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ARTICLE TYPE

Antitrypanosomal and antileishmanial activity of prenyl-1,2,3-triazoles†

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A series of prenyl 1,2,3-triazoles were prepared from isoprenyl azides and different alkynes. The dipolar cycloaddition reaction provided exclusively primary azide products as regioisomeric mixtures that were separated by column chromatography and fully characterized. Most of the compounds displayed antiparasitic activity against *Trypanosoma cruzi* and *Leishmania donovani*. The most active compounds were assayed as potential *Tc*CYP51 inhibitors.

Trypanosomatids are protist parasites which cause a series of devastating illnesses that affect millions of people worldwide. In The Americas these kinetoplastids cause Chagas disease (*Trypanosoma cruzi*) and different forms of leishmaniasis (*Leishmania spp.*). These tropical diseases are considered neglected as they incisively reduce human potential, keeping people in poverty. They are especially harmful in vulnerable populations, particularly among children or immunosuppressed people.[1]

The neglect in the public sector arises when the government agendas are pushed aside and the required resources of the already limited health budgets of most of the countries where the diseases are endemic are limited. The immediate consequence is an inadequate and inefficient chemotherapeutic arsenal to fight these diseases, which has remained virtually unchanged in the last half century. In addition, the appearance of strains resistant to commercial drugs presents an increasing threat.[1]

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Electronic Supplementary Information (ESI) available: detailed experimental procedures. Copies of ^{1}H and ^{13}C NMR spectra of all new products. See DOI: XX.XXXX/XXXXXXXX/

The main chemotherapy for the treatment of leishmaniasis is stilbogluconate (Pentosam®), which is a highly toxic antimony derivative. Other drugs, used when patients do not respond to antimony-derived drugs, are amphotericin B, which has relatively low toxicity but a high cost, and pentamidine, which is even more toxic than those derived from antimony **(Figure 1)** and must be supplied under controlled supervision. The only drugs available for the Chagas disease treatment are nifurtimox and benznidazol **(Figure 1)**,[2] which are effective for the treatment of the disease in its acute phase, with a parasitological cure in more than 80% of the treated patients. Their effectiveness varies depending on the geographical region, probably due to the difference in susceptibility of the strains of *T. cruzi* found in those areas. However, there is less than 20% chance of parasitological cure in patients who are in the chronic phase of the disease.[3] Although these drugs have several side effects, they are better tolerated by children than by adults.

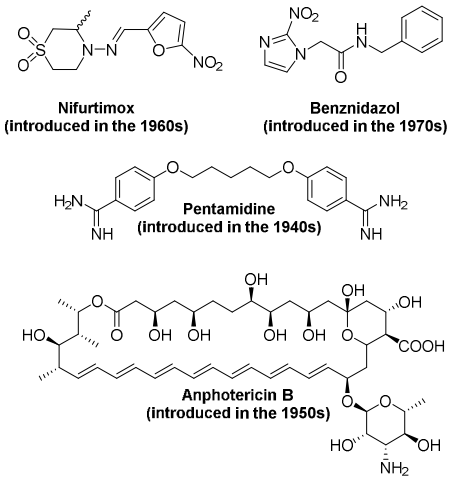

Figure 1. Chemotherapies known for leishmaniasis and Chagas disease.

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Multidisciplinary collaboration between different actors is the key to addressing the neglected diseases' problem. Governments, non-profit organizations or alliances, and the scientific community have been working together to establish a feasible drug development pipeline for diseases caused by parasites, including kinetoplastids.[4-8]

Isoprenes are very interesting structures, that can be abundantly found in nature, but also in many bioactive compounds in which they are present. Isoprenyl 1,2,3-triazoles have shown promising and varied biological activities **(Figure 2)** such as antimicrobials,[9] antibiofilms,[10,11] antioxidants,[9] and antiparasitics.[12] Additionally they also displayed activity as geranylgeranyl transferase II,[13] geranylgeranyldiphosphate synthase,[14,15] farnesyltransferase, Ras and Rab geranylgeranyl transferase inhibitors. In the same way, it is used as a precursor for the construction of analogues and metabolites, for example FPP,[16] glycolipids[17] and pharmacological drugs.[18]

