DFT Studies of New Class of Single-Headed Nucleosides Derived from the D-glucaric Acid

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ABSTRACT

The nucleoside analogues can be conveniently classified into cyclic or acyclic analogues. The goal of this study is to anticipate the structural and electronic properties of new single-headed acyclo-C-nucleosides derived from the D-glucaric acid which are able to be in equilibrium with their corresponding cyclic forms by lactonization. The heterocyclic moieties selected for this study are: the 1,3,4-oxadiazole-2-thione, the 1,2,4-triazole-3-thiol and the 4-amino-1,2,4-triazole-3-thiol. Using density functional theory, the candidate nucleosides will be compared with the D-glucaric acid and its mono-lactones that are used as references. The results indicated that incorporating of the heterocycles significantly increase the reactivity of the new nucleosides. For the cyclic forms, a high reactivity of the molecules carrying the 6,3-lactone ring are observed in comparison with those carrying the 1,4-lactone ring. Whereas for the acyclic forms, the substitution of the carboxylic acid group by the heterocyclic moiety in position of carbon C6 gives a greater stability to the molecules compared with the same substitution in position C1. The results motivate theoretically the synthesis of this new class of nucleoside analogues, but it remains to find out the experimental conditions.

Key Words: DFT, D-glucaric acid; D-glucaro-1,4-lactone; D-glucaro-6,3-lactone; .

INTRODUCTION

The D-Glucaric acid [(2R,3S,4S,5S)-2,3,4,5-tetrahydroxyhexanedioic acid] (1) is a carbohydrate derived from the D-glucose and whose different possible applications have not yet been exploited as it should, considering the low cost and abundance of its precursor (Cui, 2005). As it is presents in small quantities in various fruits and vegetables (Walaszek *et al*., 1996), the D-glucaric acid (1) is more conveniently prepared by oxidation of D-glucose using different methods. Sohst and Tollens (1888), using the nitric acid, oxidized the D-glucose to the D-glucaric acid (1) and isolated the latter in the form of potassium salts (Sohst and Tollens, 1888). However, the large-scale production by the nitric acid was not promising, due to concurrent secondary reactions giving a low rate of this diacid (1) as well as, the strongly exothermic nature of the oxidation (Smith *et al*., 2012). Some works have proposed to optimize the oxidation and extraction processes of this molecule (Armstrong *et al*., 2017; Yuan *et al*., 2017). Moreover, several patents that focused on improving yields and oxidation conditions in addition to the recovery (recycling) of the nitric acid have been deposited (Mehltretter *et al*., 1949; Ulrich *et al*., 1966; Kiely and Ponder, 2000; Donen *et al*., 2015; Kiely and Hash, 2015).

A variety of other methods exist for the synthesis of the D-glucaric acid (1) such as the oxidation catalyzed by sodium nitrite (Grigoreva *et al*., 2001), the electrocatalytic oxidation (Ibert *et al*., 2010), the biological synthesis in Escherichia coli (Moon *et al*., 2010; Qu *et al*., 2018), the oxidation using Au/C catalysts (Solmi *et al*., 2017).

Since the work of Hirasaka and Umemoto (1965), it is well known that the D-glucaric acid (1) equilibrates in aqueous solution with its mono- and di-lactone forms : D-glucaro-1,4-lactone (2), D-glucaro-6,3-lactone (3) and D-glucaro-1,4:6,3-dilactone (4) as shown in figure 1.

Various studies have examined the equilibrium of this diacid (1) in neutral medium, in acidic solution and by varying the

temperature (Hirasaka *et al*., 1965; Horton and Walaszek, 1982; Brown *et al*., 2007). All agree that switching from one mono-lactone to another is done mainly via the acyclic form, the dilactone (4) being detectable in very small amount in solution at an elevated temperature.

Also, it has been reported that the reactivity of the ring 1,4-lactone (2) was higher compared to that of the 6,3-lactone ring (3) (Davey *et al*., 2006).

Some works have described the conformations of D-glucaric acid (1) and its lactone forms in solution. Among the most recent studies, (Armstrong et al., 2017; Denton *et al*., 2011) have characterized the crystal structure of D-glucaric acid (1) in solution and indicated that it has a sickle-like (bent) $_2G^+{}_3G^+$ conformation.

