fact that 1 retains appreciable binding affinity for the progestin receptor thus confirms that the region of the binding site corresponding to C21 is fairly large and can accommodate a bulky phenylselenium group. On the other hand, the orientation of the 17β side chain of 2 is somewhat different from previously observed orientations for steroids with a bulky 17α substituent. The C16–C17–C20–O20 dihedral angle of 17α-substituted steroids tends to be small (ca. −5°)[16] but, to our knowledge, never as small as noted here (+13°) for 2 (i.e., on the α side of ring D).

The virtual lack of affinity of 2 for the progestin receptor would thus seem to be explained by its two distinguishing features: a 17β side chain oriented beyond a zone previously shown to permit hydrogen bonding[6,7] and/or steric hindrance from the bulky 17α-selenophenyl substituent. The 17α position can accommodate fairly large substituents (e.g., an acetate group) without the binding affinity being greatly affected. For instance, under our experimental conditions, after 24-h incubation at 0 °C, medroxyprogesterone acetate has an RBA of 306 ± 25 and chlormadinone acetate an RBA of 321 ± 35.[10,11] However, the presence of a selenophenyl substituent in the 17α position, because of steric hindrance and because of the 90° orbitals of selenium, affects the orientation of the 17β-acetyl side chain to the extent that the ketone group can no longer form adequate hydrogen bonds with the progestin receptor. Inspection of a model reveals that the steric hindrance between C21 and the hydrogen atoms of the phenyl ring of the 17α substituent prevents the 17β side chain from attaining high or even moderately negative values for the C16–C17–C20–O20 dihedral angle. The introduction of the selenophenyl substituent into position 21 does not have such a drastic effect. Derivative 1 may still be able to form the requisite hydrogen bonds. Other explanations relating to, for example, the charge of the molecule, cannot, however, be entirely ignored.

Acknowledgment. The helpful collaboration of M. Fortin and G. Teutsch is gratefully acknowledged. We are indebted to Professor C. Djerassi for kindly supplying us with the two steroids.

Registry No. 1, 74136-99-5; 2, 74137-00-1; progesterone, 57-83-0.

Supplementary Material Available: Atomic coordinates of compounds 1 and 2 (1 page). Ordering information is given on any current masthead page.

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N-(Substituted-phenyl)-D-glycopyranosylamines and Their *O*-Acetyl Derivatives as Potential Modifiers of the Formation of Glycosaminoglycans[1]

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D-Arabinosyl, D-ribosyl, D-glucosyl, D-galactosyl, D-mannosyl, and L-rhamnosyl *N*-glycosides of *p*-aminobenzoic acid and their *O*-acetyl derivatives have been synthesized, and their ability to (a) inhibit the replication of cultured B16 melanoma cells and (b) modify the synthesis of glycosaminoglycans by these neoplastic cells have been evaluated. The most cytotoxic compound of the series was *N*-(*p*-carboxyphenyl)-2,3,4-tri-*O*-acetyl-D-arabinopyranosylamine (8), which produced 50% inhibition of cellular proliferation at a concentration of 4 μM; a number of other compounds were relatively cytotoxic, causing 50% inhibition of cell replication at levels of 18 to 49 μM. These effects were not due to modification of glycosaminoglycan biosynthesis, since these compounds were ineffective as inhibitors or initiators of the formation of these macromolecules.

