

Supplementary Information for

**High-throughput evaluation of organic contaminant removal efficiency in a
wastewater treatment plant using direct injection UHPLC-Orbitrap-
MS/MS**

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Chemicals and reagents

Table S1. List of the native standards and their physical-chemical properties.

native standard	CAS No.	molecular formula	exact mass	ESI mode	log K _{ow} ^a	pK _a ^b	corresponding IS
2-chlorobenzoic acid	118-91-2	C ₇ H ₅ ClO ₂	155.9978	ESI-	2.23	3.07	2-chlorobenzoic acid
4-hydroxybenzotriazole	26725-51-9	C ₆ H ₅ N ₃ O	135.0433	ESI-	1.00	7.70	4-hydroxybenzotriazole
1H-benzotriazole	95-14-7	C ₆ H ₅ N ₃	119.0484	ESI+	1.30	8.63	1H-benzotriazole-d4
acesulfame	33665-90-6	C ₄ H ₅ NO ₄ S	162.9939	ESI-	0.25	3.02	acesulfame-d4
acetaminophen	103-90-2	C ₈ H ₉ NO ₂	151.0633	ESI+	0.27	9.46	acetaminophen-d4
anastrozole	120511-73-1	C ₁₇ H ₁₉ N ₅	293.1640	ESI+	3.03	2.00	anastrozole-d12
aniline	62-53-3	C ₆ H ₅ NH ₂	93.0578	ESI+	1.14	4.64	aniline-d5
atenolol	29122-68-7	C ₁₄ H ₂₂ N ₂ O ₃	266.1630	ESI+	-0.03	9.67	atenolol-d7
atorvastatin	134523-03-8	C ₃₃ H ₃₅ FN ₂ O ₅	558.2530	ESI+	6.36	4.31	atorvastatin-d5
bezafibrate	42859-67-0	C ₁₉ H ₂₀ ClNO ₄	361.1081	ESI+	4.25	3.83	bezafibrate-d4
bicalutamide	90357-06-5	C ₁₈ H ₁₄ F ₄ N ₂ O ₄ S	430.0610	ESI+	2.30	12.0	bicalutamide-d4
caffeine	58-08-2	C ₈ H ₁₀ N ₄ O ₂	194.0804	ESI+	0.16	--	caffeine-d9
carbamazepine	298-46-4	C ₁₅ H ₁₂ N ₂ O	236.0950	ESI+	2.25	13.9	carbamazepine-d8
carbamazepine-10,11-epoxide	36507-30-9	C ₁₅ H ₁₂ N ₂ O ₂	252.0899	ESI+	2.58	5.13	venlafaxine-d6
chlorothiazide	58-94-6	C ₇ H ₆ ClN ₃ O ₄ S ₂	294.9488	ESI-	-0.44	9.19	hydrochlorothiazide-13C-d2
chlorthalidone	77-36-1	C ₁₄ H ₁₁ ClN ₂ O ₄ S	338.0128	ESI-	1.60	8.76	fluconazole-d4
climbazole	38083-17-9	C ₁₅ H ₁₇ ClN ₂ O ₂	292.0979	ESI+	3.76	6.49	climbazole-d4
clofibric acid	882-09-7	C ₁₀ H ₁₁ ClO ₃	214.0397	ESI-	2.84	3.37	clofibric acid-d4
diclofenac	15307-86-5	C ₁₄ H ₁₁ Cl ₂ NO ₂	295.0167	ESI+	4.02	4.00	diclofenac-13C6
fluconazole	86386-73-4	C ₁₃ H ₁₂ F ₂ N ₆ O	306.1041	ESI+	0.25	1.70	fluconazole-d4
fluoxetine	54910-89-3	C ₁₇ H ₁₈ F ₃ NO	309.1340	ESI+	4.65	9.80	fluoxetine-d5
furosemide	54-31-9	C ₁₂ H ₁₁ ClN ₂ O ₅ S	330.0077	ESI+	2.32	4.25	furosemide-d5
gabapentin	60142-96-3	C ₉ H ₁₇ NO ₂	171.1259	ESI+	-1.27	4.63	gabapentin-d6
glimepiride	93479-97-1	C ₂₄ H ₃₄ N ₄ O ₅ S	490.2250	ESI+	4.70	4.32	glimepiride-d5
hydrochlorothiazide	58-93-5	C ₇ H ₈ ClN ₃ O ₄ S ₂	296.9645	ESI-	-0.10	9.09	hydrochlorothiazide-13C-d2
irbesartan	138402-11-6	C ₂₅ H ₂₈ N ₆ O	428.2325	ESI+	5.39	5.85	irbesartan-d6
ketoprofen	22071-15-4	C ₁₆ H ₁₄ O ₃	254.0943	ESI+	3.00	3.88	ketoprofen-13C-d3
MCPA	94-74-6	C ₉ H ₉ ClO ₃	200.0240	ESI-	2.41	3.36	MCPA-d6
metformin	657-24-9	C ₄ H ₁₁ N ₅	129.1014	ESI+	-2.64	10.27	metformin-d6
methotrexate	59-05-2	C ₂₀ H ₂₂ N ₈ O ₅	454.1713	ESI+	-0.24	3.25	methotrexate-d3
metoprolol	51384-51-1	C ₁₅ H ₂₅ NO ₃	267.1834	ESI+	1.69	9.67	metoprolol-d7
metoprolol acid	56392-14-4	C ₁₄ H ₂₁ NO ₄	267.1471	ESI+	-1.24	3.54	metoprolol acid-d5
oxazepam	604-75-1	C ₁₅ H ₁₁ N ₂ O ₂ Cl	286.0509	ESI+	1.65	4.21	oxazepam-d5
pravastatin	81093-37-0	C ₂₃ H ₃₆ O ₇	424.2461	ESI-	1.65	4.21	pravastatin-d3
propranolol	13013-17-7	C ₁₆ H ₂₁ NO ₂	259.1572	ESI+	2.60	9.67	propranolol-d7
ranitidine	66357-35-5	C ₁₃ H ₂₂ N ₄ O ₃ S	314.1413	ESI+	0.29	7.12	ranitidine-d6
sotalol	3930-20-9	C ₁₂ H ₂₀ N ₂ O ₃ S	272.1195	ESI+	0.37	9.43	sotalol-d6
sulfamethoxazole	723-46-6	C ₁₀ H ₁₁ N ₃ O ₃ S	253.0521	ESI+	0.48	6.16	sulfamethoxazole-d4
tramadol	27203-92-5	C ₁₆ H ₂₅ NO ₂	263.1885	ESI+	3.01	9.23	tramadol-d6
triclosan	3380-34-5	C ₁₂ H ₇ Cl ₃ O ₂	287.9512	ESI-	4.66	7.68	triclosan-d3
valsartan	137862-53-4	C ₂₄ H ₂₉ N ₅ O ₃	435.2270	ESI-	3.65	4.61	valsartan-d3
venlafaxine	93413-69-5	C ₁₇ H ₂₇ NO ₂	277.2042	ESI+	2.74	8.91	venlafaxine-d6

^a logK_{ow} values were predicted for the non-charged form of the molecule using the EPI Suite™ software;

^b pK_a values were predicted within the pH range of 0-14 using the MarvinSketch software from ChemAxon.

Table S2. List of the isotope-labeled standards and their physical-chemical properties.

isotope-labeled standard	molecular formula	exact mass	ESI mode	log K _{ow} ^a	pK _a ^b
1H-benzotriazole-d4	C ₆ HD ₄ N ₃	123.0735	ESI+	1.30	8.63
2-hydroxy-ibuprofen-d6	C ₁₃ H ₁₂ D ₆ O ₃	228.1633	ESI-	2.37	4.63
acesulfame-d4	C ₄ HD ₄ NO ₄ S	167.0190	ESI-	0.25	3.02
acetaminophen-d4	C ₈ H ₅ D ₄ NO ₂	155.0884	ESI+	0.27	9.46
anastrozole-d12	C ₁₇ H ₇ D ₁₂ N ₅	305.2394	ESI+	3.03	2.00
aniline-d5	C ₆ D ₅ NH ₂	98.0892	ESI+	1.14	4.64
atenolol-d7	C ₁₄ H ₁₅ D ₇ N ₂ O ₃	273.2070	ESI+	-0.03	9.67
atorvastatin-d5	C ₃₃ H ₃₀ D ₅ FN ₂ O ₅	563.2844	ESI+	6.36	4.31
bezafibrate-d4	C ₁₉ H ₁₆ D ₄ ClNO ₄	365.1332	ESI+	4.25	3.83
bicalutamide-d4	C ₁₈ H ₁₀ D ₄ F ₄ N ₂ O ₄ S	434.0862	ESI+	2.30	12.0
caffeine-d9	C ₈ HD ₉ N ₄ O ₂	203.1369	ESI+	0.16	--
carbamazepine-d8	C ₁₅ H ₄ D ₈ N ₂ O	244.1452	ESI+	2.25	13.9
carboxy-ibuprofen-d3	C ₁₃ H ₁₃ D ₃ O ₄	239.1237	ESI-	2.78	3.97
climbazole-d4	C ₁₅ H ₁₃ D ₄ ClN ₂ O ₂	296.1230	ESI+	3.76	6.49
clofibric acid-d4	C ₁₀ H ₇ D ₄ ClO ₃	218.0648	ESI-	2.84	3.37
diclofenac-13C6	C ₈ ¹³ C ₆ H ₁₁ Cl ₂ NO ₂	301.0368	ESI+	4.02	4.00
fluconazole-d4	C ₁₃ H ₈ D ₄ F ₂ N ₆ O	310.1292	ESI+	0.25	1.70
fluoxetine-d5	C ₁₇ H ₁₃ D ₅ F ₃ NO	314.1654	ESI+	4.65	9.80
furosemide-d5	C ₁₂ H ₆ D ₅ ClN ₂ O ₅ S	335.0391	ESI+	2.32	4.25
gabapentin-d6	C ₉ H ₁₁ D ₆ NO ₂	177.1636	ESI+	-1.27	4.63
glimepiride-d5	C ₂₄ H ₂₉ D ₅ N ₄ O ₅ S	495.2564	ESI+	4.70	4.32
guanyl urea-15N4	C ₂ H ₆ ¹⁵ N ₄ O	106.0423	ESI+	-2.03	5.81
hydrochlorothiazide-13C-d2	C ₆ ¹³ CH ₆ D ₂ ClN ₃ O ₄ S ₂	299.9804	ESI-	-0.10	9.09
irbesartan-d6	C ₂₅ H ₂₂ D ₆ N ₆ O	434.2701	ESI+	5.39	5.85
ketoprofen-13C-d3	C ₁₅ ¹³ CH ₁₁ D ₃ O ₃	258.1165	ESI+	3.00	3.88
MCPA-d6	C ₉ H ₃ D ₆ ClO ₃	206.0617	ESI-	2.41	3.36
metformin-d6	C ₄ H ₅ D ₆ N ₅	135.1391	ESI+	-2.64	10.27
methotrexate-d3	C ₂₀ H ₁₉ D ₃ N ₈ O ₅	457.1902	ESI+	-0.24	3.25
metoprolol acid-d5	C ₁₅ H ₂₀ D ₅ NO ₃	272.1784	ESI+	-1.24	3.54
metoprolol-d7	C ₁₄ H ₁₄ D ₇ NO ₄	274.2274	ESI+	1.69	9.67
oxazepam-d5	C ₁₅ H ₆ D ₅ N ₂ O ₂ Cl	291.0823	ESI+	1.65	4.21
pravastatin-d3	C ₂₃ H ₃₃ D ₃ O ₇	427.2649	ESI-	1.65	4.21
propranolol-d7	C ₁₆ H ₁₄ D ₇ NO ₂	266.2012	ESI+	2.60	9.67
ranitidine-d6	C ₁₃ H ₁₆ D ₆ N ₄ O ₃ S	320.1789	ESI+	0.29	7.12
sotalol-d6	C ₁₂ H ₁₄ D ₆ N ₂ O ₃ S	278.1571	ESI+	0.37	9.43
sulfamethoxazole-d4	C ₁₀ H ₇ D ₄ N ₃ O ₃ S	257.0772	ESI+	0.48	6.16
tramadol-d6	C ₁₆ H ₁₉ D ₆ NO ₂	269.2262	ESI+	3.01	9.23
triclosan-d3	C ₁₂ H ₄ D ₃ Cl ₃ O ₂	290.9700	ESI-	4.66	7.68
valsartan-d3	C ₂₄ H ₂₆ D ₃ N ₅ O ₃	438.2459	ESI+	3.65	4.61
venlafaxine-d6	C ₁₇ H ₂₁ D ₆ NO ₂	283.2418	ESI+	2.74	8.91

^a logK_{ow} values were predicted for the non-charged form of the molecule using the EPI Suite™ software;

^b pK_a values were predicted within the pH range of 0-14 using the MarvinSketch software from ChemAxon.

UHPLC-Orbitrap-MS/MS analysis

Orbitrap-MS/MS method: Full MS was operated with a resolution of 120000, AGC target of 3.0E6 and a maximum IT of 200 ms; scan range was 80 to 1000 m/z, profile spectrum data were acquired. Data-dependent MS/MS (dd-MS²) was operated with a resolution of 15000, AGC target of 1.0E5 (min. 8.0E3), maximum IT of 30 ms, top 5 precursor ions were selected for MS/MS, profile spectrum was acquired. The spray voltage was 3.5 kV for positive mode and 3.0 for negative mode.

Quality Assurance

None of the target analytes was detected in the blanks (i.e., methanol and Milli-Q water). The intraday coefficient of variation of the analytical instrument was <11% for all the compounds, derived from the quality control samples including four calibration standards. The SPE method recovery was tested by spiking deionized water with the target analytes at a final concentration of 10 µg L⁻¹. The recoveries of the analytes ranged from 42% for climbazole to 99% for gabapentin (n=3). Relative standard deviations in the triplicate wastewater samples were <18%, calculated for all the target analytes with the detected concentration in influent samples above their LOQ.

