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"Fleximers". Design and Synthesis of Two Novel Split Nucleosides

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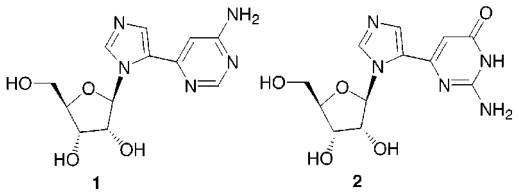
ABSTRACT



A new class of shape-modified nucleosides is introduced. The purine heterobases of adenosine and guanosine have been split into their imidazole and pyrimidine components, thereby introducing flexibility while retaining the elements necessary for recognition. As a consequence, these novel "fleximers" should find use as bioprobes for investigating enzyme–coenzyme binding sites as well as nucleic acid and protein interactions. Their design and synthesis is described.

Purines are one of the most ubiquitous heterocyclic ring systems found in nature; they are components in numerous biologically significant molecules and thus present an excellent scaffold for the construction of bioprobes. Pioneering work in this area by Leonard employed expanded purines such as his *lin*-, *prox*-, and *dist*-benzo nucleosides.[1,2] In some cases the analogues showed biological activity, however, not significant enough for the compounds to serve as prototypes for drug design based solely on enzyme inhibition. This limitation may have been due to their inherent rigidity; enzyme/substrate recognition is a "lock and key" relationship, thus the more flexible the "key", the more adaptable it can be at fitting into a variety of "locks".

One focus for our research involves the design and synthesis of novel shape-modified nucleosides for studies into the fundamental aspects of nucleic acid structure, function, and recognition. As an extension of Leonard's work, we have designed a series of innovative nucleoside "fleximers" (as in **1** and **2**), which possess a purine ring split into the imidazole and pyrimidine components. Analogous to Leonard's *dist*-benzo analogues, the rings remain connected by a single 1.5 Å carbon−carbon bond at the C-5 of the imidazole and the C-6 of the pyrimidine rings.[3,4] As a result, these novel "fleximers" will provide a unique perspective in studies of nucleic acid interactions.

Synthesis of the fleximers was envisioned from a tricyclic nucleoside containing a thiophene spacer ring.[5] As shown in Scheme 1, 4,5-dibromoimidazole (**3**) was coupled[6] to the commercially available tetraacetate-protected ribose using bis(trimethylsilyl)acetamide (BSA) and trimethylsilyltriflate (TMSOTf). Removal of the labile acetate groups and subsequent conversion to more stable benzyl ethers was accomplished with a modified benzylation procedure[7] to give **4** in a 60% overall yield from **3**. Grignard treatment of **4** with ethylmagnesium bromide and dimethylformamide produced aldehyde **5**, which was then converted to oxime **6** (80% from **4**). Dehydration of **6** provided nitrile **7** (90%).

(1) Leonard, N. J. *Acc. Chem. Res.* **1982**, *15*, 128.
(2) Leonard, N. J.; Hiremath, S. P. *Tetrahedron* **1986**, *42*, 1917.
(3) Synthesis of the *prox*-benzo isomers is presently underway.
(4) For the closest nucleoside structure, see: Van Calenbergh, S.; De Bruyn, A.; Schraml, J.; Blaton, N.; Peeters, O.; De Keukeleire, D.; Busson, R.; Herdewijn, P. *Nucleosides Nucleotides* **1997**, *16*, 291.
(5) Seley, K. L.; Januszczyk, P.; Hagos, A.; Zhang, L.; Dransfield, D. *J. Med. Chem.* **2000**, *43*, 4877.
(6) Koshkin, A. A.; Singh, S. K.; Nielsen, P.; Rajwanshi, V. K.; Kumar, R.; Meldgaard, M.; Olsen, C. E.; Wengel, J. *Tetrahedron* **1998**, *54*, 3607.
(7) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, *17*, 3535.