The sodium salt of *p*-aminobenzoic acid *N*-xyloside has been reported to be an effective inhibitor of the growth of a variety of transplanted rodent neoplasms.[3] This compound causes a number of biochemical changes in malignant cells, including modification of the metabolism of prostaglandins, cyclic nucleotides, phospholipids, and glycosaminoglycans (GAGS), and interference with amino acid and Ca^{2+} transport.[4] The action on GAGS is due to the capacity of this compound to serve as an artificial initiator of GAG synthesis, a process that results in the formation and secretion of GAGS of low molecular weight. Since alterations in the properties of GAGS may result in modification of the growth and metastatic patterns of malignant tumor cells, we have synthesized a variety of *N*-(substituted-phenyl)-D-xylopyranosylamines[5] and haloacetamidoalkyl β-D-xylopyranosides[6] and have demonstrated that members of these two series were cytotoxic

(1) This paper has been presented in part. See L. Wang, C. A. Maniglia, S. L. Mella, and A. C. Sartorelli in "Abstracts of Papers", 182nd National Meeting of the American Chemical Society, New York, Aug 23–28, 1981, American Chemical Society, Washington, DC, Abstr CARB 23.

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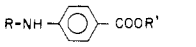
Table I. Properties of *N*-(*p*-Substituted-phenyl)glycopyranosylamines and Their Acetyl Derivatives



no.	R	R′	mp, °C	recrystn solvent	yield,[a] %	$[\alpha]^{20}_D$,[b] deg	formula	anal.[c]
1	D-arabinopyranosyl[d]	H	161–165 dec	EtOH/H_2O	51	+26.8[e]	$C_{12}H_{15}NO_6$	C, H, N
2	D-ribopyranosyl[d]	H	147–149 dec	EtOH/H_2O	47	+232.5	$C_{12}H_{15}NO_6$	C, H, N
3	D-glucopyranosyl[d]	H	126–127 dec	EtOH	51	−108.7	$C_{13}H_{17}NO_7 \cdot H_2O$	C, N; H[f]
4	D-glucopyranosyl	Na	78–82		76	+24.3[g]	$C_{13}H_{16}NO_7Na$	C, H, N
5	D-galactopyranosyl[h]	H	151–152 dec	EtOH	60	−105.7	$C_{13}H_{17}NO_7 \cdot H_2O$	C, H, N
6	D-mannopyranosyl[d]	H	174–175 dec	EtOH/H_2O	63	−170.9	$C_{13}H_{17}NO_7 \cdot H_2O$	C, H, N
7	L-rhamnopyranosyl[h]	H	165–166 dec	EtOH	57	−26.3[g]	$C_{13}H_{17}NO_6$	C, H, N
8	2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl	H	120–125	EtOH	30	−62.9[i]	$C_{18}H_{21}NO_9$	C, H, N
9	2,3,4-tri-*O*-acetyl-α-D-ribopyranosyl	$COCH_3$	93–95	EtOH	27	+30.1[i]	$C_{20}H_{23}NO_{10}$	C, H, N
10	2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl	H	96–103	EtOH/H_2O	31	−3.32[g]	$C_{21}H_{25}NO_{11} \cdot 0.5H_2O$	C, H, N
11	2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl	H	114–118	EtOH/$CHCl_3$	21	+3.05[j]	$C_{21}H_{25}NO_{11}$	C, H, N
12	2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl	$COCH_3$	168–169	EtOH/$CHCl_3$	49	−104.5[j]	$C_{23}H_{27}NO_{12}$	C, H, N
13	2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl	H	102–104	EtOH/H_2O	35	+81.4[i]	$C_{19}H_{23}NO_9$	C, H, N

[a] Yields were based on the final recrystallized products obtained. [b] Measured as 1% solutions in pyridine unless otherwise indicated. [c] The analytical results obtained for elements were within ±0.4% of theoretical values unless otherwise indicated. All compounds had IR spectra, and compounds 8–13 had NMR spectra compatible with expected structures. [d] Literature[20] values for 1, mp 192 °C, $[\alpha]_D$ +29.0° (DMF); for 2, mp 156 °C, $[\alpha]_D$ +168° (DMF); for 3, mp 134 °C, $[\alpha]_D$ −66.2° (EtOH); for 6, mp 182 °C, $[\alpha]_D$ −176.9° (DMF). [e] Measured as 1% solutions in dimethylformamide (DMF). [f] H: calcd, 6.04; found, 5.29. [g] Measured as 1% solutions in water. [h] Literature[21] values for 5, mp 154–156 °C, $[\alpha]_D$ −110.6° (EtOH); for 7, mp 169–170 °C, $[\alpha]_D$ −28.6° (EtOH). [i] Measured as 1% solutions in ethanol. [j] Measured as 1% solutions in $CHCl_3$.

