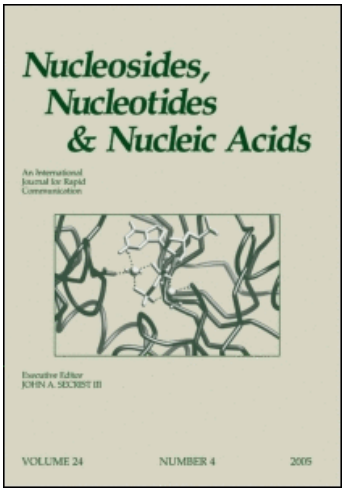

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Synthesis of Quinazoline C-Nucleosides: A New Class of 6:6 Bicyclic Purine-Like Analogues.[1]

Mallela S. P. Sarma[a]; Phyllis Wilson[a]; Brian A. Otter[a]; Robert S. Klein[a]
[a] Department of Oncology, Montefiore Medical Center, Albert Einstein College of Medicine Cancer Center and Medicinal Chemistry Laboratory, Bronx, NY

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SYNTHESIS OF QUINAZOLINE C-NUCLEOSIDES : A NEW CLASS OF 6:6 BICYCLIC PURINE-LIKE ANALOGUES.[1]

Mallela S. P. Sarma, Phyllis Wilson, Brian A. Otter and Robert S. Klein.

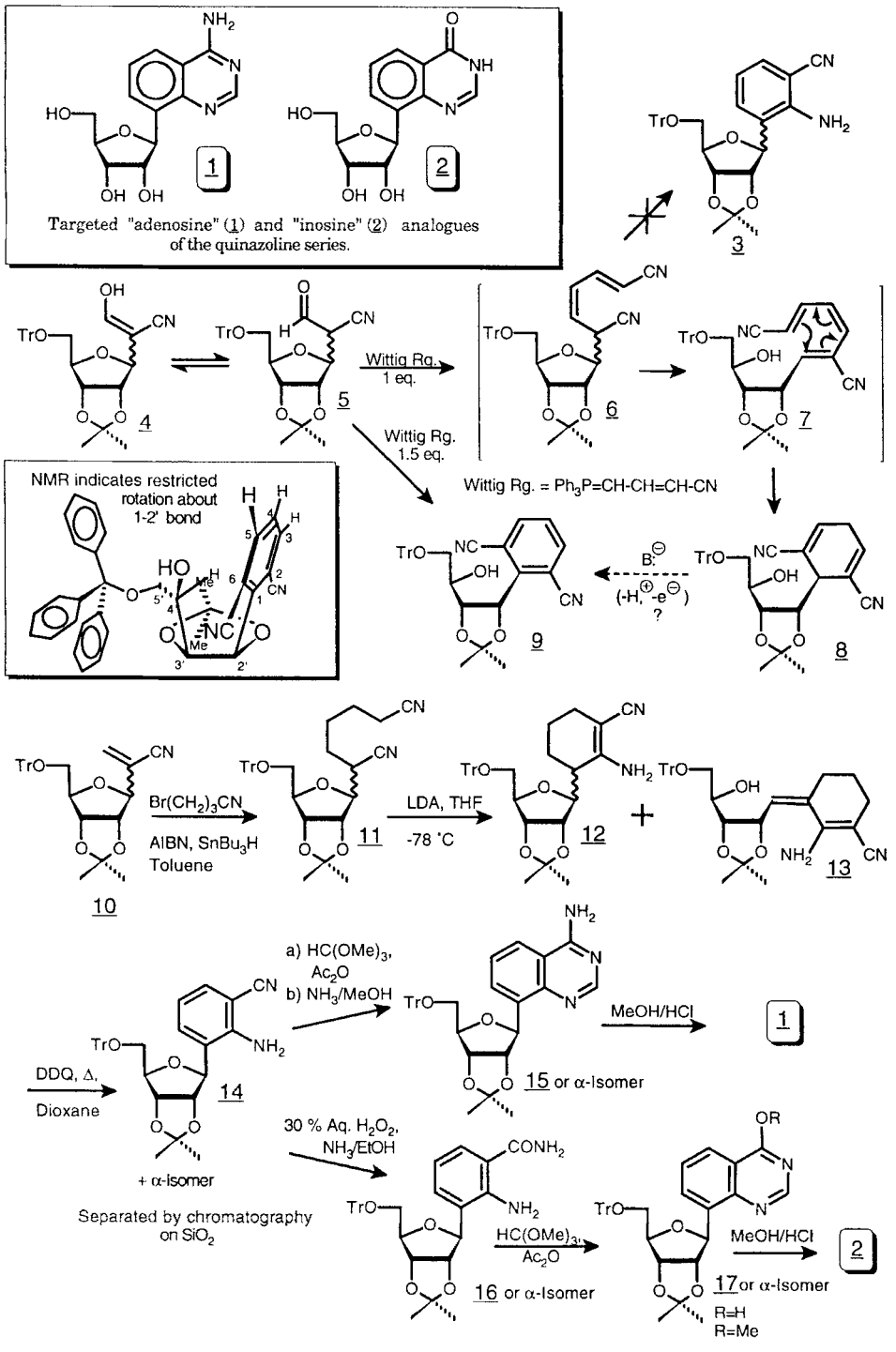
Albert Einstein College of Medicine Cancer Center and
Medicinal Chemistry Laboratory, Department of Oncology,
Montefiore Medical Center, Bronx, NY 10467-2401.

