

Title	高尿酸血症治療薬を志向した濃縮型ヌクレオシドトランスポーター2阻害薬の創製
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博士学位論文

高尿酸血症治療薬を志向した

濃縮型ヌクレオシドトランスポーター2阻害薬の創製

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略語表

本論文中、以下の略語を使用した。

Ac	acetyl
AM	apical membrane
Anal.	combustion elemental analysis
aq	aqueous
AUC	area under the curve; area under the concentration-time curve
BDCRB	$\label{eq:2-bromo-5,6-dichloro-1-\beta-D-ribofuranosyl-1} \textit{H-benzimidazole}$
BM	basolateral membrane
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
<i>t</i> -Bu	<i>tert</i> -butyl
calcd	calculated
Cbz	benzyloxycarbonyl
Cbz-OSu	N-(benzyloxycarbonyloxy)succinimide
CDI	1,1'-carbonyldiimidazole
CL _{tot}	plasma total clearance
C_{\max}	maximal plasma concentration
CNT	concentrative nucleoside transporter
compd	compound
DCE	1,2-dichloroethane
DCM	dichloromethane
dec	decomposition
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMEM	Dulbecco's modified Eagle's medium
DMF	<i>N</i> , <i>N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DRB	5,6-dichloro-1-β-D-ribofuranosyl-1 <i>H</i> -benzimidazole
ENT	equilibrative nucleoside transporter
Et	ethyl

bioavailability
human concentrative nucleoside transporter
human equilibrative nucleoside transporter
4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
human ether-a-go-go-related gene
high-performance liquid chromatography; high-pressure liquid chromatography
high-resolution mass spectrometry
isopropyl
Japanese Pharmacopoeia 2nd Fluid for dissolution test
Michaelis constant
logarithm of distribution coefficient
logarithm of distribution coefficient at pH 6.5
meta-
methyl
melting point
nitrobenzylmercaptopurine riboside; $6-[(4-nitrobenzyl)thio]-9-\beta-D-ribofuranosyl-9H-purine$
nuclear magnetic resonance
nucleoside transporter
ortho-
para-
phenyl
phthaloyl
parts per million
propyl
quality of life
quantitative
rat concentrative nucleoside transporter
reference
ribonucleic acid
room temperature
reverse transcription polymerase chain reaction
standard error of the mean
solute carrier
tert-butyldimethylsilyl
trifluoromethanesulfonyl

TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
$t_{1/2}$	elimination half-life
THF	tetrahydrofuran
<i>t</i> _{max}	time-to-maximal plasma concentration
TMS	trimethylsilyl
Tris	tris(hydroxymethyl)aminomethane
URAT1	urate transporter 1
V _{dss}	volume of distribution; apparent volume of distribution of a drug at steady state
XO	xanthine oxidase

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序論

尿酸は、プリン体の代謝産物であり、ほとんどの哺乳類では尿酸酸化酵素(ウリカーゼ)により、さら にアラントインに代謝されて排泄される。しかし、霊長類の進化の過程で起きた突然変異によりヒトで は尿酸酸化酵素の活性が失われているため^{1,2}、尿酸がプリン体の最終代謝産物として直接排泄される (図 1)³。



Figure 1. The difference in the end product of purine metabolism between most mammals and humans.

高尿酸血症は、尿酸産生量の増大、尿酸排泄量の減少、または両者の組み合わせにより、尿酸の産生量と排泄量の不均衡が生じ、血液中の尿酸濃度が異常に高まった状態である。国際的に統一された診断基準はないが、日本痛風・核酸代謝学会が発行するガイドラインによると、性や年齢を問わず、「血清尿酸値が 7.0 mg/dL を超えるもの」と定義されている⁴。高尿酸血症が持続すると、痛風関節炎や腎障害などの尿酸塩沈着症の主要な危険因子になることが広く認識されている。一方、近年の相次ぐ報告によると、高尿酸血症は生活習慣病と高率に合併し、心筋梗塞や脳梗塞などの動脈硬化性疾患の発症リスクを高める可能性が示唆されており、高尿酸血症を治療する意義が一段と深まりつつある⁴⁻¹²。

高尿酸血症の治療においては、血清尿酸値を一定水準以下にコントロールすることにより、尿酸塩沈 着症の発症を回避することが第一目標である⁴。日本国内では、生活習慣の是正を基本とする治療方針 が主流だが、血清尿酸値のコントロールが不十分な場合には、薬物治療も適宜導入される。高尿酸血症 治療薬(尿酸降下薬)は、作用機序の違いにより、尿酸生成抑制薬と尿酸排泄促進薬に大別される。現在 我が国では、臨床的にそれぞれ3剤が使用されている。

尿酸生成抑制薬(図 2)は、プリン代謝の最終段階を触媒するキサンチンオキシダーゼ(XO)を阻害する ことにより、尿酸生成量を減らし、血清尿酸値を低下させる¹³。従来は、40年以上にわたりアロプリノ ール1がグローバルスタンダードとして使用されていたが、プリン類似の化学構造を有するために核酸 代謝酵素にも影響を及ぼし、皮膚粘膜眼症候群(Stevens-Johnson syndrome)、中毒性表皮壊死症(Lyell's

1

syndrome)、剥脱性皮膚炎等の重篤な皮膚障害または過敏性血管炎を起こすリスクを内包していることから、安全性に優れた新しい薬剤の開発が望まれていた。フェブキソスタット2およびトピロキソスタット3は、このようなニーズに応えた新薬であり、1のようなプリン類似の骨格を回避した化学構造式 を有している。従って、キサンチンオキシダーゼに対する選択性が高く^{14,15}、治療効果ならびに安全性 の両面で1を凌駕している¹⁶⁻²⁰。しかし一方で、キサンチンオキシダーゼ阻害薬による治療で十分な効 果が得られない患者(ノンレスポンダー)が存在するなど依然として問題点がある^{21,22}。



Figure 2. Structural formulas of clinically used xanthine oxidase inhibitors.

尿酸排泄促進薬(図 3)は、主として近位尿細管の管腔側に発現して尿酸の再吸収を担っている尿酸ト ランスポーター(URAT1)の機能を抑制することにより、尿酸の再吸収量を減らし、血清尿酸値を低下さ せる²³。ベンズブロマロン4は、尿酸排泄促進作用が最も強く、現在我が国で最も多く用いられる尿酸 排泄促進薬である。しかし、劇症肝炎等の肝障害のリスクを秘める薬物であることから、投与開始後半 年間は定期的な肝機能検査が義務付けられている⁴。プロベネシド**5**やブコローム**6**も尿酸排泄促進薬 として使用されるが、腎障害が進行している患者では効果が減弱するほか、薬物相互作用に対するケア が必要である⁴。その他、尿酸排泄促進薬は尿路結石の形成を促進するため、尿路結石の既往ないし合 併のある患者には原則禁忌である⁴。



Figure 3. Structural formulas of clinically used uricosuric agents.

以上述べたように、有効性および安全性の両面を満たす高尿酸血症治療薬が存在していないのが現状 である。従って、既存薬の問題点を解消しうる新しい高尿酸血症治療薬を提供することは大変意義深い。 特に、既存薬には、その作用機序に起因する限界や欠点が挙げられることから、単独のみならず、既存 薬と併用して治療効果を高められるような新規作用機序の治療薬は利用価値が高いと考えられる。

血清尿酸値は、食物から摂取する外因性のプリン体、プリン体の異化、そして腎臓や腸管からの尿酸 排泄の三者を主軸とするバランスにより規定されている(図 4)^{24,25}。従って、プリン体の過剰摂取、プリ ン体の異化亢進、尿酸の排泄量低下、あるいはこれらの組み合わせにより、高尿酸血症が惹起されると 考えられる。前述の通り、既存の高尿酸血症治療薬には、プリン体の異化を抑制するキサンチンオキシ ダーゼ阻害薬と尿酸の排泄量を増加させる尿酸排泄促進薬の二つタイプが存在しているが、プリン体の 過剰摂取を抑えるような高尿酸血症治療薬はこれまで開発されていない。



Figure 4. Main factors affecting serum urate level.

一方、経口的に摂取されたプリン体と高尿酸血症の因果関係を示唆する研究結果はこれまで数多く報告されている。例えばYuらは、健常者に酵母由来のRNAを1日に4g、数日間摂取させると、血清尿酸値は2-3 mg/dL上昇し、高尿酸血症を呈することを報告している²⁶。また、Emmersonは、食事のプリン体を制限することで、血清尿酸値の著明な低下が認められる症例を報告している²⁷。さらに、Choiらは、肉類や魚介類などのプリン体を多く含む食品の消費量が多いほど血清尿酸値は高値を示すことを報告している²⁸。これらの知見は、経口摂取されたプリン体が血清尿酸値の上昇に寄与すること、およびプリン体の経口摂取を制限することが高尿酸血症の有望な治療方法になることを示唆している。しかしながら、プリン体の経口摂取を制限することは、即ち食事内容のバリエーションを狭めることであり、栄養障害に陥る危険性やQOLの低下に繋がる可能性が懸念される。従って、たとえ実践しても長期間継続することが難しく、失敗に終わるケースも多いと予想される。そこで筆者は、プリン体の吸収を強力に抑制する薬物を創製することにより、プリン体制限食に代わるような新しい作用機序の高尿酸血症

- 第一章 標的分子の選定と新規 hCNT2 阻害薬の創出
- 第二章 リード化合物の創製
- 第三章 医薬品候補化合物の創製
- 第四章 活性コンホメーションに関する考察

の順にその内容を記述する。

本論

第一章 標的分子の選定と新規 hCNT2 阻害薬の創出

第一節 標的分子の選定

食物中のプリン体には、DNA や RNA、オリゴヌクレオチド、プリンヌクレオチド、プリンヌクレオ シド、プリン塩基など様々な形態があるが、これらはいずれも高親水性(高極性)や高分子量などの特性 を有することから直接細胞膜を通過するとは考えにくい。現在、経口摂取されたプリン体は、プリンヌ クレオシドまたはプリン塩基まで分解されたのちに吸収されると考えられており²⁹、この過程にはヌク レオシドトランスポーター(NT)と呼ばれる膜タンパク質が関与することが知られている(図 1-1)³⁰⁻³³。



Figure 1-1. Purine absorption in the gastrointestinal tract.

哺乳類の NT は、濃縮型 NT (concentrative nucleoside transporter, CNT) および受動拡散型 NT (equilibrative nucleoside transporter, ENT) に大別され、現在それぞれ 3 種 (CNT1-3) および 4 種 (ENT1-4) のサブタイプ が同定されており、組織における分布や基質選択性などもかなり詳しく調べられている ³⁰⁻³⁴。表 1-1 に ヒトの NT を一覧で示す。ヒト ENT3 および ENT4 は酸性条件下で機能する特殊な NT であり、標的分子の候補から除外した。ヒト小腸上皮細胞におけるこれら NT の細胞局在については、CNTs が頂端膜 (apical membrane, AM) 側、ENT (s) が側底膜 (basolateral membrane, BM) 側であることが明らかにされて おり、輸送の方向性が明確に規定されている (図 1-2)³³。この知見から、吸収抑制薬を目指す上では、標 的分子として CNTs の方が良いと考えた。ヒト CNTs (hCNT1-3)の基質選択性を表 1-2 に示す。hCNT1 は、ピリミジンヌクレオシドとアデノシンを基質とするが、アデノシンについては高親和性かつ低容量 (high affinity and low-capacity)での輸送であり、実質的にピリミジン特異的トランスポーターである ³¹。

hCNT2 は、プリンヌクレオシドおよびウリジンを基質とするプリンヌクレオシド選択的トランスポータ ーである。hCNT3 は、すべてのヌクレオシドを基質とする非選択的トランスポーターである。また、 hCNTs はいずれも核酸塩基を基質としない。以上、薬物吸収の大半を占める小腸の上皮細胞における細 胞局在および基質選択性に関する知見から、本研究においては、小腸上皮細胞の頂端膜側でプリンヌク レオシドの吸収に関与する hCNT2、hCNT3、または両者を標的分子として選択するのが良いと考えた。 続いて、ヒトの消化管における NT の発現プロファイルを定量リアルタイム RT-PCR 法により調べた(図 1-3)³⁵。hCNT2 は消化管全般に発現量が多く、特に小腸上部の十二指腸および空腸に多く発現していた。 一方、hCNT3 は、全般的に発現量が少なく、小腸下部の回腸でのみ hCNT2 と同程度の発現が見られた。 以上のデータは、プリン体の消化管吸収において、hCNT2 が中心的な役割を果たすことを示唆している。 よって、本研究では、hCNT2 を標的分子に選択した。

Table 1-1. Human Nucleoside Transporters
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human gene name	protein name	transport type
SLC28A1	CNT1	concentrative, Na ⁺ -dependent
SLC28A2	CNT2	concentrative, Na ⁺ -dependent
SLC28A3	CNT3	concentrative, Na ⁺ and/or H ⁺ -dependent
SLC29A1	ENT1	facilitated diffusion
SLC29A2	ENT2	facilitated diffusion
SLC29A3	ENT3	unclear, possively H ⁺ -linked
SLC29A4	ENT4	unclear, possively H ⁺ -linked





Figure 1-2. Schematic representation of the plasma membrane distributions of human CNTs and ENTs in intestine.

muhatrata		nucleoside transporter ^a			
substrate	hCNT1	hCNT2	hCNT3		
purine nucleosides	adenosine	Т	Т	Т	
	guanosine	NT	Т	Т	
	inosine	NT	Т	Т	
pyrimidine nucleosides	cytidine	Т	NT	Т	
	thymidine	Т	NT	Т	
	uridine	Т	Т	Т	
nucleobases		NT	NT	NT	

Table 1-2. Substrate Selectivities of hCNTs

^{*a*}T, transported; NT, not transported.



Figure 1-3. Expression profiles of nucleoside transporters in human digestive tract tissues and HeLa cells. Quantitative real-time RT-PCR was performed with primers and Taqman probes. F. Stomach: Fundus of stomach, C. Stomach: Corpus of stomach, As. Colon: Ascending colon. (A) Expression profiles of hCNT1, hCNT2, and hCNT3 in human digestive tract tissues and HeLa cells. (B) Expression profiles of hENT1 and hENT2 in human digestive tract tissues and HeLa cells. Copy numbers per 1 ng total RNA are expressed as the mean \pm SEM (n = 3).

第二節 新規 hCNT2 阻害薬の創出³⁶

第一節では、ヒトの消化管からのプリン体の吸収には、hCNT2 が中心的な役割を果たすと推定した。 従って、その機能を阻害することにより、食事由来のプリン体による血清尿酸値の上昇を抑制すること ができるとの仮説が成り立つ。そこで、既存の hCNT2 阻害薬を用い、この仮説を検証しようと考えた。

既に医薬品の標的分子としての地位が確立されている ENT 阻害薬とは対照的に、CNT 阻害薬に関す る報告例は現在も非常に少ない。既存の情報からは、図 1-4 に示す 5-フルオロウリジン 7³⁷、2'-デオキシ -5-フルオロウリジン 8^{37,38}、フロリジン 9^{39,40}、および 7,8,3'-トリヒドロキシフラボン 10⁴⁰の 4 化合物が 比較的強力な hCNT2 阻害薬であると考えられたが、これら化合物の hCNT2 阻害活性の文献記載値は、 それぞれ異なる実験系での評価結果であり、同一条件下における活性の強弱は不明であった。そこで、 hCNT2 を一過性に発現した COS-7 細胞を用いる評価系を新たに構築し、ナトリウムイオン依存的なイ ノシン取り込みに対するこれら化合物群の影響を調べた。その結果、いずれの化合物も IC₅₀値が 100 μM を上回る弱い hCNT2 阻害薬であることが明らかとなり、より高活性な hCNT2 阻害薬を新たに見出す必 要性があると判断した。



Figure 1-4. Inhibitory effects of known hCNT2 inhibitors on Na⁺-dependent inosine uptake in COS-7 cells transiently expressing hCNT2.

前述の通り、CNT 阻害薬に関する報告例は非常に少なく、ほとんど手がかりの無い状態で新たな阻害 薬を見出さねばならなかった。そこで、hCNT2 と確実に相互作用する輸送基質に着目し、その構造を軽 微なものから段階的に修飾することにより、最終的に優れた阻害薬へと転換できないか検討することに した。表 1-2 に示した通り、hCNT2 はプリンヌクレオシドとウリジンを基質とするが、プリンヌクレオ シドの Km 値はウリジンより低値であることが知られている^{30,31,33,41}。即ち、プリンヌクレオシドの方が hCNT2 に対する親和性が高い。また、プリンヌクレオシドの中では、アデノシンの Km 値がグアノシン より低値であることも報告されている³⁰。さらに、アデノシンとイノシンの Km 値はほぼ同等だが⁴¹、ア デノシン誘導体から対応するイノシン誘導体への化学的変換は比較的容易に行える。以上より、化学修 飾する対象の輸送基質には、アデノシンを選択した。次に、実際の修飾部位について考えた。hCNT2 は、 表 1-2 に示した 4 種の天然ヌクレオシドのほかに、図 1-5 に示すリバビリン(ribavirin)やベンズイミダゾ ールヌクレオシドなど、塩基部が非天然型のヌクレオシド系化合物を基質または阻害薬として認識する ことが知られている^{38,42,43}。一方、糖部については、3'位水酸基が hCNT2 による基質または阻害薬の認 識にとって極めて重要であることや、糖部のコンホメーションの違いにより hCNT2 の基質認識性に差 が生じることなどが報告されている^{32,37,44,45}。以上より、hCNT2 は塩基部より糖部を厳密に認識してい ると考え、修飾部位は主に塩基部とした。



Figure 1-5. Structural formulas of unnatural nucleosides recognized by hCNT2.

まず、初期検討としてアデノシンの 2、 N^6 、8、および 5'位に比較的軽微な修飾を加えた化合物群 1-1– 1-24 を合成し、それらの hCNT2 阻害活性を評価した。なお、特に断らない限り、これ以降の化合物群 の一次評価は、前述の COS-7 細胞によるナトリウムイオン依存的なイノシン取り込み実験により行っ た。結果を表 1-3 に示す。塩基部を修飾した化合物群 1-1–1-12 の中では、8-(ベンジルアミノ)アデノシ ン 1-12 (IC₅₀ = 52 μ M)に最も強力な hCNT2 阻害活性が認められ、しかもその活性は、図 1-4 に示した既 知の hCNT2 阻害薬の中で最も高活性だった 7 (IC₅₀ = 216 μ M)を凌駕するものであった。一方、糖部を修 飾した化合物群 1-13–1-24 には、1-12 を上回る hCNT2 阻害活性を示すものはなかった。そこで、1-12 が シード化合物として相応しいかどうか見極めることにした。

Table 1-3. Inhibitory Effects of Compounds 1-1–1-24 on Na⁺-Dependent Inosine Uptakein COS-7 Cells Transiently Expressing hCNT2

			HO OH HO OH B 1-5: R = Me		$HO \qquad HO \qquad$		
	1-2 : R = Et 1-3 : R = pentyl		1-6 : R = Et 1-7 : R = pent	tvl	1-10: R 1-11 [·] R	= Et = pentyl	
	1-4 : R = Bn		1-8 : R = Bn	.y.	1-12 : R	= Bn	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$							
	D		E 1 17: P - Mo			4-	
1-1. 1-14	3: R = Me 4: R = Et		1-17: R = Me 1-18: R = Et		1-22 : R = Et		
1-1: 1-1(5: R = pentyl 6: R = Bn		1-19 : R = pentyl 1-20 : R = Bn		1-23 : R = pentyl 1-24 : R = Bn		
			IC 50 ($(\mathbf{M})^a$			
R		D	C	D	Б	Б	
	A	В	<u> </u>	D	E	Г	
Me	inactive ^b	>100°	>1000 ^d	>100°	>100 ^c	>100°	
Et	>100°	>100°	>1000 ^d	>100°	>100 ^c	$>1000^{d}$	
pentyl	inactive ^b	>100°	>1000 ^d	>100°	>100°	>100°	
Bn	>100 ^c	inactive ^b	52 ± 3.8	>100 ^c	>100°	>100°	
	7			$216 \pm 40 \ \mu$ l	M		

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}No inhibition was observed at the maximum concentration of 1000 μ M. ^{*c*}Inhibition was less than 50% at the maximum concentration of 1000 μ M.

まず、ベンジルアミノ基の窒素原子について検討した(表 1-4)。窒素原子を炭素、酸素、および硫黄の 各原子で置換した化合物 1-25-1-27 を合成し、hCNT2 阻害活性を評価したところ、炭素原子に置換した 1-25 に僅かな活性が認められるのみで、他は失活した。さらに、窒素原子をメチル化した 1-28 を合成し て評価したが、これも失活した。続いて、ベンジルアミノ基のメチレンリンカーについて検討した(表 1-5)。メチレン基を除去または鎖伸長した化合物群 1-29-1-31 では hCNT2 阻害活性が減弱した。また、メ チレン基にメチル基を導入した 1-32 および 1-33 では失活するか活性が大幅に減弱した。最後に、ベン ゼン環をシクロアルキル基やヘテロアリール基で置換したが、すべての化合物で hCNT2 阻害活性が減 弱または消失した(表 1-6)。以上の結果より、化合物 1-12 がシード化合物として妥当であることが示さ れた。さらに、本化合物の 8 位に結合するベンジルアミノ基が、強力な hCNT2 阻害活性の発現に必須 の部分構造であることも明らかになった。

Table 1-4. Inhibitory Effects of Compounds 1-25–1-28 on Na⁺-Dependent Inosine Uptake inCOS-7 Cells Transiently Expressing hCNT2



Table 1-5. Inhibitory Effects of Compounds 1-29–1-33 on Na+-Dependent Inosine Uptake inCOS-7 Cells Transiently Expressing hCNT2



НО ОН			Ч/ НО҅́́́́ОН		
compd	Х	$IC_{50} (\mu M)^a$	compd	R	IC ₅₀ (µM) ^a
1-25	CH ₂	>1000 ^b	1-29	Ph	289 ± 87
1-26	0	inactive ^c	1-30	PhCH ₂ CH ₂	233 ± 19
1-27	S	inactive ^c	1-31	PhCH ₂ CH ₂ CH ₂	536 ± 89
1-28	NMe	inactive ^c	1-32	(R)-PhCH(Me)	inactive ^c
1-12	NII	52 + 2.8	1-33	(S)-PhCH(Me)	>1000 ^b
	INП	32 ± 3.8	1-12	PhCH ₂	52 ± 3.8

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}Inhibition was less than 50% at the maximum concentration of 1000 μ M. ^{*c*}No inhibition was observed at the maximum concentration of 1000 μ M.

Table 1-6. Inhibitory Effects of Compounds 1-34–1-43 on Na⁺-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2



^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}No inhibition was observed at the maximum concentration of 100 μ M. ^{*c*}Inhibition was less than 50% at the maximum concentration of 1000 μ M. ^{*d*}Inhibition was less than 50% at the maximum concentration of 100 μ M.

前段の検討結果より、8-(ベンジルアミノ)アデノシンを部分構造とする化合物群に hCNT2 阻害活性 の更なる向上を期待した。そこで、1-12 のベンゼン環に単純な置換基を導入し、構造活性相関を調べた (表 1-7)。その結果、塩素原子を導入した 1-53 および 1-54 では約 10 倍の hCNT2 阻害活性の向上が認め られ、他の誘導体でも置換基の電子的性質や置換位置によらず、hCNT2 阻害活性は概ね向上した。一方、 2-メトキシ誘導体 1-47 では明らかな活性の減弱が認められたことより、1-12 が hCNT2 と相互作用する 際の 2 位周辺には空間的制限があることが示唆された。

Table 1-7. Inhibitory Effects of Compounds 1-44–1-58 on Na⁺-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2



^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}Inhibition was less than 50% at the maximum concentration of 100 μ M.

続いて、表 1-6 に示した結果を踏まえ、末端のベンゼン環を同じく炭素芳香環であるナフタレン環に 置き換えた化合物 1-59 および 1-60 を合成して評価したところ、両化合物の hCNT2 阻害活性は 1-12 に 比べ約 10 倍向上していた(表 1-8)。そこで、医薬品らしさの観点から、ナフタレン環を同じく 2 つのベ ンゼン環から構成されるビフェニルに置き換えたところ、置換様式の違いにより、明確な活性差が生じ た(表 1-8)。オルト異性体 1-61 では、hCNT2 阻害活性が減弱したが、この結果は、前段にて 2-メトキシ 誘導体 1-47 について言及したように、2 位周辺の空間的制限の存在を改めて示唆するものと理解でき る。次に、メタ異性体 1-62 では、hCNT2 阻害活性が約 2 倍向上しており、表 1-7 に示した置換基群と同 様の効果が認められた。一方、パラ異性体 1-63 では、hCNT2 阻害活性が約 80 倍向上し、導入したフェ ニル基が hCNT2 との新たな相互作用を獲得したことが示唆された。

Table 1-8. Inhibitory Effects of Compounds 1-59–1-63 on Na⁺-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2



	no on	
compd	R	IC ₅₀ (µM) ^a
1-59	1-naphthyl	5.7 ± 1.1
1-60	2-naphthyl	5.3 ± 1.7
1-61	biphenyl-2-yl	$>100^{b}$
1-62	biphenyl-3-yl	21 ± 9.8
1-63	biphenyl-4-yl	0.64 ± 0.19
1-12	Ph	52 ± 3.8

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}Inhibition was less than 50% at the maximum concentration of 100 μ M.

そこで、1-63の末端のベンゼン環の適切な位置を知る目的で、2 つのベンゼン環を炭素、酸素、および硫黄原子で繋いだ1-64-1-66をそれぞれ合成してhCNT2阻害活性を評価したところ、全例で阻害活性が減弱した(表1-9)。この結果より、2 つのベンゼン環は直接結合していることが重要だとわかった。次に、1-63の末端のフェニル基をシクロアルキル基で置換した1-67-1-69を合成して評価した(表1-10)。シクロプロピル基で置換した1-67のhCNT2阻害活性は1-63に比べやや減弱したが、1-12との比較においては約26倍強力であり、また1-64-1-66を凌駕するものであった。一方、シクロペンチル基およびシクロヘキシル基で置換した1-68および1-69は、1-63と遜色ないhCNT2阻害活性を示した。以上より、1-12のベンゼン環のパラ位に直接結合する炭素環は、hCNT2との相互作用にとって好ましく、hCNT2阻害活性を大きく向上させる効果があるとわかった。

Table 1-9. Inhibitory Effects of Compounds 1-64–1-66 on Na⁺-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2 Table 1-10. Inhibitory Effects of Compounds 1-67–1-69 on Na⁺-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2

compd	Х	$IC_{50} (\mu M)^a$	-	compd	R	$IC_{50} (\mu M)^a$
1-64	CH ₂	6.0 ± 0.8		1-67	cyclopropyl	2.0 ± 0.64
1-65	0	3.3 ± 0.8		1-68	cyclopentyl	0.53 ± 0.07
1-66	S	5.2 ± 1.4		1-69	cyclohexyl	0.87 ± 0.30
1-63	single bond	0.64 ± 0.19	-	1-63	Ph	0.64 ± 0.19

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated.

以上、本節では、新規かつ強力な hCNT2 阻害薬の創出について述べた。次章では、特に強力な hCNT2 阻害活性を示した 1-63、1-68、および 1-69 のうち、類縁体合成の難易度を考慮して優先した化合物 1-63 からのリード創製について述べる。

化合物 1-1-1-4 は、2-クロロアデノシン 11 と対応するアミンとを縮合することにより合成した(スキ ーム 1-1)。

Scheme 1-1. Synthesis of Compounds 1-1–1-4^a



^{*a*}Reagents and conditions: (a) aq MeNH₂ or aq EtNH₂, EtOH, 100 °C, in a screw tube; (b) pentylamine or BnNH₂, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube.

化合物 1-5-1-7 は、6-クロロプリンリボシド 12 と対応するアミンとを縮合することにより合成した (スキーム 1-2)。

Scheme 1-2. Synthesis of Compounds 1-5–1-7^{*a*}



^{*a*}Reagents and conditions: (a) aq MeNH₂ or aq EtNH₂, EtOH, 100 °C, in a screw tube; (b) pentylamine, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube.

化合物 1-9-1-12、1-28、1-30-1-59、1-61-1-63、および 1-65 は、8-ブロモアデノシン 13 と対応するア ミンとを縮合することにより合成した(スキーム 1-3)。各化合物の単離収率を表 1-11 に示す。なお、化 合物 1-32 の合成においては、反応が効率良く進行しなかったため、他の場合より高温かつマイクロ波照 射下で反応を行うことにより、単離収率が 43%まで向上した。また、化合物 1-33 も同様の反応条件を用 い合成したが、この場合は未反応の 13 との分離が困難であった。そこで、両者を一旦トリアセチル化体へと導き、シリカゲルカラムクロマトグラフィーにより分離したのち、トリアセチル化体 1-70 をナト リウムメトキシドで処理してアセチル基を除去することにより、通算 40%の単離収率で目的物 1-33 を 得た。

Scheme 1-3. Synthesis of Compounds 1-9–1-12, 1-28, 1-30–1-59, 1-61–1-63, and 1-65^a



^{*a*}Reagents and conditions: (a) aq R¹R²NH, EtOH, 100 °C, in a screw tube; (b) R¹R²NH, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube; (c) R¹R²NH, *i*-Pr₂NEt, EtOH, 150 °C, in a sealed tube, microwave irradiation; (d) Ac₂O, Et₃N, DMAP, MeCN, rt; (e) NaOMe, MeOH, rt.

compd	\mathbb{R}^1	\mathbb{R}^2	yield	compd	\mathbf{R}^1	\mathbb{R}^2	yield
1-9	Me	Н	61% ^{<i>a</i>}	1-40	thiophen-3-ylmethyl	Н	89% ^b
1-10	Et	Н	73% ^a	1-41	pyridin-2-ylmethyl	Н	53% ^b
1-11	pentyl	Н	81% ^b	1-42	pyridin-3-ylmethyl	Н	91% ^b
1-12	Bn	Н	93% ^b	1-43	pyridin-4-ylmethyl	Н	87% ^b
1-28	Bn	Me	91% ^b	1-44	2-methylbenzyl	Н	$87\%^b$
1-30	PhCH ₂ CH ₂	Н	82% ^b	1-45	3-methylbenzyl	Н	$80\%^b$
1-31	PhCH ₂ CH ₂ CH ₂ CH ₂	Н	86% ^b	1-46	4-methylbenzyl	Н	37% ^b
1-32	(R)-PhCH(Me)	Н	43% ^c	1-47	2-methoxybenzyl	Н	44% ^b
1-33	(S)-PhCH(Me)	Н	40% ^{c,d}	1-48	3-methoxybenzyl	Н	$88\%^b$
1-34	cyclopropylmethyl	Н	75% ^b	1-49	4-methoxybenzyl	Н	91% ^b
1-35	cyclopentylmethyl	Н	77% ^b	1-50	2-fluorobenzyl	Н	81% ^b
1-36	cyclohexylmethyl	Н	91% ^b	1-51	3-fluorobenzyl	Н	84% ^b
1-37	furan-2-ylmethyl	Н	81% ^b	1-52	4-fluorobenzyl	Н	89% ^b
1-38	furan-3-ylmethyl	Н	82% ^b	1-53	2-chlorobenzyl	Н	96% ^b
1-39	thiophen-2-ylmethyl	Н	76% ^b	1-54	3-chlorobenzyl	Н	81% ^b

Table 1-11. Isolated Yields of Compounds 1-9-1-12, 1-28, 1-30-1-59, 1-61-1-63, and 1-65

(continued on the following page)

Table 1-11. continued

compd	\mathbf{R}^1	\mathbb{R}^2	yield	compd	\mathbb{R}^1	\mathbb{R}^2	yield
1-55	4-chlorobenzyl	Н	83% ^b	1-61	biphenyl-2-ylmethyl	Н	93% ^b
1-56	2-(trifluoromethyl)benzyl	Н	50% ^b	1-62	biphenyl-3-ylmethyl	Н	86% ^b
1-57	3-(trifluoromethyl)benzyl	Н	83% ^b	1-63	biphenyl-4-ylmethyl	Н	59% ^b
1-58	4-(trifluoromethyl)benzyl	Н	85% ^b	1-65	4-phenoxybenzyl	Н	89% ^b
1-59	1-naphthylmethyl	Н	$86\%^b$				

^{*a*}Reaction condition "a" was used. ^{*b*}Reaction condition "b" was used. ^{*c*}Reaction condition "c" was used. ^{*d*}Isolated yield for 3 steps.

化合物 1-60 は、2-(ブロモメチル)ナフタレン 14 からガブリエル法により合成したアミン 1-72 と 8-ブ ロモアデノシン 13 とを縮合することにより合成した(スキーム 1-4)。

Scheme 1-4. Synthesis of Compound 1-60^a



^{*a*}Reagents and conditions: (a) phthalimide potassium salt, DMF, 50 °C, 83%; (b) H₂NNH₂·H₂O, MeOH, reflux, 97%; (c) **13**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 86%.

化合物 1-64 は、スキーム 1-5 に示す通り合成した。4-ベンジル安息香酸 15 を 1,1'-カルボニルジイミ ダゾールと反応させ、次いでアンモニア水で処理することによりアミド 1-73 へと導き、これをトリエチ ルアミンの存在下、トリフルオロ酢酸無水物で処理して脱水し、ニトリル 1-74 とした。1-74 のシアノ基 を水素化アルミニウムリチウムで還元し、生じたアミン 1-75 と 8-ブロモアデノシン 13 とを縮合するこ とにより目的物 1-64 を得た。 Scheme 1-5. Synthesis of Compound 1-64^a



^{*a*}Reagents and conditions: (a) CDI, THF, rt, then 28% aq NH₃, 99%; (b) TFAA, Et₃N, DCM, rt, 90%; (c) LiAlH₄, THF, 60 °C, 90%; (d) **13**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 88%.

化合物 1-66 は、スキーム 1-6 に示す通り合成した。Li らの方法 ⁴⁶に従い、4-ブロモベンゾニトリル 16 から合成した 4-(フェニルチオ)ベンゾニトリル 17 のシアノ基を水素化アルミニウムリチウムで還元し、 生じたアミン 1-76 と 8-ブロモアデノシン 13 とを縮合することにより目的物 1-66 を得た。

Scheme 1-6. Synthesis of Compound 1-66^a



^aReagents and conditions: (a) LiAlH₄, THF, 60 °C, 83%; (b) **13**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 85%.

化合物 1-67 は、スキーム 1-7 に示す通り合成した。4-シクロプロピルベンゾニトリル 18 のシアノ基 を水素化アルミニウムリチウムで還元し、生じたアミン 1-77 と Schoffers らの方法 ⁴⁷ に従い別途合成し たアデノシン誘導体 19 とを縮合することにより 1-78 へと導いたのち、ふっ化アンモニウムで処理して TBS 基を除去することにより目的物 1-67 を得た。なお、アミン 1-77 と 8-ブロモアデノシン 13 とを縮合 して直接 1-67 を合成することも可能であったが、その場合には生成物の溶解性の問題により精製操作 がやや煩雑になった。

Scheme 1-7. Synthesis of Compound 1-67^a



^{*a*}Reagents and conditions: (a) LiAlH₄, THF, 60 °C, quant.; (b) *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 97%; (c) NH₄F, MeOH, reflux, quant.

化合物 1-68 は、スキーム 1-8 に示す通り合成した。Kwong らの方法 ⁴⁸に従い、4-シアノフェノール 20 から合成したトリフレート 21 に対し、鈴木-宮浦カップリングによりシクロペンテニル基を導入し、さらに接触水素化により二重結合を還元してニトリル 1-80 とした。1-80 のシアノ基を水素化アルミニウムリチウムで還元し、生じたアミン 1-81 と 8-ブロモアデノシン 13 とを縮合することにより目的物 1-68 を得た。





^{*a*}Reagents and conditions: (a) (cyclopent-1-en-1-yl)boronic acid, Pd(PPh₃)₄, Na₂CO₃, DME, H₂O, reflux, 98%; (b) H₂, 5% Pt–C, AcOEt, rt, 84%; (c) LiAlH₄, THF, 60 °C, quant.; (d) **13**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube,

86%.

化合物 1-69 は、スキーム 1-9 に示す通り合成した。4-シクロヘキシル安息香酸 22 のカルボキシ基を 水素化アルミニウムリチウムで還元し、得られたアルコール 1-82 を光延反応によりフタルイミドと反 応させて化合物 1-83 としたのち、ヒドラジン一水和物で処理してフタロイル基を除去した。生じたアミ ン 1-84 とアデノシン誘導体 19⁴⁷ とを縮合して化合物 1-85 へと導いたのち、ふっ化アンモニウムで処理 して TBS 基を除去することにより目的物 1-69 を得た。

Scheme 1-9. Synthesis of Compound 1-69^a



^{*a*}Reagents and conditions: (a) LiAlH₄, THF, 60 °C, 91%; (b) phthalimide, DIAD, PPh₃, THF. rt, 90%; (c) $H_2NNH_2 \cdot H_2O$, CHCl₃, EtOH, rt, quant.; (d) **19**⁴⁷, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, quant; (e) NH₄F, MeOH, reflux, 90%.

化合物 1-13-1-24 は、スキーム 1-10 に示す通り合成した。2',3'-O-イソプロピリデンアデノシン 23 を ピリジンの存在下、無水酢酸と反応させて 5'位水酸基を選択的にアセチル化して化合物 1-86 とし、次い で 70%蟻酸水溶液で処理してイソプロピリデン基を除去することにより目的物 1-13 を得た。また、23 を DMAP の存在下、酸クロリドまたはクロロ蟻酸エステルと反応させて 5'位水酸基を選択的にアシル 化またはアルコキシカルボニル化して化合物 1-87-1-93 とし、次いで 70%蟻酸水溶液で処理してイソプ ロピリデン基を除去することにより目的物 1-14-1-20 を得た。なお、化合物 1-89 は、さらに N⁶位がフェ ニルアセチル化された副生成物との混合物として得られたため、Nowak らの方法⁴⁹を用いて N⁶位のフ ェニルアセチル基を選択的に除去することにより単一の生成物とした。さらに、23 をトリエチルアミン の存在下、クロロ蟻酸 4-ニトロフェニルと反応させて炭酸エステル 1-94 としたのち、対応するアミン と反応させることによりカルバメート体 1-95-1-98 へと導き、次いで 70%蟻酸水溶液で処理してイソプ ロピリデン基を除去することにより目的物 1-21-1-24 を得た。

Scheme 1-10 Synthesis of Compounds 1-13-1-24^a



^{*a*}Reagents and conditions: (a) Ac₂O, pyridine, 0 °C to rt; (b) RCOCl (R = Et, pentyl, MeO, EtO, pentyloxy, BnO), DMAP, MeCN, rt; (c) BnCOCl, DMAP, MeCN, rt, then MeOH, 120 °C, microwave irradiation; (d) 70% aq HCO₂H, rt; (e) 4-nitrophenyl chloroformate, Et₃N, MeCN, 0 °C to rt; (f) appropriate amine, Et₃N, THF, rt.

化合物 1-25 は、スキーム 1-11 に示す通り合成した。8-ブロモアデノシン 13 の水酸基をアセチル基で 保護し、次いで薗頭カップリングによりフェニルエチニル基を導入してアルキン 1-100 とした。1-100 の 三重結合を接触水素化により還元したのち、ナトリウムメトキシドで処理してアセチル基を除去するこ とにより目的物 1-25 を得た。 Scheme 1-11. Synthesis of Compound 1-25^{*a*}



^{*a*}Reagents and conditions: (a) Ac₂O, Et₃N, DMAP, MeCN, rt, 76%; (b) ethynylbenzene, Pd(PPh₃)₄, CuI, Et₃N, DMF, 80 °C, 87%; (c) H₂, 10% Pd–C, AcOEt, rt, 97%; (d) NaOMe, MeOH, rt, 89%.

化合物 1-26 は、スキーム 1-12 に示す通り合成した。アデノシン誘導体 19⁴⁷をカリウム *tert*-ブトキシ ドの存在下、ベンジルアルコール中で加熱することにより化合物 1-102 とし、これを単離することなく ふっ化アンモニウムで処理して TBS 基を除去することにより目的物 1-26 を得た。

Scheme 1-12. Synthesis of Compound 1-26^a



^aReagents and conditions: (a) *t*-BuOK, BnOH, 40 °C; (b) NH₄F, MeOH, reflux, 86% from **19**⁴⁷.

化合物 1-27 は、8-ブロモアデノシン 13 とベンジルメルカプタンとを縮合することにより合成した(ス キーム 1-13)。

Scheme 1-13. Synthesis of Compound 1-27^{*a*}



^aReagents and a condition: (a) BnSH, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 29%.

化合物 1-29 は、Schoffers らの方法⁴⁷に従い合成したアデノシン誘導体 24 をふっ化アンモニウムで処理し、TBS 基を除去することにより得た(スキーム 1-14)。





^aReagents and a condition: (a) NH₄F, MeOH, reflux, 87%.

第二章 リード化合物の創製 50

第一節 ビフェニルの立体配座制御による水溶性の改善

筆者が目標とする化合物は、主として小腸の管腔側で作用する必要がある。このことを念頭に置き、 第一章で見出したプロトタイプ阻害薬 1-63 の日本薬局方・溶出試験第 2 液 (pH 6.8, 以下 JP2 と略す)⁵¹ に対する 37 ℃ での溶解性を調べたところ、溶解度は 0.003 mg/mL と算出された。この数値は、日本薬 局方に記載されている溶解性を示す用語を参考にすると、"ほとんど溶けない"ことを意味しており、実 際に、この難溶性の問題から 1-63 を用いて高次評価を行うには限界があった。そこで、1-63 の強力な hCNT2 阻害活性を保持しつつ水溶性を改善することを課題にリード探索研究を進めることにした。

化合物の水溶性を改善する主な手段として、筆者は下記の3つがあると認識している。

① 極性基を導入し、化合物と溶媒(水)との相互作用を強化して熱力学的な溶解性を高める方法

② 結晶パッキングの鍵となる分子間の相互作用を弱め、速度論的な溶解性を高める方法

③ 化合物の塩フォーム、結晶フォーム、あるいは粒子状態を変えて溶解性を高める方法 これら3つの手段のうち、リード探索の段階で③に取り組むのは適切ではないと判断し、①および②に よる水溶性改善を検討したので、その結果について以下に詳述する。

1-63 の乏しい水溶性を改善するには、上記①に基づき、高い疎水性を有するビフェニル部位に極性基 を導入するのが良いと考え、まずは末端のベンゼン環をピリジン環で置換した化合物 2-1-2-3 を合成し、 hCNT2 阻害活性を評価した(表 2-1)。ピリジン-3-イル誘導体 2-2 は概ね 1-63 と同等の阻害活性を発現し たが、残りの 2 つの誘導体 2-1 および 2-3 の阻害活性は減弱傾向を示した。

Table 2-1. Inhibitory Effects of Compounds 2-1–2-3 on Na⁺-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2



compd	R	IC ₅₀ (µM) ^a
2-1	pyridin-2-yl	1.5 ± 0.5
2-2	pyridin-3-yl	1.0 ± 0.2
2-3	pyridin-4-yl	2.7 ± 0.9
1-63	Ph	0.64 ± 0.19

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated.

次に、ビフェニル部位に極性置換基を導入することにした。この場合は前述①に加えて②の方法も活 用できると考えられた。即ち、ビフェニル結合のオルト位に置換基を導入すると、オルト位置換基同士 の立体的反発が他の位置異性体より大きくなるため、ビフェニル部位はより一層ねじれた構造にシフト すると予想される。このように分子の平面性を崩すことにより結晶パッキングが妨げられ、化合物の溶 解性が向上する例が多数報告されている^{52,53}。そこで、フェニレンリンカーにメチル基を導入した2種 の誘導体を単純なモデル化合物として、置換基がビフェニル構造のねじれ角に与える影響を計算化学ソ フトウェア Spartan'14 (Wavefunction, Inc.)を用いた理論計算によりシミュレーションした。図2-1 に密度 汎関数法 (DFT 法)により得られた化合物の最安定配座を示す。ビフェニル結合のオルト位にメチルを導 入した誘導体 A のねじれ角は 57.4°であり、無置換体 1-63 のねじれ角 37.3°に比べて大きく増大してい た。一方、同メタ位にメチル基を導入した誘導体 B のねじれ角は 36.6°であり、無置換体 1-63 のねじれ 角 37.3°とほぼ同等であった。



Figure 2-1. Simulation of substituent effects on the twisted structure of the biphenyl moiety.

次に、上記のシミュレーションの妥当性を評価するため、フェニレンリンカーに置換基を導入した化 合物を実際に合成することにした。導入する置換基としては、前述①に基づく効果も評価できるように、 疎水性のメチル基に代えて、極性基であるメトキシ基およびエトキシ基を選択した。各化合物のJP2 に 対する溶解度を調べた結果を表 2-2 に示す。2-メトキシ誘導体 2-4 および 2-エトキシ誘導体 2-5 の溶解 度は、いずれも 1-63 に比べて大幅に向上した。一方で、対応する 3-アルコキシ誘導体 2-6 および 2-7 の 溶解度は 1-63 と同等であり改善効果が認められなかった。これらのデータは上記のシミュレーション の結果と良い相関性を示した。また、同じ極性置換基を導入して認められた差異であることから、①よ りも、②による溶解性改善効果の寄与率の方が高いと考えられた。

Table 2-2. Solubility of Compounds 2-4–2-7 in JP2

HO O OH						
compd	\mathbb{R}^1	\mathbb{R}^2	solubility in JP2 at 37 °C (mg/mL)			
2-4	OMe	Н	0.215			
2-5	OEt	Н	0.121			
2-6	Н	OMe	0.004			
2-7	Н	OEt	0.002			
1-63	Н	Н	0.003			

ビフェニル結合のオルト位に極性置換基を導入することにより、JP2 に対する溶解度の改善が可能と 実証できたので、当該位置に極性置換基を導入した化合物群をさらに合成し、hCNT2 阻害活性に及ぼす 影響を調べた(表 2-3)。ヒドロキシ誘導体 2-8 およびメトキシ誘導体 2-4 は、概ね 1-63 と同等の hCNT2 阻害活性を示したが、エトキシ、プロポキシ、およびイソプロポキシ誘導体 2-9-2-11 は、導入したアル コキシ基の炭素数および立体的嵩高さに依存して阻害活性が減弱した。これら結果より、導入するアル コキシ基の炭素数を増大する方向性は適切でないと考え、化合物 2-4 および 2-5 のアルコキシ基に極性 官能基を導入した化合物 2-11-2-13 を合成して評価したが、hCNT2 阻害活性の向上は認められなかった。

Table 2-3. Inhibitory Effects of Compounds 2-4, 2-5, and 2-8–2-13 on Na⁺-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2



aamud	D	IC ₅₀	$IC_{50} (\mu M)^a$			
compu	К	hCNT2	rCNT2			
2-8	ОН	1.2 ± 0.6	inactive ^b			
2-4	OMe	1.3 ± 0.2	inactive ^b			
2-5	OEt	2.3 ± 0.6	inactive ^b			
2-9	OPr	5.2 ± 1.5	inactive ^b			
2-10	OPr- <i>i</i>	10 ± 1.0	inactive ^b			
2-11	OCH ₂ CO ₂ Me	3.3 ± 0.8	inactive ^b			
2-12	OCH ₂ CONH ₂	5.5 ± 1.4	>100 (<5)°			
2-13	OCH ₂ CH ₂ OH	3.1 ± 0.3	>100 (49) ^c			
1-63	Н	0.64 ± 0.19	inactive ^b			
2-2		1.0 ± 0.2	>100 (11) ^c			

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}No inhibition was observed at the maximum concentration of 100 μ M. ^{*c*}Inhibition was less than 50% at the maximum concentration of 100 μ M. The inhibition% is shown in parentheses.

ここまでの検討の結果、化合物 1-63 の hCNT2 阻害活性を凌駕する化合物は見出せなかったものの、 ほぼ遜色ない hCNT2 阻害活性を示す化合物として、実際に JP2 に対する溶解度が改善された 2-メトキ シ誘導体 2-4 のほか、ビリジン-3-イル誘導体 2-2、およびヒドロキシ誘導体 2-8 を見出すことができた。 そこで、まずはげっ歯類を用い、in vivo 薬効試験を通じて創薬コンセプトの妥当性を評価するとともに、 CNT2 阻害という新規作用機序の薬物が、生体に対してどのような影響を及ぼすのか調べ、医薬品とし て開発可能かどうか早期かつ適切に判断する目的で、これら 3 化合物の rat CNT2 (rCNT2)に対する阻害 活性を評価した(表 2-3)。その結果、残念なことに、化合物 2-2 にわずかな活性が認められるのみで、残 りの 2-4 および 2-8 は不活性であることが明らかになった。このように天然型ヌクレオシドに対して同 様の基質選択性を示す hCNT2 および rCNT2 が、非天然型ヌクレオシドに対しては大きく異なる基質選 択性を示すことは既に知られており、hCNT2 と rCNT2 との間の C 末端側(C-terminal half)のアミノ酸残 基の違いに起因することが示唆されている ⁵⁴。そこで、他の誘導体の rCNT2 阻害活性も評価したが、カ ルバモイル基を有する 2-12 および水酸基を有する 2-13 に弱い阻害活性が認められるのみであった。

第二節 rCNT2 阻害活性改善の試み

前段の通り、in vivo 薬効試験を行うに際し、化合物のrCNT2 阻害活性の向上が新たな課題になった。 しかし、表 2-3 のデータを注視することにより、解決の糸口が一つ見て取れた。即ち、rCNT2 に対して 阻害活性を示さないエトキシ誘導体 2-5 と最も強力な rCNT2 阻害活性を示した 2-ヒドロキシエトキシ 誘導体 2-13 とを比較することにより、2-5 のエトキシ基の末端に水酸基を導入することが rCNT2 阻害活 性の発現または向上に重要な役割を果たしていると考えられた。そこで、rCNT2 阻害活性の向上を期待 して 2-13 のホモログ 2-14、2-15、および 2-16 を合成して評価したところ、すべての化合物で rCNT2 阻 害活性の向上が認められ、さらに hCNT2 阻害活性も向上した(表 2-4)。中でも 4-ヒドロキシブトキシ基 を有する 2-15 は、1-63 に匹敵する hCNT2 阻害活性を保持しながら、rCNT2 阻害活性が改善された化合 物であった。2-15 について JP2 に対する溶解性を評価したところ、溶解度は 0.190 mg/mL と算出され、 1-63 に比べて大幅に向上していることも明らかになった。これにより、"1-63 の強力な hCNT2 阻害活性 を保持しつつ水溶性を改善する"という当初の目標を達成することができた。また、2-15 は rCNT2 阻害 活性に改善の余地を残すものの、その JP2 に対する溶解度(0.190 mg/mL = 354 μ M)は、rCNT2 阻害活性 の指標である IC₃₀ 値(=38 μ M)を 10 倍近く上回っていることから、in vivo 薬効試験で有効性を評価すべ き化合物であると判断し、本化合物をリード化合物に位置付けて高次評価を実施することにした。

Table 2-4. in vitro Profiles of Compounds 2-13–2-16 and Solubility of 2-15 in JP2



J	nd n	IC ₅₀ (J	μ M) ^a	
compa		hCNT2	rCNT2	solubility in JP2 at 37 °C (mg/mL)
2-13	1	3.1 ± 0.3	193 ± 18	nd^c
2-14	2	1.1 ± 0.1	45 ± 2.9	nd^c
2-15	3	0.94 ± 0.24	38 ± 13	0.190
2-16	4	1.6 ± 0.1	60 ± 20	nd ^c
1-63		0.64 ± 0.19	inactive ^b	0.003

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}No inhibition was observed at the maximum concentration of 100 μ M. ^{*c*}nd, not determined.

化合物 2-15 の in vivo での有効性をラットを用いたプリン体負荷試験により評価した(図 2-2)。なお、 ラットでは尿酸酸化酵素(ウリカーゼ)が活性であり、血漿尿酸値は通常低値(<0.5-1.0 mg/dL)を示すた め³、プリン体負荷の 1 時間前にオキソン酸カリウム(ウリカーゼ阻害薬)を皮下投与して血漿尿酸値の ベースラインを上昇させた。該ラットにプリン体(adenosine:guanosine:inosine = 1:1:1, 50 mg/kg)を経口投 与すると、血漿尿酸値は有意に上昇した(黒塗り棒グラフ)。一方、プリン体と 2-15 (50 mg/kg)を同時に 経口投与すると、プリン体を単独投与した場合に比べて血漿尿酸値の上昇が抑えられ(斜線棒グラフ)、 抑制率は 42%と計算された。しかし残念なことに、この抑制効果は統計学的に有意ではなかった。この ような結果を招いた原因としては、①rCNT2 阻害活性が不十分、②rCNT2 以外の NT を介するプリンヌ クレオシドの吸収経路の寄与率が比較的高い、③プリン塩基に分解されたのちに吸収される経路の寄与 率が比較的高いなど、いくつか想定されるが、筆者は①を主な原因と考え、より強力な rCNT2 阻害活性 を示す化合物を探索することにした。



Figure 2-2. Effect of compound **2-15** on the elevation of plasma uric acid levels derived from orally administered purine nucleoside mixture (adenosine:guanosine:inosine =1:1:1, 50 mg/kg) in rats. Data are expressed as the mean \pm SEM (n = 5). ##: p < 0.01 versus a group treated with only potassium oxonate (100 mg/kg). NS, not significant.
第三節 スキャホールドホッピング (Scaffold Hopping)

リード化合物 2-15 の rCNT2 阻害活性を向上した化合物を探索するにあたり、これまで評価した化合物群の in vitro 活性データより、hCNT2 阻害活性と rCNT2 阻害活性に見られた大きな隔たりは、8-(ベンジルアミノ)アデノシンを部分構造とする化合物群に共通する特徴であると考えられた。そこで筆者は、8-(ベンジルアミノ)アデノシンを部分構造に持たない化合物を求め、本研究では未検討の方法で糖部および塩基部を変換することにより、新たな方向性を見出すことができるかどうか検討することにした。

まず、糖部に関しては、3'位水酸基が hCNT2 との相互作用に特に重要であることが報告されている ^{32,37,44}ことを念頭に置き、2-15 の β-D-リボフラノシル基を β-D-2'-デオキシリボフラノシル基および β-D-アラビノフラノシル基でそれぞれ置換した 2-17 および 2-18 を合成して評価した(表 2-5)。その結果、化 合物 2-17 では 2-15 と同等の in vitro 活性プロファイルが保持される一方、2-18 では、2-15 に比べ rCNT2 阻害活性のみならず、hCNT2 阻害活性も減弱することが明らかになり、糖部の限定的な修飾では rCNT2 阻害活性の向上や種差の改善は見込めないことが示唆された。

Table 2-5. Inhibitory Effects of Compounds 2-17 and 2-18 on Na⁺-Dependent Inosine Uptake inCOS-7 Cells Transiently Expressing hCNT2 or rCNT2

....

$HO HO HO R^{1}$						
1	ם ו	\mathbf{P}^2	$IC_{50} (\mu M)^a$			
compa	K	K	hCNT2	rCNT2		
2-17	Н	Н	1.5 ± 0.2	23 ± 6.8		
2-18	ОН	Н	6.1 ± 0.4	$>100 (45)^{b}$		
2-15	Н	ОН	0.94 ± 0.24	38 ± 13		

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}Inhibition was less than 50% at the maximum concentration of 100 μ M. The inhibition% is shown in parentheses.

続いて、塩基部の変換を行った。hCNT2は、すべてのプリンヌクレオシドを基質とするが、一方では、第一章第二節(pp.8-9)で述べた通り、リバビリンやベンズイミダゾールヌクレオシドなどの塩基部が非天然型のヌクレオシド系化合物を基質または阻害薬として認識することが知られている^{38,42,43}。これらの事実は、塩基部が糖部ほど厳密に認識されていないことを示唆している。

そこで、近年の創薬研究でよく用いられるスキャホールドホッピング (scaffold hopping)を検討するこ とにした。この手法は、1999 年に Schneider らにより、"*identification of isofunctional molecular structures with significantly different molecular backbones*"と定義されたものであり ⁵⁵、リード化合物などの持つ活性 や機能を損なわずに、母核 (scaffold)を跳躍的に変化 (hopping) させることと理解できる。今回は、化合物 の取り扱い易さを考慮し、2-15 のアデニンをヒポキサンチンおよびベンズイミダゾールで置換した 2-19 および 2-20 を合成して評価した (表 2-6)。その結果、2-19 では、2-15 に比べて rCNT2 および hCNT2 阻 害活性双方が減弱し、阻害活性の種差が拡大した。一方、2-20 では、対照的に両阻害活性の増強が認め られ、阻害活性の種差が縮小した。そこで、2-20 の JP2 に対する溶解性を調べたところ、溶解度は 0.120 mg/mL (= 231 μ M) と算出され、rCNT2 阻害活性の指標である IC₅₀ 値 (= 1.5 μ M) より 150 倍以上高値であ ったことから、本化合物を第二のリード化合物に位置付けて高次評価を実施することにした。

	но но	N NH H NNH HO ОН	но	
aamnd	IC ₅₀ (µ	$IC_{50} (\mu M)^a$		colubility in ID2 of 27 °C (mg/mL)
compa	hCNT2	rCNT2	rat/human	solubility in JP2 at 37°C (ing/inL)
2-19	20 ± 2.0	>1000 ^b	>50	nd^c
2-20	0.062 ± 0.017	1.5 ± 0.1	24	0.120
2-15	0.94 ± 0.24	38 ± 13	40	0.190

Table 2-6. in vitro Profiles of Compounds 2-19 and 2-20, and Solubility of 2-20 in JP2

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^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}Inhibition was less than 50% at the maximum concentration of 1000 μ M. ^{*c*}nd, not determined.

