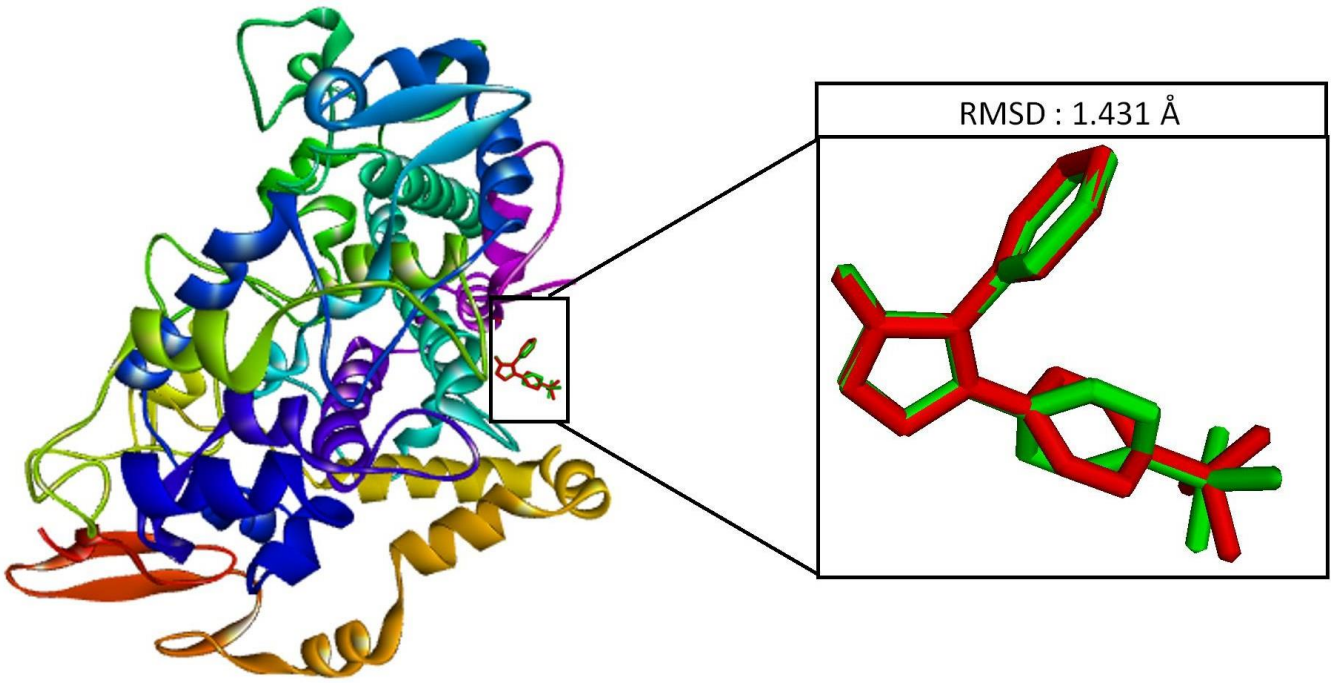
