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Synthesis, structural characterization and conformational aspects of nostoclidade analogues

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\textbf{Abstract}

The synthesis and structural analysis of a set of nostoclidade analogues with potential herbicide activity is described. The influence of intra- and intermolecular hydrogen bonding, as well as other interactions on the conformation and packing of the compounds is thoroughly described using DFT calculations and single crystal X-ray diffraction analyses. All lactones exhibited the \(Z\) configuration as confirmed by NOESY experiments and by single crystal X-ray diffraction measurements.

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\section{1. Introduction}

Marine organisms are capable of producing a myriad of structurally diverse secondary metabolites \cite{1}. More than 17,000 compounds have been described from marine sources \cite{2} including compounds from polar habitats \cite{3}. Alongside exploring the diversity found among the marine natural products for drug development \cite{4}, these metabolites can also be explored either as herbicides or novel lead structures towards the development of weed controllers \cite{5}.

The metabolites known as nostoclidades \textsuperscript{(1)} (Fig. 1) were first isolated in 1993 by Yang and co-workers. They are produced by a cyanobacterium (or blue-green algae; \textit{Nostoc} sp.), which can live free or in symbiosis, for instance, in the lichen \textit{Peltigera canina} \cite{6}, and belong to a family of compounds known as \(\gamma\)-alkylidenebutenolides \cite{7}. The nostoclidades \textsuperscript{(1)} resemble the substance cyanobacterin \textsuperscript{(2)} (Fig. 1), a lactone that is capable of inhibiting the photosynthetic electron transport in isolated chloroplasts \cite{8}.

Because of the structural similarity between the nostoclidades \textsuperscript{(1)} and cyanobacterin \textsuperscript{(2)}, we have considered the former as a potential new lead for herbicide development. As a consequence, a variety of nostoclidade analogues [general structures \textsuperscript{(3)} and \textsuperscript{(4)}, Fig. 1] have been synthesized. Their biological activities were evaluated \textit{in vitro} as the ability to interfere with light-driven reduction of ferrocyanide by isolated spinach chloroplasts \cite{9}. Several compounds exhibited inhibitory properties in the micromolar range against the basal electron flow from water to K\textsubscript{3}[Fe(CN)\textsubscript{6}]. Moreover, several of the synthesized analogues were submitted to \textit{in vitro} evaluation against different cancer cell lines using the MTT assay. Some of the evaluated compounds exhibited moderate cytotoxicity against at least one of the cell lines \cite{10}.

In addition to biological property studies, we have also been interested in the molecular properties of the nostoclidade analogues. In a previous paper \cite{11}, a combined study using XRD techniques and DFT calculations was carried out to characterize two nostoclidade analogues [compounds \textsuperscript{(5)} and \textsuperscript{(6)}, Fig. 1] namely 5(\(Z\))-3-benzyl-5-(1,3-dioxalanebenzylidene)furan-2(5\(H\))-one \textsuperscript{(5)} and 5(\(E\))-3-benzyl-5-(2,4,6-trimethoxybenzylidene)furan-2(5\(H\))-one \textsuperscript{(6)}. In order to get further insight into the molecular properties of this type of lactone, we conducted an investigation on a series of nostoclidade analogues employing a combination of NMR analyses, DFT calculations and XRD techniques. Herein we describe the results of this investigation.

\section{2. Experimental}

\subsection{2.1. Materials and methods}

All reactions were carried out under a protective atmosphere of dry nitrogen. Dichloromethane, tetrahydrofuran (THF), diethyl
ether, and amines were purified as described by Perrin and Armarego [12]. Commercially tert-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf), 8-diazabicyclo [5.4.0] undec-7-ene (DBU), and phosphoryl chloride (POCl3) were purchased from Aldrich and used without further purification. The compound 3-bromobenzaldehyde was prepared from the corresponding commercially available (Aldrich) benzylic alcohol by Swern oxidation [13]. Other aldehydes were purchased from Aldrich and used without further purifications. The preparation of the silylenol ethers from 2-hydroxybenzaldehyde and 3-hydroxybenzaldehyde was carried out by methodology previously described [14]. Lactone (7) was synthesized employing methodology described by Nasmann [15]. Commercially available n-butyllithium hexane solutions (1.6 mol L⁻¹) were titrated prior to use [16]. The 1H and 13C NMR spectra were recorded on Bruker AVANCE DRX400 spectrometer at 400 and 100 MHz. Mass spectra were recorded on a SHIMADZU GCMS-QP5050A instrument under electron impact (70 eV) conditions. IR spectra were recorded on a SHIMADZU GCMS-QP5050A instrument. T 1H and 13C NMR spectra were recorded on a Bruker AVANCE DRX400 spectrometer at 400 and 100 MHz. Mass spectra were recorded on a SHIMADZU GCMS-QP5050A instrument under electron impact (70 eV) conditions. IR spectra were recorded on a SHIMADZU GCMS-QP5050A instrument.

