Synthesis and Biological Evaluation of Certain C-4 Substituted Pyrazolo[3,4-*b*]pyridine Nucleosides

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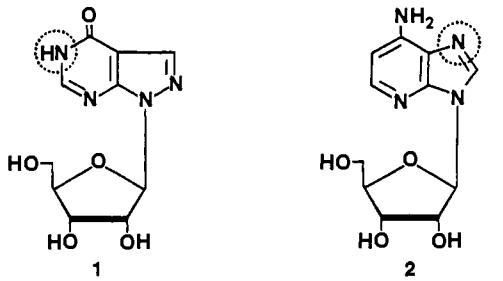
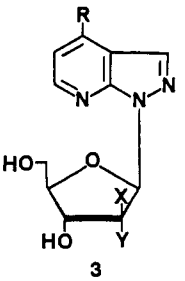
A series of C-4 substituted pyrazolo[3,4-*b*]pyridine nucleosides have been synthesized and evaluated for their biological activity. Successful synthesis of various C-4 substituted pyrazolo[3,4-*b*]pyridine nucleosides involves nucleophilic displacement by a suitable nucleophile at the C-4 position of 4-chloro-1*H*-pyrazolo[3,4-*b*]pyridine (**5**), followed by glycosylation of the sodium salt of the C-4 substituted pyrazolo[3,4-*b*]pyridines with a protected α-halopentofuranose. Use of this methodology furnished a simple and direct route to the β-D-ribofuranosyl, β-D-arabinofuranosyl, and 2-deoxy-β-D-*erythro*-pentofuranosyl nucleosides of C-4 substituted pyrazolo[3,4-*b*]pyridines, wherein the C-4 substituent was azido, amino, methoxy, chloro, or oxo. The regiospecificity of these glycosylations was determined on the basis of UV data and the anomeric configuration was established by ^{1}H NMR analysis. Conclusive structural assignment was made by a single-crystal X-ray diffraction study of three compounds, **15**, **31**, and **42**, as representatives of ribo-, 2′-deoxy-, and aranucleosides, respectively. The stereospecific attachment of all three α-halogenoses appears to occur by a Walden inversion (S_N2 mechanism) at the C-1 carbon of the halogenose by the anionic N-1 of pyrazolo[3,4-*b*]pyridine. All deprotected nucleosides were tested against various viruses and tumor cells in culture. The effects of these compounds on de novo purine and pyrimidine nucleotide biosynthesis was also evaluated. Among the compounds tested, 4-chloro-1-β-D-ribofuranosylpyrazolo[3,4-*b*]pyridine (**16**) and 1-β-D-ribofuranosyl-4,7-dihydro-4-oxopyrazolo[3,4-*b*]pyridine (**19**) were found to be moderately cytotoxic to L1210 and WI-L2 in culture.

In a search for more selective and effective inhibitors of nucleic acid metabolism, we[1] and others[2] have investigated the role of the purine nitrogens by synthesizing and studying the biological effects of various aza and deaza analogues of inosine, adenosine, and guanosine. Such structural variations in the purine ring have produced synthetic nucleosides such as allopurinol ribonucleoside [1-β-D-ribofuranosylpyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one, **1**][3] and 7-amino-3-β-D-ribofuranosylimidazo[4,5-*b*]pyridine (1-deazaadenosine, **2**)[4] possessing significant chemotherapeutic properties. In a recent study 1-deazaadenosine displayed the highest selectivity for adenosine receptors.[5] This property of the 1-deaza analogue suggests that the presence of the nitrogen atom at position 1 of the purine ring, a requirement for hydrogen bonding of base pairs in the Watson–Crick DNA model, is not so critical for interaction with adenosine receptors.

Thus the nucleoside derivatives of pyrazolo[3,4-*b*]-pyridine (**3**), which may provide selective activity without toxicity were chosen for synthesis and study. It is of particular interest that the glycosidic bond in the pyrazolo[3,4-*d*]pyrimidine nucleosides[6] is quite stable to enzymatic phosphorolysis. The absence of N-1 in the pyrimidine ring could considerably increase the basicity of the pyridine ring, which in turn may increase the potency of biologically active pyrazolo[3,4-*b*]pyridine nucleosides. The pyrazolo[3,4-*b*]pyridines, in general, represent a unique class of compounds due to a wide range of medicinal uses





reported in the literature.[7] Preobrazhenskaya et al. reported[8] the synthesis of certain C-4 substituted pyrazolo-[3,4-*b*]pyridine nucleosides, which subsequently were found[9] to be erroneous and proved to be C-6 substituted pyrazolo[3,4-*b*]pyridine isomers. We have synthesized for the first time C-4 substituted pyrazolo[3,4-*b*]pyridine nucleosides originally conceived by Preobrazhenskaya et al.[8] Furthermore we have evaluated these 1-deaza analogues

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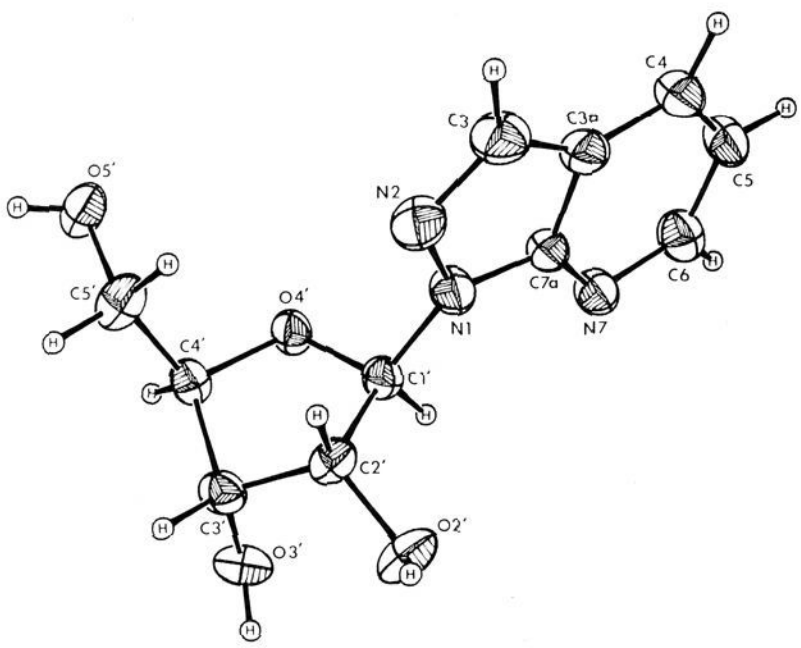


Figure 1. ORTEP drawing of **15**.