Based on previous precedents where complex prenyl 1,2,3-triazolyl steroids[12] have shown promising antitrypanosomal activities we wanted to explored simplified version of those compounds. Looking for new chemical entities with antitrypanosomal activity, we wanted to investigate if simple prenylated 1,2,3-triazoles could displayed antiparasitic activity. Therefore, we proposed a series of 1,2,3-triazoles that could be prepared by CuAAC of prenyl azides and different alkyne, also looking to obtain isomerically pure compounds. In this current article, we report the synthesis of a collection of 1,2,3-triazoles to explore the structural requirements for activity. Data is reported for all compounds against the causative organisms of visceral leishmaniasis and Chagas disease, and structure-activity relationships are discussed.

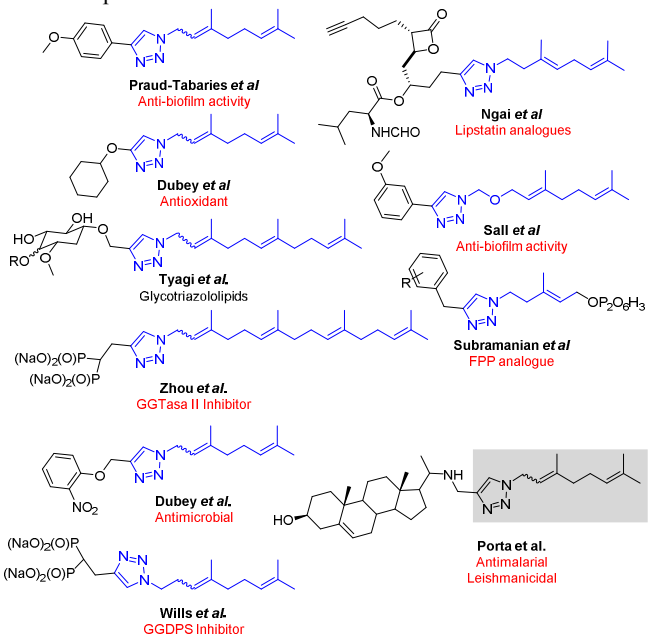

Figure 2. Bioactive prenyl 1,2,3-triazoles.

Synthesis

Prenylazides, the key intermediates, have been previously prepared as a mixture of regioisomers.[12,19] They interconvert rapidly at room temperature, due to a [3,3]-sigmatropic Winstein's rearrangement (**Figure 3**).[20,21]

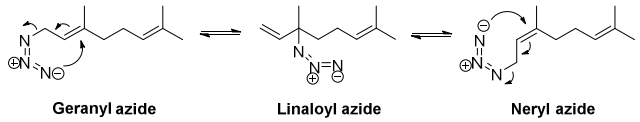

Figure 3. [3,3]-sigmatropic rearrangement geranyl azide.

The required prenylazides were prepared from the corresponding prenylalcohols following Thompson's reaction (**Figure 4**).[22]

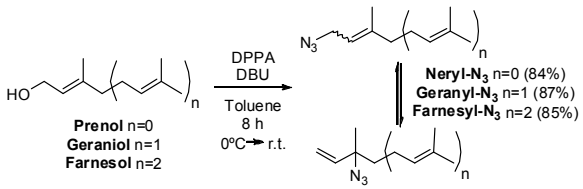

Figure 4. Prenyl azides synthesis

The azides were obtained in 8 hours with an average yield of 85%. NMR studies confirmed that geranyl and farnesyl azides were a mixture of primary (*E*,*Z*) and tertiary isomers in 5:3:1 ratio, respectively, while prenyl azide was a primary:tertiary 9:1 ratio.

