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Biotransformation reactions of a boron-modified triphenylethylene as an oral selective estrogen receptor down-regulator

Changde Zhang, Jiawang Liu, Shilong Zheng, Shanchun Guo, Qiu Zhong, Qiang Zhang and **Guangdi Wang**
Xavier University of Louisiana, USA

Statement of the Problem: Fulvestrant is the only selective estrogen receptor down-regulator (SERD) FDA has approved to fight hormonally driven metastatic breast cancer in postmenopausal women whose disease has progressed after receiving prior hormonal therapies such as tamoxifen or aromatase inhibitors (AIs). However, it is administered through intramuscular injection in clinical practice due to its poor bioavailability and poor pharmacokinetic profile. It is necessary to develop orally bioavailable SERDs to treat patients with hormonally driven metastatic breast cancer. We developed a boron-modified triphenylethylene (GLL398) as an orally bioavailable SERD. GLL398 was discovered effective in fighting inhibiting tamoxifen-resistant cancer cells *in vitro* and with a remarkable pharmacokinetic profile *in vivo*. The purpose of this study is to understand the biotransformation of GLL398. In this study, GLL398 was incubated *in vitro* with liver microsomes to study its phase I oxidative biotransformation reaction and phase II glucuronidation reaction; it was incubated *in vitro* with liver cytosols to study its sulfation biotransformation reaction. GW7604 was the major product by the oxidative transformation. Both direct glucuronidation and sulfation biotransformation of GLL398 were blocked in the incubation. These results suggest that the excellent pharmacokinetic profile of GLL 398 is attributable to reduced first past metabolism by blocking glucuronidation and sulfation at the C-4 position as compared to GW7604.

Biography

Changde Zhang is an organic chemist with expertise in the evaluation of the ADME and pharmacokinetics of drugs using advanced mass spectrometers in preclinical animal drug tests. He is also interested in using lipidomics and metabolomics in promoting biomarker discovery and drug discovery. He has the passion and dedication to contribute to the research and drug development in preventing and treating cancer diseases, brain injury, and aging-related neurodegenerative diseases. He is currently a core staff scientist working at the RCMI cancer research center and chemistry department at Xavier University. He received his PhD in organic chemistry from Louisiana State University.

czhang1@xula.edu

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