Plasma and Cerebrospinal Fluid Pharmacokinetics of O\textsuperscript{6}-Benzylguanine and Analogues in Nonhuman Primates\textsuperscript{1}

Lina Long, Stacey L. Berg, Sandip K. Roy,\textsuperscript{2} Cindy L. McCully, Hee-Won Song-Yoo, Robert C. Moschel, Frank M. Balis, and M. Eileen Dolan\textsuperscript{3}

Department of Medicine, Cancer Research Center and Committee on Clinical Pharmacology, University of Chicago, Chicago, Illinois 60637; [L. L., S. K. R., M. E. D.]; Texas Children’s Cancer Center, Texas Children’s Hospital, Baylor College of Medicine, Houston, Texas 77030 [S. L. B.]; Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland 20892 [C. L. M., F. M. B.]; and Chemistry of Carcinogenesis Laboratory, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, Maryland 21702-1201 [H-W. S-Y., R. C. M.]

ABSTRACT

O\textsuperscript{6}-Benzylguanine (BG) is a potent, specific inactivator of the DNA repair protein, O\textsuperscript{6}-alkylguanine-DNA alkyltransferase, that enhances the sensitivity of tumor cell lines and tumor xenografts to chloroethylnitrosoureas. To search for BG analogues with greater penetration into the cerebrospinal fluid (CSF), we evaluated plasma and CSF pharmacokinetics of BG, 8-aza-O\textsuperscript{6}-benzylguanine (8-azaBG), O\textsuperscript{6}-benzyl-8-bromoguanine (8-BrBG), O\textsuperscript{6}-benzyl-8-oxoguanine (8-oxoBG), O\textsuperscript{6}-benzyl-8-trifluoromethylguanine (8-tfmBG), and O\textsuperscript{6}-benzyl-2′-deoxyguanosine (B2dG) after i.v. administration of 200 mg/m\textsuperscript{2} of drug through an indwelling Omnaya reservoir in a nonhuman primate model. BG and its analogues were quantified in plasma and CSF using reverse-phase high-performance liquid chromatography assays. The plasma clearances of the four 8-substituted BG analogues were similar (0.04–0.06 l/h/kg), but half-lives ranged from <2 to >24 h. BG was converted to 8-oxoBG, an equally potent O\textsuperscript{6}-alkylguanine-DNA alkyltransferase inactivator, and the elimination of 8-oxoBG was much slower than that of BG. As a result, the plasma area under the curve of 8-oxoBG was 3.5-fold greater than that of BG. B2dG was metabolized to BG and 8-oxoBG, but this pathway accounted for only 20% of B2dG elimination. The CSF penetration percentages (based on the ratio of AUC\textsuperscript{CSF} : AUC\textsuperscript{plasma}) for BG, 8-azaBG, 8-oxoBG, 8-tfmBG, 8-BrBG, and B2dG were 3.2, 0.18, 4.1, 1.4, <0.3, and 2.0%, respectively. The CSF penetration of BG and its active metabolite 8-oxoBG is greater than the penetration of 8-azaBG, 8-BrBG, 8-tfmBG, and B2dG.

INTRODUCTION

BG\textsuperscript{4} is one of the most potent, specific inactivators of the DNA repair protein, AGT (1, 2). Inactivation of AGT leads to significant enhancement in the cytotoxic effects of alkylating agents, such as carmustine (BCNU), dacarbazine, temozolomide, and streptozotocin, in human tumor cell lines and tumor xenografts (2–4). BG treatment prior to BCNU results in greater tumor growth inhibition in human brain and colon tumor xenografts in nude mice than BCNU alone (5–7). In clinical trials of BG, AGT can be completely inactivated in tumors in vivo at tolerable doses of AGT, and Phase I trials of the combination of BG and BCNU have been completed recently (8–11). BG is rapidly metabolized in vivo to 8-oxoBG, which is also a potent AGT inactivator, in rats (12), nonhuman primates (13), and humans (8).

