Design and In Silico Profiling of Semi-Synthetic Abietane Diterpenoids with Promising Anticancer Activity

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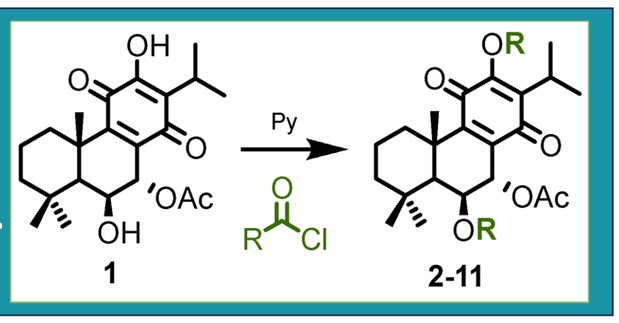
Introduction

Plants: Important source of bioactive molecules.

***Plectranthus* genus (Lamiaceae):** Rich in cytotoxic abietane diterpenoids. 7α-Acetoxy-6β-hydroxyroyleanone (**Roy 1**) isolated from *P. grandidentatus* Gürke demonstrates notable cytotoxicity across cancer cell lines. To enhance its anticancer potential, a series of semi-synthetic Roy derivatives were synthesized and examined through comprehensive in silico analyses.

Methods and Results

Synthesis:

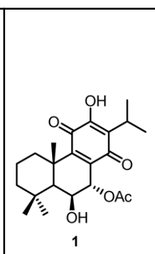
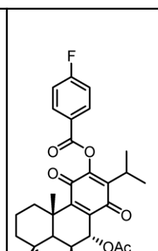
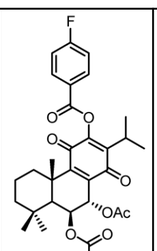
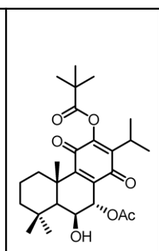
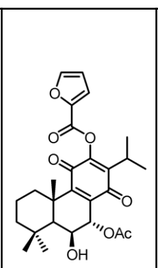
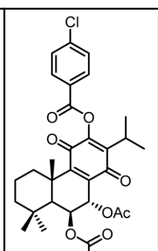
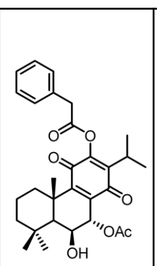
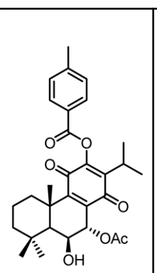
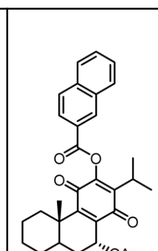
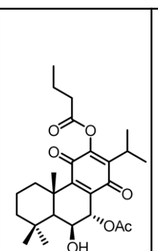
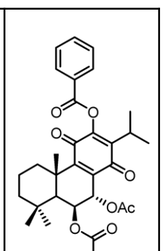
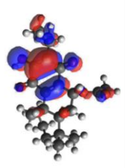
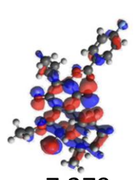
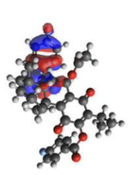
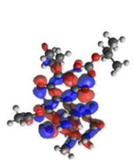
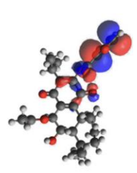
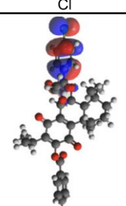
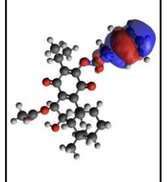
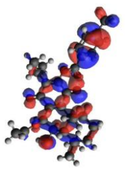
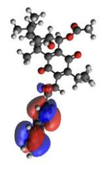
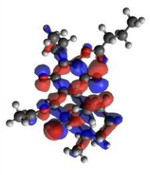
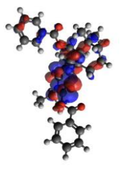
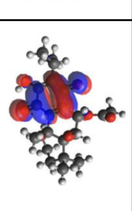
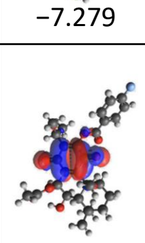
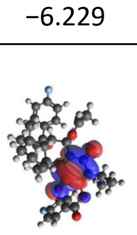
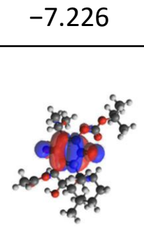
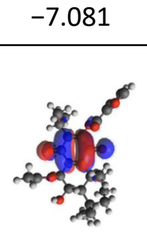
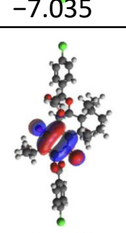
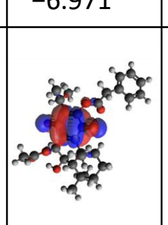
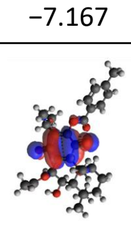
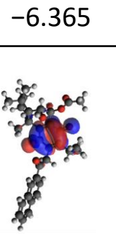
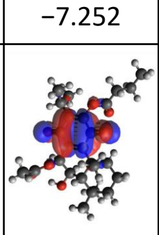
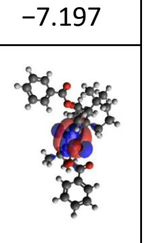


