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 | 2-bromo-5,6-dichloro-1-β-D-ribofuranosyl-1*H*-benzimidazole |
| BM | basolateral membrane |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| *t*-Bu | *tert*-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 | *N*,*N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| DRB | 5,6-dichloro-1-β-D-ribofuranosyl-1*H*-benzimidazole |
| ENT | equilibrative nucleoside transporter |
| Et | ethyl |

| | |
|---|---|
| *F* | bioavailability |
| hCNT | human concentrative nucleoside transporter |
| hENT | human equilibrative nucleoside transporter |
| HEPES | 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid |
| hERG | human ether-a-go-go-related gene |
| HPLC | high-performance liquid chromatography; high-pressure liquid chromatography |
| HRMS | high-resolution mass spectrometry |
| *i*-Pr | isopropyl |
| JP2 | Japanese Pharmacopoeia 2nd Fluid for dissolution test |
| $K_m$ | Michaelis constant |
| LogD | logarithm of distribution coefficient |
| $LogD_{6.5}$ | logarithm of distribution coefficient at pH 6.5 |
| *m*- | *meta*- |
| Me | methyl |
| mp | melting point |
| NBMPR | nitrobenzylmercaptopurine riboside; 6-[(4-nitrobenzyl)thio]-9-β-D-ribofuranosyl-9*H*-purine |
| NMR | nuclear magnetic resonance |
| NT | nucleoside transporter |
| *o*- | *ortho*- |
| *p*- | *para*- |
| Ph | phenyl |
| Phth | phthaloyl |
| ppm | parts per million |
| Pr | propyl |
| QOL | quality of life |
| quant. | quantitative |
| rCNT | rat concentrative nucleoside transporter |
| ref. | reference |
| RNA | ribonucleic acid |
| rt | room temperature |
| RT-PCR | reverse transcription polymerase chain reaction |
| SEM | standard error of the mean |
| SLC | solute carrier |
| TBS | *tert*-butyldimethylsilyl |
| Tf | trifluoromethanesulfonyl |

| | |
|---|---|
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| $t_{1/2}$ | elimination half-life |
| THF | tetrahydrofuran |
| $t_{max}$ | 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 |

目次

## 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]。

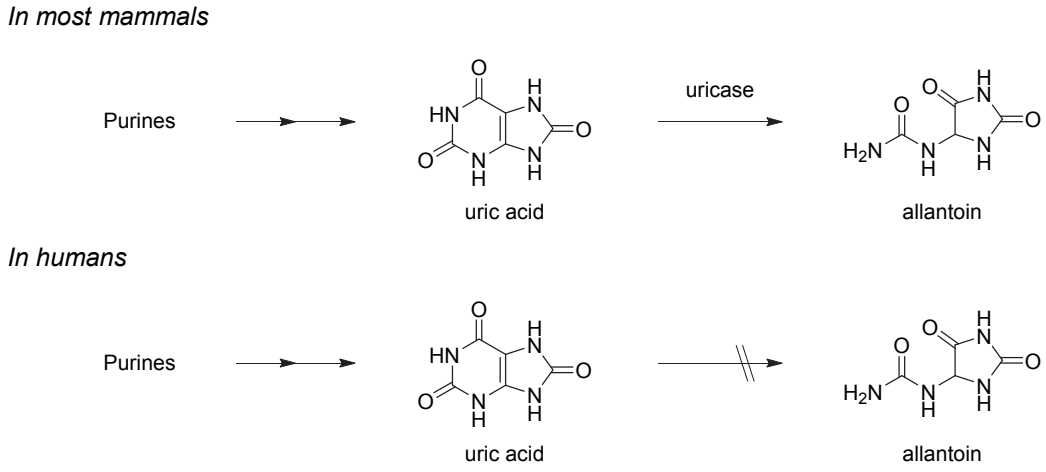



**Figure 1.** The difference in the end product of purine metabolism between most mammals and humans.

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

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]。

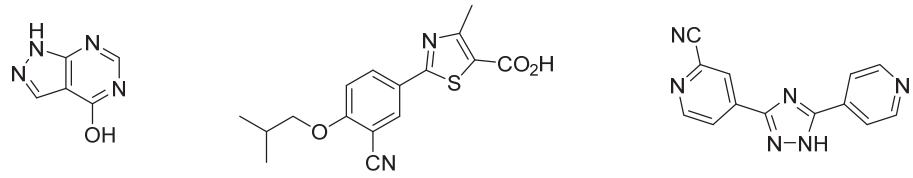



**Figure 2.** Structural formulas of clinically used xanthine oxidase inhibitors.

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]。

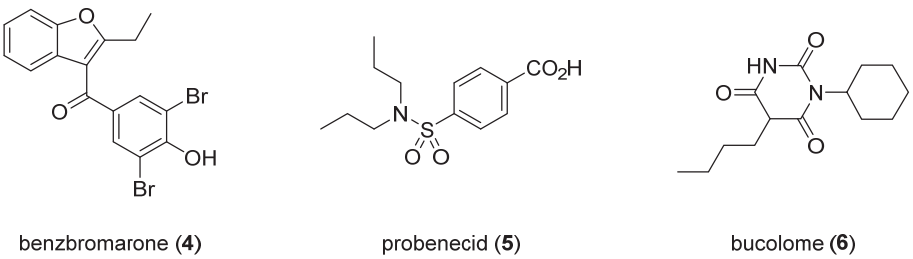



**Figure 3.** Structural formulas of clinically used uricosuric agents.

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。

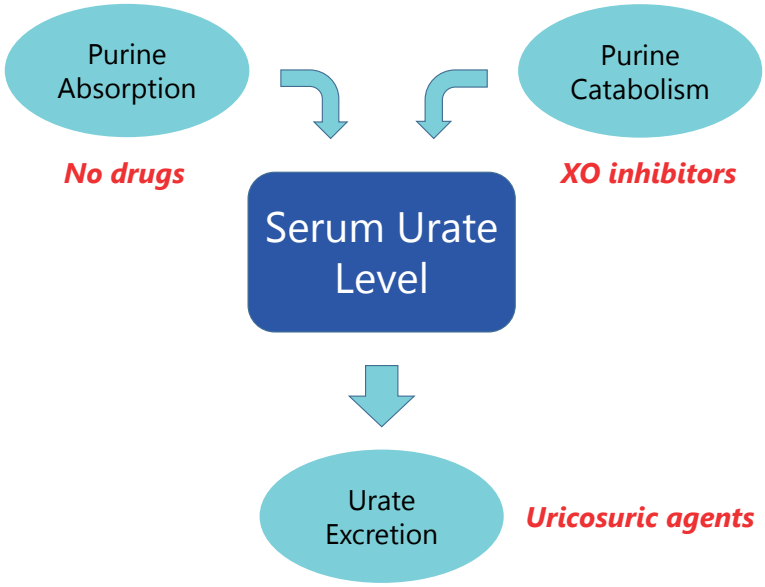



**Figure 4.** Main factors affecting serum urate level.

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 Yü らは、健常者に酵母由来の RNA を 1 日に 4 g、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治療薬を提供することを目的に本研究に着手した。以下、

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]。

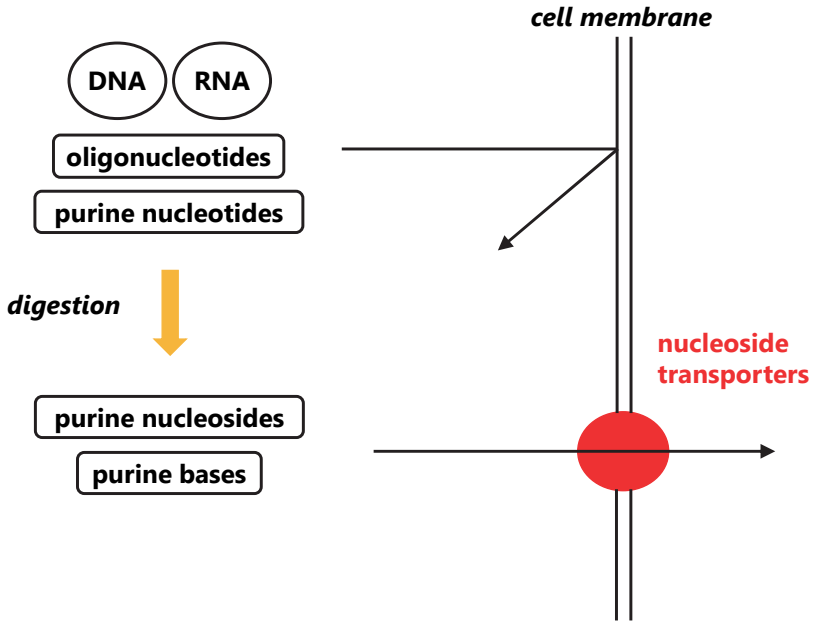



**Figure 1-1.** Purine absorption in the gastrointestinal tract.

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**

| 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 |

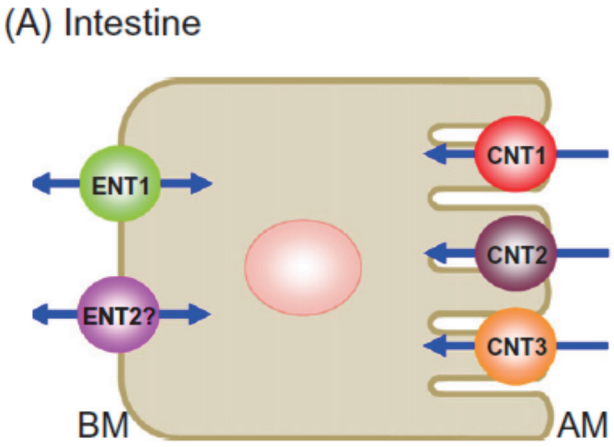



**Figure 1-2.** Schematic representation of the plasma membrane distributions of human CNTs and ENTs in intestine.

**Table 1-2. Substrate Selectivities of hCNTs**

| substrate | | nucleoside transporter[a] | | |
|---|---|---|---|---|
| | | hCNT1 | hCNT2 | hCNT3 |
| purine nucleosides | adenosine | T | T | T |
| | guanosine | NT | T | T |
| | inosine | NT | T | T |
| pyrimidine nucleosides | cytidine | T | NT | T |
| | thymidine | T | NT | T |
| | uridine | T | T | T |
| nucleobases | | NT | NT | NT |

[a]T, transported; NT, not transported.

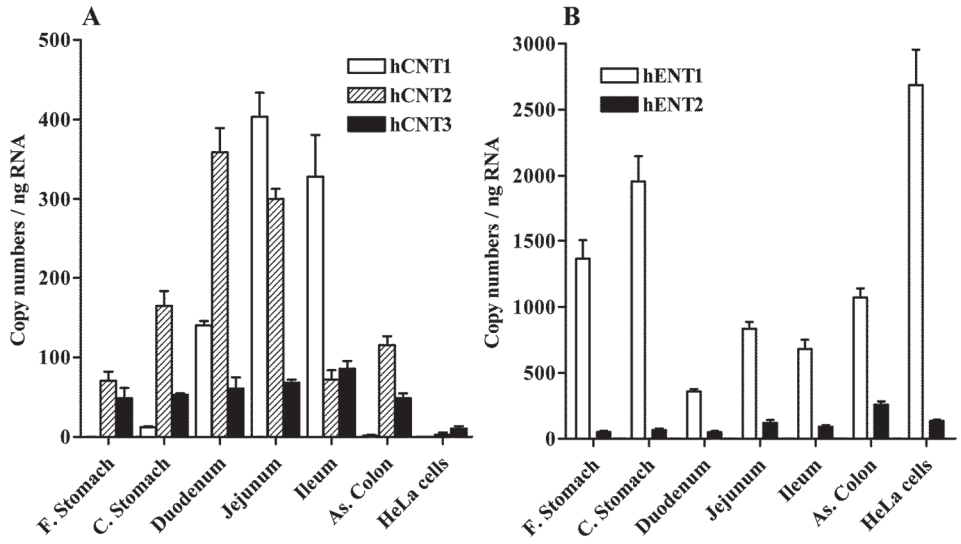



**Figure 1-3.** Expression profiles of nucleoside transporters in human digestive tract tissues and HeLa cells. Quantitative real-time RT-PCR was performed with primers and Taqman probes. F. Stomach: Fundus of stomach, C. Stomach: Corpus of stomach, As. Colon: Ascending colon. (A) Expression profiles 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 ± 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 **7**[37]、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 **10**[40] 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 $IC_{50}$ 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。

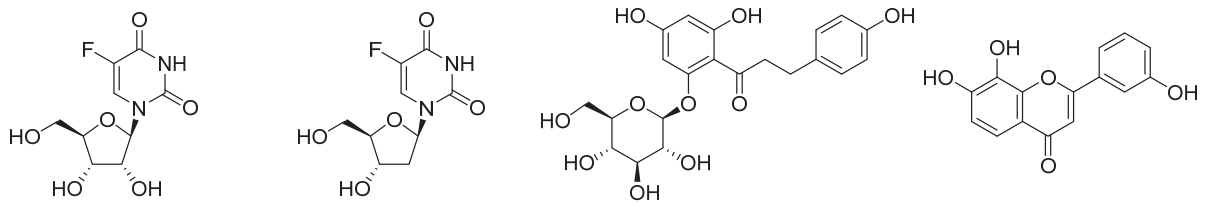



**Figure 1-4.** Inhibitory effects of known hCNT2 inhibitors on $Na^+$-dependent inosine uptake in COS-7 cells transiently expressing hCNT2.

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 $K_m$ 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 $K_m$ 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 $K_m$ 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。

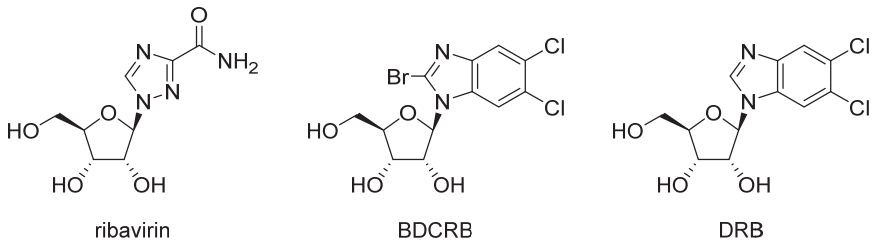
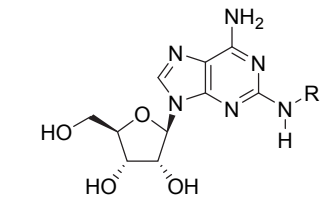



**Figure 1-5.** Structural formulas of unnatural nucleosides recognized by hCNT2.

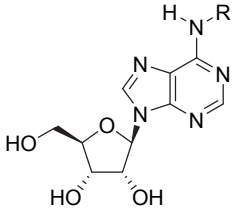
まず、初期検討としてアデノシンの 2、$N^6$、8、および 5′位に比較的軽微な修飾を加えた化合物群 **1-1**–**1-24** を合成し、それらの hCNT2 阻害活性を評価した。なお、特に断らない限り、これ以降の化合物群の一次評価は、前述の COS-7 細胞によるナトリウムイオン依存的なイノシン取り込み実験により行った。結果を表 1-3 に示す。塩基部を修飾した化合物群 **1-1**–**1-12** の中では、8-(ベンジルアミノ)アデノシン **1-12**($IC_{50}$ = 52 μM)に最も強力な hCNT2 阻害活性が認められ、しかもその活性は、図 1-4 に示した既知の hCNT2 阻害薬の中で最も高活性だった **7**($IC_{50}$ = 216 μM)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 Uptake in COS-7 Cells Transiently Expressing hCNT2**



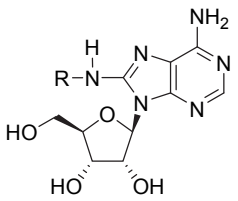
**A**

**1-1**: R = Me
**1-2**: R = Et
**1-3**: R = pentyl
**1-4**: R = Bn



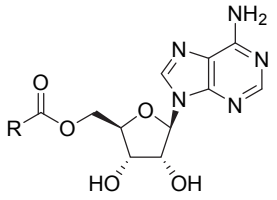
**B**

**1-5**: R = Me
**1-6**: R = Et
**1-7**: R = pentyl
**1-8**: R = Bn



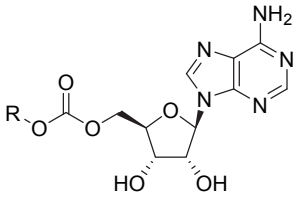
**C**

**1-9**: R = Me
**1-10**: R = Et
**1-11**: R = pentyl
**1-12**: R = Bn



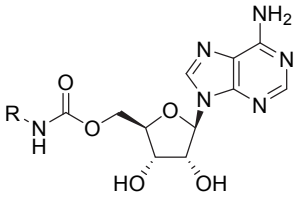
**D**

**1-13**: R = Me
**1-14**: R = Et
**1-15**: R = pentyl
**1-16**: R = Bn



**E**

**1-17**: R = Me
**1-18**: R = Et
**1-19**: R = pentyl
**1-20**: R = Bn



**F**

**1-21**: R = Me
**1-22**: R = Et
**1-23**: R = pentyl
**1-24**: R = Bn

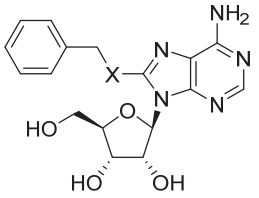
| R | $IC_{50}$ (μM)[a] | | | | | |
|---|---|---|---|---|---|---|
| | A | B | C | D | E | F |
| Me | inactive[b] | >100[c] | >1000[d] | >100[c] | >100[c] | >100[c] |
| Et | >100[c] | >100[c] | >1000[d] | >100[c] | >100[c] | >1000[d] |
| pentyl | inactive[b] | >100[c] | >1000[d] | >100[c] | >100[c] | >100[c] |
| Bn | >100[c] | inactive[b] | 52 ± 3.8 | >100[c] | >100[c] | >100[c] |
| **7** | 216 ± 40 μM | | | | | |

[a]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. [b]No inhibition was observed at the maximum concentration of 1000 μM. [c]Inhibition was less than 50% at the maximum concentration of 100 μM. [d]Inhibition was less than 50% at the maximum concentration of 1000 μM.

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

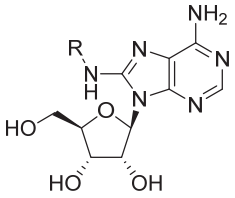
弱または消失した(表 1-6)。以上の結果より、化合物 **1-12** がシード化合物として妥当であることが示された。さらに、本化合物の 8 位に結合するベンジルアミノ基が、強力な hCNT2 阻害活性の発現に必須の部分構造であることも明らかになった。

**Table 1-4. Inhibitory Effects of Compounds 1-25–1-28 on $Na^+$-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2**



| compd | X | $IC_{50}$ (μM)[a] |
|---|---|---|
| **1-25** | $CH_2$ | >1000[b] |
| **1-26** | O | inactive[c] |
| **1-27** | S | inactive[c] |
| **1-28** | NMe | inactive[c] |
| **1-12** | NH | 52 ± 3.8 |

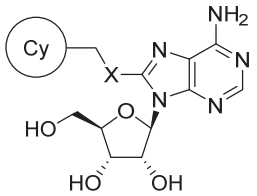
**Table 1-5. Inhibitory Effects of Compounds 1-29–1-33 on $Na^+$-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2**



| compd | R | $IC_{50}$ (μM)[a] |
|---|---|---|
| **1-29** | Ph | 289 ± 87 |
| **1-30** | $PhCH_2CH_2$ | 233 ± 19 |
| **1-31** | $PhCH_2CH_2CH_2$ | 536 ± 89 |
| **1-32** | (*R*)-PhCH(Me) | inactive[c] |
| **1-33** | (*S*)-PhCH(Me) | >1000[b] |
| **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 ± 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 μM. [c]No inhibition was observed at the maximum concentration of 1000 μM.

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

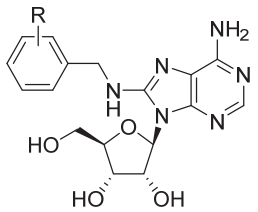



| compd | Cy | $IC_{50}$ (μM)[a] |
|---|---|---|
| **1-34** | cyclopopyl | inactive[b] |
| **1-35** | cyclopentyl | >1000[c] |
| **1-36** | cyclohexyl | >1000[c] |
| **1-37** | furan-2-yl | >1000[c] |
| **1-38** | furan-3-yl | inactive[b] |
| **1-39** | thiophen-2-yl | >100[d] |
| **1-40** | thiophen-3-yl | >100[d] |
| **1-41** | pyridin-2-yl | >100[d] |
| **1-42** | pyridin-3-yl | >100[d] |
| **1-43** | pyridin-4-yl | >100[d] |
| **1-12** | Ph | 52 ± 3.8 |

[a]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. [b]No inhibition was observed at the maximum concentration of 100 μM. [c]Inhibition was less than 50% at the maximum concentration of 1000 μM. [d]Inhibition was less than 50% at the maximum concentration of 100 μM.

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**

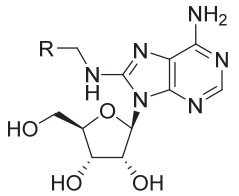



| compd | R | $IC_{50}$ (μM)[a] |
|---|---|---|
| **1-44** | 2-Me | 65 ± 5.9 |
| **1-45** | 3-Me | 19 ± 2.3 |
| **1-46** | 4-Me | 11 ± 4.2 |
| **1-47** | 2-OMe | >100[b] |
| **1-48** | 3-OMe | 13 ± 5.7 |
| **1-49** | 4-OMe | 36 ± 13 |
| **1-50** | 2-F | 15 ± 4.1 |
| **1-51** | 3-F | 16 ± 3.6 |
| **1-52** | 4-F | 63 ± 15 |
| **1-53** | 2-Cl | 5.7 ± 1.2 |
| **1-54** | 3-Cl | 5.4 ± 1.3 |
| **1-55** | 4-Cl | 11 ± 2.8 |
| **1-56** | 2-$CF_3$ | 22 ± 6.6 |
| **1-57** | 3-$CF_3$ | 11 ± 1.6 |
| **1-58** | 4-$CF_3$ | 26 ± 7.6 |
| **1-12** | H | 52 ± 3.8 |

[a]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. [b]Inhibition was less than 50% at the maximum concentration of 100 μM.

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**

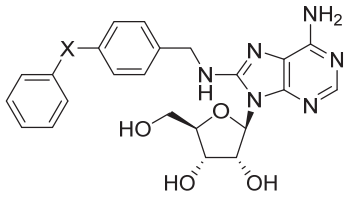


| compd | R | $IC_{50}$ (μM)[a] |
|---|---|---|
| **1-59** | 1-naphthyl | 5.7 ± 1.1 |
| **1-60** | 2-naphthyl | 5.3 ± 1.7 |
| **1-61** | biphenyl-2-yl | >100[b] |
| **1-62** | biphenyl-3-yl | 21 ± 9.8 |
| **1-63** | biphenyl-4-yl | 0.64 ± 0.19 |
| **1-12** | Ph | 52 ± 3.8 |

[a]Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean ± 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 μM.

