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Synthesis and Biological Evaluation of Guanidine-Type Iminosugars

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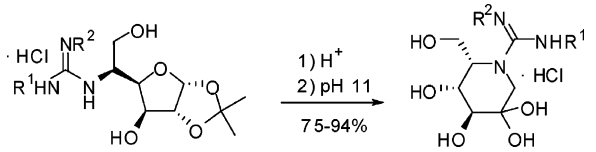
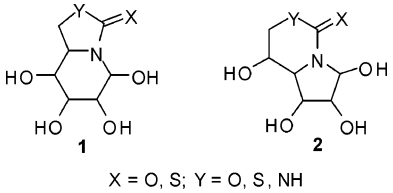


The preparation of carbohydrate mimics in which the endocyclic oxygen has been replaced by a guanidine-type nitrogen atom is reported. The synthetic strategy involves the furanose → piperidine rearrangement of 5-deoxy-5-guanidino-L-idose precursors. The reaction proceeds through elimination of water to give 3-oxopiperidines, which were isolated as the corresponding hydrates. Biological evaluation of the new glycomimetics evidenced a strong influence of the nature of the substituents at the nitrogen atoms on the glycosidase inhibitory properties.

Polyhydroxylated alkaloids with iminosugar structure, usually referred to as azasugars,[1] display a broad range of interesting biological activities potentially useful in the treatment of ailments as varied as viral infections,[2] including human immunodeficiency virus (HIV),[2a−e] human hepatitis C (HCV),[2f,g] or dengue virus,[2i] cancer,[3] diabetes,[4] tuberculosis,[5] and lysosomal storage diseases.[6] The tremendous therapeutic potential of this class of compounds has been ascribed to their ability to interact with carbohydrate-processing enzymes, acting as competitive inhibitors of glycosidases and/or glycosyltransferases, and has strongly stimulated research in this area of glycobiology.[7]

We have recently reported a new family of iminosugars in which the endocyclic sp^3 amine-type nitrogen atom has been replaced by a neutral or very weakly basic pseudoamide-type nitrogen (urea, thiourea, carbamate) with substantial sp^2 character ("sp^2-azasugars").[8] This subtle structural change substantially modifies the reactivity and the stereoelectronic properties at the pseudoanomeric region, with a dramatic increase in the anomeric effect, which has been exploited in the design of conformationally and configurationally stable reducing glycomimetics in the indolizidine series (see structures **1** and **2** for castanospermine and swainsonine analogues, respectively), some of which behaved as highly selective and potent α-glucosidase inhibitors.[9]



Our general synthetic strategy to access sp^2-azasugars is based on the ability of the masked carbonyl group of an hexose

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(1) Although the term "azasugar" is widely used in the literature to refer to glycomimetics where the endocyclic oxygen atom has been replaced by nitrogen, the term is not strictly correct according to the IUPAC−IUMB nomenclature recommendations for carbohydrates, the accepted term being "iminosugar". See: McNaught, A. D. *Pure Appl. Chem.* **1996**, *68*, 1919.

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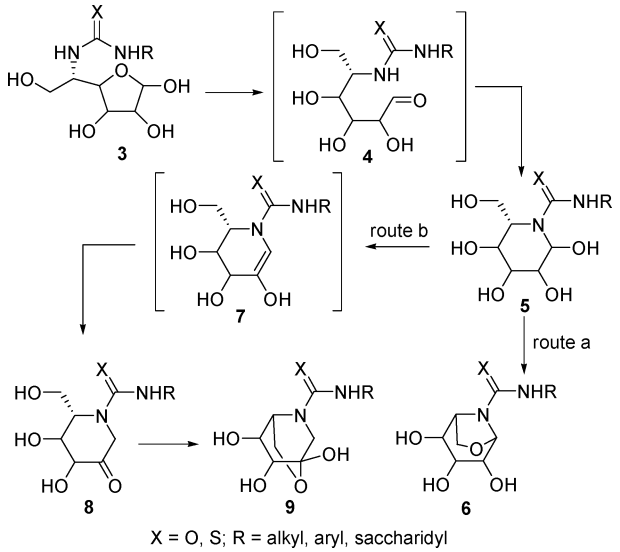
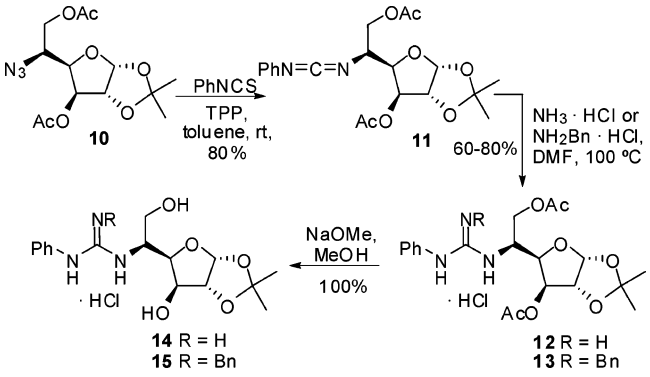
SCHEME 1. Synthesis and Reactivity of sp²-Azasugars



