separations

MDPI

*Supplementary Materials*

# Enantiomeric Separation and Molecular Modelling of Bioactive 4-aryl-3,4-dihydropyrimidin-2(1*H*)-one Ester Derivatives on Teicoplanin-Based Chiral Stationary Phase

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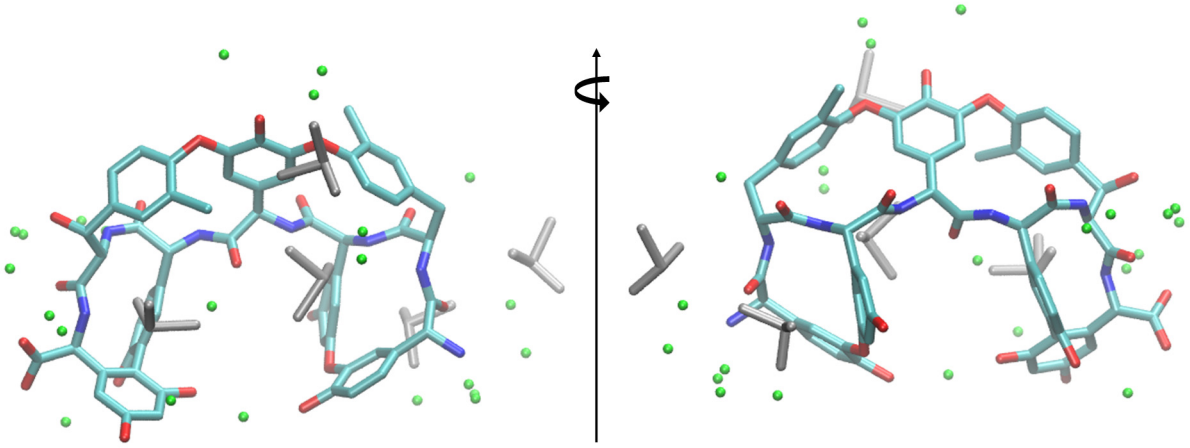

**Figure S1.** Crystal structure of teicoplanin aglycone with DMSO (grey) and water molecules (green).

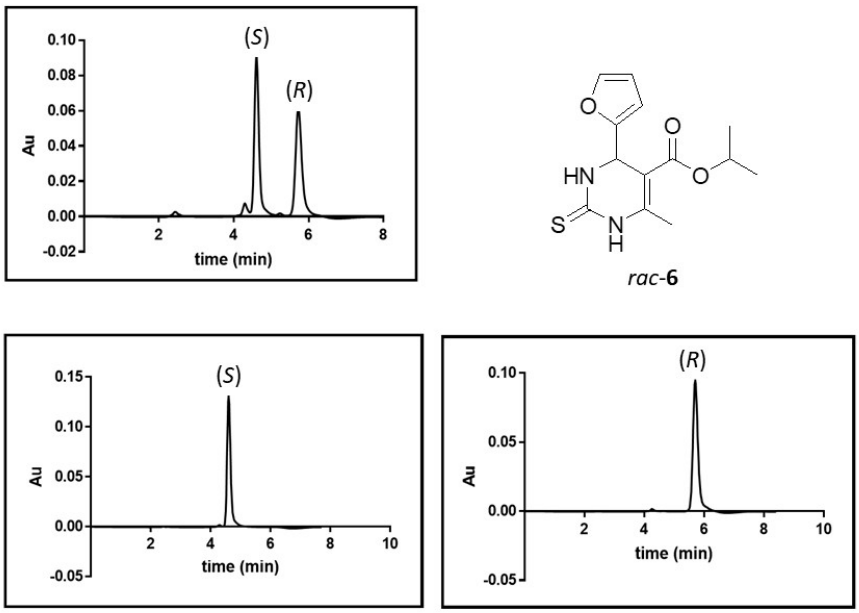


**Figure S2.** HPLC chromatograms of *rac*-**6** and single *R* and *S* enantiomers on Chirobiotic™ TAG as chiral stationary phase and MeOH as the mobile phase; flow rate: 0.7 mL·min$^{-1}$ (r.t.; 254 nm).

