Comprehensive Characterization of 76 Pharmaceuticals and Metabolites in Wastewater by LC-MS/MS

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Table S1. Anatomical Therapeutic Chemical classification system (ATC) of target pharmaceuticals.

				ATC CODE	NAME
A. Alimentary tract and metabolism	A01. Stomatological preparations	A01A. Stomatological preparations	A01AD. Other agents for local oral treatment	A01AD05	Acetylsalicylic acid
	A02. Drugs for acid related disorders	A02B. Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	A02BA. H2-receptor antagonists	A02BA02	Ranitidine
			A02BC. Proton pump inhibitor	A02BC01	Omeprazole
				A02BC02	Pantoprazole
				A02BC05	Esomeprazole
	A10. Drugs used in diabetes	A10B. Blood glucose lowering drugs, excl. insulins	A10BH. Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH02	Vildagliptin
C. Cardiovascular system	C01. Cardiac therapy	C01B. Antiarrhythmics, class I and III	C01BD. Antiarrhythmics, class III	C01BD01	Amiodarone
	C03. Diuretics	C03A. Low-ceiling diuretics, thiazides	C03AA. Thiazides, plain	C03AA03	Hydrochlorothiazide
		C03C. High-ceiling diuretics	C03CA. Sulfonamides, plain	C03CA01	Furosemide
	C04. Peripheral vasodilators	C04A. Peripheral vasodilators	C04AD. Purine derivatives	C04AD03	Pentoxifylline
	C05. Vasoprotectives	C05A. Agents for treatment of hemorrhoids and anal fissures for topical use	C05AD. Local anesthetics	C05AD01	Lidocaine
	C07. Beta blocking agents	C07A. Beta blocking agents	C07AA. Beta blocking agents, non-selective	C07AA05	Propranolol
			C07AB. Beta blocking agents, selective	C07AB03	Atenolol
	C08. Calcium channel blockers	C08D. Selective calcium channel blockers with direct cardiac effects	C08DA. Phenylalkylamine derivates	C08DA01	Verapamil
		C09A. Ace inhibitors, plain	C09AA. ACE inhibitors plain	C09AA02	Enalapril

	C09. Agents acting on the renin-angiotensin system	C09C. Angiotensin II receptor blockers (ARBs), plain	C09CA. Angiotensin II receptor blockers (ARBs), plain	C09CA01	Losartan
				C09CA03	Valsartan
	C10. Lipid modifying agents	C10A. Lipid modifying agents, plain	C10AA. HMG CoA reductase inhibitors	C10AA01	Simvastatin
				C10AA07	Rosuvastatin
			C10AX. Other lipid modifying agents	C10AX09	Ezetimibe
G. Genito urinary system and sex hormones	G03. Sex hormones and modulators of the genital system	G03C. Estrogens	G03CA. Natural and semisynthetic estrogens, plain	G03CA07	Estrone
		G03H. Antiandrogens	G03HA. Antiandrogens, plain	G03HA01	Cyproterone
	G04. Urologicals	G04C. Drugs used in benign prostatic hypertrophy	G04CB. Testosterone-5-alpha reductase inhibitors	G04CB02	Dutasteride
H. Systemic hormonal preparations, excl. sex hormones and insulins	H02. Corticosteroids for systemic use	H02A. Corticosteroids for systemic use, plain	H02AB. Glucocorticoids	H02AB07	Prednisone
J. Anti-infectives for systemic use	J01. Antibacterials for systemic use	J01C. Beta-lactam antibacterials, penicillins	J01CA. Penicillin with extended spectrum	J01CA04	Amoxicillin
		J01E. Sulfonamides and trimethoprim	J01EB. Short-acting sulfonamides	J01EB04	Sulfapyridine
			J01EC. Intermediate-acting sulfonamides	J01EC01	Sulfamethoxazole
				J01EC02	Sulfadiazine
		J01F. Macrolides, lincosamides and streptogramins	J01FA. Macrolides	J01FA01	Erythromycin
				J01FA09	Clarithromycin
		J01M. Quinolone antibacterials	J01MA. Fluoroquinolones	J01MA02	Ciprofloxacin
				J01MA06	Norfloxacin
				J01MA12	Levofloxacin
L. Antineoplastic and immunomodulating agents	L01. Antineoplastic agents	L01A. Alkylating agents	L01AA. Nitrogen mustard analogues	L01AA01	Cyclophosphamide
				L01AA06	Ifosfamide
	L02. Endocrine therapy	L02A. Hormones and related agents	L02AB. Progestogens	L02AB01	Megestrol

	L02B. Hormone antagonists and related agents	L02BB. Anti-androgens	L02BB03	Bicalutamide
	L04. Immunosuppressants	L04A. Immunosuppressants	L04AA. Selective immunosuppressants	L04AA06	Mycophenolic acid
M. Musculo-skeletal system	M01. Antiinflammatory and antirheumatic products	M01A. Antiinflammatory and antirheumatic products, non-steroids	M01AB. Acetic acid derivatives and related substances	M01AB05	Diclofenac
			M01AE. Propionic acid derivatives	M01AE01	Ibuprofen
N. Nervous system	N02. Analgesics	N02A. Opioids	N02AX. Other opioids	N02AX02	Tramadol
		N02B. Other analgesics and antipyretics	N02BE. Anilides	N02BE01	Paracetamol
	N03. Antiepileptics	N03A. Antiepileptics	N03AF. Carboxamide derivatives	N03AF01	Carbamazepine
			N03AX. Other antiepileptics	N03AX11	Topiramate
				N03AX12	Gabapentin
				N03AX14	Levetiracetam
				N03AX16	Pregabalin
	N04. Anti-parkinson drugs	N04B. Dopaminergic agents	N04BA. Dopa and dopa derivatives	N04BA01	Levodopa
			N04BD. Monoamine oxidase B inhibitors	N04BD02	Rasagiline
	N05. Psycholeptics	N05B. Anxiolytics	N05BA. Benzodiazepine derivatives	N05BA01	Diazepam
		N05C. Hypnotics and sedatives	N05CM. Other hypnotics and sedatives	N05CM02	Clomethiazole
				N05CM05	Scopolamine
	N06. Psychoanaleptics	N06A. Antidepressants	N06AB. Selective serotonin reuptake inhibitors	N06AB03	Fluoxetine
				N06AB04	Citalopram
				N06AB10	Escitalopram
			N06AX. Other antidepressants	N06AX05	Trazodone
				N06AX16	Venlafaxine

