Revista Virtual de Química
ISSN 1984-6835

Artigo

Synthesis and Cytotoxic Activity of New Alkyl 2-Azido-2,3-Dideoxy-α-D-*Lixo*-Hexopyranosides From α,β-Unsaturated Sugar Enones and Sodium Azide

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Rev. Virtual Quim., **2019**, *11* (6), 1823-1834. Data de publicação na Web: 2 de janeiro de 2020

http://rvq.sbq.org.br

Síntese e Atividade Citotóxica de Novos Alquil 2-azido-2,3-dideoxi-α-D-*Lixo*-hexopiranosídeos Obtidos a Partir de Enonas α,β-Insaturados e Azida de Sódio

Resumo: Este trabalho descreve a síntese de cinco novos alquil 2-azido-2,3-dideoxi-α-D-lixo-hexopiranosídeo (**7a-e**) a partir de enonas α,β-insaturados e azida de sódio em presença de ácido acético. Um intermediário chave, alquil 2-azido-dideoxi-α-D-treo-hexopiranosídeo-4-ulose (**6a-e**), foi utilizado para obter os compostos **7a-e**. Os compostos **7a-e** foram obtidos em bons rendimentos (65-78 %). As estruturas dos compostos sintetizados foram elucidadas usando espectrometria de infravermelho, RMN de ^{1}H e ^{13}C e análise elementar. As suas atividades antiproliferativas foram avaliadas contra quatro diferentes linhagens celulares humanas que também são descritas neste trabalho. O composto **7c** exibiu uma boa atividade citotóxica contra as linhagens celulares estudadas HL-60, NCI H292, MCF-7 e HEP com valores de 6,8 µg / mL, 9,9 µg / mL, 12,1 µg / mL e 5,1 µg / mL, respectivamente.

***Palavras-chave*:** Azido acúcar; enona α,β-insaturado; atividade citotóxica.

Abstract

The synthesis of five new alkyl 2-azido-2,3-dideoxy-α-D-*lixo*-hexopyranoside (**7a-e**) obtained from α,β-unsaturated sugar enones and sodium azide in the presence of acetic acid is described. One key intermediate, alkyl 2-azido-dideoxy-α-D-*threo*-hexopyranosid-4-ulose (**6a-e**), was used to obtain compounds **7a-e.** The compounds **7a-e** were obtained on good yields (65-78 %). The structures of the synthesized compounds were elucidated using infrared spectrometry and ^{1}H and ^{13}C NMR and elemental analysis. The antiproliferative activities were evaluated against four different human cell lines that are also described in this paper. The compound **7c** exhibited good cytotoxicity activity against cancer cell lines HL-60, NCI H292, MCF-7 and HEP with values of 6.8 µg/mL, 9.9 µg/mL, 12.1 µg/mL and 5.1 µg/mL respectively.

***Keywords*:** Azide sugar; α,β-unsaturated carbonyl; cytotoxic activity.

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DOI: 10.21577/1984-6835.20190127

Volume 11, Número 6 Novembro-Dezembro 2019

Revista Virtual de Química
ISSN 1984-6835

Synthesis and Cytotoxic Activity of New Alkyl 2-Azido-2,3-Dideoxy-α-D-Lixo-Hexopyranosides From α,β-Unsaturated Sugar Enones and Sodium Azide

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Recebido em 22 de fevereiro de 2019. Aceito para publicação em 25 de outubro de 2019

1. Introduction

The saccharides and glycoconjugates are a promising class of compounds in view of their usefulness in organic synthesis.[1, 2] These carbohydrates play a vital role in several life processes and can be used as building blocks in the synthesis of natural products.[3] Examples of carbohydrates with biological activities important are the Neocarzinostatin,[4,5] Vancomycin[6] and Macrolactin *O*[7] (Figure 1).

An interesting reaction involving carbohydrates is the introduction of the azide group in glycals. Lemieux in 1979, reported the azidonitration, an efficient methodology for the synthesis of 2-azido sugars that is still frequently used.[8] It is especially useful for the synthesis of the 2-azido derivatives, whose corresponding glycosamines lack accessibility from natural sources, as in the case of galactosamine. Aminoglycosides, however, are highly potent, broad-spectrum antibiotics, containing several amino groups presented on an oligosaccharide-like core[9-11] and polysaccharides, performing an important role in their biological activities.[12-14] The synthesis of aminoglycoside derivatives with improved properties is of great interest, once appear bacterial strains resistant all the time to these drugs.[15] Aminoglycoside antibiotics are known bactericidal agents. However, toxicity, target promiscuity and the appearance of resistance mechanisms have depreciated their clinical use.[16]

We then focused our attention on the synthesis of azide sugars in a rather simple manner. It has been shown that carbohydrate molecules possessing the enone functionality are the preferred precursors for the synthesis of branched-chain and rare sugars.[17-22] However enones are key intermediates in the synthesis of monosaccharides from non-carbohydrate precursors.[23] The stereochemical relationships at C-2, C-3 and C-4 are determined by a wise choice of reaction sequences: reduction of ketone and *cis*-hydroxylation or epoxidation.[24]

Glycopyranosid-4-uloses, derived from glycals or hydroxyl methylfurfural, are useful intermediates in many bioactive molecules, such as anthracycline antibiotics,[25,26] with proven clinical effectiveness against leukemias, lymphomas, breast carcinomas, and sarcomas.[27]

Most of the reports describing nucleophilic additions dealt with 1,4-

addition of nucleophiles to Glycopyranosid-4-uloses. As Michael addition of azide has been used as a step to obtain amino sugars,[28-30] the addition of sodium azide to α,β-unsaturated carbonyl compounds derived from sugars has been examined to a limited extent and therefore opens a new

way for the functionalization of sugar molecules. The normal conditions for Michael addition to hex-2-enopyranosid-4-uloses cannot be employed because of the sensitivity and ease of de composition of the enones on contact with alkaline solution. Some success was achieved in the presence of a potassium bicarbonate suspension in alcohol.