Abstract The quinazoline C-nucleoside congeners of adenosine (**1**) and inosine (**2**) have been obtained by radical-induced addition of 4-bromobutyronitrile to C-ribosyl acrylonitrile **10**. A base-catalyzed Ziegler-Thorpe cyclization of the dinitrile thus obtained (**11**) followed by aromatization with DDQ afforded key intermediate 6–ribosylated anthranilonitrile **14** and its α-isomer. Annulation of a pyrimidine ring onto **14** or onto the corresponding *o*–amino-amide followed by deblocking with MeOH/HCl finally gave **1** or **2** respectively.

Of the new classes of "purine-like" C-nucleoside analogues so far synthesized in this and other laboratories, those where the imidazole ring of the original purine ring has been replaced by a five-membered heterocycle (e.g. the pyrazolo[1,5-*a*]triazines[2], the pyrrolo-[3], furo-[4], and thieno[3,2-*d*]pyrimidines[5], the thieno[4,3-*d*]pyrimidines[6], the pyrrolo[2,1-*f*]1,2,4-triazines[7] and the isothiazolo[4,5-*d*]pyrimidines[8]) have shown some significant biological activities. These reflect the close structural similarity of these systems to the natural substances. Such activities include pronounced growth inhibitory effects in the case of the adenosine analogues and antitrypanosomal/antiprotozoal activity for the inosine analogues. In contrast, a preliminary evaluation of pyrido[4,3-*d*]pyrimidine C-nucleosides[9], our initial entry into 6:6 bicyclic purine nucleoside analogues, has indicated no similar activities.

In an effort to find out whether such lack of biological activity might also apply to other 6:6 bicyclic purine-like C-nucleoside analogues, we have recently completed the synthesis of some 8–β-D-ribofuranosyl quinazolines. We report herein the synthesis of the 4-amino (**1**) and 4-oxo (**2**) derivatives and the growth inhibitory activities of **1** against several tumor cell lines.

Our originally planned synthetic approach to this new class envisaged the elaboration of 1,3-diene **6** which, under basic conditions, would undergo a Thorpe-Ziegler type of reaction leading to the desired *o*-amino nitrile intermediate **3**. When treated at room temperature with 1.5



equivalents of the appropriate γ-cyanophosphorane, synthetic precursor **4** afforded 1,3-dicyanobenzene derivative **9** instead of the expected **3** or **6**.

