

Carbocyclic Isoadenosine Analogues of Neplanocin A

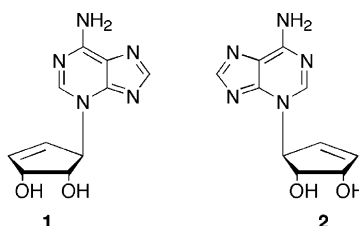
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ABSTRACT



Isoadenosine (IsoA), a structural isomer of adenosine, was shown to possess interesting biological activity but was inherently unstable. In an effort to overcome this, we have designed a series of carbocyclic IsoA analogues, combining the unique connectivity of IsoA with the structural features of some biologically significant Neplanocin A analogues. Their design, synthesis, and structural elucidation is reported.

Isoadenosine (IsoA) (Figure 1) is a structural isomer of adenosine where the purine base differs in its connectivity, being coupled to the ribofuranose moiety at the N-3 rather than the conventional N-9.

is the cross conjugation of the heterocyclic moiety and facile migration of the glycosidic C-1/N-3 bond, which occurs in an effort to restore the aromaticity of the purine ring, thereby resulting in adenosine (Figure 2).

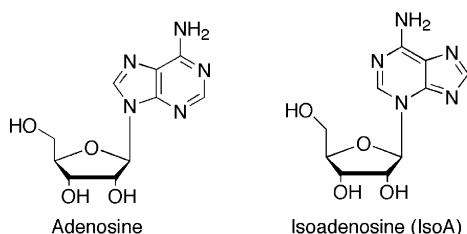


Figure 1.

IsoA initially showed promising chemotherapeutic properties; however, interest soon waned due to issues with stability.¹ IsoA is unstable for several reasons. One problem

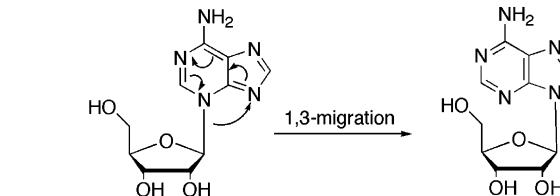


Figure 2.

A second problem is that the glycosidic bond of IsoA is highly susceptible to cleavage by both acids and bases, thereby making it difficult to work with synthetically. In contrast, the carbocyclic ring system is quite stable; replacement of the furanose oxygen by a methylene group transforms the unstable hemiaminal glycosidic bond to a more stable tertiary amine. This isosteric change not only imparts increased stability but also results in enhanced chemo-

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therapeutic effects for many modified nucleosides.^{2,3} As a class, the carbocyclic nucleosides have exhibited potent inhibitory activity against many biologically significant enzymes, in particular, *S*-adenosyl-L-homocysteine hydrolase (SAHase) and DNA methyltransferase (MeTase).^{4–6}

Two of the most well-known carbocyclic nucleosides are Aristeromycin (Ari)⁷ and Neplanocin A (NpcA)⁸ (Figure 3).

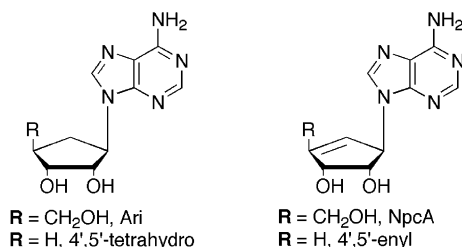


Figure 3.

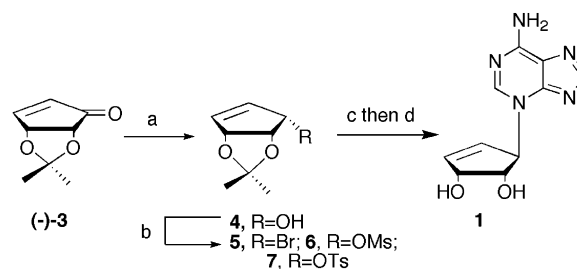
Both have exhibited potent biological activity; however, due to their close structural resemblance to adenosine, both are readily phosphorylated to the corresponding mono-, di-, and triphosphate forms, and this results in significant toxicity. As a result, many laboratories, including ours, have pursued additional structural modifications in an effort to overcome this problem.

One of the most important of these modifications was the elimination of the 4'-hydroxymethyl group of Ari and NpcA, which provided the 4',5'-enyl and tetrahydro analogues (Figure 3). The 4',5'-enyl analogues in particular have proven to be very effective inhibitors of SAHase and are much less toxic than their parent analogues.^{9,10}

Using the lead provided by IsoA, combined with the potent biological activity of the 4',5'-enyl NpcA analogues, we have designed the corresponding 4',5'-enyl carbocyclic analogues of IsoA.

