SUPPORTING INFORMATION

Metabolism of Benzalkonium Chlorides by Human Hepatic Cytochromes P450

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Table of Contents:

Figure S1. Representative MS/MS fragmentation spectra (25 eV collision energy) of (A) C_{10}-BAC, (B) C_{12}-BAC, (C) C_{14}-BAC, and (D) C_{16}-BAC are shown to demonstrate consistent loss of and detection of the unmodified benzyl cation fragment (theoretical: 91.0548 *m/z*). Parent BAC structures and retention times (t_R) are provided.

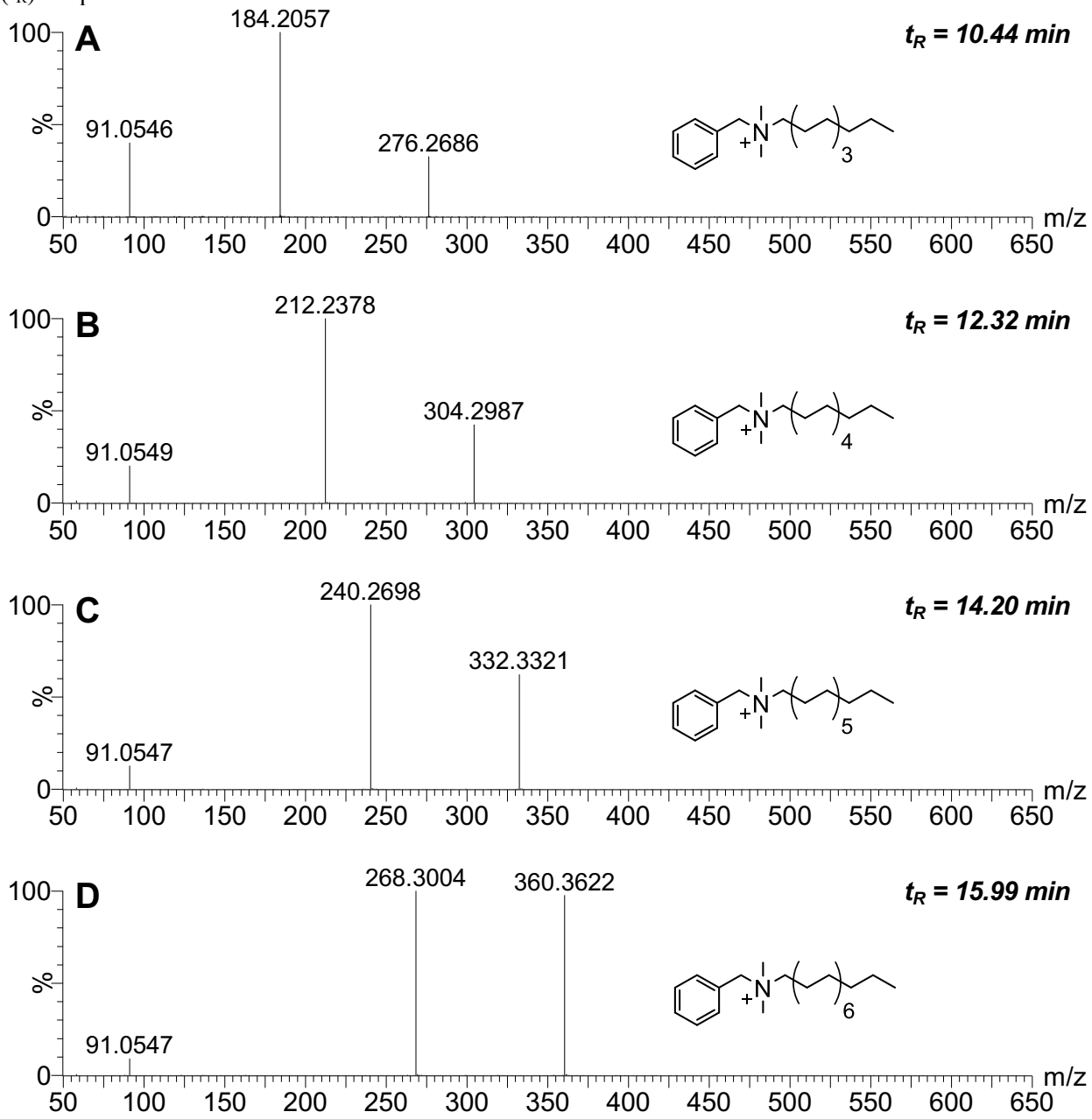

Figure S2. Representative MS/MS fragmentation spectra (25 eV collision energy) of the major +1O BAC metabolites (A) C_{10}-BAC+1O, (B) C_{12}-BAC+1O, (C) C_{14}-BAC+1O, and (D) C_{16}-BAC+1O produced by NADPH-dependent metabolism in HLM are shown to demonstrate consistent loss of and detection of the unmodified benzyl cation fragment (theoretical: 91.0548 *m/z*). Analyte retention times (t_R) and proposed metabolite structures are provided.

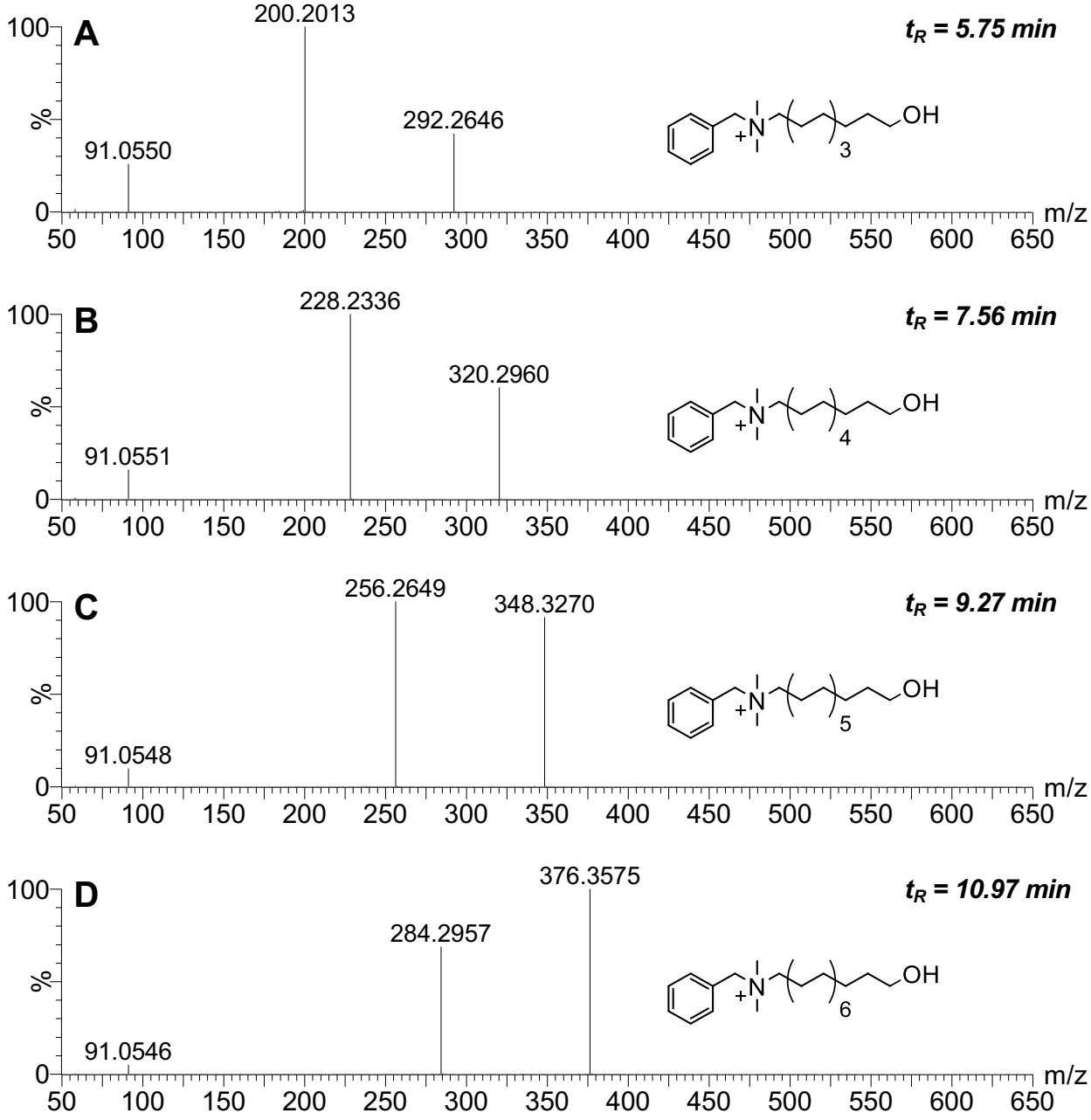

Figure S3. Representative MS/MS fragmentation spectra (25 eV collision energy) of the minor +1O BAC metabolites (A) C_{10}-BAC+1O, (B) C_{12}-BAC+1O, (C) C_{14}-BAC+1O, and (D) C_{16}-BAC+1O produced by NADPH-dependent metabolism in HLM are shown to demonstrate consistent loss of and detection of the unmodified benzyl cation fragment (theoretical: 91.0548 *m/z*). Analyte retention times (t_R) and proposed metabolite structures are provided.

