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NEW 1,2,3-TRIAZENES AND 1,2,3-TRIAZOLES AS ANTILEISHMANIAL, ANTITRYPANOSOMAL AND ANTIPLASMODIAL AGENTS

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Abstract

Trypanosomiasis, leishmaniasis and malaria are tropical diseases that affect poor populations and the classical drugs are toxic and select drug resistance. There is, therefore, an urgent need to find effective therapeutic agents accessible to developing countries that bear the brunt of morbidity and mortality.

In this study, we evaluated the *in vitro* activities of fourteen 1,2,3-triazenes and 1,2,3-triazoles against *Trypanosoma brucei gambiense*, *Leishmania donovani* and *Plasmodium falciparum*. Moreover, the synthesis of two new products among them will be described.

The 1,4-disubstituted 1,2,3-triazenes showed better activities than 1,2,3-triazoles against *Leishmania donovani* with selectivity indexes greater than 100. Thus, compound **2b** was the most effective one against axenic amastigote forms of *Leishmania donovani* LV9 with an IC₅₀ of 0.89 ± 0.41 μM, and against the intramacrophagic amastigote forms, with an IC₅₀ value at 0.99 ± 0.36 μM.

Compounds **3a**, a 1,2,3-triazene and **8**, a triazole analogue of the cholesterol side chain, showed the best trypanocidal activities against *Trypanosoma brucei gambiense* with IC₅₀ of 3.45 ± 0.09 μM and 3.99 ± 0.23 μM, respectively.

The most interesting result against the *Plasmodium falciparum* 3D7 strain was obtained with **5b** with an IC₅₀ value of 1.29 ± 0.15 μM.

The present study revealed that 1,2,3-triazenes and 1,4-disubstituted 1,2,3-triazoles are chemical entities exhibiting an antiparasite potential that could lead to a new class of drug candidates.

Keywords: trypanosomiasis, leishmaniasis, malaria, antiparasitic activity, 1,2,3-triazene, 1,2,3-triazole.

I. INTRODUCTION

Parasitic infections affect the whole planet, particularly the tropics, where populations living in poor living conditions become their prime targets. According to the World Health Organization, Neglected Tropical Diseases (NTD) affect more than one billion people with disastrous health, social and economic consequences and cause around 17% of deaths worldwide ^{[1][2]}. Among them, Human African trypanosomiasis (HAT), and leishmaniasis, have a significant impact in human morbidity and lethality whereas malaria, which is not a NTD, is responsible for many deaths a year.

Human African trypanosomiasis (HAT), a parasitic disease endemic to 36 African countries, is transmitted by tsetse flies and can affect humans and animals ^[3]. HAT is caused by two subspecies of the hemoflagellate protozoan *Trypanosoma brucei*, *T. b. rhodesiense* and *T. b. gambiense*. *Trypanosoma brucei gambiense*, responsible for a chronic infection, occurs in West and Central Africa, is reported in over 95% of cases of "sleeping sickness" whereas *Trypanosoma b. rhodesiense*, manifested in an acute form, is found in East and southern Africa ^[4]. Boseley et al. revealed that approximately 48,000 people died from trypanosomiasis in 2008 ^[5]. Relentless control efforts have reduced the number of new cases and for the first time in 50 years, only 992 cases were recorded in 2019 ^[6].

Treatment of the disease is based on the therapeutic use of trypanocides. Five drugs are used for the treatment of HAT: suramin, pentamidine, and fexinidazole are used for the haemo-lymphatic stage, whereas nifurtimox, eflornithine and fexinidazole are used for the meningo-encephalitic stage. The various degrees of toxicity noted and the appearance of resistance constitute the limits of these treatments ^{[7][8][9]}.

