1H-Cyclopenta[b]benzofuran Lignans from Aglaia Species Inhibit Cell Proliferation and Alter Cell Cycle Distribution in Human Monocytic Leukemia Cell Lines

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1H-Cyclopenta[b]benzofuran Lignans, Aglaia, Cell Cycle, Cytostatic Activity, Human Leukemia Cells

Thirteen naturally occurring 1H-cyclopenta[b]benzofuran lignans of the rocamadule type as well as one naturally occurring aglain congener all of them isolated from three Aglaia species (Aglaia duperreana, A. oligophylla and A. spectabilis) collected in Vietnam were studied for their antiproliferative effects using the human monocytic leukemia cell lines MONO-MAC-1 and MONO-MAC-6. Only rocamadule type compounds showed significant inhibition of [3H]-thymidine incorporation and the most active compound didesmethylrocamadule inhibited cell growth in a similar concentration range as the well-known anticancer drug vinblastine sulfate. Detailed structure-activity analysis indicated that the OH-group at C-8b which is a common structural feature of most naturally occurring rocamadule compounds is essential for the described antiproliferative activity since replacement of this group by methylation led to a complete loss of the inhibitory activity for the resulting derivative. Rocamadule derivatives rapidly inhibited DNA as well as protein biosynthesis of MONO-MAC-1 cells in the G2/M and probably G0/G1-phase of the cell cycle with no morphological indication of cellular damage. Our data suggest that 1H-cyclopenta[b]benzofuran lignans of the rocamadule type act primarily by a cytostatic mechanism.

Introduction

The genus Aglaia comprises over 100 species that occur in moist tropical forests in the Indo-Malaysian region (Mabberley et al., 1995). In recent years Aglaia species have attracted attention due to their unique 1H-cyclopenta[b]benzofuran lignans (also called rocamadule derivatives) that have been isolated from over 10 Aglaia species so far and are exclusively confined to members of this genus (e.g. Dumontet et al., 1996; Cui et al., 1997; Nugroho et al., 1997a; Nugroho et al., 1997b; Güssregen et al., 1997; Wu et al., 1997; Brader et al., 1998; Chaidir et al., 1999; Nugroho et al., 1999). Roacamadule derivatives (Fig. 1–2) are potent natural insecticides that are comparable with regard to their insecticidal activity to azadirachtin from the Neem tree Azadirachta indica (e.g. Ewete et al., 1996; Nugroho et al., 1999). In addition to their insecticidal activity these compounds have also attracted attention due to their cytostatic activity against human cancer cell lines in vitro (Cui et al., 1997; Wu et al., 1997) that may be as pronounced as that of the well-known anticancer drug vinblastine (Bohnenstengel et al., 1999). Recent experiments indicate that the cytostatic activity of rocamadule compounds may also extend to the in vivo level and delay tumor growth in athymic mice (Lee et al., 1998). Thus, naturally occurring rocamadules or chemical derivatives obtained from these natural products may possibly be used in future as therapeutic or investigational drugs and further studies on their potential antiproliferative activity are required.

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This prompted us to conduct a comparative study on the cytostatic activity of thirteen naturally occurring rocaglamide derivatives (1-13) (Fig. 1-2) and of an aglaine type compound (14) (Fig. 2). We selected a new series of structurally-related compounds and analyzed their effect on the proliferative machinery of fast growing tumor cells in order to identify key elements within the chemical structure conferring the cytotoxic or cytostatic activity, and possibly to elucidate intracellular targets of these 1H-cyclopenta(b)benzofuran derivatives in malignant cells.

Materials and Methods

Plant material

All examined Aglaia species were collected in Vietnam during February 1998. Flowers and stems of Aglaia duperreana were found near Ho Chi Minh City, whereas the bark and stems of A. oligophylla were harvested in Nui Cam, An-Giang Province near the border of Cambodia. Both species were specified by Le Cong Kiet, Dept. of Botany, University of Ho Chi Minh City, Vietnam. The bark of Aglaia spectabilis was collected on Phu Quoc island, Kien Giang Province and was finally specified by C. Pannell, Dep. of Plant Sciences, University of Oxford, England. Voucher specimens are on file in the Department of Botany, Vietnam National University, HCMc, Vietnam.