2.2. Synthesis of (5Z)-3-benzyl-5-(3-hydroxybenzylidene)furan-2(5H)-one (10)

To a two-neck round bottom flask, under nitrogen atmosphere, were added 3-benzylfuran-2-(5H)-one (7) (150 mg, 0.86 mmol), anhydrous dichloromethane (4 mL), TBDMSOTf (250 µL, 1.03 mmol), diisopropylethylamine (450 µL, 2.58 mmol) and m-tolualdehyde (124 mg, 1.03 mmol). The resulting mixture was stirred at room temperature for 1 h. After adding DBU (260 µL, 1.72 mmol), the reaction mixture was refluxed for an additional 3 h and dichloromethane (70 mL) was added. The resulting organic layer was washed with 3 mol L⁻¹ HCl aqueous solution (2 × 25 mL) and brine (25 mL). After separation, the organic layer was dried over MgSO4, filtered, and concentrated under reduced pressure. The resulting material was purified by column chromatography on silica gel eluted with hexane–dichloromethane (2:1 v/v) to afford compound (10) as a white solid in 66% yield (156 mg, 0.57 mmol).

Compounds (11) and (12) were prepared employing a similar procedure to that described for compound (10) using 3-bromobenzaldehyde and 2-chloro-4-(NN-dimethylamino)benzaldehyde to yield compounds (11) and (12), respectively, as presented in Fig. 2. Spectroscopic data for compounds (10–12) are available in Supplementary material.

2.3. Synthesis of (5Z)-3-benzyl-5-(3-hydroxybenzylidene)furan-2(5H)-one (13)

A 25 mL round bottom flask, under nitrogen atmosphere, was charged with 3-tert-butyldimethylsilyloxybenzaldehyde (0.243 g, 1.03 mmol), 3-benzylfuran-2-(5H)-one (7) (150 mg, 0.86 mmol), anhydrous dichloromethane (4 mL), TBDMSOTf (250 µL, 1.03 mmol) and diisopropylethylamine (450 µL, 2.58 mmol). The resulting mixture was stirred at room temperature for 1 h and after some time DBU (260 µL, 1.72 mmol) was added. The reaction mixture was then refluxed for a further 3 h before addition of dichloromethane (70 mL). The resulting organic layer was washed with 3 mol L⁻¹ aqueous HCl solution (2 × 25 mL) and brine (25 mL). After separation, the organic layer was dried over MgSO4, filtered, and concentrated under reduced pressure to afford pale yellow oil. To this oil, placed in a plastic flask, was added 3 mL of MeCN/HF (1:1 v/v) solution. The resulting mixture was stirred at room temperature for 3 h and then transferred to a separatory funnel containing ethyl acetate (80 mL). The layers were separated and the organic layer was washed with saturated sodium bicarbonate solution (3 × 25 mL). The aqueous extracts were combined and the resulting aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried over MgSO4, filtered, and concentrated under reduced pressure. The resulting crude product material was purified by silica gel column chromatography eluted with hexane–ethyl acetate (2:1 v/v)
to afford compound (13) as a yellow solid in 78% yield (187 mg, 0.67 mmol).

Compound (14) was prepared employing a similar procedure to that described for compound (13) and yield is presented in Fig. 2. Spectroscopic data for compounds (13) and (14) are available in Supplementary material.

Crystals of compounds (10–14) were obtained by gently warming each compound in hexane, followed by addition of dichloromethane dropwise until the solid was completely dissolved. The resulting solution was left undisturbed at room temperature. After 24 h, white [prisms for compound (10); needles for compound (11)] and yellow [prisms for compounds (12–14)] crystals, suitable for X-ray analyses, were formed. They were separated, washed with cold hexane, and dried.