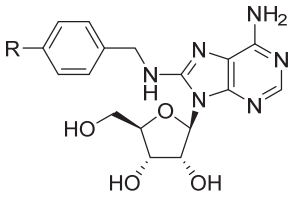
そこで、**1-63** の末端のベンゼン環の適切な位置を知る目的で、2 つのベンゼン環を炭素、酸素、および硫黄原子で繋いだ **1-64**–**1-66** をそれぞれ合成して hCNT2 阻害活性を評価したところ、全例で阻害活性が減弱した(表 1-9)。この結果より、2 つのベンゼン環は直接結合していることが重要だとわかった。次に、**1-63** の末端のフェニル基をシクロアルキル基で置換した **1-67**–**1-69** を合成して評価した(表 1-10)。シクロプロピル基で置換した **1-67** の hCNT2 阻害活性は **1-63** に比べやや減弱したが、**1-12** 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**



| compd | X | $IC_{50}$ (μM)[a] |
|---|---|---|
| **1-64** | $CH_2$ | 6.0 ± 0.8 |
| **1-65** | O | 3.3 ± 0.8 |
| **1-66** | S | 5.2 ± 1.4 |
| **1-63** | single bond | 0.64 ± 0.19 |

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



| compd | R | $IC_{50}$ (μM)[a] |
|---|---|---|
| **1-67** | cyclopropyl | 2.0 ± 0.64 |
| **1-68** | cyclopentyl | 0.53 ± 0.07 |
| **1-69** | cyclohexyl | 0.87 ± 0.30 |
| **1-63** | Ph | 0.64 ± 0.19 |

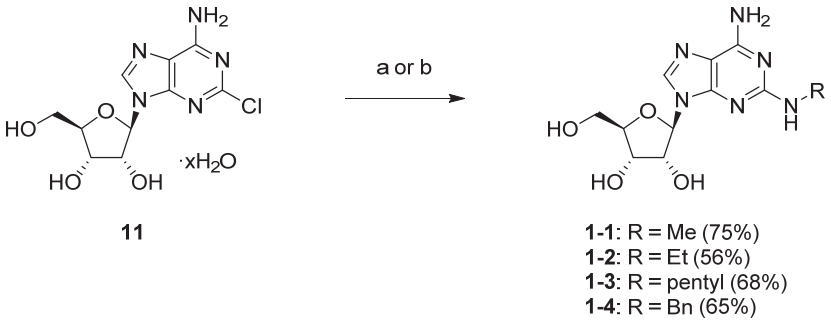
[a]Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean ± standard error of the mean (SEM) of at least three independent experiments unless otherwise stated.

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。

第三節　試験化合物の合成

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]



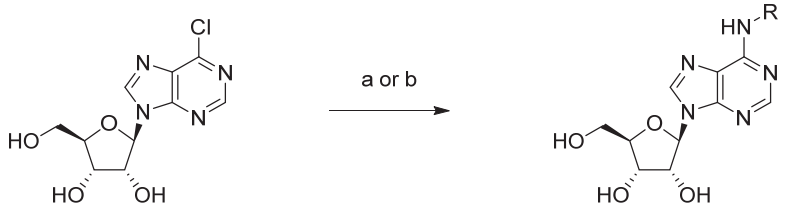

**11**

**1-1**: R = Me (75%)
**1-2**: R = Et (56%)
**1-3**: R = pentyl (68%)
**1-4**: R = Bn (65%)

[a]Reagents and conditions: (a) aq $MeNH_2$ or aq $EtNH_2$, EtOH, 100 °C, in a screw tube; (b) pentylamine or $BnNH_2$, *i*-$Pr_2NEt$, 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]




**12**

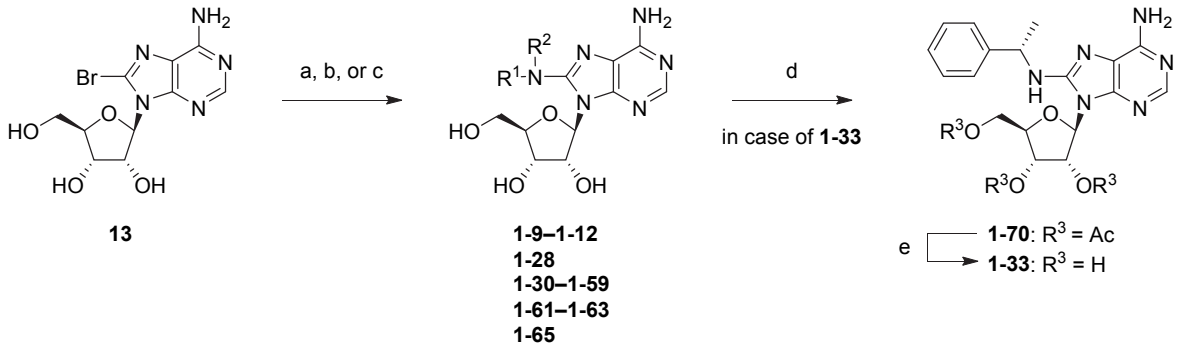
**1-5**: R = Me (54%)
**1-6**: R = Et (59%)
**1-7**: R = pentyl (88%)

[a]Reagents and conditions: (a) aq $MeNH_2$ or aq $EtNH_2$, EtOH, 100 °C, in a screw tube; (b) pentylamine, *i*-$Pr_2NEt$, 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 $R^1R^2NH$, EtOH, 100 °C, in a screw tube; (b) $R^1R^2NH$, *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube; (c) $R^1R^2NH$, *i*-$Pr_2NEt$, EtOH, 150 °C, in a sealed tube, microwave irradiation; (d) $Ac_2O$, $Et_3N$, DMAP, MeCN, rt; (e) NaOMe, MeOH, rt.

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

| compd | $R^1$ | $R^2$ | yield | compd | $R^1$ | $R^2$ | yield |
|---|---|---|---|---|---|---|---|
| **1-9** | Me | H | 61%[a] | **1-40** | thiophen-3-ylmethyl | H | 89%[b] |
| **1-10** | Et | H | 73%[a] | **1-41** | pyridin-2-ylmethyl | H | 53%[b] |
| **1-11** | pentyl | H | 81%[b] | **1-42** | pyridin-3-ylmethyl | H | 91%[b] |
| **1-12** | Bn | H | 93%[b] | **1-43** | pyridin-4-ylmethyl | H | 87%[b] |
| **1-28** | Bn | Me | 91%[b] | **1-44** | 2-methylbenzyl | H | 87%[b] |
| **1-30** | $PhCH_2CH_2$ | H | 82%[b] | **1-45** | 3-methylbenzyl | H | 80%[b] |
| **1-31** | $PhCH_2CH_2CH_2$ | H | 86%[b] | **1-46** | 4-methylbenzyl | H | 37%[b] |
| **1-32** | (*R*)-PhCH(Me) | H | 43%[c] | **1-47** | 2-methoxybenzyl | H | 44%[b] |
| **1-33** | (*S*)-PhCH(Me) | H | 40%[c,d] | **1-48** | 3-methoxybenzyl | H | 88%[b] |
| **1-34** | cyclopropylmethyl | H | 75%[b] | **1-49** | 4-methoxybenzyl | H | 91%[b] |
| **1-35** | cyclopentylmethyl | H | 77%[b] | **1-50** | 2-fluorobenzyl | H | 81%[b] |
| **1-36** | cyclohexylmethyl | H | 91%[b] | **1-51** | 3-fluorobenzyl | H | 84%[b] |
| **1-37** | furan-2-ylmethyl | H | 81%[b] | **1-52** | 4-fluorobenzyl | H | 89%[b] |
| **1-38** | furan-3-ylmethyl | H | 82%[b] | **1-53** | 2-chlorobenzyl | H | 96%[b] |
| **1-39** | thiophen-2-ylmethyl | H | 76%[b] | **1-54** | 3-chlorobenzyl | H | 81%[b] |

(continued on the following page)

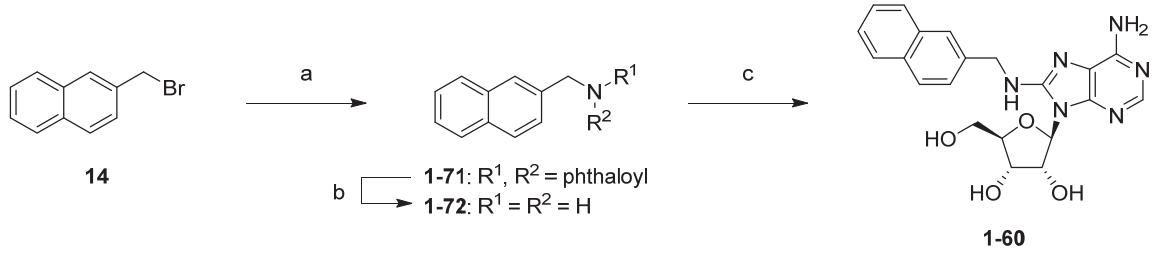
**Table 1-11. continued**

| compd | $R^1$ | $R^2$ | yield | compd | $R^1$ | $R^2$ | yield |
|---|---|---|---|---|---|---|---|
| **1-55** | 4-chlorobenzyl | H | 83%[b] | **1-61** | biphenyl-2-ylmethyl | H | 93%[b] |
| **1-56** | 2-(trifluoromethyl)benzyl | H | 50%[b] | **1-62** | biphenyl-3-ylmethyl | H | 86%[b] |
| **1-57** | 3-(trifluoromethyl)benzyl | H | 83%[b] | **1-63** | biphenyl-4-ylmethyl | H | 59%[b] |
| **1-58** | 4-(trifluoromethyl)benzyl | H | 85%[b] | **1-65** | 4-phenoxybenzyl | H | 89%[b] |
| **1-59** | 1-naphthylmethyl | H | 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)。

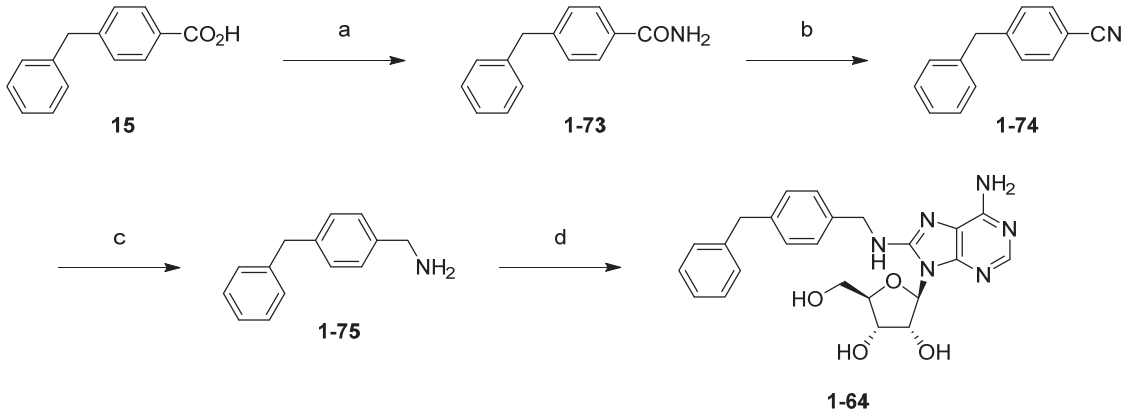
**Scheme 1-4.** Synthesis of Compound **1-60**[a]




[a]Reagents and conditions: (a) phthalimide potassium salt, DMF, 50 °C, 83%; (b) $H_2NNH_2 \cdot H_2O$, MeOH, reflux, 97%; (c) **13**, *i*-$Pr_2$NEt, 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。

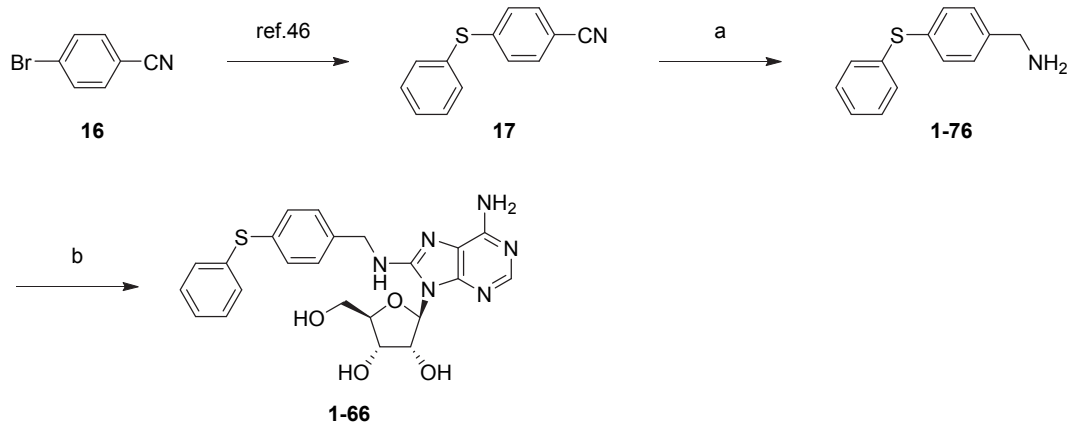
**Scheme 1-5.** Synthesis of Compound **1-64**[a]




[a]Reagents and conditions: (a) CDI, THF, rt, then 28% aq $NH_3$, 99%; (b) TFAA, $Et_3N$, DCM, rt, 90%; (c) $LiAlH_4$, THF, 60 °C, 90%; (d) **13**, *i*-$Pr_2NEt$, 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]

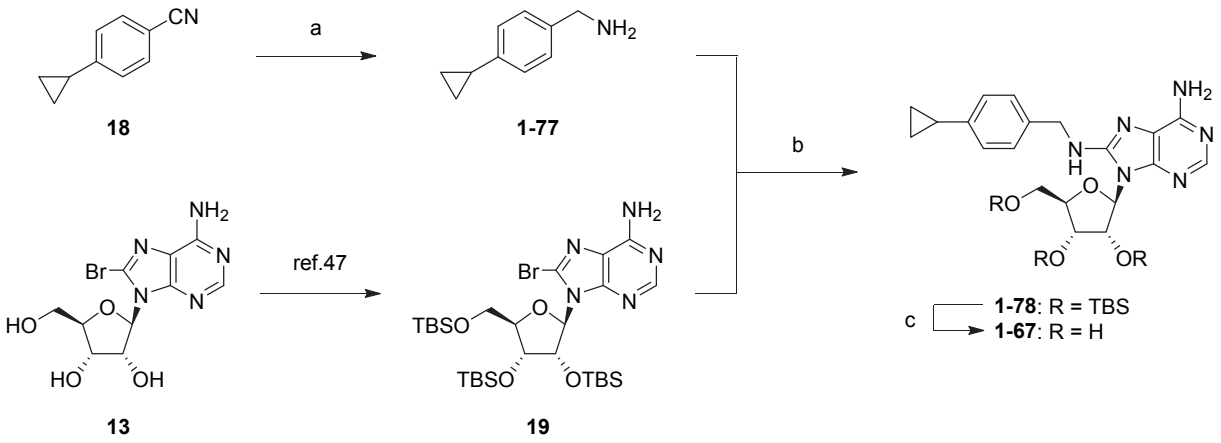



[a]Reagents and conditions: (a) $LiAlH_4$, THF, 60 °C, 83%; (b) **13**, *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube, 85%.

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。

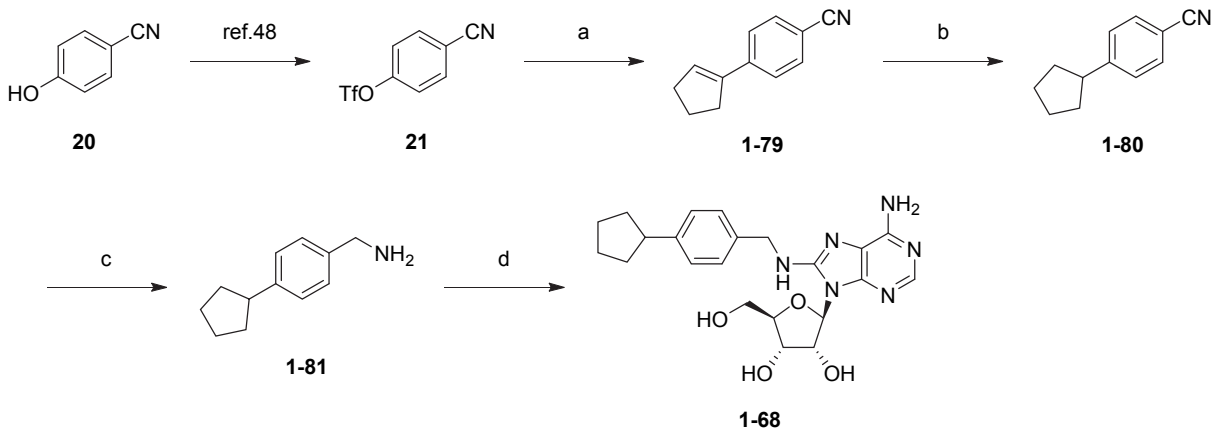
**Scheme 1-7.** Synthesis of Compound **1-67**[a]




[a]Reagents and conditions: (a) $LiAlH_4$, THF, 60 °C, quant.; (b) *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube, 97%; (c) $NH_4F$, 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。

**Scheme 1-8.** Synthesis of Compound **1-68**[a]

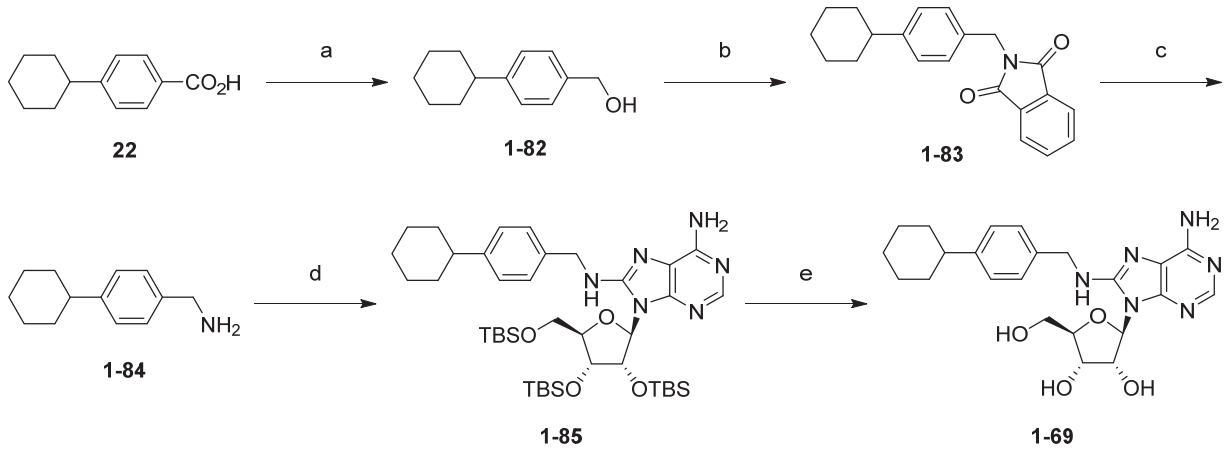



[a]Reagents and conditions: (a) (cyclopent-1-en-1-yl)boronic acid, $Pd(PPh_3)_4$, $Na_2CO_3$, DME, $H_2O$, reflux, 98%; (b) $H_2$, 5% Pt–C, AcOEt, rt, 84%; (c) $LiAlH_4$, THF, 60 °C, quant.; (d) **13**, *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube,

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 **19**[47] 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。

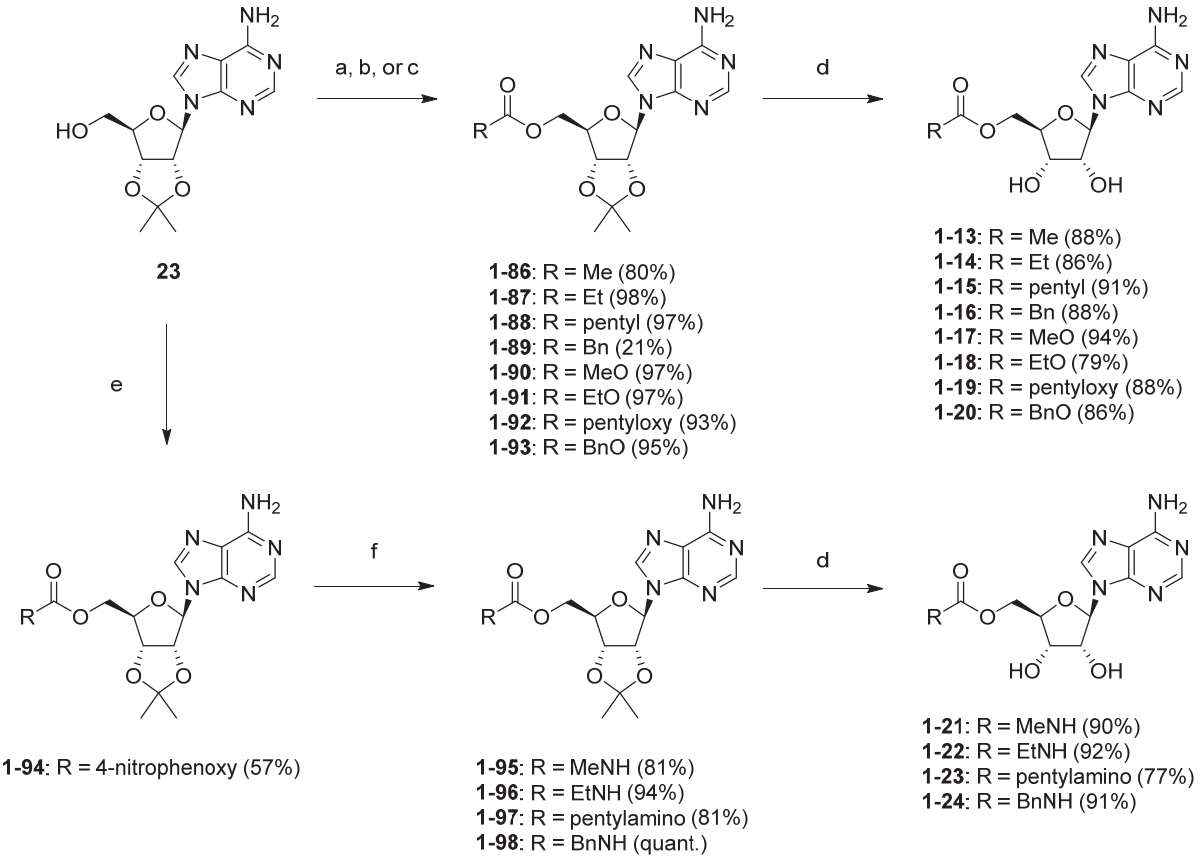
**Scheme 1-9.** Synthesis of Compound **1-69**[a]




