

Table S1 Experimental sample information table

| Drug name | Molecular formula | Molecular weight | CAS |
|-----------------------------|-----------------------|------------------|--------------|
| Norfentanyl | $C_{14}H_{20}N_2O$ | 232.32 | 1609-66-1 |
| Acetylfentanyl | $C_{21}H_{26}N_2O$ | 322.45 | 3258-84-2 |
| Isobutyryl fentanyl | $C_{23}H_{30}N_2O$ | 350.51 | 119618-70-1 |
| P-Fluorofentanyl | $C_{22}H_{27}FN_2O$ | 354.47 | 90736-23-5 |
| Ocfentanyl | $C_{22}H_{27}FN_2O_2$ | 370.47 | 101343-69-5 |
| Thiofentanyl | $C_{20}H_{26}N_2OS$ | 342.50 | 1165-22-6 |
| 4-fluoroisobutyryl fentanyl | $C_{23}H_{29}FN_2O$ | 368.50 | 244195-32-2 |
| Tetrahydrofuran fentanyl | $C_{24}H_{30}N_2O_2$ | 378.52 | 2142571-01-3 |
| Fentanyl | $C_{22}H_{28}N_2O$ | 336.48 | 437-38-7 |
| AP | $C_9H_{13}N$ | 135.21 | 300-62-9 |
| MA | $C_{10}H_{15}N$ | 149.23 | 537-46-2 |
| MDEA | $C_{12}H_{17}NO_2$ | 207.27 | 82801-81-8 |
| MDMA | $C_{11}H_{15}NO_2$ | 193.24 | 42542-10-9 |
| MDA | $C_{10}H_{13}NO_2$ | 179.22 | 4764-17-4 |
| Ephedrine | $C_{10}H_{15}NO$ | 165.12 | 299-42-3 |

Table S2 Information of instruments

| Instrument name | Model | Manufacturer |
|-----------------------------|--------------|---------------------------------|
| LC-MS/MS | TQS | Waters, The United States |
| GC-MS/MS | 7890A-7000 | Agilent, The United States |
| Ultrasound machine | Branson 8510 | Danbury, The United States |
| Nitrogen blowing instrument | N-EVAP 112 | Organomation, The United States |
| Pure water machine | Milli-Q | Millipore, The United States |
| Centrifuge | CF16RXII | HITACHI, Japan |
| Electronic balance | XP205 | Mettler Toledo, Switzerland |

Table S3 Laboratory reagent information sheet

| Reagent name | Purity | Manufacturer |
|--------------------|------------------------|---|
| Methanol | Chromatographic purity | Merck KGaA, Germany |
| Acetonitrile | Chromatographic purity | Merck KGaA, Germany |
| Dimethyl sulfoxide | >99.5% | Honeywell, The United States |
| Hydrochloric acid | Analytical purity | Beijing Institute of Chemical Reagents, China |
| Formic acid | Chromatographic purity | Honeywell, The United States |
| Ammonium acetate | Chromatographic purity | Honeywell, The United States |

Table S4 Gradient elution program table

| Time(min) | A(%) | B(%) |
|-----------|------|------|
| 0.0 | 85 | 15 |
| 4.0 | 72 | 28 |
| 5.0 | 72 | 28 |
| 10.0 | 70 | 30 |
| 13.0 | 55 | 45 |
| 13.5 | 5 | 95 |
| 14.5 | 85 | 15 |
| 20.0 | 85 | 15 |