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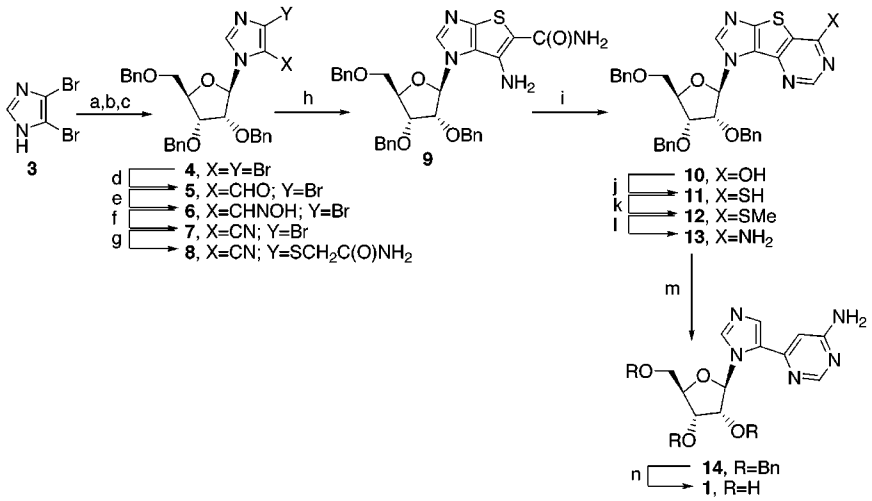
Scheme 1[a]



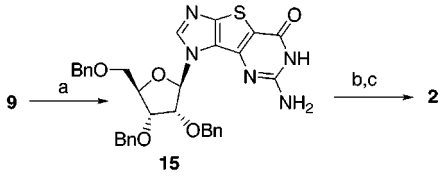
[a] (a) 1,2,3,5-Tetra-*O*-acetyl-*β*-D-ribofuranose, BSA, CH_3CN, and then TMSOTf; (b) NH_3, EtOH; (c) NaH, BnBr, Bu_4NI; (d) EtMgBr, anhydrous DMF; (e) $NH_2OH{\cdot}HCl$, $NaHCO_3$; (f) Ac_2O; (g) $NH_2C(O)CH_2SH$, K_2CO_3; (h) NaOEt, EtOH; (i) $CH(OEt)_3$, Ac_2O (1:1); (j) P_2S_5, pyridine; (k) MeI, K_2CO_3; (l) NH_3, MeOH; (m) Raney Ni, MeOH; (n) $BF_3{\cdot}OEt_2$, EtSH, CH_2Cl_2.

Displacement of the bromine at C-4 with thioglycolamide[8] yielded **8** (50%).

Closure to the thiophene ring was quite facile and yielded **9** (90%). Subsequent treatment of **9** with a 1:1 mixture of acetic anhydride and triethyl orthoformate facilitated closure of the pyrimidine ring to provide **10** (82%). Conversion of **10** to thiocarbonyl **11**, and immediate methylation gave **12** (80%). Ammonolysis of **12** yielded tricyclic nucleoside **13** (75%), which was then refluxed with Raney nickel to provide the protected "fleximer" **14** (74%). Removal of the benzyls[9] resulted in the adenosine "fleximer" **1** (91%).

Guanosine "fleximer" **2** (Scheme 2) was realized from sequential treatment[10] of **9** with sodium hydroxide and then heating with carbon disulfide, followed by addition of hydrogen peroxide, and finally ammonia provided tricyclic **15** (77%). Again using Raney nickel, the thiophene ring of **15** was successfully cleaved (76%) and, following deprotection, gave guanosine "fleximer" **2** (84%).

Scheme 2[a]



[a] (a) (i) NaOH, MeOH; (ii) CS_2, heat; (iii) H_2O_2; (iv) NH_3; (b) Raney Ni, MeOH; (c) $BF_3{\cdot}OEt_2$, EtSH, CH_2Cl_2.

In conclusion, we have introduced a new class of unique shape-modified nucleosides for use as bioprobes of enzymatic systems, as well as for use in nucleic acid structural investigations. Full experimental details[11] of the synthesis, as well as the results of the structural studies for the "fleximers" will be presented elsewhere.

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(9) Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661.

(10) Bennett, S. M.; Nguyen-Ba, N.; Ogilvie, K. K. *J. Med. Chem.* **1990**, *33*, 2162.

(11) ^1H and ^{13}C NMR, HRMS, and elemental analyses for all new compounds were consistent with their structures.