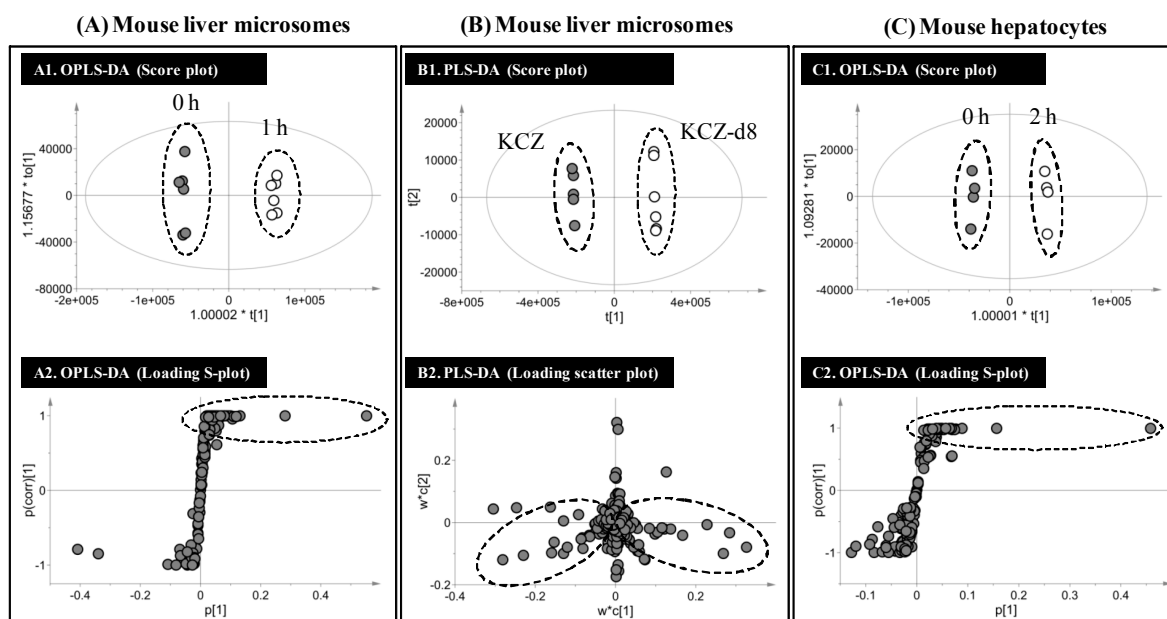


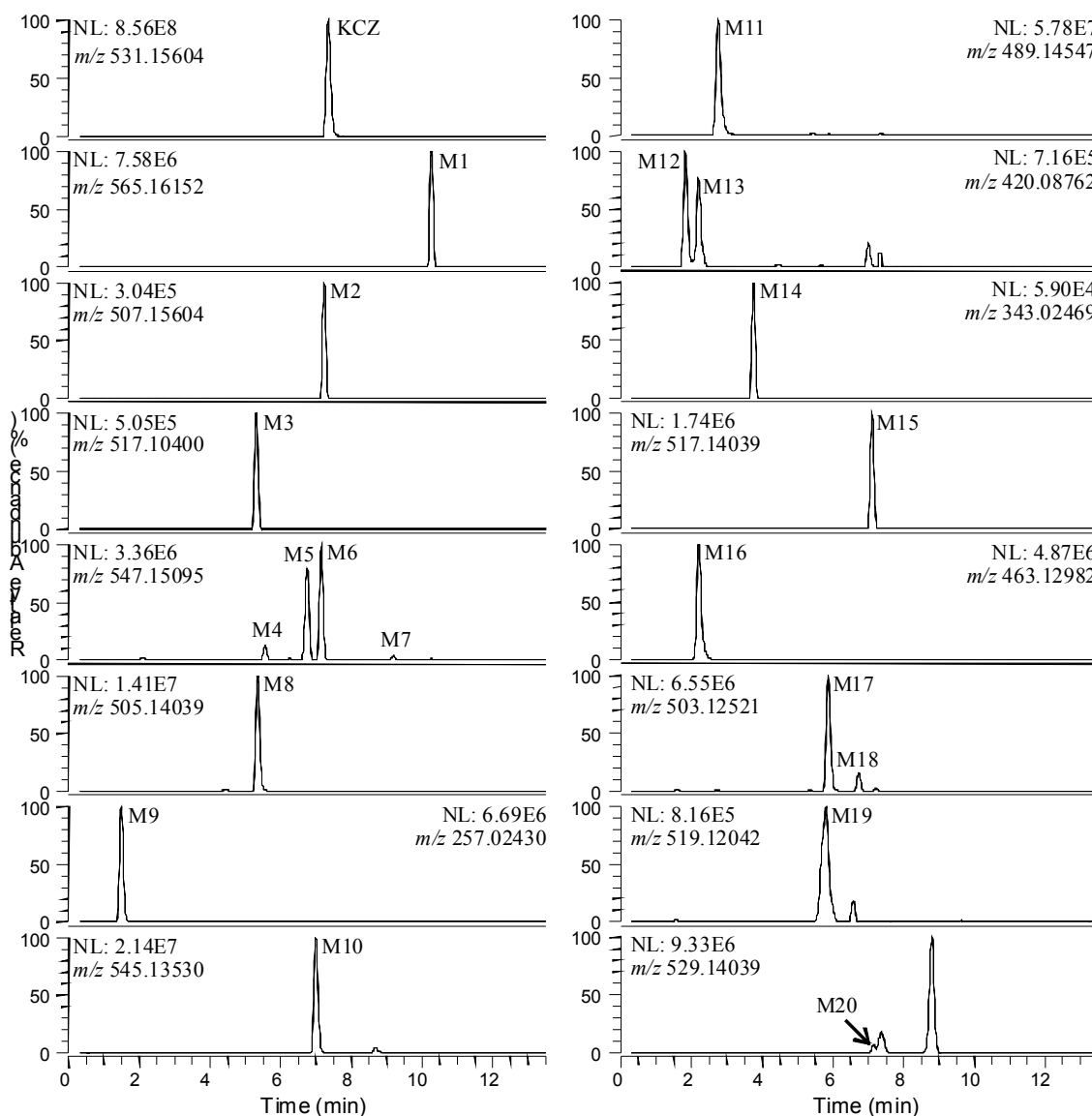
Supplementary material

## Revisiting the metabolism and bioactivation of ketoconazole in