(**3**), for their antiviral and antitumor properties in culture, as well as for their effects on de novo purine and pyrimidine biosynthesis.

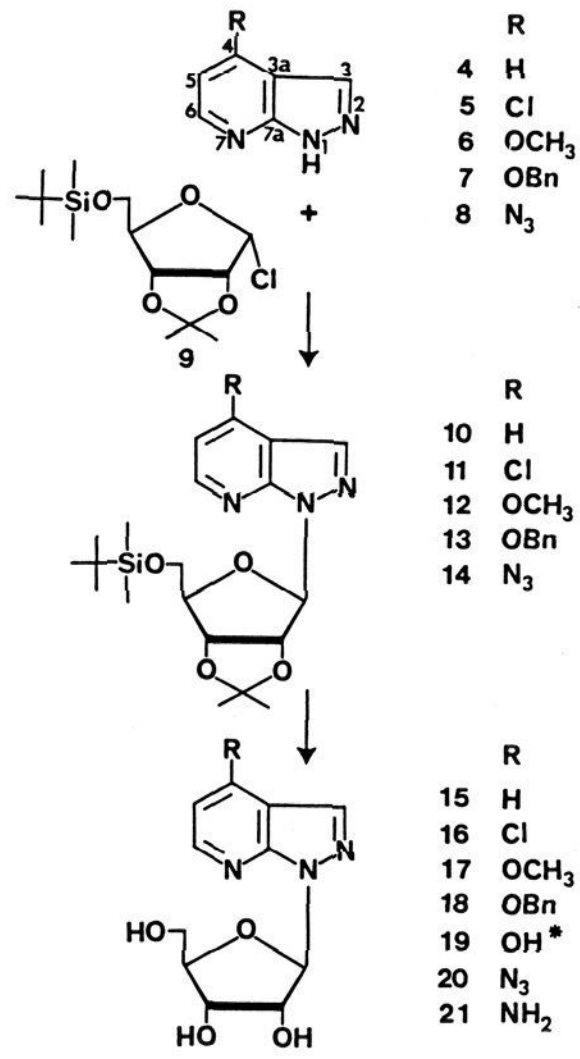
Chemistry

The aglycon 4-chloro-1*H*-pyrazolo[3,4-*b*]pyridine (**5**)[10] was chosen as our starting material for the synthetic study of the desired pyrazolo[3,4-*b*]pyridine nucleosides. The purpose for choosing **5** was due to the facile nucleophilic displacement of the 4-chloro group,[11] which should undergo a similar substitution to afford 4-substituted pyrazolo-[3,4-*b*]pyridine nucleosides, once **5** has been glycosylated.

The sodium salt of **5**, generated in situ by treatment with NaH in anhydrous CH_3CN, was reacted with 1-chloro-2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-α-D-ribofuranose (**9**)[12] at room temperature for 12 h in a dry inert atmosphere, to furnish 4-chloro-1-(2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl)pyrazolo[3,4-*b*]pyridine (**11**). Compound **11** was too hygroscopic to handle; therefore, deprotection of **11** with 90% aqueous trifluoroacetic acid (TFA) furnished 4-chloro-1-β-D-ribofuranosylpyrazolo[3,4-*b*]pyridine (**16**) in 39% overall yield. Catalytic hydrogenation of **16** gave **15** in quantitative yield. Glycosylation of **4** with **9** in a similar way as described for **5** furnished **10**, which upon deblocking with TFA gave 1-β-D-ribofuranosylpyrazolo-[3,4-*b*]pyridine (**15**) in 35% overall yield. Compound **15**, synthesized by the two different routes, was found to be identical in all respects (melting point, UV, IR, ^1H NMR). A direct comparison of the UV data obtained on our compound **15** with the data reported in the literature[8] for **15** compares with its UV but differs in its melting point by ~10 °C. Therefore, the absolute structural assignment of **15** was established by single-crystal X-ray diffraction analysis (see Figure 1).

Simple nucleophilic displacement of the 4-chloro group of **16** by hydroxide ion and ammonia appeared to be the most straightforward approach for the synthesis of inosine (**19**) and adenosine (**21**) analogues, respectively. Treatment of **16** with both of these nucleophiles at mild as well as at elevated temperature and prolonged reaction time lead to extensive decomposition of starting material. Similar difficulty in the displacement of the 4-chloro group of pyridines has been documented.[13] Thus, an alternate route to compounds **19** and **21** was considered by employing the preformed 4-(benzyloxy)-1*H*-pyrazolo[3,4-*b*]-pyridine (**7**) for the inosine analogue and 4-azido-1*H*-pyrazolo[3,4-*b*]pyridine (**8**) for the adenosine analogue. Thus, **7** and **8** on glycosylation followed by reduction and deblocking would result in the desired pyrazolo[3,4-*b*]-pyridine nucleosides.

Scheme I



*Present as the oxo tautomer.

A large number of 4-substituted pyrazolo[3,4-*b*]pyridines have been prepared[11] from the 4-chloro derivative **5**. Likewise, treatment of **5** with NaOH/aqueous MeOH or NaOBn/benzyl alcohol at elevated temperature produced 4-methoxy-1*H*-pyrazolo[3,4-*b*]pyridine (**6**, 48% yield) and 4-(benzyloxy)-1*H*-pyrazolo[3,4-*b*]pyridine (**7**, 55% yield), respectively. The structures of **6** and **7** were assigned on the basis of ^1H NMR and UV data (see Tables II and III). The synthesis of 4-azido-1*H*-pyrazolo[3,4-*b*]pyridine (**8**) was achieved from **5** after salt formation. When the TFA salt of **5** was reacted with NaN_3 in DMF, **8** was obtained in 81% yield. The structure of **8** was supported by the azido group absorption at 2135 cm^{-1} in its IR spectrum.

