**SUPPORTING INFORMATION**

**Distinguishing Between Isobaric Ions Using Microdroplet Hydrogen-Deuterium Exchange Mass Spectrometry**

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**Figure S1.** **CID-MS/MS spectra of (A) codeine and (B) hydrocodone. The black dot indicates the precursor ion.**

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**Figure S2. CID-MS/MS spectra of (A) 6-acetyl morphine and (B) naloxone. The black dot indicates the precursor ion.**

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**Figure S3. CID-MS/MS spectra of (A) morphine and (B) norcodeine. The black dot indicates the precursor ion.**

**Table S1. Isobaric ions that were frequently detected in saliva or serum and successfully distinguished by HDX-CPSI-MS.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **No** | **Exact *m/z*** | **Adduct Ions** | **Formulae** | **Metabolites** | **Number of Exchangeable** **proton sites** | **Base****peaks** |
| 1 | 118.0862  | [M+H]+ | C5H11NO2 | Betaine | 1 | D0 |
| 5-Aminopentanoic acid | 3 | D1 |
| Valine | 3 | D0 |
| 2 | 141.0789 | [M+K]+ | C5H14N2 | Cadaverine | 4 | D2 |
| N-methyl putrescine | 3 | D2 |
| 3 | 146.0459  | [M-H]- | C5H9NO4 | Glutamate | 3 | D2 |
| O-acetyl serine | 2 | D0 |
| N-acetyl serine | 2 | D1 |
| 4 | 280.0904 | [M+Na]+ | C10H15N3O5 | 5-Methylcytidine | 5 | D2 |
| 3-methylcytidine | 4 | D2 |
| 280.0920 | [M+H]+ | C8H20NO6P | glycerophosphocholine | 3 | D2 |
| 5 | 112.0369 | [M+Na]+ | C3H7NO2 | Alanine | 3 | D1 |
| Sarcosine | 2 | D1 |
| 6 | 126.0520  | [M+Na]+ | C4H9NO2 | aminobutyric acid | 3 | D1 |
| N, N-dimethylglycine | 1 | D0 |
| 7 | 137.0706 | [M+H]+ | C7H8N2O | 2-aminobenzamide | 4 | D1 |
| N-methylnicotinamide  | 1 | D0 |

**Table S2. The relative intensities in HDX patterns acquired from samples of glucose (G) and inositol (I) at different molar ratios.**

|  |  |  |
| --- | --- | --- |
| ***m/z*** | **G:I Simulated HDX Patterns** | **G:I Observed HDX Patterns** |
| 1:1 | 3:1 | 1:3 | 1:1 | 3:1 | 1:3 |
| 203.05 | 46 | 55 | 33 | 41 | 55 | 38 |
| 204.06 | 73 | 82 | 57 | 72 | 78 | 63 |
| 205.07 | 100 | 100 | 91 | 100 | 100 | 95 |
| 206.08 | 95 | 83 | 100 | 87 | 91 | 100 |
| 207.09 | 64 | 49 | 74 | 52 | 51 | 79 |
| 208.10 | 28 | 19 | 35 | 17 | 18 | 40 |
| 209.11 |  4 |  2 |  6 |  5 |  6 |  7 |