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Synthesis, NMR Studies and Theoretical Calculations of Novel 3-Spiro-branched Ribofuranoses

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Abstract: Novel spiro-branched sugar derivatives bearing a spiro-5'-(4'-amino-2'-oxazolone) or a spiro-5'-(4'-amino-1',2',3'-oxathiazole-2',2'-dioxide) rings at position-3 of the sugar moiety have been prepared. The synthesis has been achieved by a one-pot procedure from a conveniently protected sugar cyanohydrin derivative by reaction with chlorosulfonyl isocyanate or sulfamoyl chloride, respectively. The tautomeric preference in solution of these novel 3-spiro sugars are described as derived from NMR spectroscopy. Also a comparative theoretical study, by *ab-initio* methods, of the steric and electronic properties of the spiro rings present in these sugar derivatives has been performed.

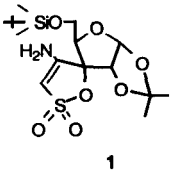
'Keywords:' Spiro compounds; Oxazolones; Oxathiazoles; Carbohydrates

Introduction

Branched-chain sugars are widely spread naturally occurring products.[1,2] They are also useful chiral synthons for the total synthesis of other naturally occurring non carbohydrate compounds.[3,4]

In the course of our studies on the synthesis of highly functionalised branched-chain sugars, we reported the unexpected behaviour of tertiary cyanomesylates of carbohydrates,[5,6] prepared from furanos-3-uloses, pyranos-3-uloses or pyranos-2-uloses, which under basic conditions underwent intramolecular aldol-type cyclocondensation to afford *C*-branched spiro derivatives having a 3-spiro-5'-(4'-amino-1',2'-oxathiole-2',2'-dioxide) ring at the branching point (*i.e.* spirosugar derivative **1**). Extension of this procedure to α-mesyloxinitriles of nucleosides lead us to discover a novel class of potent HIV-1 specific inhibitors whose prototype compound is the thymine derivative designated as TSAO-T (**2**).[7-10]

As further part of our chemical interest in the synthesis of *C*-branched-chain sugar derivatives having a highly functionalised substituent at the branching point, and paying special attention to spiro-substituted sugar derivatives, we report here the very first examples of sugar derivatives bearing a spiro-5'-(4'-amino-2'-oxazolone) or a spiro-5'-(4'-amino-1',2',3'-oxathiazole-2',2'-dioxide) rings at position-3 of the sugar moiety.



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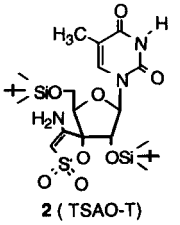

2 (TSAO-T)

These spiro sugar derivatives have been prepared by a one-pot procedure from a conveniently protected sugar cyanohydrin derivative by reaction with chlorosulfonyl isocyanate or sulfamoyl chloride, respectively.

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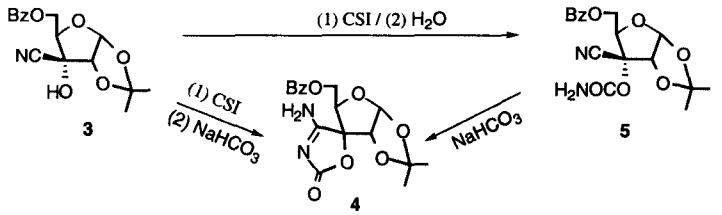
A different regioselectivity depending on the spiro substituent of these sugar derivatives was observed when these compounds were treated with methyl iodide and sodium carbonate. Additionally, a theoretical study on the reactivity of these spirosugars is also reported.

Results and Discussion

Our strategy for the synthesis of these new 3-spiro sugars has been based on the functionalisation and closure of the corresponding cyanohydrins obtained from 3-ketosugars. This strategy allowed us to obtain in one-pot two-steps procedure highly functionalised sugar derivatives starting from a common precursor. As an appropriate synthon for the synthesis of the desired 3-spiro sugars (**4** and **6**), the sugar cyanohydrin **3**, previously prepared in our laboratory,[8] was chosen (Scheme 1).



Scheme 1

For the synthesis of the new spiro derivative **4** we designed a procedure based on a reported method for the synthesis of pseudohydantoins.[11] The method consisted of the reaction between cyanohydrins and chlorosulfonyl isocyanate (CSI) in toluene at reflux or in the presence of Et_3N at room temperature. Attempts to prepare **4** following such method were unsuccessful. On the other hand, it has also been described that amino nitriles react with chlorosulfonyl isocyanate in CH_2Cl_2 to give, after hydrolysis with water, iminohydantoins.[12] However, reaction of cyanohydrin **3**[5,6] under those reaction conditions (chlorosulfonyl isocyanate followed by treatment with water) gave the carbamoyl derivative **5** (60%) instead of the expected cyclic compound **4** (Scheme 1). Finally, compound **4** was prepared in 76% yield by reaction of cyanohydrin **3** with chlorosulfonyl isocyanate followed by *in situ* treatment with saturated aqueous $NaHCO_3$. Besides, when the carbamate **5** was treated with saturated aqueous $NaHCO_3$, the spiro derivative **4** was also obtained.

Structures of the new compounds were assigned from their analytical and spectroscopic data. The ^1H NMR spectra of **5** showed the disappearance of the signal corresponding to the OH group and the presence of two new broad singlets that disappeared on D_2O exchange that were assigned to the NH_2 group of the carbamate grouping. The ^{13}C NMR spectra showed the presence of a new signal at 154.27 ppm corresponding to the -$OCONH_2$ carbon atom and the presence of the signal corresponding to the cyano group at 114.41 ppm.

The spiro moiety at the 3-position of compound **4** could exist in different tautomeric forms (Figure 1). The existence of **4** in the tautomeric form II (in acetone-d_6) was established based on the following criteria. The ^1H NMR spectra of **4** showed the presence of two new signals of NH at 8.57 and 7.32 ppm. The ^{13}C NMR spectra of **4** showed the disappearance of the signal corresponding to the cyano group and the presence of two new signals at 165.92 and 180.39 ppm corresponding to C-2' and C-4' respectively. The chemical shift value of 165.92 ppm for C-2' allowed us to discard the presence of the tautomer III (a value of 150-155 ppm for C-2'

would be expected[13] if tautomer III would be present). On the other hand, the chemical shift of C-4' is in agreement with literature data for an endocyclic C=N double bond in five membered ring systems that appear at 182-190 ppm[14,15] (exocyclic C=N double bonds appear at 158-168 ppm[6,16,17]). Therefore, the ^{13}C NMR data suggest the existence of compound **4** in the tautomeric form II as the most probable one.