まず、前記同様のプリン体負荷試験により、化合物 2-20 の有効性を評価した。結果を図 2-3 に示す。 2-20 は、低用量(0.1 mg/kg)から弱い血漿尿酸値上昇抑制効果を示し、1.0 mg/kg に増量することにより、 有意な血漿尿酸値上昇抑制効果を発揮した(抑制率 65%)。この結果は、消化管におけるプリン体の吸収 には、主として CNT2 が関与していることを示唆するものであり、筆者の当初の見立てが支持された。 しかし一方で、本化合物による血漿尿酸値上昇抑制効果は、さらに高用量(10 mg/kg)を用いても改善が ほとんど認められなかった(抑制率 67%)。このことより、消化管におけるプリン体の吸収には、CNT2 を介さない経路も一部関与していることが示唆された。



Figure 2-3. Effects of compound **2-20** on the elevation of plasma uric acid levels derived from orally administered purine mixture (50 mg/kg) in rats. Data are expressed as the mean \pm SEM. (n = 5–11). ###: p < 0.001 versus a group treated with only potassium oxonate (100 mg/kg). ***: p < 0.001 versus a group treated with potassium oxonate and purine mixture.

次に、プリン体負荷試験における薬効発現メカニズムを考察するため、ラットを用い、化合物 2-20 の 薬物動態試験を実施した。薬物動態パラメータを表 2-7 に示す。まず、分布容積(V_{dss})は 0.12 L/kg であ り、一般に組織移行性が低いと判断する基準(<0.2 L/kg)を満たす。一方、10 mg/kg の用量で経口投与し た際の最高血中濃度到達時間(t_{max})は 0.83 時間であり、薬効評価のタイミング(プリン体負荷後 1 時間) と概ね合致する。しかし、最高血中濃度(C_{max})は 0.11 μM であり、rCNT2 阻害活性の指標である IC₅₀値 (1.5 μM)の 10 分の 1 未満である。また、2-20 の薬物動態に線形性があると仮定した場合、本化合物が 有意な血漿尿酸値上昇抑制効果を示した 1 mg/kg の用量では、C_{max}は IC₅₀値の 100 分の 1 未満になる。 さらに、本化合物を 10 mg/kg の用量で経口投与した際の生物学的利用率は 0.51%であり、特筆すべき代 謝物も検出されなかったことから、本化合物は低吸収性化合物であると判断した。以上より、プリン体 負荷試験における 2-20 の作用部位は、消化管にほぼ限定されると考えられた。従って、2-20 による血漿 尿酸値上昇抑制効果は、消化管における rCNT2 阻害に基づき、プリンヌクレオシドの消化管吸収が抑制 された結果として発揮されたことが示唆された。

Table.2-7 Pharmacokinetic Parameters of Compound 2-20 in Rats after

Intravenous (iv) and Oral (po) Administrations^a

	2-20					
parameter	iv^b	po ^c				
$CL_{tot} (L h^{-1} kg^{-1})$	0.39					
V _{dss} (L/kg)	0.12					
$t_{1/2}$ (h)	1.7					
$AUC_{0\text{-}inf}\left(\mu M \cdot h\right)$	5.0					
C_{\max} (μ M)		0.11				
t_{\max} (h)		0.83				
$AUC_{0-x} \left(\mu M \cdot h \right)$		0.25				
F (%)		0.51				

^{*a*}Data are expressed as the mean (n = 3). ^{*b*}Compound **2-20** was dissolved in 50% (v/v) *N*,*N*-dimethylacetamide in 5% glucose solution and administered intravenously at a dose of 1.0 mg/kg. ^{*c*}Compound **2-20** was suspended in sodium carboxymethyl cellulose and administered orally at a dose of 10 mg/kg.

化合物 2-1 は、ニトリル 25 を水素化アルミニウムリチウムで処理し、生じたアミン 2-21 と 8-ブロモ アデノシン 13 とを縮合することにより合成した(スキーム 2-1)。

Scheme 2-1. Synthesis of Compound 2-1^{*a*}



^aReagents and conditions: (a) LiAlH₄, THF, 60 °C, 91%; (b) **13**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 84%.

化合物 2-2 は、スキーム 2-2 に示す通り合成した。3-ブロモビリジン 26 を鈴木-宮浦カップリングによ りビアリール化合物 2-22 としたのち、水素化アルミニウムリチウムで処理してシアノ基を還元した。生 じたアミンは、精製を容易にするため、トリフルオロ酢酸エチルで処理して一旦アミド 2-23 へと導き、 続くアルカリ加水分解によりトリフルオロアセチル基を除去し、生じたアミン 2-24 と 8-ブロモアデノ シン 13 とを縮合することにより目的物 2-2 を得た。





^{*a*}Reagents and conditions: (a) 4-cyanophenylboronic acid, Pd(PPh₃)₄, 2.0 M aq Na₂CO₃, MeCN, 80 °C, 73%; (b) LiAlH₄, THF, 60 °C; (c) CF₃CO₂Et, EtOH, rt, 58% from **2-22**; (d) 2.0 M aq NaOH, EtOH, rt, 93%; (e) **13**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 77%.

化合物 2-3 は、スキーム 2-3 に示す通り合成した。4-ブロモピリジン塩酸塩 27 を鈴木-宮浦カップリン グによりビアリール化合物 2-25 としたのち、水素化アルミニウムリチウムで処理してシアノ基を還元 し、生じたアミン 2-26 と 8-ブロモアデノシン 13 とを縮合することにより目的物 2-3 を得た。

Scheme 2-3. Synthesis of Compound 2-3^{*a*}



^{*a*}Reagents and conditions: (a) 4-cyanophenylboronic acid, Pd(PPh₃)₄, 2.0 M aq Na₂CO₃, MeCN, 80 °C, 79%; (b) LiAlH₄, THF, 60 °C, 71%; (c) **13**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 50%.

化合物 2-4 は、スキーム 2-4 に示す通り合成した。フェノール 28 をトリフレート 2-27 に変換後、鈴木-宮浦カップリングによりビフェニル化合物 2-28 とした。続いて、2-28 のシアノ基を水素化アルミニウムリチウムで還元し、生じたアミン 2-29 と 8-ブロモアデノシン 13 とを縮合することにより目的物 2-4 を得た。





^{*a*}Reagents and conditions: (a) Tf₂O, Et₃N, DCM, rt; (b) PhB(OH)₂, Pd(PPh₃)₄, Na₂CO₃, DMF, H₂O, 80 °C, 90% from **28**; (c) LiAlH₄, THF, 60 °C, 95%; (d) **13**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 93%.

化合物 2-5 および 2-8-2-13 は、スキーム 2-5 に示す通り合成した。メチルエーテル 2-28 を三臭化ほう 素、次いで臭化ベンジルで処理することによりベンジルエーテル 2-31 に変換した。2-31 のシアノ基を 水素化アルミニウムリチウムで還元し、生じたアミン 2-32 とアデノシン誘導体 19⁴⁷ とを縮合したのち、 接触水素化によりベンジル基を除去して共通中間体 2-34 を得た。2-34 をふっ化アンモニウムで処理し て TBS 基を除去することにより目的物 2-8 を得た。一方、2-34 の水酸基をアルキル化して 2-35-2-38 へ と導き、次いでふっ化アンモニウムで処理することにより目的物 2-5 および 2-9-2-11 を得た。さらに、 化合物 2-11 をアンモニア・メタノール溶液で処理することにより目的物 2-12、および水素化ほう素ナト リウムで処理することにより目的物 2-13 を得た。





^{*a*}Reagents and conditions: (a) BBr₃ (1.0 M in DCM), DCM, 30 °C, 96%; (b) BnBr, K₂CO₃, DMF, rt, quant.; (c) LiAlH₄, THF, 60 °C, quant.; (d) **19**⁴⁷, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 98%; (e) H₂, 10% Pd–C, AcOEt, rt, 96%; (f) NH₄F, MeOH, reflux; (g) appropriate alkyl iodide or methyl bromoacetate, K₂CO₃, DMF, 35–50 °C; (h) NH₃ (2.0 M in MeOH), rt; (i) NaBH₄, EtOH, rt.

化合物 2-6 および 2-7 は、スキーム 2-6 に示す通り合成した。ニトリル 29 の水酸基をベンジル化した のち、鈴木-宮浦カップリングによりビフェニル化合物 2-40 とした。2-40 のシアノ基を水素化アルミニ ウムリチウムで還元し、生じたアミン 2-41 とアデノシン誘導体 19⁴⁷ とを縮合したのち、接触水素化に よりベンジル基を除去して共通中間体 2-43 を得た。2-43 の水酸基をアルキル化して 2-44 および 2-45 へ と導き、次いでふっ化アンモニウムで処理して TBS 基を除去することにより目的物 2-6 および 2-7 を得 た。





^{*a*}Reagents and conditions: (a) BnBr, K₂CO₃, DMF, rt; (b) PhB(OH)₂, Pd(PPh₃)₄, Na₂CO₃, H₂O, DMF 80 °C, 94% from **29**; (c) LiAlH₄, THF, 60 °C, 96%; (d) **19**⁴⁷, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 98%; (e) H₂, 10% Pd–C, AcOEt, rt, 91%; (f) RI, K₂CO₃, DMF, rt–40 °C; (g) NH₄F, MeOH, reflux.

化合物 2-14-2-16 は、スキーム 2-7 に示す通り合成した。化合物 2-30 の水酸基をアルキル化し、次い で水素化アルミニウムリチウムで処理してシアノ基を還元することによりアミン 2-49-2-51 を得た。続 いて、2-49-2-51 と 8-ブロモアデノシン 13 とを縮合することにより 2-52-2-54 へと導いたのち、接触水 素化によりベンジル基を除去して目的物 2-14-2-16 を得た。





^{*a*}Reagents and conditions: (a) RBr, K_2CO_3 , DMF, 50 °C; (b) LiAlH₄, THF, 60 °C; (c) **13**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube; (d) H₂, 10% Pd–C, MeOH, 50 °C.

化合物 2-17 は、8-ブロモ-2'-デオキシアデノシン 30 とアミン 2-50 とを縮合して 2-55 を得たのち、接触水素化によりベンジル基を除去することにより合成した(スキーム 2-8)。

Scheme 2-8. Synthesis of Compound 2-17^{*a*}



^{*a*}Reagents and conditions: (a) **2-50**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 37%; (b) H₂, 10% Pd–C, MeOH, 50 °C, 54%.

化合物 2-18 は、Ikehara らの方法 ⁵⁶に従い、8-ブロモアデノシン 13 から合成したシクロヌクレオシド 31 を、アミン 2-50 との反応により開環させて 2-56 としたのち、接触水素化によりベンジル基を除去す ることにより合成した(スキーム 2-9)。

Scheme 2-9. Synthesis of Compound 2-18^a



^{*a*}Reagents and conditions: (a) **2-50**, PrOH, 150 °C, in a sealed tube, microwave irradiation, 26%; (b) H₂, 10% Pd– C, MeOH, 50 °C, 65%.

化合物 2-19 は、酢酸水溶液中、化合物 2-53 を亜硝酸ナトリウムで処理して脱アミノ化したのち、接触水素化によりベンジル基を除去することにより合成した(スキーム 2-10)。

Scheme 2-10. Synthesis of Compound 2-19^a



^aReagents and conditions: (a) NaNO₂, 75% aq AcOH, rt, 42%; (b) H₂, 10% Pd–C, MeOH, 50 °C, 79%.

化合物 2-20 は、スキーム 2-11 に示す通り合成した。1,2,3,5-テトラ-*O*-アセチル-β-D-リボフラノースを 糖供与体とするグリコシル化反応により、2-クロロ-1*H*-ベンズイミダゾール 32 を配糖体 2-58 に導いた のち、メタノール中、カリウム *tert*-ブトキシドで処理することによりアセチル基を除去し、ベンズイミ ダゾールヌクレオシド 2-59 を得た。続いて、2-59 とアミン 2-50 とを縮合したのち、接触水素化により ベンジル基を除去することにより目的物 2-20 を得た。 Scheme 2-11. Synthesis of Compound 2-20^{*a*}



^{*a*}Reagents and conditions: (a) *N*,*O*-bis(trimethylsilyl)acetamide, MeCN, 80 °C then TMSOTf, 1,2,3,4-tetra-*O*-acetyl-β-D-ribofuranose, rt, 84%; (b) *t*-BuOK, MeOH, rt, 84%; (c) **2-50**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 58%; (d) H₂, 10% Pd–C, MeOH, 50 °C, 88%.

第一節 hCNT2 選択的阻害薬の創製

第二章で創出したリード化合物 2-20(図 3-1)を更なる高次試験で評価するにあたり、本化合物の初期 安全性評価を実施したところ、残念ながらいくつかの問題点が洗い出された。例えば、2-20には比較的 強力な hERG チャネル阻害作用が認められ、心不全につながる QT 延長リスクを内包する化合物である とわかった。しかも、本作用はビフェニル部位の置換基が異なる代替化合物にも共通して認められる特 性であり、基本構造に起因する作用と推察された。従って、基本構造を再度変換して問題回避を図るの が望ましいと判断した。なお、第二章第三節(pp.33-34)に記載した通り、本化合物は低吸収性であり、 その作用部位は消化管に限定的であることが示唆されているため、hERG チャネル阻害作用が深刻な問 題点にはならないとも考えられた。しかし、将来的に適応拡大する可能性(例えば、正常細胞が hCNT2、 腫瘍細胞が他の NT を介して抗腫瘍薬を取り込む場合における副作用発現の回避薬として)まで視野に 入れると、本化合物を非経口的に投与するケースは十分に想定され、比較的強力な hERG チャネル阻害 作用を有する特性が致命的な問題点として浮上することも否定できない。そこで、本研究においては、 プロトタイプ阻害薬である 1-63(図 3-1)の hERG チャネル阻害作用が弱いことを確認できたことより、 本化合物に立ち戻り、"1-63 の強力な hCNT2 阻害活性を保持しつつ水溶性を改善する" ことを目標に再 びリード創製研究に取り組むことにした。



Figure 3-1. Structural formulas of lead compound 2-20 and prototype inhibitor 1-63.

化合物 1-63 の水溶性の改善には、ビフェニル結合のオルト位に極性置換基を導入することが非常に 効果的であった(第二章第一節参照)。そこで、今度は化合物 1-63 のビフェニル結合のもう一つのオルト 位に同様に極性置換基を導入して、水溶性の改善を目指すことにした(表 3-1)。hCNT2 阻害活性を評価 した結果、合成した 3-1-3-8 は対応する位置異性体 2-4、2-5、および 2-8-2-13 と類似の構造活性相関を 示した。即ち、比較的小さい極性置換基ほど強力な阻害活性を発現すること、置換基の炭素数や立体的 嵩高さに依存して阻害活性が低下すること、ならびにアルコキシ基に極性官能基を導入しても阻害活性 の向上には寄与しないことがわかった。しかし、1-63 に匹敵する hCNT2 阻害活性を有する化合物は得 られなかった。

Table 3-1. Inhibitory Effects of Compounds 3-1–3-8 on Na⁺-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2

compd	R	$IC_{50} (\mu M)^a$			
3-1	ОН	1.7 ± 0.3			
3-2	OMe	1.6 ± 0.3			
3-3	OEt	1.9 ± 0.3			
3-4	OPr	4.0 ± 0.5			
3-5	OPr- <i>i</i>	7.6 ± 1.3			
3-6	OCH ₂ CO ₂ Me	3.3 ± 0.8			
3-7	OCH ₂ CONH ₂	3.9 ± 1.0			
3-8	OCH ₂ CH ₂ OH	1.6 ± 0.5			
1-63	Н	0.64 ± 0.19			

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated.

前段の結果を受け、水溶性改善の鍵と予想されるビフェニル構造のねじれ角の増大は期待できないものの、メタおよびパラ位にも同様に極性置換基を導入して、hCNT2阻害活性を評価してみることにした。結果を表 3-2 に示す。構造活性相関は、この場合も位置異性体である 2-4、2-5、および 2-8-2-13 と同様の傾向であったが、阻害活性の強度は置換位置により異なった。即ち、メタ位に置換基を導入した 3-9-3-16 は、全体的に強力な阻害活性を発現し、エトキシ、プロポキシ、およびイソプロポキシ誘導体 3-11-3-13 を除き、すべての化合物が 1-63 と同等以上の阻害活性を示した。一方、パラ位に置換基を導入した 3-17-3-24 は、いずれの化合物も 1-63 に及ぶような強力な阻害活性を示さなかった。以上より、1-63 と同等以上の hCNT2 阻害活性を示した 3-9、3-10、および 3-14-3-16 に着目し、さらなる検討を進めた。

Table 3-2. Inhibitory Effects of Compounds 3-9–3-24 on Na⁺-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2

	НОЙОН						
compd	R	IC ₅₀ (µM) ^a	compd	R	$IC_{50} (\mu M)^a$		
3-9	<i>m</i> -OH	0.54 ± 0.10	3-17	<i>p</i> -ОН	1.6 ± 0.2		
3-10	<i>m</i> -OMe	0.61 ± 0.04	3-18	<i>p</i> -OMe	4.5 ± 0.2		
3-11	<i>m</i> -OEt	1.2 ± 0.2	3-19	<i>p</i> -OEt	21 ± 4.3		
3-12	<i>m</i> -OPr	2.5 ± 0.5	3-20	<i>p</i> -OPr	>100 (39) ^b		
3-13	<i>m</i> -OPr- <i>i</i>	1.8 ± 0.1	3-21	<i>p</i> -OPr- <i>i</i>	>100 (36) ^b		
3-14	<i>m</i> -OCH ₂ CO ₂ Me	0.89 ± 0.07	3-22	<i>p</i> -OCH ₂ CO ₂ Me	1.7 ± 0.4		
3-15	<i>m</i> -OCH ₂ CONH ₂	0.65 ± 0.09	3-23	<i>p</i> -OCH ₂ CONH ₂	2.8 ± 0.5		
3-16	<i>m</i> -OCH ₂ CH ₂ OH	0.34 ± 0.11	3-24	p-OCH ₂ CH ₂ OH	4.4 ± 1.4		
1-63	Н	0.64 ± 0.19					

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}Inhibition was less than 50% at the maximum concentration of 100 μ M. The inhibition% is shown in parentheses.

3-9、**3-10**、および **3-14-3-16** について、JP2 (pH6.8) に対する溶解度に代わる指標として、pH6.5 におけ るオクタノール/水分配係数の常用対数 (LogD_{6.5}) を計算したところ、すべての化合物で **1-63** より低値 となり、**1-63** より JP2 に対する溶解度が向上していることが示唆された。そこで、全5 化合物の rCNT2 阻害活性を評価したところ、**3-14-3-16** に相対的に強力な活性が認められた (表 3-3)。一方、**3-14-3-16** は、 大きく異なる LogD_{6.5} を有するにもかかわらず、ほぼ同等の rCNT2 阻害活性を示した。従って、これら 3 化合物の rCNT2 阻害活性を損なうことなく、さらに LogD_{6.5} を低減できる可能性があると考えた。そ こで、3 者の中で最も強力な hCNT2 阻害活性を有する **3-16** (LogD_{6.5} = 0.58) に着目し、LogD_{6.5} をより下 げるべく、水酸基をアミノ基で置換した **3-25** (LogD_{6.5} = -2.11) を合成し、rCNT2 阻害活性を評価した (表 3-4)。その結果、**3-25** は **3-16** と同等以上の阻害活性を示した。つまり、rCNT2 阻害活性を損なうことな く LogD_{6.5}の低減が図れることが実証できた。さらに **3-25** は、hCNT2 に対しても **3-16** と同等以上の阻 害活性を発現し、これまで合成したアデノシン誘導体の中では最良の in vitro 活性プロファイルを有す る化合物であった。そこで、LogD_{6.5} が **3-25** と遜色ないホモログ **3-26** (LogD_{6.5} = -2.35) および **3-27** (LogD_{6.5} = -1.90) をさらに合成して評価した。その結果、**3-26** および **3-27** いずれにおいても hCNT2 および rCNT2 阻害活性双方が強化されており、**3-25** よりさらに優れた in vitro 活性プロファイルを持つ化合物を得る ことができた(表 **3-4**)。そこで、**3-26** および **3-27** の高次評価を行うことにした。 Table 3-3. Inhibitory Effects on Na⁺-Dependent Inosine Uptake in COS-7 Cells TransientlyExpressing hCNT2 or rCNT2, and LogD_{6.5} of Compounds 3-9, 3-10, and 3-14–3-16



1	D	IC ₅₀ ($IC_{50} (\mu M)^a$		
compa	K	hCNT2	rCNT2	- LogD _{6.5} °	
3-9	ОН	0.54 ± 0.10	$>100^{b}$	1.13	
3-10	OMe	0.61 ± 0.04	$>100^{b}$	1.27	
3-14	OCH ₂ CO ₂ Me	0.89 ± 0.07	36 ^c	0.90	
3-15	OCH ₂ CONH ₂	0.65 ± 0.09	83 ± 2.7	-0.06	
3-16	OCH ₂ CH ₂ OH	0.34 ± 0.11	54 ± 5.5	0.58	
1-63	Н	0.64 ± 0.19	inactive ^d	1.43	

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}Inhibition was less than 50% at the maximum concentration of 100 μ M. ^{*c*}The data is expressed as the mean of two independent experiments. ^{*d*}No inhibition was observed at the the maximum concentration of 100 μ M. ^{*c*}LogD_{6.5} values were calculated via MarvinSketch 6.2.0 (ChemAxon).

Table 3-4. Inhibitory Effects on Na⁺-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2 or rCNT2, and LogD_{6.5} of Compounds 3-25–3-27



compd	D	IC ₅₀ (µ	LeeD h	
	K	hCNT2	rCNT2	- LogD _{6.5}
3-25	OCH ₂ CH ₂ NH ₂	0.25 ± 0.06	23 ± 4.4	-2.11
3-26	OCH ₂ CH ₂ CH ₂ NH ₂	0.11 ± 0.02	9.4 ± 3.0	-2.35
3-27	OCH ₂ CH ₂ CH ₂ CH ₂ NH ₂	0.072 ± 0.014	6.3 ± 1.0	-1.90
3-16	OCH ₂ CH ₂ OH	0.34 ± 0.11	54 ± 5.5	0.58

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}LogD_{6.5} values were calculated via MarvinSketch 6.2.0 (ChemAxon).

3-26 および 3-27 に関する高次評価は、最終的にヒトでの有効性を見積もるために霊長類を用いた薬 効試験を実施することを念頭に置き進めた。まず、創薬コンセプトの妥当性を可能な限り正確に評価で きる化合物を得るため、hCNT2 に対する選択性を調べた(表 3-5)。その結果、両化合物ともに hCNT1 に 対しては比較的弱い阻害作用しか示さず、hCNT3 に対しては比較的強力な阻害活性を有するものの、 hCNT2 に対してより選択的な阻害薬であることが確認できた。次に、hCNT2 に対してより高い選択性 を示した **3-26** を優先し、ヒト ENT1 (hENT1)および ENT2 (hENT2)に対する影響を調べた。図 1-3 (p.7) に示した発現パターンより、HeLa 細胞では hCNTs に比べて hENT1 および hENT2 の発現量が相対的に 多いため、ナトリウムイオン非存在下におけるアデノシン取り込み作用への影響を調べることにより、 hENT1 および hENT2 に対する阻害作用が評価できると考えた。実際の評価結果を図 3-2 に示す。代表 的な ENT 阻害薬であるニトロベンジルメルカプトプリンリボシド(NBMPR)が、HeLa 細胞によるナト リウムイオン非依存的なアデノシンの取り込みを強力に阻害(IC50 = ca. 0.01 μM)する一方、3-26 は NBMPR よりも明らかに高濃度(1 µM < IC50 < 10 µM)でしか阻害作用を示さなかった。また、3-26 が HeLa 細胞によるナトリウムイオン非依存的なアデノシン取り込みを阻害する濃度は、hCNT2阻害作用を示す 濃度に比べて高値であった。従って、3-26は、hENT1および hENT2よりも hCNT2 に対して選択的な化 合物だと判断した。続いて、3-26の JP2 への溶解性を調べたところ、溶解度は 0.408 mg/mL (= 782 μM) と算出され、LogD65(=-2.35)から期待された通り、1-63に比べ水溶性が大幅に改善されていた(表 3-5)。 以上より、"1-63 の強力な hCNT2 阻害活性を保持しつつ水溶性を改善する"という当初の目標を上回る 成果を得ることができた。

Table 3-5. Inhibitory Effects of Compounds 3-26 and 3-27 on hCNT1–3 Activity, and Solubility of 3-26 in JP2



3-26: $R = OCH_2CH_2CH_2NH_2$ **3-27**: $R = OCH_2CH_2CH_2CH_2NH_2$

aamnd		IC ₅₀ (µM) ^a	solubility in JP2 at 37 °C	
compa	hCNT2	hCNT1	hCNT3	(mg/mL)
2.26	0.11 ± 0.02	203 ± 28	6.4 ± 1.0	0.409
3-26	$(1)^{b}$	$(1845)^{b}$	$(58)^{b}$	0.408
2 27	0.072 ± 0.014	104 ± 14	3.5 ± 0.2	e dû
3-27	$(1)^{b}$	$(1444)^{b}$	$(49)^{b}$	nd

^{*a*}Concentration of each compound required to inhibit inosine uptake (hCNT2 and hCNT3) or thymidine uptake (hCNT1) by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}The IC₅₀ values were divided with that for hCNT2 inhibition to assess hCNT2 selectivity. The results are shown in parentheses. ^{*c*}nd, not determined.



Figure 3-2. Inhibitory effect of compound **3-26** on adenosine uptake in HeLa cells. HeLa cells were incubated for 30 min with $[^{14}C]$ -adenosine and individual compounds in Na⁺-free buffer.

第二節 フサオマキザルにおける血漿尿酸値上昇抑制効果

前節の結果を踏まえ、化合物 3-26 の高次評価を更に進めることとし、フサオマキザル(Cebus apella) を用いたプリン体負荷試験にて本化合物の有効性を評価することにした。ラットやカニクイザルなど、 広く一般に用いられる実験動物では尿酸酸化酵素(ウリカーゼ)が活性なため、血漿尿酸値は通常は低値 (<0.5-2 mg/dL)を示すが³、フサオマキザルでは本酵素の活性が低く、血漿尿酸値は比較的高値(2-4 mg/mL)になることが知られている^{57,58}。この特性から、フサオマキザルは尿酸降下薬の有効性を評価す る際によく用いられている。

まず、化合物 3-26 がフサオマキザルにおいてどの程度の CNT2 阻害活性を示すのかを類推するため、 国立生物工学情報センター(National Center for Biotechnology Information, NCBI)に登録のあるアミノ酸配 列情報⁵⁹を元に相同性を調べた。なお、実験に用いるフサオマキザル(Cebus apella)に関する情報は登録 がなかったため、その亜種で登録のあるシロガオオマキザル(Cebus capucinus imitator)の情報を代用した。 表 3-6 に示す通り、フサオマキザル CNT2 のアミノ酸配列は、hCNT2 と高い相同性(93.2%)を有してお り、rCNT2 との相同性は、hCNT2 と同様に約 80%であった。この結果より、3-26 はフサオマキザル CNT2 に対しても、hCNT2 に対するものと同様の強力な阻害活性を発現するものと判断した。

Human, Rat, and Cebus CNT2					
anaciaa	sequence		identity		
species		vs human	vs rat	vs cebus	
human	658aa	100	80.5	93.2	
rat	659aa		100	79.7	
cebus	620aa			100	

 Table 3-6. Amino Acid Sequence Identity among

 Human Rat and Cebus CNT2

次に、化合物 3-26 の hERG チャネル阻害作用を評価した。その結果、軽微な作用を示すのみであった (表 3-7)。また、Ames 試験の結果は陰性であった。

Table 3-7. Effect of Compound 3-26 on Tail Current using HEK293 cells stably expres	sing
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a a man d	conc. (µM)	tail curre	inhibition (0/)	
compa		before treatment	after treatment	Infibition (%)
3-26	30	1161	920	20.8

さらに、フサオマキザルを用い、絶食下における化合物 3-26 の経口吸収性を評価した(表 3-8)。3-26 を 0.1、1、および 10 mg/kg の各用量で経口投与し、投与後 8 時間まで血中薬物濃度を追跡したところ、いずれの評価ポイントにおいても薬物は検出されなかった(検出限界:5 ng/mL)。この結果より、本化 合物も低吸収性であり、作用部位も消化管に限定的であることが示唆された。

Table 3-8. Plasma Concentration of Compd 3-26 after Oral Administration to Fasted Cebus Apella (n = 1–3) dose (mg/kg)

times (h)	dose (mg/kg)			
time (n)	0.1	1	10	
1	$N.D^{a}$	$N.D^{a}$	$N.D^a$	
2	$N.D^a$	$N.D^a$	$N.D^a$	
4	$N.D^a$	$N.D^a$	$N.D^a$	
8	$N.D^a$	$N.D^a$	$N.D^a$	

^{*a*}N.D., not detected. The detection limit was 5 ng/mL.

以上、化合物 **3-26** はフサオマキザルを用いた薬効試験で評価するに十分なプロファイルを有していると確認できた。次に、本化合物のプリン体負荷試験を実施した。試験の概要を図 **3-3** に示す。



Figure 3-3. Schematic of the study design. BC: blood collection, Ox: potassium oxonate, UC: urine collection. Three–phase crossover studies were conducted. Study No.1: treatment with oxonic acid, Study No.2: treatment with potassium oxonate and yeast RNA (30 mg/kg), Study No.3: treatment with potassium oxoniate, yeast RNA (30 mg/kg), and compound **3-26** (50 mg/kg).

- 2頭のフサオマキザルを用いたクロス—オーバー試験
- ・ 5日間の馴化期間を経て、6日目から10日目までの5日間を評価期間とした。
- ・ 評価期間中は、血漿尿酸値のベースラインを高めるため、動物には1日2回、 オキソン酸カリウム(ウリカーゼ阻害薬)を皮下投与した。
- ・ 動物には1日1回、13:00-14:00に給餌し、動物はこれを完食した。
- ・ プリン体 (yeast RNA) の負荷および被験物質の投与は混餌により行った。
- ・ 採血は、2、5、6、8、および10日目(16:00、19:00、および翌日9:00)に行った。
- ・ 採尿は、2、5、6、8、および10日目(11:00-19:00および19:00-翌日9:00)に行った。

血漿尿酸値および尿中尿酸値の推移を図 3-4 および 3-5 に示した。評価期間中、Study No.2 (Ox.+RNA) の血漿尿酸値は、Study No.1 (Ox.) より常に高いレベルで推移したが、Study No.3 (Ox.+RNA+3-26)の血漿 尿酸値は終始 Study. No.1 と遜色なく推移した。また、クレアチニン値で補正した尿中尿酸濃度の推移に も血漿尿酸値と同様の傾向が認められた。これらの結果は、経口的に負荷された yeast RNA に由来する 血漿尿酸値の上昇を、化合物 3-26 が評価期間を通じて抑制し続けたことを示唆している。また、化合物

3-26のフサオマキザルを用いた薬物動態試験の結果(p.49)を踏まえると、本化合物が吸収されて効果を 発揮したとは考えにくく、今回確認された薬効が本化合物の消化管における CNT2 阻害に基づき、プリ ンヌクレオシドの消化管吸収が抑制された結果として発揮されたと解釈する方が受け入れ易い。さらに、 ラットを用いたプリン体負荷試験(p.33)で観察されたような薬効の頭打ちが見られないことより、フサ オマキザルの消化管におけるプリン体の吸収に関しては、CNT2 を介する経路が主経路と推察される。

以上より、当初予想した通り、消化管におけるプリン体の吸収には、CNT2が中心的な役割を果たし、 その機能を強力に阻害することにより、経口的に摂取されたプリン体に起因する血漿尿酸値の上昇をほ ぼ完璧に抑制できることが示唆された。





Figure 3-4. Effects of repeated doses of compound **3-26** on plasma uric acid level in cebus monkeys. Plasma uric acid levels were determined from samples taken at 16:00, 19:00, and then 9:00.



Figure 3-4. continued



Figure 3-5. Effects of repeated doses of compound 3-26 on urinary uric acid/creatinine value in cebus monkeys.

化合物 3-1、3-4-3-9 および 3-12-3-24 は、スキーム 3-1 および 3-2 に示す通り合成した。Howell らの 方法 ⁶⁰に従い合成したベンジルアミン誘導体 34 を鈴木-宮浦カップリングにより化合物 3-28-3-30 へと 導いたのち、酸性条件下 Boc 基を除去し、生じたアミン 3-31-3-33 とアデノシン誘導体 19⁴⁷ とを縮合す ることにより共通中間体 3-34-3-36 を得た。3-34-3-36 をふっ化アンモニウムで処理して TBS 基を除去 することにより目的物 3-1、3-9、および 3-17 を得た。一方、3-34-3-36 の水酸基をアルキル化して 3-37-3-42 および 3-44-3-48 とし、次いでふっ化アンモニウムで処理して TBS 基を除去することにより目的物 3-4-3-6、3-12-3-14 および 3-18-3-22 を得た。さらに、目的物 3-6 を、アンモニア・メタノール溶液で処 理することにより目的物 3-7、および水素化ほう素ナトリウムで処理することにより目的物 3-8 を得た。 また同様に、目的物 3-14 を水素化ほう素ナトリウムで処理して目的物 3-16 を得た。なお、目的物 3-15 および 3-23 は、アルキル化体 3-42 および 3-48 をアンモニア・メタノール溶液で処理して対応するアミ ド 3-43 および 3-49 に変換後、ふっ化アンモニウムで処理して TBS 基を除去することにより得た。また、 目的物 3-24 は、アルキル化体 3-48 を水素化ほう素ナトリウムで処理して対応するアルコール 3-50 に変 換後、ふっ化アンモニウムで処理して TBS 基を除去することにより得た。





^{*a*}Reagents and conditions: (a) appropriate hydroxyphenylboronic acid, Pd(PPh₃)₄, Na₂CO₃, H₂O, MeCN, 80 °C; (b) HCl (4 N in 1,4-dioxane), 1,4-dioxane, rt; (c) **19**⁴⁷, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube.



^{*a*}Reagents and conditions: (a) NH₄F, MeOH, reflux; (b) appropriate alkyl iodide or methyl bromoacetate, K₂CO₃, DMF, rt–50 °C; (c) NH₃ (2.0 M in MeOH), rt; (d) NaBH₄, EtOH, rt.

化合物 3-2、3-3、3-10、および 3-11 は、スキーム 3-3 に示す通り合成した。4-ブロモベンゾニトリル 16 と対応するアルコキシフェニルボロン酸との鈴木-宮浦カップリングによりニトリル 3-51-3-54 を得 たのち、水素化アルミニウムリチウムで処理してシアノ基を還元し、生じたアミン 3-55-3-58 と 8-ブロ モアデノシン 13 とを縮合することにより目的物 3-2、3-3、3-10、および 3-11 を得た。 Scheme 3-3. Synthesis of Compounds 3-2, 3-3, 3-10, and 3-11^a



*a*Reagents and conditions: (a) appropriate alkoxyphenylboronic acid, Pd(PPh₃)₄, 2.0 M aq Na₂CO₃, MeCN, 80 °C;
(b) LiAlH₄, THF, 60 °C; (c) 13, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube.

化合物 3-25 および 3-26 は、スキーム 3-4 に示す通り合成した。3-29 の水酸基をアルキル化して 3-59 および 3-60 としたのち、酸性条件下 Boc 基を除去し、生じたアミン 3-61 および 3-62 をそれぞれ 8-ブロ モアデノシン 13 と反応させて 3-63 および 3-64 へと導いた。最後に接触水素化により Cbz 基を除去し て目的物 3-25 および 3-26 を得た。





^{*a*}Reagents and conditions: (a) benzyl *N*-(2-hydroxyethyl)carbamate, DIAD, PPh₃, THF, rt; (b) benzyl 3bromopropylcarbamate, K₂CO₃, DMF, 50 °C; (c) TFA, DCM, 0 °C–rt; (d) **13**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube; (e) H₂, 10% Pd–C, MeOH, rt.

化合物 3-27 は、スキーム 3-5 に示す通り合成した。3-29 の水酸基をアルキル化して 3-65 としたのち、 ヒドラジン一水和物で処理してフタロイル基を除去し、生じたアミン 3-66 を Cbz-OSu と反応させるこ とによりカルバメート 3-67 を得た。続いて、酸性条件下 Boc 基を除去し、生じたアミン 3-68 を 8-ブロ モアデノシン 13 と反応させて 3-69 へと導いたのち、接触水素化により Cbz 基を除去して目的物 3-27 を 得た。

Scheme 3-5. Synthesis of Compound 3-27^{*a*}



^{*a*}Reagents and conditions: (a) *N*-(4-bromobutyl)phthalimide, K₂CO₃, DMF, 50 °C, 95%; (b) H₂NNH₂·H₂O, CHCl₃, EtOH, rt; (c) Cbz-OSu, THF, rt, 89% from **3-65**; (d) TFA, DCM, rt, 90%; (e) **13**, *i*-Pr₂NEt, EtOH, 120 °C, in a screw tube, 92%; (f) H₂, 10% Pd–C, MeOH, rt, 80%.

第一節 理論計算による考察

筆者は第一章第二節において、8-アミノアデノシン誘導体が強力な hCNT2 阻害活性を発現するため には、8 位の第二級アミノ基が必須であることを明らかにした。そこで本章では、いくつかのアプロー チによりその理由を考察したので、その結果を順次説明する。

ヌクレオシド系化合物と標的タンパク質との相互作用の強度を決定付ける大きな要因の1つとして、 グリコシド結合まわりのコンホメーションが挙げられる⁶¹。グリコシド結合まわりのコンホメーション には、大きく分けて2つの比較的安定な領域、*syn*領域および*anti*領域があり、ねじれ角χ(O4'-C1'-N9-C4)により定義される(図4-1)⁶²。



Figure 4-1. The syn-anti conformational equilibrium (adenosine as an example).

そこで、プロトタイプ阻害薬 **1-63** について、Spartan'10(Wavefunction, Inc.)によるコンホメーション解析を行った。その結果、図 **4-2** に示す通 り、最安定な *anti-コンホマーのエネルギーは、*最安定な *syn-コンホマー* のエネルギーよりも 5.41 kcal/mol 低く、本化合物のグリコシド結合まわ りのコンホメーションは、*syn* 配座よりも *anti* 配座の方が安定であること が示唆された。8 位の第二級アミノ基は、ドナーとして糖部との水素結合



に関与しており、anti 配座をとる際に重要な役割を果たす可能性がある。また、このことが事実だとすると、第一章第二節において、8-(ベンジルアミノ)アデノシン 1-12の8位窒素原子を炭素、酸素、もしくは硫黄原子で置換、または N-メチル化することにより hCNT2阻害活性が消失した理由がよく理解できる。



Figure 4-2. The most stable *anti* (A, $\chi = 185.3^{\circ}$) and *syn* (B, $\chi = 61.7^{\circ}$) conformers of **1-63**.

第二節 NMR による考察

第一節にて、化合物 1-63 が強力な hCNT2 阻害活性を発現できるのは、*anti* 配座を安定にとることができるためであることが示唆された。そこで、実際に *anti* 配座をとるかどうか NMR を用いて検証することにした。

Jordan らは、プリンヌクレオシドのグリコシド結合まわりのコンホメーションを評価する際に、¹H NMR における 2'位プロトンの化学シフトならびに 1'位および 2'位プロトンの化学シフトの差が有用な 判断基準になることを報告している⁶³。8 位に置換基を持たないプリンヌクレオシドは通常、グリコシ ド結合を軸とする回転が比較的容易に起こり、*syn-anti* 平衡のもと存在するが、8 位に置換基が導入され ると、*syn* 配座へのコンホメーション変化が惹起され、これに伴い 2'位プロトンの化学シフトが低磁場 側にシフトする。一方、1'位プロトンの化学シフト(通常は 2'位プロトンより低磁場側)は僅かな変化を 伴うのみであることから、両者の化学シフトの差が縮小するとのことであり、1'位と 2'位のプロトンの 化学シフトの差は、*syn-anti* 平衡における *syn* 配座の存在割合に依存して縮小すると述べている。

表4-1には、グリコシド結合まわりのコンホメーションが文献的に報告されているプリンヌクレオシ ドおよび1-63の化学シフトを一覧で示した。35は、天然のヌクレオシドであり、anti配座優位で存在する ⁶⁴。これに対し13は、様々な解析手段によりsyn配座で存在することが確認されている⁶⁵。13の化学シフ トを35のものと比較すると、2′位のプロトンの化学シフトが低磁場シフトしており、1′位のプロトンの化 学シフトとの差が縮小している。即ち、Jordanらの判断基準により、13は35よりsyn配座の割合が高い化 合物と考えられ、syn配座で存在する事実とも合致する。別の例として、X線結晶構造解析により、それ ぞれsynおよびanti配座をとることが報告されている36および37⁶⁶の化学シフトを35のものと比較した。 36では13と同様の傾向を示すことから、syn配座で存在すると評価できる一方、37では2′位のプロトンの 化学シフトの低磁場シフトは僅かであり、1'および2'位のプロトンの化学シフトの差は35のものと近い 値を示すことから、*syn-anti*平衡における*anti*配座の割合が高いと評価できる。従って、Jordanらの判断基 準による36および37のグリコシド結合まわりのコンホメーションに関する評価の結果は、両化合物のX 線結晶構造解析の結果と良く一致している。一方、1-9は、Jordanらが論文中で評価している化合物であ り、"syn-anti flexible mixture"と判定されているが、その2'位および1'位のプロトンの化学シフトは、35お よび**37**のものと近い値を示すことから、1-9は*anti*配座が優位な化合物であることが示唆される。これに 対し、1-63の2'位および1'位のプロトンの化学シフトは、35、37、および1-9のものと非常に類似している。 即ち、1-63もanti配座が優位な化合物であることが示唆される。

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Table 4-1. Selected Chemical Shifts of Compounds 1-9, 1-63, 13, and 35-37^a



compd	H2′	H1′	$\Delta_{1'-2'}{}^b$
adenosine (35)	4.61	5.88	1.26
8-bromoadenosine (13)	5.09	5.83	0.74
8-(pyrrolidin-1-yl)adenosine (36)	5.11	5.75	0.65
8-(2-hydroxyethylamino)adenosine (37)	4.69	5.87	1.18
8-(methylamino)adenosine (1-9)	4.68	5.85	1.18
8-(biphenyl-4-ylmethylamino)adenosine (1-63)	4.76	5.96	1.20

^{*a*}Nucleosides: 0.04 M in DMSO-*d*₆. ^{*b*}Difference in chemical shift: $\delta_{H1} - \delta_{H2'}$.

前段の通り、¹H NMR を用いた考察からも 1-63 が anti 配座を優先的にとることにより、強力な hCNT2 阻害活性を発現できるとの仮説が支持された。そこで、この仮説をさらに検証するために、Jordan らの 判断基準を用い、他の化合物についてもグリコシド結合まわりの syn-anti コンホメーションと hCNT2 阻 害活性の関係性を調べることにした。表 4-2 には、1-12 ならびにその 8 位窒素原子を他の原子で置換し た 1-25-1-27 および N-メチル化した 1-28 の¹H NMR データと hCNT2 阻害活性を示した。hCNT2 阻害活 性を示す 1-12 (IC50 = 52 µM)では、2'位プロトンの化学シフトは 35 のものと大差なく、1'位および 2'位 のプロトンの化学シフトの差もわずかに縮小するのみであり、1-12 が anti 配座優位で存在することが示 唆された。一方、第2級アミノ基を持たず、僅かな hCNT2 阻害活性しか示さない化合物 1-25 (IC50>1000 μM)では、1-12 に比べ 2'位のプロトンの化学シフトはより低磁場側にシフトし、1'位および 2'位のプロ トンの化学シフトの差も縮小していた。このことより、1-25 では 1-12 に比べて syn 配座の存在割合が増 大した結果、hCNT2 阻害活性の大幅な減弱に繋がった可能性がある。また、第2級アミノ基を持たず、 hCNT2 阻害活性を示さない 1-26-1-28 では、1-25 と同じく 2/位のプロトンの化学シフトが低磁場側にシ フトしていたが、1'位および2'位のプロトンの化学シフトの差は1-25より縮小していた。これらのデー タは、1-26-1-28の syn 配座の存在割合が 1-25 に比べて高いことを示唆しており、完全に hCNT2 阻害活 性を失う主因になった可能性がある。以上より、1-12も anti 配座優位で存在し、比較的強力な hCNT2 阻害活性を発現することが示唆された。

Table 4-2. Selected Chemical Shifts and IC₅₀ of Compounds 1-12 and 1-25-1-28^a



compd	Х	H2′	H1′	$\Delta_{1'-2'}{}^b$	IC ₅₀ (µM) ^c
8-(benzylamino)adenosine (1-12)	NH	4.73	5.94	1.21	52 ± 3.8
8-(2-phenylethyl)adenosine (1-25)	CH_2	4.91	5.85	0.94	$>1000^{d}$
8-(benzyloxy)adenosine (1-26)	0	4.90	5.73	0.83	inactive ^e
8-(benzylthio)adenosine (1-27)	S	4.96	5.73	0.77	inactive ^e
8-[benzyl(methyl)amino]adenosine (1-28)	NMe	5.13	5.87	0.74	inactive ^e
adenosine (35)		4.61	5.88	1.26	
8-bromoadenosine (13)		5.09	5.83	0.74	

^{*a*}Nucleosides: 0.04 M in DMSO-*d*₆. ^{*b*}Difference in chemical shift: $\delta_{H1} - \delta_{H2'}$. ^{*c*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean ± standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*d*}Inhibition was less than 50% at the maximum concentration of 1000 μ M. ^{*e*}No inhibition was observed at the maximum concentration of 1000 μ M.

理論計算に続き、NMR からも 1-63 の強力な hCNT2 阻害活性と anti 配座の強い関係性が示唆された。 そこで、さらに深く考察する目的で、X 線結晶構造解析によるコンホメーション解析を行うことにした。 しかし残念なことに、得られた 1-63 の結晶は、X 線結晶構造解析に適しておらず、第二章第一節で述べ た通り、本化合物の難溶性の性質から再結晶条件の検討も困難であった。 そこで、代替化合物を探索したところ、ビフェニル部位にメトキシ基を 導入した 3-10 が X 線結晶構造解析可能な結晶として得られた。3-10 と 1-63 の構造上の差異は比較的軽微であり、hCNT2 阻害活性(IC₅₀=0.61 μ M)

も **1-63** (IC₅₀ = 0.64 μ M) と遜色ない点で適切な代替化合物と考えられる。 しかし確認のため、本章第一節および第二節と同様の考察を加えたので 以下に示す。

図 4-3 には、Spartan'10 (Wavefunction, Inc.) によるコンホメーション解析の結果を示した。1-63 と同様 に、*anti* 配座の方が安定であることが示唆された ($\Delta E_{syn-anti} = 5.50$ kcal/mol)。



А

В



ΗÔ

3-10

ОH

Figure 4-3. The most stable *anti* (A, $\chi = 185.2^{\circ}$) and *syn* (B, $\chi = 55.9^{\circ}$) conformers of **3-10**.

表 4-3 には、化合物 1-63 および 3-10 の ¹H NMR スペクトルにおける 1'位および 2'位プロトンの化学 シフト値を示した。両化合物における差異はほとんど認められなかった。

Table 4-3. Selected Chemical Shifts of Compounds 1-63 and 3-10 ^a				
compd	H2′	H1′	$\Delta_{1'-2'}{}^b$	
1-63	4.76	5.96	1.20	
3-10	4.75	5.96	1.21	

^{*a*}Nucleosides: 0.04 M in DMSO-*d*₆. ^{*b*}Difference in chemical shift: $\delta_{H1} - \delta_{H2'}$.

図 4-4 に、化合物 3-10 の X 線結晶構造解析のデータ⁶⁷を示す。3-10 の結晶構造は、コンホメーションの異なる 2 分子を単位とする繰り返し構造から成るものであった。それぞれの分子におけるねじれ角 (O4'-C1'-N9-C4)は、χ = 102.1°および 117.1°であり、*syn* 配座(50° < χ < 80°)および *anti* 配座(180° < χ < 280°)いずれの定義⁶²にも該当しなかった。



Figure 4-4. X-ray crystallography of 3-10.

第一節から第三節にかけて3つの手段を用い考察してきたが、1-63の活性コンホメーションに関する 情報はまだ十分ではない。そこで、具体的な化合物を合成してhCNT2阻害活性を評価することにより、 更に考察を深めることにした。Spartan'10(Wavefunction, Inc.)による計算結果や¹H NMRの化学シフト値 から示唆される通り、1-63が本当に anti 配座を優先的にとるならば、1-63のビフェニル部位は5'位周辺 に存在して強力なhCNT2阻害活性の発現に寄与しているはずである。そこで、5'位水酸基にビフェニル 部位を移動させた化合物 4-1-4-3 を合成し、これら化合物が強力なhCNT2阻害活性を発現するかどうか を調べた。結果を表 4-4 に示す。4-1-4-3 は、期待するほどの強度ではなかったが、すべてがhCNT2阻 害活性を発現し、中でもビフェニル-3-イル基を有する 4-2 は、シード化合物 1-12を凌駕するhCNT2阻 害活性を発現し、中でもビフェニル-3-イル基を有する 4-2 は、シード化合物 1-12を凌駕するhCNT2阻 害活性を示した。また、1-12 から 1-63 への構造展開に伴うhCNT2阻害活性の向上と同様に、5'-O-フェ ニル誘導体 4-4 から 5'-O-ビフェニル-3-イル誘導体 4-2 へと構造展開することにより、hCNT2阻害活性 は向上した(表 4-4)。以上の結果は、1-63のビフェニル部位が 5'位周辺に存在し、強力なhCNT2阻害活 性の発現に寄与しているとする筆者の仮説を支持するものである。

Table 4-4. Inhibitory Effects of Compounds 4-1-4-4

on Na⁺-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2

	R ² -	
4-1-4-4		1-63 : R ² = Ph 1-12 : R ² = H
compd	\mathbb{R}^1	$IC_{50} (\mu M)^a$
4-1	2-Ph	>100 $(49)^b$
4-2	3-Ph	11^{c}
4-3	4-Ph	$>100 (40)^{b}$
4-4	Н	$>100 (49)^{b}$
1-63		0.64 ± 0.19
1-12		52 ± 3.8

^{*a*}Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean \pm standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. ^{*b*}Inhibition was less than 50% at the maximum concentration of 100 μ M. The inhibition% is shown in parentheses. ^{*c*}The data is expressed as the mean of two independent experiments.

化合物 4-1-4-4 は、光延反応により 2',3'-O-イソプロピリデンアデノシン 23 と適当なフェノールを反応させて 4-5-4-8 へと導いたのち、70%蟻酸水溶液で処理してイソプロピリデン基を除去することにより合成した(スキーム 4-1)。





^aReagents and conditions: (a) appropriate phenol, DIAD, PPh₃, THF, rt; (b) 70% aq HCO₂H, rt.

結語

- 1. ヒト消化管におけるプリン体の吸収には、hCNT2 が中心的役割を果たすとの仮説のもと、強力な hCNT2 阻害薬を創製し、新たな作用機序の高尿酸血症治療薬を提供すべく、創薬研究を推進した。
- 2. 8-(ベンジルアミノ)アデノシン 1-12 およびこれを共通部分構造とする化合物群が、新規かつ強力な hCNT2 阻害薬であることを見出した。
- 3. アデニンヌクレオシド 2-15 をベンズイミダゾールヌクレオシド 2-20 へ Scaffold Hopping すると、 hCNT2 および rCNT2 に対する阻害活性がいずれも強化されることを見出した。
- 4. rCNT2 阻害活性を有するベンズイミダゾールヌクレオシド 2-20 が、ラットを用いたプリン体負荷 試験において、血漿尿酸値の上昇を有意に抑制することを実証した。また、ラットを用いた薬物動 態試験の結果から、2-20 は低吸収性化合物(F=0.51%)であり、その作用は消化管にほぼ限定される と考えられた。従って、観察された 2-20 の薬効は、消化管における rCNT2 阻害に基づき、プリン ヌクレオシドの消化管吸収が抑制されて発揮されたことが示唆された。
- 5. 強力な hCNT2 阻害活性を有するアデニンヌクレオシド **3-26** が、フサオマキザルを用いたプリン体 負荷試験において、血漿尿酸値の上昇をほぼ完璧に抑制することを実証した。また、フサオマキザ ルを用いた薬物動態試験において、**3-26** が血中に検出されなかったことより、**3-26** は低吸収性であ り、その作用は消化管に限定的と考えられた。従って、観察された **3-26** の薬効は、消化管における フサオマキザル CNT2 阻害に基づき、プリンヌクレオシドの消化管吸収が抑制されて発揮されたこ とが示唆された。
- 6. 8-アミノアデノシン誘導体が強力な hCNT2 阻害活性を発現するために必須の部分構造である 8 位の第二級アミノ基の意義を、理論計算、NMR、X 線結晶構造解析、およびドラッグデザインにより考察した。その結果、8 位の第二級アミノ基が糖部酸素原子との間に水素結合を形成し、化合物のグリコシド結合まわりのコンホメーションを anti 配座優位に導くことにより、強力な hCNT2 阻害活性の発現に寄与していることが示唆された。
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2017年3月 田谷 和也

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Experimental Section

General Methods

Reagents and solvents were purchased from commercial sources and used without further purification. All moisture and air sensitive reactions were carried out in an oven-dried flask under an argon atmosphere. Microwave irradiation was carried out with Biotage initiator or initiator⁺. Reaction conditions and yields were not optimized. Reactions were monitored by thin layer chromatography (TLC) using Merck Kieselgel 60 F254 plates or Fuji Silysia Chemical Ltd. Chromatorex NH-TLC plates, Flash column chromatography was performed on Biotage prepacked columns or Yamazen Hi-Flash columns using an automated flash chromatography system Biotage Isolera One (Biotage AB, Uppsala, Sweden) or W-prep 2XY (Yamazen Corporation, Osaka, Japan). All melting points were determined on a Yanaco micro melting point apparatus (MP-J3) and are uncorrected. ¹H NMR spectra were recorded on a Bruker AV400M spectrometer at 400.1 MHz. Chemical shifts (δ) are reported in parts per million (ppm) using tetramethylsilane as an internal standard. Data are presented as follows: chemical shift, multiplicity (s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad; br s, broad singlet), coupling constant and integration. ¹³C NMR spectra were recorded on a Bruker AV400M spectrometer at 100.6 MHz with complete proton decoupling. Chemical shifts (δ) are reported in parts per million (ppm) with the solvent as the internal reference (δ 77.16 in CDCl₃, δ 39.52 in DMSO-*d*₆, or δ 49.00 in CD₃OD).⁶⁸ High resolution mass spectra (HRMS) were recorded on an Agilent Technologies 6520 Accurate-Mass Q-TOF instrument using electrospray ionization (ESI, positive or negative ion mode). The purity of all tested compounds was determined to be \geq 95% by elemental analysis and/or HPLC-UV analysis. Elemental analyses were performed by Sumika Chemical Analysis Service, Ltd. (Osaka, Japan), and the results obtained were within ±0.4% of the theoretical values. HPLC–UV analysis was performed on a Shimadzu VP series or Prominence instrument (Shimadzu Corporation, Kyoto, Japan) with the following parameters: analytical column, Inertsil ODS-3, 4.6 × 250 mm, 5 µm (GL Sciences Inc., Tokyo, Japan); gradient elution, 10–90% MeOH in 0.1% ag HCO₂H for 45 min; flow rate, 1.0 mL/min; column temperature, 40 °C; injection volume, 10 µL; compound concentration, 2 mM in DMSO; detection wavelength, 260 nm. 5-Fluorouridine (>98.0%) and 2'-deoxy-5-fluorouridine (>98.0%) were purchased from Tokyo Chemical Industry Co., Ltd. (TCI). Phloridzin dihydrate (99%) was purchased from Sigma-Aldrich Co. LLC. 7,8,3'-Trihydroxyflavone (99+%) was purchased from Indofine Chemical Campany, Inc. N^6 -Benzyladenosine (97.7%) was purchased from MP Biomedicals, Inc. Pharmacological, pharmacokinetic, and safety studies were carried out by Kissei Pharmaceutical Co., Ltd.

Synthetic Procedures and Characterization Data for Tested Compounds in Chapter 1

2-(Methylamino)adenosine (1-1)⁶⁹

A mixture of 2-chloroadenosine hydrate **11** (200 mg, 0.626 mmol as monohydrate) and ca. 40% aqueous MeNH₂ (1.25 mL, ca. 15.0 mmol) in EtOH (6.25 mL) was heated in a screw tube at 100 °C with stirring for 5.5 days. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 10–20% MeOH in DCM) followed by recrystallization from H₂O to give the title compound (138 mg, 75%) as a pale brown solid. mp 204–206 °C (lit.⁶⁹ mp 198 °C, dec). ¹H NMR (DMSO-*d*₆) δ 2.75 (d, *J* = 4.8 Hz, 3H), 3.47–3.69 (m, 2H), 3.85–3.93 (m, 1H), 4.09–4.18 (m, 1H), 4.55–4.67 (m, 1H), 5.01–5.26 (m, 2H), 5.35 (d, *J* = 6.3 Hz, 1H), 5.73 (d, *J* = 6.3 Hz, 1H), 6.08–6.22 (m, 1H), 6.73 (br s, 2H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 28.4, 61.9, 70.8, 72.9, 85.4, 87.2, 113.6, 136.5, 151.5, 156.0, 160.1. HRMS calcd for C₁₁H₁₇N₆O₄ (M+H)⁺ 297.1306, found 297.1308.