The present manuscript describes the Michael 1,4-addition of sodium azide in acetic acid to five enones **4a-e** leading the formation of five glycosyl azides **7a-e**. The antiproliferative activities were evaluated against four different human cell lines. We performed this investigation using an in vitro bioassay based on their cytotoxic effects against cancer cells, including NCI-H292 (human lung carcinoma), MCF-7 (human breast adenocarcinoma), HL-60 (human pro-myelocytic leukemia) and HEP (human uterus carcinoma) measured by the MTT method.

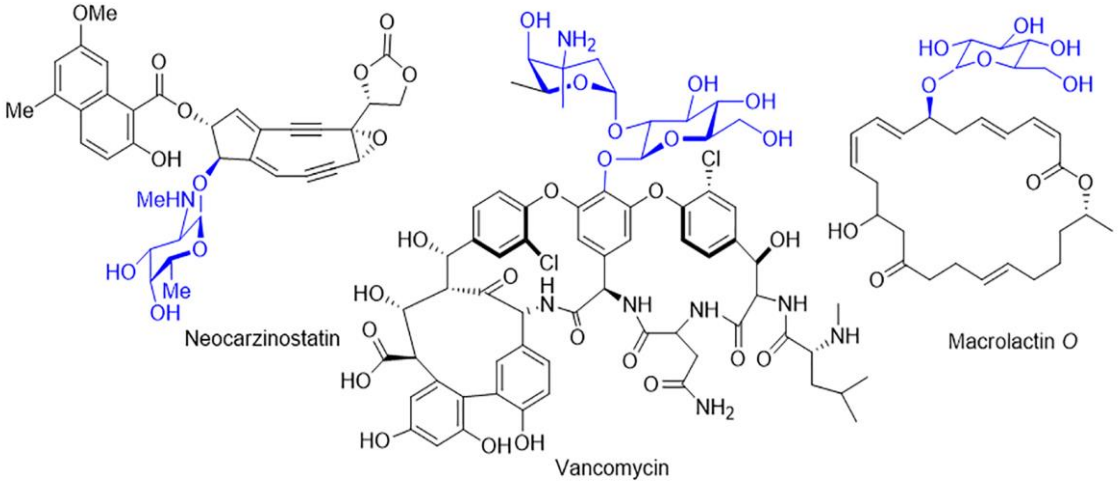
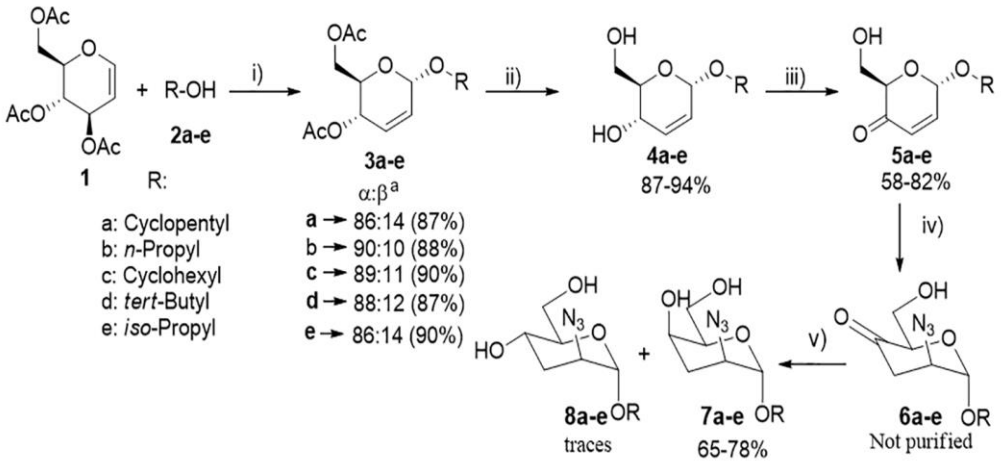


Figure 1. Examples of natural products containing an *O*-glycosidic linkage



Scheme 1. *Conditions*: i) K-10, CH_2Cl_2, reflux; ii) CH_3OH, H_2O, $(CH_3CH_2)_3N$, r.t.; iii) MnO_2, CH_2Cl_2, r.t.; iv) NaN_3, CH_3COOH, H_2O, r.t; v) $NaBH_4$, CH_3OH, 0 °C

2. Results and Discussion

The synthetic route to these azides sugars (**7a-e**) is described in Scheme 1. The starting 2,3-unsaturated glycosides (**3a-e**) were prepared by allowing tri-*O*-acetyl-D-glucal (**1**) to react with an appropriate alcohol (**2a-e)** in the presence of montmorillonite K-10 catalyst.[31,32] In all cases, the corresponding 2,3-unsaturated glycosides (**3a-e**) were obtained in good yields (65-78 %) and anomeric selectivities (Scheme 1). The anomeric ratios were obtained by HNMR and confirmed by gas chromatography. Compounds **3a-e** was then purified by chromatographic column to yield pure α-anomers. Deacetylation of alkyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides (**3a-e**), according to the method of Fraser-Reid *et al*.[33,34] furnished compounds **4a-e**, which in turn were subjected to allylic oxidation at C-4 with activated MnO_2 to afford enones **5a-e**.

Then, the compounds **5a-e** were treated with sodium azide in acetic acid via a Michael type reaction for exclusive formation of the derivatives of *threo* configuration **6a-e** (doublet δ=5.25 ppm, H_1, $J_{1,2}$ = 3.6 Hz) resulting of addition of the azide ion under kinetic control.[35] The 1,4-addition of the sodium azide

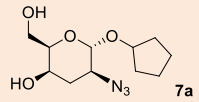
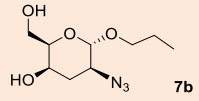
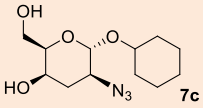
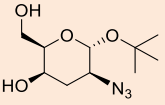
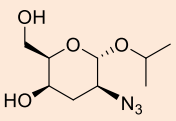
to C-2 and C-3 double bond in **5a-e** occurred from the opposite site of the aglycone to afford **6a-e**.

