The extra virgin olive oil phenolic oleacein is a dual substrate-inhibitor of catechol-O-methyltransferase

Elisabet Cuyàs, Sara Verdura, Jesús Lozano-Sánchez,
Ignacio Viciano-Gonzalo, Laura Llorach-Parés, Joaquim Bosch-Barrera,
Joan Brunet, Alfons Nonell-Canals, Antonio Segura-Carretero,
Melchor Sánchez-Martínez, José Antonio Encinar, Javier A. Menendez

SUPPLEMENTARY INFORMATION

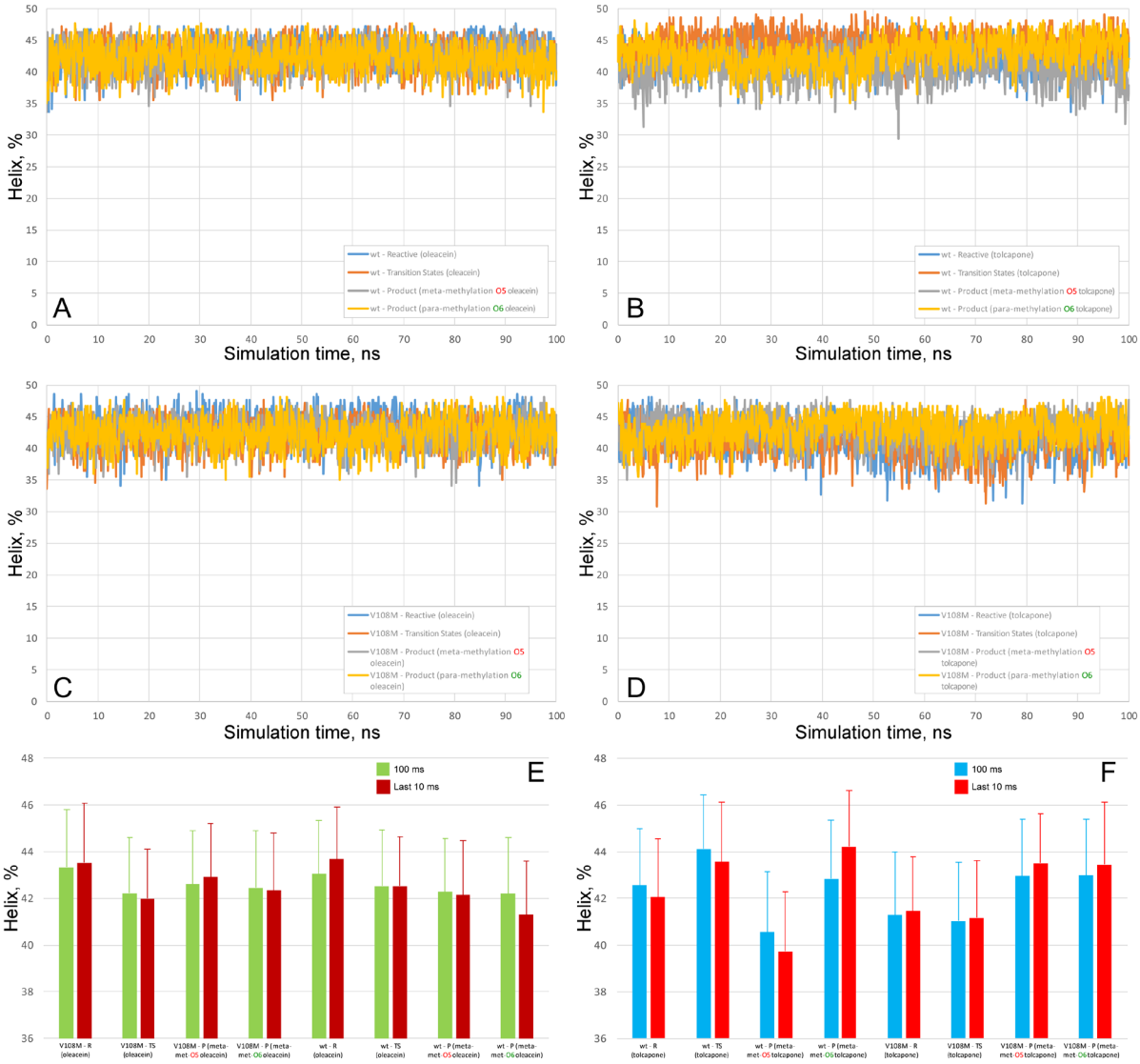


Figure S1. Result of molecular dynamics (MD) simulation showing the secondary structure helix content for COMT (**A**, **B**) and V108M COMT (**C**, **D**) in the presence of oleacein (R), intermediates (TS) or their putative catalyzed products (meta-methylation O5 oleacein and meta-methylation O6 oleacein); and in the presence of tolcapone (R), intermediates (TS) or their potentially catalyzed products (meta-methylation O5 tolcapone and meta-methylation O6 tolcapone). Panels **E** (oleacein) and **F** (tolcapone) include average values and standard deviation for the analyzed parameter at last 10 ns and all 100 ns of the MD simulation. The legends are included in each panel to facilitate reading.

