**Table S1.** Target analytes and corresponding internal standers.

| Analyte | Internal Standard |
|---|---|
| Methamphetamine | Methamphetamine-d8 |
| Amphetamine | Amphetamine-d8 |
| 3,4-Methylenedioxymethamphetamine | 3,4-Methylenedioxymethamphetamine-d5 |
| 3,4-Methylene-dioxyamphetamine | 3,4-Methylene-dioxyamphetamine -d5 |
| Ketamine | Ketamine-d4 |
| Norketamine | Norketamine-d4 |
| 6-Acetylmorphine | 6-Acetylmorphine-d6 |
| Morphine | Morphine-d3 |
| Codeine | Codeine-d6 |
| Methadone | Methadone-d9 |
| 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine | 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine-d3 |
| Cocaine | Cocaine-d3 |
| Benzoylecgonine | Benzoylecgonine-d3 |
| Cathinone | Cathinone-d5 |
| Mephedrone | Mephedrone-d3 |
| p-Methoxymethamphetamine | p-Methoxymethamphetamine-d3 |
| Benzylpiperazine | Benzylpiperazine-d7 |
| 1-(3-chlorophenyl) Piperazine | 1-(3-chlorophenyl) Piperazine-d8 |
| 3-Trifluoromethylphenylpiperazine | 3-Trifluoromethylphenylpiperazine-d4 |
| 4-Iodo-2,5-Dimethoxyphenethylamine | 4-Iodo-2,5-Dimethoxyphenethylamine-d3 |
| Tramadol | Tramadol-$^{13}$C-d3 |
| Fentanyl | Fentanyl-d5 |
| Methylone | Methylone-d3 |
| 3,4-Methylenedioxypyrovalerone | 3,4-Methylenedioxypyrovalerone-d8 |

