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Syntheses and analytical characterizations of *N*-alkyl-arylcyclohexylamines

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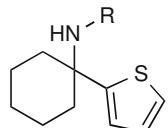
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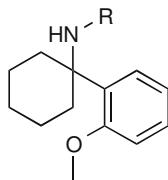
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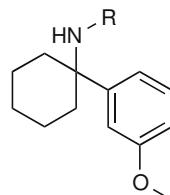
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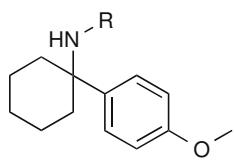
(1a) : R = CH₃ (TCMe)
(1b) : R = CH₂CH₃ (TCE)
(1c) : R = CH₂CH₂CH₃ (TCPPr)



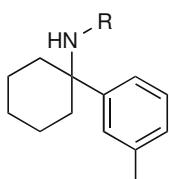
(2a) : R = CH₃ (2-MeO-PCMe)
(2b) : R = CH₂CH₃ (2-MeO-PCE)
(2c) : R = CH₂CH₂CH₃ (2-MeO-PCPr)



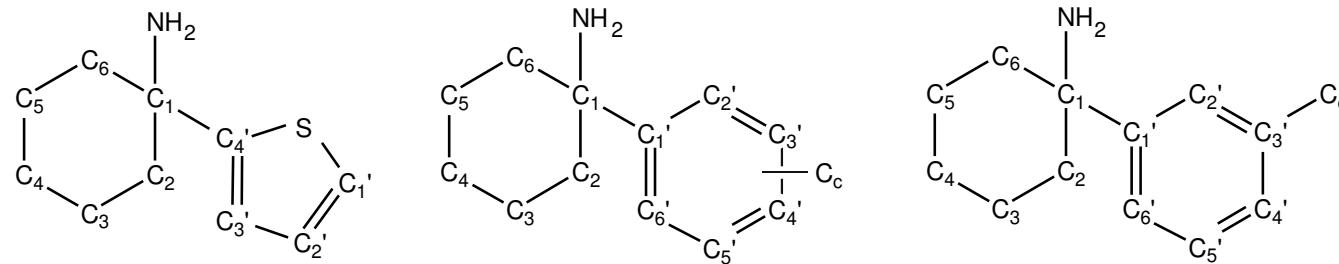
(3a) : R = CH₃ (3-MeO-PCMe)
(3b) : R = CH₂CH₃ (3-MeO-PCE)
(3c) : R = CH₂CH₂CH₃ (3-MeO-PCPr)



(4a) : R = CH₃ (4-MeO-PCMe)
(4b) : R = CH₂CH₃ (4-MeO-PCE)
(4c) : R = CH₂CH₂CH₃ (4-MeO-PCPr)

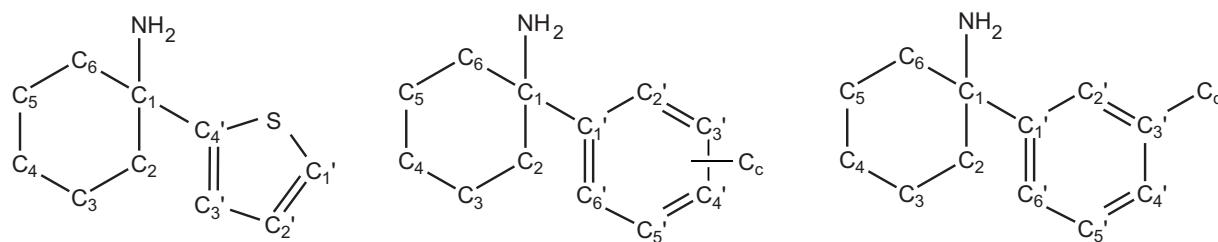


(5a) : R = CH₃ (3-Me-PCMe)
(5b) : R = CH₂CH₃ (3-Me-PCE)
(5c) : R = CH₂CH₂CH₃ (3-Me-PCPr)



| Proton | TCA | 2-MeO-PCA | 3-MeO-PCA** | 4-MeO-PCA** | 3-Me-PCA** |
|---------------------|--|--|--|--|--|
| $\text{H}_{2,6}$ | 2.27 dd (13.2, 6.2 Hz, 2 H_{eq}) 2.12–2.04 m (2 H_{ax}) | 2.54–2.41 m (2 H_{eq}) 2.29 ddd (13.3, 9.3, 3.4 Hz, 2 H_{ax}) | 2.30–2.17 m (2 H_{eq}) 2.11–2.00 m (2 H_{ax}) | 2.28–2.16 m (2 H_{eq}) 2.09–1.97 m (2 H_{ax}) | 2.27–2.17 m (2 H_{eq}) 2.11–2.00 m (2 H_{ax}) |
| $\text{H}_{3,5}$ | 1.83–1.73 m (2 H_{eq}) 1.55–1.43 m (2 H_{ax}) | 1.93–1.78 m (2 H_{eq}) 1.51–1.38 m (2 H_{ax}) | 1.85–1.71 m (2 H_{eq}) 1.58–1.34 m (2 H_{ax}) | 1.78–1.65 m (2 H_{eq}) 1.40–1.20 m (2 H_{ax}) | 1.82–1.70 m (2 H_{eq}) 1.47–1.34 m (2 H_{ax}) |
| H_4 | 1.55–1.43 s (2H) | 1.60–1.50 m (1 H_{eq}) 1.51–1.38 m (1 H_{ax}) | 1.58–1.34 m (2H) | 1.50–1.40 m (1 H_{eq}) 1.40–1.20 m (1 H_{ax}) | 1.57–1.48 m (1 H_{eq}) 1.47–1.34 m (1 H_{ax}) |
| $\text{H}_{1'}$ | – | – | – | – | – |
| $\text{H}_{2'}$ | 7.31 dd (3.7, 1.1 Hz) | – | 7.20 t (2.0 Hz) | 7.55 dm (8.9 Hz) | 7.46 bs |
| $\text{H}_{3'}$ | 6.97 dd (5.1, 3.7 Hz) | 6.85 dd (8.4, 1.0 Hz) | – | 6.87 dm (8.9 Hz) | – |
| $\text{H}_{4'}$ | 7.27 dd (5.1, 1.1 Hz) | 7.31 ddd (8.8, 7.1, 1.5 Hz) | 6.85 ddd (8.3, 2.5, 0.9 Hz) | – | 7.10 d (7.5 Hz) |
| $\text{H}_{5'}$ | – | 6.96 td (7.6, 1.0 Hz) | 7.25 t (8.0 Hz) | 6.87 dm (8.9 Hz) | 7.22 t (7.7 Hz) |
| $\text{H}_{6'}$ | – | 7.44 dd (7.8, 1.5 Hz) | 7.17 dm (7.8 Hz) | 7.55 dm (8.9 Hz) | 7.42 d (8.0 Hz) |
| H_α | – | – | – | – | – |
| H_β | – | – | – | – | – |
| H_γ | – | – | – | – | – |
| H_c | – | 3.72 s (OCH_3) | 3.81 s (OCH_3) | 3.78 s (OCH_3) | 2.35 s (CH_3) |
| NH^+ | 8.62 s (NH_3^+) | 8.49 s (NH_3^+) | 8.49 s (NH_3^+) | 8.38 s (NH_3^+) | 8.45 s (NH_3^+) |

* b = broad; d = doublet; m = multiplet; s = singlet; triplet; q = quartet; quint = quintet; sex = sextet; ** adapted from Wallach *et al.* *Drug Test. Anal.* **2014**, *6*, 633.



| 100 MHz ^{13}C NMR spectra of HCl salts in CDCl_3 . | | | | | |
|---|--------|-----------|------------|------------|-----------|
| Carbon | TCA | 2-MeO-PCA | 3-MeO-PCA* | 4-MeO-PCA* | 3-Me-PCA* |
| C ₁ | 57.04 | 58.74 | 58.56 | 58.06 | 58.43 |
| C _{2,6} | 36.11 | 33.75 | 34.77 | 34.71 | 34.67 |
| C _{3,5} | 21.72 | 22.21 | 21.62 | 21.59 | 21.58 |
| C ₄ | 24.52 | 25.06 | 24.83 | 24.88 | 24.88 |
| C _{1'} | 143.29 | 126.49 | 140.37 | 130.66 | 138.83 |
| C _{2'} | 127.19 | 156.98 | 114.79 | 128.15 | 128.95 |
| C _{3'} | 126.80 | 111.41 | 159.86 | 113.89 | 138.21 |
| C _{4'} | 125.73 | 129.66 | 111.66 | 159.27 | 128.55 |
| C _{5'} | – | 120.83 | 129.60 | 113.89 | 127.28 |
| C _{6'} | – | 128.85 | 118.75 | 128.15 | 123.65 |
| α | – | – | – | – | – |
| β | – | – | – | – | – |
| γ | – | – | – | – | – |
| C _c | – | 55.35 | 55.42 | 55.12 | 21.58 |

*Taken from Wallach *et al.* *Drug Test. Anal.* **2014**, 6, 633.

Proton chemical shifts

All ^1H chemical shift values, multiplicities and assignments for arylcyclohexylamines (**1a**) – (**5c**) are summarized in Tables 1–3. The $\text{H}_{2,6}\text{Hax}$ chemical shifts observed for secondary amines were 0.1–0.3 ppm downfield compared to their primary amine counterparts. A slightly larger $\text{H}_{2,6}\text{Hax}$ shift was seen with tertiary amines: ~0.5–0.6 ppm downfield from primary amines.^[1] The $\text{H}_{2,6}\text{Heq}$ chemical shifts of both secondary and tertiary amines were 0.2–0.5 ppm downfield of primary amines. The $\text{H}_{3,5}$ and H_4 ^1H chemical shift values showed minor differences between different amine nitrogen substituents (primary, secondary and tertiary). Likewise, the aromatic ^1H chemical shifts of equivalent aryl series showed only minor differences.