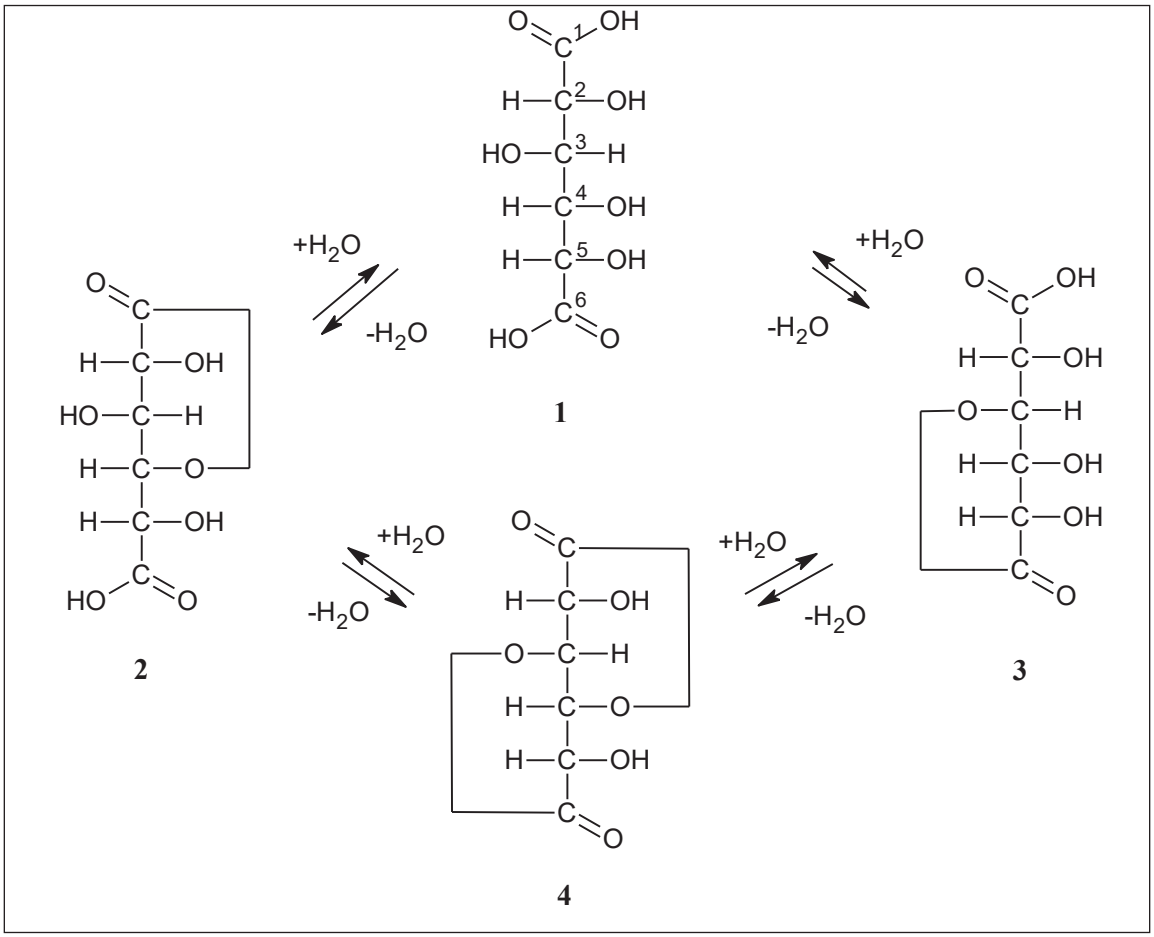


Fig 1. Equilibrium of the D-glucaric acid (1) with its mono- and di- lactones (2-4) forms in aqueous solution.

Crystal structures of the D-glucaric acid derivatives have also been reported, some of which have variable bent conformations, while others are conformationally extended (Styron *et al*., 2011). Concerning the mono-lactones, in 1982, Horton and Walaszek studied the conformations of these molecules in solution. For the D-glucaro-1,4-lactone (2), they have indicated that a conformational equilibrium ^3E(D) and E_3(D) exists in solution and that the OH group carried by C5 carbon tends to occupy the position on the lactone ring in the favored conformation E_3(D),gg (Horton and Walaszek, 1982). Whereas for the D-glucaro-6,3-lactone (3), they have indicated that the conformation of E_4(D),gt was favored with almost none ^4E(D) conformation present (Horton and Walaszek, 1982).

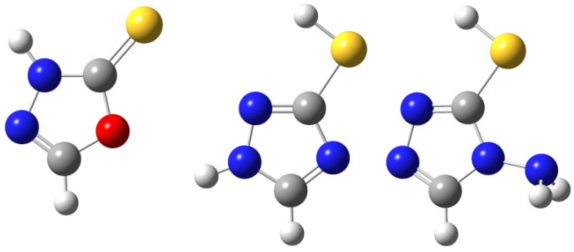
In the field of health, it has been shown that the diacid (1) in its D-glucaro-1,4-lactone (2) form has an anticancer effect, and that the risk

of developing this disease could be reduced by consumption of diets rich in D-glucaric acid (1). Indeed, the D-glucaro-1,4-lactone (2) being able to suppress β-glucuronidase, an enzyme produced by the microflora of the colon, whose activity is associated with an increased risk of various cancers (Zółtaszek *et al*., 2008).

The natural nucleosides are molecules formed by the association of a nucleobase and a sugar (Watson and Crick, 1954). A modification on one of these fragments, or both at the same time, i.e. modified sugar, modified nucleobase or modified sugar and nucleobase give, nucleoside analogues. Also it is possible to classify them into two main categories of cyclic or acyclic analogues. As well, depending on the type and number of heterocycles, it is possible to distribute them in mono-, bi-, tri-, or poly-cyclic or polymeric bases, and in double-headed, triple-headed nucleoside analogues... etc. (Kisakürek, 2000; Simons, 2000; Chu, 2002; El Ashry, 2007). It should be noted that the nucleoside analogues are in fact molecules similar to natural nucleosides, and some of which possess therapeutic activities against various diseases, bacteria and viruses such as the hepatitis B virus, the human immunodeficiency virus, among others (Romeo *et al*., 2010; Chhikara *et al*. , 2014; Wu *et al*., 2018).

In this study, we present new nucleoside analogue molecules able to be in equilibrium between cyclic and acyclic forms in a biological medium. These candidate molecules are single-headed acyclo-C-nucleosides carrying on one side a fragment of D-glucaric acid (1) or one of its mono-lactones (2 or 3), and on the other side a heterocyclic moiety.

The heterocycles that can be tested for this study are numerous: whether they are saturated or unsaturated heterocycles, that the heteroatom is the nitrogen, the oxygen, the sulfur, the phosphorus or the halogens, or that the heterocycle is carrying hydroxyl , amine or thiohydroxylated derivatives able to have a tautomeric behavior, the choice is very diversified. However, we have selected three, which are : the 1,3,4-oxadiazole-2-thione (5), the 1,2,4-triazole-3-thiol (6) and the 4-amino-1,2,4-triazole-3-thiol (7), whose structures are given in the figure 2.



5 6 7

Fig 2. Heterocycles chosen for this study.

This choice is justified by the fact that three double-headed acyclo-C-nucleosides, carriers these heterocycles, were synthesized from the D-glucaric acid (1) (Amara and Othman, 2016) and whose computational results have already been published (Amara *et al*, 2015). So, this is continuity in the path of a series of molecules already synthesized. At the same time, the selected 1,3,4-oxadiazole and 1,2,4-triazole derivatives are scaffolds that have a variety of biological importance widely reported in the literature (Othman *et al*., 2014).

Thus, we propose to design and study theoretically twelve nucleoside analogues derived from D-glucaric acid (1), then to compare them to their precursor and its mono-lactones (2 and 3) taken as reference. It's about doing a study of the stability and reactivity in order to motivate this synthesis among chemists.