A series of BG derivatives have been tested for their ability to inactivate AGT in HT29 cells and HT29 cell-free extracts (14–16). Compounds with an electron-withdrawing group at the 8-position of guanine, including 8-azaBG and 8-BrBG, were slightly more potent inactivators of AGT inHT29 cell-free extracts compared with BG (16). 8-oxoBG and 8-tfmBG were equivalent or slightly less potent than BG in extracts prepared from HT29 cells (16). The deoxyribonucleoside analogue of BG, B2dG, was 10-fold less potent in HT29 cell-free extract in vitro (14) but demonstrated higher antitumor activity than BG when combined with BCNU in human tumor xenograft studies (17) and a 10-fold greater water solubility than BG. The greater potency of B2dG observed in mice is thought to be attributable to its conversion to the more potent AGT inactivators, AGT and 8-oxoBG, providing enhanced systemic availability of active AGT-inactivating components for prolonged time periods (17–19).

To search for BG analogues with more advantageous

\textsuperscript{1}The abbreviations used are: BG, O\textsuperscript{6}-benzylguanine; 8-azaBG, 8-aza-O\textsuperscript{6}-benzylguanine; 8-BrBG, O\textsuperscript{6}-benzyl-8-bromoguanine; 8-oxoBG, O\textsuperscript{6}-benzyl-8-oxoguanine; 8-tfmBG, O\textsuperscript{6}-benzyl-8-trifluoromethylguanine; B2dG, O\textsuperscript{6}-benzyl-2′-deoxyguanosine; HPLC, high-performance liquid chromatography; BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; AGT, O\textsuperscript{6}-alkylguanine-DNA alkyltransferase; CSF, cerebrospinal fluid; AUC, area under the concentration-time curve; I.S., internal standard; UDPGA, uridine diphosphate glucoronic acid.

\textsuperscript{2}Present address: Food and Drug Administration, CDER Division of Oncology Drug Products, HFD-150, 5600 Fishers Lane, Rockville, MD 20857.

\textsuperscript{3}To whom requests for reprints should be addressed, at Section of Hematology-Oncology, University of Chicago, 5841 South Maryland Avenue, Box MC2115, Chicago, IL 60637. Phone: (773) 702-4441; Fax: (773) 702-0963; E-mail: edolan@medicine.bsd.uchicago.edu.

\textsuperscript{4}The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
plasma pharmacokinetic profiles or greater penetration into the CSF for use against brain tumors, we investigated the plasma pharmacokinetic behavior and CSF penetration of BG, 8-azaBG, 8-BrBG, 8-oxoBG, 8-tfmBG, and B2dG (see Fig. 1) in a nonhuman primate model that has been predictive of the plasma and central nervous system pharmacology of a variety of drugs in humans.

MATERIALS AND METHODS

Chemicals. BG, 8-azaBG, 8-BrBG, 8-oxoBG, 8-tfmBG, B2dG (shown in Fig. 1), $O^6$-(p-hydroxymethylbenzyl)guanine (p-CH$_2$OH-BG), $O^6$-(p-fluorobenzyl)guanine (p-F-BG), and $O^6$-(p-chlorobenzyl)guanine (p-Cl-BG) were synthesized as described previously (1, 14–16). UDPGA [glucuronyl-$^{14}$C] was obtained from ICN Pharmaceuticals, Inc. (Irvine, CA). Non-radioactive UDPGA was purchased from Sigma Chemical Co. (St. Louis, MO).

Animals and Protocol. Adult male Rhesus monkeys weighing 7.8–12.5 kg were fed Purina Monkey Chow twice daily and were group housed in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). Blood samples were drawn through a catheter placed in either the femoral or the saphenous vein contralateral to the site of drug infusion. CSF samples were drawn from a s.c. Ommaya reservoir attached to an indwelling Pudenz catheter, with its tip located in the fourth ventricle (20). This study was approved by the National Cancer Institute’s Animal Care and Use Committee.

A single 10 mg/kg (200 mg/m$^2$) dose of BG, 8-azaBG, 8-BrBG, 8-tfmBG, 8-oxoBG, and B2dG was administered i.v. over 15–20 min to two animals. Blood samples were collected before the infusion, at the end of the infusion, and at 5, 15, and 30 min and 1, 2, 3, 4, 6, 8, 10, 24, and 48 h after the end of the infusion. Plasma was separated immediately by centrifugation at 1500 rpm. CSF was collected before and at 1, 2, 4, 6, 8, 10, 24, and 48 h after completion of the drug infusion. Plasma and CSF were frozen at −70°C until analysis.