In the case of secondary and tertiary arylcyclohexylamines, ^1H chemical shifts of protons linked to carbons in the α -position of the *N*-alkyl substituent appeared further downfield relative to ^1H chemical shifts associated with β - and γ -positions due to increasing deshielding resulting from the amine nitrogen.

The ^1H chemical shifts corresponding to the α -position, were observed to shift downfield with increased *N*-alkyl chain length, i.e. *N*-ethyl and *N*-propyl counterparts. A similar effect was seen with the ^1H chemical shifts of H_β protons between the PCE and PCPr series ($\Delta\text{H}_\beta \sim 0.4$ ppm). This effect was consistent with the ^{13}C chemical shift values (shown below), and resulted from deshielding associated with increased alkyl substitution and greater electronegativity of carbon relative to hydrogen.

The ^1H chemical shifts of the protonated amine function (NH^+) appeared as a singlet or broad singlet in the case of 2-MeO-PCE (**2b**) and 2-MeO-PCPr (**2c**). The NH^+ shifts were consistently downfield (~9.0–9.5 ppm for secondary amines) as a consequence of the deshielding effect following protonation of the nitrogen atom. These shifts are useful in the identification of the protonation state of amine samples. In primary amines, the NH^+ chemical shifts appeared at ~8.4–8.6 ppm and were shifted increasingly downfield in the case of secondary amines with a Δ_{NH^+} of ~0.5–1.0 ppm for secondary relative to primary amines. Interestingly, the extent of Δ_{NH^+} decreased slightly with increased chain length. The very broad singlet NH_2^+ chemical shifts were associated with 2-MeO-PCE (10.2–8.0 ppm) and 2-MeO-PCPr (11.0–7.67 ppm). This peak broadening may be the result of intramolecular H-bond between the aryl-2 methoxyl oxygen lone pairs and the NH protons.

Carbon chemical shifts

^{13}C Chemical shift data are summarized in Tables 4–6. C_1 chemical shifts were the furthest downfield (~60 ppm) of all the aliphatic carbon shifts. The downfield position of carbons α to an amine nitrogen have been described.^[1–3] Consistent with this, an amine dependent ΔC_1 chemical shift was observed that moved progressively downfield with increasing degree of amine substitution due to increased deshielding. This shift for secondary relative to primary amines was ~4–5 ppm and the magnitude of this shift increased slightly with increasing *N*-alkyl chain length. A ~12–13 and 9–10 ppm downfield shift for hydrochlorides PCP and PCPy tertiary amines relative to primary amines respectively was observed previously.^[1]

The ^{13}C $\text{C}_{2,6}$ chemical shift showed an upfield shift for secondary ($\Delta\text{C}_{2,6} \sim 1.5$ ppm) and tertiary amines (~2–4 ppm) relative to primary amines. Again, an upfield shift of carbons β to the amine nitrogen has been reported.^[1,3] A small 0.4–0.7 ppm $\Delta\text{C}_{3,5}$ shift was seen with secondary amines shifted downfield relative to primary amines and an increasingly downfield trend was noted with increasing *N*-alkyl chain lengths. The $\Delta\text{C}_{3,5}$ downfield shift seen previously with the aryl-substituted PCPy series^[1] relative to primary amines was equivalent to that of the PCE and PCPr counterparts whereas that with the PCP series was slightly greater (~1.1 ppm).^[1]

A minor ΔC_4 was observed with secondary and tertiary amines relative to primary amines. As reported, a 0.2–0.3 ppm upfield shift occurred with tertiary amines, being consistently ~0.1 ppm greater with PCP relative to PCPy counterparts.^[1] In the case of secondary amines, a small ~0.1–0.2 ppm upfield shift was seen which increased slightly with chain length. Literature on cyclic and acyclic amines generally point toward an upfield shift for carbons delta to an amine nitrogen with both secondary

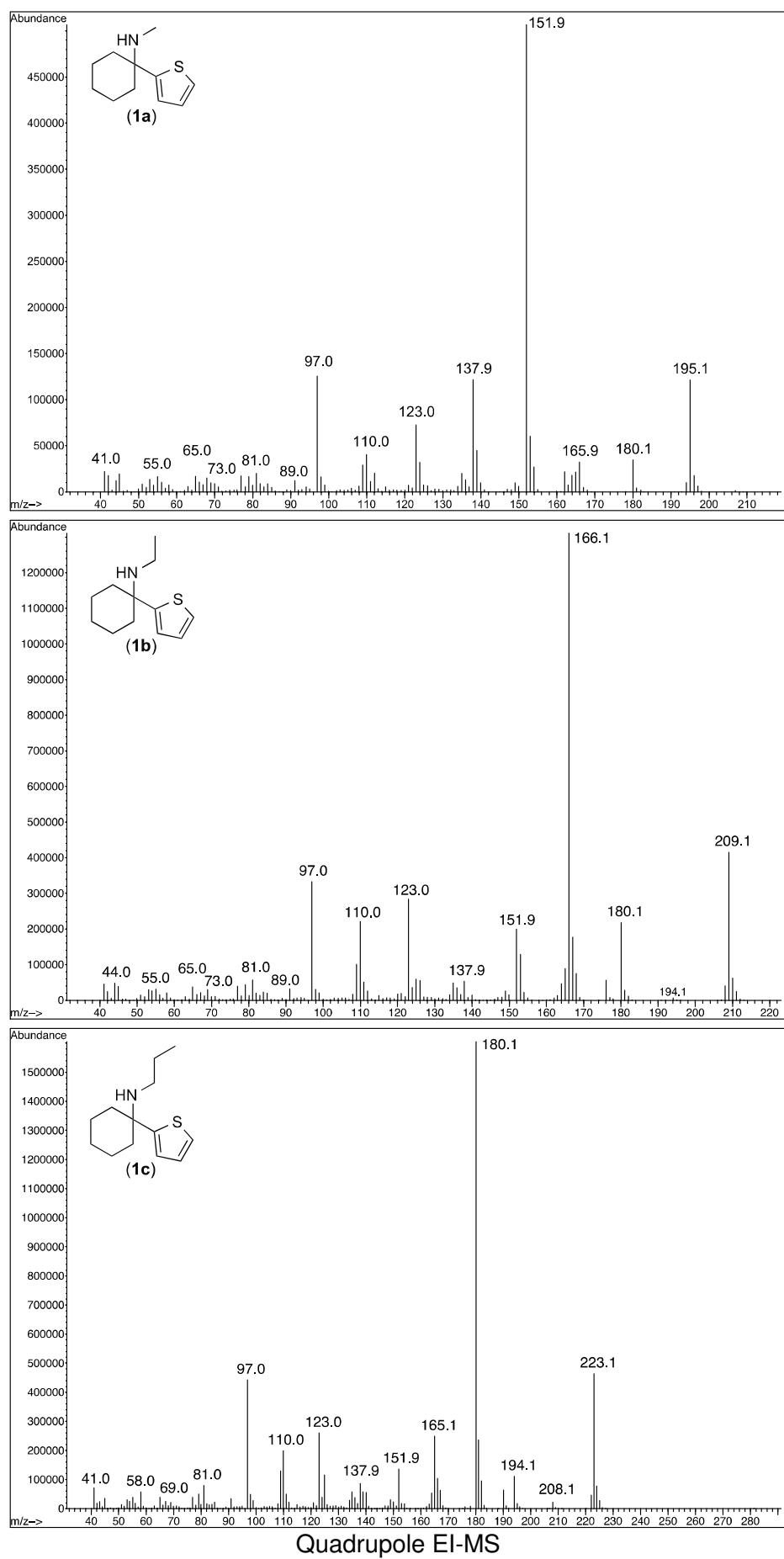
and tertiary amines relative to primary, although this appeared to be reflected only to a relatively small extent as seen here.^[2,3]

A ΔC_1 amine dependent chemical shift was detected between each series, consistent with carbons β to the amine nitrogen.^[2,3] This ΔC_1 moved progressively upfield for secondary and tertiary amines relative to primary, (~3–4 and ~7–8 ppm, respectively). A notable exception was the ^{13}C C_1 chemical shift of 3-Me-PCPr (**5c**), which shifted slightly downfield from 3-Me-PCA. Similarly, although the HCl salts exhibited a chemical shift difference, the C_1 ^{13}C chemical shift for 3-Me-PCP and 3-Me-PCPy free bases showed a minimal ΔC_1 with respect to 3-Me-PCA.^[1] Causes of these discrepancies with certain 3-Me- substituted compounds are unclear but may be related to unique conformations adopted by 3-Me-PCPr (**5c**) in the current study and related 3-Me- arylcyclohexylamines which are solvent and protonation dependent. The remaining aryl ^{13}C chemical shifts showed only minor or inconsistent chemical shift differences between equivalent aryl substituted ^{13}C chemical shifts. Generally however, secondary and tertiary amine chemical shifts were recorded downfield from primary amine counterparts.