Leishmaniasis are parasitic diseases caused by protozoa of the genus *Leishmania*, transmitted by the bite of an insect vector, the sandflies. Leishmaniasis occurs in three clinical forms: cutaneous, with skin ulcers; mucocutaneous, with ulcers of the skin, mouth and nose; and visceral, with enlarged liver and spleen, as well as bone marrow dysfunction, and it is fatal if left untreated ^{[10][11][12][13][14]} (10-12). As the second deadliest tropical disease and the fourth most morbid, leishmaniasis is present in 88 countries ^[1]. There are two million new cases each year and 12 million people are currently infected ^[15]. The most serious visceral leishmaniasis (VL) is responsible for around 50,000 deaths each year, with new cases estimated at around 500,000 per year. Five countries contain 90% of the cases: India, Bangladesh, Nepal, Sudan and Brasil ^[16]. In the South of Asia and the horn of Africa, the main mode of transmission of the parasite *Leishmania donovani* is anthroponotic ^[17]. There is currently no effective vaccine and the first-choice treatment for leishmaniasis involves the use of highly toxic antimonial compounds with severe side-effects and a prolonged treatment regimen ^{[1][11][15]}. Alternatives include paromomycin, pentamidine, miltefosine, and liposomal amphotericin-B which despite their efficacy, they exhibit either high toxicity, emergence of resistance or high cost ^{[16][18][19][20][21]}.

Malaria is one of the deadliest diseases in Africa caused by five species of *Plasmodium*: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*. *P. vivax* and *P. falciparum* are the most common and the most dangerous *P. falciparum* is predominant in sub-Saharan Africa and causes the most complications with the highest mortality rates among species. After reaching 216 million people infected worldwide and approximately 445,000 deaths in 2016, an upsurge in malaria was observed in 2020, with 241 million the number of cases and 627,000 deaths. Almost all cases are found in Africa with 95% of cases and 96% of deaths, 80% of which are children under 5 years old ^[22].

The World Health Organization recommends artemisinin-based combination therapy (ACT) as the first-line treatment for *Plasmodium falciparum* while in many countries, chloroquine remains effective for *Plasmodium vivax*. Despite the efficacy of ACTs, resistance has been reported for both artemisinin and its analogues ^[23]. Thus, there is an urgent need to develop new, safe and effective drugs to treat malaria due to the still high morbidity and mortality rates but also to the emergence of drug resistance to known antimalarials ^[24].

In addition to being known as building blocks in organic synthesis, 1,2,3-triazenes are also endowed with important biological properties and are therefore cited for their antimicrobial ^{[25][26][27][28][29][30]} antitumor ^{[31][32][33]} and antitrypanosomal ^[34] activities. The rapidity of the

increasing global spread of resistance to most of the available and affordable antiprotozoal drugs is a major concern hence the need to develop innovative strategies to control infectious diseases. In this context, new, effective, easy to administer and inexpensive chemotherapeutic compounds are urgently needed. There is also considerable interest in the chemistry of 1,2,3-triazoles due to their biological and synthetic importance. The 1,2,3-triazoles have been well exploited to gain access to numerous medicinal scaffolds exhibiting antibacterial, anti-HIV, anti-cancer activities, to cite a few [35][36][37][38].

In the present work, we describe the *in vitro* evaluation of the activity of 1,2,3-triazenes and 1,4-disubstituted-1,2,3-triazoles against *Trypanosoma brucei gambiense*, *Leishmania donovani* and *Plasmodium falciparum*.