		N06B. Psychostimulants, agents used for adhd and nootropics	N06BC. Xanthine derivatives	N06BC01	Caffeine
		N06D. Anti-dementia drugs	N06DA. Anticholinesterases	N06DA02	Donepezil
			N06DX. Other anti-dementia drugs	N06DX01	Memantine
R. Respiratory system	R02. Throat preparations	R02A. Throat preparations	R02AA. Antiseptics	R02AA03	Dichlorobenzyl alcohol
				R02AA20	Amylmetacresol
	R03. Drugs for obstructive airway diseases	R03B. Other drugs for obstructive airway diseases, inhalants	R03BA. Glucocorticoids	R03BA02	Budesonide
				R03BA05	Fluticasone
			R03BB. Anticholinergics	R03BB04	Tiotropium bromide
	R05. Cough and cold preparations	R05C. Expectorants, excl. combinations with cough suppressants	R05CB. Mucolytics	R05CB01	Acetylcysteine
		R05D. Cough suppressants, excl. combinations with expectorants	R05DA. Opium alkaloids and derivatives	R05DA09	Dextromethorphan
			R05DB. Other cough suppressants	R05DB21	Cloperastine
	R06. Antihistamines for systemic use	R06A. Antihistamines for systemic use	R06AB. Substituted alkylamines	R06AB02	Dexchlorpheniramine

Table S2. Physicochemical properties of the 76 pharmaceuticals, metabolites (*) and transformation product (**) studied. Mw: molecular weight. Values have been reported from EPI Suite [77].

Pharmaceutical	Molecular Formula	CAS number	Mw	Water solubility (mg L^{-1})	pKa	logP	Henry's law constant (atm m^3 mol^{-1})	Half-life	Excretion (%)
Acetylsalicylic acid	$C_9H_8O_4$	50-78-2	180.1	5295	3.5	1.19	1.30×10^{-9}	20 min	90
Salicylic acid *	$C_7H_6O_3$	69-72-7	138.1	3808	n. r.	2.26	1.42×10^{-8}	2 – 12 h	10
Ranitidine	$C_{13}H_{22}N_4O_3S$	66357-35-5	314.4	24660	2.7	1.93	3.42×10^{-15}	2 – 3 h	50
Omeprazole	$C_{17}H_{19}N_3O_3S$	73590-58-6	345.4	82.28	4.8	2.23	3.04×10^{-19}	1 – 1.2 h	100
Pantoprazole	$C_{16}H_{15}F_2N_3O_4S$	102625-70-7	383.4	48.84	3.92	2.22	5.84×10^{-20}	1 – 2 h	20
Esomeprazole	$C_{17}H_{19}N_3O_3S$	119141-88-7	345.4	82.28	4.78	3.40	3.04×10^{-19}	1 – 1.5 h	80
Vildagliptin	$C_{17}H_{25}N_3O_2$	274901-16-5	303.4	1336	15.05	0.79	3.14×10^{-16}	2 – 3 h	27
Amiodarone	$C_{25}H_{29}I_2NO_3$	1951-25-3	645.3	0.0002825	6.56	7.57	1.80×10^{-12}	58 d	< 1
Hydrochlorothiazide	$C_7H_8ClN_3O_4S_2$	58-93-5	297.7	1292	7.9	-0.07	4.39×10^{-12}	6 – 15 h	> 95
Furosemide	$C_{12}H_{11}ClN_2O_5S$	54-31-9	330.7	149.3	3.8	2.03	3.94×10^{-16}	2 h	99
Pentoxifylline	$C_{13}H_{18}N_4O_3$	6493-05-6	278.3	453.7	19.64	0.29	5.63×10^{-14}	0.4 – 0.8 h	99
Lidocaine	$C_{14}H_{22}N_2O$	137-58-6	234.3	237.7	7.86	2.44	1.31×10^{-10}	1.5 – 2 h	50
Propranolol	$C_{16}H_{21}NO_2$	525-66-6	259.3	228	9.42	3.48	7.98×10^{-13}	4 – 5 h	< 1
Atenolol	$C_{14}H_{22}N_2O_3$	29122-68-7	266.3	685.2	9.6	0.16	1.37×10^{-18}	6 – 7 h	50
Verapamil	$C_{27}H_{38}N_2O_4$	52-53-9	454.6	4.471	8.92	2.15	8.79×10^{-15}	3 – 7 h	11
Enalapril	$C_{20}H_{28}N_2O_5$	75847-73-3	376.4	182.5	3.0	0.07	3.34×10^{-16}	11 h	15
Enalaprilat *	$C_{18}H_{24}N_2O_5$	76420-72-9	348.4	11.32	n. r.	-0.74	7.85×10^{-19}	11 h	85
Losartan	$C_{22}H_{23}ClN_6O$	114798-26-4	422.9	0.8223	5.5	4.01	4.35×10^{-16}	1.5 – 2 h	80
Valsartan	$C_{24}H_{29}N_5O_3$	137862-53-4	435.5	1.406	3.73	3.65	3.08×10^{-18}	6 h	70
Simvastatin	$C_{25}H_{38}O_5$	79902-63-9	418.6	0.7653	14.91	4.68	2.81×10^{-10}	2 h	73
Rosuvastatin	$C_{22}H_{28}FN_3O_6S$	287714-41-4	481.5	17.96	4.0	0.13	1.50×10^{-16}	19 h	90
Ezetimibe	$C_{24}H_{21}F_2NO_3$	163222-33-1	409.4	4.41	9.73	3.94	4.41×10^{-18}	19 – 30 h	89
Estrone	$C_{18}H_{22}O_2$	53-16-7	270.4	146.8	10.25	3.13	3.80×10^{-10}	19 h	7
Cyproterone	$C_{22}H_{27}ClO_3$	2098-66-0	374.9	12.13	17.83	3.59	3.05×10^{-9}	38 h	93
Dutasteride	$C_{27}H_{30}F_6N_2O_2$	164656-23-9	528.5	0.02553	13.32	6.8	3.06×10^{-10}	4 – 5 w	5