2-(Ethylamino)adenosine (1-2)

A mixture of **11** (100 mg, 0.313 mmol as monohydrate) and ca. 70% aqueous EtNH₂ (0.620 mL, ca. 7.44 mmol) in EtOH (3.1 mL) was heated in a screw tube at 100 °C with stirring for 93 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was triturated in DCM. The precipitate was collected by filtration, washed with DCM, dried under reduced pressure, and then recrystallized from H₂O to give the title compound (54.7 mg, 56%) as an off-white solid. mp 215–217 °C. ¹H NMR (DMSO-*d*₆) δ 1.09 (t, *J* =7.2 Hz, 3H), 3.19–3.31 (m, 2H), 3.46–3.68 (m, 2H), 3.83–3.93 (m, 1H), 4.07–4.17 (m, 1H), 4.53–4.67 (m, 1H), 4.97–5.24 (m, 2H), 5.34 (d, *J* = 6.3 Hz, 1H), 5.71 (d, *J* = 6.3 Hz, 1H), 6.06–6.21 (m, 1H), 6.70 (br s, 2H), 7.88 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 15.1, 35.7, 61.8, 70.8, 72.9, 85.3, 87.2, 113.6, 136.4, 151.5, 156.1, 159.3. HRMS calcd for C₁₂H₁₉N₆O₄ (M+H)⁺ 311.1462, found 311.1458.

2-(Pentylamino)adenosine (1-3)⁷⁰

A mixture of **11** (200 mg, 0.626 mmol as monohydrate), pentylamine (164 mg, 1.88 mmol), and *i*-Pr₂NEt (485 mg, 3.75 mmol) in EtOH (6.26 mL) was heated in a screw tube at 120 °C with stirring for 6 days. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified sequentially by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM), flash column chromatography on silica gel (gradient: 10–17% MeOH in DCM), and recrystallization form aqueous EtOH to give the title compound (149 mg, 68%) as a brown solid. mp 130–131 °C. ¹H NMR (DMSO-*d*₆) δ 0.80–0.95 (m, 3H), 1.20–1.38 (m, 4H), 1.40–1.60 (m, 2H), 3.14–3.28 (m, 2H), 3.45–3.72 (m, 2H), 3.83–3.93 (m, 1H), 4.08–4.18 (m, 1H), 4.49–4.71 (m, 1H), 4.90–5.30 (m, 2H), 5.34 (d, *J* = 6.3 Hz, 1H), 5.71 (d, *J* = 6.0 Hz, 1H), 5.99–6.27 (m, 1H),

6.68 (br s, 2H), 7.88 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 14.0, 22.0, 28.8, 29.0, 41.0, 61.9, 70.8, 72.9, 85.3, 87.2, 113.6, 136.4, 151.5, 156.0, 159.5. HRMS calcd for C₁₅H₂₅N₆O₄ (M+H)⁺ 353.1932, found 353.1934.

The ¹H NMR spectral property was found to be different from the following data previously reported.⁷⁰ 2-(*n*-Amylamino)adenosine (7c). ¹H NMR (DMSO- d_6) δ 1.41 (t, 3H, C5"-H), 1.49 (p, 2H, C4"-H), 1.63 (p, 2H, C3"-H), 1.86 (p, 2H, C2"-H), 3.50 and 3.61 (2 × m, 2H, C5'-H_{a,b}), 3.86 (m, 1H, C4'-H), 4.11 (m, 2H, C3'-H and

C1"-H), 4.60 (dd, 1H, C2'-H), 5.20 (br s, 3H, *OH*), 5.70 (d, 1H, C1'-H), 6.12 (s, 1H, C2-N*H*), 6.66 (br s, 2H, N⁶-H), 7.89 (s, 1H, C8-H).

2-(Benzylamino)adenosine (1-4)^{71,72}

A mixture of **11** (200 mg, 0.626 mmol as monohydrate), BnNH₂ (201 mg, 1.88 mmol), and *i*-Pr₂NEt (485 mg, 3.75 mmol) in EtOH (6.26 mL) was heated in a screw tube at 120 °C with stirring for 6.5 days. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 2–9% MeOH in DCM) followed by flash column chromatography on silica gel (gradient: 5–12% MeOH in DCM) to give the title compound (152 mg, 65%) as a brown solid. mp 118–120 °C (lit.⁷¹ mp 126–130 °C / lit.⁷² mp 100–105 °C for monohydrate). ¹H NMR (DMSO-*d*₆) δ 3.41–3.68 (m, 2H), 3.82–3.96 (m, 1H), 4.04–4.18 (m, 1H), 4.40–4.63 (m, 3H), 4.96–5.27 (m, 2H), 5.32 (d, *J* = 6.3 Hz, 1H), 5.71 (d, *J* = 6.0 Hz, 1H), 6.61–6.94 (m, 3H), 7.14–7.44 (m, 5H), 7.91 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 44.3, 61.8, 70.6, 73.0, 85.2, 87.1, 113.7, 126.3, 127.2, 128.1, 136.4, 141.3, 151.5, 156.1, 159.4. HRMS calcd for C₁₇H₂₁N₆O₄ (M+H)⁺ 373.1619, found 373.1615.

*N*⁶-Methyladenosine (1-5)^{73,74}

A mixture of 6-chloropurine riboside **12** (150 mg, 0.523 mmol) and ca. 40% aqueous MeNH₂ (1.05 mL, ca. 12.6 mmol) in EtOH (5.25 mL) was heated in a screw tube at 100 °C with stirring for 72 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 8–15% MeOH in DCM) followed by recrystallization from aqueous EtOH to give the title compound (79.5 mg, 54%) as an off-white solid. mp 218–220 °C (lit.⁷³ mp 219–221 °C). ¹H NMR (DMSO-*d*₆, D₂O shake) δ 2.96 (br s, 3H), 3.54 (dd, *J* = 3.6, 12.2 Hz, 1H), 3.67 (dd, *J* = 3.5, 12.2 Hz, 1H), 3.92–4.01 (m, 1H), 4.14 (dd, *J* = 3.0, 4.8 Hz, 1H), 4.55–4.65 (m, 1H), 5.88 (d, *J* = 6.3 Hz, 1H), 8.23 (br s, 1H), 8.34 (s, 1H). HRMS calcd for C₁₁H₁₆N₅O₄ (M+H)⁺ 282.1197, found 282.1199.

N⁶-Ethyladenosine (1-6)⁷⁵

A mixture of **12** (150 mg, 0.523 mmol) and ca. 70% aqueous $EtNH_2$ (1.05 mL, ca. 12.6 mmol) in EtOH (5.25 mL) was heated in a screw tube at 100 °C with stirring for 72 h. The reaction mixture was allowed to cool to room

temperature and then concentrated under reduced pressure. The residual solid was recrystallized from H₂O to give the title compound (91.3 mg, 59%) as a white floc. mp 199–200 °C (lit.⁷⁵ mp 193–194 °C). ¹H NMR (DMSO-*d*₆) δ 1.17 (t, *J* = 7.0 Hz, 3H), 3.39–3.75 (m, 4H), 3.93–4.00 (m, 1H), 4.10–4.19 (m, 1H), 4.56–4.66 (m, 1H), 5.17 (d, *J* = 4.5 Hz, 1H), 5.36–5.50 (m, 2H), 5.88 (d, *J* = 6.3 Hz, 1H), 7.68–8.00 (br, 1H), 8.20 (br s, 1H), 8.33 (s, 1H). HRMS calcd for C₁₂H₁₈N₅O₄ (M+H)⁺ 296.1353, found 296.1355.

N⁶-Pentyladenosine (1-7)^{76,77}

A mixture of **12** (150 mg, 0.523 mmol), pentylamine (137 mg, 1.57 mmol), and *i*-Pr₂NEt (406 mg, 3.14 mmol) in EtOH (5.23 mL) was heated in a screw tube at 120 °C with stirring for 96 h. The reaction mixture was allowed to cool to room temperature. The precipitate was collected by filtration, washed with cold EtOH, and dried at 80 °C under reduced pressure to give the title compound (155 mg, 88%) as a white solid. An analytical sample was prepared by recrystallization from aqueous EtOH. mp 154–156 °C (lit.⁷⁶ mp 150 °C). ¹H NMR (CD₃OD) δ 0.87–1.00 (m, 3H), 1.32–1.48 (m, 4H), 1.62–1.76 (m, 2H), 3.44–3.80 (m, 3H), 3.88 (dd, *J* = 2.4, 12.7 Hz, 1H), 4.13–4.21 (m, 1H), 4.31 (dd, *J* = 2.5, 5.1 Hz, 1H), 4.74 (dd, *J* = 5.1, 6.4 Hz, 1H), 5.94 (d, *J* = 6.4 Hz, 1H), 8.13–8.30 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 14.0, 21.9, 28.6, 28.7, 61.7, 70.7, 73.5, 86.0, 88.0, 119.8, 139.7, 148.2, 152.4, 154.7. HRMS calcd for C₁₅H₂₄N₅O4 (M+H)⁺ 338.1823, found 338.1824.

8-(Methylamino)adenosine (1-9)⁷⁸

A mixture of 8-bromoadenosine **13** (200 mg, 0.578 mmol) and ca. 40% aqueous MeNH₂ (1.16 mL, 13.9 mmol) in EtOH (5.78 mL) was heated in a screw tube at 100 °C with stirring for 77 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residual solid was recrystallized from H₂O to give the title compound (105 mg, 61%) as an off-white solid. mp 251–255 °C, dec (lit.⁷⁸ mp 250 °C, dec). ¹H NMR (DMSO-*d*₆) δ 2.88 (d, *J* = 4.5 Hz, 3H), 3.55–3.71 (m, 2H), 3.92–4.00 (m, 1H), 4.07–4.17 (m, 1H), 4.62–4.74 (m, 1H), 5.13 (d, *J* = 4.0 Hz, 1H), 5.23 (d, *J* = 6.8 Hz, 1H), 5.81–5.93 (m, 2H), 6.53 (br s, 2H), 6.91 (q, *J* = 4.5 Hz, 1H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 29.1, 61.7, 70.7, 71.0, 85.7, 86.5, 117.2, 148.5, 149.8, 152.1, 152.5. HRMS calcd for C₁₁H₁₇N₆O₄ (M+H)⁺ 297.1306, found 297.1306.

8-(Ethylamino)adenosine (1-10)⁷⁸

A mixture of **13** (200 mg, 0.578 mmol) and ca. 70% aqueous EtNH₂ (1.16 mL, ca. 13.9 mmol) in EtOH (5.78 mL) was heated in a screw tube at 100 °C with stirring for 64 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residual solid was recrystallized from H₂O to give the title compound (130 mg, 73%) as a pale brown solid. mp 257–259 °C, dec (lit.⁷⁸ mp 257 °C, dec). ¹H NMR (DMSO-*d*₆) δ 1.14–1.23 (m, 3H), 3.28–3.46 (m, 2H), 3.55–3.72 (m, 2H), 3.91–4.01 (m, 1H), 4.08–4.17 (m, 1H),

4.62–4.72 (m, 1H), 5.12 (d, J = 4.0 Hz, 1H), 5.21 (d, J = 6.8 Hz, 1H), 5.81–5.92 (m, 2H), 6.48 (br s, 2H), 6.87 (t, J = 5.3 Hz, 1H), 7.88 (s, 1H). ¹³C NMR (DMSO- d_6) δ 14.7, 37.1, 61.7, 70.7, 71.0, 85.6, 86.4, 117.1, 148.4, 149.8, 151.3, 152.4. HRMS calcd for C₁₂H₁₉N₆O₄ (M+H)⁺ 311.1462, found 311.1463.

8-(Pentylamino)adenosine (1-11)

A mixture of **13** (200 mg, 0.578 mmol), pentylamine (151 mg, 1.73 mmol), and *i*-Pr₂NEt (448 mg, 3.47 mmol) in EtOH (5.78 mL) was heated in a screw tube at 120 °C with stirring for 101 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM) followed by flash column chromatography on silica gel (gradient: 10–17% MeOH in DCM) to give the title compound (164 mg, 81%) as a beige solid. mp 204–205 °C. ¹H NMR (DMSO-*d*₆) δ 0.78–0.98 (m, 3H), 1.22–1.40 (m, 4H), 1.50–1.68 (m, 2H), 3.22–3.44 (m, 2H), 3.56–3.74 (m, 2H), 3.92–4.00 (m, 1H), 4.06–4.16 (m, 1H), 4.57–4.70 (m, 1H), 5.15 (d, *J* = 4.0 Hz, 1H), 5.23 (d, *J* = 6.8 Hz, 1H), 5.81–5.95 (m, 2H), 6.48 (br s, 2H), 6.80–6.93 (m, 1H), 7.88 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 14.0, 21.9, 28.4, 28.7, 42.3, 61.7, 70.7, 71.0, 85.7, 86.3, 117.1, 148.4, 149.8, 151.4, 152.3. HRMS calcd for C₁₅H₂₅N₆O₄ (M+H)⁺ 353.1932, found 353.1936.

8-(Benzylamino)adenosine (1-12)⁷⁹

The title compound (199 mg, 93%) was obtained as a pale yellow solid from **13** (200 mg, 0.578 mmol) and benzylamine (186 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H-NMR (DMSO-*d*₆) δ 3.55–3.70 (m, 2H), 3.95–4.03 (m, 1H), 4.08–4.19 (m, 1H), 4.51–4.67 (m, 2H), 4.69–4.80 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.85–6.00 (m, 2H), 6.51 (br s, 2H), 7.19–7.44 (m, 5H), 7.54 (t, *J* = 6.0 Hz, 1H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.2, 61.8, 70.9, 71.1, 85.8, 86.5, 117.1, 126.7, 127.1, 128.2, 139.9, 148.6, 149.8, 151.4, 152.5. HRMS calcd for C₁₇H₂₁N₆O₄ (M+H)⁺ 373.1619, found 373.1621.

5'-O-Acetyladenosine (1-13)^{81,82}

5'-O-Acetyl-2',3'-O-isopropylideneadenosine (*1-86*).⁸⁰ To a stirred suspension of 2',3'-*O*-isopropylideneadenosine **23** (200 mg, 0.651 mmol) in pyridine (3.25 mL) was added Ac₂O (79.7 mg, 0.781 mmol) at 0 °C, and the resulting mixture was gradually warmed to room temperature with stirring for 15 h. The reaction mixture was quenched by addition of MeOH (1 mL), stirred for additional 1 h, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 0–10% MeOH in AcOEt) to give the title compound (181 mg, 80%) as a white solid. ¹H NMR (CD₃OD) δ 1.39 (s, 3H), 1.60 (s, 3H), 1.96 (s, 3H), 4.22 (dd, *J* = 6.0, 11.8 Hz, 1H), 4.27 (dd, *J* = 4.8, 11.8 Hz, 1H), 4.39–4.48 (m, 1H), 5.09 (dd, *J* = 3.3, 6.3 Hz, 1H), 5.51 (dd, *J* = 2.3, 6.3 Hz, 1H), 6.21 (d, *J* = 2.3 Hz, 1H), 8.22 (s, 1H), 8.24 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 20.5, 25.2, 27.0,

63.7, 81.1, 83.2, 83.7, 89.1, 113.4, 119.1, 139.8, 148.8, 152.8, 156.2, 170.0. HRMS calcd for $C_{15}H_{20}N_5O_5$ (M+H)⁺ 350.1459, found 350.1462.

5'-O-Acetyladenosine (*1-13*).^{81,82} **1-86** (173 mg, 0.495 mmol) was dissolved in 70% (v/v) aqueous HCO₂H (4.95 mL) and the solution was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on NH silica gel (gradient: 5–12% MeOH in DCM) to give the title compound (134 mg, 88%) as a white solid. mp 132–134 °C (lit.⁸² mp 131–132 °C). ¹H NMR (DMSO-*d*₆) δ 2.01 (s, 3H), 4.04–4.11 (m, 1H), 4.17 (dd, *J* = 6.2, 11.9 Hz, 1H), 4.21–4.28 (m, 1H), 4.32 (dd, *J* = 3.8, 11.9 Hz, 1H), 4.62–4.70 (m, 1H), 5.36 (d, *J* = 5.5 Hz, 1H), 5.56 (d, *J* = 5.8 Hz, 1H), 5.90 (d, *J* = 4.8 Hz, 1H), 7.30 (br s, 2H), 8.15 (s, 1H), 8.31 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 20.6, 63.9, 70.3, 72.9, 81.5, 87.8, 119.2, 139.8, 149.4, 152.7, 156.1, 170.2. HRMS calcd for C₁₂H₁₆N₅O₅ (M+H)⁺ 310.1146, found 310.1146.

5'-O-Propionyladenosine (1-14)⁸¹

2',3'-*O*-*Isopropylidene-5'-O*-*propionyladenosine (1-87)*. To a stirred ice-cold suspension of **23** (500 mg, 1.63 mmol) in MeCN (8.1 mL) was added DMAP (398 mg, 3.25 mmol) followed by propionyl chloride (181 mg, 1.95 mmol), and the resulting mixture was allowed to warm to room temperature with stirring for 4 h. The reaction mixture was quenched by addition of MeOH (1 mL), stirred for additional 30 min, and then concentrated under reduced pressure. To the residue was added AcOEt (50 mL) and the resulting suspension was filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 0–10% MeOH in AcOEt) to give the title compound (581 mg, 98%) as a white solid. mp 128–130 °C. ¹H NMR (DMSO-*d*₆) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.34 (s, 3H), 1.54 (s, 3H), 2.15–2.35 (m, 2H), 4.13 (dd, *J* = 6.4, 11.7 Hz, 1H), 4.25 (dd, *J* = 4.5, 11.7 Hz, 1H), 4.31–4.40 (m, 1H), 5.06 (dd, *J* = 3.3, 6.2 Hz, 1H), 5.48 (dd, *J* = 2.4, 6.2 Hz, 1H), 6.19 (d, *J* = 2.4 Hz, 1H), 7.35 (br s, 2H), 8.16 (s, 1H), 8.29 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 8.8, 25.2, 26.5, 27.0, 63.6, 81.1, 83.2, 83.7, 89.1, 113.4, 119.2, 139.8, 148.8, 152.8, 156.2, 173.3. HRMS calcd for C₁₆H₂₂N₅O₅ (M+H)⁺ 364.1615, found 364.1617.

5'-O-Propionyladenosine (*1-14*).⁸¹ The title compound (414 mg, 86%) was obtained as a white solid from **1-87** (541 mg, 1.49 mmol) according to a procedure similar to that described for the preparation of **1-13**. An analytical sample was prepared by recrystallization from H₂O. mp 179–181 °C. ¹H NMR (DMSO-*d*₆) δ 1.00 (t, *J* = 7.5 Hz, 3H), 2.31 (q, *J* = 7.5 Hz, 2H), 4.03–4.12 (m, 1H), 4.18 (dd, *J* = 6.0, 11.8 Hz, 1H), 4.22–4.30 (m, 1H), 4.34 (dd, *J* = 3.8, 11.8 Hz, 1H), 4.61–4.70 (m, 1H), 5.35 (d, *J* = 5.8 Hz, 1H), 5.56 (d, *J* = 5.8 Hz, 1H), 5.90 (d, *J* = 4.8 Hz, 1H), 7.30 (br s, 2H), 8.15 (s, 1H), 8.30 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 8.9, 26.7, 63.8, 70.3, 72.9, 81.5, 87.8, 119.2, 139.7, 149.4, 152.7, 156.1, 173.5. HRMS calcd for C₁₃H₁₈N₅O₅ (M+H)⁺ 324.1302, found 324.1306.

5'-O-Hexanoyladenosine (1-15)⁸³

5'-O-Hexanoyl-2',3'-O-isopropylideneadenosine (1-88). The title compound (637 mg, 97%) was obtained as a white

solid from **23** (500 mg, 1.63 mmol) and hexanoyl chloride (263 mg, 1.95 mmol) according to a procedure similar to that described for the preparation of **1-87**. ¹H NMR (DMSO- d_6) δ 0.82 (t, J = 7.0 Hz, 3H), 1.10–1.30 (m, 4H), 1.33 (s, 3H), 1.36–1.50 (m, 2H), 1.54 (s, 3H), 2.12–2.29 (m, 2H), 4.14 (dd, J = 6.4, 11.7 Hz, 1H), 4.24 (dd, J = 4.6, 11.7 Hz, 1H), 4.32–4.40 (m, 1H), 5.04 (dd, J = 3.1, 6.2 Hz, 1H), 5.49 (dd, J = 2.4, 6.2 Hz, 1H), 6.19 (d, J = 2.4 Hz, 1H), 7.35 (br s, 2H), 8.16 (s, 1H), 8.29 (s, 1H). ¹³C NMR (DMSO- d_6) δ 13.7, 21.7, 24.0, 25.2, 27.0, 30.5, 33.1, 63.6, 81.2, 83.2, 83.7, 89.2, 113.4, 119.2, 139.8, 148.8, 152.7, 156.2, 172.6. HRMS calcd for C₁₉H₂₈N₅O₅ (M+H)⁺ 406.2085, found 406.2090.

5'-O-Hexanoyladenosine (*1-15*).⁸³ The title compound (500 mg, 91%) was obtained as a white solid from **1-88** (610 mg, 1.50 mmol) according to a procedure similar to that described for the preparation of **1-13**. ¹H NMR (DMSO-*d*₆) δ 0.78–0.86 (m, 3H), 1.13–1.30 (m, 4H), 1.41–1.54 (m, 2H), 2.23–2.31 (m, 2H), 4.04–4.10 (m, 1H), 4.18 (dd, *J* = 6.0, 11.8 Hz, 1H), 4.22–4.29 (m, 1H), 4.33 (dd, *J* = 3.8, 11.8 Hz, 1H), 4.63–4.71 (m, 1H), 5.34 (d, *J* = 5.5 Hz, 1H), 5.54 (d, *J* = 5.5 Hz, 1H), 5.90 (d, *J* = 4.8 Hz, 1H), 7.28 (br s, 2H), 8.14 (s, 1H), 8.29 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 13.8, 21.7, 24.0, 30.6, 33.3, 63.7, 70.3, 72.9, 81.5, 87.8, 119.2, 139.7, 149.3, 152.7, 156.1, 172.8. HRMS calcd for $C_{16}H_{24}N_5O_5$ (M+H)⁺ 366.1772, found 366.1774.

5'-O-(Phenylacetyl)adenosine (1-16)

2',3'-O-Isopropylidene-5'-O-(phenylacetyl)adenosine (1-89). To a stirred ice-cold suspension of 23 (500 mg, 1.63 mmol) in MeCN (8.10 mL) was added DMAP (398 mg, 3.25 mmol) followed by phenylacetyl chloride (302 mg, 1.95 mmol), and the resulting mixture was stirred at room temperature for 14 h. The reaction mixture was quenched by addition of MeOH (1 mL), stirred for additional 30 min, and then concentrated under reduced pressure. The residue was suspended in AcOEt (50 mL) and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 0-10% MeOH in AcOEt) to give the title compound as a mixture with 2',3'-O-isopropylidene- $N^6,5'-O$ -bis-(phenylacetyl)adenosine (270 mg) as indicated by ¹H NMR and LC-MS analyses. The product obtained (268 mg) was dissolved in MeOH (4.20 mL) and the solution was heated in a sealed tube at 120 °C with stirring for 12 h under microwave irradiation. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 0-10% MeOH in AcOEt) to give the title compound (142 mg, 21% from 23) as an off-white foam. ¹H NMR (DMSO-*d*₆) δ 1.33 (s, 3H), 1.54 (s, 3H), 3.54– $3.71 \text{ (m, 2H)}, 4.18 \text{ (dd}, J = 6.3, 11.8 \text{ Hz}, 1\text{H}), 4.28 \text{ (dd}, J = 4.3, 11.8 \text{ Hz}, 1\text{H}), 4.34-4.45 \text{ (m, 1H)}, 5.01 \text{ (dd}, J = 3.3, 1.8 \text{ Hz}, 1.8 \text{ H$ 6.3 Hz, 1H), 5.39 (dd, J = 2.5, 6.3 Hz, 1H), 6.18 (d, J = 2.5 Hz, 1H), 7.10–7.60 (m, 7H), 8.17 (s, 1H), 8.28 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.2, 27.0, 64.1, 81.1, 83.2, 83.5, 89.2, 113.5, 119.2, 126.8, 128.3, 129.3, 134.1, 139.7, 148.8, 152.8, 156.2, 170.9. HRMS calcd for C₂₁H₂₄N₅O₅ (M+H)⁺ 426.1772, found 426.1774.

5'-O-(Phenylacetyl)adenosine (1-16). The title compound (103 mg, 88%) was obtained as an off-white solid from **1-89** (130 mg, 0.306 mmol) according to a procedure similar to that described for the preparation of **1-13**. ¹H NMR

(DMSO-*d*₆) δ 3.62–3.74 (m, 2H), 4.04–4.14 (m, 1H), 4.16–4.31 (m, 2H), 4.35 (dd, *J* = 3.6, 11.9 Hz, 1H), 4.60–4.69 (m, 1H), 5.38 (d, *J* = 5.5 Hz, 1H), 5.57 (d, *J* = 5.8 Hz, 1H), 5.90 (d, *J* = 5.0 Hz, 1H), 7.19–7.47 (m, 7H), 8.15 (s, 1H), 8.28 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 40.1, 64.3, 70.2, 72.9, 81.5, 87.7, 119.2, 126.9, 128.4, 129.4, 134.2, 139.7, 149.4, 152.7, 156.1, 171.1. HRMS calcd for C₁₈H₂₀N₅O₅ (M+H)⁺ 386.1459, found 386.1455.

5'-O-(Methoxycarbonyl)adenosine (1-17)

2',3'-O-Isopropylidene-5'-O-(methoxycarbonyl)adenosine (**1-90**). The title compound (1.15 g, 97%) was obtained as a white solid from **23** (1.00 g, 3.25 mmol) and methyl chloroformate (461 mg, 4.88 mmol) according to a procedure similar to that described for the preparation of **1-87**. ¹H NMR (DMSO-*d*₆) δ 1.33 (s, 3H), 1.54 (s, 3H), 3.66 (s, 3H), 4.22 (dd, *J* = 6.8, 11.3 Hz, 1H), 4.26–4.43 (m, 2H), 5.07 (dd, *J* = 3.3, 6.3 Hz, 1H), 5.45 (dd, *J* = 2.3, 6.3 Hz, 1H), 6.21 (d, *J* = 2.3 Hz, 1H), 7.37 (br s, 2H), 8.16 (s, 1H), 8.29 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.1, 26.9, 54.8, 67.1, 81.0, 83.2, 83.5, 89.1, 113.5, 119.1, 139.8, 148.8, 152.8, 154.8, 156.2. HRMS calcd for C₁₅H₂₀N₅O₆ (M+H)⁺ 366.1408, found 366.1409.

5'-O-(Methoxycarbonyl)adenosine (1-17). The title compound (419 mg, 94%) was obtained as an off-white solid from **1-90** (500 mg, 1.37 mmol) according to a procedure similar to that described for the preparation of **1-13**. An analytical sample was prepared by recrystallization from H₂O. mp 189–191 °C. ¹H NMR (DMSO-*d*₆) δ 3.69 (s, 3H), 4.05–4.14 (m, 1H), 4.18–4.34 (m, 2H), 4.39 (dd, J = 3.8, 11.5 Hz, 1H), 4.59–4.68 (m, 1H), 5.40 (d, J = 5.5 Hz, 1H), 5.58 (d, J = 5.8Hz, 1H), 5.91 (d, J = 5.0 Hz, 1H), 7.30 (br s, 2H), 8.14 (s, 1H), 8.28 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 54.8, 67.5, 70.3, 73.0, 81.4, 87.7, 119.2, 139.5, 149.4, 152.7, 155.0, 156.1. HRMS calcd for C₁₂H₁₆N₅O₆ (M+H)⁺ 326.1095, found 326.1102.

5'-O-(Ethoxycarbonyl)adenosine (1-18)

5'-O-(*Ethoxycarbonyl*)-2',3'-O-*isopropylideneadenosine* (**1-91**).⁸⁴ The title compound (1.20 g, 97%) was obtained as a white solid from **23** (1.00 g, 3.25 mmol) and ethyl chloroformate (530 mg, 4.88 mmol) according to a procedure similar to that described for the preparation of **1-87**. ¹H NMR (DMSO-*d*₆) δ 1.17 (t, *J* = 7.1 Hz, 3H), 1.33 (s, 3H), 1.54 (s. 3H), 4.06 (q, *J* = 7.1 Hz, 2H), 4.21 (dd, *J* = 6.9, 11.4 Hz, 1H), 4.24–4.41 (m, 2H), 5.07 (dd, *J* = 3.3, 6.3 Hz, 1H), 5.46 (dd, *J* = 2.4, 6.3 Hz, 1H), 6.21 (d, *J* = 2.4 Hz, 1H), 7.35 (br s, 2H), 8.16 (s, 1H), 8.29 (s. 1H). ¹³C NMR (DMSO-*d*₆) δ 14.0, 25.2, 26.9, 63.8, 66.9, 81.1, 83.2, 83.5, 89.1, 113.5, 119.1, 139.8, 148.8, 152.8, 154.1, 156.2. HRMS calcd for C₁₆H₂₂N₅O₆ (M+H)⁺ 380.1565, found 380.1564.

5'-O-(*Ethoxycarbonyl*)adenosine (1-18). The title compound (352 mg, 79%) was obtained as an off-white solid from 1-91 (500 mg, 1.32 mmol) according to a procedure similar to that described for the preparation of 1-13. An analytical sample was prepared by recrystallization from H₂O. mp 157–159 °C. ¹H NMR (DMSO-*d*₆) δ 1.19 (t, *J* = 7.2 Hz, 3H), 4.05–4.17 (m, 3H), 4.19–4.34 (m, 2H), 4.38 (dd, *J* = 3.9, 11.7 Hz, 1H), 4.60–4.71 (m, 1H), 5.41 (d, *J* = 5.5 Hz, 1H), 5.60 (d, *J* = 5.8 Hz, 1H), 5.91 (d, *J* = 5.3 Hz, 1H), 7.32 (br s, 2H), 8.15 (s, 1H), 8.29 (s, 1H). ¹³C

NMR (DMSO-*d*₆) δ 14.1, 63.8, 67.2, 70.3, 72.9, 81.4, 87.7, 119.1, 139.5, 149.4, 152.7, 154.4, 156.1. HRMS calcd for C₁₃H₁₈N₅O₆ (M+H)⁺ 340.1252, found 340.1254.

5'-O-(Pentyloxycarbonyl)adenosine (1-19)

2',3'-O-Isopropylidene-5'-O-(pentyloxycarbonyl)adenosine (**1-92**). The title compound (1.28 g, 93%) was obtained as a white foam from **23** (1.00 g, 3.25 mmol) and pentyl chloroformate (735 mg, 4.88 mmol) according to a procedure similar to that described for the preparation of **1-87**. ¹H NMR (DMSO-*d*₆) δ 0.77–0.94 (m, 3H), 1.18– 1.41 (m, 7H), 1.46–1.64 (m, 5H), 4.01 (t, *J* = 6.7 Hz, 2H), 4.21 (dd, *J* = 6.8, 11.3 Hz, 1H), 4.26–4.43 (m, 2H), 5.07 (dd, *J* = 3.3, 6.3 Hz, 1H), 5.46 (dd, *J* = 2.3, 6.3 Hz, 1H), 6.21 (d, *J* = 2.3 Hz, 1H), 7.36 (br s, 2H), 8.16 (s, 1H), 8.29 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 13.8, 21.7, 25.2, 26.9, 27.2, 27.7, 66.9, 67.8, 81.1, 83.2, 83.6, 89.2, 113.5, 119.2, 139.8, 148.8, 152.8, 154.2, 156.2. HRMS calcd for C₁₉H₂₈N₅O₆ (M+H)⁺ 422.2034, found 422.2042. 5'-O-(Pentyloxycarbonyl)adenosine (*1-19*). The title compound (1.02 g, 88%) was obtained as an off-white solid from **1-92** (1.28 g, 3.04 mmol) according to a procedure similar to that described for the preparation of **1-13**. An analytical sample was prepared by recrystallization from aqueous EtOH. mp 177–179 °C. ¹H NMR (DMSO-*d*₆) δ 0.77–0.93 (m, 3H), 1.19–1.34 (m, 4H), 1.48–1.65 (m, 2H), 3.99–4.15 (m, 3H), 4.19–4.34 (m, 2H), 4.38 (dd, *J* = 3.9, 11.7 Hz, 1H), 4.60–4.70 (m, 1H), 5.41 (d, *J* = 5.3 Hz, 1H), 5.59 (d, *J* = 5.8 Hz, 1H), 5.91 (d, *J* = 5.3 Hz, 1H), 7.31 (br s, 2H), 8.14 (s, 1H), 8.29 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 13.8, 21.7, 27.3, 27.7, 67.3, 67.7, 70.3, 72.9, 81.4,

5'-O-(Benzyloxycarbonyl)adenosine (1-20)

5'-O-(Benzyloxycarbonyl)-2',3'-O-isopropylideneadenosine (**1-93**). The title compound (684 mg, 95%) was obtained as a white foam from **23** (500 mg, 1.63 mmol) and benzyl chloroformate (416 mg, 2.44 mmol) according to a procedure similar to that described for the preparation of **1-87**. ¹H NMR (DMSO-*d*₆) δ 1.33 (s, 3H), 1.54 (s, 3H), 4.21–4.47 (m, 3H), 5.03–5.18 (m, 3H), 5.45 (dd, *J* = 2.4, 6.3 Hz, 1H), 6.21 (d, *J* = 2.4 Hz, 1H), 7.26–7.51 (m, 7H), 8.16 (s, 1H), 8.30 (s, 1H).¹³C NMR (DMSO-*d*₆) δ 25.2, 26.9, 67.2, 69.1, 81.0, 83.2, 83.5, 89.1, 113.5, 119.1, 128.2, 128.4, 128.5, 135.3, 139.8, 148.8, 152.8, 154.1, 156.2. HRMS calcd for C₂₁H₂₄N₅O₆ (M+H)⁺ 442.1721, found 442.1722.

87.7, 119.2, 139.5, 149.4, 152.7, 154.5, 156.1. HRMS calcd for C₁₆H₂₄N₅O₆ (M+H)⁺ 382.1721, found 382.1724.

5'-*O*-(*Benzyloxycarbonyl*)*adenosine* (**1**-20). The title compound (512 mg, 86%) was obtained as a white solid from **1-93** (658 mg, 1.49 mmol) according to a procedure similar to that described for the preparation of **1-13**. ¹H NMR (DMSO-*d*₆) δ 4.07–4.15 (m, 1H), 4.19–4.26 (m, 1H), 4.32 (dd, *J* = 6.4, 11.6 Hz, 1H), 4.41 (dd, *J* = 3.8, 11.6 Hz, 1H), 4.60–4.71 (m, 1H), 5.08–5.19 (m, 2H), 5.41 (d, *J* = 5.3 Hz, 1H), 5.59 (d, *J* = 5.8 Hz, 1H), 5.91 (d, *J* = 5.3 Hz, 1H), 7.19–7.49 (m, 7H), 8.14 (s, 1H), 8.29 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 67.6, 69.1, 70.3, 72.9, 81.4, 87.7, 119.2, 128.2, 128.4, 128.5, 135.4, 139.6, 149.4, 152.7, 154.4, 156.1. HRMS calcd for C₁₈H₂₀N₅O₆ (M+H)⁺ 402.1408, found 402.1402.

5'-O-(Methylcarbamoyl)adenosine (1-21)

2',3'-O-Isopropylidene-5'-O-(4-nitrophenoxycarbonyl)adenosine (1-94).⁸⁵ To a stirred suspension of 23 (500 mg, 1.63 mmol) in MeCN (8.10 mL) was added Et₃N (329 mg, 3.25 mmol) at 0 °C. Then 4-nitrophenyl chloroformate (492 mg, 2.44 mmol) was added in five portions, and the resulting mixture was gradually warmed to room temperature with stirring for 24 h. After being quenched with crushed ice, the reaction mixture was partitioned between AcOEt (45 mL) and saturated aqueous NaHCO₃ (20 mL). The organic layer was washed successively with saturated aqueous NaHCO₃ (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 1–8% MeOH in AcOEt) to give the title compound (439 mg, 57%) as a pale yellow foam. ¹H NMR (DMSO-*d*₆) δ 1.35 (s, 3H), 1.57 (s, 3H), 4.33–4.62 (m, 3H), 5.17 (dd, *J* = 2.9, 6.1 Hz, 1H), 5.50 (dd, *J* = 2.2, 6.1 Hz, 1H), 6.25 (d, *J* = 2.2 Hz, 1H), 7.23–7.55 (m, 4H), 8.17 (s, 1H), 8.23–8.38 (m, 3H). ¹³C NMR (DMSO-*d*₆) δ 25.2, 26.9, 68.4, 80.9, 83.3, 83.5, 89.2, 113.5, 119.2, 122.5, 125.4, 139.8, 145.2, 148.8, 151.7, 152.8, 155.1, 156.2. HRMS calcd for C₂₀H₂₁N₆O₈ (M+H)⁺ 473.1415, found 473.1407.

2',3'-O-Isopropylidene-5'-O-(methylcarbamoyl)adenosine (1-95). To a solution of 1-94 (350 mg, 0.741 mmol) in THF (7.4 mL) was added Et₃N (113 mg, 1.11 mmol) followed by MeNH₂ (40% in MeOH, 0.091 mL, ca. 0.892 mmol), and the resulting mixture was stirred at room temperature for 75 min. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on NH silica gel (gradient: 0–10% MeOH in AcOEt) to give the title compound (218 mg, 81%) as a white foam. ¹H NMR (DMSO-*d*₆) δ 1.33 (s, 3H), 1.54 (s, 3H), 2.54 (d, *J* = 4.5 Hz, 3H), 3.95–4.07 (m, 1H), 4.17 (dd, *J* = 5.0, 11.5 Hz, 1H), 4.27–4.38 (m, 1H), 5.01 (dd, *J* = 2.9, 6.1 Hz, 1H), 5.45 (d, *J* = 2.8, 6.1 Hz, 1H), 6.17 (d, *J* = 2.8 Hz, 1H), 7.05–7.15 (m, 1H), 7.34 (br s, 2H), 8.17 (s, 1H), 8.29 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.2, 26.9, 27.0, 63.8, 81.4, 83.2, 83.8, 89.1, 113.4, 119.1, 139.6, 148.9, 152.8, 156.2 (2C). HRMS calcd for C₁₅H₂₁N₆O₅ (M+H)⁺ 365.1568, found 365.1570.

5'-O-(*Methylcarbamoyl*)*adenosine* (1-21). The title compound (168 mg, 90%) was obtained as a white solid from 1-95 (209 mg, 0.574 mmol) according to a procedure similar to that described for the preparation of 1-13. An analytical sample was prepared by recrystallization from H₂O. mp 164–165 °C. ¹H NMR (DMSO-*d*₆) δ 2.57 (d, *J* = 4.8 Hz, 3H), 3.99–4.36 (m, 4H), 4.58–4.72 (m, 1H), 5.14–5.68 (m, 2H), 5.91 (d, *J* = 5.8 Hz, 1H), 7.10–7.23 (m, 1H), 7.38 (br s, 2H), 8.17 (s, 1H), 8.34 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 27.0, 64.1, 70.6, 73.0, 82.5, 87.0, 119.0, 140.0, 149.6, 152.5, 155.9, 156.5. HRMS calcd for C₁₂H₁₇N₆O₅ (M+H)⁺ 325.1255, found 325.1261.

5'-O-(Ethylcarbamoyl)adenosine (1-22)

5'-O-(Ethylcarbamoyl)-2',3'-O-isopropylideneadenosine (1-96). The title compound (75.4 mg, 94%) was obtained as a pale yellow solid from **1-94** (100 mg, 0.212 mmol) and ca. 70% aqueous EtNH₂ (0.021 mL, ca. 0.252 mmol) according to a procedure similar to that described for the preparation of **1-95**. ¹H NMR (DMSO-*d*₆) δ 0.99 (t, *J* =

7.2 Hz, 3H), 1.33 (s, 3H), 1.54 (s, 3H), 2.90–3.06 (m, 2H), 4.00 (dd, J = 6.5, 11.5 Hz, 1H), 4.17 (dd, J = 5.0, 11.5 Hz, 1H), 4.29–4.38 (m, 1H), 5.01 (dd, J = 2.8, 6.2 Hz, 1H), 5.46 (dd, J = 2.7, 6.2 Hz, 1H), 6.17 (d, J = 2.7 Hz, 1H), 7.22 (t, J = 5.5 Hz, 1H), 7.35 (br s, 2H), 8.17 (s, 1H), 8.29 (s, 1H). ¹³C NMR (DMSO- d_6) δ 14.9, 25.2, 27.0, 35.0, 63.7, 81.4, 83.1, 83.7, 89.0, 113.4, 119.0, 139.6, 148.9, 152.8, 155.5, 156.2. HRMS calcd for C₁₆H₂₃N₆O₅ (M+H)⁺ 379.1724, found 379.1730.

5'-O-(Ethylcarbamoyl)adenosine (1-22). The title compound (232 mg, 92%) was obtained as a slightly hay-colored solid from **1-96** (283 mg, 0.747 mmol) according to a procedure similar to that described for the preparation of **1-13**. An analytical sample was prepared by recrystallization from H₂O. mp 203–205 °C. ¹H NMR (DMSO-*d*₆) δ 1.01 (t, *J* = 7.2 Hz, 3H), 2.91–3.08 (m, 2H), 4.00–4.33 (m, 4H), 4.61–4.72 (m, 1H), 5.36 (d, *J* = 5.0 Hz, 1H), 5.51 (d, *J* = 6.3 Hz, 1H), 5.91 (d, *J* = 6.0 Hz, 1H), 7.15–7.45 (m, 3H), 8.15 (s, 1H), 8.32 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 15.0, 35.1, 64.0, 70.7, 73.0, 82.4, 86.9, 119.0, 139.4, 149.7, 152.7, 155.8, 156.1. HRMS calcd for C₁₃H₁₉N₆O₅ (M+H)⁺ 339.1411, found 339.1419.

5'-O-(Pentylcarbamoyl)adenosine (1-23)

2',3'-O-Isopropylidene-5'-O-(pentylcarbamoyl)adenosine (1-97). The title compound (253 mg, 81%) was obtained as a pale yellow foam from 1-94 (350 mg, 0.741 mmol) and pentylamine (77.5 mg, 0.889 mmol) according to a procedure similar to that described for the preparation of 1-95. ¹H NMR (DMSO- d_6) δ 0.76–0.92 (m, 3H), 1.06– 1.46 (m, 9H), 1.54 (s, 3H), 2.87–3.00 (m, 2H), 4.00 (dd, *J* = 6.7, 11.4 Hz, 1H), 4.16 (dd, *J* = 5.2, 11.4 Hz, 1H), 4.29– 4.39 (m, 1H), 5.00 (dd, *J* = 2.8, 6.1 Hz, 1H), 5.46 (dd, *J* = 2.8, 6.1 Hz, 1H), 6.17 (d, *J* = 2.8 Hz, 1H), 7.16–7.28 (m, 1H), 7.35 (br s, 2H), 8.16 (s, 1H), 8.30 (s, 1H). ¹³C NMR (DMSO- d_6) δ 13.9, 21.8, 25.2, 27.0, 28.4, 29.0, 40.2, 63.7, 81.4, 83.1, 83.7, 89.0, 113.4, 119.0, 139.6, 148.9, 152.8, 155.7, 156.1. HRMS calcd for C₁₉H₂₉N₆O₅ (M+H)⁺ 421.2194, found 421.2200.

5'-O-(Pentylcarbamoyl)adenosine (1-23). **1-97** (219 mg, 0.521 mmol) was dissolved in 70% (v/v) aqueous HCO₂H (5.21 mL) and the solution was stirred at room temperature for 25 h. The reaction mixture was concentrated under reduced pressure and the residual solid was recrystallized from EtOH to give the title compound (152 mg, 77%) as an off-white solid. mp 197–200 °C. ¹H NMR (DMSO-*d*₆) δ 0.76–0.93 (m, 3H), 1.12–1.48 (m, 6H), 2.88–3.01 (m, 2H), 4.00–4.31 (m, 4H), 4.61–4.72 (m, 1H), 5.36 (d, *J* = 5.0 Hz, 1H), 5.51 (d, *J* = 6.3 Hz, 1H), 5.91 (d, *J* = 6.0 Hz, 1H), 7.17–7.43 (m, 3H), 8.15 (s, 1H), 8.33 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 13.9, 21.8, 28.4, 29.0, 40.2, 64.0, 70.6, 73.0, 82.4, 86.9, 119.0, 139.5, 149.6, 152.7, 155.9, 156.1. HRMS calcd for C₁₆H₂₅N₆O₅ (M+H)⁺ 381.1881, found 381.1878.

5'-O-(Benzylcarbamoyl)adenosine (1-24)

5'-O-(*Benzylcarbamoyl*)-2',3'-O-isopropylideneadenosine (1-98). The title compound (362 mg, quant.) was obtained as a pale yellow foam from 1-94 (385 mg, 0.815 mmol) and benzylamine (105 mg, 0.978 mmol) according

to a procedure similar to that described for the preparation of **1-95**. ¹H NMR (DMSO-*d*₆) δ 1.33 (s, 3H), 1.55 (s, 3H), 4.07 (dd, *J* = 6.5, 11.5 Hz, 1H), 4.11–4.27 (m, 3H), 4.28–4.43 (m, 1H), 5.02 (dd, *J* = 2.8, 6.1 Hz, 1H), 5.46 (dd, *J* = 2.7, 6.1 Hz, 1H), 6.18 (d, *J* = 2.7 Hz, 1H), 7.15–7.54 (m, 7H), 7.82 (t, *J* = 6.0 Hz, 1H), 8.17 (s, 1H), 8.32 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.2, 27.0, 43.8, 64.0, 81.4, 83.2, 83.7, 89.1, 113.4, 119.1, 126.8, 127.0, 128.3, 139.5, 139.6, 148.9, 152.9, 156.0, 156.2. HRMS calcd for C₂₁H₂₅N₆O₅ (M+H)⁺ 441.1881, found 441.1887.

5'-O-(*Benzylcarbamoyl*)*adenosine* (1-24). 1-98 (336 mg, 0.763 mmol) was dissolved in 70% (v/v) aqueous HCO₂H (7.63 mL) and the solution was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and the residual solid was suspended in EtOH (20 mL). The suspension was heated under reflux with stirring for 1 h and then allowed to cool to room temperature. The precipitate was collected by filtration, washed with EtOH, air-dried, and dried at 80 °C under reduced pressure to give the title compound (277 mg, 91%) as a pale yellow solid. mp 198–200 °C. ¹H NMR (DMSO-*d*₆) δ 3.98–4.33 (m, 6H), 4.62–4.75 (m, 1H), 5.38 (d, *J* = 5.0 Hz, 1H), 5.52 (d, *J* = 6.3 Hz, 1H), 5.92 (d, *J* = 6.0 Hz, 1H), 7.15–7.48 (m, 7H), 7.88 (t, *J* = 6.2 Hz, 1H), 8.15 (s, 1H), 8.35 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 43.8, 64.3, 70.6, 73.0, 82.4, 86.9, 119.0, 126.8, 127.0, 128.3, 139.5, 139.6, 149.6, 152.7, 156.1, 156.3. HRMS calcd for C₁₈H₂₁N₆O₅ (M+H)⁺ 401.1568, found 401.1574.

8-(2-Phenylethyl)adenosine (1-25)

2',3',5'-*Tri-O-acetyl-8-bromoadenosine* (1-99).⁸⁶ To a stirred mixture of **13** (500 mg, 1.44 mmol), Et₃N (585 mg, 5.78 mmol), and DMAP (17.6 mg, 0.144 mmol) in MeCN (14.4 mL) was added dropwise Ac₂O (531 mg, 5.20 mmol), and the resulting mixture was stirred at room temperature for 36 h. The reaction mixture was quenched by addition of MeOH (1.5 ml), stirred for additional 6 h, and then concentrated under reduced pressure. The residue was partitioned between AcOEt (55 mL) and H₂O (15 mL). The organic layer was washed with brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 72–93% AcOEt in hexane) to give the title compound (515 mg, 76%) as a white foam. ¹H NMR (CDCl₃) δ 2.04 (s, 3H), 2.11 (s, 3H), 2.16 (s, 3H), 4.29–4.44 (m, 2H), 4.52 (dd, *J* = 3.4, 11.6 Hz, 1H), 5.54 (br s, 2H), 5.91–6.00 (m, 1H), 6.10 (d, *J* = 4.4 Hz, 1H), 6.35 (dd, *J* = 4.4, 6.0 Hz, 1H), 8.32 (s, 1H). HRMS calcd for C₁₆H₁₉BrN₅O₇ (M+H)⁺ 472.0462, found 472.0463.

2',3',5'-*Tri-O-acetyl-8-(phenylethynyl)adenosine* (**1-100**).⁸⁷ To a stirred mixture of **1-99** (159 mg, 0.337 mmol), ethynylbenzene (41.3 mg, 0.404 mmol), Et₃N (102 mg, 1.01 mmol) and CuI (3.80 mg, 0.0200 mmol) in DMF (2.69 mL) was added Pd(PPh₃)₄ (11.7 mg, 0.0101 mmol), and the resulting mixture was heated in a screw tube at 110 °C with stirring for 31 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (40 mL) and H₂O (10 mL). The organic layer was washed twice with H₂O (10 mL × 2), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 70–91% AcOEt in hexane) to give the title compound (145 mg, 87%) as a pale yellow solid. ¹H NMR (CDCl₃) δ 2.02 (s, 3H), 2.11 (s, 3H), 2.15 (s, 3H), 4.35 (dd, *J* = 6.0, 11.7 Hz, 1H), 4.38–4.45 (m, 1H), 4.54 (dd, *J* =

3.4, 11.7 Hz, 1H), 5.60 (br s, 2H), 5.95–6.02 (m, 1H), 6.29–6.38 (m, 2H), 7.39–7.52 (m, 3H), 7.62–7.72 (m, 2H), 8.39 (s, 1H). 13 C NMR (CDCl₃) δ 20.6, 20.7, 20.8, 63.2, 70.6, 72.6, 77.7, 80.1, 87.7, 96.3, 120.1, 120.5, 128.8, 130.4, 132.4, 134.7, 149.6, 154.1, 155.4, 169.5, 169.6, 170.7. HRMS calcd for C₂₄H₂₄N₅O₇ (M+H)⁺ 494.1670, found 494.1670.

2',3',5'-*Tri-O-acetyl-8-(2-phenylethyl)adenosine* (1-101). A mixture of 1-100 (261 mg, 0.529 mmol) and 10% Pd– C (56.5 wt% H₂O, 180 mg) in AcOEt (5.3 mL) was stirred at room temperature for 2.5 h under a hydrogen atmosphere. The reaction mixture was filtered through a pad of Hyflo Super-Cel and the filtrate was concentrated under reduced pressure to give the title compound (255 mg, 97%) as a beige solid. mp 202–205 °C. ¹H NMR (CDCl₃) δ 1.96 (s, 3H), 2.07 (s, 3H), 2.14 (s, 3H), 3.11–3.25 (m, 4H), 4.28–4.39 (m, 2H), 4.43–4.54 (m, 1H), 5.42 (br s, 2H), 5.90–5.99 (m, 2H), 6.32 (dd, *J* = 4.8, 5.8 Hz, 1H), 7.20–7.38 (m, 5H), 8.32 (s, 1H). ¹³C NMR (CDCl₃) δ 20.6, 20.7, 30.0, 33.5, 63.2, 70.7, 72.5, 80.1, 86.7, 118.9, 126.7, 128.5, 128.8, 140.5, 150.9, 152.2, 152.6, 154.8, 169.6, 169.7, 170.7. HRMS calcd for C₂₄H₂₈N₅O₇ (M+H)⁺ 498.1983, found 498.1982.

8-(2-Phenylethyl)adenosine (1-25). To a stirred suspension of 1-101 (253 mg, 0.509 mmol) in MeOH (5 mL) was added NaOMe (28% in MeOH, 0.030 mL), and the resulting mixture was stirred at room temperature for 26 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 8–15% MeOH in DCM) to give the title compound (168 mg, 89%) as a slightly yellow solid. mp 204–205 °C. ¹H NMR (DMSO-*d*₆) δ 3.02–3.25 (m, 4H), 3.47–3.62 (m, 1H), 3.63–3.78 (m, 1H), 3.97–4.08 (m, 1H), 4.10–4.22 (m, 1H), 4.85–4.99 (m, 1H), 5.24 (d, J = 4.5 Hz, 1H), 5.40 (d, J = 7.3 Hz, 1H), 5.85 (d, J = 7.3 Hz, 1H), 5.96 (dd, J = 3.0, 9.5 Hz, 1H), 7.15–7.46 (m, 7H), 8.07 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 29.3, 33.1, 62.3, 71.2, 72.1, 86.9, 88.4, 118.3, 126.2, 128.4, 140.7, 149.7, 151.4, 151.6, 155.6. HRMS calcd for C₁₈H₂₂N₅O₄ (M+H)⁺ 372.1666, found 372.1664.

8-Benzyloxyadenosine (1-26)⁸⁸

A mixture of 8-bromo-2',3',5'-tris-*O*-(*tert*-butyldimethylsilyl)adenosine 19^{47} (300 mg, 0.436 mmol) and *t*-BuOK (147 mg, 1.31 mmol) in BnOH (2.18 mL) was heated at 40 °C with stirring for 48 h. After being quenched with AcOH (78.5 mg, 1.31 mmol), the reaction mixture was partitioned between AcOEt (50 mL) and H₂O (15 mL). The organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give a pale yellow oil (2.40 g). To a solution of the residue in MeOH (8.71 mL) was added NH₄F (968 mg, 26.1 mmol), and the resulting mixture was heated under reflux with stirring for 48 h. The reaction mixture was allowed to cool to room temperature, diluted with DCM (25 mL), stirred for 30 min, and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 7–14% MeOH in DCM) to give the title compound (140 mg, 86% from 19^{47}) as an off-white solid. mp 193–197 °C, dec. ¹H NMR (DMSO-*d*₆) δ 3.39–3.50 (m, 1H), 3.54–3.64 (m, 1H), 3.85–3.92 (m, 1H), 4.05–4.13 (m, 1H), 4.86–4.95 (m, 1H), 5.13 (d, *J* = 4.8 Hz, 1H), 5.37 (d, *J* = 6.3

Hz, 1H), 5.43 (dd, J = 4.3, 8.3 Hz, 1H), 5.54 (d, J = 12.1 Hz, 1H), 5.57 (d, J = 12.1 Hz, 1H), 5.73 (d, J = 6.8 Hz, 1H), 7.02 (br s, 2H), 7.35–7.49 (m, 3H), 7.51–7.60 (m, 2H), 8.04 (s, 1H). ¹³C NMR (DMSO- d_6) δ 62.2, 70.9, 71.1, 71.3, 86.1, 86.7, 114.9, 128.4, 128.6 (2C), 135.4, 148.7, 150.7, 153.7, 154.1. HRMS calcd for C₁₇H₂₀N₅O₅ (M+H)⁺ 374.1459, found 374.1458.

8-(Benzylthio)adenosine (1-27)

A mixture of **13** (200 mg, 0.578 mmol), BnSH (215 mg, 1.73 mmol), and *i*-Pr₂NEt (448 mg, 3.47 mmol) in EtOH (5.78 mL) was heated in a screw tube at 120 °C with stirring for 80 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residual solid was recrystallized twice from EtOH to give the title compound (64.5 mg, 29%) as an off-white solid. mp 210–213 °C. ¹H NMR (DMSO-*d*₆) δ 3.44–3.58 (m, 1H), 3.59–3.73 (m, 1H), 3.89–4.02 (m, 1H), 4.08–4.22 (m, 1H), 4.55 (d, *J* = 13.1 Hz, 1H), 4.60 (d, *J* = 13.1 Hz, 1H), 4.91–5.05 (m, 1H), 5.19 (d, *J* = 4.5 Hz, 1H), 5.41 (d, *J* = 6.5 Hz, 1H), 5.62 (dd, *J* = 3.8, 8.8 Hz, 1H), 5.73 (d, *J* = 6.8 Hz, 1H), 7.20–7.63 (m, 7H), 8.06 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 35.9, 62.2, 71.0, 71.4, 86.7, 88.9, 119.6, 127.5, 128.5, 129.2, 137.1, 148.1, 150.6, 151.4, 154.7. HRMS calcd for C₁₇H₂₀N₅O₄S (M+H)⁺ 390.1231, found 390.1227.

8-[Benzyl(methyl)amino]adenosine (1-28)

The title compound (204 mg, 91%) was obtained as a beige solid from **13** (200 mg, 0.578 mmol) and *N*-methylbenzylamine (210 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 2.78 (s, 3H), 3.47–3.60 (m, 1H), 3.63–3.73 (m, 1H), 3.93–4.00 (m, 1H), 4.13–4.22 (m, 1H), 4.39 (d, *J* = 14.3 Hz, 1H), 4.45 (d, *J* = 14.3 Hz, 1H), 5.09–5.20 (m, 2H), 5.46 (d, *J* = 6.5 Hz, 1H), 5.78 (dd, *J* = 3.3, 9.3 Hz, 1H), 5.87 (d, *J* = 7.0 Hz, 1H), 7.02 (br s, 2H), 7.23–7.42 (m, 5H), 8.02 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 39.8, 58.4, 62.4, 71.2 (2C), 86.5, 88.3, 116.9, 127.5, 128.4, 128.5, 136.8, 149.3, 150.5, 154.4, 155.4. HRMS calcd for C₁₈H₂₃N₆O₄ (M+H)⁺ 387.1775, found 387.1771.

8-(Phenylamino)adenosine (1-29)⁸⁹

To a suspension of 2',3',5'-tris-*O*-(*tert*-butyldimethylsilyl)-8-(phenylamino)adenosine 24^{47} (108 mg, 0.154 mmol) in MeOH (3.08 mL) was added NH₄F (342 mg, 9.24 mmol), and the resulting mixture was heated under reflux with stirring for 26 h. The reaction mixture was allowed to cool to room temperature, diluted with DCM/MeOH (4/1), stirred for 10 min, and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 7–14% MeOH in DCM) to give the title compound (47.8 mg, 87%) as a brown solid. mp 206–208 °C, dec. ¹H NMR (DMSO-*d*₆) δ 3.66–3.82 (m, 2H), 4.01–4.10 (m, 1H), 4.12–4.22 (m, 1H), 4.62–4.75 (m, 1H), 5.22 (d, *J* = 4.3 Hz, 1H), 5.35 (d, *J*

= 6.8 Hz, 1H), 6.06–6.19 (m, 2H), 6.82 (br s, 2H), 6.93–7.03 (m, 1H), 7.25–7.38 (m, 2H), 7.83–7.94 (m, 2H), 8.01 (s, 1H), 8.96 (s, 1H). ¹³C NMR (DMSO- d_6) δ 61.7, 71.0, 71.2, 85.9, 86.5, 116.4, 118.3, 121.5, 128.7, 140.4, 146.6, 149.1, 150.0, 153.4. HRMS calcd for C₁₆H₁₉N₆O₄ (M+H)⁺ 359.1462, found 359.1466.