HRMS data post-processing workflow parameters in CompoundDiscoverer

Step I – Peak Picking

- RT range: 0.2 – 15 min
- m/z range: 80 – 1000 Da
- S/N threshold: 5
- Minimum scan number: 5
- Minimum intensity: 5000

Step II – Retention Time Alignment

- Alignment model: adaptive curve
- Maximum shift: 0.5 min
- Mass tolerance: 5 ppm

Step III – Compound Detection

- Considered elements: C50, H100, Br5, Cl6, F10, I5, N10, O15, P5, S5
- Isotope grouping:
mass tolerance: 5 ppm; intensity tolerance: 40%; minimum isotopes: 2
- Considered adducts:
Positive mode: [M+ACN+H]¹⁺, [M+H]¹⁺, [M+K]¹⁺, [M+Na]¹⁺
Negative mode: [2M+FA-H]¹⁻; [2M-H]¹⁻; [M-2H+K]¹⁻; [M-H]¹⁻; [M-H-H₂O]¹⁻
- Adduct grouping:

Mass tolerance: 5 ppm; intensity tolerance: 30%

Step IV – Background Subtraction

- Maximum sample/blank ratio*: 3
* *The maximum allowed peak area ratio of a compound in sample vs. blank (Milli-Q and methanol) to be considered as background.*
- Mass tolerance: 5 ppm

Step V – Database (mzCloud) Searching

- Compound classes: all
- Match ion activation type: true
- Match ion activation energy: match tolerance
- Ion activation energy tolerance: 30
- Apply intensity threshold: true
- Identity search: HighChem HighRes
- Similarity search: none
- Mass tolerance: 5 ppm
- Match score threshold: 70

Evaluation of uncertainty in the removal efficiency calculation

RE (%) of a compound was calculated as the abundance change between influent and effluent:

$$RE = \left(1 - \frac{C_{EFF}}{C_{IN}}\right) \times 100\% \quad (1)$$

The uncertainty of the mean \overline{RE} is determined by $\frac{C_{EFF}}{C_{IN}}$. Define C_{EFF} as A and C_{IN} as B. The mean value and standard deviation of A and B are: \overline{A} and $s_{\overline{A}}$, and \overline{B} and $s_{\overline{B}}$, respectively. The standard deviation of $\frac{C_{EFF}}{C_{IN}}$ can be then calculated as:

$$s_{\frac{\overline{A}}{\overline{B}}} = \frac{\overline{A}}{\overline{B}} \cdot \sqrt{\left(\frac{s_{\overline{A}}}{\overline{A}}\right)^2 + \left(\frac{s_{\overline{B}}}{\overline{B}}\right)^2} \quad (2)$$

The 95% confidence intervals for *RE* is $1 - A/B (1 + 1.96 s)$ and $1 - A/B (1 - 1.96 s)$.

The same method was applied to the uncertainty analysis for the *RE* calculated from the non-target analysis data. The measured peak areas were used instead of concentrations.

Table S3. Identification of the target standard compounds in the calibration standard samples (concentration range: 0.05-100 $\mu\text{g L}^{-1}$) using non-target analysis. The limit of detection for non-target analysis (NLOD) and both limit of detection and limit of quantification for target analysis (LOD and LOQ) are also provided.

compound	molecular formula	exact mass	expected RT (min)	NLOD ($\mu\text{g L}^{-1}$)	LOD/LOQ ($\mu\text{g L}^{-1}$)	mzCloud match score ^a	$ \Delta m/z ^a$ (ppm)	$ \Delta RT ^a$ (min)
2-chlorobenzoic acid	C ₇ H ₅ ClO ₂	155.9978	4.65	0.25	0.05/0.05	89.9	4.85	0.02
4-hydroxybenzotriazole	C ₆ H ₅ N ₃ O	135.0433	1.88	0.25	0.05/0.05	90.8	0.98	0.07
1H-benzotriazole	C ₆ H ₅ N ₃	119.0484	2.65	0.10	0.10/0.10	98.2	1.24	0.10
acesulfame	C ₄ H ₅ NO ₄ S	162.9939	1.12	0.05	0.05/0.05	93.1	4.59	0.03
acetaminophen	C ₈ H ₉ NO ₂	151.0633	2.93	0.10	0.10/0.25	88.4	0.98	0.07
anastrozole	C ₁₇ H ₁₉ N ₅	293.1640	4.78	0.25	0.05/0.05	93.5	0.67	0.09
aniline	C ₆ H ₅ NH ₂	93.0578	0.79	0.10	0.10/0.25	91.8	1.71	0.08
atenolol	C ₁₄ H ₂₂ N ₂ O ₃	266.1630	1.71	0.05	0.05/0.05	98.8	1.10	0.09
atorvastatin	C ₃₃ H ₃₅ FN ₂ O ₅	558.2530	6.53	0.50	0.25/0.50	95.3	1.50	0.03
bezafibrate	C ₁₉ H ₂₀ ClNO ₄	361.1081	5.69	0.10	0.10/0.10	99.0	0.27	0.11
bicalutamide	C ₁₈ H ₁₄ F ₄ N ₂ O ₄ S	430.0610	5.95	0.05	0.05/0.05	95.4	0.35	0.02
caffeine	C ₈ H ₁₀ N ₄ O ₂	194.0804	2.23	0.50	0.50/0.50	95.3	1.78	0.10
carbamazepine	C ₁₅ H ₁₂ N ₂ O	236.0950	4.60	0.10	0.05/0.05	96.6	0.94	0.08
carbamazepine-10,11-epoxide	C ₁₅ H ₁₂ N ₂ O ₂	252.0899	3.87	0.10	0.10/0.10	95.0	0.47	0.09
chlorothiazide	C ₇ H ₆ ClN ₃ O ₄ S ₂	294.9488	1.86	0.10	0.10/0.10	92.3	0.93	0.02
chlorthalidone	C ₁₄ H ₁₁ ClN ₂ O ₄ S	338.0128	3.37	0.50	0.25/0.25	96.0	1.37	0.01
climbazole	C ₁₅ H ₁₇ ClN ₂ O ₂	292.0979	5.08	0.25	0.10/0.10	88.7	0.91	0.09
clofibric acid	C ₁₀ H ₁₁ ClO ₃	214.0397	5.41	0.10	0.05/0.05	97.3	1.18	0.03
diclofenac	C ₁₄ H ₁₁ Cl ₂ NO ₂	295.0167	6.52	0.25	0.05/0.05	97.6	0.49	0.06
fluconazole	C ₁₃ H ₁₂ F ₂ N ₆ O	306.1041	2.99	0.50	0.50/0.50	97.3	0.28	0.10
fluoxetine	C ₁₇ H ₁₈ F ₃ NO	309.1340	5.39	0.25	0.05/0.05	92.0	1.06	0.08
furosemide	C ₁₂ H ₁₁ ClN ₂ O ₅ S	330.0077	4.44	0.50	0.10/0.10	93.9	1.39	0.04
gabapentin	C ₉ H ₁₇ NO ₂	171.1259	1.95	0.10	0.10/0.10	98.3	1.57	0.10
glimepiride	C ₂₄ H ₃₄ N ₄ O ₅ S	490.2250	6.77	5.00	2.50/2.50	90.1	0.55	0.08
hydrochlorothiazide	C ₇ H ₈ ClN ₃ O ₄ S ₂	296.9645	2.00	0.25	0.25/0.25	94.7	0.96	0.02
irbesartan	C ₂₅ H ₂₈ N ₆ O	428.2325	5.05	0.25	0.05/0.05	96.4	0.93	0.01
ketoprofen	C ₁₆ H ₁₄ O ₃	254.0943	5.46	0.25	0.10/0.25	97.6	0.17	0.07
MCPA	C ₉ H ₉ ClO ₃	200.0240	5.20	0.10	0.10/0.25	95.3	2.01	0.03
metformin	C ₄ H ₁₁ N ₅	129.1014	0.66	0.10	0.05/0.05	95.7	1.90	0.05
methotrexate	C ₂₀ H ₂₂ N ₈ O ₅	454.1713	2.27	0.50	0.50/0.50	99.3	1.35	0.02
metoprolol	C ₁₅ H ₂₅ NO ₃	267.1834	3.08	0.05	0.05/0.05	97.4	1.21	0.01
metoprolol acid	C ₁₄ H ₂₁ NO ₄	267.1471	2.17	0.25	0.05/0.05	95.8	0.82	0.08
oxazepam	C ₁₅ H ₁₁ N ₂ O ₂ Cl	286.0509	4.84	0.50	0.25/0.25	95.8	0.30	0.03
pravastatin	C ₂₃ H ₃₆ O ₇	424.2461	4.60	0.25	0.10/0.10	93.0	1.36	0.02
propranolol	C ₁₆ H ₂₁ NO ₂	259.1572	4.11	0.05	0.05/0.05	98.4	1.35	0.08
ranitidine	C ₁₃ H ₂₂ N ₄ O ₃ S	314.1413	1.69	0.05	0.05/0.05	97.4	1.69	0.08
sotalol	C ₁₂ H ₂₀ N ₂ O ₃ S	272.1195	1.57	0.10	0.05/0.05	93.8	0.75	0.09
sulfamethoxazole	C ₁₀ H ₁₁ N ₃ O ₃ S	253.0521	3.26	0.25	0.10/0.25	97.8	0.44	0.09
tramadol	C ₁₆ H ₂₅ NO ₂	263.1885	3.09	0.05	0.05/0.05	88.8	0.95	0.09
triclosan	C ₁₂ H ₇ Cl ₃ O ₂	287.9512	7.56	0.25	0.05/0.25	96.7	1.66	0.03
valsartan	C ₂₄ H ₂₉ N ₅ O ₃	435.2270	5.91	0.10	0.10/0.10	98.7	0.90	0.03
venlafaxine	C ₁₇ H ₂₇ NO ₂	277.2042	3.77	0.05	0.05/0.05	94.0	1.04	0.08

^aThe mzCloud match score, difference between theoretical and detected m/z, and difference between expected and detected RT represent average values calculated from all the calibration standard samples.

Identification of the target compounds

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #1105, RT=4.648 min, MS2, FTMS (-), (HCD, DDF, 154.9898@30, -1)
REFERENCE(bottom): mzCloud library, 2-Chlorobenzoic acid, C7 H5 Cl O2, MS2, FTMS, (HCD, 154.9905@30)

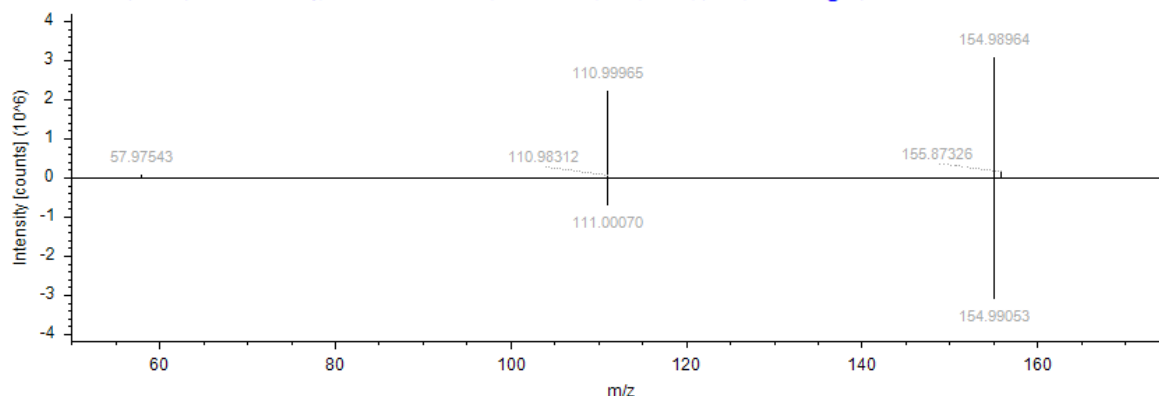


Figure S1. Identification of 2-chlorobenzoic acid (mzCloud match score: 89.9) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #449, RT=1.872 min, MS2, FTMS (-), (HCD, DDF, 134.0351@30, -1)
REFERENCE(bottom): mzCloud library, 4-Hydroxybenzotriazole, C6 H5 N3 O, MS2, FTMS, (HCD, 134.0360@45)

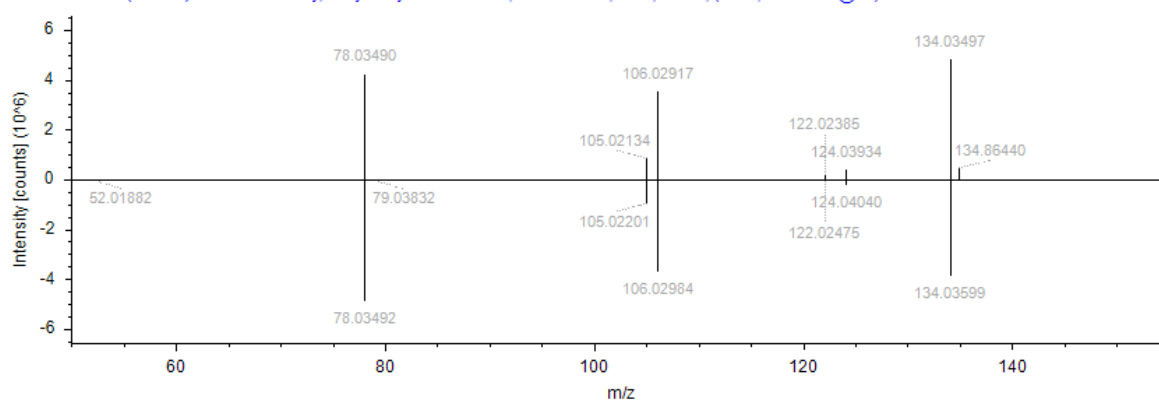


Figure S2. Identification of 4-hydroxybenzotriazole (mzCloud match score: 90.8) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #776, RT=2.623 min, MS2, FTMS (+), (HCD, DDF, 120.0556@30, +1)
REFERENCE(bottom): mzCloud library, Benzotriazole, C6 H5 N3, MS2, FTMS, (HCD, 120.0556@30)