Prednisone	$C_{21}H_{26}O_5$	53-03-2	358.4	312	13.9	1.46	2.83×10^{-10}	1 – 4 h	50
Amoxicillin	$C_{16}H_{19}N_3O_5S$	26787-78-0	365.4	3433	2.44	0.87	2.49×10^{-21}	61.3 min	75
Sulfapyridine	$C_{11}H_{11}N_3O_2S$	144-83-2	249.3	11990	8.43	0.35	1.08×10^{-13}	6 – 14 h	n. r.
Sulfadiazine	$C_{10}H_{10}N_4O_2S$	68-35-9	250.3	28140	6.36	-0.09	1.58×10^{-10}	7 – 17 h	n. r.
Sulfamethoxazole	$C_{10}H_{11}N_3O_3S$	723-46-6	253.3	3942	5.81	0.89	9.56×10^{-13}	10 h	20
N⁴-acetyl sulfamethoxazole *	$C_{12}H_{13}N_3O_4S$	21312-10-7	295.3	1216	n. r.	1.2	3.1×10^{-15}	n. r.	70
Erythromycin	$C_{37}H_{67}NO_{13}$	114-07-8	733.9	0.5168	8.88	3.06	5.42×10^{-29}	1.5 – 2 h	15
Clarithromycin	$C_{38}H_{69}NO_{13}$	81103-11-9	748.0	0.342	8.99	3.16	1.73×10^{-29}	3 – 4 h	40
Ciprofloxacin	$C_{17}H_{18}FN_3O_3$	85721-33-1	331.3	11480	6.09	0.28	5.09×10^{-19}	4 – 6 h	70
Norfloxacin	$C_{16}H_{18}FN_3O_3$	70458-96-7	319.3	177900	6.34	0.46	8.70×10^{-19}	3 – 4 h	32
Levofloxacin	$C_{18}H_{20}FN_3O_4$	100986-85-4	361.4	28300	6.24	-0.39	4.98×10^{-20}	6 – 8 h	87
Cyclophosphamide	$C_7H_{15}Cl_2N_2O_2P$	50-18-0	261.1	5943	12.78	0.63	1.36×10^{-11}	3 – 12 h	91
Ifosfamide	$C_7H_{15}Cl_2N_2O_2P$	3778-73-2	261.1	3781	13.24	0.86	1.36×10^{-11}	72 h	80
Megestrol	$C_{22}H_{30}O_3$	3562-63-8	342.5	27.02	17.83	3.41	1.14×10^{-8}	34 h	86
Bicalutamide	$C_{18}H_{14}F_4N_2O_4S$	90357-06-5	430.4	11.75	12.0	2.30	2.82×10^{-15}	6 d	77
Mycophenolic acid	$C_{17}H_{20}O_6$	24280-93-1	320.3	22.07	4.71	2.8	3.82×10^{-12}	8 – 16 h	99
Diclofenac	$C_{14}H_{11}Cl_2NO_2$	15307-86-5	296.1	4.518	4.15	4.51	4.73×10^{-12}	2 h	100
N-(2,6-dichlorophenyl)-2-indolinone *	$C_{14}H_9Cl_2NO$	15362-40-0	278.1	36.46	n. r.	3.1	6.39×10^{-9}	n. r.	n. r.
Ibuprofen	$C_{13}H_{18}O_2$	15687-27-1	206.3	41.05	5.3	3.97	1.52×10^{-7}	2 – 4 h	15
1-hydroxy ibuprofen *	$C_{13}H_{18}O_3$	53949-53-4	222.3	3192	n. r.	2.25	5.54×10^{-12}	n. r.	n. r.
2-hydroxy ibuprofen *	$C_{13}H_{18}O_3$	51146-55-5	222.3	2974	n. r.	2.3	5.54×10^{-12}	n. r.	n. r.
Tramadol	$C_{16}H_{25}NO_2$	27203-92-5	263.4	1151	9.41	3.01	1.54×10^{-11}	5 – 8 h	95
4-aminoantipyrine *	$C_{11}H_{13}N_3O$	83-07-8	203.2	2379	n. r.	-0.07	2.85×10^{-12}	2 – 4 h	9
Paracetamol	$C_8H_9NO_2$	103-90-2	151.2	30350	9.38	0.46	1.94×10^{-6}	1 – 4 h	90
Carbamazepine	$C_{15}H_{12}N_2O$	298-46-4	236.3	17.66	13.9	2.25	1.08×10^{-10}	16 – 24 h	100
Carbamazepine 10,11-epoxide *	$C_{15}H_{12}N_2O_2$	36507-30-9	252.3	276.8	n. r.	0.95	6.84×10^{-13}	n. r.	n. r.
Topiramate	$C_{12}H_{21}NO_8S$	97240-79-4	339.4	13640	8.7	-0.33	8.88×10^{-17}	19 – 25 h	75
Gabapentin	$C_9H_{17}NO_2$	60142-96-3	171.4	4491	4.72	-1.1	1.81×10^{-10}	5 – 7 h	98