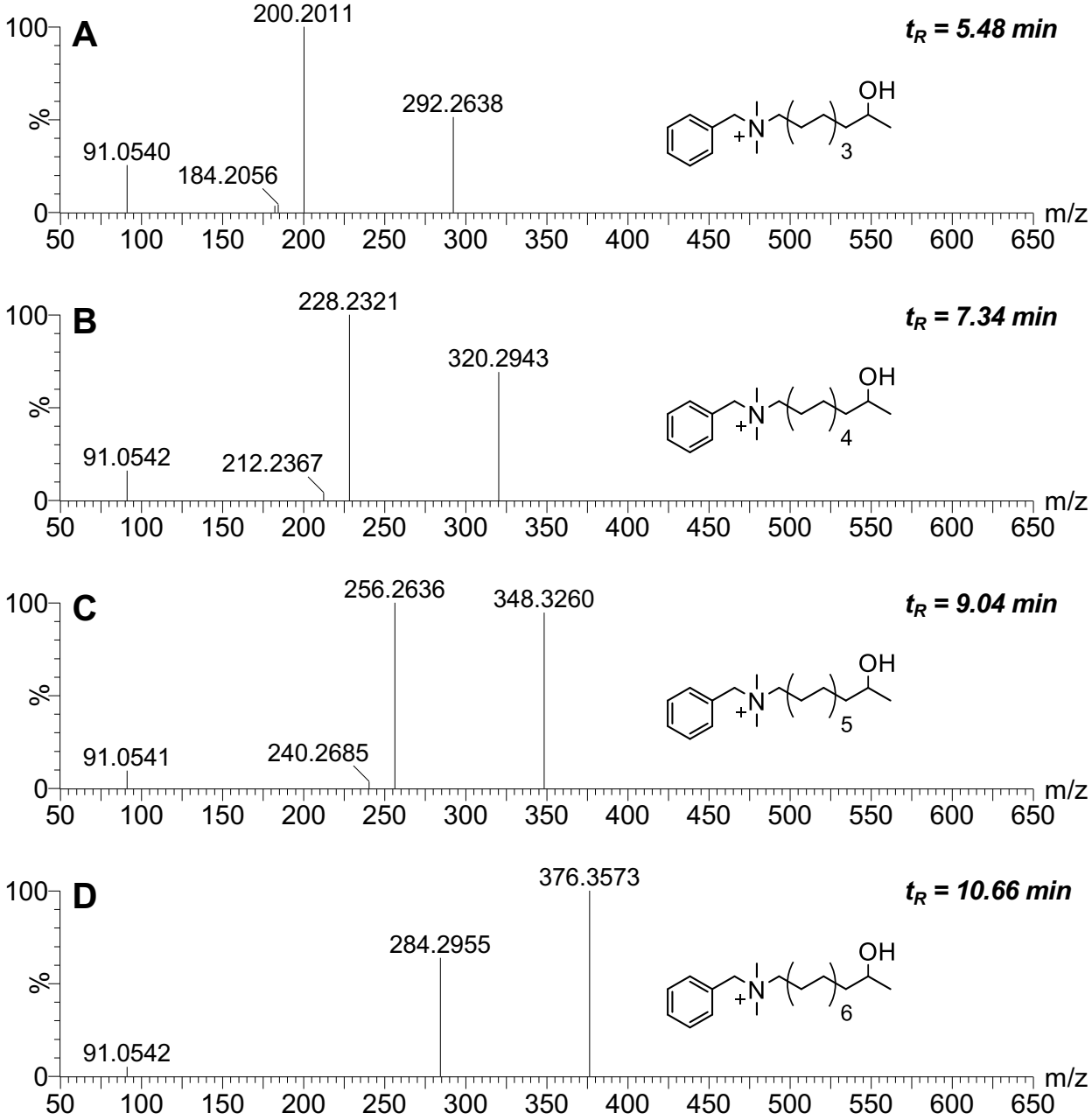

Figure S4. Representative MS/MS fragmentation spectra (25 eV collision energy) of the major +2O BAC metabolites (A) C_{10}-BAC+2O, (B) C_{12}-BAC+2O, (C) C_{14}-BAC+2O, and (D) C_{16}-BAC+2O produced by NADPH-dependent metabolism in HLM are shown to demonstrate consistent loss of and detection of the unmodified benzyl cation fragment (theoretical: 91.0548 *m/z*). Analyte retention times (t_R) and proposed metabolite structures are provided.

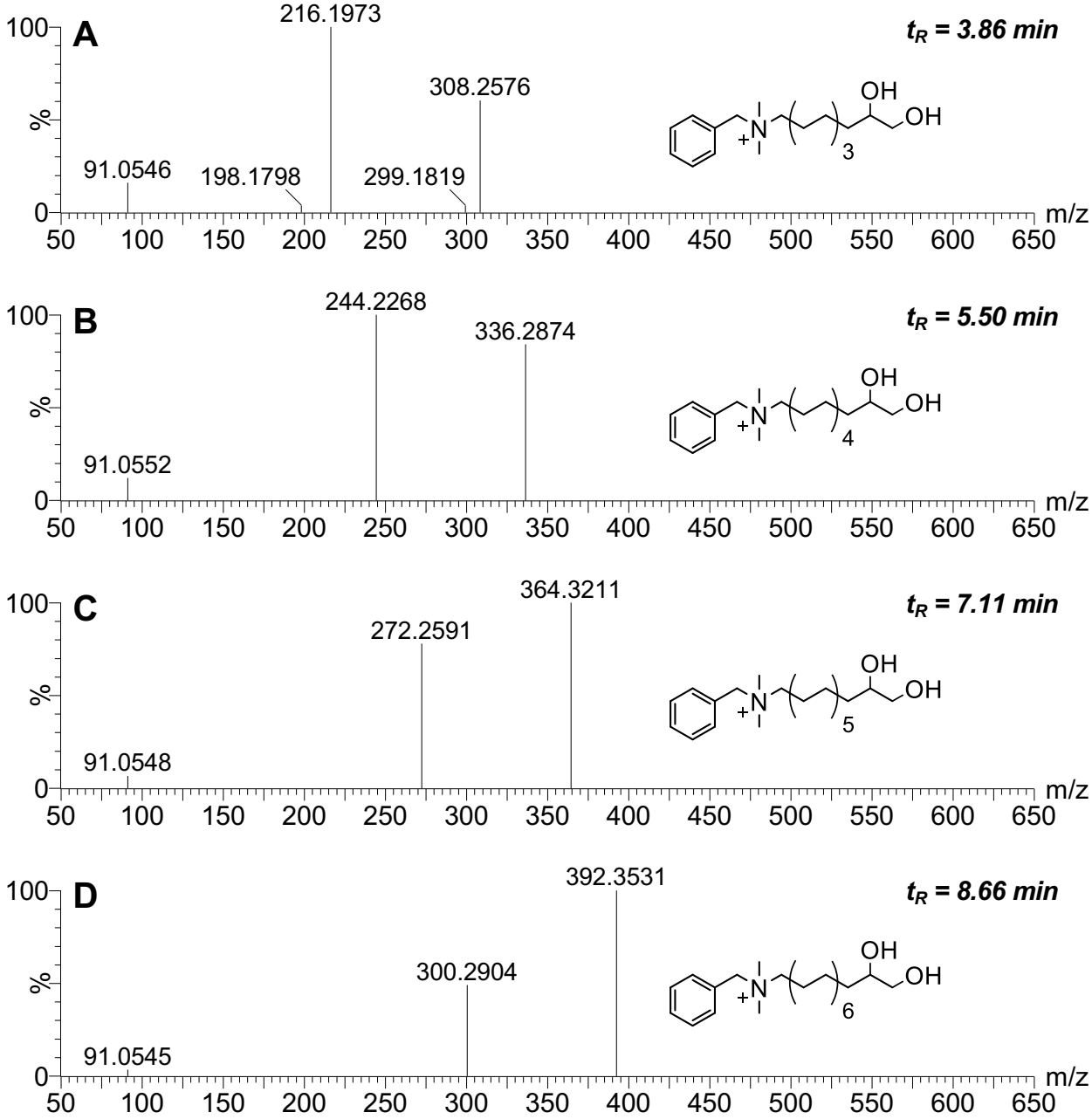

Figure S5. Representative MS/MS fragmentation spectra (25 eV collision energy) of the major +1O, -2H BAC metabolites (A) C_{10}-BAC+1O-2H, (B) C_{12}-BAC+1O-2H, (C) C_{14}-BAC+1O-2H, and (D) C_{16}-BAC+1O-2H produced by NADPH-dependent metabolism in HLM are shown to demonstrate consistent loss of and detection of the unmodified benzyl cation fragment (theoretical: 91.0548 *m/z*). Analyte retention times (t_R) and proposed metabolite structures are provided.

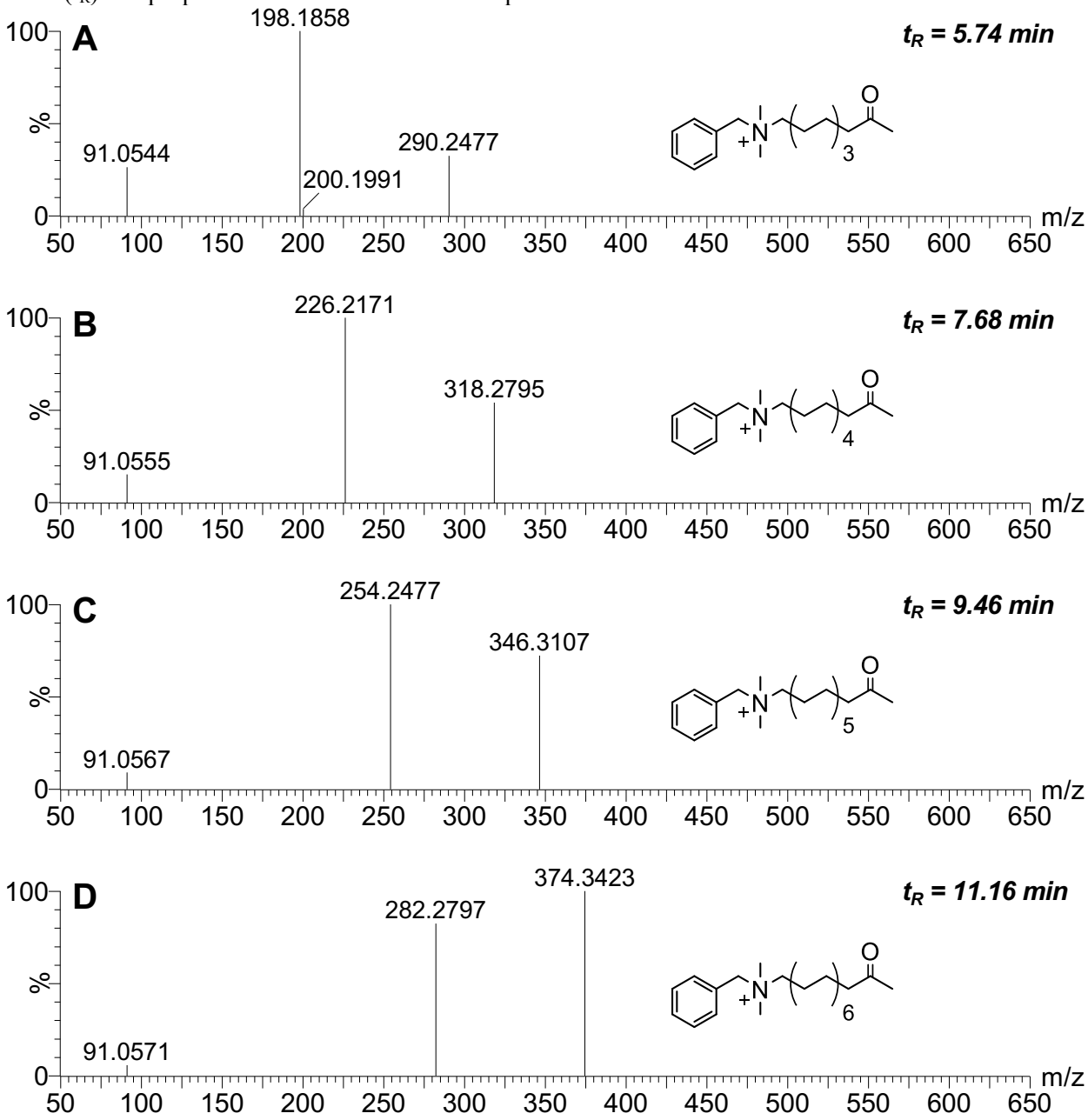

Figure S6. Representative MS/MS fragmentation spectra (25 eV collision energy) of the major +2O, -2H BAC metabolites (A) C_{10}-BAC+2O-2H, (B) C_{12}-BAC+2O-2H, (C) C_{14}-BAC+2O-2H, and (D) C_{16}-BAC+2O-2H produced by NADPH-dependent metabolism in HLM are shown to demonstrate consistent loss of and detection of the unmodified benzyl cation fragment (theoretical: 91.0548 *m/z*). Analyte retention times (t_R) and proposed metabolite structures are provided.