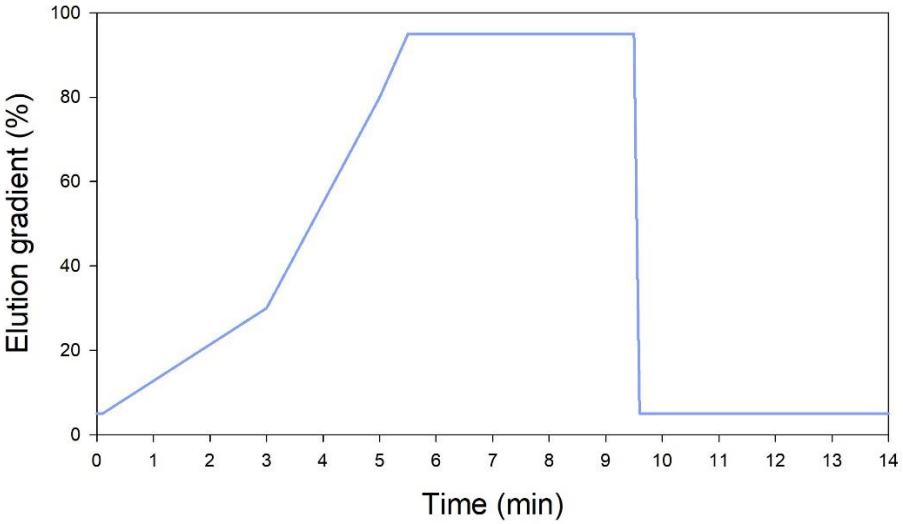


**Figure S1.** The elution gradient of mobile phase B (MeOH).

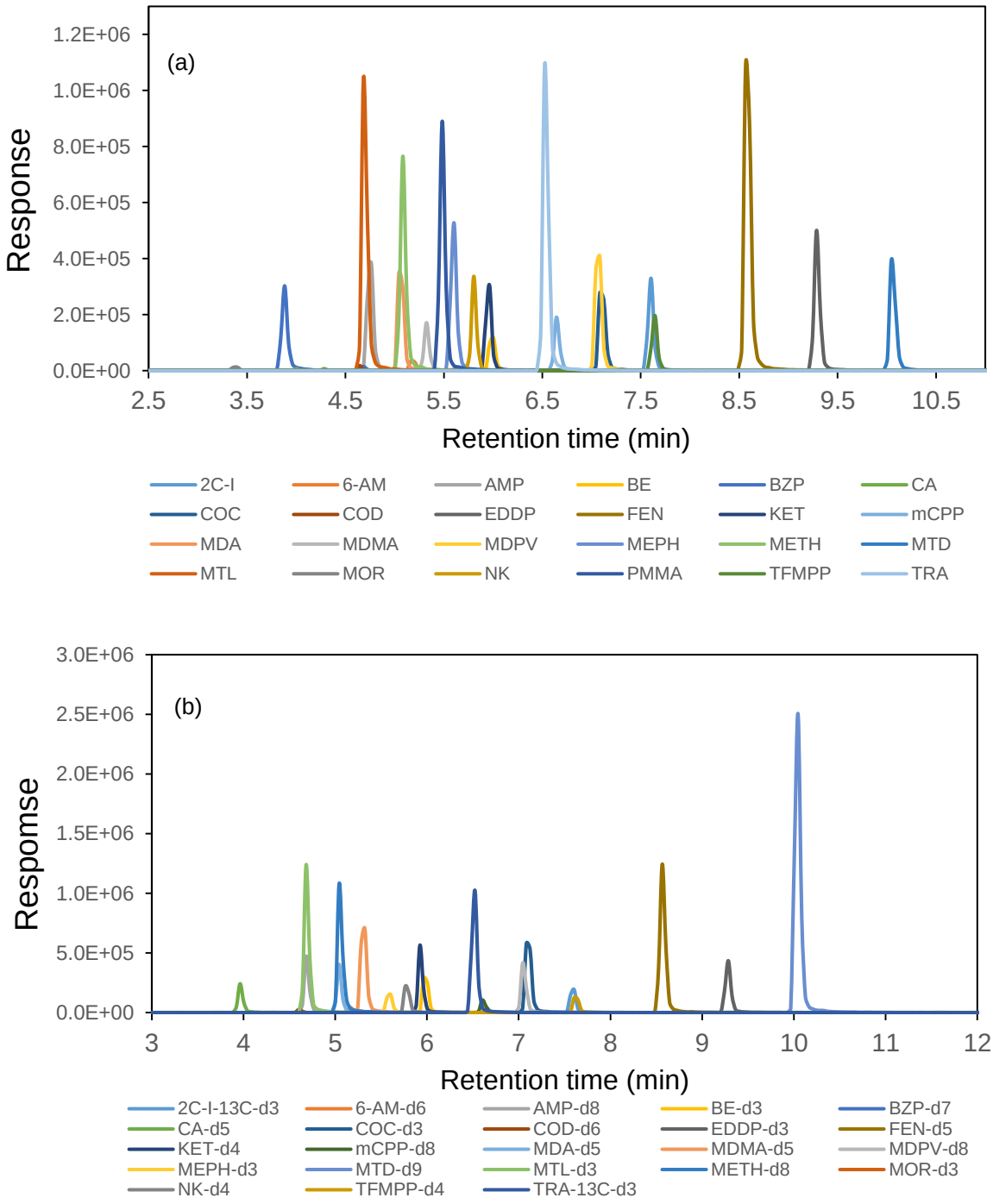


**Figure S2.** Chromatogram of 24 analyzed substances (**a**) and their corresponding deuterated (**b**).

**Table S2.** MS parameters (quantifier and qualifier ions), declustering potential, collision energy and retention time.