[a]Reagents and conditions: (a) $LiAlH_4$, THF, 60 °C, 91%; (b) phthalimide, DIAD, $PPh_3$, THF. rt, 90%; (c) $H_2NNH_2{\cdot}H_2O$, $CHCl_3$, EtOH, rt, quant.; (d) **19**[47], *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube, quant; (e) $NH_4F$, 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 $N^6$ 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 $N^6$ 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。

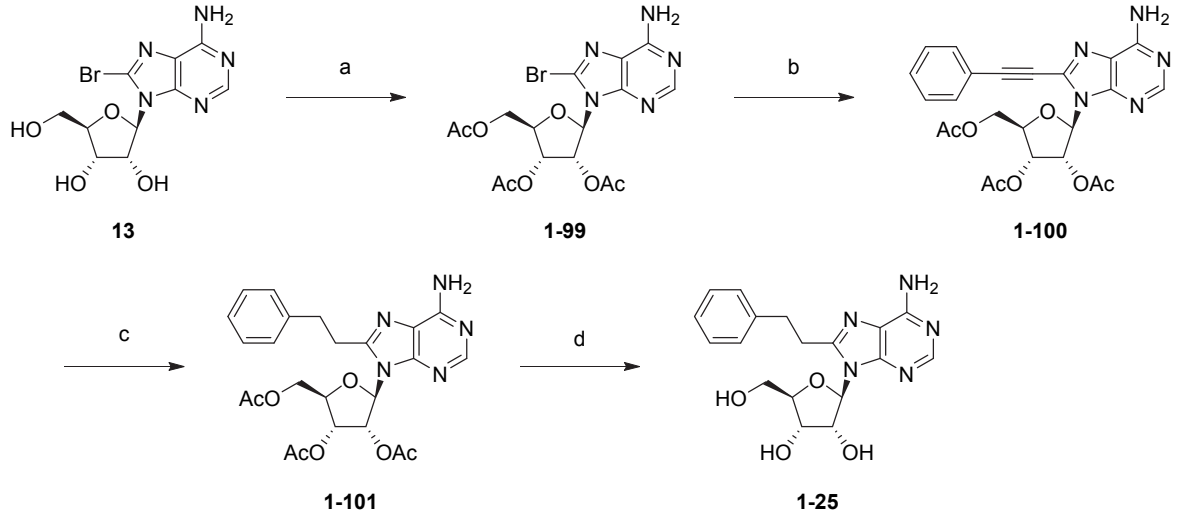
**Scheme 1-10** Synthesis of Compounds **1-13**–**1-24**[a]




[a]Reagents and conditions: (a) $Ac_2O$, 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 $HCO_2H$, rt; (e) 4-nitrophenyl chloroformate, $Et_3N$, MeCN, 0 °C to rt; (f) appropriate amine, $Et_3N$, 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。

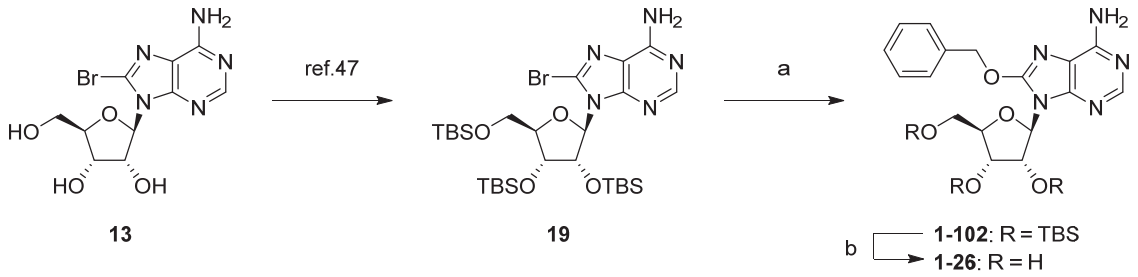
**Scheme 1-11.** Synthesis of Compound **1-25**[a]




[a]Reagents and conditions: (a) $Ac_2O$, $Et_3N$, DMAP, MeCN, rt, 76%; (b) ethynylbenzene, $Pd(PPh_3)_4$, CuI, $Et_3N$, DMF, 80 °C, 87%; (c) $H_2$, 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 **19**[47] 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。

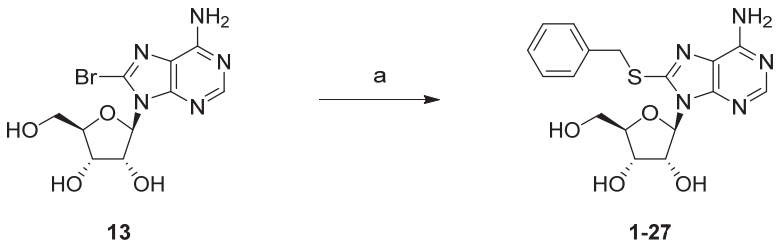
**Scheme 1-12.** Synthesis of Compound **1-26**[a]




[a]Reagents and conditions: (a) *t*-BuOK, BnOH, 40 °C; (b) $NH_4F$, 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)。

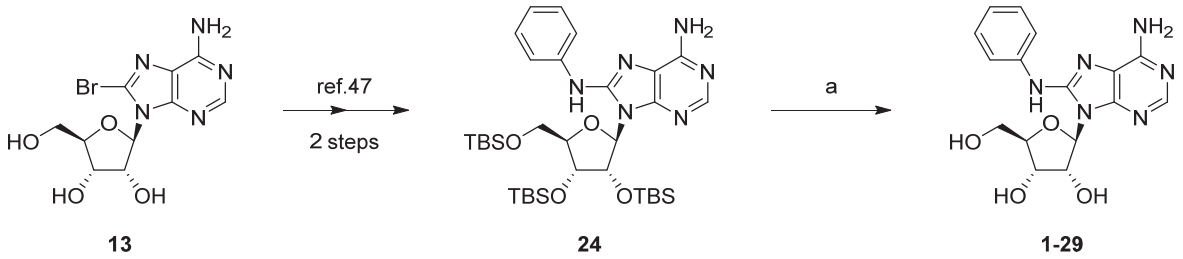
**Scheme 1-13.** Synthesis of Compound **1-27**[a]




[a]Reagents and a condition: (a) BnSH, *i*-$Pr_2$NEt, 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)。

**Scheme 1-14.** Synthesis of Compound **1-29**[a]




[a]Reagents and a condition: (a) $NH_4F$, 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 °C 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

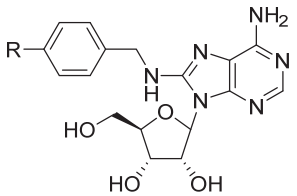
② 結晶パッキングの鍵となる分子間の相互作用を弱め、速度論的な溶解性を高める方法

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 ± 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。

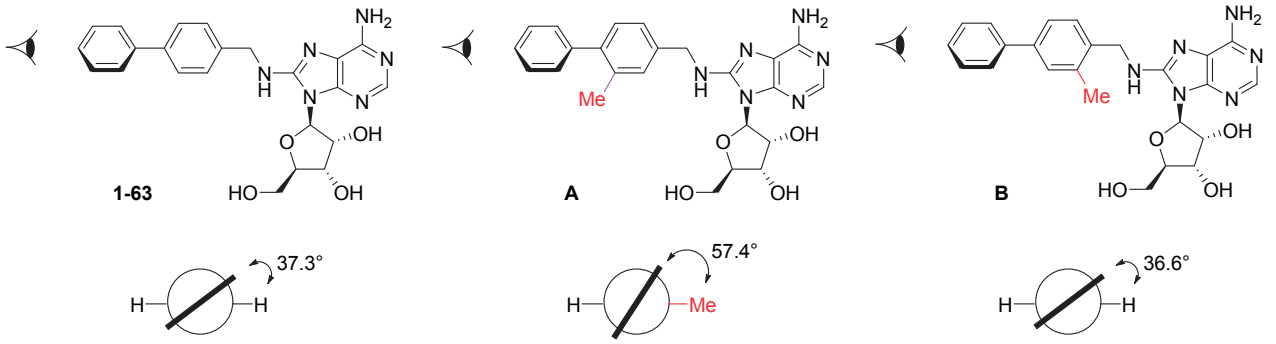
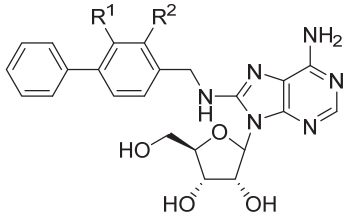



**Figure 2-1.** Simulation of substituent effects on the twisted structure of the biphenyl moiety.

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。

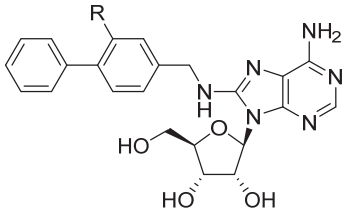
**Table 2-2. Solubility of Compounds 2-4–2-7 in JP2**




| compd | $R^1$ | $R^2$ | solubility in JP2 at 37 °C (mg/mL) |
|---|---|---|---|
| **2-4** | OMe | H | 0.215 |
| **2-5** | OEt | H | 0.121 |
| **2-6** | H | OMe | 0.004 |
| **2-7** | H | OEt | 0.002 |
| **1-63** | H | H | 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**




| compd | R | $IC_{50}$ (μM)[a] | |
|---|---|---|---|
| | | hCNT2 | rCNT2 |
| **2-8** | OH | 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* | 10 ± 1.0 | inactive[b] |
| **2-11** | $OCH_2CO_2Me$ | 3.3 ± 0.8 | inactive[b] |
| **2-12** | $OCH_2CONH_2$ | 5.5 ± 1.4 | >100 (<5)[c] |
| **2-13** | $OCH_2CH_2OH$ | 3.1 ± 0.3 | >100 (49)[c] |
| **1-63** | H | 0.64 ± 0.19 | inactive[b] |
| **2-2** | | 1.0 ± 0.2 | >100 (11)[c] |

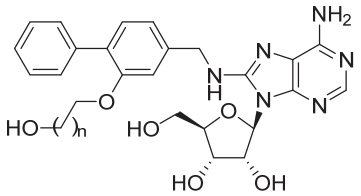
[a]Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean ± standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. [b]No inhibition was observed at the maximum concentration of 100 μM. [c]Inhibition was less than 50% at the maximum concentration of 100 μM. 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、ピリジン-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 μM）は、rCNT2 阻害活性の指標である $IC_{50}$ 値（= 38 μM）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**




| compd | n | $IC_{50}$ (μM)[a] | | solubility in JP2 at 37 °C (mg/mL) |
|---|---|---|---|---|
| | | hCNT2 | rCNT2 | |
| **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 ± 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 μM. [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。

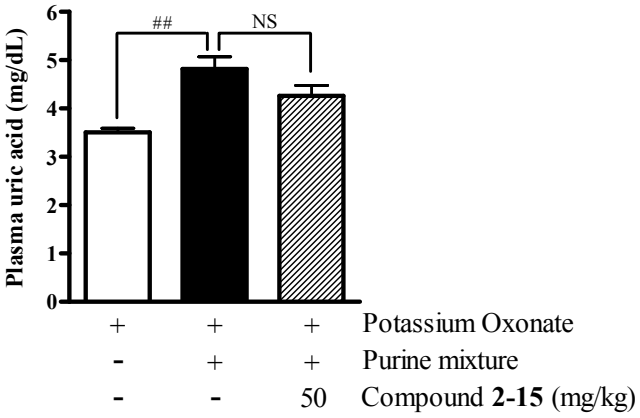


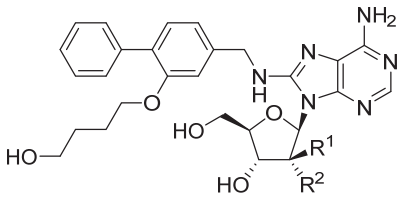

**Figure 2-2.** Effect of compound **2-15** on the elevation of plasma uric acid levels derived from orally administered purine nucleoside mixture (adenosine:guanosine:inosine =1:1:1, 50 mg/kg) in rats. Data are expressed as the mean ± SEM (n = 5). ##: $p < 0.01$ versus a group treated with only potassium 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 in COS-7 Cells Transiently Expressing hCNT2 or rCNT2**



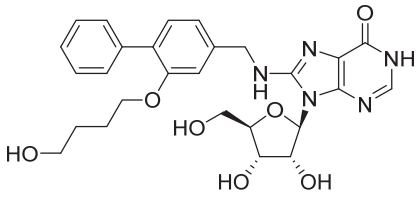

| compd | $R^1$ | $R^2$ | $IC_{50}$ (μM)[a] | |
|---|---|---|---|---|
| | | | hCNT2 | rCNT2 |
| **2-17** | H | H | 1.5 ± 0.2 | 23 ± 6.8 |
| **2-18** | OH | H | 6.1 ± 0.4 | >100 (45)[b] |
| **2-15** | H | OH | 0.94 ± 0.24 | 38 ± 13 |

[a]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. [b]Inhibition was less than 50% at the maximum concentration of 100 μM. The inhibition% is shown in parentheses.

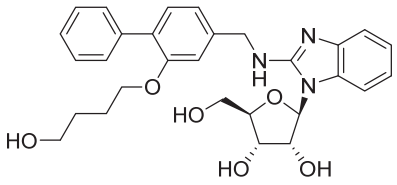
続いて、塩基部の変換を行った。hCNT2 は、すべてのプリンヌクレオシドを基質とするが、一方では、第一章第二節（pp.8–9）で述べた通り、リバビリンやベンズイミダゾールヌクレオシドなどの塩基部が非天然型のヌクレオシド系化合物を基質または阻害薬として認識することが知られている[38,42,43]。これらの事実は、塩基部が糖部ほど厳密に認識されていないことを示唆している。

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 μM）と算出され、rCNT2 阻害活性の指標である $IC_{50}$ 値（= 1.5 μM）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。

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



**2-19**



**2-20**

| compd | $IC_{50}$ (μM)[a] | | ratio | solubility in JP2 at 37 °C (mg/mL) |
|---|---|---|---|---|
| | hCNT2 | rCNT2 | rat/human | |
| **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 |

[a]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. [b]Inhibition was less than 50% at the maximum concentration of 1000 μM. [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。

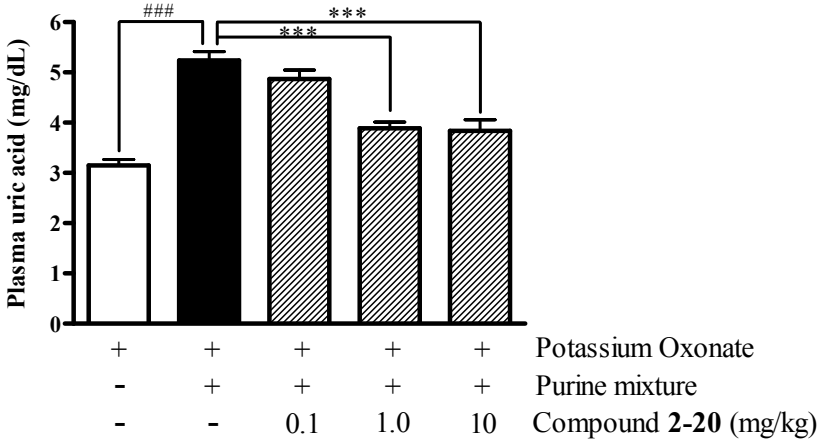
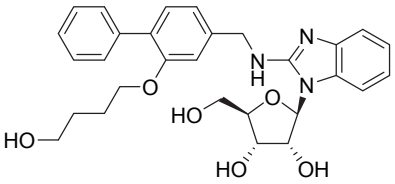



**Figure 2-3.** Effects of compound **2-20** on the elevation of plasma uric acid levels derived from orally administered purine mixture (50 mg/kg) in rats. Data are expressed as the mean ± SEM. (n = 5–11). ###: $p < 0.001$ versus a group treated with only potassium oxonate (100 mg/kg). ***: $p < 0.001$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

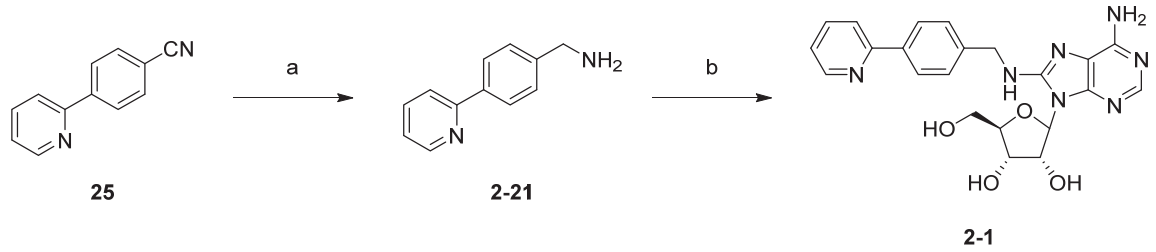
| parameter | iv[b] | po[c] |
|---|---|---|
| $CL_{tot}$ (L $h^{-1}$ $kg^{-1}$) | 0.39 | |
| $V_{dss}$ (L/kg) | 0.12 | |
| $t_{1/2}$ (h) | 1.7 | |
| $AUC_{0\text{-}inf}$ (μM·h) | 5.0 | |
| $C_{max}$ (μM) | | 0.11 |
| $t_{max}$ (h) | | 0.83 |
| $AUC_{0\text{-}x}$ (μM·h) | | 0.25 |
| $F$ (%) | | 0.51 |

[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.

第四節　試験化合物の合成

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）。

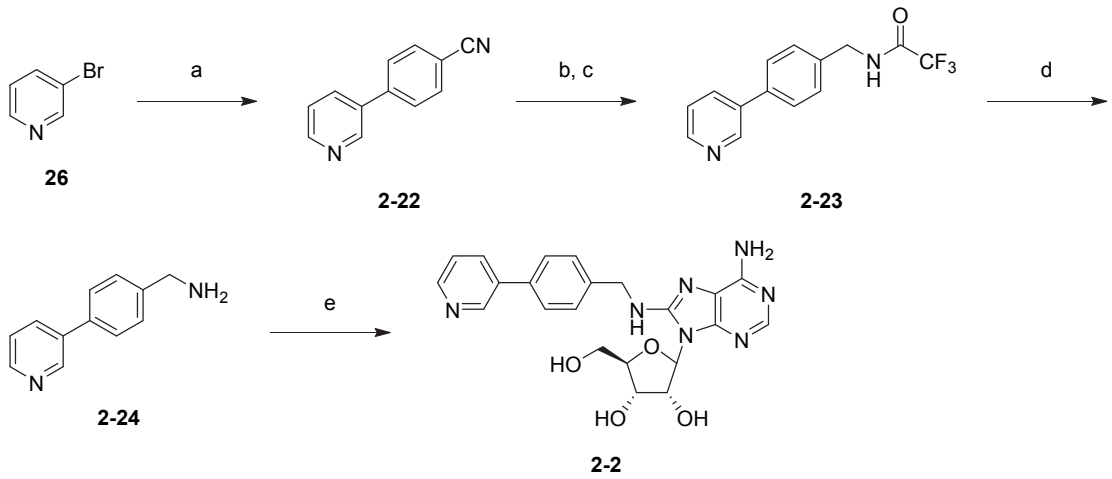
**Scheme 2-1.** Synthesis of Compound **2-1**[a]




[a]Reagents and conditions: (a) $LiAlH_4$, THF, 60 °C, 91%; (b) **13**, *i*-$Pr_2NEt$, 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-ブロモピリジン **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。

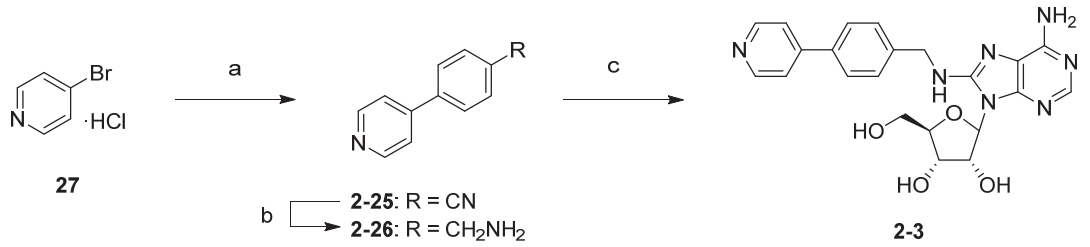
**Scheme 2-2.** Synthesis of Compound **2-2**[a]




[a]Reagents and conditions: (a) 4-cyanophenylboronic acid, $Pd(PPh_3)_4$, 2.0 M aq $Na_2CO_3$, MeCN, 80 °C, 73%; (b) $LiAlH_4$, THF, 60 °C; (c) $CF_3CO_2Et$, EtOH, rt, 58% from **2-22**; (d) 2.0 M aq NaOH, EtOH, rt, 93%; (e) **13**, *i*-$Pr_2NEt$, 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。

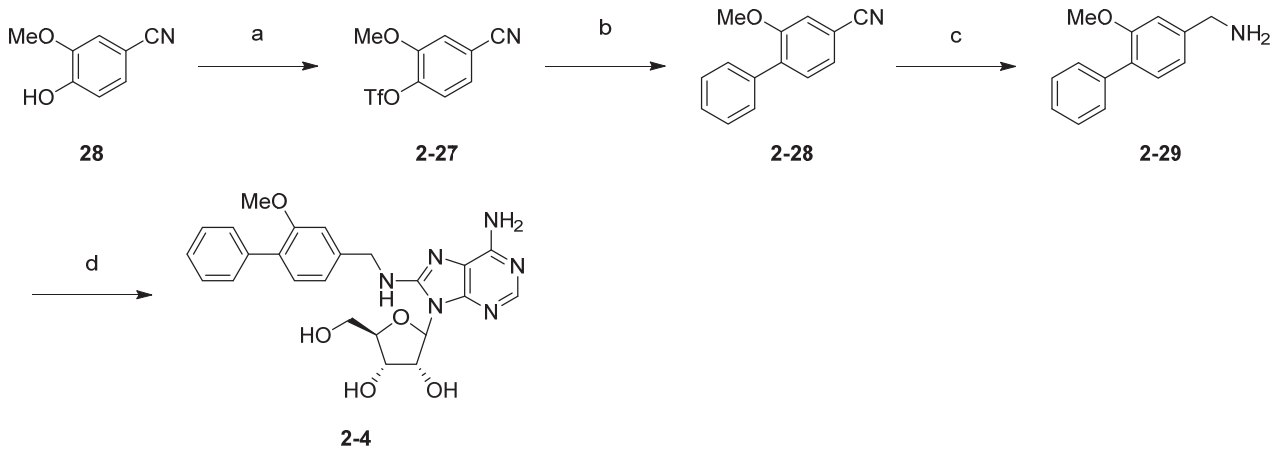
**Scheme 2-3.** Synthesis of Compound **2-3**[a]