precursor (**3**) to act as the electrophilic target for the nitrogen atom of a pseudoamide group located at the C-5 position through the open-chain aldehyde form (**4**). Interestingly, monocyclic analogues with *N*-(thio)carbamoylpiperidine structure (**5**) exhibited a strong tendency to undergo further intramolecular glycosylation involving the primary OH-6, leading to nortropane-type (calystegine-type) glycomimetics (**6**) that exhibited instead β-glucosidase inhibitory activity.[10] Concomitant β-elimination of water was observed as a minor side reaction (→**7**).[11] Attempts to isolate the resulting polyhydroxylated *N*-(thio)carbamoyloxopiperidine (**8**) or the corresponding intramolecular hemiacetal (**9**) for biological evaluation failed, however (Scheme 1). We reasoned that replacing the neutral (thio)urea or (thio)carbamate group into a strongly basic guanidine functionality should prevent the formation of the piperidine ring under the acidic conditions that promote the intramolecular glycosylation step (route a). Under more basic conditions, the elimination pathway leading to the 3-oxo derivative would be favored (route b). This hypothesis has now been translated into a practical synthesis of guanidine-type iminosugars in the piperidine series. The synthesis of the key guanidinosugar precursors, the scope of the approach, and the preliminary biological evaluation of the new glycomimetics against a panel of glycosidases are reported.

To the best of our knowledge, azasugar analogues in which the endocyclic nitrogen atom is part of a guanidine functionality, that is *N*-amidinoyliminosugars, have not been reported so far.[12] Since the guanidinium group can establish, simultaneously, strong electrostatic and bidentate hydrogen bond interactions with complementary groups,[13] it may interact favorably with the two putative carboxylic residues in the active site of glycosidases. Moreover, both the pK_a values and additional interactions with the enzyme may be modulated with appropriate

SCHEME 2. Synthesis of 5-Guanidinosugars via Carbodiimides



substituents, providing opportunity for the introduction of molecular diversity in the glycomimetic structure. In order to implement the general synthetic route shown in Scheme 1 for accessing the target compounds, the preparation of structurally diverse 5-deoxy-5-guanidino-L-idofuranose precursors, via carbodiimide intermediates, was first envisioned. On one hand, sp²-azasugar with this hydroxylation profile exhibited the strongest β-glycosidase inhibitory activity in the nortropane series. On the other hand, since intramolecular glycosylation is particularly favored for this sugar configuration, it is ideally suited to test the validity of our approach.[8b,10]

Tandem Staudinger−aza-Wittig-type condensation[14] of the 5-azido-5-deoxysugar **10**[15] with triphenylphosphine and phenyl isothiocyanate proceeded smoothly in toluene at room temperature to afford the phenylcarbodiimide derivative **11** in 80% yield.[10] Compound **11** was used as a pivotal synthetic intermediate in the preparation of the *N*′-phenyl- and *N*′-benzyl-*N*″-phenylguanidine derivatives **12** and **13** by reaction with ammonium chloride or benzylamine hydrochloride, respectively. Final de-*O*-acetylation provided the requested precursors **14** and **15** (Scheme 2).