The ¹H and ¹³C NMR spectral properties were found to be different from the following data previously reported.⁸⁹ *N-(Adenosin-8-yl)-aniline (4a).* ¹H NMR (DMSO-*d*₆) δ 3.72 (m, 2H, 5′H), 3.91 (m, 1H, 4′H), 3.96 (m, 2H, NH₂), 4.24 (m, 1H, 3′H), 4.51 (m, 1H, 2′H), 4.62 (s, 1H, 2′OH), 4.69 (s, 1H, Ar-NH), 4.81 (s, 1H, 5′OH), 4.94 (s, 1H, 3′OH), 6.18 (q, 1H, 1′H), 6.62 (d, 2H, Ar-2H, Ar-6H), 6.79 (t, 1H, Ar-4H), 7.02 (t, 2H, Ar-3H, Ar-5H), 8.42 (d, 1H, 2H). ¹³C NMR (DMSO-*d*₆) δ 63.89 (5′C), 72.93 (3′C), 77.86 (2′C), 82.27 (1′C), 92.06 (4′C), 119.34 (Ar-2C, Ar-6C), 120.78 (Ar-4C), 122.32 (C5), 128.17 (Ar-3C, Ar-5C), 141.24 (Ar-1C), 147.76 (4C), 151.39 (2C), 153.19 (6C), 161.23 (8C).

8-(2-Phenylethylamino)adenosine (1-30)

The title compound (183 mg, 82%) was obtained as an off-white solid from **13** (200 mg, 0.578 mmol) and 2phenylethylamine (210 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1**-**11**. ¹H NMR (DMSO-*d*₆) δ 2.84–3.01 (m, 2H), 3.46–3.76 (m, 4H), 3.89–4.05 (m, 1H), 4.07–4.19 (m, 1H), 4.59– 4.73 (m, 1H), 5.14 (d, *J* = 4.3 Hz, 1H), 5.21 (d, *J* = 6.8 Hz, 1H), 5.83–5.98 (m, 2H), 6.52 (br s, 2H), 7.04 (t, *J* = 5.4 Hz, 1H), 7.15–7.44 (m, 5H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 34.9, 44.1, 61.7, 70.8, 71.0, 85.7, 86.5, 117.1, 126.1, 128.4, 128.7, 139.7, 148.6, 149.8, 151.2, 152.5. HRMS calcd for C₁₈H₂₃N₆O₄ (M+H)⁺ 387.1775, found 387.1774.

8-(3-Phenylpropylamino)adenosine (1-31)

The title compound (200 mg, 86%) was obtained as a pale yellow solid from **13** (200 mg, 0.578 mmol) and 3-phenylpropylamine (234 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 1.81–2.02 (m, 2H), 2.60–2.76 (m, 2H), 3.24–3.52 (m, 2H), 3.55–3.77 (m, 2H), 3.92–4.04 (m, 1H), 4.08–4.20 (m, 1H), 4.61–4.73 (m, 1H), 5.16 (d, *J* = 4.3 Hz, 1H), 5.26 (d, *J* = 6.8 Hz, 1H), 5.85–6.01 (m, 2H), 6.50 (br s, 2H), 6.93 (t, *J* = 5.3 Hz, 1H), 7.14–7.40 (m, 5H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 30.5, 32.7, 42.1, 61.7, 70.7, 71.0, 85.7, 86.4, 117.1, 125.8, 128.3, 141.9, 148.5, 149.8, 151.3, 152.4. HRMS calcd for C₁₉H₂₅N₆O₄ (M+H)⁺ 401.1932, found 401.1938.

8-[(*R*)-1-Phenylethylamino]adenosine (1-32)

A mixture of **13** (400 mg, 1.16 mmol), (*R*)-1-phenylethylamine (420 mg, 3.47 mmol), and *i*-Pr₂NEt (896 mg, 6.93 mmol) in EtOH (11.6 mL) was heated in a sealed tube at 150 °C with stirring for 8.5 h under microwave irradiation. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The

residue was purified by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM) followed by flash column chromatography on silica gel (gradient: 12–20% MeOH in DCM) to give the title compound (194 mg, 43%) as a light beige foam. ¹H NMR (DMSO- d_6) δ 1.49 (d, J = 7.0 Hz, 3H), 3.61–3.74 (m, 2H), 3.99–4.07 (m, 1H), 4.10–4.19 (m, 1H), 4.64–4.74 (m, 1H), 5.14–5.32 (m, 3H), 5.93–6.05 (m, 2H), 6.42 (br s, 2H), 7.15–7.47 (m, 6H), 7.87 (s, 1H). ¹³C NMR (DMSO- d_6) δ 23.1, 51.3, 61.8, 70.7, 71.2, 85.8, 86.2, 116.9, 126.0, 126.5, 128.1, 145.3, 148.6, 149.9, 150.5, 152.3. HRMS calcd for C₁₈H₂₃N₆O₄ (M+H)⁺ 387.1775, found 387.1778.

8-[(S)-1-Phenylethylamino]adenosine (1-33)

2',3',5'-Tri-O-acetyl-8-[(S)-1-phenylethylamino]adenosine (1-70). A mixture of 13 (400 mg, 1.16 mmol), (S)-1phenylethylamine (420 mg, 3.47 mmol), and *i*-Pr₂NEt (896 mg, 6.93 mmol) in EtOH (11.6 mL) was heated in a sealed tube at 150 °C with stirring for 8.5 h under microwave irradiation. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM) followed by flash column chromatography on silica gel (gradient: 12–20% MeOH in DCM) to give the title compound (240 mg) as a mixture with 13. To the suspension of the impure product (236 mg) in MeCN (6.11 mL) were added Et₃N (247 mg, 2.44 mmol) and DMAP (7.5 mg, 0.0614 mmol) followed by Ac₂O (206 mg. 2.02 mmol), and the resulting mixture was stirred at room temperature for 12 h. Et₃N (124 mg, 1.22 mmol) and Ac₂O (103 mg, 1.01 mmol) were added in this order, and the reaction was continued for additional 6 h. The reaction mixture was quenched by addition of MeOH (1 mL), stirred at room temperature for 30 min, and then concentrated under reduced pressure. The residue was partitioned between AcOEt (50 mL) and H₂O (15 mL). The organic layer was washed with brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 0–10% MeOH in AcOEt) to give the title compound (257 mg, 43% from 13) as a white foam. ¹H NMR $(CDCl_3) \delta 1.54-1.76 (m, 3H), 1.79 (s, 3H), 2.05 (s, 3H), 2.15 (s, 3H), 4.29 (dd, J = 2.5, 12.2 Hz, 1H), 4.34-4.42 (m, 3H), 1.79 (s, 3H), 2.05 (s, 3H), 2.15 (s, 3H), 4.29 (dd, J = 2.5, 12.2 Hz, 1H), 4.34-4.42 (m, 3H), 1.79 (s, 3H), 1.79 (s, 3H), 2.05 (s, 3H), 2.15 (s, 3H), 4.29 (dd, J = 2.5, 12.2 Hz, 1H), 4.34-4.42 (m, 3H), 1.79 (s, 3H), 2.05 (s, 3H), 2.15 (s, 3H), 4.29 (dd, J = 2.5, 12.2 Hz, 1H), 4.34-4.42 (m, 3H), 1.79 (s, 3H), 2.05 (s, 3H), 2.15 (s, 3H), 4.29 (dd, J = 2.5, 12.2 Hz, 1H), 4.34-4.42 (m, 3H), 1.79 (s, 3H), 1.79 (s, 3H), 1.79 (s, 3H), 2.15 (s, 3H), 2.15 (s, 3H), 1.29 (s, 3H), 1.29$ 1H), 4.48 (dd, J = 4.6, 12.2 Hz, 1H), 5.04–5.30 (m, 4H), 5.53–5.59 (m, 1H), 6.00 (t, J = 5.8 Hz, 1H), 6.12 (d, 6.0 Hz, 1H), 7.24–7.31 (m, 1H), 7.32–7.47 (m, 4H), 8.16 (s, 1H). ¹³C NMR (CDCl₃) δ 20.4, 20.6, 20.7, 22.6, 52.3, 63.2, 70.3, 71.4, 80.4, 85.1, 117.8, 126.2, 127.5, 128.8, 143.7, 150.0, 150.2, 150.9, 152.4, 169.8, 169.9, 170.5. HRMS calcd for $C_{24}H_{29}N_6O_7$ (M+H)⁺ 513.2092, found 513.2096.

8-[(S)-1-Phenylethylamino]adenosine (1-33). To a stirred suspension of 1-70 (255 mg, 0.498 mmol) in MeOH (4.98 mL) was added NaOMe (28% in MeOH, 0.029 mL), and the resulting mixture was stirred at room temperature for 34 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 10–17% MeOH in DCM) to give the title compound (179 mg, 93%) as a pale brown amorphous solid. ¹H NMR (DMSO- d_6) δ 1.49 (d, J = 7.0 Hz, 3H), 3.57–3.74 (m, 2H), 3.93–4.06 (m, 1H), 4.11–4.21 (m, 1H), 4.64–4.75 (m, 1H), 5.13–5.34 (m, 3H), 5.85–5.95 (m, 1H), 5.99 (d, J = 7.5 Hz, 1H), 6.45 (br s, 2H), 7.17–7.49 (m, 6H), 7.88 (s, 1H). ¹³C NMR (DMSO- d_6) δ 22.9, 51.2, 61.7, 71.0 (2C), 85.7, 86.3, 116.9,

126.1, 126.6, 128.2, 145.2, 148.6, 149.8, 150.5, 152.4. HRMS calcd for $C_{18}H_{23}N_6O_4$ (M+H)⁺ 387.1775, found 387.1774.

8-(Cyclopropylmethylamino)adenosine (1-34)

A mixture of **13** (200 mg, 0.578 mmol) and cyclopropylmethanamine (1.23 g, 17.3 mmol) in EtOH (5.78 mL) was heated in a screw tube at 100 °C with stirring for 76 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM) followed by recrystallization from aqueous EtOH to give the title compound (145 mg, 75%) as a white solid. ¹H NMR (DMSO- d_6) δ 0.15–0.35 (m, 2H), 0.37–0.53 (m, 2H), 1.07–1.21 (m, 1H), 3.14–3.29 (m, 2H), 3.55–3.76 (m, 2H), 3.90–4.05 (m, 1H), 4.08–4.20 (m, 1H), 4.60–4.77 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.25 (d, *J* = 6.8 Hz, 1H), 5.84 (dd, *J* = 4.3, 5.8 Hz, 1H), 5.90 (d, *J* = 7.5 Hz, 1H), 6.50 (br s, 2H), 7.04 (t, *J* = 5.5 Hz, 1H), 7.88 (s, 1H). ¹³C NMR (DMSO- d_6) δ 3.4, 3.5, 10.9, 46.9, 61.7, 70.8, 71.0, 85.7, 86.4, 117.1, 148.5, 149.8, 151.5, 152.4. HRMS calcd for C₁₄H₂₁N₆O₄ (M+H)⁺ 337.1619, found 337.1624.

8-(Cyclopentylmethylamino)adenosine (1-35)

The title compound (163 mg, 77%) was obtained as an off-white solid from **13** (200 mg, 0.578 mmol) and cyclopentylmethanamine (172 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 1.15–1.33 (m, 2H), 1.39–1.82 (m, 6H), 2.17–2.35 (m, 1H), 3.17–3.38 (m, 2H), 3.56–3.73 (m, 2H), 3.93–4.03 (m, 1H), 4.07–4.19 (m, 1H), 4.56–4.71 (m, 1H), 5.15 (d, *J* = 4.3 Hz, 1H), 5.23 (d, *J* = 7.0 Hz, 1H), 5.82–5.90 (m, 1H), 5.92 (d, *J* = 7.5 Hz, 1H), 6.48 (br s, 2H), 6.91 (t, *J* = 5.5 Hz, 1H), 7.88 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 24.8, 30.0 (2C), 38.6, 47.4, 61.6, 70.7, 71.0, 85.7, 86.3, 117.0, 148.5, 149.9, 151.4, 152.3. HRMS calcd for C₁₆H₂₅N₆O₄ (M+H)⁺ 365.1932, found 365.1940.

8-(Cyclohexylmethylamino)adenosine (1-36)

The title compound (199 mg, 91%) was obtained as a beige solid from **13** (200 mg, 0.578 mmol) and cyclohexylmethanamine (196 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 0.80–1.00 (m, 2H), 1.03–1.32 (m, 3H), 1.51–1.89 (m, 6H), 3.06–3.29 (m, 2H), 3.56–3.70 (m, 2H), 3.93–4.02 (m, 1H), 4.06–4.17 (m, 1H), 4.56–4.71 (m, 1H), 5.15 (d, *J* = 4.0 Hz, 1H), 5.24 (d, *J* = 6.8 Hz, 1H), 5.82–5.90 (m, 1H), 5.91 (d, *J* = 7.5 Hz, 1H), 6.47 (br s, 2H), 6.87 (t, *J* = 5.5 Hz, 1H), 7.88 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.4 (2C), 26.2, 30.5, 30.6, 36.5, 48.6, 61.7, 70.7, 71.0, 85.7, 86.3, 117.1, 148.4, 149.8, 151.4, 152.2. HRMS calcd for C₁₇H₂₇N₆O₄ (M+H)⁺ 379.2088, found 379.2088.

8-(Furan-2-ylmethylamino)adenosine (1-37)

The title compound (169 mg, 81%) was obtained as a beige solid from **13** (200 mg, 0.578 mmol) and furan-2ylmethanamine (168 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.52–3.70 (m, 2H), 3.90–4.01 (m, 1H), 4.05–4.14 (m, 1H), 4.52 (dd, *J* = 5.8, 15.8 Hz, 1H), 4.59 (dd, *J* = 5.5, 15.8 Hz, 1H), 4.64–4.75 (m, 1H), 5.15 (d, *J* = 4.0 Hz, 1H), 5.27 (d, *J* = 7.0 Hz, 1H), 5.87 (dd, *J* = 4.3, 6.5 Hz, 1H), 5.90 (d, *J* = 7.3 Hz, 1H), 6.32 (dd, *J* = 0.6, 3.2 Hz, 1H), 6.39 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.59 (br s, 2H), 7.46 (t, *J* = 5.8 Hz, 1H), 7.57 (dd, *J* = 0.6, 1.8 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 39.0, 61.8, 70.9, 71.1, 85.8, 86.5, 107.0, 110.5, 117.0, 142.0, 148.7, 149.8, 151.1, 152.6, 152.8. HRMS calcd for C₁₅H₁₉N₆O₅ (M+H)⁺ 363.1411, found 363.1410.

8-(Furan-3-ylmethylamino)adenosine (1-38)

The title compound (171 mg, 82%) was obtained as a beige solid from **13** (200 mg, 0.578 mmol), furan-3-ylmethanamine hydrochloride (232 mg, 1.73 mmol), and *i*-Pr₂NEt (523 mg, 4.04 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.53–3.70 (m, 2H), 3.91–4.00 (m, 1H), 4.05–4.15 (m, 1H), 4.25–4.46 (m, 2H), 4.61–4.73 (m, 1H), 5.15 (d, *J* = 4.3 Hz, 1H), 5.26 (d, *J* = 6.8 Hz, 1H), 5.82–5.92 (m, 2H), 6.49–6.54 (m, 1H), 6.58 (br s, 2H), 7.24–7.34 (m, 1H), 7.54–7.66 (m, 2H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 36.9, 61.8, 70.9, 71.1, 85.8, 86.5, 111.0, 117.1, 123.4, 140.2, 143.1, 148.6, 149.8, 151.3, 152.6. HRMS calcd for C₁₅H₁₉N₆O₅ (M+H)⁺ 363.1411, found 363.1415.

8-(Thiophen-2-ylmethylamino)adenosine (1-39)

The title compound (165 mg, 76%) was obtained as a pale yellow solid from **13** (200 mg, 0.578 mmol) and thiophen-2-ylmethanamine (196 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1**-**11**. ¹H NMR (DMSO-*d*₆) δ 3.50–3.70 (m, 2H), 3.88–4.01 (m, 1H), 4.02–4.17 (m, 1H), 4.60–4.83 (m, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.26 (d, *J* = 6.8 Hz, 1H), 5.78–5.98 (m, 2H), 6.57 (br s, 2H), 6.96 (dd, *J* = 3.4, 5.1 Hz, 1H), 7.07 (dd, *J* = 1.2, 3.4 Hz, 1H), 7.37 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.61 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO*d*₆) δ 40.6, 61.8, 71.1, 85.8, 86.5, 117.0, 124.8, 125.4, 126.7, 143.0, 148.7, 149.8, 151.0, 152.6. HRMS calcd for C₁₅H₁₉N₆O₄S (M+H)⁺ 379.1183, found 379.1183.

8-(Thiophen-3-ylmethylamino)adenosine (1-40)

The title compound (195 mg, 89%) was obtained as a pale yellow foam from **13** (200 mg, 0.578 mmol) and thiophen-3-ylmethanamine (196 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.52–3.71 (m, 2H), 3.88–4.01 (m, 1H), 4.04–4.19 (m, 1H), 4.42–4.62 (m, 2H), 4.63– 4.77 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.79–5.98 (m, 2H), 6.56 (br s, 2H), 7.13 (dd, *J* = 1.3, 5.0 Hz, 1H), 7.30–7.54 (m, 3H), 7.89 (s, 1H). ¹³C NMR (DMSO- d_6) δ 41.1, 61.8, 70.9, 71.1, 85.8, 86.5, 117.1, 121.7, 126.1, 127.7, 140.9, 148.6, 149.8, 151.3, 152.5. HRMS calcd for C₁₅H₁₉N₆O₄S (M+H)⁺ 379.1183, found 379.1186.

8-(Pyridin-2-ylmethylamino)adenosine (1-41)

A mixture of **13** (200 mg, 0.578 mmol), pyridin-2-ylmethanamine (188 mg, 1.73 mmol), and *i*-Pr₂NEt (448 mg, 3.47 mmol) in EtOH (4.82 mL) was heated in a screw tube at 120 °C with stirring for 82 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was suspended in DCM (20 mL) and stirred at room temperature for 3 h. The precipitate was collected by filtration, washed with DCM, air-dried, and then recrystallized from aqueous EtOH to give the title compound (114 mg, 53%) as a pale yellow solid. ¹H NMR (DMSO-*d*₆) δ 3.54–3.72 (m, 2H), 3.97–4.05 (m, 1H), 4.08–4.18 (m, 1H), 4.61–4.82 (m, 3H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.34 (d, *J* = 6.8 Hz, 1H), 5.88 (dd, *J* = 4.1, 6.2 Hz, 1H), 5.97 (d, *J* = 7.5 Hz, 1H), 6.53 (br s, 2H), 7.21–7.29 (m, 1H), 7.32–7.41 (m, 1H), 7.60–7.69 (m, 1H), 7.70–7.80 (m, 1H), 7.90 (s, 1H), 8.48–8.56 (m, 1H). ¹³C NMR (DMSO-*d*₆) δ 47.1, 61.8, 71.0, 71.1, 85.9, 86.6, 117.0, 120.5, 122.0, 136.8, 148.7, 148.9, 149.9, 151.3, 152.6, 159.3. HRMS calcd for C₁₆H₂₀N₇O₄ (M+H)⁺ 374.1571, found 374.1567.

8-(Pyridin-3-ylmethylamino)adenosine (1-42)

A mixture of **13** (200 mg, 0.578 mmol), pyridin-3-ylmethanamine (188 mg, 1.73 mmol), and *i*-Pr₂NEt (448 mg, 3.47 mmol) in EtOH (4.82 mL) was heated in a screw tube at 120 °C with stirring for 5 days. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM) to give the title compound (197 mg, 91%) as a pale yellow solid. ¹H NMR (DMSO-*d*₆) δ 3.53–3.72 (m, 2H), 3.93–4.04 (m, 1H), 4.05–4.18 (m, 1H), 4.47–4.81 (m, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.84–5.98 (m, 2H), 6.57 (br s, 2H), 7.30–7.41 (m, 1H), 7.62 (t, *J* = 6.0 Hz, 1H), 7.73–7.84 (m, 1H), 7.90 (s, 1H), 8.40–8.50 (m, 1H), 8.57–8.66 (m, 1H). ¹³C NMR (DMSO-*d*₆) δ 43.1, 61.8, 70.9, 71.1, 85.8, 86.5, 117.0, 123.4, 135.2 (2C), 148.1, 148.7, 149.0, 149.8, 151.1, 152.6. HRMS calcd for C₁₆H₂₀N₇O₄ (M+H)⁺ 374.1571, found 374.1562.

8-(Pyridin-4-ylmethylamino)adenosine (1-43)

The title compound (188 mg, 87%) was obtained as a yellow solid from **13** (200 mg, 0.578 mmol) and pyridin-4ylmethanamine (188 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-42**. ¹H NMR (DMSO-*d*₆) δ 3.55–3.72 (m, 2H), 3.93–4.04 (m, 1H), 4.06–4.17 (m, 1H), 4.50–4.81 (m, 3H), 5.19 (d, *J* = 3.8 Hz, 1H), 5.36 (d, *J* = 6.8 Hz, 1H), 5.92 (dd, *J* = 4.1, 5.9 Hz, 1H), 5.96 (d, *J* = 7.5 Hz, 1H), 6.53 (br s, 2H), 7.28– 7.40 (m, 2H), 7.67 (t, *J* = 6.0 Hz, 1H), 7.91 (s, 1H), 8.43–8.53 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 44.3, 61.8, 71.0, 71.2, 85.9, 86.6, 116.9, 122.1, 148.8, 149.1, 149.5, 149.9, 151.1, 152.6. HRMS calcd for $C_{16}H_{20}N_7O_4$ (M+H)⁺ 374.1571, found 374.1570.

8-(2-Methylbenzylamino)adenosine (1-44)

The title compound (195 mg, 87%) was obtained as a beige solid from **13** (200 mg, 0.578 mmol) and 2methylbenzylamine (210 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 2.32 (s, 3H), 3.53–3.70 (m, 2H), 3.95–4.03 (m, 1H), 4.08–4.18 (m, 1H), 4.46–4.64 (m, 2H), 4.69–4.82 (m, 1H), 5.15 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 7.0 Hz, 1H), 5.85 (dd, *J* = 4.0, 6.3 Hz, 1H), 5.96 (d, *J* = 7.5 Hz, 1H), 6.51 (br s, 2H), 7.08–7.24 (m, 3H), 7.27–7.47 (m, 2H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 18.7, 43.5, 61.8, 71.0, 71.1, 85.9, 86.5, 117.1, 125.7, 126.6, 126.9, 129.8, 135.5, 137.5, 148.6, 149.9, 151.4, 152.5. HRMS calcd for C₁₈H₂₃N₆O₄ (M+H)⁺ 387.1775, found 387.1774.

8-(3-Methylbenzylamino)adenosine (1-45)

The title compound (179 mg, 80%) was obtained as a pale yellow solid from **13** (200 mg, 0.578 mmol) and 3methylbenzylamine (210 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 2.28 (s, 3H), 3.55–3.70 (m, 2H), 3.96–4.02 (m, 1H), 4.08–4.19 (m, 1H), 4.48–4.64 (m, 2H), 4.67–4.81 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.85–5.99 (m, 2H), 6.51 (br s, 2H), 7.00– 7.08 (m, 1H), 7.11–7.26 (m, 3H), 7.50 (t, *J* = 6.0 Hz, 1H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 21.1, 45.2, 61.8, 71.0, 71.1, 85.9, 86.5, 117.1, 124.2, 127.3, 127.7, 128.1, 137.2, 139.9, 148.5, 149.8, 151.4, 152.5. HRMS calcd for C₁₈H₂₃N₆O₄ (M+H)⁺ 387.1775, found 387.1776.

8-(4-Methylbenzylamino)adenosine (1-46)

The title compound was synthesized from **13** (200 mg, 0.578 mmol) and 4-methylbenzylamine (210 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**, purified by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM) followed by recrystallization from EtOH, and isolated as a pale yellow solid (83.5 mg, 37%). mp 226–228 °C. ¹H NMR (DMSO-*d*₆) δ 2.27 (s, 3H), 3.49–3.72 (m, 2H), 3.94–4.01 (m, 1H), 4.08–4.18 (m, 1H), 4.44–4.64 (m, 2H), 4.67–4.76 (m, 1H), 5.14 (d, *J* = 4.0 Hz, 1H), 5.26 (d, *J* = 7.0 Hz, 1H), 5.87 (dd, *J* = 4.3, 6.3 Hz, 1H), 5.92 (d, *J* = 7.3 Hz, 1H), 6.49 (br s, 2H), 7.08–7.17 (m, 2H), 7.21–7.32 (m, 2H), 7.47 (t, *J* = 6.0 Hz, 1H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 20.7, 45.1, 61.8, 70.9, 71.1, 85.8, 86.5, 117.1, 127.2, 128.8, 135.7, 136.9, 148.5, 149.8, 151.4, 152.4. HRMS calcd for C₁₈H₂₃N₆O₄ (M+H)⁺ 387.1775, found 387.1777.

8-(2-Methoxybenzylamino)adenosine (1-47)

The title compound (103 mg, 44%) was obtained as an off-white solid from **13** (200 mg, 0.578 mmol) and 2methoxybenzylamine (238 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-46**. mp 155–158 °C. ¹H NMR (DMSO-*d*₆) δ 3.54–3.70 (m, 2H), 3.83 (s, 3H), 3.97–4.05 (m, 1H), 4.09–4.18 (m, 1H), 4.48–4.64 (m, 2H), 4.70–4.82 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.32 (d, *J* = 6.8 Hz, 1H), 5.80–5.88 (m, 1H), 5.98 (d, *J* = 7.5 Hz, 1H), 6.50 (br s, 2H), 6.83–7.01 (m, 2H), 7.17–7.29 (m, 2H), 7.30–7.41 (m, 1H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 40.7, 55.2, 61.8, 70.9, 71.1, 85.8, 86.5, 110.1, 117.0, 120.1, 126.7, 127.3, 127.7, 148.5, 149.9, 151.4, 152.4, 156.6. HRMS calcd for C₁₈H₂₃N₆O₅ (M+H)⁺ 403.1724, found 403.1721.

8-(3-Methoxybenzylamino)adenosine (1-48)

The title compound (204 mg, 88%) was obtained as a yellow solid from **13** (200 mg, 0.578 mmol) and 3methoxybenzylamine (238 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11.** ¹H NMR (DMSO-*d*₆) δ 3.56–3.70 (m, 2H), 3.72 (s, 3H), 3.95–4.03 (m, 1H), 4.08–4.17 (m, 1H), 4.49–4.64 (m, 2H), 4.67–4.78 (m, 1H), 5.15 (d, *J* = 4.0 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.89 (dd, *J* = 4.3, 6.0 Hz, 1H), 5.94 (d, *J* = 7.3 Hz, 1H), 6.51 (br s, 2H), 6.75–6.83 (m, 1H), 6.89–6.99 (m, 2H), 7.18–7.27 (m, 1H), 7.46–7.60 (m, 1H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.2, 55.0, 61.8, 71.0, 71.1, 85.9, 86.5, 112.0, 112.8, 117.0, 119.3, 129.3, 141.6, 148.6, 149.9, 151.4, 152.5, 159.3. HRMS calcd for C₁₈H₂₃N₆O₅ (M+H)⁺ 403.1724, found 403.1724.

8-(4-Methoxybenzylamino)adenosine (1-49)

The title compound (212 mg, 91%) was obtained as a beige foam from **13** (200 mg, 0.578 mmol) and 4methoxybenzylamine (238 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.54–3.69 (m, 2H), 3.72 (s, 3H), 3.93–4.02 (m, 1H), 4.08–4.18 (m, 1H), 4.40–4.62 (m, 2H), 4.66–4.78 (m, 1H), 5.14 (d, *J* = 4.0 Hz, 1H), 5.24 (d, *J* = 7.0 Hz, 1H), 5.82–5.99 (m, 2H), 6.50 (br s, 2H), 6.83– 6.94 (m, 2H), 7.26–7.53 (m, 3H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 44.8, 55.0, 61.8, 70.9, 71.1, 85.8, 86.5, 113.6, 117.1, 128.6, 131.8, 148.5, 149.8, 151.4, 152.4, 158.2. HRMS calcd for C₁₈H₂₃N₆O₅ (M+H)⁺ 403.1724, found 403.1720.

8-(2-Fluorobenzylamino)adenosine (1-50)

The title compound (183 mg, 81%) was obtained as a pale yellow solid from **13** (200 mg, 0.578 mmol) and 2-fluorobenzylamine (217 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.54–3.70 (m, 2H), 3.95–4.03 (m, 1H), 4.08–4.18 (m, 1H), 4.64 (d, *J* = 5.9 Hz, 2H), 4.70–4.79 (m, 1H), 5.17 (d, *J* = 3.8 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.88 (dd, *J* = 4.3, 6.0 Hz, 1H), 5.95 (d, *J* = 7.5 Hz, 1H), 6.54 (br s, 2H), 7.10–7.23 (m, 2H), 7.25–7.35 (m, 1H), 7.39–7.48 (m, 1H), 7.53 (t, *J* = 5.9 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 61.8, 71.0, 71.1, 85.9, 86.5, 115.0 (d, ²*J*_{C-F} = 21.3 Hz), 117.0, 124.3 (d, ⁴*J*_{C-F} = 2.9 Hz), 126.5 (d, ²*J*_{C-F} = 14.7 Hz), 128.7 (d, ³*J*_{C-F} = 8.1 Hz), 129.0 (d, ³*J*_{C-F} = 4.4 Hz), 148.7, 149.9, 151.2, 152.6, 160.2 (d, ¹*J*_{C-F} = 243.6 Hz). HRMS calcd for C₁₇H₂₀FN₆O₄ (M+H)⁺ 391.1525, found 391.1525.

8-(3-Fluorobenzylamino)adenosine (1-51)

The title compound (189 mg, 84%) was obtained as a pale yellow solid from **13** (200 mg, 0.578 mmol) and 3-fluorobenzylamine (217 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1**-**11**. ¹H NMR (DMSO-*d*₆) δ 3.54–3.73 (m, 2H), 3.96–4.04 (m, 1H), 4.09–4.20 (m, 1H), 4.60 (d, *J* = 6.0 Hz, 2H), 4.68–4.80 (m, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.32 (d, *J* = 6.5 Hz, 1H), 5.85–6.02 (m, 2H), 6.54 (br s, 2H), 7.01–7.11 (m, 1H), 7.12–7.29 (m, 2H), 7.31–7.45 (m, 1H), 7.61 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 44.8, 61.8, 71.0, 71.1, 85.9, 86.6, 113.5 (d, ²*J*_{C-F} = 20.5 Hz), 113.8 (d, ²*J*_{C-F} = 21.3 Hz), 117.0, 123.1 (d, ⁴*J*_{C-F} = 2.2 Hz), 130.2 (d, ³*J*_{C-F} = 8.1 Hz), 143.1 (d, ³*J*_{C-F} = 7.3 Hz), 148.7, 149.9, 151.2, 152.5, 162.3 (d, ¹*J*_{C-F} = 243.6 Hz). HRMS calcd for C₁₇H₂₀FN₆O₄ (M+H)⁺ 391.1525, found 391.1529.

8-(4-Fluorobenzylamino)adenosine (1-52)⁹⁰

The title compound (201 mg, 89%) was obtained as a beige solid from **13** (200 mg, 0.578 mmol) and 4-fluorobenzylamine (217 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1**-**11**. ¹H NMR (DMSO-*d*₆) δ 3.53–3.73 (m, 2H), 3.92–4.02 (m, 1H), 4.06–4.19 (m, 1H), 4.45–4.65 (m, 2H), 4.66–4.79 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.89 (dd, *J* = 4.1, 6.1 Hz, 1H), 5.92 (d, *J* = 7.5 Hz, 1H), 6.53 (br s, 2H), 7.08–7.24 (m, 2H), 7.36–7.48 (m, 2H), 7.55 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 44.7, 61.8, 71.0, 71.1, 85.9, 86.5, 114.9 (d, ²*J*_{C-F} = 20.5 Hz), 117.0, 129.2 (d, ³*J*_{C-F} = 8.1 Hz), 136.1 (d, ⁴*J*_{C-F} = 2.9 Hz), 148.7, 149.9, 151.3, 152.5, 161.2 (d, ¹*J*_{C-F} = 242.1 Hz). HRMS calcd for C₁₇H₂₀FN₆O₄ (M+H)⁺ 391.1525, found 391.1531.

8-(2-Chlorobenzylamino)adenosine (1-53)

The title compound (225 mg, 96%) was obtained as a pale yellow solid from **13** (200 mg, 0.578 mmol) and 2-chlorobenzylamine (245 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.55–3.72 (m, 2H), 3.97–4.05 (m, 1H), 4.09–4.18 (m, 1H), 4.56–4.81 (m, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.35 (d, *J* = 6.8 Hz, 1H), 5.87 (dd, *J* = 4.0, 6.0 Hz, 1H), 5.99 (d, *J* = 7.3 Hz, 1H), 6.54 (br s, 2H), 7.23–7.35 (m, 2H), 7.38–7.49 (m, 2H), 7.58 (t, *J* = 6.0 Hz, 1H), 7.91 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 43.3, 61.8, 71.0, 71.1, 85.9, 86.6, 116.9, 127.1, 128.2, 128.4, 129.1, 131.9, 136.8, 148.8, 149.9, 151.1, 152.6. HRMS calcd for C₁₇H₂₀ClN₆O₄ (M+H)⁺ 407.1229, found 407.1232.

8-(3-Chlorobenzylamino)adenosine (1-54)

The title compound (190 mg, 81%) was obtained as a yellow solid from **13** (200 mg, 0.578 mmol) and 3-chlorobenzylamine (245 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.54–3.72 (m, 2H), 3.96–4.04 (m, 1H), 4.08–4.19 (m, 1H), 4.59 (d, *J* = 6.0 Hz, 2H), 4.68–4.79 (m, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.32 (d, *J* = 6.8 Hz, 1H), 5.86–5.99 (m, 2H), 6.54 (br s, 2H), 7.25–7.46 (m, 4H), 7.61 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 44.8, 61.8, 71.0, 71.1, 85.9, 86.6, 117.0, 125.8, 126.7, 126.9, 130.1, 133.0, 142.7, 148.7, 149.9, 151.2, 152.5. HRMS calcd for C₁₇H₂₀ClN₆O₄ (M+H)⁺ 407.1229, found 407.1230.

8-(4-Chlorobenzylamino)adenosine (1-55)

The title compound (195 mg, 83%) was obtained as a pale yellow solid from **13** (200 mg, 0.578 mmol) and 4-chlorobenzylamine (245 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.54–3.70 (m, 2H), 3.95–4.01 (m, 1H), 4.08–4.17 (m, 1H), 4.47–4.64 (m, 2H), 4.67–4.77 (m, 1H), 5.15 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.88 (dd, *J* = 4.3, 6.0 Hz, 1H), 5.92 (d, *J* = 7.3 Hz, 1H), 6.52 (br s, 2H), 7.32–7.45 (m, 4H), 7.57 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 44.7, 61.8, 70.9, 71.1, 85.8, 86.5, 117.0, 128.2, 129.1, 131.3, 139.0, 148.7, 149.8, 151.2, 152.5. HRMS calcd for C₁₇H₂₀ClN₆O₄ (M+H)⁺ 407.1229, found 407.1231.

8-[2-(Trifluoromethyl)benzylamino]adenosine (1-56)

The title compound (128 mg, 50%) was obtained as a pale yellow solid from **13** (200 mg, 0.578 mmol) and 2-(trifluoromethyl)benzylamine (304 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.53–3.71 (m, 2H), 3.94–4.05 (m, 1H), 4.08–4.18 (m, 1H), 4.69–4.90 (m, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.34 (d, *J* = 6.8 Hz, 1H), 5.85 (dd, *J* = 4.0, 6.0 Hz, 1H), 5.98 (d, *J* = 7.3 Hz, 1H), 6.50 (br s, 2H), 7.42–7.52 (m, 1H), 7.55–7.69 (m, 3H), 7.70–7.78 (m, 1H), 7.92 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 42.0 (q, ³*J*_{C-F} = 2.9 Hz), 61.8, 71.0, 71.2, 85.9, 86.6, 116.9, 124.6 (q, ¹*J*_{C-F} = 273.9 Hz), 125.8 (q, ³*J*_{C-F} = 5.9 Hz), 126.1 (q, ²*J*_{C-F} = 30.1 Hz), 127.3, 128.2, 132.7, 138.1, 148.9, 150.0, 151.2, 152.6. HRMS calcd for C₁₈H₂₀F₃N₆O₄ (M+H)⁺ 441.1493, found 441.1495.

8-[3-(Trifluoromethyl)benzylamino]adenosine (1-57)

The title compound (212 mg, 83%) was obtained as a pale yellow solid from **13** (200 mg, 0.578 mmol) and 3-(trifluoromethyl)benzylamine (304 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.53–3.72 (m, 2H), 3.95–4.04 (m, 1H), 4.09–4.18 (m, 1H), 4.58–4.81 (m, 3H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.5 Hz, 1H), 5.90 (dd, *J* = 4.3, 6.0 Hz, 1H), 5.93 (d, *J* = 7.5 Hz, 1H),

6.52 (br s, 2H), 7.52–7.76 (m, 5H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 44.9, 61.8, 71.0, 71.1, 85.9, 86.6, 117.0, 123.5 (q, ³*J*_{C-F} = 3.7 Hz), 123.7 (q, ³*J*_{C-F} = 3.7 Hz), 124.4 (q, ¹*J*_{C-F} = 272.2 Hz), 129.1 (q, ²*J*_{C-F} = 31.3 Hz), 129.3, 131.3, 141.5, 148.8, 149.9, 151.2, 152.6. HRMS calcd for C₁₈H₂₀F₃N₆O₄ (M+H)⁺ 441.1493, found 441.1493.

8-[4-(Trifluoromethyl)benzylamino]adenosine (1-58)

The title compound (215 mg, 85%) was obtained as a pale yellow solid from **13** (200 mg, 0.578 mmol) and 4-(trifluoromethyl)benzylamine (304 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.55–3.71 (m, 2H), 3.96–4.05 (m, 1H), 4.09–4.19 (m, 1H), 4.56–4.80 (m, 3H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.88 (dd, *J* = 4.0, 6.0 Hz, 1H), 5.94 (d, *J* = 7.3 Hz, 1H), 6.51 (br s, 2H), 7.55–7.76 (m, 5H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 44.9, 61.8, 71.0, 71.1, 85.9, 86.6, 117.0, 124.4 (q, ¹*J*_{C-F} = 271.9 Hz), 125.1 (q, ³*J*_{C-F} = 3.7 Hz), 127.5 (q, ²*J*_{C-F} = 31.5 Hz), 127.8, 144.9 (q, ⁴*J*_{C-F} = 1.5 Hz), 148.7, 149.9, 151.2, 152.6. HRMS calcd for C₁₈H₂₀F₃N₆O₄ (M+H)⁺ 441.1493, found 441.1496.

8-(1-Naphthylmethylamino)adenosine (1-59)

The title compound (210 mg, 86%) was obtained as a yellow solid from **13** (200 mg, 0.578 mmol) and 1-naphthylmethylamine (273 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.52–3.72 (m, 2H), 3.96–4.05 (m, 1H), 4.08–4.18 (m, 1H), 4.71–4.84 (m, 1H), 5.00–5.20 (m, 3H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.88 (dd, *J* = 4.0, 6.3 Hz, 1H), 5.99 (d, *J* = 7.5 Hz, 1H), 6.53 (br s, 2H), 7.41–7.70 (m, 5H), 7.79–8.00 (m, 3H), 8.11–8.24 (m, 1H). ¹³C NMR (DMSO-*d*₆) δ 43.4, 61.9, 71.0, 71.1, 85.9, 86.5, 117.1, 123.3, 124.2, 125.5, 125.8, 126.2, 127.2, 128.5, 130.9, 133.2, 135.0, 148.6, 149.9, 151.4, 152.5. HRMS calcd for C₂₁H₂₃N₆O₄ (M+H)⁺ 423.1775, found 423.1772.

8-(2-Naphthylmethylamino)adenosine (1-60)

*N-(2-Naphthylmethyl)phthalimide (1-71).*⁹¹ A mixture of 2-(bromomethyl)naphthalene **14** (3.00 g, 13.6 mmol) and phthalimide potassium salt (2.76 g, 14.9 mmol) in DMF (67.8 mL) was heated at 50 °C with stirring for 19 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (250 mL) and H₂O (200 mL). The organic layer was washed successively with H₂O (80 mL \times 2) and brine (80 mL), dried (MgSO₄), and concentrated under reduced pressure. The residual solid was triturated in Et₂O (50 mL), sonicated, collected by filtration, washed with Et₂O, and then dried at 40 °C under reduced pressure to give the title compound (3.23 g, 83%) as a white solid. ¹H NMR (CDCl₃) δ 5.01 (s, 2H), 7.40–7.52 (m, 2H), 7.52–7.60 (m, 1H), 7.67–7.94 (m, 8H). HRMS calcd for C₁₉H₁₄NO₂ (M+H)⁺ 288.1019, found 288.1016.

2-Naphthylmethylamine (1-72).⁹² To a stirred suspension of 1-71 (500 mg, 1.74 mmol) in MeOH (105 mL) was added $H_2NNH_2 \cdot H_2O$ (7 mL), and the resulting mixture was heated under reflux with stirring for 4 h. The reaction

mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was partitioned between DCM (100 mL) and saturated aqueous NaHCO₃ (40 mL). The organic layer was washed twice with saturated aqueous NaHCO₃ (40 mL × 2), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel eluting with AcOEt to give the title compound (264 mg, 97%) as a pale yellow solid. ¹H NMR (CDCl₃) δ 4.04 (s, 2H), 7.35–7.53 (m, 3H), 7.71–7.90 (m, 4H). HRMS calcd for C₁₁H₁₂N (M+H)⁺ 158.0964, found 158.0964.

8-(2-Naphthylmethylamino)adenosine (1-60). The title compound (211 mg, 86%) was obtained as a yellow solid from 13 (200 mg, 0.578 mmol) and 1-72 (273 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of 1-11. ¹H NMR (DMSO- d_6) δ 3.55–3.71 (m, 2H), 3.97–4.04 (m, 1H), 4.10–4.17 (m, 1H), 4.66–4.86 (m, 3H), 5.15 (d, *J* = 4.0 Hz, 1H), 5.32 (d, *J* = 6.8 Hz, 1H), 5.90 (dd, *J* = 4.0, 6.3 Hz, 1H), 5.97 (d, *J* = 7.5 Hz, 1H), 6.52 (br s, 2H), 7.42–7.58 (m, 3H), 7.65 (t, *J* = 6.0 Hz, 1H), 7.80–7.95 (m, 5H). ¹³C NMR (DMSO- d_6) δ 45.5, 61.8, 71.0, 71.1, 85.9, 86.6, 117.1, 125.2, 125.6, 125.9, 126.1, 127.5, 127.6, 127.8, 132.1, 132.9, 137.5, 148.6, 149.9, 151.4, 152.5. HRMS calcd for C₂₁H₂₃N₆O₄ (M+H)⁺ 423.1775, found 423.1775.

8-(2-Phenylbenzylamino)adenosine (1-61)

The title compound (241 mg, 93%) was obtained as a yellow solid from **13** (200 mg, 0.578 mmol) and 2phenylbenzylamine (318 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.49–3.70 (m, 2H), 3.93–4.02 (m, 1H), 4.07–4.15 (m, 1H), 4.41–4.59 (m, 2H), 4.69– 4.80 (m, 1H), 5.15 (d, *J* = 4.3 Hz, 1H), 5.27 (d, *J* = 6.8 Hz, 1H), 5.81 (dd, *J* = 4.0, 6.8 Hz, 1H), 5.94 (d, *J* = 7.3 Hz, 1H), 6.45 (br s, 2H), 7.18–7.26 (m, 1H), 7.28–7.56 (m, 9H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 43.6, 61.8, 71.1, 85.9, 86.6, 117.1, 126.8, 127.2, 127.4, 127.5, 128.4, 129.1, 129.7, 136.5, 140.5, 140.8, 148.6, 149.8, 151.4, 152.5. HRMS calcd for C₂₃H₂₅N₆O₄ (M+H)⁺ 449.1932, found 449.1939.

8-(3-Phenylbenzylamino)adenosine (1-62)

The title compound (223 mg, 86%) was obtained as a yellow solid from **13** (200 mg, 0.578 mmol) and 3-phenylbenzylamine (318 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.55–3.72 (m, 2H), 3.96–4.04 (m, 1H), 4.09–4.20 (m, 1H), 4.67 (d, *J* = 5.8 Hz, 2H), 4.71–4.81 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.87–6.01 (m, 2H), 6.52 (br s, 2H), 7.30–7.76 (m, 10H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.3, 61.8, 71.0, 71.1, 85.9, 86.5, 117.1, 125.1, 125.6, 126.3, 126.7, 127.5, 128.9, 129.0, 140.1, 140.2, 140.7, 148.6, 149.9, 151.4, 152.5. HRMS calcd for C₂₃H₂₅N₆O₄ (M+H)⁺ 449.1932, found 449.1928.

8-(4-Phenylbenzylamino)adenosine (1-63)

A mixture of **13** (200 mg, 0.578 mmol), 4-phenylbenzylamine (318 mg, 1.73 mmol), and *i*-Pr₂NEt (448 mg, 3.47 mmol) in PrOH (5.78 mL) was heated in a screw tube at 120 °C with stirring for 73 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was suspended in DCM. The precipitate was collected by filtration, washed with EtOH, and dried at 80 °C under reduced pressure to give a pale yellow solid (329 mg), which was recrystallized from EtOH to give the title compound (153 mg, 59%) as a pale yellow solid. mp 246–248 °C, dec. ¹H NMR (DMSO-*d*₆) δ 3.56–3.72 (m, 2H), 3.96–4.03 (m, 1H), 4.10–4.18 (m, 1H), 4.55–4.80 (m, 3H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.87–5.98 (m, 2H), 6.52 (br s, 2H), 7.31–7.38 (m, 1H), 7.40–7.51 (m, 4H), 7.52–7.70 (m, 5H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 61.8, 70.9, 71.1, 85.8, 86.5, 117.1, 126.6 (2C), 127.3, 127.7, 128.9, 138.7, 139.2, 140.1, 148.6, 149.8, 151.4, 152.5. HRMS calcd for C₂₃H₂₅N₆O₄ (M+H)⁺ 449.1932, found 449.1928.

8-(4-Benzylbenzylamino)adenosine (1-64)

4-Benzylbenzamide (1-73).⁹³ To a stirred solution of 4-benzylbenzoic acid 15 (1.00 g, 4.71 mmol) in THF (23.5 mL) was added CDI (1.53 g, 9.42 mmol), and the resulting mixture was stirred at room temperature for 24 h. Then 28% aqueous NH₃ (4.7 mL) was added dropwise, and stirring was continued for additional 4 h. The reaction mixture was quenched with 1.0 M hydrochloric acid (40 mL), and the whole was extracted with AcOEt (60 mL). The organic layer was washed successively with 1.0 M hydrochloric acid (40 mL), saturated aqueous NaHCO₃ (40 mL), and brine (40 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give the title compound (981 mg, 99%) as a white solid. ¹H NMR (DMSO-*d*₆) δ 3.98 (s, 2H), 7.12–7.39 (m, 8H), 7.70–7.84 (m, 2H), 7.89 (br s, 1H). HRMS calcd for C₁₄H₁₄NO (M+H)⁺ 212.1070, found 212.1067.

4-Benzylbenzonitrile (1-74).⁹⁴ To a stirred ice-cold mixture of 1-73 (979 mg, 4.63 mmol) and Et₃N (2.34 g, 23.2 mmol) in DCM (23.2 mL) was added dropwise TFAA (2.43 g, 11.6 mmol), and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with MeOH (2.5 mL), stirred for additional 30 min, and then concentrated under reduced pressure. The residue was partitioned between AcOEt (60 mL) and H₂O (20 mL). The organic layer was washed with brine (20 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 0–13% AcOEt in hexane) to give the title compound (802 mg, 90%) as a slightly yellow oil. ¹H NMR (CDCl₃) δ 4.03 (s, 2H), 7.12–7.20 (m, 2H), 7.21–7.35 (m, 5H), 7.53–7.60 (m, 2H). ¹³C NMR (CDCl₃) δ 42.1, 110.1, 119.1, 126.8, 128.9, 129.1, 129.8, 132.4, 139.4, 146.9. HRMS calcd for C₁₄H₁₂N (M+H)⁺ 194.0964, found 194.0961.

4-Benzylbenzylamine (1-75).⁹⁵ To a stirred ice-cold suspension of LiAlH₄ (103 mg, 2.72 mmol) in THF (10.9 mL) was added dropwise a solution of 1-74 (350 mg, 1.81 mmol) in THF (7.24 mL), and the resulting mixture was heated at 60 $^{\circ}$ C with stirring for 3 h. After being allowed to cool to room temperature, the reaction mixture was quenched

by sequential addition of H₂O (0.103 mL), 15% aqueous NaOH (0.103 mL), and H₂O (0.103 mL). The resulting suspension was stirred at room temperature for 3 h and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on NH silica gel (gradient: 0–10% MeOH in AcOEt) to give the title compound (323 mg, 90%) as a slightly yellow oily material. ¹H NMR (CDCl₃) δ 3.83 (s, 2H), 3.97 (s, 2H), 7.06–7.32 (m, 9H). ¹³C NMR (CDCl₃) δ 41.7, 46.3, 126.2, 127.3, 128.6, 129.0, 129.2, 139.8, 141.2, 141.3. HRMS calcd for C₁₄H₁₆N (M+H)⁺ 198.1277, found 198.1276. *8-(4-Benzylbenzylamino)adenosine (1-64)*. The title compound (206 mg, 88%) was obtained as a pale yellow solid from **13** (176 mg, 0.509 mmol) and **1-75** (301 mg, 1.53 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.52–3.68 (m, 2H), 3.90 (s, 2H), 3.93–4.02 (m, 1H), 4.06–4.18 (m, 1H), 4.40–4.63 (m, 2H), 4.64–4.77 (m, 1H), 5.15 (d, *J* = 4.0 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.81–5.99 (m, 2H), 6.51 (br s, 2H), 7.09–7.34 (m, 9H), 7.50 (t, *J* = 6.0 Hz, 1H), 7.88 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 40.8, 45.0, 61.8, 70.9, 71.1, 85.8, 86.5, 117.1, 126.0, 127.3, 128.5 (2C), 128.7, 137.5, 139.8, 141.5, 148.6, 149.8, 151.4, 152.5. HRMS calcd for C₂₄H₂₇N₆O₄ (M+H)⁺ 463.2088, found 463.2089.

8-(4-Phenoxybenzylamino)adenosine (1-65)

The title compound (239 mg, 89%) was obtained as a pale yellow foam from **13** (200 mg, 0.578 mmol) and 4phenoxybenzylamine (345 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.53–3.71 (m, 2H), 3.92–4.03 (m, 1H), 4.06–4.18 (m, 1H), 4.45–4.66 (m, 2H), 4.67– 4.80 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.84–5.97 (m, 2H), 6.54 (br s, 2H), 6.90–7.06 (m, 4H), 7.07–7.17 (m, 1H), 7.30–7.44 (m, 4H), 7.54 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 44.8, 61.8, 70.9, 71.1, 85.9, 86.5, 117.1, 118.5, 118.6, 123.3, 129.0, 130.1, 135.1, 148.6, 149.8, 151.4, 152.5, 155.4, 156.9. HRMS calcd for C₂₃H₂₅N₆O₅ (M+H)⁺ 465.1881, found 465.1880.

8-[4-(Phenylthio)benzylamino]adenosine (1-66)

4-(Phenylthio)benzylamine (1-76). The title compound (276 mg, 83%) was obtained as a yellow oil from 4-(phenylthio)benzonitrile 17^{46} (326 mg, 1.54 mmol) according to a procedure similar to that described for the preparation of 1-75. ¹H NMR (CDCl₃) δ 3.86 (s, 2H), 7.19–7.38 (m, 9H). ¹³C NMR (CDCl₃) δ 46.1, 126.9, 128.1, 129.2, 130.6, 131.9, 133.7, 136.4, 142.6. HRMS calcd for C₁₃H₁₃NNaS (M+Na)⁺ 238.0661, found 238.0665.

8-[4-(Phenylthio)benzylamino]adenosine (1-66). The title compound (163 mg, 85%) was obtained as a yellow solid from **13** (138 mg, 0.399 mmol) and **1-76** (258 mg, 1.20 mmol) according to a procedure similar to that described for the preparation of **1-11**. ¹H NMR (DMSO-*d*₆) δ 3.55–3.69 (m, 2H), 3.93–4.01 (m, 1H), 4.08–4.18 (m, 1H), 4.47–4.66 (m, 2H), 4.69–4.79 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.89 (dd, *J* = 4.1, 6.2 Hz, 1H), 5.92 (d, *J* = 7.5 Hz, 1H), 6.53 (br s, 2H), 7.24–7.45 (m, 9H), 7.57 (t, *J* = 6.0 Hz, 1H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 44.9, 61.8, 70.9, 71.1, 85.8, 86.5, 117.0, 127.2, 128.4, 129.6, 130.3, 131.2, 132.5, 135.4, 139.7, 148.6, 149.8,

8-(4-Cyclopropylbenzylamino)adenosine (1-67)

4-Cyclopropylbenzylamine (1-77). To a stirred ice-cold suspension of LiAlH₄ (119 mg, 3.14 mmol) in THF (12.6 mL) was added dropwise a solution of 4-cyclopropylbenzonitrile **18** (300 mg, 2.10 mmol) in THF (8.4 mL), and the resulting mixture was heated under reflux with stirring for 5 h. After being allowed to cool to room temperature, the reaction mixture was quenched by sequential addition of H₂O (0.119 mL), 15% aqueous NaOH (0.119 mL), and H₂O (0.119 mL). The resulting mixture was stirred at room temperature for 3 h and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure to give the title compound (313 mg, quant.) as a pale yellow oil, which was used in the next step without further purification. ¹H NMR (CDCl₃) δ 0.63–0.72 (m, 2H), 0.90–0.99 (m, 2H), 1.83–1.93 (m, 1H), 3.82 (s, 2H), 7.02–7.09 (m, 2H), 7.17–7.23 (m, 2H). HRMS calcd for C₁₀H₁₄N (M+H)⁺ 148.1121, found 148.1115.

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(4-cyclopropylbenzylamino)adenosine (1-78).* A mixture of 19⁴⁷ (480 mg, 0.697 mmol), 1-77 (308 mg, 2.09 mmol), and *i*-Pr₂NEt (540 mg, 4.18 mmol) in EtOH (6.26 mL) was heated in a screw tube at 120 °C with stirring for 76 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was partitioned between AcOEt (50 mL) and saturated aqueous NaHCO₃ (15 mL). The organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 30–51% AcOEt in hexane) to give the title compound (508 mg, 97%) as a slightly yellow foam. ¹H NMR (CDCl₃) δ –0.32 (s, 3H), –0.06 (s, 3H), –0.03 (s, 3H), –0.01 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.61–0.71 (m, 2H), 0.75 (s, 9H), 0.81 (s, 9H), 0.88–1.00 (m, 11H), 1.81–1.93 (m, 1H), 3.71 (dd, *J* = 2.6, 11.5 Hz, 1H), 3.82 (dd, *J* = 3.0, 11.5 Hz, 1H), 4.03–4.13 (m, 1H), 4.28 (dd, *J* = 2.6, 4.6 Hz, 1H), 4.47 (dd, *J* = 4.0, 15.3 Hz, 1H), 4.78–4.92 (m, 2H), 4.99–5.25 (m, 2H), 5.81 (dd, *J* = 4.0, 7.8 Hz, 1H), 6.01 (d, *J* = 6.8 Hz, 1H), 6.97–7.07 (m, 2H), 7.18–7.29 (m, 2H), 8.15 (s, 1H). HRMS calcd for C₃₈H₆7N₆O₄Si₃ (M+H)⁺ 755.4526, found 755.4520.

8-(4-Cyclopropylbenzylamino)adenosine (1-67). To a solution of 1-78 (504 mg, 0.667 mmol) in MeOH (13.3 mL) was added NH₄F (1.48 g, 40.0 mmol), and the resulting mixture was heated under reflux with stirring for 24 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. To the residue was added H₂O (45 mL), and the resulting suspension was stirred at room temperature for 2 h. The precipitate was collected by filtration, washed with H₂O, and air-dried to give the title compound (275 mg, quant.) as a pale yellow solid. An analytical sample was prepared by recrystallization from EtOH. ¹H NMR (DMSO-*d*₆) δ 0.55–0.68 (m, 2H), 0.83–0.97 (m, 2H), 1.82–1.92 (m, 1H), 3.54–3.70 (m, 2H), 3.95–4.02 (m, 1H), 4.07–4.18 (m, 1H), 4.44–4.61 (m, 2H), 4.65–4.78 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.27 (d, *J* = 7.0 Hz, 1H), 5.89 (dd, *J* = 4.3, 6.3 Hz, 1H), 5.92 (d, *J* = 7.5 Hz, 1H), 6.51 (br s, 2H), 6.96–7.07 (m, 2H), 7.19–7.28 (m, 2H), 7.48 (t, *J* = 6.0 Hz, 1H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 9.3, 14.8, 45.0, 61.8, 70.9, 71.1, 85.8, 86.5, 117.1, 125.2, 127.2, 136.8, 142.1,

8-(4-Cyclopentylbenzylamino)adenosine (1-68)

*4-(Cyclopent-1-en-1-yl)benzonitrile (1-79).*⁹⁶ A mixture of 4-cyanophenyl trifluoromethanesulfonate **21**⁴⁸ (500 mg, 1.99 mmol), (cyclopent-1-en-1-yl)boronic acid (334 mg, 2.99 mmol), Pd(PPh₃)₄ (230 mg, 0.199 mmol), Na₂CO₃ (232 mg, 2.19 mmol), and H₂O (4.00 mL) in DME (16.0 mL) was heated under reflux with stirring for 6 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was partitioned between AcOEt (70 mL) and H₂O (20 mL). The organic layer was washed with brine (20 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 0–8% AcOEt in hexane) to give the title compound (331 mg, 98%) as a slightly yellow solid. ¹H NMR (CDCl₃) δ 1.98–2.14 (m, 2H), 2.51–2.80 (m, 4H), 6.32–6.42 (m, 1H), 7.45–7.55 (m, 2H), 7.56–7.66 (m, 2H). ¹³C NMR (CDCl₃) δ 23.3, 33.0, 33.7, 110.0, 119.3, 126.1, 130.8, 132.2, 141.3 (2C). HRMS calcd for C₁₂H₁₂N (M+H)⁺ 170.0964, found 170.0964.