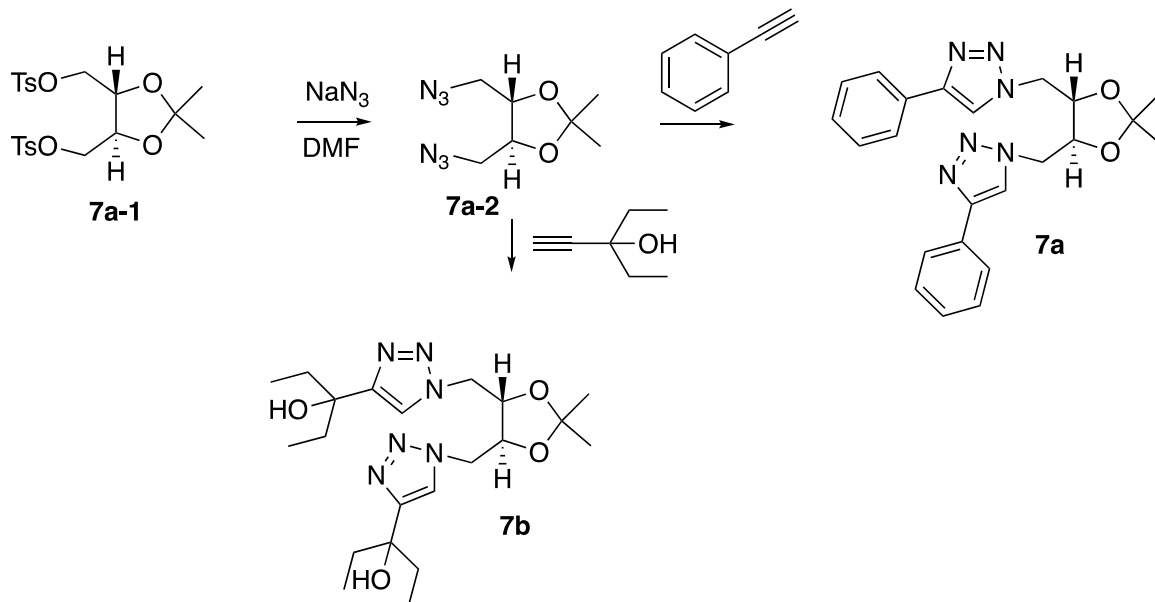
II. MATERIALS AND METHODS

II.1. Materials

The 1,2,3-triazenes **1a**, **1b**, **2a**, **2b**, **3a**, **3b**, and **4**, were obtained by the diazocoupling synthesis method [29] and the 1,4-disubstituted-1,2,3-triazoles **5a**, **5b**, **6a**, **6b**, and **8** by 1,3-dipolar cycloaddition [30][39]. The synthesis was carried out at the Organic Chemistry Laboratory of the Organic Chemistry Department of the University of Vigo. Figure 1 shows all the tested 1,2,3-triazenes and 1,4-disubstituted 1,2,3-triazoles. The biological tests were carried out at the "Antiparasite chemotherapy" team of the Faculty of Pharmacy of Châtenay-Malabry (Paris-Saclay University). The macrophages RAW 264.7 were used for cytotoxicity evaluation. *Trypanosoma brucei gambiense* (FéoITMAP/1893), *Leishmania donovani* (MHOM/ET/67/HU3/LV9) and *Plasmodium falciparum* 3D7 have been used as *in vitro* models for antiparasitic evaluation.

II.2. Methods

II.2.1. Synthesis of molecules **7a** and **7b**



Scheme 1: Access to molecules **7a** and **7b**

According to Rubin the ditosyl compound **7a-1** was obtained by reacting p-TsCl with a very high yield of 90% [40]. Azide **7a-2** was obtained by reacting with **7a-1** NaN_3 in DMF with a yield of 92%. Compound **7a-2** reacts with acetylenic derivatives to give bistriazole compounds **7a** and **7b**. In this part of the work we tried to develop a new strategy for the synthesis of nitrogen heterocycles from tartaric acid. The overall yield of the synthesis of **7a** was 79.12% from **7a-1** in two steps. While access to **7b** was achieved with a yield of 73.60% over two steps as well. These synthesized molecules have an optical activity with specific optical powers of - 38.76 in CHCl_3 at 23 °C for

compound **7b** and + 82.31 in CHCl₃ at 23 °C for compound **7a**. Tartaric acid has therefore allowed the preparation of enantiomerically pure bistriazole compounds.

II.2.2. Biological evaluation

II.2.2.1. Evaluation of compound cytotoxicity

Cytotoxicity was evaluated on RAW 264.7 macrophages using the procedure describe by [41].

II.2.2.2. In vitro evaluation against *Trypanosoma brucei gambiense*

Trypanosoma brucei gambiense (strain FéoITMAP/1893) was engaged in a procedure described by Jagu *et al.* [41]. The activity of the compounds was expressed as IC₅₀ in μM (concentration of drug inhibiting 50% of the parasite growth, comparatively to the controls treated with the excipient only). The reference drug used was pentamidine diisethionate.

II.2.2.3. In vitro antileishmanial evaluation against *Leishmania donovani*

Promastigotes of *Leishmania donovani* (MHOM/ET/67/HU3/LV9) were used in this part of the Ghozlani *et al.* procedure that we have adopted [42]. Pentamidine was used as the reference drug.