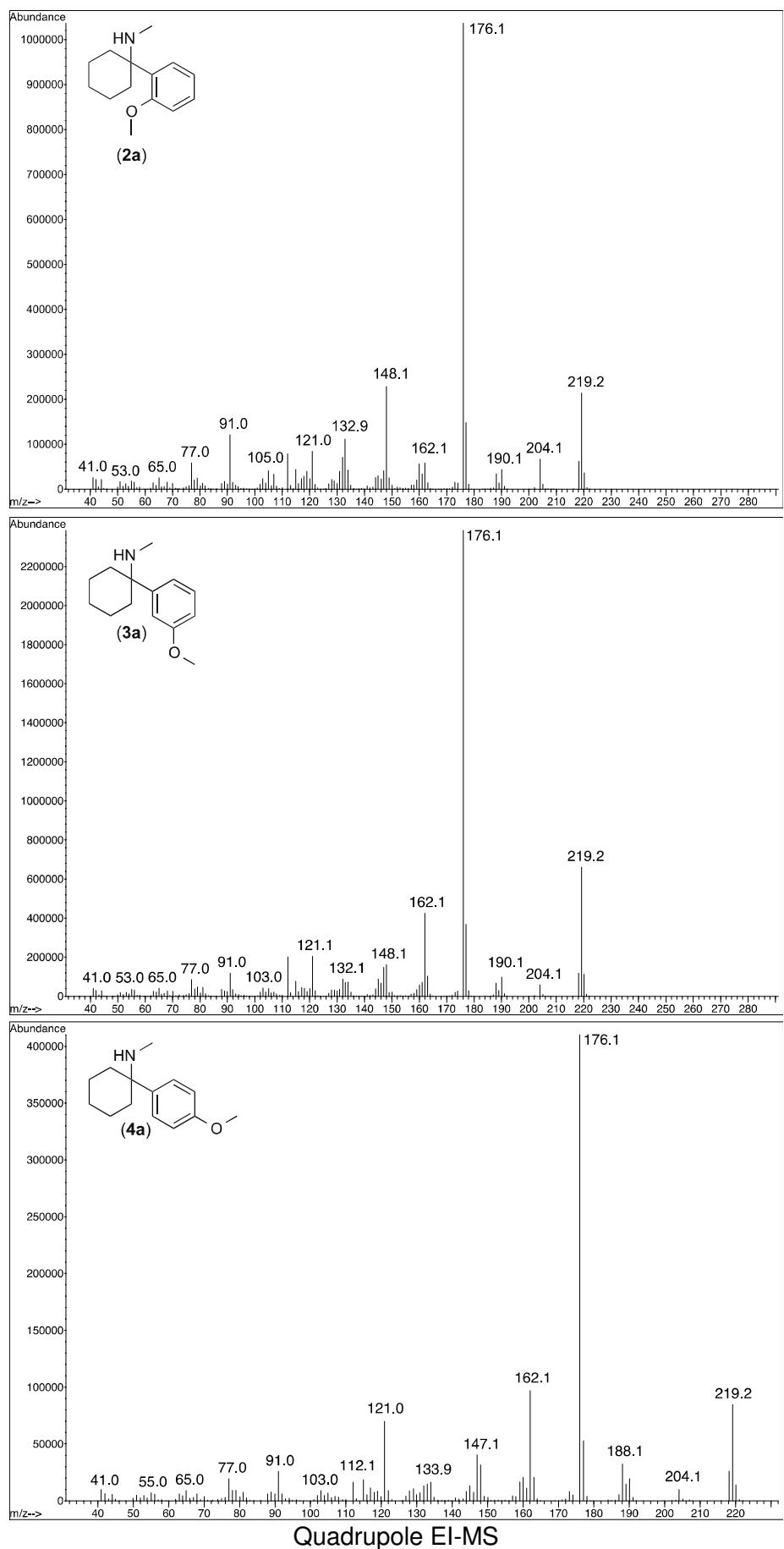
N-Alkyl substitutions of the secondary amines were shifted several ppm upfield with respect to equivalent ^{13}C chemical shifts of tertiary amines. Likewise, terminal aliphatic carbons were always found further upfield from their non-terminal counterparts. For example, the difference with the α ^{13}C chemical shift between 3-MeO-PCMe (**3a**) and 3-MeO-PCE (**3b**) was 10.69 ppm. In the case of 3-MeO-PCPr (**3c**), the α resonance shifted 17.25 ppm downfield and this shift is common in the ^{13}C spectra of various *N*-alkyl-amines and reflects greater deshielding with increasing alkyl substitution.^[2,4] This effect was also observed with the equivalent ^1H chemical shifts (Tables 1–3). Finally, the C_c ^{13}C chemical shifts of equivalent aryl substituents exhibited minimal chemical shift differences.