Once the intermediates were synthetized, the Sharpless´ conditions were used to prepare the 1,4-disubstituted 1,2,3-triazole, using $CuSO_4$ as the copper source, and sodium ascorbate as a reductant.[23] Five terminal alkynes were used as a synthetic counterpart of the three allylic azides mixtures. The dipolarophiles were selected by using cheminformatic tools considering three factors: Lipinsky's rules of five,[24] a hydrophobic nature, and the physicochemical profiles of active reported isoprenyltriazoles. Based on those factors, commercially available phenylacetylene, methyl propiolate, 1-pentyne, 1-heptyne and 1-decyne, were selected. The combination of the three mixtures of prenyl azides and five alkynes allowed the efficient synthesis of 25 compounds with 83% average yield in an 8-hour reaction at room temperature **(Table 1)**. In all cases, a mixture of the regiomeric primary azides were obtained. The lack of reactivity of the tertiary azides in the 1,3-dipolar cycloaddition was not unexpected because has been described by Fokin and Sharpless in 2005.[25] They showed that, under dynamic equilibrium, only primary azides react, while the mixture interconverts to restore the initial composition.

After that, contradicting the literature precedents,[9-15] a careful chromatographic procedure allowed the separation of the regioisomeric mixture when it was present **(IT- 6** to **IT-25).** This approach becomes a powerful tool to develop new regioisomerically pure molecular entities with potential pharmacological action.

Chemically pure isomers of two standards were assigned unambiguously and reliably by nOe experiments. The analysis of the composition of the isomers by GC-MS reveals that geranyl triazoles has a Z/*E* relationship of 33:67, and farnesyl triazoles of 35:65. Compared with the Z/*E* ratio of the azide there has not been a significant change in the regiomeric composition after the reaction. This might indicate that the dipolar cycloaddition has a

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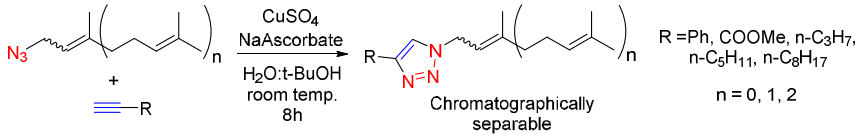
lower relative rate than the Winstein´s rearrangement.

Table 1. Synthesized isoprenyl-1,2,3-triazoles library.



R=	COOMe[a]		Phenyl[a]		Propyl[a]		Pentyl[a]		Octyl[a]	
n=0; Prenyl	**IT-1**	83%	**IT-2**	93%	**IT-3**	74%	**IT-4**	83%	**IT-5**	80%
n=1; Z-geranyl	**IT-6** (1.0)	86%	**IT-7** (1.0)	75%	**IT-8** (1.0)	87%	**IT-9** (1.0)	85%	**IT-10** (1.0)	82%
E-geranyl	**IT-11** (2.0)		**IT-12** (2.0)		**IT-13** (2.0)		**IT-14** (2.0)		**IT-15** (2.0)	
n=2; Z,E-farnesyl	**IT-16** (1.0)	72%	**IT-17** (1.0)	81%	**IT-18** (1.0)	83%	**IT-19** (1.0)	89%	**IT-20** (1.0)	69%
E,E-farnesyl	**IT-21** (1.9)		**IT-22** (1.9)		**IT-23** (1.9)		**IT-24** (1.9)		**IT-25** (1.9)	

[a]*Regioisomers relationship is specified in parentheses*

Cheminformatics Analysis

In chemogenomics, cheminformatics tools and molecular similarity methods are frequently used. An analysis of the structural similarity using the ChemMine Tools platform[26] of our chemical library reveals that it has a high degree of similarity, particularly in the area defined in **Figure 5**.