Quantification of BG Analouges. Total plasma and CSF concentration of BG analogues were measured by HPLC using diode array or fluorescence detection. Aliquots of 500 µl of plasma were spiked with I.S., $O^6$-(p-hydroxymethylbenzyl)guanine for 8-tfmBG and B2dG, $O^6$-(p-fluorobenzyl)guanine for BG, $O^6$-(p-chlorobenzyl)guanine for 8-oxoBG and 8-azaBG, and BG for 8-BrBG analysis. Protein was precipitated by the addition of 1 ml of cold methanol, and the samples were centrifuged at 1320 $\times$ g for 20 min. The supernatant was evaporated to dryness under nitrogen gas and reconstituted in the mobile phase. CSF samples were spiked with the same I.S. and injected directly onto the HPLC. CSF injection volume varied between 230 and 400 µl depending on sample availability.

BG and 8-oxoBG were eluted isocratically with 28% methanol in 10 mM potassium phosphate (pH 7.5), using a Waters Novapak 4-µm phenyl column (3.9 × 150 mm; Waters Corp., Milford, MA) at a flow rate of 1.5 ml/min. Retention times were 20, 23, and 30 min for 8-oxoBG, BG, and $O^6$-(p-fluorobenzyl)guanine (I.S.). B2dG was separated using an acetonitrile gradient and 50 mM sodium phosphate buffer (pH 4.0), starting with 2% of acetonitrile for 6 min and increasing linearly to 30% acetonitrile over 54 min, on a Supelco C18-DB reverse phase column (Supelco, Bellefonte, PA). The retention times for $O^6$-(p-hydroxymethylbenzyl)guanine (I.S.), BG, 8-oxoBG, and B2dG were 39, 54, 55, and 57 min. All other compounds were separated using a methanol gradient and 50 mM ammonium formate buffer (pH 4.5) on a Beckman C18 reverse phase column (4.6 × 250 mm; Beckman Instruments, Inc. Fullerton, CA) at a flow rate 1 ml/min. The conditions used to elute 8-tfmBG, 8-azaBG, and 8-BrBG consisted of a linear gradient.
Pharmacokinetics of 8-oxoBG and 8-azaBG

After incubation at 37°C for 1 h, reactions were stopped by the addition of collecting samples every minute for 25–60% methanol over 45 min. The retention times for 8-tfmBG and Oβ-(p-hydroxymethylbenzyl)guanine (I.S.) were 43 and 23 min, respectively. The retention times for 8-azaBG and Oβ-(p-chlorobenzyl)guanine (I.S.) were 36 and 42 min, respectively. The retention times for BG (I.S.) and 8-BG were 26 and 32 min, respectively. The condition used to analyze 8-oxoBG consisted of a linear gradient of 10–60% methanol over 50 min, with 8-oxoBG and Oβ-(p-chlorobenzyl)guanine (I.S.) eluting at 43 and 48 min, respectively.

Table 1 One-compartment model-fitted and derived pharmacokinetic parameters for 8-oxoBG and 8-azaBG

<table>
<thead>
<tr>
<th>Parameter</th>
<th>8-oxoBG</th>
<th>8-azaBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vc (l/kg)</td>
<td>0.79</td>
<td>0.70</td>
</tr>
<tr>
<td>k1 (h−1)</td>
<td>0.084</td>
<td>0.070</td>
</tr>
<tr>
<td>CL (l/h/kg)</td>
<td>0.067</td>
<td>0.067</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>8.2</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Table 2 Two-compartment model-fitted and derived pharmacokinetic parameters for 8-tfmBG and 8-BrBG

<table>
<thead>
<tr>
<th>Parameter</th>
<th>8-tfmBG</th>
<th>8-BrBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vc (l/kg)</td>
<td>0.096</td>
<td>0.098</td>
</tr>
<tr>
<td>k1 (h−1)</td>
<td>0.070</td>
<td>0.070</td>
</tr>
<tr>
<td>CL (l/h/kg)</td>
<td>0.067</td>
<td>0.067</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>8.2</td>
<td>5.5</td>
</tr>
</tbody>
</table>

RESULTS

Fig. 1 illustrates the chemical structure of BG and analogues evaluated in this study. The effective dose required to inactivate 50% of AGT activity in HT29 cell-free extracts for 8-azaBG, 8-BrBG, BG, 8-oxoBG, 8-tfmBG, and B2dG are 0.07, 0.08, 0.2, 0.3, 0.4, and 2 μM, respectively (19, 21).