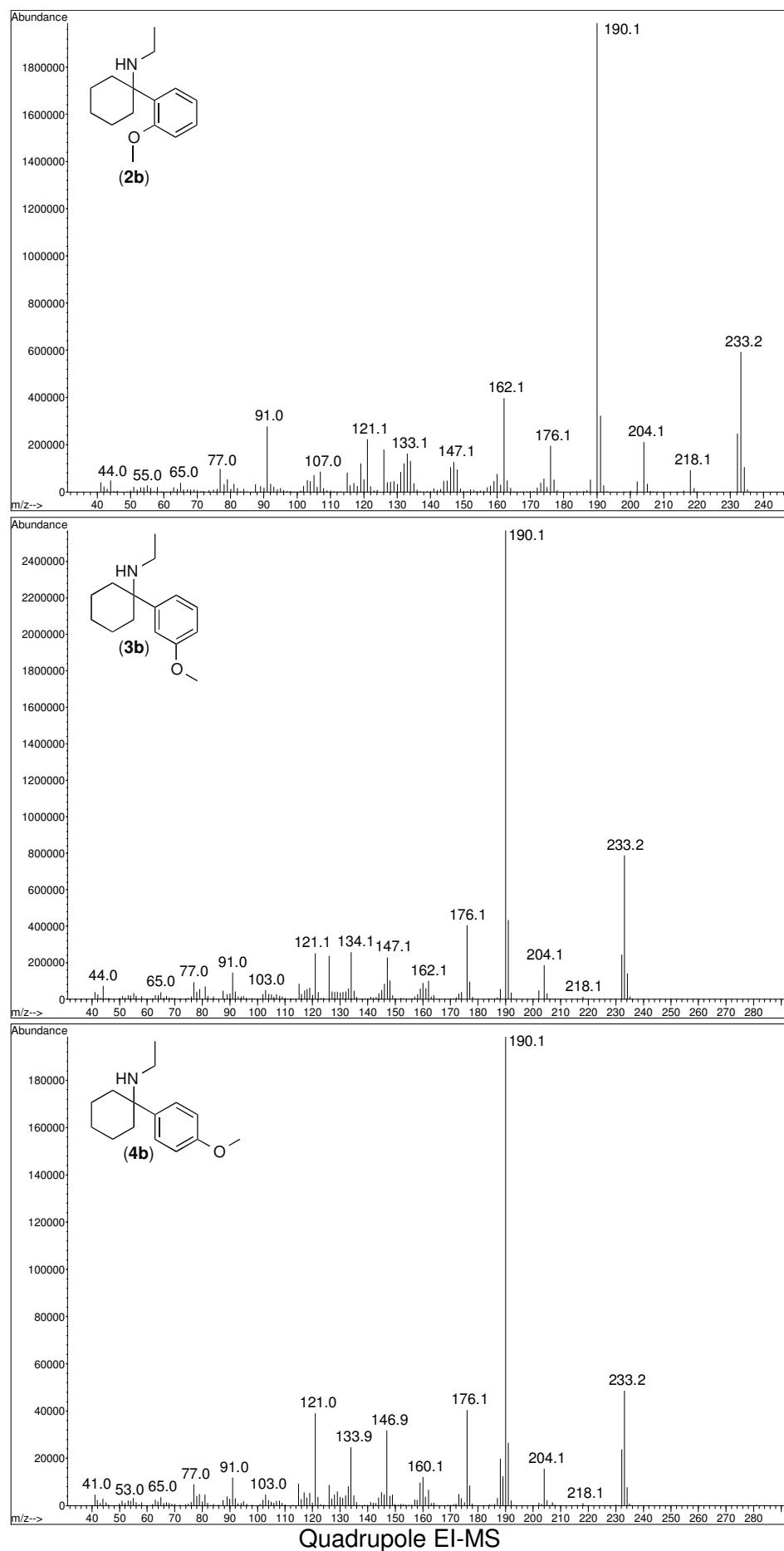
References

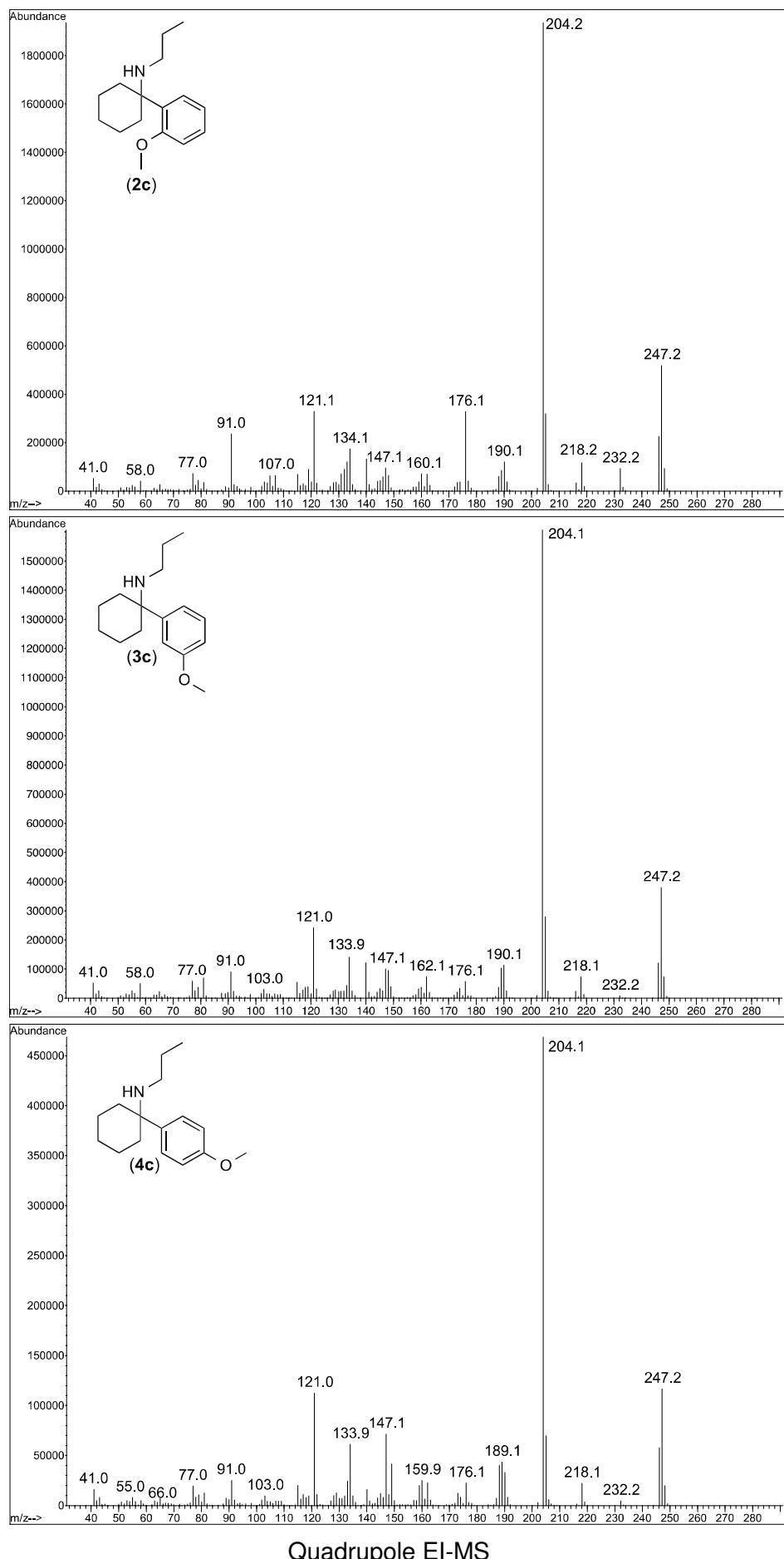
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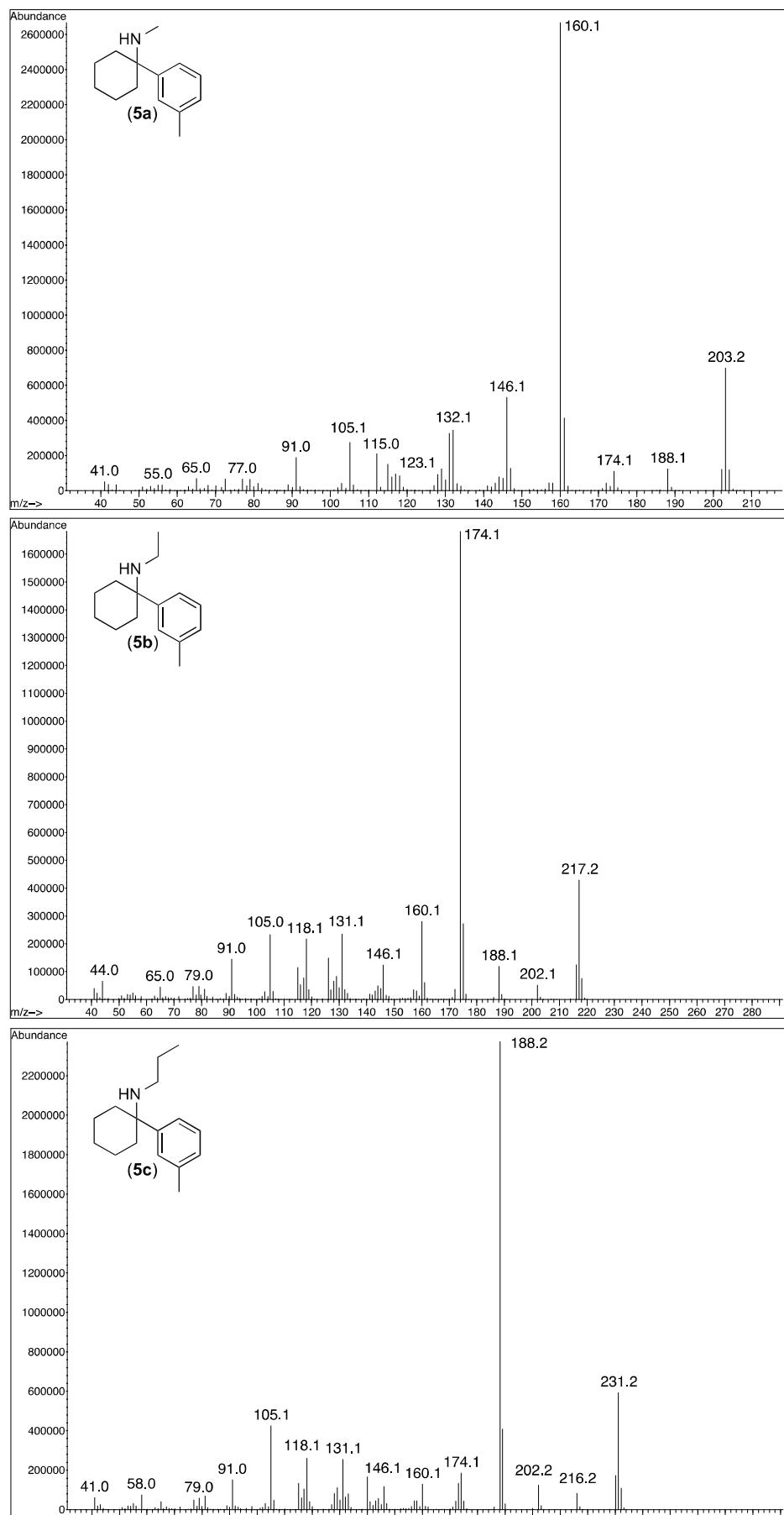