MATERIALS AND METHODS

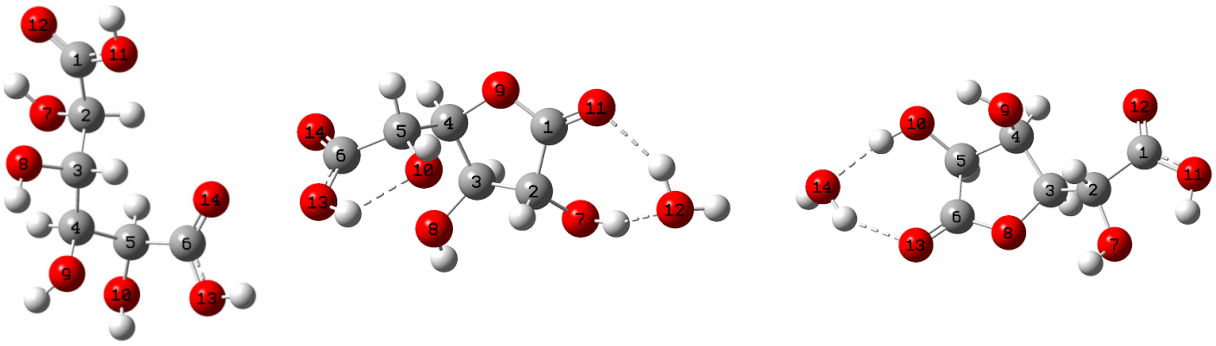
Concerning the modeling of the molecules, as developed in the introductory part, some researches have described the privileged conformations of the D-glucaric acid (1) and its D-glucaro-monolactones (2 and 3) forms in solution. These favored conformations are taken as a starting point for this study. The molecules were optimized, via Gaussian09 software (Frisch *et al*., 2009), by the density functional theory (DFT), using the hybrid functional B3LYP (Lee *et al*., 1988; Becke,

1993) and the basis set 6-31+G(d,p). The results have been visualized through the GaussView 5.0.8 graphical interface (Dennington *et al.*, 2009). Finally, and in order to simulate more closely the biological medium, which is essentially formed of water, the effects of solvent in aqueous medium have been taken into account implicitly using, in calculations, the polarizable continuum model (PCM) (Miertus *et al.*,1981 ; Cammi and Tomasi, 1995). Regarding the explicit consideration, we are content with a mono hydration, where the water molecule is positioned near the lactone function, thus allowing equilibrium between cyclic and acyclic forms.

RESULT AND DISCUSSION

Structures and electronic properties of the D-glucaric acid and its mono-lactones

The D-glucaric acid in sickle-like conformation (8) and its mono-hydrated mono-lactone forms including D-glucaro-1,4-lactone in E_3(D),gg conformation (9) and D-glucaro-6,3-lactone in E_4(D),gt conformation (10) were optimized by DFT in the gas phase but also in an implicit aqueous medium. In total, three reference systems are described. The optimized structures in the implicit aqueous medium, with the numbering of carbon and oxygen atoms, are given in figure 3.



8 9 10

Fig 3. Optimized structures of the D-glucaric acid (8) and its mono-hydrated cyclic forms (9 and 10), obtained by DFT in implicit aqueous medium.

No intramolecular hydrogen bond appeared in the optimized structures of the D-glucaric acid (8). This is in agreement with the structure of this diacid characterized in solution (Denton el al., 2011). For cyclic forms, only the mono-hydrated D-glucaro-1,4-lactone (9) has, in the implicit aqueous medium, an intramolecular hydrogen bond in its structure. Also, two intermolecular hydrogen bonds appear respectively in each mono-hydrated system (9 and 10), and this between the explicit water molecule and the cyclic γ-lactone.

Total energies (E_T), zero point energies (*ZPE*), enthalpies ($H_{298\ K}$), frontier orbital energies: highest occupied molecular orbital (E_{HOMO}) and lowest unoccupied molecular orbital (E_{LUMO}), as well as the HOMO-LUMO energy gaps (E_{gap}) of the three reference systems in the gas phase and in the implicit aqueous medium are given in Table 1.

We emphasize that D-glucaric acid, D-glucaro-1,4-lactone and D-glucaro-6,3-lactone, regardless of their conformations are numbered respectively (1), (2) and (3). However, in their favorable conformations that we have modeled we number them, respectively (8), (9) and (10). For this reason, when we report the experimental results we will use the first numbering.

Table 1. Total energies (E_T), zero point energies (ZPE), enthalpies ($H_{298\,K}$), HOMO energies (E_{HOMO}), LUMO energies (E_{LUMO}), HOMO-LUMO energy gaps (E_{gap}) in atomic units (a.u.) for the systems (8-10) by DFT.

Molecules	E_T (u.a.)	*ZPE* (u.a.)	$H_{298\,K}$ (u.a.)	E_{LUMO} (u.a.)	E_{HOMO} (u.a.)	E_{gap} (u.a.)
D-glucaric acid (8)						
Gas phase	-836.5163	-836.3351	-836.3191	-0.03668	-0.28684	0.25016
Implicit medium	-836.5363	-836.3565	-836.3399	-0.03197	-0.28553	0.25356
Mono-hydrated D-glucaro-1,4-lactone (9)						
Gas phase	-836.5224	-836.3423	-836.3262	-0.03198	-0.27831	0.24633
Implicit medium	-836.5438	-836.3646	-836.3481	-0.03458	-0.28370	0.24912
Mono-hydrated D-glucaro-6,3-lactone (10)						
Gas phase	-836.5221	-836.3417	-836.3257	-0.04386	-0.29350	0.24964
Implicit medium	-836.5443	-836.3648	-836.3486	-0.03710	-0.29111	0.25401

In table 1, the values of the energies indicate that for each system, a greater stability is observed when passing from gas phase to implicit aqueous medium. This is due to the effect exerted by the implicit solvent. The results of the optimizations of the systems (9 and 10) indicate that in the gas phase, the mono-hydrated D-glucaro-1,4-lactone (9) presents a greater stability than its counterpart the 6,3-lactone (10), while in implicit aqueous medium the opposite is observed.

According to the experimental results available in the literature, when the D-glucaric acid (1) and its mono-lactone forms (2-3) are in equilibrium in aqueous solution, the D-glucaro-6,3-lactone (3) presents in a quantity slightly higher than that of the D-glucaro-1,4-lactone (2), (Hirasaka *et al*., 1965; Brown *et al*., 2007). This indicated the greater stability for the 6,3-lactone ring (3). Thus, it is possible to conclude, that the simple explicit mono-hydration is not enough to describe this system, and that the introduction of an implicit solvation is necessary for the study of this equilibrium.

The HOMO-LUMO energy gap allows obtaining clues on the reactivity (Todeschini and Consonni, 2009). Concerning the values of the gaps HOMO-LUMO, and by comparing the systems (9 and 10) that the mono-hydrated D-glucaro-1,4-lactone (9) has lower E_{gap} values than its counterpart mono-hydrated D-glucaro-6,3-lactone (10). Thus, according to these results, the system (9) is more reactive than the system (10). This is consistent with the experimental results on the reactivity of D-glucaro-monolactones (Davey *et al*., 2006).