4-Cyclopentylbenzonitrile (**1-80**).⁹⁷ A mixture of **1-79** (308 mg, 1.82 mmol) and 5% Pt–C (61.6 mg) in THF (9.10 mL) was stirred at room temperature for 1 h under a hydrogen atmosphere. The reaction mixture was filtered through a pad of Hyflo Super-Cel and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 0–8% AcOEt in hexane) to give the title compound (263 mg, 84%) as a pale yellow oil. ¹H NMR (CDCl₃) δ 1.48–1.90 (m, 6H), 2.01–2.18 (m, 2H), 2.97–3.11 (m, 1H), 7.29–7.37 (m, 2H), 7.53–7.61 (m, 2H). HRMS calcd for C₁₂H₁₄N (M+H)⁺ 172.1121, found 172.1128.

4-Cyclopentylbenzylamine (1-81). The title compound (294 mg, quant.) was obtained as a pale yellow oil from 1-80 (261 mg, 1.52 mmol) according to a procedure similar to that described for the preparation of 1-77. ¹H NMR (DMSO-*d*₆) δ 1.42–2.28 (m, 10H), 2.86–3.00 (m, 1H), 3.65 (s, 2H), 7.11–7.29 (m, 4H). ¹³C NMR (DMSO-*d*₆) δ 25.0, 34.3, 45.0, 45.4, 126.6, 127.0, 141.6, 143.7. HRMS calcd for C₁₂H₁₈N (M+H)⁺ 176.1434, found 176.1432.

8-(4-Cyclopentylbenzylamino)adenosine (1-68). The title compound (194 mg, 86%) was obtained as a pale yellow foam from 13 (178 mg, 0.514 mmol) and 1-81 (270 mg, 1.54 mmol) according to a procedure similar to that described for the preparation of 1-11. ¹H NMR (DMSO-*d*₆) δ 1.40–1.81 (m, 6H), 1.90–2.05 (m, 2H), 2.86–3.01 (m, 1H), 3.54–3.70 (m, 2H), 3.94–4.02 (m, 1H), 4.07–4.18 (m, 1H), 4.47–4.63 (m, 2H), 4.66–4.77 (m, 1H), 5.17 (d, J = 4.3 Hz, 1H), 5.28 (d, J = 6.8 Hz, 1H), 5.87–5.97 (m, 2H), 6.52 (br s, 2H), 7.14–7.23 (m, 2H), 7.23–7.33 (m, 2H), 7.50 (t, J = 6.2 Hz, 1H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.0, 34.3, 45.1, 61.8, 71.0, 71.1, 85.8, 86.5, 117.1, 126.8, 127.2, 137.3, 144.3, 148.6, 149.8, 151.4, 152.5. HRMS calcd for C₂₂H₂₉N₆O₄ (M+H)⁺ 441.2245, found 441.2242.

8-(4-Cyclohexylbenzylamino)adenosine (1-69)

(4-Cyclohexylphenyl)methanol (1-82).98 To a stirred suspension of LiAlH₄ (223 mg, 5.88 mmol) in THF (10 mL)

was added dropwise a solution of 4-cyclohexylbenzoic acid **22** (1.00 g, 4.90 mmol) in THF (9.6 mL), and the resulting mixture was heated under reflux with stirring for 5 h. After being allowed to cool to room temperature, the reaction mixture was quenched by sequential addition of H₂O (0.223 mL), 15% aqueous NaOH (0.223 mL), and H₂O (0.223 mL). The resulting mixture was stirred at room temperature for 3 h and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 9–30% AcOEt in hexane) to give the title compound (850 mg, 91%) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.12–1.48 (m, 5H), 1.63–1.88 (m, 5H), 2.39–2.56 (m, 1H), 4.43 (d, *J* = 5.8 Hz, 2H), 5.07 (t, *J* = 5.8 Hz, 1H), 7.11–7.28 (m, 4H). ¹³C NMR (DMSO-*d*₆) δ 25.6, 26.4, 34.1, 43.6, 62.8, 126.3, 126.6, 140.0, 146.0. HRMS calcd for C₁₃H₁₈NaO (M+Na)⁺ 213.1250, found 213.1244.

N-(4-Cyclohexylbenzyl)phthalimide (1-83). To a stirred mixture of **1-82** (810 mg, 4.26 mmol), PPh₃ (1.34 g, 5.11 mmol), and phthalimide (689 mg, 4.68 mmol) in THF (21.3 mL) was added dropwise DIAD (40% in toluene, ca. 1.9 mol/L, 2.69 mL, ca. 5.11 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 0–17% AcOEt in hexane) to give the title compound (1.22 g, 90%) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.12–1.43 (m, 5H), 1.62–1.84 (m, 5H), 2.37–2.56 (m, 1H), 4.72 (s, 2H), 7.13–7.27 (m, 4H), 7.82–7.95 (m, 4H). ¹³C NMR (DMSO-*d*₆) δ 25.6, 26.4, 33.9, 40.6, 43.5, 123.3, 126.9, 127.5, 131.6, 134.2, 134.6, 146.9, 167.8. HRMS calcd for C₂₁H₂₂NO₂ (M+H)⁺ 320.1645, found 320.1648.

4-Cyclohexylbenzylamine (*1-84*). To a stirred solution of **1-83** (1.19 g, 3.73 mmol) in CHCl₃/EtOH (5/1, 24.8 mL) was added dropwise H₂NNH₂·H₂O (933 mg, 18.6 mmol), and the resulting mixture was stirred at room temperature for 48 h. The reaction mixture was filtered through a pad of Hyflo Super-Cel and the filtrate was concentrated under reduced pressure. The residue was partitioned between DCM (50 mL) and H₂O (20 mL). The organic layer was washed with H₂O (20 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give the title compound (714 mg, quant.) as a pale yellow oil, which was used in the next step without further purification. ¹H NMR (DMSO-*d*₆) δ 1.10–1.47 (m, 5H), 1.63–2.02 (m, 7H), 2.38–2.56 (m, 1H), 3.65 (s, 2H), 7.09–7.16 (m, 2H), 7.18–7.25 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 25.6, 26.4, 34.1, 43.5, 45.5, 126.3, 127.0, 141.7, 145.5. HRMS calcd for C₁₃H₂₀N (M+H)⁺ 190.1590, found 190.1590.

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(4-cyclohexylbenzylamino)adenosine (1-85)*. The title compound (468 mg, quant.) was obtained as an off-white foam from 19^{47} (400 mg, 0.581 mmol) and 1-84 (330 mg, 1.74 mmol) according to a procedure similar to that described for the preparation of 1-78. ¹H NMR (CDCl₃) δ –0.31 (s, 3H), –0.06 (s, 3H), –0.05 (s, 3H), –0.03 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.80 (s, 9H), 0.94 (s, 9H), 1.16–1.48 (m, 5H), 1.64–1.92 (m, 5H), 2.40–2.55 (m, 1H), 3.72 (dd, *J* = 2.8, 11.5 Hz, 1H), 3.84 (dd, *J* = 2.8, 11.5 Hz, 1H), 4.03–4.11 (m, 1H), 4.25–4.35 (m, 1H), 4.44–4.54 (m, 1H), 4.81–4.95 (m, 2H), 5.15 (br s, 2H), 5.83 (dd, *J* = 4.0, 7.8 Hz, 1H), 6.01 (d, *J* = 6.5 Hz, 1H), 7.11–7.20 (m, 2H), 7.21–7.32 (m, 2H), 8.15 (s, 1H). HRMS calcd for C₄₁H₇₃N₆O₄Si₃ (M+H)⁺ 797.4996, found 797.4989.

8-(4-Cyclohexylbenzylamino)adenosine (1-69). To a solution of 1-85 (396 mg, 0.497 mmol) in MeOH (9.93 mL) was added NH₄F (1.10 g, 29.8 mmol), and the resulting mixture was heated under reflux with stirring for 24 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. To the residue was added H₂O (40 mL), and the resulting suspension was stirred at room temperature for 2 h. The precipitate was collected by filtration, washed with H₂O, and air-dried to give a pale yellow solid (242 mg), which was purified by flash column chromatography on silica gel (gradient: 10–17% MeOH in DCM) to give the title compound (202 mg, 90%) as an off-white foam. ¹H NMR (DMSO-*d*₆) δ 1.09–1.47 (m, 5H), 1.60–1.90 (m, 5H), 2.37–2.54 (m, 1H), 3.53–3.75 (m, 2H), 3.92–4.03 (m, 1H), 4.05–4.16 (m, 1H), 4.45–4.64 (m, 2H), 4.68–4.79 (m, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.86–5.97 (m, 2H), 6.52 (br s, 2H), 7.10–7.19 (m, 2H), 7.22–7.31 (m, 2H), 7.43–7.56 (m, 1H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.7, 26.4, 34.1, 43.5, 45.0, 61.9, 71.0, 71.1, 85.9, 86.5, 117.1, 126.5, 127.2, 137.4, 146.1, 148.6, 149.8, 151.4, 152.5. HRMS calcd for C₂₃H₃₁N₆O₄ (M+H)⁺ 455.2401, found 455.2401.

Purity of Tested Compounds in Chapter 1

compd	formula	calcd				found	$t_{\rm R}^a$	area	
		С	Н	Ν	С	Н	Ν	(min)	(%)
1-1	$C_{11}H_{16}N_6O_4{\cdot}0.4H_2O$	43.53	5.58	27.69	43.44	5.62	27.65		
1-2	$C_{12}H_{18}N_6O_4$	46.45	5.85	27.08	46.27	5.85	27.38		
1-3	$C_{15}H_{24}N_6O_4{\cdot}0.3H_2O$	50.35	6.93	23.49	50.33	6.96	23.19	19.1	99.0
1-4	$C_{17}H_{20}N_6O_4{\cdot}0.4H_2O$	53.79	5.52	22.14	54.05	5.51	21.85	16.0	99.0
1-5	$C_{11}H_{15}N_5O_4{\cdot}0.5H_2O$	45.51	5.56	24.13	45.38	5.59	24.08	9.7	99.5
1-6	$C_{12}H_{17}N_5O_4{\cdot}0.85H_2O$	46.40	6.07	22.55	46.01	6.09	22.51	13.9	99.6
1-7	$C_{15}H_{23}N_5O_4{\cdot}0.4H_2O$	52.28	6.96	20.32	52.38	6.92	20.33	32.1	99.9
1-8	purchased								
1-9	$C_{11}H_{16}N_6O_4{\cdot}0.1H_2O$	44.32	5.48	28.19	44.41	5.43	27.93		
1-10	$C_{12}H_{18}N_6O_4$	46.45	5.85	27.08	46.14	5.87	26.71	10.0	99.3
1-11	$C_{15}H_{24}N_6O_4$	51.13	6.86	23.85	51.03	7.00	23.61	21.6	99.5
1-12	$C_{17}H_{20}N_6O_4{\cdot}0.4H_2O$	53.79	5.52	22.14	53.92	5.56	21.89	18.1	98.5
1-13	$C_{12}H_{15}N_5O_5{\cdot}0.3H_2O$	45.80	5.00	22.16	45.71	5.07	21.97	10.5	97.9
1-14	$C_{13}H_{17}N_5O_5{\cdot}0.4H_2O$	47.24	5.43	21.19	47.34	5.44	21.10	15.1	98.5
1-15	$C_{16}H_{23}N_5O_5{\cdot}0.5H_2O$	51.33	6.46	18.71	51.39	6.42	18.50	29.9	98.7
1-16	$C_{18}H_{19}N_5O_5$	56.10	4.97	18.17	56.11	4.98	17.92	23.8	97.9
1-17	$C_{12}H_{15}N_5O_6$	44.31	4.65	21.53	44.58	4.71	21.25	11.7	99.1
1-18	$C_{13}H_{17}N_5O_6\cdot 0.3H_2O$	45.30	5.15	20.32	45.22	5.18	20.38	15.9	99.8
1-19	$C_{16}H_{23}N_5O_6$	50.39	6.08	18.36	50.47	6.04	18.29	31.1	99.7
1-20	$C_{18}H_{19}N_5O_6$	53.86	4.77	17.45	53.68	4.75	17.33		
1-21	$C_{12}H_{16}N_6O_5{\cdot}0.5H_2O$	43.24	5.14	25.21	43.36	5.11	25.08	8.7	98.5
1-22	$C_{13}H_{18}N_6O_5{\cdot}0.6H_2O$	44.72	5.54	24.07	44.95	5.59	23.84	11.9	99.7
1-23	$C_{16}H_{24}N_6O_5{\cdot}0.8H_2O$	48.67	6.54	21.29	48.68	6.46	21.43	26.4	97.9
1-24								21.7	99.3
1-25	$C_{18}H_{21}N_5O_4{\cdot}0.2H_2O$	57.65	5.75	18.68	57.80	5.81	18.61	28.3	99.5
1-26	$C_{17}H_{19}N_5O_5$	54.69	5.13	18.76	54.94	5.23	18.54	24.0	99.7
1-27	$C_{17}H_{19}N_5O_4S$	52.43	4.92	17.98	52.25	4.94	17.92	29.8	99.0

Table E1. Elemental Analysis and/or HPLC–UV Analysis Data for Tested Compounds in Chapter 1

 $^{a}t_{\rm R}$ is the retention time of the compound.

(continued on the following page)

Table E1.	continued

compd	formula	calcd			found			$t_{\rm R}{}^a$	area
		С	Н	Ν	С	Н	Ν	(min)	(%)
1-28	$C_{18}H_{22}N_6O_4{\cdot}0.2H_2O$	55.43	5.79	21.55	55.48	5.83	21.50	19.5	97.9
1-29								19.0	96.1
1-30	$C_{18}H_{22}N_6O_4{\cdot}0.4H_2O$	54.93	5.84	21.35	55.03	5.84	21.16	21.0	98.7
1-31	$C_{19}H_{24}N_6O_4{\cdot}0.5H_2O$	55.74	6.15	20.53	55.67	6.10	20.24	25.2	99.2
1-32	$C_{18}H_{22}N_6O_4{\cdot}0.8H_2O$	53.94	5.93	20.97	54.09	5.89	20.67	20.7	95.2
1-33	$C_{18}H_{22}N_6O_4{\cdot}0.3H_2O$	55.18	5.81	21.45	55.26	5.86	21.25	19.1	99.2
1-34	$C_{14}H_{20}N_6O_4{\cdot}0.2H_2O$	49.46	6.05	24.72	49.56	6.08	24.34	14.3	98.8
1-35	$C_{16}H_{24}N_6O_4{\cdot}0.65H_2O$	51.39	6.74	21.98	51.09	6.78	22.34	21.5	99.5
1-36	$C_{17}H_{26}N_6O_4{\cdot}0.5H_2O$	52.70	7.02	21.69	52.84	7.03	21.66	24.9	98.8
1-37	$C_{15}H_{18}N_6O_5$	49.72	5.01	23.19	49.32	5.08	22.84	13.5	98.3
1-38	$C_{15}H_{18}N_6O_5$	49.72	5.01	23.19	49.54	5.11	23.56		
1-39	$C_{15}H_{18}N_6O_4S\!\cdot\!0.2H_2O$	47.16	4.85	22.00	47.33	4.90	21.91	15.9	97.1
1-40	$C_{15}H_{18}N_6O_4S$	47.61	4.79	22.21	47.26	4.92	21.85	16.4	97.2
1-41	$C_{16}H_{19}N_7O_4{\cdot}0.25H_2O$	50.86	5.20	25.95	50.94	5.10	25.84		
1-42	$C_{16}H_{19}N_7O_4{\cdot}0.25H_2O$	50.86	5.20	25.95	51.16	5.19	25.65		
1-43	$C_{16}H_{19}N_7O_4{\cdot}0.4H_2O$	50.50	5.24	25.76	50.53	5.28	25.43		
1-44	$C_{18}H_{22}N_6O_4{\cdot}0.3H_2O$	55.18	5.81	21.45	55.20	5.81	21.32	21.3	97.5
1-45	$C_{18}H_{22}N_6O_4{\cdot}0.2H_2O$	55.43	5.79	21.55	55.52	5.83	21.18	22.0	96.9
1-46	$C_{18}H_{22}N_6O_4$	55.95	5.74	21.75	55.72	5.75	21.63		
1-47	$C_{18}H_{22}N_6O_5$	53.73	5.51	20.88	53.33	5.59	20.60	19.5	97.9
1-48	$C_{18}H_{22}N_6O_5{\cdot}0.4H_2O$	52.78	5.61	20.52	52.79	5.65	20.40	19.1	96.9
1-49	$C_{18}H_{22}N_6O_5{\cdot}0.2H_2O$	53.25	5.56	20.70	53.30	5.56	20.55	18.8	98.6
1-50	$C_{17}H_{19}FN_6O_4{\cdot}0.7H_2O$	50.67	5.10	20.85	50.69	5.09	20.65	18.8	98.0
1-51	$C_{17}H_{19}FN_6O_4{\cdot}0.6H_2O$	50.90	5.08	20.95	51.06	5.11	20.90	19.8	98.3
1-52	$C_{17}H_{19}FN_6O_4 \cdot 1.1H_2O$	49.78	5.21	20.49	49.40	5.22	20.15	19.7	97.8
1-53	$C_{17}H_{19}ClN_6O_4 \cdot 0.3H_2O$	49.53	4.79	20.39	49.88	4.87	20.06	22.0	99.1
1-54	$C_{17}H_{19}ClN_6O_4{\cdot}0.3H_2O$	49.53	4.79	20.39	49.64	4.82	20.18	23.9	96.3
1-55	$C_{17}H_{19}ClN_6O_4 \cdot 1.1H_2O$	47.86	5.01	19.70	47.61	5.01	19.41	24.3	97.0
1-56	$C_{18}H_{19}F_{3}N_{6}O_{4}{\cdot}0.4H_{2}O$	48.30	4.46	18.78	48.31	4.54	18.65		

 $^{a}t_{\mathrm{R}}$ is the retention time of the compound.

(continued on the following page)

Table E1. continued

compd	formula	calcd			found			$t_{\rm R}{}^a$	area
		С	Н	Ν	С	Н	Ν	(min)	(%)
1-57	$C_{18}H_{19}F_{3}N_{6}O_{4}{\cdot}0.2H_{2}O$	48.69	4.40	18.93	48.68	4.52	18.81	26.4	98.9
1-58	$C_{18}H_{19}F_{3}N_{6}O_{4}{\cdot}0.2H_{2}O$	48.69	4.40	18.93	48.73	4.51	18.78	27.2	96.9
1-59	$C_{21}H_{22}N_6O_4{\cdot}0.5H_2O$	58.46	5.37	19.48	58.53	5.36	19.30	26.2	98.8
1-60	$C_{21}H_{22}N_6O_4{\cdot}0.2H_2O$	59.20	5.30	19.73	59.14	5.33	19.50	26.7	97.5
1-61	$C_{23}H_{24}N_6O_4{\cdot}0.3H_2O$	60.86	5.46	18.52	60.93	5.51	18.41	29.2	97.2
1-62	$C_{23}H_{24}N_6O_4{\cdot}0.2H_2O$	61.11	5.44	18.59	61.10	5.50	18.31	31.1	98.3
1-63	$C_{23}H_{24}N_6O_4$	61.60	5.39	18.74	61.37	5.39	18.73	31.3	99.0
1-64	$C_{24}H_{26}N_6O_4{\cdot}0.25H_2O$	61.72	5.72	18.00	61.72	5.74	18.07		
1-65	$C_{23}H_{24}N_6O_5{\cdot}0.3H_2O$	58.79	5.28	17.89	58.80	5.33	17.78	31.4	96.2
1-66	$C_{23}H_{24}N_6O_4S$	57.49	5.03	17.49	57.33	5.18	17.19	34.8	95.5
1-67	$C_{20}H_{24}N_6O_4$	58.24	5.87	20.38	58.23	5.81	20.47		
1-68	$C_{22}H_{28}N_6O_4{\cdot}0.6H_2O$	58.55	6.52	18.62	58.57	6.46	18.51	34.2	98.3
1-69	$C_{23}H_{30}N_6O_4{\cdot}0.8H_2O$	58.91	6.79	17.92	58.93	6.64	17.92	37.3	99.5

 $^{a}t_{\rm R}$ is the retention time of the compound.

Synthetic Procedures and Characterization Data for Tested Compounds in Chapter 2

8-[4-(Pyridin-2-yl)benzylamino]adenosine (2-1)

4-(Pyridin-2-yl)benzylamine (2-21). To a stirred ice-cold suspension of LiAlH₄ (126 mg, 3.33 mmol) in THF (13.3 mL) was added dropwise a solution of 4-(pyridin-2-yl)benzonitrile **25** (400 mg, 2.22 mmol) in THF (8.88 mL), and the resulting mixture was heated at 60 °C with stirring for 5 h. After being allowed to cool to room temperature, the reaction mixture was quenched by sequential addition of H₂O (0.126 mL), 15% aqueous NaOH (0.126 mL), and H₂O (0.126 mL). The resulting suspension was stirred at room temperature for 7 h and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on NH silica gel (gradient: 0–10% MeOH in AcOEt) to give the title compound (371 mg, 91%) as a yellow solid. ¹H NMR (DMSO-*d*₆) δ 1.86 (br s, 2H), 3.77 (s, 2H), 7.28–7.37 (m, 1H), 7.39–7.49 (m, 2H), 7.79–8.07 (m, 4H), 8.61–8.71 (m, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.4, 120.0, 122.3, 126.3, 127.4, 136.7, 137.2, 145.4, 149.5, 156.1. HRMS calcd for C₁₂H₁₃N₂ (M+H)⁺ 185.1073, found 185.1068.

8-[4-(Pyridin-2-yl)benzylamino]adenosine (2-1). A mixture of 8-bromoadenosine **13** (215 mg, 0.621 mmol), **2-21** (343 mg, 1.86 mmol), and *i*-Pr₂NEt (482 mg, 3.73 mmol) in EtOH (5.18 mL) was heated in a screw tube at 120 °C with stirring for 90 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM) followed by flash column chromatography on silica gel (gradient: 10–20% MeOH in DCM) to give the title compound (235 mg, 84%) as a yellow foam. ¹H NMR (DMSO-*d*₆) δ 3.53–3.73 (m, 2H), 3.96–4.05 (m, 1H), 4.09–4.17 (m, 1H), 4.55–4.81 (m, 3H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.32 (d, *J* = 6.8 Hz, 1H), 5.92 (dd, *J* = 4.0, 6.3 Hz, 1H), 5.96 (d, *J* = 7.5 Hz, 1H), 6.54 (br s, 2H), 7.28–7.37 (m, 1H), 7.43–7.53 (m, 2H), 7.55–7.67 (m, 1H), 7.80–7.97 (m, 3H), 7.99–8.10 (m, 2H), 8.60–8.69 (m, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.1, 61.8, 71.0, 71.2, 85.9, 86.6, 117.1, 120.1, 122.5, 126.5, 127.5, 137.3 (2C), 140.9, 148.7, 149.6, 149.9, 151.4, 152.5, 156.0. HRMS calcd for C₂₂H₂₄N₇O₄ (M+H)⁺ 450.1884, found 450.1886.

8-[4-(Pyridin-3-yl)benzylamino]adenosine (2-2)

4-(Pyridin-3-yl)benzonitrile (2-22).⁹⁹ To a mixture of 3-bromopyridine 26 (430 mg, 2.72 mmol), 4cyanophenylboronic acid (440 mg, 2.99 mmol), and 2.0 M aqueous Na₂CO₃ (2.72 mL) in MeCN (13.6 mL) was added Pd(PPh₃)₄ (157 mg, 0.136 mmol), and the resulting mixture was heated at 80 °C with stirring for 24 h. After being allowed to cool to room temperature, the reaction mixture was filtered through a pad of Hyflo Super-Cel and the filtrate was concentrated under reduced pressure. The residue was partitioned between AcOEt (60 mL) and H₂O/brine (1/1, 40 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was dissolved in DCM, pre-adsorbed onto silica gel, and then purified by flash column chromatography on silica gel (gradient: 52–73% AcOEt in hexane) to give the title compound (358 mg, 73%) as an off-white solid. ¹H NMR
$(CDCl_3) \delta 7.36-7.50 \text{ (m, 1H)}, 7.60-7.98 \text{ (m, 5H)}, 8.61-8.74 \text{ (m, 1H)}, 8.80-8.94 \text{ (m, 1H)}. {}^{13}C NMR (CDCl_3) \delta 112.0, 118.7, 123.9, 127.9, 133.0, 134.6, 134.9, 142.4, 148.4, 149.9. HRMS calcd for C₁₂H₉N₂ (M+H)⁺ 181.0760, found 181.0756.$

N-[4-(Pyridin-3-yl)benzyl]trifluoroacetamide (2-23). To a stirred ice-cold suspension of LiAlH₄ (105 mg, 2.76 mmol) in THF (11.0 mL) was added dropwise a solution of 2-22 (332 mg, 1.84 mmol) in THF (7.40 mL), and the resulting mixture was heated at 60 °C with stirring for 3 h. After being allowed to cool to room temperature, the reaction mixture was quenched by sequential addition of H₂O (0.105 mL), 15% aqueous NaOH (0.105 mL), and H₂O (0.105 mL). The resulting suspension was stirred at room temperature for 10 h and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 65–86% AcOEt in hexane) to give the title compound (299 mg, 58% from 2-22) as a pale yellow solid. ¹H NMR (DMSO-*d*₆) δ 4.45 (d, *J* = 6.0 Hz, 2H), 7.35–7.56 (m, 3H), 7.65–7.78 (m, 2H), 8.02–8.12 (m, 1H), 8.53–8.60 (m, 1H), 8.85–8.92 (m, 1H), 9.97–10.16 (m, 1H). HRMS calcd for C₁₄H₁₂F₃N₂O (M+H)⁺ 281.0896, found 281.0892.

4-(Pyridin-3-yl)benzylamine (2-24).¹⁰⁰ To a solution of 2-23 (296 mg, 1.06 mmol) in EtOH (10.6 mL) was added 2.0 M aqueous NaOH (1.59 mL, 3.18 mmol), and the resulting mixture was heated at 60 °C with stirring for 3 h. After being allowed to cool to room temperature, the reaction mixture was concentrated under reduced pressure to remove EtOH. The residue was partitioned between DCM (30 mL) and H₂O (10 mL). The aqueous layer was extracted twice with DCM (10 mL × 2). The combined organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 0–10% MeOH in AcOEt) to give the title compound (181 mg, 93%) as a yellow solid. ¹H NMR (DMSO-*d*₆) δ 1.84 (br s, 2H), 3.76 (s, 2H), 7.35–7.54 (m, 3H), 7.57–7.71 (m, 2H), 7.97–8.10 (m, 1H), 8.49–8.59 (m, 1H), 8.82–8.93 (m, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.3, 123.9, 126.6, 127.8, 133.9, 135.0, 135.6, 144.4, 147.5, 148.2. HRMS calcd for C₁₂H₁₃N₂ (M+H)⁺ 185.1073, found 185.1070.

8-[4-(Pyridin-3-yl)benzylamino]adenosine (2-2). The title compound (99.9 mg, 77%) was obtained as a beige amorphous solid from **13** (100 mg, 0.289 mmol) and **2-24** (160 mg, 0.867 mmol) according to a procedure similar to that described for the preparation of **2-1**. ¹H NMR (DMSO-*d*₆) δ 3.55–3.74 (m, 2H), 3.96–4.06 (m, 1H), 4.10–4.20 (m, 1H), 4.54–4.82 (m, 3H), 5.16 (d, J = 4.0 Hz, 1H), 5.30 (d, J = 6.8 Hz, 1H), 5.85–6.00 (m, 2H), 6.53 (br s, 2H), 7.44–7.55 (m, 3H), 7.61 (t, J = 6.0 Hz, 1H), 7.64–7.73(m, 2H), 7.90 (s, 1H), 8.02–8.10 (m, 1H), 8.55 (dd, J = 1.8, 4.8 Hz, 1H), 8.84–8.91 (m, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 61.8, 71.0, 71.1, 85.9, 86.6, 117.0, 123.9, 126.8, 127.9, 134.0, 135.5 (2C), 140.0, 147.6, 148.3, 148.5, 149.9, 151.4, 152.4. HRMS calcd for C₂₂H₂₄N₇O₄ (M+H)⁺ 450.1884, found 450.1879.

8-[4-(Pyridin-4-yl)benzylamino]adenosine (2-3)

4-(Pyridin-4-yl)benzonitrile (2-25).⁹⁹ The title compound (147 mg, 79%) was obtained as a white solid from 4bromopyridine hydrochloride 27 (200 mg, 1.03 mmol) and 4-cyanophenylboronic acid (166 mg, 1.13 mmol) according to a procedure similar to that described for the preparation of 2-22. ¹H NMR (CDCl₃) δ 7.46–7.57 (m, 2H), 7.67–7.89 (m, 4H), 8.68–8.80 (m, 2H). ¹³C NMR (CDCl₃) δ 112.9, 118.5, 121.7, 127.9, 133.0, 142.7, 146.5, 150.7. HRMS calcd for C₁₂H₉N₂ (M+H)⁺ 181.0760, found 181.0755.

4-(Pyridin-4-yl)benzylamine (2-26).¹⁰¹ The title compound (260 mg, 71%) was obtained as an orange-brown solid from 2-25 (360 mg, 2.00 mmol) according to a procedure similar to that described for the preparation of 2-21. ¹H NMR (DMSO-*d*₆) δ 1.83 (br s, 2H), 3.77 (s, 2H), 7.42–7.52 (m, 2H), 7.63–7.84 (m, 4H), 8.55–8.65 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 45.3, 121.0, 126.5, 127.8, 135.0, 145.7, 146.9, 150.2. HRMS calcd for C₁₂H₁₃N₂ (M+H)⁺ 185.1073, found 185.1068.

8-[4-(Pyridin-4-yl)benzylamino]adenosine (2-3). A mixture of **13** (142 mg, 0.410 mmol), **2-26** (227 mg, 1.23 mmol), and *i*-Pr₂NEt (318 mg, 2.46 mmol) in EtOH (4.10 mL) was heated in a screw tube at 120 °C with stirring for 96 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. To the suspension of the residue in DCM (20.0 mL) was added *i*-Pr₂NEt (159 mg, 1.23 mmol), and the resulting mixture was stirred at room temperature for 20 h. The precipitate was collected by filtration, washed with DCM, air-dried, and then dried under reduced pressure to give an orange brown solid (256 mg). The solid (252 mg) was suspended in EtOH (30.0 mL) and heated under reflux with stirring for 1 h before being allowed to cool to room temperature. The precipitate was collected by filtration, washed with EtOH, air-dried, and then dried under reduced pressure to give an orange brown solid. ¹H NMR (DMSO-*d*₆) δ 3.54–3.71 (m, 2H), 3.96–4.06 (m, 1H), 4.10–4.20 (m, 1H), 4.52–4.84 (m, 3H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.90 (dd, *J* = 4.0, 6.0 Hz, 1H), 5.95 (d, *J* = 7.5 Hz, 1H), 6.52 (br s, 2H), 7.48–7.59 (m, 2H), 7.62 (t, *J* = 6.2 Hz, 1H), 7.66–7.86 (m, 4H), 7.90 (s, 1H), 8.58–8.69 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 61.8, 71.0, 71.1, 85.8, 86.5, 117.0, 121.1, 126.7, 127.9, 135.6, 141.3, 146.8, 148.6, 149.9, 150.2, 151.3, 152.5. HRMS calcd for C₂₂H₂₄N₇O₄ (M+H)⁺ 450.1884, found 450.1884.

8-(2-Methoxybiphenyl-4-ylmethylamino)adenosine (2-4)

4-Cyano-2-methoxyphenyl trifluoromethanesulfonate (2-27).¹⁰² To a stirred ice-cold solution of 4-hydroxy-3methoxybenzonitrile **28** (2.00 g, 13.4 mmol) in DCM (26.8 mL) was added Et₃N (2.04 g, 20.1 mmol). Then Tf₂O (4.92 g, 17.4 mmol) was added dropwise, and the resulting mixture was allowed to warm to room temperature with stirring for 2.5 h. After being quenched with crushed ice, the reaction mixture was partitioned between AcOEt (75 mL) and saturated aqueous NaHCO₃ (30 mL). The organic layer was washed successively with H₂O/brine (2/1, 30 mL) and brine (30 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give the title compound (3.98 g) as a dark brown solid, which was used in the next step without further purification. ¹H NMR (CDCl₃) δ 3.98 (s, 3H), 7.28–7.32 (m, 1H), 7.32–7.36 (m, 2H).

2-Methoxybiphenyl-4-carbonitrile (**2-28**). To a mixture of **2-27** (3.98 g, as 13.4 mmol), PhB(OH)₂ (1.80 g, 14.8 mmol), Na₂CO₃ (2.84 g, 26.8 mmol), and H₂O (4.5 mL) in DMF (25.5 mL) was added Pd(PPh₃)₄ (775 mg, 0.671 mmol), and the resulting mixture was heated at 80 °C with stirring for 6 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (100 mL) and H₂O (50 mL). The organic layer was washed successively with H₂O (40 mL) and brine (40 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 0–17% AcOEt in hexane) to give the title compound (2.53 g, 90% from **28**) as a yellow syrup. ¹H NMR (CDCl₃) δ 3.85 (s, 3H), 7.17–7.24 (m, 1H), 7.31–7.63 (m, 7H). ¹³C NMR (CDCl₃) δ 56.0, 112.0, 114.3, 119.0, 125.0, 128.2, 128.4, 129.5, 131.6, 135.9, 136.8, 156.7. HRMS calcd for C₁₄H₁₂NO (M+H)⁺ 210.0913, found 210.0906.

2-Methoxybiphenyl-4-ylmethanamine (2-29). The title compound (387 mg, 95%) was obtained as a pale yellow oil from **2-28** (400 mg, 1.91 mmol) according to a procedure similar to that described for the preparation of **2-21**. ¹H NMR (CDCl₃) δ 1.20–1.80 (br, 2H), 3.83 (s, 3H), 3.92 (s, 2H), 6.94–7.02 (m, 2H), 7.23–7.45 (m, 4H), 7.48–7.55 (m, 2H). ¹³C NMR (CDCl₃) δ 46.6, 55.7, 110.2, 119.5, 127.0, 128.1, 129.4, 129.6, 131.1, 138.5, 144.3, 156.7. HRMS calcd for C₁₄H₁₅NNaO (M+Na)⁺ 236.1046, found 236.1041.

8-(2-Methoxybiphenyl-4-ylmethylamino)adenosine (2-4). The title compound (257 mg, 93%) was obtained as a yellow solid from **13** (200 mg, 0.578 mmol) and **2-29** (370 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **2-1**. mp 137–139 °C. ¹H NMR (DMSO-*d*₆) δ 3.57–3.72 (m, 2H), 3.75 (s, 3H), 3.97–4.05 (m, 1H), 4.08–4.21 (m, 1H), 4.51–4.82 (m, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.87–6.03 (m, 2H), 6.53 (br s, 2H), 6.98–7.08 (m, 1H), 7.13–7.51 (m, 7H), 7.52–7.64 (m, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.3, 55.5, 61.8, 71.0, 71.1, 85.9, 86.5, 110.7, 117.1, 119.5, 126.7, 128.0, 128.2, 129.2, 130.2, 138.1, 141.0, 148.6, 149.9, 151.3, 152.5, 156.0. HRMS calcd for C₂₄H₂₇N₆O₅ (M+H)⁺ 479.2037, found 479.2036.

8-(2-Ethoxybiphenyl-4-ylmethylamino)adenosine (2-5)

4-Cyanobiphenyl-2-ol (2-30). To a stirred solution of **2-28** (6.17 g, 29.5 mmol) in DCM (17 mL) was added dropwise a 1.0 M solution of BBr₃ in DCM (100 mL) at 30 °C, and the resulting mixture was stirred at the same temperature for 37 h. The reaction mixture was poured into crushed ice (300 g) and left at room temperature until a bilayer mixture was formed. The aqueous layer was separated and extracted with DCM (100 mL). The combined organic layers were washed successively with 1.0 M hydrochloric acid (100 mL), saturated aqueous NaHCO₃ (100 mL), and brine (100 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 15–36% AcOEt in hexane) to give the title compound (5.51 g, 96%) as a pale brown solid. ¹H NMR (DMSO-*d*₆) δ 7.26 (d, *J* = 1.5 Hz, 1H), 7.30–7.50 (m, 5H), 7.51–7.62 (m, 2H), 10.39 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 110.6, 118.8 (2C), 123.2, 127.7, 128.2, 129.1, 131.5, 133.2, 136.8, 154.8. HRMS

calcd for C₁₃H₈NO (M–H)⁻ 194.0611, found 194.0614.

2-Benzyloxybiphenyl-4-carbonitrile (2-31). To a stirred solution of 2-30 (100 mg, 0.512 mmol) in DMF (1.02 mL) was added K₂CO₃ (92.0 mg, 0.666 mmol) followed by BnBr (96.4 mg, 0.564 mmol), and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was partitioned between Et₂O (30 mL) and H₂O (10 mL). The organic layer was washed successively with H₂O (10 mL × 2) and brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give the title compound (146 mg, quant.) as a white solid. ¹H NMR (CDCl₃) δ 5.11 (s, 2H), 7.23–7.48 (m, 11H), 7.51–7.59 (m, 2H). ¹³C NMR (CDCl₃) δ 70.8, 111.9, 116.3, 119.0, 125.4, 127.0, 128.2 (2C), 128.3, 128.8, 129.6, 131.7, 136.0, 136.5, 136.8, 155.8. HRMS calcd for C₂₀H₁₅NNaO (M+Na)⁺ 308.1046, found 308.1045.

2-Benzyloxybiphenyl-4-ylmethanamine (*2-32*). The title compound (1.45 g, quant.) was obtained as a pale yellow oil from **2-31** (1.40 g, 4.91 mmol) according to a procedure similar to that described for the preparation of **2-21**. ¹H NMR (DMSO-*d*₆) δ 1.87 (br s, 2H), 3.73 (s, 2H), 5.12 (s, 2H), 6.97–7.05 (m, 1H), 7.19–7.44 (m, 10H), 7.48–7.56 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 45.7, 69.6, 112.0, 119.7, 126.6, 127.2, 127.6, 127.9, 128.1, 128.3, 129.3, 130.2, 137.2, 138.3, 145.5, 155.1. HRMS calcd for C₂₀H₂₀NO (M+H)⁺ 290.1539, found 290.1536.

8-(2-Benzyloxybiphenyl-4-ylmethylamino)-2',3',5'-tris-O-(tert-butyldimethylsilyl)adenosine (2-33). A mixture of 8-bromo-2',3',5'-tris-*O-(tert-*butyldimethylsilyl)adenosine **19**⁴⁷ (400 mg, 0.581 mmol), **2-32** (504 mg, 1.74 mmol), and *i*-Pr₂NEt (338 mg, 2.61 mmol) in EtOH (5.81 mL) was heated in a screw tube at 120 °C for 102 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (45 mL) and saturated aqueous NaHCO₃ (15 mL). The organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 46–67% AcOEt in hexane) to give the title compound (509 mg, 98%) as a slightly yellow foam. ¹H NMR (CDCl₃) δ –0.32 (s, 3H), –0.06 (s, 3H), –0.01 (s, 3H), 0.01 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.82 (s, 9H), 0.94 (s, 9H), 3.73 (dd, *J* = 2.5, 11.7 Hz, 1H), 3.81 (dd, *J* = 2.6, 11.7 Hz, 1H), 4.06–4.12 (m, 1H), 4.27 (dd, *J* = 2.3, 4.8 Hz, 1H), 4.48 (dd, *J* = 3.6, 15.9 Hz, 1H), 4.83 (dd, *J* = 4.8, 7.0 Hz, 1H), 4.95–5.20 (m, 5H), 6.00 (dd, *J* = 3.6, 8.4 Hz, 1H), 6.09 (d, *J* = 7.0 Hz, 1H), 6.97–7.10 (m, 2H), 7.16–7.45 (m, 9H), 7.52–7.62 (m, 2H), 8.18 (s, 1H). HRMS calcd for C₄₈H₇₃N₆O₅Si₃ (M+H)⁺ 897.4945, found 897.4936.

2',3',5'-Tris-O-(tert-butyldimethylsilyl)-8-(2-hydroxybiphenyl-4-ylmethylamino)adenosine (2-34). A mixture of 2-33 (506 mg, 0.564 mmol) and 10% Pd–C (56.5 wt% H₂O, 349 mg) in AcOEt (11.3 mL) was stirred at room temperature for 24 h under a hydrogen atmosphere. The reaction mixture was filtered through a pad of Hyflo Super-Cel and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 54–75% AcOEt in hexane) to give the title compound (435 mg, 96%) as a yellow foam. ¹H NMR (CDCl₃) δ –0.47 (s, 3H), –0.15 (s, 3H), –0.04 (s, 3H), –0.02 (s, 3H), 0.10 (s, 3H), 0.13 (s, 3H), 0.68 (s, 9H), 0.76 (s, 9H), 0.96 (s, 9H), 3.57–3.74 (m, 2H), 3.93–4.01 (m, 1H), 4.08 (dd, *J* = 1.0, 5.0 Hz, 1H), 4.30 (dd, *J* = 3.0, 16.9 Hz, 1H), 4.45 (dd, *J* = 5.0, 8.0 Hz, 1H), 5.05 (dd, *J* = 9.5, 16.9 Hz, 1H), 5.22 (br s, 2H), 5.97 (d, J = 8.0 Hz, 1H), 6.14 (dd, J = 3.0, 9.5 Hz, 1H), 6.60–6.75 (m, 2H), 7.02 (d, J = 7.8 Hz, 1H), 7.23–7.51 (m, 5H), 8.15 (s, 1H), 9.50–10.90 (br, 1H). HRMS calcd for C₄₁H₆₇N₆O₅Si₃ (M+H)⁺ 807.4475, found 807.4472.

2',3',5'-Tris-O-(tert-butyldimethylsilyl)-8-(2-ethoxybiphenyl-4-ylmethylamino)adenosine (2-35). To a solution of 2-34 (400 mg, 0.496 mmol) in DMF (3.30 mL) was added K₂CO₃ (137 mg, 0.991 mmol) followed by iodoethane (116 mg, 0.743 mmol), and the resulting mixture was heated at 40 °C with stirring for 27 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (45 mL) and H₂O (15 mL). The organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 35–56% AcOEt in hexane) to give the title compound (354 mg, 86%) as a pale yellow foam. ¹H NMR (CDCl₃) δ –0.31 (s, 3H), -0.05 (s, 3H), 0.00 (s, 3H), 0.02 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.83 (s, 9H), 0.94 (s, 9H), 1.32 (t, *J* = 7.0 Hz, 3H), 3.76 (dd, *J* = 2.5, 11.5 Hz, 1H), 3.87 (dd, *J* = 2.8, 11.5 Hz, 1H), 3.99 (q, *J* = 7.0 Hz, 2H), 4.07–4.13 (m, 1H), 4.29 (dd, *J* = 2.3, 4.8 Hz, 1H), 4.52 (dd, *J* = 3.8, 15.6 Hz, 1H), 4.85 (dd, *J* = 4.8, 7.0 Hz, 1H), 4.98 (dd, *J* = 8.2, 15.6 Hz, 1H), 5.18 (br s, 2H), 5.99 (dd, *J* = 3.8, 8.2 Hz, 1H), 6.07 (d, *J* = 7.0 Hz, 1H), 6.95–7.06 (m, 2H), 7.24–7.44 (m, 4H), 7.49–7.58 (m, 2H), 8.16 (s, 1H). HRMS calcd for C₄₃H₇₁N₆O₅Si₃ (M+H)⁺ 835.4788, found 835.4779.

8-(2-Ethoxybiphenyl-4-ylmethylamino)adenosine (2-5). To a solution of 2-35 (350 mg, 0.419 mmol) in MeOH (8.38 mL) was added NH₄F (931 mg, 25.1 mmol), and the resulting mixture was heated under reflux with stirring for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with DCM (34.0 mL), stirred for 1 h, and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 10–17% MeOH in DCM) to give the title compound (146 mg, 71%) as a pale yellow solid. mp 128–130 °C. ¹H NMR (DMSO-*d*₆) δ 1.24 (t, *J* = 6.9 Hz, 3H), 3.56–3.73 (m, 2H), 3.94–4.21 (m, 4H), 4.61 (d, *J* = 6.0 Hz, 2H), 4.70–4.81 (m, 1H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.90–6.04 (m, 2H), 6.54 (br s, 2H), 6.98–7.06 (m, 1H), 7.11–7.55 (m, 7H), 7.58 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 14.6, 45.2, 61.8, 63.5, 71.0, 71.2, 85.9, 86.5, 111.8, 117.1, 119.5, 126.7, 128.0, 128.3, 129.2, 130.3, 138.2, 140.9, 148.6, 149.9, 151.3, 152.5, 155.3. HRMS calcd for C₂₅H₂₉N₆O₅ (M+H)⁺ 493.2194, found 493.2199.

8-(3-Methoxybiphenyl-4-ylmethylamino)adenosine (2-6)

2-Benzyloxy-4-bromobenzonitrile (2-39).¹⁰³ To a stirred mixture of 4-bromo-2-hydroxybenzonitrile 29 (3.00 g, 15.2 mmol) and K₂CO₃ (2.72 g, 19.7 mmol) in DMF (30.3 mL) was added BnBr (2.85 g, 16.7 mmol), and the resulting mixture was stirred at room temperature for 27 h. The reaction mixture was partitioned between AcOEt (100 mL) and H₂O (100 mL). The organic layer was washed successively with H₂O (40 mL) and brine (40 mL), dried (Na₂SO₄), and concentrated under reduced pressure to give the title compound (4.29 g) as a pale brown solid, which was used in the next step without further purification. ¹H NMR (CDCl₃) δ 5.20 (s, 2H), 7.15–7.22 (m, 2H), 7.32–

7.53 (m, 6H). HRMS calcd for $C_{14}H_{14}BrN_{2}O$ (M+NH₄)⁺ 305.0284, found 305.0283.

3-Benzyloxybiphenyl-4-carbonitrile (2-40). To a mixture of 2-39 (4.29 g, as 14.9 mmol), PhB(OH)₂ (2.03 g, 16.7 mmol), Na₂CO₃ (3.21 g, 30.3 mmol), and H₂O (7.5 mL) in DMF (30 mL) was added Pd(PPh₃)₄ (876 mg, 0.758 mmol), and the resulting mixture was heated at 80 °C with stirring for 24 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (120 mL) and H₂O (60 mL). The organic layer was washed successively with H₂O (50 mL) and brine (50 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was dissolved in DCM and purified by flash column chromatography on silica gel (gradient: 0–13% AcOEt in hexane) to give the title compound (4.06 g, 94% from **29**) as a white solid. ¹H NMR (CDCl₃) δ 5.29 (s, 2H), 7.16–7.25 (m, 2H), 7.31–7.59 (m, 10H), 7.64 (d, *J* = 8.0 Hz, 1H). ¹³C NMR (CDCl₃) δ 70.8, 101.2, 111.8, 116.7, 120.2, 127.2, 127.4, 128.4, 128.9 (2C), 129.2, 134.2, 135.8, 139.6, 147.7, 160.7. HRMS calcd for C₂₀H₁₉N₂O (M+NH₄)⁺ 303.1492, found 303.1489.

3-Benzyloxybiphenyl-4-ylmethanamine (2-41). The title compound (3.88 g, 96%) was obtained as a pale yellow waxy solid from 2-40 (4.00 g, 14.0 mmol) according to a procedure similar to that described for the preparation of 2-21. ¹H NMR (DMSO-*d*₆) δ 1.69 (br s, 2H), 3.76 (s, 2H), 5.25 (s, 2H), 7.21 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.26–7.57 (m, 10H), 7.58–7.74 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 40.7, 69.2, 110.2, 118.7, 126.7, 127.3, 127.4, 127.7, 128.4, 128.5, 128.8, 131.6, 137.5, 139.6, 140.3, 156.1. HRMS calcd for C₂₀H₁₉NNaO (M+Na)⁺ 312.1359, found 312.1354. *8-(3-Benzyloxybiphenyl-4-ylmethylamino)-2',3',5'-tris-O-(tert-butyldimethylsilyl)adenosine* (2-42). The title compound (512 mg, 98%) was obtained as a yellow foam from 19⁴⁷ (400 mg, 0.581 mmol) and 2-41 (504 mg, 1.74 mmol) according to a procedure similar to that described for the preparation of 2-33. ¹H NMR (CDCl₃) δ -0.30 (s, 3H), -0.08 (s, 3H), -0.05 (s, 3H), -0.03 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.76 (s, 9H), 0.94 (s, 9H), 3.71 (dd, *J* = 2.5, 11.5 Hz, 1H), 3.83 (dd, *J* = 2.8, 11.5 Hz, 1H), 4.05–4.13 (m, 1H), 4.33 (dd, *J* = 2.8, 4.8 Hz, 1H), 4.66 (dd, *J* = 4.1, 16.2 Hz, 1H), 4.92–5.12 (m, 4H), 5.17 (d, *J* = 11.9 Hz, 1H), 5.21 (d, *J* = 11.9 Hz, 1H), 5.91 (dd, *J* = 4.1, 8.0 Hz, 1H), 6.00 (d, *J* = 6.5 Hz, 1H), 7.10–7.18 (m, 2H), 7.29–7.58 (m, 11H), 8.15 (s, 1H). HRMS calcd for C₄₈H₇₃N₆O₅Si₃ (M+H)⁺ 897.4945, found 897.4945.

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(3-hydroxybiphenyl-4-ylmethylamino)adenosine* (2-43). The title compound (428 mg, 91%) was obtained as a pale yellow foam from 2-42 (521 mg, 0.581 mmol) according to a procedure similar to that described for the preparation of 2-34. ¹H NMR (CDCl₃) δ –0.36 (s, 3H), –0.07 (s, 3H), 0.10 (s, 3H), 0.13 (s, 3H), 0.14 (s, 3H), 0.18 (s, 3H), 0.72 (s, 9H), 0.93 (s, 9H), 0.95 (s, 9H), 3.81 (dd, J = 2.5, 11.8 Hz, 1H), 3.96 (dd, J = 2.3, 11.8 Hz, 1H), 4.04–4.12 (m, 1H), 4.28 (dd, J = 2.8, 4.8 Hz, 1H), 4.42 (dd, J = 5.4, 14.9 Hz, 1H), 4.65 (dd, J = 7.3, 14.9 Hz, 1H), 4.83 (dd, J = 4.8, 6.6 Hz, 1H), 5.07 (minor) and 5.09 (major) (each br s, 2H), 5.98 (d, J = 6.6 Hz, 1H), 6.20–6.40 (m, 1H), 7.09 (dd, J = 1.8, 7.9 Hz, 1H), 7.20 (d, J = 1.8 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 7.28–7.46 (m, 3H), 7.50–7.62 (m, 2H), 8.17 (s, 1H), 11.80–12.20 (br, 1H). HRMS calcd for C₄₁H₆₇N₆O₅Si₃ (M+H)⁺ 807.4475, found 807.4469.

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(3-methoxybiphenyl-4-ylmethylamino)adenosine (2-44)*. To a solution of **2-43** (500 mg, 0.619 mmol) in DMF (4.13 mL) was added K₂CO₃ (171 mg, 1.24 mmol) followed by iodomethane (132 mg, 0.929 mmol), and the resulting mixture was stirred at room temperature for 25 h. The reaction mixture was partitioned between AcOEt (45 mL) and H₂O (15 mL). The organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 19–40% AcOEt in hexane) to give the title compound (389 mg, 77%) as a yellow foam. ¹H NMR (CDCl₃) δ –0.30 (s, 3H), -0.05 (s, 3H), -0.04 (s, 3H), 0.01 (s, 3H), 0.11 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.79 (s, 9H), 0.94 (s, 9H), 3.74 (dd, *J* = 2.9, 11.4 Hz, 1H), 3.88 (dd, *J* = 3.4, 11.4 Hz, 1H), 3.93 (s, 3H), 4.06–4.13 (m, 1H), 4.33 (dd, *J* = 2.8, 4.8 Hz, 1H), 4.59 (dd, *J* = 4.1, 15.8 Hz, 1H), 4.89 (dd, *J* = 8.1, 15.8 Hz, 1H), 4.97 (dd, *J* = 4.8, 6.4 Hz, 1H), 5.03 (br s, 2H), 5.88 (dd, *J* = 4.1, 8.1 Hz, 1H), 5.98 (d, *J* = 6.4 Hz, 1H), 7.07 (d, *J* = 1.7 Hz, 1H), 7.12 (dd, *J* = 1.7, 7.7 Hz, 1H), 7.30–7.48 (m, 4H), 7.53–7.63 (m, 2H), 8.14 (s, 1H). HRMS calcd for C₄₂H₆₉N₆O₅Si₃ (M+H)⁺ 821.4632, found 821.4635.

8-(3-Methoxybiphenyl-4-ylmethylamino)adenosine (2-6). To a solution of 2-44 (384 mg, 0.468 mmol) in MeOH (9.35 mL) was added NH₄F (1.04 g, 28.1 mmol), and the resulting mixture was heated under reflux with stirring for 26 h. The reaction mixture was allowed to cool to room temperature, diluted with H₂O (40 mL), and then stirred for 1 h. The precipitate was collected by filtration, washed with H₂O, air-dried, and then recrystallized from EtOH to give the title compound (167 mg, 75%) as a pale yellow solid. mp 236–238 °C, dec. ¹H NMR (DMSO-*d*₆) δ 3.57–3.72 (m, 2H), 3.93 (s, 3H), 3.98–4.05 (m, 1H), 4.10–4.19 (m, 1H), 4.51–4.68 (m, 2H), 4.73–4.83 (m, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.33 (d, *J* = 6.8 Hz, 1H), 5.86 (dd, *J* = 4.0, 6.0 Hz, 1H), 5.99 (d, *J* = 7.3 Hz, 1H), 6.51 (br s, 2H), 7.14–7.26 (m, 2H), 7.28–7.52 (m, 5H), 7.63–7.73 (m, 2H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 40.6, 55.4, 61.8, 70.9, 71.2, 85.9, 86.5, 108.8, 117.1, 118.5, 126.6, 126.8, 127.3, 127.4, 128.9, 140.1, 140.4, 148.6, 149.9, 151.4, 152.5, 157.0. HRMS calcd for C₂₄H₂₇N₆O₅ (M+H)⁺ 479.2037, found 479.2046.

8-(3-Ethoxybiphenyl-4-ylmethylamino)adenosine (2-7)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(3-ethoxybiphenyl-4-ylmethylamino)adenosine* (2-45). The title compound (326 mg, 90%) was obtained as a pale yellow foam from 2-43 (352 mg, 0.436 mmol) and iodoethane (102 mg, 0.654 mmol) according to a procedure similar to that described for the preparation of 2-35. ¹H NMR (CDCl₃) δ -0.28 (s, 3H), -0.07 (s, 3H), -0.04 (s, 3H), -0.02 (s, 3H), 0.11 (s, 3H), 0.15 (s, 3H), 0.76 (s, 9H), 0.77 (s, 9H), 0.94 (s, 9H), 1.47 (t, *J* = 7.0 Hz, 3H), 3.72 (dd, *J* = 2.8, 11.5 Hz, 1H), 3.86 (dd, *J* = 3.4, 11.5 Hz, 1H), 4.06-4.12 (m, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 4.35 (dd, *J* = 2.9, 4.7 Hz, 1H), 4.61 (dd, *J* = 4.0, 16.0 Hz, 1H), 4.92 (dd, *J* = 7.8, 16.0 Hz, 1H), 5.03 (dd, *J* = 4.7, 6.3 Hz, 1H), 5.06 (br s, 2H), 5.88 (dd, *J* = 4.0, 7.8 Hz, 1H), 5.95 (d, *J* = 6.3 Hz, 1H), 7.05 (d, *J* = 1.5 Hz, 1H), 7.11 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.30-7.49 (m, 4H), 7.52-7.60 (m, 2H), 8.14 (s, 1H). HRMS calcd for C₄₃H₇₁N₆O₅Si₃ (M+H)⁺ 835.4788, found 835.4779.