The structure of **9** was unambiguously assigned by ^{1}H and ^{13}C nmr spectroscopy. One of its most notable structural features is the restricted rotation about the 1-2' bond which had been suggested by molecular modeling studies and confirmed by the observed doubling of some of the aromatic ring signals. In the ^{1}H nmr spectrum, for example, H 3/5 have chemical shifts of δ 7.91 and 7.81 (CDCl3, 200 MHz) while in the ^{13}C spectrum C 3/5 appear at δ 138.9 and 135.8 ($CDCl_3$, 125 MHz). In DMSO d_6, the two signals for H 3/5 coalesce at ~85 °C and reseparate upon cooling to 25 °C. Treatment of **5** with one equivalent of that same γ-cyanophosphorane reagent afforded the dihydro derivative **8** (presumably the synthetic precursor of **9**) which is formed by the electrocyclic rearrangement of 1,3,5-triene intermediate **7** to a 1,3-cyclohexadiene followed by tautomerization to the more stable 1,4-diene isolated product **8**.

A successful synthesis of **1** and **2** was finally achieved through a conventional Thorpe-Ziegler cyclization reaction utilizing the fully saturated dinitrile **11**. This synthetic precursor was obtained in 88% yield as a mixture of α:β isomers by the radical induced 1,4-addition of 4-bromobutanonitrile[10] to 2-ribosyl acrylonitrile **10**. Previously, we had used synthon **10** in the synthesis of pyrido[4,3-*d*]pyrimidine C-nucleosides[9].

Cyclization of **11** with 1.2 eq. of LDA:THF complex in dry THF at -78 °C afforded a mixture of products **12** and **13** separated initially by PTLC for the purpose of characterization. When the reaction was subsequently repeated, the mixture was treated directly with DDQ in warm dioxane for aromatization of both **12** and **13** to *o*-aminonitrile **14** and its α-isomer (1:4, 32% total yield). These could be readily separated by silica gel column chromatography to serve as synthetic precursors of the subsequent series of derivatives in either the α or β series.

Treatment of **14** (or its α-isomer) with trimethyl orthoformate and acetic anhydride and direct cyclization of the resulting formimino ether with methanolic ammonia[11] afforded the protected 4-aminoquinazoline C-nucleoside 15 in 87% yield (or its α-isomer in 85% yield). Final deblocking of **15** (or its α-isomer) with methanolic HCl afforded the adenosine analogue **1** in 95% yield (or its α-isomer in 86% yield).

For the synthesis of the inosine analogue, aminonitrile **14** (or its α-isomer) was readily converted to the corresponding amide **16** (53% for the β- and 80% for the α-isomer) by treatment with 30% H_2O_2 and conc. ammonia in ethanol at room temperature. Cyclization to the quinazoline system was carried out by treatment of the *o*-aminocarboxamide **16** (or its α-isomer) with trimethylorthoformate and acetic anhydride[11] at 65 °C to give the blocked inosine analogue **17** (R=H) in 70 % yields (90% for the α-isomer). Higher reaction temperatures led also to the formation of varying amounts of the 4-OMe derivative (**17**, R=OMe). Deprotection of **17** (R=H) by treatment with 7% methanolic HCl finally afforded **2** in 95% yield (68% for the α-isomer).

In Vitro Growth Inhibitory Activity of 9-DAA and 1 (ID_{50} in μM) in Several Tumor Cell Lines.			
	S180	**L1210-C2**	**HL60**
9-Deazaadenosine (9-DAA)	0.0083	0.0018	0.0011
4–Amino-Quinazoline Riboside 1	0.0025	0.0028	0.0071

As shown in the table, 4-aminoquinazoline nucleoside **1** was found to have pronounced growth inhibitory activities against a number of tumor cell lines at levels comparable to that of 9–deaza-adenosine itself. This finding presumably indicates that significant structural similarities exist between **1** and adenosine and that the former might act as an antimetabolite. The range of biological activities in this new series of C-nucleoside analogues is now under investigation.

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