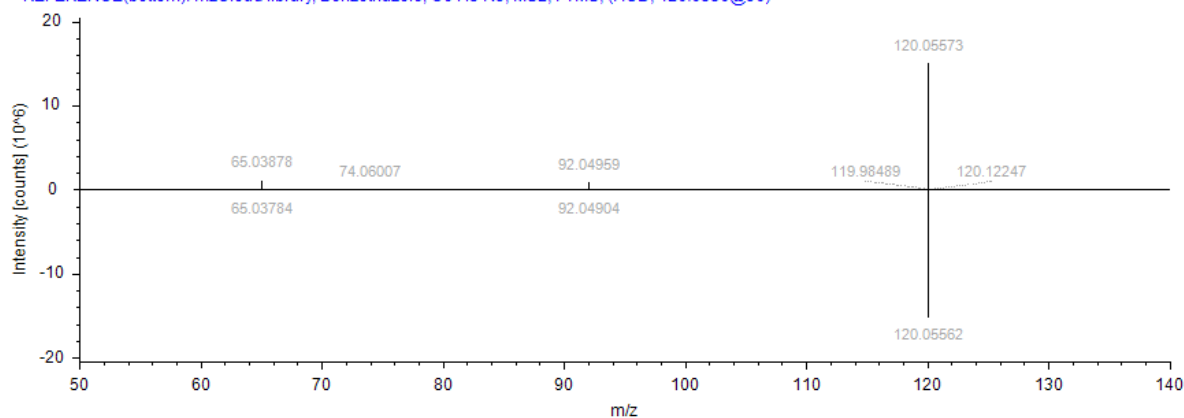


Figure S3. Identification of 1H-benzotriazole (mzCloud match score: 98.2) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #278, RT=1.112 min, MS2, FTMS (-), (HCD, DDF, 161.9859@30, -1)
REFERENCE(bottom): mzCloud library, Acesulfame, C4 H5 N O4 S, MS2, FTMS, (HCD, 161.9867@60)

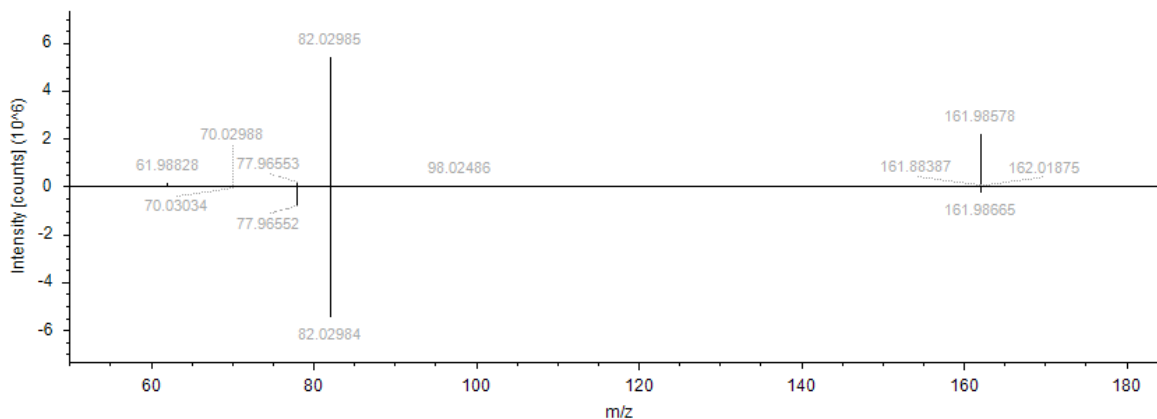


Figure S4. Identification of acesulfame (mzCloud match score: 93.1) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-33-SPE-In-pos (F28) #1544, RT=2.962 min, MS2, FTMS (+), (HCD, DDF, 152.0164@30, +1)
REFERENCE(bottom): mzCloud library, Paracetamol, C8 H9 N O2, MS2, FTMS, (HCD, 152.0706@30)

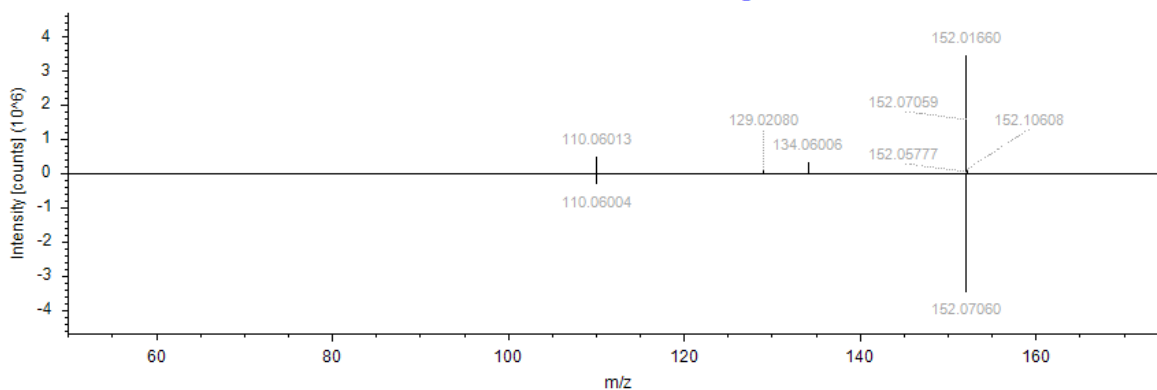


Figure S5. Identification of acetaminophen (mzCloud match score: 88.4) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-33-SPE-In-pos (F28) #226, RT=0.839 min, MS2, FTMS (+), (HCD, DDF, 94.0650@30, +1)
REFERENCE(bottom): mzCloud library, Aniline, C6 H7 N, MS2, FTMS, (HCD, 94.0651@20)

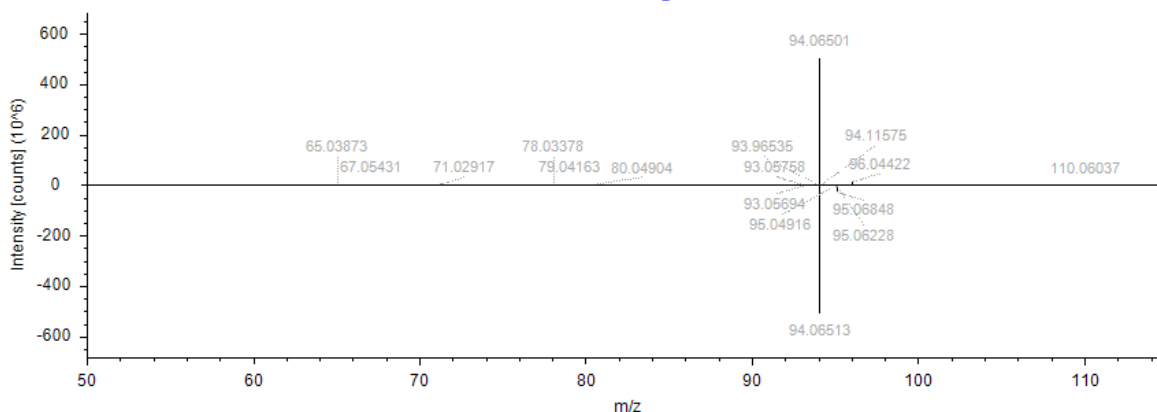


Figure S6. Identification of aniline (mzCloud match score: 91.8) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #517, RT=1.784 min, MS2, FTMS (+), (HCD, DDF, 267.1703@30, +1)
REFERENCE(bottom): mzCloud library, Atenolol, C₁₄H₂₂N₂O₃, MS2, FTMS, (HCD, 267.1703@30)

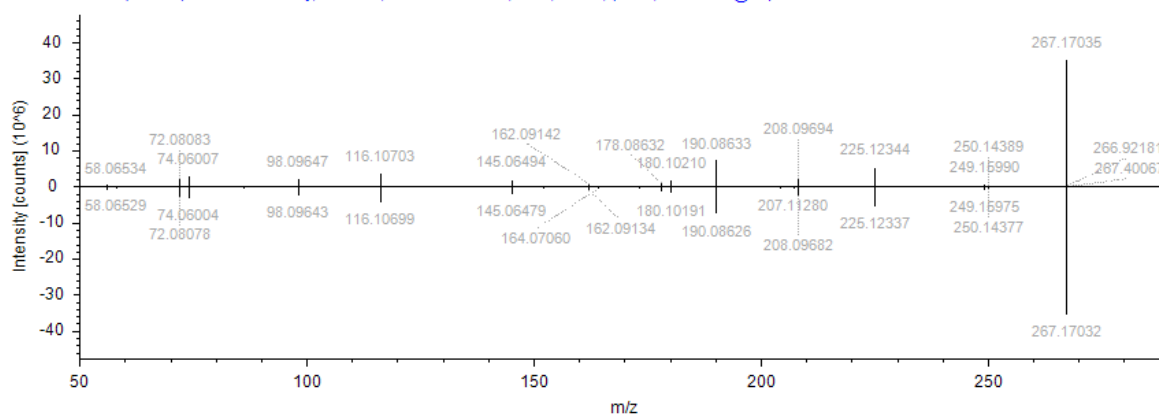


Figure S7. Identification of atenolol (mzCloud match score: 98.8) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #1593, RT=6.549 min, MS2, FTMS (-), (HCD, DDF, 557.2464@30, -1)
REFERENCE(bottom): mzCloud library, Atorvastatin, C₃₃H₃₅F N₂O₅, MS2, FTMS, (HCD, 557.2457@30)

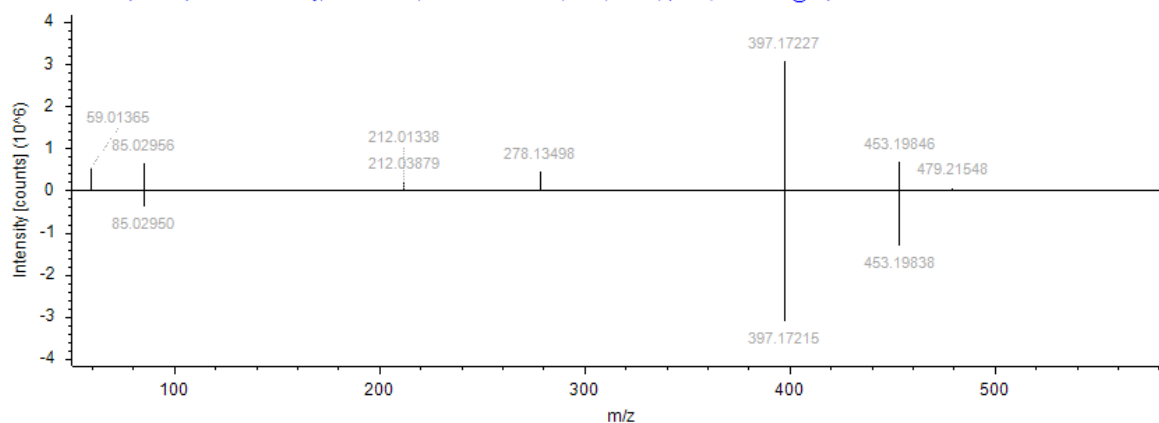


Figure S8. Identification of atorvastatin (mzCloud match score: 95.3) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #1805, RT=5.826 min, MS2, FTMS (+), (HCD, DDF, 362.1155@30, +1)
REFERENCE(bottom): mzCloud library, Bezafibrate, C₁₉H₂₀Cl N O₄, MS2, FTMS, (HCD, 362.1154@30)

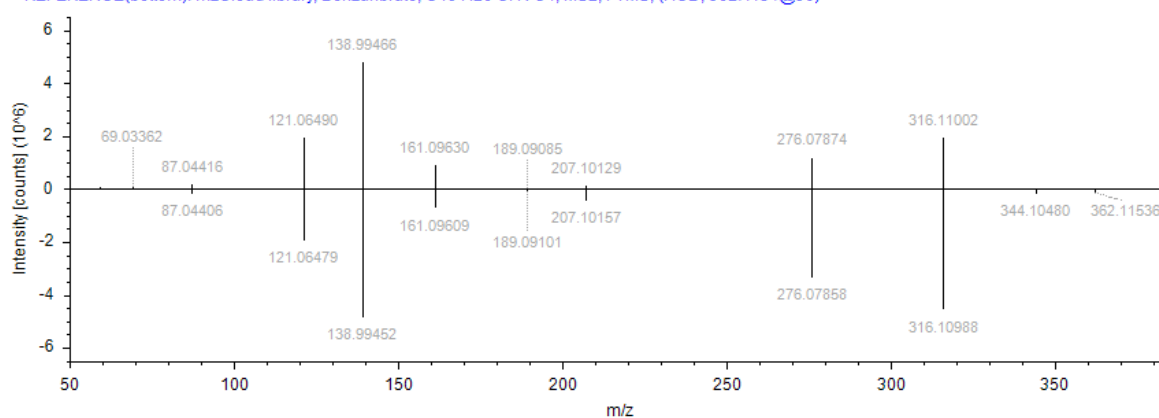


Figure S9. Identification of bezafibrate (mzCloud match score: 99.0) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #1438, RT=5.944 min, MS2, FTMS (-), (HCD, DDF, 429.0543@30, -1)
 REFERENCE(bottom): mzCloud library, Bicalutamide, C18 H14 F4 N2 O4 S, MS2, FTMS, (HCD, 429.0538@45)