The instability of the 1,4-lactone ring (2) has been treated in different works. Indeed, Hirasaka and Umemoto (1965) indicated that the fast mutarotation of the D-glucaro-1,4:6,3-dilactone (4) in aqueous solution was attributable to the instability of its 1,4-lactone ring. Also, Brown *et al*. (2007) argued that the opening of the dilactone (4) molecule, rapidly produces 6,3-lactone (3), due to the instability of the 1,4-lactone ring.

However, our results do not indicate such an important instability of the system (9)! If we observe more closely the conformations of the D-glucaro-1,4-lactone (2), we find that no contradiction exists. Indeed, the instability indicated in the works of Hirasaka and Umemoto (1965), as well as Brown *et al*. (2007) related to the conformation ^3E(D) of the 1,4-lactone ring of the D-glucaro-1,4:6,3-dilactone (4), the conformation of the latter being ^3E:E_4(D). Meanwhile, the privileged conformation of the D-glucaro-1,4-lactone (2), described by Horton and Walaszek (1982) as well as the crystallized form given by Gress and Jeffrey (1976) are all of type E_3(D),gg. In addition, the results of Brown *et al*. who pointed out that D-glucaro-1,4-

lactone (2), dissolved in aqueous solution under neutral conditions, was relatively stable with regard to equilibration (Brown *et al*., 2007).

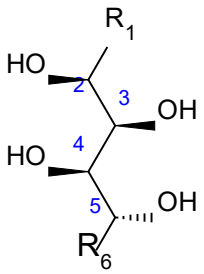
For the geometrical parameters of these different systems, it is possible to note that, in general, the values of the bonds and angles vary only slightly from the gas phase to the implicit aqueous medium. However, by comparing the dihedral angles of the D-glucaric acid (8) with the two systems (9 and 10), the important, and necessary structural deformations, which the diacid (8) must undergo to allow the formation of its mono-lactones, is noticed.

Structures and electronic properties of cyclic and acyclic forms of nucleoside analogues candidates

In the molecule of the D-glucaric acid (8), the substitution of the carboxylic acid group carried at the C1 carbon by the 1,3,4-oxadiazole-2-thione (5) gives nucleoside (11) coded as Oxa(1)-acyclic. The aliphatic moiety can lactonize via release a molecule of water to form the 6,3-lactone ring. The resulting new molecule (12) will be symbolized as Oxa(1)-cyclic-6,3 (Figure 4). If this same substitution is performed by the 1,2,4-triazole-3-thiol (6), the acyclic form (15) that is coded as Tri(1)-acyclic is produced, that will equilibrate with the molecule (16) coded as Tri(1)-cyclic-6,3 (Figure 5).

Similarly, if the substitution is made by the 4-amino-1,2,4-triazole-3-thiol (7), the acyclic form (19) coded ATri(1)-acyclic is obtained, and which equilibrate with the molecule (20) code as ATri (1)-cyclic-6,3 (Figure 6). By analogy, the substitution of the carboxylic acid group at the C6 carbon by one of the heterocycles (5, 6 or 7), allows obtaining the molecules: Oxa(6)-acyclic (13) in equilibrium with Oxa(6)-cyclic-1,4 (14) (Figure 4), Tri(6)-acyclic (17) in equilibrium with Tri(6)-cyclic-1,4 (18) (Figure 5) and ATri(6)-acyclic (21) in equilibrium with ATri(6)-cyclic-1,4 (22), respectively (Figure 6). Table 2 summarizes all these nomenclatures.

Table 2. Nomenclature of the studied nucleoside analogues.

Molecule	R_1	R_6	Code of the acyclic form	Code of the cyclic form
	1,3,4-oxadiazole-2-thione (5)	COOH	Oxa(1)-acyclic (11)	Oxa(1)-cyclic-6,3 (12)
	COOH	1,3,4-oxadiazole-2-thione (5)	Oxa(6)-acyclic (13)	Oxa(6)-cyclic-1,4 (14)
	1,2,4-triazole-3-thiol (6)	COOH	Tri(1)-acyclic (15)	Tri(1)-cyclic-6,3 (16)
	COOH	1,2,4-triazole-3-thiol (6)	Tri(6)-acyclic (17)	Tri(6)-cyclic-1,4 (18)
	4-amino-1,2,4-triazole-3-thiol (7)	COOH	ATri(1)-acyclic (19)	ATri(1)-cyclic -6,3 (20)
	COOH	4-amino-1,2,4-triazole-3-thiol (7)	ATri(6)-acyclic (21)	ATri(6)-cyclic-1,4 (22)

R_1 and R: Carboxylic acid or heterocycles carried respectively by carbons C1 and C6.

In the end, the twelve molecules (11-22) have been modeled and optimized by DFT in gas phase and in aqueous medium using the PCM model (Figures 4-6). Note that the three-dimensional representations of these nucleoside analogues are oriented so as to have the fragment of D-glucaric acid or its mono-lactone forms oriented in space exactly in the same way that the reference systems (8-10) in order to facilitate the recognition of the numbering given in the figure 3.

