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RESEARCH ARTICLE

Identification of 1-Aryl-1*H*-1,2,3-Triazoles as Potential New Antiretroviral Agents

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Abstract: ***Background*:** Low molecular weight 1-Aryl-1*H*-1,2,3-triazoles are endowed with various types of biological activities, such as against cancer, HIV and bacteria. Despite the existence of six different classes of antiretroviral drugs in clinical use, HIV/AIDS continue to be an on growing public health problem.

***Objective*:** In the present study, we synthesized and evaluated thirty 1-Aryl-1*H*-1,2,3-triazoles against HIV replication.

***Method*:** The compounds were prepared by Huisgen 1,3-dipolar cycloaddition protocol catalyzed by Cu(I) between aryl azides and propargylic alcohol followed by further esterification and etherification from a nucleophilic substitution with acid chlorides or alkyl bromides in good yields. The compounds were submitted to the inhibition of HIV replication and evaluation of their cytotoxicity. Initially, the compounds were screened at 10 μM and the most active were further evaluated in order to obtain some pharmacological parameters.

***Results*:** Thirty molecules were evaluated, six were selected – because they inhibited more than 80% HIV replication. We further showed that two of these compounds are 8-times more potent, and less cytotoxic, than nevirapine, an antiretroviral drug in clinical use.

***Conclusion*:** We identified very simple triazoles with promissing antiretroviral activities that led to the development of new drugs against AIDS.

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1. INTRODUCTION

The acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). Despite the success of highly active antiretroviral therapy (HAART), which increases the lifespan of HIV-infected individuals, it is estimated that over 35 million people are infected by this virus worldwide. Among these, around 2 million people die of AIDS yearly, of which 330,000 are children [1].

HIV-1 enters T helper lymphocytes, monocyte/macrophages and dendritic cells, by using the CD4 molecule and chemokine receptors CCR5 or CXCR4 onto cellular surface. During HIV-1 life cycle, viral RNA undergoes reverse transcription, which is accomplished by the action of the viral enzyme reverse transcriptase (RT), and the resulting cDNA is further integrated in the host cell genome. New progeny virions are assembled bud through the cell membrane and get mature due to the effect of viral protease [2]. In order to suppress HIV-1 replication and delay clinical progression to AIDS, several drugs have been studied [3]. Currently, there are 24 drugs approved for clinical use against HIV, these are distributed in six distinct classes due to their mechanisms of action and resistance [4] (Fig. **1**): (i) nucleoside reverse transcriptase inhibitors (NRTIs), such as azidovudine, better known as AZT (**1**); (ii) non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as efavirenz (**2**); (iii) (iv) protease inhibitors (PIs), like ritonavir (**3**); (iv) integrase inhibitors,

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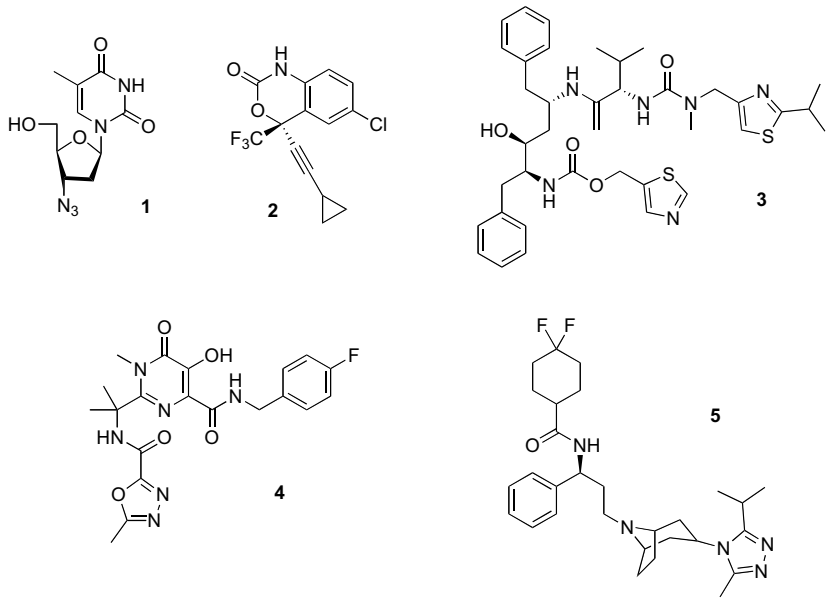


Fig. (1). Representative molecules of the HAART.