and capable of markedly elevating the formation of GAGS.[5,7,8]

The galactosyltransferase enzyme system, which normally recognizes the xylose moiety linked to the hydroxyl group of a seryl residue in a polypeptide of the endoplasmic reticulum, appears to have absolute specificity for the xylose constituent of the initiating GAG chain;[9,10] therefore, it appeared to be possible by varying the sugar residue to evaluate the importance of initiation of GAG biosynthesis to the cytotoxic action of these compounds. Additionally, since it was conceivable that the specificity of the galactosyltransferase present in neoplastic cells was relaxed, modification of the carbohydrate component attached to *p*-aminobenzoic acid permitted an evaluation of such specificity. This report, therefore, describes the synthesis of a series of *N*-(substituted-phenyl)-D-glycopyranosylamines and their peracetyl derivatives, designed to improve the uptake of these compounds, presumably by passive diffusion, and the capacity of these agents to affect both the replication of B16 melanoma cells in culture and the biosynthesis of GAGS by these neoplastic cells.

Chemistry. *N*-(*p*-Carboxyphenyl)glycopyranosylamines (1–7) were synthesized by condensation of molar equivalent amounts of *p*-aminobenzoic acid (or its sodium salt) with various penta- and hexapyranoses in the presence of glacial acetic acid as a catalyst[11] (Scheme I). The amines (I) were each acetylated[12] with an excess of acetic anhydride in pyridine at 5 °C to give the corresponding *O*-peracetyl derivatives (8–13) (II).[13] Acetylation of 2 and 6 under these conditions, however, gave the corresponding mixed acetic anhydride derivatives 9 and 12 in which both the hydroxyl and carboxyl groups were acetylated. The structures of 9 and 12 were confirmed by NMR and IR spectroscopy. The acetoxy methyl signals that appeared at relatively low field (δ 2.35 for 9, and δ 2.36 for 12) indicated the existence of a $COOCOCH_3$ substituent. The *O*-acetyl signals were observed at higher field,[14,15] with δ 2.22, 2.13, and 2.10 (each of 3 H) in 9 and δ 2.08, 2.07, and 2.03 (each of 3 H) in 12. Characteristic anhydride IR absorptions[16] of compounds 9 (1795 cm^{-1}) and 12 (1795

Scheme I

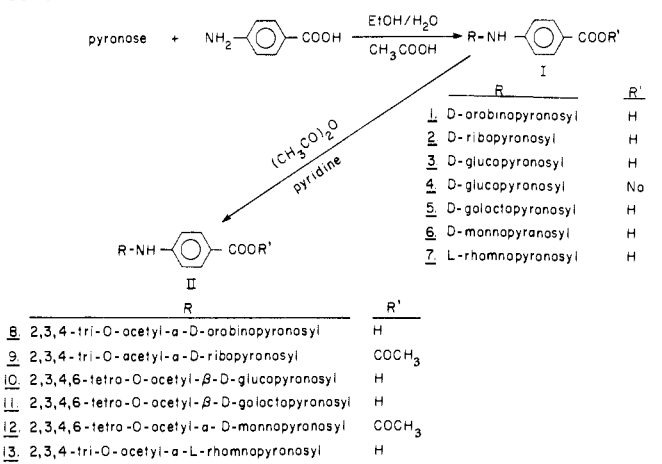


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Table II. Effect of N-(p-Substituted-phenyl)-D-glycopyranosylamines on the Growth of B16 Melanoma Cells in Culture

no.	ID_{50},[a] μM
1	100
2	38
3	100
4	100
5	30
6	39
7	37
8	4
9	25
10	18
11	49
12	25
13	20

[a] Each compound was tested at concentrations of 0.1 μM to 0.1 mM in at least two replicate experiments and the 50% inhibitory level (ID_{50}) was determined graphically.

cm^{-1}) further indicated the formation of $COOCOCH_3$ during acetylation. The properties of amines **1–13** are listed in Table I.