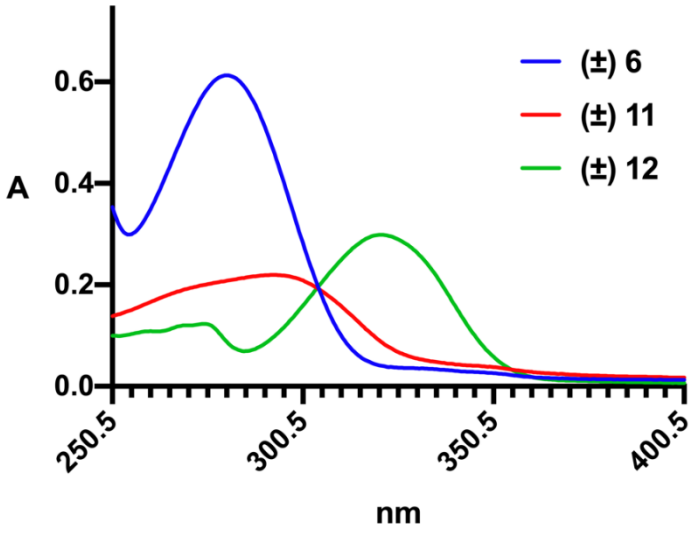


**Figure S3.** UV spectra of racemic compounds **6**, **11** and **12** recorded on a Jasco V770 system equipped with a Peltier-type thermostatic accessory. Measurements were carried out at 20 ± 1 °C using a 1 mm quartz cell in a volume of 800 µL. Compounds (1 mg) were dissolved in MeOH (1.0 mL) and then 100-fold diluted in MeOH. The instrument settings were as follows: data interval, 0.5 nm; UV/Vis bandwidth, 2.0 nm; UV/Vis response, 0.06 sec; scan speed, 1000 nm/min; number of cycles, 1; wavelengths, 500–250 nm.