mouse and human using liquid chromatography–mass spectroscopy-based metabolomics

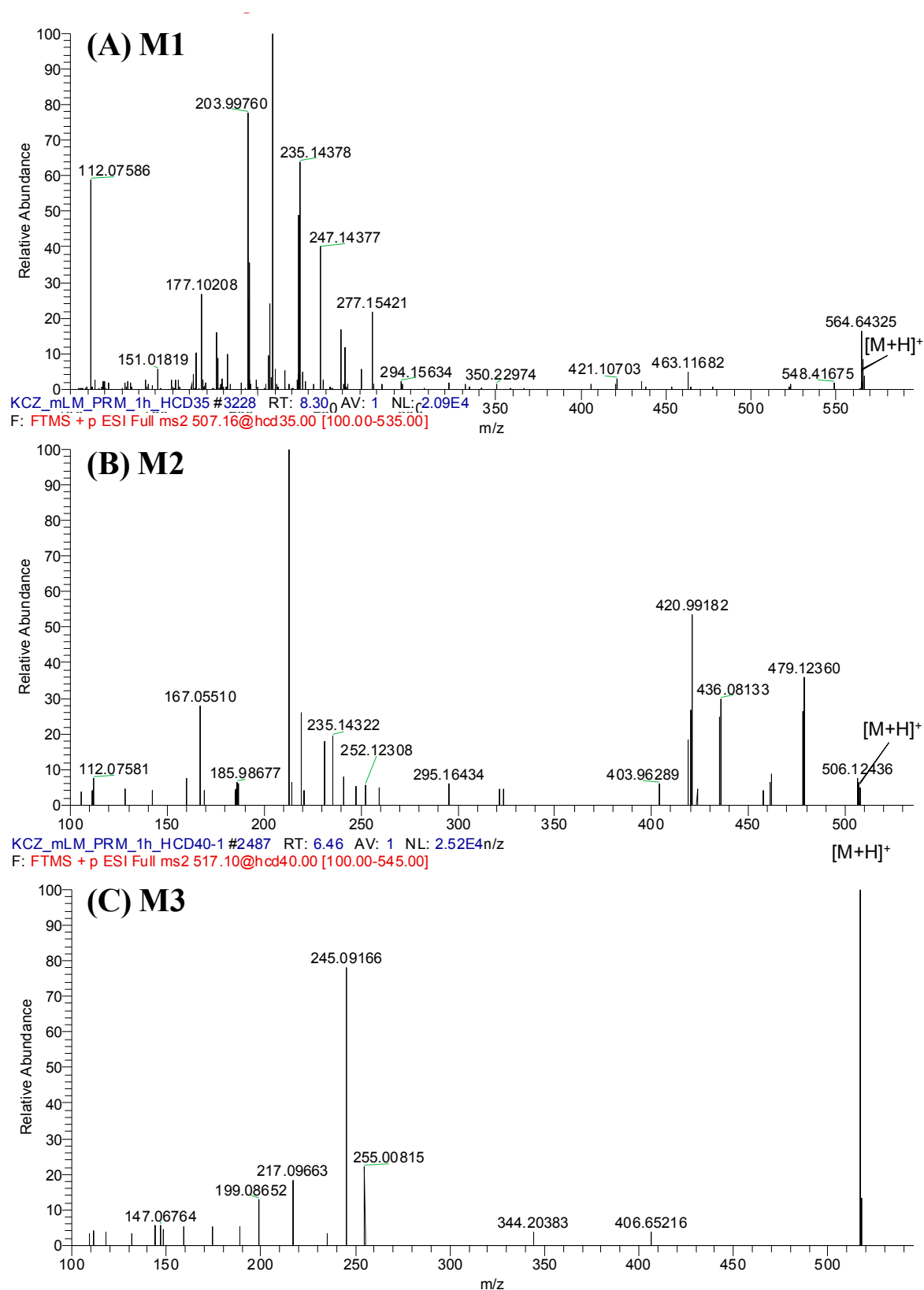
Ju-Hyun Kim, Won-Gu Choi, Sangkyu Lee and Hye Suk Lee