2.4. X-ray Crystallography

Fig. 2. Scheme for the synthesis of the nostoclide analogues (10–14). (i) DBU, CH2Cl2, reflux (compounds 10, 11, and 12), (ii) DBU, CH2Cl2, reflux then MeCN/HF (1:1) (compounds 13 and 14).

Table 1: Crystal data and structure refinement for compounds 10–14 (R = 3-ethylphenyl; Y = 3-methylphenyl, 3-bromophenyl, 2-chloro-4-dimethylaminophenyl, 3-hydroxyphenyl, 2-hydroxyphenyl; X = TBDMSO, P, NEt2; Ar = 3-methylphenyl, 3-bromophenyl, 2-chloro-4-dimethylaminophenyl, 3-hydroxyphenyl, 2-hydroxyphenyl).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar Group</th>
<th>Yield*(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>3-methylphenyl</td>
<td>66</td>
</tr>
<tr>
<td>11</td>
<td>3-bromophenyl</td>
<td>33</td>
</tr>
<tr>
<td>12</td>
<td>2-chloro-4-dimethylaminophenyl</td>
<td>16</td>
</tr>
<tr>
<td>13</td>
<td>3-hydroxyphenyl</td>
<td>78</td>
</tr>
<tr>
<td>14</td>
<td>2-hydroxyphenyl</td>
<td>74</td>
</tr>
</tbody>
</table>

*Yields based on compound (7)
The molecular conformation analyses of (10–14) were carried out using the MOGUL [25], a knowledge base of molecular geometry derived from the CSD-Cambridge Structural Database that provides rapid access to information on the preferred values of bond lengths, valence angles and acyclic torsion angles (see Supplementary material) [26]. It was found that all bond lengths and bond angles are in agreement with the expected values. The main differences occurred in the acyclic torsion angles, which are influenced either by intermolecular or intramolecular forces.

Crystallographic data for the structures in this paper have been deposited in the Cambridge Crystallographic Data Centre as a Supplementary publication (10, CCDC 665352; 11, CCDC 665353; 12, CCDC 665354; 13, CCDC 665355; 14, CCDC 665356). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB1 2EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

2.5. Computational details

To determine the most stable conformers for each derivative, the semi-empirical AM1 procedure [27] was employed using the conformation distribution subroutine of the TITAN software [28]. The six most stable, albeit not identical conformers in each case were fully optimized at the DFT level using the B3LYP functional [29] with the 6-31g(d) basis set [30]. Relative energies are given at this level. Solvent effects were evaluated by reoptimization of the geometries using the CPCM continuum solvation model [31], again with the B3LYP/6-31g(d) combination. Solvent effects were simulated in water and in n-heptane. All DFT calculations were carried out using the Gaussian03W software package [32].

3. Results and discussion

As previously reported [11], the synthesis of compounds (10–14) was accomplished via the vinylogous aldol reaction between the silyloxy diene furan synthon and the appropriate aldehydes. Briefly, reaction of lactone (7), prepared as shown in Fig. 2, with pertinent aldehydes in the presence of tert-butylidimethylsilyltri-fluoromethanesulfonate and diisopropylketylamine followed by treatment of the silyl ether generated in situ with DBU afforded compounds (10–14) in yields ranging from 16% to 78% (Fig. 2). It is important to note that in the preparation of compounds (13) and (14), tert-butylidimethylsilyloxy aldehydes were employed. After various attempts, the removal of the tert-butylidimethylsilyl protecting group was achieved with a mixture of MeCN/HF (1:1 v/v) [33].

The identity of the synthesized lactones (10–14) was confirmed based on spectroscopic (NMR and IR) as well as spectrometric (MS) data. The presence of the correlation peak from H4 and H6 in the NOESY contour plots of the lactones led to the Z configuration assignment concerning the exocyclic double bounds. This stereochemical assignment was unambiguously confirmed by single crystal X-ray diffraction. Table 1 summarizes the main crystallographic data for compounds (10–14).