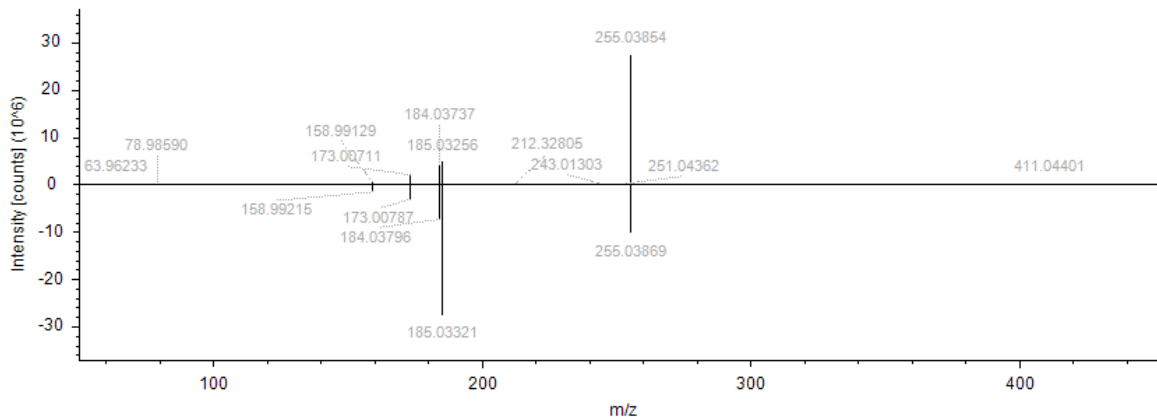


Figure S10. Identification of bicalutamide (mzCloud match score: 95.4) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-33-SPE-In-pos (F28) #1206, RT=2.409 min, MS2, FTMS (+), (HCD, DDF, 195.0875@30, +1)
 REFERENCE(bottom): mzCloud library, Caffeine, C8 H10 N4 O2, MS2, FTMS, (HCD, 195.0877@45)

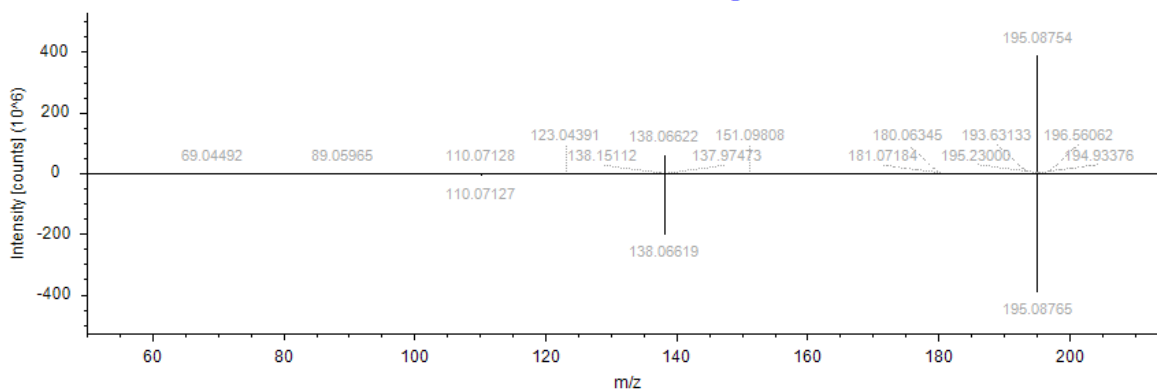


Figure S11. Identification of caffeine (mzCloud match score: 95.3) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #1468, RT=4.800 min, MS2, FTMS (+), (HCD, DDF, 237.1020@30, +1)
 REFERENCE(bottom): mzCloud library, Carbamazepine, C15 H12 N2 O, MS2, FTMS, (HCD, 237.1022@10)

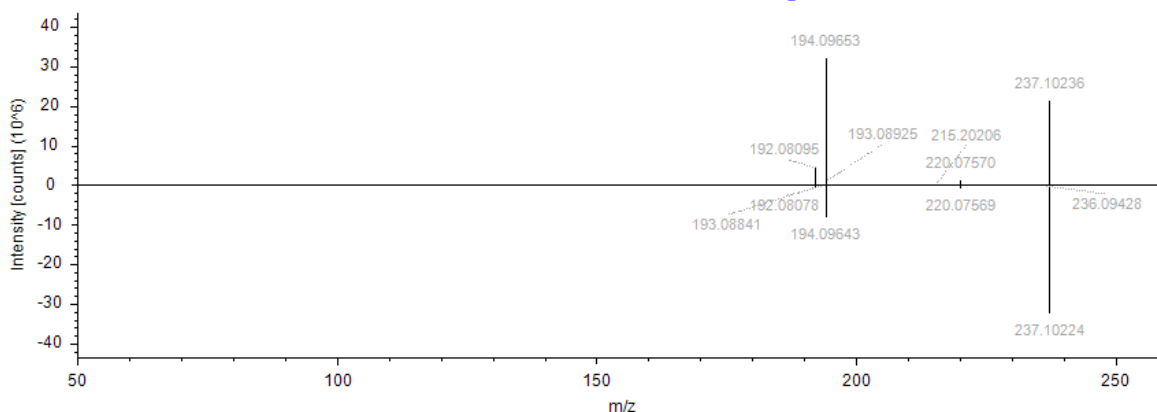


Figure S12. Identification of carbamazepine (mzCloud match score: 96.6) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #1230, RT=4.047 min, MS2, FTMS (+), (HCD, DDF, 253.0972@30, +1)
 REFERENCE(bottom): mzCloud library, Carbamazepine 10,11-epoxide, C15 H12 N2 O2, MS2, FTMS, (HCD, 253.0972@30)

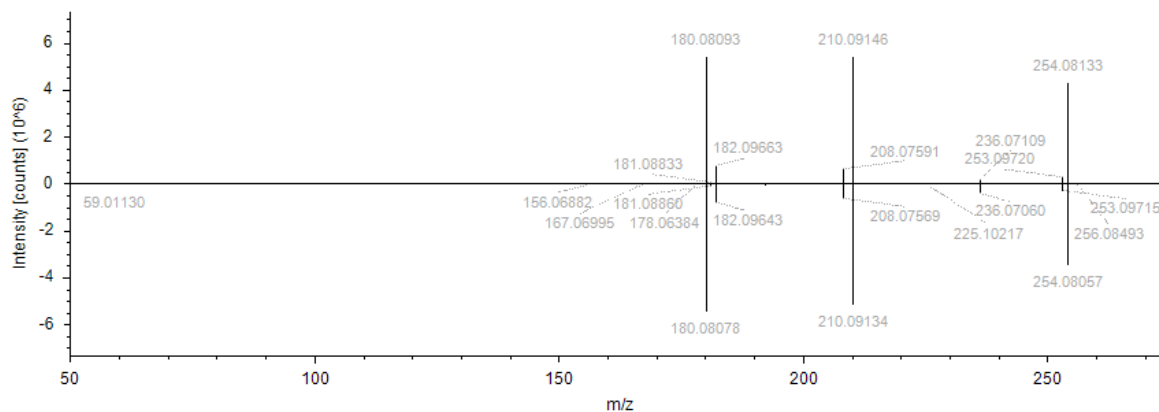


Figure S13. Identification of carbamazepine-10,11-epoxide (mzCloud match score: 95.0) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #445, RT=1.857 min, MS2, FTMS (-), (HCD, DDF, 293.9420@30, -1)
 REFERENCE(bottom): mzCloud library, Chlorothiazide, C7 H6 Cl N3 O4 S2, MS2, FTMS, (HCD, 293.9415@30)

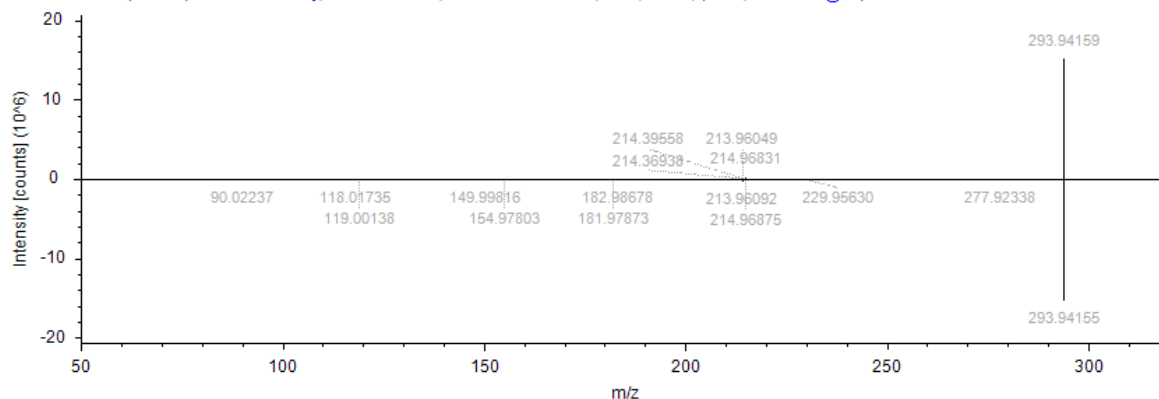


Figure S14. Identification of chlorothiazide (mzCloud match score: 92.3) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #804, RT=3.364 min, MS2, FTMS (-), (HCD, DDF, 337.0061@30, -1)
 REFERENCE(bottom): mzCloud library, Chlorthalidone, C14 H11 Cl N2 O4 S, MS2, FTMS, (HCD, 337.0055@30)

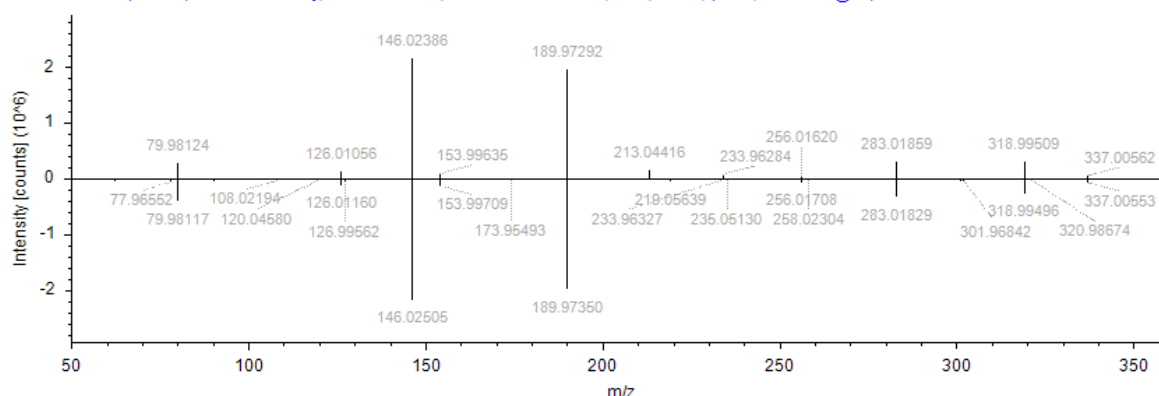


Figure S15. Identification of chlorthalidone (mzCloud match score: 96.0) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #1616, RT=5.233 min, MS2, FTMS (+), (HCD, DDF, 293.1049@30, +1)
REFERENCE(bottom): mzCloud library, Climbazole, C15 H17 Cl N2 O2, MS2, FTMS, (HCD, 293.1051@30)

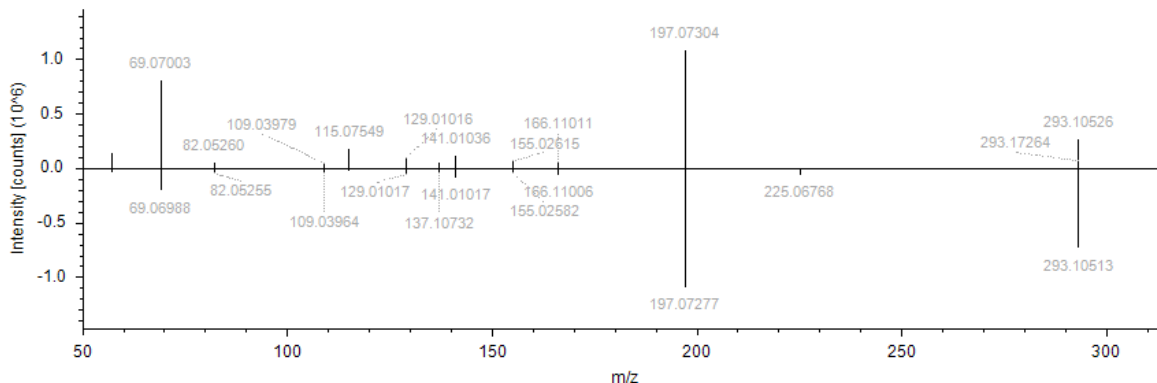


Figure S16. Identification of climbazole (mzCloud match score: 88.7) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-13-CalMix9-neg (F13) #1282, RT=5.419 min, MS2, FTMS (-), (HCD, DDF, 213.0322@30, -1)
REFERENCE(bottom): mzCloud library, Clofibric acid, C10 H11 Cl O3, MS2, FTMS, (HCD, 213.0324@30)

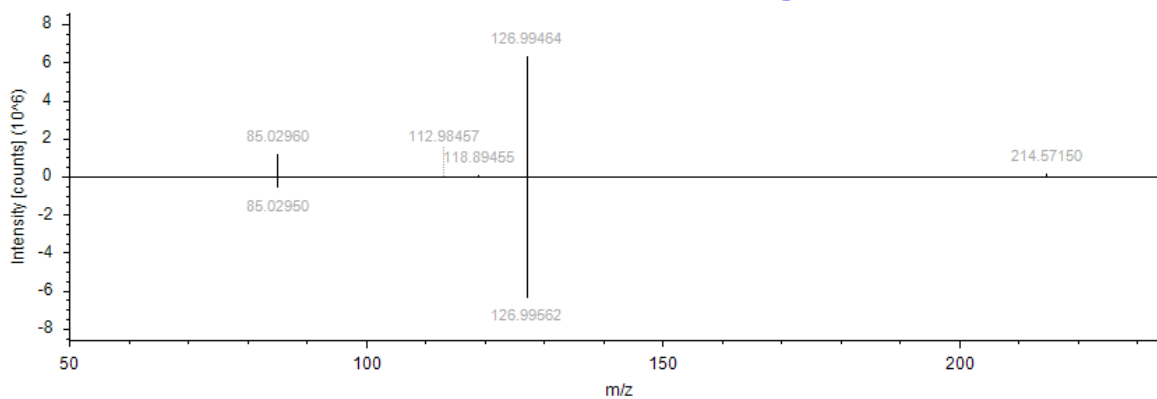


Figure S17. Identification of clofibric acid (mzCloud match score: 97.3) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-13-CalMix9-pos (F48) #2026, RT=6.677 min, MS2, FTMS (+), (HCD, DDF, 296.0240@30, +1)
REFERENCE(bottom): mzCloud library, Diclofenac, C14 H11 Cl2 N O2, MS2, FTMS, (HCD, 296.0240@30)