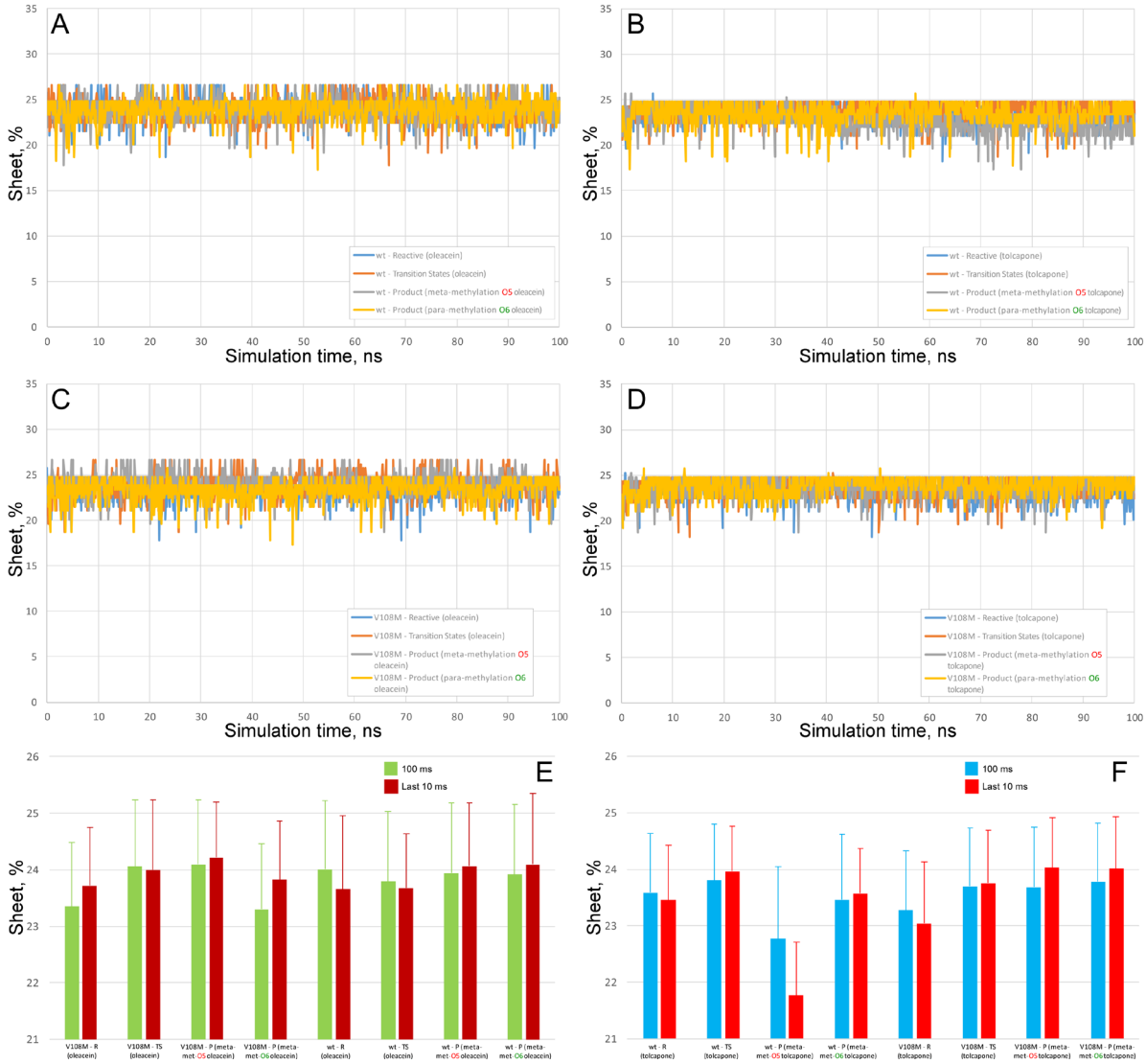


Figure S2. Result of molecular dynamics (MD) simulation showing the secondary structure sheet content for COMT (**A**, **B**) and V108M COMT (**C**, **D**) in the presence of oleacein (R), intermediates (TS) or their putative catalyzed products (meta-methylation O5 oleacein and meta-methylation O6 oleacein); and in the presence of tolcapone (R), intermediates (TS) or their potentially catalyzed products (meta-methylation O5 tolcapone and meta-methylation O6 tolcapone). Panels **E** (oleacein) and **F** (tolcapone) include average values and standard deviation for the analyzed parameter at last 10 ns and all 100 ns of the MD simulation. The legends are included in each panel to facilitate reading.

