# SUPPLEMENTARY INFORMATION

## Selected anthraquinones as potential free radical scavengers and P-glycoprotein inhibitors

Svetlana Jeremić[1,*], Ana Amić[2], Marijana Stanojević-Pirković[3], Zoran Marković[1]

[1]Department of Chemical-Technological Sciences, State University of Novi Pazar, Vuka Karadžića bb, 36300 Novi Pazar, Serbia

[2]Department of Chemistry, Josip Juraj Strossmayer University of Osijek, Cara Hadrijana 8a, 31000 Osijek, Croatia

[3]Faculty of Medical Sciences, University of Kragujevac, Svetozara Markovića 69, 34000 Kragujevac, Serbia.

* Corresponding author. Tel.: 00381 20 317 754; fax: 00381 20 337 669.

E-mail address: sjeremic@np.ac.rs (S. Jeremić)

**Table S1**. The PCM/SMD/M06-2X/6-311++G(d,p) reaction enthalpies and Gibbs free energies (in kJ $mol^{-1}$) for HAT mechanism of free radical formation from corresponding neutral molecules in polar and nonpolar environment.

| Free radical | Benzene | | Pentyl ethanoate | | DMSO | | Water | |
|---|---|---|---|---|---|---|---|---|
| | $\Delta_r H_{BDE}$ | $\Delta_r G_{BDE}$ | $\Delta_r H_{BDE}$ | $\Delta_r G_{BDE}$ | $\Delta_r H_{BDE}$ | $\Delta_r G_{BDE}$ | $\Delta_r H_{BDE}$ | $\Delta_r G_{BDE}$ |
| $^{\bullet}OH$ | 489.55 | 458.51 | 490.53 | 459.49 | 491.87 | 460.83 | 503.56 | 472.53 |
| $(CH_3)_3C–O^{\bullet}$ | 437.57 | 403.02 | 437.77 | 403.30 | 438.53 | 404.13 | 451.87 | 417.12 |
| $^{\bullet}OCH_3$ | 429.77 | 395.80 | 429.48 | 395.54 | 429.72 | 395.81 | 443.43 | 409.55 |
| $CCl_3–O–O^{\bullet}$ | 386.12 | 351.58 | 387.31 | 352.64 | 388.34 | 353.49 | 405.83 | 370.90 |
| $PhO^{\bullet}$ | 369.19 | 333.80 | 368.88 | 333.46 | 369.01 | 333.56 | 377.19 | 341.78 |
| $^{\bullet}OOH$ | 359.06 | 324.52 | 358.19 | 325.32 | 357.11 | 323.97 | 372.65 | 339.94 |
| $CH_2=CH–O–O^{\bullet}$ | 354.33 | 322.13 | 353.25 | 322.38 | 352.51 | 321.43 | 370.09 | 339.05 |
| $CH_3–O–O^{\bullet}$ | 351.38 | 318.95 | 349.40 | 315.67 | 348.26 | 314.66 | 366.53 | 332.68 |
| $CH_2=CH–CH_2–O–O^{\bullet}$ | 350.35 | 317.43 | 349.19 | 316.05 | 348.05 | 314.39 | 366.59 | 332.54 |
| $O_2^{\bullet-}$ | 257.54 | 229.94 | 259.17 | 231.55 | 260.49 | 232.85 | 298.06 | 270.38 |

**Figure S1.** Numerical values of spin density distribution (SDD) for the most stable radicals of investigated anthraquinones, calculated in pentyl ethanoate.

