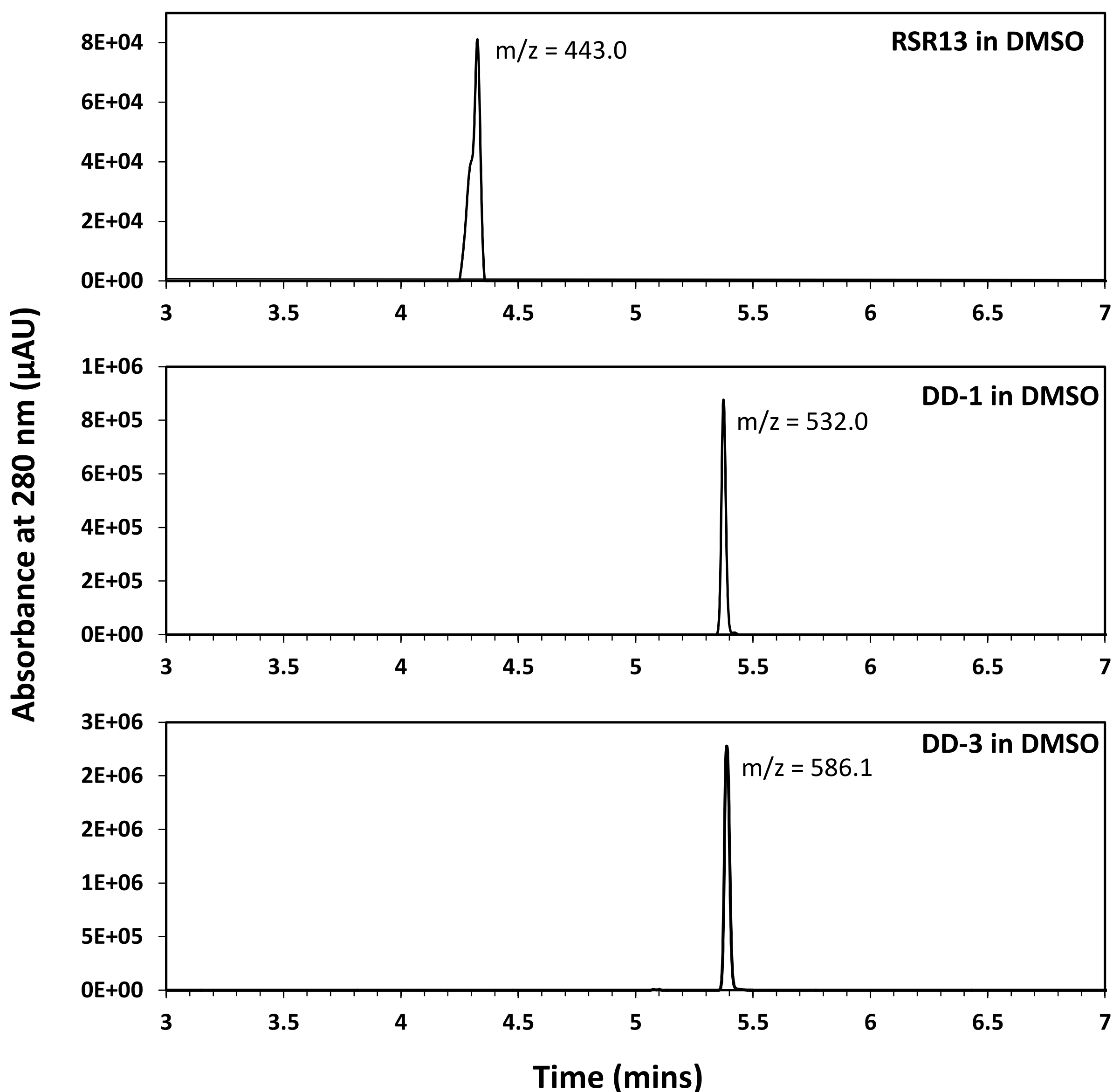

Figure S1: UPLC-MS chromatograms of RSR13 (first panel), DD-1 (middle panel), and DD-3 (bottom panel) when incubated in DMSO for 24 hrs at 37°C. The parent m/z peak for each compound is provided next to each peak. RSR13 has a $[M+HXA]^+$ peak at m/z 443.0, DD-1 has a $[M+HXA]^+$ peak at m/z 532.0, and DD-3 has an $[M+HXA]^+$ peak at m/z 586.1. HXA (hexylammonium) is the ion pairing agent. Similar chromatogram was observed when the reaction was performed in room temperature. No degradation product, including RSR13 was formed.