The model-fitted and derived pharmacokinetic parameters for each drug and its metabolites are listed in Tables 1–4. The models described in Fig. 2 adequately described the time course of drug and metabolite disposition for all of the BG analogues (Figs. 3–6). The 8-substituted BG analogues (8-oxoBG, 8-azaBG, 8-tfmBG, and 8-BrBG) had similar plasma clearances, which ranged from 0.04 to 0.06 l/h/kg. However, the half-lives varied from <2 h to >24 h, and the volume of distribution of 8-BrBG was at least 10-fold larger than the volumes of distribution of the other 8-substituted BG analogues.

BG and B2dG are both converted to active metabolites, and both drugs were rapidly cleared from plasma in nonhuman primates. BG is converted to 8-oxoBG, and the pharmacokinetic model fit to the BG and 8-oxoBG plasma concentrations (Fig. 2C) predicted that 50% of the parent drug is converted to its 8-oxo-metabolite, based on the ratio of the elimination rate constants

$$\frac{k_{\text{elu}}}{k_{\text{elu}} + k_{\text{elz}}}$$

The elimination rate constant for 8-oxoBG (k_elz) is approximately one-tenth of the elimination rate constant for BG (k_elz + k_elu), which accounts for the 3.5-fold greater plasma drug exposure (AUC) to 8-oxoBG compared with BG after administration of BG. The mean plasma AUC of BG in the 2 animals was 173 μg·h, and the mean AUC of the 8-oxo-metabolite was 636 μg·h.
B2dG is converted to BG and 8-oxoBG. The elimination rate constant for conversion of B2dG to 8-oxoBG ($k_{celm2}$) was substantially smaller than the elimination rate constant for conversion of B2dG to BG ($k_{celm1}$), indicating that the primary pathway for the formation of 8-oxoBG was via conversion of B2dG to BG and then conversion of BG to 8-oxoBG. The model predicted that only 20% of B2dG is converted to BG, based on the ratio of the elimination rate constants

$$\frac{k_{celm1}}{k_{celm1} + k_{celm2} + k_{celo}}$$

and drug exposures to BG (mean AUC, 12 $\mu$g$\cdot$h) and 8-oxoBG (mean AUC, 225 $\mu$g$\cdot$h) were lower than those achieved by administering BG. An unidentified metabolite of B2dG eluted ~10 min earlier than parent drug. Incubation of B2dG with liver microsomes and [14C]UDPGA for 1 h resulted in a radioactive product with the same retention time and UV spectrum as the metabolite, suggesting a glucuronic acid conjugate of B2dG. Glucoronicidation of B2dG has been noted in rats (22). The metabolite, suggesting a glucoronic acid conjugate of B2dG.

The pharmacokinetic behavior of 8-substituted BGs and B2dG varied considerably from BG. BG and 8-oxoBG were detected in plasma and CSF after direct i.v. administration and also as a result of metabolism of other compounds. BG and its metabolite 8-oxoBG penetrate into the CSF slightly better than the other compounds, but the overall CSF penetration of these agents is low. Both BG and 8-oxoBG appeared after administration of B2dG, and 8-oxoBG was also detected after administration of BG. We did not detect known active metabolites after administration of any of the other compounds. Assuming the administration of equimolar doses, administration of 8-tfmBG and 8-BrBG results in the greatest total plasma exposure to AGT-inactivating compounds, followed by administration of 8-azaBG; BG, 8-oxoBG, and B2dG. There is only an ~2-fold difference in the plasma exposures to AGT-inactivating compounds among all of the agents except B2dG, which produces a much smaller total exposure of parent drug.