Levetiracetam	$C_8H_{14}N_2O_2$	102767-28-2	170.2	7910	16.09	-0.49	2.67×10^{-10}	6 – 8 h	66
Pregabalin	$C_8H_{17}NO_2$	148553-50-8	159.2	19630	4.23	-1.78	3.08×10^{-10}	6.3 h	90
Levodopa	$C_9H_{11}NO_4$	59-92-7	197.2	320100	2.32	-2.39	1.30×10^{-18}	0.75 – 1.5 h	75
Rasagiline	$C_{12}H_{13}N$	136236-51-6	171.2	3733	8.69	2.6	1.89×10^{-7}	3 h	67
Diazepam	$C_{16}H_{13}ClN_2O$	439-14-5	284.7	58.78	3.4	2.82	3.64×10^{-9}	50 h	n. r.
Clomethiazole	C_6H_8ClNS	533-45-9	161.7	1041	3.22	2.12	2.18×10^{-6}	3.6 – 5 h	50
Scopolamine	$C_{17}H_{21}NO_4$	51-34-3	303.4	55310	7.75	0.98	3.36×10^{-16}	4.5 h	> 10
Fluoxetine	$C_{17}H_{18}F_3NO$	54910-89-3	309.3	60.28	9.8	4.05	8.90×10^{-8}	4 – 6 d	95
Citalopram	$C_{20}H_{21}FN_2O$	59729-33-8	324.4	31.09	9.78	3.74	2.69×10^{-11}	35 h	100
Escitalopram	$C_{20}H_{21}FN_2O$	128196-01-0	324.4	31.09	9.80	3.74	2.69×10^{-11}	27 – 32 h	80
Trazodone	$C_{19}H_{22}ClN_5O$	19794-93-5	371.9	8.24	6.74	3.21	1.74×10^{-15}	5 – 9 h	96
Venlafaxine	$C_{17}H_{27}NO_2$	93413-69-5	277.4	266.7	10.09	3.20	2.87×10^{-11}	3 – 7 h	5
Caffeine	$C_8H_{10}N_4O_2$	58-08-2	194.2	2632	10.4	-0.07	3.58×10^{-11}	3 – 7 h	100
Donepezil	$C_{24}H_{29}NO_3$	120014-06-4	379.5	2.93	8.62	4.86	1.22×10^{-12}	70 h	15
Memantine	$C_{12}H_{21}N$	19982-08-2	179.3	31.09	10.27	3.28	2.69×10^{-11}	60 – 100 h	48
Dichlorobenzyl alcohol	$C_7H_6Cl_2O$	1777-82-8	177.0	1762	n. r.	2.36	3.38×10^{-8}	n. r.	90
Amylmetacresol	$C_{12}H_{18}O$	1300-94-3	178.3	26.6	10.54	4.57	2.12×10^{-6}	1.15 h	50
Budesonide	$C_{25}H_{34}O_6$	51333-22-3	430.5	11.61	17.87	1.90	6.56×10^{-13}	2 – 3.6 h	60
Fluticasone	$C_{22}H_{27}F_3O_4S$	90566-53-3	444.5	102	n. r.	1.40	2.29×10^{-9}	10 h	< 5
Tiotropium bromide	$C_{19}H_{22}NO_4S_2$	139404-48-1	392.5	34140	10.35	-1.76	2.33×10^{-21}	5 – 6 d	74
Acetylcysteine	$C_5H_9NO_3S$	616-91-1	163.2	242900	3.24	-0.66	1.72×10^{-13}	5.6 h	33
Dextromethorphan	$C_{18}H_{25}NO$	125-71-3	271.4	74.65	9.13	3.97	1.20×10^{-7}	2 – 4 h	50
Cloperastine	$C_{20}H_{24}ClNO$	3703-76-2	329.9	3.593	8.69	5.11	2.83×10^{-9}	n. r.	50
Dexchlorpheniramine	C16H19ClN2	25523-97-1	274.8	4529	9.2	3.38	4.07×10^{-10}	21 – 27 h	50

Results and discussion

Mass spectral characterization

Mass spectral characterization for target compounds was organized by ATC code for selected pharmaceuticals, including their metabolites, and the internal standards. **Error! Reference source not found.** shows the fragments of the compounds studied.

Alimentary tract and metabolism class (A)

Herein, the pharmaceuticals studied were acetylsalicylic acid, salicylic acid, ranitidine, omeprazole, pantoprazole, esomeprazole and vildagliptin. Acetylsalicylic acid, also called aspirin, is one of the most common nonsteroidal anti-inflammatory drugs (NSAIDs) which has a molecular weight of 180 g mol^{-1}. The compound showed the intense protonated molecule at m/z 137 [M-COCH$_3$]$^-$ because in solution rapidly degrades to salicylic acid (Mw 137 g mol^{-1}). Product ions from this precursor were reported at m/z 93 [C$_6$H$_5$O]$^-$ and at m/z 65 [C$_5$H$_5$]$^-$. The main metabolite of aspirin is salicylic acid, produced by the loss of an acetyl group. The protonated molecular ion was at m/z 137, sharing the molecular ion and the product ions with aspirin. Similar results for salicylic acid were reported by R. López-Serna et al. who included the formation of the same product ions (López-Serna et al., 2012).

On the other hand, ranitidine is described as a pharmaceutical for acid disorders. It had the molecular ion at m/z 315 [M+H]$^+$, and the product ions at m/z 176 [C$_5$H$_{10}$N$_3$SO$_2$]$^+$ and m/z 130 [C$_4$H$_8$N$_3$O$_2$]$^+$. The transitions 315>176 and 315>130 were used as a quantification and confirmation purposes. Althakafy et al. determined this pharmaceutical in treated wastewater samples with the same precursor ion and confirmation ion at m/z 176, but reported another confirmation ion at m/z 224 (Althakafy et al., 2017). Pedrouzo et al. studied eleven pharmaceuticals in various water sources and reported another confirmation ion at m/z 270 corresponding to the fragment [C$_{11}$H$_{16}$N$_3$SO$_3$]$^+$ (Pedrouzo et al., 2008). Esomeprazole is the S-isomer of omeprazole, both with the same molecular weight and as result, they share the molecular ion 346 [M+H]$^+$. Moreover, they have the same product ions, which were formed at m/z 198 [C$_9$H$_{12}$NSO$_2$]$^+$ and at m/z 136 [C$_8$H$_{10}$NO]$^+$. A previous study about the determination of voriconazole and other co-administered drugs in plasma of pediatric cancer patients using UPLC-MS/MS reported the same transition than in the present work (Al-ghobashy et al., 2018). Another study determined EOCs that included omeprazole with the transitions 346>197 and 346>179 for quantification and confirmation purposes (Jiang et al., 2014). Pantoprazole gave in the full scan spectrum the protonate molecular ion at m/z 384 [M+H]$^+$, with two product ions at m/z 200 [C$_8$H$_{10}$NO$_3$S]$^+$ and m/z 138 [C$_7$H$_8$NO$_2$]$^+$.