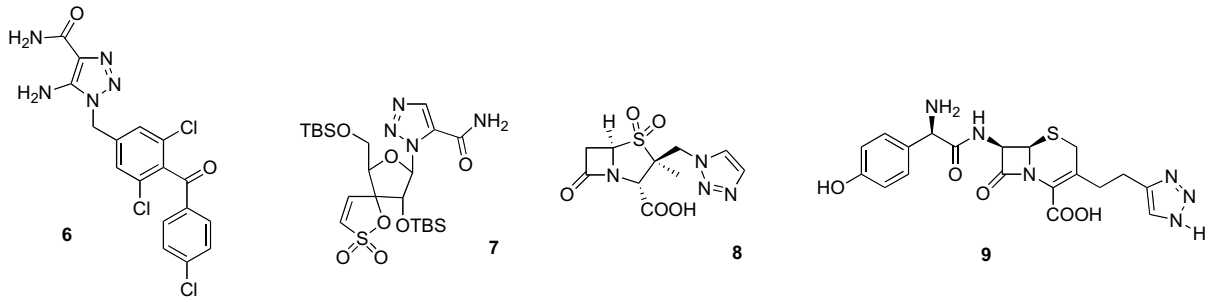


Fig. (2). Drugs containing the heterocycle 1,2,3-triazole.

for example raltegravir (**4**); (v) fusion inhibitors, *e.g.* enfuvirtide, a 36 amino acids peptide; and (vi) coreceptor antagonists as maraviroc (**5**). The above mentioned classes I to V target viral proteins, whereas the sixth category aims at a cellular component [4]. The combination of drugs from three distinct classes composes the HAART, which aims to reduce the viral load and thereby recover some cellular parameters such as the number and functionality of CD4 + T cells [2]. However, this combination is not able to eliminate HIV-1 from infected tissues [2]. In addition, multiresistant strains have been described [5-8]. It was expected that at least the fitness of multiresistant viruses would be reduced, but surprisingly, primary infections with these strains have been described [5-9]. The combination of compounds that comprises HAART also presents another limitation, high cytotoxicity, which leads the host to metabolic disorders [4, 10]. Therefore, the continuous search for new antiretroviral drugs is pivotal.

A variety of biological activities are found for heterocycles containing 1,2,3-triazole nucleus [11] and some examples of drugs with this core heterocycle (Fig. **2**) are: anticancer carboxyanidatriazole (**6**), NNRTI known as TSAO (**7**) and antibiotics beta-lactams such as tazobactam (**8**) and cephalosporinacefatrizine (**9**) [12].

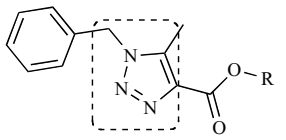
Recently, we can find some 1*H*-1,2,3-triazoles capable of inhibition of HIV virus replication. Fang and coworkers [13] synthesized a series of dihydroalkylthiobenzyl-oxopyrimidines (S-DABO) derivatives with the substituted 1*H*-1,2,3-triazole moiety with significative anti HIV-1 potency (EC_{50} up to 3.22 μM) compared with the drug 3TC (EC_{50} 2.24 μM). In another study, Wu *et al.* [14] developed new 1*H*-1,2,3-triazoles conjugated with nucleosides leading to new compounds that exhibited potent anti-HIV-1 activity with no cytotoxicity at concentration up to 25 μM.