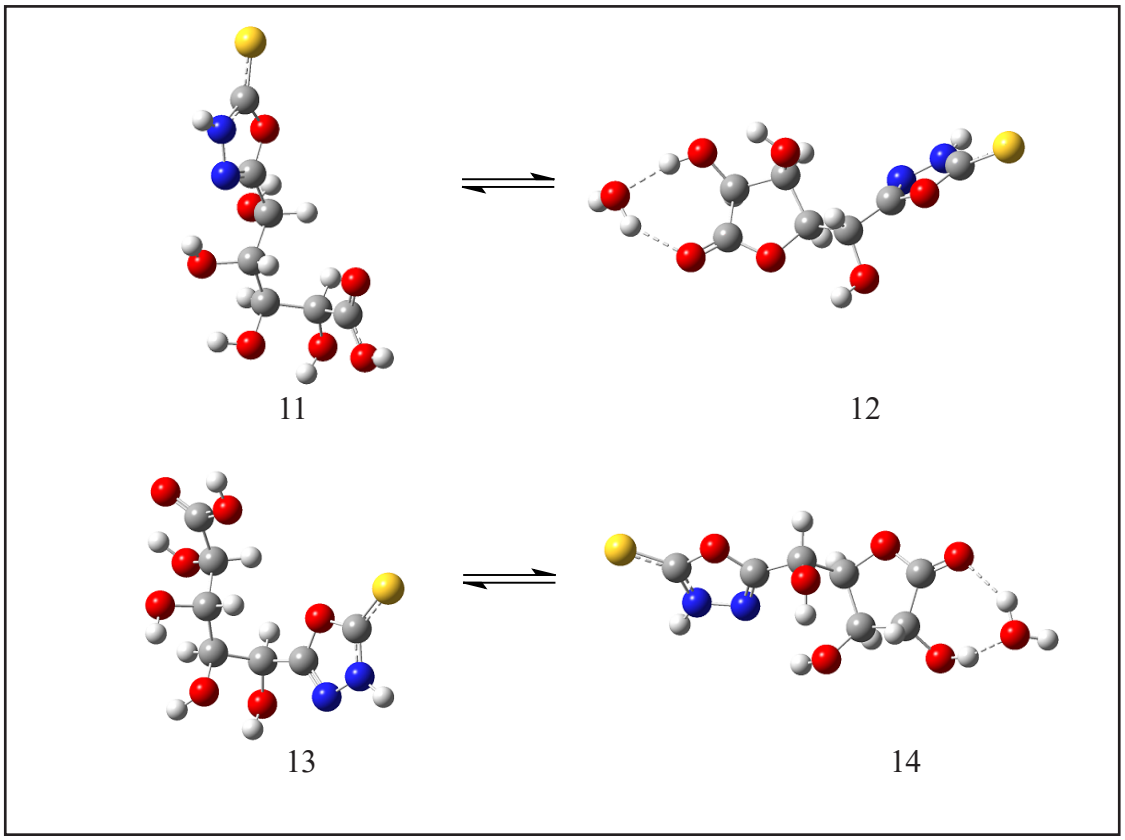


Fig 4. Structures of nucleoside analogues having 1,3,4-oxadiazole-2-thione in implicit aqueous medium by the DFT method.

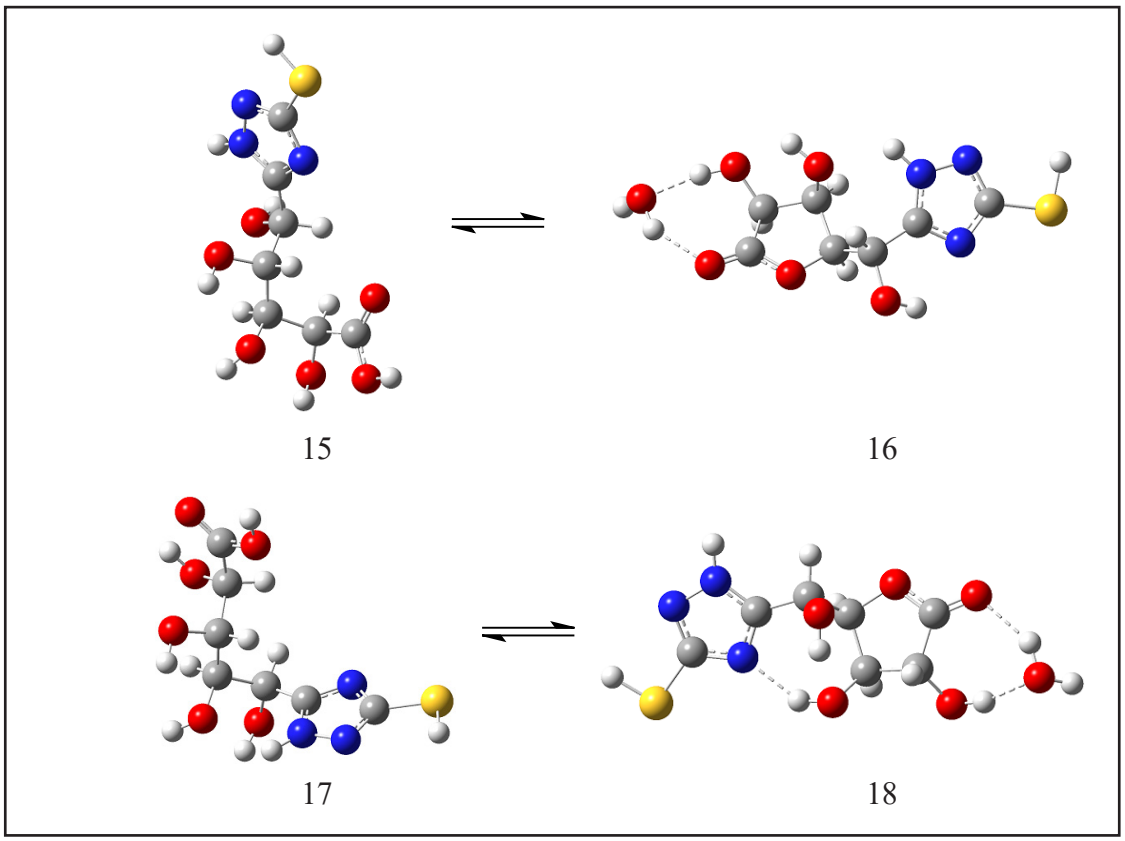


Fig 5. Structures of nucleoside analogues having 1,2,4-triazole-3-thiol moiety in implicit aqueous medium by the DFT method.