The synthesis of **1** and **2** was first envisioned via displacement of the C-1 bromide by adenine. To achieve the requisite cyclopentenyl intermediate, our synthetic efforts begin with the enantiospecific synthesis of cyclopentenones (–)-**3** and (+)-**3** using literature procedures.^{11,12} As shown in Scheme 1 on the next page, stereospecific reduction of

Scheme 1^a



^a Reaction conditions: (a) NaBH₄, CeCl₃·7H₂O, MeOH, 0 °C, 1 h. (b) for **5**, (i) *p*-NO₂BzOH, DIAD, PPh₃, dry THF, rt, 2 days; (ii) KOH, MeOH, H₂O, 2 h; (iii) PPh₃, NBS, DMF, 0 °C to rt, 3 h; for **6**, MsCl, pyridine 0 °C, for **7**, TsCl, pyridine, rt, 15 h. (c) **5**, **6**, or **7**, adenine, dry *N,N*-dimethylacetamide, reflux, 2 days. (d) 2:1 TFA/H₂O.

(–)-**3** to allylic alcohol **4** was carried out using Luche¹³ conditions employing NaBH₄ and CeCl₃·7H₂O (90%). Next, conversion of the allylic alcohol of **4** into **5** was undertaken. The hydroxyl group must first undergo inversion using standard Mitsunobu conditions in order to ultimately achieve the correct conformation for the bromine substituent. Once inverted, standard hydrolysis of the ester, followed by bromination using an S_N2 displacement gave **5** in moderate yield (60%). Subsequently, refluxing **5** and adenine in *N,N*-dimethylacetamide in the absence of base afforded the coupled product in 55% yield (under normal coupling conditions employing a base, the major product is coupled at N-9 instead of at N-3).¹⁴

In an attempt to increase the overall yield in addition to alleviating the number of steps required when using the bromide intermediate, we then tried converting the hydroxyl group into the corresponding mesylate and tosylate. Treatment of allylic alcohol **4** with methanesulfonyl chloride at 0 °C in pyridine provided **6** in 80% yield, while tosylation of allylic alcohol **4** with *p*-toluenesulfonyl chloride in pyridine at room temperature afforded tosylate **7** in an 82% yield.

The desired IsoA analogue was then realized by the deprotection of the isopropylidene group using a 2:1 mixture of TFA/H₂O to give **1** (99%) in a 31% overall yield from (–)-**3**. Enantiomer **2** was synthesized in an analogous manner using the identical series of reactions used for **1**, however, starting with (+)-**3** (43% in six steps). In both cases, the N-9 product was formed in around 15%, as well as traces of the N-7 product, but both were easily isolated during purification by column chromatography. Unfortunately, despite the shorter synthetic routes to the mesylate and tosylate intermediates, a better overall yield for the coupling was obtained using the bromide intermediate.

Structural elucidation of **1** and **2** was then undertaken. While the most direct way to accomplish this would be to obtain a crystal structure, unfortunately both **1** and **2** proved

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to be difficult to crystallize, as they were both fine powders. Assessment of the UV spectra for **1** and **2**, however, provided initial evidence that the coupling had occurred at N-3. Our observed value of 274 nm fell perfectly in line with the reported 277 nm for isoadenosine¹ and 270 nm for the 2',3'-dideoxyisoadenosine analogue,¹⁵ as opposed to adenosine analogues, which fall around 260 nm; as a result, we felt reasonably confident in our structure and turned to NMR for final verification.

All proton and carbon peaks could easily be identified through comparison of various literature values of other purine shifts, with the exception of H-2, H-8, C-2, and C-8.¹⁰

It has been noted in the literature that coupling at either the N-9 or N-3 position results in a greater downfield shift in the ¹H NMR spectra for H-2 than is seen for H-8.¹⁶ In cases involving N-3 coupled products, however, the difference in ppm between the two peaks is much larger than is seen for N-9 coupled products, which often overlap. The corresponding ¹³C NMR spectra for N-9- and N-3-coupled nucleosides exhibit a different trend; C-2 for N-9-coupled products is shifted further downfield than C-8, but in the case of N-3 coupling, the order is reversed; the signal for the C-8 is shifted further downfield than that for C-2.

The ¹H NMR for both **1** and **2** showed a marked difference of 0.20 ppm in the chemical shifts between H-2 and H-8,

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which strongly suggested coupling at N-3 versus N-9; however, the ¹³C spectra was inconclusive. Using two-dimensional NMR techniques, however, the correct assignments for **1** and **2** could be made. The HMQC spectra, which correlates the ¹H to the ¹³C spectrum, showed that the signal for C-8 was shifted further downfield than that for C-2, suggesting once again that the coupling had occurred at N-3. This was confirmed by HMBC; if coupled at N-3, the signal for H-2 must exhibit long-range coupling to C-1', C-4, and C-6, and H-8 would be coupled to C-4 and C-5. This was indeed the case, thereby establishing that **1** and **2** were indeed coupled at N-3.

In conclusion, we have synthesized and successfully characterized the first two analogues in a series of carbocyclic N-3-coupled IsoA nucleosides that we hope will prove to be biologically interesting. Details of the biological investigation underway will be provided elsewhere soon.

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Supporting Information Available: Experimental details and two-dimensional NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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