The configuration and conformation of compounds **8–13** were determined by 270- and 500-MHz spectroscopy. The detailed NMR properties of compounds **8–13** have been presented in part[17] and will be reported in detail elsewhere.

Biological Evaluation. Growth inhibitory activity of the synthesized N-(p-substituted-phenyl)glycopyranosylamines (**1–13**) was evaluated against B16/F10 melanoma cells in culture. Most of these compounds exhibited significant inhibition of cellular proliferation in vitro as shown in Table II. The free sugars **1**, **3**, and **4**, each tested up to a concentration of 100 μM, were not effective inhibitors of cell proliferation. In contrast, the corresponding peracetylated derivatives **8** and **10** were the most potent agents tested, exhibiting 50% inhibitory concentrations (ID_{50} values) of 4 and 18 μM, respectively. In general, acetylated derivatives inhibited cellular replication better than the corresponding nonacetylated derivatives, except for compound **11**. Furthermore, the acetyl groups appeared to be necessary for the cytotoxicity of compounds **8** and **10**, since the corresponding free sugars were relatively inactive at similar concentrations. The greater inhibitory activity of the peracetates compared to their corresponding free sugars suggests that differences in transport properties of the more lipophilic derivatives may be operative.

The effects of these compounds upon GAG biosynthesis was analyzed. Unlike several of the xylopyranosylamines, which exhibited both cytotoxic and GAG-modifying activity,[5] the glycopyranosylamines described in the present report neither inhibited the synthesis of GAGS nor served as artificial initiators. This finding implies that (a) modification of GAG biosynthesis is not a prerequisite for cytotoxic activity, and (b) the specificity of the galactosyltransferase enzyme for the xylose moiety as an initiator of GAG chain formation is maintained in these malignant melanoma cells.

Experimental Section

Chemistry. All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were obtained with a Bruker 270 HX spectrometer at 270 MHz and a Brucker WM 500 spectrometer at 500 MHz with Me_4Si as an internal standard. IR absorption spectra were obtained with a Perkin-Elmer 15 spectrometer using KBr pellets of solids. All analytical samples were homogeneous by thin-layer chromatography performed on EM silica gel 60 F_{254} sheets (0.2 mm) with $C_6H_6/C_2H_5OH/H_2O$ (1:3:1, v/v) or $CHCl_3/CH_3OH$ (2:1, v/v) as the developing solvent; spots were detected with iodine. Elemental analyses and optical rotations were carried out by Baron Consulting Co., Orange, CT.

General Procedure for the Preparation of Glycosylamines (1–7) and Their Corresponding Acetyl Derivatives (8–13). N-(p-Substituted-phenyl)glycopyranosylamines (1–7). A solution of 0.45 g (3.3 mmol) of p-aminobenzoic acid (or its sodium salt) in 10 mL of ethanol was reacted with molar equivalent amounts of various D-pyranoses (except for rhamnose, where the L form was employed) in 2 mL of water; except for 4, 3 drops of glacial acetic acid was added to catalyze the reaction. The resulting solutions were refrigerated overnight. Crystallization occurred in some instances, and in others, the solutions were concentrated under reduced pressure at a temperature below 30 °C. Crystals were collected by filtration, washed with ethanol, and recrystallized with either ethanol or ethanol–water. Recrystallization solvents, yields, and melting points are given in Table I.