The sodium salt glycosylation[14] of **8** with the α-halogenose **9** in anhydrous CH_3CN furnished 4-azido-1-(2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-β-D-ribofuranosyl)pyrazolo[3,4-*b*]pyridine (**14**) as a crystalline product. Compound **14** on treatment with aqueous TFA gave 4-azido-1-β-D-ribofuranosylpyrazolo[3,4-*b*]pyridine (**20**) in 87% yield. Catalytic (Pd/C) hydrogenation of **20** furnished the desired adenosine analogue 4-amino-1-β-D-ribofuranosylpyrazolo[3,4-*b*]pyridine (**21**). In a similar way, glycosylation of **7** with **9** furnished compound **13** as a hygroscopic solid, which on deprotection of the glycon moiety

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Table I. Preparation and Physical Properties of Pyrazolo[3,4-*b*]pyridine Nucleosides

starting material (intermediate)	product	method of prepn[a]	yield, %	mp, °C (solvent for crystn)	molecular formula[c]
8	**14**	A	50	85 (hexanes)	$C_{20}H_{30}N_6O_4Si$
4 (**10**)	**15**	A followed by D	35[b]	144 (EtOAc)	$C_{11}H_{13}N_3O_4$
5 (**11**)	**16**	A followed by D	39[b]	141 (EtOH)	$C_{11}H_{12}ClN_3O_4$
6 (**12**)	**17**	A followed by D	40[b]	128 (EtOAc)	$C_{12}H_{15}N_3O_5$
7 (**13**)	**18**	A followed by D	42[b]	95, foam	$C_{18}H_{19}N_3O_5$
18	**19**	E	94	209 (EtOH)	$C_{11}H_{13}N_3O_5$
14	**20**	D	87	165 (EtOH)	$C_{11}H_{12}N_6O_4$
20	**21**	E	42	228[d] (EtOH)	$C_{11}H_{14}N_4O_4$
4	**23**	B	95	91 (hexanes)	$C_{27}H_{25}N_3O_5$
5	**24**	B	63	120 (hexanes)	$C_{27}H_{24}ClN_3O_5$
6	**25**	B	64	108 (EtOH)	$C_{28}H_{27}N_3O_6$
7	**26**	B	78	70, foam	$C_{34}H_{31}N_3O_6$
8	**27**	B	61	68, foam	$C_{27}H_{24}N_6O_5$
23	**28**	F	66	177 (EtOH)	$C_{11}H_{13}N_3O_3$
24	**29**	F	82	70 (EtOH)	$C_{11}H_{12}ClN_3O_3 \cdot 0.5H_2O$
25	**30**	F	94	160 (EtOH)	$C_{12}H_{15}N_3O_4$
26 (**26a**)	**31**	E followed by F	60[b]	198 (EtOH)	$C_{11}H_{13}N_3O_4$
27 (**27a**)	**32**	E followed by F	55[b]	270[d] (EtOH)	$C_{11}H_{14}N_4O_3$
4 (**34**)	**39**	C followed by H	60[b]	160 (acetone)	$C_{11}H_{13}N_3O_4$
5 (**35**)	**40**	C followed by G	63[b]	95 (acetone)	$C_{11}H_{12}ClN_3O_4$
6 (**36**)	**41**	C followed by H	44[b]	145 (EtOH)	$C_{12}H_{15}N_3O_5$
7 (**37**)	**42**	C followed by H	64[b]	227 (EtOH)	$C_{11}H_{13}N_3O_5$
8 (**38**)	**43**	C followed by H	41[b]	177 (acetone)	$C_{11}H_{14}N_4O_4$

[a] See text of Experimental Section for the details of the methods A–H. [b] Overall yield in two steps without isolation of intermediate. [c] Satisfactory analytical data (±0.4% for C, H, and N) were obtained for all new compounds listed in the table. [d] Decomposed.

Table II. UV Spectral Data of Pyrazolo[3,4-*b*]pyridines in Water

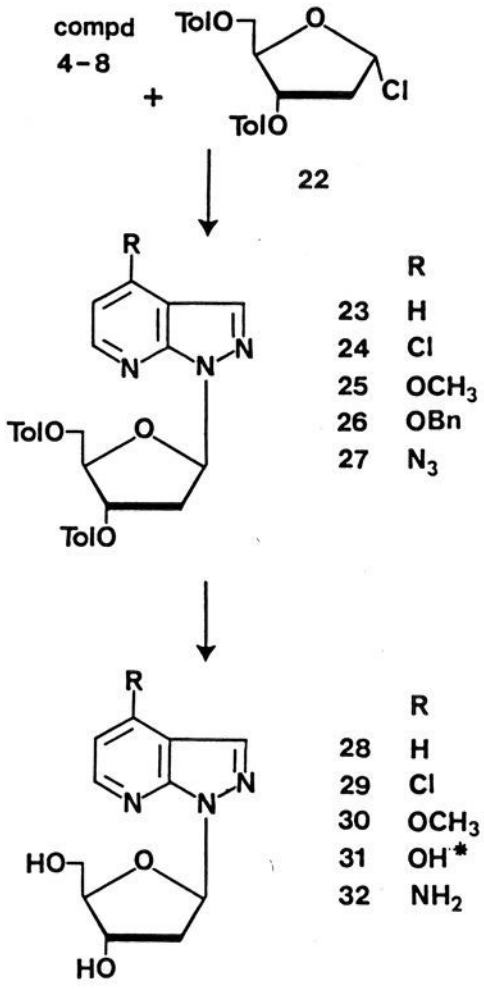
compd no.	λ_{max}, nm ($\epsilon \times 10^{-3}$)		
	pH 1	pH 7	pH 11
6	235 (5.1), 261 (10.0), 313 (5.8)	250 (6.7), 285 (6.8), 290 (sh, 5.7)	253 (6.0), 285 (5.7), 290 (sh, 5.2)
7	235 (7.5), 262 (11.7), 314 (6.7)	251 (3.9), 285 (3.7), 290 (sh, 3.1)	255 (3.7), 286 (3.4), 290 (sh, 3.0)
8	214 (18.5), 283 (21.8), 340 (8.9)	213 (16.8), 270 (11.1), 276 (11.2), 303 (11.2)	268 (sh, 9.5), 276 (10.1), 302 (9.0)
15	261 (5.0), 299 (5.4), 304 (sh, 5.1)	257 (4.8), 294 (6.2), 304 (sh, 5.0)	258 (4.7), 294 (6.1), 304 (sh, 5.0)
16	214 (19.8), 260 (4.1), 296 (4.4)	214 (23.1), 261 (4.4), 296 (4.9)	260 (4.9), 296 (5.3)
17	257 (17.5), 291 (12.7)	249 (14.3), 256 (sh, 13.5), 286 (14.0), 295 (sh, 12.1)	286 (14.6), 296 (sh, 12.4)
18	257 (20.4), 292 (14.7)	250 (15.7), 287 (15.6), 295 (sh, 23.5)	287 (15.4), 295 (sh, 13.5)
19	254 (10.5), 286 (12.1), 295 (sh, 10.3)	253 (6.37), 258 (sh, 7.8), 287 (15.8), 293 (16.2)	295 (17.4), 300 (sh, 16.4)
20	220 (8.4), 278 (6.3), 310 (4.4)	221 (7.9), 267 (4.6), 276 (4.5), 305 (4.5)	220 (8.2), 268 (4.7), 275 (4.6), 307 (4.3)
21	261 (8.1), 294 (15.5), 302 (12.5)	258 (6.9), 262 (7.3), 299 (13.3)	257 (6.9), 262 (7.3), 299 (13.3)
28	264 (4.4), 297 (4.4)	258 (4.3), 295 (5.5)	258 (4.3), 295 (5.5)
29	261 (6.6), 297 (7.2)	260 (6.6), 296 (7.6)	260 (7.0), 295 (7.9)
30	211 (20.5), 234 (7.0), 257 (8.7), 290 (5.4)	241 (8.8), 257 (sh, 7.3), 286 (6.1), 294 (sh, 4.8)	249 (7.7), 257 (sh, 7.3), 286 (5.9), 295 (sh, 4.8)
31	256 (9.7), 288 (9.2), 295 (sh, 8.4)	254 (7.7), 260 (sh, 7.1), 290 (13.8), 295 (13.7)	254 (7.7), 259 (7.7), 296 (15.5), 302 (sh, 14.6)
32	212 (12.5), 262 (5.4), 295 (8.3), 303 (7.5)	215 (13.5), 257 (4.7), 263 (5.0), 299 (8.3)	257 (4.7), 263 (5.0), 299 (8.3)
39	213 (20.3), 264 (5.5), 297 (4.5)	258 (4.8), 295 (5.5)	257 (4.7), 296 (5.4)
40	262 (4.9), 296 (5.3)	260 (5.1), 296 (5.6)	260 (5.4), 296 (5.9)
41	258 (9.9), 292 (6.9)	250 (7.4), 258 (sh, 6.9), 287 (7.4)	250 (7.6), 258 (sh, 6.9), 287 (7.3)
42	254 (11.6), 287 (12.7), 295 (sh, 11.1)	254 (9.6), 258 (sh, 9.5), 287 (17.9), 294 (17.1)	253 (9.2), 259 (9.2), 295 (19.5), 302 (sh, 17.8)
43	262 (8.2), 294 (15.0), 302 (12.0)	258 (7.3), 262 (7.4), 298 (12.9)	257 (6.9), 262 (7.3), 298 (12.7)