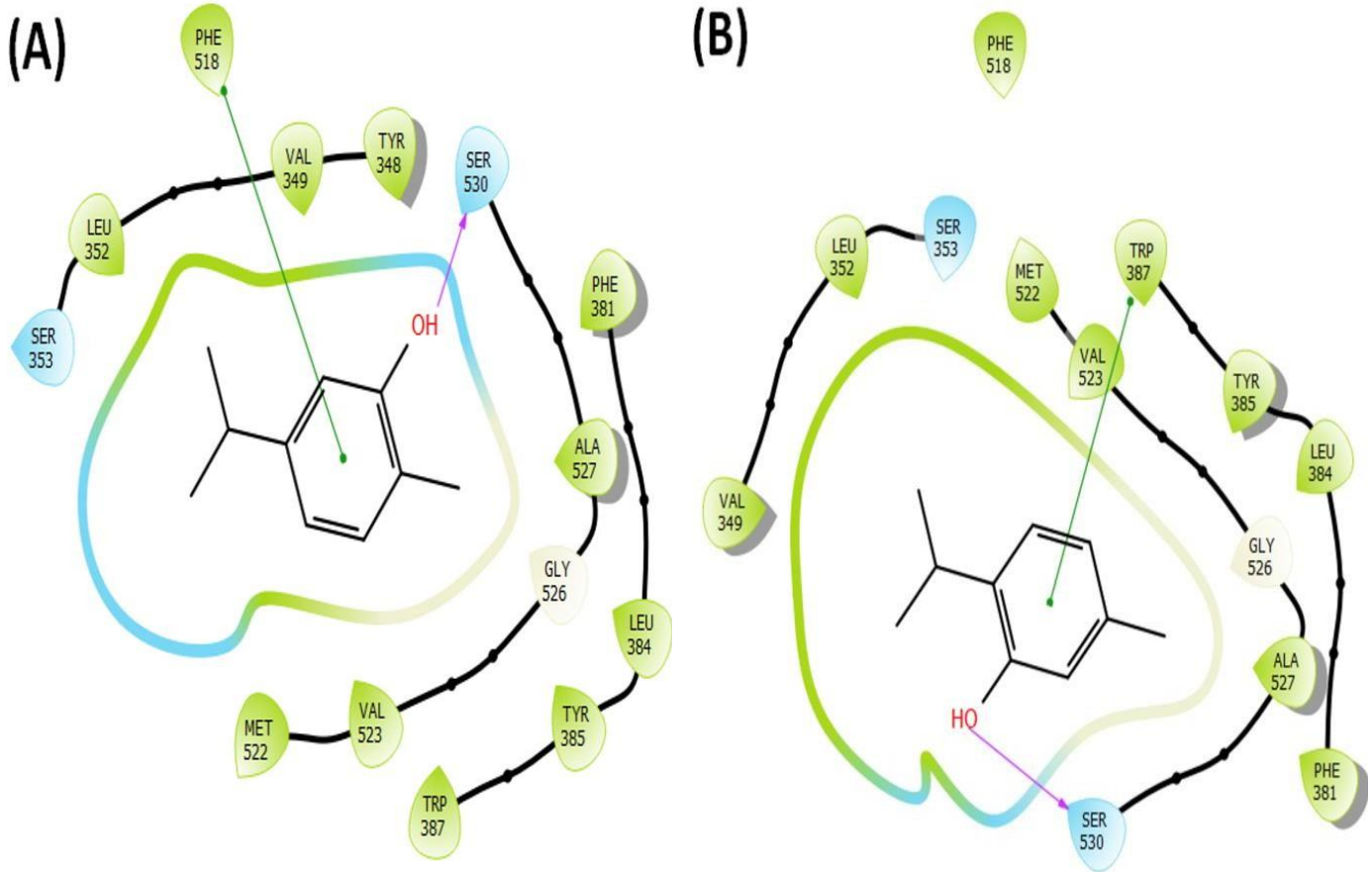