Unequivocal assignment of the predominant tautomer (in acetone-d_6) was carried out by heteronuclear inverse detection ^{1}H-^{15}N (HMQC) correlation spectroscopy experiments.[18] Thus, an HMQC experiment carried out on compound **4** indicated that the proton of the spiro moiety appearing at 7.32 ppm was directly bonded to a nitrogen which appeared shielded 292 ppm with respect to nitromethane (reference signal). This result is in agreement with literature data for enamine-type nitrogens (as in tautomer II), whose signals appear shielded around 300 ppm[19,20] with respect to nitromethane. Imine-type nitrogens (as in tautomers I and III), on the other hand appear shielded around 190-200 ppm.[20] Therefore, tautomer II is the only form that can be detected by ^{15}N-NMR.

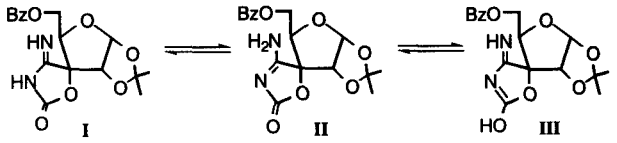
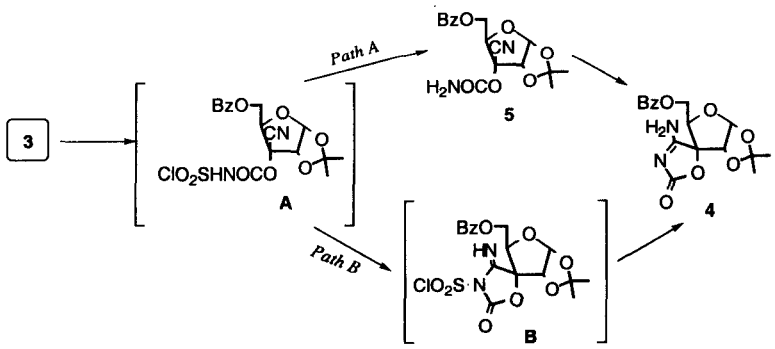


Figure 1: Tautomeric forms of spiromoiety of compound 4

The absolute configuration at C-3 for the spiro derivative **4** was unequivocally determined by a NOESY experiment. The correlation peaks observed between the NH-4' protons and the H-2 and H-5 protons were only compatible with a *ribo* configuration.

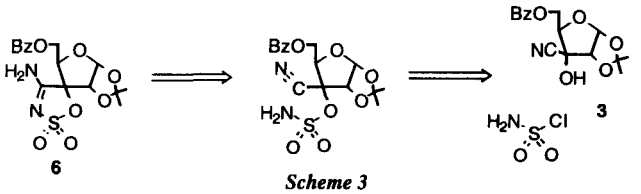
The isolation of intermediate **5** allows speculation concerning the mechanism of the spirooxazolone formation reaction. A possible rationale for the formation of the 3-spirooxazolone derivative **4** is shown in Scheme 2. The initial adduct of cyanohydrin **3** and chlorosulfonylisocyanate is presumably **A** which could hydrolyze to **5** (path A) or cyclise to **B** (path B). Then, either cyclisation of **5** or hydrolysis of **B**, would lead to the spirooxazolone derivative **4**. The fact that treatment of **5** under basic conditions afforded the cyclized compound **4** seems to indicate that the carbamate intermediate **5** is involved in the mechanism of the oxazolone forming reaction and points to path A as the most probable, although the possibility of path B cannot be completely discarded.



Scheme 2

For the synthesis of 3-spiro-oxathiazoledioxide derivative **6** the retrosynthesis outlined in Scheme 3 was devised. Thus, the 3-spirooxathiazoledioxide could be obtained by cyclization of the intermediate generated by reaction of the cyanohydrin **3** with sulfamoyl chloride. The sulfamoylation reaction requires the activation of the

hydroxyl group using basic conditions[21,22] or by reacting with bis(tributyltin)oxide.[21,23] Initial attempts to activate the hydroxynitrile **3** with bis(tributyltin)oxide followed by the addition of sulfamoyl chloride were unfruitful, and the starting material was recovered unchanged. However, treatment of cyanohydrin **3** with DMAP and sulfamoyl chloride in dry dioxane,[24] afforded the cyclised compound **6** (63%). In this reaction the formation of acyclic intermediates was not detected. Cyclizations between a CN group and the NH_2 group of the sulfamoyl grouping under basic conditions have been described.[25]



Scheme 3

The structure of **6** was determined as follows. The IR spectra showed the dissapearance of the band corresponding to the CN group and the presence of new bands at 1360 and 1180 cm^{-1} characteristic of the SO_2 group. The ^1H NMR spectra showed the presence of two signals at 7.21 and 8.47 ppm. The ^{13}C NMR showed the disappearance of the cyano function and the presence of a new signal at 167.6 ppm corresponding to C-4'. From the spectroscopic data we could not discriminate between the possible tautomeric forms of the spiro aminooxathiazoledioxide ring at 3-position (Figure 2). The existence of **6** in the tautomeric form II (in acetone-d_6) was unequivocally determined by a ^1H-^{15}N (HMQC) experiment as indicated for compound **4**. The experiment showed that the protons of the spiro moiety appearing at 7.21 and 8.47 ppm were directly bonded to a nitrogen which appeared shielded 292 ppm with respect to nitromethane (reference signal). This result was only compatible an enamine type structure and therefore with tautomer II.