**Figure S 1.** Multivariate data analysis for the profiling of ketoconazole metabolites. (A) Score plot and loading S-plot generated by orthogonal partial least squares-discriminant analysis (OPLS-DA) from mouse liver microsomal incubates of ketoconazole. (B) Score plot and loading scatter plot generated by partial least squares-discriminant analysis (PLS-DA) from mouse liver microsomal incubates of ketoconazole and ketoconazole-d8. (C) Score plot and loading S-plot generated by (OPLS-DA) from mouse hepatocytes incubates of ketoconazole.



**Figure S 2.** Extracted ion chromatograms of ketoconazole and its possible metabolites after incubation of 20  $\mu$ M ketoconazole with mouse liver microsomes for 1 h at 37°C. The chromatograms were extracted with mass accuracy of 3 ppm.



**Figure S 3.** Product ion spectra of (A) M1, (B) M2, and (C) M3.

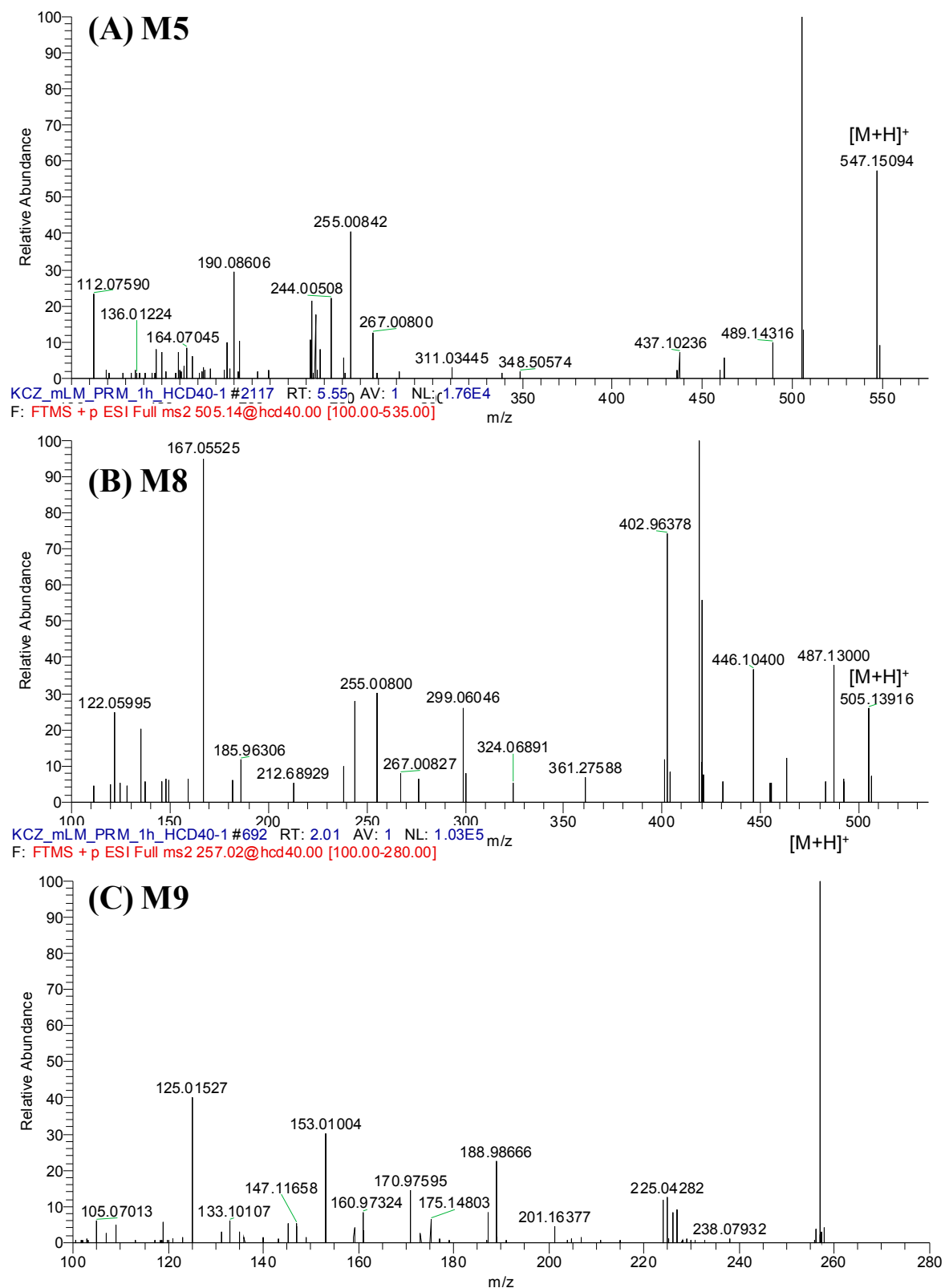
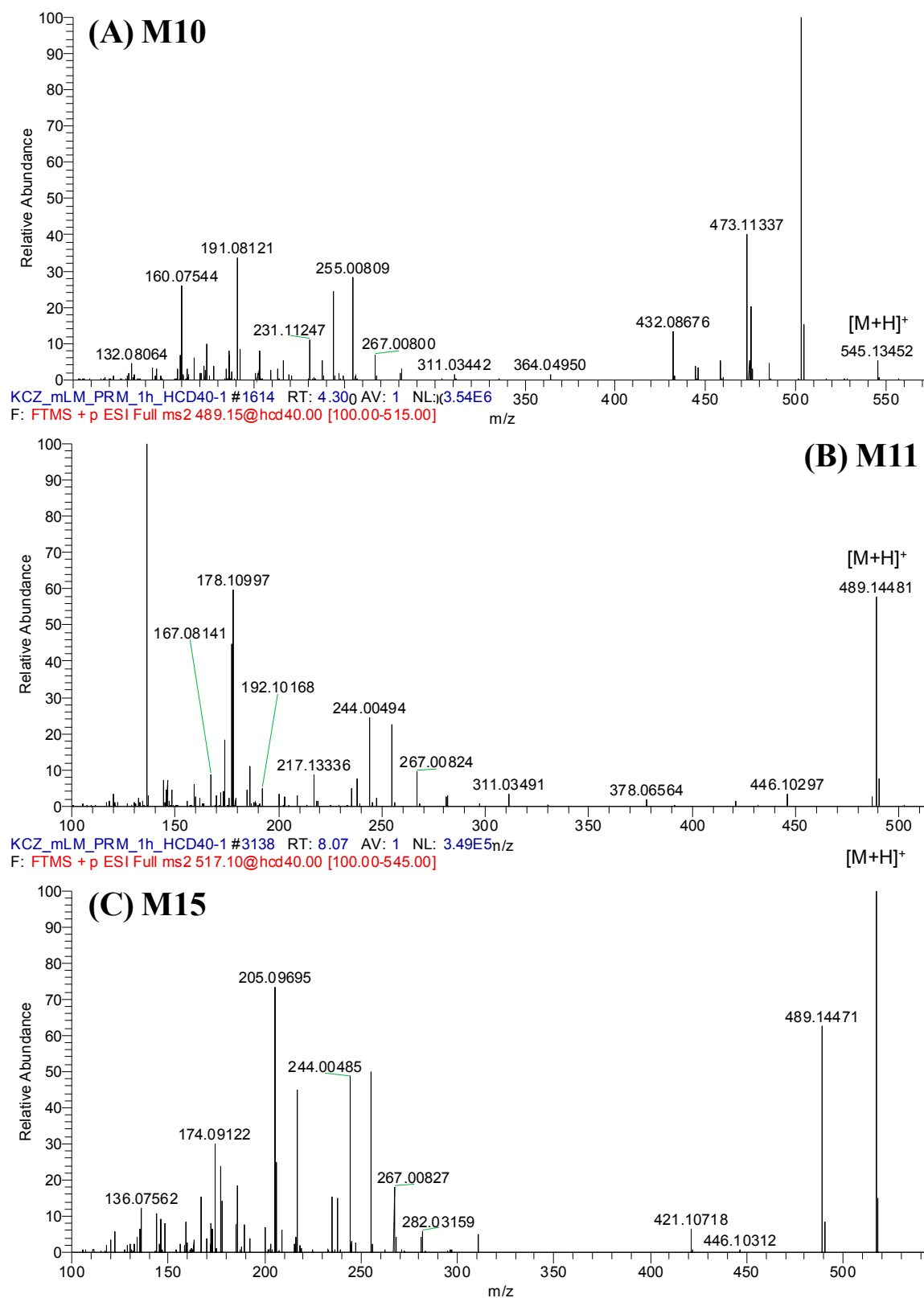


Figure S 4. Product ion spectra of (A) M5, (B) M8, and (C) M9.