**DISCUSSION**

These studies establish plasma and CSF pharmacokinetic parameters for BG, 8-azaBG, 8-BrBG, 8-oxoBG, 8-tfmBG, and B2dG. The pharmacokinetic behavior of 8-substituted BGs and B2dG varied considerably from BG. BG and 8-oxoBG were detected in plasma and CSF after direct i.v. administration and also as a result of metabolism of other compounds. BG and its metabolite 8-oxoBG penetrate into the CSF slightly better than the other compounds, but the overall CSF penetration of these agents is low. Both BG and 8-oxoBG appeared after administration of B2dG, and 8-oxoBG was also detected after administration of BG. We did not detect known active metabolites after administration of any of the other compounds. Assuming the administration of equimolar doses, administration of 8-tfmBG and 8-BrBG results in the greatest total plasma exposure to AGT-inactivating compounds, followed by administration of 8-azaBG; BG, 8-oxoBG, and B2dG. There is only an ~2-fold difference in the plasma exposures to AGT-inactivating compounds among all of the agents except B2dG, which produces a much smaller total exposure of parent drug.

Human tumor xenograft studies in mice have revealed that B2dG combined with BCNU is superior to BG plus BCNU (19, 21). In rodents, similar to nonhuman primates, B2dG is metabol-
Fig. 2 Pharmacokinetic models fit to the plasma concentrations of the 8-substituted analogues and their metabolites. The differential equations below each model describe the concentration or amount of drug or metabolite in each compartment. For the one-compartment model (A) fit to the 8-azaBG and 8-oxoBG plasma concentrations, $C$ is the concentration of drug at time $t$, $k_0$ is the drug infusion rate, $V_d$ is the volume of distribution, and $k_{el}$ is the first-order elimination rate constant. For the two-compartment model (B) fit to the 8-tfmBG and 8-BrBG plasma concentrations, $C_c$ is the concentration of drug in the central compartment, $X_p$ is the amount of drug in the peripheral compartment, $k_{el}$ is the first-order elimination rate constant, $V_c$ is the volume of the central compartment, and $k_p$ and $k_{pe}$ are the rate constants for exchange of drug between the central and peripheral compartments. For the model fit to BG and its metabolite, 8-oxoBG, $C$ is the concentration of BG, $M$ is the concentration of 8-oxoBG, $k_{elim}$ is the rate constant for the conversion of BG to 8-oxoBG, $k_{el}$ is the first-order elimination rate constant for all other routes of elimination (other than conversion to 8-oxoBG), and $V_d$ is the volume of distribution for BG, and $V_{dm}$ is the volume of distribution for 8-oxoBG. For the model fit to B2dG and its metabolites BG and 8-oxoBG, $C_c$ is the concentration of B2dG in the central compartment, $X_p$ is the amount of B2dG in the peripheral compartment, $M_1$ is the concentration of BG, $M_2$ is the concentration of 8-oxoBG, $k_{elim1}$ is the first-order rate constant for conversion of B2dG to BG, $k_{elim2}$ is the first-order rate constant for conversion of B2dG to 8-oxoBG (not via BG), $k_{cel}$ is the first-order elimination rate constant for all other routes of elimination of B2dG, $k_{elm}$ is the first-order rate constant for conversion of BG to 8-oxoBG, $k_{elor}$ is the first-order elimination rate constant for 8-oxoBG, $V_{dm1}$ is the volume of the BG compartment, and $V_{dm2}$ is the volume of the 8-oxoBG compartment.
olized to BG, 8-oxoBG, and a glucoronic acid derivative of B2dG. It is thought that the metabolic conversion to more effective AGT inactivators (BG and 8-oxoBG), the distribution of these metabolites, and glucoronidation in the intestinal epithelium to a less active metabolite (glucoronic acid derivative of B2dG) is responsible for its greater antitumor activity in mice (18, 22). On the basis of studies in rodents and structure-activity relations (14, 15), the introduction of a glucoronic acid would be expected to result in a dramatic reduction of the effectiveness of this product to deplete AGT activity. Therefore, extensive glucoronidation in the intestinal epithelium would result in protection of this tissue from sensitization to alkylating agents. We present evidence for a glucoronic acid conjugate of B2dG in plasma of nonhuman primates and as a product of the reaction between B2dG and human liver microsomes in the presence of UDPGA. Although the structure of the derivative is not confirmed, evidence from the UV spectrum and retention time suggests glucoronicidation of the sugar rather than the purine similar to that seen in rats (22). This pathway is considered in our model as a route of elimination.