It is important to note that lactone (11) crystallizes in the noncentrosymmetric space group Pca21 with two independent molecules in the asymmetric unit hereafter labeled as (11A) and (11B) (Fig. 3). Comparison of these molecules by the method of Kabsch shown them to be very similar, related by improper non-crystallographic symmetry (the approximate rotational matrix is $-1000-10.00-1$ and with a root mean square deviation between the 21 homologous atoms of 0.1 Å. These facts suggested that the crystal could belong to a centrosymmetric space group, with just one molecule per asymmetric unit. Closer scrutiny, however, showed this not to be the case, since the affin transformation (rotation + translation) relating the two moieties did not match any of those belonging to another space group. The refined Flack parameter observed for compound (11) is 0.48(1). Therefore, compound (11) can be considered an inversion twin, which consists of centrosymmetrically related crystalline domain. The symmetry operation relating domain structures is that of a center of inversion operation relating domain structures is that of a center of inversion

Table 1

<table>
<thead>
<tr>
<th>Compounds</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C10H12O2</td>
<td>C10H14BrO4</td>
<td>C10H17ClN2O2</td>
<td>C7H11O2</td>
<td>C6H11O2</td>
</tr>
<tr>
<td>Formula weight</td>
<td>276.32</td>
<td>682.39</td>
<td>339.80</td>
<td>278.29</td>
<td>278.29</td>
</tr>
<tr>
<td>Temperature</td>
<td>298(2)</td>
<td>150(2)</td>
<td>298(2)</td>
<td>298(2)</td>
<td>298(2)</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
<td>Orthorhombic</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21 21 21</td>
<td>Pca21</td>
<td>P21/c</td>
<td>P21/c</td>
<td>P21</td>
</tr>
<tr>
<td>Unit cell (Å)</td>
<td>a = 6.1227(4)</td>
<td>b = 13.6325(4)</td>
<td>c = 17.601(1)</td>
<td>c = 35.270(1)</td>
<td>c = 6.7234(3)</td>
</tr>
<tr>
<td>Volume (Å³)</td>
<td>1484.3(2)</td>
<td>2858.8(2)</td>
<td>1714.0(1)</td>
<td>1440.7(1)</td>
<td>708.56(8)</td>
</tr>
<tr>
<td>Density (Mg/m³)</td>
<td>1.236</td>
<td>1.585</td>
<td>1.317</td>
<td>1.283</td>
<td>1.304</td>
</tr>
<tr>
<td>μ (mm⁻¹)</td>
<td>0.079</td>
<td>2.877</td>
<td>0.234</td>
<td>0.087</td>
<td>0.088</td>
</tr>
<tr>
<td>F(000)</td>
<td>584</td>
<td>1376</td>
<td>712</td>
<td>584</td>
<td>292</td>
</tr>
<tr>
<td>Crystal size (mm³)</td>
<td>0.05 × 0.17 × 0.23</td>
<td>0.03 × 0.05 × 0.31</td>
<td>0.14 × 0.25 × 0.29</td>
<td>0.06 × 0.15 × 0.20</td>
<td>0.08 × 0.10 × 0.14</td>
</tr>
<tr>
<td>θ Range (°)</td>
<td>3.18 to 27.53</td>
<td>3.05 to 25.68</td>
<td>2.94 to 26.02</td>
<td>2.97 to 27.46</td>
<td>3.25 to 26.59</td>
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<tr>
<td>Reflections collected</td>
<td>7316</td>
<td>24302</td>
<td>12518</td>
<td>17530</td>
<td>8569</td>
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<tr>
<td>Independent reflections</td>
<td>1946</td>
<td>5398</td>
<td>3326</td>
<td>3057</td>
<td>1558</td>
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<tr>
<td>R(int)</td>
<td>0.0459</td>
<td>0.0811</td>
<td>0.0579</td>
<td>0.0639</td>
<td>0.0607</td>
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<tr>
<td>Completeness to θmax</td>
<td>98.5 %</td>
<td>99.9%</td>
<td>98.4%</td>
<td>93.1%</td>
<td>97.1%</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>1946/0/190</td>
<td>5398/1/380</td>
<td>3326/0/217</td>
<td>3057/0/194</td>
<td>1558/1/194</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.018</td>
<td>0.993</td>
<td>1.025</td>
<td>1.019</td>
<td>1.059</td>
</tr>
<tr>
<td>Final R indices</td>
<td>R₁ = 0.0486,</td>
<td>R₁ = 0.0399,</td>
<td>R₁ = 0.0474,</td>
<td>R₁ = 0.0497,</td>
<td>R₁ = 0.0624,</td>
</tr>
<tr>
<td>R₁ [Z ref]</td>
<td>wR₂ = 0.1174</td>
<td>wR₂ = 0.0835</td>
<td>wR₂ = 0.1238</td>
<td>wR₂ = 0.1294</td>
<td>wR₂ = 0.0915</td>
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<tr>
<td>R indices (all data)</td>
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<td>R₁ = 0.0551,</td>
<td>R₁ = 0.0828,</td>
<td>R₁ = 0.0737,</td>
<td>R₁ = 0.0624,</td>
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<tr>
<td></td>
<td>wR₂ = 0.1381</td>
<td>wR₂ = 0.0893</td>
<td>wR₂ = 0.1398</td>
<td>wR₂ = 0.1500</td>
<td>wR₂ = 0.1026</td>
</tr>
<tr>
<td>Δρmax and Δρmin (e Å⁻³)</td>
<td>0.158 and –0.167</td>
<td>1.173 and –0.413</td>
<td>0.232 and –0.242</td>
<td>0.118 and –0.121</td>
<td>0.117 and –0.115</td>
</tr>
</tbody>
</table>