The above methodology was much less efficient in the case of compounds bearing exclusively alkyl substituents at the nitrogen atoms. An alternative three-step synthetic strategy via thiourea adducts was devised.[16] Nucleophilic addition of 5-amino-5-deoxy-1,2-*O*-isopropylidene-L-idofuranose **16**[15] to benzyl isothiocyanate yielded the corresponding thiourea **17**,[10] which was further *O*-acetylated (→**18**)[17] and subjected to desulfuration with mercuric oxide to give carbodiimide **19** (51% overall yield). Subsequent addition of benzylamine hydrochloride to the heteroallene group afforded the *N*′,*N*″-dibenzylguanidine derivative **20**, which was finally deacetylated to the corresponding diol **21**. An analogous reaction sequence using methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato-α-D-glucopyranoside (**22**)[18] provided the guanidine-linked pseudodis-

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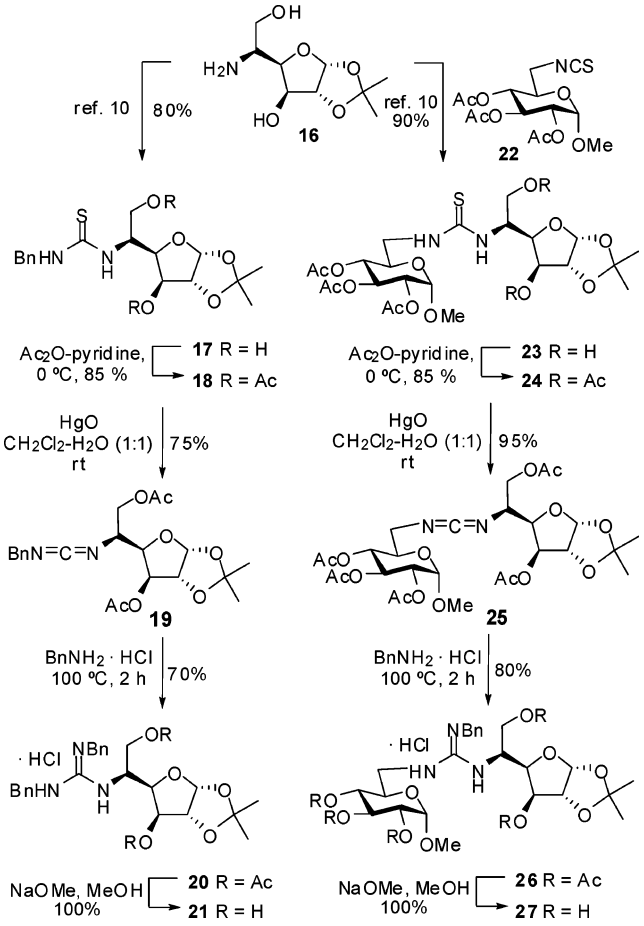
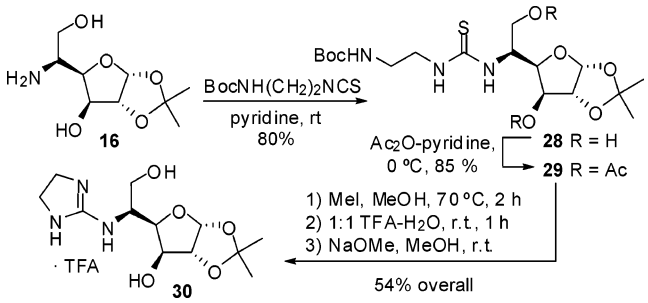
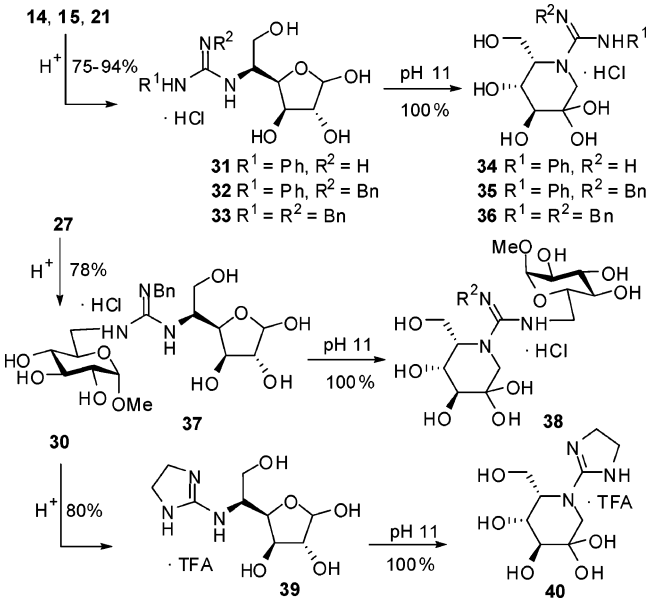
SCHEME 3. Synthesis of 5-Guanidinosugars via Thioureas