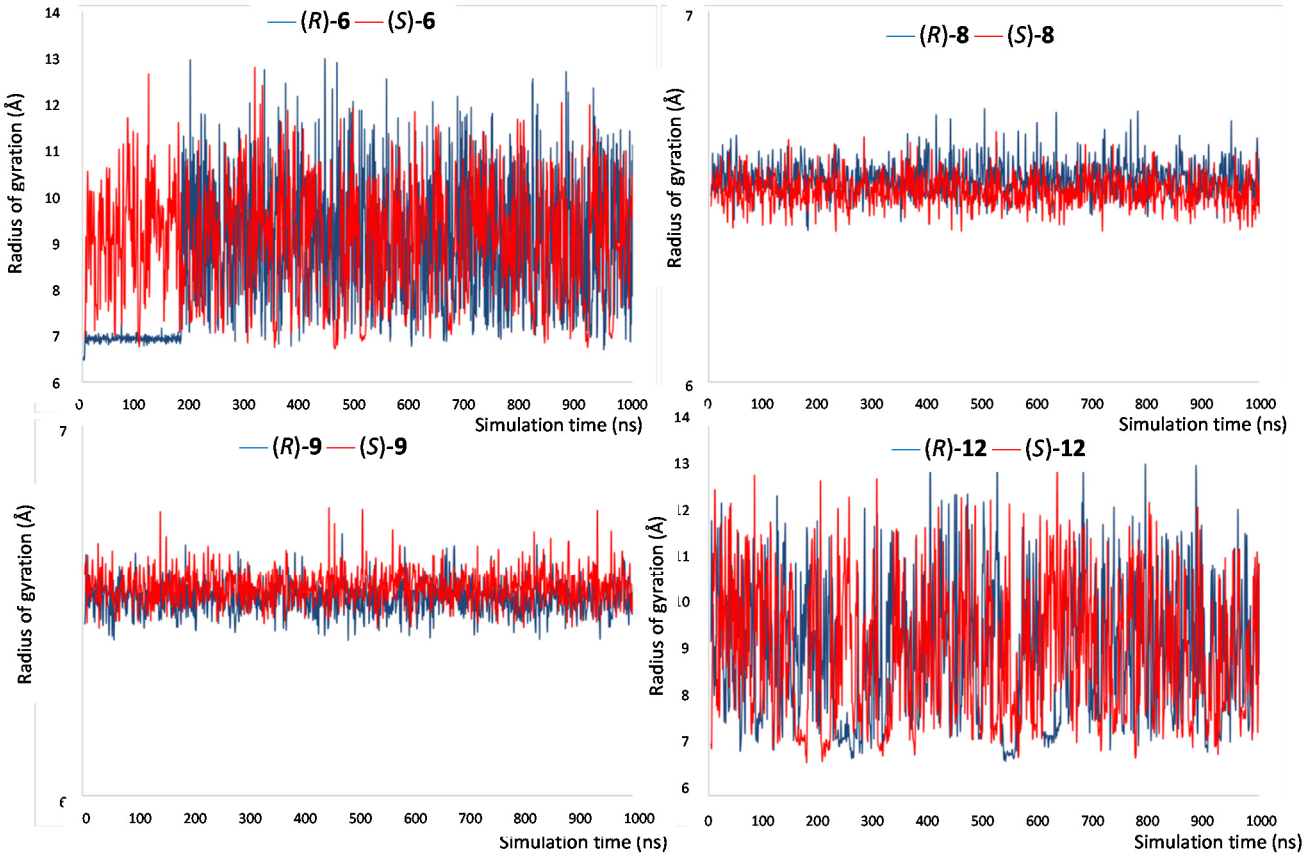


**Figure S4.** Radius of gyration of compounds **6**, **8**, **9**, **12** as a function of time of the molecular dynamics' trajectory.