[a]Reagents and conditions: (a) 4-cyanophenylboronic acid, $Pd(PPh_3)_4$, 2.0 M aq $Na_2CO_3$, MeCN, 80 °C, 79%; (b) $LiAlH_4$, THF, 60 °C, 71%; (c) **13**, *i*-$Pr_2NEt$, 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。

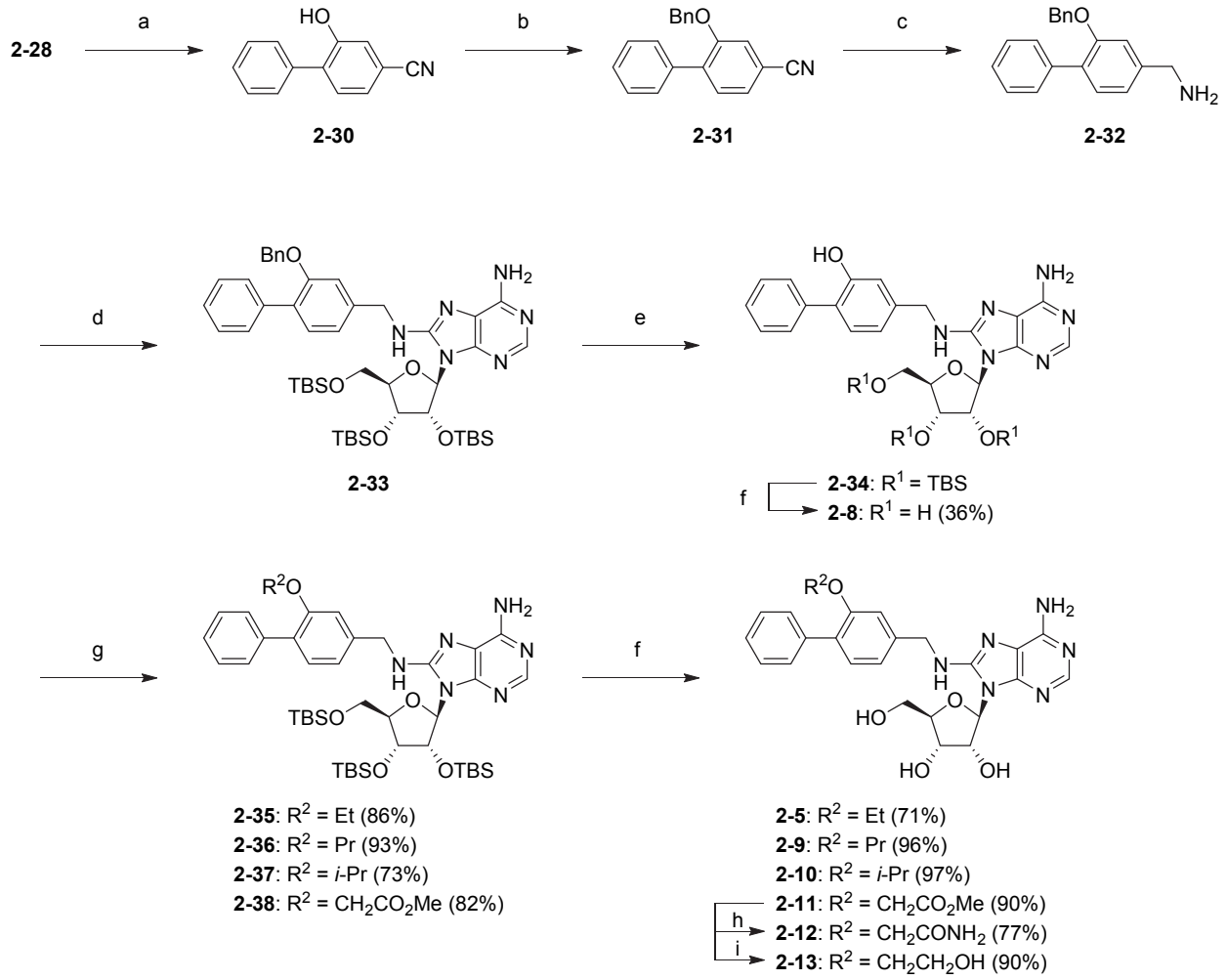
**Scheme 2-4.** Synthesis of Compound **2-4**[a]




[a]Reagents and conditions: (a) $Tf_2O$, $Et_3N$, DCM, rt; (b) $PhB(OH)_2$, $Pd(PPh_3)_4$, $Na_2CO_3$, DMF, $H_2O$, 80 °C, 90% from **28**; (c) $LiAlH_4$, THF, 60 °C, 95%; (d) **13**, *i*-$Pr_2NEt$, 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 **19**[47] 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。

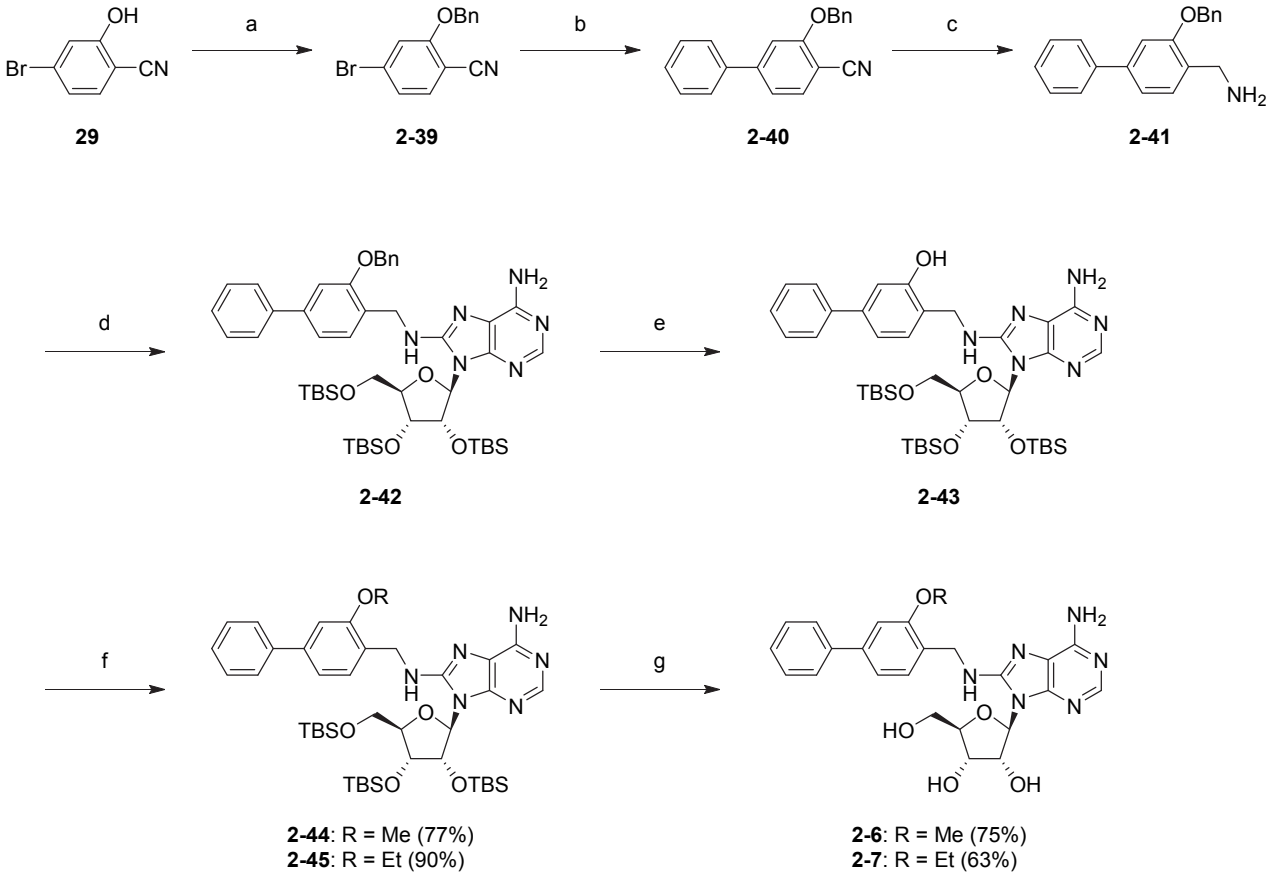
**Scheme 2-5.** Synthesis of Compounds **2-5** and **2-8**–**2-13**[a]




[a]Reagents and conditions: (a) $BBr_3$ (1.0 M in DCM), DCM, 30 °C, 96%; (b) BnBr, $K_2CO_3$, DMF, rt, quant.; (c) $LiAlH_4$, THF, 60 °C, quant.; (d) **19**[47], *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube, 98%; (e) $H_2$, 10% Pd–C, AcOEt, rt, 96%; (f) $NH_4F$, MeOH, reflux; (g) appropriate alkyl iodide or methyl bromoacetate, $K_2CO_3$, DMF, 35–50 °C; (h) $NH_3$ (2.0 M in MeOH), rt; (i) $NaBH_4$, 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 **19**[47] 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。

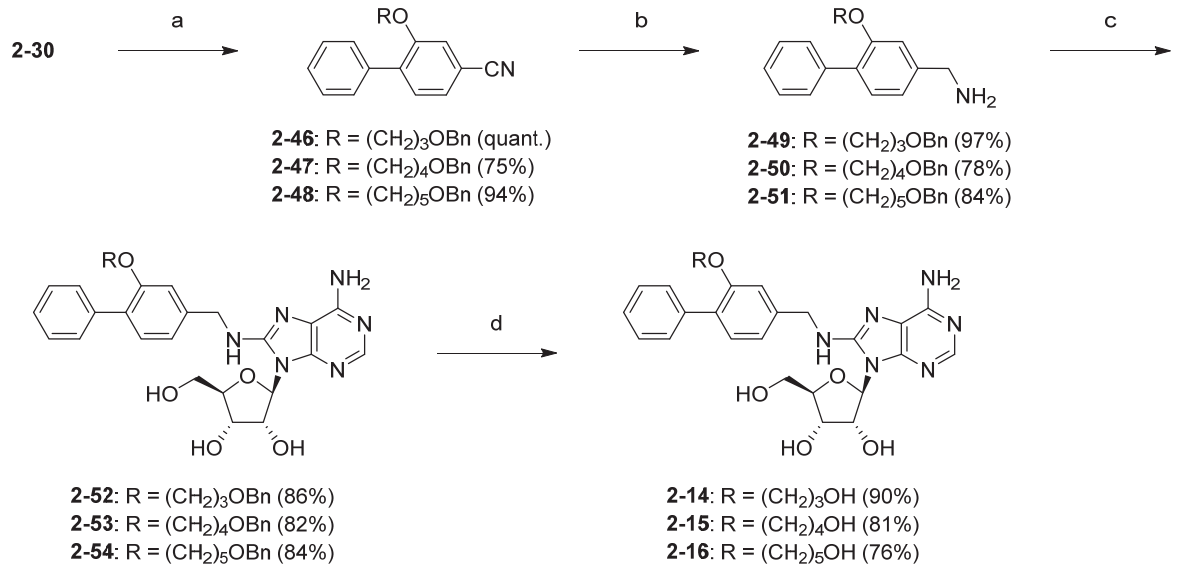
**Scheme 2-6.** Synthesis of Compounds **2-6** and **2-7**[a]




[a]Reagents and conditions: (a) BnBr, $K_2CO_3$, DMF, rt; (b) $PhB(OH)_2$, $Pd(PPh_3)_4$, $Na_2CO_3$, $H_2O$, DMF 80 °C, 94% from **29**; (c) $LiAlH_4$, THF, 60 °C, 96%; (d) **19**[47], *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube, 98%; (e) $H_2$, 10% Pd–C, AcOEt, rt, 91%; (f) RI, $K_2CO_3$, DMF, rt–40 °C; (g) $NH_4F$, 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。

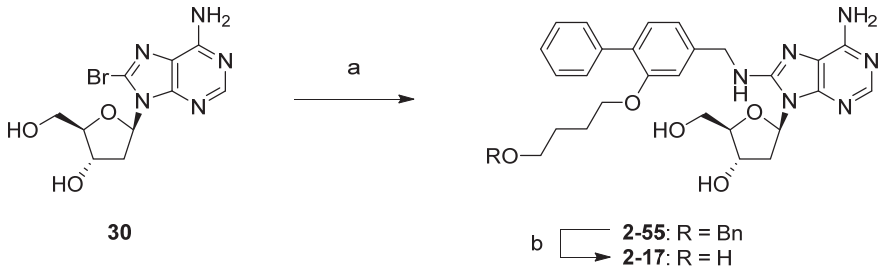
**Scheme 2-7.** Synthesis of Compounds **2-14**–**2-16**[a]




[a]Reagents and conditions: (a) RBr, $K_2CO_3$, DMF, 50 °C; (b) $LiAlH_4$, THF, 60 °C; (c) **13**, *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube; (d) $H_2$, 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)。

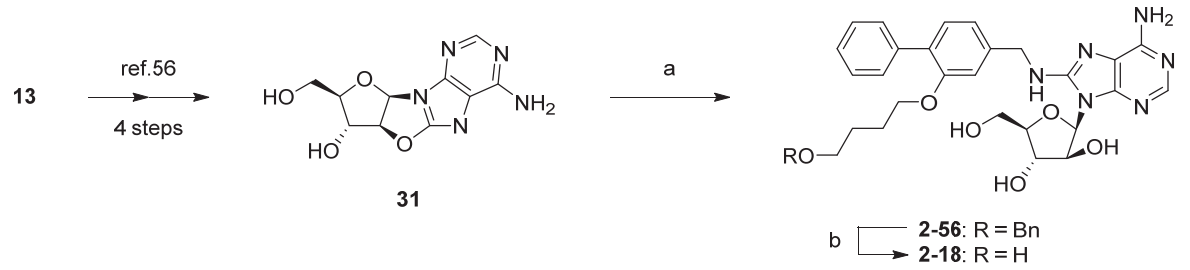
**Scheme 2-8.** Synthesis of Compound **2-17**[a]




[a]Reagents and conditions: (a) **2-50**, *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube, 37%; (b) $H_2$, 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)。

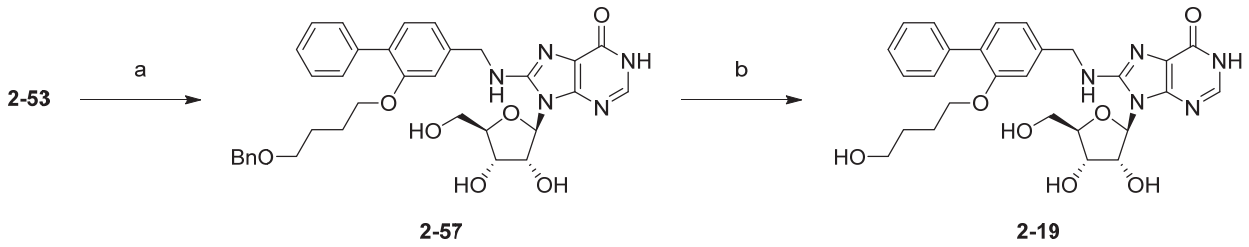
**Scheme 2-9.** Synthesis of Compound **2-18**[a]




[a]Reagents and conditions: (a) **2-50**, PrOH, 150 °C, in a sealed tube, microwave irradiation, 26%; (b) $H_2$, 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)。

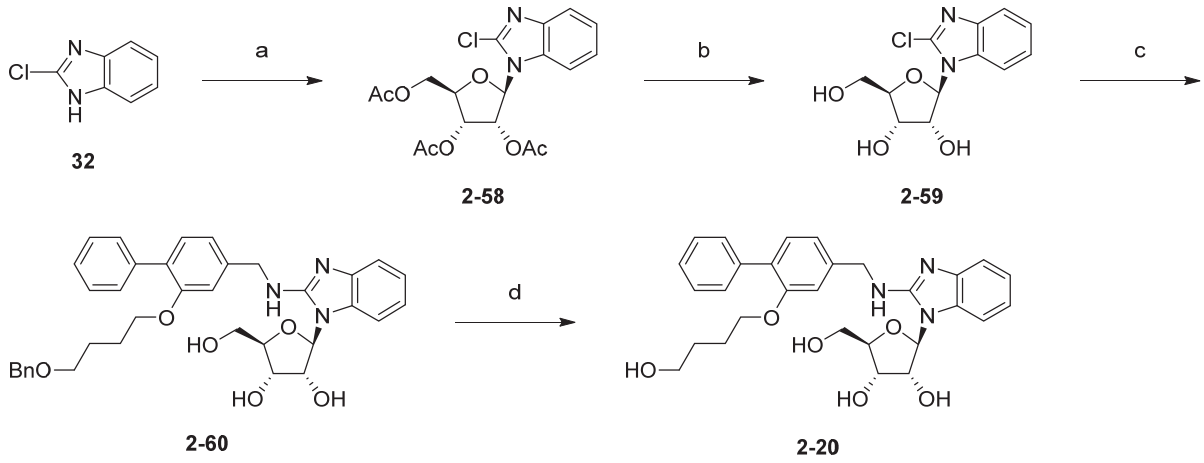
**Scheme 2-10.** Synthesis of Compound **2-19**[a]




[a]Reagents and conditions: (a) $NaNO_2$, 75% aq AcOH, rt, 42%; (b) $H_2$, 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]

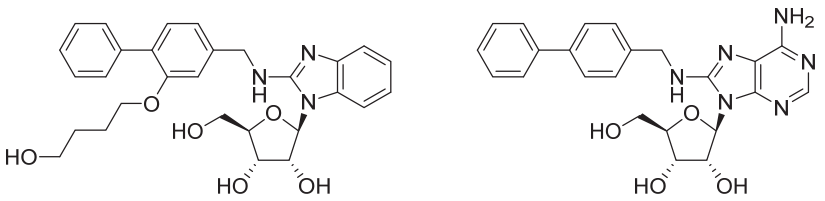



[a]Reagents and conditions: (a) *N*,*O*-bis(trimethylsilyl)acetamide, MeCN, 80 °C then TMSOTf, 1,2,3,4-tetra-*O*-acetyl-β-D-ribofuranose, rt, 84%; (b) *t*-BuOK, MeOH, rt, 84%; (c) **2-50**, *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube, 58%; (d) $H_2$, 10% Pd–C, MeOH, 50 °C, 88%.

# 第三章　医薬品候補化合物の創製

## 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。

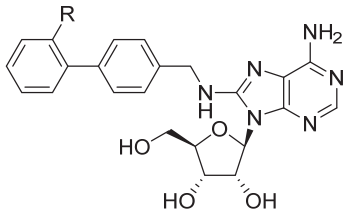



**2-20**, relatively strong hERG blockage　　**1-63**, relatively weak hERG blockage

**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**

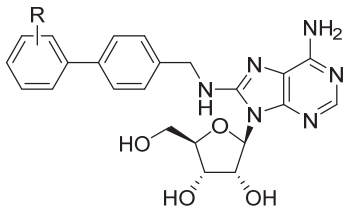



| compd | R | $IC_{50}$ (μM)[a] |
|---|---|---|
| **3-1** | OH | 1.7 ± 0.3 |
| **3-2** | OMe | 1.6 ± 0.3 |
| **3-3** | OEt | 1.9 ± 0.3 |
| **3-4** | OPr | 4.0 ± 0.5 |
| **3-5** | OPr-*i* | 7.6 ± 1.3 |
| **3-6** | $OCH_2CO_2Me$ | 3.3 ± 0.8 |
| **3-7** | $OCH_2CONH_2$ | 3.9 ± 1.0 |
| **3-8** | $OCH_2CH_2OH$ | 1.6 ± 0.5 |
| **1-63** | H | 0.64 ± 0.19 |

[a]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.

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**

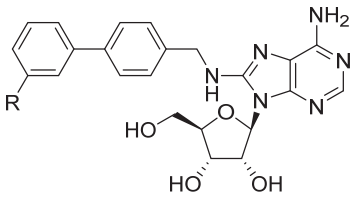


| compd | R | $IC_{50}$ (μM)[a] | compd | R | $IC_{50}$ (μM)[a] |
|---|---|---|---|---|---|
| **3-9** | *m*-OH | 0.54 ± 0.10 | **3-17** | *p*-OH | 1.6 ± 0.2 |
| **3-10** | *m*-OMe | 0.61 ± 0.04 | **3-18** | *p*-OMe | 4.5 ± 0.2 |
| **3-11** | *m*-OEt | 1.2 ± 0.2 | **3-19** | *p*-OEt | 21 ± 4.3 |
| **3-12** | *m*-OPr | 2.5 ± 0.5 | **3-20** | *p*-OPr | >100 (39)[b] |
| **3-13** | *m*-OPr-*i* | 1.8 ± 0.1 | **3-21** | *p*-OPr-*i* | >100 (36)[b] |
| **3-14** | *m*-$OCH_2CO_2Me$ | 0.89 ± 0.07 | **3-22** | *p*-$OCH_2CO_2Me$ | 1.7 ± 0.4 |
| **3-15** | *m*-$OCH_2CONH_2$ | 0.65 ± 0.09 | **3-23** | *p*-$OCH_2CONH_2$ | 2.8 ± 0.5 |
| **3-16** | *m*-$OCH_2CH_2OH$ | 0.34 ± 0.11 | **3-24** | *p*-$OCH_2CH_2OH$ | 4.4 ± 1.4 |
| **1-63** | H | 0.64 ± 0.19 | | | |

[a]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. [b]Inhibition was less than 50% at the maximum concentration of 100 μM. 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。

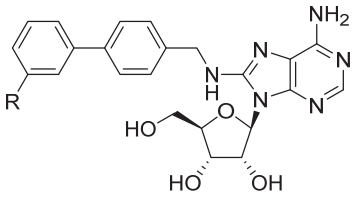
**Table 3-3. Inhibitory Effects on $Na^+$-Dependent Inosine Uptake in COS-7 Cells Transiently Expressing hCNT2 or rCNT2, and $LogD_{6.5}$ of Compounds 3-9, 3-10, and 3-14–3-16**



| compd | R | $IC_{50}$ (μM)[a] | | $LogD_{6.5}$[e] |
|---|---|---|---|---|
| | | hCNT2 | rCNT2 | |
| **3-9** | OH | 0.54 ± 0.10 | >100[b] | 1.13 |
| **3-10** | OMe | 0.61 ± 0.04 | >100[b] | 1.27 |
| **3-14** | $OCH_2CO_2Me$ | 0.89 ± 0.07 | 36[c] | 0.90 |
| **3-15** | $OCH_2CONH_2$ | 0.65 ± 0.09 | 83 ± 2.7 | −0.06 |
| **3-16** | $OCH_2CH_2OH$ | 0.34 ± 0.11 | 54 ± 5.5 | 0.58 |
| **1-63** | H | 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 ± 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 μM. [c]The data is expressed as the mean of two independent experiments. [d]No inhibition was observed at the the maximum concentration of 100 μM. [e]$LogD_{6.5}$ 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**

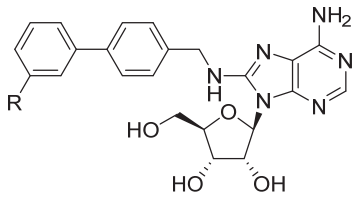


| compd | R | $IC_{50}$ (μM)[a] | | $LogD_{6.5}$[b] |
|---|---|---|---|---|
| | | hCNT2 | rCNT2 | |
| **3-25** | $OCH_2CH_2NH_2$ | 0.25 ± 0.06 | 23 ± 4.4 | −2.11 |
| **3-26** | $OCH_2CH_2CH_2NH_2$ | 0.11 ± 0.02 | 9.4 ± 3.0 | −2.35 |
| **3-27** | $OCH_2CH_2CH_2CH_2NH_2$ | 0.072 ± 0.014 | 6.3 ± 1.0 | −1.90 |
| **3-16** | $OCH_2CH_2OH$ | 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 ± 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($IC_{50}$ = ca. 0.01 μM)する一方、**3-26** は NBMPR よりも明らかに高濃度(1 μM < $IC_{50}$ < 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、$LogD_{6.5}$(= −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 = $OCH_2CH_2CH_2CH_2NH_2$

| compd | $IC_{50}$ (μM)[a] | | | solubility in JP2 at 37 °C (mg/mL) |
|---|---|---|---|---|
| | hCNT2 | hCNT1 | hCNT3 | |
| **3-26** | 0.11 ± 0.02 (1)[b] | 203 ± 28 (1845)[b] | 6.4 ± 1.0 (58)[b] | 0.408 |
| **3-27** | 0.072 ± 0.014 (1)[b] | 104 ± 14 (1444)[b] | 3.5 ± 0.2 (49)[b] | nd[c] |

[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 ± standard error of the mean (SEM) of at least three independent experiments unless otherwise stated. [b]The $IC_{50}$ values were divided with that for hCNT2 inhibition to assess hCNT2 selectivity. The results are shown in parentheses. [c]nd, not determined.