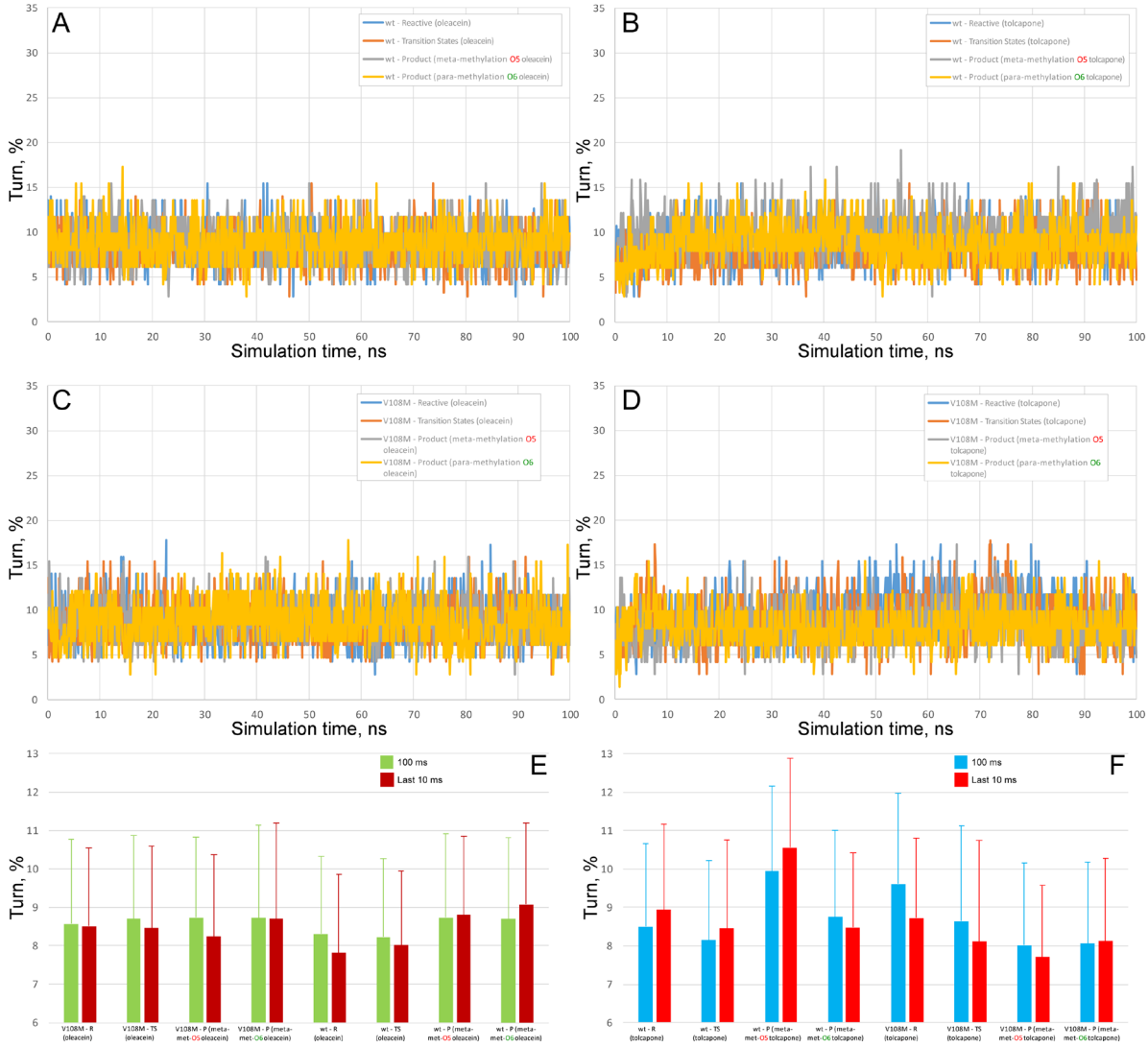


Figure S3. Result of molecular dynamics (MD) simulation showing the secondary structure turn content for COMT (**A**, **B**) and COMT V108M (**C**, **D**) in the presence of oleacein (R), intermediates (TS) or their putative catalyzed products (meta-methylation O5 oleacein and meta-methylation O6 oleacein); and in the presence of tolcapone (R), intermediates (TS) or their potentially catalyzed products (meta-methylation O5 tolcapone and meta-methylation O6 tolcapone). Panels **E** (oleacein) and **F** (tolcapone) include average values and standard deviation for the analyzed parameter at last 10 ns and all 100 ns of the MD simulation. The legends are included in each panel to facilitate reading.