Isolation of the rocaglamide derivatives

The isolation and structural elucidation of the rocaglamide derivatives with complete data of MS, 1H- and 13C-, 2D-NMR, CD and optical rotation were previously described (Dryer, 1999; Hiort et al., 1999; Nugroho et al., 1999; Schneider, 1999).

Chemicals

RPMI 1640-Cell culture medium and supplements, penicillin and streptomycin were obtained from Gibco-BRL (Eggenstein, Germany). Actinomycin D, cycloheximide, propidium iodide, fetal bovine serum (FBS) and RNAse A were from Sigma (Deisenhofen, Germany). EGMME (ethylene glycol monomethyl ether) was from Merck (Darmstadt, Germany). Methyl-[3H]-thymidine (specific activity 74 GBq/mmol) and methyl-

Proliferation assays

The rocaglamide derivatives and the aglaine derivative were tested for their antiproliferative activity using the two human monocytic leukemia cell lines MONO-MAC-1 and MONO-MAC-6 (Ziegler-Heitbrock et al., 1988). The cell lines are deposited at the German Collection of Microorganisms and Cell Cultures (DSMZ, Braunschweig, Germany).

The cells were grown in plastic flasks (Nunc, Wiesbaden, Germany). All cultures were propagated using standardized media supplemented with 10–20% heat-inactivated fetal bovine serum and were cultivated at 37 °C in a humidified atmosphere containing 5% CO2. Details are outlined in the DSMZ Catalogue of Human and Animal Cell Lines (Drexler et al., 1999).

The freeze-dried rocaglamides were dissolved in EGMME (ethylene glycol monomethyl ether), diluted in RPMI-1640 culture medium and stored frozen at −20 °C. At the final dilution used in the experiments, the EGMME concentration was 0.1%. For the experiments, exponentially growing cells (viability of >90% as measured by trypan blue exclusion) were harvested, washed and resuspended in fresh medium at a final concentration ranging between 2 and 4 x 10^5 cells/ml (depending on the cell line). Proliferation assay was carried out as described (Steube et al., 1992): Aliquots of 90 μl were seeded out into 96-well flat-bottom culture plates (Nunc, Wiesbaden, Germany). Ten microliters with medium, medium with the solvent EGMME or with different concentrations of the rocaglamide derivatives were added. After a 45 h cultivation period 1 μCi of [methyl-3H]-thymidine was given to each well and the cultures were further incubated for 3 h. Cells were harvested on glass fiber filters with a multiple automatic sample harvester, and incorporated radioactivity was determined in a liquid scintillation counter (1209 Rackbeta, LKB, Freiburg, Germany). Total cell number and viability were determined in a cell counting chamber after staining the cells with trypan blue.

All experiments were carried out in triplicates and repeated three times. As controls, cells were
incubated with 0.1% EGMME in culture medium. To avoid bacterial contamination all experiments were carried out in the presence of 100 IU/ml penicillin G and 100 μg/ml streptomycin.

Short term exposure to rocaglamide derivatives:

MONO-MAC-6 cells (density 2 x 10^5 cells/ml) were plated out in 96-well flat-bottom culture plates. After an overnight incubation, the cells were treated with various rocaglamide derivatives for 1 h, followed by a pulsing with 1 μCi [3H]thymidine or [3H]leucine. Radioactive incorporation was determined 2, 4, 6, 8 hours thereafter.

Cell cycle analysis:

Cells were harvested by centrifugation for 10 min at 400xg at 4°C. To the sedimented cells ice-cold 70% ethanol was added drop wise and the samples were fixed in ethanol overnight at 4°C. After washing with PBS, 1 x 10^6 cells were incubated for 15 min. at 37°C with RNase (1 ml of 100 μg/ml RNAse A). After two more washing steps, cells were resuspended in 500 μl PBS. Propidium iodide was added to a final concentration of 20 μg/ml. After 10 min the DNA content of at least 10,000 cells was determined by flow cytometry on a FACScan (Becton Dickinson, Heidelberg, Germany).