Table S5 Mass spectrometry parameters of fentanyl and amphetamines in LC-MS/MS

| Drug name | Molecular weight | Parent ion (m/z) | Daughter ion (m/z) | Cone (V) | CE (V) |
|----------------------------|------------------|------------------|--------------------|----------|--------|
| Norfentanyl | 232.32 | 233.25 | 84.25* | 82 | 18 |
| Acetylfentanyl | 322.45 | 323.31 | 188.29* | 10 | 20 |
| | | | 105.23 | 10 | 32 |
| Ocfentanyl | 370.47 | 371.33 | 188.29* | 10 | 24 |
| | | | 105.23 | 10 | 34 |
| Thiofentanyl | 342.50 | 343.23 | 194.27* | 16 | 20 |
| | | | 111.21 | 16 | 46 |
| Fentanyl | 336.48 | 337.34 | 188.29* | 4 | 20 |
| | | | 105.23 | 4 | 34 |
| P-Fluorofentanyl | 354.47 | 355.33 | 188.29* | 8 | 26 |
| | | | 105.23 | 8 | 34 |
| Isobutyryl fentanyl | 350.51 | 351.37 | 188.29* | 16 | 24 |
| | | | 105.23 | 16 | 34 |
| 4-fluoroisobutyrylfentanyl | 368.50 | 369.36 | 188.29* | 6 | 24 |
| | | | 105.23 | 6 | 36 |
| Tetrahydrofuranylfentanyl | 378.52 | 379.29 | 188.29* | 94 | 38 |
| | | | 105.23 | 94 | 22 |
| AP | 135.00 | 137.10 | 92.15* | 55 | 25 |
| | | | 119.00 | 55 | 15 |
| MA | 149.23 | 148.24 | 133.24* | 64 | 18 |
| | | | 117.26 | 64 | 16 |
| MDEA | 207.00 | 208.22 | 105.23* | 28 | 22 |
| | | | 132.85 | 28 | 24 |
| MDMA | 194.00 | 194.22 | 163.27* | 32 | 12 |
| | | | 105.23 | 32 | 22 |
| MDA | 179.20 | 181.10 | 135.00 | 70 | 26 |
| | | | 164.20* | 70 | 13 |
| Ephedrine | 148.00 | 148.16 | 114.91 | 42 | 16 |
| | | | 133.24* | 42 | 16 |
| MA-D5 | 154.23 | 155.17 | 92.11 | 20 | 4 |
| | | | 114.14* | 10 | 4 |

Table S6 Retention times and characteristic ions of fentanyl and amphetamines in GC-MS/MS

| Drug name | Characteristic ions | RT(min) |
|-----------------------------|---------------------|---------|
| AP | 44*,91,117,65 | - |
| MA | 58*,91,56 | 6.40 |
| MDEA | 72*,135,136,77 | 11.57 |
| MDMA | 58*,77,59,135 | 11.01 |
| MDA | 44*,136,77,51 | 10.37 |
| Ephedrine | 58*,77,105 | 9.12 |
| MA-D5 | 62*,66,92,139 | 6.37 |
| Norfentanyl | 120,159,175,83* | 15.89 |
| Acetylfentanyl | 231*,146,188 | 23.28 |
| Isobutyryl fentanyl | 259*,146,189 | 23.64 |
| P-Fluorofentanyl | 263*,164,220 | 23.45 |
| Ocfentanyl | 279*,176,280 | 24.53 |
| Thiofentanyl | 245*,146,93 | 23.91 |
| 4-fluoroisobutyryl fentanyl | 277,164*,207 | 24.05 |
| Tetrahydrofuran fentanyl | 287*,189,146,158 | 26.98 |
| Fentanyl | 245*,146,189,280 | 23.79 |