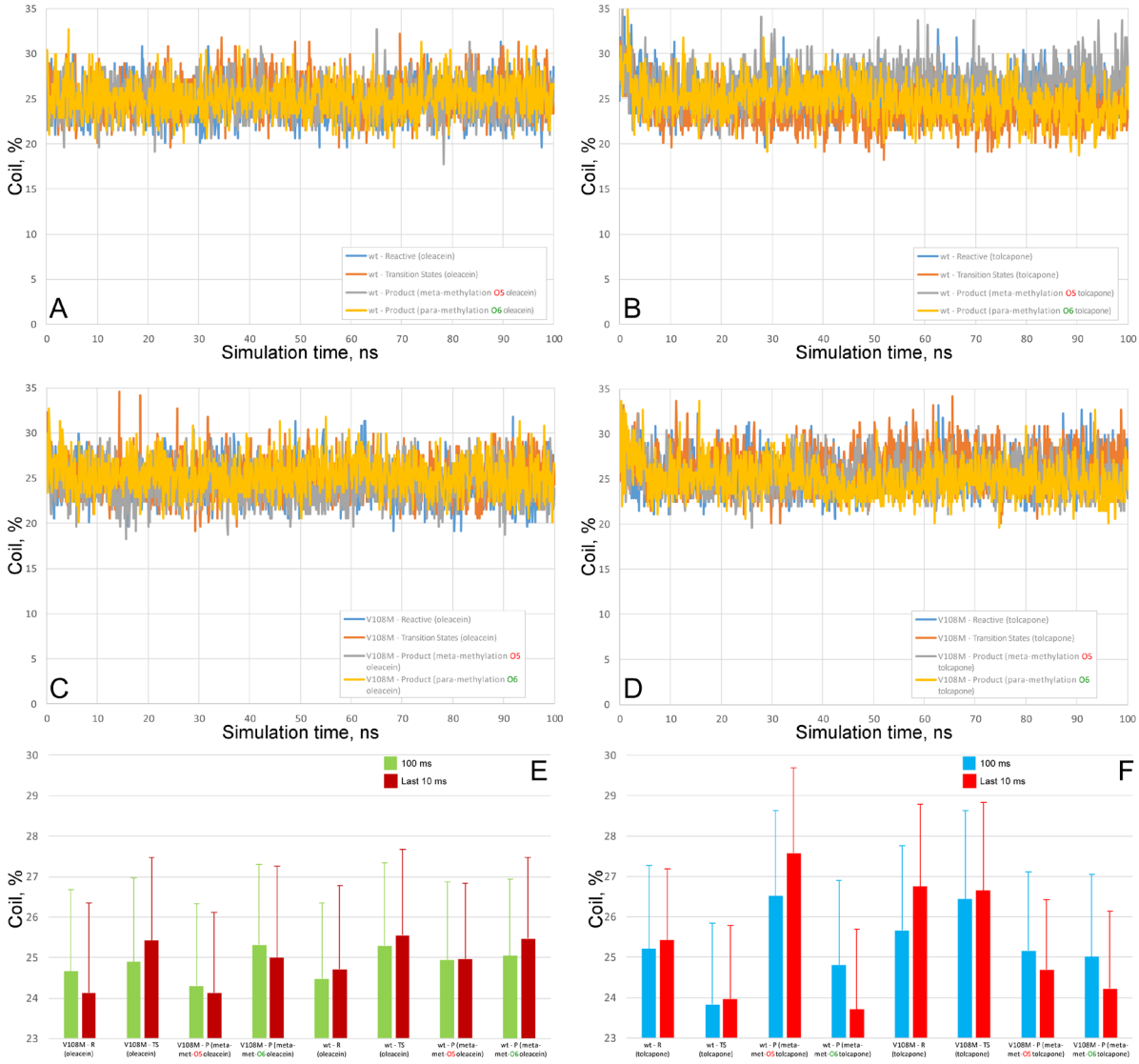


Figure S4. Result of molecular dynamics (MD) simulation showing the secondary structure coil content for COMT (**A**, **B**) and V108M COMT (**C**, **D**) in the presence of oleacein (R), intermediates (TS) or their putative catalyzed products (meta-methylation O5 oleacein and meta-methylation O6 oleacein); and in the presence of tolcapone (R), intermediates (TS) or their potentially catalyzed products (meta-methylation O5 tolcapone and meta-methylation O6 tolcapone). Panels **E** (oleacein) and **F** (tolcapone) include average values and standard deviation for the analyzed parameter at last 10 ns and all 100 ns of the MD simulation. The legends are included in each panel to facilitate reading.