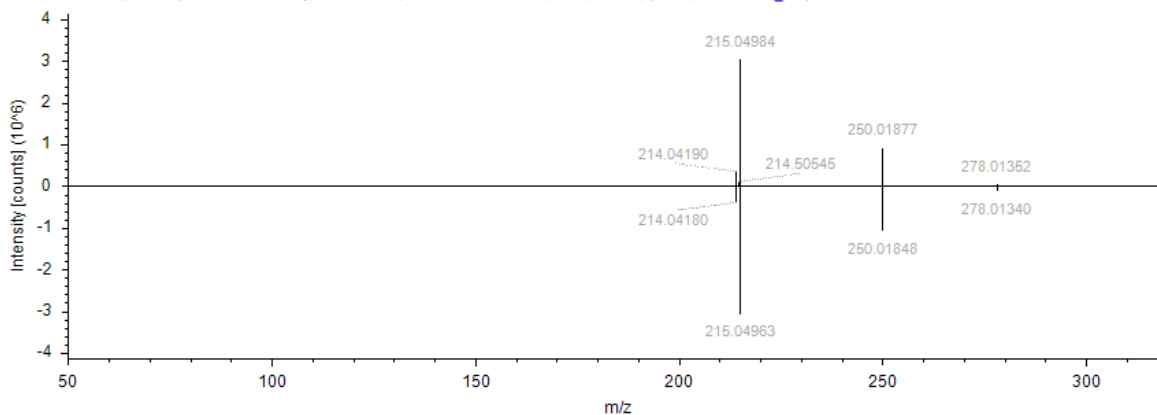


Figure S18. Identification of diclofenac (mzCloud match score: 97.6) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #938, RT=3.164 min, MS2, FTMS (+), (HCD, DDF, 307.1114@30, +1)
REFERENCE(bottom): mzCloud library, Fluconazole, C₁₃H₁₂F₂N₆O, MS2, FTMS, (HCD, 307.1113@30)

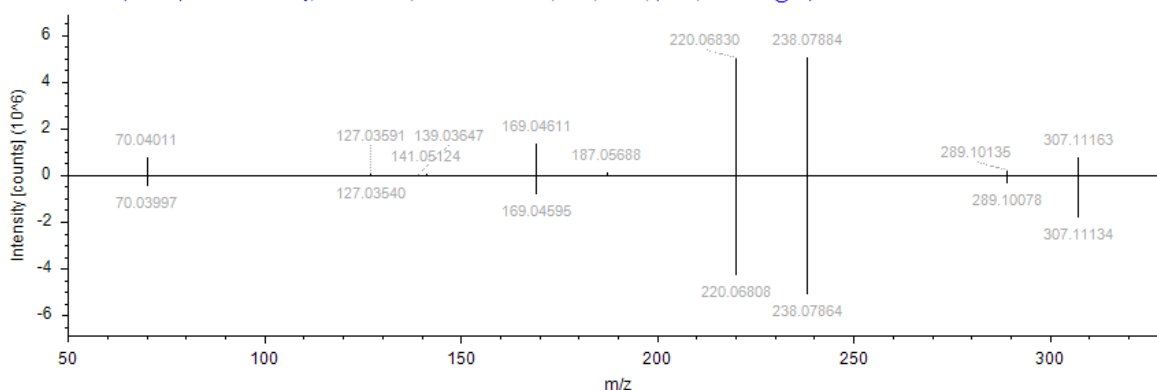


Figure S19. Identification of fluconazole (mzCloud match score: 97.3) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #1059, RT=4.463 min, MS2, FTMS (-), (HCD, DDF, 329.0010@30, -1)
REFERENCE(bottom): mzCloud library, Furosemide, C₁₂H₁₁ClN₂O₅S, MS2, FTMS, (HCD, 329.0004@20)

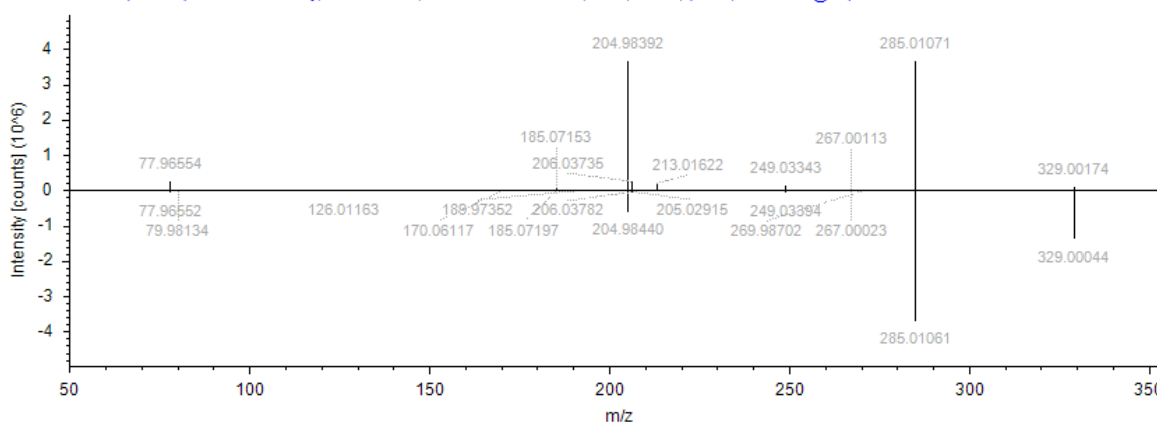


Figure S20. Identification of furosemide (mzCloud match score: 93.9) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-32-SPE-Eff-pos (F29) #864, RT=2.139 min, MS2, FTMS (+), (HCD, DDF, 172.1330@30, +1)
REFERENCE(bottom): mzCloud library, Gabapentin, C₉H₁₇N₂O₂, MS2, FTMS, (HCD, 172.1332@20)

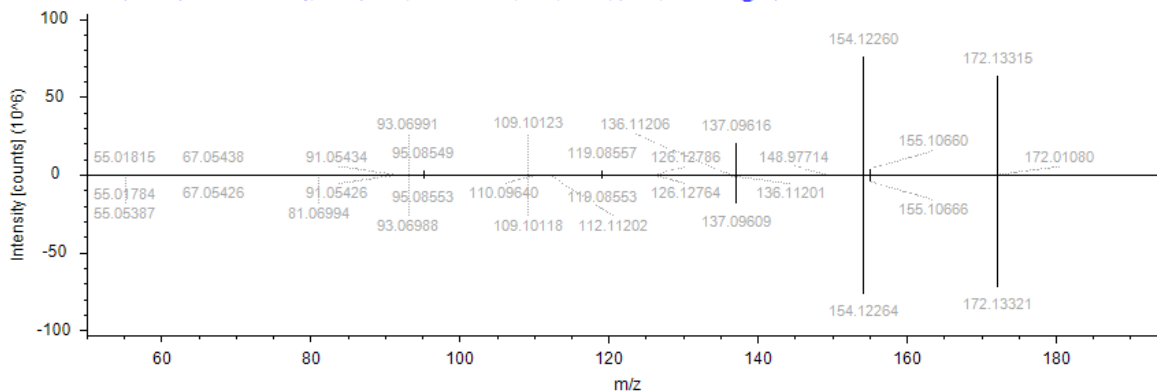


Figure S21. Identification gabapentin (mzCloud match score: 98.3) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #2141, RT=6.956 min, MS2, FTMS (+), (HCD, DDF, 491.2320@30, +1)
 REFERENCE(bottom): mzCloud library, Glimepiride, C24 H34 N4 O5 S, MS2, FTMS, (HCD, 491.2323@20)

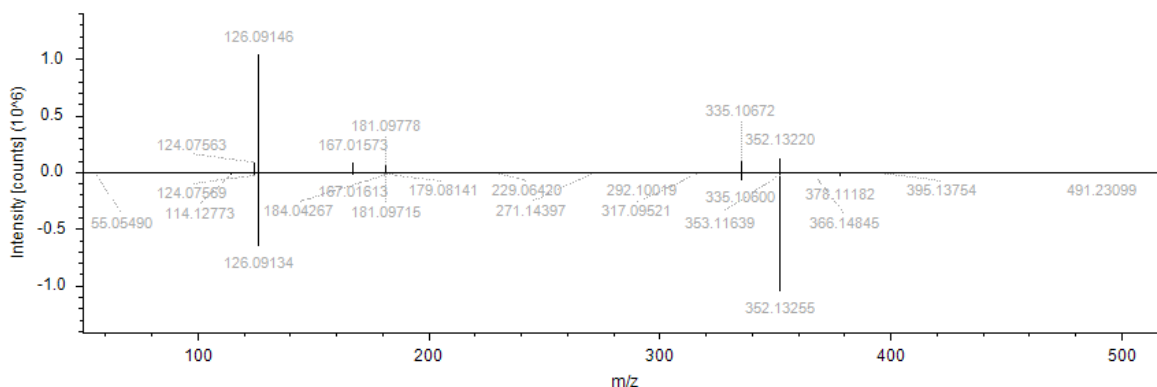


Figure S22. Identification glimepiride (mzCloud match score: 90.1) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #486, RT=2.010 min, MS2, FTMS (-), (HCD, DDF, 295.9576@30, -1)
 REFERENCE(bottom): mzCloud library, Hydrochlorothiazide, C7 H8 Cl N3 O4 S2, MS2, FTMS, (HCD, 295.9572@20)

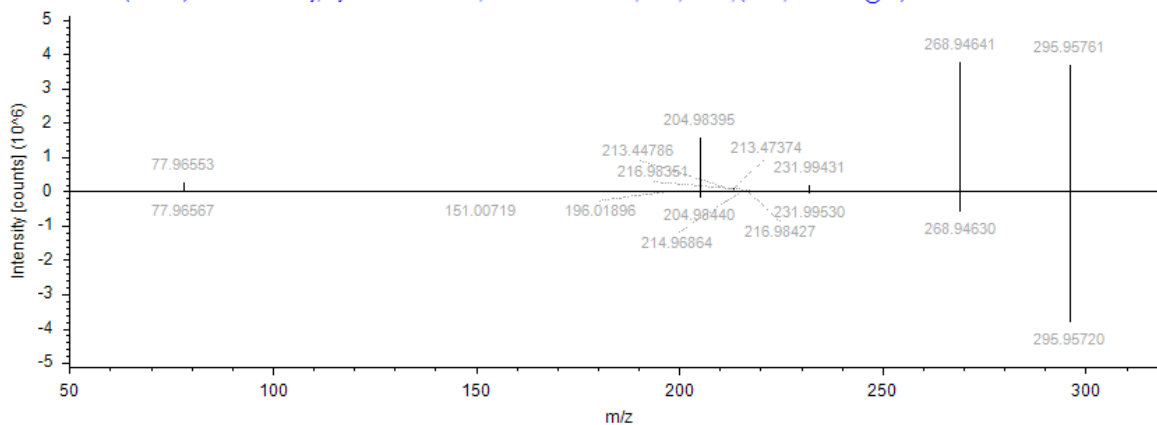


Figure S23. Identification of hydrochlorothiazide (mzCloud match score: 94.7) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #1622, RT=5.243 min, MS2, FTMS (+), (HCD, DDF, 429.2398@30, +1)
 REFERENCE(bottom): mzCloud library, Irbesartan, C25 H28 N6 O, MS2, FTMS, (HCD, 429.2397@30)

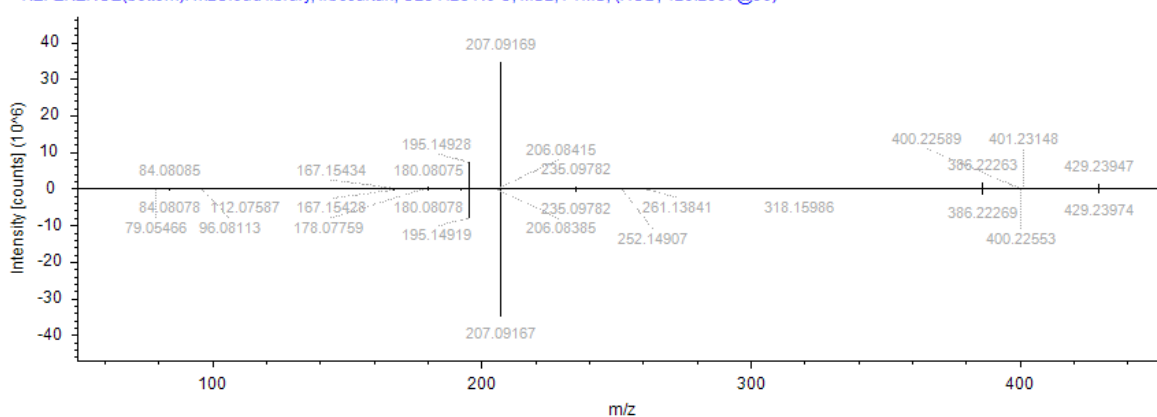


Figure S24. Identification of irbesartan (mzCloud match score: 96.4) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #1748, RT=5.641 min, MS2, FTMS (+), (HCD, DDF, 255.1015@30, +1)
REFERENCE(bottom): mzCloud library, Ketoprofen, C₁₆H₁₄O₃, MS2, FTMS, (HCD, 255.1016@30)