| Analyte | Retention time (min) | Precursor Ion (m/z) | Declustering Potential (V) | Quantifier | | Qualifier | |
|---|---|---|---|---|---|---|---|
| | | | | Product Ion (m/z) | Collision Energy (V) | Product Ion (m/z) | Collision Energy (V) |
| Methamphetamine | 5.08 | 150.1 | 35 | 119.2 | 15 | 91.2 | 20 |
| Amphetamine | 4.76 | 136.1 | 40 | 119.1 | 15 | 91.2 | 20 |
| Ketamine | 5.96 | 238.1 | 50 | 207.1 | 20 | 125.1 | 38 |
| Norketamine | 5.80 | 224.1 | 40 | 125.1 | 32 | 207.1 | 16 |
| Morphine | 3.40 | 286.2 | 90 | 165.1 | 50 | 201.3 | 35 |
| Codeine | 4.64 | 300.1 | 108 | 199.1 | 40 | 165.1 | 54 |
| 6-Acetylmorphine | 5.16 | 328.1 | 90 | 165.2 | 49 | 211.1 | 35 |
| Cocaine | 7.08 | 304.1 | 114 | 182.2 | 26 | 150.3 | 34 |
| Benzoylecgonine | 6.00 | 290.1 | 107 | 168.1 | 26 | 105.1 | 40 |
| 3,4-Methylenedioxymethamphetamine | 5.32 | 193.8 | 70 | 162.9 | 15 | 134.9 | 25 |
| 3,4-Methylene-dioxyamphetamine | 5.04 | 180.1 | 41 | 162.9 | 15 | 135.0 | 26 |
| Methadone | 10.05 | 310.3 | 110 | 265.1 | 20 | 105.1 | 40 |
| 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine | 9.29 | 278.2 | 100 | 234.2 | 33 | 249.2 | 33 |
| p-Methoxymethamphetamine | 5.48 | 180.2 | 50 | 149.2 | 23 | 121.2 | 30 |
| Methylone | 4.68 | 208.2 | 55 | 160.0 | 25 | 190.1 | 16 |
| 4-Iodo-2,5-Dimethoxyphenethylamine | 7.60 | 308.2 | 55 | 291.0 | 20 | 275.8 | 30 |
| Mephedrone | 5.60 | 178.1 | 80 | 160.0 | 19 | 145.2 | 29 |
| Cathinone | 4.28 | 150.0 | 80 | 132.1 | 19 | 117.1 | 32 |
| 3,4-Methylenedioxypyrovalerone | 7.08 | 276.1 | 80 | 126.1 | 34 | 135.0 | 38 |
| Benzylpiperazine | 3.88 | 177.1 | 80 | 91.0 | 32 | 85.1 | 22 |
| 3-Trifluoromethylphenylpiperazine | 7.64 | 231.0 | 80 | 188.0 | 33 | 119.0 | 42 |
| 1-(3-chlorophenyl) Piperazine | 6.64 | 197.0 | 80 | 154.1 | 27 | 119.2 | 35 |
| Tramadol | 6.52 | 264.4 | 50 | 58.1 | 30 | 246.3 | 15 |
| Fentanyl | 8.57 | 337.4 | 50 | 188.1 | 30 | 216.1 | 30 |
| Methamphetamine-d8 | 5.04 | 158.1 | 40 | 124.2 | 16 | - | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Amphetamine-d8 | 4.68 | 144.1 | 40 | 127.1 | 13 | - | - |
| 3,4-Methylenedioxymethamphetamine-d5 | 5.32 | 199.1 | 65 | 165.0 | 17 | - | - |
| 3,4-Methylene-dioxyamphetamine-d5 | 5.04 | 185.1 | 55 | 168.0 | 15 | - | - |
| Ketamine-d4 | 5.92 | 242.1 | 60 | 129.1 | 37 | - | - |
| Norketamine-d4 | 5.76 | 228.1 | 45 | 129.1 | 30 | - | - |
| 6-Acetylmorphine-d6 | 5.16 | 334.2 | 90 | 211.2 | 36 | - | - |
| Morphine-d3 | 3.44 | 289.1 | 90 | 181.1 | 51 | - | - |
| Codeine-d6 | 4.60 | 306.2 | 103 | 165.2 | 55 | - | - |
| Methadone-d9 | 10.05 | 319.3 | 60 | 268.2 | 22 | - | - |
| 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine-d3 | 9.29 | 281.2 | 100 | 234.2 | 33 | - | - |
| Cocaine-d3 | 7.08 | 307.1 | 105 | 185.1 | 28 | - | - |
| Benzoylecgonine-d3 | 5.96 | 293.2 | 93 | 171.2 | 27 | - | - |
| Cathinone-d5 | 3.96 | 155.3 | 50 | 137.1 | 16 | - | - |
| Mephedrone-d3 | 5.60 | 181.1 | 80 | 163.0 | 19 | - | - |
| Benzylpiperazine-d7 | 7.08 | 184.1 | 80 | 98.0 | 32 | - | - |
| 1-(3-chlorophenyl) Piperazine-d8 | 6.60 | 205.1 | 80 | 158.1 | 31 | - | - |
| 3-Trifluoromethylphenylpiperazine-d4 | 7.60 | 235.1 | 80 | 190.0 | 32 | - | - |
| 4-Iodo-2,5-Dimethoxyphenethylamine-$^{13}$C-d3 | 7.60 | 312.3 | 53 | 294.9 | 19 | - | - |
| Fentanyl-d5 | 8.57 | 342.3 | 90 | 187.9 | 30 | - | - |
| Tramadol-$^{13}$C-d3 | 6.52 | 268.4 | 50 | 58.1 | 40 | - | - |
| Methylone-d3 | 4.68 | 211.3 | 50 | 162.9 | 23 | - | - |
| 3,4-Methylenedioxypyrovalerone-d8 | 7.04 | 284.1 | 80 | 134.2 | 39 | - | - |