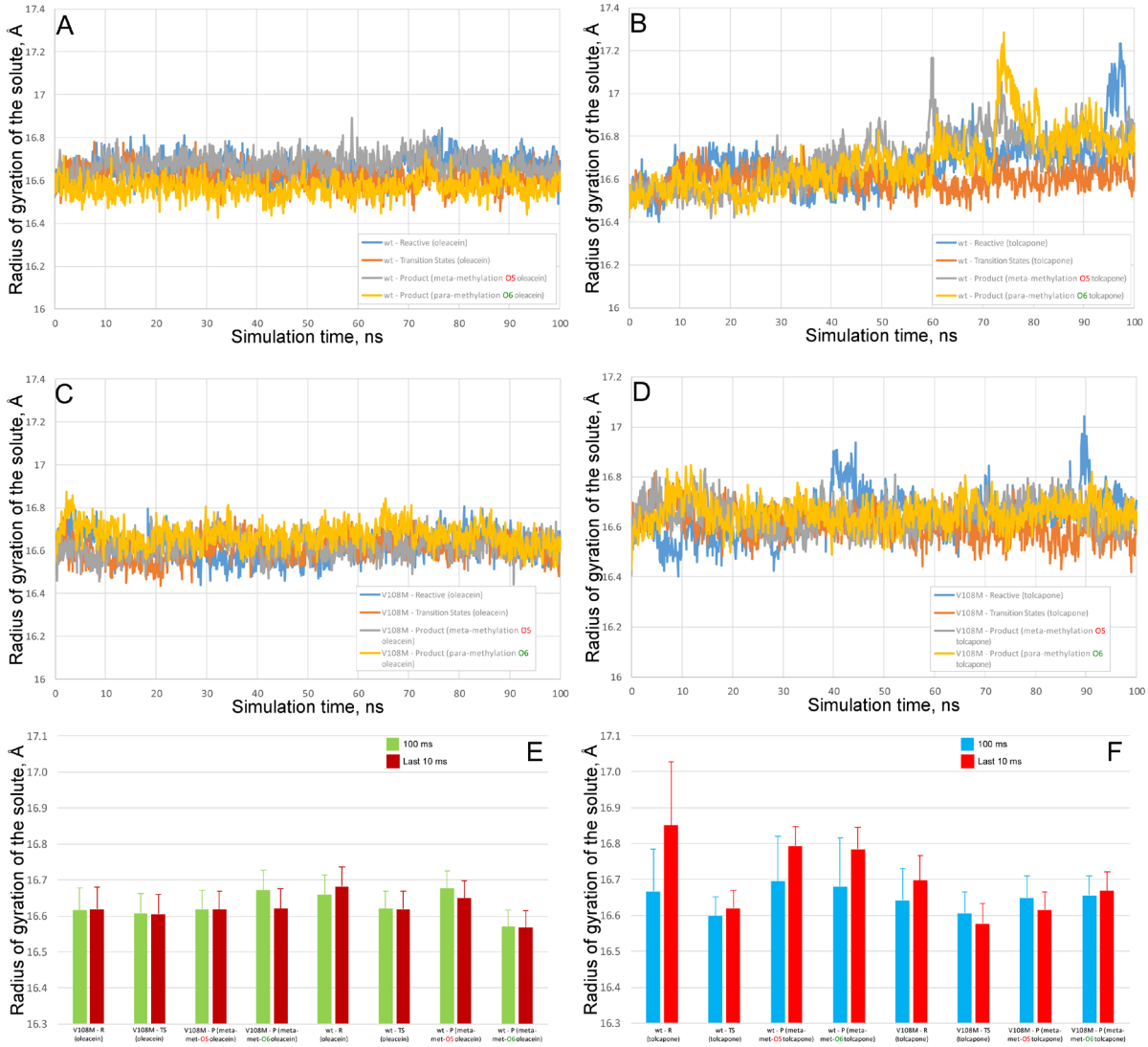


Figure S5. Result from molecular dynamics (MD) simulation showing the radius of gyration of the solute measured in Å for COMT (**A**, **B**) and V108M COMT (**C**, **D**) in the presence of oleacein (R), intermediates (TS) or their putative catalyzed products (meta-methylation O5 oleacein and meta-methylation O6 oleacein); and in the presence of tolcapone (R), intermediates (TS) or their potentially catalyzed products (meta-methylation O5 tolcapone and meta-methylation O6 tolcapone). Panels **E** (oleacein) and **F** (tolcapone) include average values and standard deviation for the analyzed parameter at last 10 ns and all 100 ns of the MD simulation. The legends are included in each panel to facilitate reading.