As part of our research program on the synthesis of new biologically active compounds, we prepared several new triazoles and evaluated their inhibitory profile against the HIV virus. We now report our results of the synthesis and in vitro evaluation of low molecular weight 1-Aryl-1*H*-1,2,3-triazoles against HIV virus growth.

2. MATERIALS AND METHODS

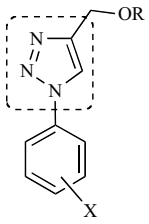
2.1. Chemistry

The reagents were purchased from Sigma-Aldrich Brazil and were used without further purification. Column chromatography was performed with silica gel 60 (Merck 70-230



R = Ribofuranose (Inhibition 63.6%)

Xylofuranose (Inhibition 64.7%)



	Inhibition
11e, R = Propyl, X = 4-Cl	89%
11h, R = Propyl, X = 2,5-Cl	91%
11k, R = Propyl, X = 3,5-Cl	90%
11n, R = Propyl, X = 4-OMe	88%
12e, R = Hexanoyl, X = 2,5-Cl	85%
12i, R = Hexanoyl, X = 4-OMe	81%

Fig. (3). HIV inhibition of glycotriazoles versus 1-Aryl-1*H*-1,2,3-triazoles.

mesh). Analytical thin layer chromatography was performed with silica gel plates (Merck, TLC silica gel 60 F254), hexane:ethyl acetate (7:3) as eluent, and the plots were visualized using UV light or aqueous solutions of ammonium sulfate. The indicated yields refer to chromatographically and spectroscopically homogeneous materials. Melting points were obtained on a Fischer-Johns apparatus and were uncorrected. Infrared spectra were measured with KBr pellets on a Perkin-Elmer model 1420 FT-IR Spectrophotometer, and the spectra were calibrated relative to the 1601.8 cm^{-1} absorbance of polystyrene. NMR spectra were recorded on a Varian Unity Plus VXR (500 MHz) instrument in DMSO-d_6 solutions. The chemical shift data were reported in the units of d (ppm) downfield from tetramethylsilane or the solvent, either of which was used as an internal standard; coupling constants (*J*) are reported in hertz and refer to apparent peak multiplicities. CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer.

2.1.1. General Procedure for Preparing 1,2,3-Triazoles

The protocols for preparing all of the 1*H*-1,2,3-triazoles and the physical and spectroscopic data for **10a-e, 11a, 11c-d, 11f, 11i, 11m, 12a-e, 12g-h, 12j** were previously reported in our studies [15, 16]. All the triazoles were fully characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and CHN elemental analysis.

2.1.2. 4-(Propoxymethtyl)-1-phenyl-1H-1,2,3-Triazole (11b)

Obtained in 62 % as a yellow oil, R_f = 0.82; IR (KBr, cm^{-1}): 2961, 2933, 2872, 1730, 1598, 1503, 1465, 1377, 1339, 1229, 1095, 1040, 989, 814, 757, 690; NMR ^{1}H (500 MHz, DMSO-d_6) δ: 0.87 (3H, t, *J* 7.0 Hz); 1.54 (2H, sext, *J* 7.0 Hz); 3.45 (2H, t, *J* 7.0 Hz); 4.58 (2H, s); 7.75 (1H, t, *J* 7.7 Hz); 7.59 (2H, t, *J* 7.7 Hz); 7.89 (2H, d, *J* 7.7 Hz); 8.76 (1H, s); NMR ^{13}C (125 MHz APT, DMSO-d_6) δ: 10.6; 22.5, 63.3, 71.5, 120.2, 122.2, 128.8, 130.0, 136.8, 145.6; Anal. Calcd for. $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.54; H, 7.12; N, 18.89.