8-(3-Ethoxybiphenyl-4-ylmethylamino)adenosine (2-7). To a solution of **2-45** (322 mg, 0.386 mmol) in MeOH (7.71 mL) was added NH₄F (857 mg, 23.1 mmol), and the resulting mixture was heated under reflux with stirring for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with DCM (24 mL), stirred for 1 h, and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was triturated in DCM. The precipitate was collected by filtration, washed with DCM, air-dried, and then recrystallized from EtOH to give the title compound (120 mg, 63%) as a pale yellow solid. mp 219–221 °C. ¹H NMR (DMSO-*d*₆) δ 1.40 (t, *J* = 6.9 Hz, 3H), 3.56–3.71 (m, 2H), 3.97–4.06 (m, 1H), 4.10–4.27 (m, 3H), 4.52–4.69 (m, 2H), 4.73–4.84 (m, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.34 (d, *J* = 6.8 Hz, 1H), 5.85 (dd, *J* = 4.0, 6.0 Hz, 1H), 6.00 (d, *J* = 7.5 Hz, 1H), 6.50 (br s, 2H), 7.12–7.52 (m, 7H), 7.61–7.74 (m, 2H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 14.8, 40.6, 61.8, 63.3, 70.9, 71.2, 85.9, 86.5, 109.5, 117.1, 118.4, 126.7, 126.8, 127.2, 127.3, 128.9, 140.0, 140.4, 148.6, 149.9, 151.5, 152.5, 156.3. HRMS calcd for C₂₅H₂₉N₆O₅ (M+H)⁺ 493.2194, found 493.2191.

8-(2-Hydroxybiphenyl-4-ylmethylamino)adenosine (2-8)

To a solution of **2-34** (367 mg, 0.455 mmol) in MeOH (9.09 mL) was added NH₄F (1.01 g, 27.3 mmol), and the resulting mixture was heated under reflux with stirring for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with H₂O (9.09 mL), and then stirred for 1 h. The precipitate was collected by filtration, washed with MeOH/H₂O (1/1), air-dried, and then recrystallized from EtOH to give the title compound (75.0 mg, 36%) as an off-white solid. mp 240–242 °C. ¹H NMR (DMSO-*d*₆) δ 3.56–3.75 (m, 2H), 3.96–4.08 (m, 1H), 4.10–4.19 (m, 1H), 4.46–4.63 (m, 2H), 4.72–4.82 (m, 1H), 5.17 (d, *J* = 4.3 Hz, 1H), 5.24 (d, *J* = 6.8 Hz, 1H), 5.85–5.93 (m, 1H), 5.95 (d, *J* = 7.3 Hz, 1H), 6.51 (br s, 2H), 6.84–6.91 (m, 1H), 6.92–6.99 (m, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.23–7.31 (m, 1H), 7.33–7.43 (m, 2H), 7.47–7.62 (m, 3H), 7.90 (s, 1H), 9.46 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 61.8, 71.1, 85.8, 86.6, 114.7, 117.1, 118.2, 126.2, 126.4, 127.9, 129.0, 130.1, 138.6, 140.5, 148.5, 149.8, 151.5, 152.5, 154.2. HRMS calcd for C₂₃H₂₅N₆O₅ (M+H)⁺ 465.1881, found 465.1873.

8-(2-Propoxybiphenyl-4-ylmethylamino)adenosine (2-9)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(2-propoxybiphenyl-4-ylmethylamino)adenosine* (2-36). The title compound (418 mg, 93%) was obtained as a yellow foam from 2-34 (428 mg, 0.530 mmol) and 1-iodopropane (135 mg, 0.795 mmol) according to a procedure similar to that described for the preparation of 2-35. ¹H NMR (CDCl₃) δ -0.31 (s, 3H), -0.05 (s, 3H), -0.01 (s, 3H), 0.02 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.82 (s, 9H), 0.89–0.99 (m, 12H), 1.56–1.85 (m, 2H), 3.75 (dd, J = 2.8, 11.5 Hz, 1H), 3.81–3.95 (m, 3H), 4.06–4.15 (m, 1H), 4.30 (dd, J = 2.5, 4.8 Hz, 1H), 4.52 (dd, J = 3.8, 15.5 Hz, 1H), 4.88 (dd, J = 4.8, 6.7 Hz, 1H), 4.98 (dd, J = 8.1, 15.5 Hz, 1H), 5.02–5.14 (m, 2H), 5.92 (dd, J = 3.8, 1Hz, 1H), 6.05 (d, J = 6.7 Hz, 1H), 6.95–7.05 (m, 2H), 7.24–7.43 (m, 4H), 7.49–7.59 (m, 2H), 8.17 (s, 1H). HRMS calcd for C₄₄H₇₃N₆O₅Si₃ (M+H)⁺ 849.4945, found 849.4938.

8-(2-Propoxybiphenyl-4-ylmethylamino)adenosine (2-9). The title compound was obtained (236 mg, 96%) as a pale yellow foam from **2-36** (414 mg, 0.487 mmol) according to a procedure similar to that described for the preparation of **2-5**. ¹H NMR (DMSO-*d*₆) δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.56–1.71 (m, 2H), 3.57–3.72 (m, 2H), 3.92 (t, *J* = 6.4 Hz, 2H), 3.97–4.05 (m, 1H), 4.10–4.18 (m, 1H), 4.61 (d, *J* = 6.0 Hz, 2H), 4.70–4.81 (m, 1H), 5.19 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.89–6.01 (m, 2H), 6.54 (br s, 2H), 6.98–7.07 (m, 1H), 7.11–7.18 (m, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.25–7.33 (m, 1H), 7.33–7.64 (m, 5H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 10.6, 22.1, 45.2, 61.8, 69.3, 71.0, 71.1, 85.9, 86.5, 111.6, 117.1, 119.4, 126.7, 127.9, 128.3, 129.2, 130.2, 138.2, 140.9, 148.6, 149.9, 151.3, 152.5, 155.4. HRMS calcd for C₂₆H₃₁N₆O₅ (M+H)⁺ 507.2350, found 507.2350.

8-(2-Isopropoxybiphenyl-4-ylmethylamino)adenosine (2-10)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(2-isopropoxybiphenyl-4-ylmethylamino)adenosine (2-37).* To a solution of **2-34** (409 mg, 0.507 mmol) in DMF (3.38 mL) was added K₂CO₃ (140 mg, 1.01 mmol) followed by 2-iodopropane (129 mg, 0.760 mmol), and the resulting mixture was heated at 50 °C with stirring for 27 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (50 mL) and H₂O (20 mL). The organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 38–59% AcOEt in hexane) to give the title compound (313 mg, 73%) as a brownish yellow foam. ¹H NMR (CDCl₃) δ –0.31 (s, 3H), –0.05 (s, 3H), 0.00 (s, 3H), 0.03 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.83 (s, 9H), 0.94 (s, 9H), 1.17–1.26 (m, 6H), 3.75 (dd, *J* = 2.6, 11.6 Hz, 1H), 3.87 (dd, *J* = 2.8, 11.6 Hz, 1H), 4.06–4.12 (m, 1H), 4.30 (dd, *J* = 2.5, 4.8 Hz, 1H), 4.33–4.45 (m, 1H), 4.50 (dd, *J* = 3.8, 15.6 Hz, 1H), 4.88 (dd, *J* = 4.8, 6.8 Hz, 1H), 4.97 (dd, *J* = 8.1, 15.6 Hz, 1H), 5.08 (br s, 2H), 5.94 (dd, *J* = 3.8, 8.1 Hz, 1H), 6.05 (d, *J* = 6.8 Hz, 1H), 6.94–7.05 (m, 2H), 7.23–7.43 (m, 4H), 7.48–7.57 (m, 2H), 8.16 (s, 1H). HRMS calcd for C₄₄H₇₃N₆O₅Si₃ (M+H)⁺ 849.4945, found 849.4940.

8-(2-Isopropoxybiphenyl-4-ylmethylamino)adenosine (2-10). The title compound (180 mg, 97%) was obtained as an ivory-colored foam from 2-37 (310 mg, 0.365 mmol) according to a procedure similar to that described for the preparation of 2-5. ¹H NMR (DMSO-*d*₆) δ 1.11–1.24 (m, 6H), 3.55–3.74 (m, 2H), 3.95–4.05 (m, 1H), 4.09–4.18 (m, 1H), 4.48–4.81 (m, 4H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.88–6.03 (m, 2H), 6.53 (br s, 2H), 6.96–7.05 (m, 1H), 7.10–7.18 (m, 1H), 7.19–7.52 (m, 6H), 7.59 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 21.8 (2C), 45.2, 61.8, 69.8, 71.0, 71.1, 85.9, 86.5, 113.5, 117.1, 119.6, 126.6, 127.9, 129.1, 129.2, 130.5, 138.4, 140.8, 148.6, 149.9, 151.3, 152.5, 154.1. HRMS calcd for C₂₆H₃₁N₆O₅ (M+H)⁺ 507.2350, found 507.2345.

8-[2-(2-Methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (2-11)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-[2-(2-methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine* (2-38). To a solution of 2-34 (378 mg, 0.468 mmol) in DMF (3.12 mL) was added K₂CO₃ (97.1 mg, 0.703 mmol) followed

by methyl bromoacetate (93.1 mg, 0.609 mmol), and the resulting mixture was stirred at 35 °C for 24 h. The reaction mixture was partitioned between AcOEt (45 mL) and H₂O (15 mL). The organic layer was washed successively with H₂O (10 mL) and brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 55–76% AcOEt in hexane) to give the title compound (339 mg, 82%) as a tan foam. ¹H NMR (CDCl₃) δ –0.33 (s, 3H), –0.06 (s, 3H), 0.01 (s, 3H), 0.04 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.84 (s, 9H), 0.94 (s, 9H), 3.69 (s, 3H), 3.76 (dd, *J* = 2.4, 11.7 Hz, 1H), 3.88 (dd, *J* = 2.4, 11.7 Hz, 1H), 4.06–4.13 (m, 1H), 4.27 (dd, *J* = 2.3, 4.8 Hz, 1H), 4.48 (dd, *J* = 3.7, 15.6 Hz, 1H), 4.56 (s, 2H), 4.83 (dd, *J* = 4.8, 7.0 Hz, 1H), 4.99 (dd, *J* = 8.3, 15.6 Hz, 1H), 5.04–5.20 (m, 2H), 6.03 (dd, *J* = 3.7, 8.3 Hz, 1H), 6.08 (d, *J* = 7.0 Hz, 1H), 6.91–6.97 (m, 1H), 7.01–7.08 (m, 1H), 7.23–7.49 (m, 4H), 7.54–7.66 (m, 2H), 8.17 (s, 1H). HRMS calcd for C₄₄H₇₁N₆O₇Si₃ (M+H)⁺ 879.4687, found 879.4677.

8-[2-(2-Methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (2-11). To a solution of **2-38** (335 mg, 0.381 mmol) in MeOH (7.62 mL) was added NH₄F (847 mg, 22.9 mmol), and the resulting mixture was heated under reflux with stirring for 27 h. The reaction mixture was allowed to cool to room temperature, diluted with DCM (24 mL), stirred for 1 h, and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 9–16% MeOH in DCM) to give the title compound (184 mg, 90%) as a pale brown solid. mp 121–123 °C. ¹H NMR (DMSO-*d*₆) δ 3.56–3.79 (m, 5H), 3.96–4.07 (m, 1H), 4.10–4.23 (m, 1H), 4.59 (d, *J* = 6.0 Hz, 2H), 4.69–4.78 (m, 1H), 4.80 (s, 2H), 5.19 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 7.0 Hz, 1H), 5.88–6.07 (m, 2H), 6.55 (br s, 2H), 7.00–7.16 (m, 2H), 7.22–7.71 (m, 7H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.1, 51.8, 61.8, 64.5, 71.0, 71.1, 85.8, 86.5, 111.2, 117.1, 120.1, 126.8, 128.0, 128.4, 129.3, 130.5, 137.9, 140.9, 148.6, 149.8, 151.3, 152.5, 154.3, 169.3. HRMS calcd for C₂₆H₂₉N₆O₇ (M+H)⁺ 537.2092, found 537.2092.

8-[2-(2-Amino-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (2-12)

To **2-11** (195 mg, 0.363 mmol) was added a 2.0 M solution of NH₃ in MeOH (14.5 mL), and the resulting mixture was stirred at room temperature for 72 h. The reaction mixture was diluted with MeOH (15 mL) and CHCl₃ (20 mL). The resulting suspension was heated under reflux until a clear solution was formed. The solution was allowed to cool to room temperature while stirring. The precipitate was collected by filtration, washed with MeOH/CHCl₃ (6/4), air-dried, and dried at 60 °C under reduced pressure to give the title compound (145 mg, 77%) as a white solid. mp 166–169 °C. ¹H NMR (DMSO-*d*₆) δ 3.56–3.72 (m, 2H), 3.97–4.03 (m, 1H), 4.10–4.18 (m, 1H), 4.43 (s, 2H), 4.52–4.64 (m, 2H), 4.70–4.80 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.91 (dd, *J* = 4.0, 6.0 Hz, 1H), 5.95 (d, *J* = 7.5 Hz, 1H), 6.53 (br s, 2H), 7.01–7.13 (m, 3H), 7.23–7.45 (m, 5H), 7.51–7.62 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.2, 61.8, 67.4, 71.0, 71.1, 85.9, 86.5, 112.2, 117.1, 120.3, 126.9, 128.1, 128.7, 129.3, 130.4, 138.0, 140.9, 148.6, 149.9, 151.3, 152.5, 154.6, 170.1. HRMS calcd for C₂₅H₂₈N₇O₆ (M+H)⁺ 522.2096, found 522.2092.

8-[2-(2-Hydroxyethoxy)biphenyl-4-ylmethylamino]adenosine (2-13)

To a stirred suspension of **2-11** (194 mg, 0.362 mmol) in EtOH (3.62 mL) was added NaBH₄ (68.4 mg, 1.81 mmol) in small portions, and the resulting mixture was stirred at room temperature for 25 h. The reaction mixture was quenched carefully by addition of AcOH (434 mg, 7.23 mmol) and then concentrated under reduced pressure. To the residue was added DCM/MeOH (6/1), and the insoluble material was filtered out. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on NH silica gel (gradient: 7–15% MeOH in DCM) to give the title compound (165 mg, 90%) as a pale yellow solid. mp 143–146 °C. ¹H NMR (DMSO-*d*₆) δ 3.52–3.79 (m, 4H), 3.92–4.22 (m, 4H), 4.61 (d, *J* = 6.3 Hz, 2H), 4.70–4.82 (m, 2H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.90–6.04 (m, 2H), 6.54 (br s, 2H), 6.98–7.07 (m, 1H), 7.13–7.20 (m, 1H), 7.21–7.43 (m, 4H), 7.51–7.68 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.2, 59.5, 61.8, 69.9, 71.0, 71.1, 85.9, 86.5, 111.9, 117.1, 119.6, 126.6, 128.0, 128.3, 129.3, 130.3, 138.1, 140.9, 148.6, 149.9, 151.3, 152.5, 155.4. HRMS calcd for C₂₅H₂₉N₆O₆ (M+H)⁺ 509.2143, found 509.2142.

8-[2-(3-Hydroxypropoxy)biphenyl-4-ylmethylamino]adenosine (2-14)

2-(3-Benzyloxypropoxy)biphenyl-4-carbonitrile (2-46). The title compound (881 mg, quant.) was obtained as a slightly yellow oil from 2-30 (500 mg, 2.56 mmol) and benzyl 3-bromopropyl ether (704 mg, 3.07 mmol) according to a procedure similar to that described for the preparation of 2-47. ¹H NMR (CDCl₃) δ 1.98–2.08 (m, 2H), 3.54 (t, J = 6.2 Hz, 2H), 4.10 (t, J = 6.2 Hz, 2H), 4.46 (s, 2H), 7.18–7.57 (m, 13H). ¹³C NMR (CDCl₃) δ 29.5, 65.8, 66.4, 73.2, 111.9, 115.5, 119.1, 125.0, 127.8 (2C), 128.0, 128.2, 128.5, 129.5, 131.5, 136.0, 136.9, 138.4, 156.1. HRMS calcd for C₂₃H₂₁NNaO₂ (M+Na)⁺ 366.1465, found 366.1463.

2-(3-Benzyloxypropoxy)biphenyl-4-ylmethanamine (2-49). The title compound (867 mg, 97%) was obtained as a pale yellow oil from 2-46 (885 mg, 2.58 mmol) according to a procedure similar to that described for the preparation of 2-21. ¹H NMR (DMSO-*d*₆) δ 1.65–2.10 (m, 4H), 3.50 (t, *J* = 6.4 Hz, 2H), 3.72 (s, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 4.43 (s, 2H), 6.92–7.00 (m, 1H), 7.05–7.13 (m, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.22–7.47 (m, 10H). ¹³C NMR (DMSO-*d*₆) δ 29.1, 45.7, 64.8, 66.3, 71.9, 111.5, 119.4, 126.5, 127.4 (2C), 127.8, 127.9, 128.2, 129.2, 130.0, 138.3, 138.5, 145.5, 155.3. HRMS calcd for C₂₃H₂₆NO₂ (M+H)⁺ 348.1958, found 348.1959.

8-[2-(3-Benzyloxypropoxy)biphenyl-4-ylmethylamino]adenosine (2-52). The title compound (304 mg, 86%) was obtained as a slightly yellow foam from **13** (200 mg, 0.578 mmol) and **2-49** (602 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **2-53**. ¹H NMR (DMSO-*d*₆) δ 1.83–1.97 (m, 2H), 3.48 (t, J = 6.3 Hz, 2H), 3.55–3.73 (m, 2H), 3.97–4.20 (m, 4H), 4.41 (s, 2H), 4.61 (d, J = 6.0 Hz, 2H), 4.71–4.81 (m, 1H), 5.19 (d, J = 4.0 Hz, 1H), 5.31 (d, J = 6.8 Hz, 1H), 5.91–6.02 (m, 2H), 6.54 (br s, 2H), 6.99–7.06 (m, 1H), 7.12–7.51 (m, 12H), 7.59 (t, J = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 29.1, 45.2, 61.8, 64.8, 66.3, 71.0, 71.1, 71.9, 85.9, 86.5, 111.7, 117.1, 119.5, 126.7, 127.4, 127.5, 127.9, 128.3 (2C), 129.2, 130.2, 138.1, 138.5, 141.0, 148.6,

149.8, 151.3, 152.5, 155.3. HRMS calcd for C₃₃H₃₇N₆O₆ (M+H)⁺ 613.2769, found 613.2770.

8-[2-(3-Hydroxypropoxy)biphenyl-4-ylmethylamino]adenosine (2-14). The title compound (214 mg, 90%) was obtained as an off-white foam from **2-52** (278 mg, 0.454 mmol) according to a procedure similar to that described for the preparation of **2-15**. ¹H NMR (DMSO-*d*₆) δ 1.71–1.88 (m, 2H), 3.42–3.55 (m, 2H), 3.57–3.73 (m, 2H), 3.96–4.18 (m, 4H), 4.45–4.52 (m, 1H), 4.61 (d, *J* = 6.1 Hz, 2H), 4.70–4.81 (m, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.88–6.01 (m, 2H), 6.52 (br s, 2H), 6.97–7.07 (m, 1H), 7.12–7.53 (m, 7H), 7.58 (t, *J* = 6.1 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 32.1, 45.3, 57.4, 61.8, 64.8, 71.0, 71.1, 85.9, 86.5, 111.6, 117.1, 119.4, 126.7, 127.9, 128.2, 129.2, 130.2, 138.2, 140.9, 148.6, 149.8, 151.3, 152.5, 155.4. HRMS calcd for C₂₆H₃₁N₆O₆ (M+H)⁺ 523.2300, found 523.2292.

8-[2-(4-Hydroxybutoxy)biphenyl-4-ylmethylamino]adenosine (2-15)

2-(4-Benzyloxybutoxy)biphenyl-4-carbonitrile (2-47). To a solution of 2-30 (200 mg, 1.02 mmol) in DMF (2.00 mL) was added K₂CO₃ (283 mg, 2.05 mmol) followed by benzyl 4-bromobutyl ether (90%, 333 mg, 1.23 mmol), and the resulting mixture was heated at 50 °C with stirring for 24 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (35 mL) and H₂O (10 mL). The organic layer was washed successively with H₂O (10 mL) and brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 0-18% AcOEt in hexane) to give the title compound (276 mg, 75%) as a slightly yellow oil. ¹H NMR (CDCl₃) δ 1.65–1.76 (m, 2H), 1.79–1.91 (m, 2H), 3.46 (t, J = 6.3 Hz, 2H), 4.00 (t, J = 6.3 Hz, 2H), 4.46 (s, 2H), 7.14-7.19 (m, 1H), 7.24-7.45 (m, 10H), 7.47-7.53(m, 2H). ¹³C NMR (CDCl₃) δ 26.0, 26.3, 68.7, 69.7, 72.9, 111.9, 115.3, 119.1, 124.9, 127.7 (2C), 128.0, 128.2, 128.5, 129.5, 131.5, 136.0, 136.9, 138.6, 156.2. HRMS calcd for $C_{24}H_{24}NO_2 (M+H)^+$ 358.1802, found 358.1805. 2-(4-Benzyloxybutoxy)biphenyl-4-ylmethanamine (2-50). To a stirred suspension of LiAlH₄ (44.6 mg, 1.18 mmol) in THF (4.70 mL) was added dropwise a solution of 2-47 (280 mg, 0.783 mmol) in THF (3.10 mL), and the resulting mixture was heated at 60 °C with stirring for 3 h. After being allowed to cool to room temperature, the reaction mixture was quenched by sequential addition of H₂O (0.045 mL), 15% aqueous NaOH (0.045 mL), and H₂O (0.135 mL). The resulting suspension was stirred at room temperature for 8.5 h and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on NH silica gel (gradient: 0–10% MeOH in AcOEt) to give the title compound (221 mg, 78%) as a pale yellow oil. ¹H NMR (DMSO- d_6) δ 1.52–2.10 (m, 6H), 3.42 (t, J = 6.3 Hz, 2H), 3.72 (s, 2H), 4.00 (t, J = 6.1 Hz, 2H), 4.41 (s, 2H), 6.93–7.00 (m, 1H), 7.04–7.13 (m, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.24–7.42 (m, 8H), 7.43– 7.52 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 25.7, 25.9, 45.6, 67.6, 69.2, 71.7, 111.5, 119.3, 126.5, 127.3, 127.4, 127.8 (2C), 128.2, 129.2, 130.0, 138.3, 138.7, 145.4, 155.4. HRMS calcd for C₂₄H₂₈NO₂ (M+H)⁺ 362.2115, found 362.2108.

8-[2-(4-Benzyloxybutoxy)biphenyl-4-ylmethylamino]adenosine (2-53). A mixture of 13 (88.5 mg, 0.256 mmol), 2-50 (277 mg, 0.767 mmol), and *i*-Pr₂NEt (132 mg, 1.02 mmol) in EtOH (2.56 mL) was heated in a screw tube at 120 °C with stirring for 96 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 2-9% MeOH in DCM) followed by flash column chromatography on silica gel (gradient: 5–12% MeOH in DCM) to give the title compound (132 mg, 82%) as a vellow foam. ¹H NMR (DMSO- d_6) δ 1.52–1.80 (m, 4H), 3.39 (t, J = 6.3 Hz, 2H), 3.54–3.73 (m, 2H), 3.91–4.07 (m, 3H), 4.09–4.21 (m, 1H), 4.39 (s, 2H), 4.61 (d, J = 6.0 Hz, 2H), 4.70– 4.81 (m, 1H), 5.18 (d, J = 4.0 Hz, 1H), 5.30 (d, J = 6.8 Hz, 1H), 5.87–6.04 (m, 2H), 6.54 (br s, 2H), 6.98–7.06 (m, 1H), 7.10–7.53 (m, 12H), 7.58 (t, J = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO- d_6) δ 25.6, 25.9, 45.2, 61.8, 67.6, 69.2, 71.0, 71.1, 71.7, 85.9, 86.5, 111.7, 117.1, 119.4, 126.7, 127.3, 127.4, 127.9, 128.2, 128.3, 129.2, 130.2, 138.2, 138.7, 140.9, 148.6, 149.9, 151.3, 152.5, 155.4. HRMS calcd for $C_{34}H_{39}N_6O_6$ (M+H)⁺ 627.2926, found 627.2929. 8-[2-(4-Hydroxybutoxy)biphenyl-4-ylmethylamino]adenosine (2-15). A mixture of 2-53 (354 mg, 0.565 mmol) and 10% Pd–C (51.7 wt% H₂O, 220 mg) in MeOH (11.3 mL) was heated at 50 °C with stirring for 50 h under a hydrogen atmosphere. The reaction mixture was allowed to cool to room temperature and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on NH silica gel (gradient: 3–15% MeOH in DCM) to give the title compound (245 mg, 81%) as a pale yellow foam. ¹H NMR (DMSO-*d*₆) δ 1.42–1.55 (m, 2H), 1.59–1.75 (m, 2H), 3.29–3.44 (m, 2H), 3.56–3.74 (m, 2H), 3.90-4.08 (m, 3H), 4.08-4.20 (m, 1H), 4.42 (t, J = 5.1 Hz, 1H), 4.61 (d, J = 6.0 Hz, 2H), 4.70-4.82 (m, 1H), 4.61 (d, J = 6.0 Hz, 2H), 4.70-4.82 (m, 1H), 4.61 (d, J = 6.0 Hz, 2H), 4.70-4.82 (m, 1H), 4.61 (d, J = 6.0 Hz, 2H), 4.70-4.82 (m, 1H), 4.61 (d, J = 6.0 Hz, 2H), 4.70-4.82 (m, 1H), 4.61 (d, J = 6.0 Hz, 2H), 4.70-4.82 (m, 1H), 4.61 (d, J = 6.0 Hz, 2H), 4.70-4.82 (m, 1H), 4.61 (m, 1H), 4.61 (m, 2H), 4.61 (m, 2H), 4.70-4.82 (m, 2H), 4.82 (m, 2H), 4.70-4.82 (m, 2H), 4.70-4.821H), 5.19 (d, J = 4.0 Hz, 1H), 5.31 (d, J = 7.0 Hz, 1H), 5.90–6.03 (m, 2H), 6.55 (br s, 2H), 6.97–7.07 (m, 1H), 7.11– 7.19 (m, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.25–7.33 (m, 1H), 7.34–7.43 (m, 2H), 7.43–7.53 (m, 2H), 7.58 (t, J = 6.0Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.5, 29.0, 45.2, 60.4, 61.8, 67.8, 71.0, 71.2, 85.9, 86.5, 111.6, 117.1, 119.4, 126.7, 127.9, 128.3, 129.2, 130.3, 138.2, 140.9, 148.6, 149.9, 151.3, 152.5, 155.4. HRMS calcd for $C_{27}H_{33}N_6O_6 (M+H)^+ 537.2456$, found 537.2458.

8-[2-(5-Hydroxypentyloxy)biphenyl-4-ylmethylamino]adenosine (2-16)

2-(5-Benzyloxypentyloxy)biphenyl-4-carbonitrile (2-48). The title compound (894 mg, 94%) was obtained as a slightly yellow oil from 2-30 (500 mg, 2.56 mmol) and benzyl 5-bromopentyl ether (790 mg, 3.07 mmol) according to a procedure similar to that described for the preparation of 2-47. ¹H NMR (CDCl₃) δ 1.42–1.83 (m, 6H), 3.44 (t, J = 6.3 Hz, 2H), 3.98 (t, J = 6.4 Hz, 2H), 4.49 (s, 2H), 7.16–7.22 (m, 1H), 7.24–7.45 (m, 10H), 7.47–7.55 (m, 2H). ¹³C NMR (CDCl₃) δ 22.9, 28.8, 29.4, 68.8, 70.2, 73.0, 111.9, 115.3, 119.1, 124.9, 127.7 (2C), 128.0, 128.2, 128.5, 129.5, 131.5, 136.0, 136.9, 138.7, 156.2. HRMS calcd for C₂₅H₂₅NNaO₂ (M+Na)⁺ 394.1778, found 394.1773. *2-(5-Benzyloxypentyloxy)biphenyl-4-ylmethanamine (2-51)*. The title compound (740 mg, 84%) was obtained as a pale yellow oil from 2-48 (867 mg, 2.33 mmol) according to a procedure similar to that described for the preparation of 2-21. ¹H NMR (DMSO-*d*₆) δ 1.36–2.04 (m, 8H), 3.40 (t, J = 6.3 Hz, 2H), 3.72 (s, 2H), 3.98 (t, J = 6.3 Hz, 2H),

4.43 (s, 2H), 6.93–6.99 (m, 1H), 7.07–7.13 (m, 1H), 7.17–7.52 (m, 11H). ¹³C NMR (DMSO-*d*₆) δ 22.4, 28.5, 28.8, 45.7, 67.6, 69.6, 71.8, 111.5, 119.3, 126.5, 127.3, 127.4, 127.7, 127.8, 128.2, 129.2, 130.0, 138.3, 138.7, 145.5, 155.4. HRMS calcd for C₂₅H₃₀NO₂ (M+H)⁺ 376.2271, found 376.2275.

8-[2-(5-Benzyloxypentyloxy)biphenyl-4-ylmethylamino]adenosine (2-54). The title compound (342 mg, 84%) was obtained as a slightly yellow foam from **13** (220 mg, 0.636 mmol) and **2-51** (716 mg, 1.91 mmol) according to a procedure similar to that described for the preparation of **2-53**. ¹H NMR (DMSO-*d*₆) δ 1.30–1.75 (m, 6H), 3.37 (t, *J* = 6.3 Hz, 2H), 3.56–3.73 (m, 2H), 3.89–4.07 (m, 3H), 4.10–4.20 (m, 1H), 4.42 (s, 2H), 4.61 (d, *J* = 6.1 Hz, 2H), 4.69–4.81 (m, 1H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.90–6.06 (m, 2H), 6.54 (br s, 2H), 6.97–7.08 (m, 1H), 7.11–7.52 (m, 12H), 7.58 (t, *J* = 6.1 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 22.4, 28.4, 28.8, 45.2, 61.8, 67.7, 69.5, 71.0, 71.1, 71.8, 85.9, 86.5, 111.6, 117.1, 119.4, 126.6, 127.3, 127.4, 127.9, 128.2, 128.3, 129.2, 130.2, 138.1, 138.7, 140.9, 148.6, 149.9, 151.3, 152.5, 155.4. HRMS calcd for C₃₅H₄₁N₆O₆ (M+H)⁺ 641.3082, found 641.3077.

8-[2-(5-Hydroxypentyloxy)biphenyl-4-ylmethylamino]adenosine (2-16). The title compound (204 mg, 76%) was obtained as an off-white foam from 2-54 (314 mg, 0.490 mmol) according to a procedure similar to that described for the preparation of 2-15. ¹H NMR (DMSO- d_6) δ 1.28–1.45 (m, 4H), 1.55–1.70 (m, 2H), 3.28–3.43 (m, 2H), 3.56–3.75 (m, 2H), 3.90–4.06 (m, 3H), 4.09–4.21 (m, 1H), 4.30–4.38 (m, 1H), 4.61 (d, *J* = 6.1 Hz, 2H), 4.71–4.81 (m, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.89–6.03 (m, 2H), 6.52 (br s, 2H), 6.98–7.06 (m, 1H), 7.11–7.52 (m, 7H), 7.57 (t, *J* = 6.1 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO- d_6) δ 22.0, 28.4, 32.0, 45.2, 60.6, 61.8, 67.7, 70.9, 71.1, 85.8, 86.5, 111.6, 117.0, 119.3, 126.6, 127.8, 128.2, 129.2, 130.2, 138.1, 140.8, 148.6, 149.8, 151.2, 152.4, 155.4. HRMS calcd for C₂₈H₃₅N₆O₆ (M+H)⁺ 551.2613, found 551.2607.

2'-Deoxy-8-[2-(4-hydroxybutoxy)biphenyl-4-ylmethylamino]adenosine (2-17)

8-[2-(4-Benzyloxybutoxy)biphenyl-4-ylmethylamino]-2'-deoxyadenosine (2-55). A mixture of 8-bromo-2'deoxyadenosine **30** (120 mg, 0.364 mmol), **2-50** (394 mg, 1.09 mmol), and *i*-Pr₂NEt (188 mg, 1.45 mmol) in EtOH (3.64 mL) was heated in a screw tube at 120 °C with stirring for 12 h. The reaction mixture was allowed to cool to room temperature. The precipitate was filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 3–10% MeOH in DCM) followed by flash column chromatography on silica gel (gradient: 5–15% MeOH in DCM) to give the title compound (82.2 mg, 37%) as a yellow foam. ¹H NMR (DMSO-*d*₆) δ 1.49–1.76 (m, 4H), 1.99–2.12 (m, 1H), 2.70–2.85 (m, 1H), 3.30–3.45 (m, 2H), 3.59–3.77 (m, 2H), 3.88–4.08 (m, 3H), 4.34–4.49 (m, 3H), 4.51–4.70 (m, 2H), 5.33 (d, *J* = 3.8 Hz, 1H), 5.80–5.91 (m, 1H), 6.42 (dd, *J* = 5.8, 9.3 Hz, 1H), 6.55 (br s, 2H), 6.96–7.06 (m, 1H), 7.10–7.18 (m, 1H), 7.20–7.52 (m, 11H), 7.68 (t, *J* = 6.2 Hz, 1H), 7.91 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.6, 25.9, 37.9, 45.3, 61.8, 67.6, 69.2, 71.6, 71.7, 83.2, 87.6, 111.6, 116.9, 119.4, 126.7, 127.4 (2C), 127.9, 128.3 (2C), 129.2, 130.3, 138.2, 138.7, 141.0, 148.7, 149.5, 151.1, 152.5, 155.4. HRMS calcd for C₃₄H₃₉N₆O₅ (M+H)⁺ 611.2976, found 611.2974. 2'-Deoxy-8-[2-(4-hydroxybutoxy)biphenyl-4-ylmethylamino]adenosine (2-17). The title compound (60.4 mg, 54%) was obtained as a pale yellow amorphous solid from 2-55 (132 mg, 0.217 mmol) according to a procedure similar to that described for the preparation of 2-15. ¹H NMR (DMSO-*d*₆) δ 1.39–1.58 (m, 2H), 1.58–1.79 (m, 2H), 2.00–2.14 (m, 1H), 2.70–2.85 (m, 1H), 3.28–3.45 (m, 2H), 3.59–3.73 (m, 2H), 3.88–4.05 (m, 3H), 4.37–4.50 (m, 2H), 4.50–4.73 (m, 2H), 5.33 (d, *J* = 3.8 Hz, 1H), 5.80–5.92 (m, 1H), 6.36–6.48 (m, 1H), 6.53 (br s, 2H), 6.97–7.06 (m, 1H), 7.10–7.20 (m, 1H), 7.20–7.34, (m, 2H), 7.34–7.43 (m, 2H), 7.44–7.55 (m, 2H), 7.61–7.74 (m, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.5, 29.0, 37.9, 45.3, 60.4, 61.8, 67.8, 71.6, 83.2, 87.6, 111.6, 116.9, 119.4, 126.7, 127.9, 128.2, 129.2, 130.3, 138.2, 140.9, 148.7, 149.5, 151.1, 152.5, 155.4. HRMS calcd for C₂₇H₃₃N₆O₅ (M+H)⁺ 521.2507, found 521.2504.

9-β-D-Arabinofuranosyl-8-[2-(4-hydroxybutoxy)biphenyl-4-ylmethylamino]adenine (2-18)

9-β-D-Arabinofuranosyl-8-[2-(4-benzyloxybutoxy)biphenyl-4-ylmethylamino]adenine (2-56). A mixture of 8, 2'anhydro-8-hydroxy-9-β-D-arabinofuranosyladenine **31**³⁴ (65.9 mg, 0.249 mmol) and **2-50** (270 mg, 0.746 mmol) in PrOH (2.49 mL) was heated in a sealed tube at 150 °C with stirring for 24 h under microwave irradiation. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM) followed by flash column chromatography on silica gel (gradient: 10–17% MeOH in DCM) to give the title compound (41.0 mg, 26%) as a cream-colored solid. ¹H NMR (DMSO-*d*₆) δ 1.53–1.75 (m, 4H), 3.29–3.48 (m, 2H), 3.64–3.81 (m, 3H), 3.90–4.04 (m, 2H), 4.18–4.33 (m, 2H), 4.39 (s, 2H), 4.53 (dd, *J* = 6.5, 16.1 Hz, 1H), 4.69 (dd, *J* = 6.0, 16.1 Hz, 1H), 5.51 (d, *J* = 4.8 Hz, 1H), 5.54 (t, *J* = 4.5 Hz, 1H), 5.75 (d, *J* = 5.3 Hz, 1H), 6.28 (d, *J* = 5.3 Hz, 1H), 6.43 (br s, 2H), 7.00–7.08 (m, 1H), 7.14–7.55 (m, 13H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.6, 25.9, 45.1, 59.3, 67.7, 69.3, 71.7, 74.8, 76.9, 82.4, 84.3, 111.2, 116.7, 119.1, 126.6, 127.3, 127.4, 127.9, 128.0, 128.3, 129.2, 130.1, 138.3, 138.7, 141.2, 148.5, 150.0, 152.1, 152.5, 155.4. HRMS calcd for C₃₄H₃₉N₆O₆ (M+H)⁺ 627.2926, found 627.2922.

9-β-D-Arabinofuranosyl-8-[2-(4-hydroxybutoxy)biphenyl-4-ylmethylamino]adenine (2-18). The title compound (56.8 mg, 65%) was obtained as an off-white solid from **2-56** (102 mg, 0.162 mmol) according to a procedure similar to that described for the preparation of **2-15**. ¹H NMR (DMSO-*d*₆) δ 1.41–1.54 (m, 2H), 1.59–1.74 (m, 2H), 3.29–3.43 (m, 2H), 3.64–3.81 (m, 3H), 3.89–4.04 (m, 2H), 4.16–4.30 (m, 2H), 4.40 (t, *J* = 5.1 Hz, 1H), 4.53 (dd, *J* = 6.7, 16.1 Hz, 1H), 4.68 (dd, *J* = 5.8, 16.1 Hz, 1H), 5.46–5.60 (m, 2H), 5.74 (d, *J* = 5.5 Hz, 1H), 6.28 (d, *J* = 5.3 Hz, 1H), 6.43 (br s, 2H), 7.00–7.09 (m, 1H), 7.16–7.33 (m, 4H), 7.34–7.43 (m, 2H), 7.44–7.55 (m, 2H), 7.89 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.5, 29.0, 45.1, 59.3, 60.4, 67.8, 74.9, 76.9, 82.5, 84.3, 111.3, 116.7, 119.1, 126.6, 127.9, 128.0, 129.2, 130.1, 138.3, 141.2, 148.5, 150.0, 152.1, 152.5, 155.5. HRMS calcd for C₂₇H₃₃N₆O₆ (M+H)⁺ 537.2456, found 537.2452.

8-[2-(4-Hydroxybutoxy)biphenyl-4-ylmethylamino]inosine (2-19)

8-[2-(4-Benzyloxybutoxy)biphenyl-4-ylmethylamino]inosine (2-57). To a solution of **2-53** (311 mg, 0.496 mmol) in 75% (v/v) aqueous AcOH (4.96 mL) was added NaNO₂ (445 mg, 6.45 mmol) in small portions, and the resulting mixture was stirred at 25 °C for 24 h. The reaction mixture was concentrated under reduced pressure and the residue was triturated in MeOH. The insoluble material was filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 10–25% MeOH in DCM) to give the title compound (131 mg, 42%) as an orange-brown solid. ¹H NMR (DMSO-*d*₆) δ 1.53–1.76 (m, 4H), 3.40 (t, *J* = 6.3 Hz, 2H), 3.60–3.74 (m, 2H), 3.90–4.08 (m, 3H), 4.08–4.19 (m, 1H), 4.40 (s, 2H), 4.54 (d, *J* = 6.0 Hz, 2H), 4.61–4.71 (m, 1H), 5.19 (d, *J* = 4.0 Hz, 1H), 5.37 (d, *J* = 6.8 Hz, 1H), 5.75 (t, *J* = 4.5 Hz, 1H), 5.95 (d, *J* = 7.5 Hz, 1H), 6.95–7.04 (m, 1H), 7.05–7.13 (m, 1H), 7.17–7.42 (m, 9H), 7.43–7.62 (m, 3H), 7.82 (s, 1H), 12.10 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 25.6, 25.9, 45.1, 61.5, 67.6, 69.2, 70.7, 71.0, 71.7, 85.7, 86.6, 111.4, 119.2, 121.7, 126.6, 127.3, 127.4, 127.9, 128.2, 129.2, 130.2, 138.2, 138.7, 141.1, 142.3, 147.7, 150.5, 155.4 (2C). HRMS calcd for C₃₄H₃₈N₅O₇ (M+H)⁺ 628.2766, found 628.2761.

8-[2-(4-Hydroxybutoxy)biphenyl-4-ylmethylamino]inosine (2-19). The title compound (75.2 mg, 79%) was obtained as a pale yellow amorphous solid from 2-57 (111 mg, 0.177 mmol) according to a procedure similar to that described for the preparation of 2-15. ¹H NMR (DMSO- d_6) δ 1.41–1.57 (m, 2H), 1.60–1.79 (m, 2H), 3.29–3.47 (m, 2H), 3.60–3.76 (m, 2H), 3.91–4.08 (m, 3H), 4.09–4.21 (m, 1H), 4.41 (t, *J* = 5.3 Hz, 1H), 4.54 (d, *J* = 6.0 Hz, 2H), 4.61–4.74 (m, 1H), 5.20 (d, *J* = 4.3 Hz, 1H), 5.38 (d, *J* = 6.8 Hz, 1H), 5.77 (t, *J* = 4.5 Hz, 1H), 5.94 (d, *J* = 7.5 Hz, 1H), 6.94–7.03 (m, 1H), 7.06–7.14 (m, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.24–7.63 (m, 6H), 7.83 (s, 1H), 12.11 (s, 1H). ¹³C NMR (DMSO- d_6) δ 25.5, 29.0, 45.1, 60.4, 61.5, 67.7, 70.7, 71.0, 85.8, 86.6, 111.4, 119.2, 121.7, 126.6, 127.9, 128.2, 129.2, 130.2, 138.2, 141.1, 142.4, 147.7, 150.5, 155.4 (2C). HRMS calcd for C₂₇H₃₂N₅O₇ (M+H)⁺ 538.2296, found 538.2287.

2-[2-(4-Hydroxybutoxy)biphenyl-4-ylmethylamino]-1-β-D-ribofuranosyl-1*H*-benzimidazole (2-20)

1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-2-chloro-1H-benzimidazole (2-58).¹⁰⁴ To a stirred suspension of 2-chloro-1H-benzimidazole **32** (7.50 g, 49.2 mmol) in MeCN (150 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (15.2 g, 74.8 mmol), and the resulting mixture was heated at 80 °C with stirring for 1 h before being allowed to cool to room temperature. TMSOTf (21.8 g, 98.3 mmol) was added dropwise and the whole was stirred at room temperature for 15 min. 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (17.2 g, 54.1 mmol) was added in four equal portions, and stirring was continued for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between AcOEt (150 mL) and saturated aqueous NaHCO₃ (100 mL). The organic layer was washed successively with saturated aqueous NaHCO₃ (60 mL), H₂O (60 mL), and brine (60 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 32–48% AcOEt in hexane) to give the title compound (17.0 g, 84%) as a white solid. ¹H NMR (CDCl₃) δ 2.05 (s, 3H), 2.17 (s, 3H), 2.22 (s, 3H), 4.35–4.52 (m, 3H), 5.51 (dd, J = 4.1, 6.7 Hz, 1H), 5.61–5.70 (m, 1H), 6.24 (d, J = 7.3 Hz, 1H), 7.23–7.37 (m, 2H), 7.58–7.65 (m, 1H), 7.68–7.75 (m, 1H). ¹³C NMR (CDCl₃) δ 20.3, 20.7, 20.9, 63.2, 69.7, 71.1, 80.3, 87.1, 111.3, 120.2, 123.7, 123.9, 133.1, 140.1, 142.2, 169.3, 169.7, 170.4. HRMS calcd for C₁₈H₁₉ClN₂NaO₇ (M+Na)⁺ 433.0773, found 433.0774.

2-Chloro-1-β-D-ribofuranosyl-1H-benzimidazole (2-59).^{104,105} To a stirred solution of **2-58** (3.00 g, 7.30 mmol) in MeOH (73.0 mL) was added *t*-BuOK (246 mg, 2.19 mmol), and the resulting mixture was stirred at room temperature for 6 h. The reaction mixture was quenched with AcOH (132 mg, 2.19 mmol) and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 10–20% MeOH in DCM) to give the title compound (1.74 g, 84%) as an off-white solid. ¹H NMR (DMSO-*d*₆) δ 3.58–3.81 (m, 2H), 3.91–4.02 (m, 1H), 4.05–4.21 (m, 1H), 4.43–4.61 (m, 1H), 5.20 (t, *J* = 5.1 Hz, 1H), 5.26 (d, *J* = 4.8 Hz, 1H), 5.48 (d, *J* = 6.5 Hz, 1H), 5.89 (d, *J* = 7.8 Hz, 1H), 7.20–7.37 (m, 2H), 7.56–7.71 (m, 1H), 7.93–8.08 (m, 1H). ¹³C NMR (DMSO-*d*₆) δ 61.4, 69.8, 71.2, 86.1, 89.0, 113.2, 118.9, 122.9, 123.2, 133.2, 140.0, 141.5. HRMS calcd for C₁₂H₁₄ClN₂O₄ (M+H)⁺ 285.0637, found 285.0628.

2-[2-(4-Benzyloxybutoxy)biphenyl-4-ylmethylamino]-1-β-D-ribofuranosyl-1H-benzimidazole (2-60). A mixture of 2-59 (175 mg, 0.615 mmol), 2-50 (667 mg, 1.84 mmol), and *i*-Pr₂NEt (477 mg, 3.69 mmol) in EtOH (6.15 mL) was heated in a screw tube at 120 °C with stirring for 98 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 2–9% MeOH in DCM) followed by flash column chromatography on silica gel (gradient: 3–11% MeOH in DCM) to give the title compound (217 mg, 58%) as a pale yellow amorphous solid. ¹H NMR (DMSO-*d*₆) δ 1.54–1.78 (m, 4H), 3.39 (t, *J* = 6.3 Hz, 2H), 3.64–3.78 (m, 2H), 3.90–4.06 (m, 3H), 4.07–4.18 (m, 1H), 4.35–4.51 (m, 3H), 4.60 (d, *J* = 6.0 Hz, 2H), 5.23 (d, *J* = 4.5 Hz, 1H), 5.31 (d, *J* = 7.5 Hz, 1H), 5.60–5.69 (m, 1H), 5.84 (d, *J* = 7.5 Hz, 1H), 6.83–7.07 (m, 3H), 7.09–7.59 (m, 15H). ¹³C NMR (DMSO-*d*₆) δ 25.6, 25.9, 45.5, 61.2, 67.6, 69.2, 70.4, 71.3, 71.7, 85.4, 87.6, 108.7, 111.4, 115.2, 118.6, 119.3, 120.7, 126.6, 127.3, 127.4, 127.9, 128.2 (2C), 129.2, 130.2, 134.1, 138.2, 138.7, 141.4, 142.5, 154.0, 155.3. HRMS calcd for C₃₆H₄₀N₃O₆ (M+H)⁺ 610.2912, found 610.2915.

2-[2-(4-Hydroxybutoxy)biphenyl-4-ylmethylamino]-1-β-D-ribofuranosyl-1H-benzimidazole (2-20). A mixture of 2-60 (192 mg, 0.315 mmol) and 10% Pd–C (56.5 wt% H₂O, 133 mg) in MeOH (6.30 mL) was heated at 50 °C with stirring for 24 h under a hydrogen atmosphere. The reaction mixture was allowed to cool to room temperature and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 8-15% MeOH in DCM) to give the title compound (144 mg, 88%) as an off-white amorphous solid. ¹H NMR (DMSO-*d*₆) δ 1.42–1.54 (m, 2H), 1.61–1.73 (m, 2H), 3.28–3.43 (m, 2H), 3.64–3.78 (m, 2H), 3.90–4.05 (m, 3H), 4.08–4.16 (m, 1H), 4.37–4.50 (m, 2H), 4.59 (d, J = 6.0 Hz, 2H), 5.23 (d, J = 4.5 Hz, 1H), 5.31 (d, J = 7.3 Hz, 1H), 5.62–5.70 (m, 1H), 5.83 (d, J = 7.5 Hz, 1H), 6.84–7.06 (m, 3H), 7.10–7.60 (m, 10H). ¹³C NMR (DMSO-*d*₆) δ 25.5, 29.0, 45.5, 60.3, 61.2, 67.7, 70.4, 71.3, 85.4, 87.6, 108.7, 111.4, 115.2, 118.6, 119.3, 120.7, 126.6, 127.9, 128.1, 129.2, 130.2, 134.1, 138.2, 141.3, 142.5, 154.0, 155.4. HRMS calcd for C₂₉H₃₄O₃N₆ (M+H)⁺ 520.2442, found 520.2441.

Purity of Tested Compounds in Chapter 2

	v			v			•	1	
compd	formula		calcd			found		$t_{\rm R}{}^a$	area
		С	Н	Ν	С	Н	Ν	(min)	(%)
2-1	$C_{22}H_{23}N_7O_4{\cdot}0.7H_2O$	57.18	5.32	21.22	57.31	5.31	21.10	15.1	98.8
2-2	$C_{22}H_{23}N_7O_4{\cdot}0.6H_2O$	57.41	5.30	21.30	57.55	5.37	20.91	12.7	98.5
2-3	$C_{22}H_{23}N_7O_4{\cdot}0.25H_2O$	58.21	5.22	21.60	58.48	5.19	21.22	9.3	96.7
2-4	$C_{24}H_{26}N_6O_5{\cdot}0.25H_2O$	59.68	5.53	17.40	59.74	5.56	17.35	26.7	99.6
2-5	$C_{25}H_{28}N_6O_5{\cdot}0.5H_2O$	59.87	5.83	16.76	59.89	5.84	16.65	31.0	97.7
2-6	$C_{24}H_{26}N_6O_5{\cdot}0.2H_2O$	59.79	5.52	17.43	59.80	5.53	17.37	31.9	98.7
2-7	$C_{25}H_{28}N_6O_5{\cdot}0.5H_2O$	59.87	5.83	16.76	59.81	5.87	16.81	34.6	98.4
2-8	$C_{23}H_{24}N_6O_5$	59.48	5.21	18.09	59.28	5.30	18.13	34.0	98.6
2-9	$C_{26}H_{30}N_6O_5{\cdot}0.2H_2O$	61.21	6.01	16.47	61.21	6.08	16.21	37.1	98.9
2-10	$C_{26}H_{30}N_6O_5{\cdot}0.25H_2O$	61.10	6.02	16.44	61.14	6.09	16.25	35.7	98.8
2-11	$C_{26}H_{28}N_6O_7{\cdot}0.3H_2O$	57.62	5.32	15.51	57.60	5.39	15.40	30.2	96.3
2-12	$C_{25}H_{27}N_7O_6{\cdot}0.8H_2O$	56.03	5.38	18.29	55.99	5.31	18.21	26.5	97.8
2-13	$C_{25}H_{28}N_6O_6{\cdot}0.4H_2O$	58.22	5.63	16.30	58.24	5.71	16.07	27.2	97.8
2-14	$C_{26}H_{30}N_6O_6{\cdot}0.7H_2O$	58.35	5.91	15.70	58.38	5.87	15.45	29.4	98.5
2-15	$C_{27}H_{32}N_6O_6{\cdot}0.3H_2O$	59.83	6.06	15.51	59.88	6.19	15.29	30.7	96.0
2-16	$C_{28}H_{34}N_6O_6{\cdot}0.5H_2O$	60.09	6.30	15.02	60.18	6.29	14.92	32.7	98.9
2-17								31.4	98.1
2-18	$C_{27}H_{32}N_6O_6{\cdot}0.7H_2O$	59.05	6.13	15.30	59.08	6.12	14.92	29.0	98.2
2-19	$C_{27}H_{31}N_5O_7{\cdot}0.7H_2O$	58.94	5.94	12.73	59.06	5.94	12.57	34.0	96.1
2-20	$C_{29}H_{33}N_3O_6{\cdot}0.25H_2O$	66.46	6.44	8.02	66.48	6.53	7.90	28.5	98.8

 Table E2. Elemental Analysis and/or HPLC–UV Analysis Data for Tested Compounds in Chapter 2

 $^{a}t_{\rm R}$ is the retention time of the compound.

Synthetic Procedures and Characterization Data for Tested Compounds in Chapter 3

8-(2'-Hydroxybiphenyl-4-ylmethylamino)adenosine (3-1)

tert-Butyl (2'-hydroxybiphenyl-4-ylmethyl)carbamate (3-28). To a mixture of *tert*-butyl (4-bromobenzyl)carbamate **34**⁶⁰ (3.00 g, 10.5 mmol), 2-hydroxyphenylboronic acid (1.59 g, 11.5 mmol), Na₂CO₃ (2.22 g, 21.0 mmol), and H₂O (9 mL) in MeCN (45 mL) was added Pd(PPh₃)₄ (606 mg, 0.524 mmol), and the resulting mixture was heated at 80 °C with stirring for 14 h. The reaction mixture was allowed to cool to room temperature and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure. The residue was partitioned between AcOEt (70 mL) and H₂O (30 mL). The organic layer was washed with brine (30 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 12–33% AcOEt in hexane) to give the title compound (2.25 g, 72%) as an apricot-colored solid. ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 4.38 (d, *J* = 5.8 Hz, 2H), 4.76–5.08 (br, 1H), 5.23 (s, 1H), 6.94–7.03 (m, 2H), 7.19–7.31 (m, 2H), 7.36–7.51 (m, 4H). ¹³C NMR (CDCl₃) δ 28.6, 44.5, 79.9, 116.0, 120.9, 128.0, 128.3, 129.2, 129.5, 130.4, 136.4, 138.6, 152.7, 156.2. HRMS calcd for C₁₈H₂₁NNaO₃ (M+Na)⁺ 322.1414, found 322.1413.

4'-(Aminomethyl)biphenyl-2-ol hydrochloride (3-31). To a stirred solution of 3-28 (1.00 g, 3.34 mmol) in 1,4dioxane (13.4 mL) was added dropwise a 4 N solution of HCl in 1,4-dioxane (13.4 mL), and the resulting mixture was stirred at room temperature for 45 h. The precipitate was collected by filtration, washed with 1,4-dioxane, and then air-dried to give the title compound (751 mg, 95%) as an off-white solid. ¹H NMR (DMSO-*d*₆) δ 4.04 (s, 2H), 6.82–7.03 (m, 2H), 7.11–7.30 (m, 2H), 7.45–7.66 (m, 4H), 8.38 (br s, 3H), 9.64 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 42.0, 116.1, 119.4, 127.1, 128.6, 128.7, 129.2, 130.2, 132.2, 138.8, 154.5. HRMS calcd for C₁₃H₁₄NO (M+H)⁺ 200.1070, found 200.1069.

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(2'-hydroxybiphenyl-4-ylmethylamino)adenosine* (**3-34**). A mixture of 8-bromo-2',3',5'-tris-*O*-(*tert*-butyldimethylsilyl)adenosine **19**⁴⁷ (400 mg, 0.581 mmol), **3-31** (411 mg, 1.74 mmol), and *i*-Pr₂NEt (375 mg, 2.90 mmol) in EtOH (5.81 mL) was heated in a screw tube at 120 °C with stirring for 83 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (45 mL) and saturated aqueous NaHCO₃ (15 mL). The organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was suspended in DCM and the precipitate was filtered out. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 68–89% AcOEt in hexane) to give the title compound (458 mg, 98%) as a pale yellow foam. ¹H NMR (CDCl₃) δ –0.31 (s, 3H), -0.06 (s, 3H), 0.02 (s, 3H), 0.03 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.83 (s, 9H), 0.94 (s, 9H), 3.79 (dd, *J* = 2.5, 11.5 Hz, 1H), 3.93 (dd, *J* = 2.8, 11.5 Hz, 1H), 4.07–4.19 (m, 1H), 4.27 (dd, *J* = 2.1, 4.9 Hz, 1H), 4.49 (dd, *J* = 3.7, 15.9 Hz, 1H), 4.86 (dd, *J* = 4.9, 7.2 Hz, 1H), 4.95 (dd, *J* = 8.4, 15.9 Hz, 1H), 5.12 (minor) and 5.14 (major) (each br s, 2H), 6.12 (d, *J* = 7.2 Hz, 1H), 6.16 (dd, *J* = 3.7, 8.4 Hz, 1H), 6.91–7.05 (m, 2H), 7.17–7.29 (m, 2H), 7.32–7.44 (m, 4H), 8.12 (s, 1H). HRMS calcd

for C₄₁H₆₇N₆O₅Si₃ (M+H)⁺ 807.4475, found 807.4468.

8-(2'-Hydroxybiphenyl-4-ylmethylamino)adenosine (3-1). To a solution of 3-34 (350 mg, 0.434 mmol) in MeOH (8.67 mL) was added NH₄F (964 mg, 26.0 mmol), and the resulting mixture was heated under reflux with stirring for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with DCM (26 mL), stirred for 75 min, and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 10–17% MeOH in DCM) to give the title compound (200 mg, 99%) as a pale yellow foam. ¹H NMR (DMSO-*d*₆) δ 3.55–3.72 (m, 2H), 3.96–4.04 (m, 1H), 4.10–4.17 (m, 1H), 4.53–4.80 (m, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.88–6.01 (m, 2H), 6.53 (br s, 2H), 6.80–6.95 (m, 2H), 7.08–7.25 (m, 2H), 7.34–7.53 (m, 4H), 7.54–7.64 (m, 1H), 7.90 (s, 1H), 9.48 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.1, 61.8, 71.0, 71.1, 85.9, 86.5, 116.0, 117.1, 119.5, 126.7, 127.7, 128.4, 129.0, 130.3, 137.0, 138.2, 148.6, 149.9, 151.4, 152.4, 154.3. HRMS calcd for C₂₃H₂₅N₆O₅ (M+H)⁺ 465.1881, found 465.1882.