ADMET and Drug-Likeness Analysis Results:

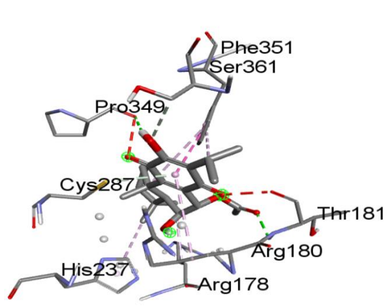
- Compounds **1** and **10** followed all five filters (Lipinski, Ghose, Veber, Egan, and Muegge).
- The calculated bioavailability score for all compounds placed them within the 56% probability class.

DFT Calculations:

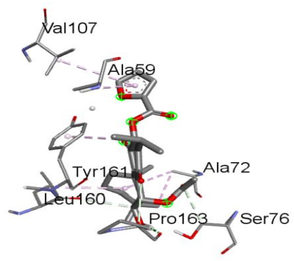
Table 1. HOMO-LUMO diagram of compound **1** and derivatives (**2**–**11**) synthetized from **1**. The LUMO energy refers to the electron-accepting aptitude of a molecule while the HOMO energy determines its electron-donating ability. A smaller HOMO–LUMO gap indicates a more polarizable molecule with lower kinetic stability and higher chemical reactivity.

Derivative Structure	 1	 2	 3	 4	 5	 6	 7	 8	 9	 10	 11
HOMO E_{HOMO} (eV)	 −6.885	 −7.279	 −6.229	 −7.226	 −7.081	 −7.035	 −6.971	 −7.167	 −6.365	 −7.252	 −7.197
LUMO E_{LUMO} (eV)	 −3.433	 −3.572	 −3.599	 −3.488	 −3.429	 −3.493	 −3.579	 −3.462	 −2.862	 −3.537	 −3.412

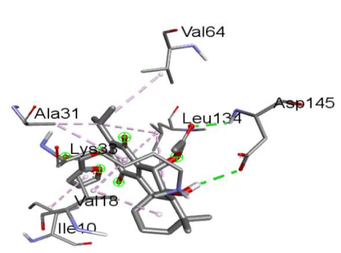
Molecular docking and MD simulations :



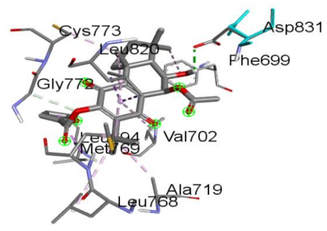
(A)
−10.60 Kcal/mol



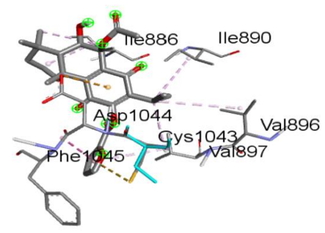
(B)
-10.90 kcal/mol



(C)
-13.42 kcal/mol



(D)
-10,12 kcal/mol



(E)
-12.29 kcal/mol

(F)
−11.65 kcal/mol

(G)
−12.84 kcal/mol

(H)
−11.86 kcal/mol

(I)
−13.49 kcal/mol

(J)
-12.39 kcal/mol

(K)
−11.40 kcal/mol

Figure 2. Interaction and binding energy between compounds (**1**, **5** and **9**) and the active sites of target proteins implicated in cancer-related pathway. Compound **1** against caspase 9 (**A**); compound **5** against BCL-2 (**B**), CDK2 (**C**), EGFR (**D**) and VEGFR (**E**); compound **9** against EGFR (**F**), BCL-XL (**G**), caspase 3 (**H**), CDK2 (**I**), VEGFR (**J**), p53 (**K**).

Conclusion

- ADMET predictions indicated favourable attributes and acceptable toxicity profiles for all compounds
- Quantum mechanical calculations and DFT models revealed modifications in HOMO–LUMO gaps (3.39–3.79 eV) and global reactivity indices.
- Molecular docking and MD simulations highlighted favourable binding against key cancer-related proteins
- These findings suggest that Roy and its derivatives are effective molecules with significant anticancer properties, supporting future experimental validation.

Acknowledgments

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Fundação para a Ciência e a Tecnologia

References

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[2] Isca, V.M.S., et. al., Rijo, P., Kowalczyk, T. 2024. Molecules, 29, 1807.
[3] Merecz-Sadowska, A., Isca, V.M.S., et. al., Rijo, P., Zajdel, R. 2024. Int. J. Mol. Sci., 25, 4529.