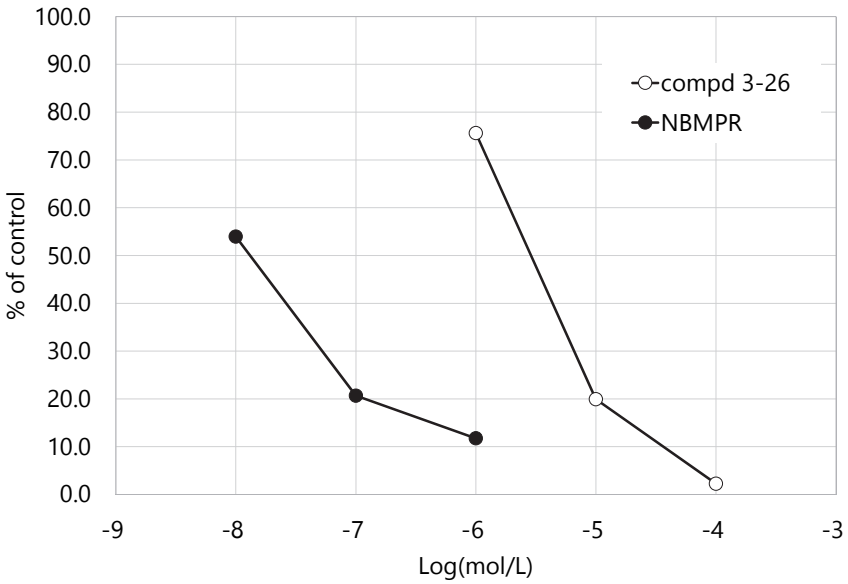



**Figure 3-2.** Inhibitory effect of compound **3-26** on adenosine uptake in HeLa cells. HeLa cells were incubated for 30 min with [$^{14}$C]-adenosine and individual compounds in $Na^+$-free buffer.

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。

**Table 3-6. Amino Acid Sequence Identity among Human, Rat, and Cebus CNT2**

| species | sequence | identity | | |
|---|---|---|---|---|
| | | vs human | vs rat | vs cebus |
| human | 658aa | 100 | 80.5 | 93.2 |
| rat | 659aa | | 100 | 79.7 |
| cebus | 620aa | | | 100 |

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 expressing hERG Channel**

| compd | conc. (μM) | tail current (nA) | | inhibition (%) |
|---|---|---|---|---|
| | | before treatment | after treatment | |
| **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)**

| time (h) | dose (mg/kg) | | |
|---|---|---|---|
| | 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。

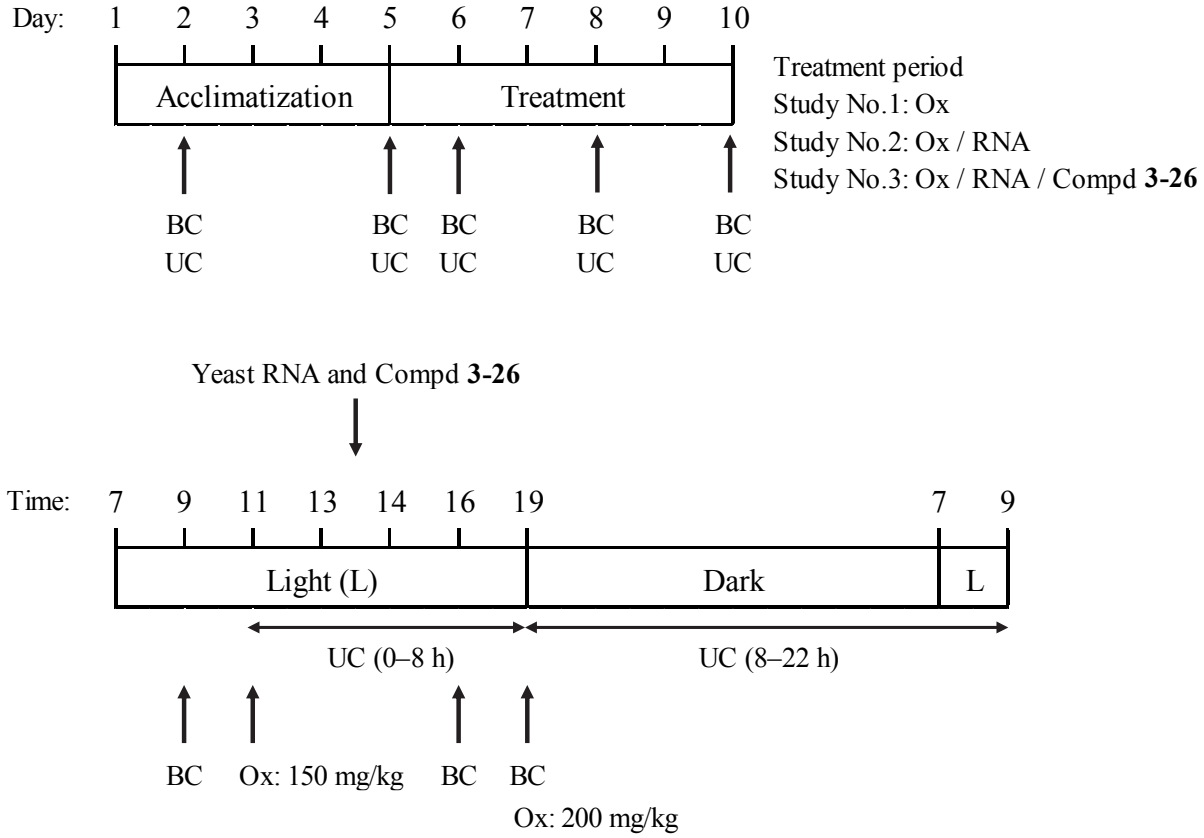



**Figure 3-3.** Schematic of the study design. BC: blood collection, Ox: potassium oxonate, UC: urine collection. Three–phase crossover studies were conducted. Study No.1: treatment with oxonic acid, Study No.2: treatment with potassium oxonate and yeast RNA (30 mg/kg), Study No.3: treatment with potassium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

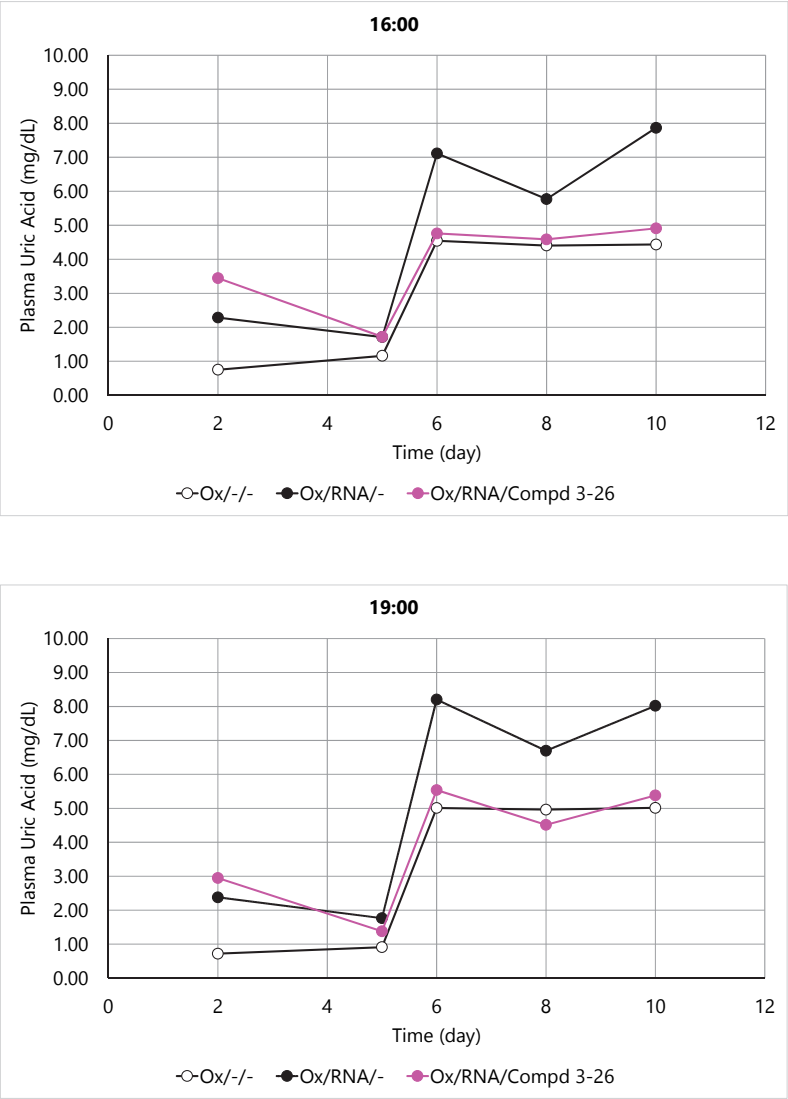



**Figure 3-4.** Effects of repeated doses of compound **3-26** on plasma uric acid level in cebus monkeys. Plasma uric acid levels were determined from samples taken at 16:00, 19:00, and then 9:00.

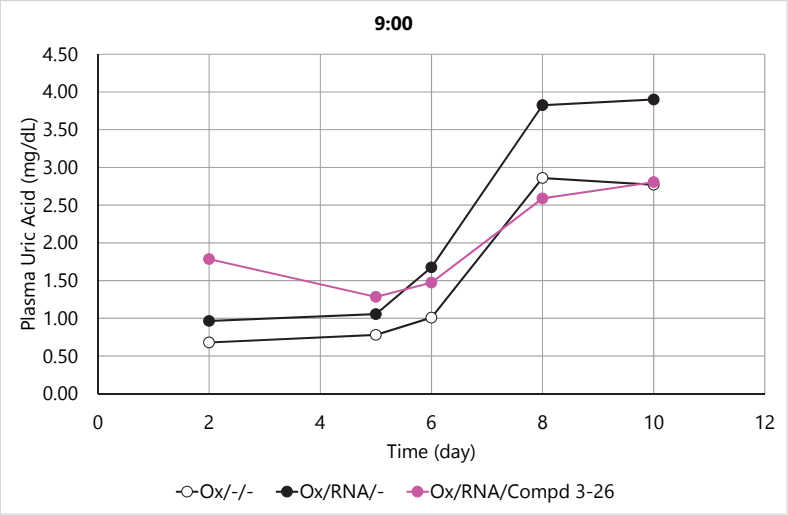



**Figure 3-4. continued**

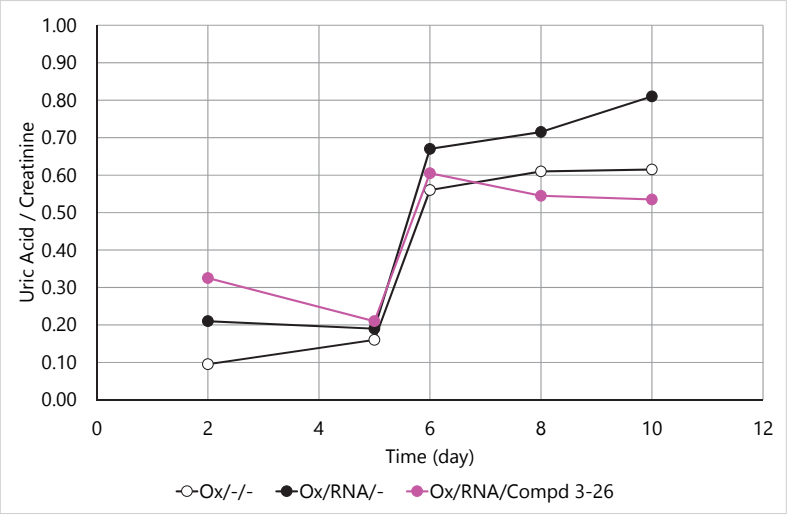
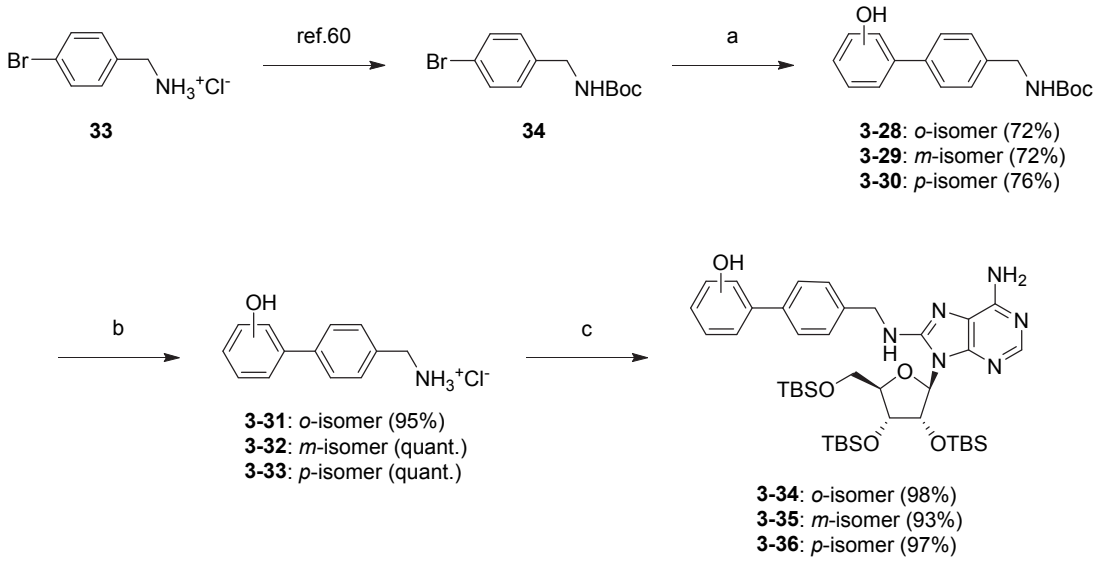



**Figure 3-5.** Effects of repeated doses of compound **3-26** on urinary uric acid/creatinine value in cebus monkeys.

第三節　試験化合物の合成

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 **19**[47] 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。

**Scheme 3-1.** Synthesis of Common Intermediates **3-34**–**3-36**[a]




**33**

**34**

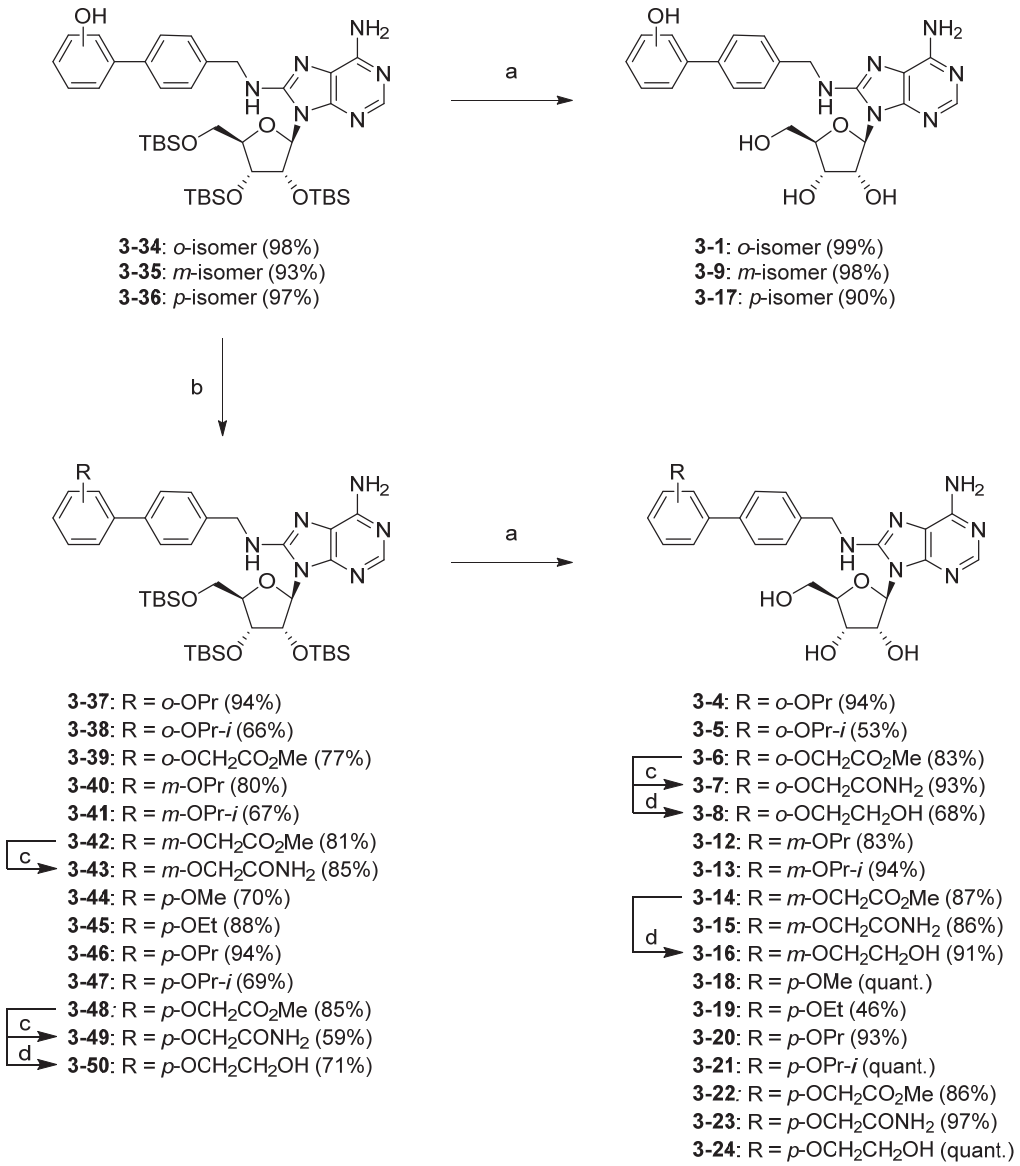
**3-28**: *o*-isomer (72%)
**3-29**: *m*-isomer (72%)
**3-30**: *p*-isomer (76%)

**3-31**: *o*-isomer (95%)
**3-32**: *m*-isomer (quant.)
**3-33**: *p*-isomer (quant.)

**3-34**: *o*-isomer (98%)
**3-35**: *m*-isomer (93%)
**3-36**: *p*-isomer (97%)

[a]Reagents and conditions: (a) appropriate hydroxyphenylboronic acid, $Pd(PPh_3)_4$, $Na_2CO_3$, $H_2O$, MeCN, 80 °C; (b) HCl (4 N in 1,4-dioxane), 1,4-dioxane, rt; (c) **19**[47], *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube.