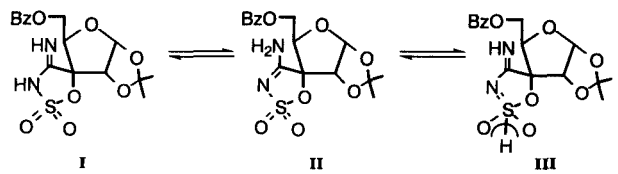
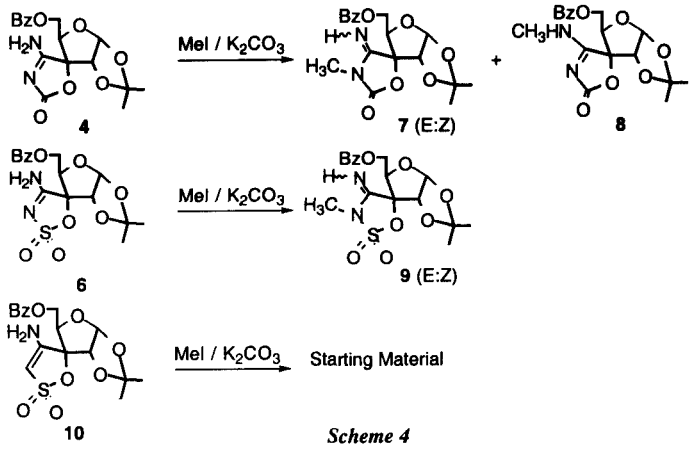


Figure 2: Tautomeric forms of spiromoiety of compound 6

The absolute configuration at C-3 for the spiro derivative **6** was unequivocally determined by NOE experiments. Thus, irradiation of the NH_2-4' group caused enhancements of the signals for H-1 and H-2. These correlations indicated that the NH_2 group is in the upper side (β) of the furanose ring, and where only compatible with a *ribo* configuration of the furanose moiety.

Treatment of compound **4** (Scheme 4) with methyl iodide in the presence of K_2CO_3 gave a (1:1) mixture of isomeric 4-imino-3-*N*-methyl-spiro oxazolidinone derivatives **7*E*** and **7*Z*** in 58% yield, toghether with the 4-*N*-methyl-spiro-oxazolone compound **8** as the minor derivative (15%), the ratio af *E* and *Z* isomers was established as 1:1 by the integration of the signal for each isomer in the ^{1}H NMR spectrum. A similar alkylation of compound **6** (methyl iodide / K_2CO_3) afforded, exclusively an isomeric mixture of the *E* and *Z* imino



Scheme 4

derivatives **9** in 90% yield, resulting from the methylation of the endocyclic nitrogen, no methylation was observed on the exocyclic NH_2 group. Finally, when the spiroaminooxatioldioxide derivative (**10**), prepared from **1**[5,6] by removal of the 5'-TBDMS group followed by benzoylation of the 5'-OH, was subjected to similar reaction conditions, no alkylation took place and the starting material was recovered unchanged.

The site of methylation and the stereochemistry (*E, Z*) of N-methyl spiroderivatives **7-9** were determined by ^1H, ^{13}C and ^{15}N NMR spectroscopy using mono and bidimensional techniques (HMQC[18] and HMBC[26] and NOE experiments). The ^1H and ^{13}C NMR spectra of **7**, in acetone-d_6 and in DMSO-d_6, showed duplicated signals corresponding to two forms. This fact suggests the presence of the *E* and *Z* imino isomers due to the two possible orientations of the NH proton. The location of the methyl group was unambiguously established from the HMBC spectrum. The NMe protons of the *E* and *Z* forms (δ 2.98 ppm, δ 3.00 ppm) showed long-range correlations with the C4' carbon (δ 161.8 ppm, δ 158.8 ppm) and the carbonyl carbon C2' (δ 155.7 ppm, δ 155.3 ppm), this indicates that the Me is attached to the endocyclic N3' nitrogen.

The ^1H-NMR spectrum of compound **8**, in DMSO-d6, showed signals corresponding to a single compound. The location of the methyl group attached to the exocyclic nitrogen (N-4') was unambiguously established from the HMBC spectrum. The NMe protons (δ 2.85 ppm) showed long-range correlation only with the C4' carbon (δ 177.8 ppm), thus indicating that the Me is attached to the N4' nitrogen. Furthermore, the observed correlation between H4 proton of the ribose (δ 4.59 ppm) and C 4' (δ 177.8 ppm) of the spiro ring, supported this result.

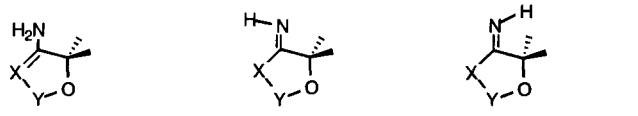
The presence of a SO_2 group , in compound **9**, instead of a CO as in compounds **7** or **8**, precluded the use of HMBC experiment to unambiguously determine the position of the methyl group. ^{15}N NMR spectroscopy is a more suitable technique for this purpose. Thus, the position of the methyl group was unequivocally determined by a ^1H-^{15}N (HMQC) correlation spectroscopy experiment,[18] as shown for compounds **4** and **6**. This experiment carried out, in acetone-d_6, with compound **9** showed that the NH proton appearing at δ 7.45 ppm was directly bonded to an imine-type nitrogen[20] which appeared shielded 167.86 ppm with respect to nitromethane. This result is only compatible with the existence of an imino-type nitrogen at C4' and therefore the methyl group is attached to the endocyclic N3' nitrogen. A NOE experiment irradiating the NH proton (δ 7.45 ppm) showed enhancements in H1, H2 and NMe resonances (δ 6.19, δ 4.94 and δ 3.02 ppm).

This confirms the proposed imine-type structure and indicates the existence of imino isomers *E* and *Z*. It should be pointed out that when the ^1H NMR spectrum of compound **9**,was registered in $CDCl_3$, at room temperature, broad signals were observed that did not collapse upon heating. This suggests that the energy barrier between tautomers shold be too high to allow to "collapse" to average signals as those observed when the spectrum was registered in acetone.

Theoretical Calculations

In order to explain the different reactivity observed in the methylation of spiro sugars **4**, **6** and **10** and parallel to the synthesis and NMR studies, an *ab initio* [27] theoretical study using the 6-31G** basis set was carried out with amines **4a**, **6a** and **10a** (Figure 3) which can be taken as a simplification of the different spiro rings present in the molecules (**4**, **6** and **10**). Also, their imino forms **4i**, **6i** and **10i** (Figure 3) were studied.