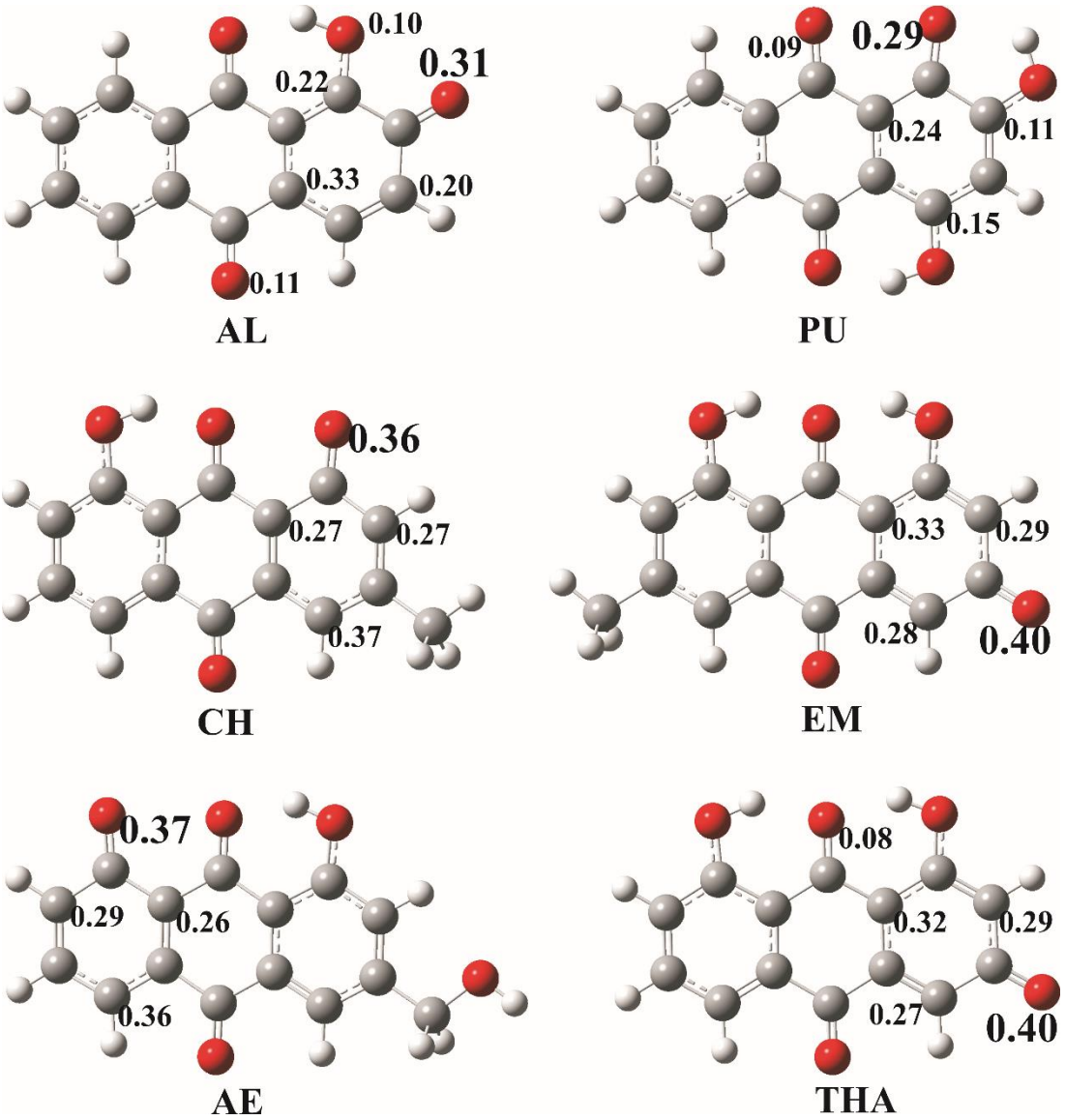

**Figure S2.** Optimized structures of four selected anthracycline and anthracene drugs: doxorubicin (DX), daunorubicin (DA), mitoxantrone (MX) and bisantrene (BA).