Table III. ^1H NMR Data of Pyrazolo[3,4-*b*]pyridines in $(CD_3)_2SO$

compd no.	characteristic peaks					
	$C_1'H^a$	C_3H	R	C_5H^a	C_6H^a	N*H*
6		8.09 (s)	4.01 (s)	6.70 (d) (6)	8.35 (d) (6)	13.54 (br s)
7		8.13 (s)	5.39 (s), 7.39 (m)	6.78 (d) (6.0)	8.34 (d) (6.0)	13.56 (br s)
8		8.14 (s)		7.0 (d) (5.6)	8.44 (d) (5.6)	13.82 (br s)
15	6.33 (d) (5.3)	8.27 (s)	8.30 (m)	7.29 (m)	8.57 (m)	
16	6.32 (d) (5.3)	8.40 (s)		7.45 (d) (5.6)	8.55 (d) (5.6)	
17	6.25 (d) (5.3)	8.21 (s)	4.01 (s)	6.79 (d) (6.0)	8.39 (d) (6.0)	
18	6.26 (d) (5.3)	8.26 (s)	7.34–7.54 (m)	6.90 (d) (6.3)	8.40 (d) (6.3)	
19	6.19 (d) (5.13)	8.14 (s)		6.16 (d) (5.4)	8.10 (d) (5.4)	11.5 (br s)
20	6.29 (d) (5.16)	8.27 (s)		7.13 (d) (5.6)	8.50 (d) (5.6)	
21	6.11 (d) (5.16)	8.30 (s)	7.98 (br s)	6.36 (d) (6.8)	7.09 (d) (6.8)	
28	6.80 (t)	8.21 (s)	8.24 (m)	7.27 (m)	8.52 (d) (5.0)	
29	6.77 (t)	8.38 (s)		7.45 (d) (5.5)	8.55 (d) (5.5)	
30	6.73 (t)	8.21 (s)	4.02 (s)	6.79 (d) (6.1)	8.41 (d) (6.1)	
31	6.64 (t)	8.13 (s)		6.43 (d) (6.1)	8.03 (d) (6.1)	11.8 (br s)
32	6.59 (t)	8.13 (s)	6.95 (br s)	6.19 (d) (6.1)	7.91 (d) (6.1)	
39	6.61 (d) (6.2)	8.25 (s)	8.27 (m)	7.27 (m)	8.55 (d) (5.0)	
40	6.59 (d) (6.5)	8.36 (s)		7.42 (d) (5.5)	8.52 (d) (5.5)	
41	6.54 (d) (6.5)	8.20 (s)	4.03 (s)	6.77 (d) (6.1)	8.38 (d) (6.1)	
42	6.28 (d) (6.6)	8.05 (s)		6.24 (d) (6.1)	7.84 (d) (6.1)	11.5 (br s)
43	6.40 (s) (7.1)	8.14 (s)	6.92 (br s)	6.19 (d) (6.1)	7.90 (d) (6.1)	

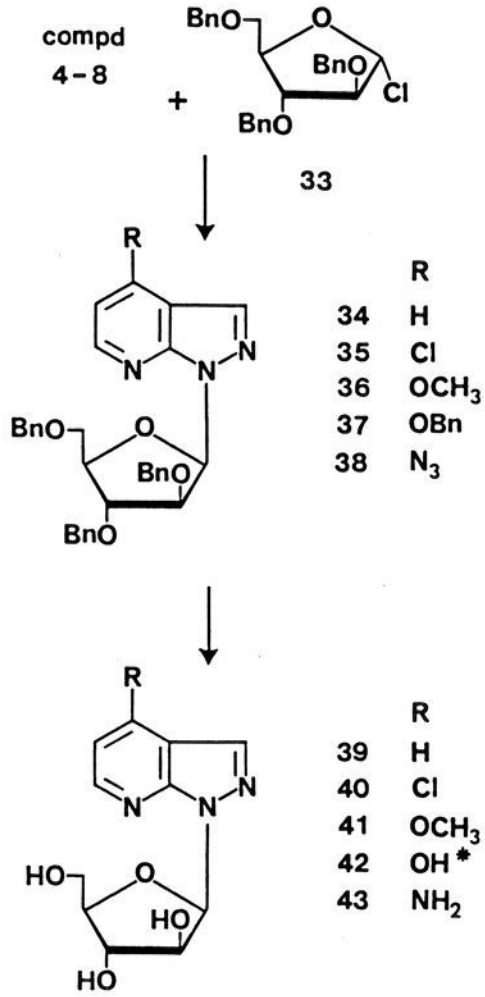
[a] Coupling constant in hertz.