*: quantitative ion

-: not detected

Table S7 Linearity and range of 15 drugs

| Drug name | GC-MS/MS | | | LC-MS/MS | | |
|----------------------------|--------------------------------------|---------------------|--------|--------------------------------------|---------------------|--------|
| | Linear range/ ng·mg ⁻¹ | Regression equation | r | Linear range/ ng·mg ⁻¹ | Regression equation | r |
| Norfentanyl | 0.4-4.5 | y=0.1311x+0.1568 | 0.9998 | 0.01-0.2 | y=21.173x+0.1193 | 0.9997 |
| Acetylfentanyl | 0.9-4.5 | y=0.2019x+0.3706 | 0.9996 | 0.01-0.2 | y=61.131x+0.3503 | 0.9996 |
| Isobutyryl fentanyl | 0.4-4.5 | y=0.27x+0.6094 | 0.9997 | 0.01-0.2 | y=51.327x+1.2441 | 0.9996 |
| P-Fluorofentanyl | 0.4-4.5 | y=0.2233x+0.4528 | 0.9996 | 0.01-0.2 | y=71.813x+0.0265 | 0.9995 |
| Ocfentanyl | 0.4-4.5 | y=0.2182x+0.4271 | 0.9997 | 0.01-0.2 | y=84.916x+0.462 | 0.9995 |
| Thiofentanyl | 0.4-4.5 | y=0.175x+0.4698 | 0.9996 | 0.01-0.2 | y=45.938x+0.1992 | 0.9995 |
| 4-fluoroisobutyrylfentanyl | 0.4-4.5 | y=0.1424x+0.3142 | 0.9997 | 0.01-0.2 | y=16.077x+3.8265 | 0.9998 |
| Tetrahydrofuranylfentanyl | 0.9-4.5 | y=0.1195x+0.2369 | 0.9995 | 0.01-0.2 | y=31.942x+0.0672 | 0.9997 |
| Fentanyl | 0.4-4.5 | y=0.1425x+0.3061 | 0.9996 | 0.01-0.2 | y=56.917x+0.1109 | 0.9999 |
| AP | 0.9-4.3 | y=0.5144x+0.9685 | 0.9996 | 0.06-0.5 | y=0.1779x+0.0163 | 0.9995 |
| MA | 0.9-4.5 | y=1.0571x+1.0671 | 0.9998 | 0.01-0.2 | y=7.689x-0.0435 | 0.9997 |
| MDEA | 0.9-4.4 | y=1.056x+4.1112 | 0.9996 | 0.01-0.2 | y=23.794x+0.1312 | 0.9996 |
| MDMA | 0.9-4.4 | y=0.6487x+2.0984 | 0.9995 | 0.01-0.2 | y=38.361x+0.12 | 0.9998 |
| Ephedrine | 0.9-4.4 | y=0.604x+0.8299 | 0.9997 | 0.01-0.2 | y=10.336x-0.0034 | 0.9999 |
| MDA | 0.9-4.4 | y=0.3614x+0.5927 | 0.9997 | 0.06-0.5 | y=0.0566+0.0062 | 0.9996 |

Table S8 Repeatability results of 15 drugs

| Drug name | GC-MS/MS | LC-MS/MS |
|-----------|----------|----------|
|-----------|----------|----------|

| | ME/% | | ME/% | |
|---------------------------|---------------|---------------|---------------|---------------|
| | Intraday(n=6) | Daytime(n=30) | Intraday(n=6) | Daytime(n=30) |
| Norfentanyl | 5.1 | 6.7 | 1.9 | 2.6 |
| Acetylfentanyl | 3.6 | 8.0 | 1.2 | 1.4 |
| Isobutyryl fentanyl | 4.0 | 6.8 | 1.2 | 1.5 |
| P-Fluorofentanyl | 3.5 | 7.5 | 1.0 | 1.6 |
| Ocfentanyl | 5.1 | 7.7 | 1.2 | 1.6 |
| Thiofentanyl | 2.5 | 7.9 | 0.9 | 1.4 |
| 4-fluoroisobutyrfentanyl | 2.7 | 8.1 | 1.1 | 1.6 |
| Tetrahydrofuranylfentanyl | 3.6 | 9.3 | 1.2 | 2.1 |
| Fentanyl | 2.7 | 9.6 | 1.0 | 2.1 |
| AP | - | - | - | - |
| MA | 2.1 | 3.8 | 3.1 | 5.1 |
| MDEA | 1.3 | 2.1 | 1.6 | 2.7 |
| MDMA | 1.5 | 3.3 | 1.2 | 1.5 |
| Ephedrine | 2.9 | 8.8 | 1.4 | 3.6 |
| MDA | 1.6 | 5.8 | 2.6 | 5.0 |