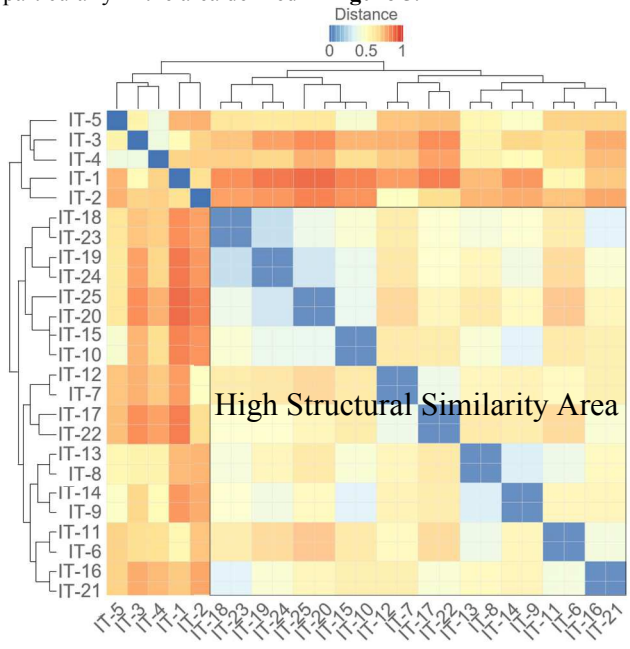


Figure 5. Analysis of molecular similarity of the chemical library. High similarity area is delimited.

Additionally, an inferential analysis of the potential mechanisms *in silico* ADME-Tox gave substantial information for a feasible and pharmacotherapeutic use of a chemical library. On the one hand, the toxicology analysis given by the OSIRIS Property Explorer platform[27] indicates that none of the products prepared are potentially mutagenic, irritant, teratogenic or toxic for sexual reproduction.

On the other hand, the most relevant parameters (molecular weight, polar surface area and logP) of the collection allow us to predict the potential of the compounds as leaders, possible administration routes and they complemented the structure-activity studies. **Figure 6** shows the physicochemical profile and distribution of the prepared compounds per molecular weight, polar surface area and octanol/water partition coefficient.

None of the prepared compounds contains more than 5 hydrogen bond donors or more than 10 oxygen and/or nitrogen atoms and all of them have molecular weights below 500 Da. Also, in all cases the total polar surface area is less than 100 A^3. These parameters augured good oral and passive absorption in the body and may also potentially penetrate the blood-brain barrier. The Hammett and Hansch's principle allowed the use of the descriptor like logP as lipophilicity, considering that, for a homologous series of compounds, generally parabolic relationships between partition coefficients and biological activity are obtained. In our case, the distribution of logP values of the 25 compounds fluctuates between 1 and 9.

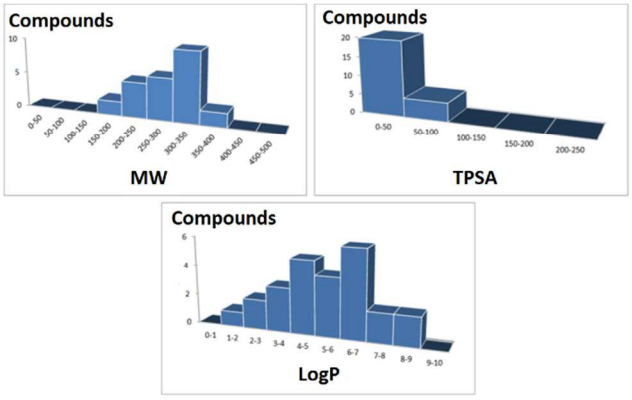


Figure 6. Distribution of physicochemical parameters of the chemical library.

Biological activity

The *in vitro* activity in two of the trypanosomatid pathogens, the etiological agents of Chagas disease (*T. cruzi* epimastigotes) and visceral leishmaniasis (*L. donovani* promastigotes) were assayed. **Table 2** displayed the activity on both parasites, the

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physicochemical and the structural parameters.

None of the prepared triazoles shown cytotoxicity in VERO cells at a maximum concentration of 20 μM. From the analysis of the *in vitro* activity of the compounds in both parasites, those containing prenyl in their structure are inactive at concentrations lower than 100 μM in both parasites, excluding **IT-5 (Entry 5)** in *T. cruzi*. This compound has the higher logP, PM and volume values of this subfamily. The triazoles that are decorated with neryl group (*Z*) in their structures (**Entries 6** to **10**) have moderate IC_{50} values in both parasites, except for the **IT-10** which contains octyl (**Entry 10**), with an IC_{50} of 16 μM in *L. donovani*. That compound also has the highest values in the physicochemical properties of the subfamily. The activity in *T. cruzi* of those analogs were active when they lack of oxygenated functional groups in their structure. However, there is no difference in their activity (between 34 and 44 μM).