2.1.3. 1-(4-Chlorophenyl)-4-(Propoxymethyl)-1H-1,2,3-triazole (11e)

Obtained in 45% as a yellow solid, R_f = 0.74, m.p. 75-76ºC; IR (KBr, cm^{-1}): 3160, 2968, 2932, 2871, 1721, 1563, 1502, 1456, 1341, 1229, 1194, 1092, 984, 954, 837, 817, 783, 737, 697, 753; NMR ^{1}H (500 MHz, DMSO-d_6) δ: 0.99 (3H, t, *J* 7.0 Hz); 1.66 (2H, sext, *J* 7.0 Hz); 3.56 (2H, t, *J* 7.0 Hz); 4.70 (2H, s); 7.77-7.79 (2H, m); 8.05-8.07 (2H, m); 8.90 (1H, s); NMR ^{13}C (125 MHz APT, DMSO-d_6) δ: 10.6, 22.5, 63.3, 71.5, 121.9, 122.2, 129.9, 133.1, 135.6, 145.7; Anal. Calcd for. $C_{12}H_{14}ClN_3O$: C, 57.26; H 5.61; N, 16.69. Found: C, 57.42; H, 5.82; N, 16.37.

2.1.4. 1-(2,5-Dichlorophenyl)-4-ethoxy-1H-1,2,3-Triazole (11g)

Obtained in 50 % as a yellow oil, R_f = 0.70; IR (KBr, cm^{-1}): 3141, 2975, 2868, 1732, 1588, 1487, 1448, 1376, 1231, 1097, 1038, 874, 809, 698, 671, 651; NMR ^{1}H (500 MHz, DMSO-d_6) δ: 1.27 (3H, t, *J* 3.9 Hz); 3.67 (2H, q, *J* 3.9 Hz); 4.70 (s, 2H); 7.84 (1H, dd, *J* 5.4 and 1.5 Hz); 7.92 (1H, d, *J* 5.4 Hz); 8.02 (1H, d, *J* 1.5 Hz); 8.63 (1H, s); NMR ^{13}C (125 MHz APT, DMSO-d_6) δ: 14.9, 62.8, 65.0, 125.8, 127.4, 128.0, 131.2, 131.8, 132.4, 135.5, 144.4; Anal. Calcd for. $C_{11}H_{11}Cl_2N_3O$: C, 48.55; H 4.07; N, 15.44. Found: C, 48.63; H, 4.02; N, 15.37.

2.1.5. 1-(2,5-Dichlorophenyl)-4-propoxy-1H-1,2,3-triazole (11h)

Obtained in 50 % as a yellow oil, R_f = 0.73; IR (KBr, cm^{-1}): 2962, 2872, 1588, 1486, 1450, 1369, 1231, 1096, 1037, 1000, 874, 811, 760, 694, 651; NMR ^{1}H (500 MHz, DMSO-d_6) δ: 0.99 (3H, t, *J* 7.0 Hz); 1.67 (2H, pent, *J* 7.0 Hz); 3.58 (2H, t, *J* 7.0 Hz); 3.61 (2H, t, J 6.9 Hz); 4.72 (2H, s); 7.85 (1H, dd, *J* 9.0 and 2.5 Hz); 7.92 (1H, d, *J* 9.0 Hz); 8.01 (1H, d, *J* 3.0 Hz); 8.66 (1H, s); NMR ^{13}C (125 MHz APT, DMSO-d_6) δ: 10.5, 22.4, 63.0, 71.3, 125.9, 127.5, 128.2, 131.4, 131.9, 132.5, 135.5, 144.4; Anal. Calcd for. $C_{12}H_{13}Cl_2N_3O$: C, 50.37; H 4.58; N, 14.68. Found: C, 50.24; H, 4.52; N, 14.88.