Evaluation on axenic amastigotes

The evaluations of activity on the axenic amastigotes of *L. donovani* were adapted from the protocols previously described by Balaraman *et al.* [43].

Evaluation on intramacrophage amastigotes

Concerning the evaluation on the intramacrophage amastigotes, RAW 264.7 macrophages were used and the activity of the compounds was expressed as IC₅₀ in μM.

II.2.2.4. In vitro evaluation against *Plasmodium falciparum* 3D7

Parasite culture of *Plasmodium falciparum*

The chloroquine-sensitive 3D7 *P. falciparum* strain and W2 chloroquine-resistant stain were obtained from Malaria French National Reference Center (CNR Paludisme, Hôpital Bichat Claude Bernard, Paris). The strains were maintained in O⁺ human erythrocytes in albumin supplemented RPMI medium under continuous culture using the candle-jar method [44]. The parasites were synchronized to the ring stage by repeated sorbitol treatment [45].

In vitro antiplasmodial activity on *Plasmodium falciparum*

The *in vitro* antiplasmodial activity on *Plasmodium falciparum* was evaluated by using a method described by Ortiz *et al.* [46].

III. RESULTS AND DISCUSSION

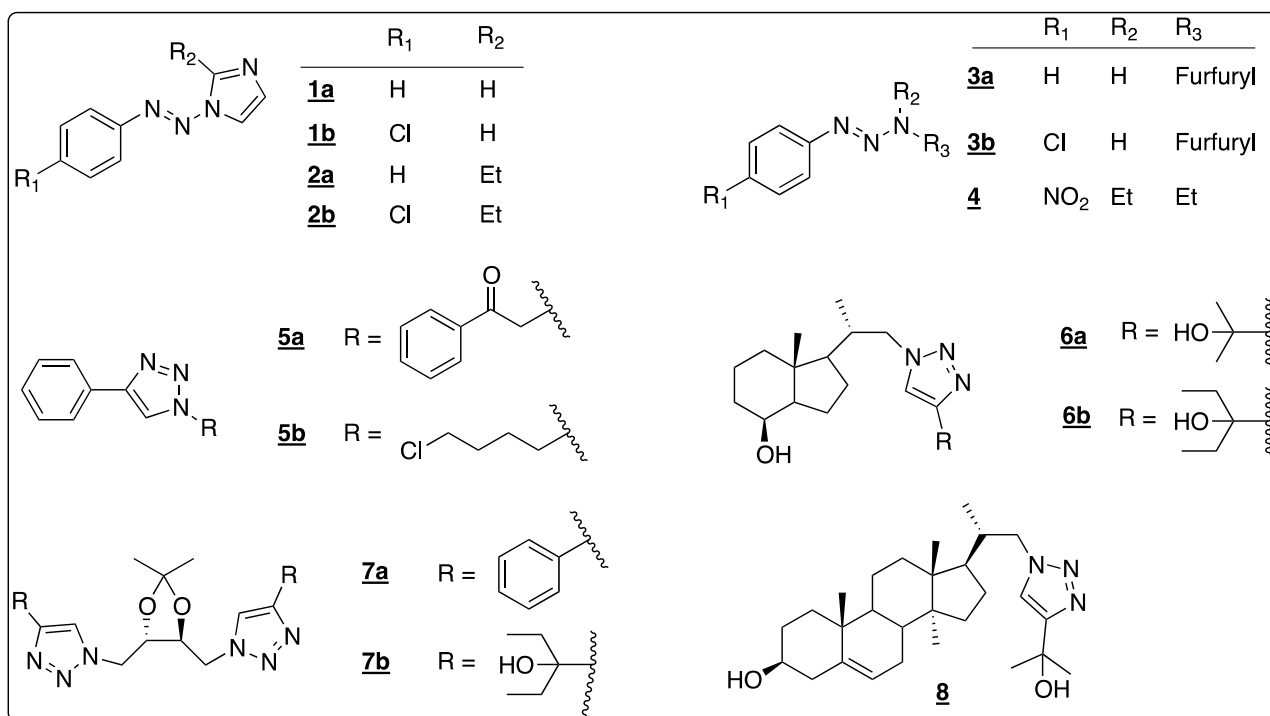


Figure 1: 1,2,3-triazenes and 1,4-disubstituted 1,2,3-triazoles tested

In this work, 14 compounds were evaluated whose seven 1,2,3-triazenes and seven 1,2,3-triazoles-1,4-disubstituted for their cytotoxicity and against four parasites: *Leishmania donovani* LV9 (axenic amastigote forms and macrophagic amastigote forms), *Trypanosoma brucei gambiense* (trypomastigote forms) and *Plasmodium falciparum* 3D7 (drug sensitive form). Concerning the cytotoxicity, no compound was toxic at 100 μM . Therefore, the Cytotoxic Concentrations 50% (CC_{50}) of all compounds were all superior to 100 μM . The results presented in Table 1 show that the tested compounds exhibited a large panel of *in vitro* activity with IC_{50} values in a range from $0.89 \pm 0.41 \mu\text{M}$ to values greater than 100 μM .