On the other hand, vildagliptin gave the protonate molecular ion at m/z 304 [M+H]$^+$. Two product ions were formed at m/z 154 [C$_7$H$_{12}$N$_3$O]$^+$ and at m/z 97 [C$_5$H$_9$N$_2$]$^+$, agree with the transitions obtained by the study of vildagliptin and other antidiabetic drugs in aqueous environmental samples analysed by HPLC-TOF (Martín et al., 2012) and in human plasma by HILIC-MS/MS (Pontarolo et al., 2014). Ascorbic acid gave in the full scan spectrum the precursor ion at m/z 177 [M+H]$^+$, and two product ions at m/z 141 [M+H-2H$_2$O]$^+$ and at m/z 95 [C$_5$H$_3$O$_2$]$^+$.

Cardio-vascular system (C)

Herein, the pharmaceuticals studied in this group were amiodarone, hydrochlorothiazide, furosemide, pentoxifylline, lidocaine, propranolol, atenolol, verapamil, enalapril, enalaprilat, losartan, valsartan, simvastatin, rosuvastatin and ezetimibe. Amiodarone was analysed by UPLC-MS/MS providing a full scan spectrum with a precursor ion at m/z 646 [M+H]$^+$. From this molecular ion, two fragment ions were formed at m/z 201 [C$_{13}$H$_{13}$O$_2$]$^+$ and at m/z 100 [C$_6$H$_{14}$N]$^+$. Hydrochlorothiazide is a diuretic medication used to treat high blood pressure and swelling due to fluid build-up. It presented a molecular ion at m/z 296 [M-H]$^-$ as it was ionized better in negative mode. From this precursor ion, two fragments ions were formed at m/z 269 [C$_6$H$_5$ClN$_2$O$_4$S$_2$]$^-$ and at m/z 205, these transitions were used for confirmation and quantification purposes, respectively. Baena-Nogueras et al. developed and validated an analytical method for the determination of 83 pharmaceuticals in aqueous samples, including hydrochlorothiazide, and also reported the

same protonated ion and fragment ions (Baena-Nogueras et al., 2016). In addition, López-Serna et al. developed and validated another analytical method to determine 58 pharmaceuticals and 19 metabolites in environmental samples, which also confirmed the same transitions for quantification and confirmation purposes of hydrochlorothiazide (López-Serna et al., 2012). Furosemide is used to treat fluid build-up due to heart failure, liver scarring, or kidney disease. Using m/z 329 $[M-H]^-$ as precursor ion, it exhibited at m/z 285 $[C_{11}H_{10}ClN_2O_3S]^-$ the most intense product ion and at m/z 205 $[C_{11}H_8ClNO]^-$ the second major product ion, at 13 eV and 20 eV of C.E. respectively. The SRM transition of both m/z were used for confirmation and quantification purposes, and the same product ions were reported in study mentioned before, carried out by Baena-Nogueras et al. (Baena-Nogueras et al., 2016).

Pentoxifylline gave in the full scan spectrum the molecular ion at m/z 279 $[M+H]^+$. From this precursor ion, two transitions were reported at m/z 181 $[C_7H_9N_4O_2]^+$ and m/z 138 $[C_6H_8N_3O]^+$, corresponding to the highest intense transitions obtained. Gurke et al. developed a SPE-HPLC-MS/MS method to determinate pharmaceuticals and related metabolites in urban sewage samples of Germany, using the same transitions to quantify pentoxifylline in water samples (Gurke et al., 2015). Lidocaine is a local anhestesic that gave a full scan spectrum with the precursor ion at m/z 235 $[M+H]^+$ and two fragment ions at m/z 86 $[C_5H_{12}N]^+$ and at m/z 58 $[C_4H_{10}]^+$. Propranolol is a nonselective beta blocker widely prescribed to treat high blood pressure and a number of heart dysrhythmias. When it was analysed with the MS/MS detector, it showed a molecular ion at m/z 260 $[M+H]^+$, and two fragment ions at m/z 183 $[C_{10}H_{17}NO_2]^+$ corresponding to the quantification transition and m/z 157 $[C_{11}H_9O]^+$ for confirmation purposes. Oertel et al. developed an analytical method to quantify antidiabetic drugs using an HILIC column to acquire the chromatographic separation. They used the same precursor ions reported before for lidocaine and propranolol, but for propranolol proposed fragment ions at m/z 116 and m/z 183 (Oertel et al., 2018).

Another pharmaceutical included in this group is atenolol that gave in the full scan spectrum the precursor ion at m/z 267 $[M+H]^+$, obtaining its highest intensity at 41 V of C.V. A SIM-SCAN method was performed obtaining two transitions at m/z 145 corresponding to the fragment $[C_7H_{15}NO_2]^+$ and at m/z 74 $[C_4H_{12}N]^+$. This compound was analysed by Baena-Nogueras et al., who optimized and validated an analytical method for pharmaceuticals in Spain, reporting the transitions 267>145 for quantification purposes and 267>73 for confirmation purposes for atenolol (Baena-Nogueras et al., 2016). However, López-Serna et al., who developed an analytical method for pharmaceuticals and metabolites in environmental water samples, reported two different fragment ions at m/z 145 for both compounds, and at m/z 190 for atenolol (López-Serna et al., 2012). Verapamil is a phenylalkylamine derivative used as calcium channel blocker with direct cardiac effects. It gave a full scan spectrum with a protonated molecule at m/z 455 $[M+H]^+$ at 31 V of C.V. MS/MS spectrum from this precursor ion produced a fragment ion at m/z 165 $[C_{10}H_{13}O_2]^+$ using 30 eV of C.E., whereas the other fragment ion was obtained using 40 eV of C.E. at m/z 150 $[C_9H_{10}O_2]^+$. The same transitions 455>165 and 455>150 were reported by García-Galán et al., who developed an analytical methodology based on dual column liquid chromatography coupled to tandem mass spectrometry to analyse 12 pharmaceuticals and 20 metabolites in influent and effluent wastewaters and surface water (García-Galán et al., 2016).