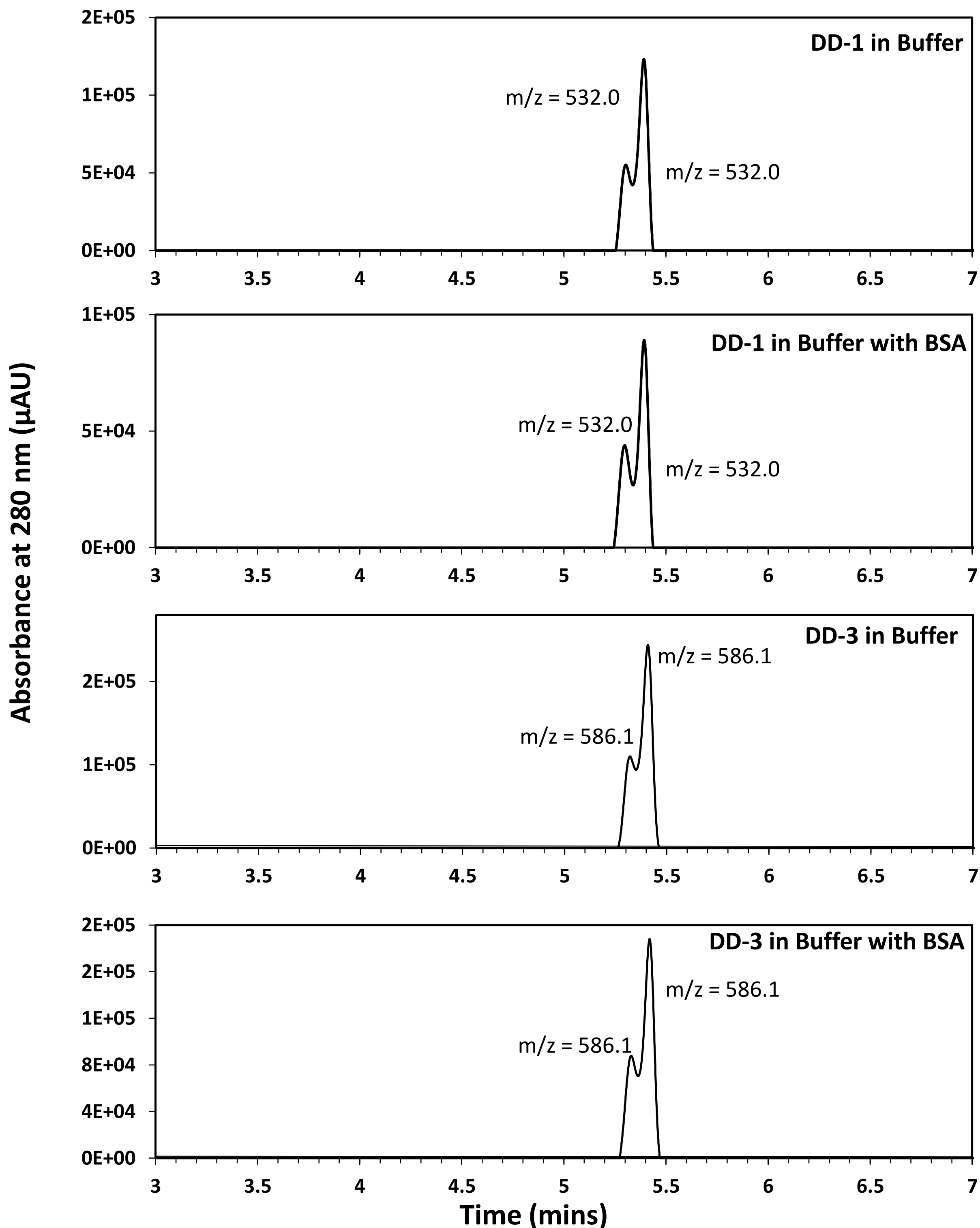

Figure S2: UPLC-MS chromatograms of DD-1 when incubated with only buffer (top panel), buffer containing BSA (second panel) for 16 hrs at 37°C. UPLC-MS chromatograms of DD-3 when incubated with only buffer (third panel), buffer containing BSA (last panel) for 16 hrs at 37°C. Note that the DD-1 and DD-3 showed two peaks with identical masses ($[M+HXA]^+$ peak at m/z 532.0 and 586.1, respectively), which is probably due to partial ion pairing with other buffer components, causing separate retention times. No degradation product, including RSR13 was formed.