**Figure S 5.** Product ion spectra of (A) M10, (B) M11, and (C) M15.

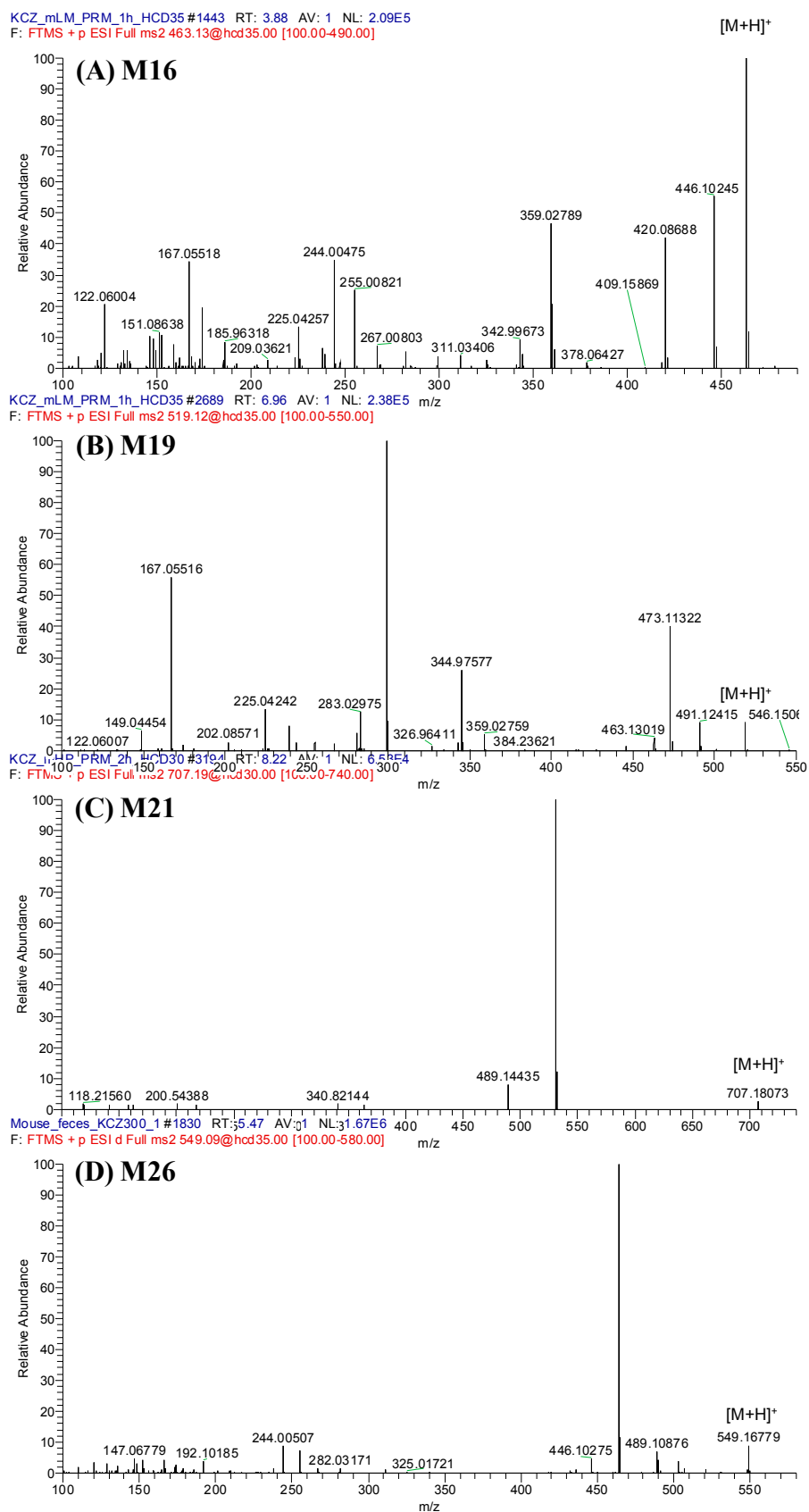
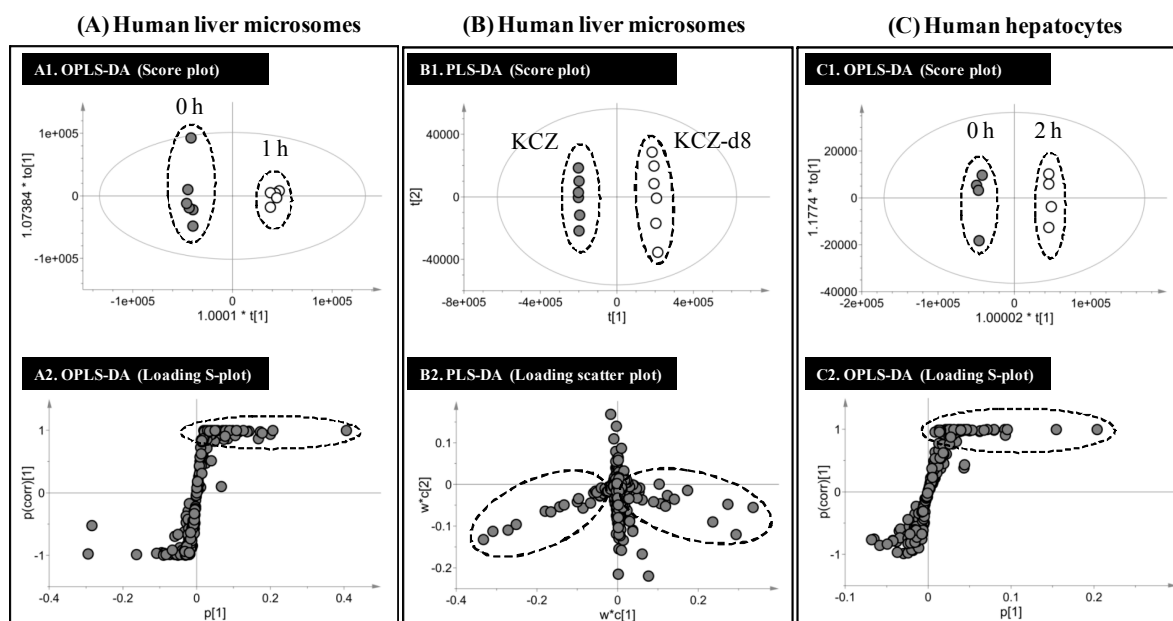
