Introduction

The ATP-binding cassette (ABC) transporter family comprises 49 members, some of which have been linked to the transport of drugs. Apart from P-glycoprotein (P-gp, MDR1/ABCB1) and the multidrug resistance-related proteins (MRPs/ABCCs), which have been well analysed during the past years, the breast cancer resistance protein (BCRP/ABCG2) has also been shown to be associated with drug transport and multidrug resistance. Although originally identified in P-gp-negative multidrug-resistant breast cancer cells, its expression is not confined to breast cancer cells. It can also be found in other tumour types and in several normal tissues such as placental syncytiotrophoblasts, in enteroctyes, in the liver canalicular membrane, in ducts and lobules of the breast, in the veins and capillaries of blood vessels, in lymphocytes, in haematopoietic stem cell side populations and at the blood–brain barrier. This widespread localization mostly overlapping with P-gp indicates that BCRP is involved in physiological transport processes to protect tissues from xenobiotics and endogenous toxins. In addition to the transport of various antineoplastic agents, BCRP has also been shown to transport a number of drugs not related to cancer chemotherapy, e.g. cimetidine and fluoroquinolone antibiotics. As expected, it may also be responsible for pharmacokinetic drug–drug interactions.

Previous investigations indicated that drugs used for the treatment of human immunodeficiency virus (HIV) might also...
interact with BCRP.\textsuperscript{9–11} Highly active antiretroviral therapy (HAART) for the treatment of HIV infection consists of a combination of three or four antiretroviral drugs of different classes. Among them are the HIV-protease inhibitors (PIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs), the nucleoside reverse transcriptase inhibitors (NRTIs) and the nucleotide reverse transcriptase inhibitors (NtRTIs). The complexity of antiretroviral drug regimens and the need for additional drugs to treat co-morbidities lead to an increased risk for drug interactions in patients infected with HIV.\textsuperscript{12–14}

PIs are substrates, inhibitors and, to some extent, inducers of P-gp.\textsuperscript{15–20} Indeed, there is unambiguous evidence that P-gp accounts for some drug interactions seen with HAART. Inhibition of P-gp leads to modified oral bioavailability, disposition and penetration into the central nervous system and accumulation of HIV-PIs in leucocytes.\textsuperscript{21} Hence, it is of particular importance for the effectiveness and safety of antiretroviral therapy. Moreover, PIs themselves can influence the bioavailability, distribution or elimination of concomitant drugs by inhibition or induction of P-gp.\textsuperscript{22,23} For some MRPs relevance in HIV-therapy has also been demonstrated.\textsuperscript{24–27} In contrast, the role of BCRP for interactions with PIs and the other antiviral drug classes is far from being evident. So far, only substrate characteristics of isolated NRTIs and PIs and the inhibition of BCRP by some PIs have been investigated.\textsuperscript{9–11} BCRP inhibition by NRTIs, NNRTIs, NtRTIs and by numerous PIs has not been analysed up to now. Inhibition of BCRP by antiretrovirals might lead to increased toxicity of concurrently administered BCRP substrates like doxorubicin or daunorubicin\textsuperscript{28} used for the treatment of AIDS-associated Kaposi’s sarcoma but also to the superior effectiveness of HAART. We, therefore, systematically tested the 19 most frequently used antiretroviral drugs (Table 1) for their potential to inhibit BCRP. As a cell model MDCKII–BCRP, generated by transfection of the canine kidney epithelial cell line MDCKII with human BCRP, and the corresponding parental cell line was used and after careful evaluation of several probe substrates for BCRP, we selected phophoribide A (PhA) as the most suitable.