Quadrupole EI-MS

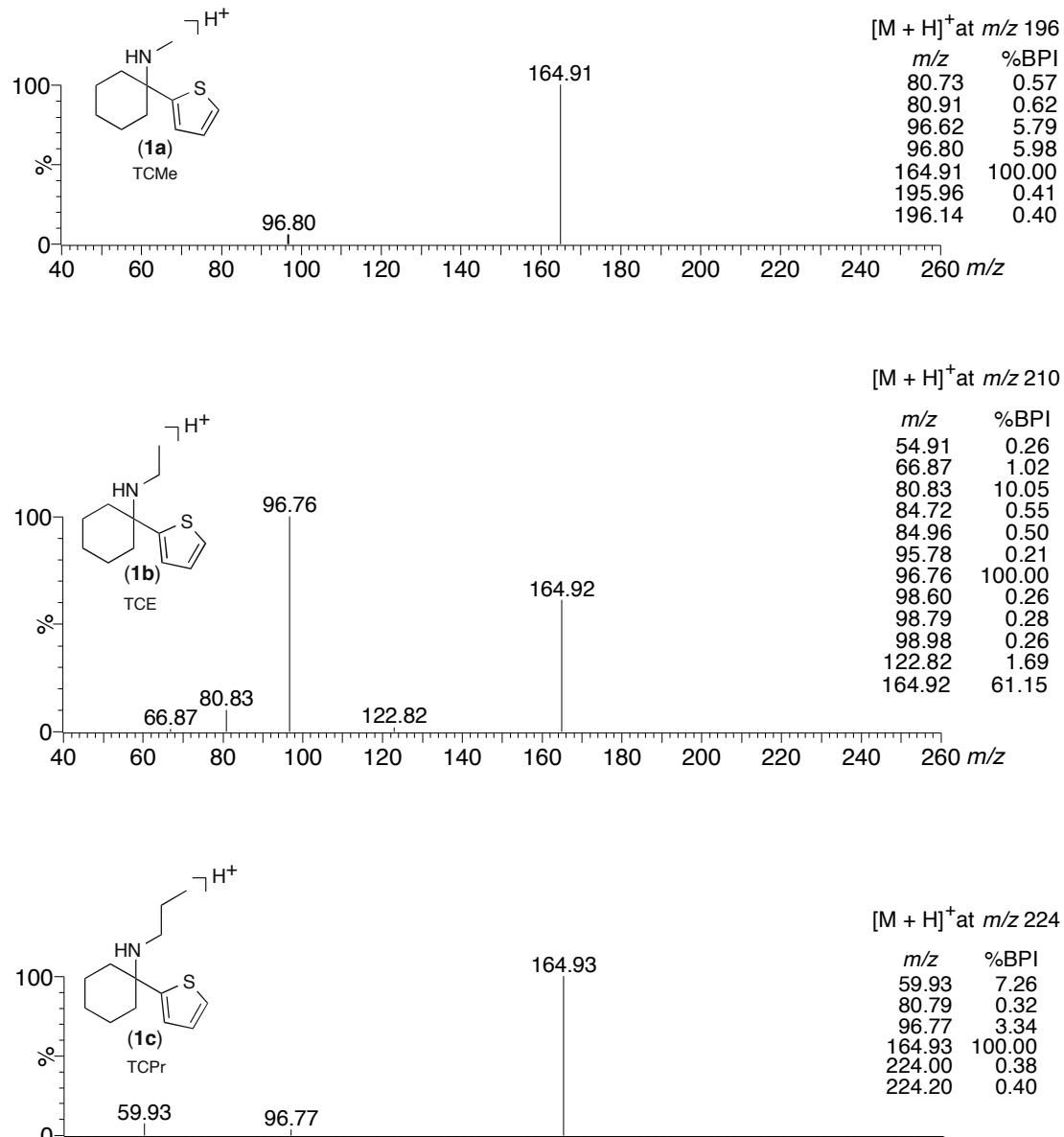




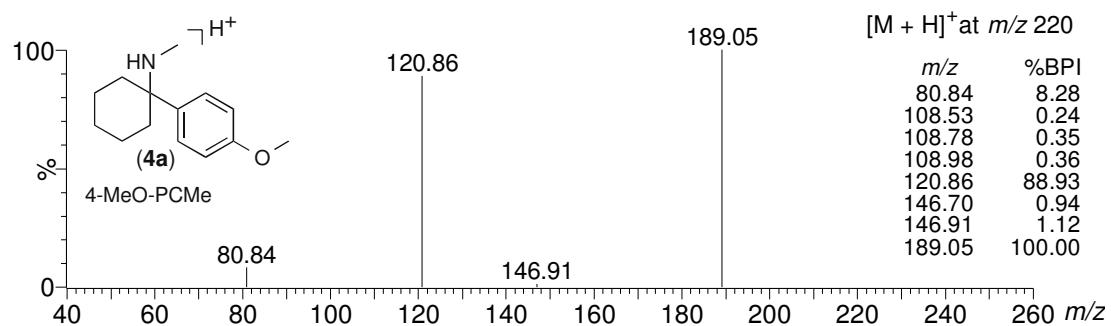
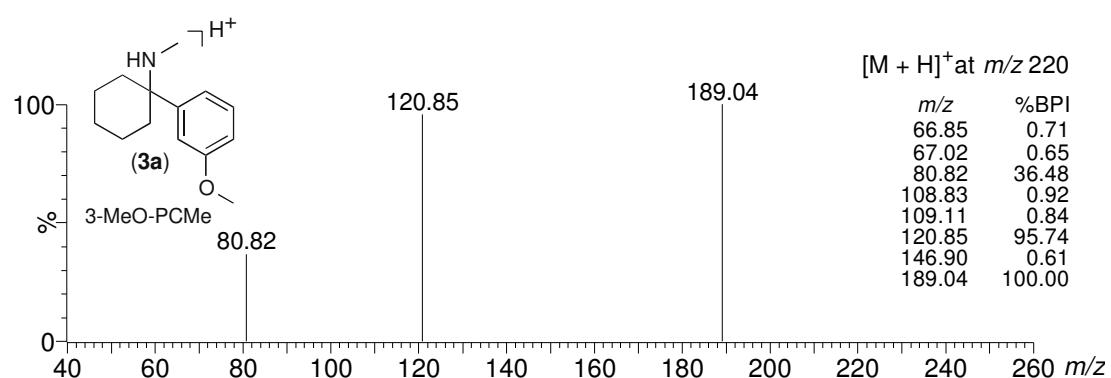