The total electronic energy values (E_{elect}, Table 1) show that the imine **4i*Z***, and the amines **6a** and **10a** are energetically the most stable tautomers. However, among the tautomers of **4**, the energy differences are very low (less than 1.1 Kcal/mol between **4a** and both **4i*Z*** and **4i*E***). Moreover, the computed dipole moment value of the amine **4a** is much larger than those of the imine isomers **4i*E*** and **4i*Z*** (8.44 vs 4.21 and 2.85 Debye, respectively) which indicates that, in polar solvents, the amine **4a** should be more stable than the imines. Therefore, in polar solvents, the small energy differences could be reversed and the three forms are equally possible. Whereas in the case of **6** and **10**, the energy differences among tautomers (~ 9-11 kcal/mol) together with the computed dipole moments values (see Table 1) indicate that, in both polar and apolar solvents, the amines **6a** and **10a** would be the only forms present. These results are in agreement with the experimental results observed in the NMR study *vide supra*.



4a; X = N; Y = C=O
6a; X = N; Y = SO_2
10a; X = CH; Y = SO_2

4i*Z*; X = NH; Y = C=O
6i*Z*; X = NH; Y = SO_2
10i*Z*; X = CH_2; Y = SO_2

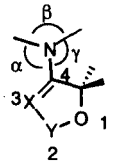
4i*E*; X = NH; Y = C=O
6i*E*; X = NH; Y = SO_2
10i*E*; X = CH_2; Y = SO_2

Figure 3

Geometry Calculations

Table 1 shows the most relevant geometrical parameters, that may account for the reactivity of these structures as nucleophiles.[28] These are the dihedral angle N4-C4-X3-Y2 (ϕ_1), the flip angle Ψ_1[29] (Ψ_1 = H4-N4-C4-X3 angle), the distance d_{C4-N4} and the sum of the bond angles (Σ) at the amino group that gives a measure of the planar or pyramidal nature of the amino group, and can be related with the hybridization type. Thus, a planar geometry (sp^2) should give a value of $\Sigma = 360°$, while a tetrahedral one (sp^3) should give a value around $\Sigma = 329°$.[30] As shown in Table 1, in the amines **4a** and **6a**, the nitrogen is in the same plane as the spiro ring ($\Psi_1 = 0$; $\phi_1 = 180°$), whereas in the amine **10a** a flip angle is observed ($\Psi_1 = 6.9$; $\phi_1 < 180°$). On the other hand, **4a** and **6a** show an sp^2 planar geometry ($\Sigma = 360°$), whereas amine **10a** shows a certain sp^3 tetrahedral geometry ($\Sigma = 348°$). Also, the distance (d_{C4-N4}) shows the tendency to adopt an sp^2 geometry (values ranging from 1.38 Å in the planar geometry to 1.43 Å in a tetrahedral one), this distance is slightly shorter in **4a** and **6a** with

TABLE 1. Geometrical parameters of amines **4a**, **6a** and **10a** and imines **4i**, **6i** and **10i**.



4; X = N; Y = C=O
6; X = N; Y = SO_2
10; X = CH; Y = SO_2

Comp.	[a]d_{C4-N4} (Å)	[b]Σ (°)	[c]ψ_1 (°)	[d]Φ_1 (°)	$E_{elect.}$ (Kcal/mol)	μ (Debye)
4a	1.332	360	0.0	180	-284056.55	8.44
4iZ	1.248	—	—	—	-284057.48	2.85
4iE	1.248	—	—	—	-284057.30	4.21
6a	1.332	360	0.0	180	-556647.58	9.75
6iZ	1.247	—	—	—	-556636.20	4.07
6iE	1.247	—	—	—	-556635.61	5.40
10a	1.350	348	6.9	175.5	-546597.10	9.17
10iZ	1.246	—	—	—	-546588.57	5.01
10iE	1.246	—	—	—	-546587.87	5.73

[a] Distance between the exocyclic nitorgen and C-4. [b] Sum of the bond angles at the amino group (Σ = α + β + γ). [c] Flip angle (ψ_1 = angle H4-N4-C4-X3). [d] angle N4-C4-X3-Y2.

respect to **10a**, this indicates a lower conjugation in **10a** between the amino group and the double bond and therefore, a higher reactivity as nucleophile.

The sp^2 or sp^3 character of amines has been related with their basicity.[31] When an amino group is directly linked to a conjugated system the lone-pair electrons tend to become delocalized and to participate in the conjugated system. Thus, it is well known that aromatic amines are much weaker bases than their aliphatic analogues.[32] The maximum mesomeric effect of the amino group could be exerted only if the hydrogen atoms of the amino group became coplanar with the ring, for this to occur it is necessary a trigonal geometry (sp^2) of the nitrogen atom. The certain tendency to the sp^3 character of the nitrogen atom of ring **10a** suggests that the amino group present in this ring is slightly more basic than the corresponding amino groups of **4a** and **6a**.

The geometrical parameters for imine forms (**4i** and **6i**) are all very similar with deviations smaller than 1% among them.

Electronic Parameters

The main electronic parameters of the amines **4a**, **6a** and **10a** and the corresponding imines **4i**, **6i** and **10i** are shown in Table 2. Using quantum mechanical theory, an expression can be derived for the energy (ΔE) gained or lost when the orbitals of one reactant overlap with the orbitals of another. This equation, is known as the Fukui-Klopman-Salem (FKS)[33-35] equation ($\Delta E = Term_{Endoergic} + Term_{Charge} + Term_{Orbitalic}$).

According to the concept of HSBA (hard and soft acids and bases), first developed by Pearson[36-39] and later rigorously formalized in the frame of density functional theory,[40,41] a process will be charge-controlled when the number of electrons interchanged between the reactants of the chemical reaction (ΔN) is zero or nearly zero, and will be an orbital-controlled process when the mentioned ΔN is high. The equation to calculate ΔN of a chemical reaction A + B → C is the following:

TABLE 2. Electronic parameters of amines **4a**, **6a** and **10a** and imines **4i**, **6i** and **10i**.