**Figure S1**: Superimposition of the docked co-crystal ligand (in green color) and the co-crystal ligand (in red color) with RMSD of 1.431 Å, (validation of docking study).



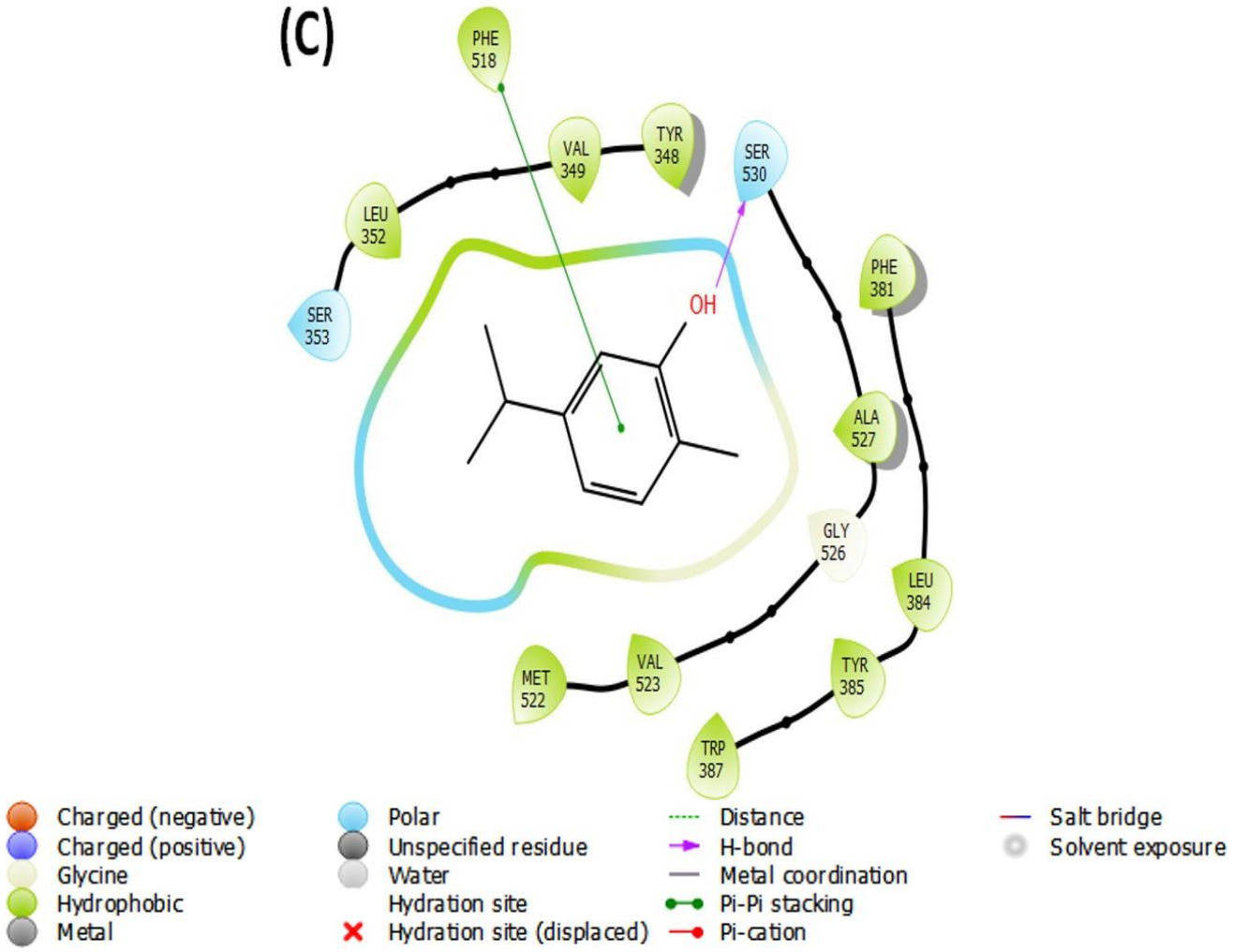
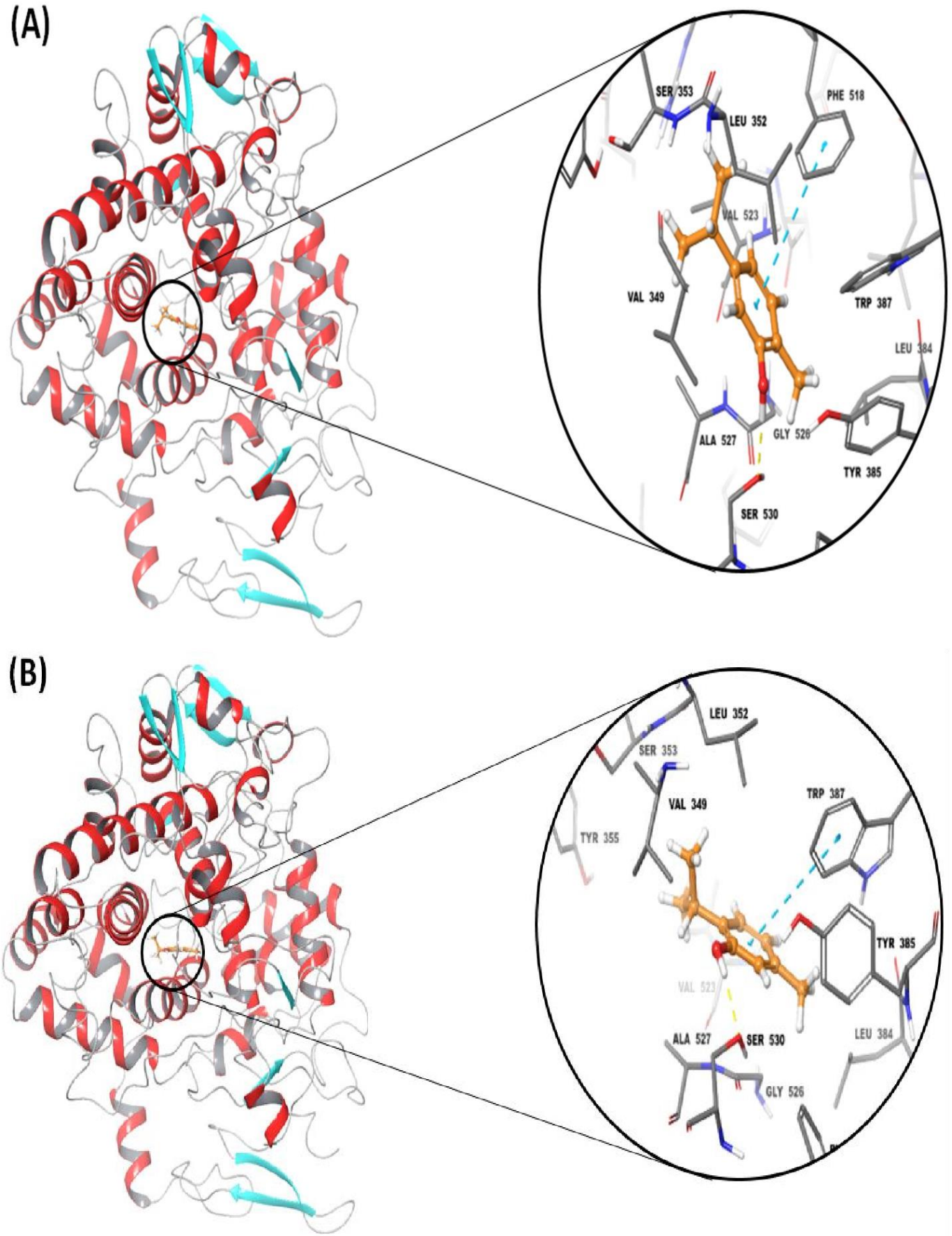