Scheme II



*Present as the oxo tautomer.

Scheme III



*Present as the oxo tautomer.

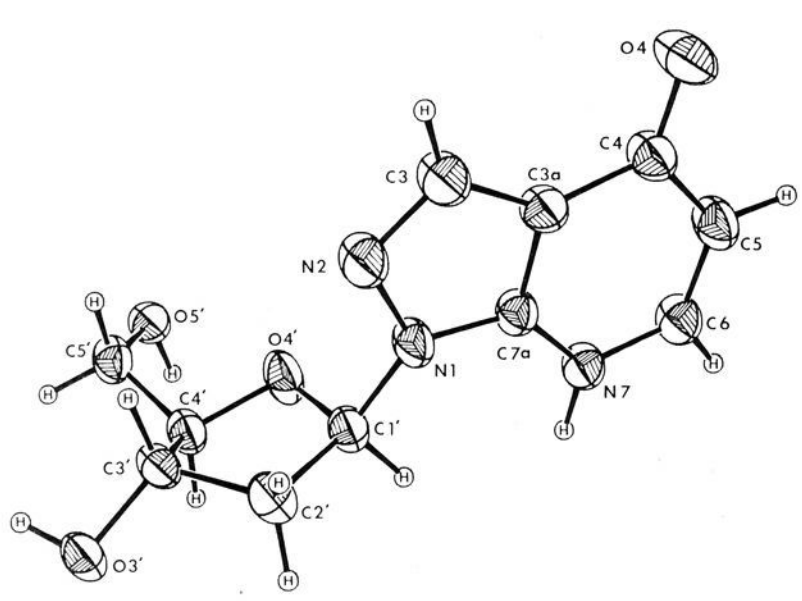


Figure 2. ORTEP drawing of **31**.

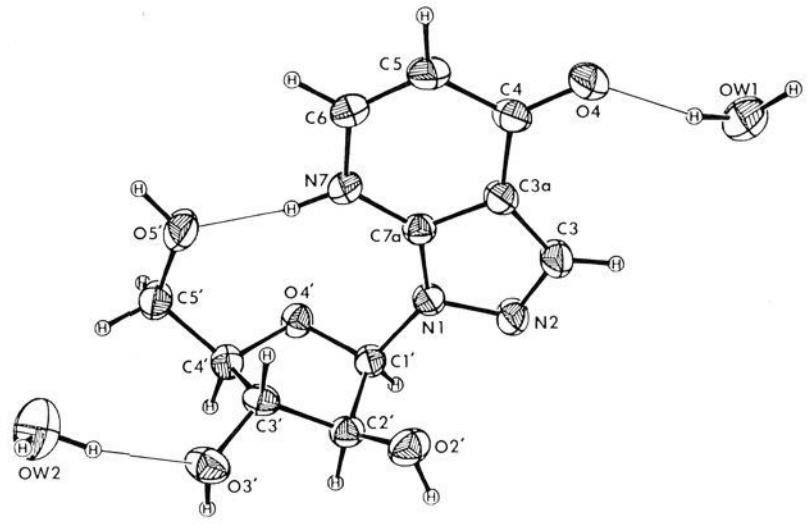


Figure 3. ORTEP drawing of **42**.

furnished **18** (Table I). Hydrogenation of **18** gave the inosine analogue 1-β-D-ribofuranosyl-4,7-dihydropyrazolo[3,4-*b*]pyridin-4-one (**19**). The above glycosylation procedure was also applied to the synthesis of 4-methoxy-1-β-D-ribofuranosylpyrazolo[3,4-*b*]pyridine (**17**) in two steps starting from **6** (Scheme I).

This general and versatile glycosylation procedure[15] was also utilized for the preparation of the corresponding 2′-deoxypyrazolo[3,4-*b*]pyridine nucleosides, **28–32** (Scheme II), in good yield (Table I). As a representative example, the sodium salt of **7**, generated in situ, was treated with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose (**22**)[16] to furnish the blocked nucleoside **26** in 78% yield. Hydrogenation of **26**, followed by deblocking, gave the 2′-deoxyinosine analogue 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-4,7-dihydropyrazolo[3,4-*b*]pyridin-4-one (**31**). The structure of **31** was based on elemental analysis and spectroscopic studies and was confirmed by single-crystal X-ray diffraction analysis (Figure 2).

This general glycosylation procedure[15] was also applied to the synthesis of the β-D-arabinofuranosyl nucleosides **39–43** (Scheme III). The sodium salt of **7** was treated with 1-chloro-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose (**33**)[17] to obtain the intermediate 4-(benzyloxy)-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)pyrazolo[3,4-*b*]pyridine (**37**). Catalytic [$Pd(OH)_2$] hydrogenation of **37** gave 1-β-D-arabinofuranosyl-4,7-dihydropyrazolo[3,4-*b*]pyridin-4-one (**42**). The ^1H NMR and UV spectra of **42** were in agreement with that of **31** and **19**. In order to further establish the structural assignment for **42**, an X-ray crystallographic study (Figure 3) was carried out, which unequivocally confirmed the site of glycosylation and anomeric configuration. It should be noted that **19**, **31**, and **42** were assigned

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Table IV. Crystal Data for Compounds 15, 31, and 42

	15	31	42
formula	$C_{11}H_{13}N_3O_4$	$C_{11}H_{13}N_3O_4$	$C_{11}H_{13}N_3O_5 \cdot 2H_2O$
a, Å	6.9252 (6)	17.506 (3)	4.8604 (3)
b, Å	8.288 (6)	8.512 (2)	12.6573 (15)
c, Å	19.431 (3)	7.941 (3)	10.9802 (17)
β, deg	90	110.59 (3)	91.17 (6)
Z	4	4	2
system	orthorhombic	monoclinic	monoclinic
space group	$P2_12_12_1$	$C2$	$P2_1$
R	0.0298	0.0369	0.0291
reflections ($F \geq 4\sigma_F$)	2045	1874	2692

the 4-oxo tautomeric structures based on X-ray, ^{1}H NMR, and IR data which indicated the presence of an NH group and a C=O group as well. The general synthetic pathways for glycosylations of various 4-substituted pyrazolo[3,4-*b*]pyridine nucleosides are shown in Schemes I–III and listed in Table I, while UV and ^{1}H NMR data are given in Tables II and III, respectively.

