Identification of potential molecular targets related to cancer for the formicamycin's family

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INTRODUCTION

According to the Global Cancer Observatory, 18 million new cases and 9.5 million deaths were estimated for all types of cancer in 2018. The World Health Organization predicts that in 2030 there will be a 70% increase in new cases and 45% in deaths. Due to the rise of cancer incidence and mortality, it is necessary to invest in the discovery and development of new antineoplastic drugs.

The novel family of molecules called formicamycin, active against some antibiotic-resistant microorganisms, had a tyrosine kinase enzyme predicted as one of its molecular targets. As this enzyme plays a role in the progression of cancer, the potential antineoplastic action of the formicamycins has been studied.

AIM

To identify the potential molecular targets for an antineoplastic action of the formicamycins through:

- Reverse virtual screening to establish molecular targets which interact with these compounds;
- Literature review to verify the influence of these targets in carcinogenesis; and
- Molecular docking and dynamics to estimate the free energy of binding (EFEB) and the variation of Gibbs free energy (ΔG), respectively, between target and molecule.

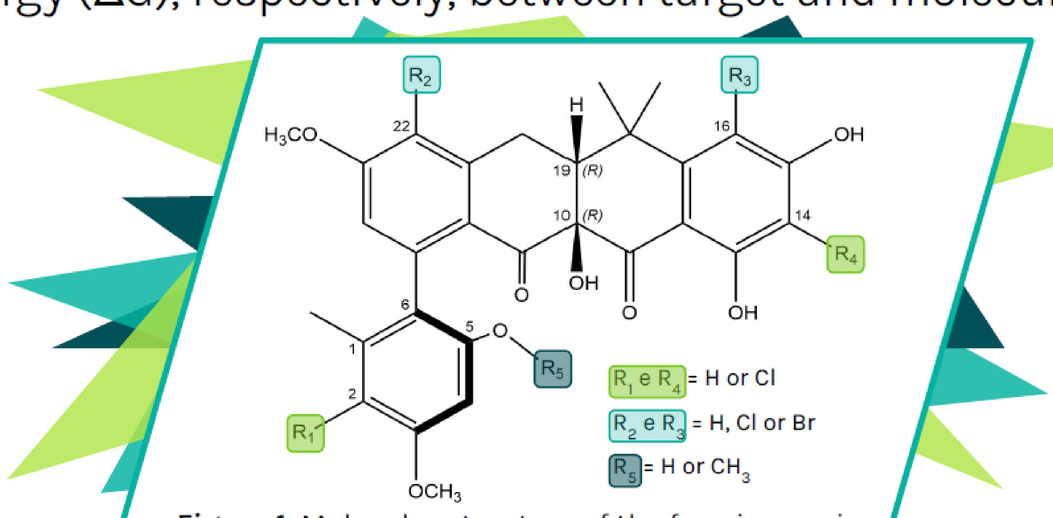
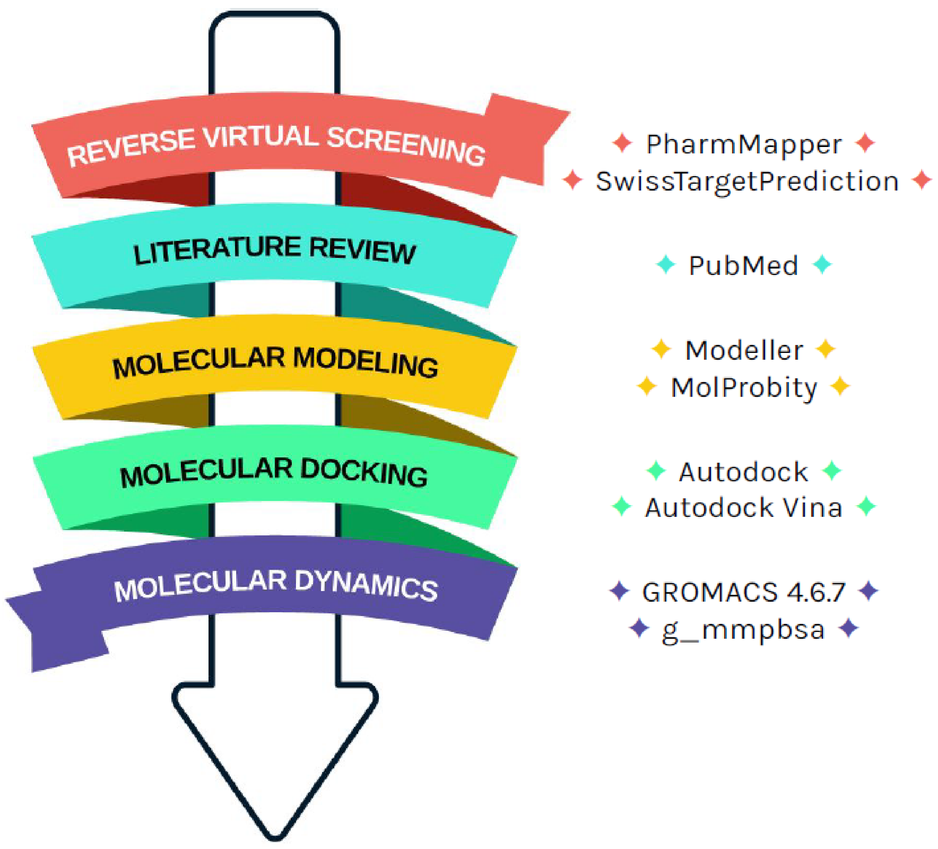