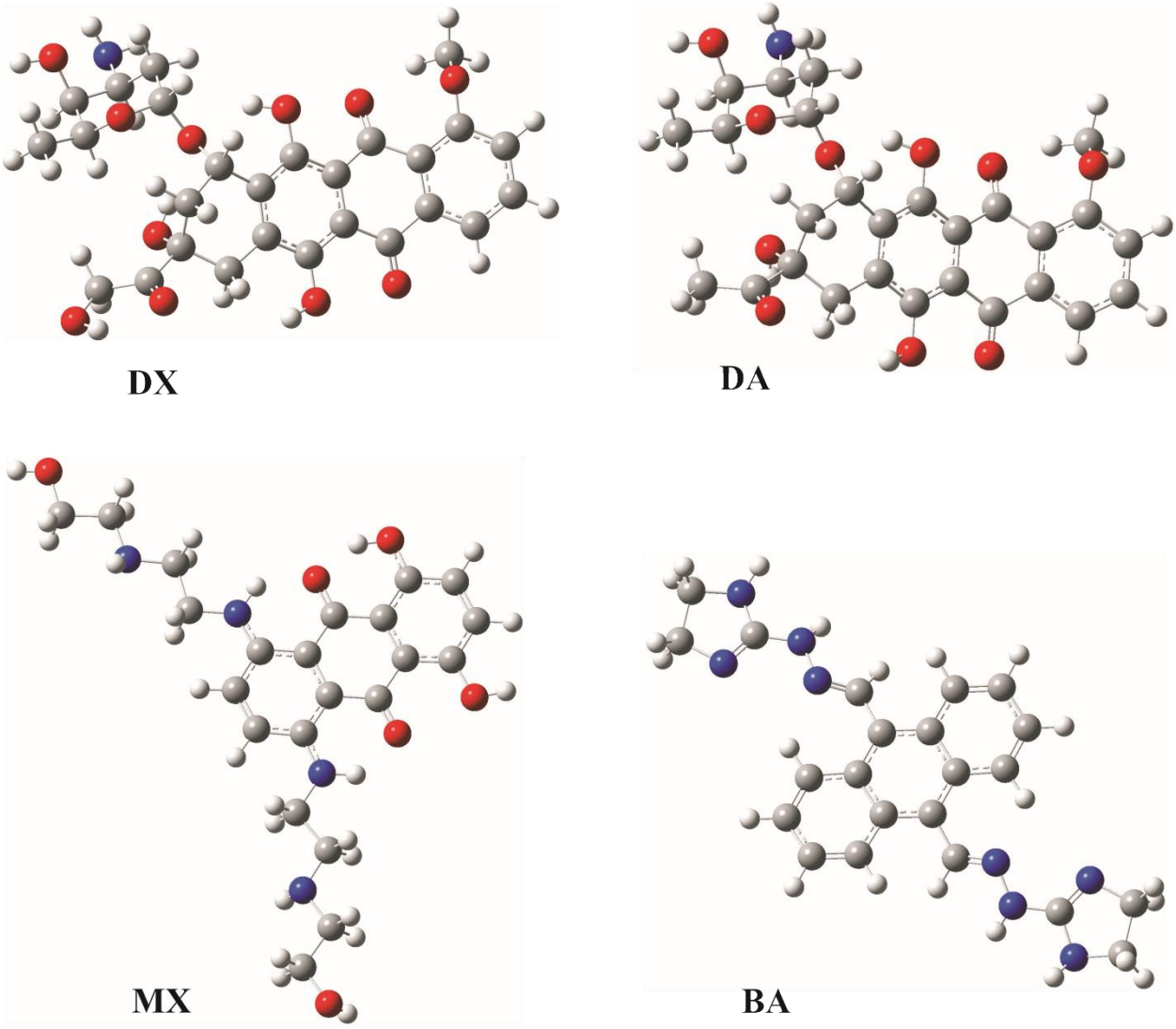

**Table S2.** Results of docking analysis of monoanions of AL, PU, CH, AE and TA, and selected anticancer drugs DX, DA and BA, in reaction with P-glycoprotein: type of antraquinone monoanion / anticancer drug with its role in bond formation; corresponding amino acid with its position in the primary structure of protein, and with its role in bond formation; type of interaction during bond formation; distance in Å between respective active cites of ligand and amino acids; pairwise interaction energy ($E_i$) in kcal $mol^{-1}$; estimated total free energy of binding ($E_b$) in kcal $mol^{-1}$, estimated inhibition constant ($K_i$) in μM.

| **Ligand** | | **Amino acid** | | **Type of interaction** | **Atom distance** | **$E_i$** | **$E_b$** | **$K_i$** |
|---|---|---|---|---|---|---|---|---|
| $AL^-$ | π-orbitals electron donor | **Lys 884** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 4.474 | 0.02 | -4.68 | 372.34 |
| | H-donor | **Glu 885** | H-acceptor | Conventional hydrogen bond | 2.134 | 0.60 | | |
| | π-orbitals electron acceptor | **Glu 885** | C-H bond is electron donor | π – σ hydrophobic | 3.140 | 0.06 | | |
| | H-acceptor | **Gly 888** | H-donor | Conventional hydrogen bond | 2.422 | 0.37 | | |
| | π-orbitals electron donor | **Pro 923** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 4.481 | 0.02 | | |
| $PU^-$ | π-orbitals electron donor | **Lys 884** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 5.395 | 0.01 | -4.67 | 376.63 |
| | H-donor | **Glu 885** | H-acceptor | Conventional hydrogen bond | 2.003 | 0.60 | | |
| | H-acceptor | **Gly 888** | H-donor | Conventional hydrogen bond | 2.509 | 0.27 | | |
| | H-donor | **Ser 919** | H-acceptor | Conventional hydrogen bond | 2.159 | 0.58 | | |
| | π-orbitals electron donor | **Pro 923** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 4.519 | 0.02 | | |
| $CH^-$ | Alkyl group is electron donor | **Lys 884** | Alkyl group is electron acceptor | alkyl – alkyl hydrophobic | 4.584 | 0.02 | -4.89 | 261.11 |
| | H-donor | **Glu 885** | H-acceptor | Conventional hydrogen bond | 1.965 | 0.60 | | |