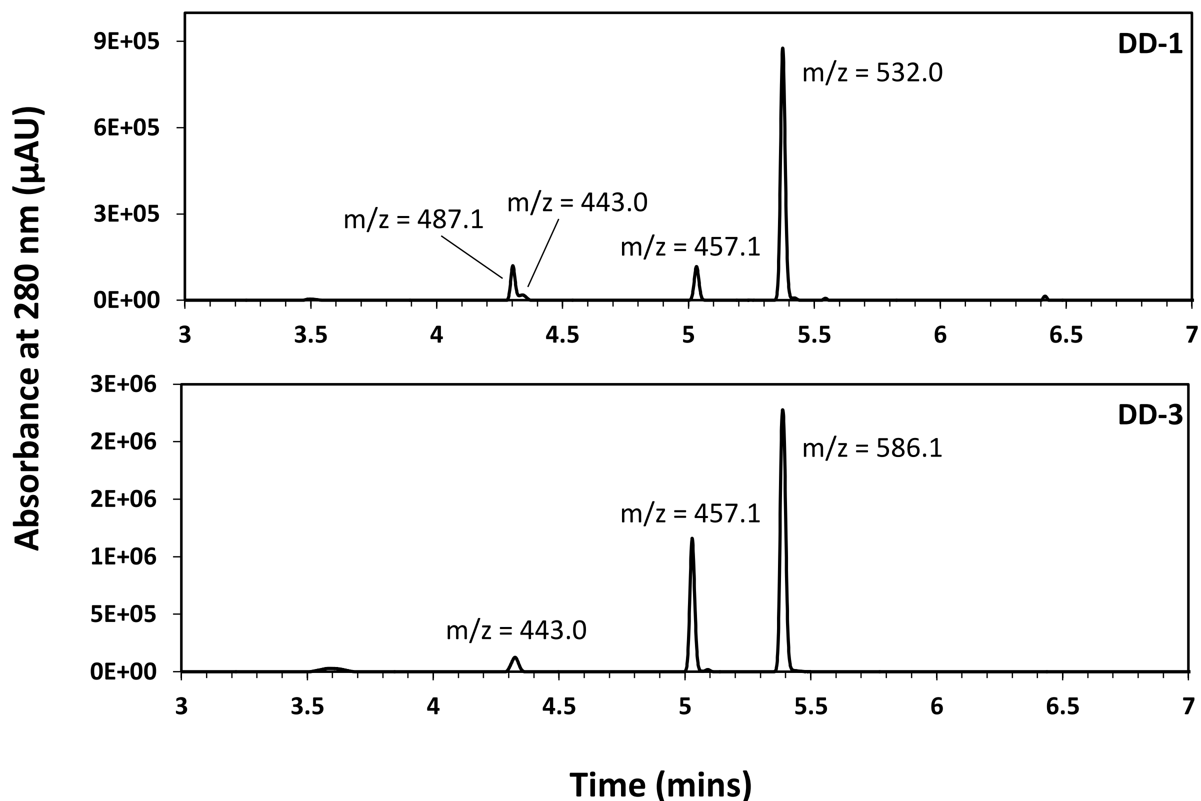

Figure S3: UPLC-MS chromatograms of DD-1 (first panel) and DD-3 (second panel) when incubated with buffer containing L-cysteine for 24 hours at 37 °C. DD-1 produced three peaks, including $[M+HXA]^+$ at m/z 532 corresponding to DD-1, $[M+Cys]^+$ at m/z 457.1 corresponding to RSR13, $[M+HXA]^+$ at m/z 443.0 corresponding to RSR13, and $[M+HXA]^+$ at m/z 487.1 corresponding to RSR13-CH_2CH_2OH. DD-3 produced three peaks, including $[M+HXA]^+$ at m/z 586.1 corresponding to DD-3, $[M+Cys]^+$ at m/z 457.1 and $[M+HXA]^+$ at m/z 443.0, all corresponding to RSR13. HXA is hexylammonium