similar (Fig. 3), only structure (11A) will be discussed in terms of intramolecular geometry.

In spite of not having the property of chirality, the compounds (10) and (14) spontaneously crystallized into the chiral space group under the aforementioned re-crystallization conditions. In fact, a number of space groups that strongly favors molecules with symmetry C1 are chiral. Thus, an enantiomerically pure substance can be obtained when a molecule that does not possess an inversion centre or mirror plane crystallizes in a chiral space group. However, any molecule (possessing any symmetry) may crystallize in a chiral crystal structure [35], and there is hundreds of known chiral crystal structures formed of achiral molecules [36]. Examining the space-group preference in the CSD [26] (updated JAN 2008), in which can be found more than 430,000 structures deposited, it is noted that the majority of the organic compounds can be found within one of three space groups, P21/c, P21, and P212121. This skewed distribution, which contain the two chiral space groups observed for (10) and (14), is related to the presence of specific symmetry elements within these space groups that, in turns, optimize intermolecular interactions between neighboring molecules [36].

It is important to note that (14) can be considered a donor-acceptor π-electron chromophore having conjugated bridges, which is a requirement for molecular compounds to exhibit second order non-linear optical (NLO) properties. More recently, organic materials are under investigation since their potential NLO efficiency is significantly higher than that of inorganic ones. Another obligatory requirement for NLO materials is non-centrosymmetric orientation of polar molecules in bulk samples [37]. This requirement might be achieved by creating acentric crystal structures, which is considered a challenging goal in crystal engineering applied to crystalline NLO materials. Since this requirement is achieved by the molecule (14), it can be considered a promising chromophore for opto-electronic applications.

In the structural investigation carried out with compounds 5(Z)-3-benzyl-5-(1,3-dioxalanbenzylidene)furan-2(5H)-one (5) and 5(E)-3-benzyl-5-(2,4,6-trimethoxybenzylidene)furan-2(5H)-one (6) (Fig. 1), it was demonstrated that the fact the isomers 5Z and 6E are found within the solid state, is not the result of supramolecular forces, but rather is due to the fact that these two structures being the lowest energy forms [11]. In the present investigation, compounds (10–14) were obtained as Z stereoisomers, as exemplified in Fig. 4 for compound (10).

The weak non-classical intramolecular hydrogen bond involving C6–H6...O2, shown in Fig. 4 (single dotted line), is a common feature for all the remaining structures investigated (Table 2) as well as for compound (5) (Fig. 1). Therefore, this hydrogen-bonding motif appears to play an important role in the stabilization of the Z isomer. For compound (6) (Fig. 1), the presence of the methoxy groups attached to the ortho positions precludes the formation of the hydrogen bond aforementioned leading to the adoption of the E configuration.