### Materials and methods

**Materials**

Culture media, fetal calf serum (FCS), medium supplements, antibiotics and phosphate-buffered saline (PBS) were purchased from Invitrogen (Karlsruhe, Germany), DMSO, MES, aprotinin and mitoxantrone (MX) were from Sigma-Aldrich (Taufkirchen, Germany), NaCl (sodium chloride), Tris [2-amino-2-(hydroxymethyl)-1, 3-propaniol], SDS, glycerol and β-mercaptoethanol were from AppliChem (Darmstadt, Germany), cultivating bottles were from Nunc (Wiesbaden, Germany), PhA was from Frontier Scientific Europe (Carnforth, Lancashire, UK), bodipy-prazosin (BPZ) was from Molecular Probes (MoBiTec, Göttingen, Germany), pefabloc was from Serva (Heidelberg, Germany) and leupeptin and pepstatin were from Biomol (Hamburg, Germany). Drugs were obtained from Sigma-Aldrich (Taufkirchen, Germany) or from the corresponding manufacturer. The concentration ranges tested in the flow cytometry assay are indicated in Table 1.

**Stock solutions and test solutions**

Stock solutions of test compounds were prepared strictly following the manufacturers’ instructions. All test compounds were dissolved in DMSO, only tenofovir, emtricitabine and stavudine were dissolved in PBS. The maximum DMSO concentration in the assays was limited to 1%, a concentration without effect on BCRP efflux activity. All anti-HIV drugs were used up to the highest concentration soluble in PBS or up to 1 mM.

### MDCKII and MDCKII–BCRP cells

MDCKII–BCRP cells were generated by transfection of the canine kidney epithelial cell line MDCKII with the human full-length wild-type BCRP cDNA and the green fluorescence protein (GFP)\textsuperscript{6} and were kindly provided by Dr A. H. Schinkel (Amsterdam, The Netherlands). The parental cell line MDCKII (available at ATCC, Manassas, USA) was used as a control. The cells were cultured in Dulbecco’s modified Eagle’s medium (DMEM) with 10% FCS, 2 mM glutamine, 100 U/mL penicillin and 100 μg/mL streptomycin.

**Western-blot analysis of BCRP**

Expression of BCRP in MDCKII and MDCKII–BCRP cells was demonstrated by western-blot analysis. Trypsinized cells were washed once with PBS. The pellet was homogenized on ice in 500 μL of lysis buffer (pH 6.5) containing 25 mM MES, 150 mM NaCl and a combination of protease inhibitors (1 mg/mL pefabloc, 5 μg/mL leupeptin, 1 μg/mL pepstatin and 1 μg/mL aprotinin). Protein concentrations in the lysates were determined using a BCA protein assay kit from Pierce (Rockford, USA) according to the manufacturer’s instructions. Protein (20 μg) preheated for 5 min at 99°C in sample buffer (containing Tris–HCl, SDS, β-mercaptoethanol, Bromophenol Blue and glycerol) was subjected to 12% PAGE and

### Table 1. Tested concentration ranges of antiviral drugs and controls

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tested concentration range (μM)</th>
</tr>
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<tbody>
<tr>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>fumitremorgin C</td>
<td>0.1–20</td>
</tr>
<tr>
<td>Ko143</td>
<td>0.004–0.4</td>
</tr>
<tr>
<td>LY335979</td>
<td>0.01–1</td>
</tr>
<tr>
<td>NRTIs/NtRTIs</td>
<td></td>
</tr>
<tr>
<td>abacavir</td>
<td>10–500</td>
</tr>
<tr>
<td>didanosine</td>
<td>10–500</td>
</tr>
<tr>
<td>emtricitabine</td>
<td>10–1000</td>
</tr>
<tr>
<td>lamivudine</td>
<td>10–1000</td>
</tr>
<tr>
<td>stavudine</td>
<td>50–1000</td>
</tr>
<tr>
<td>tenofovir</td>
<td>10–1000</td>
</tr>
<tr>
<td>zalcitabine</td>
<td>10–1000</td>
</tr>
<tr>
<td>zidovudine</td>
<td>10–1000</td>
</tr>
<tr>
<td>NNRTIs</td>
<td></td>
</tr>
<tr>
<td>delavirdine</td>
<td>1–100</td>
</tr>
<tr>
<td>efavirenz</td>
<td>5–100</td>
</tr>
<tr>
<td>nevirapine</td>
<td>10–1000</td>
</tr>
<tr>
<td>PIs</td>
<td></td>
</tr>
<tr>
<td>amprenavir</td>
<td>1–100</td>
</tr>
<tr>
<td>atazanavir</td>
<td>1–100</td>
</tr>
<tr>
<td>indinavir</td>
<td>1–50</td>
</tr>
<tr>
<td>lopinavir</td>
<td>0.2–20</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>0.2–20</td>
</tr>
<tr>
<td>ritonavir</td>
<td>0.1–5</td>
</tr>
<tr>
<td>saquinavir</td>
<td>1–50</td>
</tr>
<tr>
<td>tipranavir</td>
<td>0.4–20</td>
</tr>
</tbody>
</table>
Becton Dickinson LSR II flow cytometer with a solid state coherent laser and a 530 bandpass filter for BPZ and GFP and a 633 nm helium/neon laser and a 660 bandpass filter for MX and PhA.