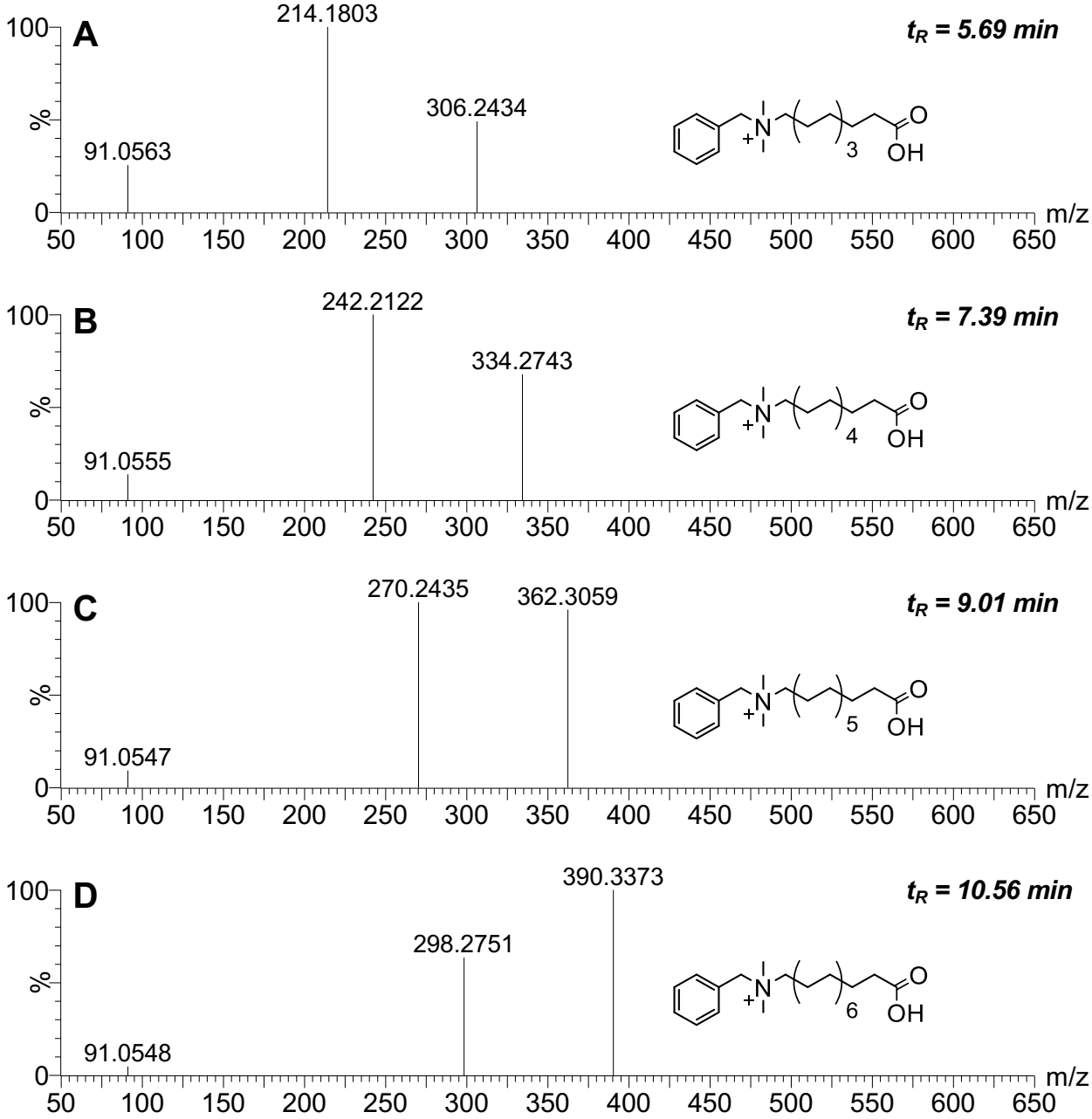

Figure S7. Representative MS/MS fragmentation spectra (25 eV collision energy) of authentic C_{10}-BAC metabolite standards synthesized in-house (A) (ω-1)-hydroxy C_{10}-BAC, (B) ω-hydroxy C_{10}-BAC, (C) (ω, ω-1)-dihydroxy C_{10}-BAC, (D) (ω-1)-ketone C_{10}-BAC, and (E) ω-carboxylic acid C_{10}-BAC are shown to demonstrate consistent loss of and detection of the unmodified benzyl cation fragment (theoretical: 91.0548 *m/z*). Analyte retention times (t_R) and the chemical structures (confirmed by ^{1}H-NMR) are provided.

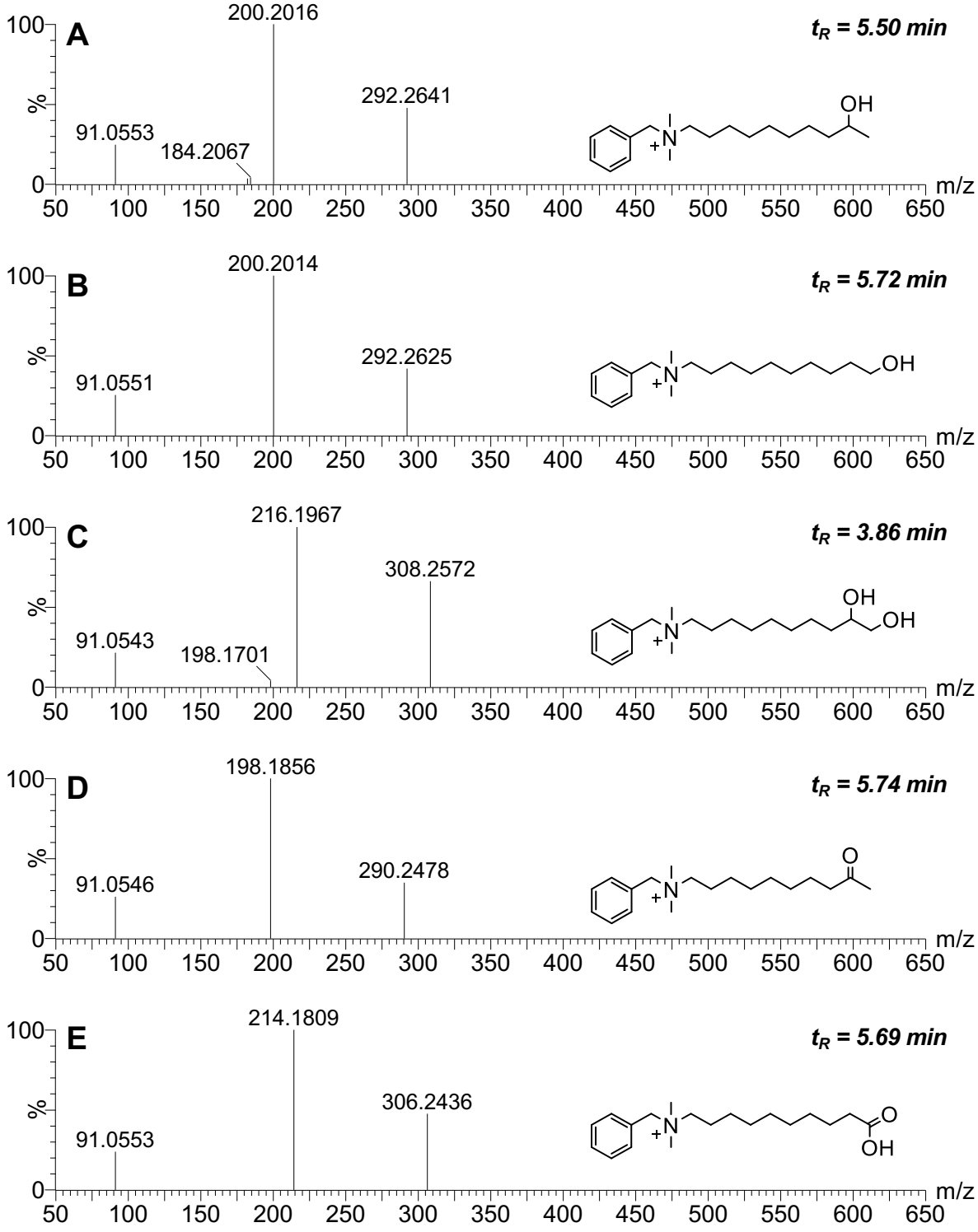

Figure S8. LC-MS chromatograms of authentic C_{10}-BAC metabolite standards synthesized in-house (A) (ω-1)-hydroxy C_{10}-BAC, (B) ω-hydroxy C_{10}-BAC, (C) (ω, ω-1)-dihydroxy C_{10}-BAC, (D) (ω-1)-ketone C_{10}-BAC, and (E) ω-carboxylic acid C_{10}-BAC are shown. Analyte peaks are labeled with retention times. The mass (*m/z*) filtered (±0.005 *m/z*) and maximum peak height are also provided. In Panels A and D, respectively, (ω-2)-hydroxy C_{10}-BAC and (ω-2)-ketone C_{10}-BAC are noted as minor impurities.

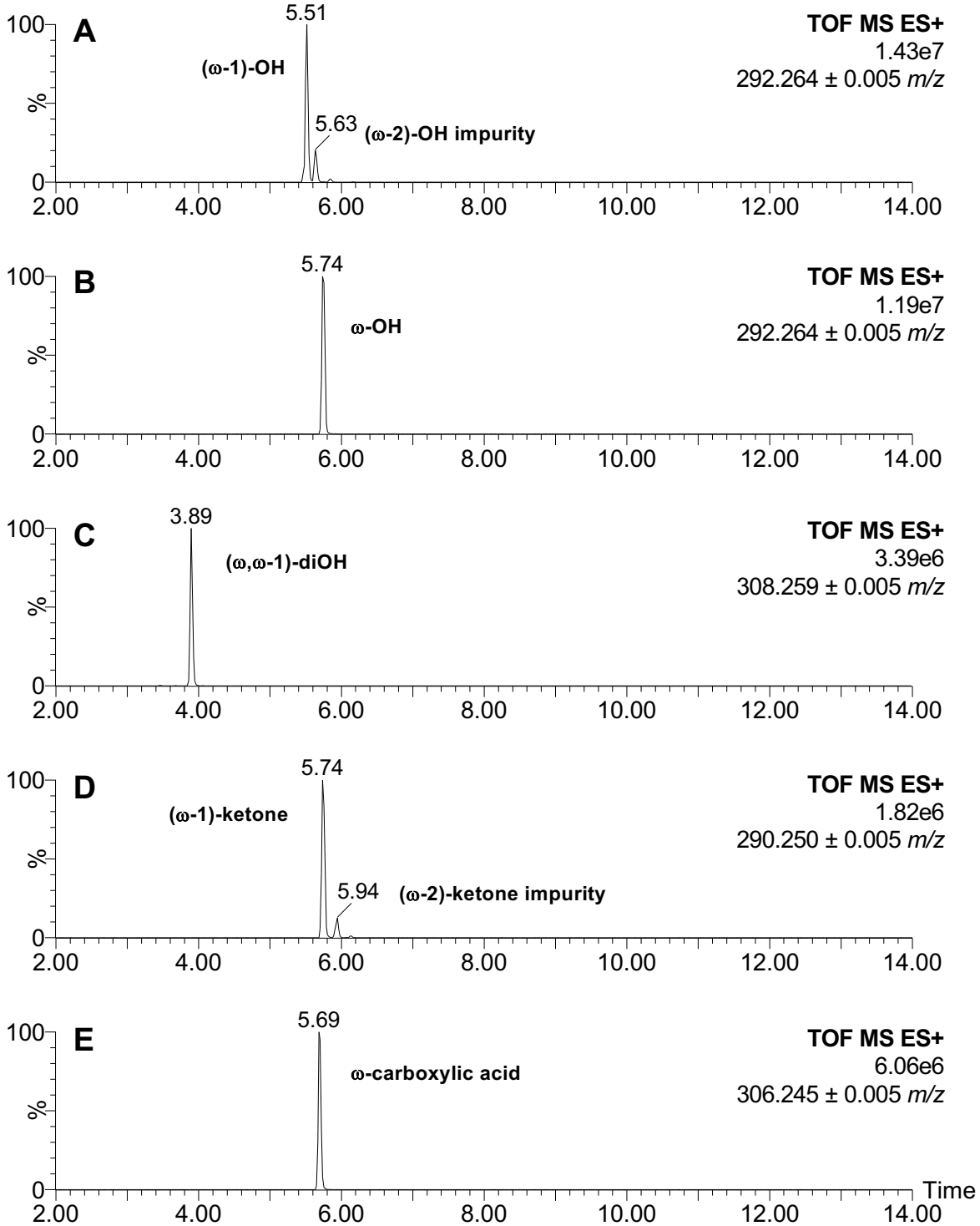

Figure S9. LC-MS chromatograms displaying +1O BAC metabolites of the substrates (A) C_{10}-BAC, (B) C_{12}-BAC, (C) C_{14}-BAC, and (D) C_{16}-BAC produced by NADPH-dependent metabolism in HLM are shown. Analyte peaks are labeled with retention times. The mass (*m/z*) filtered (±0.005 *m/z*) and maximum peak height are also provided.