Tableau 1: *In vitro* antileishmanial, trypanocidal and antiplasmodial activities of 1,2,3-triazenes and 1,2,3-triazoles

Compounds	<i>T. brucei gambiense</i> IC_{50} (μM) \pm SD	<i>L. donovani</i> LV9 axenic amastigote forms IC_{50} (μM) \pm SD	<i>L. donovani</i> intramacrophage amastigote forms IC_{50} (μM) \pm SD	<i>P. falciparum</i> 3D7 IC_{50} (μM) \pm SD
1a	> 100	> 100	> 100	5.25 ± 0.36
2a	15.67 ± 3.17	0.98 ± 0.22	1.25 ± 0.46	>50
1b	10.19 ± 0.92	>100	>100	>50
2b	18.57 ± 5.83	0.89 ± 0.41	0.99 ± 0.36	12.26 ± 2.24
3a	3.45 ± 0.09	10.75 ± 1.23	5.25 ± 0.20	6.07 ± 0.82
3b	11.48 ± 2.05	46.20 ± 2.25	45.25 ± 5.2	11.42 ± 1.13
4	5.98 ± 1.57	8.60 ± 0.98	12.30 ± 1.45	5.63 ± 0.17
5a	14.71 ± 1.14	7.60 ± 0.84	5.85 ± 1.20	5.74 ± 0.74
5b	16.54 ± 0.18	52.20 ± 1.32	>100	1.29 ± 0.15
7a	10.04 ± 5.04	>100	75.10 ± 1.50	>50
7b	63.58 ± 0.59	>100	>100	8.91 ± 0.44

6a	22.51 ± 2.37	38.50 ± 4.1	48.10 ± 2.3	3.29 ± 0.56
6b	8.49 ± 0.28	46.50 ± 3.2	38.20 ± 0.80	>50
8	3.99 ± 0.23	>100	>100	>50
PMD	0.0051 ± 0.0006	10.35 ± 1.27	11.32 ± 1.14	
CQ				0.02 ± 0.01

PMD: Pentamidine

CQ: Chloroquine

Against *Trypanosoma brucei gambiense*, the most active compounds (**3a**, **8** and **4**) exhibit IC₅₀ values (3.45, 3.99, and 5.98 μM, respectively) about one thousand higher than those of pentamidine (5.1 nM), the reference compound. The Selectivity Indexes (SI) relative to the antitrypanosomal activity, defined as the ratio CC₅₀/IC₅₀, were > 29, > 25 and > 17, for compounds **3a**, **8** and **4**, respectively. Our results can therefore be compared favorably with those of Abdulsalam et al.^[47] who reports the activity of oxadiazole with 1,2,3-triazole on *T. brucei brucei* (WT) and *T. brucei brucei* (B48) with IC₅₀ of 8.6 ± 0.2 μM and 10.7 ± 0.7 μM respectively.