Crystallographic Analysis

Colorless, transparent needles of **15** and **42** crystallized from ethanol, **42** as a dihydrate. Crystals of the 2′-deoxy **31** were obtained from 1:1 ethanol/water solution as thin, colorless, transparent plates. Crystal data for each is tabulated in Table IV. Each compound was confirmed to be the β anomer as shown in Figures 1–3 (ORTEPII[18]); in particular, **31** and **42** exist in the solid state in the 4-oxo tautomeric form as suggested by NMR for the solution state. The nitrogen N7 bears the proton in each case. The dihedral angles between the planes of the fused rings of the heterocycles are 1° or less in the three structures. Compounds **15**, **31**, and **42** have glycosidic torsion angles (χ = O4′–C1′–N1–N2) of 72.7 (2), 67.7 (3), and −155.55 (12)°, respectively, corresponding to the anti conformation for the first two and the syn conformation for the latter. The syn conformation of **42** is stabilized by an N7–H7···O5′ intramolecular hydrogen bond [the H7···O5′ distance is 1.78 (3) Å] which requires the C5′–O5′ side chain to be gauche-gauche. The side chains of the other two, **15** and **31**, are both gauche-trans. The sugar conformations, pseudorotation angles (P) and the amplitudes of pucker (τ_m)[19] are as follows: $C_{3'}$ exo, 192.2° and 38.8° for **15**; $C_{4'}$ exo, 48.9° and 38.7° for **31**; and, $C_{3'}$ endo, 26.2° and 41.4° for **42**. Each hydroxyl group, O2′, O3′, and O5′, in **15** participates in hydrogen bonding as a donor. The corresponding acceptors are O5′, N7, and O3′ with hydrogen to acceptor (H···A) distances of 1.87 (2), 2.16 (3), and 1.96 (3) Å, respectively. In **31**, each possible donor, N7, O3′, and O5′, is involved in hydrogen bonding with the acceptors, O5′, N2, and O4, respectively. The corresponding H···A distances are 1.85 (4), 2.12 (6), and 1.71 (4) Å. Due to the hydration of **42**, there is considerably more hydrogen bonding involved in its crystal structure. In addition to the intramolecular N–H···O hydrogen bonding mentioned above, every OH proton is donated to an acceptor. The intermolecular hydrogen bonds are O2′ → OW1, O3′ → N2, O5′ → O4, OW1 → O4, OW1 → OW2, OW2 → O3′ and OW2 → OW1 with H···A distances ranging from 1.72 (5) to 2.01 (4) Å (see Figure 3 for atom labeling). Details of these structures will be presented elsewhere.[20]

Biological Evaluation of Pyrazolo[3,4-*b*]pyridine Nucleosides 15–21, 28–32, and 39–43

All compounds were tested against herpes 2 (in Vero cells), adeno 2 (in HeLa cells), rhino 1-A (in HeLa cells), Para Flu 3 (in Vero cells), Semliki forest (in Vero cells), and Visna virus (in SCP cells). The inosine analogue **19** exhibited a virus rating of 0.6 against rhino 1-A; the other compounds were inactive against the viruses used.

Cytotoxicity of the compounds was determined with the following cell lines: L1210 (a murine leukemia), WI-L2 (a human B-lymphoblast), and LoVo/L (a human colon carcinoma) (see ref 21 for experimental details). Only two compounds, **16** and **19**, demonstrated appreciable cytotoxicity. The 4-chloro compound **16** had an ID_{50} = 18 μM (WI-L2) and 20 μM (L1210); the inosine analogue **19** had an ID_{50} = 20 μM (WI-L2) and >100 μM (L1210). Therefore, cytotoxicity of **16** and **19** was further studied in WI-L2 cells deficient in either adenosine kinase or HPRT activity. The HPRT-deficient cell line was not resistant to growth inhibition by either compound. The adenosine kinase deficient lymphoblast line was resistant to compound **16**, indicating that adenosine kinase is responsible for phosphorylating the compound to an active species. On the other hand, the adenosine kinase deficient cell line was not resistant to the toxicity of **19**. This suggested that compound **19** was either metabolized to the monophosphate by another route or may be active without further metabolism.

The pyrazolo[3,4-*b*]pyridine nucleosides were tested for effects on de novo purine nucleotide biosynthesis by using the [^{14}C]formate incorporation method with cultures of human lymphoblast cells (see ref 22 for experimental details). At a concentration of 100 μM, the following compounds were found to inhibit de novo purine nucleotide biosynthesis by 20% or greater: **16**, 94%; **19**, 80%; **20**, 46%; **21**, 36%. All compounds were further studied by using a similar method which utilizes [^{14}C]bicarbonate incorporation and evaluates both purine and pyrimidine de novo biosynthesis.[22] The 4-chloropyrazolo[3,4-*b*]-pyridine **16** and, less strikingly, **20** and **21** appear to primarily inhibit de novo purine nucleotide biosynthesis. On the other hand, **16** appears to preferentially inhibit de novo pyrimidine biosynthesis; furthermore, carbamyl aspartate, orotate, and OMP were observed to accumulate, which suggested that the primary site of inhibition of **16** was most likely at OMP decarboxylase. Therefore, compound **16** provided a nucleotide profile indistinguishable from the aza congener **1** (allopurinol ribonucleoside), which as a monophosphate inhibits the OMP decarboxylase activity of the UMP synthetase complex.[23]

The compounds were tested as inhibitors of adenosine deamination to inosine by calf intestinal mucosa adenosine deaminase.[24] At a 20:1 inhibitor to substrate ratio, only compound **20**, was found to provide significant inhibition, which was 64%. Under similar conditions coformycin provided a 98% inhibition of adenosine deaminase activity. In a further test, the 4-azido **20** displayed no substrate activity in 16 h of incubation with adenosine deaminase,

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wherein the reaction mixtures were analyzed by reverse-phase HPLC.[25]

In summary, the present study provided for the first time a general use of our sodium salt glycosylation methodology[15] for the preparation of pyrazolo[3,4-*b*]pyridines with three different halogenoses **9**, **22**, and **33** (Schemes I–III) to furnish β-D-ribofuranosyl, 2-deoxy-β-D-*erythro*-pentofuranosyl, and β-D-arabinofuranosyl nucleosides, respectively, in high regio- and stereoselectivity. These compounds are devoid of any specificity or potency against the viral and tumor models used in this study.