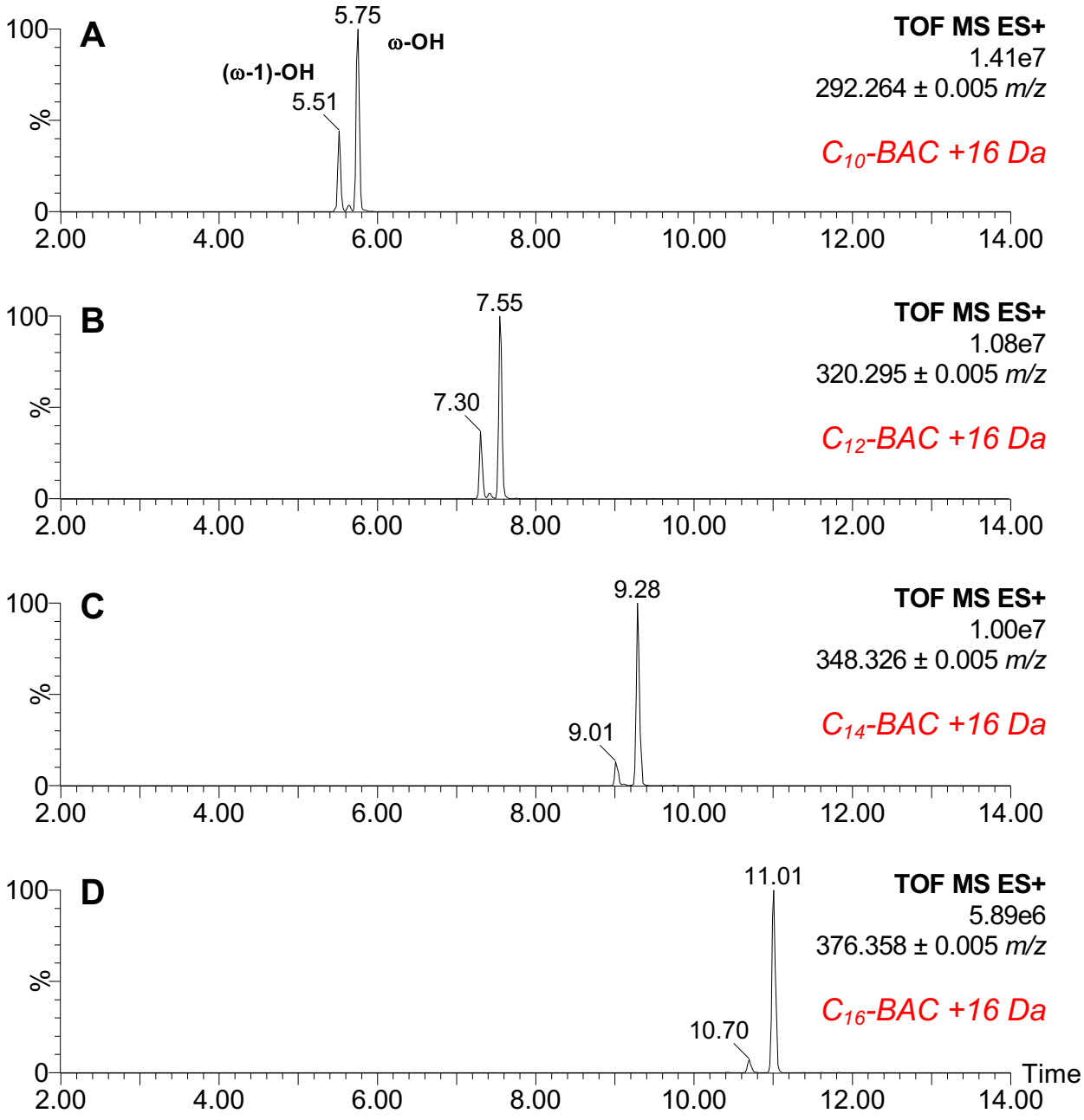

Figure S10. LC-MS chromatograms displaying +2O BAC metabolites of the substrates (A) C_{10}-BAC, (B) C_{12}-BAC, (C) C_{14}-BAC, and (D) C_{16}-BAC produced by NADPH-dependent metabolism in HLM are shown. Analyte peaks are labeled with retention times. The mass (*m/z*) filtered (±0.005 *m/z*) and maximum peak height are also provided.

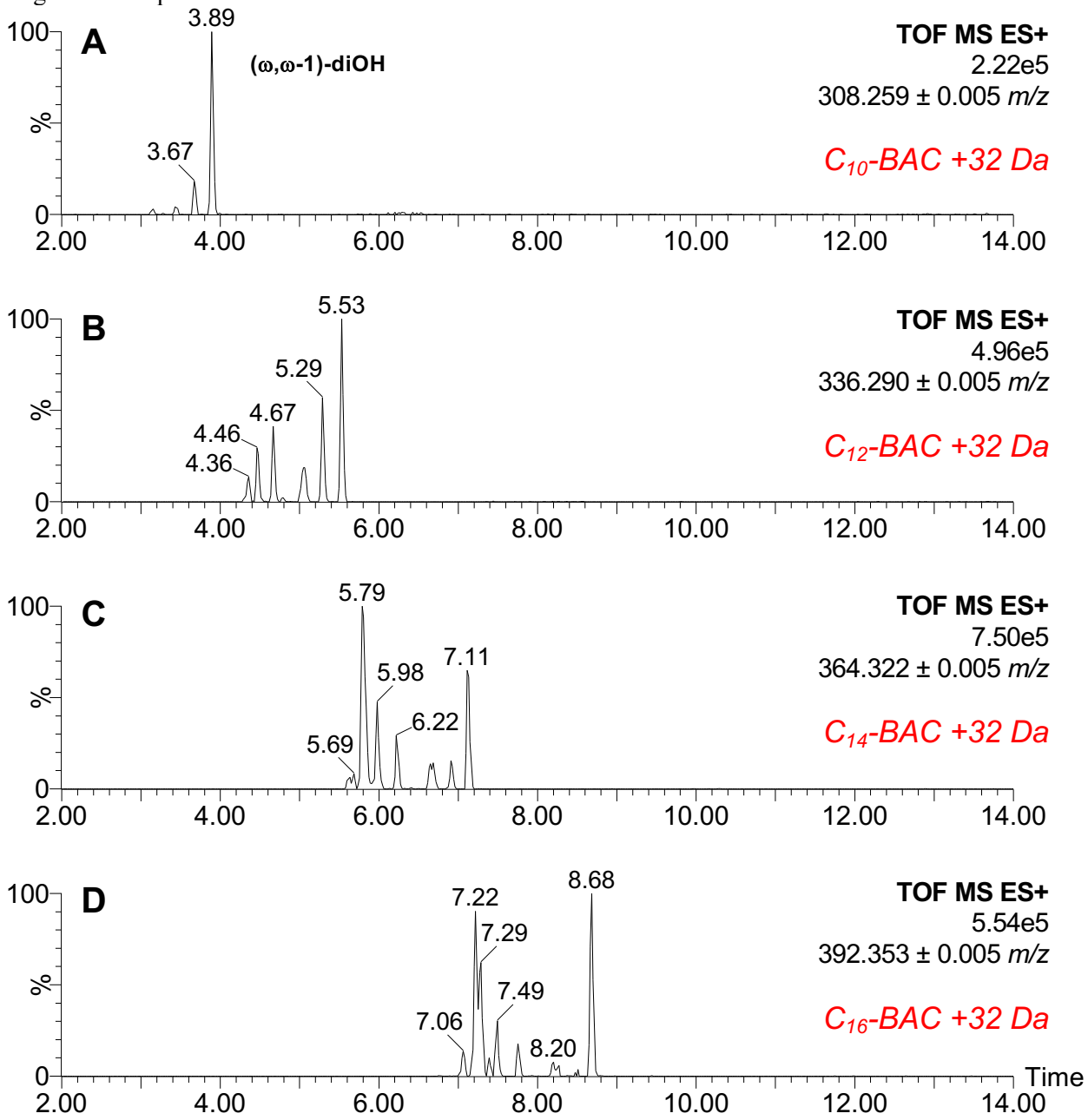

Figure S11. LC-MS chromatograms displaying +1O, -2H BAC metabolites of the substrates (A) C_{10}-BAC, (B) C_{12}-BAC, (C) C_{14}-BAC, and (D) C_{16}-BAC produced by NADPH-dependent metabolism in HLM are shown. Analyte peaks are labeled with retention times. The mass (*m/z*) filtered (±0.005 *m/z*) and maximum peak height are also provided.