Preliminary studies in our laboratory demonstrate that B2dG is converted to BG and 8-oxoBG in humans as well. Although we demonstrate conversion of BG to 8-oxoBG after administration of BG, our data do not rule out the possibility that B2dG is oxidized, then debrlosylated, to form 8-oxoBG. More likely, the route of metabolic conversion is debrlosylation of B2dG to BG and then oxidation to 8-oxoBG.

The AUC_{CSF}/AUC_{plasma} ratio was greatest for BG and 8-oxoBG, resulting in concentrations of BG plus 8-oxoBG (after administration of BG) or 8-oxoBG (after administration of 8-oxoBG) between 1 and 3 μM in the CSF for up to 12 h after drug administration. The effective dose required to produce 50% inactivation in HT29 colon cancer cells upon incubation for 4 h is 0.05 and 0.15 μM for BG and 8-oxoBG, respectively. Therefore, it is likely that the concentrations measured in the CSF would be adequate for AGT suppression in a disease such as neoplastic meningitis.

Because it takes hours after nitrosourea administration for irreversible DNA cross-linking to occur (23), the prolonged...
inactivation of AGT is probably critical to the success of biochemical modulators like BG in sensitizing tumors to DNA alkylating agents. It is possible that the duration of target tissue concentrations above a certain threshold, rather than total plasma drug exposure, is the most important determinant of AGT inactivation. Previous studies in nonhuman primates suggested that administration of BG results in prolonged inhibition of lymphocyte AGT activity, probably because of the long half-life of 8-oxoBG (13). In a Phase I trial in patients with cancer, similar conversion to 8-oxoBG was observed, with depletion of lymphocyte AGT activity at doses as low as 20 mg/m² (8); however, doses of 100 and 120 mg/m² BG were required for tumor AGT inactivation (9, 10). These studies demonstrated that lymphocytes are not an adequate surrogate for assessment of biochemical modulation by BG because of a lack of correlation in the extent of AGT depletion between lymphocytes and tumor (10, 11). Thus, target tissue concentration rather than plasma concentration may be a better predictor of modulation.

Currently, Phase II clinical trials are under way to determine the efficacy of the combination of BG and BCNU. Preclinical and clinical work demonstrated that BG sensitizes normal cells, such as bone marrow progenitors, to the toxic effects of alkylating agents, resulting in lowering the alkylating agent dose as compared with the dose administered alone (6, 9–11, 24, 25). However, in animal studies even at these lower alkylating agent doses, significant tumor responses were seen, suggesting that there is a therapeutic window in which the combination might be effective without inducing undue toxicity (6, 9).
ongoing clinical trials will be critical to determine whether the strategy of AGT inactivation is useful for enhancing the anticancer activity of alkylating agents. The results of our study do not suggest an important pharmacological advantage for any of the BG analogues over BG with relation to the treatment of tumors in the CSF or brain. Thus, of the AGT-inactivating agents tested preclinically to date, BG remains a logical choice for clinical trials testing the ability of modulating AGT activity to improve the efficacy of anticancer therapy with DNA alkylating agents. B2dG warrants further investigation.

REFERENCES


The table below lists the CSF:plasma ratio for the 8-substituted BG analogues.

<table>
<thead>
<tr>
<th>Drug and animal</th>
<th>Plasma AUC (μMh)</th>
<th>CSF AUC (μMh)</th>
<th>CSF:Plasmaa</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-azaBG</td>
<td>RQ293 735</td>
<td>1.6</td>
<td>0.0021</td>
</tr>
<tr>
<td></td>
<td>D-16 1301</td>
<td>2.0</td>
<td>0.0015</td>
</tr>
<tr>
<td>8-frmBG</td>
<td>R838A 434</td>
<td>11</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>B9078 747</td>
<td>2.9</td>
<td>0.0034</td>
</tr>
<tr>
<td>8-BrBG</td>
<td>R838A 1015</td>
<td>2.8</td>
<td>0.0028</td>
</tr>
<tr>
<td></td>
<td>B9078 979</td>
<td>NDb</td>
<td></td>
</tr>
</tbody>
</table>

a CSF:plasma ratio is the ratio of the AUC in CSF to the AUC in plasma.

b ND, not detectable.


The table above lists the CSF:plasma ratio for the 8-substituted BG analogues.