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The Metabolite Profiling of Fulvestrant-3 Boronic Acid under Biological Oxidation

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Abstract : Fulvestrant was approved by FDA to treat breast cancer as a selective estrogen receptor downregulator (SERD) with intramuscular injection administration. ZB716, a fulvestarnt-3 boronic acid, is an SERD with comparable anticancer effect to fulvestrant, but could produce good pharmacokinetic properties under oral administration with mice or rat models. To understand why ZB716 produced much better oral bioavailability, it was proposed that the boronic acid blocked the phase II direct biotransformation with the hydroxyl group on the 3 position of the aromatic ring on fulvestrant. In this study, ZB716 or fulvestrant was incubated with human liver microsome and oxidation cofactor NADPH in vitro. Their metabolites after oxidation were profiled with the Q-Exactive, a high-resolution mass spectrometer. The result showed that ZB716 blocked the forming of hydroxyl groups on its benzene ring except for the oxidation of C-B bond forming fulvestrant in its metabolites, and the concentration of fulvestrant with one more hydroxyl group found in the metabolites from incubation with fulvestrant was about 34 fold high as that formed from incubation with ZB716. Compared to fulvestrant, ZB716 is expected to be much difficult to be further bio-transformed into more hydrophilic compounds, to be difficult excreted out of blood system, and to have longer residence time in blood, which can lead to higher oral bioavailability. This study provided evidence to explain the high bioavailability of ZB716 after oral administration from the perspective of its difficulty of oxidation, a phase I biotransformation, on positions on its aromatic ring.

Keywords : biotransformation, fulvestrant, metabolite profiling, ZB716
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