Results and Discussion

Thirteen naturally occurring 1H-cyclopenta[b]benzofuran lignans of the rocaglamide type (1–13) (Fig. 1–2) as well as a naturally occurring aglal congener (14) (Fig. 2) were studied for their antiproliferative effect on the human monocytic leukemia cell line MONO-MAC-6. This cell line is a well established and characterized model system in hematology and immunology (Ziegler-Heitbrock et al., 1988; Ziegler-Heitbrock et al., 1994) and we have used it in previous studies (Bohnenstengel et al., 1999; Eder et al., 1998; Steube et al., 1998). Therefore we were able to directly discuss and compare our new results with those reported recently (Bohnenstengel et al., 1999).

The rocaglamide congeners were selected for these experiments based on structural considerations which allow independent determination of the activity modulating effects of different substituents present at positions 1, 2, 6, 7, 8b, 3′ or 4′ of the basic rocaglamide skeleton (Fig. 1–2).

Whereas most rocaglamide derivatives except compounds (6) and (7) were found to clearly inhibit [3H]thymidine incorporation of MONO-MAC-6 cells, there were nevertheless marked differences in the degree of antiproliferative activity that could be related to distinct structural features of the various compounds (Table I). Didesmethylocaglamide (1) and methylrocaglate (2) (Fig. 1), are the most active rocaglamide congeners encountered in this study, exhibiting IC_{50} values of 0.013 and 0.016 μM, respectively. With regard to their growth inhibitory activity they are in the same order of magnitude as the well-known anticancer drug vinblastine sulfate (IC_{50} 0.009 μM) which we have analyzed recently in the same system (Bohnenstengel et al., 1999). Comparison of the IC_{50} values and of the structures of compounds (1) and (2) indicated that the amide substituent as present in (1) can be replaced by a methyl ester group like in (2) with no apparent loss of activity. In contrast, if C-2 was unsubstituted as in rocaglaol (3) (Fig. 1) the antiproliferative activity of the
latter was decreased at least by a factor of four compared to the former derivatives (1) and (2) (Table I). This is in congruence with an earlier report on antiproliferative effects of rocaglamide congeners (Lee et al., 1998). A similar decrease in the antiproliferative activity as from (2) to (3) was observed from (8) to (9). In both weaker compounds (3) and (9) the polar ester substituent at position C-2 is replaced by a hydrogen, again emphasizing the importance of a polar residue at C-2.

Addition of a methylenedioxy group to the rocaglamide skeleton was found to influence activity of the resulting derivatives in a position specific manner. Compound (11) (Fig. 2) that differs from methylrocaglate (2) by a methylenedioxy group linked to C-6 and C-7 of ring A exhibited an IC\textsubscript{50} value of 0.045 \(\mu\)M compared to the IC\textsubscript{50} of 0.016 \(\mu\)M for the parent compound (2) (Table I). Interestingly, compound (8) (4'-demethoxy-3',4'-methylenedioxy-methylrocaglate) with an IC\textsubscript{50} value of 0.020 \(\mu\)M that differs from methylrocaglate (2) by presence of a methylenedioxy group at positions C-3' and C-4' of ring B is nearly as active as the parent compound (2) (Table I).

The influence of the substitution pattern at ring B on the cytostatic properties of rocaglamide derivatives is strictly documented by the low and missing proliferative activity of compounds (5) and (12); both congeners carry a methoxy group at C-3' (instead of -H or methylenedioxy).

To summarize, the comparison of the IC\textsubscript{50} values of (3, 5, 9, 12) indicates that both, a methoxy group in ring B and an unpolar substituent at C-2 have negative influence on the antiproliferative activity of rocaglamide derivatives.