SCHEME 4. Synthesis of the 5-Imidazolin-2-ylaminosugar 30



SCHEME 5. Synthesis of Guanidine-Type Iminosugars



accharide **27** through the corresponding thiourea (**23**, **24**), carbodiimide (**25**)[19] and penta-*O*-acetylated guanidinosugar (**26**) intermediates (Scheme 3).[20]

The preparation of compound **30**, incorporating an aminoimidazoline moiety, was next considered. This fragment has been previously used in the rational design of artificial receptors for phosphodiester and carboxylates.[21] Coupling reaction of amine **16** with 2-(*N*-*tert*-butoxycarbonylamino)ethyl isothiocyanate gave the corresponding thiourea adduct **28**, which was transformed into the required cyclic guanidine through a two-step reaction sequence involving *S*-alkylation with methyl iodide and aqueous TFA-promoted hydrolysis of the carbamate group (Scheme 4).

Trifluoroacetic acid-promoted deisopropylidination of the 1,2-*O*-isopropylidene-5-deoxy-5-guanidino-L-idofuranose derivatives **14**, **15**, **21**, **27**, and **30** afforded the fully unprotected furanose compounds **31**−**33**, **37**, and **39** as mixtures of the corresponding α- and *β*-anomers. Contrary to that previously observed for the urea and thiourea counterparts,[10] no formation of nitrogen-in-the-ring isomers was observed neither during coevaporation of the acid with water nor after neutralization with Amberlite IRA-68 (OH^-) ion-exchange resin. At pH 11, spontaneous rearrangement to the corresponding amidinoylpiperidine was accompanied by concomitant dehydration reaction. The resulting 3-oxopiperidines (see structure **8** in Scheme 1) were isolated in quantitative yield as the corresponding hydrates **34**−**36**, **38**, and **40**. No formation of intramolecular hemiacetals occurred even after acidification of the reaction products (Scheme 5).

The ^1H NMR spectra of the final compounds were in agreement with the presence of two methylene groups in the molecule, one of them coupled to the piperidine ring spin system and the other one showing exclusively the geminal coupling constant, corresponding to the hydroxymethyl substituent at C-2 and the pseudoanomeric protons (H-6a, H-6b), respectively. The coupling constant values between vicinal protons at the piperidine ring ($J_{2,3}$ and $J_{3,4} \geq 9.0$ Hz) were indicative of either anti (180°) or eclipsed (0°) relative dispositions, suggesting that the $^{1,4}B$ boat conformation (H-2/H-3 eclipsed; H-3/H-4 anti) largely predominates over the $^4C_1$ chair conformation (H-2/H-3 gauche; H-3/H-4 anti) typical of L-ido-configured *N*-(thio)carbamoylpiperidine-derived intramolecular glycosides (see, as an example, the structures of the *N*′-phenylamidinoyl, phenylcarbamoyl, and phenylthiocarbamoyl derivatives **34**, **41**, and **42**).

(19) Compound **25** has been previously prepared by the Staudiger−aza-Wittig-type condensation of azide **10** and isothiocyanate **22** in a much lower (30%) yield. See ref 10.