Figure 1. Molecular structure of the formicamycins.

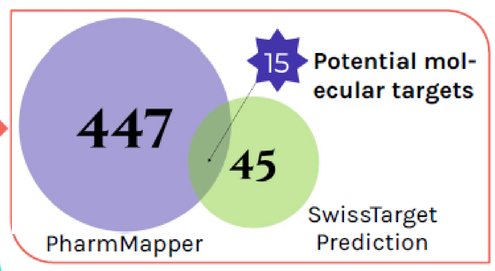
METHODOLOGY



- PharmMapper
- SwissTargetPrediction
- PubMed
- Modeller
- MolProbity
- Autodock
- Autodock Vina
- GROMACS 4.6.7
- g_mmpbsa

RESULTS

Molecular targets: 492 → 15 → 12 → 4 → 12 → 12 → 3



- cGMP-specific 3'-5'-cyclic phosphodiesterase
- Coagulation factor VII
- Coagulation factor X
- Glucocorticoid receptor
- Heat shock protein 90 α
- Insulin-like growth factor 1 receptor
- **Matrix metalloproteinase 3 (MP3)**
- **Matrix metalloproteinase 12 (MP12)**
- Matrix metalloproteinase 13
- **Nuclear receptor subfamily 1 group I member 2 (NR1I2)**
- Progesterone receptor
- Tyrosine-protein phosphatase non-receptor type 1

Top 3 results of the variation of Gibbs Free Energy (ΔG) estimated by g_mmpbsa from the molecular dynamics' simulations

Molecular targets		NR1I2	MP3	MP12
PDB ID		4X1F*	1HY7*	2WO9
Ligand	ID	3WF	MBS	068
	ΔG	-102.73	-53.72	-39.53
Formicamycin (Autodock)	ID	F	A	D
	ΔG	-224.84	-155.39	-125.94
Formicamycin (Vina)	ID	F	D	B
	ΔG	-236.23	-107.79	-141.09

PDB ID, alphanumeric identification code at the Protein Data Bank (PDB); ID, molecular identification code in the PDB of the crystallographic ligands and identification of the formicamycin family representative who obtained the lowest EFEB in the dockings; ΔG (kcal/mol), variation of Gibbs free energy calculated by g_mmpbsa from the molecular dynamics simulation data; *Structures modeled due to missing parts; 3WF, ethinylestradiol.

CONCLUSION

In this work, we were able to establish a reverse virtual screening protocol for the identification of potential molecular targets for an antineoplastic action of formicamycins. After all the steps, three potential molecular targets for the formicamycins were identified. Among these macromolecules, nuclear receptor subfamily 1 group I member 2 and matrix metalloproteinase 3 are the most promising targets for an antineoplastic action of these compounds.

Acknowledgements

CAPES

UFCSPA Universidade Federal de Ciências da Saúde de Porto Alegre