The most dramatic structure activity relation as revealed in this study, however, was detected by analyzing compounds (6) and (7) (Fig. 1) which...
were both devoid of antiproliferative activity even when tested at a concentration of 2.0 μM (Table I). Both rocaglamide congeners are characterized by an unusual OCH₃ substituent at C-8b whereas the majority of naturally occurring rocaglamide type compounds (Fig. 1–2) features a hydroxyl group at this position. Presence of a OH rather than of an OCH₃ substituent at C-8b is therefore essential for the antiproliferative activity of rocaglamide type compounds. Interestingly, 1H-cyclopenta[b]benzofuran type compounds with a methoxy group at C-8b, e.g. (6) and (7) were previously shown to lack also insecticidal activity, whereas their corresponding demethyl parent compounds (2) and (3) are strong natural insecticides (Hiort et al., 1999). It is therefore conceivable to assume that the intracellular target(s) of rocaglamide congeners are similar or identical both in insects and in human cancer cells.

Aglain derivatives such as compound (14) (Fig. 2) that often cooccur with structurally related rocaglamide type compounds in Aglaiá species (Dumontet et al., 1996; Nugroho et al., 1999) differ from the latter by the nature of the heterocycle (bridged benzopyran vs. benzofuran) and usually by a larger and more spacious amide substituent than encountered with rocaglamide derivatives. In a previous study we reported that aglain type compounds show no antiproliferative activity (Bohnenstengel et al., 1999) and assumed this to be due to the different heterocycles present in both types of compounds, even though a negative influence of the large amide group on the biological activity of aglains could not be ruled out at that time. With the structurally closely related rocaglamide derivative (13) (Fig. 2) and the aglain congener (14) now being available for comparative biological studies it could be unequivocally proven for the first time that the loss of antiproliferative activity associated with aglain type compounds can indeed be attributed to the presence of the bridged benzopyran moiety of the aglains vs. the benzofuran system of rocaglamide type compounds. In a previous communication we had demonstrated that rocaglamide derivatives act on MONO-MAC-6 cells by a cytostatic rather than by a cytotoxic mechanism (Bohnenstengel et al., 1999). Since the monocytic leukemia cell line MONO-MAC-6 contains both, diploid and tetraploid cells, an exact cell cycle analysis by flow cytometry was not possible. To evaluate more precisely the cell cycle distribution we have chosen the near-diploid cell line MONO-MAC-1 (Steube et al., 1997), which has been established from the same patient as MONO-MAC-6 (Ziegler-Heitbrock et al., 1988). Thus, flow cytometry was carried out with MONO-MAC-1 cells, in presence of the most active compound, didesmethylrocaglamide (1) for a time period of up to 96 h and compared to controls (Fig. 3) (Table II).

Prior to the drug treatment about 70% of the cells were in G1-, 20% in S- and 10% in G2/M-phase. The number of cells in G2/M increased continuously to 27% during the 96 hours incubation period, in parallel to a decrease of cells in S-phase (Fig. 3). In addition to the cell cycle analysis we determined cell viability and [³H]thymidine incorporation. The control culture steadily increased its cell number and [³H]thymidine incorporation while the amount of viable cells in the didesmethylrocaglamide-treated culture remained constant (or slightly decreased), and an almost complete stop of [³H]thymidine incorporation was observed (Table II). These data, together with the fact that we did not detect any significant increase of cells

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**Table I. IC₅₀ values of compounds (1–14) determined for MONO-MAC-6 (human monocytic leukemia cell line).**

<table>
<thead>
<tr>
<th>Compound</th>
<th>MONO-MAC-6 (µg/ml)</th>
<th>MONO-MAC-6 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.006</td>
<td>(0.013)</td>
</tr>
<tr>
<td>2</td>
<td>0.008</td>
<td>(0.016)</td>
</tr>
<tr>
<td>3</td>
<td>0.031</td>
<td>(0.071)</td>
</tr>
<tr>
<td>4</td>
<td>0.029</td>
<td>(0.056)</td>
</tr>
<tr>
<td>5</td>
<td>0.091</td>
<td>(0.174)</td>
</tr>
<tr>
<td>6</td>
<td>N. A.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>N. A.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.010</td>
<td>(0.020)</td>
</tr>
<tr>
<td>9</td>
<td>0.041</td>
<td>(0.092)</td>
</tr>
<tr>
<td>10</td>
<td>0.022</td>
<td>(0.042)</td>
</tr>
<tr>
<td>11</td>
<td>0.023</td>
<td>(0.045)</td>
</tr>
<tr>
<td>12</td>
<td>N. A.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>0.032</td>
<td>(0.051)</td>
</tr>
<tr>
<td>14</td>
<td>N. A.</td>
<td></td>
</tr>
</tbody>
</table>