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|---|---|---|---|---|---|---|---|---|
| | π-orbitals electron acceptor | **Glu 885** | C-H bond is electron donor | π – σ hydrophobic | 3.160 | 0.03 | | |
| | H-acceptor | **Gly 888** | H-donor | Conventional hydrogen bond | 2.422 | 0.37 | | |
| | π-orbitals electron donor | **Pro 923** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 4.353 | 0.02 | | |
| $AE^-$ | H-acceptor | **Lys 884** | H-donor | Carbon hydrogen bond | 3.701 | 0.03 | -4.61 | 414.40 |
| | H-donor | **Glu 885** | H-acceptor | Conventional hydrogen bond | 1.731 | 0.60 | | |
| | π-orbitals electron acceptor | **Glu 885** | C-H bond is electron donor | π – σ hydrophobic | 3.483 | 0.02 | | |
| | H-acceptor | **Gly 888** | H-donor | Conventional hydrogen bond | 2.278 | 0.48 | | |
| | H-donor | **Ser 919** | H-acceptor | Conventional hydrogen bond | 1.960 | 0.60 | | |
| | π-orbitals electron donor | **Pro 923** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 4.867 | 0.02 | | |
| $TA^-$ | H-donor | **Lys 884** | H-acceptor | Conventional hydrogen bond | 2.085 | 0.60 | -4.81 | 298.24 |
| | π-orbitals electron donor | **Lys 884** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 4.887 | 0.02 | | |
| | H-donor | **Glu 885** | H-acceptor | Conventional hydrogen bond | 2.029 | 0.60 | | |
| | π-orbitals electron acceptor | **Glu 885** | C-H bond is electron donor | π – σ hydrophobic | 3.175 | 0.03 | | |
| | H-acceptor | **Gly 888** | H-donor | Conventional hydrogen bond | 2.325 | 0.48 | | |
| | H-acceptor | **Pro 923** | H-donor | Carbon hydrogen bond | 3.124 | 0.02 | | |
| DX | Alkyl group is electron donor | **Lys 884** | Alkyl group is electron acceptor | alkyl – alkyl hydrophobic | 4.528 | 0.02 | **-3.02** | **$6.12 \cdot 10^3$** |
| | H-donor | **Glu 887** | H-acceptor | Conventional hydrogen bond | 2.434 | 0.37 | | |

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|---|---|---|---|---|---|---|---|---|
| | H-donor | **Glu 887** | H-acceptor | Conventional hydrogen bond | 2.110 | 0.60 | | |
| | H-acceptor | **Ser 919** | H-donor | Carbon hydrogen bond | 2.929 | 0.01 | | |
| | π-orbitals electron acceptor | **Ile 922** | C-H bond is electron donor | π – σ hydrophobic | 3.813 | 0.02 | | |
| | π-orbitals electron acceptor | **Ile 922** | C-H bond is electron donor | π – σ hydrophobic | 3.946 | 0.02 | | |
| | π-orbitals electron donor | **Ile 922** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 5.367 | 0.01 | | |
| | π-orbitals electron donor | **Pro 923** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 5.493 | 0.01 | | |
| DA | Alkyl group is electron donor | **Lys 884** | Alkyl group is electron acceptor | alkyl – alkyl hydrophobic | 4.260 | 0.02 | **-3.95** | **$1.26 \cdot 10^3$** |
| | H-donor | **Glu 887** | H-acceptor | Conventional hydrogen bond | 2.233 | 0.58 | | |
| | H-donor | **Glu 887** | H-acceptor | Conventional hydrogen bond | 1.957 | 0.60 | | |
| | π-orbitals electron acceptor | **Ile 922** | C-H bond is electron donor | π – σ hydrophobic | 3.452 | 0.02 | | |
| | π-orbitals electron acceptor | **Ile 922** | C-H bond is electron donor | π – σ hydrophobic | 3.258 | 0.01 | | |
| | π-orbitals electron donor | **Ile 922** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 5.354 | 0.01 | | |
| BA | H-donor | **Lys 884** | H-acceptor | Carbon hydrogen bond | 3.095 | 0.02 | **-5.08** | **187.80** |
| | π-orbitals electron donor | **Lys 884** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 5.289 | 0.01 | | |
| | π-orbitals electron acceptor | **Glu 885** | C-H bond is electron donor | π – σ hydrophobic | 3.176 | 0.03 | | |
| | H-donor | **Glu 887** | H-acceptor | Conventional hydrogen bond | 1.750 | 0.60 | | |