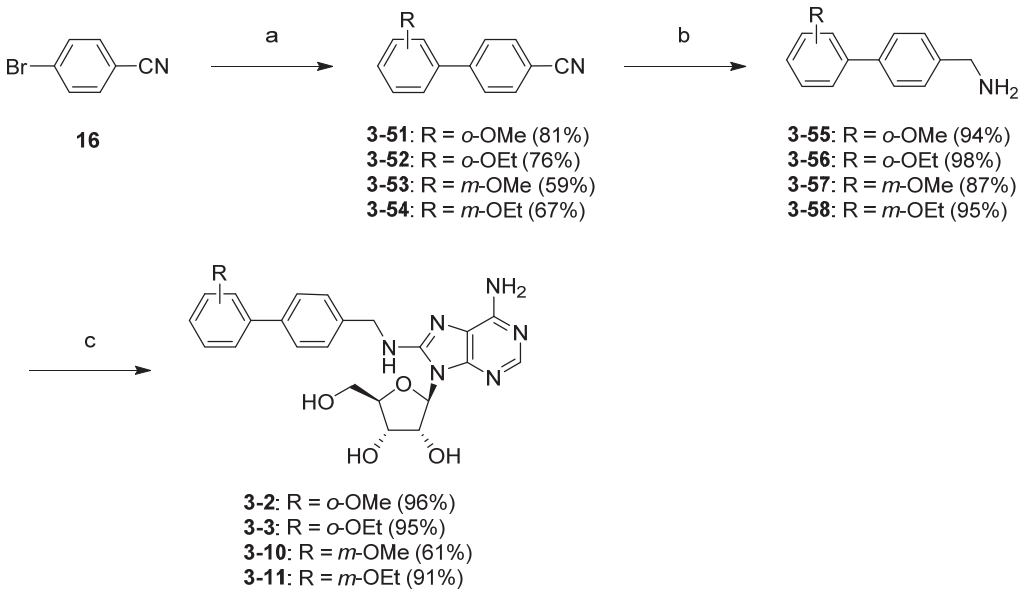
**Scheme 3-2.** Synthesis of Compounds **3-1**, **3-4**–**3-9**, and **3-12**–**3-24**[a]




[a]Reagents and conditions: (a) $NH_4F$, MeOH, reflux; (b) appropriate alkyl iodide or methyl bromoacetate, $K_2CO_3$, DMF, rt–50 °C; (c) $NH_3$ (2.0 M in MeOH), rt; (d) $NaBH_4$, 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。

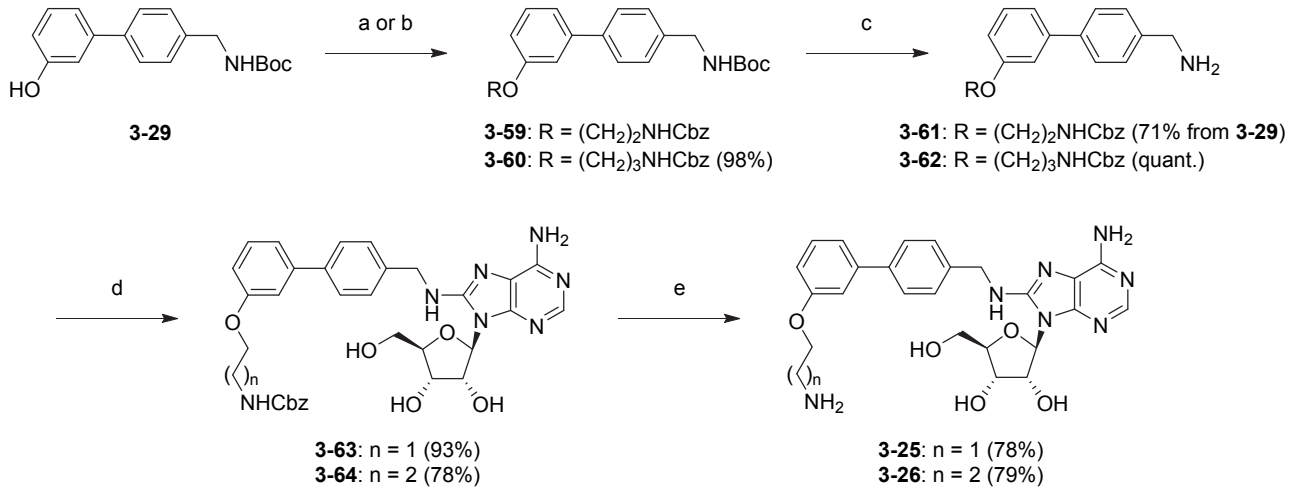
**Scheme 3-3.** Synthesis of Compounds **3-2**, **3-3**, **3-10**, and **3-11**[a]




[a]Reagents and conditions: (a) appropriate alkoxyphenylboronic acid, $Pd(PPh_3)_4$, 2.0 M aq $Na_2CO_3$, MeCN, 80 °C; (b) $LiAlH_4$, THF, 60 °C; (c) **13**, *i*-$Pr_2NEt$, 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。

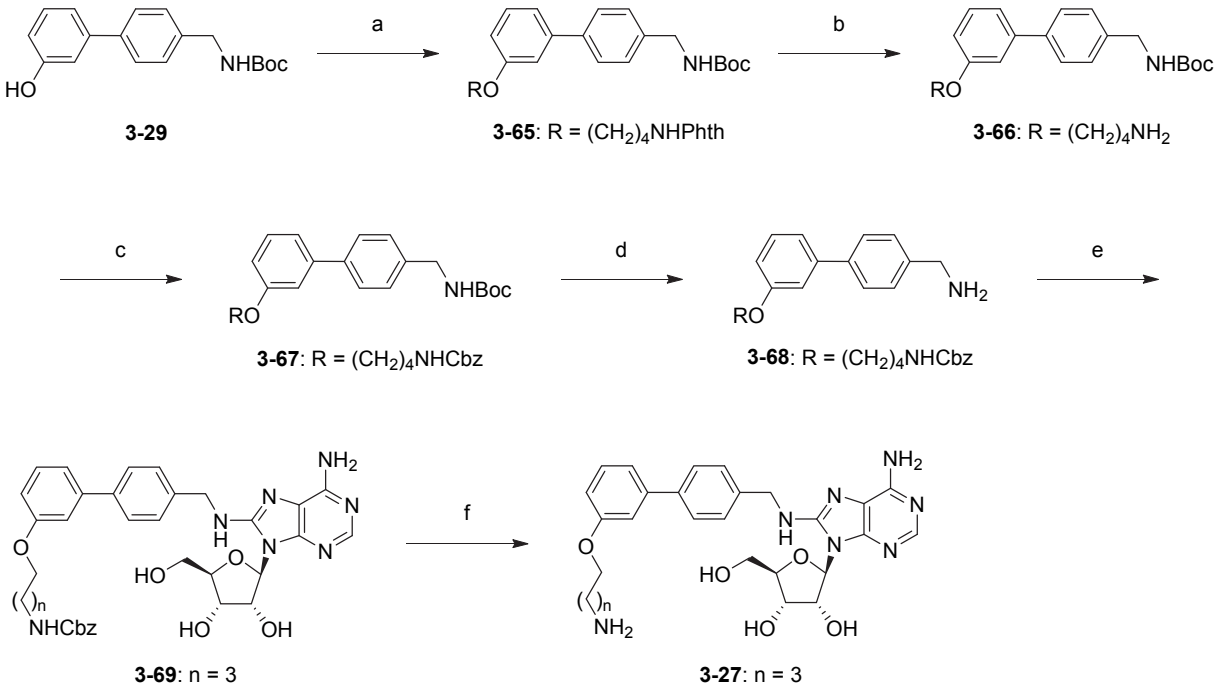
**Scheme 3-4.** Synthesis of Compounds **3-25** and **3-26**[a]



[a]Reagents and conditions: (a) benzyl *N*-(2-hydroxyethyl)carbamate, DIAD, $PPh_3$, THF, rt; (b) benzyl 3-bromopropylcarbamate, $K_2CO_3$, DMF, 50 °C; (c) TFA, DCM, 0 °C–rt; (d) **13**, *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube; (e) $H_2$, 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, $K_2CO_3$, DMF, 50 °C, 95%; (b) $H_2NNH_2 \cdot H_2O$, $CHCl_3$, EtOH, rt; (c) Cbz-OSu, THF, rt, 89% from **3-65**; (d) TFA, DCM, rt, 90%; (e) **13**, *i*-$Pr_2NEt$, EtOH, 120 °C, in a screw tube, 92%; (f) $H_2$, 10% Pd–C, MeOH, rt, 80%.

# 第四章　活性コンホメーションに関する考察

## 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]。

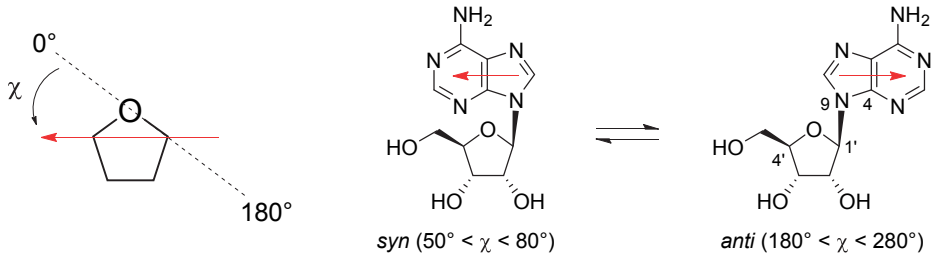
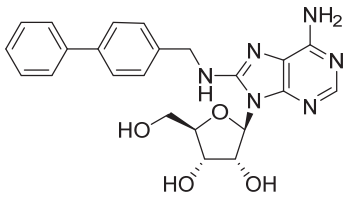


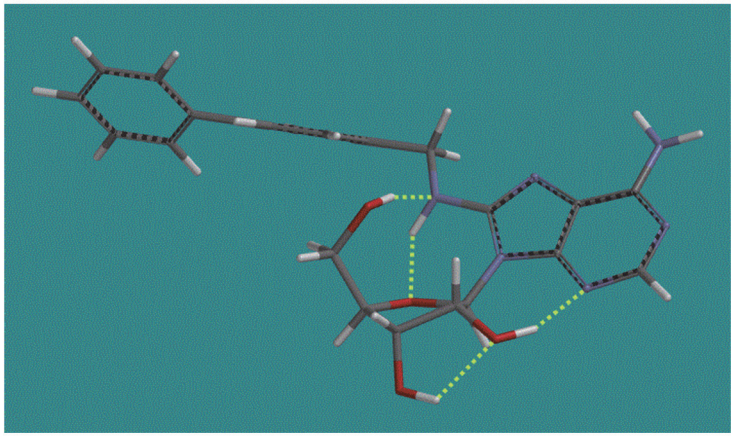

**Figure 4-1.** The *syn-anti* conformational equilibrium (adenosine as an example).

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。




**1-63**

A



$\Delta E_{syn\text{-}anti}$ = 5.41 kcal/mol

B

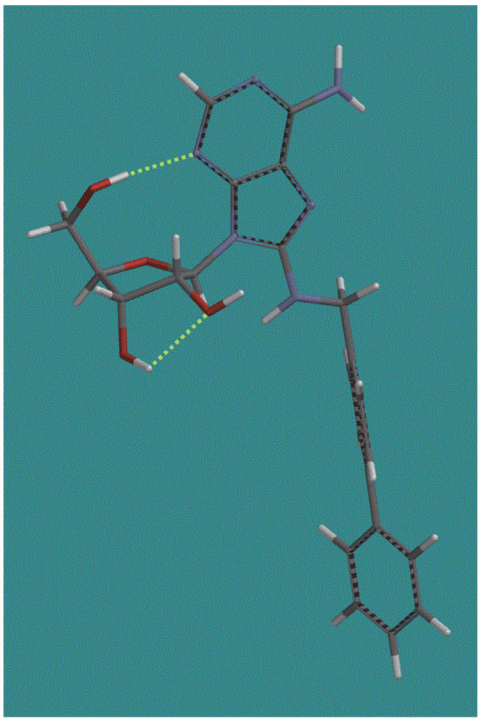


**Figure 4-2.** The most stable *anti* (A, $\chi$ = 185.3°) and *syn* (B, $\chi$ = 61.7°) conformers of **1-63**.

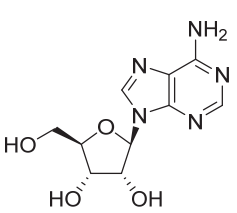
第二節　NMR による考察

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。

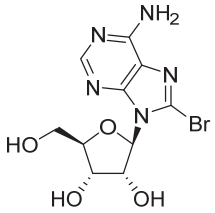
Jordan らは、プリンヌクレオシドのグリコシド結合まわりのコンホメーションを評価する際に、$^{1}$H NMR における 2′位プロトンの化学シフトならびに 1′位および 2′位プロトンの化学シフトの差が有用な判断基準になることを報告している [63]。8 位に置換基を持たないプリンヌクレオシドは通常、グリコシド結合を軸とする回転が比較的容易に起こり、*syn-anti* 平衡のもと存在するが、8 位に置換基が導入されると、*syn* 配座へのコンホメーション変化が惹起され、これに伴い 2′位プロトンの化学シフトが低磁場側にシフトする。一方、1′位プロトンの化学シフト（通常は 2′位プロトンより低磁場側）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**37**[66]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。

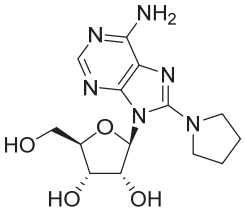
**Table 4-1. Selected Chemical Shifts of Compounds 1-9, 1-63, 13, and 35–37**[a]



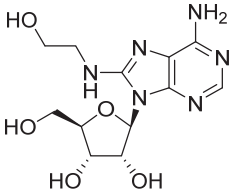
**35**



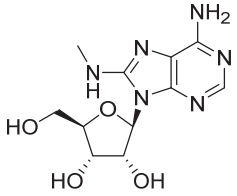
**13**



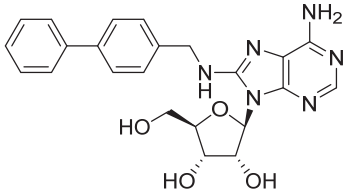
**36**



**37**



**1-9**



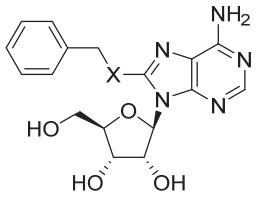
**1-63**

| 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、$^1$H 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 $^1$H NMR データと hCNT2 阻害活性を示した。hCNT2 阻害活性を示す **1-12**（$IC_{50}$ = 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**（$IC_{50}$ > 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 $IC_{50}$ of Compounds 1-12 and 1-25–1-28**[a]

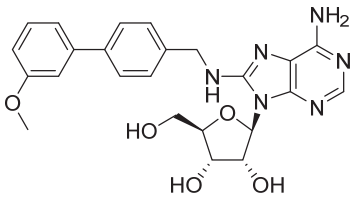



| compd | X | H2′ | H1′ | $\Delta_{1'-2'}$[b] | $IC_{50}$ (μM)[c] |
|---|---|---|---|---|---|
| 8-(benzylamino)adenosine (**1-12**) | NH | 4.73 | 5.94 | 1.21 | 52 ± 3.8 |
| 8-(2-phenylethyl)adenosine (**1-25**) | $CH_2$ | 4.91 | 5.85 | 0.94 | >1000[d] |
| 8-(benzyloxy)adenosine (**1-26**) | O | 4.90 | 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 μM. [e]No inhibition was observed at the maximum concentration of 1000 μM.

第三節　X 線結晶構造解析による考察

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。



**3-10**

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（$IC_{50}$ = 0.61 μM）も **1-63**（$IC_{50}$ = 0.64 μM）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（$\Delta E_{syn\text{-}anti}$ = 5.50 kcal/mol）。

A　　B

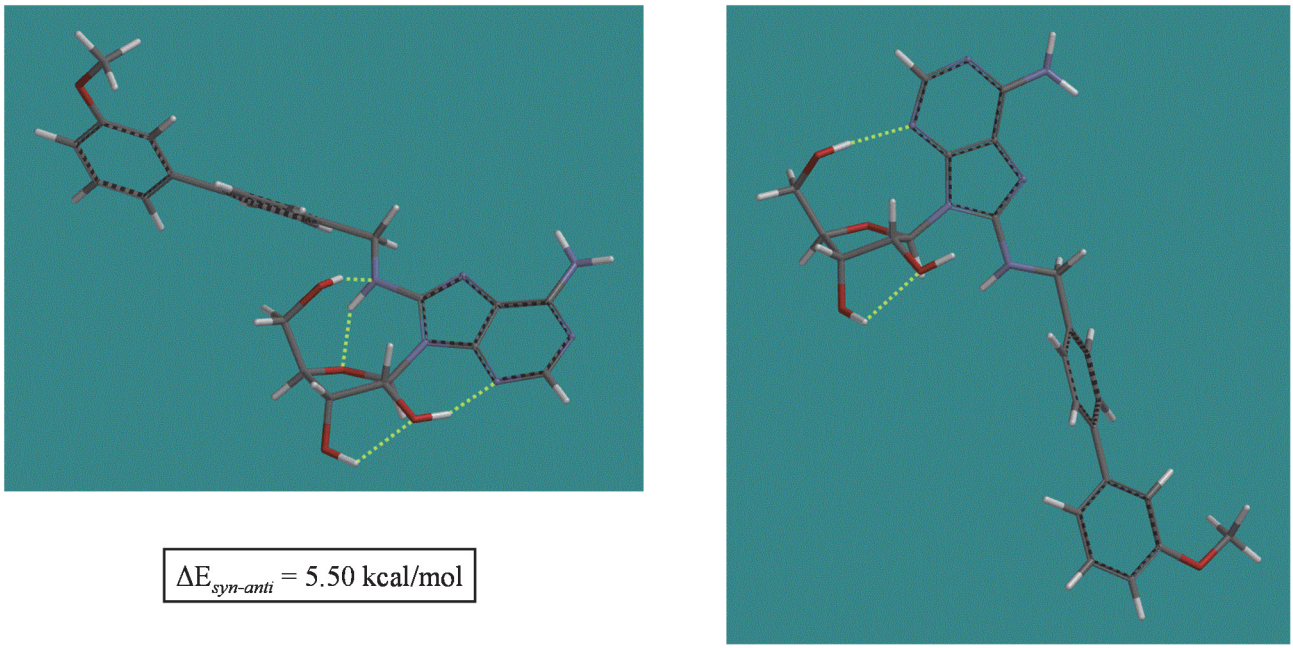



**Figure 4-3.** The most stable *anti* (A, χ = 185.2°) and *syn* (B, χ = 55.9°) conformers of **3-10**.

表 4-3 には、化合物 **1-63** および **3-10** の $^{1}$H 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、$\chi$ = 102.1°および 117.1°であり、*syn* 配座（50° < $\chi$ < 80°）および *anti* 配座（180° < $\chi$ < 280°）いずれの定義 [62] にも該当しなかった。

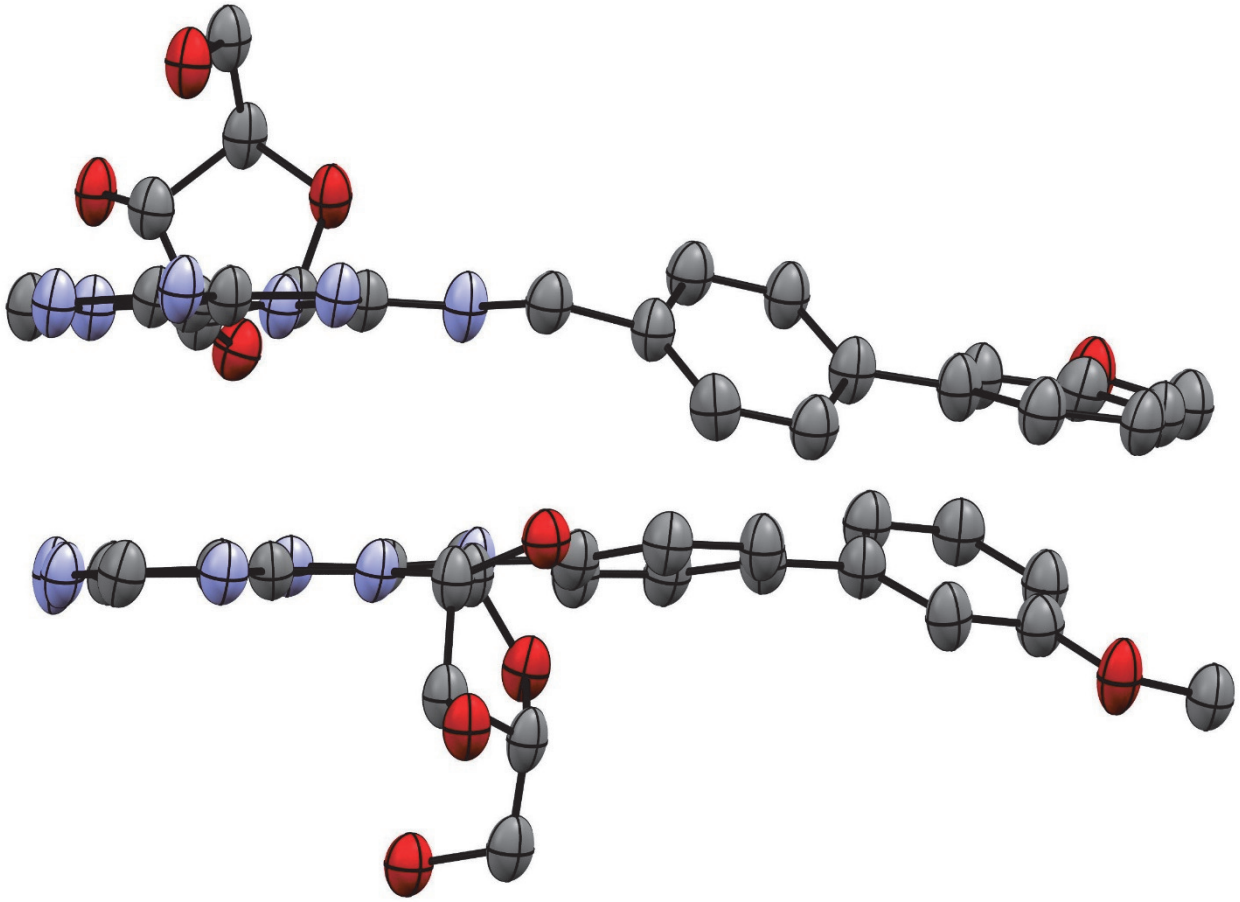
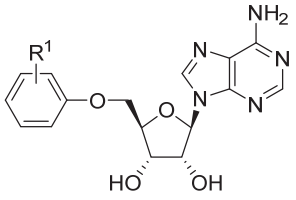


**Figure 4-4.** X-ray crystallography of **3-10**.

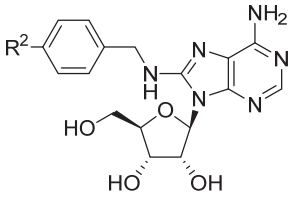
第四節　ドラッグデザインによる考察

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 $^1$H 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**




**4-1–4-4**




**1-63**: $R^2$ = Ph
**1-12**: $R^2$ = H

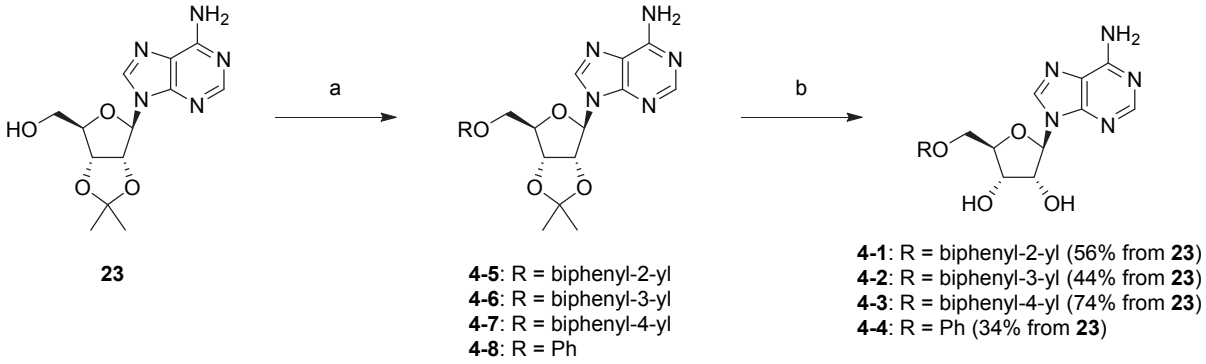
| compd | $R^1$ | $IC_{50}$ (μM)[a] |
|---|---|---|
| **4-1** | 2-Ph | >100 (49)[b] |
| **4-2** | 3-Ph | 11[c] |
| **4-3** | 4-Ph | >100 (40)[b] |
| **4-4** | H | >100 (49)[b] |
| **1-63** | | 0.64 ± 0.19 |
| **1-12** | | 52 ± 3.8 |

[a]Concentration of each compound required to inhibit inosine uptake by 50%. Data are expressed as the mean ± 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 μM. The inhibition% is shown in parentheses. [c]The data is expressed as the mean of two independent experiments.