The NOESY experiments showed one important aspect with respect to compounds (12) and (14). The expected NOE correlation peak from H2 and H6 was not observed. It was hypothesized that this fact should be related to a preferential conformation attained by the compounds. In order to alleviate the non-bonding steric repulsion between the O–I electronic lone pairs and the X ortho group, the aforementioned compounds preferentially attain conformation II (Fig. 5). In this conformation, the distance between the hydrogen atoms H2 and H6 is longer when compared with the corresponding distance in conformation I. Thus, the cross-peak between these hydrogen atoms is not observed. To shed light on this proposal, DFT calculations and XRD analyses were carried out.

DFT calculations, conducted with compounds (12) and (14), revealed a divergent behavior in the gas phase. As predicted in the case of (12), steric interactions (or Pauli repulsion) between the two electronegative chlorine and oxygen atoms strongly destabilize conformation I (Fig. 5) by 6.8 kcal mol⁻¹. On the other hand, in the case of the hydroxyl substituted derivative (14), conformation I is more stable than conformation II by 1.7 kcal mol⁻¹. In this case, a strong hydrogen bond between the hydrogen of the hydroxyl group and the oxygen atom of the lactone group is responsible for this preferential stabilization. This order of stability is contrary to that found in the solid state by crystallographic XRD analyses.
(vide infra). One reason to this divergence may be found in the medium effect, although supramolecular interactions in the solid state may also operate. Therefore we decided to calculate solvent effects on the relative stability of the several conformations.

Solvent effects were calculated in both polar (water) and non-polar (n-heptane) solvents. While differential solvation effects are negligible for compound (12), with both solvents changing relative stabilities by no more than 0.4 kcal mol$^{-1}$, for compound (14), the solvent effect is relatively large. Even in the non-polar solvent n-heptane conformation II becomes more stable by 0.4 kcal mol$^{-1}$. The preferential stabilization of conformation II is much stronger in the case of the polar solvent water. In this solvent, conformation II is more stable by 3.4 kcal mol$^{-1}$ therefore completely reversing the stability order. This result comes from differential solvation of both conformers. While the solvation energy (in water) of conformation II is 16.8 kcal mol$^{-1}$, for conformation I, it is only 11.7 kcal mol$^{-1}$. Based on these results, we were led to conclude that a hydrogen bond between the ortho hydroxyl substituent and the lactone oxygen atom stabilizes conformation I in the gas phase. This stabilization vanishes in a non-polar solvent, however, and is reversed in the case of a polar solvent, where conformation II is more stable.

The most stable conformer (Conformer II, Fig. 5) was found within the crystal structure of compounds (12) and (14), as exemplified in Fig. 6 for compound (12). The presence of the most stable conformer can be ascribed to the hindrance effect that keeps the substituent away from O2 atom, and to the formation of the intra-molecular hydrogen bond C6–H6...O2 (Table 2) and is much stronger in the case of a polar solvent, where conformation II is more stable.

Table 2
Main hydrogen bonding for nostoclide derivatives (10–14) (Å$^1$). Others non-classical H bonds that stabilized the packing are shown in the Supplementary material figures

<table>
<thead>
<tr>
<th>Lactone</th>
<th>D–H...A</th>
<th>H...A</th>
<th>D...A</th>
<th>D–H...A</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>C6–H6...O2</td>
<td>2.340</td>
<td>2.970(4)</td>
<td>124</td>
</tr>
<tr>
<td>11A</td>
<td>C6–H6...O2</td>
<td>2.380</td>
<td>3.009(6)</td>
<td>125</td>
</tr>
<tr>
<td>12</td>
<td>C6–H6...O2</td>
<td>2.420</td>
<td>3.012(2)</td>
<td>122</td>
</tr>
<tr>
<td>12</td>
<td>C7–H7...O1$^i$</td>
<td>2.564</td>
<td>3.343(2)</td>
<td>149</td>
</tr>
<tr>
<td>12</td>
<td>C9–H9...O1$^i$</td>
<td>2.608</td>
<td>3.343(2)</td>
<td>136</td>
</tr>
<tr>
<td>13</td>
<td>C6–H6...O2</td>
<td>2.320</td>
<td>2.957(2)</td>
<td>125</td>
</tr>
<tr>
<td>13</td>
<td>O3–O3...O1$^i$</td>
<td>1.853</td>
<td>2.802(2)</td>
<td>169</td>
</tr>
<tr>
<td>14</td>
<td>C6–H6...O2</td>
<td>2.310</td>
<td>2.955(4)</td>
<td>126</td>
</tr>
<tr>
<td>14</td>
<td>O3–O3...O1$^i$</td>
<td>1.810</td>
<td>2.787(4)</td>
<td>167</td>
</tr>
<tr>
<td>14</td>
<td>C14$^{iii}$–H14$^{iii}$...O1</td>
<td>2.962</td>
<td>3.674(2)</td>
<td>133</td>
</tr>
<tr>
<td>14</td>
<td>C17$^{v}$–H17$^{v}$...Ct</td>
<td>3.075</td>
<td>3.827(4)</td>
<td>139</td>
</tr>
</tbody>
</table>