**Figure S2.** 2D Diagrams of protein-ligand interaction: (**A**): Carvacrol-COX-2 complex; (**B**): Thymol-COX-2 complex; (**C**): Diclofenac-COX-2 complex.


(A)
SER 353
LEU 352
PHE 518
VAL 523
VAL 349
TRP 387
LEU 384
ALA 527
GLY 526
TYR 385
SER 530
(B)
LEU 352
SER 353
TRP 387
VAL 349
TYR 355
TYR 385
VAL 523
ALA 527
SER 530
LEU 384
GLY 526

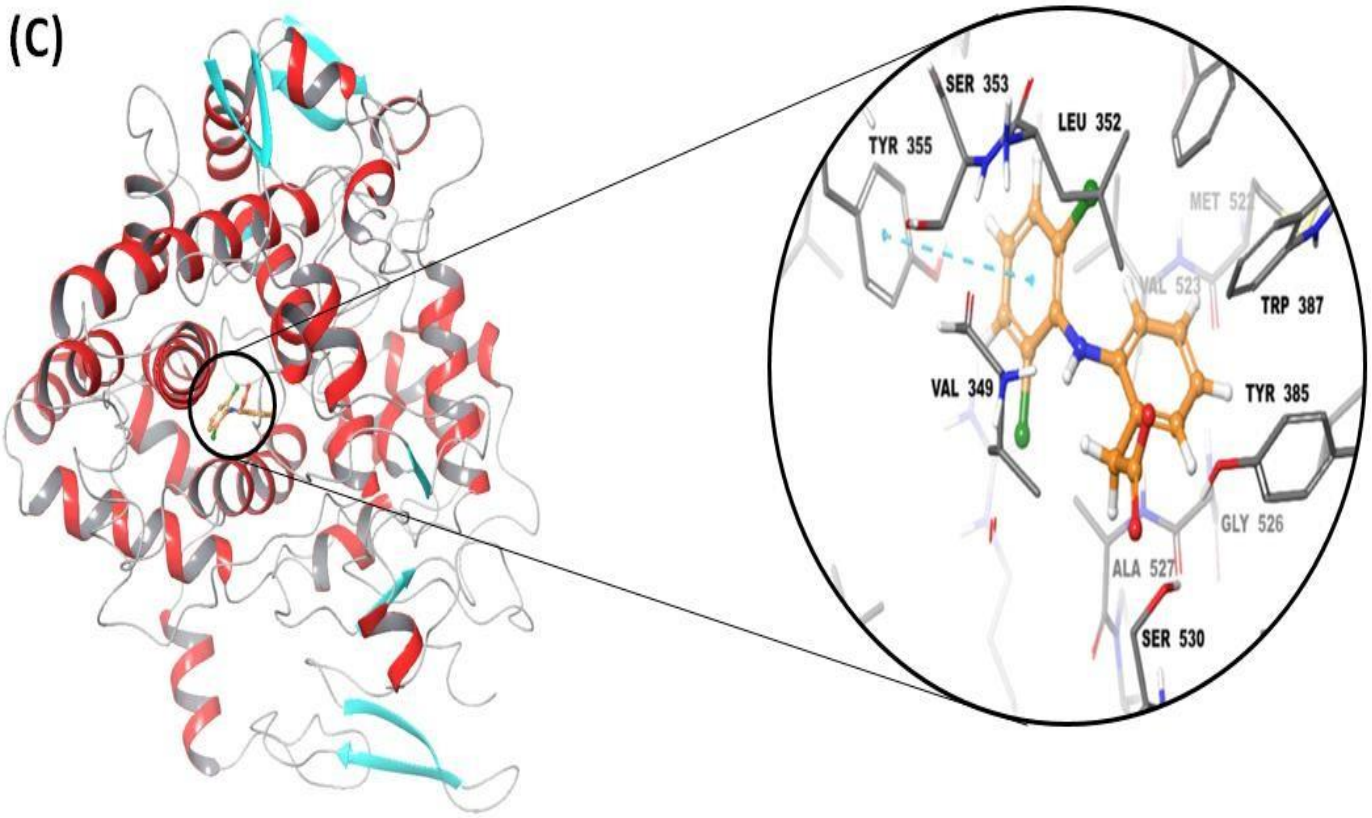



**Figure S3.** 3D molecular interactions of the best hits and diclofenac at COX-2 active site: (**A**) carvacrol-COX-2 complex; (**B**) thymol-COX-2 complex; (C) diclofenac-COX-2 complex.

**Table S1**. Biochemical parameters for rats treated by AVEO (acute toxicity).

| Biochemical parameters | Group I: control | Group II: (1000 mg/kg ) | Group III: (2000 mg/kg ) |
|---|---|---|---|
| Triglycerides (g/l) | 0.55 ± 0.06 | 0.48 ± 0.02 | 0.50 ± 0.03 |
| Total cholesterol (g/l) | 0.56 ± 0.02 | 0.46 ± 0.07 | 0.48 ± 0.02 |
| GOT (UI/l) | 51.04 ± 2.86 | 54.77 ± 3.48 | 57.17 ± 4.16 |
| GPT (UI/l) | 23.42 ± 1.26 | 26.83 ± 3.26 | 25.53 ± 1.29 |
| ALP (UI/l) | 104.90 ± 7.05 | 98.85 ± 3.29 | 112.00 ± 4.68 |
| Uric acid (mg/l) | 20.57 ± 0.93 | 19.38 ± 2.18 | 18.63 ± 1.01 |
| Creatinine (mg/l) | 4.75 ± 0.86 | 5.25 ± 0.25 | 5.73 ± 0.26 |

GOT (glutamic oxaloacetic transaminase/aspartate aminotransferase), GPT (glutamic pyruvic transaminase/alanine aminotransferase), ALP (alkaline phosphatase). Values are expressed as mean ± SEM.