In each sample 30,000 cells were counted. Cell debris was eliminated by gating the living cells in the forward versus side scatter. BCRP-positive MDCKII-BCRP cells were additionally gated using their GFP signal. To quantify the inhibitory effects of the compounds, the ratio between the median fluorescence (MF) with inhibitor and without inhibitor during the efflux period was calculated and normalized to the effect observed in the corresponding parental cell line according to the following equation:

\[
\text{Inhibition ratio} = \frac{\text{MF}_{\text{overexpressing cell line with test compound}}}{\text{MF}_{\text{overexpressing cell line without test compound}}} \]

\[
\frac{\text{MF}_{\text{parental cell line with test compound}}}{\text{MF}_{\text{parental cell line without test compound}}}
\]

When using BPZ as substrate, the MF of the corresponding unstained cells was subtracted from all MF values due to the GFP signal detected in the same channel (530 nm bandpass filter) as BPZ. Each experiment was performed at least three times. In each experiment 10 μM of the selective BCRP inhibitor fumitremorgin C served as a positive control. In the optimized assay, the even more potent fumitremorgin C derivative Ko143 was additionally tested.

Statistical analysis

For calculation of the inhibitor effects in flow cytometry assays, \( P \) values for differences between the inhibition ratio compared with the hypothetical ratio of 1 (for no BCRP inhibition) were determined by Student’s unpaired, two-tailed \( t \)-test. A \( P \) value of \( \leq 0.05 \) was considered significant.

For better comparison of the inhibitory potencies IC50 values (concentration leading to half-maximal inhibition) were estimated on the basis of the mean concentration–response curves fitted non-linearly with four parameters according to the following formula:

\[
y = \frac{I_{\text{max}} - I_{\text{min}}}{1 + \left( \frac{x}{\text{IC}_{50}} \right)^{s}} + I_{\text{min}}
\]

where \( I_{\text{max}} \) (maximal inhibition) was constrained to the ratio obtained with 10 μM fumitremorgin C in the corresponding series of experiments, \( I_{\text{min}} \) (background) was constrained to 1 (no inhibition) and \( s \) is the slope factor.

Results

Establishment of a specific BCRP inhibition assay: selection of a suitable probe substrate

To establish an optimized assay for BCRP inhibition, we screened the BCRP substrates MX, BPZ and PhA for their suitability by investigating the effect of the selective BCRP inhibitor fumitremorgin C (10 μM) and the selective P-gp inhibitor LY335979 (1 μM) on the efflux of the corresponding substrate. Figure 2 demonstrates that of all substrates tested the highest ratio between MDCKII-BCRP and MDCKII was obtained with PhA as a substrate and compared with the effect of the selective inhibitor fumitremorgin C the effect of LY335979 was only minor. In the control cell line, fumitremorgin C did not increase intracellular fluorescence except in experiments with BPZ as a substrate. In contrast, LY335979 slightly increased the fluorescence to some extent.
extent in both cell lines depending on the substrate used (Figure 2). The selective and highly potent BCRP inhibitor Ko143, which was only tested with PhA as substrate, only increased intracellular fluorescence in MDCKII-BCRP and not in MDCKII cells.