The intermediate **6a-e** was reduced with sodium borohydride in methanol to a furnish the diastereomeric mixture of alkyl 2-azido-2,3-dideoxy-α-D-*lixo*-hexopyranoside (**7a-e**) and alkyl 2-azido-2,3-dideoxy-α-D-*arabino*-hexopyranoside (**8a-e**). However, it was possible to separate compounds (**7a-e**) of compounds (**8a-e**) them by a very careful liquid chromatography over silica gel.

The structures and configurations of products **7a–e** were deduced through their ^{1}H NMR spectra. Compound **7c** was chosen for examination by 300 MHz ^{1}H NMR spectroscopy in order to deduce the configuration and conformation of this compound. The signal for H-1 appeared as a broad singlet at δ 4.90 ppm. The proton signal of H-4 appeared at δ 4.28 ppm as a broad singlet. Since, the *J* value between H-4 and H-5 is small (*J* 4.8 Hz), it is inferred that the OH group at C-4 is axial indicating a lyxo configuration for **7a-e.** The stereochemistry at C-2 was established on the basis of $J_{2,3eq}$ and $J_{2,3ax}$ (3.6 and 6.9 Hz, respectively) that clearly showed that the azide group was axially oriented.

The antiproliferative activity of the compounds **7a-e** was evaluated using an MTT assay[36] against four human cell lines: NCI-H292 (lung carcinoma), HL-60 (pro-myelocytic leukemia), MCF-7 (breast adenocarcinoma) and HEP (uterus carcinoma). Initially the compounds **7a-e** were screened at 25 µg/mL initial concentration was determined and then the IC_{50} concentration values. IC_{50} results are summarized in Table 1, where the compound **7c** exhibited good cytotoxicity activity against cancer cell lines HL-60, NCI H292, MCF-7 and HEP with values of 6.8 µg/mL, 9.9 µg/mL, 12.1 µg/mL and 5.1 µg/mL respectively.

Table 1. IC_{50} values µg/mL and the confidence interval for compounds **7a-e**

Entry	Compound	HL-60 (SD)	NCI H292 (SD)	MCF-7 (SD)	HEP (SD)
1	 **7a**	>25	>25	>25	>25
2	 **7b**	>25	>25	>25	>25
3	 **7c**	6.8 (±1.8)	9.9 (±3.9)	12.1 (±4.2)	5.1(±1.0)
4	 **7d**	ND	ND	ND	ND
5	 **7e**	>25	>25	>25	>25
3	**DOX**	0.2 (±0.1)	0.6 (±0.5)	0.6 (±0.03)	1.3 (±1.0)

DOX = Doxorubicin; ND = Not determined; SD = Standard deviatio

According to Table 1 the compound **7c** showed better cytotoxicity activity against

human cell lineage HEP compared to human cell lineage HL-60 with IC_{50} values of 5.1 and 6.8 respectively (entry 3). This result is very interesting because the literature reports the human cell lineage HL-60 human cell is more sensitive to oxidative stress, thus presenting a low level of antioxidant defense compared to other strains.[37,38] Doxorubicin was used as a positive control and their IC_{50} values against the three lineage cells are shown in Table 1. Additionally, the compounds **7a-b** and **7d-e** showed no cytotoxic activity against the concentration study none of the four human cell lines, however, this initial study has demonstrated the potential for this azides sugars compound **7c** exhibit good activity.

3. Experimental

3.1. General consideration

All commercially available reagents were used directly without purification unless otherwise stated. All the solvents used in reactions were distilled for purity. IR spectra were recorded as KBr films on a Brucker IFFS66 series Fourier transform spectrophotometer. ^{1}H NMR and ^{13}C NMR data were recorded in $CDCl_3$. The chemical shifts are reported as delta (δ) units in parts per million (ppm) relative to the solvent residual peak as the internal reference. Coupling constants (J) are given in Hz. Thin Layer Chromatography (TLC) was performed using Merck Silica gel 60 F_{254} plates. The solvent system for running the TLC plates was a mixture of CH_2Cl_2:EtOAc (9:1). The melting points (mp) are not corrected. Optical rotation was obtained in a Perkin-Elmer Model 141 or 241 Polarimeter 10 cm, 1 mL microcell. Microanalyses were performed at the Department of Chemistry, Universidade Federal de Pernambuco, Recife, Brazil. High-resolution mass spectra were obtained using electrospray ionization (ESI). ChemDraw-Ultra-8.0 was used to generate the nomenclature of the prepared compounds.

3.2. General procedure for the preparation of *Cyclohexyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside* (**3a**):Isolated as a colorless oil; 0.26 g (87 %); $[\alpha]_D^{25}$ +99.0 (*c* 0.98, $CHCl_3$)]; IR (thin film) ν_{max} 2940, 2861, 2673, 2137, 1746, 1456, 1373, 1234, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (br d, J =10.5 Hz, 1H, H-3), 5.74 (dt, J_{2-3} =10.5 Hz, J_{2-1} =J_{2-4} =2.4 Hz, 1H, H-2), 5.23 (dd, J_{4-5} =9.6 Hz, J_{4-3} =1.2 Hz, 1H, H-4), 5.04 (br s, 1H, H-1), 4.20 (dd, $J_{6-6'}$=12.0 Hz, J_{6-5} =5.4 Hz, 1H, H-6), 4.12 (dd, $J_{6'-6}$ =12.0 Hz, $J_{6'-5}$ =2.4 Hz, 1H, H-6'), 4.06 (ddd, J_{5-4} = 9.6 Hz, J_{5-6} = 5.4 Hz, $J_{5-6'}$ = 2.4 Hz, 1H, H-5), 2.04 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.76–1.47 (m, 9H, –OCH(CH_2)$_4$ and –OC*H*(CH_2)$_4$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 170.2, 128.5, 128.3, 93.5, 80.5, 66.6, 65.2, 62.9, 33.4, 32.2, 23.4, 23.0, 20.8, 20.7.