The IC₅₀ values reported represent means of three independent experiments.

Results are expressed as IC₅₀ values in µg/ml (µM).

- **a** Not active up to 1 µg/ml (2.0 µM)
- **b** Not active up to 0,1 µg/ml (0.2 µM)
- **c** Not active up to 3 µg/ml (4.6 µM).
Fig. 3. MONO-MAC-1 cells (starting conc. of 0.3 x 10^6 cells/ml) were incubated with or without 0.050 μg/ml didesmethylrocaglamide (1). At different time periods (24h, 48h, 72h, 96h) cell cycle analysis was performed as described in Materials and Methods. Shown is the diagram after 96h incubation without (left) and with the rocaglamide derivative (right). Percentage of distribution is given in Table II.

Table II. Effect of 0.050 μg/ml didesmethylrocaglamide (1) on cell cycle distribution, total cell number and viability of MONO-MAC-1 cells.

<table>
<thead>
<tr>
<th></th>
<th>G1/G0 (%)</th>
<th>S (%)</th>
<th>G2/M (%)</th>
<th>Cell number (10^6 cells/ml)</th>
<th>Viability (%)</th>
<th>[3H]thymidine incorporation (cpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h</td>
<td>Control</td>
<td>65</td>
<td>26</td>
<td>9</td>
<td>0.38</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Roca (1)</td>
<td>67</td>
<td>21</td>
<td>12</td>
<td>0.35</td>
<td>96</td>
</tr>
<tr>
<td>48h</td>
<td>Control</td>
<td>63</td>
<td>25</td>
<td>12</td>
<td>0.49</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Roca (1)</td>
<td>67</td>
<td>17</td>
<td>16</td>
<td>0.38</td>
<td>95</td>
</tr>
<tr>
<td>72h</td>
<td>Control</td>
<td>63</td>
<td>28</td>
<td>9</td>
<td>N. D.a</td>
<td>N. D.a</td>
</tr>
<tr>
<td></td>
<td>Roca (1)</td>
<td>63</td>
<td>14</td>
<td>23</td>
<td>N. D.a</td>
<td>N. D.a</td>
</tr>
<tr>
<td>96h</td>
<td>Control</td>
<td>61</td>
<td>29</td>
<td>10</td>
<td>1.07</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Roca (1)</td>
<td>60</td>
<td>13</td>
<td>27</td>
<td>0.37</td>
<td>84</td>
</tr>
</tbody>
</table>

* a Not determined.

Thus, our data differ to a certain degree to those of a recent study (Lee et al., 1998) that claimed a transient arrest of the cells in the G1/G0 phases of the cell cycle. In contrast to our system Lee et al. (1998) have used a lung cancer cell line (Lu1) which seems not to be further certified or characterized, since the cells are not published and are not available from an international recognized cell bank. They carried out flow cytometry at seven time points, but only 24 hours after start a significant difference between control and drug treated cultures was observed. It is not discussed why the reported G1/G0 arrest is only transient, although the total cell number remained constant throughout the whole 72 hours cultivation time. The MONO-MAC-1 cells we used grow as suspension culture whereas lung cells grow adherent and must be trypsinized prior to flow cytometry. It is possible that drug-treated lung-cells are less resistant to the trypsin-treatment than the control cells and only an unrepresentative fraction of the culture was analyzed.