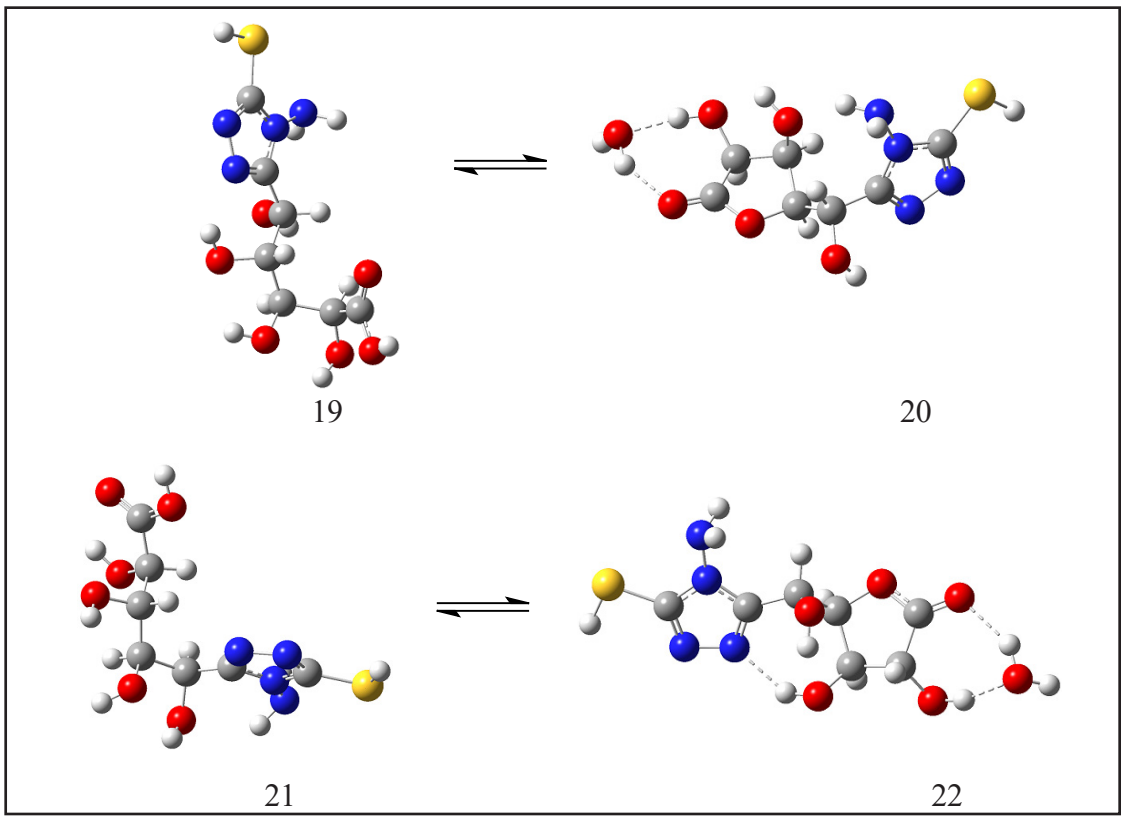


Fig 6. Structures of nucleoside analogues having 4-amino-1,2,4-triazole-3-thiol moiety in implicit aqueous medium by the DFT method.

Total energies (E_T), zero point energie.s (*ZPE*), enthalpies ($H_{298\ K}$), frontier orbital energies (E_{HOMO} and E_{LUMO}), as well as the HOMO-LUMO energy gaps (E_{gap}) of the different molecules (11-22) are given in table 3. Overall, it is possible to see the effect of the solvent, which increases the stability of all the systems (11-22) in the implicit aqueous medium.

However, for a better analysis, we discuss the results of the table 3 by groups of nucleoside analogues, each group characterized by the type of heterocycle that it carries.

Table 3. Total energies (E_T), zero point energies (*ZPE*), enthalpies ($H_{298\ K}$), HOMO energies (E_{HOMO}), LUMO energies (E_{LUMO}), HOMO-LUMO energy gaps (E_{gap}) in atomic units (a.u.) for the candidates analogues of nucleosides by DFT.

Molecules	E_T (u.a.)	*ZPE* (u.a.)	$H_{298\ K}$ (u.a.)	E_{LUMO} (u.a.)	E_{HOMO} (u.a.)	E_{gap} (u.a.)
Oxa(1)-acyclic (11)						
Gas phase	-1307.0519	-1306.8557	-1306.8375	-0.04481	-0.23166	0.18685
Implicit medium	-1307.0752	-1306.8798	-1306.8614	-0.05062	-0.24918	0.19856
Oxa(1)-cyclic-6,3 (12)						
Gas phase	-1307.0597	-1306.8648	-1306.8464	-0.05117	-0.24060	0.18943
Implicit medium	-1307.0843	-1306.8903	-1306.8716	-0.05276	-0.24950	0.19674
Oxa(6)-acyclic (13)						
Gas phase	-1307.0532	-1306.8573	-1306.8390	-0.05151	-0.24840	0.19689
Implicit medium	-1307.0772	-1306.8818	-1306.8633	-0.04787	-0.24726	0.19939
Oxa(6)-cyclic-1,4 (14)						
Gas phase	-1307.0562	-1306.8610	-1306.8427	-0.04722	-0.24397	0.19675
Implicit medium	-1307.0828	-1306.8876	-1306.8695	-0.05343	-0.25055	0.19712

Table 3, cont

Molecules	E_T (u.a.)	*ZPE* (u.a.)	$H_{298\,K}$ (u.a.)	E_{LUMO} (u.a.)	E_{HOMO} (u.a.)	E_{gap} (u.a.)
Tri(1)-acyclic (15)						
Gas phase	-1287.1968	-1286.9907	-1286.9721	-0.04151	-0.23363	0.19212
Implicit medium	-1287.2177	-1287.0128	-1286.9936	-0.03034	-0.24599	0.21565
Tri(1)-cyclic-6,3 (16)						
Gas phase	-1287.2061	-1287.0013	-1286.9825	-0.04063	-0.24109	0.20046
Implicit medium	-1287.2292	-1287.0251	-1287.0063	-0.03702	-0.24892	0.21190
Tri(6)-acyclic (17)						
Gas phase	-1287.2002	-1286.9941	-1286.9755	-0.03475	-0.24329	0.20854
Implicit medium	-1287.2213	-1287.0162	-1286.9973	-0.02843	-0.24751	0.21908
Tri(6)-cyclic-1,4 (18)						
Gas phase	-1287.2047	-1286.9986	-1286.9804	-0.04378	-0.25994	0.21616
Implicit medium	-1287.2290	-1287.0240	-1287.0054	-0.03588	-0.25368	0.21780
ATri(1)-acyclic (19)						
Gas phase	-1342.5075	-1342.2850	-1342.2651	-0.04263	-0.24906	0.20643
Implicit medium	-1342.5357	-1342.3139	-1342.2938	-0.03264	-0.25137	0.21873
Atri(1)-cyclic-6,3 (20)						
Gas phase	-1342.5190	-1342.2972	-1342.2775	-0.04242	-0.24670	0.20428
Implicit medium	-1342.5463	-1342.3254	-1342.3053	-0.03701	-0.24954	0.21253
Atri(6)-acyclic (21)						
Gas phase	-1342.5089	-1342.2863	-1342.2665	-0.03478	-0.23937	0.20459
Implicit medium	-1342.5362	-1342.3147	-1342.2943	-0.02718	-0.24802	0.22084
Atri(6)-cyclic-1,4 (22)						
Gas phase	-1342.5190	-1342.2967	-1342.2770	-0.03620	-0.25833	0.22213
Implicit medium	-1342.5462	-1342.3248	-1342.3048	-0.03536	-0.25405	0.21869