n-*Propyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**3b**)*: Isolated as a colorless oil; 0.24g (88 %); $[\alpha]_D^{31.7}$+118.2 (*c* 1.00, $CHCl_3$)]; IR (thin film) ν_{max} 2964, 2881, 1747, 1450, 1371, 1234, 1182, 1105 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.92–5.78 (m, 2H, H-2 and H-3), 5.29–5.25 (m, 1H, H-4), 4.99 (br s, 1H, H-1), 4.21 (dd, $J_{6-6'}$= 12.0 Hz, J_{6-5} =5.4Hz, 1H, H-6), 4.14 (dd, $J_{6'-6}$=12.0 Hz, $J_{6'-5}$=2.1 Hz, 1H, H-6'), 4.08 (ddd, J_{5-4} =9.6 Hz, J_{5-6} =5.1 Hz, $J_{5-6'}$ =2.1 Hz, 1H, H-5), 3.68 (dt, J =9.6, 7.5 Hz, 1H, –C*H*$_2$CH$_2$CH$_3$), 3.45 (dt, J =9.6, 7.5 Hz, 1H, –C*H*$_2$CH$_2$CH$_3$), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.61 (q, J =7.5 Hz, 2H,–CH$_2$C*H*$_2$CH$_3$), 0.91 (t, J =7.5 Hz, 3H, –CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 170.2,128.9, 127.8, 94.2, 70.5, 66.7, 65.2, 62.9, 22.9, 20.9, 20.7, 10.6.

D-erythro-*hex-2-enopyranoside* (**3c**): Isolated

alkyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-erythro-hex-2enopyranosides (3a–e)

The reaction of **2a–d** with compound **1** to provide the alkyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-erythro-hex-2enopyranosides **(3a-e)** was conducted according to the method of Toshima *et al*.[28] The details are given below.

Characterization data of the compounds:

as a colorless oil; 0.28 g (90 %); $[\alpha]_D^{31.7}$ +110.7 (*c* 1.00, $CHCl_3$)]; IR (thin film) ν_{max} 2933, 2858, 2659, 2134, 1747, 1450, 1370, 1233, 1187, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.82 (br d, J =10.5 Hz, 1H, H-3), 5.76 (dt, J_{2-3} =10.5 Hz, J_{2-1}=J_{2-4}=1.5 Hz, 1H, H-2), 5.24 (dd, J_{4-5} =9.3 Hz, J_{4-3} =1.2 Hz, 1H, H-4), 5.12 (br s, 1H, H-1), 4.20 (m, 3H, H-5, H-6 and H-6'), 3.64–3.55 (m, 1H, –OC*H*$(CH_2)_5$), 2.04 (s, 3H, OAc), 2.03 (s, 3H, OAc), 1.92–1.82 (m, 2H, –OCH(C*H*$_2)_5$), 1.71–1.68 (m, 2H, OCH(C*H*$_2)_5$), 1.52–1.48 (m, 1H, –OCH(C*H*$_2)_5$), 1.37–1.15 (m, 5H, –OCH(C*H*$_2)_5$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 170.2, 128.6, 128.4, 92.6, 76.6, 66.5, 65.3, 63.0, 33.6, 32.0, 25.4, 24.3, 24.0, 20.9, 20.6.

tert-*Butyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside* (**3d**): Isolated as a colorless oil; 0,25 g (87 %); $[\alpha]_D^{25}$ +100.0 (*c* 1.00, $CHCl_3$)]; IR (thin film) ν_{max} 2958, 2904, 2129, 1747, 1463, 1371, 1333, 1234, 1186, 1104 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.82 (br d, J =10.2 Hz, 1H, H-3), 5.72 (dt, J_{2-3} = 10.2 Hz, J_{2-1} = J_{2-4} =2.7 Hz, 1H, H-2), 5.31 (br s, 1H, H-1), 5.25 (br d, J_{4-5} = 9.6 Hz, 1H, H-4), 4.26–4.10 (m, 3H, H-5, H-6 and H-6'), 2.07 (s, 3H, OAc), 2.05 (s, 3H, OAc), 1.27 (s, 9H, –C(C*H*$_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 170.3, 129.5, 128.1, 88.9, 75.3, 66.4, 65.2, 63.2, 28.7, 20.9, 20.8.

3.3. General procedure for the preparation of alkyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (4a-e)

The hydrolysis of **3a–e** in 9:6:1 MeOH–H_2O–Et_3N (32 mL) required 3h at room temperature for deacetylation as determined by TLC. Solvent evaporation under reduced pressure, followed by chromatography on silica (1:1 CH_2Cl_2 – EtOAc), gave diols **4a–e** in almost quantitative yield.

iso-Propyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (**3e**): Isolated as a colorless oil; 0.24 g (90 %); $[\alpha]_D^{20}$ +97.0 (c 0.70, MeOH)]; IR (thin film) ν_{max} 2971, 2902, 1745, 1450, 1372, 1317, 1233, 1184, 1127 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76 (br d, J =11.7 Hz, 1H, H-3), 5.69 (dt, $J_{2,3}$ =11.7 Hz, $J_{2,1}$=$J_{2,4}$=1.8 Hz, 1H, H-2), 5.19-5.15 (m,1H, H-4), 5.02 (br s,1H, H-1), 4.17-4.01 (m, 3H, H-5, H-6 and H6'), 3.98-3.84 (m,1H,-CH$(CH_3)_2$),1.98 (s, 3H, OAc), 1.97 (s, 3H, OAc), 1.14 (d, J =6.3 Hz, 3H,-CH$(CH_3)_2$), 1.07 (d, J =6.0 Hz, 3H, -CH$(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 169.9, 128.5, 128.2, 92.5, 70.4, 66.5, 65.1, 62.8, 23.2, 21.7, 20.7, 20.5.