**Table S3.** Method validation parameters: recovery, matrix effect, repeatability, reproducibility, LOD, LOQ and procedure bank.

| Analyte | Recovery | Matrix | Repeatability | Reproducibility | LOD [a] | LOQ [b] | Procedure Bank |
|---|---|---|---|---|---|---|---|
| | 400 ng/L ($n$ = 3) (%) | | 10 µg/L ($n$ = 5) (RSD %) [c] | | ng/L | ng/L | ng/L ($n$ = 5) |
| Methamphetamine | 92.2 ± 4.2 | −5.5 ± 8.8 | 2.3 | 4.3 | 0.2 | 0.8 | <LOD |
| Amphetamine | 98.7 ± 5.5 | −2.1 ± 0.9 | 5.8 | 8.8 | 2.0 | 4.0 | <LOD |
| Ketamine | 97.6 ± 5.5 | −3.0 ± 2.3 | 4.3 | 5.8 | 0.2 | 0.8 | <LOD |
| Norketamine | 98.2 ± 6.2 | 4.9 ± 5.8 | 2.5 | 3.9 | 2.0 | 0.8 | <LOD |
| Morphine | 95.6 ± 13.6 | −6.1 ± 4.7 | 1.6 | 6.1 | 0.5 | 2.0 | <LOD |
| Codeine | 95.3 ± 6.2 | 0.2 ± 10.0 | 4.9 | 9.1 | 0.5 | 2.0 | <LOD |
| 6-Acetylmorphine | 83.6 ± 10.1 | 17.2 ± 7.3 | 3.6 | 3.6 | 0.5 | 0.8 | <LOD |
| Cocaine | 95.1 ± 8.2 | −4.2 ± 2.0 | 4.8 | 5.5 | 0.2 | 0.8 | <LOD |
| Benzoylecgonine | 96.1 ± 3.6 | −6.3 ± 1.3 | 2.0 | 3.7 | 0.2 | 0.8 | <LOD |
| 3,4-Methylenedioxymethamphetamine | 104.9 ± 6.2 | 10.9 ± 8.3 | 3.4 | 3.3 | 0.2 | 0.8 | <LOD |
| 3,4-Methylene-dioxyamphetamine | 90.2 ± 5.5 | −5.8 ± 2.1 | 0.5 | 1.4 | 2.0 | 4.0 | <LOD |
| Methadone | 102.4 ± 4.1 | −1.2 ± 5.5 | 1.2 | 5.1 | 0.2 | 0.8 | <LOD |
| 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine | 104.9 ± 3.8 | 0.6 ± 4.1 | 3.9 | 4.0 | 0.2 | 0.8 | <LOD |
| p-Methoxymethamphetamine | 86.4 ± 4.8 | −10.3 ± 3.5 | 2.8 | 6.4 | 2.0 | 4.0 | <LOD |
| Methylone | 104.8 ± 7.6 | 2.2 ± 4.0 | 3.9 | 2.5 | 0.2 | 0.8 | <LOD |
| 4-Iodo-2,5-Dimethoxyphenethylamine | 100.2 ± 7.0 | −3.0 ± 1.7 | 6.9 | 8.7 | 0.2 | 0.8 | <LOD |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mephedrone | 101.2 ± 3.7 | 5.3 ± 3.5 | 1.1 | 5.9 | 0.2 | 0.8 | <LOD |
| Cathinone | 99.6 ± 11.7 | −7.2 ± 2.5 | 2.3 | 2.4 | 0.2 | 0.8 | <LOD |
| 3,4-Methylenedioxypyrovalerone | 102.7 ± 5.1 | 6.2 ± 2.6 | 6.1 | 7.1 | 0.2 | 0.8 | <LOD |
| Benzylpiperazine | 88.2 ± 9.7 | 8.3 ± 9.6 | 6.3 | 14.8 | 0.2 | 0.8 | <LOD |
| 3-Trifluoromethylphenylpiperazine | 102.3 ± 8.7 | 1.8 ± 2.7 | 4.6 | 9.3 | 0.2 | 0.8 | <LOD |
| 1-(3-chlorophenyl) Piperazine | 96.7 ± 5.2 | −0.4 ± 3.6 | 4.0 | 6.7 | 0.2 | 0.8 | <LOD |
| Tramadol | 91.0 ± 5.1 | −10.1 ± 6.6 | 3.8 | 6.3 | 0.2 | 0.8 | <LOD |
| Fentanyl | 100.4 ± 5.7 | −1.8 ± 1.9 | 1.6 | 3.0 | 0.2 | 0.8 | <LOD |