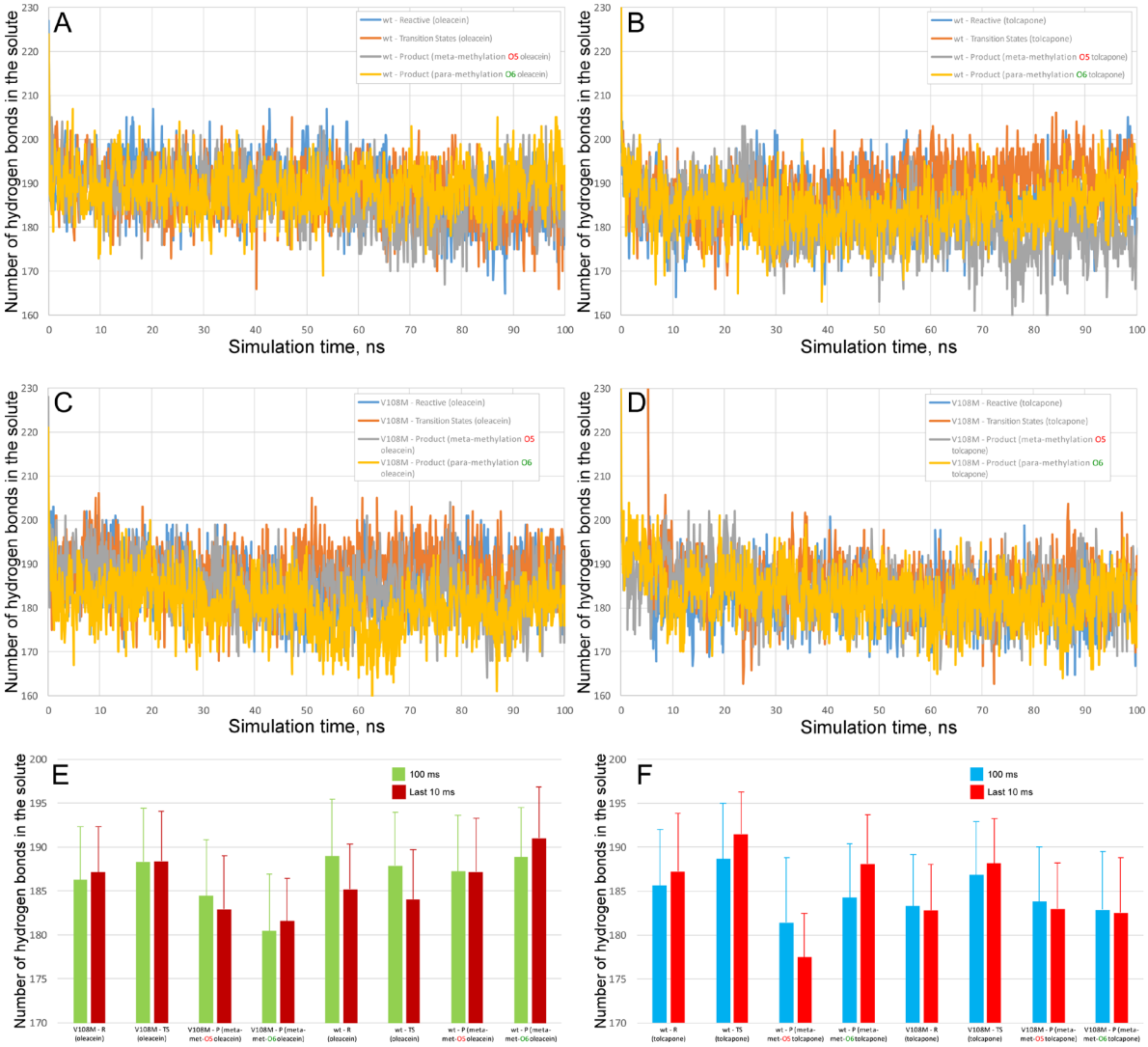


Figure S6. Result from molecular dynamics (MD) simulation showing the number of hydrogen bonds in the solute for COMT (**A**, **B**) and V108M COMT (**C**, **D**) in the presence of oleacein (R), intermediates (TS) or their putative catalyzed products (meta-methylation O5 oleacein and meta-methylation O6 oleacein); and in the presence of tolcapone (R), intermediates (TS) or