Nevertheless, enalapril is a medication used to treat high blood pressure, diabetic kidney disease and heart failure. The mass spectral produced the precursor ion at m/z 377 $[M+H]^+$, and two fragment ions selected at m/z 234 $[C_{14}H_{20}NO_2]^+$ and at m/z 117 $[C_5H_{10}NO_2]^+$. For this pharmaceutical was chosen a metabolite called enalaprilat, that has a molecular weight of 348.4 g mol^{-1} corresponding a protonated molecule at m/z 349 $[M+H]^+$. MS/MS spectra from the precursor ion produced a fragment ion at m/z 206 $[C_{12}H_{16}NO_2]^+$ using 16 eV of C.E., whereas a fragment ion at m/z 91 $[C_7H_7]^+$ was obtained using 40 eV of C.E. Similar results were reported by Gurke et al., who analysed prescribed pharmaceuticals and metabolites in influent and effluent samples of the sewage treatment plant with SPE-HPLC-MS/MS. They acquired the same product ions for enalapril (Gurke et al., 2015). On the other hand, López-Serna et al. developed an analytical method for the determination of pharmaceuticals and metabolites in environmental waters, and also reported the same product ions for enalapril and enalaprilat, according with the transitions acquired in this study (López-Serna et al., 2012).

Losartan gave a full scan spectrum with a precursor ion at m/z 423 [M+H]$^+$, and two intense fragments at m/z 377 and at m/z 207. Valsartan is an angiotensin II receptor antagonist that showed its protonated molecule at m/z 436 [M+H]$^+$. Using 20 V for C.V., valsartan produced two main fragments ions at m/z 291 [$C_{16}H_{13}N_5O$]$^+$ and at m/z 235 [$C_{14}H_{11}N_4$]$^+$ corresponding to the loss of $C_{10}H_{17}NO_2$ molecule. Both pharmaceuticals were reported in an analytical method developed to analyse pharmaceuticals and metabolites in urban sewage, with the same transitions for parent ions and fragments ions (Gurke et al., 2015). Simvastatin showed a full scan spectrum with a protonated ion at m/z 419 [M+H]$^+$. Using 34 V of C.V., two intense product ions were acquired at m/z 199 [$C_{11}H_{19}O_3$]$^+$ for quantification purposes and at m/z 285 for confirmation purposes. Similar results were reported by Kafeenah et al. who analysed multi-class pharmaceutical residues in tap water and hospital residues, and reported the same fragment ions and transitions for this drug (Kafeenah et al., 2018). In another way, rosuvastatin is a hydroxy-methyl glutaryl coenzyme A reductase inhibitor. Using m/z 482 [M+H]$^+$ as precursor ion, it exhibited m/z 258 [300-C_3H_6]$^+$ as the most intense product ion and m/z 300 [M-$C_4H_{11}N_3O_2SF$]$^+$ as the second major product ion. The last pharmaceutical included in this group is ezetimibe, which is a cholesterol-lowering medication, used to prevent the absorption of cholesterol in the intestine. In this case, the precursor ion was acquired at m/z 392 [M-H_2O+H]$^+$ as corresponded to the loss of a water molecule from the initial structure, and two product ions with highest intensity were at m/z 133 [C_9H_9O]$^+$ and at m/z 105 [C_7H_5O]$^+$.

Genito urinary system and sex hormones (G)

Herein, the pharmaceuticals studied were estrone, cyproterone and dutasteride. Estrone is an estrogenic hormone. When it was analysed by LC-MS/MS provided a molecular ion at m/z 271 [M+H]$^+$ with the highest intensity at 40 V of C.V. This precursor ion exhibited at m/z 253 [$C_{18}H_{21}O$]$^+$ and at m/z 133 [C_9H_9O]$^+$ two fragment ions used to quantify and confirm. The transition 271>53 corresponded to the loss of a water molecule and the transition 271>133 is formed by the loss of a $C_9H_{13}O$ molecule. Cyproterone is a steroidal antiandrogen with a molecular weight of 374.9 g mol^{-1}, while its precursor ion (cyproterone acetate) was found at m/z 417 [$C_{24}H_{29}ClO_4$]$^+$. Cyproterone exhibited at m/z 313 [M-$C_4H_6O_3$]$^+$ and at m/z 357 [M-$C_2H_3O_2$]$^+$ two fragment ions used to quantify and confirm it. On the other hand, dutasteride had also studied as it is a medication used to treat the symptoms of an enlarged prostate, it gave a full scan mass spectra with a protonated molecule at m/z 529 [M+H]$^+$ and two fragment ions were reported at m/z 461 [$C_{26}H_{32}F_3N_2O_2$]$^+$ and at m/z 69 [C_3H_3NO]$^+$.

Systemic hormonal preparations, excl. sex hormones and insulins (H)

With full scan LC-MS/MS, prednisone produced the protonated molecule at m/z 359 [M+H]$^+$. MS/MS spectra from this precursor ion using 11 eV of C.E. produced the fragment ions at m/z 341 [M-H_2O]$^+$ and using 36 eV of C.E. produced m/z 147 [$C_{10}H_{11}O$]$^+$. Both 359>341 and 359>147 were used as SRM transitions and are depicted in **Error! Reference source not found.**.