* Symmetry codes for (12), (13), and (14) as in Figs. 7, 10, and 11, respectively.

Fig. 6. ORTEP-3 view of (12) showing the arbitrary atom labelling. Ellipsoids represent 30% probability level. The intramolecular H bond is shown as single dotted line.

Fig. 7. ORTEP-3 view of (12) showing two neighboring molecules (symmetry code: x, y–1, z). Ellipsoids represent 30% probability level. The intermolecular H bonds are shown as single dotted line.
2) are the structural features responsible for maintaining the coplanarity of the rings A and C.

Compound (12) is an exception to the generalization mentioned above. In this case, the lack of planarity between the rings A and C was attributed to the presence of the bulky chlorine atom attached to the ortho position in the C ring, which gives rise to a hindrance effect between neighbor molecules in the crystalline solid state (Fig. 7). If all atoms in the rings A and C were in a plane, the intramolecular distance Cl...O2 (i = x, y = -1, z) would become very short, < 3 Å. The chlorine and oxygen atoms have van der Waals radii equal to 1.90 and 1.50 Å, respectively [38]. Since no hydrogen is present between these two electronegative atoms, the distance Cl...O2 cannot fall below that expected from the van der Waals radii sum (~ 3.4 Å). As a consequence, in spite of being individually planar, the least-squares plane through the phenyl C ring (Rms deviation of fitted atoms = 0.0058 Å) forms an angle of 19.2(1)° with the least-square plane) passing through the lactone A ring (Rms deviation of fitted atoms = 0.0062 Å. In this way, the chlorine atom deviates 1.031(1) Å from the individual least-square plane through A ring resulting in a distance Cl...O2 equal to 3.496(2) Å, which is greater than the sum of their van der Waals radii. The break of the extended electron delocalization cannot be invoked to explain the aforementioned absence of planarity since the

bond lengths and bond angles found for compound (12) do not differ significantly when compared with the structures of the other derivatives investigated regarding the moiety involving the dihedral angle C8—C7—C1—C2 (see Supplementary material).

Similar to what was previously described for compounds (12) and (14), two preferential conformers may be considered regarding the orientation of the meta substituent attached to the C ring, one with the substituent faced to the lactone ring, and the other one with the substituent faced to the opposite direction (Fig. 8).

Regarding compound (10), DFT calculations found that there is no remarkable energy difference between the conformers III and IV. On the other hand, for compound (11) conformer IV is more stable by 0.3 kcal mol⁻¹, while for compound (13) conformer III is more stable by 1.0 kcal mol⁻¹. Although the energy differences are small, it is worth to note that the most stable conformer in each case [compounds (11) and (13)] nicely fits the experimental X-ray diffraction observation, as observed in Fig. 3 for compound (11).

Even though there is some agreement between the results found by DFT calculations in gas phase and XRD analysis, it seems that the presence of conformer III or IV (Fig. 8) in the crystal structure of compounds (10), (11), and (13) is a result of crystal packing forces or intermolecular bonding motifs as depicted in Fig. 9 for compound (11) [crystal packing figures for compounds (10) and (13) can be found in the Supplementary material].

It is observed that the substituent attached to the C ring plays an important role in the formation of the double chains for the nostoclide derivatives (10) and (11). For compound (13), the formation of a 16-fold ring, leading to a planar dimer, seems to be responsible for the most stable conformer observed (Fig. 10).