We, therefore, chose PhA as probe substrate for the assessment of BCRP inhibitory effects. To further minimize unspecific effects, the ratio between the effect in the overexpressing and the parental cell line was calculated (inhibition ratio) according to the formula presented in the Materials and methods section. Figure 3 depicts the extent of fluorescence shift provoked by 10 \( \mu M \) fumitremorgin C. Figure 4 demonstrates the significant and concentration-dependent inhibition of BCRP in MDCKII-BCRP cells by the selective BCRP inhibitors fumitremorgin C and Ko143, whereas the inhibition ratio of the selective P-gp inhibitor LY335979 did not differ significantly from 1 (no inhibition), when the ratio between overexpressing and parental cell line was calculated.

**Effects of anti-HIV drugs on BCRP-mediated PhA efflux in MDCKII-BCRP cells**

In the MDCK cell system only efavirenz induced cytotoxic effects at concentrations \( \geq 50 \mu M \) (at 50 \( \mu M \): 41% in MDCKII and 37% in MDCKII-BCRP cells; at 100 \( \mu M \): 95% in MDCKII and 79% in MDCK-BCRP cells). Moreover, because cells drifted out of the gate at efavirenz concentrations above 50 \( \mu M \) indicating cell damage, these concentrations were not included in the data analysis.

There were large differences in the effect on BCRP activity between anti-HIV drug classes and also within individual classes. As shown in Figure 5 from all PIs lopinavir, nelfinavir and saquinavir exhibited the most potent concentration-dependent BCRP inhibition, followed by atazanavir, tipranavir and amprenavir. Ritonavir and indinavir had no influence on PhA transport. All NNRTIs significantly inhibited BCRP in a concentration-dependent manner, with delavirdine and efavirenz being more potent than nevirapine (Figure 6). The NRTIs/NtRTIs demonstrated the lowest impact on PhA transport, with abacavir and zidovudine exerting moderate inhibition and all other NRTIs/NtRTIs being devoid of an effect (Figure 7). According to the \( IC_{50} \) estimation, the rank order for BCRP inhibition was lopinavir > nelfinavir > delavirdine > efavirenz > saquinavir > atazanavir >
amprenavir > abacavir (Table 2). The IC_{50} values of ritonavir and tipranavir could not be estimated due to their low solubility.

Generally, fumitremorgin C was at least one order of magnitude and Ko143 more than two orders of magnitude more potent than the compounds tested.

**Discussion**

Drug interactions between and with anti-HIV drugs as well as viral resistance to antiretrovirals represent a considerable problem for the safety and effectiveness of HAART. Whereas evidence for the central role of the ABC transporter P-gp in the pharmacokinetics of and the interaction with antiretroviral drugs is accumulating,15,18,20,22 the influence of BCRP is far from being elucidated. The aim of this study was therefore to investigate the influence of all frequently used and recommended by the US Department of Health and Human Services32 PIs, NNRTIs, NRTIs and the NtRTI tenofovir on BCRP activity in vitro and to

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Figure 4. (a–c) PhA efflux assay measured by flow cytometry. Inhibition of BCRP in MDCKII-BCRP cells by the selective BCRP inhibitors fumitremorgin C and Ko143 and the selective P-gp inhibitor LY335979. Inhibition ratio = ratio between the median fluorescence (MF) with and without inhibitor during the efflux period, normalized to the effect in the parental cell line MDCKII. Data are expressed as mean ± SEM of n = 4 experiments. P values for differences between the inhibition ratio compared with the hypothetical ratio of 1 (no BCRP inhibition) were determined by unpaired two-tailed t-test. *P < 0.05; **P < 0.01; ***P < 0.001.

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assess all in one assay to allow unrestricted comparison of the results.

As a cell model the thoroughly characterized MDCKII-BCRP cells were used after confirming exclusive BCRP expression in the transfected cell line and its absence in the parental control cells by western-blot. Although it is unknown whether the monoclonal antibody BXP-21 raised against human BCRP cross-reacts with canine BCRP, a modulation of the results by fumitremorgin C.