Table S9 Stability test results of 15 drugs

| Drug name | GC-MS/MS | LC-MS/MS |
|-----------|----------|----------|
|-----------|----------|----------|

| | Stability/% | | | | | Stability/% | | | | |
|----------------------------|-------------|------|------|------|------|-------------|------|------|------|------|
| | 1 h | 24 h | 48 h | 72 h | 96 h | 1 h | 24 h | 48 h | 72 h | 96 h |
| Norfentanyl | 5.1 | 4.7 | 5.3 | 6.3 | 6.7 | 1.9 | 1.8 | 2.9 | 2.7 | 2.6 |
| Acetylfentanyl | 3.6 | 4.4 | 4.5 | 5.4 | 8.0 | 1.2 | 1.3 | 1.4 | 1.5 | 1.4 |
| Isobutyryl fentanyl | 4.0 | 4.5 | 4.6 | 4.8 | 6.8 | 1.2 | 1.5 | 1.4 | 1.5 | 1.5 |
| P-Fluorofentanyl | 3.5 | 7.9 | 6.9 | 6.3 | 7.5 | 1.0 | 1.2 | 1.2 | 1.6 | 1.6 |
| Ocfentanyl | 5.1 | 6.1 | 6.4 | 6.9 | 7.7 | 1.2 | 1.7 | 1.6 | 1.7 | 1.6 |
| Thiofentanyl | 2.5 | 6.4 | 5.9 | 6.1 | 7.9 | 0.9 | 1.0 | 1.0 | 1.3 | 1.4 |
| 4-fluoroisobutyrylfentanyl | 2.7 | 6.3 | 6.8 | 6.8 | 8.1 | 1.1 | 1.8 | 1.5 | 1.6 | 1.6 |
| Tetrahydrofuranylfentanyl | 3.6 | 5.6 | 5.8 | 7.4 | 9.3 | 1.2 | 2.3 | 2.2 | 2.2 | 2.1 |
| Fentanyl | 2.7 | 6.1 | 5.8 | 5.7 | 9.6 | 1.0 | 1.3 | 1.7 | 2.1 | 2.1 |
| AP | - | - | - | - | - | - | - | - | - | - |
| MA | 2.1 | 2.6 | 2.8 | 3.3 | 3.8 | 3.1 | 3.6 | 4.0 | 4.3 | 5.1 |
| MDEA | 1.3 | 1.8 | 2.1 | 2.0 | 2.1 | 1.6 | 1.5 | 2.4 | 2.6 | 2.7 |
| MDMA | 1.5 | 1.8 | 2.3 | 2.6 | 3.3 | 1.2 | 1.0 | 1.5 | 1.5 | 1.5 |
| Ephedrine | 2.9 | 5.2 | 6.0 | 6.6 | 8.8 | 1.4 | 2.4 | 2.7 | 3.1 | 3.6 |
| MDA | 1.6 | 1.7 | 3.0 | 4.1 | 5.8 | 2.6 | 5.3 | 4.9 | 5.3 | 5.0 |

Table S10 Recovery and matrix effect of 15 drugs

| Drug name | GC-MS/MS | LC-MS/MS |
|-----------|----------|----------|
|-----------|----------|----------|