2.1.6. 1-(3,5-Dichlorophenyl)-4-(Dthoxymethyl)-1H-1,2,3-triazole (11j)

Obtained in 54% as a yellow solid, R_f = 0.55, m.p. 49-50ºC; IR (KBr, cm^{-1}): 2974, 2927, 2865, 1728, 1585, 1475, 1440, 1374, 1334, 1278, 1094, 1039, 851, 807, 666; NMR ^{1}H (500 MHz, DMSO-d_6) δ: 1.28 (3H, t, *J* 6.5 Hz); 3.67 (2H, t, *J* 6.5 Hz); 4.71 (2H, s); 7.86 (1H, t, *J* 2.0); 8.19 (1H, d, *J* 2.0 Hz); 9.03 (1H, s); NMR ^{13}C (125 MHz APT, DMSO-d_6) δ: 15.0, 63.0, 65.1, 118.6, 122.4, 127.9, 135.2, 138.3, 145.7; Anal. Calcd for. $C_{11}H_{11}Cl_2N_3O$: C, 48.55; H 4.07; N, 15.44. found: C, 48.66; H, 3.98; N, 15.40.

2.1.7. 1-(3,5-Dichlorophenyl)-4-(Propoxymethyl)-1H-1,2,3-triazole (11k)

Obtained in 68% as a yellow solid, R_f = 0.65, m.p. 49-50ºC; IR (KBr, cm^{-1}): 3142, 3048, 2922, 2872, 1585, 1476, 1436,

1365, 1337, 1228, 1088, 1036, 1004, 955, 889, 853, 811, 667; NMR ^{1}H (500 MHz, DMSO-d_6) δ: 0.88 (3H, t, *J* 7.5 Hz); 1.55 (2H, sext, *J* 7.5 Hz); 3.45 (2H, t, *J* 7.5 Hz); 4.58 (2H, s); 7.74 (2H, t, *J* 2.0 Hz); 8.07 (2H, d, *J* 2.0 Hz); 8.91 (1H, s); NMR ^{13}C (125 MHz APT, DMSO-d_6) δ: 10.5, 22.4, 63.2, 71.4, 118.5, 122.3, 127.8, 135.2, 138.2, 145.7; Anal. Calcd for. $C_{12}H_{13}Cl_2N_3O$: C, 50.37; H 4.58; N, 14.68. Found: C, 50.44; H, 4.59; N, 14.34.

2.1.8. 1-(3,5-Dichlorophenyl)-4-(butoxymethyl)-1H-1,2,3-triazole (11l)

Obtained in 54% as a yellow solid, R_f = 0.74, m.p. 47-48ºC; IR (KBr, cm^{-1}): 3139, 2932, 2863, 1586, 1475, 1443, 1371, 1335, 1264, 1091, 1040, 1003, 852, 810, 666; NMR ^{1}H (500 MHz, DMSO-d_6) δ: 1.00 (3H, t, *J* 7.0 Hz); 1.45 (2H, pent, *J* 7.0 Hz); 1.61-1.67 (2H, m); 3.61 (2H, t, *J* 7.0 Hz); 4.70 (2H, s); 7.86 (1H, t, *J* 2.0, Hz); 8.19 (1H, d, *J* 2.0 Hz); 9.03 (1H, s); NMR ^{13}C (125,0 MHz APT, DMSO-d_6) δ: 13.7, 18.8, 31.3, 63.2, 69.5, 118.6, 122.3, 127.8, 135.3, 138.3, 145.8; Anal. Calcd for. $C_{13}H_{15}Cl_2N_3O$: C, 52.01; H 5.04; N, 14.00. Found: C, 52.24; H, 5.22; N, 14.30.

2.1.9. 1-(4-Methoxyphenyl)-4-(proproxymethyl)-1H-1,2,3-triazol (11n)

Obtained in 65% as a yellow oil, R_f = 0.74; IR (KBr, cm^{-1}): 2873, 1611, 1518, 1461, 1377, 1303, 1253, 1190, 1094, 1037, 989, 832, 768, 695; NMR ^{1}H (500 MHz, DMSO-d_6) δ: 0.99 (3H, t, *J* 7.0 Hz); 1.67 (2H, sext, *J* 7.0 Hz); 3.56 (2H, t, *J* 7.0 Hz); 3.95 (3H, s); 4.69 (2H, s); 7.23-7.26 (2H, m); 7.90-7.94 (2H, m); 8.78 (1H, s); NMR ^{13}C (125 MHz APT, DMSO-d_6) δ: 10.5, 22.4, 55.6, 63.3, 71.3, 114.9, 121.7, 122.0, 130.1, 145.1, 159.3; Anal. Calcd for. $C_{13}H_{17}N_3O_2$: C, 63.14; H 6.93; N, 16.99. found: C, 63.44; H, 6.72; N, 16.55.