Comp.	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE	ΔN	Q (eu) *Nendo*	[a]Qg (eu) *Nendo*	Q (eu) *Nexo*	[a]Qg (eu) *Nexo*	[b]$Coeff_{HOMO}$ *Nendo*	[b]$Coeff_{HOMO}$ *Nexo*
4a	-10.64	4.01	13.77	0.003	-0.647	-0.647	-0.769	-0.104	0.393	0.337
4iZ	-10.90	4.55	14.03	0.002	-0.800	-0.466	-0.656	-0.398	0.365	0.398
4iE	-10.79	4.51	13.93	0.003	-0.758	-0.413	-0.646	-0.383	0.376	0.395
6a	-11.19	3.95	14.33	0.014	-0.674	-0.674	-0.745	-0.067	0.397	0.341
6iZ	-11.21	4.50	14.35	0.005	-0.861	-0.508	-0.641	-0.377	0.371	0.391
6iE	-11.11	4.43	14.19	0.004	-0.821	-0.456	-0.631	-0.363	0.383	0.385
10a	-9.73	4.26	12.86	0.003	—	—	-0.776	-0.127		0.335
10iZ	-11.89	3.21	15.02	0.042	—	—	-0.569	-0.295		
10iE	-11.90	3.24	15.03	0.042	—	—	-0.559	-0.288		

[a] Global charge ($Q_g = Q_N + Q_{H1} + Q_{H2}$). [b] Coefficient of the HOMO orbital centered at this atom.

$$\Delta N = \frac{\chi_A - \chi_B}{2(\eta_A + \eta_B)} \quad \text{with} \quad \eta = \frac{-(E_{HOMO} - E_{LUMO})}{2} \quad \text{and} \quad \chi = \frac{-(E_{HOMO} + E_{LUMO})}{2}$$

The above expression was applied to the reaction between all the studied amines or imines and methyl iodide. As shown in Table 2, the calculated values of ΔN are close to zero which indicates that the methylation reaction should be a charge controlled process with the orbital term playing a minor role.

The electronic density values (Table 2) on the nitrogens of the amines (**4a**, **6a** and **10a**) and imines (**4i**, **6i** and **10i**) are high, consequently, these compounds should be good nucleophiles. Nevertheless, the global electronic density on the nitrogens or sum of the electronic densities of the nitrogen and the hydrogens attached to it ($Q_g = Q_N + Q_{H1} + Q_{H2}$) is not very high in all cases. According to this electronic parameter for the amines **4a** and **6a** the highest value of electronic density is located on the *endo* nitrogens (N3) whereas for the imines **4i**, **6i** and **10i** the highest electronic density is located on the *exo* nitrogens (N4). Thus, in a charge-controlled reaction, the methylation of amines **4a** and **6a** would take place on the N3 (*endo* nitrogen), and on the N4 (*exo* nitrogen) in the imines **4i** and **6i**. This is in agreement with the experimental results. Thus, methylation of compound **4**, which as previously mentioned, may exist in solution in all three possible tautomers (amine **4a** and imines **4i*E*** and **4i*Z***) and consequently the reaction is possible on both nitrogens, gives two products (compounds **7** and **8**, see scheme 4). The major compound **7** would arise from methylation of amine form **4a** (preferred tautomer) whereas the minor compound **8** would arise by methylation of imine forms **4i** (energetically less favourable). In the reaction of **6** with MeI only the methylated compound on the *endo* nitrogen (**9**) was obtained, resulting from alkylation of the amine form **6a** (the only tautomer present in solution). Finally, since, compound **10** only exists in solution as the amine tautomer (**10a**) and has no *endo* nitrogen, methylation does not occurr. Therefore, it might be assumed that the *exo* nitrogen only reacts through the imine form.

The HOMO energies (E_{HOMO}) of the amines (**4a**, **6a** and **10a**) are very low (< -9.73 eV), which correspond to amines with very low reactivity towards electrophiles.[42,43] The E_{HOMO} of the amines is slightly higher than that of the imines, indicating a slightly softer electronic behaviour[34,35] for the latter. According to

this electronic parameter, the order of reactivity should be **6a** < **4a** < **10a**. The reactivity of **6a** is much lower than that of **10a**, thus, the presence of a nitrogen at position-3 decreases the value of E_{HOMO}.

On the other hand, the HOMO electronic density distribution is the main electronic parameter which determines the regioselectivity of molecules on electrophilic reactions.[42,44] The highest value of the HOMO coefficients ($Coeff_{HOMO}$, Table 2) is located on the *endo* nitrogen (N3) for the amines **4a** and **6a** whereas, for the imine forms (**4i** and **6i**), the highest value of this coefficient is located on the *exo* nitrogen (N4). Therefore, if the electrophilic reaction is orbital-controlled, it would take place preferentially on the *endo* nitrogen for the amines and on the *exo* nitrogen for the imines. These results are in agreement with the experimental results of the methylation of **4** and **6**. Finally, the energy differences between the frontier orbitals of the amines or imines and methyl iodide ($\Delta E = E_{LUMO}$ MeI – E_{HOMO} amine or imine) are high, with values ranging from 12.86 eV for **10a** to 15.03 eV for **10iZ**, which indicates that the value of the orbitalic term in the FKS[33-35] equation should not be very important in comparison with the charge term. This result agrees with that obtained by using the Pearson treatment.

In conclusion, the experimental regioselectivity of the methylation of **4**, **6** and **10** can be established according to electronic parameters as electronic density (charge) and energy of HOMO orbital. Owing to the large energy gap between HOMO of the amines or imines and LUMO of the methyl iodide, the reactivity will be mainly determined by the electronic density.

The *ab initio* calculations were carried out with simplified structures of **4**, **6** and **10** without taking into consideration the rest of the sugar structure of these molecules (that on the other hand are too complex to be afordable by CPU-time consuming *ab initio* methods). Semiempirical quantum mechanical AM1[45] calculations were also performed with the same compounds, in order to compare the results of this method with those obtained by *ab initio* calculations. The results obtained were always comparable, giving the same differential reactivity regarding the molecular orbital energies. The same tendency found by *ab initio* regarding the values of the electronic densities on the nitrogens and calculated dipole moments was maintained. Hence, the semiempirical quantum mechanical method AM1 could be used to study other similar more complex spiro molecules, such as spiro sugars or spiro nucleosides that cannot be afforded by *ab ib initio* methods, to determine "*a priori*" their reactivity.