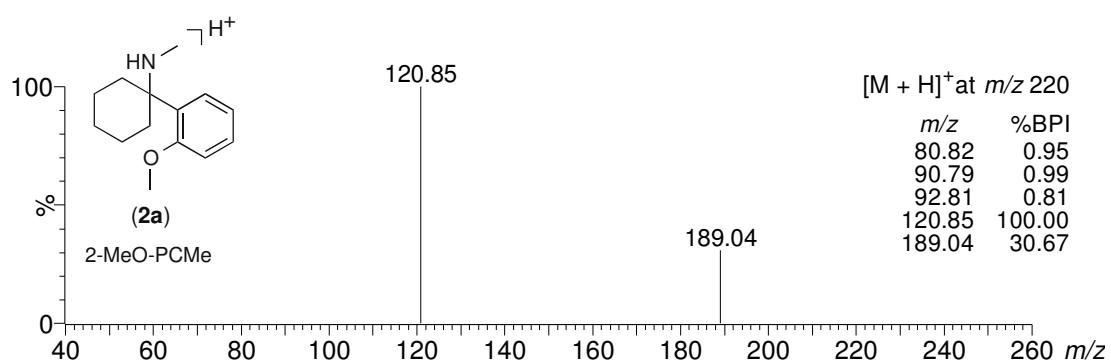




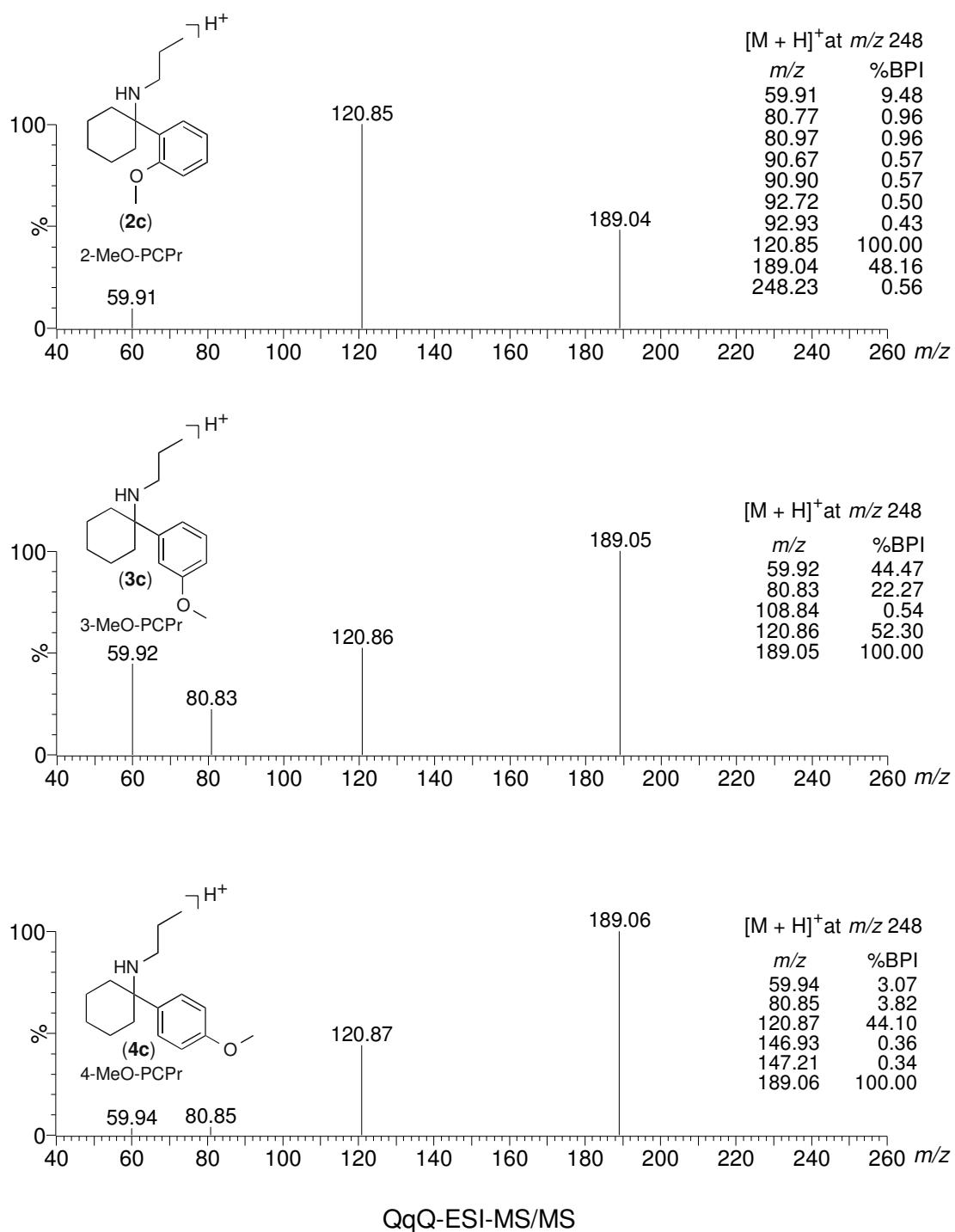
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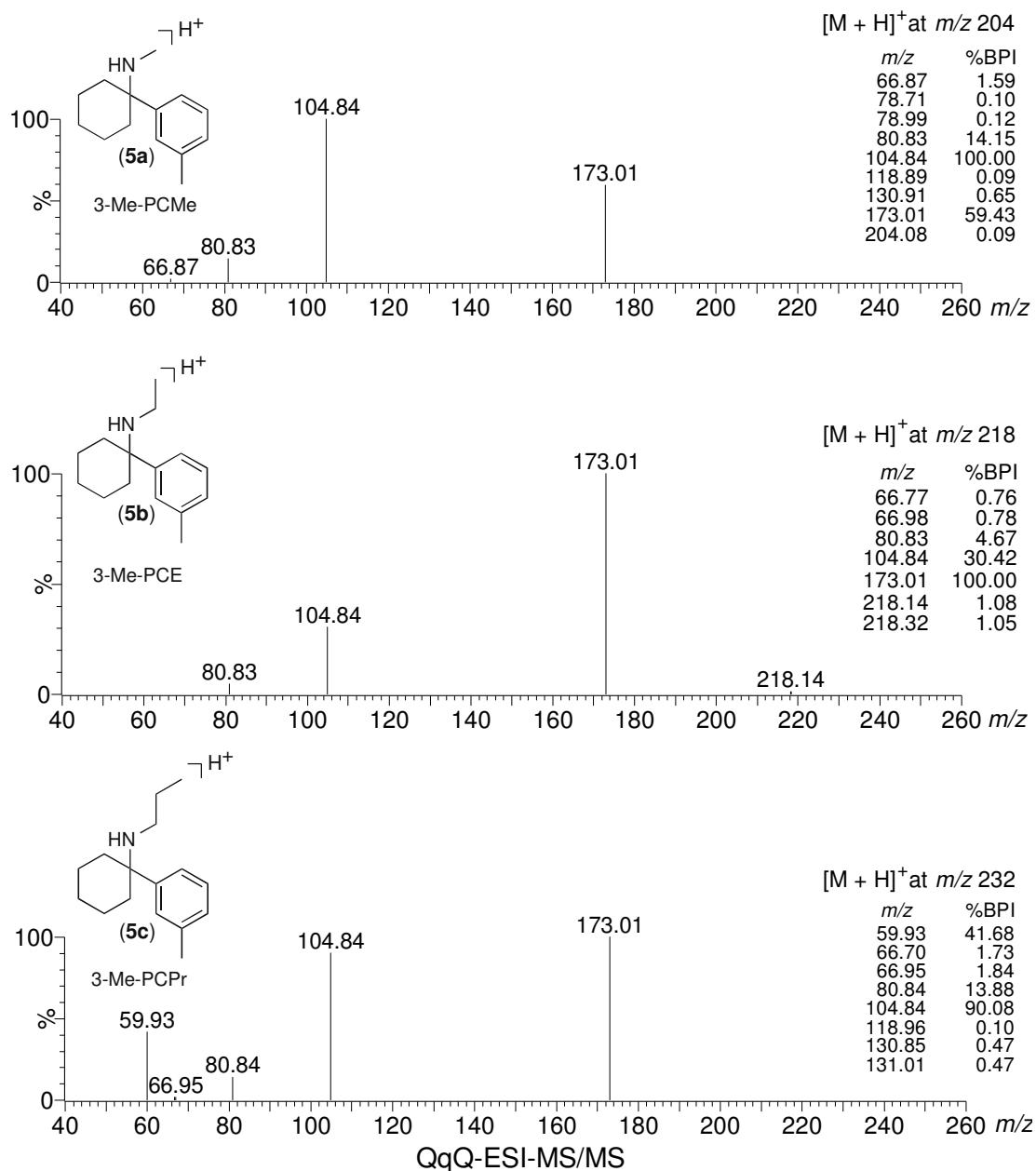