2.1.10. 4-(Butoxymethyl)-1-(4-metoxyphenyl)-1H-1,2,3-triazole (11o)

Obtained in quantitative yield as brown solid, R_f = 0.35, m.p. 63-64ºC; IR (KBr, cm^{-1}): 2932, 2866, 1610, 1517, 1462, 1375, 1304, 1254, 1190, 1095, 1039, 989, 831, 767, 695; NMR ^{1}H (500 MHz, DMSO-d_6) δ: 0.99 (3H, t, *J* 6.9 Hz); 1.41-1.48 (2H, m); 1.60-1.67 (2H, m); 3.60 (2H, t, *J* 6.6 Hz); 3.95 (3H, s); 4.68 (2H, s); 7.25 (2H, d, *J* 9.2 Hz); 7.92 (2H, d, *J* 9.2 Hz); 8.78 (1H, s); NMR ^{13}C (125 MHz APT, DMSO-d_6) δ: 13.8, 18.9, 31.2, 55.6, 63.3, 69.4, 114.9, 121.8, 122.0, 130.2, 145.2, 159.3; Anal. Calcd for. $C_{14}H_{19}N_3O_2$: C, 64.35; H 7.33; N, 16.08. Found: C, 64.44; H, 7.13; N, 16.35.

2.1.11. (1-(2,5-Dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl decanoate (12f)

Obtained in 95% as a white solid, R_f = 0.81, m.p. 35-36ºC; IR (KBr, cm^{-1}): 3664, 2919, 2852, 1741, 1588, 1489, 1451, 1377, 1285, 1252, 1210, 1168, 1102, 1074, 1043, 1018, 874, 822, 722, 651; NMR ^{1}H (500 MHz, DMSO-d_6) δ: 0.97 (3H, t, *J* 7.0 Hz); 1.30-1.41 (12H, m); 1.59-1.67 (2H, m); 2.46 (2H, t, *J* 7.0 Hz); 5.36 (2H, s, H-6); 7.85 (2H, dd, *J* 8.0 e 2.0 Hz); 7.93 (1H, d, *J* 8.0 Hz); 8.01 (1H, d, *J* 2,0 Hz); 8,42 (1H, s); NMR ^{13}C (125 MHz APT, DMSO-d_6) δ; 13.9, 22.0, 24.4, 28.4, 28.6, 28.8, 31.3, 33.4, 33.7, 56.7, 126.7, 127.5, 128.1, 131.5, 131.9, 132.5, 135.3, 142.3, 172.6; Anal. Calcd for. $C_{19}H_{25}Cl_2N_3O_2$: C, 57.29; H, 6.33; N, 10.55. Found: C, 57.00; H, 6.25; N, 10.65.

2.1.12. (1-(4-Methoxyphenyl)-1H-1,2,3-triazole-4-il)metyl hexanoate (12i)

Obtained in 55 % as a yellow oil R_f = 0.58; IR (KBr, cm^{-1}): 2932, 2870, 1734, 1611, 1518, 1462, 1304, 1253, 1164, 1109, 1034, 989, 832, 770; NMR ^{1}H (500 MHz, DMSO-d_6) δ: 0,96 (3H, t, *J* 7.4 Hz); 1.35-1.40 (4H, m); 1.52 (2H, pent, *J* 7.4 Hz); 2.45 (2H, t, *J* 7.34 Hz); 3.95 (3H, s); 5.33 (2H, s); 7.25 (2H, d, *J* 9.0 Hz); 7,91 (2H, d, *J* 9.0 Hz); 8.82 (1H, s); NMR ^{13}C (125 MHz APT, DMSO-d_6) δ: 13.7, 21.7, 24.1, 30.6, 33.3, 55.6, 56.9, 114.9, 121.8, 122.8, 130.0, 142.9, 159.4, 172.6; Anal. Calcd for. $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.05; H, 7.12; N, 13.89.