第五節　試験化合物の合成

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)。

**Scheme 4-1.** Synthesis of Compounds **4-1**–**4-4**[a]




**23**

**4-5**: R = biphenyl-2-yl
**4-6**: R = biphenyl-3-yl
**4-7**: R = biphenyl-4-yl
**4-8**: R = Ph

**4-1**: R = biphenyl-2-yl (56% from **23**)
**4-2**: R = biphenyl-3-yl (44% from **23**)
**4-3**: R = biphenyl-4-yl (74% from **23**)
**4-4**: R = Ph (34% from **23**)

[a]Reagents and conditions: (a) appropriate phenol, DIAD, $PPh_3$, THF, rt; (b) 70% aq $HCO_2H$, 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

## 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 $F_{254}$ 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. $^{1}$H 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. $^{13}$C 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 $CDCl_3$, δ 39.52 in DMSO-$d_6$, or δ 49.00 in $CD_3OD$).[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 ≥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% aq $HCO_2H$ 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 $MeNH_2$ (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 $H_2O$ to give the title compound (138 mg, 75%) as a pale brown solid. mp 204–206 °C (lit.[69] mp 198 °C, dec). $^1$H 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). $^{13}$C 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 $C_{11}H_{17}N_6O_4$ $(M+H)^+$ 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 $EtNH_2$ (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 $H_2O$ to give the title compound (54.7 mg, 56%) as an off-white solid. mp 215–217 °C. $^1$H 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). $^{13}$C 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 $C_{12}H_{19}N_6O_4$ $(M+H)^+$ 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 $i$-$Pr_2NEt$ (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. $^1$H 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). $^{13}$C 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 $C_{15}H_{25}N_6O_4$ $(M+H)^+$ 353.1932, found 353.1934.

The $^1$H NMR spectral property was found to be different from the following data previously reported.[70]

*2-(n-Amylamino)adenosine (7c).* $^1$H 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, $N^6$-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), $BnNH_2$ (201 mg, 1.88 mmol), and *i*-$Pr_2NEt$ (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). $^1$H 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). $^{13}$C 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 $C_{17}H_{21}N_6O_4$ $(M+H)^+$ 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 $MeNH_2$ (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 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). $^1$H NMR (DMSO-$d_6$, $D_2O$ 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 $C_{11}H_{16}N_5O_4$ $(M+H)^+$ 282.1197, found 282.1199.

***N*$^6$-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 $H_2O$ to give the title compound (91.3 mg, 59%) as a white floc. mp 199–200 °C (lit.[75] mp 193–194 °C). $^1$H 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 $C_{12}H_{18}N_5O_4$ $(M+H)^+$ 296.1353, found 296.1355.

**$N^6$-Pentyladenosine (1-7)**[76,77]

A mixture of **12** (150 mg, 0.523 mmol), pentylamine (137 mg, 1.57 mmol), and *i*-$Pr_2NEt$ (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). $^1$H NMR ($CD_3OD$) 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). $^{13}$C 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 $C_{15}H_{24}N_5O_4$ $(M+H)^+$ 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 $MeNH_2$ (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 $H_2O$ to give the title compound (105 mg, 61%) as an off-white solid. mp 251–255 °C, dec (lit.[78] mp 250 °C, dec). $^1$H 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). $^{13}$C 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 $C_{11}H_{17}N_6O_4$ $(M+H)^+$ 297.1306, found 297.1306.

**8-(Ethylamino)adenosine (1-10)**[78]

A mixture of **13** (200 mg, 0.578 mmol) and ca. 70% aqueous $EtNH_2$ (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 $H_2O$ to give the title compound (130 mg, 73%) as a pale brown solid. mp 257–259 °C, dec (lit.[78] mp 257 °C, dec). $^1$H 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). $^{13}$C 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 $C_{12}H_{19}N_6O_4$ $(M+H)^+$ 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*-$Pr_2NEt$ (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. $^1$H 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). $^{13}$C 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 $C_{15}H_{25}N_6O_4$ $(M+H)^+$ 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**. $^1$H-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). $^{13}$C 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 $C_{17}H_{21}N_6O_4$ $(M+H)^+$ 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 $Ac_2O$ (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. $^1$H NMR ($CD_3OD$) 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). $^{13}$C 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 $HCO_2H$ (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). $^1$H 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). $^{13}$C 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 $C_{12}H_{16}N_5O_5$ $(M+H)^+$ 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. $^1$H 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). $^{13}$C 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 $C_{16}H_{22}N_5O_5$ $(M+H)^+$ 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 $H_2O$. mp 179–181 °C. $^1$H 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). $^{13}$C 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 $C_{13}H_{18}N_5O_5$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{19}H_{28}N_5O_5$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $^1$H 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. $^1$H NMR (DMSO-$d_6$) δ 1.33 (s, 3H), 1.54 (s, 3H), 3.54–3.71 (m, 2H), 4.18 (dd, $J$ = 6.3, 11.8 Hz, 1H), 4.28 (dd, $J$ = 4.3, 11.8 Hz, 1H), 4.34–4.45 (m, 1H), 5.01 (dd, $J$ = 3.3, 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). $^{13}$C 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 $C_{21}H_{24}N_5O_5$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{18}H_{20}N_5O_5$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{15}H_{20}N_5O_6$ $(M+H)^+$ 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 $H_2O$. mp 189–191 °C. $^1$H 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). $^{13}$C 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 $C_{12}H_{16}N_5O_6$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{16}H_{22}N_5O_6$ $(M+H)^+$ 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 $H_2O$. mp 157–159 °C. $^1$H 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). $^{13}$C

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 $C_{13}H_{18}N_5O_6$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{19}H_{28}N_5O_6$ $(M+H)^+$ 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. $^1$H 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). $^{13}$C NMR (DMSO-$d_6$) δ 13.8, 21.7, 27.3, 27.7, 67.3, 67.7, 70.3, 72.9, 81.4, 87.7, 119.2, 139.5, 149.4, 152.7, 154.5, 156.1. HRMS calcd for $C_{16}H_{24}N_5O_6$ $(M+H)^+$ 382.1721, found 382.1724.

**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**. $^1$H 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).$^{13}$C 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 $C_{21}H_{24}N_5O_6$ $(M+H)^+$ 442.1721, found 442.1722.

*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**. $^1$H 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). $^{13}$C 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 $C_{18}H_{20}N_5O_6$ $(M+H)^+$ 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 $Et_3N$ (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 $NaHCO_3$ (20 mL). The organic layer was washed successively with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H 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). $^{13}$C 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 $C_{20}H_{21}N_6O_8$ $(M+H)^+$ 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 $Et_3N$ (113 mg, 1.11 mmol) followed by $MeNH_2$ (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. $^1$H 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). $^{13}$C 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 $C_{15}H_{21}N_6O_5$ $(M+H)^+$ 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 $H_2O$. mp 164–165 °C. $^1$H 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). $^{13}$C 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 $C_{12}H_{17}N_6O_5$ $(M+H)^+$ 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 $EtNH_2$ (0.021 mL, ca. 0.252 mmol) according to a procedure similar to that described for the preparation of **1-95**. $^1$H 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). $^{13}$C 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 $C_{16}H_{23}N_6O_5$ $(M+H)^+$ 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 $H_2O$. mp 203–205 °C. $^1$H 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). $^{13}$C 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 $C_{13}H_{19}N_6O_5$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{19}H_{29}N_6O_5$ $(M+H)^+$ 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 $HCO_2H$ (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. $^1$H 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). $^{13}$C 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 $C_{16}H_{25}N_6O_5$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{21}H_{25}N_6O_5$ $(M+H)^+$ 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 $HCO_2H$ (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. $^1$H 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). $^{13}$C 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 $C_{18}H_{21}N_6O_5$ $(M+H)^+$ 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), $Et_3N$ (585 mg, 5.78 mmol), and DMAP (17.6 mg, 0.144 mmol) in MeCN (14.4 mL) was added dropwise $Ac_2O$ (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 $H_2O$ (15 mL). The organic layer was washed with brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{16}H_{19}BrN_5O_7$ $(M+H)^+$ 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), $Et_3N$ (102 mg, 1.01 mmol) and CuI (3.80 mg, 0.0200 mmol) in DMF (2.69 mL) was added $Pd(PPh_3)_4$ (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 $H_2O$ (10 mL). The organic layer was washed twice with $H_2O$ (10 mL × 2), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 ($CDCl_3$) 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 $C_{24}H_{24}N_5O_7$ $(M+H)^+$ 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% $H_2O$, 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. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{24}H_{28}N_5O_7$ $(M+H)^+$ 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. $^1$H 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). $^{13}$C 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 $C_{18}H_{22}N_5O_4$ $(M+H)^+$ 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 $H_2O$ (15 mL). The organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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 $NH_4F$ (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. $^1$H 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). $^{13}$C 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 $C_{17}H_{20}N_5O_5$ $(M+H)^+$ 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*-$Pr_2$NEt (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. $^1$H 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). $^{13}$C 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 $C_{17}H_{20}N_5O_4S$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{18}H_{23}N_6O_4$ $(M+H)^+$ 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 $NH_4F$ (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. $^1$H 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). $^{13}$C 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 $C_{16}H_{19}N_6O_4$ $(M+H)^+$ 359.1462, found 359.1466.

The $^1$H and $^{13}$C NMR spectral properties were found to be different from the following data previously reported.[89]

*N-(Adenosin-8-yl)-aniline (4a).* $^1$H NMR (DMSO-$d_6$) δ 3.72 (m, 2H, 5′H), 3.91 (m, 1H, 4′H), 3.96 (m, 2H, $NH_2$), 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). $^{13}$C 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 2-phenylethylamine (210 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. $^1$H 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). $^{13}$C 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 $C_{18}H_{23}N_6O_4$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{19}H_{25}N_6O_4$ $(M+H)^+$ 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*-$Pr_2$NEt (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. $^1$H 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). $^{13}$C 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 $C_{18}H_{23}N_6O_4$ $(M+H)^+$ 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*)-1-phenylethylamine (420 mg, 3.47 mmol), and *i*-$Pr_2$NEt (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 $Et_3N$ (247 mg, 2.44 mmol) and DMAP (7.5 mg, 0.0614 mmol) followed by $Ac_2O$ (206 mg. 2.02 mmol), and the resulting mixture was stirred at room temperature for 12 h. $Et_3N$ (124 mg, 1.22 mmol) and $Ac_2O$ (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 $H_2O$ (15 mL). The organic layer was washed with brine (10 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) δ 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, 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, $J$ = 6.0 Hz, 1H), 7.24–7.31 (m, 1H), 7.32–7.47 (m, 4H), 8.16 (s, 1H). $^{13}$C NMR ($CDCl_3$) 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. $^1$H 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). $^{13}$C 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. $^1$H 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). $^{13}$C 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 $C_{14}H_{21}N_6O_4$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{16}H_{25}N_6O_4$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{17}H_{27}N_6O_4$ $(M+H)^+$ 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-2-ylmethanamine (168 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. $^1$H 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). $^{13}$C 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 $C_{15}H_{19}N_6O_5$ $(M+H)^+$ 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*-$Pr_2$NEt (523 mg, 4.04 mmol) according to a procedure similar to that described for the preparation of **1-11**. $^1$H 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). $^{13}$C 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 $C_{15}H_{19}N_6O_5$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{15}H_{19}N_6O_4S$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{15}H_{19}N_6O_4S$ $(M+H)^+$ 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*-$Pr_2NEt$ (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. $^1$H 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). $^{13}$C 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 $C_{16}H_{20}N_7O_4$ $(M+H)^+$ 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*-$Pr_2NEt$ (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. $^1$H 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). $^{13}$C 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 $C_{16}H_{20}N_7O_4$ $(M+H)^+$ 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-4-ylmethanamine (188 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-42**. $^1$H 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). $^{13}$C 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 2-methylbenzylamine (210 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. $^1$H 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). $^{13}$C 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 $C_{18}H_{23}N_6O_4$ $(M+H)^+$ 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 3-methylbenzylamine (210 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. $^1$H 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). $^{13}$C 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 $C_{18}H_{23}N_6O_4$ $(M+H)^+$ 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. $^1$H 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). $^{13}$C 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 $C_{18}H_{23}N_6O_4$ $(M+H)^+$ 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 2-methoxybenzylamine (238 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-46**. mp 155–158 °C. $^1$H 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). $^{13}$C 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 $C_{18}H_{23}N_6O_5$ $(M+H)^+$ 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 3-methoxybenzylamine (238 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11.** $^1$H 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). $^{13}$C 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 $C_{18}H_{23}N_6O_5$ $(M+H)^+$ 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 4-methoxybenzylamine (238 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. $^1$H 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). $^{13}$C 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 $C_{18}H_{23}N_6O_5$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{17}H_{20}FN_6O_4$ $(M+H)^+$ 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**. $^{1}$H 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). $^{13}$C 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 $C_{17}H_{20}FN_6O_4$ $(M+H)^+$ 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**. $^{1}$H 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). $^{13}$C 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 $C_{17}H_{20}FN_6O_4$ $(M+H)^+$ 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**. $^{1}$H 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). $^{13}$C 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 $C_{17}H_{20}ClN_6O_4$ $(M+H)^+$ 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**. $^{1}$H 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). $^{13}$C 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 $C_{17}H_{20}ClN_6O_4$ $(M+H)^+$ 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**. $^{1}$H 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). $^{13}$C 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 $C_{17}H_{20}ClN_6O_4$ $(M+H)^+$ 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**. $^{1}$H 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). $^{13}$C 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 $C_{18}H_{20}F_3N_6O_4$ $(M+H)^+$ 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**. $^{1}$H 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). $^{13}$C 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 $C_{18}H_{20}F_3N_6O_4$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{18}H_{20}F_3N_6O_4$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{21}H_{23}N_6O_4$ $(M+H)^+$ 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 $H_2O$ (200 mL). The organic layer was washed successively with $H_2O$ (80 mL × 2) and brine (80 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residual solid was triturated in $Et_2O$ (50 mL), sonicated, collected by filtration, washed with $Et_2O$, and then dried at 40 °C under reduced pressure to give the title compound (3.23 g, 83%) as a white solid. $^1$H NMR ($CDCl_3$) 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 $C_{19}H_{14}NO_2$ $(M+H)^+$ 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 $NaHCO_3$ (40 mL). The organic layer was washed twice with saturated aqueous $NaHCO_3$ (40 mL × 2), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) δ 4.04 (s, 2H), 7.35–7.53 (m, 3H), 7.71–7.90 (m, 4H). HRMS calcd for $C_{11}H_{12}N$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{21}H_{23}N_6O_4$ $(M+H)^+$ 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 2-phenylbenzylamine (318 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. $^1$H 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). $^{13}$C 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 $C_{23}H_{25}N_6O_4$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{23}H_{25}N_6O_4$ $(M+H)^+$ 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*-$Pr_2NEt$ (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. $^1$H 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). $^{13}$C 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 $C_{23}H_{25}N_6O_4$ $(M+H)^+$ 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 $NH_3$ (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 $NaHCO_3$ (40 mL), and brine (40 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure to give the title compound (981 mg, 99%) as a white solid. $^1$H 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 $C_{14}H_{14}NO$ $(M+H)^+$ 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 $Et_3N$ (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 $H_2O$ (20 mL). The organic layer was washed with brine (20 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) δ 4.03 (s, 2H), 7.12–7.20 (m, 2H), 7.21–7.35 (m, 5H), 7.53–7.60 (m, 2H). $^{13}$C NMR ($CDCl_3$) δ 42.1, 110.1, 119.1, 126.8, 128.9, 129.1, 129.8, 132.4, 139.4, 146.9. HRMS calcd for $C_{14}H_{12}N$ $(M+H)^+$ 194.0964, found 194.0961.

*4-Benzylbenzylamine (**1-75**).*[95] To a stirred ice-cold suspension of $LiAlH_4$ (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 °C with stirring for 3 h. After being allowed to cool to room temperature, the reaction mixture was quenched

by sequential addition of $H_2O$ (0.103 mL), 15% aqueous NaOH (0.103 mL), and $H_2O$ (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. $^1$H NMR ($CDCl_3$) δ 3.83 (s, 2H), 3.97 (s, 2H), 7.06–7.32 (m, 9H). $^{13}$C NMR ($CDCl_3$) δ 41.7, 46.3, 126.2, 127.3, 128.6, 129.0, 129.2, 139.8, 141.2, 141.3. HRMS calcd for $C_{14}H_{16}N$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{24}H_{27}N_6O_4$ $(M+H)^+$ 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 4-phenoxybenzylamine (345 mg, 1.73 mmol) according to a procedure similar to that described for the preparation of **1-11**. $^1$H 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). $^{13}$C 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 $C_{23}H_{25}N_6O_5$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) δ 3.86 (s, 2H), 7.19–7.38 (m, 9H). $^{13}$C NMR ($CDCl_3$) δ 46.1, 126.9, 128.1, 129.2, 130.6, 131.9, 133.7, 136.4, 142.6. HRMS calcd for $C_{13}H_{13}NNaS$ $(M+Na)^+$ 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**. $^1$H 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). $^{13}$C 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,

151.3, 152.5. HRMS calcd for $C_{23}H_{25}N_6O_4S$ $(M+H)^+$ 481.1653, found 481.1653.

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

*4-Cyclopropylbenzylamine (**1-77**).* To a stirred ice-cold suspension of $LiAlH_4$ (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 $H_2O$ (0.119 mL), 15% aqueous NaOH (0.119 mL), and $H_2O$ (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. $^1$H NMR ($CDCl_3$) 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 $C_{10}H_{14}N$ $(M+H)^+$ 148.1121, found 148.1115.

*2',3',5'-Tris-O-(tert-butyldimethylsilyl)-8-(4-cyclopropylbenzylamino)adenosine (**1-78**).* A mixture of **19**[47] (480 mg, 0.697 mmol), **1-77** (308 mg, 2.09 mmol), and *i*-$Pr_2$NEt (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 $NaHCO_3$ (15 mL). The organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{38}H_{67}N_6O_4Si_3$ $(M+H)^+$ 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 $NH_4F$ (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 $H_2O$ (45 mL), and the resulting suspension was stirred at room temperature for 2 h. The precipitate was collected by filtration, washed with $H_2O$, 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. $^1$H 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). $^{13}$C 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,

148.6, 149.8, 151.4, 152.5. HRMS calcd for $C_{20}H_{25}N_6O_4$ $(M+H)^+$ 413.1932, found 413.1930.

**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), $Pd(PPh_3)_4$ (230 mg, 0.199 mmol), $Na_2CO_3$ (232 mg, 2.19 mmol), and $H_2O$ (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 $H_2O$ (20 mL). The organic layer was washed with brine (20 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) δ 23.3, 33.0, 33.7, 110.0, 119.3, 126.1, 130.8, 132.2, 141.3 (2C). HRMS calcd for $C_{12}H_{12}N$ $(M+H)^+$ 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. $^1$H NMR ($CDCl_3$) 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 $C_{12}H_{14}N$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C NMR (DMSO-$d_6$) δ 25.0, 34.3, 45.0, 45.4, 126.6, 127.0, 141.6, 143.7. HRMS calcd for $C_{12}H_{18}N$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{22}H_{29}N_6O_4$ $(M+H)^+$ 441.2245, found 441.2242.

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

*(4-Cyclohexylphenyl)methanol (**1-82**).*[98] To a stirred suspension of $LiAlH_4$ (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 $H_2O$ (0.223 mL), 15% aqueous NaOH (0.223 mL), and $H_2O$ (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. $^1$H 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). $^{13}$C 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 $C_{13}H_{18}NaO$ $(M+Na)^+$ 213.1250, found 213.1244.

*N-(4-Cyclohexylbenzyl)phthalimide (**1-83**).* To a stirred mixture of **1-82** (810 mg, 4.26 mmol), $PPh_3$ (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. $^1$H 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). $^{13}$C 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 $C_{21}H_{22}NO_2$ $(M+H)^+$ 320.1645, found 320.1648.

*4-Cyclohexylbenzylamine (**1-84**).* To a stirred solution of **1-83** (1.19 g, 3.73 mmol) in $CHCl_3$/EtOH (5/1, 24.8 mL) was added dropwise $H_2NNH_2 \cdot H_2O$ (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 $H_2O$ (20 mL). The organic layer was washed with $H_2O$ (20 mL), dried ($Na_2SO_4$), 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. $^1$H 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). $^{13}$C 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 $C_{13}H_{20}N$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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 $C_{41}H_{73}N_6O_4Si_3$ $(M+H)^+$ 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 $NH_4F$ (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 $H_2O$ (40 mL), and the resulting suspension was stirred at room temperature for 2 h. The precipitate was collected by filtration, washed with $H_2O$, 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. $^1$H 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). $^{13}$C 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 $C_{23}H_{31}N_6O_4$ $(M+H)^+$ 455.2401, found 455.2401.

## Purity of Tested Compounds in Chapter 1

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

| compd | formula | calcd | | | found | | | $t_R$[a] | area |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | C | H | N | (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 |

[a] $t_R$ is the retention time of the compound.

(continued on the following page)

**Table E1. continued**

| compd | formula | calcd | | | found | | | $t_R$[a] | area |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | C | H | N | (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** | $C_{18}H_{19}F_3N_6O_4 \cdot 0.4H_2O$ | 48.30 | 4.46 | 18.78 | 48.31 | 4.54 | 18.65 | | |

[a] $t_R$ is the retention time of the compound.

(continued on the following page)

**Table E1. continued**

| compd | formula | calcd | | | found | | | $t_R$[a] | area |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | C | H | N | (min) | (%) |
| **1-57** | $C_{18}H_{19}F_3N_6O_4 \cdot 0.2H_2O$ | 48.69 | 4.40 | 18.93 | 48.68 | 4.52 | 18.81 | 26.4 | 98.9 |
| **1-58** | $C_{18}H_{19}F_3N_6O_4 \cdot 0.2H_2O$ | 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] $t_R$ 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 $LiAlH_4$ (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 $H_2O$ (0.126 mL), 15% aqueous NaOH (0.126 mL), and $H_2O$ (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. $^1$H 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). $^{13}$C 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 $C_{12}H_{13}N_2$ $(M+H)^+$ 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*-$Pr_2$NEt (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. $^1$H 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). $^{13}$C 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 $C_{22}H_{24}N_7O_4$ $(M+H)^+$ 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), 4-cyanophenylboronic acid (440 mg, 2.99 mmol), and 2.0 M aqueous $Na_2CO_3$ (2.72 mL) in MeCN (13.6 mL) was added $Pd(PPh_3)_4$ (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 $H_2O$/brine (1/1, 40 mL). The organic layer was dried ($Na_2SO_4$) 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. $^1$H NMR

($CDCl_3$) δ 7.36–7.50 (m, 1H), 7.60–7.98 (m, 5H), 8.61–8.74 (m, 1H), 8.80–8.94 (m, 1H). $^{13}$C NMR ($CDCl_3$) δ 112.0, 118.7, 123.9, 127.9, 133.0, 134.6, 134.9, 142.4, 148.4, 149.9. HRMS calcd for $C_{12}H_9N_2$ $(M+H)^+$ 181.0760, found 181.0756.