Characterization data of the compounds

Cyclopentyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside **(4a):** Isolated as a colorless oil; 1.74 g (93 %); R_f 0.16 (9:1 CH_2Cl_2 – EtOAc); $[\alpha]_D^{25}$+ 54° (c 1.0, $CHCl_3$); IR (KBr): 3404 cm^{-1} (υ OH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.95 (d, 1 H, $J_{3,2}$ = 10.2 Hz, H-3), 5.70 (dd, 1 H, $J_{2,3}$ = 10.2, $J_{2,4}$ = 2.4 Hz, H-2), 5.04 (bs, 1 H, H-1), 4.23 (m, 1 H, OCH), 4.21 (bd, $J_{4,5}$ = 9.3 Hz, 1 H, H-4), 3.87 (bd, 2 H, $J_{6,5}$ = 3.7 Hz, H-6, H-6'), 3.70 (dt, $J_{5,4}$ = 9.4, $J_{6,5}$ = 3.7 Hz, 1 H, H-5), 2.33 and 2.22 (bs, exchangeable, 2 H, 2 OH), 1.83–1.51 (m, 8 H, 4 CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.9, 126.8, 93.6, 80.3, 70.6, 67.2, 65.7, 34.8, 18.6. Anal.Calcd for $C_{11}H_{18}O_4$ (214.12): C, 61.70; H, 8.47. Found: C, 61.28; H, 8.37.

n-Propyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside **(4b):** Isolated as a colorless oil; 1.74 g (94 %); R_f 0.20 (9:1 CH_2Cl_2 – EtOAc); $[\alpha]_D^{25}$+ 52° (c 0.52, $CHCl_3$); IR (KBr): 3384 cm^{-1} (υ OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 (d, 1 H, $J_{3,2}$ = 10 Hz, H-3), 5.76 (d, 1 H, $J_{2,3}$ = 10 Hz, H-2), 4.97 (bs, 1 H, H-1), 4.20 (bd, 1 H, J = 8.4 Hz, H-4), 3.86 (bs, 2 H, H-6, H-6'), 3.73-3.70 (m, 2H, H-5 and O-C$\underline{H}_2CH_2CH_3$), 3.73-3.70 (m, 1H, O-C$\underline{H}_2CH_2CH_3$), 2.68 (bs, exchangeable, 1H, 1OH), 2.42 (bs, exchangeable, 1 H, 1OH), 1.65–1.58 (m, 2 H, O-$CH_2C\underline{H}_2CH_3$), 0.94 (t, 3 H, J 7.2Hz, O-$CH_2CH_2C\underline{H}_3$). ^{13}C NMR (100 MHz, $CDCl_3$): ***δ*** 133.28, 126.34, 94.29, 71.39, 70.50, 64.22, 62.70, 22.94, 20.61. HRMS (ESI, MeOH:H_2O) calcd for $C_9H_{15}O_4Na$ $[M + Na]^+$, 211.2180, found 211.1024.

Cyclohexyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside **(4c):** Isolated as a colorless oil; 1.62 g (87 %); R_f 0.20 (9:1 CH_2Cl_2 – EtOAc); $[\alpha]_D^{25}$+ 46° (c 3.4, $CHCl_3$); IR: 3100 – 3600 cm^{-1}

5.95 (ddd, 1 H, $J_{3,2}$ = 10.2, $J_{3,1}$ = 1.3, $J_{3,4}$ = 1.3

Hz, H-3), 5.73 (ddd, 1 H, $J_{2,3}$ = 10.5, $J_{2,4}$ = 2.4, $J_{2,1}$ = 2.7 Hz, H-2), 5.13 (m, 1 H, H-1), 4.20 (bd, $J_{4,5}$ = 9.0 Hz, H-4), 3.85 (d, 2 H, $J_{6,5}$ = 3.9 Hz, H-6, H-6'), 3.75 (dt, 1 H, $J_{5,4}$ = 9.0, $J_{5,6}$ = 3.9 Hz, H-5), 3.62 (m, 1 H, OCH), 2.63 and 2.37 (bs, exchangeable, 2H, 2OH), 2.04–1.10 (m, 10H, $5CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.9, 125.1, 102.3, 92.7, 70.6, 67.2, 65.7, 34.2, 32.5, 18.6. Anal. Calcd for $C_{12}H_{20}O_4$ (228.29): C, 63.13; H, 8.83. Found: C, 63.25; H, 9.10.

tert-*Butyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside* **(4d):** Isolated as a colorless oil; 1.74 g (93 %); R_f 0.16 (9:1 CH_2Cl_2 – EtOAc); $[\alpha]_D^{25}$+ 64° (c 0.96, $CHCl_3$); IR (KBr): 3405 cm $^{-1}$ (υ OH); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91 (d, 1 H, $J_{3,2}$ = 9.9 Hz, H-3), 5.60 (dd, 1 H, $J_{2,3}$ = 9.9, $J_{1,2}$ = 2.4 Hz, H-2), 5.28 (d, 1 H, J = 1.2 Hz, H-1), 4.15 (bd, $J_{4,5}$ = 9.3 Hz, 1 H, H-4), 3.81 (d, 2 H, $J_{5,6}$ = 4.2 Hz, H-6, H-6'), 3.76 (dd, $J_{4,5}$ = 9.3 Hz, $J_{5,6}$ = 4.2 Hz, 1 H, H-5), 2.37 (bs, exchangeable, 2H, 2OH), 1.28 (s, 9 H, 3 CH_3). ^{13}C NMR (75MHz, $CDCl_3$): ***δ*** 132.7, 125.7, 91.5, 72.2, 70.43, 62.68, 23.6, 20.8. Anal.Calcd for $C_{10}H_{18}O_4.1/4H_2O$ (206.75): C, 58.09; H, 9.01. Found: C, 57.73; H, 9.00.