Experimental

General methods. Microanalyses (uncorrected) were obtained with a Heraeus CHN-O-RAPID instrument. NMR spectra were recorded on a Varian UNITY-500 spectrometer operating at 499.84 MHz (^{1}H), at 125.71 MHz (^{13}C) and at 50.66 MHz (^{15}N), using acetone-d_6 or DMSO-d_6 as solvent at 30°C. ^{1}H and ^{13}C monodimensional experiments were performed using standard conditions. HMQC[27] and HMBC[18] ^{1}H-^{13}C experiments were acquired with the following conditions: Data were collected in a 2048 x 512 matrix with a spectral width of 4350 Hz in the proton domain and 8000 Hz in the carbon domain, and processed in a 2048 x 1024 matrix. The experiment was optimized for one bond heteronuclear coupling constant of 160 Hz. The null time following the BIRD pulse was empirically optimized at 300 ms. The quaternary carbons were assigned from the HMBC[18] spectra. The experiments were optimized for long range coupling constants of 8 Hz and the data were processed using parameters very similar to those used in the HMQC experiments.HMQC ^{1}H-^{15}N experiments were acquired as follows: Data were collected in a 1024 x 512 matrix with a spectral width of 3635

Hz in the proton domain and 19324 Hz in the nitrogen domain. The experiment was optimized optimized for one bond heteronuclear coupling constant of 90 Hz. The null time following the BIRD pulse was empirically optimized at 100 ms. IR spectra were recorded with a Shimadzu IR-435 spectrometer.

Analytical TLC was performed on silica gel 60 F_{254} (Merck). Separations on silica gel were performed by preparative centrifugal circular thin layer chromatography (CCTLC) on a Chromatotron (Kiesegel 60 PF 254 gipshaltig (Merck)), layer thickness (1mm), flow rate (5 mL/min). Flash column chromatography was performed with silica gel 60 (230-400 mesh) (Merck).

Computational methods. Semiempirical calculations were performed using the original parameters of the program AM1[45] based on the restricted Hartree-Fock (RHF) method, included in MOPAC version 6.0,[45] using as graphics interface and data analysis the Cerius2 program.[46] This semiempirical method is commonly accepted to allow a better description of the lone-pair/lone-pair repulsion in several compounds.[47] Thus, the calculation of hypervalent molecules and heterocyclic compounds has been improved with respect to other semiempirical calculations. The MOPAC v 6.0 program ran on a Silicon Graphics Indigo2 R-10000 workstation.

Ab initio calculations were made with the Gaussian 94 v.D4 package[48] using as data and graphical interface the Cerius2 program. Through the Z-matrix input data from AM1 calculation, the geometry and the total electronic energy werecalculated by the RHF method with 6-31G(d,p) (RHF/6-31G**) basis set. The semiempirical and *ab initio* calculations wre carried out with full geometry optimization (bond lengths, bond angles and dihedral angles) without any assumption of symmetry for both methodologies.

Initial geometries were obtained by AM1 semiempirical calculations by means of MOPAC program included in the Cerius2 package. The results of these optimizations were used as input data for the semiempirical calculations. Geometries were optimized as internal coordinates. The optimization was stopped when Herbert or Peter tests were satisfied in the Broyden-Fletcher-Goldfarb-Shanno (BFGS) method.[49] The PRECISE option was applied for semiempirical calculations during the optimization process, with the gradient norm set to 0.01, whereas the FOPT keyword was used for all *ab initio* calculations. Mulliken population analyses[50] used to discuss the electronic distributions (charges) are adequate for present purposes since they reflect the trends in populations and charges which seem to be important rather than their actual values.

(5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-ribofuranose)-3-spiro-5'-(4'-amino-2'-oxazolone) (4)
To a solution of the cyanohydrin **3**[8] (0.5 g, 1.56 mmol) in dry CH_2Cl_2 (10 mL) was added CSI (0.15 mL, 1.71 mmol). The mixture was stirred at room temperature for 5h and then CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (20 mL) were added. After stirring at room temperature for 1h the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4) and filtered. The solvent was evaporated to dryness. The residue was purified by flash-column chromatography ($CHCl_3$ / MeOH, 25:1) to give spiro sugar **4** (0.431 g, 76%) as a white amorphous solid, m.p. 190 °C (decomp.); [Found: C, 56.04; H, 4.88; N, 7.66. $C_{17}H_{18}N_2O_7$ requires C, 56.35; H, 5.01; N, 7.73%]; $[\alpha]_D^{20}$ +1.7 (*c* 1, MeOH); ν_{max} (KBr) 3400, 3310, 1770, 1710, 1645 cm^{-1}; δ_H (Acetone-d_6) 1.36, 1.49 (6 H, 2 s, $(C\underline{H}_3)_2C$), 4.37 (1 H, dd, H-5a, $J_{a,b}$ 11.4, $J_{4,5a}$ 5.2 Hz), 4.59 (1 H, dd, H-5b, $J_{4,5b}$ 6.4 Hz), 4.75 (1 H, dd, 1H, H-4), 4.84 (1 H, d, H-2), 6.22 (1 H, d, H-1, $J_{1,2}$ 3.8 Hz), 7.32, 8.57 (2 H, 2 bs, NH_2-4'), 7.46-8.01 (5 H, m, OBz); δ_C ($CDCl_3$) 26.21, 26.43 [$(\underline{C}H_3)_2$-C], 60.84

(C-5), 74.58, 80.72 (C-2, C-4), 87.43 (C-3), 103.74 (C-1), 114.80 [$(CH_3)_2$-C], 128.47, 128.94, 129.84, 133.46 (C_6H_5), 165.17, 165.92 (CO ester, C-2'), 180.93 (C-4').