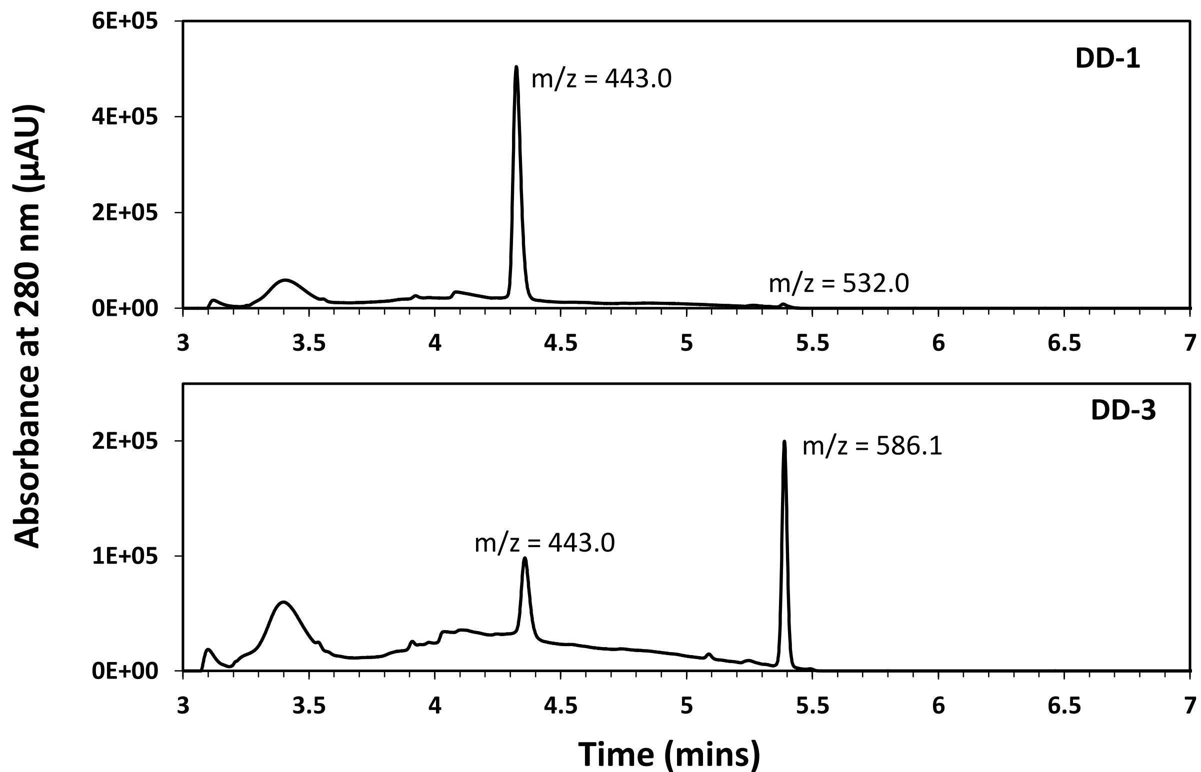

Figure S4: UPLC-MS chromatograms of DD-1 (first panel) and DD-3 (second panel) when incubated with serum containing esterases for 24 hrs at 37°C. DD-1 produced almost 100% RSR13 with $[M+HXA]^+$ peak at m/z 443. DD-3 produced two peaks, including (m/z 586.1) corresponding to DD-3 and (m/z 457.1 and 443.0) corresponding to RSR13. The data is noisy because it's likely other components of serum (the supernatant was used without precipitating the proteins) absorb at 280 nm.

