Glycosyltriazoles from 1,4-naphthoquinones: a search for active compounds against *P. falciparum*

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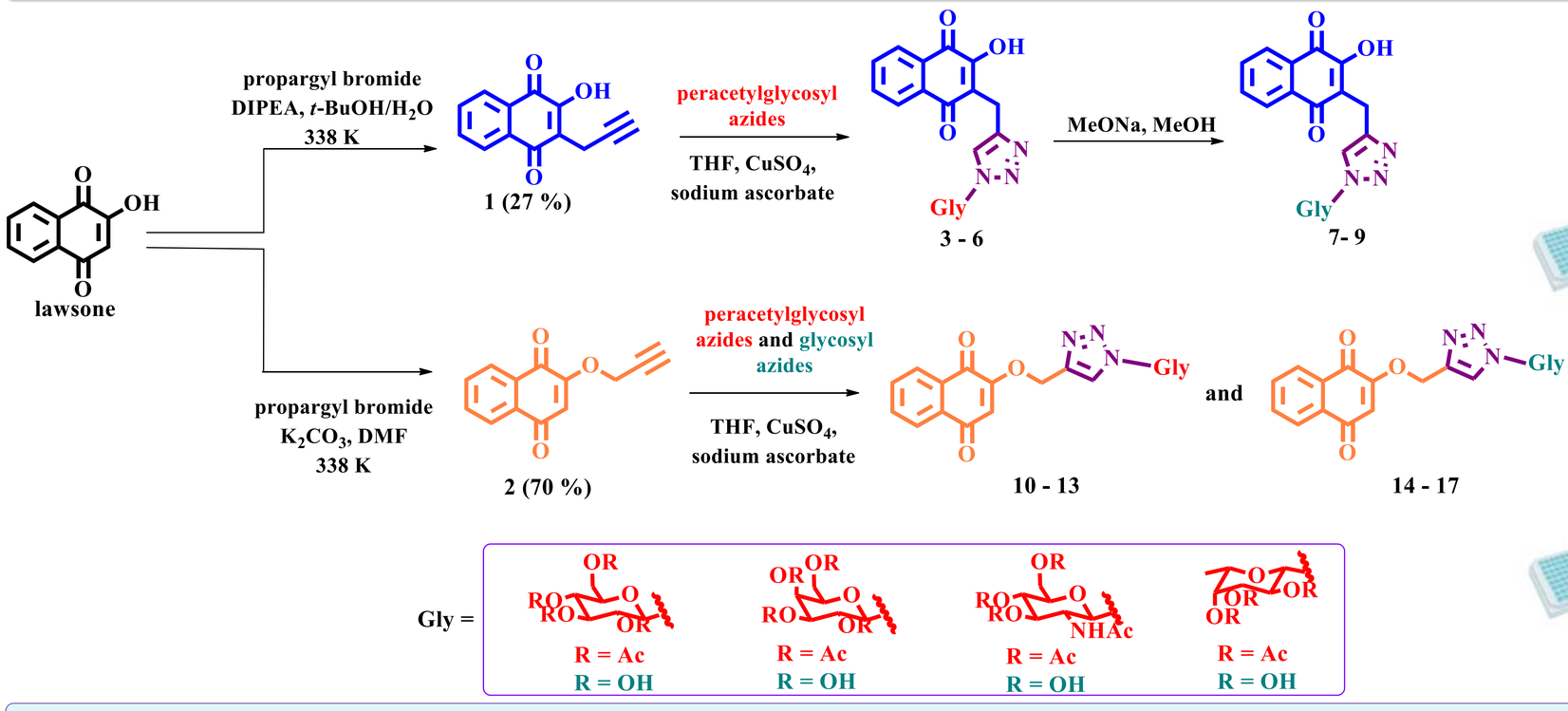
INTRODUCTION

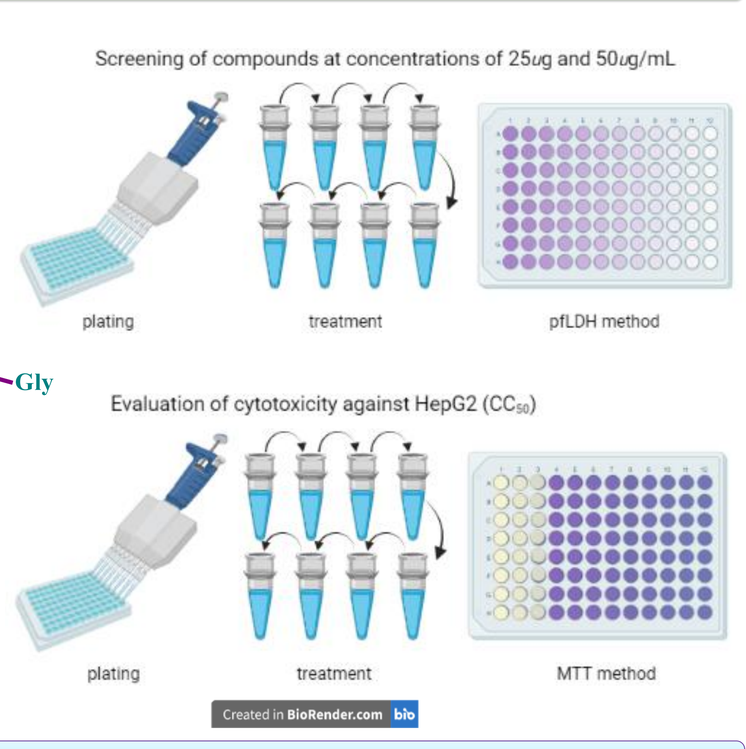
Malaria is a parasitic disease considered one of the most serious public health problems in the world and was responsible in the previous year for the deaths of 627,000 people and 241 million cases diagnosed according to the 2021 World Malaria Report. The 1,4-naphthoquinones present several biological activities, including antimalarial and this is related to their redox behavior. Thus, 1,4-naphthoquinones are privileged structures in the search for new compounds with antimalarial activity. An important representative of this class is atovaquone, one of the drugs used in the treatment of malaria, whose mechanism of action is related to the structural similarity of this drug with ubiquinone.