5-*O*-Benzoyl-3-*O* - c a r b a m o y l -3-*C*-cyano-1,2-*O*-isopropylidene-α-D-ribofuranose (5)

To a solution of **3**[8] (0.2 g, 0.62 mmol) in dry CH_2Cl_2 (5 mL), CSI (0.06 mL, 0.68 mmol) was added. The mixture was stirred at room temperature for 4h and then CH_2CL_2 (5 mL) and water (10 mL) were added. After stirring at room temperature for 30 min, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4), filtered and the solvent was evaporated *in vacuo*. The residue was purified by CCTLC on the chromatotron (CH_2Cl_2 / MeOH, 40:1), to give the *title compound* **5** (0.134 g, 60%) as a white foam. [Found: C, 56.16; H, 4.90; N, 7.68. $C_{17}H_{18}N_2O_7$ requires C, 56.35; H, 5.01; N, 7.73%]; $[\alpha]_D^{20}$ +1.3 (*c* 1, MeOH); ν_{max} (KBr) 3450, 3350, 2200, 1760, 1720cm^{-1}; δ_H (Acetone-d_6) 1.36, 1.49 (6 H, 2 s, $(C\underline{H}_3)_2C$), 4.54 (1 H, dd, H-4), 4.65 (1 H, dd, H-5a, $J_{a,b}$ 11.8, $J_{4,5a}$ 6.3 Hz), 4.72 (1 H, dd, H-5b, $J_{4,5b}$ 4.9 Hz), 5.31 (1 H, d, H-2), 6.13 (1 H, d, H-1, $J_{1,2}$ 3.9 Hz), 6.50, 6.80 (2 H, 2 bs, NH_2CO_2), 7.65 (5 H, m, OBz); δ_C (Acetone-d_6) 26.42, 26.88 [$(\underline{C}H_3)_2$-C], 63.14 (C-5), 76.61 (C-3), 77.61, 82.10 (C-2, C-4), 105.29 (C-1), 114.41 [$(CH_3)_2$-$\underline{C}$], 116.17 (CN), 129.45, 130.44, 134.25 (C_6H_5), 154.27 (O-CO-NH_2), 166.32 (CO ester).

(5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-ribofuranose)-3-spiro-5'-(4'-amino-1',2',3'-oxathiazole-2',2'-dioxide) (6)

To a solution of the cyanohydrin **3**[8] (0.5 g, 1.56 mmol) in dry dioxane (40 mL), sulfamoyl chloride[21] (0.72 g, 6.24 mmol) and a solution of DMAP in pyridine (up to pH≈8) were added. The reaction mixture was stirred at room temperature for 5 days. The solvent was evaporated to dryness, and the residue was purified by column chromatography (CH_2Cl_2 / MeOH, 20:1), to give 0.396 g (63%) of the *title compound* **6** as a white amorphous solid, m.p. 202 °C (decomp.); [Found: C, 48.13; H, 4.50; N, 6.88; S, 7.93. $C_{16}H_{18}N_2O_8S$ requires C, 48.24; H, 4.55; N, 7.03; S, 8.05%]; $[\alpha]_D^{20}$ +30.45 (*c* 0.5, MeOH); ν_{max} (KBr) 1665, 1360, 1180 cm^{-1}; δ_H (Acetone-d_6) 1.39, 1.59 (6 H, 2 s, $(C\underline{H}_3)_2C$), 4.60 (2 H, m, H-5), 4.77 (1 H, m, H-4), 4.97 (1 H, d, H-2), 6.24 (1 H, d, H-1, $J_{1,2}$ 3.8 Hz), 7.21, 8.47 (2 H, 2 bs, NH_2-4'), 7.45-8.06 (5 H, m, OBz); δ_C (Acetone-d_6) 26.44, 26.64 [$(\underline{C}H_3)_2$-C], 61.51 (C-5), 76.35, 81.16 (C-2, C-4), 91.54 (C-3), 105.01 (C-1), 115.22 [$(CH_3)_2$-$\underline{C}$], 129.02, 130.22, 134.22 (C_6H_5), 166.32, 167.66 (CO ester, C-4').

***(E* and *Z)* (5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-ribofuranose)-3-spiro-5'-(4'-imino-3'-*N*-methyl-oxazolidin-2-one) and (5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-ribofuranose)-3-spiro-5'-(4'-*N*-methylamino-2-oxazolone) (7*E*, 7*Z* and 8)**

To a solution of spiro oxazolone derivative **4** (0.1 g, 0.27 mmol) in dry acetone (6 mL), K_2CO_3 (0.019 g, 0.13 mmol) and MeI (0.07 mL) were added. The reaction mixture was heated to reflux, while additional portions of MeI (0.07 mL) were added at 2, 4, and 6 h. Volatiles were removed, and the residue thus obtained was dissolved in ethyl acetate (50 mL) and washed successively with aqueous $NaHCO_3$ (20 mL) and brine (20 mL) and dried (Na_2SO_4). After filtration and evaporation of the solvent, the residue was purified by CCTLC on the chromatotron (CH_2Cl_2 / acetone, 3:1). The fastest moving band afforded **7** (0.06 g, 58 %) as a white amorphous solid, that was a 1:1 mixture of the *E* and *Z* isomers. [Found: C, 57.38; H, 5.32; N, 7.42. $C_{18}H_{20}N_2O_7$ requires C, 57.44; H, 5.36; N, 7.44%]; ν_{max} (KBr) 3460, 1810, 1730, 1680 cm^{-1}; δ_H

(Acetone-d_6) 1.36, 1.57 (2s, $(C\underline{H}_3)_2C$), 2.98 (s, NCH_3 *E*), 3.00 (NCH_3 *Z*), 4.35 (dd, H-5b *E*, $J_{a,b}$ 11.7, $J_{4,5b}$ 6.4 Hz), 4.42 (dd, H-5b *Z*, $J_{a,b}$ 11.2, $J_{4,5b}$ 7.0 Hz), 4.58 (m, H-5a *E*, H-5a *Z*), 4.69 (pt, H-4 *E*), 4.76 (pt, H-4 *Z*), 4.72 (d, H-2 *Z*), 4.83 (d, H-2 *E*), 5.99 (d, H-1 *Z*, $J_{1,2}$ 3.4 Hz), 6.25 (d, H-1 *E*, $J_{1,2}$ 3.6 Hz), 7.50 (m, BzO-H*m*), 7.65 (m, BzO-H*p*), 7.94 (m, BzO-H*o*), 8.06, 8.36 (bs, NH *E*, NH *Z*); δ_C (Acetone-d_6) 26.0, 26.4 [$(\underline{C}H_3)_2C$], 26.2 (NCH_3 *Z*), 26.4 (NCH_3 *E*), 62.2 (C-5 *E*), 62.6 (C-5 *Z*), 75.8 (C-4 *E*), 76.7 (C-4 *Z*), 82.4 (C-2 *E*), 83.2 (C-2 *Z*), 87.2 (C-3' *E*), 87.6 (C-3' *Z*), 105.0 (C-1 *E*), 106.1 (C-1 *Z*), 115.3 [$(CH_3)_2$-*C*], 129.3 (C*m*), 130.0 (C*o*), 134.1 (C*p*), 155.3 (CO-2' *Z*), 155.7 (CO-2' *E*), 158.8 (C-4' *Z*, 161.8 (C-4' *E*), 166.2 (CO ester).