iso-Propyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside **(4e):** Isolated as a colorless oil; 1.74 g (90 %); R_f 0.18 (9:1 CH_2Cl_2 – EtOAc); $[\alpha]_D^{25}$+ 63° (c 0.9, $CHCl_3$); IR (KBr): 3391 cm $^{-1}$ (υ OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94 (d, 1 H, $J_{3,2}$ = 10.0 Hz, H-3), 5.70(dt, 1 H, $J_{2,3}$ = 10.0 and $J_{2,1}$ = 2.4 Hz, H-2), 5.07(bs, 1 H, H-1), 4.19 (d, 1 H, J = 8.4 Hz, H-4), 3.96 (q, 1H, J = 6.0 Hz, C*H*$(CH_3)_2$), 3.85-3.83 (m, 2H, H-6 and H-6'), 3.75-3.70 (m, 1H, H-5), 2.71 (bs, 1H, 1OH), 2.42 (bs, 1 H, 1OH), 1.23 (d, 3 H, J = 6.0 Hz, CH(C*H*$_3)_2$), 1.17 (d, 3 H, J = 6.0 Hz, CH(C*H*$_3)_2$). ^{13}C NMR (100MHz, $CDCl_3$): ***δ*** 133.17, 126.78, 92.55, 71.26, 70.43, 64.24, 62.68, 23.64, 21.84. HRMS (ESI, MeOH:H_2O) calcd for $C_9H_{15}O_4Na$ $[M + Na]^+$, 211.2180, found 211.1147.

3.4. General procedure for the preparation of alkyl 2,3-dideoxy-α-D-glycero-2-enopyranosid-4-uloses (5a–e)

The appropriate diol **4** (4.67 mmol) was dissolved in CH_2Cl_2 (150 mL), activated MnO_2 (4.61 g, 53 mmol) was added, and the contents stirred at rt until the completion of the reaction. The progress of the reaction was monitored by TLC using 9:1 CH_2Cl_2 EtOAc followed by spot viewing under UV light. Filtration and solvent evaporation produced analytically pure **5a–e** after recrystallization from ether – hexane.

Characterization data of the compounds

Cyclopentyl-2,3-dideoxy-α-D-glycero-hex-2-enopyranosid-4-ulose **(5a)**: Solid white; 0.79 g (76 %); mp 76.4–77.0 °C; R_f 0.39 (9:1 CH_2Cl_2–EtOAc); $[\alpha]_D^{25}$–30° (c 0.92, $CHCl_3$); IR (KBr): 3457 (υ OH), 1692 cm $^{-1}$ (υ C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (dd, 1 H, $J_{2,3}$ = 10.2, $J_{2,1}$ = 3.6 Hz, H-2), 6.09 (d, 1 H, $J_{3,2}$ = 10.2 Hz, H-3), 5.32 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 4.49 (dd, 1 H, $J_{5,6}$ = 4.5, $J_{5,6'}$ = 4.5 Hz, H-5), 4.34 (m, 1 H, OCH), 4.01 (dd, $J_{6,6'}$ = 11.7, $J_{6,5}$ = 4.5 Hz, H-6), 3.91 (dd, $J_{6',6}$ = 11.7, $J_{6',5}$ = 4.5 Hz, H-6'), 2.27 (bs, exchangeable, 1 H, OH), 1.87–1.55 (m, 8 H, $4CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 144.9, 128.1, 92.5, 81.1, 62.2, 33.6, 32.5, 18.6. Anal. Calcd for $C_{11}H_{18}O_4$ (212.24): C, 62.25; H, 7.59. Found: C, 62.15; H, 7.39.

n-Propyl-2,3-dideoxy-α-D-glycero-hex-2-enopyranosid-4-ulose **(5b)**: Pale yellow viscous liquid; 0.69 g (80 %); $[\alpha]_D^{25}$ -16.6 (c 1,0 $CHCl_3$); IR (KBr): 3370 (υ OH), 1701 cm^{-1} (υ C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (dd, 1H, $J_{2,1}$ = 3.6 Hz, $J_{2,3}$=10.2 Hz, H-2); 6.14 (d, 1H, $J_{3,2}$ = 10.2Hz, H-3); 5.27 (d, 1H, $J_{2,1}$ = 3.6 Hz, H-1); 4.49 (t, 1H, J = 4.5 Hz, H-5); 4.05-3,76 (m, 2H, H-6 and H-6'); 3.54 (dd, 2H, J = 2.7 Hz and J = 9.3Hz, CH_2,); 2.02 (bs, exchangeable, 1H, OH); 1.64 (q, 2H, CH_2); 0.96 (t, 3H, J = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.9, 144.0, 127.6, 93.1, 74.1, 71.2, 61.6, 22.8, 10.5. Anal. Calcd for $C_9H_{14}O_4$ (186.08): C, 58.05; H, 7.58. Found: C, 58.97; H, 7.83.

Cyclohexyl-2,3-dideoxy-α-D-glycero-hex-2-enopyranosid-4-ulose **(5c)**: Solid white; 0.73 g (69 %); mp 99.0 – 100 °C; R_f 0.42 (9:1 CH_2Cl_2–EtOAc); $[\alpha]_D^{25}$ -30 (c 1,0 $CHCl_3$); IR (KBr): 3100 – 3600 (υ OH), 1690 cm^{-1} (υ C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (dd, 1 H, $J_{2,3}$ = 10.2, $J_{2,1}$ = 3.6 Hz, H-2), 6.11 (d, 1 H, $J_{3,2}$ = 10.2 Hz, H-

3), 5.17 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 4.53 (dd, 1 H, $J_{5,6}$ = 4.2, $J_{5,6'}$ = 4.2 Hz, H-5), 4.02 (dd, $J_{6',6}$ = 11.8, $J_{6',5}$ = 4.2 Hz, H-6'), 3.92 (dd, 2 H, $J_{6,6'}$ = 11.8, $J_{6,5}$ = 4.2 Hz, H-6), 3.80–3.62 (m, 1 H, OCH), 2.22 (bs, exchangeable, 1 H, OH), 2.20–0.80 (m, 10 H, 5 CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.3, 145.0, 128.9, 93.5, 63.7, 62.9, 33.9, 32.9, 24.4, 18.6. Anal. Calcd for $C_{12}H_{18}O_4$ (226.26): C, 63.72; H, 7.96. Found: C, 63.42; H, 8.07.