**Table S2.** Docking scores and binding energies of AVEO constituents against COX-2.

| Compound | PubChem CID | Docking score (Kcal/mol) | Glide score (Kcal/mol) | MMGBSA (Kcal/mol) |
|---|---|---|---|---|
| Diclofenac (reference inhibitor) | 3033 | -7.837 | -7.837 | -34.62 |
| Carvacrol | 10364 | -7.381 | -7.381 | -51.50 |
| Thymol | 6989 | -6.939 | -6.939 | -42.35 |
| (*E*)–Sabinene hydrate | 6430763 | -6.640 | -6.640 | -56.52 |
| Terpinen–4–ol | 11230 | -6.561 | -6.561 | -52.19 |
| Iso-menthone | 6986 | -6.500 | -6.500 | -56.82 |
| Carvacrol methyl ether | 80790 | -6.379 | -6.379 | -50.71 |
| *gamma*–Terpinene | 7461 | -6.370 | -6.370 | -61.64 |
| Thymyl methyl oxide | 14104 | -6.283 | -6.283 | -51.17 |
| *alpha*-Thujene | 17868 | -6.268 | -6.268 | -50.08 |
| *para*–Cymene | 7463 | -6.255 | -6.255 | -46.95 |
| *alpha*–Terpineol | 17100 | -5.785 | -5.785 | -57.00 |
| *alpha*–Pinene | 6654 | -5.764 | -5.764 | -49.93 |
| Limonene | 22311 | -5.666 | -5.666 | -53.05 |
| *beta*–Pinene | 14896 | -5.423 | -5.423 | -53.68 |
| Camphor | 2537 | -5.353 | -5.353 | -36.47 |
| Borneol | 64685 | -5.065 | -5.065 | -39.37 |
| Myrcene | 31253 | -4.342 | -4.342 | -57.22 |
| Linalool | 6549 | -4.239 | -4.239 | -52.14 |

**Table S3.** Molecular interactions of minor (remaining) compounds of AVEO with the COX-2 active site.

| Protein-ligand interactions | Hydrogen bonds (distance) | Hydrophobic bonds | Polar interactions | Charged (+) interactions | Pi-Pi stacking |
|---|---|---|---|---|---|
| | | **Interacting residues** | | | |
| 5KIR-(E)-Sabinene hydrate | - | Tyr355, Leu352, Val349, Phe518, Met522, Val523, Ala527, Leu531, Leu359, Phe381, Leu384, Tyr385, Trp387 | Ser353, Ser530 | Arg120 | - |
| 5KIR-Terpinen–4–ol | Ser530 (2.50 Å) | Tyr348, Val349, Leu352, Tyr355, Leu531, Ala527, Val523, Met522, Phe518, Phe381, Leu384, Tyr385, Trp387 | Ser353, Ser530 | Arg120 | - |
| 5KIR-Iso-menthone | - | Tyr348, Val349, Leu352, Leu531, Ala527, Val523, Met522, Phe518, Tyr385, Trp387, Phe381 | Ser353, Ser530 | - | - |
| 5KIR-Carvacrol methyl ether | - | Tyr348, Val349, Leu352, Met522, Val523, Ala527, Phe518, Phe381, Leu384, Tyr385, Trp387, Phe205 | Ser353, Ser530 | - | - |
| 5KIR-Thymyl methyl oxide | - | Tyr348, Val349, Leu352, Val344, Met522, Val523, Ala527, Phe518, Phe381, Leu384, Tyr385, Trp387 | Ser353, Ser530 | - | Trp387 |
| 5KIR-*Alpha*-Thujene | - | Val349, Leu352, Met522, Val523, Ala527, Phe518, Phe381, Leu384, Tyr385, Trp387 | Ser353, Ser530 | - | - |

