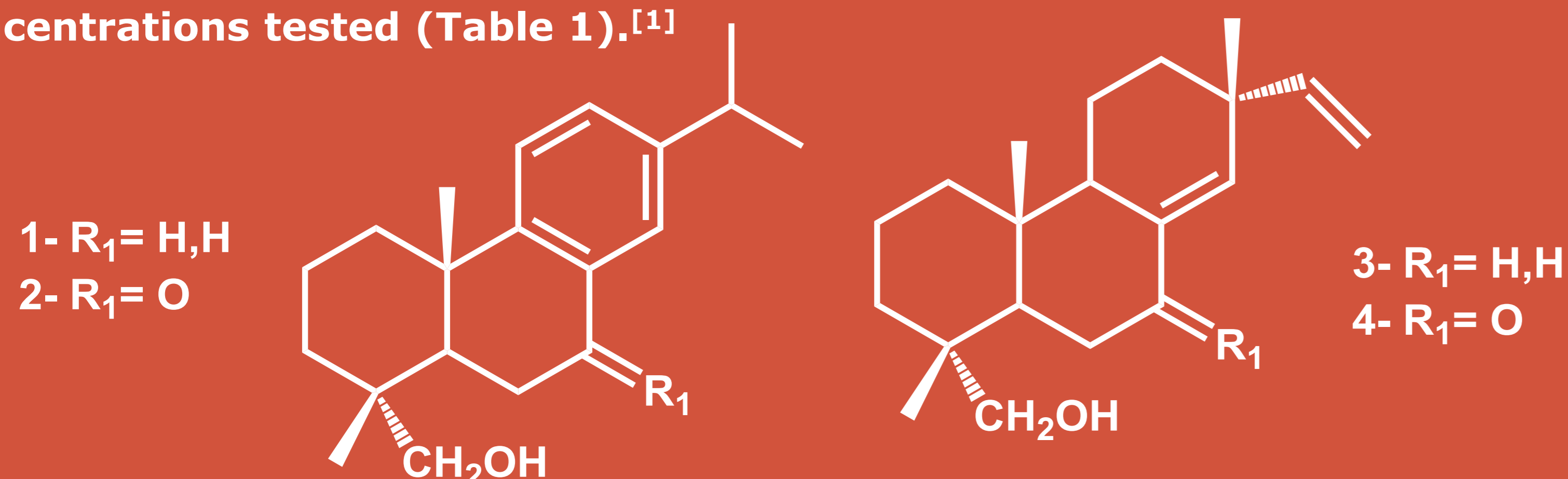


## INTRODUCTION:

Several dehydroabietane and sandaracopimarane derivatives, (1-4) isolated from leaves of *Juniperus brevifolia*,<sup>[1]</sup> an endemic conifer from Azores, displayed antiproliferative activity against cancer cell lines (HeLa, A-549 and MCF-7) and bactericidal effect against *Bacillus cereus* at different concentrations tested (Table 1).<sup>[1]</sup>



**Table 1:** Cytotoxic (IC<sub>50</sub> μM) and antimicrobial (μg/mL) activities of secondary metabolites from *J. brevifolia* leaves.

Comp.	HeLa		MCF-7		A-549		Vero		<i>B. cereus</i>	
	Lag phase	Log phase	Lag phase	Log phase	Lag phase	Log phase	Lag phase	Log phase	MIC	MBC
<b>1</b>	15.7	25.9	31.7	40.4	23.6	44.4	28.0	54.5	2.5 – 5	10 – 20
<b>2</b>	49.0	52.7	>60	>60	46.2	60.0	54.4	>60	-	-
<b>3</b>	46.5	52.1	58.5	>60	53.7	>60	>60	>60	20	20 – 40
<b>4</b>	49.6	>60	>60	>60	>60	>60	nd	nd	-	-

## RESULTS:

In this work, protein-ligand docking was performed, using the FlexScreen program, in order to pick molecular targets, from a large set of common anticancer (63) and antimicrobial (39) targets, for the selected compounds 1-4.

The preferred targets for anticancer and antimicrobial compounds 1-4 and their interaction energies are shown in Tables 2 and 3.