Anti-infective for systemic use (J)

Herein, the pharmaceuticals studied were amoxicillin, sulfapyridine, sulfamethoxazole, N^4-acetyl-sulfamethoxazole, sulfadiazine, erythromycin, clarithromycin, ciprofloxacin, norfloxacin and levofloxacin. Amoxicillin is a common antibiotic and it gave a full scan spectrum with a protonated molecule with the loss of a water molecule at m/z 349 [M-H_2O+H]$^+$ at 56 V of C.V. and two intense product ions at m/z 255 [$C_{10}H_{13}N_3O_3S$]$^+$ which corresponds to the loss of the ring of six carbon atoms connected to the alcohol group and at m/z 107 (**Error! Reference source not found.**). The SRM transitions 349>107 and 349>255 were chosen for quantification and confirmation purposes. A study carried out by Althakafy et al. developed an analytical method to detect 13 PPCPs in water samples, they reported a precursor ion at m/z 366 and two fragment ions at m/z 160 and at m/z 207 to identify amoxicillin (Althakafy et al., 2017). Whereas another study by Baena-Nogueras et al., who developed an analytical method to determine 83 pharmaceuticals in aqueous samples, reported two other fragment ions at m/z 349 and at m/z 114 (Baena-Nogueras et al., 2016). Otherwise, sulfapyridine was a sulphanilamide antibacterial medication, no longer

prescribed to treat infections in humans, only employed in veterinary medicine. At m/z 250 [M+H]+ was obtained the precursor ion, and also, the most intense fragment ions were at m/z 156 [$C_6H_6NO_2S$]+ and at m/z 95 [$C_5H_7N_2$]+. The fragment ion at m/z 156 was in accordance with one reported by García-Galán et al., who developed an analytical methodology based on dual column liquid chromatography coupled to tandem mass spectrometry to analyse 12 pharmaceuticals and 20 metabolites in influent and effluent wastewaters and surface water, the other fragment ion reported by these authors was at m/z 92 with 26 eV as C.E. (García-Galán et al., 2016).

Sulfamethoxazole gave a full scan spectrum with a protonated molecule at m/z 254 [M+H]+. From this precursor ion, the product ions selected were at m/z 108 [C_6H_6NO]+ and at m/z 92 [C_6H_6N]+ as quantification and confirmation purposes. Pedrouzo et al. described a method to determine 11 pharmaceuticals in various water sources by SPE-LC-ESI-MS. The fragment ions reported by Pedrouzo et al. were in accordance with the transition 254>108, and also, acquired other fragment ion at m/z 156 corresponding to a $C_6H_6NO_2S$ molecule (Pedrouzo et al., 2008). Another scientific group comprised by Babié et al. developed an analytical method for multi-class pharmaceuticals in wastewater, and also, reported the fragment ion at m/z 92. In addition, in accordance with the study of Pedrouzo et al., reported the transition of 254>156 as the second product ion (Babié et al., 2010). Moreover, this pharmaceutical has several metabolites including N^4-acetyl-sulfamethoxazole that was selected to be analysed in this study. Its precursor ion was obtained at m/z 296 [M+H]+ with 21 V, whereas the two fragment ions selected were at m/z 198 [$C_8H_8NO_3S$]+ and at m/z 65 [SO_2]+. Similar results were reported by García-Galán et al. who developed an analytical methodology based on dual column liquid chromatography coupled to tandem mass spectrometry to analyse 12 pharmaceuticals and 20 metabolites in aqueous samples, and also, indicated two product ion from this metabolite at m/z 65 and at m/z 134 (García-Galán et al., 2016).

Sulfadiazine is an antibiotic that produced a protonated molecule at m/z 251 [M+H]+, the most intense fragment ions were at m/z 156 [$C_6H_6NO_2S$]+ and at m/z 96 [$C_4H_6N_3$]+. Similar results were reported by García-Galán et al. (García-Galán et al., 2016)   and Babié et al. (Babié et al., 2010) providing the fragment ions at m/z 156 and at m/z 92, in accordance with one of the product ions acquired. Also, Pedrouzo et al. described a method to determine eleven pharmaceuticals in various water sources by SPE and LC-MS, and reported another fragment ion at m/z 108 which correspond to a protonated fragment of [C_6H_6NO]+ (Pedrouzo et al., 2008). Clarithromycin is the 6-O-methyl ether of erythromycin, they are macrolide antibiotics used in the treatment of respiratory-tract, skin and soft-tissue infections. Clarithromycin produced a protonated molecule at m/z 748 [M+H]+ whereas erythromycin's protonated molecule was at m/z 734 [M+H]+. Both pharmaceuticals formed the same fragment ions at m/z 158 [$C_8H_{16}NO_2$]+ and at m/z 116 [$C_6H_{14}NO$]+. In addition, both compounds were analysed by SPE-UPLC-MS/MS by Baena-Nogueras et al., who developed and validated an analytical method for 83 pharmaceuticals in aqueous samples, and obtained the product ion at m/z 158. Moreover, erythromycin was characterised by the transition 734>575 and clarithromycin by 748>590 (Baena-Nogueras et al., 2016).

Ciprofloxacin is another antibiotic used to treat bacterial infections, and when it is analysed by LC-MS/MS produced a protonated molecule at m/z 332 [M+H]+. Using 40 V as C.V., two fragment ions were reported at m/z 314 [$C_{17}H_{17}FN_3O_2$]+ and at m/z 245 [$C_{13}H_9FNO_3$]+. Apart from the reported product ions, Babié et al. developed an analytical method for multi-class pharmaceuticals in wastewater and reported another fragment ion at m/z 288 (Babié et al., 2010). In accordance with them, Althakafy et al. who developed an analytical method to detect and confirm 13 PPCPs in water samples, also reported the same fragment ion at m/z 288 (Althakafy et al., 2017). Norfloxacin belong to a class of fluoroquinolone antibiotics, and it gave a full scan spectrum with a precursor ion at m/z 320 [M+H]+. Using 22 V of C.V., two fragment ions were obtained at m/z 302 [$C_{16}H_{17}FN_3O_2$]+ and at m/z 276 [$C_{14}H_{13}FN_2O_3$]+. Similar results were reported by Babié et al. (Babié et al., 2010) who determine the same product ions, and also, Baenas-Nogueras et al. used the fragment ion at m/z 231 to identify norfloxacin in their samples (Baena-Nogueras et al., 2016). The last pharmaceutical included in this group is levofloxacin, that gave a protonated ion at m/z 362 [M+H]+ and two fragment ions at m/z 318 [$C_{17}H_{21}FN_3O_2$]+ and at m/z 261 [$C_{13}H_8FNO_4$]+, with a C.V. of 44 V and C.E. of 18 eV and 26 eV, respectively. The transitions 362>318 and 362>261 were in accordance with those reported by Oertel et al., who developed an analytical method to quantify

antidiabetic drugs in WWTPs in Germany using an HILIC column to acquire the chromatographic separation to retain the most polar compounds from the aqueous matrix (Oertel et al., 2018).