(20) For a recent report on the synthesis of guanidine-linked pseudo-oligosaccharides from thiourea precursors, see: Jiménez Blanco, J. L.; Bootello, P.; Benito, J. M.; Ortiz Mellet, C.; García Fernández, J. M. *J. Org. Chem.* **2006**, *71*, 5136.

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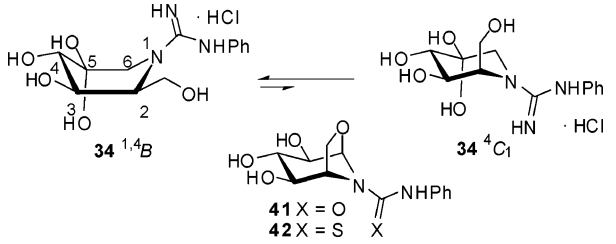

The inhibitory activities of the *N*-amidinoylpiperidine azasugars **34**−**36**, **38**, and **40** for α-glucosidase (yeast), *β*-glucosidase (almonds), *β*-glucosidase (bovine liver, cytosolic), and α-galactosidase (green coffee beans), in comparison with data for the related bicyclic compounds **41** and **42**,[10] are summarized in Table 1. The *N*′-phenylamidinoyl derivative **34** behaved as a selective but weak inhibitor of both *β*-glucosidases, in stark contrast with the very selective and strong inhibition of the bovine *β*-glucosidase by the calystegine-type *N*′-phenyl(thio)-carbamoyl glycomimetics **41** and **42**. The selectivity toward the mammalian enzyme is recovered in the case of the *N*′,*N*″-disubstituted derivatives **35** and **36**, though the inhibition potency remains over 1 order of magnitude weaker. Interestingly, the presence of the hydrophilic sugar substituent in **38** results in a full reversion of the *β*-glucosidase selectivity. The inhibition was totally abolished for the *N*-imidazolinylpiperidine **40**. None of these compounds inhibited α-glucosidase, in agreement with the linkage specificity previously encountered in the L-idose-derived sp^2-azasugars **41** and **42**. Inhibition of α-galactosidase, a typical feature of calystegine-type glycomimetics, does not occur for the monocyclic piperidine derivatives **34**−**36**, **38**, and **40**.

TABLE 1. Inhibition Constants (K_i, μM) for the *N*-Amidinoylpiperidine Derivatives 34−36, 38, and 40 in Comparison with Data for the Calystegine-Type *N*-(Thio)carbamoyl Derivatives 41 and 42

enzyme	34	35	36	38	40	41	42
α-glucosidase (yeast)	926	n.i.[a]	n.i.	n.i.	n.i.	n.i.	n.i.
β-glucosidase (almonds)	217	n.i.	n.i.	323	n.i.	1500	970
β-glucosidase (bovine liver)	367	732	303	n.i.	n.i.	30	2.5
α-galactosidase (green coffee)	n.i.	n.i.	n.i.	n.i.	n.i.	137	172

[a] No inhibition detected at 2 mM.

In summary, we have described an efficient synthetic route to guanidine-type iminosugars based on the ability of the carbonyl group of an l-idose precursor to act as the electrophilic target for the nitrogen atom of a guanidine substituent located at the C-5 position. The approach is compatible, in principle, with the introduction of molecular diversity both at the level of the piperidine ring configurational pattern and at the number and nature of the N-substituents, being ideally suited for structure−activity studies and inhibitor optimization. Research in that direction is currently underway in our laboratories.

Experimental Section

General Procedure for the Preparation of 5-Deoxy-5-guanidinium-L-idofuranose Salts (31−33, 37, and 39). A solution of **14, 15, 21**, **27**, or **30** (0.47 mmol) in a mixture of TFA/H_2O (9:1, 2.6 mL) was stirred at 0 °C for 30 min until disappearance of the starting material (TLC). The solvent was removed under vacuum and the residue coevaporated several times with water. Finally, HCl 0.1 M was added to an aqueous solution of the residue until pH 5.0, and the resulting solution was freeze-dried.