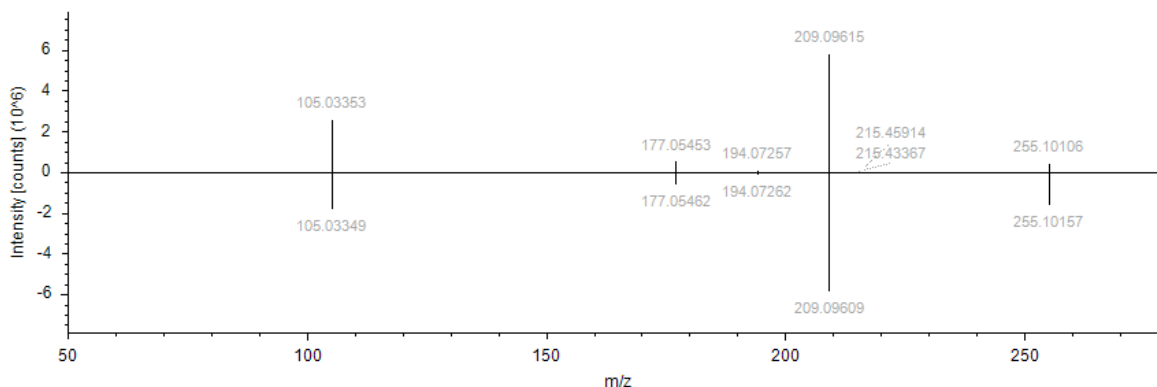


Figure S25. Identification of ketoprofen (mzCloud match score: 97.6) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #1241, RT=5.206 min, MS2, FTMS (-), (HCD, DDF, 199.0164@30, -1)
REFERENCE(bottom): mzCloud library, 2-Methyl-4-chlorophenoxyacetic acid (MCPA), C₉H₉ClO₃, MS2, FTMS, (HCD, 199.0167@20)

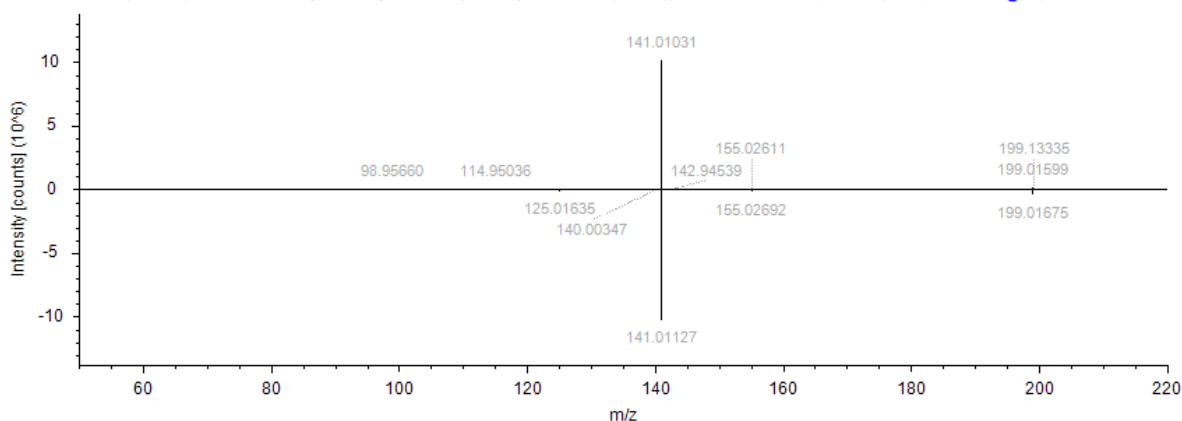


Figure S26. Identification of MCPA (mzCloud match score: 95.3) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-33-SPE-In-pos (F28) #232, RT=0.849 min, MS2, FTMS (+), (HCD, DDF, 130.1086@30, +1)
REFERENCE(bottom): mzCloud library, Metformin, C₄H₁₁N₅, MS2, FTMS, (HCD, 130.1087@60)

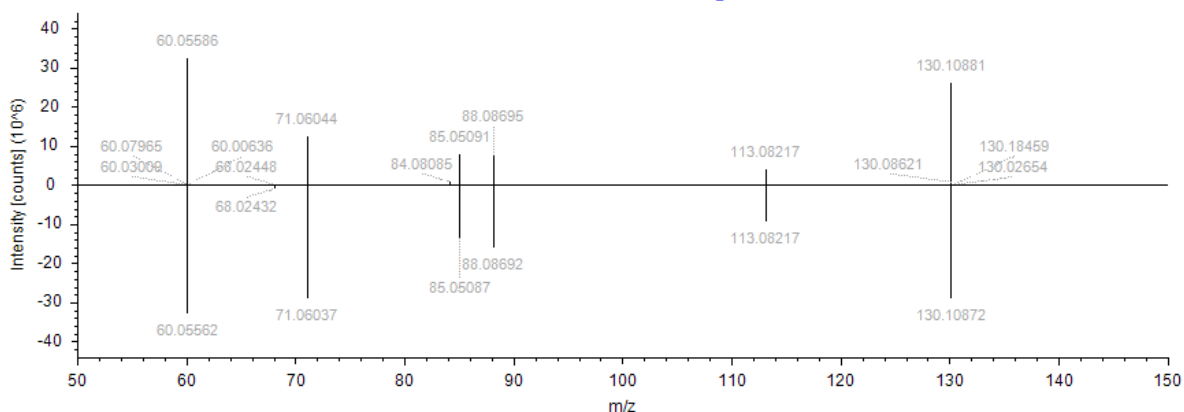


Figure S27. Identification of metformin (mzCloud match score: 95.7) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #547, RT=2.284 min, MS2, FTMS (-), (HCD, DDF, 453.1646@30, -1)
REFERENCE(bottom): mzCloud library, Methotrexate, C20 H22 N8 O5, MS2, FTMS, (HCD, 453.1640@30)

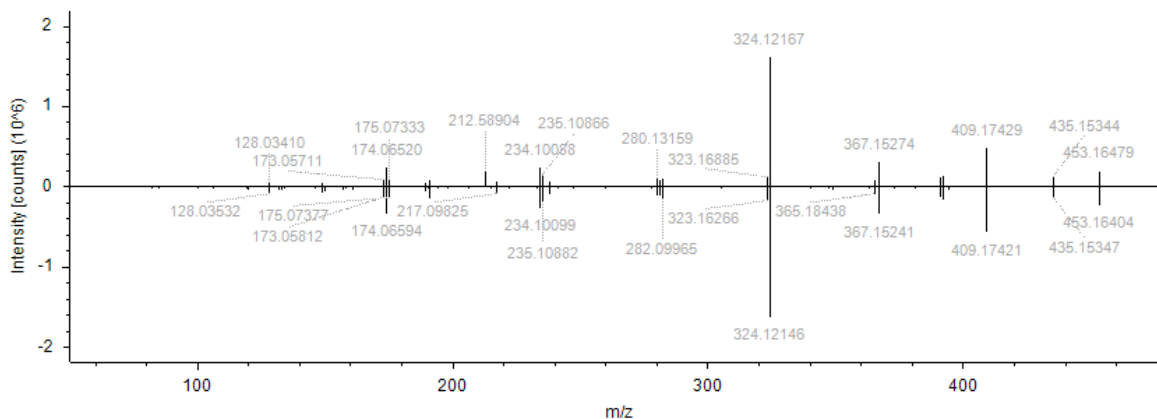


Figure S28. Identification of methotrexate (mzCloud match score: 99.3) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-32-SPE-Eff-pos (F29) #1384, RT=3.262 min, MS2, FTMS (+), (HCD, DDF, 268.1905@30, +1)
REFERENCE(bottom): mzCloud library, Metoprolol, C15 H25 N O3, MS2, FTMS, (HCD, 268.1907@10)

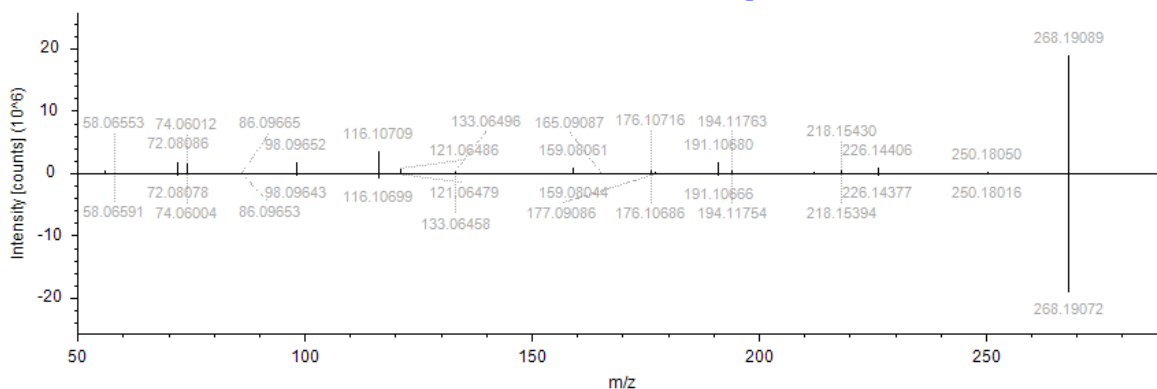


Figure S29. Identification of metoprolol (mzCloud match score: 97.4) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #696, RT=2.335 min, MS2, FTMS (+), (HCD, DDF, 268.1544@30, +1)
REFERENCE(bottom): mzCloud library, Atenolol acid, C14 H21 N O4, MS2, FTMS, (HCD, 268.1543@30)

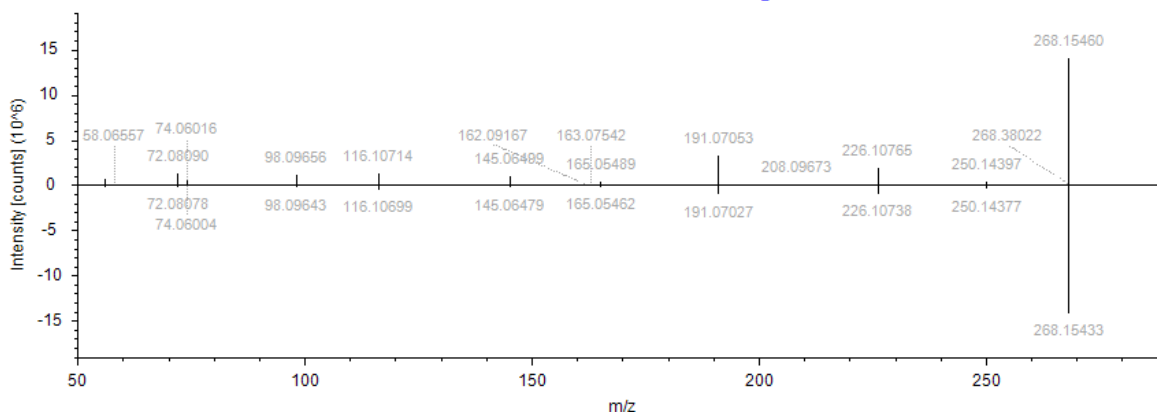


Figure S30. Identification of metoprolol acid (mzCloud match score: 95.8) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #1547, RT=5.023 min, MS2, FTMS (+), (HCD, DDF, 287.0581@30, +1)
REFERENCE(bottom): mzCloud library, Oxazepam, C15 H11 Cl N2 O2, MS2, FTMS, (HCD, 287.0582@30)

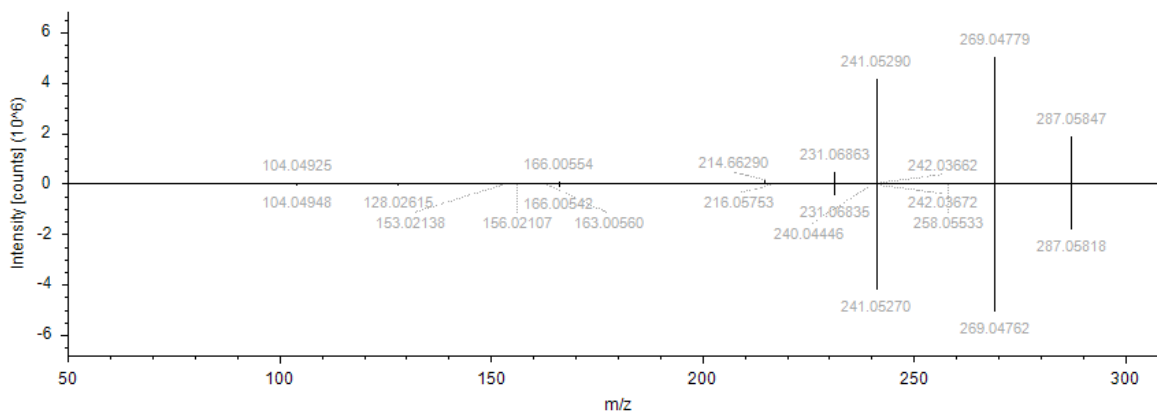


Figure S31. Identification of oxazepam (mzCloud match score: 95.8) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #1094, RT=4.608 min, MS2, FTMS (-), (HCD, DDF, 423.2395@30, -1)
REFERENCE(bottom): mzCloud library, Pravastatin, C23 H36 O7, MS2, FTMS, (HCD, 423.2388@30)

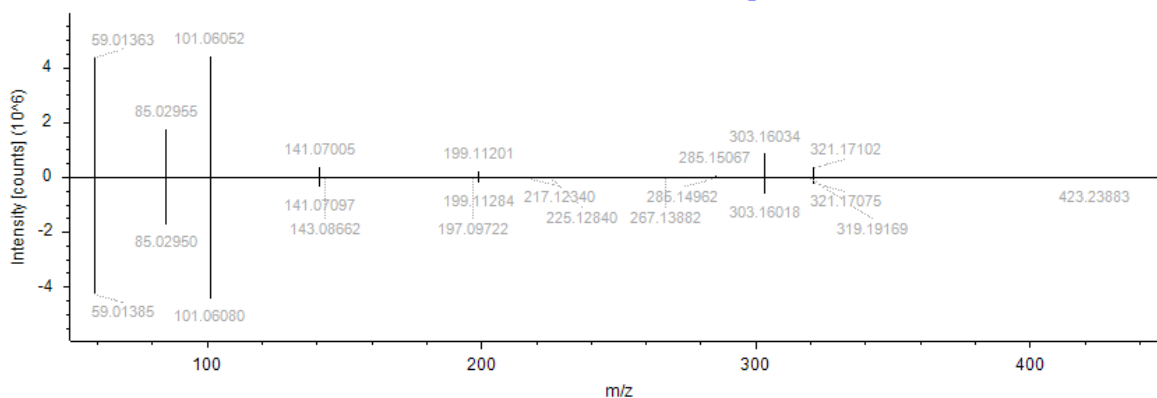


Figure S32. Identification of pravastatin (mzCloud match score: 93.0) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #1303, RT=4.269 min, MS2, FTMS (+), (HCD, DDF, 260.1643@30, +1)
REFERENCE(bottom): mzCloud library, Propranolol, C16 H21 N O2, MS2, FTMS, (HCD, 260.1645@10)