| | | | | | |
|---|---|---|---|---|---|
| 5KIR-*alpha*–Terpineol | - | Tyr348, Val349, Leu352, Met522, Val523, Ala527, Met522, Val523, Ala527, Phe518, Phe381, Leu384, Tyr385, Trp387 | Ser353, Ser530 | - | - |
| 5KIR-*alpha*–Pinene | - | Tyr348, Val349, Leu352, Met522, Val523, Ala527, Phe518, Phe381, Leu384, Tyr385, Trp387 | Ser353, Ser530 | - | - |
| 5KIR-*beta*–Pinene | - | Val349, Leu352, Tyr355, Met522, Val523, Ala527, Leu531, Phe518, Tyr385, Trp387 | Ser353, Ser530 | Arg120 | - |
| 5KIR-Camphor | - | Tyr348, Val349, Leu352, Met522, Val523, Ala527, Leu531, Phe518, Tyr385, Trp387 | Ser353, Ser530 | - | - |
| 5KIR-Borneol | - | Met522, Val523, Ala527, Leu531, Val349, Leu352, Phe518, Tyr385, Trp387 | Ser353, Ser530 | - | - |
| 5KIR-Myrcene | - | Tyr348, Val349, Leu352, Met522, Val523, Ala527, Phe518, Phe381, Leu384, Tyr385, Trp387 | Ser353, Ser530 | - | - |
| 5KIR-Linalool | Ser530 (2.39 Å) | Tyr348, Val349, Leu352, Tyr355, Met522, Val523, Ala527, Leu531, Phe518, Phe381, Tyr385, Trp387 | Ser353, Ser530 | Arg120 | - |

**Table S4.** *In silico* prediction of drug-likeness of AVEO's main components with important physicochemical characteristics.

| **Compound** | **QPlog S** | **QPlog $P_{o/w}$** | **TPSA (Å)** | **Lipinski rule** | **Veber rule** | **Bioavailability score** |
|---|---|---|---|---|---|---|
| Carvacrol | -2.324 | 3.293 | 20.23 | Yes | Yes | 0.55 |
| Thymol | -2.321 | 3.295 | 20.23 | Yes | Yes | 0.55 |
| *gamma*-Terpinene | -4.128 | 4.045 | 0.00 | Yes | Yes | 0.55 |
| *para*-Cymene | -3.689 | 3.648 | 0.00 | Yes | Yes | 0.55 |
| Limonene | -4.004 | 3.981 | 0.00 | Yes | Yes | 0.55 |

QPlog S: Water solubility; QPlog $P_{o/w}$: Lipophilicity, o/w for octanol/water; TPSA: Topological polar surface area.

**Table S5.** Predicted pharmacokinetics properties of AVEO's main compounds.

| Compound | % HO absorption (<25% is poor) (>80% is high) | Caco-2 permeability (nm/sec) | QPlogIC$_{50}$hERG (Concentration below -5) | QPlogKp (cm/h) | QPlog BB (-3 to 1.2) | CNS activity (-2 to +2) | QPlogKhasa (-1.5 to 1.5) |
|---|---|---|---|---|---|---|---|
| Carvacrol | 100 | 3709 | -3.578 | -1.813 | 0.075 | +1 | 0.046 |
| Thymol | 100 | 3835 | -3.576 | -1.779 | 0.088 | +1 | 0.043 |
| *gamma*-Terpinene | 100 | 9906 | -3.333 | -1.229 | 0.863 | +2 | 0.388 |
| *para*-Cymene | 100 | 9906 | -3.695 | -0.969 | 0.700 | +2 | 0.336 |
| Limonene | 100 | 9906 | -3.262 | -1.203 | 0.840 | +2 | 0.380 |

HO absorption: for human oral absorption; Caco-2 permeability: for Caco-2 cells permeability, a model for human intestinal absorption; QPloghERG: Predicted IC$_{50}$ value for the human-ether-a-go-go related gene (hERG) potassium channels blockage; QPlogKp: Predicted skin permeability; QPlog BB: Blood-brain coefficient; CNS activity: For central nervous system activity; QPlogKhasa: Predicted human serum albumin binding.