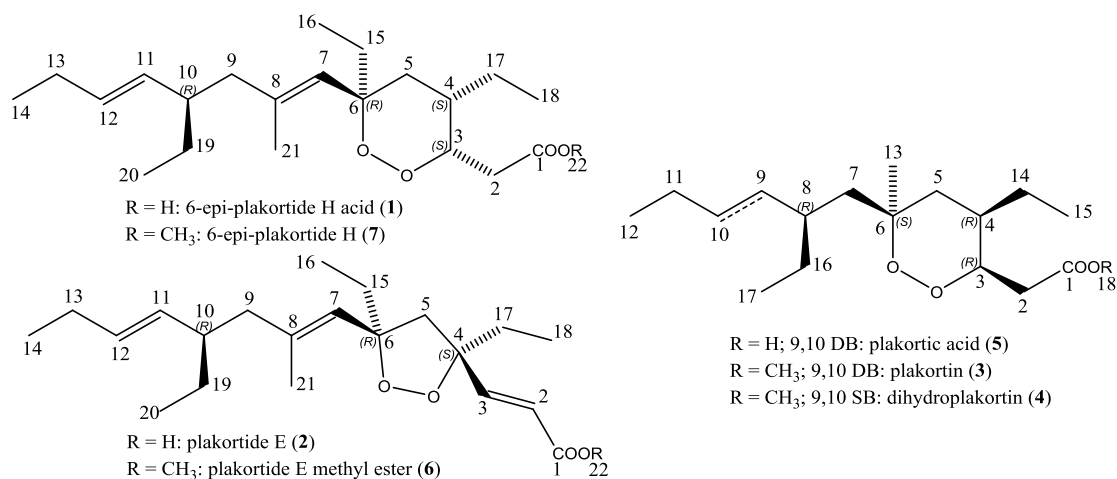


## Supplementary Materials: Cytotoxicity of endoperoxides from the Caribbean sponge *Plakortis halichondrioides* towards sensitive and multidrug-resistant leukemia cells: acids vs. esters activity evaluation



**Figure S1:** Structures of natural (1, 2, 3, 4) and semi-synthetic (5, 6, 7) endoperoxides from a sample of the sponge *Plakortis halichondrioides*: 6-epi-plakortide H acid (1), plakortide E (2), plakortin (3), dihydroplakortin (4), plakortie acid (5), plakortide E methyl ester (6), and 6-epi-plakortide H (7).

**Table S1:** NMR data of plakortin (3)

| Position | $\delta_C$ | mult            | $\delta_H$                | mult     | $J$ in Hertz           |
|----------|------------|-----------------|---------------------------|----------|------------------------|
| 1        | 172.45     | C               |                           |          |                        |
| 2        | 31.57      | CH <sub>2</sub> | 3.01<br>2.36              | dd<br>dd | 15.6, 9.4<br>15.6, 3.6 |
| 3        | 79.12      | CH              | 4.52 – 4.46               | m        |                        |
| 4        | 34.87      | CH              | 2.20 – 2.09               | m        |                        |
| 5        | 36.10      | CH <sub>2</sub> | 1.55<br>1.30 <sup>a</sup> | dd       | 13.5, 4.4              |
| 6        | 81.50      | C               |                           |          |                        |
| 7        | 46.56      | CH <sub>2</sub> | 1.47                      | dd       | 14.1, 4.2              |
| 8        | 40.34      | CH              | 2.09 – 1.95               | m        |                        |
| 9        | 134.41     | CH              | 5.11                      | dd       | 15.3, 9.1              |
| 10       | 131.78     | CH              | 5.38                      | dt       | 15.3, 6.3              |
| 11       | 25.67      | CH <sub>2</sub> | 2.09 – 1.95               | m        |                        |

|    |       |                 |  |        |     |
|----|-------|-----------------|--|--------|-----|
| 12 | 14.03 | CH <sub>3</sub> | 0.97                                   | t      | 7.5 |
| 13 | 21.37 | CH <sub>3</sub> | 1.37                                   | s      |     |
| 14 | 25.26 | CH <sub>2</sub> | 1.21 <sup>a</sup><br>1.08 <sup>a</sup> |        |     |
| 15 | 11.20 | CH <sub>3</sub> | 0.90                                   | t      | 7.4 |
| 16 | 30.06 | CH <sub>2</sub> | 1.42 <sup>a</sup><br>1.15 <sup>a</sup> | m<br>m |     |
| 17 | 11.62 | CH <sub>3</sub> | 0.81                                   | t      | 7.4 |
| 18 | 51.94 | CH <sub>3</sub> | 3.70                                   | s      |     |

NMR solvent: CDCl<sub>3</sub>; <sup>a</sup>overlap with other signals. Mult: multiplicity