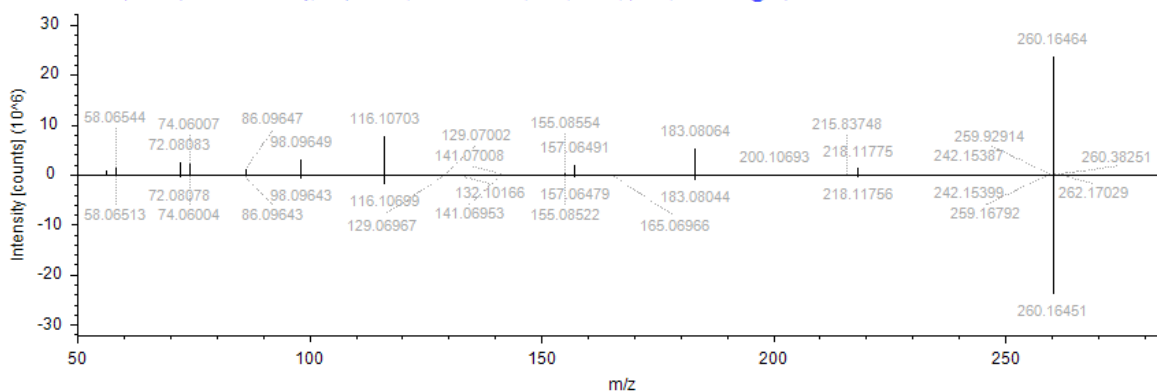


Figure S33. Identification of propranolol (mzCloud match score: 98.4) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #541, RT=1.852 min, MS2, FTMS (+), (HCD, DDF, 315.1484@30, +1)
 REFERENCE(bottom): mzCloud library, Ranitidine, C13 H22 N4 O3 S, MS2, FTMS, (HCD, 315.1485@30)

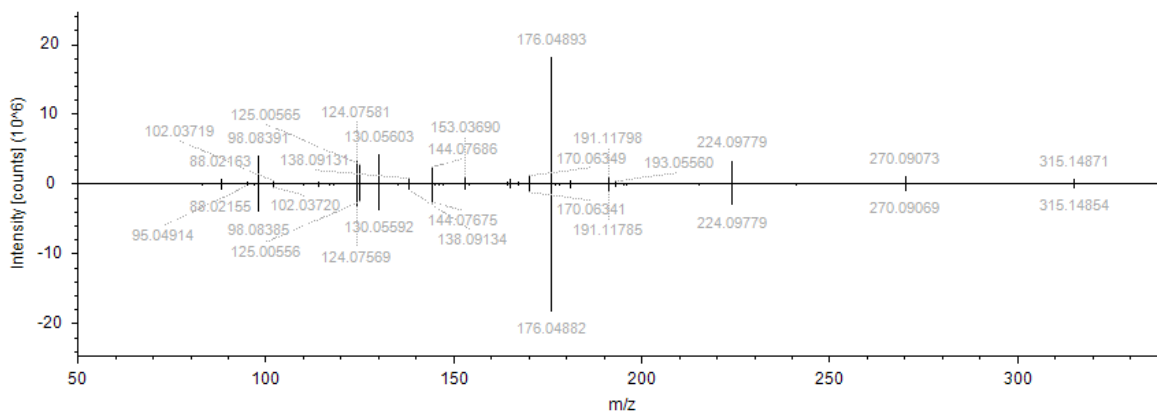


Figure S34. Identification of ranitidine (mzCloud match score: 97.4) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #497, RT=1.739 min, MS2, FTMS (+), (HCD, DDF, 273.1267@30, +1)
 REFERENCE(bottom): mzCloud library, Sotalol, C12 H20 N2 O3 S, MS2, FTMS, (HCD, 273.1267@30)

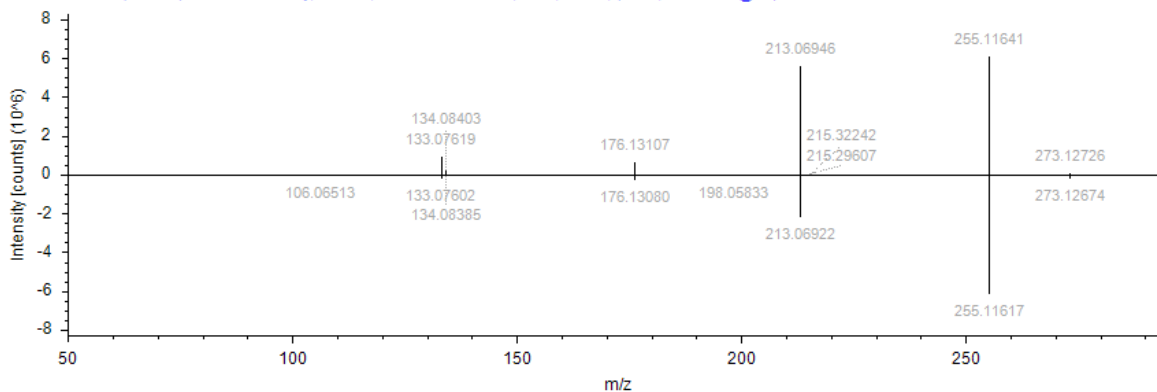


Figure S35. Identification of sotalol (mzCloud match score: 93.8) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #1031, RT=3.439 min, MS2, FTMS (+), (HCD, DDF, 254.0594@30, +1)
 REFERENCE(bottom): mzCloud library, Sulfamethoxazole, C10 H11 N3 O3 S, MS2, FTMS, (HCD, 254.0594@30)

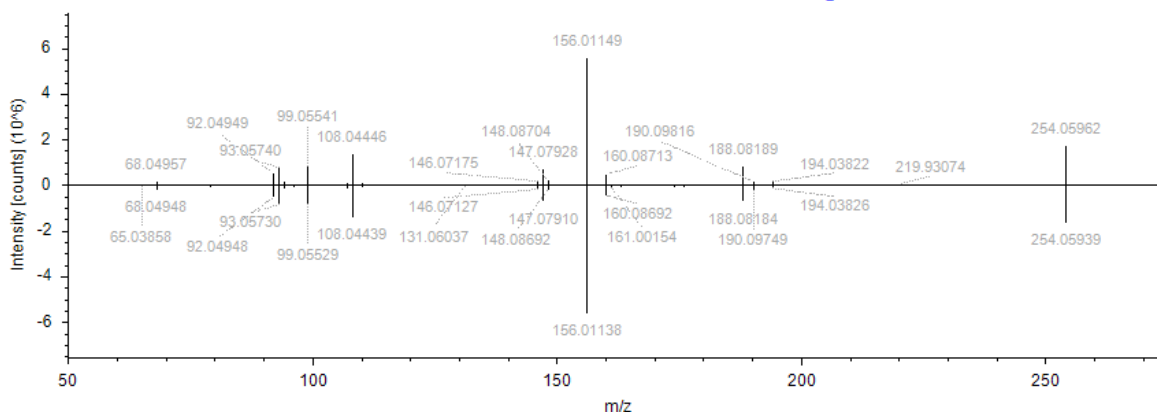


Figure S36. Identification of sulfamethoxazole (mzCloud match score: 97.8) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #970, RT=3.260 min, MS2, FTMS (+), (HCD, DDF, 264.1956@30, +1)
 REFERENCE(bottom): mzCloud library, Tramadol, C₁₆H₂₅N O₂, MS2, FTMS, (HCD, 264.1958@10)

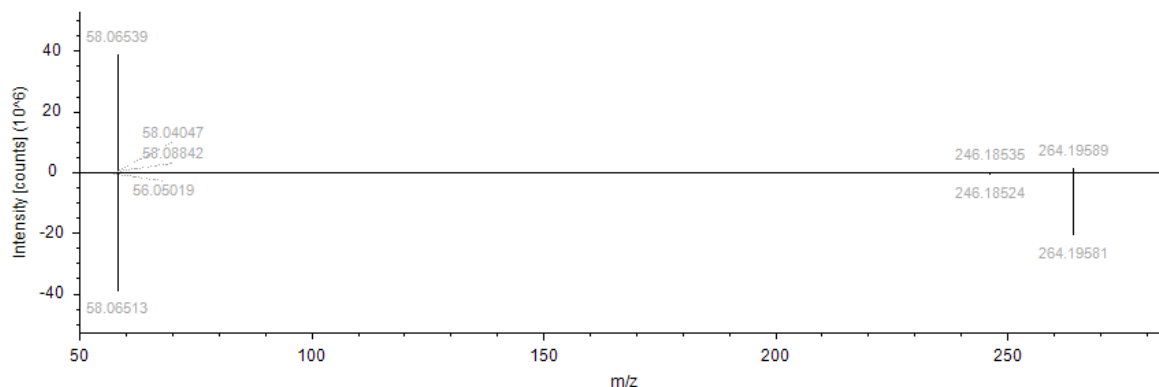


Figure S37. Identification of tramadol (mzCloud match score: 88.8) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20171002-14-CalMix10-neg (F14) #1427, RT=5.910 min, MS2, FTMS (-), (HCD, DDF, 434.2204@30, -1)
 REFERENCE(bottom): mzCloud library, Valsartan, C₂₄H₂₉N₅O₃, MS2, FTMS, (HCD, 434.2198@30)

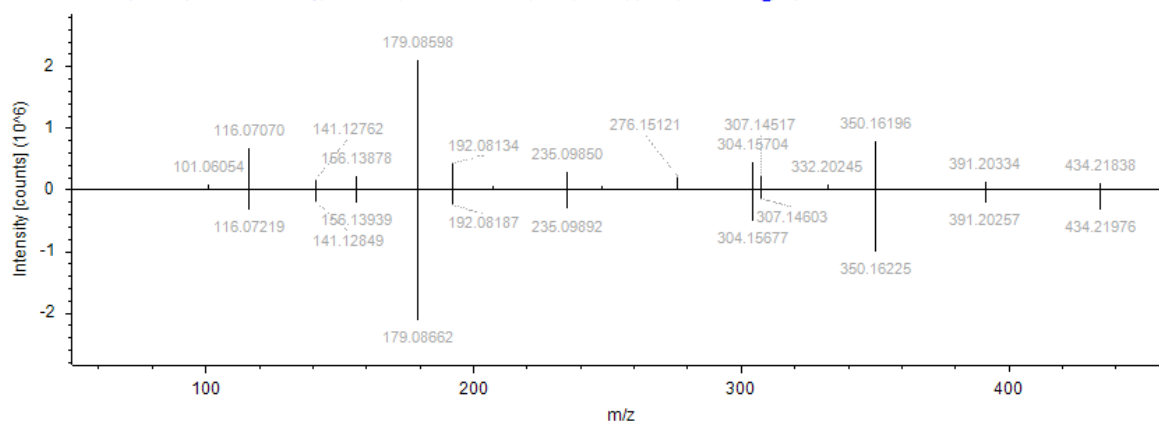


Figure S38. Identification of valsartan (mzCloud match score: 98.7) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

RAWFILE(top): 20170927-14-CalMix10-pos (F47) #1187, RT=3.924 min, MS2, FTMS (+), (HCD, DDF, 278.2115@30, +1)
 REFERENCE(bottom): mzCloud library, Venlafaxine, C₁₇H₂₇N O₂, MS2, FTMS, (HCD, 278.2115@30)

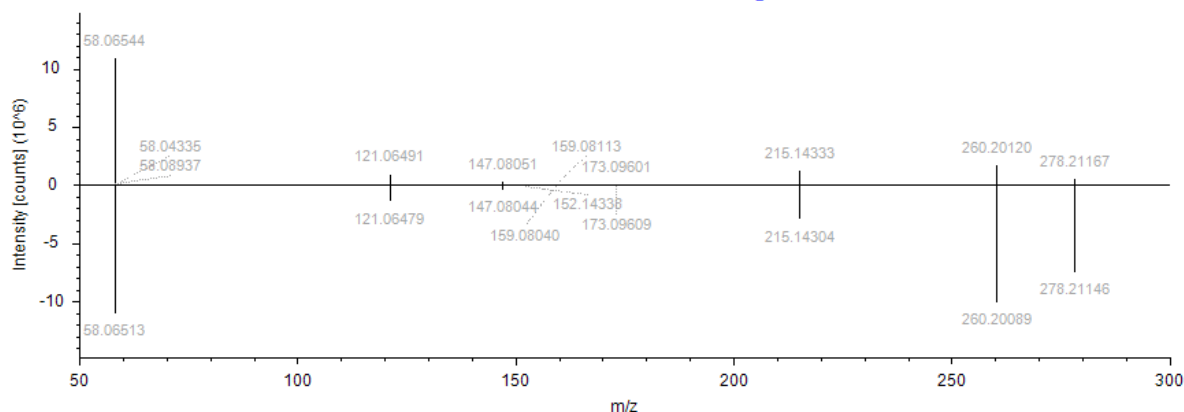


Figure S39. Identification of venlafaxine (mzCloud match score: 94.0) in the calibration standard. Shown is the matching of the detected MS/MS of the compound (top) to the library record (bottom).

Table S4. Concentrations of the target compounds detected in the influent and effluent water.

	influent ($\mu\text{g l}^{-1}$) ^a	effluent ($\mu\text{g l}^{-1}$) ^a
1H-benzotriazole	0.91	0.53
2-chlorobenzoic acid	0.22	n.d.
4-hydroxy-benzotriazole	0.82	0.76
acesulfame	51	4.3
acetaminophen	68	0.25
anastrozole	n.d.	n.d.
aniline	1.9	0.25
atenolol	0.70	0.25
atorvastatin	0.30	n.d.
bezafibrate	0.37	n.d.
bicalutamide	0.24	0.22
caffeine	273	0.062
carbamazepine	0.63	0.64
carbamazepine-10,11-epoxide	0.24	0.22
chlorothiazide	n.d.	0.056
chlorthalidone	n.d.	n.d.
climbazole	0.14	0.050
clofibric acid	n.d.	n.d.
diclofenac	1.2	0.75
fluconazole	0.21	0.18
fluoxetine	n.d.	n.d.
furosemide	0.72	0.51
gabapentin	6.1	4.7
glimepiride	n.d.	n.d.
hydrochlorothiazide	1.9	1.6
irbesartan	0.22	0.52
ketoprofen	0.85	0.16
MCPA	n.d.	n.d.
metformin	98	3.0
methotrexate	n.d.	n.d.
metoprolol	2.2	1.8
metoprolol acid	8.4	2.3
oxazepam	0.42	0.41
pravastatin	0.49	n.d.
propranolol	0.11	0.090
ranitidine	0.062	n.d.
sotalol	0.35	0.32
sulfamethoxazole	0.37	n.d.
tramadol	0.55	0.48
triclosan	0.34	n.d.
valsartan	1.6	0.56
venlafaxine	0.52	0.43

^a n.d. indicates the compound was not detected (<LOD).