tert-Butyl-2,3-dideoxy-α-D-glycero-hex-2-enopyranosid-4-ulose **(5d)**: Pale yellow viscous liquid; 0.54 g (58 %).; $[\alpha]_D^{25}$ -7^0± 2^0 (c=1,7 CH_2Cl_3); IR (KBr): 3409 (υ OH), 1722 cm^{-1} (υ C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.81 (dd, 1H, $J_{2,1}$ = 3.9 Hz, $J_{2,3}$ = 10.2 Hz, H-2); 6.10 (d, 1H, $J_{3,2}$ = 10.2 Hz, H-3); 5.55 (d, 1H, $J_{2,1}$ = 3.9 Hz, H-1); 4.58 (t, 1H, J = 4.5 Hz, H-5); 3.98 (dd, 1H, $J_{6,6'}$ = 12.3 Hz, $J_{6,5}$ = 4.5 Hz, H-6); 3.89 (dd, 1H, $J_{6',6}$ = 12.3 Hz, $J_{6,5}$ = 4.5 Hz, H-6'); 2.20 (bs, exchangeable, 1H, OH); 1.30 (s, 9H, 3CH_3); 0.96 (t, 3H, J = 7.2Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.9, 144.0, 127.6, 93.1, 74.1, 71.2, 61.6, 22.8, 10.5. Anal. Calcd for $C_{10}H_{16}O_6$.1/2H_2O (209.24): C, 57.40; H, 8.18. Found: C, 57.31; H, 7.13.

iso-Propyl-2,3-dideoxy-α-D-glycero-hex-2-enopyranosid-4-ulose ***(5e)****:* Pale yellow viscous liquid: 0.71 g (82 %); $[\alpha]_D^{25}$= +128 (c 0.87, $CHCl_3$), IR (KBr): 3390 (υ OH), 1711 cm^{-1} (υ C=O); ^{1}H NMR (300 MHz, CDC_{l3}): δ 6.91 (dd, 1H, $J_{2,1}$ = 3.6 Hz, $J_{2,3}$ =10.2 Hz, H-2); 6.14 (d, 1H, $J_{3,2}$ = 10.2Hz, H-3); 5.27 (d, 1H, $J_{2,1}$ = 3.6 Hz, H-1); 4.49 (t, 1H, J= 4.5 Hz, H-5); 4.05-3,76 (m, 2H, H-6 and H-6'); 3.99 (sept., 1H, $OCH(CH_3)_2$, J = 6.1 Hz), 2.02 (bs, exchangeable, 1H, OH); 1.22 (d, 3H, $OCH(CH_3)_2$, J = 6.2 Hz), 1.18 (d, 3H, $OCH(CH_3)_2$, J = 6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 144.0, 126.3, 93.1, 70.8, 69.9, 64.8, 22.8, 20.8. Anal. calcd for $C_9H_{16}O_4$: C, 57.41; H, 8.57. Found: C, 57.30; H, 8.74.

3.5. General procedure for the preparation of alkyl 2-azido-2,3-dideoxy-α-D-*threo*-hexopyranosid-4-ulose (6a-e)

The mixture of the alkyl 2,3-dideoxy-α-D-glycero-2-enopyranosid-4-uloses **5a-e** (1.114 mmol), HOAc (4 mmol) and NaN_3 (4 mmol) was stirred in 2 mL of H_2O at room temperature for 10 min. After addition of aqueous $NaHCO_3$, the products were extracted with ethyl acetate. Because the compound **6a-e** decomposes easily, the solvent evaporated the next stage was reached.

3.6. General procedure for the preparation of alkyl 2-azido-2,3-dideoxy-α-D-*lixo*-hexopyranoside (7a-e).

$NaBH_4$ (200 mg, 5.0 mmol) was added portion-wise to a stirred solution of the ketone **6a-e** (0.74 mmol) in MeOH (30 mL). The mixture was treated with AcOH (10 % aq.) dropwise to destroy the excess reducing agent and the solvent evaporated. The residue was subjected to workup (EtOAc) yielding the compounds **7a-e** as a pale-yellow oil.

Characterization data of the compounds

Cyclopentyl-2-azido-2,3-dideoxy-α-D-lixo-hexopyranoside **(7a):** From **6a** (0.190 g, 0.74 mmol); yields 78 %; R_f 0.16 (8:2 $CHCl_3$– EtOAc); $[\alpha]_D^{28}$= +75.8 (c 0.6, $CHCl_3$); IR (KBr): 3402 (υ OH), 2100 cm^{-1} (υ N_3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.90 (s, 1 H, H-1), 4.28 (d, 1 H, $J_{4,5}$= 4.8 Hz, H-4), 3.92-3.75 (m, 4H, H-5, H-6, H-6' and CH-O), 3.62 (dt, 1 H, $J_{2,3eq}$=3.6Hz and $J_{2,3ax}$ = 6.9 Hz, H-2), 2.46 (bs, exchangeable, 2 H, OH), 2.19-1.98 (m, 1H, $J_{3,2eq}$=3.6Hz and $J_{3,2ax}$ = 6.9 Hz H-3), 1.82-1.54 (m, 8H, 5 CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 93.7, 74.2, 71.9, 70.0, 58.7, 49.0, 26.1, 24.5, 23.7.

n-Propyl-2-azido-2,3-dideoxy-α-D-lixo-hexopyranoside **(7b):** From **6b** (0.171 g, 0.74 mmol); yields 68 %; R_f 0.16 (8:2 $CHCl_3$– EtOAc); $[\alpha]_D^{28}$= +86 (c 0.5, $CHCl_3$); IR (KBr): 3399 (υ OH), 2102 cm^{-1} (υ N_3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80 (s, 1 H, H-1), 3.83 (d, 1 H, J 7.1 Hz, H-4), 3.59-3.39 (m, 4H, H-5, H-6, H-6' and CH_2-O), 2.50 (s, 1 H, H-2), 2.05 (bs, exchangeable, 2 H, OH), 1.29 (s, 1H, H-3), 1.25-1.08 (m, 2H, CH_2), 0.87 (t, J= 8.0 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 84.7, 73.3, 72.8, 66.16, 56.4, 49.2, 22.7, 21.2, 17.2.