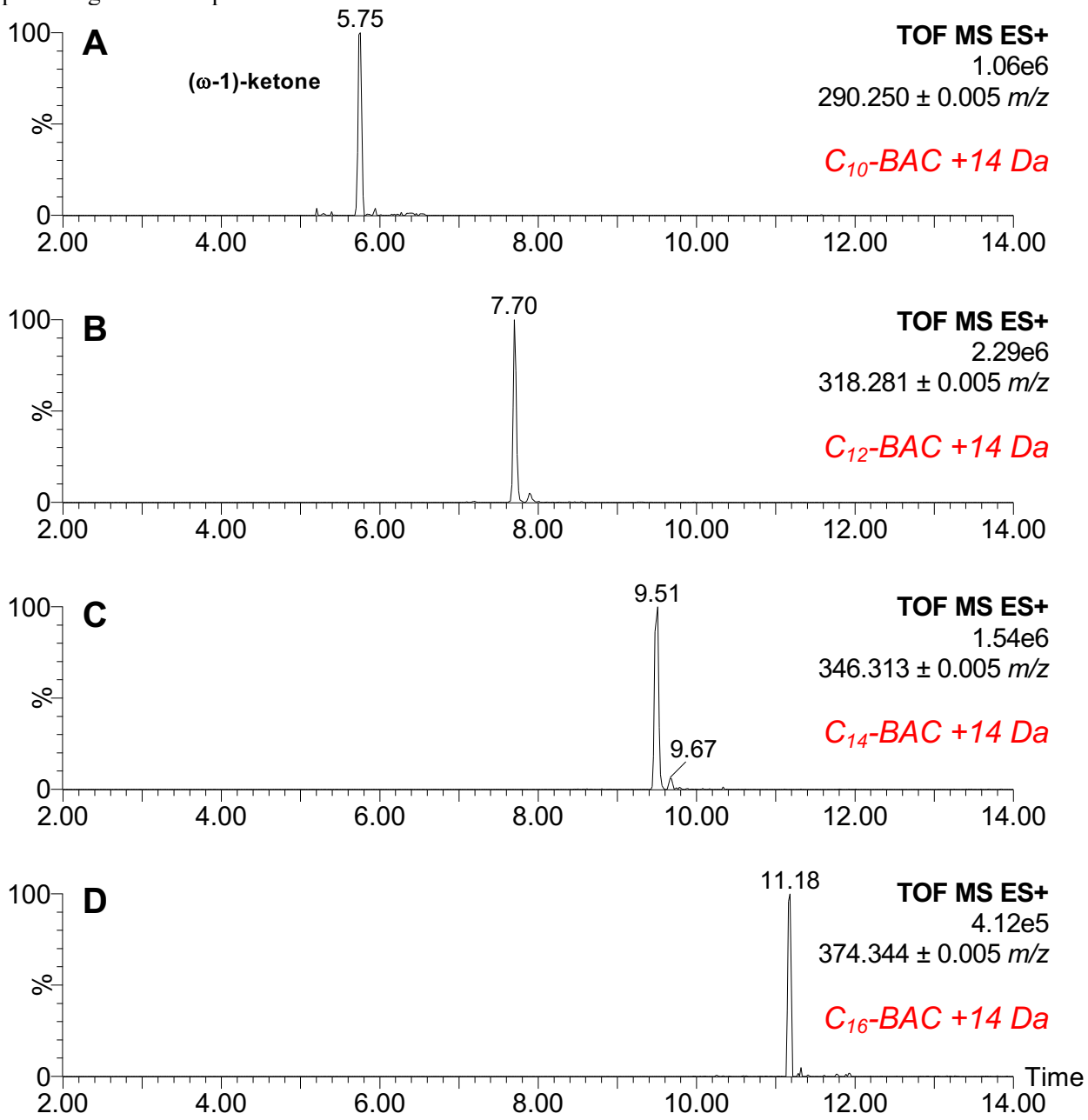

Figure S12. LC-MS chromatograms displaying +2O, -2H BAC metabolites of the substrates (A) C_{10}-BAC, (B) C_{12}-BAC, (C) C_{14}-BAC, and (D) C_{16}-BAC produced by NADPH-dependent metabolism in HLM are shown. Analyte peaks are labeled with retention times. The mass (*m/z*) filtered (±0.005 *m/z*) and maximum peak height are also provided.

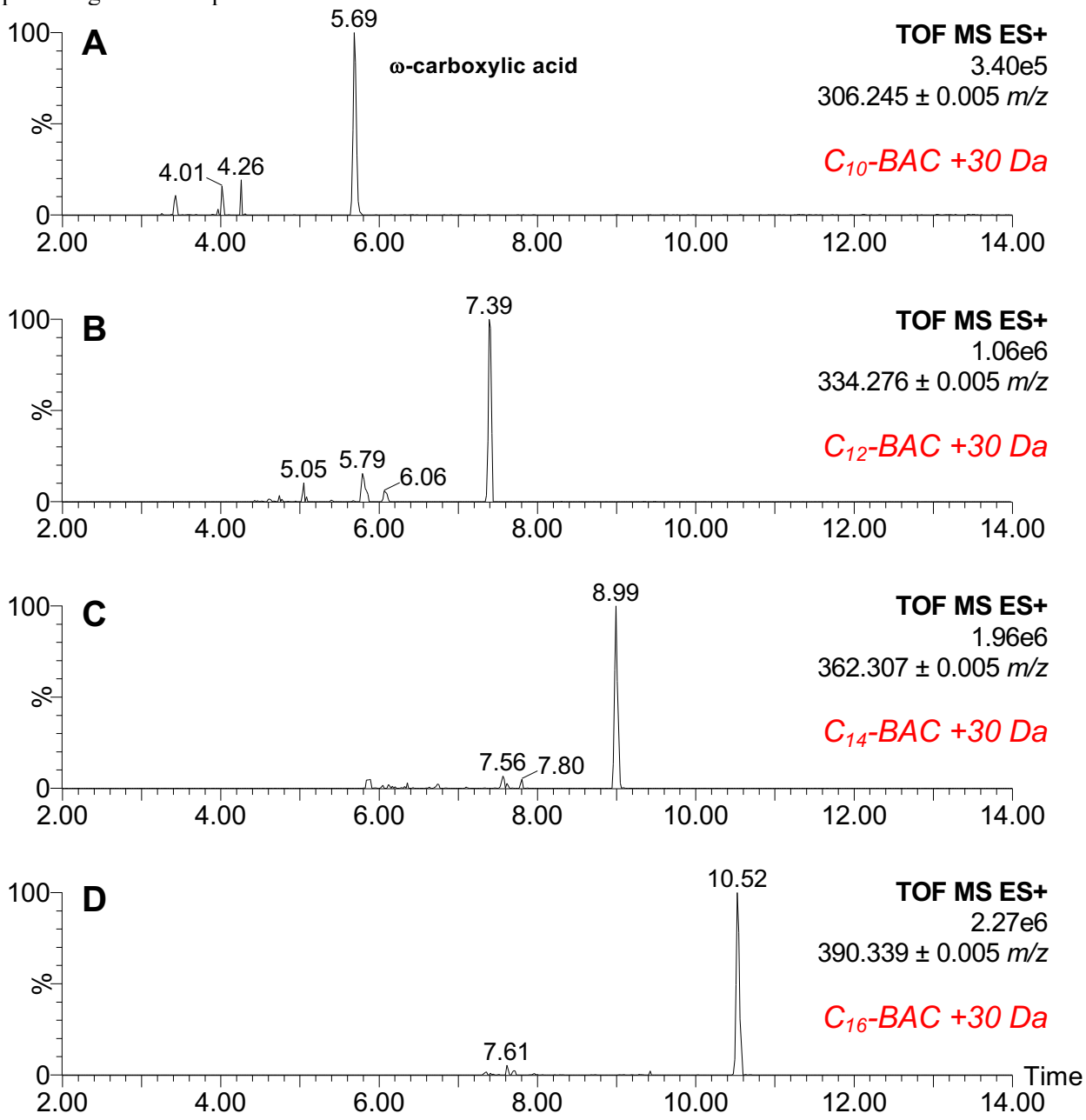

Figure S13. LC-MS chromatograms displaying (A) +1O (B) +2O (C) +1O, -2H, and (D) +2O, -2H metabolites of C_{10}-BAC produced by NADPH-dependent metabolism in recombinant CYP2D6 are shown. Analyte peaks are labeled with retention times. The mass (*m/z*) filtered (±0.005 *m/z*) and maximum peak height are also provided.

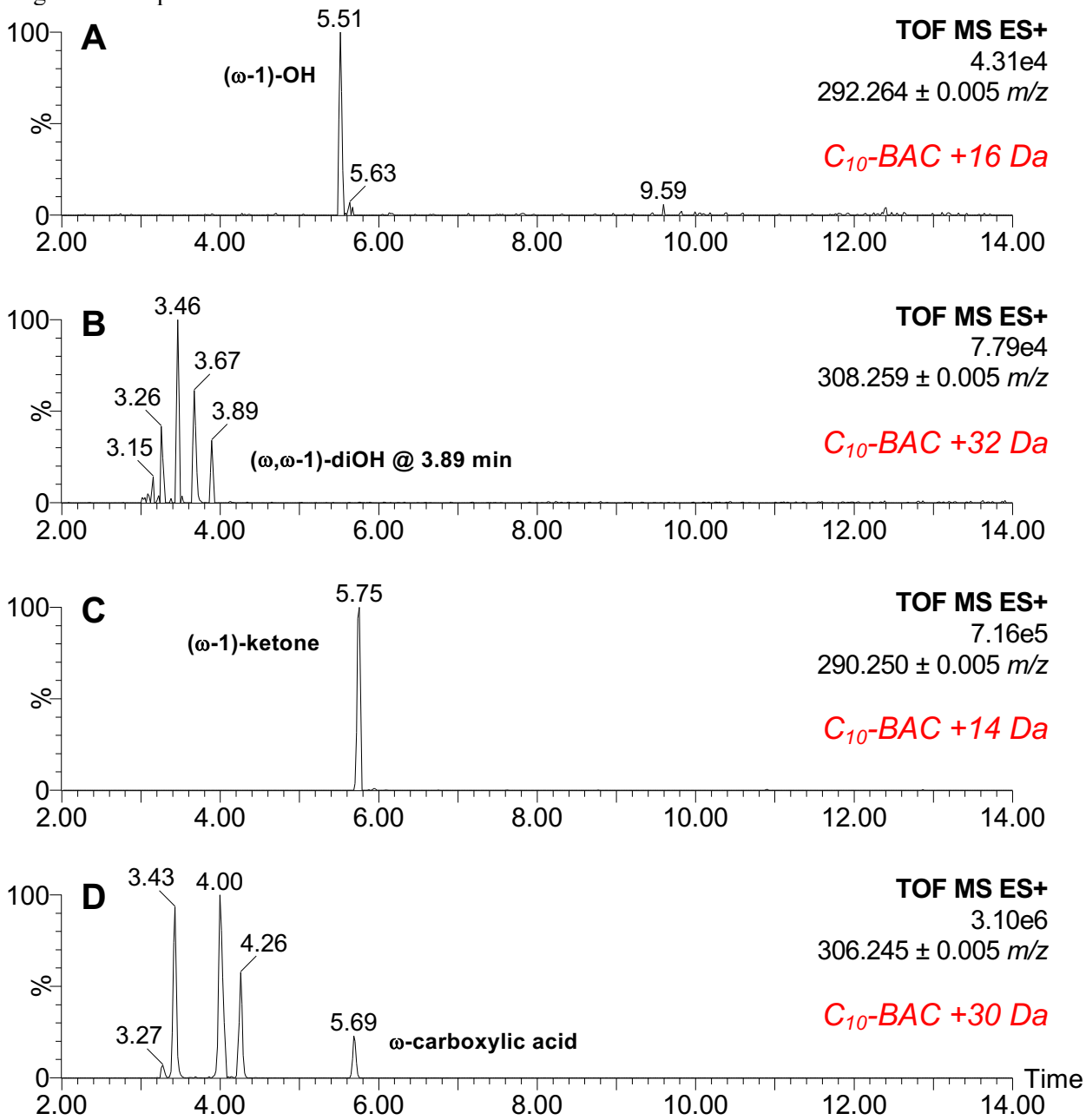

Figure S14. LC-MS chromatograms displaying (A) +1O (B) +2O (C) +1O, -2H, and (D) +2O, -2H metabolites of C_{10}-BAC produced by NADPH-dependent metabolism in recombinant CYP4F12 are shown. Analyte peaks are labeled with retention times. The mass (*m/z*) filtered (±0.005 *m/z*) and maximum peak height are also provided.