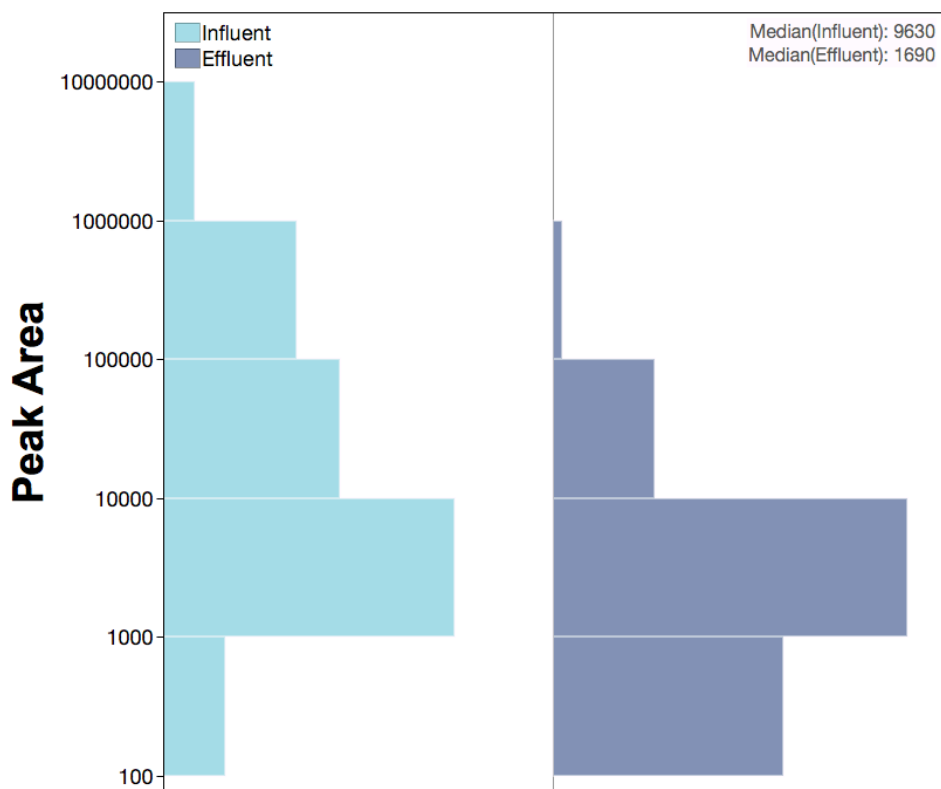


Figure S40. Distribution of the peak areas of all the compounds identified in the influent (left) and effluent water (right) using the non-target analysis. The results are from the direct injection approach.

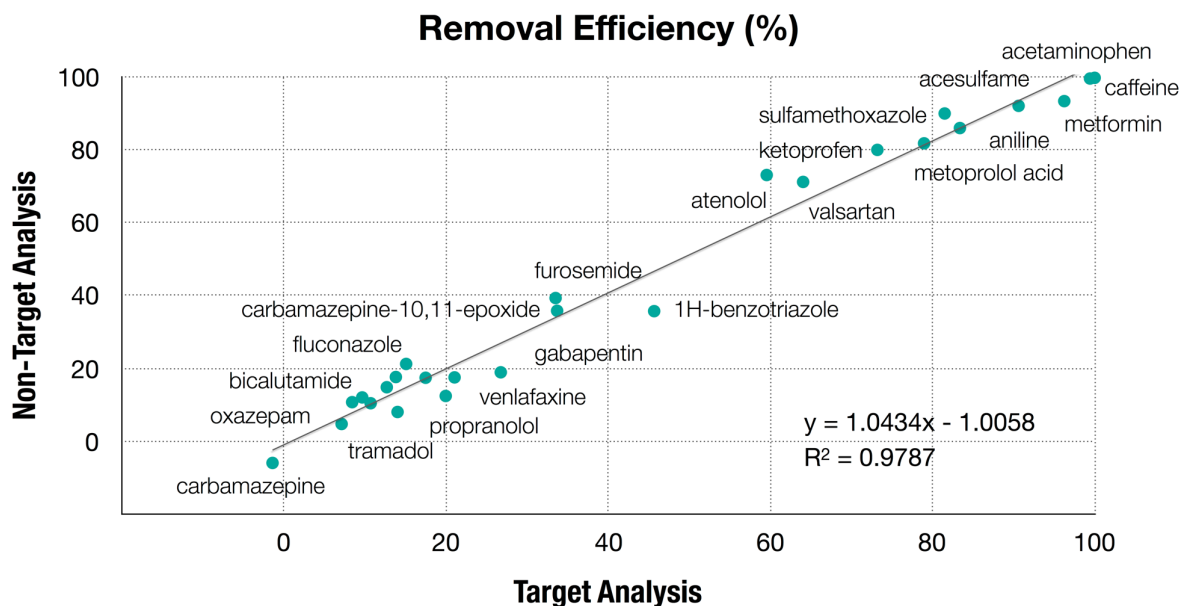


Figure S41. Comparison of the RE (%) values for the tested target compounds calculated using the target and non-target approaches with direct injection.

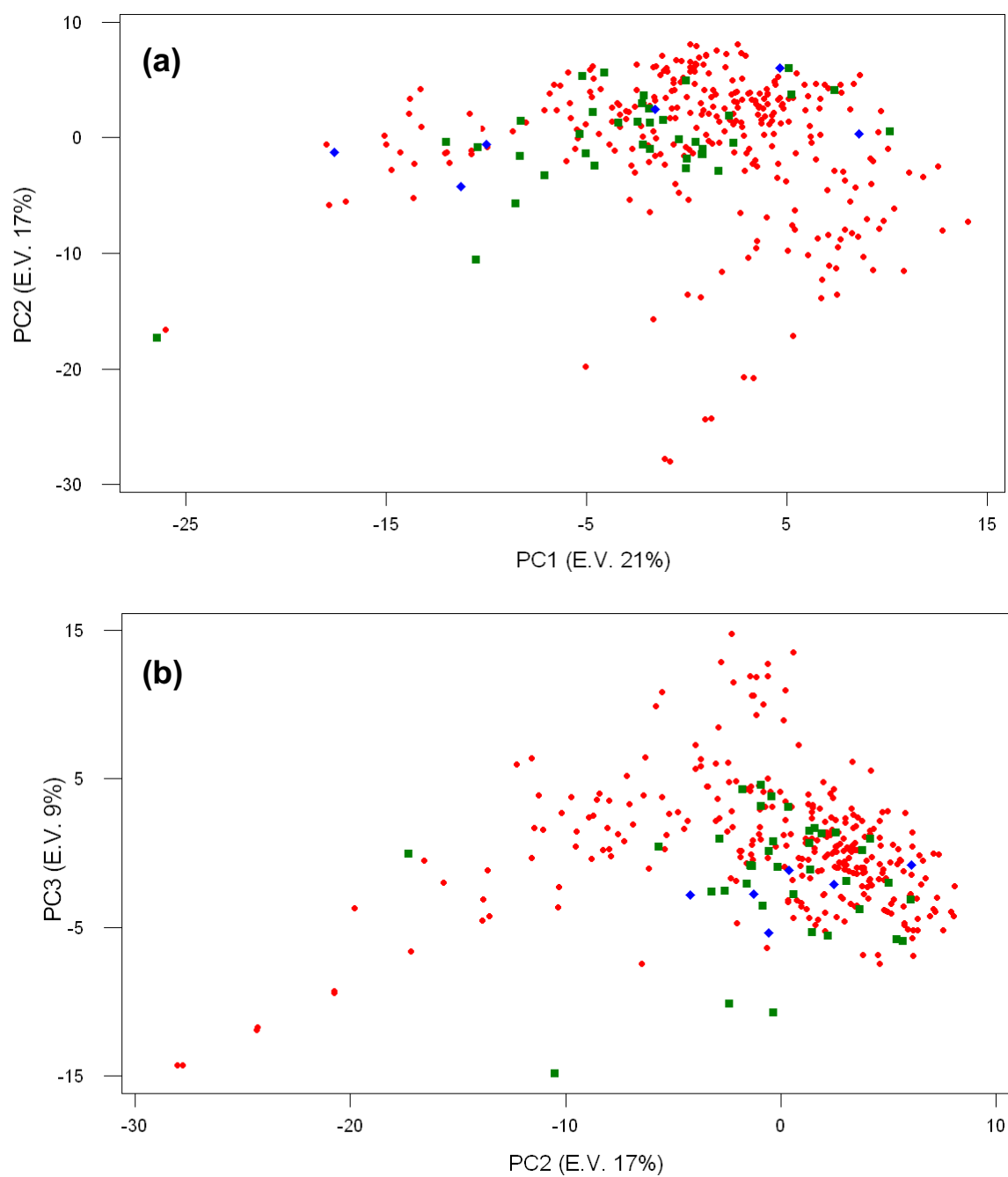


Figure S42. PCA analysis of chemical domain covering all the compounds identified by the mzCloud database (red circles) as well as the 34 isotope-labelled standards for which matrix effect was similar between influent and effluent (green triangles): (a) Score plot of PC1 and PC2 (showing chemical positions in relation to PC1 and PC2); (b) Score plot of PC2 and PC3 (showing chemical positions in relation to PC2 and PC3). Blue diamonds represent the random distribution of the six isotope-labelled standards that had significant differences in matrix effects.

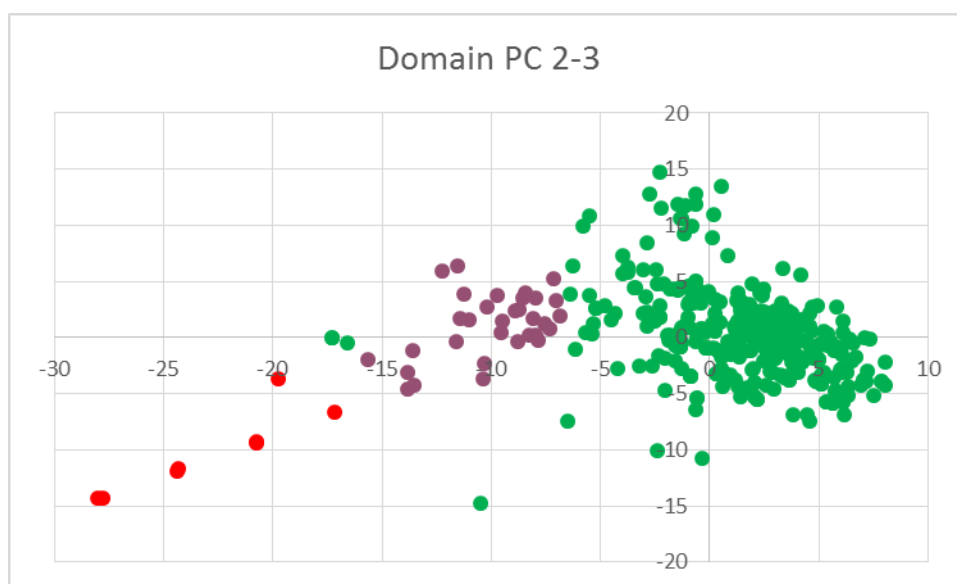
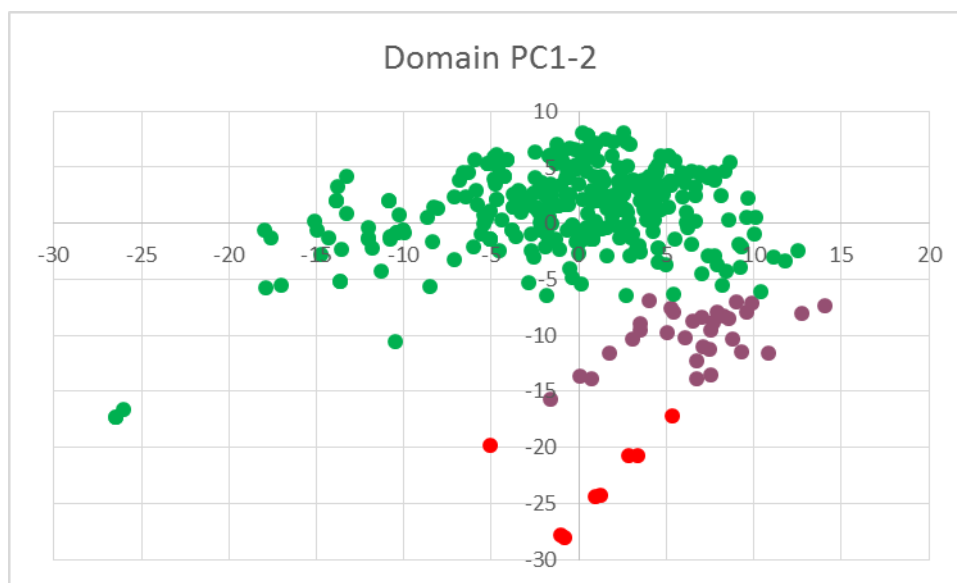


Figure S43. Chemical domain in the space of PC1-PC2-PC3 (cumulative explained variance: 47%). Green circles represent the chemicals that are inside of the structural domain of the standards; violet circles represent the chemicals for which the structures are scarcely represented by the standards; red circles represent the chemicals that are severely out of domain (unreliable RE%) (PEG n8-n15 and PPG 10).