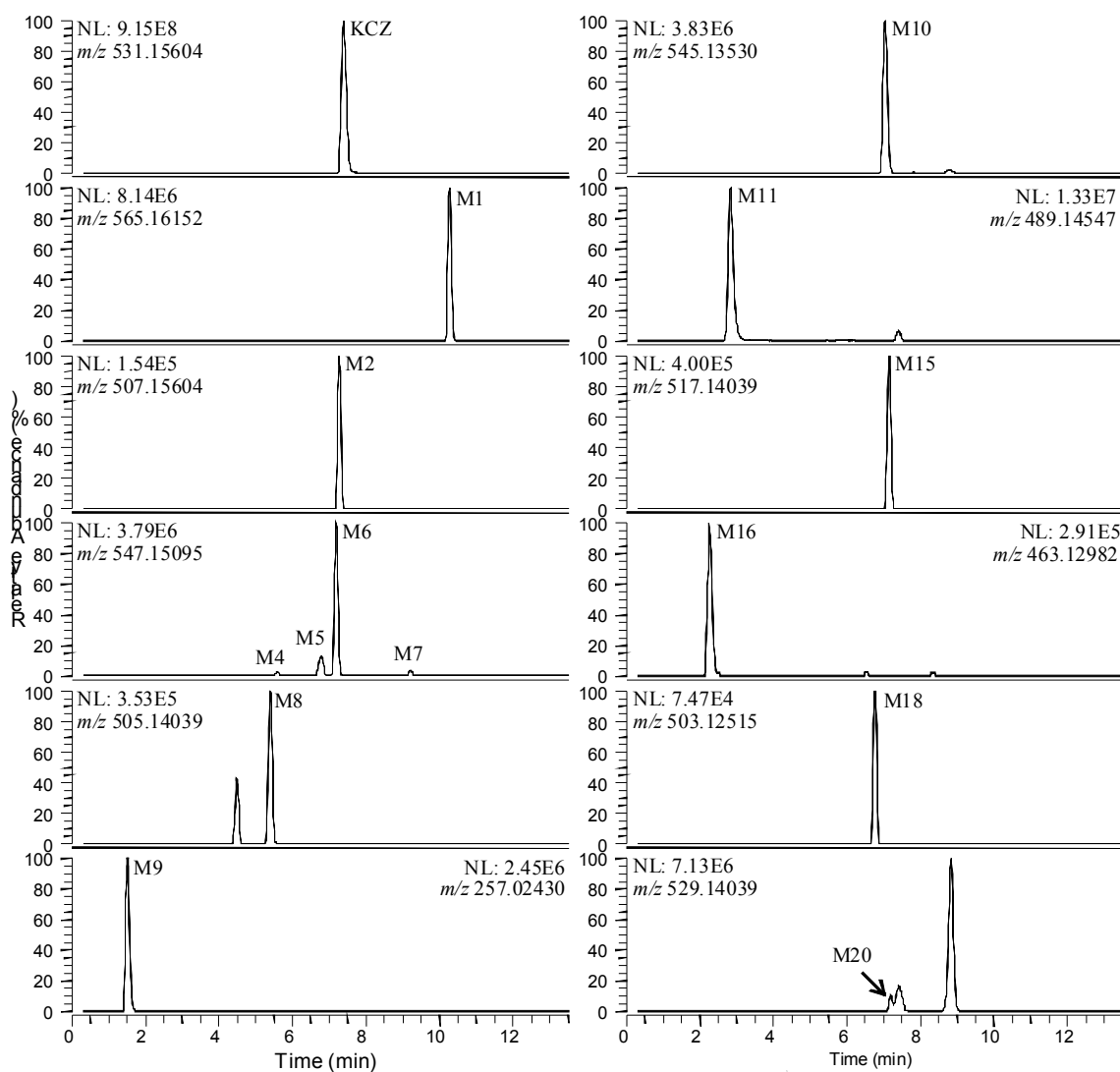


Figure S 6. Product ion spectra of (A) M16, (B) M19, (C) M21, and (D) M26.