Experimental Section

Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting point apparatus. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ. Thin-layer chromatography (TLC) was conducted on plates of silica gel 60 F-254 (EM Reagents). Silica gel (E. Merck; 230–400 mesh) was used for flash column chromatography. All solvents used were reagent grade. Detection of nucleoside components in TLC was by UV light and with 10% H_2SO_4 in MeOH spray followed by heating. Evaporations were conducted under diminished pressure with the bath temperature below 30 °C. Infrared (IR) spectra were recorded with a Beckman Acculab 2 spectrophotometer and ultraviolet (UV) spectra were recorded on a Beckman DU-50 spectrophotometer. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz with an IBM NR/300 spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. The signals are described as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). The presence of solvent as indicated by elemental analysis was verified by ^{1}H NMR spectroscopy.

Starting Materials. The following compounds were prepared according to literature procedures: 4-chloro-1*H*-pyrazolo[3,4-*b*]pyridine (**5**);[10] 1*H*-pyrazolo[3,4-*b*]pyridine (**4**);[7] 1-chloro-2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-α-D-ribofuranose (**9**);[12] 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose (**22**);[16] 1-chloro-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose (**33**).[17]

4-Methoxy-1*H*-pyrazolo[3,4-*b*]pyridine (6). A mixture of **5** (1.53 g, 10 mmol), NaOH pellets (1.32 g, 33 mmol), and aqueous MeOH (30 mL; 98%) was stirred in a sealed reaction vessel and heated at 150 °C for 16 h. The resulting clear solution was treated with decolorizing carbon (2 g) and filtered. The filtrate was acidified with AcOH to pH 5, the precipitate was collected by filtration, washed with cold water (25 mL), and crystallized from EtOH to give 0.72 g (48%) of **6**.

4-(Benzyloxy)-1*H*-pyrazolo[3,4-*b*]pyridine (7). To a solution of sodium (0.3 g, 13 mmol) in BnOH (10 mL) was added **5** (0.91 g, 6 mmol) and the mixture was heated at 170 °C for 16 h. The reaction mixture was cooled and triturated with hexanes (3 × 50 mL) to remove excess BnOH. The gummy residue was dissolved in EtOH and the solution was acidified with AcOH to pH 5. The solution was adsorbed on silica gel (5 g) and the product was purified by flash chromatography using $CHCl_3$/MeOH (9:1) to furnish 0.74 g of **7** in 55% yield; mp 164 °C (crystallized from EtOH/Et_2O).

4-Azido-1*H*-pyrazolo[3,4-*b*]pyridine (8). The substrate **5** (3.12 g, 20 mmol) was added to cold (0 °C) TFA (15 mL) in one portion and the solution was stirred for 1 h at room temperature. The excess TFA was removed by coevaporation with EtOH (3 × 50 mL). The residue was dissolved in dry DMF (30 mL), to which NaN_3 (2.64 g, 40 mmol) was added, and the mixture heated at 110 °C for 2 h. The reaction mixture was poured onto ice (100 g), the solution was acidified with AcOH to pH 5, and the precipitate was collected by filtration. The product was crystallized from EtOH to furnish 2.32 g of **8** in 72% yield; mp 203 °C dec.

General Methods. 1-Chloro-2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-α-D-ribofuranose[12] (9). A mixture of 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranose[26] (0.91 g, 3 mmol), dry THF (15 mL), and CCl_4 (0.35 mL, 3.6 mmol) was stirred and cooled to −78 °C, under an atmosphere of dry argon. Hexamethylphosphorus triamide (0.56 mL, 3.1 mmol) was added dropwise to the above solution over a period of 15 min. On complete addition, the reaction mixture became gelatinous. The reaction temperature was raised to −40 °C (to ease the stirring) and held for 1 h. Then the solution was allowed to warm up to room temperature in about 1 h and used immediately for method A described below.

General Procedures for Glycosylation of Pyrazolo[3,4-*b*]pyridines 4–8. Method A (E.g., 4 → 10, 5 → 11, 6 → 12, 7 → 13) (8 → 14: A Representative Example). To a suspension of 4-azido-1*H*-pyrazolo[3,4-*b*]pyridine (**8**, 0.32 g, 2 mmol) in dry CH_3CN (60 mL) was added NaH (60% in oil, 0.10 g, 2.5 mmol) under anhydrous and inert (argon) conditions. The suspension was stirred at room temperature for 1 h. A freshly prepared solution of 1-chloro-2,3-*O*-isopropylidene-5-*O*-(*tert*-butyldimethylsilyl)-α-D-ribofuranose[12] (**9**, 0.92 g, 3 mmol) in 15 mL of dry THF was added; stirring was continued for 12 h at room temperature. The reaction mixture was then adsorbed onto silica gel (5 g), which was subsequently loaded onto the top of a flash silica gel column (4 × 30 cm, 80 g) prepacked in hexanes/EtOAc (8:2, v/v). Elution with the same solvent mixture furnished purified **14** as the only UV-absorbing and charring (10% H_2SO_4 in MeOH) material. Appropriate fractions were pooled and evaporated to yield 0.45 g (50%) of **14**. Glycosylations of **4–7** were carried out in a similar way as described above to furnish nucleosides **10–13**, respectively.

Method B (E.g., 4 → 23, 5 → 24, 6 → 25, 8 → 27) (7 → 26: A Representative Example). To a suspension of the sodium salt of **7** (0.45 g, 2 mmol) generated in situ (as described in method A) in CH_3CN was added finely powdered 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride[16] (**22**, 0.694 g, 2 mmol) in one portion and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then purified in a similar way as described in method A (chromatography using hexanes/EtOAc; 8:2, v/v) to furnish 0.9 g (78%) of **26** as white foam. Glycosylations of **4–6** and **8** were carried out in a similar manner as described above to furnish nucleosides **23–25** and **27**, respectively (Table I).

Method C (E.g., 4 → 34, 5 → 35, 6 → 36, 8 → 38) (7 → 37: A Representative Example). To a suspension of the sodium salt of **7** (0.45 g, 2 mmol) generated in situ (as described in method A) in CH_3CN was added 1-chloro-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose[17] (**33**, 3 mmol, freshly prepared from 1-*O*-(*p*-nitrobenzoyl)-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose) in dry CH_3CN (60 mL); the resulting mixture was stirred at room temperature for 12 h. After the usual workup, the product was purified by flash column chromatography as described in method A (chromatography using hexanes/EtOAc; 8:2, v/v) to furnish 0.80 g (64%) of **37** as a syrup. Glycosylations of **4–6** and **8** were carried out in a similar way as described above to furnish nucleosides **34–36** and **38**, respectively.