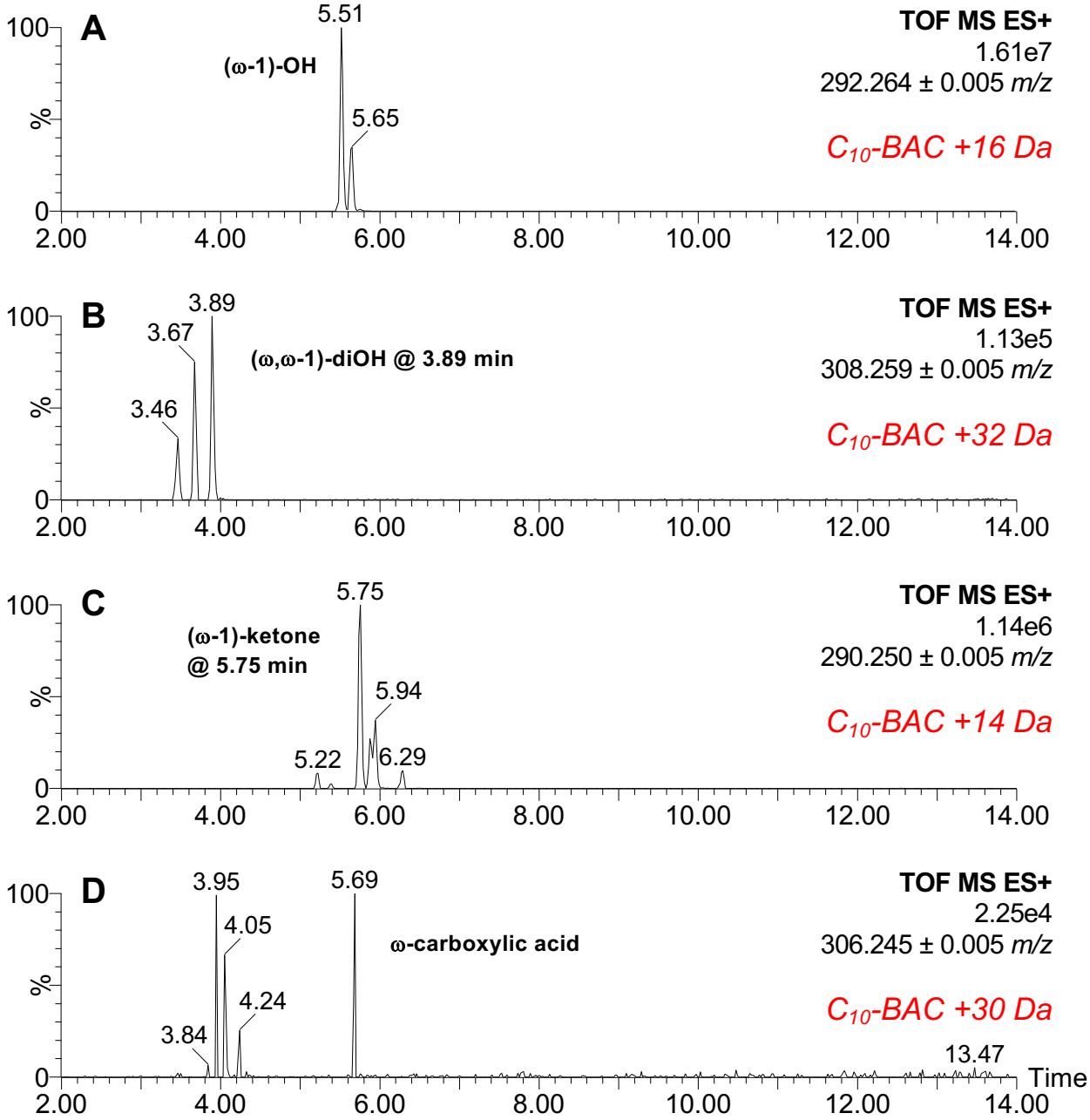

Figure S15. LC-MS chromatograms displaying (A) +1O (B) +2O (C) +1O, -2H, and (D) +2O, -2H metabolites of C_{16}-BAC produced by NADPH-dependent metabolism in recombinant CYP2D6 are shown. Analyte peaks are labeled with retention times. The mass (*m/z*) filtered (±0.005 *m/z*) and maximum peak height are also provided.

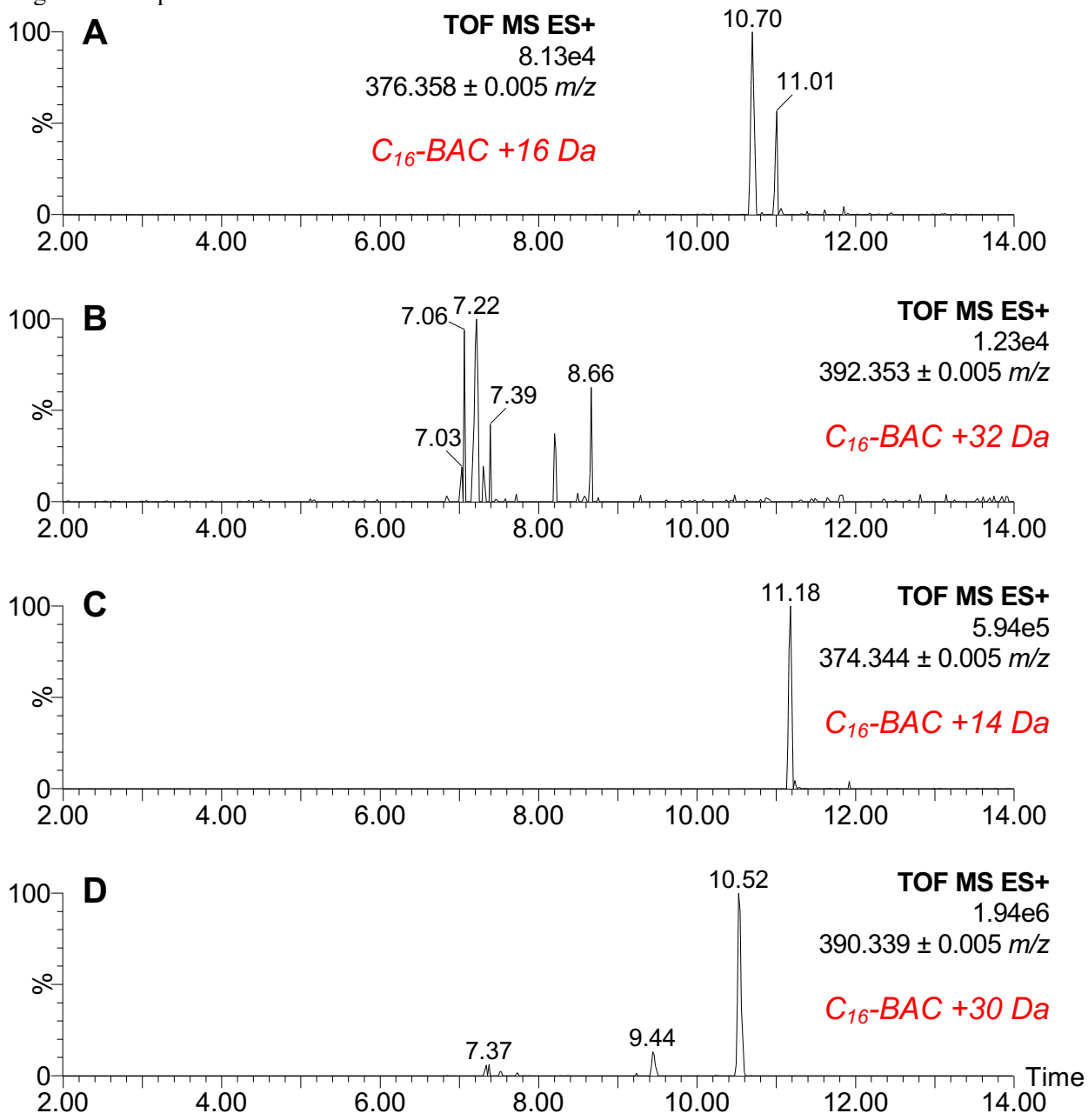

Figure S16. LC-MS chromatograms displaying (A) +1O (B) +2O (C) +1O, -2H, and (D) +2O, -2H metabolites of C_{16}-BAC produced by NADPH-dependent metabolism in recombinant CYP4F12 are shown. Analyte peaks are labeled with retention times. The mass (*m/z*) filtered (±0.005 *m/z*) and maximum peak height are also provided.

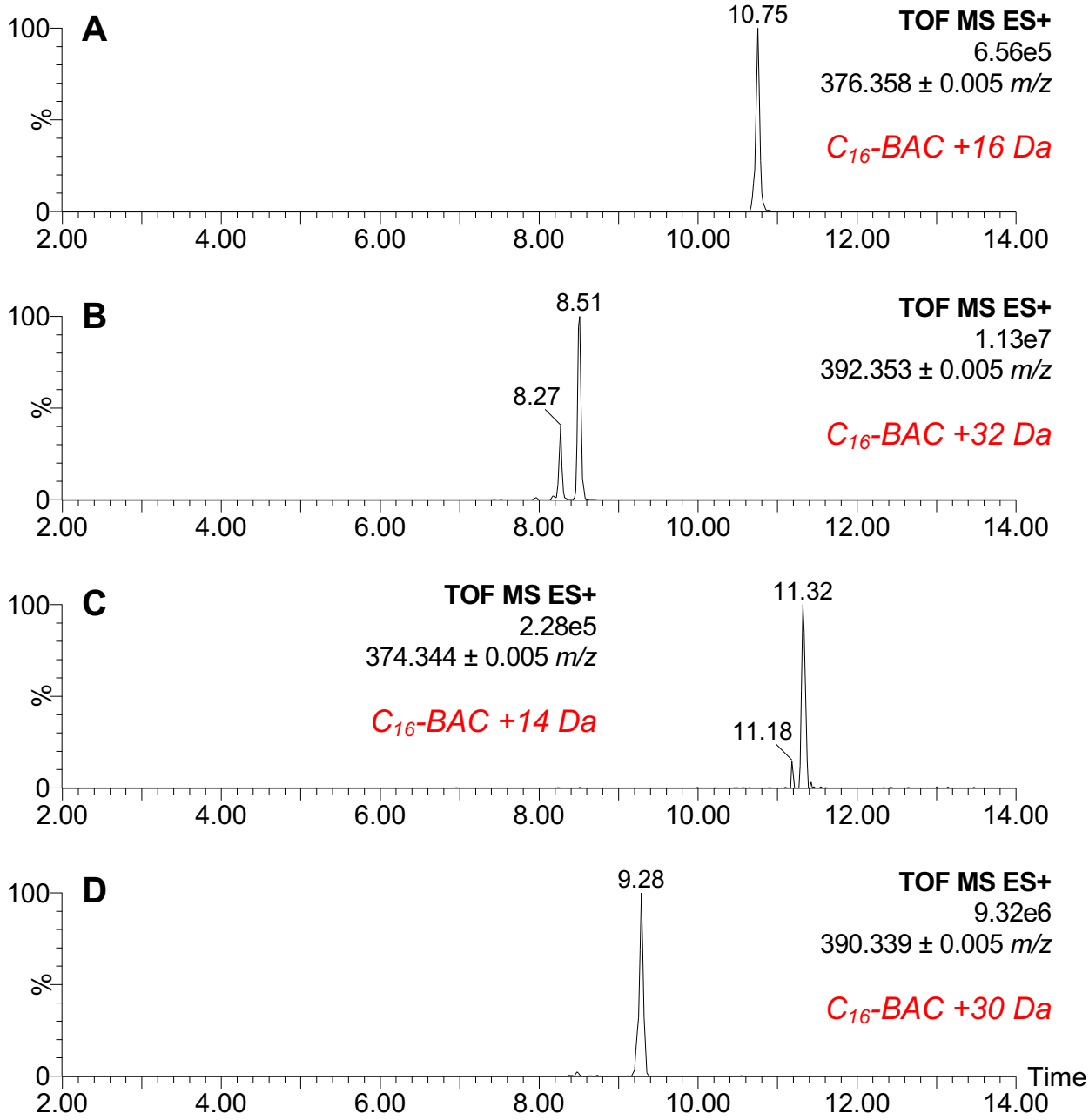

Figure S17. LC-MS chromatograms displaying (A) +1O (B) +2O (C) +1O, -2H, and (D) +2O, -2H metabolites of C_{16}-BAC produced by NADPH-dependent metabolism in recombinant CYP4F2 are shown. Analyte peaks are labeled with retention times. The mass (*m/z*) filtered (±0.005 *m/z*) and maximum peak height are also provided.