Against the *Leishmania donovani* parasites, compounds **2a** and **2b** exhibited the best activities against axenic amastigotes with IC₅₀ values at the micromolar range. Interestingly, these activities were kept on the intramacrophage amastigote model. The Selectivity Indexes (SI) relative to the intramacrophage antileishmanial activity, were > 83, and >101 for compounds **2a** and **2b**, respectively. The presence of the ethyl group on the imidazole ring seems to have a strong positive influence on the activity against *L. donovani*. Indeed, by comparing compounds **1a** and **1b** to compounds **2a** and **2b** on which the ethyl group is present, we note IC₅₀ values greater than 100 μM for compounds **1a** and **1b**, whereas they vary from 0.89 to 1.25 μM for compounds **2a** and **2b**. On the other hand, these results suggested that the effect of the conjugation of the triazole ring with the aromatic system (phenyl, imidazole) could play an important positive role in the antileishmanial activity. In fact, the compound **2a**, which does not differ from **2b** except by the presence of chlorine in para position to the 1,2,3-triazene on compound **2b**, is found to be the most active after the compound **2b**. The IC₅₀ of **2a** are with IC₅₀ of 0.98 ± 0.22 μM and 1.25 ± 0.46 μM respectively against the axenic and intramacrophage amastigote forms of *L. donovani*. The influence of this chlorine, although relatively weak, seems to play in favor of the activity. Compared to the pentamidine used as reference, we note that these two compounds are more than ten times more active one than pentamidine with IC₅₀ values of 10.35 ± 1.27 μM and 11.32 ± 1.14 μM respectively against the axenic and intramacrophage amastigote forms. At the same time, we can note that many compounds in this study showed better or equal efficacy than pentamidine, these are: compound **3a** with IC₅₀ values of 10.75 ± 1.23 μM and 5.25 ± 0.20 μM; compound **5a** with IC₅₀ values of 7.60 ± 0.84 μM and 5.85 ± 0.12 μM and compound **4**, the only one triazole of this group with IC₅₀ values of 8.86 ± 0.98 μM and 12.30 ± 1.45 μM against the axenic and intramacrophage amastigote forms, respectively. Some of these results can be compared favorably with those described by Daligaux et al.^[48] with guanosines bound to 1,2,3-triazole-5-substituted motifs whose best IC₅₀ of 8.6 ± 3.6 μM is obtained on *L. donovani* LV9 axenic amastigote forms.

The tests carried out on the drug sensitive strain *Plasmodium falciparum* 3D7 have made it possible to record CI₅₀ of 1.29 μM in the best case to CI₅₀ μM greater than 50 μM, in the worst cases. Nine compounds out of fourteen had IC₅₀ between 1.29 and 12.26 μM. Although the best activity noted for 1,2,3-triazole **5b** (1.29 ± 0.15 μM) is interesting, it remains low compared to the IC₅₀ of chloroquine (0.02 ± 0.01 μM) used here as a reference. The Selectivity Index (SI) relative to the antimalarial activity for compound **5b** is > 77. Devender and co-workers^[49] reported the

preliminary *in vitro* anti-plasmodial results of triazole tethered adamantyl/cycloheptyl indoleamide derivatives which displayed two compounds with IC₅₀ of 2.25 and 3.83 μM against CQ-sensitive (CQ-S) pf3D7. Balabadra et al^[50] evaluated the activity of triazole tethered naphthyl derivatives against pyrimethamine sensitive and resistant strains of *P. falciparum*. The best compound result displayed IC₅₀ values of 14.7 μM against *P. falciparum* 3D7. These results, although less interesting than chloroquine, allow us to positively reconsider our first results with these 1,2,3-triazene and 1,2,3-triazole derivatives with respect to their activity on *P. falciparum* 3D7 strains.

IV. CONCLUSION

This study allowed to monitor antiparasitic activities of 1,2,3-triazenes and 1,2,3-triazoles in a range from 1 to 10 μM for the best compounds against three parasites, *Trypanosoma brucei gambiense*, *Leishmania donovani* and *Plasmodium falciparum*. These results are encouraging and pave the way for further investigations. Thus, 1,2,3-triazenes and 1,2,3-triazoles are promising scaffolds to be explored in the field of medicinal chemistry for tropical infectious diseases, such as trypanosomiasis, leishmaniasis and malaria. Four compounds (**2b**, **3a**, **4** and **5a**) proved to be broad-spectrum, being active on the four strains of this study. The compound with the strongest activity for each strain can be selected for docking experiments to improve activities. Compound **2b** could be taken as a lead to explore solutions against leishmaniasis.