The conformational behavior of nostoclide analogues (10–14) is determined not only by rotation around the Cl—C6 single bond but also by rotation around the C3—C7 bond. The several conformers obtained by rotation around the latter single bond have relative energies that differ by less than 0.4 kcal mol⁻¹. The gas-phase calculations for the derivatives (10–14) showed that in the most stable arrangement they assume a conformation where the C4—C3—C7—C1' dihedral angle is near or equal to 0.0°. This result is significantly different from the results found by XRD analyses. The observed dihedral angles are −25.1(4)° [compound (10)], −91.4(8)° [compound (11)], −99.4(2)° [compound (12)], −28.5(3)° [compound (13)].
[compound (13)], and \(-27.4(4)^\circ\) [compound (14)]. Another way to analyze this structural feature can be made by looking at the angle between the individual least-square planes through rings A and B. It is observed that the unsubstituted phenyl B ring in the lactones (10–14) adopts angles of 81.8(2) [compound (10)], 72.5(4)° [compound (11)], 72.6(1)° [compound (12)], 77.9(1)° [compound (13)], and 83.2(2)° [compound (14)] with the corresponding lactone rings. The fact that the lowest energy form determined by DFT calculations for the C9–C10–C12–C13 moiety (dihedral angle = 0.0°) is not found within the solid state is the result of crystal packing forces or intermolecular bonding motifs such as hydrogen bonds, aromatic π–π stacking, steric repulsion, and van der Waals forces.

One last point, regarding the crystal structures of the investigated lactones, deserves comments. All nostoclide analogues, with the exception of compound (14), form infinite double chains linked in a head-to-tail fashion along specific crystallographic directions, as depicted in Figs. 3 and 9 for compound (11). Considering (11), the intermolecular force that stabilizes the double chain corresponds to the halogen...π-aryl interaction (Br1...C102 = 3.515(5) Å and Br2...C01 = 3.604(5) Å). This indicates that the independent molecules (11A) and (11B) (Fig. 3) are linked together by halogen...π-aryl interactions. On the other hand, the double chain found in the crystal structure of compound (10), which takes place along [100] direction, is linked by intermolecular non-classical hydrogen bonds of the type H...π-aryl. Considering compounds (12) or (13), their double chains raise along the [010] direction. In the case of compound (12), the double chain is stabilized by the intermolecular hydrogen bonds of the type H...π-aryl between the methylic hydrogen of the dimethylamino group (donor) and the π acceptor of the B ring. Taking compound (13) into consideration, the double chains are linked by the H...π-aryl interactions involving the hydrogen attached directly to the C ring (donor) and the π acceptor of the B ring.

Finally, in the case of compound (14), it forms an infinite chain along the [101] direction in which the molecules are linked by the classical hydrogen bond involving the hydroxyl group of the C ring and the carboxyl group of the lactone ring (Fig. 11).

Different interactions involved in the formation of the double chains and infinite chain can account for the different dihedral angle values, between rings A and B, found by XRD analyses. In addition, non-classical hydrogen bonds, van der Waals interactions, and aromatic π–π stacking forces link the double chains together stabilizing the packing along other crystallographic directions and forming 2D and 3D infinite structural networks (all crystal packing are available in the Supplementary material).

4. Conclusions

The structural investigation of a series of nostoclide analogues using DFT calculations and single crystal XRD techniques was carried out and the compounds were described in terms of relevant inter- and intramolecular geometric features including the stereoisomerism Z and E, and the conformers determined by the substitution pattern in the benzylidene moiety. All lactones exhibited the Z configuration, confirmed by bidimensional NOESY experiments and by single crystal X-ray diffraction measurements. The preferred conformer of the ortho substituted benzylidene derivatives found within the crystal structure showed the substituent in an anti-orientation in relation to the lactone ring. For the meta-substituted analogues, although there is some agreement between the results from DFT calculations in the gas phase and XRD analyses, it seems that the preferential conformation in the crystal structure is a result of crystal packing forces or intermolecular bonding motifs. The knowledge gained from this investigation will aid in the analysis of new compounds and, importantly, aid future exploration of struc-
ture-activity relationships for ascertaining the nostoclide phosphomacrophore and the binding requirements of the receptor.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2008.06.019.

References