8-(2'-Methoxybiphenyl-4-ylmethylamino)adenosine (3-2)

2'-Methoxybiphenyl-4-carbonitrile (3-51).¹⁰⁶ To a mixture of 4-bromobenzonitrile 16 (500 mg, 2.75 mmol), 2methoxyphenylboronic acid (438 mg, 2.88 mmol), and 2.0 M aqueous Na₂CO₃ (2.75 mL) in MeCN (13.7 mL) was added Pd(PPh₃)₄ (317 mg, 0.275 mmol), and the resulting mixture was heated at 80 °C with stirring for 24 h. The reaction mixture was allowed to cool to room temperature and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure. The residue was partitioned between AcOEt (50 mL) and H₂O/brine (1/1, 20 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 2–23% AcOEt in hexane) to give the title compound (468 mg, 81%) as a white solid. ¹H NMR (CDCl₃) δ 3.83 (s, 3H), 6.98–7.11 (m, 2H), 7.30 (dd, J = 1.8, 7.5 Hz, 1H), 7.34–7.43 (m, 1H), 7.60–7.72 (m, 4H). HRMS calcd for C₁₄H₁₂NO (M+H)⁺ 210.0913, found 210.0913. 2'-Methoxybiphenyl-4-ylmethanamine (3-55).¹⁰⁷ To a stirred ice-cold suspension of LiAlH₄ (127 mg, 3.33 mmol) in THF (13.3 mL) was added dropwise a solution of 3-51 (465 mg, 2.22 mmol) in THF (8.88 mL), and the resulting mixture was heated at 60 °C with stirring for 4 h. After being allowed to cool to room temperature, the reaction mixture was quenched by sequential addition of H₂O (0.127 mL), 15% aqueous NaOH (0.127 mL), and H₂O (0.127 mL). The resulting suspension was stirred at room temperature for 8 h and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on NH silica gel (gradient: 0–8% MeOH in AcOEt) to give the title compound (447 mg, 94%) as a pale vellow solid. ¹H NMR (DMSO- d_6) δ 1.35–2.20 (br, 2H), 3.59–3.80 (m, 5H), 6.89–7.49 (m, 8H). ¹³C NMR (DMSO-d₆) δ 45.5, 55.4, 111.7, 120.7, 126.7, 128.6, 129.0, 129.9, 130.3, 136.1, 142.9, 156.2. HRMS calcd for C₁₄H₁₆NO (M+H)⁺ 214.1226, found 214.1224.

8-(2'-Methoxybiphenyl-4-ylmethylamino)adenosine (3-2). A mixture of 8-bromoadenosine **13** (217 mg, 0.627 mmol), **3-55** (401 mg, 1.88 mmol), and *i*-Pr₂NEt (486 mg, 3.76 mmol) in EtOH (6.27 mL) was heated in a screw

tube at 120 °C with stirring for 77 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM) followed by flash column chromatography on silica gel (gradient: 10–20% MeOH in DCM) to give the title compound (288 mg, 96%) as a yellow foam. ¹H NMR (DMSO-*d*₆) δ 3.56–3.72 (m, 2H), 3.74 (s, 3H), 3.95–4.04 (m, 1H), 4.09–4.19 (m, 1H), 4.55–4.81 (m, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.88–6.01 (m, 2H), 6.54 (br s, 2H), 6.95–7.15 (m, 2H), 7.21–7.46 (m, 6H), 7.60 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.1, 55.5, 61.9, 71.0, 71.2, 85.9, 86.6, 111.7, 117.1, 120.8, 126.8, 128.8, 129.2, 129.7, 130.3, 136.6, 138.5, 148.6, 149.9, 151.4, 152.5, 156.2. HRMS calcd for C₂₄H₂₇N₆O₅ (M+H)⁺ 479.2037, found 479.2032.

8-(2'-Ethoxybiphenyl-4-ylmethylamino)adenosine (3-3)

2'-*Ethoxybiphenyl-4-carbonitrile* (**3-52**). The title compound (468 mg, 76%) was obtained as a white solid from **16** (500 mg, 2.75 mmol) and 2-ethoxyphenylboronic acid (502 mg, 3.02 mmol) according to a procedure similar to that described for the prepraration of **3-51**. ¹H NMR (CDCl₃) δ 1.35 (t, J = 7.0 Hz, 3H), 4.06 (q, J = 7.0 Hz, 2H), 6.94–7.09 (m, 2H), 7.27–7.41 (m, 2H), 7.56–7.74 (m, 4H). ¹³C NMR (CDCl₃) δ 14.8, 64.1, 110.4, 112.6, 119.4, 121.1, 128.8, 130.0, 130.4, 130.8, 131.8, 143.7, 155.9. HRMS calcd for C₁₅H₁₄NO (M+H)⁺ 224.1070, found 224.1068. *2'-Ethoxybiphenyl-4-ylmethanamine* (**3-56**). The title compound (456 mg, 98%) was obtained as a pale yellow oil from **3-52** (458 mg, 2.05 mmol) according to a procedure similar to that described for the preparation of **3-55**. ¹H NMR (DMSO-*d*₆) δ 1.26 (t, J = 6.9 Hz, 3H), 1.54–2.20 (br, 2H), 3.73 (s, 2H), 4.03 (q, J = 6.9 Hz, 2H), 6.94–7.12 (m, 2H), 7.18–7.50 (m, 6H). ¹³C NMR (DMSO-*d*₆) δ 14.6, 45.5, 63.5, 112.8, 120.7, 126.6, 128.6, 129.0, 129.9, 130.4, 136.1, 142.8, 155.4. HRMS calcd for C₁₅H₁₈NO (M+H)⁺ 228.1383, found 228.1380.

8-(2'-Ethoxybiphenyl-4-ylmethylamino)adenosine (3-3). The title compound (300 mg, 95%) was obtained as a yellow foam from **13** (221 mg, 0.639 mmol) and **3-56** (435 mg, 1.92 mmol) according to a procedure similar to that described for the preparation of **3-2**. ¹H NMR (DMSO-*d*₆) δ 1.26 (t, *J* = 6.9 Hz, 3H), 3.54–3.72 (m, 2H), 3.95–4.20 (m, 4H), 4.55–4.82 (m, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.86–6.02 (m, 2H), 6.54 (br s, 2H), 6.94–7.12 (m, 2H), 7.22–7.52 (m, 6H), 7.59 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 14.6, 45.1, 61.9, 63.5, 71.0, 71.2, 85.9, 86.6, 112.7, 117.1, 120.8, 126.7, 128.7, 129.1, 129.7, 130.5, 136.7, 138.5, 148.6, 149.9, 151.5, 152.5, 155.4. HRMS calcd for C₂₅H₂₉N₆O₅ (M+H)⁺ 493.2194, found 493.2192.

8-(2'-Propoxybiphenyl-4-ylmethylamino)adenosine (3-4)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(2'-propoxybiphenyl-4-ylmethylamino)adenosine (3-37).* To a solution of **3-34** (454 mg, 0.562 mmol) in DMF (3.75 mL) was added K₂CO₃ (156 mg, 1.13 mmol) followed by 1-iodopropane (143 mg, 0.844 mmol), and the resulting mixture was heated at 40 °C with stirring for 27 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (45 mL) and H₂O (15 mL). The

organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 39-60% AcOEt in hexane) to give the title compound (448 mg, 94%) as a pale yellow foam. ¹H NMR (CDCl₃) δ –0.30 (s, 3H), -0.05 (s, 3H), -0.02 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.76 (s, 9H), 0.81 (s, 9H), 0.90-1.01 (m, 12H), 1.64-1H), 4.30 (dd, J = 2.5, 4.8 Hz, 1H), 4.58 (dd, J = 3.6, 15.6 Hz, 1H), 4.89 (dd, J = 4.8, 6.7 Hz, 1H), 4.98 (dd, J = 8.0, 15.6 Hz, 1H), 5.04–5.20 (m, 2H), 5.93 (dd, J = 3.6, 8.0 Hz, 1H), 6.05 (d, J = 6.7 Hz, 1H), 6.93–7.05 (m, 2H), 7.25– 7.42 (m, 4H), 7.47–7.57 (m, 2H), 8.16 (s, 1H). HRMS calcd for $C_{44}H_{73}N_6O_5Si_3$ (M+H)⁺ 849.4945, found 849.4937. 8-(2'-Propoxybiphenyl-4-ylmethylamino)adenosine (3-4). To a solution of 3-37 (445 mg, 0.524 mmol) in MeOH (10.5 mL) was added NH₄F (1.16 g, 31.4 mmol), and the resulting mixture was heated under reflux with stirring for 25 h. The reaction mixture was allowed to cool to room temperature, diluted with DCM (42 mL), stirred for 2 h, and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 10–17% MeOH in DCM) to give the title compound (250 mg, 94%) as a pale yellow foam. ¹H NMR (DMSO- d_6) δ 0.92 (t, J = 7.4 Hz, 3H), 1.58–1.74 (m, 2H), 3.55–3.73 (m, 2H), 3.89–4.06 (m, 3H), 4.10–4.20 (m, 1H), 4.54–4.71 (m, 2H), 4.72–4.84 (m, 1H), 5.17 (d, J = 4.0 Hz, 1H), 5.30 (d, J = 6.8 Hz, 1H), 5.89–6.04 (m, 2H), 6.55 (br s, 2H), 6.95–7.14 (m, 2H), 7.23–7.35 (m, 2H), 7.35–7.53 (m, 4H), 7.54–7.65 (m, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 10.6, 22.1, 45.0, 61.9, 69.3, 71.0, 71.1, 85.9, 86.5, 112.6, 117.1, 120.7, 126.6, 128.7, 129.1, 129.7, 130.4, 136.7, 138.4, 148.5, 149.9, 151.5, 152.5, 155.5. HRMS calcd for $C_{26}H_{31}N_6O_5$ (M+H)⁺ 507.2350, found 507.2350.

8-(2'-Isopropoxybiphenyl-4-ylmethylamino)adenosine (3-5)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(2'-isopropoxybiphenyl-4-ylmethylamino)adenosine* (**3-38**). To a solution of **3-34** (454 mg, 0.562 mmol) in DMF (3.75 mL) was added K₂CO₃ (156 mg, 1.13 mmol) followed by 2-iodopropane (143 mg, 0.844 mmol), and the resulting mixture was heated at 50 °C with stirring for 27 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (50 mL) and H₂O (20 mL). The organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 23–58% AcOEt in hexane) to give the title compound (317 mg, 66%) as a yellow foam. ¹H NMR (CDCl₃) δ –0.30 (s, 3H), –0.05 (s, 3H), –0.02 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.81 (s, 9H), 0.94 (s, 9H), 1.24 (d, *J* = 6.0 Hz, 6H), 3.74 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.87 (dd, *J* = 2.6, 11.6 Hz, 1H), 4.06–4.13 (m, 1H), 4.30 (dd, *J* = 2.5, 4.9 Hz, 1H), 4.40–4.51 (m, 1H), 4.58 (dd, *J* = 3.8, 15.6 Hz, 1H), 4.88 (dd, *J* = 4.9, 6.9 Hz, 1H), 4.99 (dd, *J* = 8.0, 15.6 Hz, 1H), 5.07–5.16 (m, 2H), 5.95 (dd, *J* = 3.8, 8.0 Hz, 1H), 6.06 (d, *J* = 6.9 Hz, 1H), 6.94–7.05 (m, 2H), 7.23–7.40 (m, 4H), 7.48–7.56 (m, 2H), 8.16 (s, 1H). HRMS calcd for C₄₄H₇₃N₆O₅Si₃ (M+H)⁺ 849.4945, found 849.4946.

8-(2'-Isopropoxybiphenyl-4-ylmethylamino)adenosine (3-5). To a solution of **3-38** (314 mg, 0.370 mmol) in MeOH (7.39 mL) was added NH₄F (822 mg, 22.2 mmol), and the resulting mixture was heated under reflux with stirring for 27 h. The reaction mixture was allowed to cool to room temperature, diluted with DCM (30 mL), stirred for 1 h, and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residual solid was recrystallized from EtOH to give the title compound (98.4 mg, 53%) as a slightly yellow solid. mp 230–233 °C, dec. ¹H NMR (DMSO-*d*₆) δ 1.20 (d, *J* = 6.0 Hz, 6H), 3.53–3.73 (m, 2H), 3.96–4.05 (m, 1H), 4.09–4.20 (m, 1H), 4.52–4.84 (m, 4H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.32 (d, *J* = 6.8 Hz, 1H), 5.87–6.04 (m, 2H), 6.56 (br s, 2H), 6.93–7.02 (m, 1H), 7.03–7.15 (m, 1H), 7.22–7.52 (m, 6H), 7.60 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 21.8, 45.0, 61.9, 69.5, 71.0, 71.2, 85.9, 86.5, 114.3, 117.1, 120.7, 126.6, 128.6, 129.1, 130.5, 130.7, 136.9, 138.4, 148.6, 149.8, 151.5, 152.5, 154.2. HRMS calcd for C₂₆H₃₁N₆O₅ (M+H)⁺ 507.2350, found 507.2351.

8-[2'-(2-Methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (3-6)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-[2'-(2-methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine* (**3-39**). To a solution of **3-34** (100 mg, 0.124 mmol) in DMF (0.826 mL) was added K₂CO₃ (25.7 mg, 0.186 mmol) followed by methyl bromoacetate (24.6 mg, 0.161 mmol), and the resulting mixture was stirred at room temperature for 27.5 h. The reaction mixture was partitioned between AcOEt (35 mL) and H₂O (10 mL). The organic layer was washed successively with H₂O (10 mL) and brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 50–71% AcOEt in hexane) to give the title compoiund (83.6 mg, 77%) as a brownish yellow foam. ¹H NMR (CDCl₃) δ –0.29 (s, 3H), -0.04 (s, 3H), -0.01 (s, 3H), 0.01 (s, 3H), 0.15 (s, 3H), 0.76 (s, 9H), 0.82 (s, 9H), 0.94 (s, 9H), 3.69–3.81 (m, 4H), 3.89 (dd, J = 2.6, 11.7 Hz, 1H), 4.07–4.14 (m, 1H), 4.31 (dd, J = 2.8, 4.8 Hz, 1H), 4.56 (dd, J = 3.8, 15.8 Hz, 1H), 4.60 (s, 2H), 4.90 (dd, J = 4.8, 6.8 Hz, 1H), 4.97 (dd, J = 7.9, 15.8 Hz, 1H), 5.17 (br s, 2H), 5.96 (dd, J = 3.8, 7.9 Hz, 1H), 6.04 (d, J = 6.8 Hz, 1H), 6.84–6.91 (m, 1H), 7.04–7.12 (m, 1H), 7.25–7.43 (m, 4H), 7.53–7.62 (m, 2H), 8.16 (s, 1H). HRMS calcd for C₄₄H₇₁N₆O₇Si₃ (M+H)⁺ 879.4687, found 879.4682.

8-[2'-(2-Methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (**3-6**). The title compound (338 mg, 83%) was obtained as a brown foam from **3-39** (670 mg, 0.762 mmol) according to a procedure similar to that described for the preparation of **3-1**. ¹H NMR (DMSO-*d*₆) δ 3.53–3.79 (m, 5H), 3.94–4.08 (m, 1H), 4.09–4.23 (m, 1H), 4.53–4.91 (m, 5H), 5.16 (d, J = 4.0 Hz, 1H), 5.30 (d, J = 6.8 Hz, 1H), 5.93 (dd, J = 4.0, 6.3 Hz, 1H), 5.96 (d, J = 7.5 Hz, 1H), 6.53 (br s, 2H), 6.93–7.12 (m, 2H), 7.23–7.56 (m, 6H), 7.60 (t, J = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 51.9, 61.9, 64.6, 71.0, 71.2, 85.9, 86.6, 112.3, 117.1, 121.5, 126.8, 128.6, 129.2, 129.9, 130.7, 136.4, 138.6, 148.6, 149.9, 151.4, 152.5, 154.4, 169.4. HRMS calcd for C₂₆H₂₉N₆O₇ (M+H)⁺ 537.2092, found 537.2088.

8-[2'-(2-Amino-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (3-7)

To **3-6** (120 mg, 0.224 mmol) was added a 2.0 M solution of NH₃ in MeOH (8.95 mL), and the resulting mixture was stirred at room temperature for 73 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 10–25% MeOH in DCM) to give the title compound (109 mg, 93%) as a slightly yellow foam. ¹H NMR (DMSO-*d*₆) δ 3.54–3.73 (m, 2H), 3.97–4.04 (m, 1H), 4.10–4.18 (m, 1H), 4.43 (s, 2H), 4.55–4.82 (m, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.32 (d, *J* = 6.8 Hz, 1H), 5.89–6.01 (m, 2H), 6.55 (br s, 2H), 6.92–7.11 (m, 2H), 7.21 (br s, 1H), 7.25–7.46 (m, 5H), 7.49–7.67 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 61.8, 67.3, 71.0, 71.2, 85.9, 86.5, 112.9, 117.1, 121.5, 126.8, 128.7, 129.3, 130.1, 130.6, 136.5, 138.7, 148.6, 149.9, 151.4, 152.4, 154.8, 170.0. HRMS calcd for C₂₅H₂₈N₇O₆ (M+H)⁺ 522.2096, found 522.2098.

8-[2'-(2-Hydroxyethoxy)biphenyl-4-ylmethylamino]adenosine (3-8)

To a stirred solution of **3-6** (120 mg, 0.224 mmol) in EtOH (2.24 mL) was added NaBH₄ (42.3 mg, 1.12 mmol) in small portions, and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was quenched carefully by addition of AcOH (269 mg, 4.47 mmol) and then concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM) followed by flash column chromatography on silica gel (gradient: 8–18% MeOH in DCM) to give the title compound (77.5 mg, 68%) as a beige amorphous solid. ¹H NMR (DMSO-*d*₆) δ 3.55–3.75 (m, 4H), 3.94–4.20 (m, 4H), 4.55–4.84 (m, 4H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 7.0 Hz, 1H), 5.88–6.02 (m, 2H), 6.56 (br s, 2H), 6.96–7.05 (m, 1H), 7.06–7.14 (m, 1H), 7.24–7.43 (m, 4H), 7.47–7.56 (m, 2H), 7.60 (t, *J* = 6.0 Hz, 1H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.1, 59.5, 61.8, 69.9, 71.0, 71.1, 85.9, 86.5, 112.9, 117.1, 120.9, 126.7, 128.7, 129.2, 129.7, 130.5, 136.7, 138.4, 148.5, 149.9, 151.5, 152.4, 155.6. HRMS calcd for C₂₅H₂₉N₆O₆ (M+H)⁺ 509.2143, found 509.2136.

8-(3'-Hydroxybiphenyl-4-ylmethylamino)adenosine (3-9)

tert-Butyl (3'-hydroxybiphenyl-4-ylmethyl)carbamate (3-29). The title compound (2.25 g, 72%) was obtained as a pale yellow solid from **34**⁶⁰ (3.00 g, 10.5 mmol) and 3-hydroxyphenylboronic acid (1.59 g, 11.5 mmol) according to a procedure similar to that described for the preparation of **3-28**. ¹H NMR (DMSO-*d*₆) δ 1.40 (s, 9H), 4.15 (d, *J* = 6.3 Hz, 2H), 6.71–6.79 (m, 1H), 6.96–7.15 (m, 2H), 7.20–7.37 (m, 3H), 7.43 (t, *J* = 6.3 Hz, 1H), 7.50–7.62 (m, 2H), 9.51 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 28.3, 43.1, 77.8, 113.4, 114.3, 117.4, 126.5, 127.5, 129.9, 138.8, 139.4, 141.5, 155.8, 157.8. HRMS calcd for C₁₈H₂₀NO₃ (M–H)[–] 298.1449, found 298.1457.

4'-(*Aminomethyl*)*biphenyl-3-ol hydrochloride* (**3-32**). The title compound (552 mg, quant.) was obtained as a white solid from **3-29** (700 mg, 2.34 mmol) according to a procedure similar to that described for the preparation of **3-31**. ¹H NMR (DMSO-*d*₆) δ 4.06 (s, 2H), 6.76–6.83 (m, 1H), 7.01–7.12 (m, 2H), 7.22–7.30 (m, 1H), 7.49–7.59 (m, 2H),

7.61–7.70 (m, 2H), 8.28 (br s, 3H), 9.58 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 41.8, 113.6, 114.7, 117.4, 126.7, 129.6, 130.0, 133.2, 140.4, 140.9, 158.0. HRMS calcd for C₁₃H₁₄NO (M+H)⁺ 200.1070, found 200.1068.

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(3'-hydroxybiphenyl-4-ylmethylamino)adenosine (3-35).* A mixture of 19^{47} (540 mg, 0.784 mmol), 3-32 (554 mg, 2.35 mmol), and *i*-Pr₂NEt (507 mg, 3.92 mmol) in EtOH (5.60 mL) was heated in a screw tube at 120 °C with stirring for 98 h. The reaction mixture was allowed to cool to room temperature and then filtered. The filtrate was concentrated under reduced pressure. The residue was partitioned between AcOEt (60 mL) and saturated aqueous NaHCO₃ (20 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was filtered out. The filtrate was concentrated in Et₂O and the precipitate was filtered out. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 64–85% AcOEt in hexane) to give the title compound (586 mg, 93%) as a pale yellow foam. ¹H NMR (CDCl₃) δ –0.35 (s, 3H), –0.06 (s, 3H), 0.01 (s, 3H), 0.05 (s, 3H), 0.10 (s, 3H), 0.14 (s, 3H), 0.73 (s, 9H), 0.79 (s, 9H), 0.94 (s, 9H), 3.79 (dd, *J* = 2.0, 11.8 Hz, 1H), 3.92 (dd, *J* = 1.8, 11.8 Hz, 1H), 4.11–4.17 (m, 1H), 4.18–4.25 (m, 1H), 4.46 (dd, *J* = 3.8, 16.8 Hz, 1H), 4.69 (dd, *J* = 4.9, 8.0 Hz, 1H), 5.06 (dd, *J* = 9.3, 16.8 Hz, 1H), 5.23 (minor) and 5.25 (major) (each br s, 2H), 6.25 (d, *J* = 8.0 Hz, 1H), 6.47–6.65 (m, 2H), 6.77–6.84 (m, 1H), 6.88–6.95 (m, 1H), 6.98–7.13 (m, 4H), 7.15–7.24 (m, 1H), 8.19 (s, 1H), 9.50–11.10 (br, 1H). HRMS calcd for C4₁H₆₇N₆O₅Si₃ (M+H)⁺ 807.4475, found 807.4471.

8-(3'-Hydroxybiphenyl-4-ylmethylamino)adenosine (3-9). To a solution of **3-35** (536 mg, 0.664 mmol) in MeOH (13.3 mL) was added NH₄F (1.48 g, 39.8 mmol), and the resulting mixture was heated under reflux with stirring for 23 h. The reaction mixture was allowed to cool to room temperature, diluted with DCM (26.6 mL), stirred for 1 h, and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 10–17% MeOH in DCM) to give the title compound (301 mg, 98%) as a yellow solid. mp 159–164 °C. ¹H NMR (DMSO-*d*₆) δ 3.50–3.75 (m, 2H), 3.93–4.05 (m, 1H), 4.08–4.21 (m, 1H), 4.53–4.82 (m, 3H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.84–6.01 (m, 2H), 6.55 (br s, 2H), 6.71–6.79 (m, 1H), 6.96–7.10 (m, 2H), 7.19–7.28 (m, 1H), 7.38–7.48 (m, 2H), 7.49–7.68 (m, 3H), 7.90 (s, 1H), 9.51 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 61.8, 71.0, 71.1, 85.9, 86.5, 113.4, 114.3, 117.1, 117.4, 126.5, 127.7, 130.0, 138.9, 139.2, 141.5, 148.6, 149.9, 151.4, 152.5, 157.8. HRMS calcd for C₂₃H₂₅N₆O₅ (M+H)⁺ 465.1881, found 465.1877.

8-(3'-Methoxybiphenyl-4-ylmethylamino)adenosine (3-10)

*3'-Methoxybiphenyl-4-carbonitrile (3-53).*¹⁰⁸ The title compound (341 mg, 59%) was obtained as a colorless oil from **16** (500 mg, 2.75 mmol) and 3-methoxyphenylboronic acid (438 mg, 2.88 mmol) according to a procedure similar to that described for the preparation of **3-51**. ¹H NMR (CDCl₃) δ 3.88 (s, 3H), 6.93–7.01 (m, 1H), 7.08–7.20 (m, 2H), 7.36–7.44 (m, 1H), 7.64–7.76 (m, 4H). ¹³C NMR (CDCl₃) δ 55.4, 111.0, 113.1, 113.9, 118.9, 119.7, 127.8, 130.2, 132.6, 140.6, 145.5, 160.1. HRMS calcd for C₁₄H₁₂NO (M+H)⁺ 210.0913, found 210.0911.

3'-Methoxybiphenyl-4-ylmethanamine (3-57). The title compound (277 mg, 87%) was obtained as a yellow oil from **3-53** (312 mg, 1.49 mmol) according to a procedure similar to that described for the preparation of **3-55**. ¹H NMR (CDCl₃) δ 3.87 (s, 3H), 3.92 (s, 2H), 6.85–6.93 (m, 1H), 7.07–7.22 (m, 2H), 7.30–7.43 (m, 3H), 7.49–7.62 (m, 2H). ¹³C NMR (CDCl₃) δ 46.3, 55.4, 112.7, 112.9, 119.7, 127.4, 127.6, 129.9, 139.8, 142.6 (2C), 160.0. HRMS calcd for C₁₄H₁₆NO (M+H)⁺ 214.1226, found 214.1228.

8-(3'-Methoxybiphenyl-4-ylmethylamino)adenosine (3-10). A mixture of **13** (139 mg, 0.402 mmol), **3-57** (257 mg, 1.21 mmol), and *i*-Pr₂NEt (311 mg, 2.41 mmol) in EtOH (4.02 mL) was heated in a screw tube at 120 °C with stirring for 73 h. The reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The residue was suspended in DCM (20 mL) and stirred at room temperature for 13 h. The precipitate was collected by filtration, air-dried, and then recrystallized from EtOH to give the title compound (117 mg, 61%) as a pale yellow solid. mp 232–235 °C. ¹H NMR (DMSO-*d*₆) δ 3.55–3.72 (m, 2H), 3.81 (s, 3H), 3.97–4.04 (m, 1H), 4.10–4.20 (m, 1H), 4.55–4.70 (m, 2H), 4.70–4.80 (m, 1H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.90 (d, *J* = 4.0, 6.3 Hz, 1H), 5.95 (d, *J* = 7.3 Hz, 1H), 6.51 (br s, 2H), 6.88–6.97 (m, 1H), 7.13–7.23 (m, 2H), 7.30–7.40 (m, 1H), 7.41–7.50 (m, 2H), 7.53–7.66 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 55.1, 61.8, 71.0, 71.1, 85.8, 86.5, 112.1, 112.8, 117.1, 118.9, 126.7, 127.7, 130.0, 138.6, 139.4, 141.6, 148.6, 149.9, 151.4, 152.5, 159.7. HRMS calcd for C₂₄H₂₇N₆O₅ (M+H)⁺ 479.2037, found 479.2036.

8-(3'-Ethoxybiphenyl-4-ylmethylamino)adenosine (3-11)

3'-Ethoxybiphenyl-4-carbonitrile (3-54). The title compound (410 mg, 67%) was obtained as a colorless oil from **16** (500 mg, 2.75 mmol) and 3-ethoxyphenylboronic acid (502 mg, 3.02 mmol) according to a procedure similar to that described for the preparation of **3-51**. ¹H NMR (CDCl₃) δ 1.45 (t, *J* = 7.0 Hz, 3H), 4.10 (q, *J* = 7.0 Hz, 2H), 6.92–6.99 (m, 1H), 7.07–7.20 (m, 2H), 7.34–7.42 (m, 1H), 7.64–7.76 (m, 4H). ¹³C NMR (CDCl₃) δ 14.9, 63.7, 111.1, 113.8, 114.5, 119.1, 119.6, 127.9, 130.3, 132.7, 140.7, 145.7, 159.6. HRMS calcd for C₁₅H₁₄NO (M+H)⁺ 224.1070, found 224.1069.

3'-Ethoxybiphenyl-4-ylmethanamine (3-58). The title compound (372 mg, 95%) was obtained as a yellow oil from **3-54** (386 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **3-55**. ¹H NMR (DMSO-*d*₆) δ 1.35 (t, *J* = 7.0 Hz, 3H), 1.89 (br s, 2H), 3.74 (s, 2H), 4.09 (q, *J* = 7.0 Hz, 2H), 6.85–6.94 (m, 1H), 7.09–7.25 (m, 2H), 7.29–7.46 (m, 3H), 7.51–7.63 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 14.7, 45.4, 63.0, 112.5, 113.1, 118.8, 126.5, 127.6, 129.9, 138.0, 141.7, 143.8, 159.0. HRMS calcd for C₁₅H₁₈NO (M+H)⁺ 228.1383, found 228.1382.

8-(3'-Ethoxybiphenyl-4-ylmethylamino)adenosine (3-11). The title compound (226 mg, 91%) was obtained as a pale yellow solid from 13 (174 mg, 0.503 mmol) and 3-58 (343 mg, 1.51 mmol) according to a procedure similar to that described for the preparation of 3-2. mp 116–121 °C. ¹H NMR (DMSO-*d*₆) δ 1.34 (t, *J* = 7.0 Hz, 3H), 3.55–3.74 (m, 2H), 3.96–4.22 (m, 4H), 4.51–4.84 (m, 3H), 5.16 (d, *J* = 4.0 Hz, 1H), 5.29 (d, *J* = 6.8 Hz, 1H), 5.91 (dd, *J* = 4.1, 6.1

Hz, 1H), 5.95 (d, J = 7.5 Hz, 1H), 6.52 (br s, 2H), 6.86–6.97 (m, 1H), 7.10–7.23 (m, 2H), 7.30–7.40 (m, 1H), 7.41–7.51 (m, 2H), 7.55–7.69 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 14.7, 45.0, 61.8, 63.0, 71.0, 71.1, 85.8, 86.5, 112.6, 113.3, 117.1, 118.8, 126.6, 127.7, 130.0, 138.6, 139.3, 141.6, 148.6, 149.9, 151.4, 152.5, 159.0. HRMS calcd for C₂₅H₂₉N₆O₅ (M+H)⁺ 493.2194, found 493.2192.

8-(3'-Propoxybiphenyl-4-ylmethylamino)adenosine (3-12)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(3'-propoxybiphenyl-4-ylmethylamino)adenosine* (**3-40**). The title compound (489 mg, 80%) was obtained as a yellow foam from **3-35** (581 mg, 0.720 mmol) and 1-iodopropane (184 mg, 1.08 mmol) according to a procedure similar to that described for the preparation of **3-37**. ¹H NMR (CDCl₃) δ -0.31 (s, 3H), -0.05 (s, 3H), -0.02 (s, 3H), 0.00 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.81 (s, 9H), 0.94 (s, 9H), 1.05 (t, *J* = 7.4 Hz, 3H), 1.77–1.89 (m, 2H), 3.74 (dd, *J* = 2.5, 11.5 Hz, 1H), 3.86 (dd, *J* = 2.8, 11.5 Hz, 1H), 3.97 (t, *J* = 6.5 Hz, 2H), 4.06–4.13 (m, 1H), 4.28 (dd, *J* = 2.4, 5.0 Hz, 1H), 4.57 (dd, *J* = 3.8, 15.6 Hz, 1H), 4.86 (dd, *J* = 5.0, 6.9 Hz, 1H), 4.98 (dd, *J* = 8.2, 15.6 Hz, 1H), 5.04 (minor) and 5.06 (major) (each br s, 2H), 5.95 (dd, *J* = 3.8, 8.2 Hz, 1H), 6.06 (d, *J* = 6.9 Hz, 1H), 6.85–6.92 (m, 1H), 7.07–7.19 (m, 2H), 7.29–7.44 (m, 3H), 7.49–7.59 (m, 2H), 8.17 (s, 1H). HRMS calcd for C₄₄H₇₃N₆O₅Si₃ (M+H)⁺ 849.4945, found 849.4937.

8-(3'-Propoxybiphenyl-4-ylmethylamino)adenosine (3-12). To a solution of **3-40** (485 mg, 0.571 mmol) in MeOH (11.4 mL) was added NH₄F (1.27 g, 34.3 mmol), and the resulting mixture was heated under reflux with stirring for 26 h. The reaction mixture was allowed to cool to room temperature, diluted with DCM (45 mL), stirred for 75 min, and then filtered through a pad of Hyflo Super-Cel. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 10–17% MeOH in DCM) followed by flash column chromatography on NH silica gel (gradient: 8–15% MeOH in DCM) to give the title compound (241 mg, 83%) as a slightly yellow solid. mp 120–125 °C. ¹H NMR (DMSO-*d*₆) δ 0.99 (t, *J* = 7.4 Hz, 3H), 1.66–1.83 (m, 2H), 3.56–3.73 (m, 2H), 3.93–4.07 (m, 3H), 4.09–4.18 (m, 1H), 4.54–4.81 (m, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.92 (dd, *J* = 4.0, 6.3 Hz, 1H), 5.95 (d, *J* = 7.3 Hz, 1H), 6.53 (br s, 2H), 6.86–6.94 (m, 1H), 7.12–7.23 (m, 2H), 7.29–7.52 (m, 3H), 7.55–7.71 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 10.5, 22.1, 45.0, 61.8, 68.9, 71.0, 71.1, 85.8, 86.5, 112.6, 113.3, 117.1, 118.8, 126.7, 127.7, 130.0, 138.6, 139.3, 141.6, 148.6, 149.9, 151.4, 152.5, 159.2. HRMS calcd for C₂₆H₃₁N₆O₅ (M+H)⁺ 507.2350, found 507.2343.

8-(3'-Isopropoxybiphenyl-4-ylmethylamino)adenosine (3-13)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(3'-isopropoxybiphenyl-4-ylmethylamino)adenosine (3-41)*. To a solution of **3-35** (302 mg, 0.374 mmol) in DMF (2.49 mL) was added K₂CO₃ (103 mg, 0.748 mmol) followed by 2-iodopropane (95.4 mg, 0.561 mmol), and the resulting mixture was heated at 50 °C with stirring for 27 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (50 mL) and H₂O (20 mL). The organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and

concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 37-58% AcOEt in hexane) to give the title compound (212 mg, 67%) as a pale yellow foam. ¹H NMR (CDCl₃) δ -0.31 (s, 3H), -0.05 (s, 3H), -0.01 (s, 3H), 0.00 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.81 (s, 9H), 0.94 (s, 9H), 1.36 (d, *J* = 6.0 Hz, 6H), 3.75 (dd, *J* = 2.6, 11.7 Hz, 1H), 3.86 (dd, *J* = 2.6, 11.7 Hz, 1H), 4.05–4.14 (m, 1H), 4.28 (dd, *J* = 2.5, 4.8 Hz, 1H), 4.52–4.67 (m, 2H), 4.85 (dd, *J* = 4.8, 6.9 Hz, 1H), 4.97 (dd, *J* = 8.1, 15.6 Hz, 1H), 5.12 (br s, 2H), 5.99 (dd, *J* = 4.0, 8.1 Hz, 1H), 6.07 (d, *J* = 6.9 Hz, 1H), 6.83–6.91 (m, 1H), 7.07–7.16 (m, 2H), 7.28–7.36 (m, 1H), 7.37–7.45 (m, 2H), 7.50–7.60 (m, 2H), 8.16 (s, 1H). HRMS calcd for C₄₄H₇₃N₆O₅Si₃ (M+H)⁺ 849.4945, found 849.4939.

8-(3'-Isopropoxybiphenyl-4-ylmethylamino)adenosine (*3-13*). The title compound (117 mg, 94%) was obtained as a pale yellow foam from **3-41** (208 mg, 0.245 mmol) according to a procedure similar to that described for the preparation of **3-1**. ¹H NMR (DMSO-*d*₆) δ 1.28 (d, *J* = 6.0 Hz, 6H), 3.56–3.74 (m, 2H), 3.96–4.04 (m, 1H), 4.09–4.21 (m, 1H), 4.54–4.85 (m, 4H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.86–6.02 (m, 2H), 6.55 (br s, 2H), 6.85–6.94 (m, 1H), 7.08–7.21 (m, 2H), 7.28–7.38 (m, 1H), 7.40–7.52 (m, 2H), 7.55–7.68 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 21.9, 45.0, 61.8, 69.1, 71.0, 71.1, 85.9, 86.5, 113.9, 114.4, 117.1, 118.8, 126.7, 127.7, 130.1, 138.6, 139.3, 141.7, 148.6, 149.9, 151.4, 152.4, 158.0. HRMS calcd for C₂₆H₃₁N₆O₅ (M+H)⁺ 507.2350, found 507.2355.

8-[3'-(2-Methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (3-14)

2',3',5'-Tris-O-(tert-butyldimethylsilyl)-8-[3'-(2-methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (3-42). The title compound (589 mg, 81%) was obtained as a pale yellow foam from **3-35** (670 mg, 0.830 mmol) and methyl bromoacetate (152 mg, 0.990 mmol) according to a procedure similar to that described for the preparation of **3-39**. ¹H NMR (CDCl₃) δ -0.31 (s, 3H), -0.05 (s, 3H), -0.01 (s, 3H), 0.01 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.82 (s, 9H), 0.94 (s, 9H), 3.75 (dd, J = 2.6, 11.7 Hz, 1H), 3.82 (major) and 3.83 (minor) (each s, 3H), 3.88 (dd, J = 2.6, 11.7 Hz, 1H), 3.82 (major) and 3.83 (minor) (each s, 3H), 3.88 (dd, J = 2.6, 11.7 Hz, 1H), 3.82 (major) and 3.83 (minor) (each s, 3H), 3.88 (dd, J = 2.6, 11.7 Hz, 1H), 3.82 (major) and 3.83 (minor) (each s, 3H), 3.88 (dd, J = 2.6, 11.7 Hz, 1H), 3.82 (major) and 3.83 (minor) (each s, 3H), 3.88 (dd, J = 2.6, 1H), 3.82 (major) (2.6, 11.7 Hz, 1H), 4.07–4.13 (m, 1H), 4.27 (dd, *J* = 2.3, 4.8 Hz, 1H), 4.57 (dd, *J* = 3.8, 15.7 Hz, 1H), 4.69 (major) and 4.71 (minor) (each s, 2H), 4.83 (dd, J = 4.8, 6.9 Hz, 1H), 4.97 (dd, J = 8.0, 15.7 Hz, 1H), 5.15 (br s, 2H), 6.03 (dd, J = 3.8, 8.0 Hz, 1H), 6.09 (d, J = 6.9 Hz, 1H), 6.84–6.90 (m, 1H), 7.11–7.17 (m, 1H), 7.18–7.25 (m, 1H), 7.32– 7.44 (m, 3H), 7.49–7.56 (m, 2H), 8.16 (s, 1H). HRMS calcd for $C_{44}H_{71}N_6O_7Si_3$ (M+H)⁺ 879.4687, found 879.4681. 8-[3'-(2-Methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (3-14). The title compound (215 mg, 87%) was obtained as a yellow amorphous solid from **3-42** (405 mg, 0.461 mmol) according to a procedure similar to that described for the preparation of **3-4**. ¹H NMR (DMSO-*d*₆) δ 3.55–3.75 (m, 5H), 3.96–4.03 (m, 1H), 4.10–4.17 (m, 1H), 4.55–4.80 (m, 3H), 4.88 (s, 2H), 5.17 (d, J = 4.0 Hz, 1H), 5.31 (d, J = 6.8 Hz, 1H), 5.88–5.99 (m, 2H), 6.53 (br s, 2H), 6.87–6.95 (m, 1H), 7.14–7.20 (m, 1H), 7.21–7.28 (m, 1H), 7.31–7.40 (m, 1H), 7.41–7.51 (m, 2H), 7.54– 7.68 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 51.9, 61.8, 64.6, 71.0, 71.1, 85.9, 86.5, 112.7, 113.4, 117.1, 119.7, 126.7, 127.7, 130.0, 138.3, 139.5, 141.6, 148.6, 149.9, 151.4, 152.5, 158.1, 169.4. HRMS calcd for

8-[3'-(2-Amino-2-oxoethoxy)biphenyl-4-ylmethylamino|adenosine (3-15)

8-[3'-(2-Amino-2-oxoethoxy)biphenyl-4-ylmethylamino]-2',3',5'-tris-O-(tert-butyldimethylsilyl)adenosine (3-43). To 3-42 (180 mg, 0.205 mmol) was added a 2.0 M solution of NH₃ in MeOH (8.19 mL), and the resulting mixture was stirred at room temperature for 72 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (gradient: 71–100% AcOEt in hexane) to give the title compound (150 mg, 85%) as a yellow solid. ¹H NMR (CDCl₃) δ –0.31 (s, 3H), –0.05 (s, 3H), 0.02 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.82 (s, 9H), 0.94 (s, 9H), 3.76 (dd, *J* = 2.5, 11.5 Hz, 1H), 3.88 (dd, *J* = 2.5, 11.5 Hz, 1H), 4.06–4.14 (m, 1H), 4.28 (dd, *J* = 2.3, 4.8 Hz, 1H), 4.51–4.62 (m, 3H), 4.84 (dd, *J* = 4.8, 6.9 Hz, 1H), 4.99 (dd, *J* = 8.2, 15.7 Hz, 1H), 5.09 (br s, 2H), 5.62 (br s, 1H), 6.02 (dd, *J* = 3.9, 8.2 Hz, 1H), 6.08 (d, *J* = 6.9 Hz, 1H), 6.57 (br s, 1H), 6.87–6.95 (m, 1H), 7.10–7.15 (m, 1H), 7.22–7.29 (m, 1H), 7.34–7.46 (m, 3H), 7.49–7.58 (m, 2H), 8.17 (s, 1H). HRMS calcd for C₄₃H₇₀N₇O₆Si₃ (M+H)⁺ 864.4690, found 864.4687.

8-[3'-(2-Amino-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (3-15). The title compound (75.4 mg, 86%) was obtained as a yellow solid from 3-43 (146 mg, 0.169 mmol) according to a procedure similar to that described for the preparation of 3-9. mp 147–151 °C. ¹H NMR (DMSO-*d*₆) δ 3.54–3.72 (m, 2H), 3.96–4.04 (m, 1H), 4.09–4.17 (m, 1H), 4.49 (s, 2H), 4.57–4.80 (m, 3H), 5.17 (d, J = 4.0 Hz, 1H), 5.31 (d, J = 6.8 Hz, 1H), 5.87–6.01 (m, 2H), 6.53 (br s, 2H), 6.89–6.98 (m, 1H), 7.18–7.24 (m, 2H), 7.32–7.69 (m, 8H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 61.8, 66.8, 71.0, 71.1, 85.9, 86.5, 113.0, 113.6, 117.1, 119.5, 126.6, 127.7, 130.0, 138.4, 139.4, 141.5, 148.6, 149.9, 151.4, 152.5, 158.3, 170.1. HRMS calcd for C₂₅H₂₈N₇O₆ (M+H)⁺ 522.2096, found 522.2090.

8-[3'-(2-Hydroxyethoxy)biphenyl-4-ylmethylamino]adenosine (3-16)

The title compound (123 mg, 91%) was obtained as a yellow solid from **3-14** (143 mg, 0.267 mmol) according to a procedure similar to that described for the preparation of **3-8**. mp 143–146 °C. ¹H NMR (DMSO-*d*₆) δ 3.52–3.79 (m, 4H), 3.97–4.18 (m, 4H), 4.54–4.81 (m, 3H), 4.88 (t, *J* = 5.4 Hz, 1H), 5.18 (d, *J* = 3.8 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.85–6.01 (m, 2H), 6.56 (br s, 2H), 6.88–6.95 (m, 1H), 7.12–7.23 (m, 2H), 7.30–7.38 (m, 1H), 7.40–7.51 (m, 2H), 7.55–7.68 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 59.6, 61.8, 69.5, 71.0, 71.1, 85.9, 86.5, 112.7, 113.4, 117.1, 118.9, 126.7, 127.7, 130.0, 138.6, 139.3, 141.6, 148.5, 149.9, 151.4, 152.4, 159.2. HRMS calcd for C₂₅H₂₉N₆O₆ (M+H)⁺ 509.2143, found 509.2140.

8-(4'-Hydroxybiphenyl-4-ylmethylamino)adenosine (3-17)

tert-Butyl (4'-hydroxybiphenyl-4-ylmethyl)carbamate (3-30). The title compound (794 mg, 76%) was obtained as a brownish yellow solid from **34**⁶⁰ (1.00 g, 3.49 mmol) and 4-hydroxyphenylboronic acid (530 mg, 3.84 mmol)

according to a procedure similar to that described for the prepraration of **3-28**. ¹H NMR (DMSO-*d*₆) δ 1.40 (s, 9H), 4.13 (d, *J* = 6.2 Hz, 2H), 6.79–6.89 (m, 2H), 7.20–7.32 (m, 2H), 7.39 (t, *J* = 6.2 Hz, 1H), 7.42–7.58 (m, 4H), 9.50 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 28.3, 43.1, 77.8, 115.7, 125.8, 127.5, 127.6, 130.8, 138.3, 138.7, 155.8, 157.0. HRMS calcd for C₁₈H₂₁NNaO₃ (M+Na)⁺ 322.1414, found 322.1413.

4'-(*Aminomethyl*)*biphenyl-4-ol hydrochloride* (**3-33**). The title compound (607 mg, quant.) was obtained as an offwhite solid from **3-30** (764 mg, 2.55 mmol) according to a procedure similar to that described for the preparation of **3-31**. ¹H NMR (DMSO-*d*₆) δ 4.03 (br s, 2H), 6.79–6.94 (m, 2H), 7.45–7.75 (m, 6H), 8.40 (br s, 3H), 9.64 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 41.9, 115.8, 126.0, 127.8, 129.6, 130.2, 132.1, 140.3, 157.5. HRMS calcd for C₁₃H₁₄NO (M+H)⁺ 200.1070, found 200.1066.

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(4'-hydroxybiphenyl-4-ylmethylamino)adenosine* (**3-36**). A mixture of **19**⁴⁷ (400 mg, 0.581 mmol), **3-33** (411 mg, 1.74 mmol), and *i*-Pr₂NEt (525 mg, 4.06 mmol) in EtOH (5.81 mL) was heated in a screw tube at 120 °C with stirring for 96 h. The reaction mixture was allowed to cool to room temperature and then filtered. The filtrate was concentrated under reduced pressure. The residue was partitioned between AcOEt (50 mL) and saturated aqueous NaHCO₃ (15 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 53–74% AcOEt in hexane) to give the title compound (454 mg, 97%) as a pale yellow foam. ¹H NMR (CDCl₃) δ –0.30 (s, 3H), -0.03 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.12 (s, 3H), 0.16 (s, 3H), 0.76 (s, 9H), 0.82 (s, 9H), 0.96 (s, 9H), 3.84 (dd, J = 2.1, 11.7 Hz, 1H), 3.98 (dd, J = 2.0, 11.7 Hz, 1H), 4.13–4.21 (m, 1H), 4.27 (dd, J = 1.5, 5.0 Hz, 1H), 4.60 (dd, J = 4.5, 17.0 Hz, 1H), 4.80 (dd, J = 5.0, 7.5 Hz, 1H), 4.92 (dd, J = 8.5, 17.0 Hz, 1H), 5.37 (minor) and 5.39 (major) (each br s, 2H), 6.25 (d, J = 7.5 Hz, 1H), 6.31–6.43 (m, 2H), 6.58 (dd, J = 4.5, 8.5 Hz, 1H), 6.87–7.17 (m, 6H), 8.19 (s, 1H), 9.85–10.80 (br, 1H). HRMS calcd for C₄₁H₆₇N₆O₅Si₃ (M+H)⁺ 807.4475, found 807.4466.

8-(4'-Hydroxybiphenyl-4-ylmethylamino)adenosine (3-17). To a solution of 3-36 (446 mg, 0.553 mmol) in MeOH (11.1 mL) was added NH₄F (1.23 g, 33.2 mmol), and the resulting mixture was heated under reflux with stirring for 27 h. The reaction mixture was allowed to cool to room temperature, diluted with H₂O (22.2 mL), and then stirred for 1 h. The insoluble material was collected by filtration, washed with MeOH/H₂O (1/2), air-dried, and then purified by flash column chromatography on silica gel (gradient: 10–17% MeOH in DCM) to give the title compound (231 mg, 90%) as a yellow foam. ¹H NMR (DMSO-*d*₆) δ 3.53–3.73 (m, 2H), 3.96–4.06 (m, 1H), 4.09–4.19 (m, 1H), 4.53–4.68 (m, 2H), 4.69–4.82 (m, 1H), 5.15 (d, *J* = 4.3 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 5.90 (dd, *J* = 4.0, 6.3 Hz, 1H), 5.94 (d, *J* = 7.3 Hz, 1H), 6.51 (br s, 2H), 6.78–6.88 (m, 2H), 7.36–7.63 (m, 7H), 7.90 (s, 1H), 9.50 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 61.8, 71.0, 71.1, 85.8, 86.5, 115.7, 117.1, 125.8, 127.6, 127.7, 130.8, 138.0, 138.7, 148.6, 149.9, 151.4, 152.5, 157.0. HRMS calcd for C₂₃H₂₅N₆O₅ (M+H)⁺ 465.1881, found 465.1876.

8-(4'-Methoxybiphenyl-4-ylmethylamino)adenosine (3-18)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(4'-methoxybiphenyl-4-ylmethylamino)adenosine (3-44)*. To a solution of **3-36** (500 mg, 0.619 mmol) in DMF (4.13 mL) was added K₂CO₃ (171 mg, 1.24 mmol) followed by iodomethane (132 mg, 0.929 mmol), and the resulting mixture was stirred at room temperature for 27 h. The reaction mixture was partitioned between AcOEt (50 mL) and H₂O (15 mL). The organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 49–70% AcOEt in hexane) to give the title compound (354 mg, 70%) as a yellow solid. ¹H NMR (CDCl₃) δ –0.31 (s, 3H), -0.05 (s, 3H), -0.01 (s, 3H), 0.01 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.82 (s, 9H), 0.94 (s, 9H), 3.74 (dd, *J* = 2.8, 11.5 Hz, 1H), 3.82–3.90 (m, 4H), 4.06–4.13 (m, 1H), 4.28 (dd, *J* = 2.5, 4.8 Hz, 1H), 4.55 (dd, *J* = 3.9, 15.5 Hz, 1H), 4.85 (dd, *J* = 4.8, 6.9 Hz, 1H), 4.95 (dd, *J* = 8.0, 15.5 Hz, 1H), 5.16 (br s, 2H), 5.99 (dd, *J* = 3.9, 8.0 Hz, 1H), 6.07 (d, *J* = 6.9 Hz, 1H), 6.93–7.03 (m, 2H), 7.35–7.43 (m, 2H), 7.47–7.58 (m, 4H), 8.16 (s, 1H). HRMS calcd for C₄₂H₆₉N₆N₅O₃ (M+H)⁺ 821.4632, found 821.4628.

8-(4'-Methoxybiphenyl-4-ylmethylamino)adenosine (3-18). To a solution of 3-44 (351 mg, 0.427 mmol) in MeOH (8.55 mL) was added NH₄F (950 mg, 25.6 mmol), and the resulting mixture was heated under reflux with stirring for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with H₂O (17.1 mL), and then stirred for 2 h. The insoluble material was collected by filtration, washed with H₂O, and air-dried to give the title compound (206 mg, quant.) as a pale yellow solid. ¹H NMR (DMSO-*d*₆) δ 3.55–3.72 (m, 2H), 3.78 (s, 3H), 3.96–4.04 (m, 1H), 4.09–4.18 (m, 1H), 4.53–4.68 (m, 2H), 4.69–4.80 (m, 1H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.86–5.99 (m, 2H), 6.53 (br s, 2H), 6.94–7.06 (m, 2H), 7.35–7.71 (m, 7H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 55.2, 61.8, 70.9, 71.1, 85.8, 86.5, 114.4, 117.1, 126.0, 127.6, 127.7, 132.4, 138.3, 138.4, 148.6, 149.8, 151.4, 152.5, 158.8. HRMS calcd for C₂₄H₂₇N₆O₅ (M+H)⁺ 479.2037, found 479.2038.

8-(4'-Ethoxybiphenyl-4-ylmethylamino)adenosine (3-19)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(4'-ethoxybiphenyl-4-ylmethylamino)adenosine (3-45)*. To a solution of **3-36** (454 mg, 0.562 mmol) in DMF (3.75 mL) was added K₂CO₃ (156 mg, 1.13 mmol) followed by iodoethane (132 mg, 0.844 mmol), and the resulting mixture was heated at 40 °C with stirring for 24 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (45 mL) and H₂O (15 mL). The organic layer was washed successively with H₂O (15 mL) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 49–70% AcOEt in hexane) to give the title compound (414 mg, 88%) as a yellow foam. ¹H NMR (CDCl₃) δ –0.31 (s, 3H), -0.05 (s, 3H), -0.02 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.81 (s, 9H), 0.94 (s, 9H), 1.44 (t, *J* = 7.0 Hz, 3H), 3.74 (dd, *J* = 2.6, 11.7 Hz, 1H), 3.86 (dd, *J* = 2.6, 11.7 Hz, 1H), 4.02–4.15 (m, 3H), 4.29 (dd, *J* = 2.5, 4.8 Hz, 1H), 4.55 (dd, J = 3.8, 15.4 Hz, 1H), 4.87 (dd, J = 4.8, 6.8 Hz, 1H), 4.95 (dd, J = 8.0, 15.4 Hz, 1H), 5.06 (minor) and 5.08 (major) (each br s, 2H), 5.93 (dd, J = 3.8, 8.0 Hz, 1H), 6.05 (d, J = 6.8 Hz, 1H), 6.92–6.99 (m, 2H), 7.35–7.42 (m, 2H), 7.46–7.56 (m, 4H), 8.16 (s, 1H). HRMS calcd for C₄₃H₇₁N₆O₅Si₃ (M+H)⁺ 835.4788, found 835.4779.

8-(4'-Ethoxybiphenyl-4-ylmethylamino)adenosine (3-19). To a solution of 3-45 (411 mg, 0.492 mmol) in MeOH (9.84 mL) was added NH₄F (1.09 g, 29.5 mmol), and the resulting mixture was heated under reflux with stirring for 25 h. The reaction mixture was allowed to cool to room temperature, diluted with H₂O (19.7 mL), and then stirred for 1.5 h. The insoluble material was collected by filtration, washed with H₂O, air-dried, and then recrystallized from EtOH-DCE to give the title compound (111 mg, 46%) as a yellow solid. mp 250–252 °C, dec. ¹H NMR (DMSO-*d*₆) δ 1.34 (t, *J* = 6.9 Hz, 3H), 3.54–3.74 (m, 2H), 3.96–4.02 (m, 1H), 4.05 (q, *J* = 6.9 Hz, 2H), 4.10–4.18 (m, 1H), 4.53–4.81 (m, 3H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.86–5.99 (m, 2H), 6.53 (br s, 2H), 6.95–7.05 (m, 2H), 7.37–7.47 (m, 2H), 7.50–7.64 (m, 5H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 14.7, 45.0, 61.8, 63.1, 71.0, 71.1, 85.8, 86.5, 114.8, 117.1, 126.0, 127.6, 127.7, 132.3, 138.4, 148.6, 149.9, 151.4, 152.5, 158.1. HRMS calcd for C₂₅H₂₉N₆O₅ (M+H)⁺ 493.2194, found 493.2189.

8-(4'-Propoxybiphenyl-4-ylmethylamino)adenosine (3-20)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-(4'-propoxybiphenyl-4-ylmethylamino)adenosine* (**3-46**). The title compound (590 mg, 94%) was obtained as a yellow solid from **3-36** (599 mg, 0.742 mmol) and 1-iodopropane (189 mg, 1.11 mmol) according to a procedure similar to that described for the preparation of **3-37**. ¹H NMR (CDCl₃) δ -0.31 (s, 3H), -0.05 (s, 3H), -0.02 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.81 (s, 9H), 0.94 (s, 9H), 1.05 (t, *J* = 7.4 Hz, 3H), 1.77–1.89 (m, 2H), 3.73 (dd, *J* = 2.6, 11.6 Hz, 1H), 3.86 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.96 (t, *J* = 6.7 Hz, 2H), 4.06–4.12 (m, 1H), 4.29 (dd, *J* = 2.5, 4.8 Hz, 1H), 4.55 (dd, *J* = 3.8, 15.4 Hz, 1H), 4.87 (dd, *J* = 4.8, 6.8 Hz, 1H), 4.96 (dd, *J* = 8.0, 15.4 Hz, 1H), 5.07 (br s, 2H), 5.92 (dd, *J* = 3.8, 8.0 Hz, 1H), 6.05 (d, *J* = 6.8 Hz, 1H), 6.92–7.01 (m, 2H), 7.35–7.42 (m, 2H), 7.46–7.54 (m, 4H), 8.16 (s, 1H). HRMS calcd for C₄₄H₇₃N₆N₅O₃ (M+H)⁺ 849.4945, found 849.4953.

8-(4'-Propoxybiphenyl-4-ylmethylamino)adenosine (3-20). 3-46 (587 mg, 0.691 mmol) was dissolved in MeOH (13.8 mL) by heating. To the solution was added NH₄F (1.54 g, 41.5 mmol), and the resulting mixture was heated under reflux with stirring for 30 h. The reaction mixture was allowed to cool to room temperature, diluted with H₂O (27.6 mL), and then stirred for 3 h. The insoluble material was collected by filtration, washed with H₂O, and airdried to give the title compound (327 mg, 93%) as a pale yellow solid. ¹H NMR (DMSO-*d*₆) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.67–1.80 (m, 2H), 3.56–3.70 (m, 2H), 3.91–4.03 (m, 3H), 4.09–4.17 (m, 1H), 4.54–4.68 (m, 2H), 4.70–4.79 (m, 1H), 5.17 (d, *J* = 4.3 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.88–5.98 (m, 2H), 6.53 (br s, 2H), 6.95–7.03 (m, 2H), 7.37–7.46 (m, 2H), 7.51–7.62 (m, 5H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 10.4, 22.1, 45.0, 61.8, 69.0, 71.0, 71.1, 85.9, 86.5, 114.9, 117.1, 126.0, 127.6, 127.7, 132.3, 138.4, 148.6, 149.9, 151.4, 152.5, 158.3. HRMS calcd for C₂₆H₃₁N₆O₅ (M+H)⁺ 507.2350, found 507.2343.