When the triazoles contain a geranyl substituent (*E*; **Entries 11** to **15**), a significant loss of antileishmanial activity in this subfamily is observed. Conversely, the larger compound, **IT-15**, is the best candidate in the family of monoterpenyl triazoles against *T. cruzi,* with an IC_{50} of 27 μM. Interestingly, it appears that a change in the regiochemistry of the proximal double bond to the triazole ring modulates the activity towards one parasite, revealing the importance of the chromatographic separation of the products.

Globally in monoterpenyl triazoles, if oxygenated groups (**IT-6** and **IT-11**) are present, compounds lose their activity in *T. cruzi* and *L. donovani.*

The last two subfamilies are the compounds that have the best activities in both parasites. **IT-16** (*Z, E*-farnesyl, R=COOMe) and **IT-19** (*Z,E*-farnesyl, R=pentyl) are the best candidates as leishmanicidal agents with an IC_{50} of 11 μM, that doubled the IC_{50} of pentamidine (**Entry 27**) and is thirty time less active than amphotericin B (**Entry 28**). In contrast, the best compound in the entire collection against *T. cruzi* is **IT-21** (*E,E*-farnesyl, R=COOMe) with a IC_{50} of 9 μM, slightly more active that benznidazole (**Entry 26**). The subtle change in the regiochemistry of the first isoprene unit governs the antiparasitic activity.

Compounds **IT-20** and **IT-25** are inactive in *T. cruzi* at concentrations lower than 100 μM and moderately active in *L. donovani*. These two analogs have the highest MW, volume and logP of the entire collection, suggesting that above a threshold of values (logP > 8.76; volume > 427 $Å^3$ and PM > 385 Da), these structures begin to lose activity.

Table 2. Physicochemical parameters and activities of the synthesized structures.

Entry	Compound	Regio_ chemistry	R=	TPSA	logP	MW	Volume	*T. cruzi* IC_{50} (μM)	*L. donovani* IC_{50} (μM)
1	**IT-1**	-	COOMe	57.01	1.30	195.22	182.968	>100	>100
2	**IT-2**	-	Ph	30.71	2.82	213.28	209.847	>100	>100
3	**IT-3**	-	C_3H_7	30.71	2.47	179.10	188.603	>100	>100
4	**IT-4**	-	C_5H_{11}	30.71	3.46	207.20	222.207	>100	>100
5	**IT-5**	-	C_8H_{17}	30.71	4.92	249.20	272.612	27	>100
6	**IT-6**	*Z*	COOMe	57.01	3.20	263.15	260.549	87	>100
7	**IT-7**	*Z*	Ph	30.71	4.91	281.20	287.428	39	49
8	**IT-8**	*Z*	C_3H_7	30.71	4.05	247.38	266.184	44	44
9	**IT-9**	*Z*	C_5H_{11}	30.71	5.45	275.20	299.788	36	40
10	**IT-10**	*Z*	C_8H_{17}	30.71	6.92	317.52	350.193	34	16
11	**IT-11**	*E*	COOMe	57.01	3.20	263.15	260.549	87	>100
12	**IT-12**	*E*	Ph	30.71	4.91	281.28	287.428	39	49
13	**IT-13**	*E*	C_3H_7	30.71	4.50	247.39	266.184	31	72
14	**IT-14**	*E*	C_5H_{11}	30.71	5.45	275.20	299.788	51	94
15	**IT-15**	*E*	C_8H_{17}	30.71	6.92	317.52	350.193	27	57
16	**IT-16**	*Z,E*	COOMe	57.01	5.25	331.15	338.130	15	11
17	**IT-17**	*Z,E*	Ph	30.71	6.95	349.28	365.010	32	49
18	**IT-18**	*Z,E*	C_3H_7	30.71	6.50	315.39	343.766	17	33
19	**IT-19**	*Z,E*	C_5H_{11}	30.71	7.50	343.20	377.369	18	11
20	**IT-20**	*Z,E*	C_8H_{17}	30.71	8.76	385.52	427.775	>100	52
21	**IT-21**	*E,E*	COOMe	57.01	5.25	331.15	338.130	9.0	31
22	**IT-22**	*E,E*	Ph	30.71	6.95	349.28	365.010	34	48
23	**IT-23**	*E,E*	C_3H_7	30.71	6.50	315.39	343.766	18	51
24	**IT-24**	*E,E*	C_5H_{11}	30.71	7.50	343.20	377.369	29	44
25	**IT-25**	*E,E*	C_8H_{17}	30.71	8.76	385.52	427.775	>100	36
26	**Benznidazole**	-	-	92.75	0.78	260.25	224.99	10	-
27	**Pentamidine**	-	-	118.22	1.49	340.43	324.60	-	6.2
28	**Amphotericin B**	-	-	319.61	-2.49	924.09	865.48	-	0.35