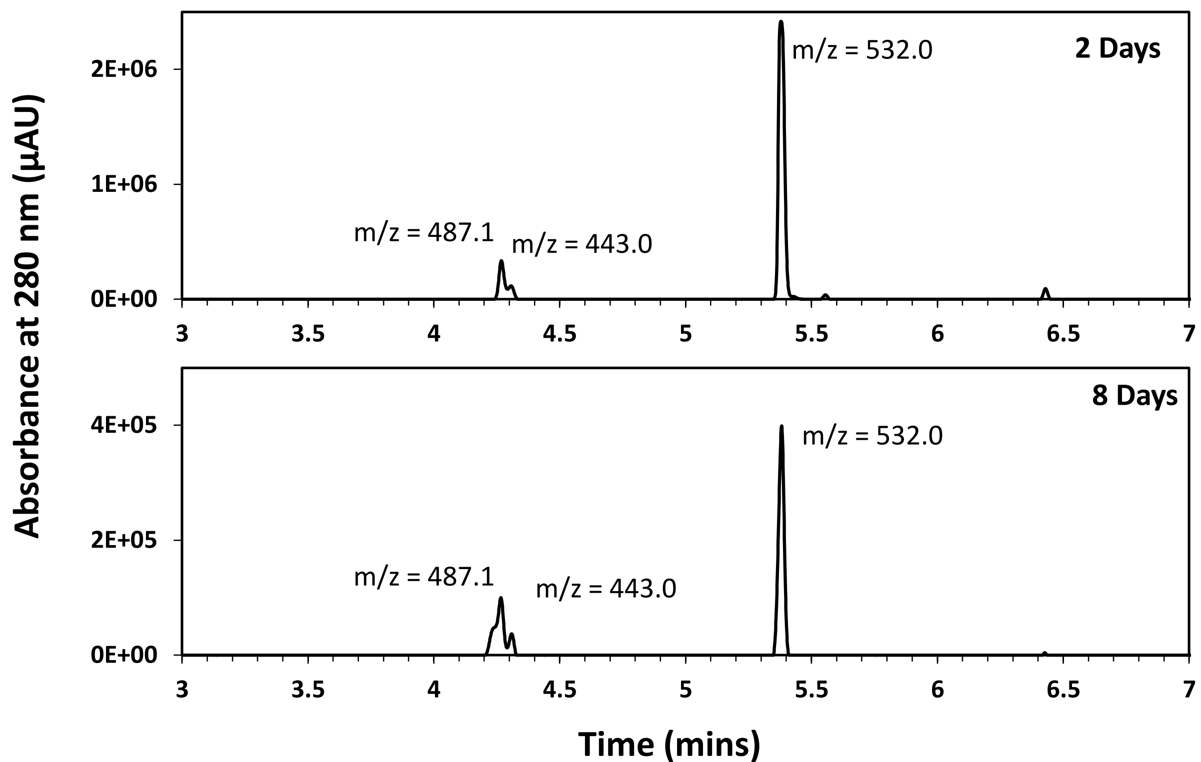

Figure S5: UPLC-MS chromatograms of DD-1 when incubated with solution containing sodium dithionite (mimicking the condition used to co-crystallize deoxyHb and DD-1) at room temperature for 2 days (first panel) or 8 days (second panel). In both figures, we observe presence of DD-1 with $[M+HXA]^+$ peak at m/z 532, RSR13-CH_2CH_2OH with $[M+HXA]^+$ peak at m/z 487.1, and RSR13 with $[M+HXA]^+$ peak at m/z 443.0