N-(p-Substituted-phenyl)-O-peracetylglycopyranosylamines (9–13). A mixture of 5 mL of acetic anhydride and 5 mL of pyridine was cooled to 5 °C, 0.5 g of glycosylamine (I) was added, and the mixture was stirred at 5 °C until solubilization was complete. Solutions were maintained at 5 °C for 48 h and then poured with stirring into 100 mL of ice–water. The resulting syrups were stirred vigorously with successive quantities of ice and water to give white solids, which were collected, washed with water at 0 °C, and recrystallized from ethanol to obtain the desired acetyl derivatives, which are listed in Table I.

Cell Culture. B16/F10 melanoma cells were maintained in monolayer culture at 37 °C in a 5% humidified atmosphere by twice weekly passage of 3×10^6 cells/flask in Eagle's minimal essential medium and Hanks' salts supplemented with 10% fetal calf serum (Flow Laboratories), nonessential amino acids, sodium pyruvate, streptomycin (110 μg/mL), penicillin (100 units/mL), minimal essential medium vitamins, and L-glutamine. Exponentially growing B16/F10 melanoma cells were seeded at 1.5 to 3×10^5 cells/25-cm^2 flask. The appropriate glycosides **1–13** were added to each flask at various concentrations at the time of cell seeding, and at the end of a 72-h incubation period, cells were removed from the tissue culture flask by treatment with 0.25% trypsin–EDTA, and the cell number was determined with a Coulter Model ZBI electronic particle counter. The 50% inhibitory concentration for each agent was determined graphically.

Analysis of Glycosaminoglycans. B16/F10 melanoma cells were seeded at a level of 3×10^5 cells/25-cm^2 flask in the presence of glycosides at a concentration of 10^{-5} M. Cultures were incubated at 37 °C, and after 24 h, 10 μCi/mL of [^{35}S]sulfate (1 Ci/mmol, New England Nuclear Corp.) was added, and the cells were incubated for another 24 h. At the end of this period, cells were washed with phosphate-buffered saline (pH 7.2) and treated with 0.25% trypsin–EDTA for approximately 1 to 2 min, and an equal volume of complete medium was added. The cell number was determined as described above, and radiolabeled GAGS were isolated by a modification of the method of Cohn et al.[18] Cellular and medium samples were treated with proteinase K (0.1 mg/flask) at 37 °C, and 24 h later, DNase (0.08 mg/mL) was added, and the samples were incubated at 37 °C for an additional 24 h. Samples were then stored frozen. After the samples were thawed, radiolabeled GAGS were assayed by cetylpyridinium chloride (CPC) precipitation according to the method of Glimelius et al.[19] Each aliquot was incubated in 1 mL of 2% CPC and 40 mM

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Na_2SO_4 at 45 °C. One hour later, samples were collected on 0.45-μm HA filters (Millipore Corp.), washed with 15 mL of 1% CPC and 40 mM Na_2SO_4, and dried, and radioactivity was measured in Biofluor (New England Nuclear Corp.) with a Beckman 7500 scintillation spectrometer.

Acknowledgment. This research was supported in part by U. S. Public Health Service Grants CA-02817, CA-28852, and CA-16359 from the National Cancer Institute.

Registry No. 1, 86195-92-8; 2, 86195-93-9; 3, 4103-32-6; 4, 78990-31-5; 5, 86195-94-0; 6, 86195-95-1; 7, 72880-47-8; 8, 86163-12-4; 9, 86163-13-5; 10, 86195-96-2; 11, 86195-97-3; 12, 86163-14-6; 13, 86163-15-7; D-arabinopyranose, 28697-53-2; D-ribopyranose, 10257-32-6; D-glucopyranose, 2280-44-6; D-galactopyranose, 10257-28-0; D-mannopyranose, 530-26-7; L-rhamnopyranose, 73-34-7; 4-aminobenzoic acid, 150-13-0.