For an organism, it is more efficient to transport xenobiotic compounds by redundant transport systems with rather little selectivity than by single transporters. Therefore, it is crucial to identify fluorescent probes with large differences in affinity to competing transporters to make them suitable tools for the evaluation of distinct transporters. Published evidence from functional assays suggests that MDCKII cell lines express endogenous P-gp. Moreover, MX is reported to be transported not only by BCRP but also by P-gp and at least prazosin seems to be a very sensitive probe for P-gp. Recent investigations showed that PhA is transported selectively by BCRP and not by P-gp or other ABC transporters. We, therefore, reassessed the suitability of MX, BPZ and PhA as probe substrates in the MDCKII cell system. Of all substrates tested the highest ratio between MDCKII-BCRP and MDCKII was obtained with PhA as a substrate. This high ratio also

Figure 6. (a–c) PhA efflux assay measured by flow cytometry. Inhibition of BCRP in MDCKII-BCRP cells by NNRTIs. Inhibition ratio = ratio between the median fluorescence (MF) with and without inhibitor during the efflux period, normalized to the effect in the parental cell line MDCKII. Data are expressed as mean ± SEM of n = 3–6 experiments. P values for differences between the inhibition ratio compared with the hypothetical ratio of 1 (no BCRP inhibition) were determined by unpaired two-tailed t-test. *P < 0.05; **P < 0.01; ***P < 0.001. Control = 10 µM fumitremorgin C. DLV, delavirdine; EFV, efavirenz; NVP, nevirapine.

Figure 7. (a–h) PhA efflux assay measured by flow cytometry. Inhibition of BCRP in MDCKII-BCRP by NRTIs and the NRTI tenofovir. Inhibition ratio = ratio between the median fluorescence (MF) with and without inhibitor during the efflux period, normalized to the effect in the parental cell line MDCKII. Data are expressed as mean ± SEM of n = 3–6 experiments. P values for differences between the inhibition ratio compared with the hypothetical ratio of 1 (no BCRP inhibition) were determined by unpaired two-tailed t-test. *P < 0.05; **P < 0.01; ***P < 0.001. Control = 10 µM fumitremorgin C. ABV, abacavir; ddI, didanosine; ETB, emtricitabine; 3TC, lamivudine; d4T, stavudine; TFV, tenofovir; ddC, zalcitabine; ZDV, zidovudine.
IC\textsubscript{50} values were calculated from the mean concentration–response curves in which \( I \) was constrained to a minimum of 1 (no inhibition) and \( I \) to the maximum inhibition (ratio obtained with 10 \( \mu \)M fumitremorgin C) in the corresponding series of experiments.

Table 2. Estimated IC\textsubscript{50} values for BCRP inhibition of anti-HIV drugs and positive controls

<table>
<thead>
<tr>
<th>Compound</th>
<th>Estimated IC\textsubscript{50} values (( \mu )M) for BCRP inhibition in MDCKII-BCRP cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fumitremorgin C</td>
<td>0.47</td>
</tr>
<tr>
<td>Ko143</td>
<td>0.01</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>181</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>69.1</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>7.66</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>13.5</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>27.4</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>18.7</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>20.6</td>
</tr>
<tr>
<td>Abacavir</td>
<td>385</td>
</tr>
</tbody>
</table>

IC\textsubscript{50} values were calculated from the mean concentration–response curves in which \( I \) was constrained to a minimum of 1 (no inhibition) and \( I \) to the maximum inhibition (ratio obtained with 10 \( \mu \)M fumitremorgin C) in the corresponding series of experiments.

The first evidence for a possible role of BCRP for the cellular resistance towards NRTIs was published by Wang et al.\textsuperscript{10} Wang et al. demonstrated impaired anti-HIV-1 activity of zidovudine and lamivudine in the CD4+ cell line MT-4/DOX\textsubscript{500} over-expressing the mutant BCRP\textsubscript{P\textsubscript{ELE82M}} suggesting transport at least by the mutant BCRP. In contrast, the activity of stavudine, nevirapine, indinavir and nelfinavir was not affected in this cell line. For zidovudine, zalcitabine, didanosine and stavudine the same investigators also found diminished activity in MT-4 cells transfected with wild-type BCRP indicating transport of these NRTIs.\textsuperscript{11} Unlike the NRTIs the PIs amprenavir, indinavir, nelfinavir, ritonavir and saquinavir are not transported by BCRP, but nelfinavir, ritonavir and saquinavir act as inhibitors of BCRP.\textsuperscript{9} Other PIs as well as the NNRTIs or the NRTIs have not been tested so far for BCRP inhibition.