2.2. Biological Assays

2.2.1. Cells

Peripheral blood mononuclear cells (PBMCs) from healthy human donors were obtained by density gradient centrifugation (Hystopaque, Sigma). Cells were resuspended in RPMI 1640 (LGCBio, São Paulo, BR) supplemented with 10 % heat-inactivated fetal bovine serum (FBS, Hyclone, Logan, UT), penicillin (100 U/mL), streptomycin (100 µg/mL), 2 mM glutamine and 10 mM HEPES, stimulated with 2 µg/mL of phytohemagglutinin (PHA, Sigma) during two to three days. PHA-stimulated cells were further maintained in culture medium containing 5 U/mL of recombinant human interleukin-2 (Sigma).

2.2.2. Effects of the Compounds on Cell Viability

To evaluate the safety of tested compounds to human cells, activated human PBMCs were plated in 96-well culture plates (2 x 10^5 cells/well) and exposed to increasing concentrations of the compounds for seven days. Thus, cell viability was examined using the Trypan blue dye exclusion assay, and the resulting CC_{50} values were calculated by linear regression [17].

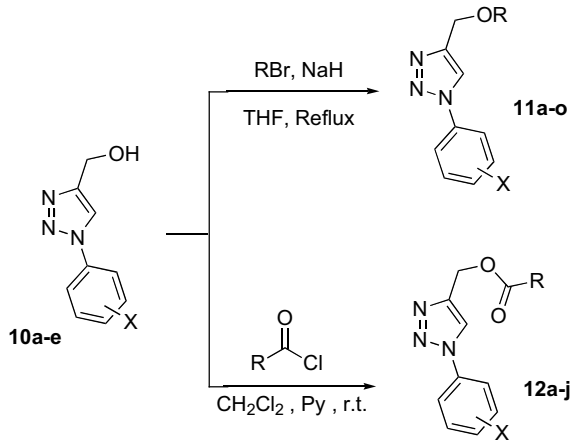
2.2.3. Effect of Compounds on HIV-1 Replication

PBMCs were initially exposed during two to three hours to viral suspensions containing 10 ng/mL of HIV-1_{BA-L} p24 Ag. Cells were washed, resuspended in complete medium, plated in 96-well culture plates (2x10^5 cells/well) in triplicates, and treated with compounds at various concentrations [17]. After 7 days at 37ºC in 5 % CO_2, viral replication was assessed by measuring the HIV-1 p24 Ag in culture supernatants using an ELISA capture assay (ZeptoMetrix Co., Buffalo, NY). Viral replication was evaluated by measuring the HIV-1 p24 Ag in culture supernatants, as described above.

3. RESULTS AND DISCUSSION

The 1,2,3-1*H*-triazoles (**10a-e**) were prepared by Huisgen 1,3-dipolar cycloaddition protocol in which a reaction of aryl azides and propargylic alcohol was catalyzed by Cu(I), providing only regioisomer 1,4-disubstituted at high yields (65-95%). The etherified (**11a-n**) and esterified (**12a-q**) deriva-

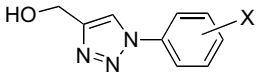
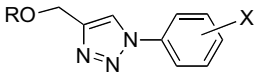
tives were made from acylation or alkylation reaction between the alcohol (**10**) and acid chlorides or alkyl bromides in basic medium, respectively (Scheme **1**).