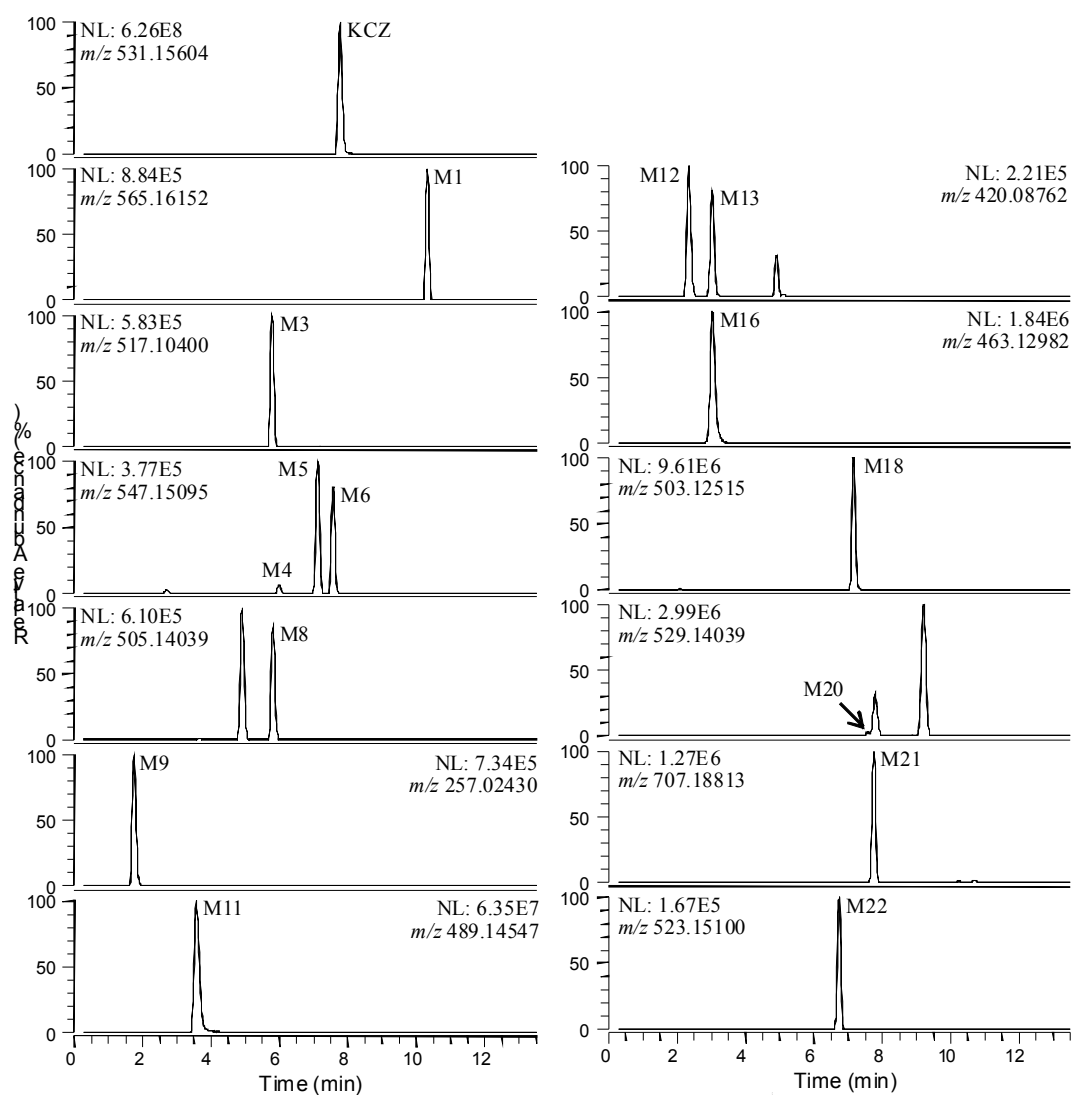


**Figure S 7.** Multivariate data analysis for the profiling of ketoconazole metabolites. (A) Score plot and loading S-plot generated by orthogonal partial least squares-discriminant analysis (OPLS-DA) from human liver microsomal incubates of ketoconazole. (B) Score plot and loading scatter plot generated by partial least squares-discriminant analysis (PLS-DA) from human liver microsomal incubates of ketoconazole and ketoconazole-d8. (C) Score plot and loading S-plot generated by (OPLS-DA) from human hepatocytes incubates of ketoconazole.