Data for 5-deoxy-5-(*N*′-phenylguanidino)-L-idofuranose hydrochloride (31) as an example: yield 150 mg (94%); R_f 0.56 (6:3:1 MeCN−H_2O−NH_4OH); $[\alpha]_D = -3$ (*c* 1.0, H_2O); ^{1}H NMR (300 MHz, D_2O, 323 K) δ 7.47−7.26 (m, 10 H, Ph), 5.42 (d, 1 H, $J_{1,2} = 4.1$ Hz, H-1α), 5.21 (d, 1 H, $J_{1,2} = 0.9$ Hz, H-1*β*), 4.29 (m, 2 H, H-3α, H-4α), 4.23 (dd, 1 H, $J_{4,5} = 7.2$ Hz, $J_{3,4} = 4.7$ Hz, H-4*β*), 4.18 (dd, 1 H, $J_{2,3} = 1.9$ Hz, H-3*β*), 4.05 (m, 3 H, H-2α, H-2*β*, H-5*β*), 3.92 (m, 1 H, H-5α), 3.80 (dd, 1 H, $J_{6a,6b} = 11.8$ Hz, $J_{5,6a} = 4.0$ Hz, H-6a*β*), 3.75 (dd, 1 H, $J_{6a,6b} = 11.7$ Hz, $J_{5,6a} = 4.4$ Hz, H-6aα), 3.65 (dd, 1 H, $J_{5,6a} = 6.9$ Hz, H-6b*β*), 3.63 (dd, 1 H, $J_{5,6b} = 7.5$ Hz, H-6bα); ^{13}C NMR (75.5 MHz, D_2O, 323 K) δ 156.2 (CN), 134.5−125.8 (Ph), 102.0 (C-1*β*), 96.1 (C-1α), 80.8 (C-2*β*), 80.7 (C-4*β*), 77.2 (C-4α), 76.3 (C-2α), 74.7 (C-3α), 74.5 (C-3*β*), 61.5 (C-6α), 61.3 (C-6*β*), 54.8 (C-5*β*), 54.0 (C-5α); FABMS *m*/*z* 298 (100, $[M - Cl]^+$). Anal. Calcd for $C_{13}H_{20}N_3O_5Cl$: C, 46.78; H, 6.04; N, 12.60. Found: C, 46.67; H, 5.94; N, 12.41.

General Procedure for the Preparation of *N*-Amidinoylpiperidine Salts (34−36, 38, and 40). An aqueous solution of the corresponding guanidinium salt **31**−**33**, **37**, or **39** (0.15 mmol) was treated with Amberlite IRA 68 (OH^-) ion-exchange resin until pH 11. The resin was filtered and the aqueous solution neutralized and freeze-dried.

Data for (2*R*,3*R*,4*S*)-1-(*N*′-phenylamidinoyl)-3,4,5,5-tetrahydroxy-2-hydroxymethylpiperidine hydrochloride (34) as an example: yield 50 mg (100%); R_f 0.39 (6:3:1 CH_3CN−H_2O−NH_4OH); $[\alpha]_D = -6$ (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O, 313 K) δ 7.59−7.39 (m, 5 H, Ph), 3.85 (m, 5 H, H-3, H-2, H-6a, H-6b, CH_aOH), 3.66 (d, 1 H, $J_{3,4} = 9.2$ Hz, H-4), 3.57 (m, 1 H, CH_b-OH); ^{13}C NMR (125.7 MHz, D_2O, 313 K) δ 156.2 (CN), 135.1−125.9 (Ph), 98.1 (C-5), 72.3 (C-3), 71.1 (C-4), 63.6 (CH_2OH), 60.0 (C-6), 54.0 (C-2). FABMS *m*/*z* 298 (80, $[M - Cl]^+$). Anal. Calcd for $C_{13}H_{20}N_3O_5Cl \cdot H_2O$: C, 44.38; H, 6.30; N, 11.94. Found: C, 44.43; H, 6.43; N, 11.54.

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Supporting Information Available: General experimental details, full purification and characterization data for the prepared compounds, and experimental procedures for determination of glycosidase inhibition constants (K_i). This material is available free of charge via the Internet at http://pubs.acs.org.

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