TPSA: Total polar surface area; logP: hydrophobicity of a compound, expressed as the logarithm of the partition coefficient water/octanol.

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In conclusion, the two best compounds against *L. donovani* (**IT-16** and **IT-19**) and the best compound against *T. cruzi* (**IT-21**) have similarities and comparable physicochemical parameters. The logP of these three compounds are found between 5.25 and 7.50, the molecular weights between 331 and 343 and the volume between 338 and 377 Å^3.

T. cruzi CYP51 inhibition assay.

Molecules with volumes lower than 260 Å^3 or greater than 400 Å^3 lose activity in both parasites. Similarly, molecules with logP below 5 or above 8 result in inefficient trypanosomacidal activity (**Figure S1,** supplementary material). We described that as an "Island of activity" (IC_{50} < 40 μM) delimited by these three selected physicochemical parameters.

In general, structures such as imidazoles or 1,2,4-triazoles, present in fluconazole, ketoconazole or itraconazole **(Figure 7)** may act as inhibitors of sterol 14α-demethylase (CYP51). CYP51 is the cytochrome P450 enzyme that is widely distributed throughout different biological kingdoms. It is found in animals, plants, fungi, yeasts, protozoa and bacteria[28] and is considered the oldest member of the P450 superfamily.[29] In all cases, CYP51 catalyzes the same three-step reaction that removes the 14α-methyl group form the cyclized sterol precursors, each step requires an oxygen molecule and NADPH. During the first step of the CYP51 reaction, the sterol 14α-methyl group is converted into the alcohol, subsequently into the aldehyde and is finally removed as formic acid. The CYP51 reaction is a required step upon biosynthesis of sterols.

Trypanosomatids are sensitive to CYP51's inhibitors because they synthesize ergosterol and cannot use host cholesterol for their cellular membranes. Blocking this enzyme also alters the structure of various organelles and decreases the total level of sterols in the parasite. Furthermore, accumulation of 14α–methylated sterols in trypanosomatids produces cytostatic and cytotoxic effects.[30]

The inhibitory effect of selected hits of the "island of activity" (**IT-16**, **IT-18**, **IT-19**, **IT-21**, **IT-23** and **IT-24)** was determined on *T. cruzi* CYP51. The methodology employed involves the expression and purification of *T. cruzi* CYP51 and the use of cytochrome P450 reductase as an electron donor.[31] The inhibitory potency of the compounds was expressed as the percentage of enzymatic activity of *T. cruzi* CYP51 in the presence of the tested compounds at a fixed concentration (100 μM, a 100-fold molar excess over the enzyme) at two time periods (5 and 60 minutes).

The results are shown in **Table 3**. Overall, the inhibitory effect is rather moderate, because, as we have shown previously, at these experimental conditions the most potent azoles completely abolish *T. cruzi* CYP51 activity at 1:1 molar ratio enzyme/inhibitor.[32] Amongst all tested analogs the strongest effects were produced by **IT-19** and **IT-24.** Interestingly, the inhibition is persistent over time, suggesting that the compounds might have a relatively low initial binding affinity to the enzyme, but also a limited tendency to be replaced by the substrate during the CYP51 reaction.[32]

Thus, there would be a contribution to their antiparasitic activity by inhibiting CYP51, these compounds must also possess one or more alternative targets. Having shown the inhibitory action of the compounds, the binding mode of these novel chemical entities was determined. The interaction between the CYP51 enzyme and its sterol substrate produces a blue shift in the Soret band (from 417 to 394 nm) caused by the expulsion of a water molecule from the coordination sphere of the iron in the heme. This spectral response (type 1) reflects the transition of the iron from the hexacoordinated low spin state to the pentacoordinated high-spin state. On the contrary, the direct coordination of a basic atom to the heme iron causes a red shift in the Soret band (from 417 to 421-424 nm) called a type 2 response, that is characteristic of azoles.