General Procedures for Transformations of C-4 Substituted Pyrazolo[3,4-*b*]pyridine Nucleosides. Method D (E.g., 10 → 15, 11 → 16, 12 → 17, 13 → 18) (14 → 20: A Typical Example). A solution of **14** (0.44 g, 1 mmol) in TFA/water (5 mL; 9:1, v/v) was stirred at room temperature for 30 min. The excess TFA was removed under a stream of argon. The residue was coevaporated with EtOH (3 × 50 mL), redissolved in EtOH (3 mL), and precipitated by dropwise addition of dry diethyl ether (200 mL). The precipitate was collected by filtration and crystallized from EtOH to furnish 0.25 g (87%) of **20**. Following this method, nucleosides **10–13** were deblocked to furnish **15–18**, respectively, in good yield (Table I).

Method E [E.g., 18 → 19, 20 → 21, 26 → 1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)-4,7-dihydropyrazolo[3,4-*b*]pyridin-4-one (26a)] [27 → 4-Amino-1-(2-deoxy-3,5-di-*O*-toluoyl-β-D-*erythro*-pentofuranosyl)-pyrazolo[3,4-*b*]pyridine (27a): A Representative Example]. A mixture of **27** (0.51 g, 1 mmol) and Pd/C (10%, 0.1 g) in absolute EtOH (100 mL) was shaken in a pressure bottle on a Parr hydrogenator at 45 psi for 2 h at room temperature. The catalyst

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was removed by filtration and washed with EtOH (2 × 25 mL). The combined filtrates were evaporated to furnish 0.44 g (91%) of **27a** as a white foam. In a similar way compounds **18**, **20**, and **26** were hydrogenated to furnish **19**, **21**, and **26a**, respectively (Table I).

Method F (E.g., 23 → 28, 24 → 29, 25 → 30, 26a → 31) (27a → 32: A Representative Example). To a suspension of **27a** (0.24 g, 0.5 mmol) in dry MeOH (25 mL) was added freshly prepared NaOMe in MeOH (1 N) until a pH of 9 was reached. After 2 h, TLC of the reaction mixture indicated no further reaction. To the clear solution, Dowex 50 (H^+) resin was added to adjust the pH to pH ~6. The resin was removed by filtration, washed with MeOH (25 mL) and the filtrate evaporated to dryness. Crystallization of the residue from EtOH furnished 0.10 g (87%) of **32**. Detoluoylation of **23–25** and **26a** by this method furnished **28–31**, respectively (Table I).

Method G (35 → 40). To a solution of **35** (1.66 g, 3 mmol) in dry dichloromethane (50 mL) at −78 °C was added BCl_3 (25 mL, 1 M in dichloromethane). The reaction mixture was stirred at this temperature for 2 h and then at −40 °C for an additional 2 h. To the reaction mixture was added MeOH (50 mL) at −40 °C and stirring was continued at room temperature for 30 min. The mixture was then neutralized with NH_4OH and filtered to remove inorganic salts. The filtrate was evaporated and the residue was purified by flash silica gel column chromatography using $CHCl_3$/MeOH (6:1, v/v) to yield **40** (0.8 g, 93%) after crystallization from acetone.

Method H (E.g., 34 → 39, 36 → 41, 37 → 42) (38 → 43: A Representative Example). To a solution of **38** (0.56 g, 1 mmol) in absolute EtOH (30 mL) were added cyclohexene (30 mL) and $Pd(OH)_2$ (0.2 g of 20%), and the mixture was refluxed for 48 h. After filtration of the reaction mixture through a Celite pad, the filtrate was evaporated to dryness and the residue was purified by flash silica gel column chromatography using $CHCl_3$/MeOH (6:1, v/v) to give 0.18 g (70%) of **43**. Following this method nucleosides **34**, **36**, and **37** were converted to **39**, **41**, and **42**, respectively (Table I).

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Registry No. **4**, 271-73-8; **5**, 29274-28-0; **6**, 119368-03-5; **7**, 119368-04-6; **8**, 119368-05-7; **9**, 102690-94-8; **10**, 119391-46-7; **11**, 119368-06-8; **12**, 119368-07-9; **13**, 119391-47-8; **14**, 119368-08-0; **15**, 49834-63-1; **16**, 35010-60-7; **17**, 119368-09-1; **18**, 119368-10-4; **19**, 119368-11-5; **20**, 119368-12-6; **21**, 49834-61-9; **22**, 4330-21-6; **23**, 119368-13-7; **24**, 119368-14-8; **25**, 119368-15-9; **26**, 119368-16-0; **26a**, 119368-31-9; **27**, 119368-17-1; **27a**, 119368-32-0; **28**, 119368-18-2; **29**, 119368-19-3; **30**, 119368-20-6; **31**, 119368-21-7; **32**, 119391-48-9; **33**, 4060-34-8; **34**, 119368-22-8; **35**, 119368-23-9; **36**, 119368-24-0; **37**, 119391-49-0; **38**, 119368-25-1; **39**, 119368-26-2; **40**, 119368-27-3; **41**, 119368-28-4; **42**, 119368-29-5; **43**, 119368-30-8; 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribose, 68703-51-5.

The Binding of Benzenesulfonamides to Carbonic Anhydrase Enzyme. A Molecular Mechanics Study and Quantitative Structure–Activity Relationships

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Molecular mechanics methods have been applied to study the interaction between a series of 20 deprotonated benzenesulfonamides and the enzyme carbonic anhydrase. The different contributions to the binding energy have been evaluated and correlated with experimental inhibition data and molecular orbital indices of the sulfonamides in their bound conformation. The results suggest that the discrimination shown by the enzyme toward these inhibitors is dominated by the short-range van der Waals forces.

Calculating binding energies between inhibitors and macromolecular targets is not enough. If the results are to be usable in molecular design, we need to be able to partition the energies into the various contributing aspects. Here this is done for sulfonamides binding to carbonic anhydrase.

The zinc metalloenzyme carbonic anhydrase (EC 4.2.1.1) catalyzes the reversible hydration of carbon dioxide. Aromatic and heterocyclic sulfonamides with an unsubstituted sulfonamido group constitute a class of highly active inhibitors possessing unusual selectivity toward different carbonic anhydrase isozymes.[1] The structure–activity relationships of sulfonamides have been analyzed both qualitatively[2,3] and quantitatively.[4-14] In earlier studies[12,14] we showed that certain calculated properties of these molecules, such as charge distribution and frontier molecular orbital indices, are good predictors of the inhibitory activities of sulfonamides on carbonic anhydrase.

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