their potentially catalyzed products (meta-methylation O5 tolcapone and meta-methylation O6 tolcapone). Panels **E** (oleacein) and **F** (tolcapone) include average values and standard deviation for the analyzed parameter at last 10 ns and all 100 ns of the MD simulation. The legends are included in each panel to facilitate reading.

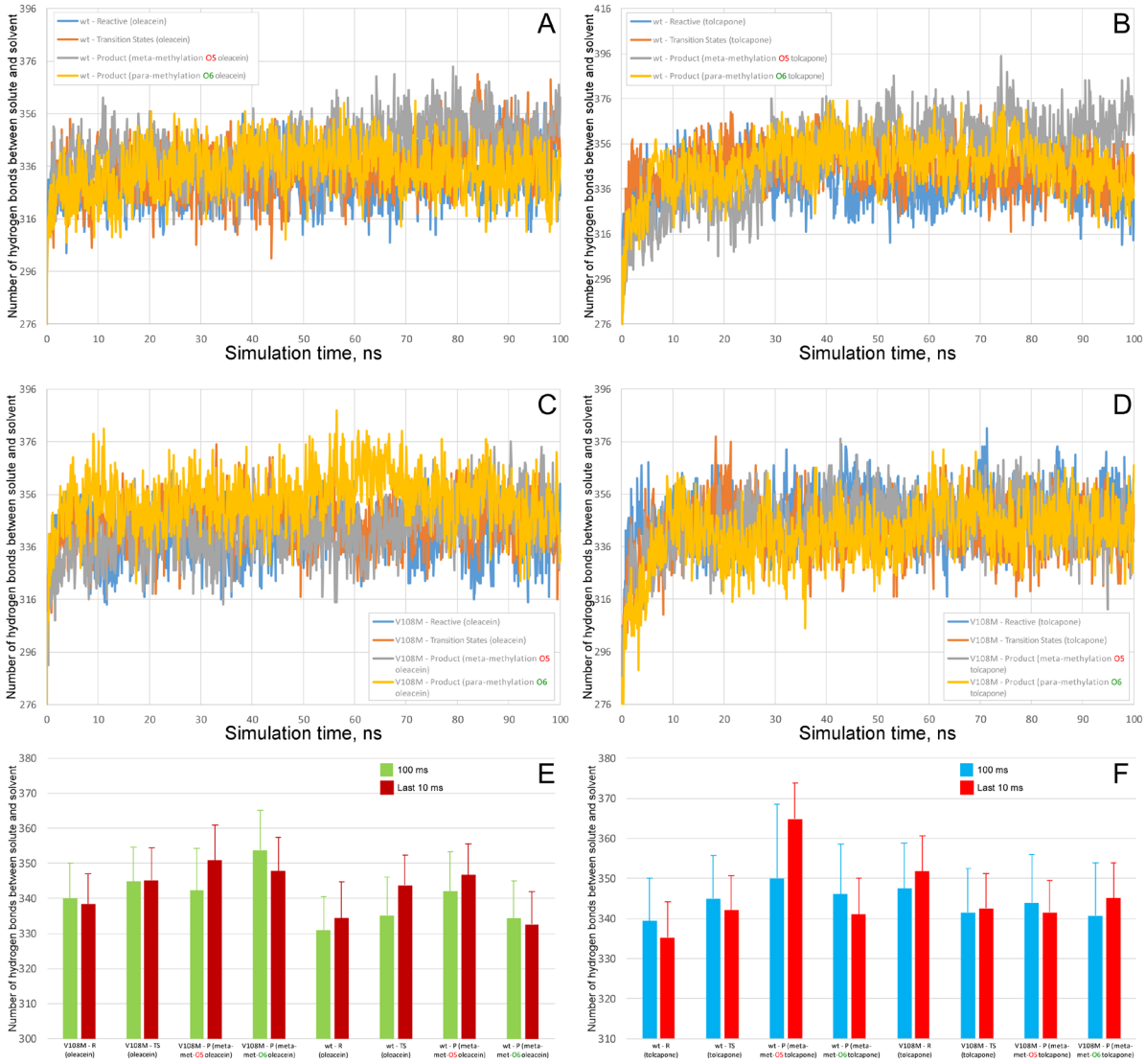
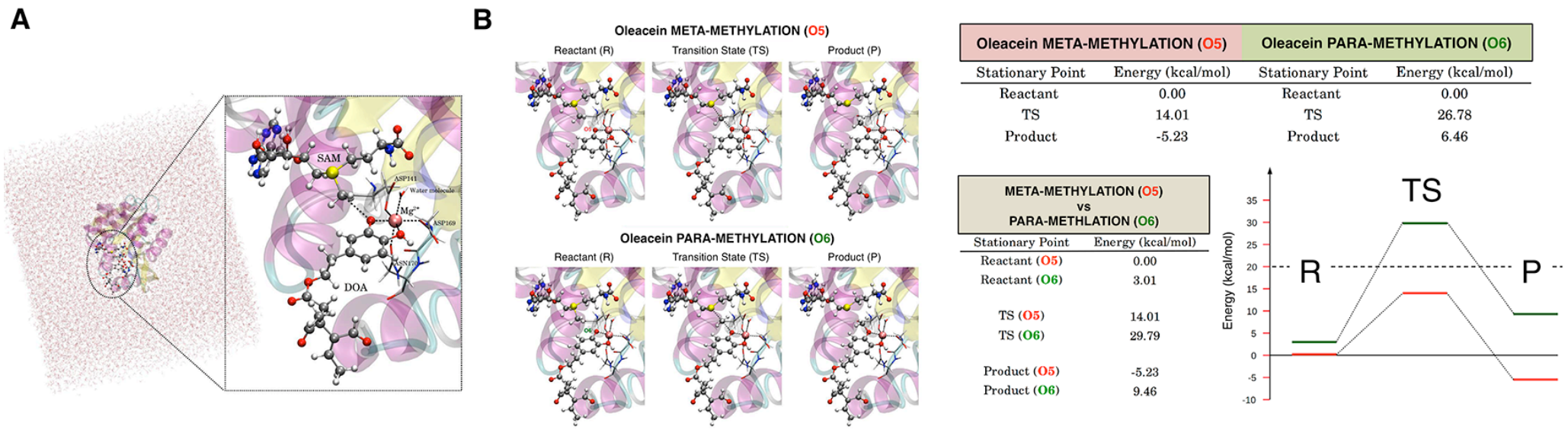