The results of the first group of nucleoside analogues with the heterocycle 1,3,4-oxadiazole-2-thione, comprising the molecules (11-14), indicate that the molecule Oxa(6)-acyclic (13) is more stable than the Oxa(1)-acyclic (11) either in the gas phase or in the implicit aqueous medium. The gap HOMO-LUMO, indicates a greater reactivity of the molecule (11) compared to the (13) in the gas phase. Regarding the PCM medium, although the gap values become much closer than they were in the gas phase, the molecule (11) still has the lowest E_{gap} value. For the cyclic forms, whatever the medium, it is always the system carrying the 6,3-lactone ring (12) which presents a greater stability than that carrying the 1,4-lactone ring (14). However, the difference HOMO-LUMO in the system (12) is lower than in the (14), making the system incorporating the 6,3-lactone ring more reactive than its counterpart. It should be noted that, as for the acyclic forms of this group, the values of the gaps are getting closer while passing from the gas phase to the aqueous medium. In the comparison of each cyclic form with its corresponding acyclic form, we find that in the gas phase, the acyclic molecule (11) is more reactive than the (12), whereas the acyclic molecule (13) is less reactive than the (14). However, the implicit solvation gives greater reactivity to all cyclic forms compared to their corresponding acyclic forms.

Considering the second group of nucleoside analogues with the heterocycle 1,2,4-triazole-3-thiol, comprising the molecules (15-18), the acyclic form (17) presents a greater stability and a lower reactivity than its isomer the molecule (15). Concerning the cyclic forms, in the gas phase and the implicit aqueous medium, a greater stability is observed in the system (16) carrying the 6.3-lactone ring

compared to the system (18) carrying the 1,4-lactone ring. Regarding the reactivity, the gap HOMO-LUMO presents a lower value in the system (16) compared to the system (18), making the first one more reactive. By comparing the cyclic and acyclic forms of this group, we notice that, unlike gas phase, the implicit solvation increases the reactivity of the cyclic systems (16 and 18) than their corresponding acyclic forms (15 and 17).

For this last group of nucleoside analogues with the heterocycle 4-amino-1,2,4-triazole-3-thiol, comprising the molecules (19-22),the molecule (21) ATri(6)-acyclic (21) has a greater stability compared with the ATri(1)-acyclic (19). Regarding the reactivity, it is higher for (21) compared to (19) in the gas phase, while the opposite is observed in the implicit aqueous medium. For the cyclic forms, the system (20) which corresponds to the cyclic form 6,3-lactone is more stable, whatever the medium, compared to its counterpart the system (22). Whereas, (20) has a greater reactivity with an E_{gap} lower than that for (22) in the gas phase and in implicit medium. The comparison between cyclic and acyclic forms indicates that, in each equilibrium, the implicit solvation increases the reactivity of the cyclic forms than the acyclic forms. While in the gas phase, this is true only for the equilibrium between molecules (19) and (20).

Analysis of the geometrical parameters for both of the twelve new nucleoside analogues and the reference systems (8-10) shows that changes occur especially in the values of the dihedral angles, some of which are given in the tables 4 and 5.

Table 4. Geometrical parameters of the molecules (8-10) calculated by DFT.

Dihedral angles (°)	Reference systems					
	Gas phase			Implicit aqueous medium		
	8	9	10	8	9	10
O11-C1-C2-C3	63.34	-161.55	-142.74	64.31	-162.44	-137.11
C1-C2-C3-C4	165.246	-28.15	-77.00	171.352	-25.98	-71.41
C2-C3-C4-C5	54.76	-89.03	-150.68	59.45	-92.32	-150.85
C3-C4-C5-C6	56.57	-69.71	33.73	55.93	-72.75	33.34
C4-C5-C6-O13	122.18	-49.36	157.66	105.73	131.69	157.57
O9-C1-C2-C3	*	17.82	*	*	17.27	*
C4-C5-C6-O8	*	*	-24.18	*	*	-23.58
C3-C4-O9-C1	*	-19.49	*	*	-16.86	*
C4-C3-O8-C6	*	*	19.42	*	*	19.80

Table 5. Geometrical parameters of the molecules (11-22) calculated by DFT.

Dihedral angles (°)	Candidate nucleoside analogues							
	Gas phase				Implicit aqueous medium			
	11	12	13	14	11	12	13	14
O11-C1-C2-C3	*	*	62.98	-162.66	*	*	64.07	-165.08
C1-C2-C3-C4	175.85	-66.86	164.88	-25.44	176.04	-65.69	171.21	-19.9
C2-C3-C4-C5	55.91	-147.21	55.43	-93.97	56.86	-147.94	62.05	-100.77
C3-C4-C5-C6	54.45	31.54	61.22	-83.83	57.44	31.96	57.41	-82.85
C4-C5-C6-O13	121.49	158.58	*	*	109.25	157.98	*	*
O9-C1-C2-C3	*	*	*	18.01	*	*	*	15.71
C4-C5-C6-O8	*	-23.46	*	*	*	-23.43	*	*
C3-C4-O9-C1	*	*	*	-14.58	*	*	*	-9.12
C4-C3-O8-C6	*	16.8	*	*	*	17.68	*	*

Table 5, cont

Dihedral angles (°)	Candidate nucleoside analogues							
	Gas phase				Implicit aqueous medium			
	15	16	17	18	15	16	17	18
O11-C1-C2-C3	*	*	63.04	-168.51	*	*	64.29	-166.16
C1-C2-C3-C4	168.77	-76.1	169.16	-16.1	174.61	-56.79	173.05	-18.23
C2-C3-C4-C5	56.49	-150.6	58.68	-103.69	59.09	-147.24	67.46	-103.37
C3-C4-C5-C6	57.77	33.62	57.17	-81.91	56.58	30.32	60.47	-81.11
C4-C5-C6-O13	124.1	157.84	*	*	105.6	158.89	*	*
O9-C1-C2-C3	*	*	*	11.42	*	*	*	14.7
C4-C5-C6-O8	*	-24.04	*	*	*	-22.52	*	*
C3-C4-O9-C1	*	*	*	-9.58	*	*	*	-7.9
C4-C3-O8-C6	*	19.47	*	*	*	16.22	*	*
	19	20	21	22	19	20	21	22
O11-C1-C2-C3	*	*	50.83	-168.04	*	*	64.06	-165.68
C1-C2-C3-C4	174.09	-57.19	161.06	-17.2	175.54	-58.73	171.6	-19.2
C2-C3-C4-C5	58.55	-151.04	52.83	-102.05	62.63	-150.69	57.86	-101.78
C3-C4-C5-C6	54.27	31.26	49.55	-79.94	56.86	31.92	54.45	-80.19
C4-C5-C6-O13	104.3	159	*	*	106.7	158.17	*	*
O9-C1-C2-C3	*	*	*	11.84	*	*	*	15.06
C4-C5-C6-O8	*	-22.55	*	*	*	-22.99	*	*
C3-C4-O9-C1	*	*	*	-10.77	*	*	*	-8.97
C4-C3-O8-C6	*	17.94	*	*	*	18.31	*	*

*: Angle inexistent in the studied system.