[a] LOD—limit of detection; [b] LOQ—limit of quantification; [c] RSD—relative standard deviation.

**Table S4.** The human excretion factors of the target drugs, molecular weight ratio of parent and metabolite and typical dose.

| Drug | Selected Biomarker | Excretion Factor (%) | $MW_P/MW_m$ [a] | Typical Dose (mg) |
|---|---|---|---|---|
| Methamphetamine | Methamphetamine | 43 [1] | 1.00 | 30 [2] |
| Ketamine | Ketamine | 16 [b] [2,3] | 1.00 | 75 [2] |
| MDMA [c] | MDMA | 26 [4] | 1.00 | 100 [1] |
| Codeine | Codeine | 30 [5] | 1.00 | 38 [3] |
| Tramadol | Tramadol | 30 [2] | 1.00 | 50 [2] |
| Cocaine | Benzoylecgonine | 29 [6] | 1.05 | 100 [1] |
| Methadone | EDDP | 55 [5] | 1.12 | 25 [4] |
| Morphine | Morphine | 77.7 [7] | 1.00 | 20 [d] [8] |
| Heroin | Morphine | 42 [1] | 1.29 | 15 [9] |

[a] $MW_P/MW_m$—molecular weight ratio of parent and metabolite; [b] Mean excretion factor; [c] MDMA—3,4-Methylenedioxymethamphetamine; [d] Assume the typical dose is same to heroin based on the similar structures;.

**Table S5.** Number of drug dependents of amphetamine-type stimulants and opiates in Malaysia from 2013–2017 [10].

| Year | Opiates | Methamphetamine | Amphetamine-type stimulants tablets [a] |
|---|---|---|---|
| 2013 | 16041 | 3008 | 476 |
| 2014 | 14502 | 5356 | 1774 |
| 2015 | 16616 | 8807 | 1309 |
| 2016 | 16985 | 12738 | 3395 |
| 2017 | 10154 | 14785 | 5130 |

[a] Includes methamphetamine, ecstasy type (MDMA) and amphetamine.

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