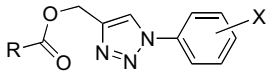
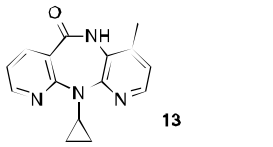
Scheme 1. Synthesis of esters and ethers 1-aryl-1H-1,2,3-triazoles.

Initially, the most active compounds were selected by their ability to inhibit HIV replication at 10 μM. We observed the percentage of inhibition (%) superior to 80 % for 6 out of the 30 compounds tested (Table **1**). For comparison, the NNRTI nevirapine (**13**) inhibited HIV replication by 98%.

Table 1. Percentage of inhibition of 1*H*-1,2,3-triazoles.

Compounds	Substitutents	Inhibition (%)
10a-e 		
10a	X = H	32
10b	X = 4-Cl	29
10c	X = 2,5-Cl	28
10d	X = 3,5-Cl	32
10e	X = 4-OMe	29
11a-o 		
11a	R = C_2H_5 X = H	37
11b	R = C_3H_7 X = H	63
11c	R = C_4H_9 X = H	20
11d	R = C_2H_5 X = 4-Cl	21
11e	R = C_3H_7 X = 4-Cl	89
11f	R = C_4H_9 X = 4-Cl	21

(Table 1) Contd….

Compounds	Substitutents	Inhibition (%)
11g	R = C_2H_5 X = 2,5-Cl	0
11h	R = C_3H_7 X = 2,5-Cl	91
11i	R = C_4H_9 X = 2,5-Cl	35
11j	R = C_2H_5 X = 3,5-Cl	66
11k	R = C_3H_7 X = 3,5-Cl	90
11l	R = C_4H_9 X = 3,5-Cl	54
11m	R = C_2H_5 X = 4-OMe	27
11n	R = C_3H_7 X = 4-OMe	88
11o	R = C_4H_9 X = 4-OMe	23
12a-j 		
12a	R = COC_5H_{11} X = H	54
12b	R = COC_9H_{19} X = H	35
12c	R = COC_5H_{11} X = 4-Cl	11
12d	R = COC_9H_{19} X = 4-Cl	20
12e	R = COC_5H_{11} X = 2,5-Cl	85
12f	R = COC_9H_{19} X = 2,5-Cl	20
12g	R = COC_5H_{11} X = 3,5-Cl	20
12h	R = COC_9H_{19} X = 3,5-Cl	53
12i	R = COC_5H_{11} X = 4-OMe	81
12j	R = COC_9H_{19} X = 4-OMe	27
 **13**		98

Among the aforementioned most active triazoles analogues in Table **1**, we further examined some pharmacological parameters related with the antiviral potency and cytotoxicity. We observed that all series of 1*H*-1,2,3-triazoles are less cytotoxic than antiretrovirals in clinical use, such as nevirapine (**13**, Table **2**). With respect to antiretroviral potency, the best triazole (**11h**) was up to 8 times more active

Table 2. IC_{50}, CC_{50} and selective index of 1*H*-1,2,3-triazoles.

Compounds	IC_{50} (μM)	CC_{50} (μM)	Selective Index*
11e	0.4	1285	3212
11h	0.1	1349	13490
11k	0.1	1281	12810
11n	0.5	1089	2178
12e	1.3	1201	924
12i	0.3	1345	4483
13	0.8	890	1112

*Selective index is calculated based on the ratio between CC_{50} and IC_{50} values.

than nevirapine (**13**, Table **2**). Consequently, the hits were over 10-fold more selective than reference antiretrovirals in clinical use (Table **2**) [4, 18] (Fig. **3**).

CONCLUSION

In summary, several 1*H*-1,2,3-triazol were synthesized by Huisgen 1,3-dipolar cycloaddition protocol and submitted to inhibition of HIV replication and cytotoxicity. Some triazoles were less cytotoxic and more active than nevirapine (**13**). The compounds **11h** and **11k** were 8 times more active and 10-fold more selective than reference antiretrovirals in clinical use suggesting potential therapeutic value as antiviral agents against HIV.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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