| | | | | | |
|---|---|---|---|---|---|
| H-acceptor | **Gly 888** | H-donor | Carbon hydrogen bond | 3.344 | 0.02 |
| π-orbitals electron donor | **Pro 923** | Alkyl group is electron acceptor | π – alkyl hydrophobic | 4.984 | 0.01 |

**Figure S3.** Docking positions of anions of alizarin (a), purpurin (b), chrysophanol (c), aloe-emodin (d) and 1,3,8- trihydroxyanthraquinone (e) with P-glycoprotein.

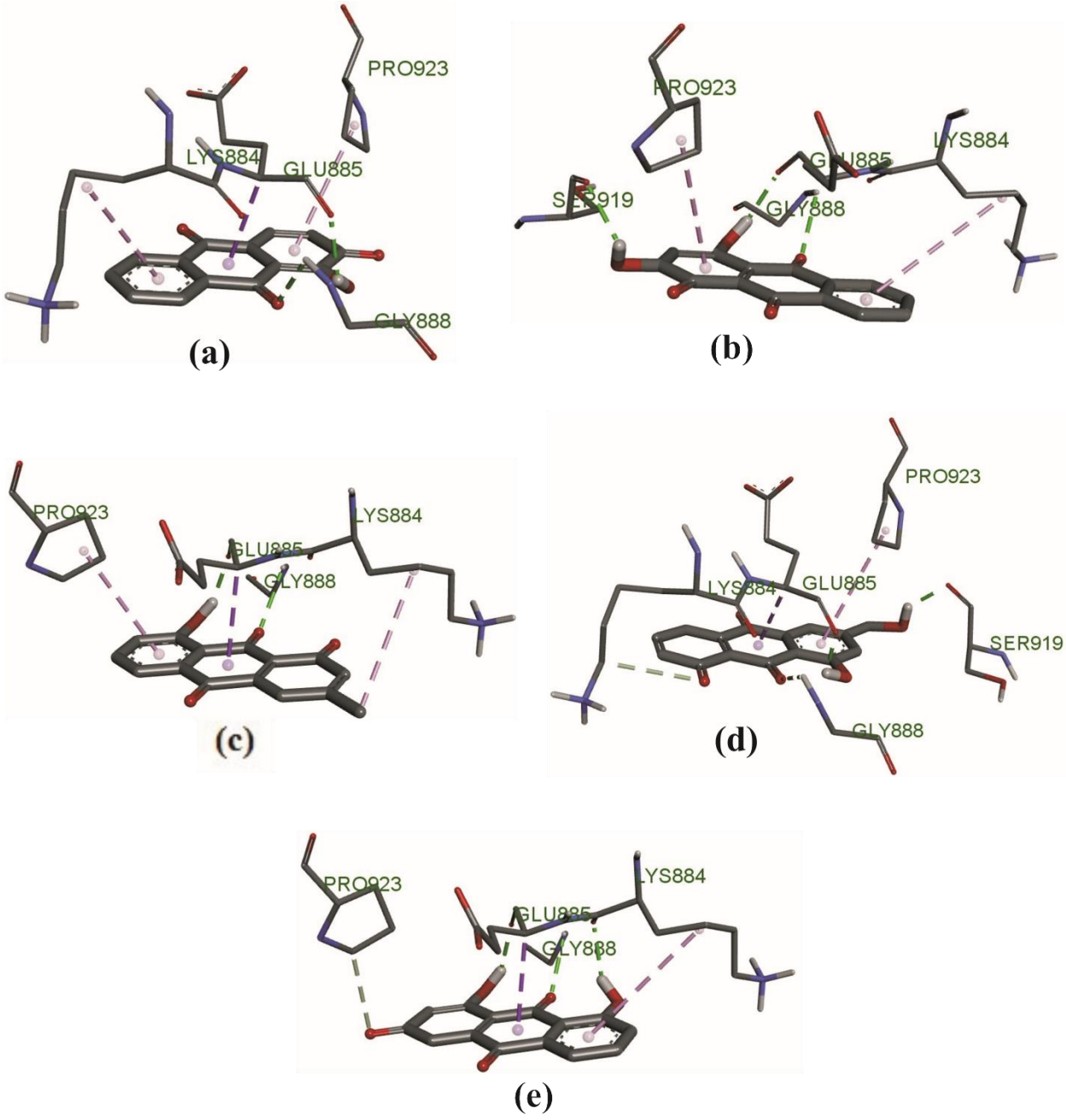

**Figure S4.** Docking positions of doxorubicin (a), daunorubicin (b) and bisantrene (c) with P-glycoprotein.

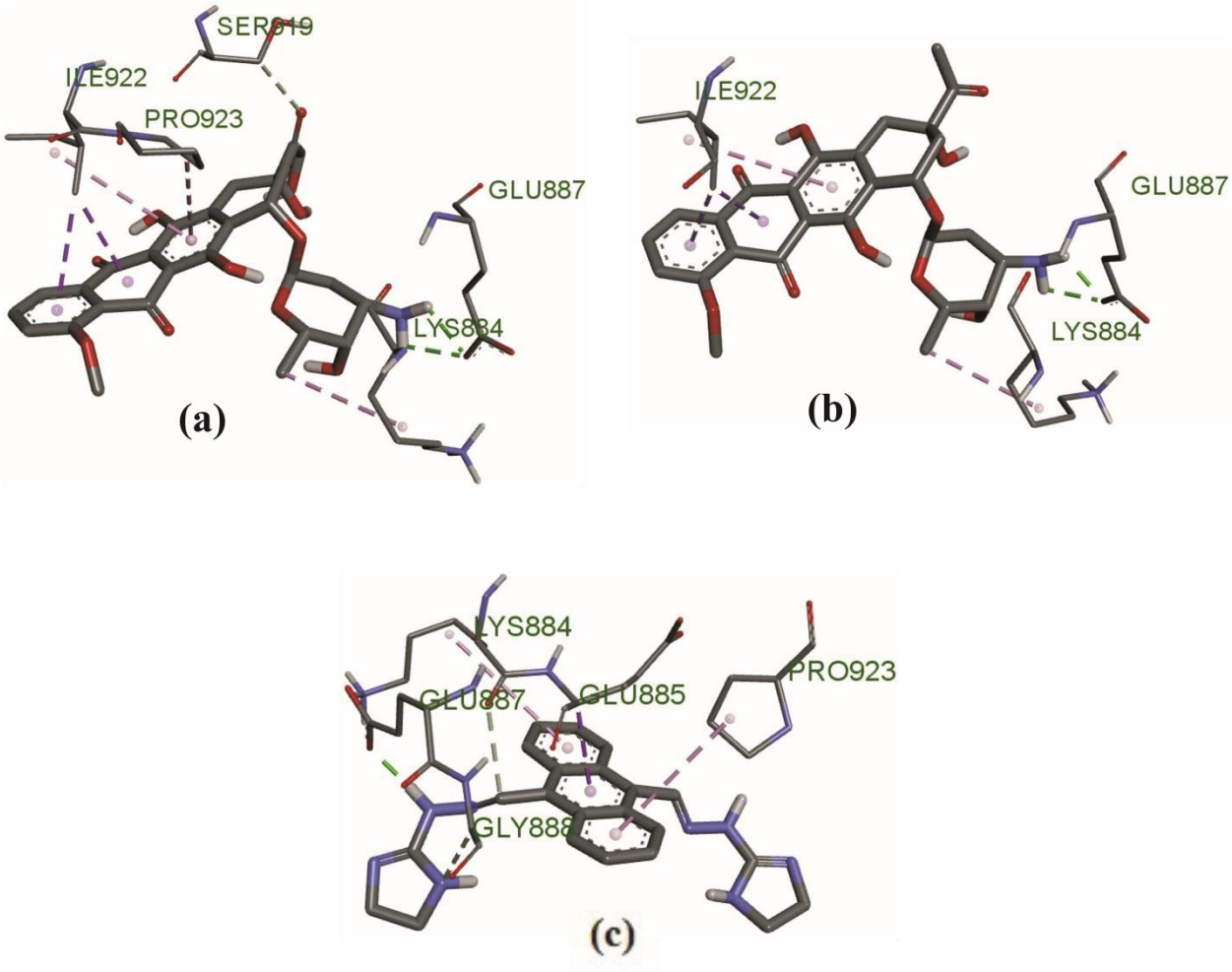

**Figure S5.** Position of docking of emodin-anion (rounded) with P-glycoprotein tertiary structure.