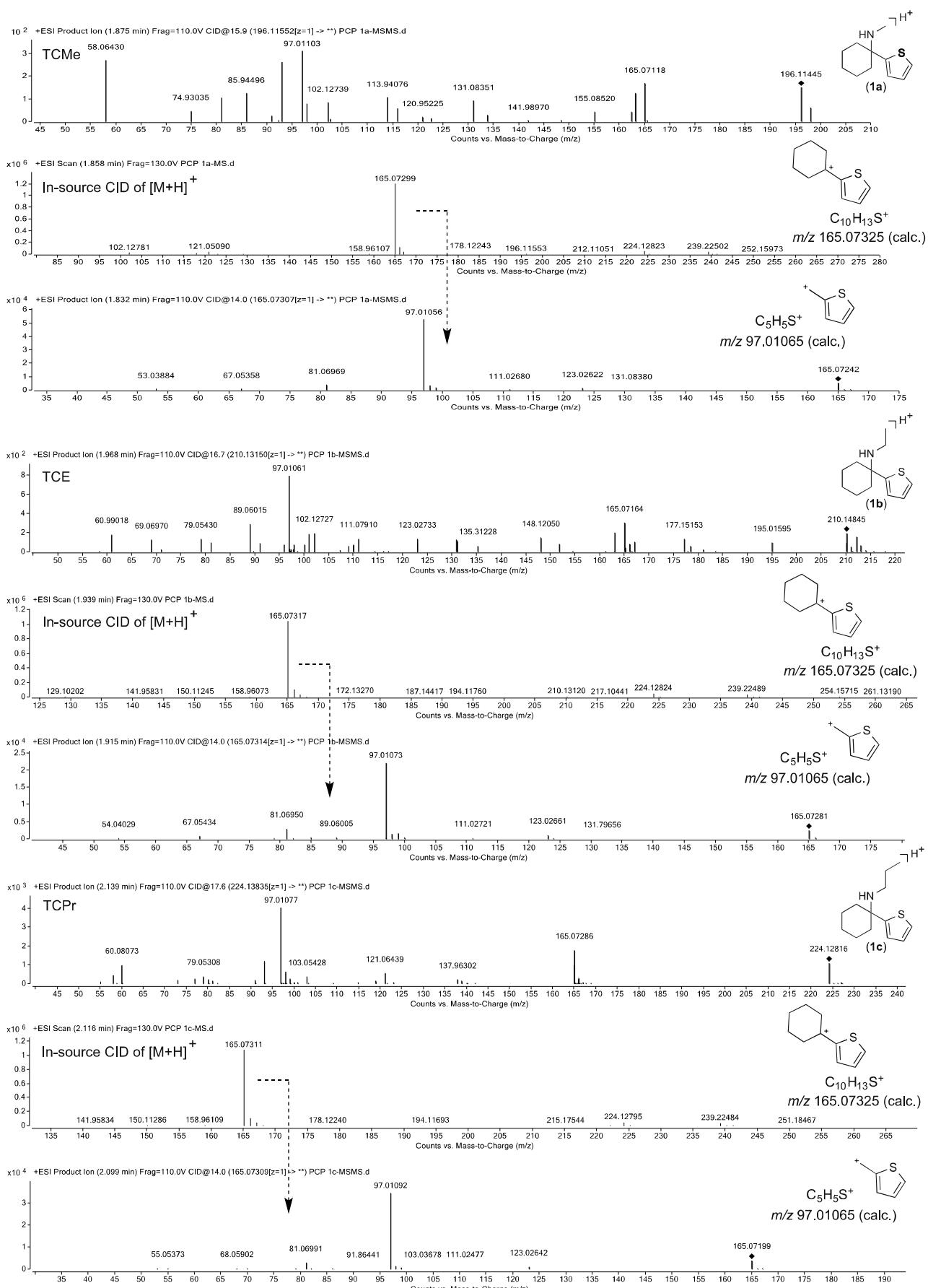
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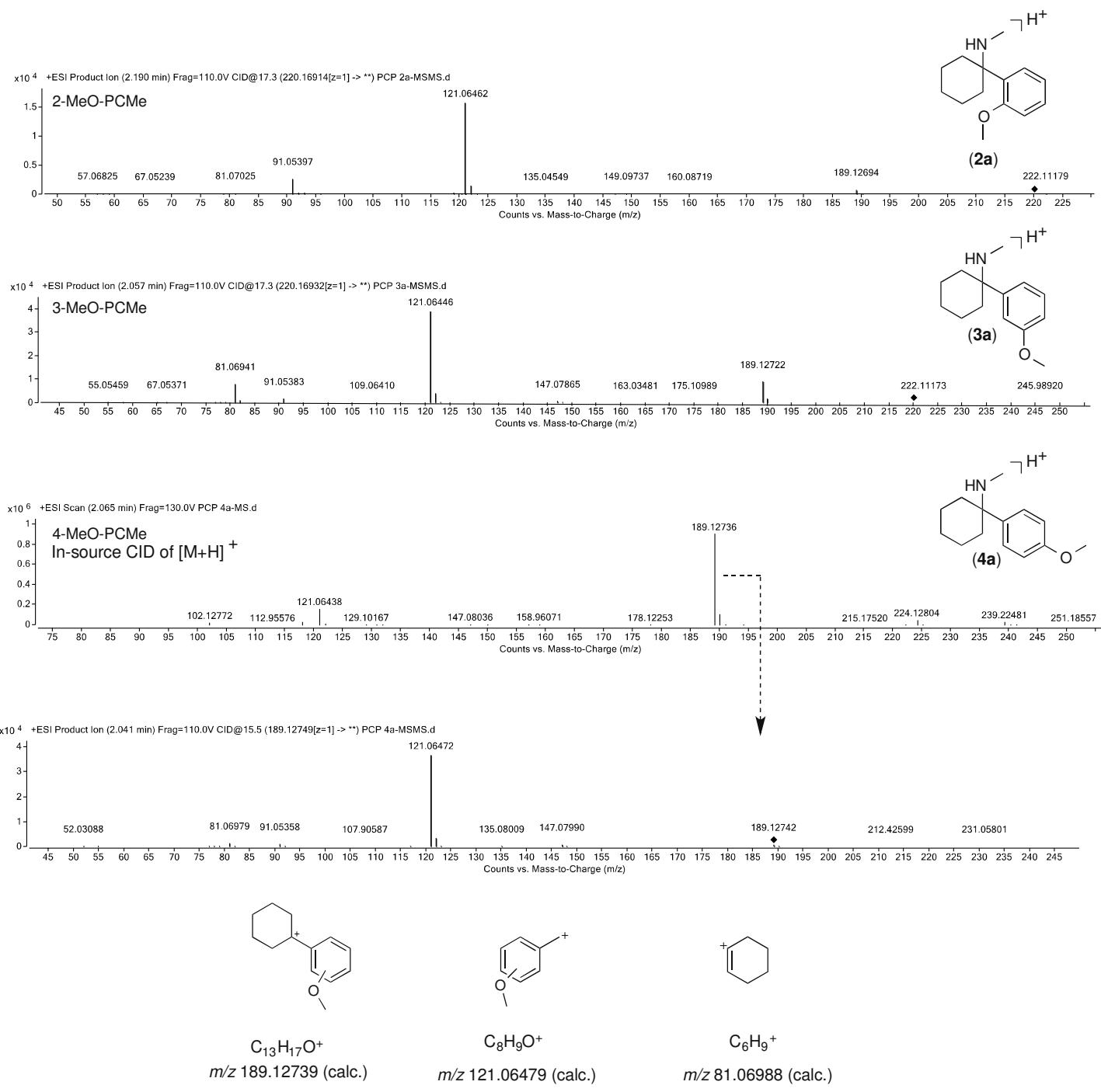
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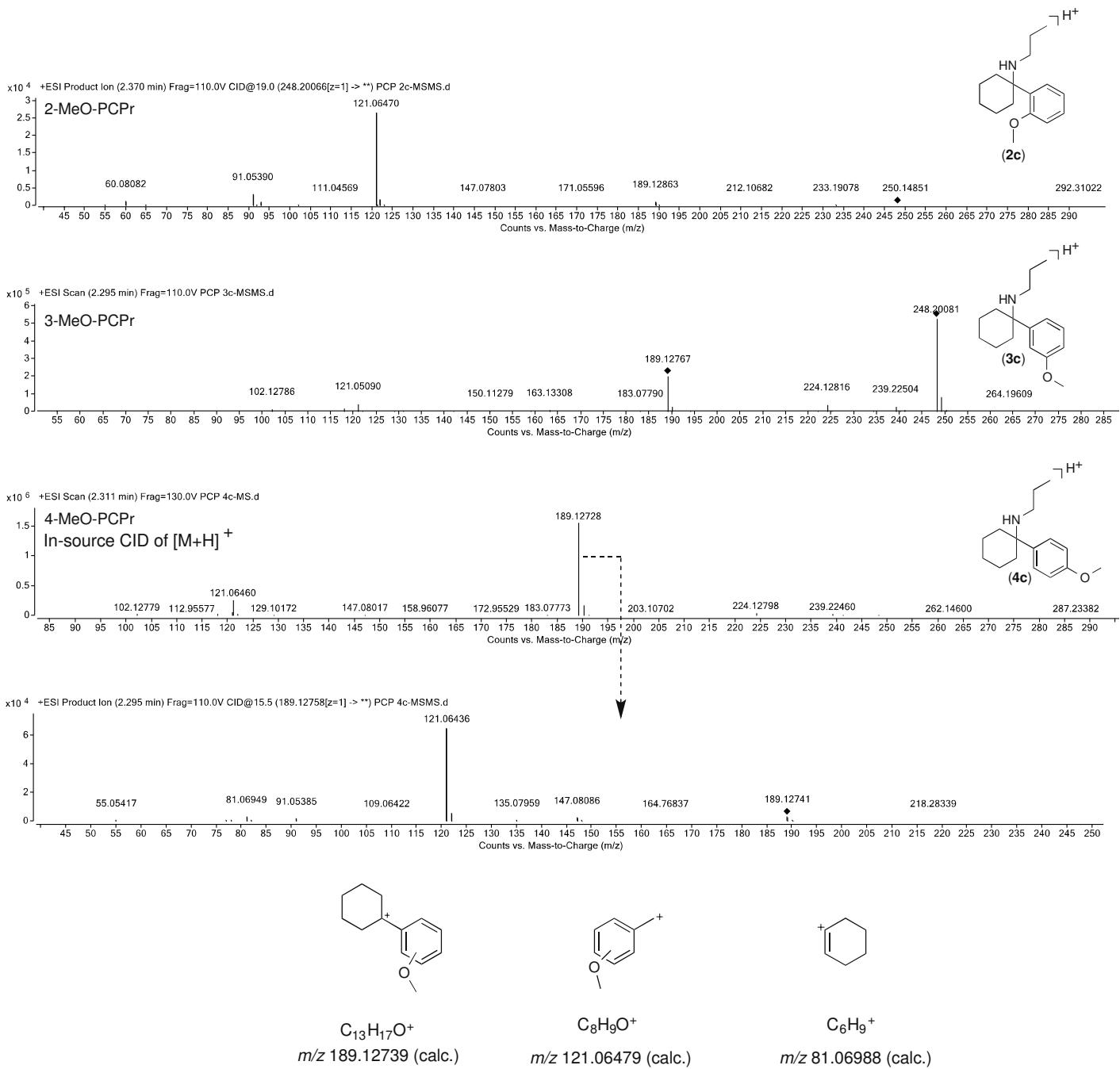