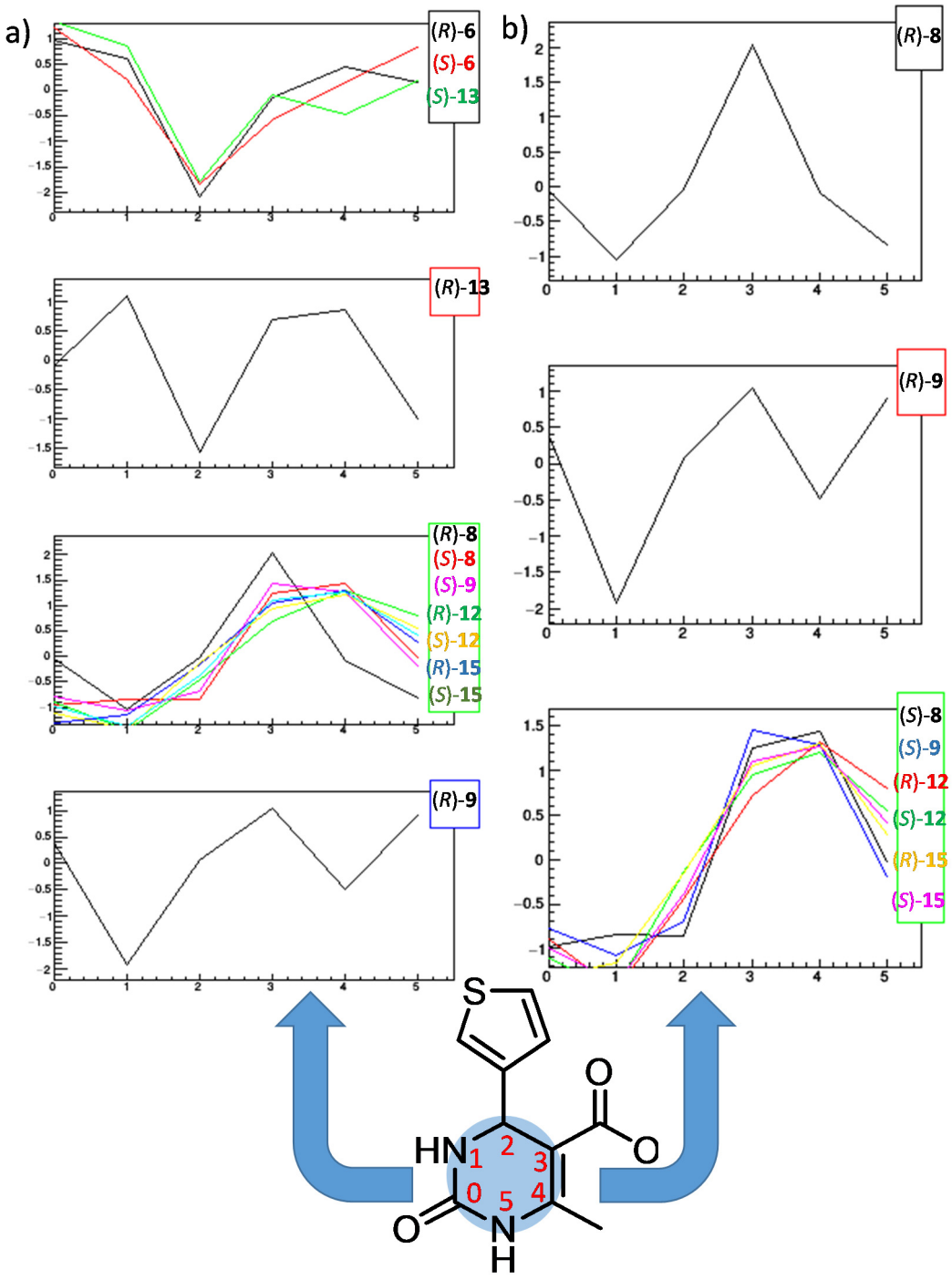


**Figure S5.** Root mean square fluctuations (RMSF) of the atoms numbered in the scheme below, which are in common to all chiral DHP derivatives examined in this study. RMSF profiles are grouped according to a PCA and clustering procedure applied on compounds **6**, **8**, **9**, **12**, **13**, **15** (a) and compounds **8**, **9**, **12**, **15** (b)..

**Table S1.** Enantiomer separation values of representative racemic DHP derivatives on Chirobiotic™ TAG stationary phase at different mobile phase compositions (flow rate: 0.7 mL/min; r.t.; UV detection at 254 nm).

| Mobile phase (%, v/v) | separation factor ($\alpha$) | | | | | |
|---|---|---|---|---|---|---|
| | **6** | **9** | **11** | **12** | **13** | **14** |
| EtOH/ACN (40:60) | 1.57 | 3.97 | 1.30 | 1 | 1 | 1 |
| EtOH/ACN (50:50) | 1.70 | 4.00 | 1.19 | 1 | 1 | 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| EtOH/ACN (60:40) | 1.71 | 4.48 | 1.23 | 1 | 1 | 1 |
| EtOH/ACN (70:30) | 1.77 | 3.80 | 1.25 | 1 | 1 | 1 |
| EtOH (100) | 2.12 | 5.52 | 1.45 | 1 | 1 | 1 |
| MeOH (100) | 2.41 | 6.04 | 1.50 | 1 | 1 | 1 |
| MeOH/ACN (50:50) | 2.06 | 4.98 | 1.31 | 1 | 1 | 1 |
| MeOH/$H_2O$ (70:30) | 1.42 | 3.00 | 1.16 | 1 | 1 | 1 |

**Table S2.** HPLC enantiomer separation factors ($\alpha$) on Chirobiotic™ TAG stationary phase [a] and molecular descriptors [b] of racemic 4-aryl 3,4-dihydropyrimidin-2(1*H*)-one (DHP) alkoxycarbonyl ester derivatives **1**-**15**.

| cmpd | $\alpha$ | MV | MSA | PSA | HBA | HBD |
|---|---|---|---|---|---|---|
| **1** | 4.24 | 255.48 | 407.01 | 67.43 | 2 | 2 |
| **2** | 3.88 | 257.98 | 398.92 | 84.50 | 3 | 2 |
| **3** | 2.96 | 289.91 | 468.22 | 85.89 | 4 | 2 |
| **4** | 1.61 | 289.97 | 466.50 | 85.89 | 4 | 2 |
| **5** | 1 | 249.69 | 442.88 | 41.57 | 1 | 1 |
| **6** | 2.41 | 245.67 | 380.00 | 63.50 | 1 | 2 |
| **7** | 2.00 | 257.51 | 398.87 | 99.65 | 5 | 2 |
| **8** | 8.76 | 231.21 | 365.22 | 95.07 | 5 | 1 |
| **9** | 6.04 | 247.54 | 390.54 | 95.07 | 5 | 1 |
| **10** | 1 | 287.74 | 456.74 | 82.18 | 4 | 1 |
| **11** | 1.50 | 296.73 | 470.13 | 108.48 | 5 | 1 |
| **12** | 1 | 299.70 | 465.43 | 69.29 | 3 | 1 |
| **13** | 1 | 228.77 | 354.00 | 67.43 | 2 | 2 |
| **14** | 1 | 267.13 | 481.06 | 79.94 | 4 | 1 |
| **15** | 1 | 273.76 | 490.00 | 95.06 | 5 | 2 |