*N-[4-(Pyridin-3-yl)benzyl]trifluoroacetamide (**2-23**).* To a stirred ice-cold suspension of $LiAlH_4$ (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 $H_2O$ (0.105 mL), 15% aqueous NaOH (0.105 mL), and $H_2O$ (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 residue was dissolved in EtOH (9.21 mL). To the solution was added $CF_3CO_2Et$ (393 mg, 2.76 mmol), and the resulting mixture 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. $^1$H 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 $C_{14}H_{12}F_3N_2O$ $(M+H)^+$ 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 $H_2O$ (10 mL). The aqueous layer was extracted twice with DCM (10 mL × 2). The combined organic extracts were dried ($Na_2SO_4$) 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. $^1$H 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). $^{13}$C 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 $C_{12}H_{13}N_2$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{22}H_{24}N_7O_4$ $(M+H)^+$ 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 4-bromopyridine 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**. $^1$H NMR ($CDCl_3$) δ 7.46–7.57 (m, 2H), 7.67–7.89 (m, 4H), 8.68–8.80 (m, 2H). $^{13}$C NMR ($CDCl_3$) δ 112.9, 118.5, 121.7, 127.9, 133.0, 142.7, 146.5, 150.7. HRMS calcd for $C_{12}H_9N_2$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C NMR (DMSO-$d_6$) δ 45.3, 121.0, 126.5, 127.8, 135.0, 145.7, 146.9, 150.2. HRMS calcd for $C_{12}H_{13}N_2$ $(M+H)^+$ 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*-$Pr_2$NEt (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*-$Pr_2$NEt (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 the title compound (93.0 mg, 50%) as a pale brown solid. $^1$H 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). $^{13}$C 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 $C_{22}H_{24}N_7O_4$ $(M+H)^+$ 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-3-methoxybenzonitrile **28** (2.00 g, 13.4 mmol) in DCM (26.8 mL) was added $Et_3N$ (2.04 g, 20.1 mmol). Then $Tf_2O$ (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 $NaHCO_3$ (30 mL). The organic layer was washed successively with $H_2O$/brine (2/1, 30 mL) and brine (30 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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), $Na_2CO_3$ (2.84 g, 26.8 mmol), and $H_2O$ (4.5 mL) in DMF (25.5 mL) was added $Pd(PPh_3)_4$ (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 $H_2O$ (50 mL). The organic layer was washed successively with $H_2O$ (40 mL) and brine (40 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) δ 3.85 (s, 3H), 7.17–7.24 (m, 1H), 7.31–7.63 (m, 7H). $^{13}$C NMR ($CDCl_3$) 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 $C_{14}H_{12}NO$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{14}H_{15}NNaO$ $(M+Na)^+$ 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. $^1$H 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). $^{13}$C 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 $C_{24}H_{27}N_6O_5$ $(M+H)^+$ 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 $BBr_3$ 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 $NaHCO_3$ (100 mL), and brine (100 mL), dried ($Na_2SO_4$), 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. $^1$H 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). $^{13}$C 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 $C_{13}H_8NO$ $(M-H)^-$ 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 $K_2CO_3$ (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 $Et_2O$ (30 mL) and $H_2O$ (10 mL). The organic layer was washed successively with $H_2O$ (10 mL × 2) and brine (10 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure to give the title compound (146 mg, quant.) as a white solid. $^1$H NMR ($CDCl_3$) δ 5.11 (s, 2H), 7.23–7.48 (m, 11H), 7.51–7.59 (m, 2H). $^{13}$C NMR ($CDCl_3$) 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 $C_{20}H_{15}NNaO$ $(M+Na)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{20}H_{20}NO$ $(M+H)^+$ 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*-$Pr_2NEt$ (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 $NaHCO_3$ (15 mL). The organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{48}H_{73}N_6O_5Si_3$ $(M+H)^+$ 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% $H_2O$, 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. $^1$H NMR ($CDCl_3$) 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 $C_{41}H_{67}N_6O_5Si_3$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (15 mL). The organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{43}H_{71}N_6O_5Si_3$ $(M+H)^+$ 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 $NH_4F$ (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. $^1$H 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). $^{13}$C 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 $C_{25}H_{29}N_6O_5$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (100 mL). The organic layer was washed successively with $H_2O$ (40 mL) and brine (40 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) δ 5.20 (s, 2H), 7.15–7.22 (m, 2H), 7.32–

7.53 (m, 6H). HRMS calcd for $C_{14}H_{14}BrN_2O$ $(M+NH_4)^+$ 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), $Na_2CO_3$ (3.21 g, 30.3 mmol), and $H_2O$ (7.5 mL) in DMF (30 mL) was added $Pd(PPh_3)_4$ (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 $H_2O$ (60 mL). The organic layer was washed successively with $H_2O$ (50 mL) and brine (50 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{20}H_{19}N_2O$ $(M+NH_4)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{20}H_{19}NNaO$ $(M+Na)^+$ 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 **19**[47] (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**. $^1$H NMR ($CDCl_3$) 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 $C_{48}H_{73}N_6O_5Si_3$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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 $C_{41}H_{67}N_6O_5Si_3$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (15 mL). The organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{42}H_{69}N_6O_5Si_3$ $(M+H)^+$ 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 $NH_4F$ (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 $H_2O$ (40 mL), and then stirred for 1 h. The precipitate was collected by filtration, washed with $H_2O$, 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. $^1$H 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). $^{13}$C 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 $C_{24}H_{27}N_6O_5$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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 $C_{43}H_{71}N_6O_5Si_3$ $(M+H)^+$ 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 $NH_4F$ (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. $^1$H 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). $^{13}$C 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 $C_{25}H_{29}N_6O_5$ $(M+H)^+$ 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 $NH_4F$ (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 $H_2O$ (9.09 mL), and then stirred for 1 h. The precipitate was collected by filtration, washed with MeOH/$H_2O$ (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. $^1$H 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). $^{13}$C 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 $C_{23}H_{25}N_6O_5$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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, 8.1 Hz, 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 $C_{44}H_{73}N_6O_5Si_3$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{26}H_{31}N_6O_5$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (20 mL). The organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{44}H_{73}N_6O_5Si_3$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{26}H_{31}N_6O_5$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (15 mL). The organic layer was washed successively with $H_2O$ (10 mL) and brine (10 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{44}H_{71}N_6O_7Si_3$ $(M+H)^+$ 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 $NH_4F$ (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. $^1$H 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). $^{13}$C 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 $C_{26}H_{29}N_6O_7$ $(M+H)^+$ 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 $NH_3$ 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 $CHCl_3$ (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/$CHCl_3$ (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. $^1$H 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). $^{13}$C 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 $C_{25}H_{28}N_7O_6$ $(M+H)^+$ 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 $NaBH_4$ (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. $^1$H 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). $^{13}$C 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 $C_{25}H_{29}N_6O_6$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{23}H_{21}NNaO_2$ $(M+Na)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{23}H_{26}NO_2$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{33}H_{37}N_6O_6$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{26}H_{31}N_6O_6$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (10 mL). The organic layer was washed successively with $H_2O$ (10 mL) and brine (10 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $LiAlH_4$ (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 $H_2O$ (0.045 mL), 15% aqueous NaOH (0.045 mL), and $H_2O$ (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. $^1$H 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). $^{13}$C 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 $C_{24}H_{28}NO_2$ $(M+H)^+$ 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*-$Pr_2NEt$ (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 yellow foam. $^1$H 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). $^{13}$C 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% $H_2O$, 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. $^1$H 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), 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, $J$ = 6.0 Hz, 1H), 7.90 (s, 1H). $^{13}$C 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**. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{25}H_{25}NNaO_2$ $(M+Na)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{25}H_{30}NO_2$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{35}H_{41}N_6O_6$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{28}H_{35}N_6O_6$ $(M+H)^+$ 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*-Pr$_2$NEt (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. $^1$H 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). $^{13}$C 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 $C_{34}H_{39}N_6O_5$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{27}H_{33}N_6O_5$ $(M+H)^+$ 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. $^1$H 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). $^{13}$C 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 $C_{34}H_{39}N_6O_6$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{27}H_{33}N_6O_6$ $(M+H)^+$ 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 $NaNO_2$ (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. $^1$H 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). $^{13}$C 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 $C_{34}H_{38}N_5O_7$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{27}H_{32}N_5O_7$ $(M+H)^+$ 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-1*H*-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 $NaHCO_3$ (100 mL). The organic layer was washed successively with saturated aqueous $NaHCO_3$ (60 mL), $H_2O$ (60 mL), and brine (60 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{18}H_{19}ClN_2NaO_7$ $(M+Na)^+$ 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. $^1$H 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). $^{13}$C 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 $C_{12}H_{14}ClN_2O_4$ $(M+H)^+$ 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*-$Pr_2$NEt (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. $^1$H 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). $^{13}$C 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 $C_{36}H_{40}N_3O_6$ $(M+H)^+$ 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% $H_2O$, 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. $^1$H 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). $^{13}$C 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 $C_{29}H_{34}O_3N_6$ $(M+H)^+$ 520.2442, found 520.2441.

## Purity of Tested Compounds in Chapter 2

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

| compd | formula | calcd | | | found | | | $t_R$[a] | area |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | C | H | N | (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 |

[a] $t_R$ 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), $Na_2CO_3$ (2.22 g, 21.0 mmol), and $H_2O$ (9 mL) in MeCN (45 mL) was added $Pd(PPh_3)_4$ (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 $H_2O$ (30 mL). The organic layer was washed with brine (30 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{18}H_{21}NNaO_3$ $(M+Na)^+$ 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 1,4-dioxane (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. $^1$H 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). $^{13}$C 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 $C_{13}H_{14}NO$ $(M+H)^+$ 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*-$Pr_2$NEt (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 $NaHCO_3$ (15 mL). The organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{41}H_{67}N_6O_5Si_3$ $(M+H)^+$ 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 $NH_4F$ (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. $^1$H 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). $^{13}$C 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 $C_{23}H_{25}N_6O_5$ $(M+H)^+$ 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), 2-methoxyphenylboronic acid (438 mg, 2.88 mmol), and 2.0 M aqueous $Na_2CO_3$ (2.75 mL) in MeCN (13.7 mL) was added $Pd(PPh_3)_4$ (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 $H_2O$/brine (1/1, 20 mL). The organic layer was dried ($Na_2SO_4$) 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. $^1$H NMR ($CDCl_3$) 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 $C_{14}H_{12}NO$ $(M+H)^+$ 210.0913, found 210.0913.

*2′-Methoxybiphenyl-4-ylmethanamine (**3-55**).*[107] To a stirred ice-cold suspension of $LiAlH_4$ (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 $H_2O$ (0.127 mL), 15% aqueous NaOH (0.127 mL), and $H_2O$ (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 yellow solid. $^1$H NMR (DMSO-$d_6$) δ 1.35–2.20 (br, 2H), 3.59–3.80 (m, 5H), 6.89–7.49 (m, 8H). $^{13}$C NMR (DMSO-$d_6$) 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 $C_{14}H_{16}NO$ $(M+H)^+$ 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*-$Pr_2NEt$ (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. $^1$H 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). $^{13}$C 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 $C_{24}H_{27}N_6O_5$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{15}H_{14}NO$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{15}H_{18}NO$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{25}H_{29}N_6O_5$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (15 mL). The

organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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), 1.64–1.82 (m, 2H), 3.74 (dd, *J* =2.5, 11.6 Hz, 1H), 3.87 (dd, *J* = 2.6, 11.6 Hz, 1H), 3.92 (t, *J* = 6.4 Hz, 2H), 4.06–4.13 (m, 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 $NH_4F$ (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. $^1$H 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). $^{13}$C 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 $K_2CO_3$ (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 $H_2O$ (20 mL). The organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{44}H_{73}N_6O_5Si_3$ $(M+H)^+$ 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 $NH_4F$ (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. $^1$H 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). $^{13}$C 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 $C_{26}H_{31}N_6O_5$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (10 mL). The organic layer was washed successively with $H_2O$ (10 mL) and brine (10 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) δ −0.29 (s, 3H), −0.04 (s, 3H), −0.01 (s, 3H), 0.01 (s, 3H), 0.10 (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 $C_{44}H_{71}N_6O_7Si_3$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{26}H_{29}N_6O_7$ $(M+H)^+$ 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 $NH_3$ 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. $^1$H 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). $^{13}$C 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 $C_{25}H_{28}N_7O_6$ $(M+H)^+$ 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 $NaBH_4$ (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. $^1$H 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). $^{13}$C 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 $C_{25}H_{29}N_6O_6$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{18}H_{20}NO_3$ $(M-H)^-$ 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**. $^1$H 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). $^{13}$C 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 $C_{13}H_{14}NO$ $(M+H)^+$ 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*-$Pr_2NEt$ (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 $NaHCO_3$ (20 mL). The organic layer was dried ($Na_2SO_4$) and concentrated under reduced pressure. The residue was triturated in $Et_2O$ 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. $^1$H NMR ($CDCl_3$) 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 $C_{41}H_{67}N_6O_5Si_3$ $(M+H)^+$ 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 $NH_4F$ (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. $^1$H 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). $^{13}$C 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 $C_{23}H_{25}N_6O_5$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{14}H_{12}NO$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{14}H_{16}NO$ $(M+H)^+$ 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*-$Pr_2$NEt (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. $^1$H 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 (dd, $J$ = 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). $^{13}$C 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 $C_{24}H_{27}N_6O_5$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{15}H_{14}NO$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{15}H_{18}NO$ $(M+H)^+$ 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. $^1$H 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). $^{13}$C 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 $C_{25}H_{29}N_6O_5$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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 $C_{44}H_{73}N_6O_5Si_3$ $(M+H)^+$ 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 $NH_4F$ (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. $^1$H 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). $^{13}$C 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 $C_{26}H_{31}N_6O_5$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (20 mL). The organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{44}H_{73}N_6O_5Si_3$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{26}H_{31}N_6O_5$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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), 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**. $^1$H 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). $^{13}$C 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

$C_{26}H_{29}N_6O_7$ $(M+H)^+$ 537.2092, found 537.2094.

**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 $NH_3$ 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. $^1$H NMR ($CDCl_3$) 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 $C_{43}H_{70}N_7O_6Si_3$ $(M+H)^+$ 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. $^1$H 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). $^{13}$C 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 $C_{25}H_{28}N_7O_6$ $(M+H)^+$ 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. $^1$H 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). $^{13}$C 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 $C_{25}H_{29}N_6O_6$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{18}H_{21}NNaO_3$ $(M+Na)^+$ 322.1414, found 322.1413.

*4'-(Aminomethyl)biphenyl-4-ol hydrochloride (**3-33**).* The title compound (607 mg, quant.) was obtained as an off-white solid from **3-30** (764 mg, 2.55 mmol) according to a procedure similar to that described for the preparation of **3-31**. $^1$H 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). $^{13}$C 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 $C_{13}H_{14}NO$ $(M+H)^+$ 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*-$Pr_2$NEt (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 $NaHCO_3$ (15 mL). The organic layer was dried ($Na_2SO_4$) 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. $^1$H NMR ($CDCl_3$) 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 $C_{41}H_{67}N_6O_5Si_3$ $(M+H)^+$ 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 $NH_4F$ (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 $H_2O$ (22.2 mL), and then stirred for 1 h. The insoluble material was collected by filtration, washed with MeOH/$H_2O$ (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. $^1$H 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). $^{13}$C 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 $C_{23}H_{25}N_6O_5$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (15 mL). The organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{42}H_{69}N_6N_5O_3$ $(M+H)^+$ 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 $NH_4F$ (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 $H_2O$ (17.1 mL), and then stirred for 2 h. The insoluble material was collected by filtration, washed with $H_2O$, and air-dried to give the title compound (206 mg, quant.) as a pale yellow solid. $^1$H 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). $^{13}$C 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 $C_{24}H_{27}N_6O_5$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (15 mL). The organic layer was washed successively with $H_2O$ (15 mL) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{43}H_{71}N_6O_5Si_3$ $(M+H)^+$ 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 $NH_4F$ (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 $H_2O$ (19.7 mL), and then stirred for 1.5 h. The insoluble material was collected by filtration, washed with $H_2O$, 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. $^1$H 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). $^{13}$C 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 $C_{25}H_{29}N_6O_5$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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 $C_{44}H_{73}N_6N_5O_3$ $(M+H)^+$ 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 $NH_4F$ (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 $H_2O$ (27.6 mL), and then stirred for 3 h. The insoluble material was collected by filtration, washed with $H_2O$, and air-dried to give the title compound (327 mg, 93%) as a pale yellow solid. $^1$H 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). $^{13}$C 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 $C_{26}H_{31}N_6O_5$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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), 0.82 (s, 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 $NH_4F$ (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 $H_2O$ (16.7 mL), and then stirred for 2.5 h. The insoluble material was collected by filtration, washed with $H_2O$, and air-dried to give the title compound (211 mg, quant.) as a pale yellow solid. $^1$H 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). $^{13}$C 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 $C_{26}H_{31}N_6O_5$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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 $C_{44}H_{71}N_6O_7Si_3$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{26}H_{29}N_6O_7$ $(M+H)^+$ 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**. $^1$H NMR ($CDCl_3$) 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 $C_{43}H_{70}N_7O_6Si_3$ $(M+H)^+$ 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 $NH_4F$ (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 $H_2O$ (13.7 mL), and then stirred for 3 h. The insoluble material was collected by filtration, washed with $H_2O$, 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. $^1$H 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). $^{13}$C 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 $C_{25}H_{28}N_7O_6$ $(M+H)^+$ 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 $NaBH_4$ (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 $NaHCO_3$ (10 mL) and brine (10 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{43}H_{71}N_6O_6Si_3$ $(M+H)^+$ 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 $NH_4F$ (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 $H_2O$ (8.22 mL), and then stirred for 3 h. The insoluble material was collected by filtration, washed with $H_2O$, and air-dried to give the title compound (105 mg, quant.) as a pale yellow solid. $^1$H 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). $^{13}$C 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 $C_{25}H_{29}N_6O_6$ $(M+H)^+$ 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 $PPh_3$ (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. $^1$H 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 $NaHCO_3$ (30 mL) and extracted with AcOEt (50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (30 mL), dried ($Na_2SO_4$), 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. $^1$H 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). $^{13}$C 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**. $^1$H 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). $^{13}$C 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 $C_{33}H_{36}N_7O_7$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{25}H_{30}N_7O_5$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (15 mL). The organic layer was washed successively with $H_2O$ (15 mL × 2) and brine (15 mL), dried ($Na_2SO_4$), 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. $^1$H 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). $^{13}$C 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 $C_{29}H_{34}N_2NaO_5$ $(M+Na)^+$ 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 $H_2O$ (20 mL). The organic layer was washed

successively with $H_2O$ (15 mL × 2) and brine (15 mL), dreid ($Na_2SO_4$), 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 $^1$H NMR). $^1$H 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). $^{13}$C 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 $C_{24}H_{27}N_2O_3$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{34}H_{38}N_7O_7$ $(M+H)^+$ 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% $H_2O$, 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. $^1$H 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). $^{13}$C 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 $C_{26}H_{32}N_7O_5$ $(M+H)^+$ 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 $K_2CO_3$ (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 $H_2O$ (30 mL). The organic layer was washed successively with $H_2O$ (30 mL × 2) and brine (30 mL), dried ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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). $^{13}$C NMR ($CDCl_3$) 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 $C_{30}H_{36}N_3O_5$ $(M+NH_4)^+$ 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 $CHCl_3$ (15.5 mL) was added dropwise a solution of $H_2NNH_2{\cdot}H_2O$ (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 $H_2O$/brine (1/1, 40 mL), dreid ($Na_2SO_4$), 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. $^1$H NMR ($CDCl_3$) 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 $C_{22}H_{31}N_2O_3$ $(M+H)^+$ 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. $^1$H 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). $^{13}$C 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 $C_{30}H_{40}N_3O_5$ $(M+NH_4)^+$ 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 $NaHCO_3/H_2O$ (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 ($Na_2SO_4$), 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. $^1$H 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). $^{13}$C 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-ylmethylamino]adenosine (**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**. $^1$H 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). $^{13}$C 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 $C_{35}H_{40}N_7O_7$ $(M+H)^+$ 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**. $^1$H 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). $^{13}$C 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 $C_{27}H_{34}N_7O_5$ $(M+H)^+$ 536.2616, found 536.2616.

## Purity of Tested Compounds in Chapter 3

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

| compd | formula | calcd | | | found | | | $t_R$[a] | area |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | C | H | N | (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** | $C_{26}H_{28}N_6O_7$ | 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 | | |

[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**). $^{1}$H 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). $^{13}$C 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 $C_{22}H_{22}N_5O_4$ $(M+H)^+$ 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**). $^{1}$H 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). $^{13}$C 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 $C_{22}H_{22}N_5O_4$ $(M+H)^+$ 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. $^{1}$H 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). $^{13}$C 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 $C_{22}H_{22}N_5O_4$ $(M+H)^+$ 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 $PPh_3$ (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 $HCO_2H$ (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. $^1$H 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). $^{13}$C 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 $C_{16}H_{18}N_5O_4$ $(M+H)^+$ 344.1353, found 344.1354.

## Purity of Tsted Compounds in Chapter 4

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

| compd | formula | calcd | | | found | | | $t_R$[a] | area |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | C | H | N | (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 |

[a] $t_R$ is the retention time of the compound. [b] Isocratic elution was employed (MeOH/0.1% aq $HCO_2H$ = 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 Taqman 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 $5 \times 10^4$ 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 [$^{14}$C]-inosine, whereas the activities in COS-7 cells expressing hCNT1 were examined with [$^{14}$C]-thymidine. The transfected cells were incubated with pretreatment buffer (2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 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 $^{14}$C-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 $CaCl_2$, 1 mM $MgCl_2$, 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 ($IC_{50}$ 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 ± 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 μL) 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 × 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 μm, 50 mm × 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)) × (dose (iv) / dose (po)) × 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 $^{14}C$-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 $CaCl_2$, 1 mM $MgCl_2$, 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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