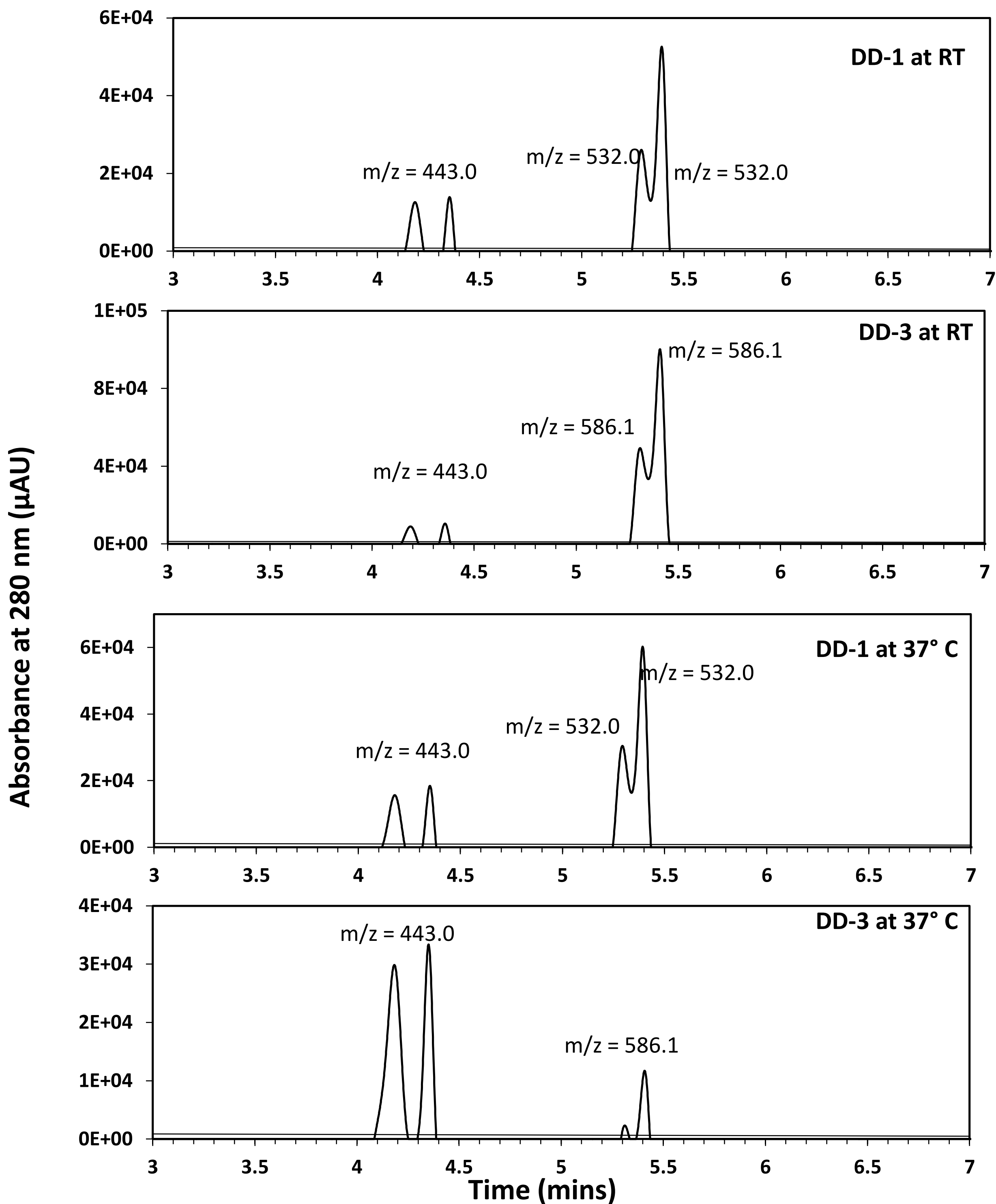

Figure S6: UPLC-MS chromatograms of DD-1 (top panel), DD-3 (second panel) when incubated with whole blood for 16 hrs at room temperature. UPLC-MS chromatograms of DD-1 (third panel), DD-3 (last panel) when incubated with whole blood for 16 hrs at 37° C. In all experiments, there is formation of RSR13 with $[M+HXA]^+$ peak at m/z 443.0. Formation of two peaks with identical masses is possibly due to partial ion pairing with other buffer components, causing separate retention times.