Interestingly, our analogs produced a blue shift in the Soret band maximum of the enzyme (a modified type 1 spectral response, **Figure 9a**), indicating that their binding mode is different from the binding mode of antifungal azoles. This means that they bind in the CYP51 active site, but do not coordinate directly to the heme iron. The shift in the Soret band suggest that binding of **IT-19** might be changing the position of the heme coordinated water molecule, pushing it away from the iron and thus weakening the Fe-O coordination bond.[33]

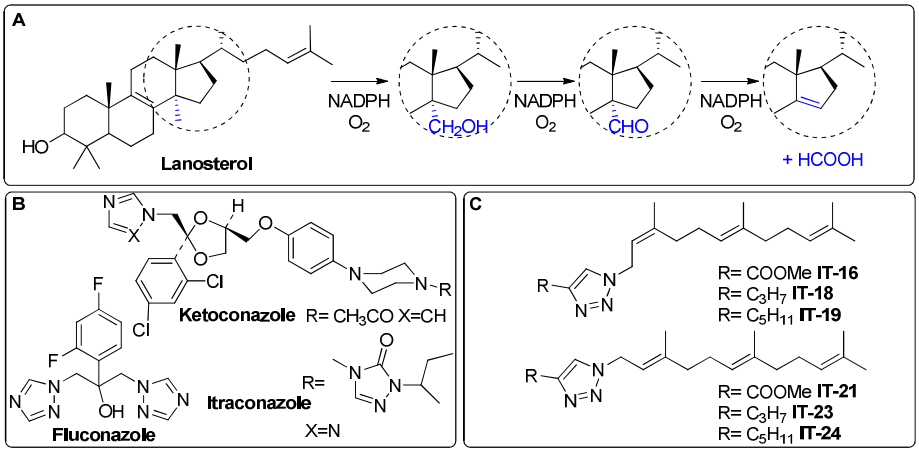

Figure 7. a. Mechanism of CYP51. b. Known CYP51 inhibitors. c. Isoprenyltriazoles tested in *Tc*CYP51.

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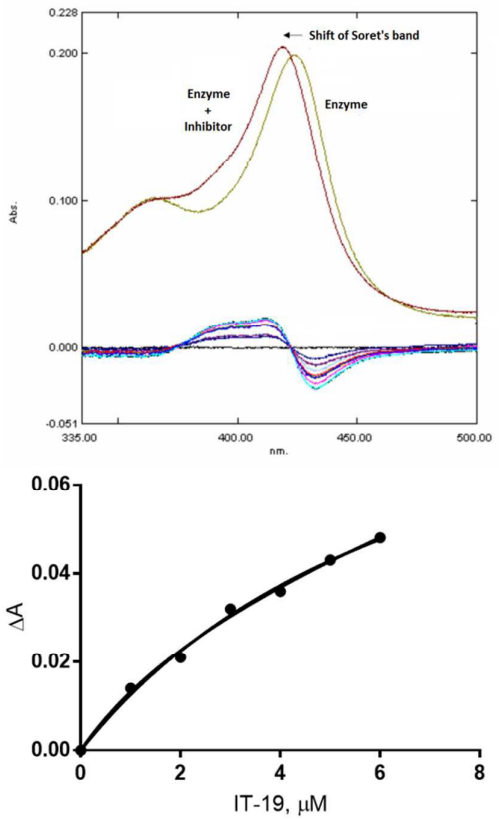

Figure 8. Shift in the *T. cruzi* CYP51 Soret band in response to the binding of compound **IT-19.**Top – absolute spectra, bottom - type 1–like difference spectra upon titration. CYP51 concentration was 2 μM, **IT-19** titration range 1-6 μM, titration step 1 μM. The apparent K_d=7.6±1.4 μM.