In the same study the authors claimed that rocaglamide derivatives act on Lu1 cells primarily by selective inhibition of protein synthesis rather than by inhibition of nucleic acid synthesis (Lee et al., 1998). They reported further that short term exposure (2–3h) of Lu1 cells to compound (8) causes severe reduction of protein synthesis (the IC₅₀ value of (8) was 0.025 μg/ml) whereas even significantly higher concentrations of (8) (up to 1.0 μg/ml) failed to reduce DNA synthesis under similar experimental conditions (Lee et al., 1998).

We have selected 6 rocaglamide derivatives including also compound (8) (4'-demethoxy-3',4'-
Compounds (0.100 μg/ml)

Fig. 4. MONO-MAC-6 cells were plated out in 96-well culture plates and incubated overnight. Followed by addition of rocaglamide derivatives at a final concentration of 0.100 μg/ml. After 1 h incubation 3H-thymidine was added. After an additional 2 h cells were harvested and incorporation of 3H-thymidine was measured. Results are expressed as% incorporation relative to control cultures.

methylenedioxy-methylrocaglate) and investigated their effect on DNA synthesis by measuring [3H]thymidine incorporation for only 3 h (Fig. 4). Five congeners including compound (8) were able to significantly reduce DNA-synthesis, albeit higher concentrations were needed than in the long-term experiments leading to the IC50 values. Further time-course experiments measuring [3H]thymidine incorporation after 4, 24, and 48 h in this and our previous study (Bohnenstengel et al., 1999) unequivocally showed that DNA-synthesis is indeed affected by more than 20 different rocaglamide derivatives. Studies carried out earlier using various human leukemia cell lines revealed also a dose dependent inhibition of RNA-synthesis (Steube et al., unpublished results).

Didesmethylrocaglamide (1) being the most active compound detected in this study, reduced DNA and protein synthesis roughly by 50% at concentrations of 0.050 – 0.100 μg/ml and compares thus favorably to well-known inhibitors of DNA or protein synthesis such as actinomycin D.

Fig. 5. MONO-MAC-6 cells (density 2 x 10^5 cells/ml) were precultured for 24 h in leucine and serum-free medium. Cells were treated with three concentrations (0.001, 0.005 and 0.050 μg/ml) of didesmethylrocaglamide (1) for 1 hour, followed by pulsing with [3H]leucine (1μCi, 7h). Cycloheximide served as a positive control (1.0 μg/ml). [3H]leucine incorporation of cells treated with didesmethylrocaglamide (1) or cycloheximide was compared with control cells.

Fig. 5. Inhibition of protein biosynthesis caused by didesmethylrocaglamide (1) and cycloheximide.
F. I. Bohnenstengel et al. • 1H-Cyclopenta[b]benzofurans Alter Cell Cycle Distribution in MONO-MAC-6 Cells (Fig. 4) or cycloheximide (Fig. 5) which were used as positive controls.

However, our experimental design could not distinguish whether inhibition of DNA or protein synthesis are direct or indirect effects of the compounds investigated.

Antiproliferative natural compounds exert their biological effects on various intracellular targets. For example, vinblastine inhibits tubulin polymerization, cytochalasin actin polymerization, whereas actinomycin D, mitomycin and anthracyclines act on DNA replication. Cycloheximide and amanitin inhibit protein biosynthesis via the ribosomal machinery and RNA polymerase II, respectively. Other natural products interfere with the signal transduction pathway by inhibition of protein kinases or phosphatases (staurosporines, calyculines, genistein, herbimycine and many others). And, many if not all applications of these drugs finally results in an inhibition of cell proliferation depending on the concentration used in the individual experiments. Thus a large number of possible targets may exist and a thorough study in isolated cell fractions or cell-free systems should be performed before a specific mode of action can be suggested for the 1H-cyclopenta[b]benzofuran ligands.

Taken together, rocalagamide type compounds have proven to be inhibitors of cellular proliferation in a cytostatic, rather than a cytotoxic manner. These substances are promising candidates for future work aiming to improve their biological activity by site directed chemical modification thus opening a possible application for rocalagamides as tools in cancer biology.

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