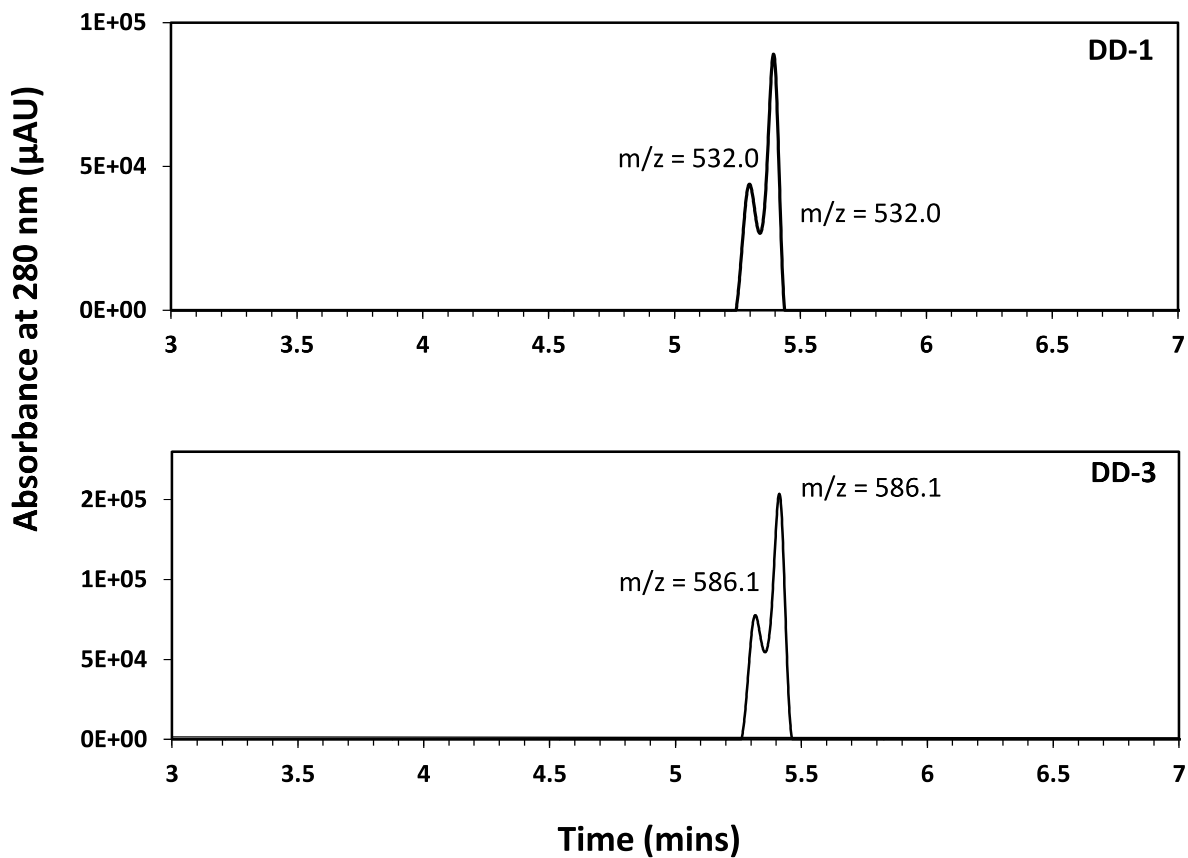

Figure S7: UPLC-MS chromatograms of DD-1 (top pane) and DD-3 (bottom panel) when incubated with Hb for 16 hrs in room temperature. No degradation product observed.