| | Recovery /% | RSD/ % | ME/ % | RSD/ % | Recovery /% | RSD/ % | ME/ % | RSD/ % |
|----------------------------|----------------|-----------|----------|-----------|----------------|-----------|----------|-----------|
| | 91.32 | 2.7 | 105.3 | 14.6 | 98.08 | 0.8 | 98.70 | 1.5 |
| Norfentanyl | 98.24 | 2.8 | 111.8 | 0.7 | 98.88 | 1.6 | 98.50 | 1.6 |
| | 93.04 | 3.0 | 102.3 | 5.6 | 99.04 | 0.4 | 98.80 | 0.8 |
| Acetylfentanyl | 92.62 | 2.2 | 94.40 | 10.1 | 97.71 | 1.2 | 99.10 | 1.1 |
| | 85.50 | 7.4 | 86.40 | 2.3 | 98.83 | 0.7 | 98.40 | 1.0 |
| | 92.74 | 6.9 | 98.20 | 0.8 | 93.94 | 0.7 | 93.50 | 1.2 |
| | 104.1 | 2.8 | 95.10 | 8.6 | 98.69 | 0.5 | 101.0 | 0.9 |
| Isobutyryl fentanyl | 90.25 | 4.1 | 88.30 | 4.3 | 98.39 | 0.8 | 97.90 | 0.9 |
| | 98.82 | 7.9 | 100.9 | 1.0 | 97.89 | 0.4 | 98.40 | 0.5 |
| | 95.63 | 2.6 | 95.00 | 4.9 | 99.21 | 1.9 | 100.2 | 1.6 |
| P-Fluorofentanyl | 102.1 | 7.9 | 86.90 | 3.4 | 99.34 | 1.4 | 98.90 | 1.2 |
| | 95.90 | 8.6 | 99.20 | 3.4 | 98.71 | 0.7 | 99.40 | 0.9 |
| | 89.92 | 2.3 | 99.50 | 10.1 | 98.40 | 1.5 | 99.60 | 1.4 |
| Ocfentanyl | 99.59 | 6.0 | 83.80 | 1.5 | 97.77 | 1.2 | 97.80 | 1.4 |
| | 96.61 | 3.4 | 96.60 | 3.4 | 99.12 | 1.1 | 99.10 | 1.0 |
| | 94.31 | 2.5 | 109.1 | 5.7 | 101.2 | 7.4 | 101.3 | 5.3 |
| Thiofentanyl | 97.56 | 2.5 | 85.60 | 2.5 | 99.09 | 1.1 | 100.7 | 1.1 |
| | 97.44 | 2.6 | 96.10 | 2.6 | 99.77 | 0.3 | 100.8 | 0.9 |
| 4-fluoroisobutyrylfentanyl | 96.56 | 1.6 | 99.70 | 4.5 | 98.02 | 2.3 | 99.80 | 2.1 |
| | 88.57 | 8.5 | 86.50 | 4.2 | 97.87 | 1.2 | 97.50 | 1.3 |
| | 101.5 | 7.1 | 96.00 | 1.5 | 98.19 | 0.4 | 98.80 | 0.9 |
| Tetrahydrofuranlylfentanyl | 92.42 | 3.6 | 86.40 | 8.6 | 97.90 | 1.7 | 99.20 | 1.4 |
| | 99.59 | 1.9 | 86.80 | 1.5 | 96.70 | 0.7 | 96.30 | 1.4 |
| | 103.9 | 5.8 | 91.50 | 3.9 | 100.7 | 0.8 | 99.60 | 1.1 |
| Fentanyl | 92.43 | 1.9 | 105.7 | 7.6 | 96.04 | 0.8 | 99.50 | 0.9 |
| | 97.84 | 5.9 | 114.9 | 2.2 | 98.72 | 1.2 | 98.40 | 1.1 |
| | 112.9 | 2.3 | 94.20 | 3.0 | 98.45 | 0.3 | 99.10 | 1.0 |
| AP | 95.83 | 6.0 | 102.3 | 1.7 | 102.3 | 1.8 | 91.80 | 6.3 |
| | 89.42 | 1.9 | 96.70 | 1.5 | 84.46 | 0.9 | 86.30 | 2.8 |
| | 104.0 | 1.3 | 108.1 | 1.5 | 88.69 | 4.4 | 87.10 | 4.6 |
| MA | 87.66 | 1.1 | 101.8 | 6.1 | 110.8 | 10.2 | 109.0 | 7.4 |
| | 89.69 | 2.3 | 115.9 | 10.3 | 104.3 | 2.8 | 103.2 | 3.6 |
| | 86.14 | 4.0 | 101.7 | 6.2 | 100.6 | 1.4 | 100.3 | 2.2 |
| MDEA | 91.13 | 1.4 | 97.10 | 8.9 | 97.41 | 2.2 | 99.10 | 1.5 |
| | 91.30 | 6.9 | 90.80 | 1.3 | 98.70 | 1.0 | 98.90 | 1.0 |
| | 106.3 | 7.5 | 103.9 | 3.0 | 98.78 | 0.2 | 99.70 | 0.6 |
| MDMA | 97.20 | 7.2 | 102.7 | 8.0 | 98.67 | 2.3 | 99.70 | 1.5 |
| | 90.90 | 1.8 | 96.80 | 2.2 | 100.2 | 0.8 | 99.40 | 0.7 |
| | 112.8 | 3.5 | 108.3 | 1.9 | 98.70 | 0.4 | 99.00 | 0.5 |
| Ephedrine | 86.84 | 2.2 | 108.5 | 13.2 | 106.6 | 1.9 | 103.4 | 2.6 |
| | 90.88 | 1.4 | 88.30 | 4.2 | 104.1 | 0.3 | 103.7 | 1.6 |
| | 105.6 | 3.2 | 89.40 | 2.3 | 100.3 | 1.2 | 100.5 | 1.1 |