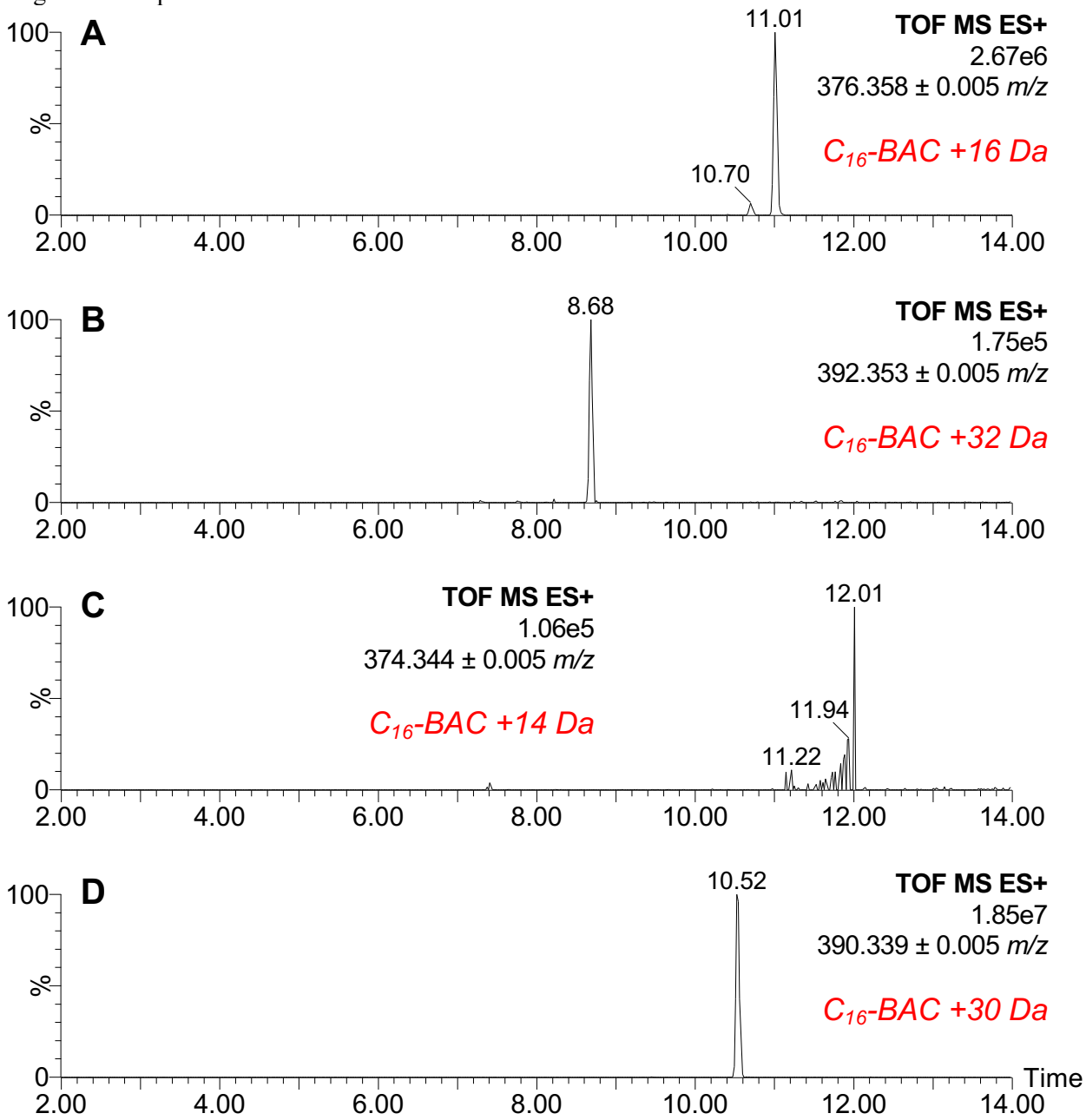

Figure S18. ^{1}H-NMR spectrum of ω-hydroxy-C_{10}-BAC in $CDCl_3$.

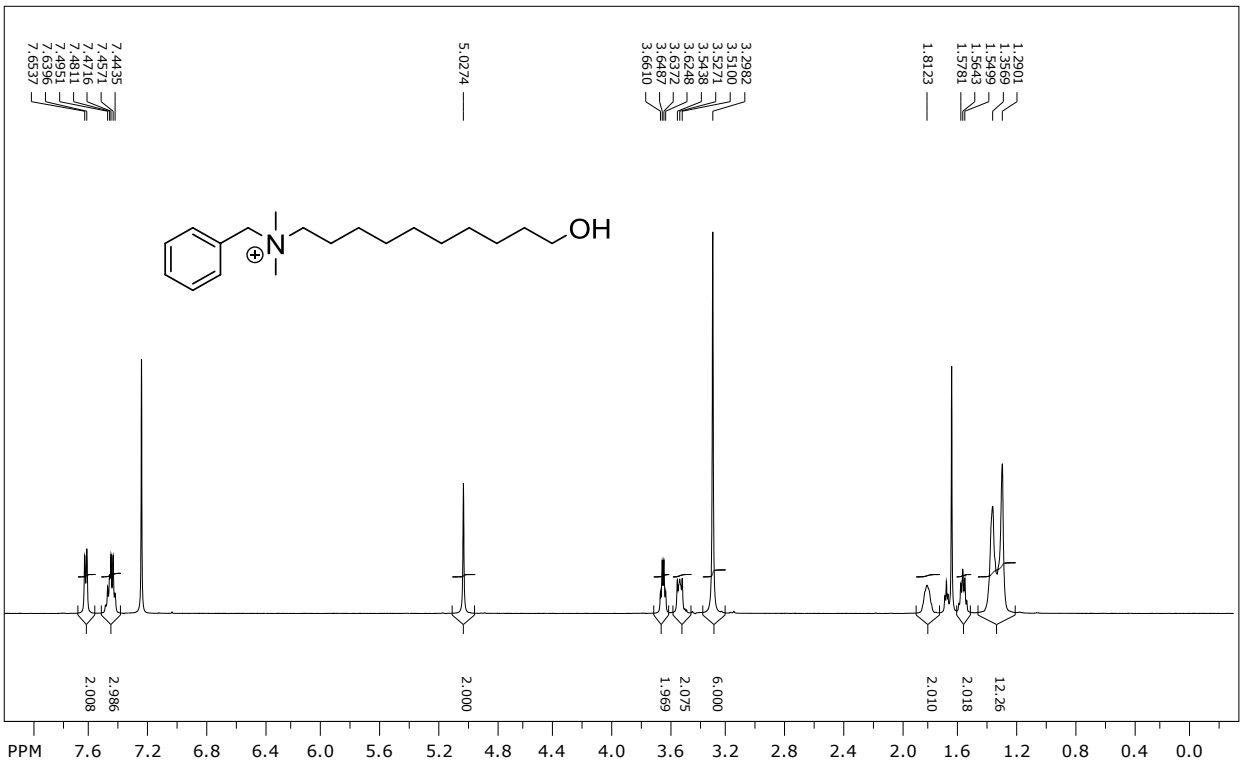

Figure S19. ^{1}H-NMR spectrum of ω-alkene-C_{10}-BAC in $CDCl_3$.

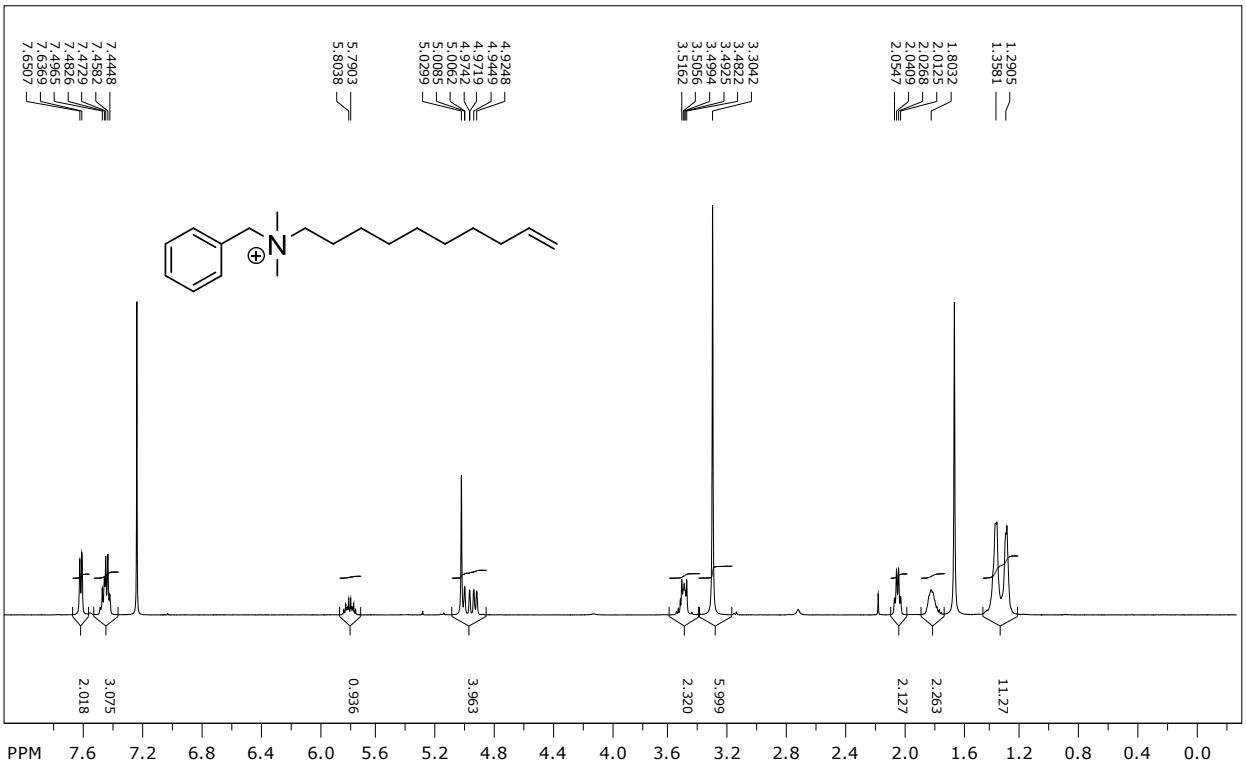

Figure S20. ^{1}H-NMR spectrum of (ω-1)-hydroxy-C_{10}-BAC in $CDCl_3$. The small triplet at 0.94 ppm is due to the presence of (ω-2)-hydroxy-C_{10}-BAC as a minor impurity.