❖ The structural differences between the skeleton-type dehydroabietane and sandaracopimarane, do not seem to be relevant in the interaction with the targets

**Table 2:** Preferred anticancer targets and interaction energies.

Comp.	Anticancer target			
	Target	PDB code	Energy (arbitrary units)	
			Sample 1	Sample 2
<b>1</b>	SHIP2	3RN8	-76,512	-76,156
<b>2</b>	PDF	3G5K	-86,313	-85,542
<b>3</b>	SHIP2	3RN8	-76,983	-76,831
<b>4</b>	TUBA	Model	-98,136	-97,943

**Table 3:** Preferred antimicrobial targets and interaction energies.

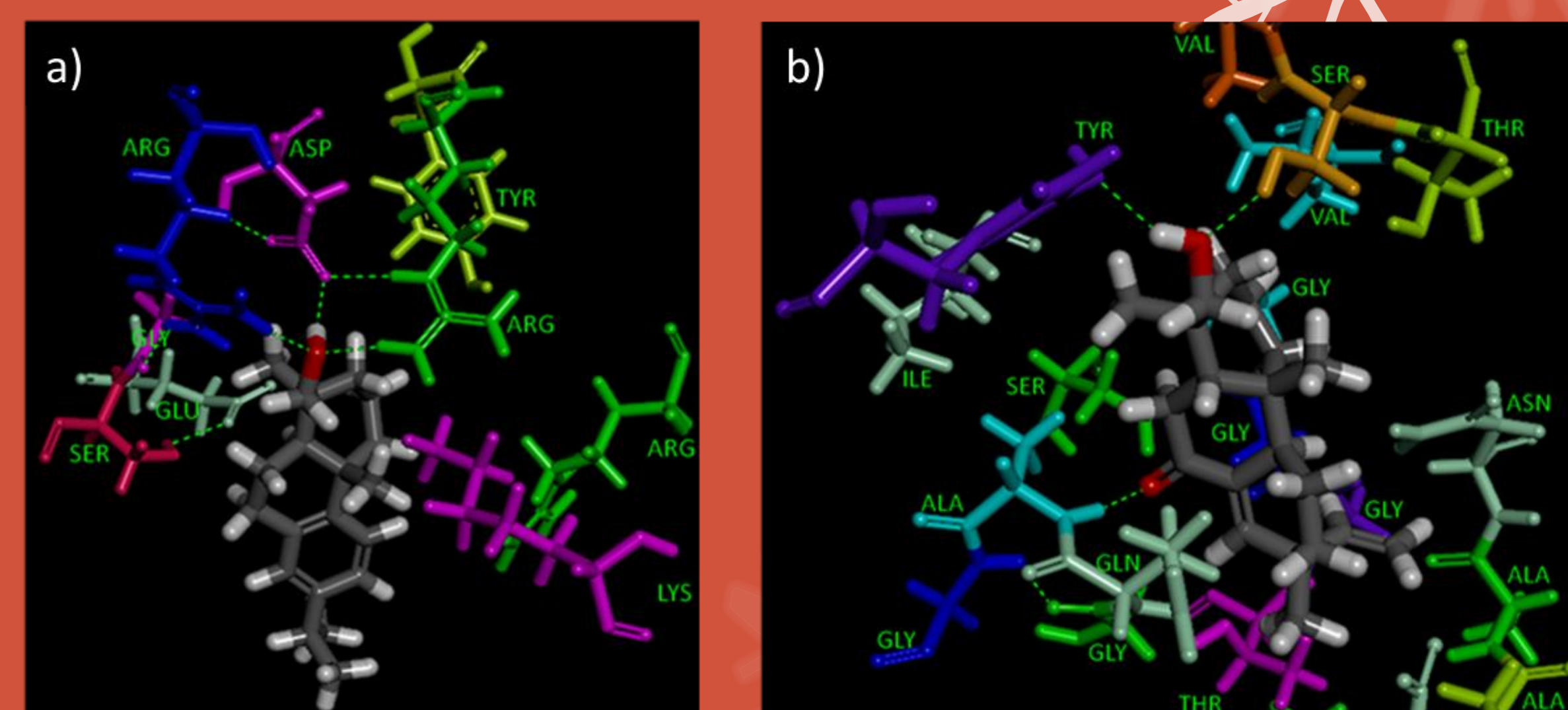
Comp.	Antimicrobial target			
	Target	PDB Code	Energy (arbitrary units)	
			Sample 1	Sample 2
<b>1</b>	RNAP	1EIK	-230,447	-212,083
<b>3</b>	RNAP	1EIK	-234,812	-234,152
<b>1</b>	PDF	2AIA	-76,970	-76,476
<b>3</b>	PDF	2AIA	-75,318	-72,259