| | | | | | | | | |
|-----|-------|-----|-------|------|-------|-----|-------|-----|
| | 116.4 | 6.1 | 93.90 | 12.8 | 97.52 | 6.7 | 97.10 | 5.7 |
| MDA | 89.68 | 3.1 | 101.7 | 5.5 | 104.2 | 5.0 | 99.50 | 3.7 |
| | 92.11 | 1.7 | 109.4 | 1.4 | 90.00 | 3.7 | 90.50 | 3.2 |

Table S11 Comparison of GC-MS/MS and LC-MS/MS results (ng/mg)

| Drug name | LC-MS/MS | GC-MS/MS | ME/% | Mean |
|-----------|----------|----------|------|------|
|-----------|----------|----------|------|------|

| | Mean | RSD/% | Mean | RSD/% | | |
|----------------------------|-------|-------|-------|-------|-------|-------|
| Norfentanyl | 1.012 | 1.6 | 1.087 | 3.7 | -3.8 | 1.050 |
| Acetylfentanyl | 4.788 | 0.6 | 4.821 | 2.0 | -1.6 | 4.805 |
| Isobutyryl fentanyl | 4.826 | 0.3 | 4.816 | 1.9 | 0.5 | 4.821 |
| P-Fluorofentanyl | 5.830 | 0.2 | 5.786 | 1.6 | 2.2 | 5.808 |
| Ocfentanyl | 3.188 | 1.1 | 3.031 | 2.2 | 7.9 | 3.110 |
| Thiofentanyl | 5.010 | 0.6 | 4.925 | 2.0 | 4.3 | 4.968 |
| 4-fluoroisobutyrylfentanyl | 6.303 | 0.4 | 6.028 | 1.7 | 13.8 | 6.166 |
| Tetrahydrofuranylfentanyl | 3.444 | 0.2 | 3.451 | 3.0 | -0.3 | 3.448 |
| Fentanyl | 7.830 | 0.3 | 7.712 | 1.9 | 5.9 | 7.771 |
| AP | - | - | - | - | - | - |
| MA | 1.789 | 1.3 | 2.015 | 2.0 | -11.3 | 1.902 |
| MDEA | 1.321 | 0.3 | 1.322 | 1.2 | -0.05 | 1.322 |
| MDMA | 3.284 | 0.7 | 3.325 | 1.2 | -2.1 | 3.305 |
| Ephedrine | 1.667 | 1.3 | 1.667 | 1.6 | -0.02 | 1.667 |
| MDA | 1.938 | 1.6 | 2.112 | 2.7 | -8.7 | 2.025 |