An analysis of the crystal structure of the CYP51 in complex with its substrate analog[34] shows that it possesses three distinguishable regions: a hydrophobic arm (isoprenylic motive) that is immersed in the deepest portion of a single hydrophobic cavity, characteristic of the CYP51 family.[35] This deep cavity allows the enzyme to interact efficiently with the substrate and to maintain its correct placement in the active site during the three steps of catalysis. In the steroid fraction, the oxygen atom is in an area near the substrate entrance channel and at a 3.5 Å distance from the main chain oxygen of methionine 358, with which it interacts through a hydrogen bridge. Finally, the 14α-methylenecyclopropyl group of the sterol is located perpendicularly to the heme plane and forms contacts with leucine 356 and threonine 295.

Table 3 Antiparasitic activity and CYP51 inhibition of selected analogs.

Compound	Antiparasitic activity		*T. cruzi* CYP51	
	T. cruzi IC_{50} (μM)	*L. donovani* IC_{50} (μM)	5 min % inh	60 min % inh
IT-16	15	11	26	59
IT-21	9	31	35	63
IT-18	17	33	14	49
IT-23	18	51	27	56
IT-19	18	11	7	39
IT-24	29	44	9	33

The binding mode to **IT-19** might comprise the interaction of the isoprenyl chain with the hydrophobic cavity deep in the enzyme, the triazole ring with the catalytic water molecule above the heme plane (the blue shift in the Soret band) and finally positioning the alkyl chain along the substrate access channel.

Conclusions

The prenyl triazole motif is an interesting structure to prepare new bioactive molecular entities. Thus, we prepared a library of 25 compounds including a cheminformatics design. When a mixture of regioisomers was obtained, the products were carefully resolved by chromatography. The complete collection was tested against the etiological agents of Chagas disease (*T. cruzi*) and visceral leishmaniasis (*L. donovani*). An island of high activity was defined by their physicochemical parameters and similarity structures. Compounds **IT-16** and **IT-19** are the best candidates as leishmanicidal agents and **IT-21** as antichagasic chemotherapy. Finally, the sum of the results of biological activities with the physicochemical parameters allows us to propose the SAR detailed in **Figure 9**. In addition, the inhibition of *T. cruzi* CYP51 by some of the most active analogs demonstrated that it might be a contributing factor to their antiprotozoan activity, the compound binding to the enzyme in a different way than the azoles (modified type 1). The lack of toxicity (predicted *in silico* and experimentally determined) and their structural and synthetic simplicity prompted us to continue working on this structure as a promising lead to trypanocidal drugs.

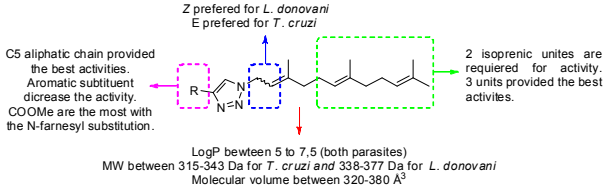

Figure 9. Analysis structure/activity of the chemical library of isoprenyltriazoles.

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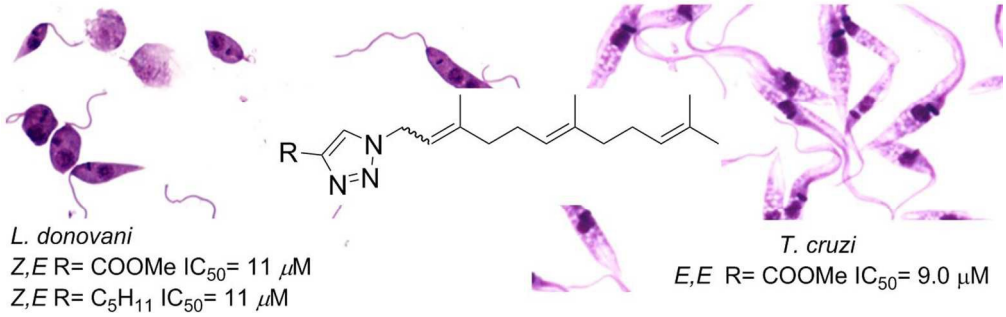

Graphical abstract

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