Figure S7. Result from molecular dynamics (MD) simulation showing the number of hydrogen bonds between solute and solvent for COMT (**A**, **B**) and V108M COMT (**C**, **D**) in the presence of oleacein (R), intermediates (TS) or their putative catalyzed products (meta-methylation O5 oleacein and meta-methylation O6 oleacein); and in the presence of tolcapone (R), intermediates (TS) or their potentially catalyzed products (meta-methylation O5 tolcapone and meta-methylation O6 tolcapone). Panels **E** (oleacein) and **F** (tolcapone) include average values and standard deviation for the analyzed parameter at last 10 ns and all 100 ns of the MD simulation. The legends are included in each panel to facilitate reading.



Oleacein META-METHYLATION (O5)		Oleacein PARA-METHYLATION (O6)	
Stationary Point	Energy (kcal/mol)	Stationary Point	Energy (kcal/mol)
Reactant	0.00	Reactant	0.00
TS	14.01	TS	26.78
Product	-5.23	Product	6.46

META-METHYLATION (O5) vs PARA-METHLATION (O6)	
Stationary Point	Energy (kcal/mol)
Reactant (O5)	0.00
Reactant (O6)	3.01
TS (O5)	14.01
TS (O6)	29.79
Product (O5)	-5.23
Product (O6)	9.46

Figure S8. A. Representation of the bidentate Mg^{2+} coordination established by oleacein at the catechol-binding place of COMT. **B.** Representation of the stationary structures corresponding to the reactants (R), Transition States (TS), and products (P) by methylation of a single oleacein hydroxyl to form the meta- (O5) or para- (O6) product. *Right panels.* Potential energies obtained for the COMT-catalyzed meta- and para-methylation of oleacein and their associated energy profiles. Several groups have calculated the reaction barrier for catechol to be approximately 20 kcal/mol in height (dashed line) (Roca et al., 2003).