8-(4'-Isopropoxybiphenyl-4-ylmethylamino)adenosine (3-21)

2',3',5'-Tris-O-(tert-butyldimethylsilyl)-8-(4'-isopropoxybiphenyl-4-ylmethylamino)adenosine (3-47). The title compound (357 mg, 69%) was obtained as a pale yellow solid from **3-36** (491 mg, 0.608 mmol) and 2-iodopropane (155 mg, 0.912 mmol) according to a procedure similar to that described for the preparation of **3-38**. ¹H NMR $(CDCl_3) \delta - 0.31$ (s, 3H), -0.05 (s, 3H), -0.01 (s, 3H), 0.00 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.82 (s, 0.15) 9H), 0.94 (s, 9H), 1.36 (d, J = 6.0 Hz, 6H), 3.74 (dd, J = 2.8, 11.5 Hz, 1H), 3.86 (dd, J = 2.5, 11.5 Hz, 1H), 4.06-4.13 (m, 1H), 4.28 (dd, J = 2.3, 4.8 Hz, 1H), 4.50–4.65 (m, 2H), 4.85 (dd, J = 4.8, 6.9 Hz, 1H), 4.95 (dd, J = 8.0, 15.6 Hz, 1H), 5.16 (br s, 2H), 5.98 (dd, J = 4.0, 8.0 Hz, 1H), 6.07 (d, J = 6.9 Hz, 1H), 6.84–7.01 (m, 2H), 7.34–7.42 (m, 2H), 7.45–7.55 (m, 4H), 8.16 (s, 1H). HRMS calcd for $C_{44}H_{73}N_6O_5Si_3$ (M+H)⁺ 849.4945, found 849.4946. 8-(4'-Isopropoxybiphenyl-4-ylmethylamino)adenosine (3-21). To a suspension of 3-47 (354 mg, 0.417 mmol) in MeOH (8.34 mL) was added NH₄F (926 mg, 25.0 mmol), and the resulting mixture was heated under reflux with stirring for 27 h. The reaction mixture was allowed to cool to room temperature, diluted with H₂O (16.7 mL), and then stirred for 2.5 h. The insoluble material was collected by filtration, washed with H₂O, and air-dried to give the title compound (211 mg, quant.) as a pale vellow solid. ¹H NMR (DMSO- d_6) δ 1.28 (d, J = 6.0 Hz, 6H), 3.55–3.71 (m, 2H), 3.96-4.04 (m, 1H), 4.09-4.19 (m, 1H), 4.52-4.81 (m, 4H), 5.17 (d, J = 4.0 Hz, 1H), 5.30 (d, J = 6.8 Hz, 1H), 5.92 (dd, J = 4.0, 6.3 Hz, 1H), 5.95 (d, J = 7.3 Hz, 1H), 6.53 (br s, 2H), 6.93–7.03 (m, 2H), 7.37–7.48 (m, 2H), 7.51–7.63 (m, 5H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 21.9, 45.0, 61.8, 69.2, 71.0, 71.1, 85.8, 86.5, 116.0, 117.1, 126.0, 127.7 (2C), 132.2, 138.4 (2C), 148.6, 149.9, 151.4, 152.5, 157.0. HRMS calcd for C₂₆H₃₁N₆O₅ (M+H)⁺ 507.2350, found 507.2352.

8-[4'-(2-Methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (3-22)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-[4'-(2-methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine* (3-48). The title compound (556 mg, 85%) was obtained as a brownish yellow foam from 3-36 (602 mg, 0.746 mmol) and methyl bromoacetate (148 mg, 0.969 mmol) according to a procedure similar to that described for the preparation of 3-39. ¹H NMR (CDCl₃) δ -0.31 (s, 3H), -0.05 (s, 3H), -0.02 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.81 (s, 9H), 0.94 (s, 9H), 3.74 (dd, *J* = 2.8, 11.6 Hz, 1H), 3.80–3.90 (m, 4H), 4.06–4.13 (m, 1H), 4.28 (dd, *J* = 2.5, 4.8 Hz, 1H), 4.55 (dd, *J* = 3.8, 15.6 Hz, 1H), 4.68 (major) and 4.69 (minor) (each s, 2H), 4.86 (dd, *J* = 4.8, 6.8 Hz, 1H), 4.96 (dd, *J* = 8.0, 15.6 Hz, 1H), 5.04 (minor) and 5.06 (major) (each br s, 2H), 5.94 (dd, *J* = 3.8, 8.0 Hz, 1H), 6.06 (d, *J* = 6.8 Hz, 1H), 6.93–7.03 (m, 2H), 7.36–7.43 (m, 2H), 7.45–7.52 (m, 4H), 8.16 (s, 1H). HRMS calcd for C₄₄H₇₁N₆O₇Si₃ (M+H)⁺ 879.4687, found 879.4678.

8-[4'-(2-Methoxy-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (3-22). The title compound (289 mg, 86%) was obtained as a pale yellow foam from 3-48 (552 mg, 0.628 mmol) according to a procedure similar to that described for the preparation of 3-4. ¹H NMR (DMSO-*d*₆) δ 3.55–3.76 (m, 5H), 3.96–4.03 (m, 1H), 4.10–4.17 (m,

1H), 4.54–4.69 (m, 2H), 4.70–4.79 (m, 1H), 4.84 (s, 2H), 5.17 (d, J = 4.0 Hz, 1H), 5.30 (d, J = 6.8 Hz, 1H), 5.86–6.00 (m, 2H), 6.53 (br s, 2H), 6.96–7.05 (m, 2H), 7.38–7.48 (m, 2H), 7.50–7.70 (m, 5H), 7.90 (s, 1H). ¹³C NMR (DMSO- d_6) δ 45.0, 51.9, 61.8, 64.6, 71.0, 71.1, 85.8, 86.5, 115.0, 117.1, 126.1, 127.7 (2C), 133.2, 138.2, 138.6, 148.6, 149.9, 151.4, 152.5, 157.2, 169.3. HRMS calcd for C₂₆H₂₉N₆O₇ (M+H)⁺ 537.2092, found 537.2094.

8-[4'-(2-Amino-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (3-23)

8-[4'-(2-Amino-2-oxoethoxy)biphenyl-4-ylmethylamino]-2',3',5'-tris-O-(tert-butyldimethylsilyl)adenosine (3-49). The title compound (152 mg, 59%) was obtained as a yellow solid from 3-48 (261 mg, 0.297 mmol) according to a procedure similar to that described for the preparation of 3-43. ¹H NMR (CDCl₃) δ -0.31 (s, 3H), -0.05 (s, 3H), 0.00 (s, 3H), 0.01 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.82 (s, 9H), 0.94 (s, 9H), 3.75 (dd, *J* = 2.5, 11.6 Hz, 1H), 3.87 (dd, *J* = 2.6, 11.6 Hz, 1H), 4.07-4.13 (m, 1H), 4.28 (dd, *J* = 2.3, 4.8 Hz, 1H), 4.50-4.60 (m, 3H), 4.84 (dd, *J* = 4.8, 6.9 Hz, 1H), 4.96 (dd, *J* = 7.9, 15.8 Hz, 1H), 5.18 (br s, 2H), 5.69 (br s, 1H), 6.02 (dd, *J* = 3.8, 7.9 Hz, 1H), 6.08 (d, *J* = 6.9 Hz, 1H), 6.56 (br s, 1H), 6.95-7.03 (m, 2H), 7.35-7.44 (m, 2H), 7.46-7.58 (m, 4H), 8.16 (s, 1H). HRMS calcd for C₄₃H₇₀N₇O₆Si₃ (M+H)⁺ 864.4690, found 864.4684.

8-[4'-(2-Amino-2-oxoethoxy)biphenyl-4-ylmethylamino]adenosine (3-23). To a solution of 3-49 (148 mg, 0.171 mmol) in MeOH (6.85 mL) was added NH4F (381 mg, 10.3 mmol), and the resulting mixture was heated under reflux with stirring for 25 h. The reaction mixture was allowed to cool to room temperature, diluted with H₂O (13.7 mL), and then stirred for 3 h. The insoluble material was collected by filtration, washed with H₂O, air-dried, and then dried at 80 °C under reduced pressure to give the title compound (86.4 mg, 97%) as a pale yellow solid. ¹H NMR (DMSO-*d*₆) δ 3.55–3.70 (m, 2H), 3.95–4.03 (m, 1H), 4.07–4.17 (m, 1H), 4.46 (s, 2H), 4.54–4.68 (m, 2H), 4.70–4.80 (m, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.87–5.98 (m, 2H), 6.53 (br s, 2H), 6.97–7.07 (m, 2H), 7.34–7.47 (m, 3H), 7.49–7.66 (m, 6H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 61.8, 66.8, 71.0, 71.1, 85.9, 86.5, 115.2, 117.1, 126.1, 127.6, 127.7, 133.0, 138.3, 138.5, 148.6, 149.9, 151.4, 152.5, 157.3, 170.0. HRMS calcd for C₂₅H₂₈N₇O₆ (M+H)⁺ 522.2096, found 522.2096.

8-[4'-(2-Hydroxyethoxy)biphenyl-4-ylmethylamino]adenosine (3-24)

2',3',5'-*Tris-O-(tert-butyldimethylsilyl)-8-[4'-(2-hydroxyethoxy)biphenyl-4-ylmethylamino]adenosine* (3-50). To a stirred solution 3-48 (260 mg, 0.296 mmol) in EtOH (2.96 mL) was added NaBH₄ (55.9 mg, 1.48 mmol) in small portions, and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was quenched carefully by addition of 10% aqueous citric acid (10 mL) and the whole was extracted with AcOEt (40 mL). The organic layer was washed successively with saturated aqueous NaHCO₃ (10 mL) and brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 60–81% AcOEt in hexane) to give the title compound (178 mg, 71%) as a pale yellow solid. ¹H NMR (CDCl₃) δ –0.31 (s, 3H), –0.05 (s, 3H), –0.02 (s, 3H), 0.00 (s, 3H), 0.10 (s, 3H), 0.15 (s, 3H), 0.75 (s, 9H), 0.81 (s,

9H), 0.94 (s, 9H), 2.14–2.32 (br, 1H), 3.74 (dd, *J* = 2.5, 11.5 Hz, 1H), 3.86 (dd, *J* = 2.8, 11.5 Hz, 1H), 3.93–4.03 (m, 2H), 4.06–4.17 (m, 3H), 4.28 (dd, *J* = 2.5, 4.8 Hz, 1H), 4.55 (dd, *J* = 3.8, 15.6 Hz, 1H), 4.86 (dd, *J* = 4.8, 6.8 Hz, 1H), 4.96 (dd, *J* = 8.0, 15.6 Hz, 1H), 5.09 (br s, 2H), 5.95 (dd, *J* = 3.8, 8.0 Hz, 1H), 6.06 (d, *J* = 6.8 Hz, 1H), 6.93–7.01 (m, 2H), 7.34–7.43 (m, 2H), 7.46–7.55 (m, 4H), 8.16 (s, 1H). HRMS calcd for C₄₃H₇₁N₆O₆Si₃ (M+H)⁺ 851.4737, found 851.4733.

8-[4'-(2-Hydroxyethoxy)biphenyl-4-ylmethylamino]adenosine (**3-24**). To a solution of **3-50** (175 mg, 0.206 mmol) in MeOH (4.11 mL) was added NH₄F (457 mg, 12.3 mmol), and the resulting mixture was heated under reflux with stirring for 24 h. The reaction mixture was allowed to cool to room temperature, diluted with H₂O (8.22 mL), and then stirred for 3 h. The insoluble material was collected by filtration, washed with H₂O, and air-dried to give the title compound (105 mg, quant.) as a pale yellow solid. ¹H NMR (DMSO-*d*₆) δ 3.54–3.78 (m, 4H), 3.95–4.06 (m, 3H), 4.09–4.17 (m, 1H), 4.54–4.68 (m, 2H), 4.70–4.80 (m, 1H), 4.88 (t, *J* = 5.5 Hz, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 5.88–5.99 (m, 2H), 6.53 (br s, 2H), 6.97–7.07 (m, 2H), 7.39–7.48 (m, 2H), 7.50–7.63 (m, 5H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 59.6, 61.8, 69.6, 71.0, 71.1, 85.9, 86.5, 114.9, 117.1, 126.0, 127.6, 127.7, 132.4, 138.4 (2C), 148.6, 149.9, 151.4, 152.5, 158.3. HRMS calcd for C₂₅H₂₉N₆O₆ (M+H)⁺ 509.2143, found 509.2140.

8-[3'-(2-Aminoethoxy)biphenyl-4-ylmethylamino]adenosine (3-25)

Benzyl 2-[4'-(tert-butoxycarbonylaminomethyl)biphenyl-3-yloxy]ethylcarbamate (3-59). To a stirred mixture of **3-29** (500 mg, 1.67 mmol), benzyl *N*-(2-hydroxyethyl)carbamate (391 mg, 2.00 mmol), and PPh₃ (526 mg, 2.00 mmol) in THF (6.68 mL) was added dropwise DIAD (40% in toluene, ca. 1.9 mol/L, 1.05 mL, ca. 2.00 mmol), and the resulting mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on NH silica gel (gradient: 21–42% AcOEt in hexane) to give the title compound (1.09 g) in milky liquid form, which was a mixture containing mainly diisopropyl hydrazine-1,2-dicarboxylate. ¹H NMR (DMSO-*d*₆) δ 1.30–1.46 (m, 9H), 3.29–3.48 (m, 2H), 3.98–4.21 (m, 4H), 4.98–5.11 (m, 2H), 6.85–6.96 (m, 1H), 7.02–7.70 (m, 14H).

Benzyl 2-[4'-(aminomethyl)biphenyl-3-yloxy]ethylcarbamate (3-61). To a stirred ice-cold solution of the above impure product (1.09 g) in DCM (6.27 mL) was added dropwise TFA (2.09 mL), and the resulting mixture was allowed to warm to room temperature with stirring for 5 h. The reaction mixture was added carefully to saturated aqueous NaHCO₃ (30 mL) and extracted with AcOEt (50 mL). The organic layer was washed with saturated aqueous NaHCO₃ (30 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 0–3% MeOH in AcOEt) to give the title compound (443 mg, 71% from **3-29**) as an off-white solid. ¹H NMR (DMSO-*d*₆) δ 1.83 (br s, 2H), 3.29–3.48 (m, 2H), 3.74 (s, 2H), 4.07 (t, *J* = 5.8 Hz, 2H), 5.04 (major) and 5.08 (minor) (s and br s, 2H), 6.84–6.99 (m, 1H), 7.08–7.69 (m, 13H). ¹³C NMR (DMSO-*d*₆) δ 45.4, 65.4, 66.4, 112.7, 113.3, 119.1, 126.5, 127.6, 127.8, 128.4, 130.0, 137.2, 137.9, 141.7,
143.8, 156.3, 158.9. HRMS calcd for $C_{23}H_{25}N_2O_3$ (M+H)⁺ 377.1860, found 377.1859.

8-[3'-(2-Benzyloxycarbonylaminoethoxy)biphenyl-4-ylmethylamino]adenosine (3-63). The title compound (345 mg, 93%) was obtained as a pale yellow foam from 13 (200 mg, 0.578 mmol) and 3-61 (653 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of 3-2. ¹H NMR (DMSO-*d*₆) δ 3.30–3.45 (m, 2H), 3.55–3.72 (m, 2H), 3.96–4.17 (m, 4H), 4.55–4.70 (m, 2H), 4.71–4.80 (m, 1H), 5.03 (major) and 5.07 (minor) (s and br s, 2H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.88–5.99 (m, 2H), 6.54 (br s, 2H), 6.84–6.95 (m, 1H), 7.07–7.67 (m, 14H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 45.0, 48.6, 61.8, 65.4, 66.4, 71.0, 71.1, 85.9, 86.5, 112.7, 113.5, 117.1, 119.1, 126.7, 127.7, 127.8 (2C), 128.4, 130.0, 137.2, 138.5, 139.4, 141.6, 148.6, 149.9, 151.4, 152.5, 156.3, 158.9. HRMS calcd for C₃₃H₃₆N₇O₇ (M+H)⁺ 642.2671, found 642.2669.

8-[3'-(2-Aminoethoxy)biphenyl-4-ylmethylamino]adenosine (3-25). The title compound (198 mg, 78%) was obtained as an off-white solid from 3-63 (320 mg, 0.499 mmol) according to a procedure similar to that described for the preparation of 3-26. ¹H NMR (DMSO-*d*₆) δ 1.40–1.94 (br, 2H), 2.88 (t, J = 5.8 Hz, 2H), 3.56–3.72 (m, 2H), 3.92–4.02 (m, 3H), 4.10–4.17 (m, 1H), 4.56–4.80 (m, 3H), 5.18 (d, J = 4.0 Hz, 1H), 5.31 (d, J = 6.8 Hz, 1H), 5.89–5.99 (m, 2H), 6.54 (br s, 2H), 6.88–6.95 (m, 1H), 7.13–7.23 (m, 2H), 7.30–7.39 (m, 1H), 7.41–7.50 (m, 2H), 7.55–7.66 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 41.0, 45.0, 61.8, 70.1, 71.0, 71.2, 85.9 (2C), 86.6, 112.8, 113.4, 117.1, 118.9, 126.7, 127.7, 130.0, 138.6, 139.4, 141.6, 148.7, 149.9, 151.4, 152.5, 159.2. HRMS calcd for C₂₅H₃₀N₇O₅ (M+H)⁺ 508.2303, found 508.2300.

8-[3'-(3-Aminopropoxy)biphenyl-4-ylmethylamino]adenosine (3-26)

Benzyl 3-[4'-(*tert-butoxycarbonylaminomethyl*)*biphenyl-3-yloxy*]*propylcarbamate* (3-60). To a solution of 3-29 (500 mg, 1.67 mmol) and benzyl 3-bromopropylcarbamate (591 mg, 2.17 mmol) in DMF (3.34 mL) was added K₂CO₃ (346 mg, 2.51 mmol), and the resulting mixture was heated at 50 °C with stirring for 42 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (50 mL) and H₂O (15 mL). The organic layer was washed successively with H₂O (15 mL × 2) and brine (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient: 35–56% AcOEt in hexane) to give the title compound (801 mg, 98%) as a white solid. ¹H NMR (DMSO-*d*₆) δ 1.26–1.53 (m, 9H), 1.82–1.96 (m, 2H), 3.13–3.27 (m, 2H), 3.98–4.27 (m, 4H), 4.97–5.08 (m, 2H), 6.86–6.95 (m, 1H), 7.11–7.49 (m, 12H), 7.55–7.67 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 28.3, 29.2, 37.4, 43.1, 65.2 (2C), 77.8, 112.6, 113.4, 118.9, 126.7, 127.5, 127.8, 128.4, 130.0, 137.3, 138.5, 139.6, 141.5, 155.9, 156.2, 159.1. HRMS calcd for C₂₉H₃₄N₂NaO₅ (M+Na)⁺ 513.2360, found 513.2369.

Benzyl 3-[4'-(aminomethyl)biphenyl-3-yloxy]propylcarbamate (3-62). To a stirred ice-cold solution of **3-60** (800 mg, 1.63 mmol) in DCM (4.08 mL) was added dropwise TFA (3.72 g, 32.6 mmol), and the resulting mixture was stirred under cooling with ice-water bath for 2 h. After being quenched with 2.0 M aqueous NaOH (17.1 mL), the reaction mixture was partitioned between DCM (50 mL) and H₂O (20 mL). The organic layer was washed

successively with H₂O (15 mL × 2) and brine (15 mL), dreid (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 0–10% MeOH in AcOEt) to give the title compound (702 mg, quant.) as an off-white waxy solid, which contained AcOEt as a residual solvent (8.0 wt% by ¹H NMR). ¹H NMR (DMSO-*d*₆) δ 1.60–2.00 (m, 4H), 3.12–3.28 (m, 2H), 3.74 (s, 2H), 3.97–4.14 (m, 2H), 5.01 (s, 2H), 6.83–7.52 (m, 12H), 7.55–7.65 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 29.2, 37.4, 45.4, 65.1, 65.2, 112.6, 113.3, 118.9, 126.5, 127.6, 127.8, 128.4, 129.9, 137.3, 138.0, 141.7, 143.8, 156.2, 159.1. HRMS calcd for C₂₄H₂₇N₂O₃ (M+H)⁺ 391.2016, found 391.2026.

8-[3'-(3-Benzyloxycarbonylaminopropoxy)biphenyl-4-ylmethylamino]adenosine (3-64). The title compound (270 mg, 78%) was obtained as a pale yellow solid from **13** (183 mg, 0.529 mmol) and **3-62** (619 mg, 1.59 mmol) according to a procedure similar to that described for the preparation of **3-2**. ¹H NMR (DMSO-*d*₆) δ 1.80–1.95 (m, 2H), 3.11–3.26 (m, 2H), 3.56–3.72 (m, 2H), 3.93–4.17 (m, 4H), 4.56–4.70 (m, 2H), 4.70–4.80 (m, 1H), 4.97–5.07 (m, 2H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.92 (dd, *J* = 4.3, 6.3 Hz, 1H), 5.95 (d, *J* = 7.3 Hz, 1H), 6.53 (br s, 2H), 6.83–6.94 (m, 1H), 7.08–7.23 (m, 2H), 7.24–7.51 (m, 9H), 7.53–7.68 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 29.2, 37.4, 45.0, 61.8, 65.1, 65.2, 70.9, 71.1, 85.8, 86.5, 112.7, 113.4, 117.1, 118.9, 126.6, 127.7 (2C), 127.8, 128.4, 130.0, 137.2, 138.5, 139.3, 141.5, 148.6, 149.8, 151.4, 152.5, 156.2, 159.1. HRMS calcd for C₃₄H₃₈N₇O₇ (M+H)⁺ 656.2827, found 656.2837.

8-[3'-(3-Aminopropoxy)biphenyl-4-ylmethylamino]adenosine (3-26). A mixture of 3-64 (251 mg, 0.383 mmol) and 10% Pd–C (56.5 wt% H₂O, 289 mg) in MeOH (5.1 mL) was stirred at room temperature for 20 h under a hydrogen atmosphere. The reaction mixture was filtered through a pad of Hyflo Super-Cel and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (14% MeOH in DCM) to give the title compound (157 mg, 79%) as a pale yellow solid. ¹H NMR (DMSO-*d*₆) δ 1.39–2.05 (m, 4H), 2.69 (t, *J* = 6.7 Hz, 2H), 3.55–3.73 (m, 2H), 3.95–4.20 (m, 4H), 4.54–4.82 (m, 3H), 5.12–5.40 (m, 2H), 5.88–5.99 (m, 2H), 6.54 (br s, 2H), 6.86–6.94 (m, 1H), 7.11–7.23 (m, 2H), 7.29–7.38 (m, 1H), 7.41–7.50 (m, 2H), 7.56–7.69 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 32.2, 38.2, 45.0, 61.8, 65.5, 71.0, 71.1, 85.9, 86.5, 112.6, 113.4, 117.1, 118.8, 126.7, 127.7, 130.0, 138.6, 139.4, 141.6, 148.6, 149.9, 151.4, 152.5, 159.2. HRMS calcd for C₂₆H₃₂N₇O₅ (M+H)⁺ 522.2459, found 522.2460.

8-[3'-(4-Aminobutoxy)biphenyl-4-ylmethylamino]adenosine (3-27)

tert-Butyl 3'-[4-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)butoxy]biphenyl-4-ylmethylcarbamate (3-65). To a solution of 3-29 (810 mg, 2.71 mmol) in DMF (5.41 mL) was added K₂CO₃ (561 mg, 4.06 mmol) followed by *N*-(4-bromobutyl)phthalimide (992 mg, 3.52 mmol), and the resulting mixture was heated at 50 °C with stirring for 28 h. After being allowed to cool to room temperature, the reaction mixture was partitioned between AcOEt (70 mL) and H₂O (30 mL). The organic layer was washed successively with H₂O (30 mL × 2) and brine (30 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on

NH silica gel (gradient: 19–40% AcOEt in hexane) to give the title compound (1.29 g, 95%) as a white solid. ¹H NMR (CDCl₃) δ 1.47 (s, 9H), 1.81–1.98 (m, 4H), 3.79 (t, *J* = 6.8 Hz, 2H), 4.05 (t, *J* = 5.9 Hz, 2H), 4.36 (d, *J* = 5.5 Hz, 2H), 4.78–4.96 (br, 1H), 6.82–6.90 (m, 1H), 7.05–7.18 (m, 2H), 7.28–7.39 (m, 3H), 7.48–7.59 (m, 2H), 7.67–7.76 (m, 2H), 7.80–7.88 (m, 2H). ¹³C NMR (CDCl₃) δ 25.5, 26.8, 28.5, 37.8, 44.5, 67.3, 79.7, 113.3, 113.6, 119.6, 123.3, 127.5, 128.0, 129.9, 132.2, 134.1, 138.2, 140.3, 142.4, 156.0, 159.4, 168.6. HRMS calcd for C₃₀H₃₆N₃O₅ (M+NH₄)⁺ 518.2649, found 518.2648.

tert-Butyl 3'-(4-aminobutoxy)biphenyl-4-ylmethylcarbamate (3-66). To a stirred solution of **3-65** (1.29 g, 2.58 mmol) in CHCl₃ (15.5 mL) was added dropwise a solution of H₂NNH₂·H₂O (645 mg, 12.9 mmol) in EtOH (3.1 mL), and the resulting mixture was stirred at room temperature for 80 h. The reaction mixtue was filtered through a pad of Hyflo Super-Cel and the pad was washed with DCM (100 mL). The filtrate was washed with H₂O/brine (1/1, 40 mL), dreid (Na₂SO₄), and concentrated under reduced pressure to give the title compound (1.03 g) as a pale yellow oil, which was used in the next step without further purification. ¹H NMR (CDCl₃) δ 1.48 (s, 9H), 1.59–1.70 (m, 2H), 1.80–1.94 (m, 2H), 2.72–2.84 (m, 2H), 4.04 (t, *J* = 6.4 Hz, 2H), 4.36 (d, *J* = 6.0 Hz, 2H), 4.76–5.01 (br, 1H), 6.84–6.93 (m, 1H), 7.07–7.20 (m, 2H), 7.29–7.40 (m, 3H), 7.49–7.60 (m, 2H). HRMS calcd for C₂₂H₃₁N₂O₃ (M+H)⁺ 371.2329, found 371.2329.

Benzyl 4-[4'-(tert-butoxycarbonylaminomethyl)biphenyl-3-yloxy]butylcarbamate (3-67). To a solution of **3-66** (1.03 g, as 2.58 mmol) in THF (12.9 mL) was added Cbz-OSu (771 mg, 3.09 mmol), and the resulting mixture was stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on NH silica gel (gradient: 29–50% AcOEt in hexane) to give the title compound (1.16 g, 89% from **3-65**) as an off-white solid. ¹H NMR (DMSO-*d*₆) δ 1.34 (minor) and 1.40 (major) (br s and s, 9H), 1.51–1.64 (m, 2H), 1.66–1.82 (m, 2H), 3.01–3.16 (m, 2H), 4.03 (t, *J* = 6.3 Hz, 2H), 4.16 (d, *J* = 6.3 Hz, 2H), 5.01 (major) and 5.05 (minor) (s and br s, 2H), 6.84–6.95 (m, 1H), 7.10–7.52 (m, 12H), 7.56–7.71 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 26.1 (2C), 28.3, 40.0, 43.1, 65.1, 67.1, 77.8, 112.6, 113.4, 118.8, 126.7, 127.5, 127.7, 128.4, 130.0, 137.3, 138.5, 139.6, 141.5, 155.9, 156.2, 159.1. HRMS calcd for C₃₀H₄₀N₃O₅ (M+NH₄)⁺ 522.2962, found 522.2962.

Benzyl 4-[4'-(aminomethyl)biphenyl-3-yloxy]butylcarbamate (3-68). To a stirred ice-cold solution of **3-67** (1.45 g, 2.87 mmol) in DCM (10.8 mL) was added dropwise TFA (3.60 mL), and the resulting mixture was allowed to warm to room temperature for 20 h. The reaction mixture was added carefully to saturated aqueous NaHCO₃/H₂O (3/1, 144 mL) while stirring and the whole was extracted with DCM (100 mL). The organic layer was washed with brine (50 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (gradient: 0–3% MeOH in AcOEt) to give the title compound (1.04 g, 90%) as a slightly yellow solid. ¹H NMR (DMSO-*d*₆) δ 1.50–1.64 (m, 2H), 1.67–1.79 (m, 2H), 1.90–2.37 (br, 2H), 3.01–3.15 (m, 2H), 3.75 (s, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 5.01 (major) and 5.05 (minor) (s and br s, 2H), 6.83–7.48 (m, 12H), 7.53–7.68 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ 26.1, 26.2, 40.0, 45.3, 65.1, 67.1, 112.6, 113.2, 118.8, 126.5, 127.6,

127.8, 128.4, 129.9, 137.3, 138.1, 141.7, 143.5, 156.2, 159.1. HRMS calcd for $C_{25}H_{29}N_2O_3$ (M+H)⁺ 405.2173, found 405.2169.

8-[3'-(4-Benzyloxycarbonylaminobutoxy)biphenyl-4-ylmethylaminoJadenosine (3-69). The title compound (356 mg, 92%) was obtained as a pale yellow foam from **13** (200 mg, 0.578 mmol) and **3-68** (701 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **3-2**. ¹H NMR (DMSO-*d*₆) δ 1.50–1.62 (m, 2H), 1.65–1.78 (m, 2H), 3.01–3.13 (m, 2H), 3.56–3.72 (m, 2H), 3.95–4.17 (m, 4H), 4.56–4.70 (m, 2H), 4.70–4.80 (m, 1H), 5.01 (major) and 5.04 (minor) (s and br s, 2H), 5.18 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 6.8 Hz, 1H), 5.89–6.01 (m, 2H), 6.54 (br s, 2H), 6.83–6.93 (m, 1H), 7.10–7.23 (m, 2H), 7.26–7.50 (m, 9H), 7.55–7.68 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 26.1, 26.2, 40.0, 45.0, 61.8, 65.2, 67.2, 71.0, 71.1, 85.9, 86.5, 112.7, 113.4, 117.1, 118.9, 126.7, 127.7, 127.8 (2C), 128.4, 130.0, 137.3, 138.6, 139.4, 141.6, 148.6, 149.9, 151.4, 152.5, 156.2, 159.1. HRMS calcd for C₃₅H₄₀N₇O₇ (M+H)⁺ 670.2984, found 670.2980.

8-[3'-(4-Aminobutoxy)biphenyl-4-ylmethylamino]adenosine (3-27). The title compound (212 mg, 80%) was obtained as a pale yellow solid from **3-69** (333 mg, 0.497 mmol) according to a procedure similar to that described for the preparation of **3-26**. ¹H NMR (DMSO-*d*₆) δ 1.43–1.54 (m, 2H), 1.68–1.80 (m, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 3.56–3.72 (m, 2H), 3.97–4.08 (m, 3H), 4.10–4.19 (m, 1H), 4.56–4.70 (m, 2H), 4.70–4.82 (m, 1H), 5.12–5.44 (m, 2H), 5.90–6.03 (m, 2H), 6.54 (br s, 2H), 6.87–6.93 (m, 1H), 7.12–7.23 (m, 2H), 7.30–7.38 (m, 1H), 7.41–7.51 (m, 2H), 7.57–7.69 (m, 3H), 7.90 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 26.3, 29.7, 41.4, 45.0, 61.8, 67.5, 71.0, 71.2, 85.9, 86.5, 112.6, 113.4, 117.1, 118.8, 126.7, 127.7, 130.0, 138.6, 139.4, 141.6, 148.6, 149.9, 151.4, 152.5, 159.2. HRMS calcd for C₂₇H₃₄N₇O₅ (M+H)⁺ 536.2616, found 536.2616.

Purity of Tested Compounds in Chapter 3

compd	formula	calcd			found			$t_{\rm R}^{a}$	area
		С	Н	Ν	С	Н	Ν	(min)	(%)
3-1	$C_{23}H_{24}N_6O_5 \cdot 0.9H_2O$	57.47	5.41	17.48	57.44	5.39	17.40	25.8	99.6
3-2	$C_{24}H_{26}N_6O_5{\cdot}0.4H_2O$	59.35	5.56	17.30	59.46	5.57	17.26	30.6	97.3
3-3	$C_{25}H_{28}N_6O_5{\cdot}0.4H_2O$	60.09	5.81	16.82	60.22	5.83	16.71	33.6	96.1
3-4	$C_{26}H_{30}N_6O_5{\cdot}0.3H_2O$	61.00	6.02	16.42	61.04	6.04	16.28	36.6	99.6
3-5	$C_{26}H_{30}N_6O_5{\cdot}0.25H_2O$	61.10	6.02	16.44	61.04	5.93	16.45	35.4	98.7
3-6	C ₂₆ H ₂₈ N ₆ O ₇	58.20	5.26	15.66	57.90	5.40	15.66	29.1	98.6
3-7	$C_{25}H_{27}N_7O_6{\cdot}0.8H_2O$	56.03	5.38	18.29	56.01	5.33	18.30	25.7	99.7
3-8	$C_{25}H_{28}N_6O_6{\cdot}0.25H_2O$	58.53	5.60	16.38	58.79	5.76	15.99	27.0	99.7
3-9	$C_{23}H_{24}N_6O_5{\cdot}0.4H_2O$	58.57	5.30	17.82	58.55	5.43	17.82	24.4	98.3
3-10	$C_{24}H_{26}N_6O_5$	60.24	5.48	17.56	59.91	5.47	17.52	31.2	98.5
3-11	$C_{25}H_{28}N_6O_5{\cdot}0.25H_2O$	60.41	5.78	16.91	60.40	5.80	16.85	34.2	98.1
3-12	$C_{26}H_{30}N_6O_5{\cdot}0.25H_2O$	61.10	6.02	16.44	61.12	6.09	16.24	37.8	99.3
3-13	$C_{26}H_{30}N_6O_5{\cdot}0.5H_2O$	60.57	6.06	16.30	60.59	6.11	16.23	35.9	99.6
3-14	$C_{26}H_{28}N_6O_7{\cdot}0.3H_2O$	57.62	5.32	15.51	57.62	5.29	15.49	29.0	97.5
3-15	$C_{25}H_{27}N_7O_6{\cdot}0.9H_2O$	55.84	5.40	18.23	55.97	5.33	17.98	23.9	96.8
3-16	$C_{25}H_{28}N_6O_6{\cdot}0.8H_2O$	57.42	5.71	16.07	57.46	5.65	15.78	25.7	97.5
3-17	$C_{23}H_{24}N_6O_5{\cdot}0.3H_2O$	58.79	5.28	17.89	58.70	5.41	17.91	22.9	97.0
3-18	$C_{24}H_{26}N_6O_5$	60.24	5.48	17.56	59.98	5.51	17.51	30.8	99.4
3-19	$C_{25}H_{28}N_6O_5{\cdot}0.3H_2O$	60.30	5.79	16.88	60.25	5.71	16.82	33.9	98.4
3-20	$C_{26}H_{30}N_6O_5$	61.65	5.97	16.59	61.56	5.94	16.52	37.6	99.1
3-21	$C_{26}H_{30}N_6O_5$	61.65	5.97	16.59	61.46	5.86	16.58	35.7	98.8
3-22	$C_{26}H_{28}N_6O_7{\cdot}0.3H_2O$	57.62	5.32	15.51	57.64	5.39	15.33	28.3	96.6
3-23	$C_{25}H_{27}N_7O_6$	57.57	5.22	18.80	57.28	5.14	18.53	22.5	95.7
3-24	$C_{25}H_{28}N_6O_6{\cdot}0.3H_2O$	58.43	5.61	16.35	58.40	5.52	16.31	24.4	99.3
3-25	$C_{25}H_{29}N_7O_5{\cdot}0.5H_2O$	58.13	5.85	18.98	58.14	5.82	18.61	14.2	97.9
3-26	$C_{26}H_{31}N_7O_5{\cdot}0.6H_2O$	58.66	6.10	18.42	58.66	6.08	18.22	15.9	96.3
3-27	$C_{27}H_{33}N_7O_5 \cdot 0.3H_2O$	59.94	6.26	18.12	59.96	6.42	17.86		

 Table E3. Elemental Analysis and/or HPLC–UV Analysis Data for Tested Compounds in Chapter 3

 $^{a}t_{R}$ is the retention time of the compound.

Synthetic Procedures and Characterization Data for Tested Compounds in Chapter 4

5'-O-Biphenyl-2-yladenosine (4-1)

The title compound was synthesized from **23** (200 mg, 0.651 mmol) and 2-phenylphenol (133 mg, 0.781 mmol) according to a procedure similar to that described for the preparation of **4-4**, purified by flash column chromatography on NH silica gel (gradient: 0–10% MeOH in DCM), and isolated as an off-white amorphous solid (152 mg, 56% from **23**). ¹H NMR (DMSO-*d*₆) δ 4.15–4.33 (m, 4H), 4.48–4.60 (m, 1H), 5.38 (d, *J* = 5.0 Hz, 1H), 5.49 (d, *J* = 6.3 Hz, 1H), 5.88 (d, *J* = 6.3 Hz, 1H), 7.00–7.10 (m, 1H), 7.11–7.19 (m, 1H), 7.20–7.45 (m, 7H), 7.46–7.55 (m, 2H), 7.70 (s, 1H), 8.12 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 68.6, 70.6, 73.0, 82.8, 86.7, 112.9, 118.9, 121.3, 127.0, 128.1, 128.9, 129.3, 130.1, 130.7, 138.1, 138.7, 149.7, 152.8, 155.2, 156.1. HRMS calcd for C₂₂H₂₂N₅O₄ (M+H)⁺ 420.1666, found 420.1663.

5'-O-Biphenyl-3-yladenosine (4-2)

The title compound was synthesized from **23** (200 mg, 0.651 mmol) and 3-phenylphenol (133 mg, 0.781 mmol) according to a procedure similar to that described for the preparation of **4-4**, purified by flash column chromatography on NH silica gel (gradient: 0–10% MeOH in DCM), and isolated as an off-white amorphous solid (121 mg, 44% from **23**). ¹H NMR (DMSO-*d*₆) δ 4.22–4.42 (m, 4H), 4.69–4.78 (m, 1H), 5.43 (d, *J* = 5.3 Hz, 1H), 5.61 (d, *J* = 5.8 Hz, 1H), 5.98 (d, *J* = 5.0 Hz, 1H), 6.93–7.02 (m, 1H), 7.18–7.53 (m, 8H), 7.61–7.71 (m, 2H), 8.15 (s, 1H), 8.37 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 67.9, 70.5, 73.3, 82.4, 87.6, 112.8, 113.7, 119.1, 119.4, 126.8, 127.7, 128.9, 130.1, 139.4, 140.0, 141.8, 149.5, 152.8, 156.1, 158.8. HRMS calcd for C₂₂H₂₂N₅O₄ (M+H)⁺ 420.1666, found 420.1666.

5'-O-Biphenyl-4-yladenosine (4-3)

The title compound was synthesized from **23** (200 mg, 0.651 mmol) and 4-phenylphenol (133 mg, 0.781 mmol) according to a procedure similar to that described for the preparation of **4-4**, purified by recrystallization from EtOH, and isolated as a white solid (107 mg, 74% from **23**). mp 238–241 °C. ¹H NMR (DMSO-*d*₆) δ 4.21–4.42 (m, 4H), 4.68–4.78 (m, 1H), 5.43 (d, *J* = 5.3 Hz, 1H), 5.62 (d, *J* = 6.0 Hz, 1H), 5.98 (d, *J* = 5.0 Hz, 1H), 7.02–7.14 (m, 2H), 7.26–7.49 (m, 5H), 7.57–7.69 (m, 4H), 8.17 (s, 1H), 8.37 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 67.9, 70.5, 73.3, 82.3, 87.6, 115.0, 119.1, 126.3, 126.8, 127.9, 128.9, 132.9, 139.4, 139.8, 149.5, 152.8, 156.1, 158.0. HRMS calcd for C₂₂H₂₂N₅O₄ (M+H)⁺ 420.1666, found 420.1662.

5'-O-Phenyladenosine (4-4)

To a stirred mixture of 2',3'-O-isopropylideneadenosine 23 (200 mg, 0.651 mmol), PhOH (73.5 mg, 0.781 mmol),

and PPh₃ (205 mg, 0.781 mmol) in THF (2.84 mL) was added dropwise DIAD (40% in toluene, ca.1.9 mol/L, 0.411 mL, ca. 0.781 mmol), and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (95% AcOEt in hexane) to give 2',3'-*O*-isopropylidene-5'-*O*-phenyladenosine containing triphenylphosphine oxide as main impurity (294 mg). This impure product was dissolved in 70% (v/v) aqueous HCO₂H (6.51 mL) and stirred at room temperature for 27.5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on NH silica gel (gradient: 0–10% MeOH in DCM) to give the title compound (76.5 mg, 34% from **23**) as an off-white solid. An analytical sample was obtained by recrystallization from EtOH. mp 191–195 °C. ¹H NMR (DMSO-*d*₆) δ 4.12–4.38 (m, 4H), 4.65–4.76 (m, 1H), 5.41 (d, *J* = 5.5 Hz, 1H), 5.61 (d, *J* = 5.8 Hz, 1H), 5.96 (d, *J* = 5.0 Hz, 1H), 6.90–7.02 (m, 3H), 7.20–7.42 (m, 4H), 8.16 (s, 1H), 8.34 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ 67.7, 70.5, 73.3, 82.3, 87.6, 114.5, 119.1, 120.9, 129.6, 139.4, 149.5, 152.8, 156.1, 158.3. HRMS calcd for C₁₆H₁₈N₅O₄ (M+H)⁺ 344.1353, found 344.1354.

Purity of Tsted Compounds in Chapter 4

compd	formula	calcd			found			$t_{\rm R}{}^a$	area
		С	Н	Ν	С	Н	Ν	(min)	(%)
4-1	$C_{22}H_{21}N_5O_4{\cdot}0.6H_2O$	61.42	5.20	16.28	61.51	5.22	16.20	18.8^{b}	98.3 ^b
4-2	$C_{22}H_{21}N_5O_4{\cdot}0.7H_2O$	61.16	5.23	16.21	61.32	5.24	16.12	38.0	97.6
4-3	$C_{22}H_{21}N_5O_4{\cdot}0.8H_2O$	60.91	5.25	16.14	60.85	5.38	15.95	38.3	98.8
4-4	$C_{16}H_{17}N_5O_4 \cdot 0.4H_2O$	54.82	5.12	19.98	54.69	5.17	19.98	24.9	97.9

Table E4. Elemental Analysis and HPLC–UV Analysis Data for Tested Compounds in Chapter 4

 $^{a}t_{R}$ is the retention time of the compound. b Isocratic elution was employed (MeOH/0.1% aq HCO₂H = 1/1).

Experimental Procedures for Physicochemical Evaluation

Conformational analysis

The most stable conformation for compound **1-63** was determined by the following procedure using Spartan'14. First, the systematic conformational search was carried out for compound **1-63**, and then the generated conformer was optimized by the molecular mechanics (MM) method at MMF94 force field. We used the Conformation Distribution option in Spartan'14. Finally, among the conformers optimized by the MM method, 20 conformers were selected in order of increasing energy and further optimized by DFT methods at B3LYP/6-31G* level. The lowest energy conformation was selected as the most stable one.

The most stable conformations of compound A, B, and 3-10 were determined by the same procedure as above.

Determination of solubility in JP2

Approximately 1 mg of a compound was shaken with 1 mL of JP2 in an incubator at 37 °C for 1 h. The resulting mixture was filtered through a syringe filter (GL Chromatodisc Type 13N, Pore Size 0.45 µm, GL Sciences Inc., Tokyo, Japan). An aliquot of the filtrate was mixed with an equal volume of internal standard solution (a 1 mg/mL solution of 8-(propylamino)adenosine in DMSO) to give a sample solution. The sample solution was subjected to HPLC–UV analysis under the same condition used for determining purity of the tested compounds, and the solubility was calculated using a previously determined calibration curve.

Experimental Procedures for Biochemical and Biological Evaluation

Quantitative real-time RT-PCR

Human total RNAs derived from stomach, intestine, and colon were purchased from BIOCHAIN (Hayward, CA), and total RNA from HeLa cells was prepared by using Isogen (Nippongene, Toyama, Japan). RNA concentrations were determined by use of RiboGreen RNA quantification reagent and kit (Molecular Probes, Eugene, OR). Quantitative real-time RT-PCR was performed with a Tagman EZ RT-PCR kit (Applied Biosystems, Carlsbad, CA). Primers and TaqMan probes were as follows: for human CNT1 (hCNT1), 5'-ATT TAC CAG TGC TGC CGT GAG-3' (forward) and 5'-AAA CCG ACA GCA GTT GTC CAG-3' (reverse), with probe 5'-AGA GCG TCA ATC CAG AGT TCA GCC CA-3'; for human CNT2 (hCNT2), 5'-GGC AGC TTG CAT CTT GAA TTT C-3' (forward) and 5'-CAA AAA CGA GTG AAC CAG GAC A-3' (reverse), with probe 5'-CCT TGT TTG TCA TCA CCT GCT TGG TGA TCT-3'; for human CNT3 (hCNT3), 5'-GCT GGT CCG ACC ATA TTT ACC TTA C-3' (forward) and 5'-CGC TTC CAG CAA TGG TAG AGA-3' (reverse), with probe 5'-TCA CCA AGT CTG AAC TCC ACG CCA TC-3'; for human ENT1 (hENT1), 5'-GGC CAC TCA GTA TTT CAC AAA CC-3' (forward) and 5'-GGC GTC CTT GCT CAG TTC A-3' (reverse), with probe 5'-CAT GTC CCA GAA TGT GTC CTT GGT CAC TG-3'; and for human ENT2 (hENT2), 5'-ACT TTA TCA CGC CCT GTG TGG-3' (forward) and 5'-GGA TGA TTT ATT GGC CAG GTA GTA G-3' (reverse), with probe 5'-CAT CCT CAT GTC CAT GGT GTG TTA CCT GA-3'. PCR was performed under the following conditions: 1 cycle at 50 °C for 2 min, 1 cycle at 60 °C for 30 min, 1 cycle at 95 °C for 5 min, 40 cycles at 94 °C for 20 sec and at 62 °C for 1 min. Samples were analyzed with serially (1:10) diluted plasmid DNA to prepare the standard curve.

Inosine or thymidine uptake assay in COS-7 cells

The cDNA encoding hCNT1, hCNT2 or rCNT2 was subcloned into the pCI-neo mammalian expression vector (Promega, Madison, WI). The cDNA encoding hCNT3 was subcloned into the pcDNA3.1 vector (Thermo Fischer Scientific, MA, USA). COS-7 cells (RIKEN, Japan) were then transfected with a given expression vector by using Lipofectamine 2000 (Thermo Fischer Scientific, MA, USA). Briefly, COS-7 cells were seeded at 5×10^4 cells into each well of collagen type I-coated 96-well plates containing DMEM (Thermo Fischer Scientific, MA, USA) with 10% fetal calf serum and cultured for 2 h. Then, for use in each well, 0.3 µg plasmid DNA was diluted in 25 µL of OPTI-MEM (Thermo Fischer Scientific, MA, USA). Zero point five microliter of Lipofectamine 2000 was also diluted in 25 µL of OPTI-MEM and incubated at room temperature for 5 min. After the incubation, the diluted plasmid DNA was mixed with the diluted Lipofectamine 2000; and the mixture was incubated at room temperature for 25 min. Finally, the incubated mixture was added to each well, and the cells were cultured for 2 days, after which the inhibition assay was performed.

Transport assays were performed with a modification of the method described by Schaner et al.¹⁰⁹ Transport activities in COS-7 cells transiently expressing hCNT2, hCNT3, or rCNT2 were examined with [¹⁴C]-inosine, whereas the activities in COS-7 cells expressing hCNT1 were examined with [¹⁴C]-thymidine. The transfected cells were incubated with pretreatment buffer (2 mM KCl, 1 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES, 5 mM Tris, and 140 mM choline chloride; pH 7.4) at 37 °C twice for 10 min each time. Following aspiration of the pretreatment buffer, uptake buffer containing 10 µM inosine or thymidine prepared with ¹⁴C-labeled and unlabeled inosine or thymidine was added to the cells, which were then incubated at 37 °C for 30 min. All uptake studies were carried out in the presence of 10 µM nitrobenzylmercaptopurine riboside (NBMPR), which is an ENT inhibitor but not effective against CNTs. Uptake was measured in the presence of Na⁺ (140 mM NaCl, 2 mM KCl, 1 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES, 5 mM Tris, 5 mM glucose; pH 7.4) or absence of Na⁺, in which case NaCl was replaced by choline chloride (140 mM). The transport was stopped by aspiration of the reaction mixture, and the cells were washed twice with ice-cold Na⁺-free buffer including 10 µM unlabeled inosine or thymidine. Then, they were solubilized with 0.2 M sodium hydroxide. Radioactivity of the cell lysates was measured by means of a liquid scintillation counter. One-hundred percent transport was set as the difference between the uptake in the presence and the absence of Na⁺, and the percentage of inosine or thymidine uptake at each compound concentration was calculated. The half maximal inhibitory concentration (IC50 value) was calculated by nonlinear regression analysis of inosine or thymidine uptake assays (at least three independent experiments) using GraphPad Prism (GraphPad Software, CA, USA).

Animals

Male Sprague-Dawley (SD) rats were purchased from Charles River Laboratories Japan, Inc. (Kanagawa, Japan). Throughout the study, the rodents were housed in a constant-temperature room with a 12-h/12-h lighting cycle (lights on 8:00 a.m. to 8:00 p.m.) and allowed access to laboratory chow diet (CE-2 pellets; CLEA Japan, Inc.) and water ad libitum. All studies using rats were performed in accordance with guidelines approved by the laboratory animal committee of Kissei Pharmaceutical Co., Ltd.

Male cebus monkeys (*Cebus apella*) were also used in the present study. During the study period, the animals were given apples or oranges and a pellet diet (New World Primate Diet #5040, PMI Nutrition International, LLC, Brentwood, MO) at 1:00–2:00 p.m. Water was freely available for intake during the study period, but water intake was restricted on days of urine collection in repeated doses studies using compound **3-26**; instead, 10 mL/kg of distilled water was orally administered to the monkeys at 11:00 a.m. and 7:00 p.m. The monkeys were housed in a constant-temperature room with a 12-h/12-h lighting cycle (lights on 7:00 a.m. to 7:00 p.m.). All studies using monkeys were carried out in the facilities of Japan Biological Science Inc. (JBS Inc), and were performed in accordance with the guidelines approved by the laboratory animal committee of JBS, Inc.

Purine load test in rats

Male SD rats (5 weeks old) were fasted overnight and subcutaneously treated with potassium oxonate (Sigma-Aldrich, MO, USA; 100 mg/kg), and after 1 hour, purine mixture (adenosine:inosine:guanosine = 1:1:1, 50 mg/kg) and compound **2-15** (50 mg/kg) or **2-20** (0.1, 1.0, or 10 mg/kg) were orally administered simultaneously. A control group was treated with potassium oxonate and purine mixture, and a group treated with only potassium oxonate represented endogenous plasma uric acid level. After 1 hour, blood was collected from the abdominal aorta under anesthesia, and uric acid levels in plasma were measured by phosphotungstic acid method.

Data were presented as means \pm SEM for each group. Statistical analysis was performed by using SAS System Version 9.3 (SAS Institute Inc., NC, USA). The statistical significance of the results was analyzed by the Student's t-test or the Dunnett's test.

Pharmacokinetic study of compound 2-20 in rats

Pharmacokinetics was investigated in male SD rats (6 weeks old, fasted for 16 h) after intravenous and oral administration. Compound 2-20 was dissolved in a mixture of dimethylacetamide and 5 % glucose solution (1:1v/v)for intravenous bolus injections at a dose of 1.0 mg/mL/kg. The intravenous dose was administered via tail-vein. Compound 2-20 was suspended in 0.5% sodium calboxymethylcellulose solution for oral administration at a dose of 10 mg/5 mL/kg. Blood samples (about 200 μ L) were collected from the jugular vein by use of heparinized syringe at 2 min, 0.25, 1, 2, 4, 6, 8, and 24 h after intravenous administration, and at 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h after oral administration. Plasma was prepared by centrifugation at $2280 \times g$ for 10 min at 4 °C. The collected plasma samples were stored at -20 °C until analysis. Aliquots of the plasma (50 µL) were deproteined with 150 µL of acetonitrile and added 50 µL of internal standard (100 nmol/L warfarin). The samples were then centrifuged at 2280 × g, for 20 minutes at 4 °C. The supernatant (5 µL) was injected into LC/MS. Samples were analyzed using a LC system coupled to a Q Exactive orbitrap mass spectrometer (Thermo Fisher scientific, MA, USA). For MS detection, the heated ESI source was operated in positive ion mode. Ions monitored in the SIM mode were m/z 520.2442 for compound 2-20. LC separation was performed using an Ultimate 3000 system (Thermo Fisher scientific, MA, USA) with a gradient elution from a Cadenza CD-C18 HT column (3 μ m, 50 mm \times 2.0 mm ID; Imtakt, Kyoto, JAPAN). The flow rate and column temperature were set at 0.4 ml/min and 50 °C, respectively. The mobile phase consisted of solvent A, 10 mM ammonium acetate aqueous solution, and solvent B, acetonitrile containing 0.1% formic acid and 20% 2-propanol. The gradient program is shown as follows: 10% B at 0-0.1 min; 90% at 0.1-0.5 min; 90% at 0.5–1.7 min; 10% at 1.7–1.8 min. The flow rate at 1.7–1.8 min was set at 1.4 ml/min for reequilibration. The standard curve was prepared in a concentration range from 1 to 5000 ng/mL for compound 2-20. Pharmacokinetic calculation was performed by noncompartmental analysis using WinNonlin version 6 (Pharsight Corporation, CA, USA) to obtain the maximal plasma concentration (C_{max}), and the area under the curve (AUC). Bioavailability (F) was

calculated as $F = (AUC (po) / AUC (iv)) \times (dose (iv) / dose (po)) \times 100$. The plasma total clearance (CL_{tot}), the volume of distribution (V_{dss}) and the elimination half–life ($t_{1/2}$) were calculated after intravenous administration.

Adenosine uptake assay in HeLa cells

Adenosine uptake by ENTs was studied by using HeLa cells (RIKEN, Japan). HeLa cells were incubated with the pretreatment buffer described above at 37 °C twice for 10 min each time. Following aspiration of the pretreatment buffer, uptake buffer containing 10 µM adenosine prepared with ¹⁴C-labeled and unlabeled adenosine was added to the cells, which were then incubated at 37 °C for 30 min. Uptake was measured in the presence of Na⁺-free buffer (140 mM choline chloride, 2 mM KCl, 1 mM CaCl₂, 1 mM MgCl₂, 10 mM HEPES, 5 mM Tris, 5 mM glucose; pH 7.4). The transport was stopped by aspiration of the reaction mixture and washing twice with ice-cold Na⁺-free buffer including 10 µM unlabeled adenosine. Then, the cells were solubilized with 0.2 M sodium hydroxide. Radioactivity of the cell lysates was measured by use of the liquid scintillation counter. The percentage of adenosine uptake at each compound concentration against the control was calculated.

Effects of repeated doses compound 3-26 in cebus monkeys

A schematic of the study design is shown in Figure 3-3 (p.50). The study was a 3-phase crossover design using 2 cebus monkeys and included once daily dosing with compound 3-26 or the vehicle for 5 consecutive days with 5 days of acclimatization period (Figure 3-3). These 3 studies were sequentially performed on the 2 monkeys, the orders of studies being study No.3, No.2, and No.1 in monkey No.1 and study No.2, No.1, and No.3 in monkey No.2. During the study period, approximately 100 g of mashed sweet potato, 100 g of fresh fruits (apple, banana, or orange), and 100 g of pancake were provided to each animal daily between 1:00 p.m. and 2:00 p.m. Potassium oxonate, yeast RNA and potassium oxonate, or the latter plus 3-26 were administered from day 6 to day 10. Yeast RNA (100 mg/kg) and 3-26 (50 mg/kg) were mixed with the mashed sweet potato and were provided to the monkeys between 1:00 p.m. and 2:00 p.m. Potassium oxonate was suspended in saline containing 10% ethanol and 40% PEG 400 and subcutaneously administered twice a day (11:00 a.m.: 150 mg/kg, 7:00 p.m.: 200 mg/kg). Blood and urine were collected on days 2, 5, 6, 8, and 10. Blood was collected into a heparinized syringe via the saphenous vein of a lower limb at 9:00 a.m., 4:00 p.m., and 7:00 p.m.; and the plasma was obtained after centrifugation. Urine collection was started at 11:00 a.m. and collected until 7:00 p.m. (0-8 h) and from 7:00 p.m. until 9:00 a.m. of the next day (8–22 h). Uric acid levels of plasma and urine were measured with a Uric acid Test Wako kit (Wako Pure Chemical Industries, Ltd.). Urinary creatinine was measured by using a Creatinine-test Wako kit (Wako Pure Chemical Industries, Ltd.).

Pharmacokinetic study of compound 3-26 in cebus monkeys

Chromatographic separation was carried out on an Alliance 2690 HPLC system (Waters, Milford, MA) equipped with a Capsulepak UG C18 column (3 µm, 50 × 4.6 mm) purchased from Shiseido (Tokyo, Japan). A mobile phase consisting of acetonitrile and 0.1% acetic acid in water (50:50, v/v) was used with a flow rate of 0.2 mL/min. The column temperature was maintained at 50 °C. Sample preparation was performed by using a PROSPECT system (PROSPEKT2[®], Spark Holland, The Netherlands), which involves automated solid-phase extraction on-line linked to the HPLC system. Mass spectra were obtained with an API 365 mass spectrometer (Perkin-Elmer Wellesley, MA) equipped with a turbo ion-spray source. The positive mode was used for the analysis. The strongest fragment was selected and used as the Q3 ion to be monitored.

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