[a] Experimental HPLC conditions: Mobile phase net MeOH; flow rate 0.7 mL·min$^{-1}$; room temperature; UV detection at 254 nm. [b] Molecular descriptors calculated with ChemAxon chemoinformatic tools: MV, molar volume; MSA, molecular surface area; PSA, polar surface area; HBA, sum of H-bond acceptors; HAD, sum of H-bond donors.

**Table S3.** Squared correlation matrix ($r^2$) of the enantioseparation ratios on Chirobiotic™ TAG stationary phase and the calculated molecular descriptors of 4-aryl 3,4-dihydropyrimidin-2(1*H*)-one (DHP) alkoxycarbonyl ester derivatives **1**-**15**.

| | $\alpha$ | MV | MSA | PSA | HBA | HBD |
|---|---|---|---|---|---|---|
| **$\alpha$** | 1 | | | | | |
| **MV** | 0.239 | 1 | | | | |
| **MSA** | 0.324 | 0.723 | 1 | | | |
| **PSA** | 0.083 | 0.075 | 0.017 | 1 | | |
| **HBA** | 0.068 | 0.101 | 0.080 | 0.858 | 1 | |
| **HBD** | 0.014 | 0.019 | 0.043 | 0.000 | 0.046 | 1 |

**Table S4.** Crystallographic data collection (in brackets the outer shell) and refinement parameters for teicoplanin aglycone.

| **Data Collection** | |
|---|---|
| Beamline | Diamond Light Source I03 |
| Wavelength (Å) | 0.7293 |
| Resolution range (Å) | 18.14 - 0.77 (0.79 - 0.77) |
| Space group | C 2 |
| Unit cell parameters (Å)<br>*a*, *b*, *c*<br>$\alpha$, $\beta$, $\gamma$, | 35.722 13.113 21.717<br>90.00 123.34 90.00 |

| | |
|---|---|
| Total number of reflection | 134537 (1587) |
| Total number of unique reflection | 9030 (209) |
| <I/σ(I)> | 12.8 (2.4) |
| Rmerge % | 13.3 (67.7) |
| Completeness % | 89.2 (28.9) |
| Multiplicity | 14.9 (7.6) |
| | |
| **Refinement** | |
| Working resolution range (Å) | 18.14 - 0.77 |
| Reflections used in refinement | 8642 |
| Reflections used for Rfree | 388 |
| Rwork % | 9.7 |
| Rfree % | 11.4 |
| Average B factor | 3.82 |
| Number of non-H atoms | 103 |
| Heterogen atoms | 80 |
| Solvent atoms | 23 |

**Table S5.** Statistical summary of the radius of gyration values (in Å) from molecular dynamics trajectories.

| | **(*R*)-6** | **(*S*)-6** | **(*R*)-8** | **(*S*)-8** | **(*R*)-9** | **(*S*)-9** | **(*R*)-12** | **(*S*)-12** |
|---|---|---|---|---|---|---|---|---|
| min | 5.97 | 6.15 | 5.91 | 5.89 | 5.91 | 5.93 | 6.24 | 6.22 |
| max | 12.46 | 12.26 | 6.24 | 6.18 | 6.21 | 6.34 | 13.20 | 12.70 |
| Mean | 8.17 | 8.52 | 6.05 | 6.02 | 6.03 | 6.06 | 8.66 | 8.59 |
| σ | 1.41 | 1.27 | 0.04 | 0.04 | 0.04 | 0.05 | 1.48 | 1.42 |