V. Acknowledgements

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VI. SPECTRAL DATA

VI.1 4-(2-azidoethyl)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolane (**7a-2**)

NaN₃ is added to a flask containing the tosylated product, then the whole is dissolved in DMF under argon. The reaction mixture is stirred for 6 h at room temperature. Add water and extract with AcOEt. The organic phase is washed several times with a saturated NaCl solution to eliminate the DMF. The pure product is obtained by chromatography on a column of silica gel using hexane as eluent. The product is a yellow liquid 404.6 mg (91.6%). R_f = 0.71 (AcOEt/Hex, 3:7). C₇H₁₂N₆O₂. MW = 212.21. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 4.06 (2 H, td, J = 2.7; 1.4 Hz); 3.45 (4 H, dddd, J = 89.7; 13.2; 2.9; 1.6 Hz); 1.47 (6 H, s). ¹³C NMR (101 MHz, CDCl₃) δ (ppm): 110.38; 76.88; 51.54; 26.86.

VI.2 1-((2,2-dimethyl-5-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-1,3-dioxolan-4-yl)methyl)-4-phenyl-1H-1, 2,3-triazole (**7a**)

To a solution of 165 mg (1.05 mmol) of **7a-2** in 4.38 ml of tBuOH/H₂O (2:1) solvents are added 13.11 mg of CuSO₄ · 5H₂O; 0.16 mmol (0.16 mL) of sodium ascorbate (1 M) and finally 126.75 mg (1.13 mmol) of alkyne. The reaction mixture is stirred for 3 hours at room temperature at the end of the reaction 4.38 mL of water are added. The aqueous phase is extracted with AcOEt (4 x 3 mL). The organic fractions are combined, dried with Na₂SO₄, filtered, and evaporated under reduced pressure. The product obtained is purified by chromatography on silica gel using as eluent (250 mL of CH₂Cl₂ and 250 mL of 5% MeOH/CH₂Cl₂). The product obtained is a yellow solid. Bp = 237-239 °C. R_f = 0.25 (AcOEt/Hex 2:8). C₂₃H₂₄N₆O₂. MW = 416.47. [α]_D^{23,2} = + 82,31 (CHCl₃; C = 0.2). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.94 (1 H, s); 7.87 (2 H, d, J = 7.6 Hz); 7.46 (2 H, t, J = 7.5 Hz); 7.38 (1 H, t, J = 7.3

Hz); 4.68 (2 H, d, $J = 2.3$ Hz); 4.22 - 4.01 (1 H, m); 1.26 (6 H, s). ^{13}C NMR (101 MHz, CDCl_3) δ (ppm): 149.17; 128.93; 128.33; 125.78; 121.61; 107.97; 75.20; 49.87; 26.80.

VI.3 3,3'-(1,1'-((4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(1H-1,2,3-triazole-4,1-diyl)) dipentan-3-ol (7b) ^[30]

Product was synthesized with the same procedure of **7a**. The product obtained was purified by chromatography on silica gel used as eluent (250 mL of CH_2Cl_2 and 250 mL of 5% $\text{MeOH}/\text{CH}_2\text{Cl}_2$). The product was a colorless oil. $R_f = 0.26$ (AcOEt/Hex 3:7); $[\alpha]_D^{23.1} = -38.76$ (CHCl_3 ; c 0.97); ^1H NMR (400 MHz, CDCl_3) δ (ppm): 7.58 (1 H, s); 4.66 - 4.53 (4 H, m); 4.28 (1 H, dt, $J = 8.4$; 4.3 Hz); 3.85 (1 H, dt, $J = 8.3$; 4.1 Hz); 3.58 (1 H, dd, $J = 13.4$; 4.1 Hz); 3.27 (1 H, dd, $J = 13.3$; 4.1 Hz); 2.49 (2 H, s); 1.46 (3 H, s); 1.29 (3 H, s); 0.83 (12 H, td, $J = 7.4$; 3.4 Hz) ^{13}C NMR (101 MHz, CDCl_3) δ (ppm): 153.31; 122.28; 110.31; 75.78; 74.08; 50.74; 33.85; 26.87; 7.83. IR-(CDCl_3 , ν (cm^{-1})): 3387; 2965; 2924; 2853; 2103; 1457; 1373; 1222; 1079.

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