Ciclohexyl-2-azido-2,3-dideoxy-α-D-lixo-hexopyranoside **(7c):** From **6c** (0.201 g, 0.74 mmol); yields 75 %; R_f 0.15 (8:2 $CHCl_3$– EtOAc); $[\alpha]_D^{28}$= +97.5 (c 1.0, $CHCl_3$); IR (KBr): 3429 (υ

OH), 2103 cm $^{-1}$ (υ N_3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (d, 1 H, $J_{1,2}$= 3.6 Hz, H-1), 4.22 (d, 1 H, *J* =7.1 Hz, H-4), 3.88-3.11 (m, 4H, H-5, H-6, H-6' and CH-O), 3.65 (dt, 1 H, $J_{2,3eq}$=3.5Hz and $J_{2,3ax}$ = 7.1 Hz, H-2), 2.47 (bs, exchangeable, 2 H, OH), 2.24-2.02 (dt, 1H, $J_{3,2eq}$=3.5Hz and $J_{3,2ax}$ = 7.1 Hz H-3), 1.82-1.34 (m, 10H, 5 CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 94.4, 75.1, 72.8, 70.2, 59.9, 57.0, 33.2, 25.5, 24.0, 23.7.

tert-Butyl-2-azido-2,3-dideoxy-α-D-lixo-hexopyranoside **(7d):** From **6d** (0.181 g, 0.74 mmol); yields 65 %; R_f 0.16 (8:2 $CHCl_3$– EtOAc); $[\alpha]_D^{28}$= +10.8 (c 0.6, $CHCl_3$); IR (KBr): 3390 (υ OH), 2103 cm $^{-1}$ (υ N_3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08 (s, 1 H, H-1), 3.90-3.60 3.92-3.75 (m, 4H, H-4, H-5, H-6, and H-6'), 2.20-2.10 (m, 2 H, H-2 and H-3), 2.46 (bs, exchangeable, 2 H, OH), 1.31 (s, 9H, 3 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 91.5, 71.4, 66.4, 62.8, 56.2, 31.0, 28.4, 14.2.

iso-Propyl-2-azido-2,3-dideoxy-α-D-lixo-hexopyranoside **(7e):** From **6e** (0.171 g, 0.74 mmol); yields 70 %; R_f 0.16 (8:2 $CHCl_3$– EtOAc); $[\alpha]_D^{28}$= +78.5 (c 0.6, $CHCl_3$); IR (KBr): 3342 (υ OH), 2104 cm $^{-1}$ (υ N_3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.73 (s, 1 H, H-1), 4.16 (t, 1 H, $J_{4,5}$ = 4.0 Hz, H-4), 3.77-3.40 (m, 4H, H-5, H-6, H-6' and CH-O), 2.11 (dt, 1 H, $J_{2,3eq}$ = 4.0 Hz and $J_{2,3ax}$ = 7.4 Hz, H-2), 2.09 (bs, exchangeable, 2 H, OH), 1.61 (d, 1H, $J_{3,2eq}$ =4.0 Hz and $J_{3,2ax}$ = 7.4 Hz, H-3), 1.26-0.83 (m, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 97.0, 71.9, 69.7, 68.1, 56.4, 38.7, 23.7, 22.7, 14.0.

3.7. Cytotoxicity assay

The antiproliferative activities alkyl 2-azido-2,3-dideoxy-α-D-*lixo*-hexopyranoside (**7a-e**) were evaluated in the following human cancer cells lines: NCI-H292 (lung carcinoma), HL-60 (pro-myelocytic leukemia), MCF-7 (breast adenocarcinoma) and HEP (uterus carcinoma) provided by the Rio de Janeiro Cell Bank (RJ-Brazil). All cancer cells were maintained in RPMI 1640 medium and DMEN supplemented with 10 % fetal bovine serum, 2mM glutamine, 100 U/mL penicillin, 100μg/mL streptomycin at 37°C with 5 % CO_2. The cytotoxicity of all compounds was tested using a 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-*2H* tetrazolium bromide (MTT) (Sigma Aldrich Co., St. Louis, MO, USA) reduction assay. For all experiments, tumor cells were plated in 96-well plates (10^5 cells/mL for adherent cells or 3×10^5 cells/mL for Leukemia). Tested Compounds (0.1-25 μg/mL) dissolved in DMSO 1 % were added to each well and incubated for 72 h. Control groups received the same amount of DMSO. After 69 h of treatment, 25 μL of MTT (5mg/mL) was added. Three hours later, the MTT formazan product was dissolved in 100 μL of DMSO, and absorbance was measured at 595 nm in a plate spectrophotometer. The IC_{50} values and their 95 % confidence intervals for two different experiments were obtained by nonlinear regression using the Graphpad Prism program (Intuitive Software for Science, San Diego, CA).

4. Conclusions

In summary, we have described the synthesis of novel compounds **7a-e** in five reaction steps. The final products were obtained in times 5 hours with good yields (65-78 %). Five synthetic compounds **7a-e** were tested as potential cytotoxic agents against four human cell lines: NCI H292 (lung carcinoma), HL-60 (pro-myelocytic leukemia), MCF-7 (breast adenocarcinoma) and HEP (uterus carcinoma). The initial screening was performed at an initial compound concentration of 25 μg/mL. Of the five compounds tested, only the compound **7c** exhibited good cytotoxicity activity against cancer cell lines HL-60, NCI H292, MCF-7 and HEP with values of 6.8 μg/mL, 9.9 μg/mL, 12.1 μg/mL and 5.1 μg/mL respectively. In addition, the results indicate that these azides sugars are important precursors in the synthesis of new biologically active drugs, also allow further structural modifications as may increase its cytotoxic activity.

Acknowledgments

The authors are grateful to the Brazilian National Research Council (CNPq), Pernambuco State Foundation for Science and Technology (FACEPE) and (CAPES) for financial help.

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