**Table S2:** Dihydroplakortin (4)

| Position | $\delta_C$ | mult            | $\delta_H$                            | mult     | <i>J</i> in Hertz           |
|----------|------------|-----------------|---------------------------------------|----------|-----------------------------|
| 1        | 172.38     | C               |                                       |          |                             |
| 2        | 31.52      | CH <sub>2</sub> | 3.01<br>2.37                          | dd<br>dd | 3.66, 15.53<br>9.55, 15.52  |
| 3        | 78.75      | CH              | 4.51                                  | m        |                             |
| 4        | 34.94      | CH              | 2.20                                  | m        |                             |
| 5        | 35.42      | CH <sub>2</sub> | 1.45<br>1.33 <sup>a</sup>             | ddt      | 5.35, 5.35, 10.62,<br>15.07 |
| 6        | 81.47      | C               |                                       |          |                             |
| 7        | 45.48      | CH <sub>2</sub> | 1.35 <sup>a</sup>                     |          |                             |
| 8        | 34.13      | CH              | 1.45                                  |          |                             |
| 9        | 34.56      | CH <sub>2</sub> | 1.24 <sup>a</sup>                     |          |                             |
| 10       | 29.03      | CH <sub>2</sub> | 1.23 <sup>a</sup>                     |          |                             |
| 11       | 23.19      | CH <sub>2</sub> | 1.29 <sup>a</sup> – 1.23 <sup>a</sup> |          |                             |
| 12       | 14.32      | CH <sub>3</sub> | 0.89                                  | m        |                             |
| 13       | 21.54      | CH <sub>3</sub> | 1.37                                  | s        |                             |
| 14       | 25.28      | CH <sub>2</sub> | 1.22 <sup>a</sup> – 1.15 <sup>a</sup> |          |                             |
| 15       | 11.21      | CH <sub>3</sub> | 0.92                                  | t        | 7.96                        |
| 16       | 27.45      | CH <sub>2</sub> | 1.34 <sup>a</sup> – 1.29 <sup>a</sup> |          |                             |
| 17       | 10.74      | CH <sub>3</sub> | 0.82                                  | td       | 4.91, 8.49, 7.40            |
| 18       | 51.99      | CH <sub>3</sub> | 3.71                                  | s        |                             |

NMR solvent: CDCl<sub>3</sub>; <sup>a</sup> overlap with other signals.

**Table S3:** Plakortic acid (5)

| Position | $\delta_C$ | mult            | $\delta_H$   | mult     | <i>J</i> in Hertz      |
|----------|------------|-----------------|--------------|----------|------------------------|
| 1        | 175.45     | C               |              |          |                        |
| 2        | 31.57      | CH <sub>2</sub> | 3.05<br>2.40 | dd<br>dd | 15.8, 9.6<br>15.8, 3.5 |
| 3        | 78.63      | CH              | 4.52 – 4.46  | m        |                        |
| 4        | 34.62      | CH              | 2.25 – 2.09  | tdd      | 12.6, 7.3, 5.0         |

|    |        |                 |  |     |              |
|----|--------|-----------------|--|-----|--------------|
| 5  | 35.67  | CH <sub>2</sub> | 1.55<br>1.34 <sup>a</sup>              | dd  | 13.5, 4.4    |
| 6  | 81.50  | C               |  |     |              |
| 7  | 46.33  | CH <sub>2</sub> | 1.47                                   | m   |              |
| 8  | 40.16  | CH              | 2.09 <sup>a</sup> – 1.95 <sup>a</sup>  |     |              |
| 9  | 134.15 | CH              | 5.11                                   | ddt | 15.3,9.1,1.3 |
| 10 | 131.65 | CH              | 5.39                                   | dt  | 15.3, 6.3    |
| 11 | 25.46  | CH <sub>2</sub> | 2.09 <sup>a</sup> – 1.95 <sup>a</sup>  |     |              |
| 12 | 13.83  | CH <sub>3</sub> | 0.97                                   | t   | 7.5          |
| 13 | 21.25  | CH <sub>3</sub> | 1.38                                   | s   |              |
| 14 | 25.00  | CH <sub>2</sub> | 1.21 <sup>a</sup><br>1.08 <sup>a</sup> |     |              |
| 15 | 10.96  | CH <sub>3</sub> | 0.90                                   | t   | 7.3          |
| 16 | 29.86  | CH <sub>2</sub> | 1.42 <sup>a</sup> – 1.15 <sup>a</sup>  |     |              |
| 17 | 11.42  | CH <sub>3</sub> | 0.81                                   | t   | 7.4          |

NMR solvent: CDCl<sub>3</sub>; <sup>a</sup>overlap with other signals.

