Supporting Information

Macrocyclic Gq protein inhibitors

FR900359 and/or YM-254890 – fit for translation?

*Jonathan G. Schlegel,[1§] Mariam Tahoun,[1§] Alexander Seidinger,[2] Jan H. Voss,[1] Markus Kuschak,[1] Stefan Kehraus,[3] Marion Schneider,[1] Michaela Matthey,[2] Bernd K. Fleischmann,[4] Gabriele M. König,[3] Daniela Wenzel,[2,4] and Christa E. Müller[1]**

[1]PharmaCenter Bonn, Pharmaceutical Institute, Pharmaceutical & Medicinal Chemistry, University of Bonn, Bonn, Germany
[2]Department of Systems Physiology, Medical Faculty, Ruhr University Bochum, Bochum, Germany
[3]Institute for Pharmaceutical Biology, University of Bonn, Bonn, Germany
[4] Institute of Physiology I, Life & Brain Center, Medical Faculty, University of Bonn, Bonn, Germany

[§]Equal contribution

*Address correspondence to
Prof. Dr. Christa E. Müller
Pharmazeutisches Institut
Pharmazeutische & Medizinische Chemie
An der Immenburg 4
D-53121 Bonn, Germany
Email: christa.mueller@uni-bonn.de
Phone: +49 228 73 2301

Cytochrome P450 enzyme inhibition

Most drugs undergo first-phase biotransformation reactions in the human liver which is catalyzed by enzymes of the cytochrome P450 (CYP450) family. High-affinity interactions between a drug and CYP enzymes may interfere with the metabolism of other drugs or natural products present as food constituents. Experiments investigating potential inhibition of CYP enzymes that are known to be important for drug metabolism showed no critical CYP-inhibitory effects, neither by FR nor YM. Both compounds displayed a similar profile. At a concentration of 1 µM, they exhibited only negligible effects on the investigated CYP enzymes. At a very high concentration of 10 µM, inhibition was still negligible to low (Figure 6), except for CYP3A4, which was inhibited by about 50% (FR: 50%, YM:56%). FR at 10 µM also displayed moderate inhibition of CYP2C8 (30 %) and CYP2C19 (38 %), whereas inhibition by 10 µM of YM was below 25%. These results indicate that both Gq inhibitors are not expected to interfere with hepatic metabolism of other drug molecules.

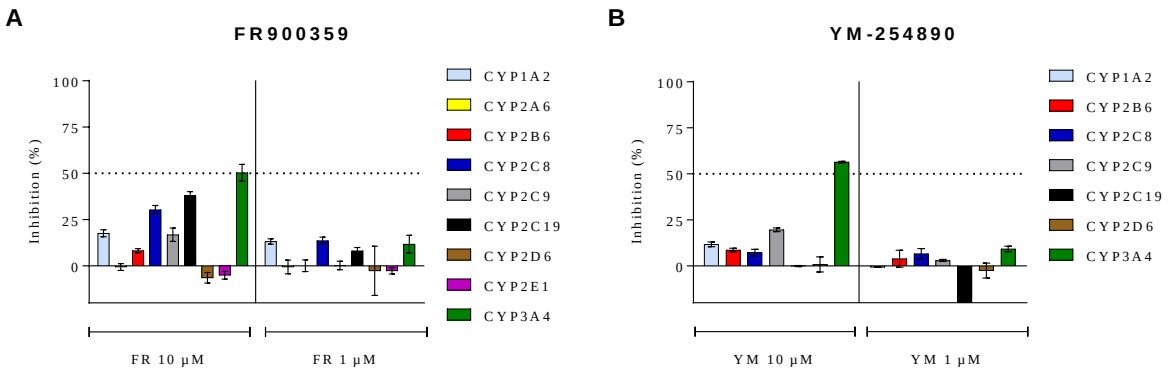

Figure S1. **A**. Percentage inhibition of CYP450 enzymes by FR at a concentration of 10 µM (left) and 1 µM (right). **B**. Percentage inhibition of CYP450 enzymes by YM at a concentration of 10 µM (left) and 1 µM (right).

CYP inhibition

The interactions of FR and YM with different recombinant human cytochrome P450 (CYP) enzymes were investigated by Pharmacelsus GmbH (Saarbrücken, Germany) using a fluorescence-based assay system. FR and YM were screened at 1 and 10 µM for inhibition of CYP1A2, CAP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Additionally, FR was screened at 1 and 10 µM for inhibition of CYP2E and CYP2A6 enzymes. Assay was performed in a NADPH regenerating system containing 100 mM phosphate buffer and coumarine derivatives as substrates. Data represent means ± SEM (FR n=3; YM n=2).