In our study, for the first time all NNRTIs, the most important PIs and NRTIs, and tenofovir have been investigated for their ability to inhibit BCRP. Besides and in contrast to earlier experiments,\textsuperscript{9} all test compounds were only used up to their highest maximal solubility thus avoiding misinterpretation of the results.\textsuperscript{35} The substantial BCRP inhibition by saquinavir and nelfinavir\textsuperscript{9} reported previously was confirmed as was the absence of an interaction with indinavir and the weak inhibition induced by amprenavir. In contrast to these earlier experiments we did not detect an inhibitor effect of ritonavir up to 5 \( \mu \)M. This apparent discrepancy may be caused by the use of ritonavir doses beyond its maximum solubility.

NNRTIs, which have not been tested so far, also proved to inhibit BCRP. Indeed, delavirdine and efavirenz were as potent BCRP inhibitors as saquinavir and nelfinavir. In contrast, the influence of the NRTIs and tenofovir on BCRP activity was either absent or weak as demonstrated for abacavir and zidovudine. Together with the recent findings that zidovudine and possibly also zalcitabine, didanosine and stavudine are transported by BCRP\textsuperscript{10,11} our findings suggest that they might bind to BCRP only with low affinity.

Taken together, our study for the first time demonstrates significant BCRP inhibition \textit{in vitro} by NNRTIs, weak inhibition by some NRTIs and potent inhibition by most of the PIs analysed, thus confirming the effects of saquinavir and nelfinavir reported in an earlier study. These results expand these findings and suggest that inhibition of BCRP might contribute to drug–drug interactions observed during HAART \textit{in vivo}. However, because many antiretroviral drugs and particularly the PIs efavirenz and nevirapine are highly plasma protein bound, extrapolation to \textit{in vivo} situations should consider free and not total plasma concentrations. Whether the free plasma concentrations reached in regular treatment regimens, which are in the nanomolar or lower micromolar range, will be high enough to prompt such interactions will have to be tested in appropriately designed clinical studies. However, the high concentrations reached in the gut after oral administration suggest that such interactions may at least play a role in the absorption process of concurrently administered BCRP substrates. Moreover, BCRP inhibition at HAART target sites like lymphocytes, which express substantial amounts of BCRP,\textsuperscript{38} should also be evaluated to assess whether this mechanism is also contributing to the superior effectiveness of combination antiretroviral therapy.

Acknowledgements

We thank Abbott (Wiesbaden, Germany) for providing ritonavir and lopinavir, GlaxoSmithKline (Brentford, UK) for abacavir, amprenavir, lamivudine and zidovudine, Roche (Basle, Switzerland) for zalcitabine, saquinavir and nelfinavir, Gilead Sciences (Foster City, CA, USA) for tenofovir and emtricitabine, Bristol-Myers Squibb (München, Germany) for atazanavir and efavirenz, Merck Sharp & Dohme (Haar, Germany) for indinavir, Boehringer Ingelheim Pharmaceuticals (Ingelheim, Germany) for tipranavir and nevirapine, Pharmacia (Kalamazoo, USA) for delavirdine, Eli Lilly Company (Bad Homburg, Germany) for LY335979, the National Cancer Institute (Rockville, USA) for fumitremorgin C, Dr Gerrit-Jan Koomen (Amsterdam, The Netherlands) for Ko143 and Dr Alfred H. Schinkel (Amsterdam, The Netherlands) for generously providing the cell lines MDCKII-BCRP.

Transparency declarations

None to declare.

References


HIV-drugs and BCRP