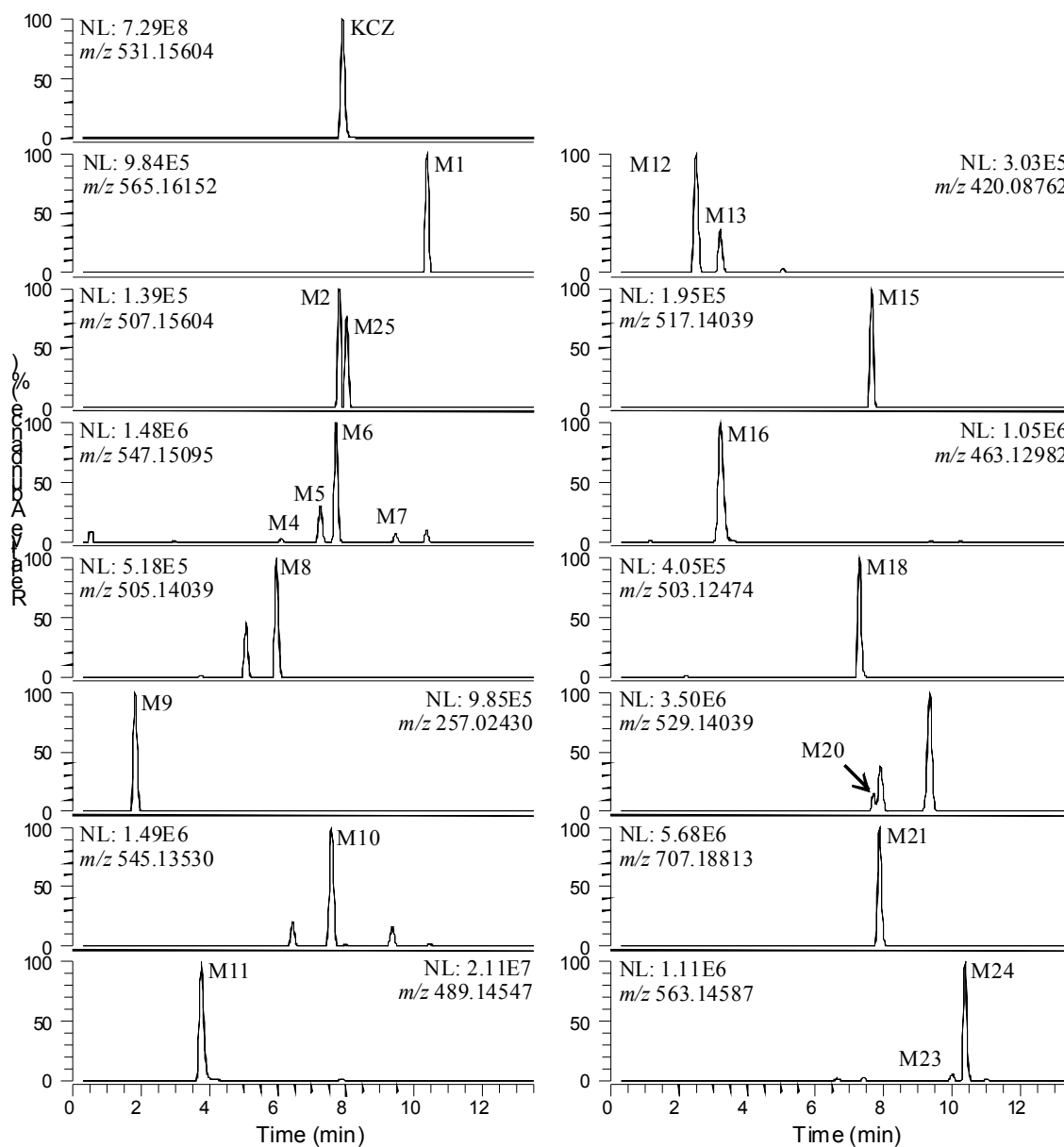


**Figure S 8.** Extracted ion chromatograms of ketoconazole and its possible metabolites after incubation of 20  $\mu$ M ketoconazole with human liver microsomes for 1 h at 37°C. The chromatograms were extracted with mass accuracy of 3 ppm.





**Figure S 9.** Extracted ion chromatograms of ketoconazole and its possible metabolites after incubation of 20  $\mu$ M ketoconazole with mouse hepatocytes for 2 h at 37°C in a humidified CO<sub>2</sub> static incubator. The chromatograms were extracted with mass accuracy of 3 ppm.



**Figure S 10.** Extracted ion chromatograms of ketoconazole and its possible metabolites after incubation of 20  $\mu$ M ketoconazole with human hepatocytes for 2 h at 37°C in a humidified CO<sub>2</sub> static incubator. The chromatograms were extracted with mass accuracy of 3 ppm.