**Table S4:** Plakortide E methyl ester (6)

| Position | <sup>δ</sup> c | mult            | <sup>δ</sup> H | mult   | J in Hertz   |
|----------|----------------|-----------------|----------------|--------|--------------|
| 1        | 167.18         | C               |                |        |              |
| 2        | 120.03         | CH              | 6.08           | d      | 15.8         |
| 3        | 149.85         | CH              | 6.86           | d      | 15.8         |
| 4        | 87.32          | C               |                |        |              |
| 5        | 56.10          | CH <sub>2</sub> | 2.54<br>2.44   | d<br>d | 12.0<br>12.0 |
| 6        | 89.39          | C               |                |        |              |
| 7        | 126.81         | CH              | 5.12           | s      |              |
| 8        | 136.82         | C               |                |        |              |
| 9        | 46.65          | CH <sub>2</sub> | 1.97<br>1.86   | m<br>m |              |
| 10       | 42.66          | CH              | 1.98           | m      |              |
| 11       | 132.91         | CH              | 5.07           | dd     | 15.2,8.2     |
| 12       | 132.07         | CH              | 5.35           | m      |              |
| 13       | 25.72          | CH <sub>2</sub> | 1.95           | m      |              |
| 14       | 14.20          | CH <sub>3</sub> | 0.93           | m      |              |
| 15       | 32.33          | CH <sub>2</sub> | 1.88<br>1.63   | m<br>m |              |

|    |       |                 |              |        |     |
|----|-------|-----------------|--------------|--------|-----|
| 16 | 9.03  | CH <sub>3</sub> | 0.87         | m      |     |
| 17 | 30.97 | CH <sub>2</sub> | 1.76         | m      |     |
| 18 | 8.97  | CH <sub>3</sub> | 0.88         | m      |     |
| 19 | 27.73 | CH <sub>2</sub> | 1.35<br>1.09 | m<br>m |     |
| 20 | 11.72 | CH <sub>3</sub> | 0.81         | t      | 7.3 |
| 21 | 17.91 | CH <sub>3</sub> | 1.61         | d      | 1.0 |
| 22 | 51.73 | CH <sub>3</sub> | 3.74         | s      |     |

NMR solvent: CDCl<sub>3</sub>

**Table S5:** 6-epi-Plakortide H (methyl ester) (7)

| Positions | $\delta_C$ | mult            | $\delta_H$                            | mult     | <i>J</i> in Hertz      |
|-----------|------------|-----------------|---------------------------------------|----------|------------------------|
| 1         | 172.53     | C               |                                       |          |                        |
| 2         | 31.44      | CH <sub>2</sub> | 3.04<br>2.38                          | dd<br>dd | 15.8, 9.4<br>15.8, 3.4 |
| 3         | 78.90      | CH              | 4.46                                  | ddd      | 2.2, 4.3, 5.51         |
| 4         | 35.43      | CH              | 2.09 <sup>a</sup>                     |          |                        |
| 5         | 35.53      | CH <sub>2</sub> | 1.69 <sup>a</sup> – 1.20 <sup>a</sup> | m        |                        |
| 6         | 84.34      | C               |                                       |          |                        |
| 7         | 127.34     | CH              | 5.13                                  | s        |                        |
| 8         | 137.32     | C               |                                       |          |                        |
| 9         | 47.60      | CH <sub>2</sub> | 2.06 <sup>a</sup> – 1.94 <sup>a</sup> |          |                        |
| 10        | 42.60      | CH              | 2.02 <sup>a</sup>                     |          |                        |
| 11        | 133.14     | CH              | 5.08                                  | m        |                        |
| 12        | 131.87     | CH              | 5.37                                  | dt       | 15.1, 6.2, 6.2         |
| 13        | 25.77      | CH <sub>2</sub> | 1.97 <sup>a</sup>                     |          |                        |
| 14        | 14.15      | CH <sub>3</sub> | 0.98                                  | t        | 7.4                    |
| 15        | 32.56      | CH <sub>2</sub> | 1.55                                  | m        |                        |
| 16        | 7.78       | CH <sub>3</sub> | 0.86                                  | t        | 7.4                    |

|    |       |                 |                           |   |     |
|----|-------|-----------------|---------------------------|---|-----|
| 17 | 25.12 | CH <sub>2</sub> | 1.17 <sup>a</sup>         |   |     |
| 18 | 11.15 | CH <sub>3</sub> | 0.92                      | t | 7.6 |
| 19 | 28.05 | CH <sub>2</sub> | 1.40<br>1.18 <sup>a</sup> | m |     |
| 20 | 11.78 | CH <sub>3</sub> | 0.84                      | t | 7.4 |
| 21 | 17.03 | CH <sub>3</sub> | 1.70                      | d |     |
| 22 | 52.01 | CH <sub>3</sub> | 3.71                      | s |     |

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NMR solvent: CDCl<sub>3</sub>; <sup>a</sup>overlap with other signals.