Studies of *N*-Hydroxy-*N'*-aminoguanidine Derivatives by Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy and as Ribonucleotide Reductase Inhibitors[1]

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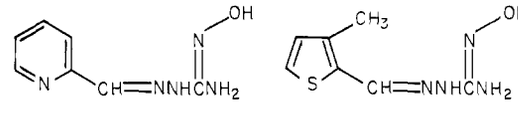
Hydroxyguanidine, with the imino group of guanidine and the hydroxyamino group of hydroxyurea, has functional groups believed to be important for both anticancer and antiviral activities (Adamson, R. H. *Nature (London)* **1972**, *236*, 400–401). Three new *N*-hydroxy-*N'*-aminoguanidine derivatives have been synthesized and found to be 20–30 times more active than the hydroxyguanidine itself as inhibitors of ribonucleotide reductase from rat Novikoff tumors (Tai, W. A.; Lai, M. M.; Lien, E. J. "Novel *N*-Hydroxyguanidine Derivatives as Antiviral Agents", North American Medicinal Chemistry Symposium, University of Toronto, Toronto, Canada, June 20–24, 1982; Abstr, p 144). The character of the tautomeric equilibria, the pK_a values, and the protonation sites of these hydroxyguanidine derivatives have been determined by ^{15}N NMR spectroscopy.

Hydroxyguanidine, a compound with the combined functional groups of anticancer hydroxyurea and antiviral guanidine, has been reported to have anticancer activity, especially against solid tumors like Walker 256 carcinoma in rats.[3] In vitro, hydroxyguanidine has an ID_{50} of 2 μg/mL against Moloney sarcoma virus.[4] Young has reported that *N*-hydroxyguanidine is equal to hydroxyurea in its ability to inhibit DNA synthesis in HeLa cells.[5] The biochemical target is generally believed to be ribonucleotide reductase, an enzyme needed for the reduction of ribonucleotides required for de novo DNA synthesis.[5] Brockman et al. have reported that 2-formylpyridine thiosemicarbazone increased the life span of mice bearing L1210 leukemia.[6] Later, French and Blanz synthesized 1-formylisoquinoline thiosemicarbazone and other α-N-heterocyclic-substituted carboxaldehyde thiosemicarbazones.[7] These compounds have shown anticancer activity against a wide spectrum of transplanted rodent neoplasms, including sarcoma 180, Ehrlich carcinoma, leukemia L1210, Lewis lung carcinoma, hepatoma 129, hepatoma 134, adenocarcinoma 755, and B16 melanoma.[7,8] The α-N-heterocyclic-substituted carboxaldehyde thiosemicarbazones have demonstrated potential as both antineoplastic and antiviral agents. these agents have been shown to inhibit DNA synthesis as a consequence of inhibiting ribonucleoside diphosphate reductase.[9] However, low water solubilities and high toxicities have limited practical therapeutic applications of these compounds.

We report here three new *N*-hydroxy-*N'*-aminoguanidines (1–3; shown here as particular tautomers in accordance with the NMR data to be discussed later), which have been designed to combine structural elements



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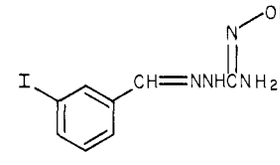
2



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of hydroxyguanidine with carboxaldehyde thiosemicarbazones. The *N*-hydroxy group was expected to enhance water solubilities, and the ring substituent groups were chosen to provide a range of lipophilic/hydrophilic balance.

[†] University of Southern California.
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[§] California Institute of Technology.
[⊥] On leave from the Institute of Photographic Chemistry of the Academia Sinica, Peking, 1979–1981.

(1) (a) Taken in part from the Ph.D. dissertation of A.W.T., University of Southern California, 1982. Supported in part by BRSG Grant 2S07RR 05792-05 to the USC School of Pharmacy and by the Clinical Cancer Education Program of the NCI (Grant 5R 25 CA 24426) to A.W.T. (b) Supported by the American Cancer Society (Grant CH122). (c) Supported by the National Science Foundation and by the Public Health Service (Grant No. GM-11072) from the Division of General Medical Sciences.
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