OBJECTIVE

The objective this work was to synthesize 3-*C*-propargyllawsone (**1**) and 2-*O*-propargillawsone (**2**) and their corresponding peracetylated and deacetylated glycosyltriazoles (**3**-**17**) from the azide-alkyne cycloaddition reaction of **1** or **2** with peracetylated glycosylazides derived from D-glucose, D-galactose, D-*N*-acetylglucosamine and L-fucose in order to evaluate the antiplasmodial activity of these derivatives against chloroquine-resistant strains of *P.falciparum (W2).*

METHODOLOGY



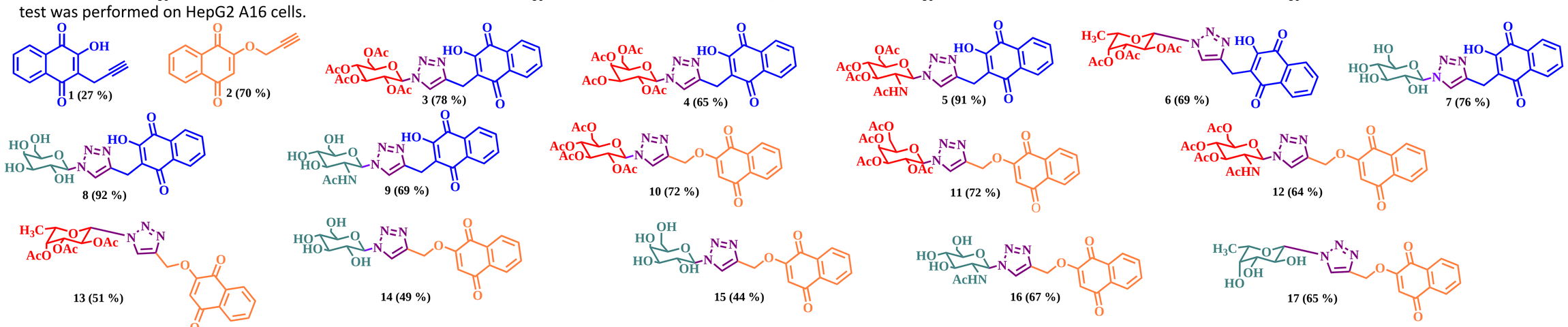


RESULTS

The compounds **1** and **2** were obtained by alkylation of lawsone with propargyl bromide in 27 % and 70 % yield, respectively. The glycosyltriazoles **3** – **17** were obtained with yields in the range of 41 – 92 %, as show bellow.

Compound	% reduction (µg/mL)* 50	25	IC_{50}	CC_{50}	SI	activity**
1	90	85	9.38±1.06	14.79±1,84	1.58	Active
2	79	77	1.74±0.40	1.43±0.23	0.82	Active
3	37	32	-	>100	-	Inactive
4	36	30	-	>100	-	Inactive
5	43	34	-	>100	-	Inactive
6	50	43	-	>100	-	Inactive
7	27	26	-	>100	-	Inactive
8	22	16	-	>100	-	Inactive
9	24	18	-	>100	-	Inactive
10	75	71	4.66±0.33	12.66±0.06	2.72	Active
11	90	86	3.16±0.52	11.36±0.88	3.59	Active
12	79	69	5.60±1.23	11.74±1.74	2.10	Active
13	83	81	6.73±0.78	25.89±3.58	3.85	Active
14	83	79	6.55±1.22	24.62±2.45	3.76	Active
15	85	75	7.60±1.80	51.05±5.69	6.72	Active
16	65	63	24.51±1.32	47.71±0.81	1.95	low active
17	74	71	5.18±0.71	54.87±4.96	10.59	Active
Chloroquine	99	97	0.0979±0.0023	29.36±2.78	302.68	Very active

*the compounds that presented a percentage of parasitemia reduction equal to or greater than 50% in the two concentrations tested were selected for determination of the CI_{50}. **Very Active – IC_{50} values below 1µg/mL; Active - IC_{50} values from 1 to 15µg/mL; Moderately Active - IC_{50} values between 15.1 and 25 µg/mL; Low active – IC_{50} values between 25.1 and 50 µg/mL; Inactive - IC_{50} above 50 µg/mL. The cytotoxicity test was performed on HepG2 A16 cells.



CONCLUSIONS

The glycosyltriazoles **3**-**17** were obtained in moderate to good yields. Of the seventeen compounds evaluated, nine were active (**1**, **2**, **10**-**13**, **15**-**17**), one was moderately active (**14**) and the others were considered inactive and showed no cytotoxicity up to 100 µg/mL. The compounds **15** and **17** showed the highest selectivity indices with values of respectively 6.72 and 10.59.

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