This is obviously due to the presence of heterocycles that can cause steric hindrance, or electrostatic interactions favoring the modification of the spatial arrangement of atoms.

By comparing the three groups of candidate nucleosides with each other, and with the references, it is found that, all the heterocycles selected for this study offered greater molecular stability and lower reactivity for the acyclic forms when localized at the C6 carbon compared to their localization at the C1 carbon.

Comparing the reactivity of all acyclic forms (11, 13, 15, 17, 19 and 21) with that of the D-glucaric acid (8), it is observed that the presence of these heterocycles significantly increases the reactivity with oxa(1)-acyclic (11) being the most reactive as the E_{gap} value is changed in the gas phase from 0.25016 a.u. for D-glucaric acid (8) up to 0.18685 a.u., and in the implicit aqueous medium from 0.25356 a.u. for the reference diacid (8) up to 0.19856 a.u. smaller with value always for the Oxa(1)-acyclic (11).

Overall, for the cyclic forms, the results obtained reveal that, whatever the simulation medium, the systems bearing the 6,3-lactone ring are all more stable than those carrying the 1,4-lactone ring. However, and unlike the reference systems (9 and 10), a greater reactivity is observed in acid having the 6,3-lactone ring (10). Also, the incorporation of these heterocycles in the cyclic forms greatly increased their reactivity to the reference systems (9 and 10).

Furthermore, the cyclic forms in aqueous medium are found to be more reactive than their corresponding acyclic forms. This is in agreement with our reference systems.

Also, it is evident that the new nucleoside analogues, significantly increase reactivity

compared to the reference acids. Finally, the substitution of the carboxylic acid function, by one of the selected heterocycles (5-7) on the C6 carbon, compared to the substitution on C1, increases the stability for the acyclic forms and decreases it for the cyclic forms.

Also, it is important to emphasize that the nucleoside analogues carrying the heterocycle 1,3,4-oxadiazoles-2-thione (5) have the highest reactivity among all.

Conclusion

Twelve new single-headed cyclic and acyclic C-nucleosides derived from the D-glucaric acid have been simulated in gas phase and implicitly in water. The obtained results indicate the high stability and reactivity of the molecules carrying the 6,3-lactone ring compared to with the molecules carrying the 1,4-lactone ring. This is the crucial point that differs with the molecules taken as references where, the mono-hydrated D-glucaro-6,3-lactone (10) was certainly more stable, but the least reactive of the two monolactone systems.

The heterocylic rings either on C1 or C6, significantly increase the reactivity of all molecules (cyclic or acyclic) compared to the reference systems (8-10).

Also, the higher reactivity of cyclic forms compared to their corresponding acyclic forms is observed.

It would be very interesting to synthesize these molecules and to test them by comparing their biological activity with that of the D-glucaric acid and its mono-lactones. This equilibrium between two forms could eventually be biologically interesting.

It remains to establish the experimental conditions that would allow the formation of the heterocycle at only one end of the diacid, leaving thus possible the formation of an equilibrium between cyclic and acyclic forms in aqueous medium. It should be noted that the products of this synthesis would be either acyclic molecules in the form of salts, or the mono-lactone cyclic forms, the carboxylic acid function not being isolatable as such.

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دراسات نظرية الكثافة الوظيفية لفئة جديدة من النوكليوزيد أحادية الرأس مشتقة من حمض د - جلوكارك

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ملخص

يمكن تصنيف مضاهئ النوكليوزيد بشكل ملائم كجزيئات حلقية أو غير حلقية. الهدف من هذه الدراسة هو توقع الخصائص الهيكلية والإلكترونية لمضاهئ نوكليوزيد جديدة غير حلقية من نوع «أحادية الرَّأس بارتباط كربوني» مشتقَّة من حمض د -جلوكارك وقادرة على أن تكون متوازنة مع أشكالها الحلقية المقابلة من خلال آلية تكوين اللاكتونات.

المركَّبات الحلقية غير المتجانسة المختارة لهذه الدراسة هي 1،3،4 - أكسادیازول -2- ثيون و 1، 2، 4- تريازول -3- ثيول و 4- أمينو-1، 2، 4- تريازول -3- ثيول. باستخدام نظرية الكثافة الوظيفية تمت مقارنة النيوكليوسيدات المرشحة مع حمض د -جلوكارك ولاكتوناته أحادية الحلقة التي تستخدم كمراجع.

أشارت النتائج إلى أن دمج المركبات الحلقية غير المتجانسة يزيد بشكل كبير من تفاعلية النيوكليوسيدات الجديدة. بشأن المركبات الحلقية، لوحظ أنَّ الجزيئات التي تحمل الحلقة 6-3 لاكتون أكثر نشاطية بالمقارنة مع تلك التي تحمل الحلقة 1-4 لاكتون. أما بشأن الأشكال غير الحلقيَّة، فإن استبدال مجموعة حمض الكربوكسيل الوظيفية بالمركبات الحلقية غير المتجانسة في موضع الكربون رقم 6 يعطي استقرارًا أكبر للجزيئات مقارنة مع الاستبدال نفسه في موضع الكربون رقم 1. تحفز النتائج النظرية تحضير هذه الفئة الجديدة من مضاهئ نوكليوزيد، ويتبقى معرفة ظروف التشييد الكيميائي.

الكلمات المفتاحية: حمض د-جلوكارك ، د-جلوكارو-4،1-لاكتون، د-جلوكارو -6 ، 3- لاكتون، ، نظرية الكثافة الوظيفية.