The next moving band gave 0.016g (15 %) of **8** as a white foam. [Found: C, 57.40; H, 5.31; N, 7.40. $C_{18}H_{20}N_2O_7$ requires C, 57.44; H, 5.36; N, 7.44%]; $[\alpha]_D^{20}$ +11 (*c* 0.5, MeOH); ν_{max} (KBr) 3340, 1770, 1730, 1615 cm^{-1}; δ_H (DMSO-d_6) 1.30, 1.53 (6 H, 2 s, $(C\underline{H}_3)C$), 2.85 (3 H, s, NCH_3), 4.25 (1 H, dd, H-5b, $J_{a,b}$ 11.9, $J_{4,5b}$ 4.4 Hz), 4.46 (1 H, dd, H-5a, $J_{4,5a}$ 6.0 Hz), 4.59 (1 H, dd, H-4), 4.78 (1 H, d, H-2), 6.12 (1 H, d, H-1, $J_{1,2}$ 3.7 Hz), 7.52 (2 H, m, BzO-H*m*), 7.67 (1 H, m, BzO-H*p*), 7.91 (2 H, m, BzO-H*o*), 8.32 (1 H, bs, NH-4'); δ_C (DMSO-d_6) 26.19, 26.29 [$(\underline{C}H_3)_2C$], 30.22 (NCH_3), 60.80 (C-5), 74.18 (C-4), 80.04 (C-2), 86.56 (C-3), 103.48 (C-1), 113.37 [$(CH_3)_2$-$\underline{C}$], 128.76 (C*m*), 129.37 (C*o*), 133.73 (C*p*), 164.55 (CO-2'), 165.12 (CO ester), 177.77 C-4').

The slowest moving band afforded 0.020 g (20 %) of unreacted starting material (**4**).

(*E,Z*) (5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-ribofuranose)-3-spiro-5'-(4'-imino-3'-*N*-methyl-1',2',3'-oxathiazolidine-2',2'-dioxide) (9)

Compound **6** (0.18 g, 0.45 mmol) was dissolved in dry acetone (12 mL) and K_2CO_3 (32 mg, 0.23 mmol) and MeI (0.10 mL) were successively added, and the mixture was heated to reflux. Additional portions of MeI (0.10 mL) were added after 1 and 3 h. After 4 h from starting, volatiles were removed. The residue was dissolved in ethyl acetate (100 mL) and successively washed with aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by CCTLC on the chromatotron (CH_2Cl_2 / acetone, 15:1), to afford the *title compound* **9** (0.167 g, 90 %) as a white foam. [Found: C, 49.49; H, 4.85; N, 6.75; S, 7.75. $C_{17}H_{20}N_2O_8S$ requires C, 49.51; H, 4.89; N, 6.79; S,7.78%]; ν_{max} (KBr) 3390, 1730, 1645, 1360, 1190 cm^{-1}; δ_H (Acetone-d_6) 1.39, 1.60 (6 H, 2 s, $(C\underline{H}_3)_2C$), 3.02 (3 H, s, NCH_3), 4.52 (1 H, dd, H-5b, $J_{a,b}$ 12.4, $J_{4,5b}$ 7.1 Hz), 4.62 (1 H, dd, H-5a, $J_{4,5a}$ 3.4 Hz), 4.75 (1 H, dd, H-4), 4.94 (1 H, d, H-2), 6.19 (1 H, d, H-1, $J_{1,2}$ 3.9 Hz), 7.40 (1 H, bs, NH-4'), 7.52 (2 H, m, BzO-H*m*), 7.66 (1 H, m, BzO-H*p*), 8.04 (2 H, m, BzO-H*o*); δ_C (Acetone-d_6) 25.59, 25.82 [$(\underline{C}H_3)_2C$], 30.21 (NCH_3), 60.59 (C-5), 75.51 (C-4), 80.31 (C-2), 90.44 (C-3), 104.06 (C-1), 114.36 [$(CH_3)_2$-$\underline{C}$], 128.59 (C*m*), 129.36 (C*o*), 133.43 (C*p*), 165.78 (C-4').

(5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-ribofuranose)-3-spiro-5'-(4'-amino-1',2'-oxathiole-2',2'-dioxide) (10)

To a solution of **1**[6] (0.20 g, 0.5 mmol) in THF (4 mL), TBAF • $3H_2O$ (0.173 g, 0.55 mmol) was added. The mixture was stirred at room temperature for 30 min. It was then filtered through wet silica gel in THF and further eluted with acetone. The filtrate was evaporated under reduced pressure and co-evaporated with pyridine. The residue was dissolved in dry pyridine (4mL) and benzoyl chloride (0.064 mL, 0.55 mmol) was added. The mixture was stitrred at room temperature overnight. Solvents were removed and the residue was

purified by CCTLC on the chromatotron (CH_2Cl_2 / MeOH, 20:1) to afford 0.155 g (78 %) of **10** as a white solid, m.p. 196 °C (decomp.); [Found: C, 51.03; H, 4.73; N, 3.38. $C_{17}H_{19}NO_8S$ requires C, 51.38; H, 4.82; N, 3.52%]; $[\alpha]_D^{20}$ +0.5 (*c* 1, MeOH); ν_{max} (KBr) 3440, 3240, 1720, 1660, 1340, 1160 cm^{-1}; δ_H (Acetone-d_6) 1.38, 1.58 (6 H, 2s, $(CH_3)_2C$), 4.57 (2 H, d, H-5), 4.70 (1 H, t, H-4, $J_{4,5}$ 5.2 Hz), 4.85 (1 H, d, H-2), 5.76 (1 H, s, H-3'), 6.10 (1 H, bs, NH_2-4'), 6.16 (1 H, d, H-1, $J_{1,2}$ 3.8 Hz), 7.50-8.06 (5 H, m, BzO).

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