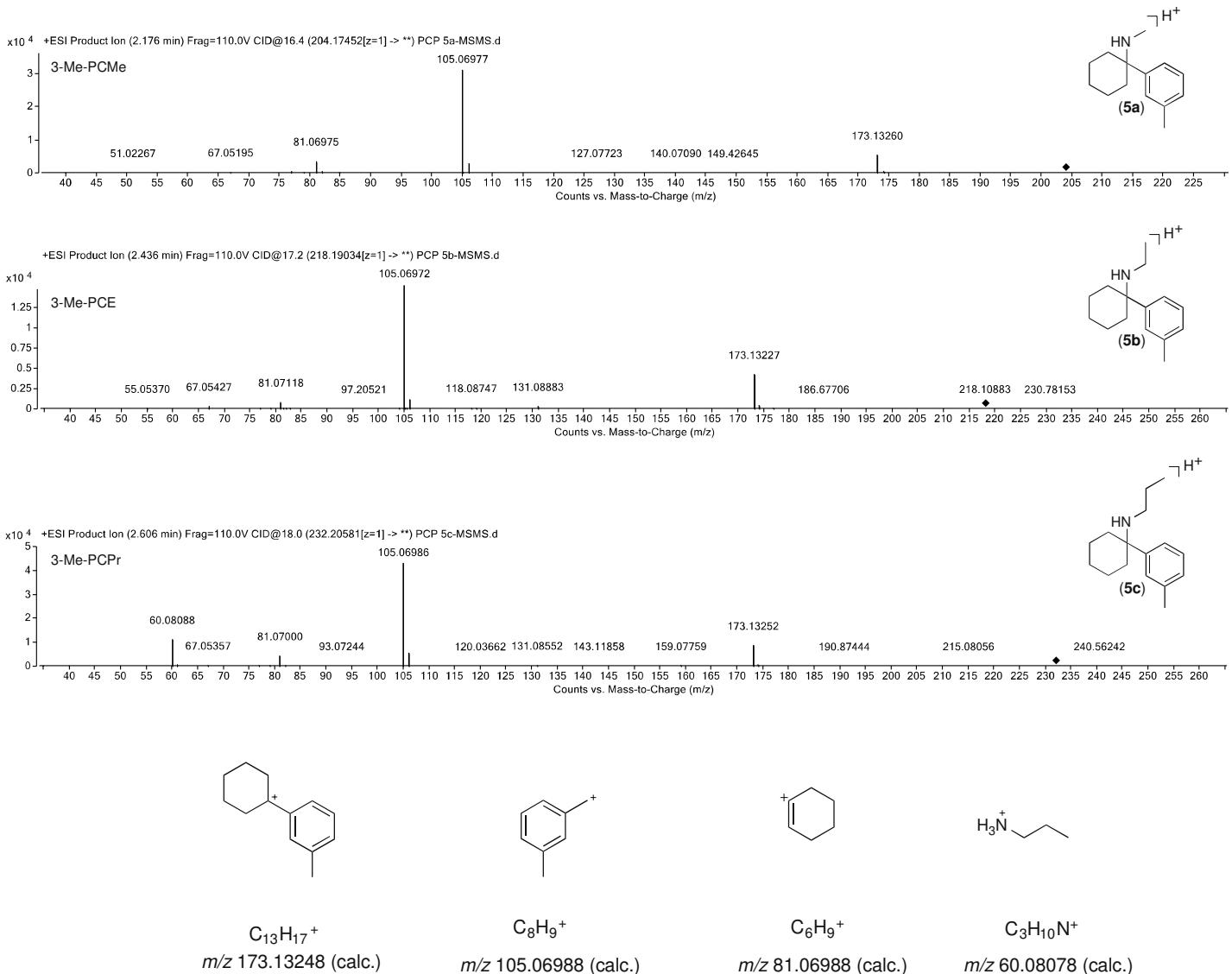


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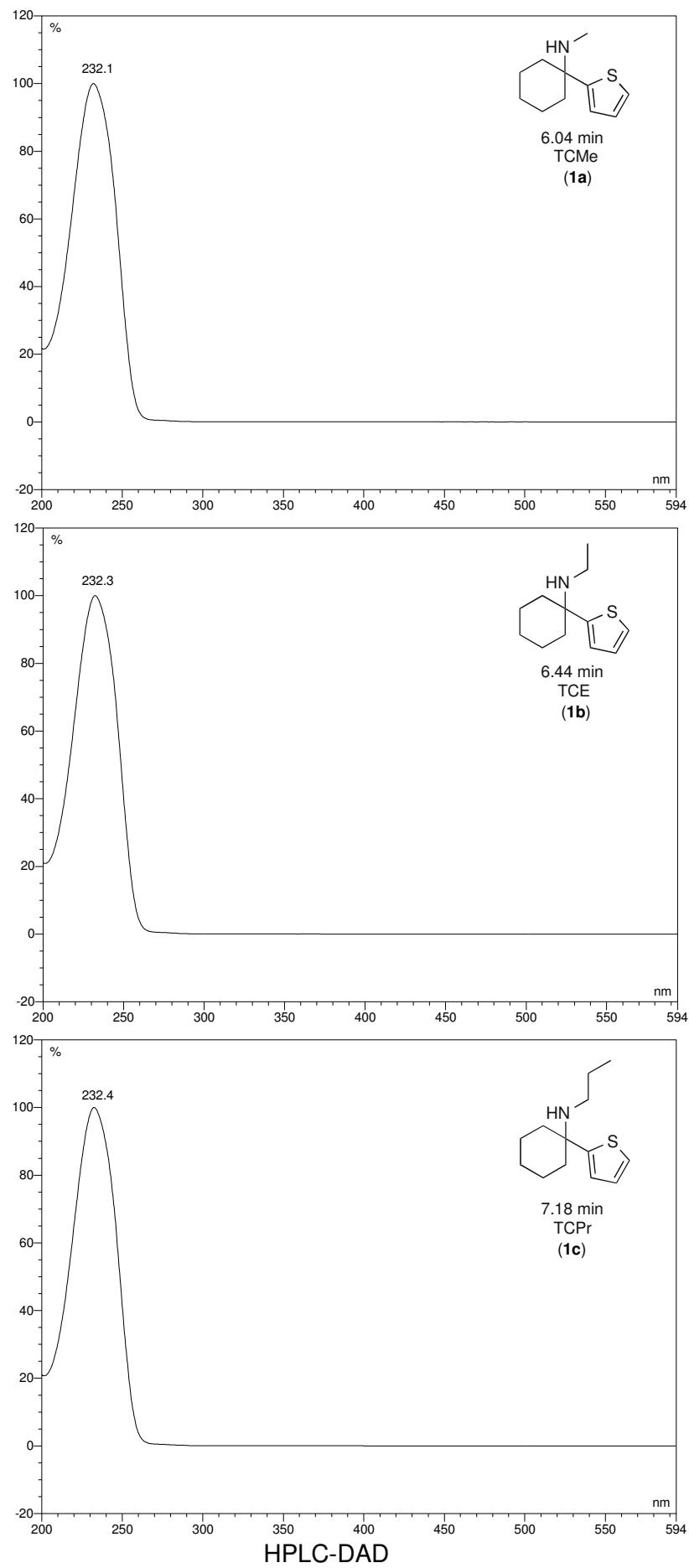


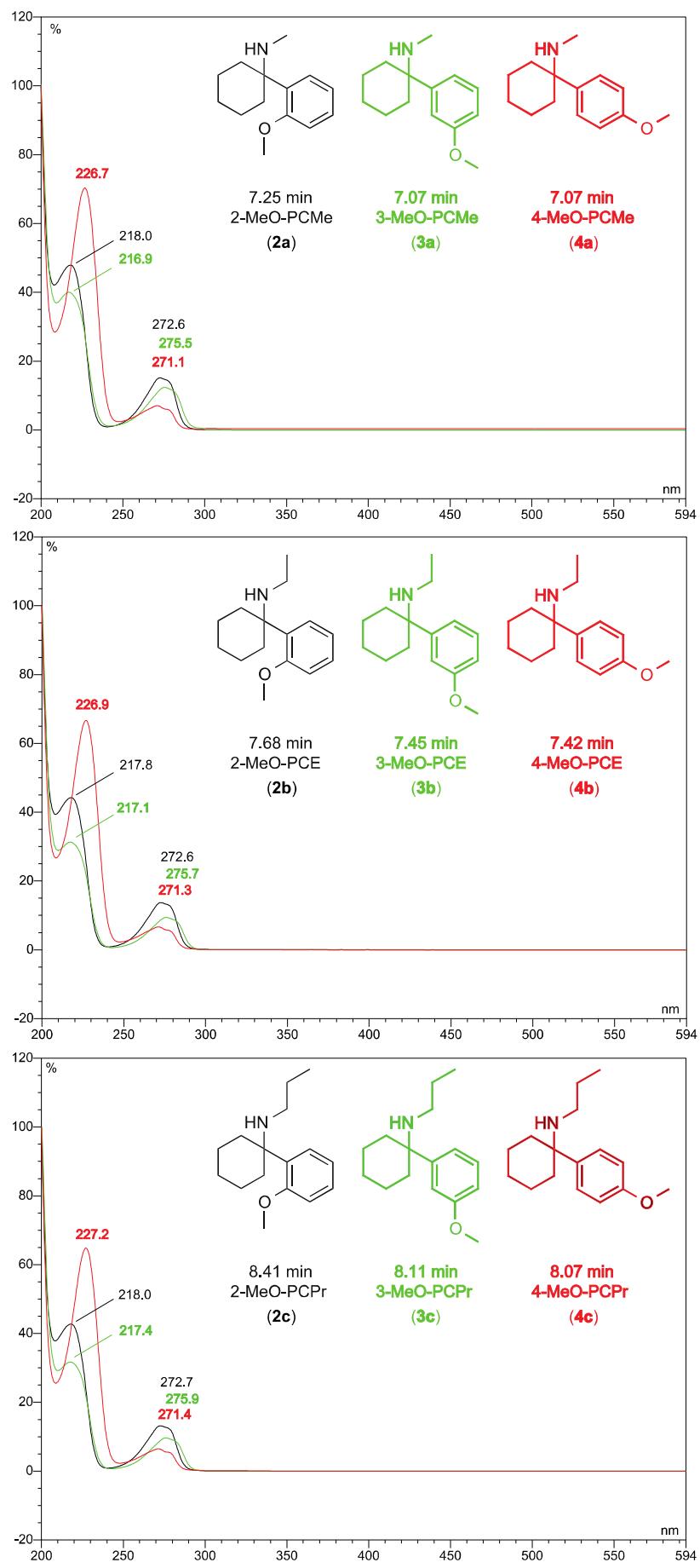
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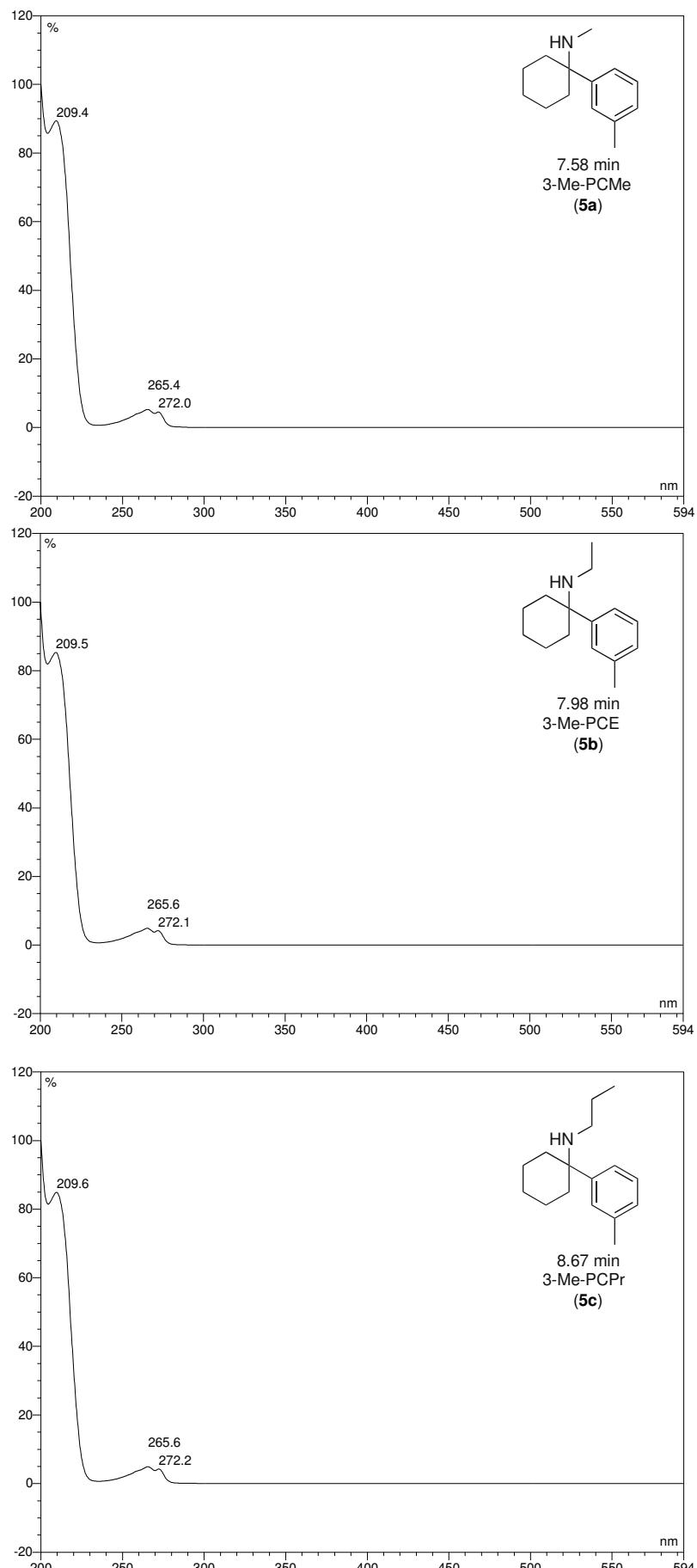


UHPLC-ESI-QTOF-MS/MS





HPLC-DAD



HPLC-DAD