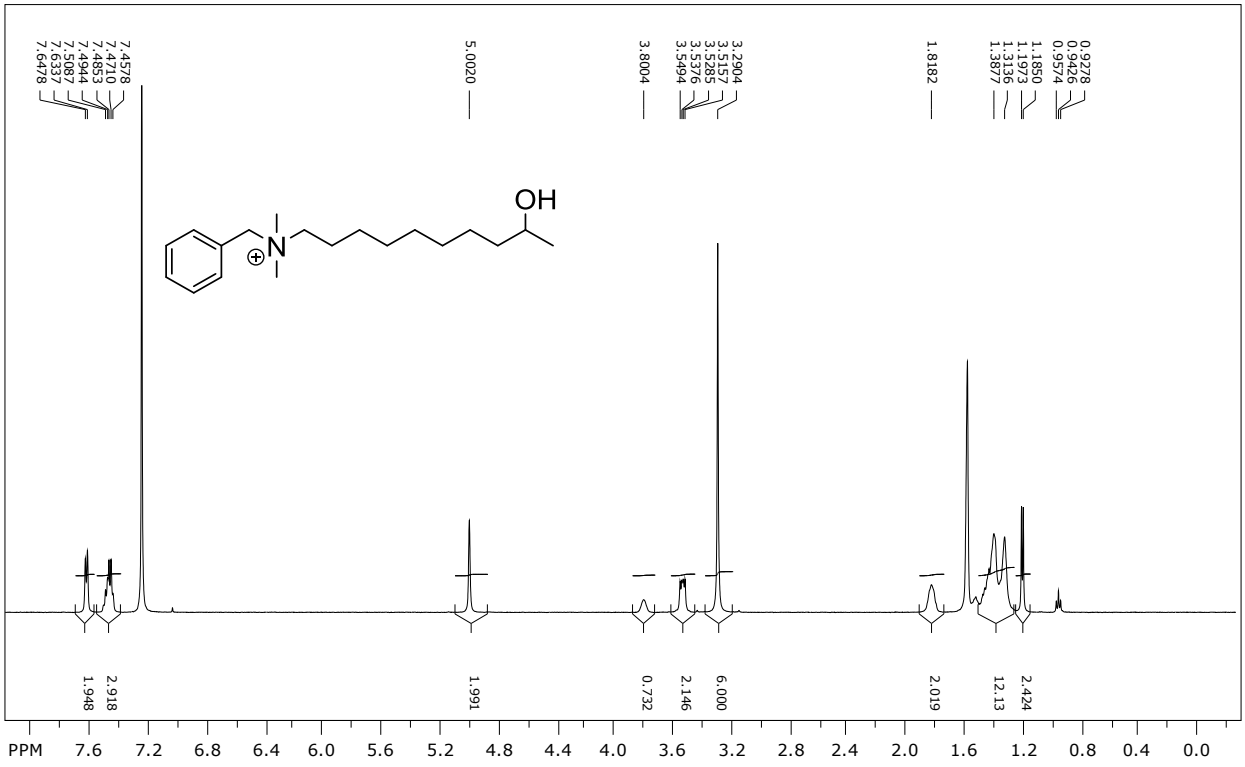

Figure S21. ^{1}H-NMR spectrum of (ω, ω-1)-dihydroxy-C_{10}-BAC in $CDCl_3$.

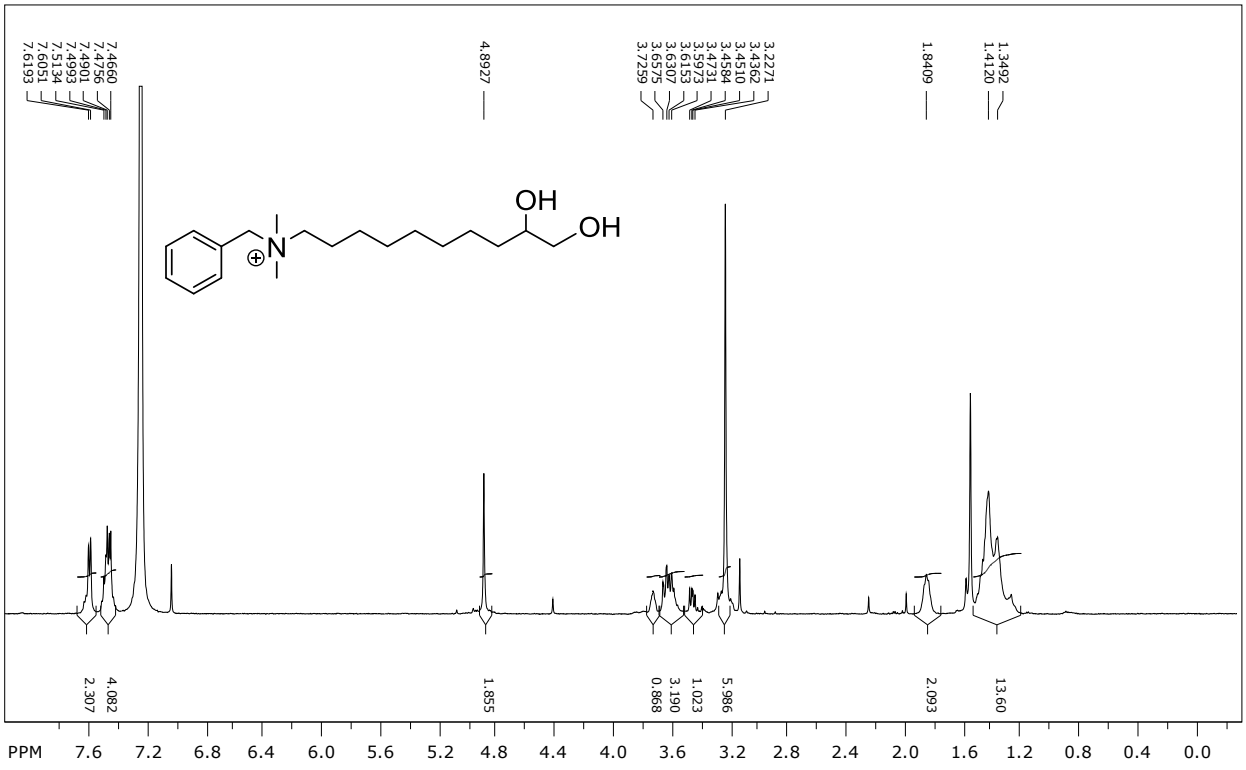

Figure S22. ^{1}H-NMR spectrum of (ω-1)-ketone-C_{10}-BAC in $CDCl_3$. The triplet at 1.04 ppm is due to the presence of (ω-2)-ketone-C_{10}-BAC as a minor impurity.

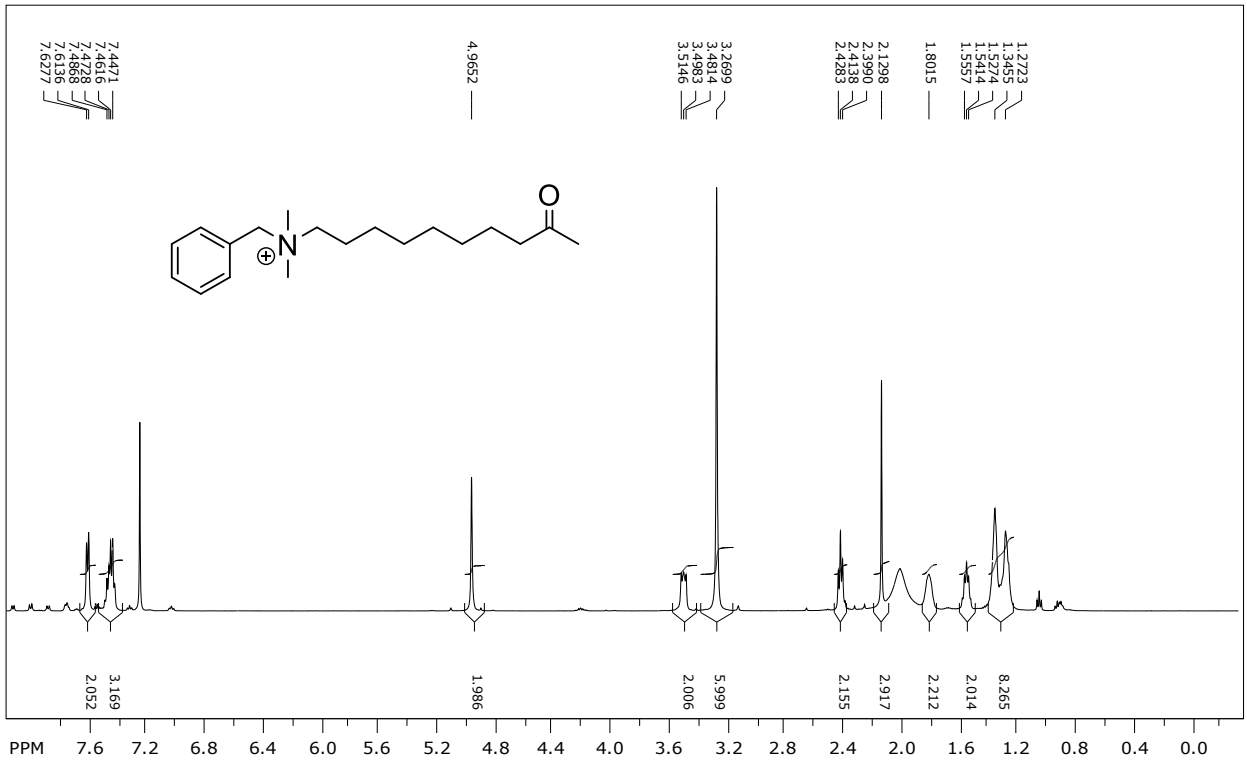

Figure S23. ^{1}H-NMR spectrum of ω-carboxylic acid-C_{10}-BAC in $CDCl_3$.

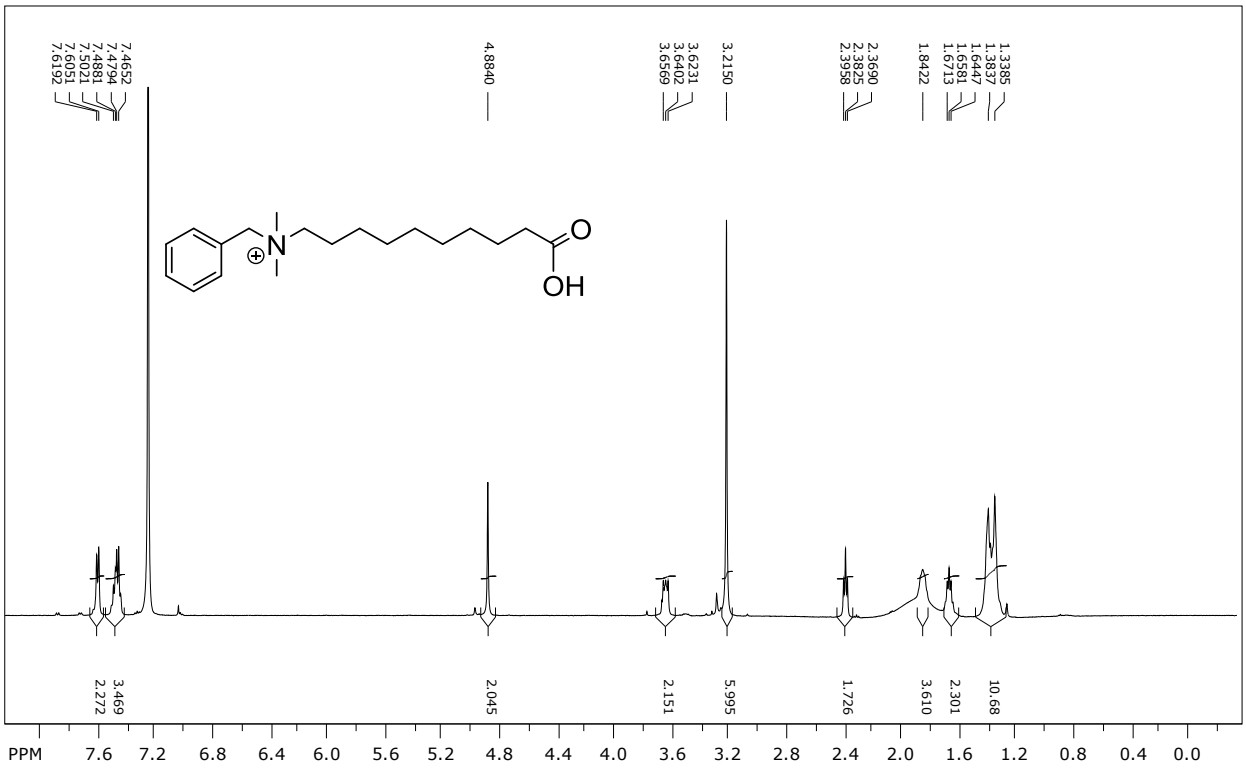

Figure S24. ^{1}H-NMR spectrum of ω-carboxylic acid-C_{10}-BAC in d_6-DMSO.