## Anticancer targets

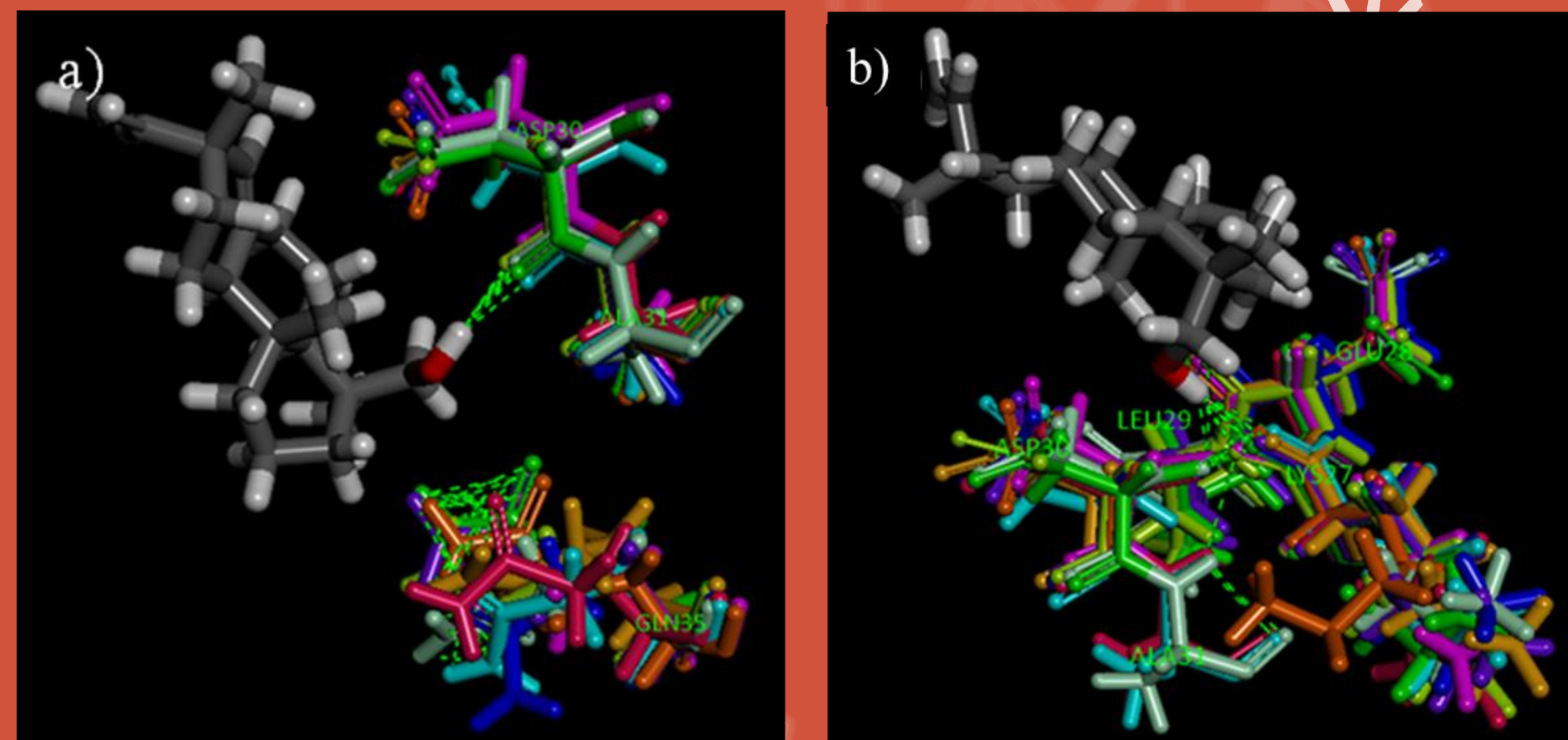
- ❖ The compounds 1 and 3 interact preferentially with phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase 2, (SHIP2), a clinically relevant novel anticancer target. This enzyme has high therapeutic index given its over-expression in cancer and its dispensability for normal cell survival.<sup>[3]</sup>
- ❖ The hydroxyl groups and their ability to form H-bond, seem to play a significant role in these interactions since the H atom interacts with the carbonyl group of the aspartate residue and the oxygen atom interact with H-N of Arginine residue (Fig 1a).
- ❖ The compound 4 interact preferentially with  $\alpha$ -tubulin (Fig 1b), the protein that makes up microtubules, not only by its OH group (H-bond with serine and tyrosine residue), but also by its carbonyl group (H-bond between N-H group of the alanine residue and oxygen atom from carbonyl group).
- ❖ The correlation between experimental and calculated data for anticancer targets show that the compounds probably inhibited the targets TNKS-1, CDK1 and HIF1A in the assay against cancer cell line Vero. Against cancer cells lines HeLa, MCF-7 and A-59, the compounds probably inhibited PPAR- $\gamma$ .

## Antimicrobial targets

- ❖ Compounds 1 and 3 interact, both by H-bond, preferentially with RNA polymerase (RNAP), an enzyme that in bacteria catalyzes the synthesis of mRNA and ncRNA.
- ❖ The hydroxyl group of compound 3 interacts with carbonyl group of aspartate (ASP30) (Fig 2 a). The hydroxyl groups of the compound 1 and 3, also interact with the carbonyl group of lysine residue (LYS27) (Fig 2b).



**Fig 1.** Representation of the obtained interactions between a) compound 1 and target SHIP2 and b) compound 4 and target TUBA.



**Fig 2.** Representation of the obtained interactions between compound 3 and target RNAP a) interactions with ASP30, b) interactions with LYS27.

## Acknowledgments

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