Antineoplastic and immunomodulating agents (L)

Herein, the pharmaceuticals studied were cyclophosphamide, ifosfamide, bicalutamide and mycophenolic acid. Cyclophosphamide and ifosfamide are a chemotherapy medication and showed a common protonated ion at m/z 261 [M+H]$^+$ as they are structural isomers. Even though, different product ions were obtained for both pharmaceuticals. Using 26 V of C.V., cyclophosphamide reported two product ions at m/z 140 [C$_4$H$_8$NCl$_2$]$^+$ and at m/z 106 [C$_4$H$_8$NCl]$^+$, and using 42 V of C.V. for ifosfamide were at m/z 154 [C$_3$H$_7$NO$_2$PCl]$^+$ and at m/z 78 [C$_2$H$_5$NCl]$^+$.

Megestrol is a progestin of the 17-α-hydroxyprogesterone group included in this study that provided a protonated ion at m/z 385 [M+H]$^+$. From this precursor, two fragment ions were obtained at m/z 325 [C$_{22}$H$_{29}$O$_2$]$^+$ and at m/z 267 for quantification and confirmation purposes. Bicalutamide is an antiandrogen medication that showed a full scan mass spectrum with a precursor ion at m/z 431 [M+H]$^+$. Using 33 V as C.V., two product ions were formed at m/z 217 [C$_9$H$_{10}$O$_3$SF]$^+$ with 14 eV of C.E. and at m/z 95 [C$_6$H$_4$F]$^+$ with 50 eV of C.E. The last pharmaceutical included in this group is mycophenolic acid, classified as a common immunosuppressant drug, that provided a protonated ion at m/z 321 [M+H]$^+$. Two product ions were obtained at m/z 207 [C$_{11}$H$_{11}$O$_4$]$^+$ formed by the loss of a C$_6$H$_8$O$_2$ molecule and at m/z 159 [C$_9$H$_3$O$_3$]$^+$, for quantification and confirmation purposes.

Musculoskeletal system (M)

Herein, the pharmaceuticals studied were diclofenac, N-(2,6-dichlorophenyl)-2-indolinone, ibuprofen, 1-hydroxy and 2-hydroxy ibuprofen. Diclofenac is an analgesic and anti-inflammatory drug that gave the protonated ion at m/z 296 [M+H]$^+$ at 9 V of C.V. From this precursor, the two transitions optimized at 296>215 and 296>250 were chosen for quantification and confirmation purposes, with a C.E. of 20 eV and 12 eV, respectively. Larabie et al. determine diclofenac and other residue of pharmaceuticals in fish plasma using LC-MS/MS, and also, they reported the same product ions as had been indicated previously (Larabie et al., 2017). Whereas another study published the analysis of this pharmaceutical in aqueous environmental matrices by SPE-UHPLC-MS/MS in negative ionization mode, reporting a precursor ion at m/z 294 [M-H]$^-$ and two product ions at m/z 250 as quantifier and at m/z 35 as qualifier (Paíga et al., 2017). Moreover, for this pharmaceutical was selected a metabolite called N-(2,6-dichlorophenyl)-2-indolinone with a precursor ion *at* m/z 278 [M+H]$^+$. Using 40 V as a C.V., the two fragment ions with the highest intensity were at m/z 208 [C$_{14}$H$_9$NO]$^+$ and at m/z 214 with 20 eV as C.E. both. Similar results were reported by García-Galán, who developed an analytical method based on dual column LC-MS/MS to analyse 12 pharmaceuticals and 20 metabolites in wastewaters and surface waters (García-Galán et al., 2016).

Another pharmaceutical included in this group is ibuprofen, a NSAID used to treat pain, fever and inflammation. It gave a full scan spectrum with a protonated molecule with the loss of carboxylic acid moiety at m/z 161 [M-COOH]$^+$, and two intense fragment ions at m/z 119 [C$_9$H$_{11}$]$^+$ and at m/z 105 [C$_8$H$_9$]$^+$. As had been observed for the other analgesic mentioned before, some studies reported the ionization in positive mode whereas others acquired the ionization of the pharmaceutical in negative mode. For instance, Paíga et al. determined seven pharmaceuticals and two metabolites by SPE-UHPLC-MS/MS in seawater samples of Atlantic Ocean (Paíga et al., 2017) and Kafeenah et al. analysed multi-class pharmaceutical residues in tap water and hospital residues (Kafeenah et al., 2018), both reporting the ionization of ibuprofen in negative mode, with the precursor ion at m/z 205 [M-H]$^-$ and the product ions at m/z 159 [M-H-CO$_2$]$^+$ and at m/z 161.

On the other hand, similar results as reported previously in this study in positive mode were acquired by Hijosa-Valsero et al. who studied the behaviour of PPCPs in constructed wetland compartments like influent, effluent, pore water, substrate and plants roots (Hijosa-Valsero et al., 2016). Ibuprofen is one of the most prescribed pharmaceuticals, for this reason, studying its metabolites was of interest. The selected metabolites are 1-hydroxy and 2-hydroxy ibuprofen, they

are isomers and has the same molecular weight. When they were analysed by LC-MS/MS, produced a protonated molecule at m/z 223 [M+H]$^+$ and two fragment ions at m/z 207 [C$_{12}$H$_{15}$O$_3$]$^+$ and m/z 193 [C$_{11}$H$_{13}$O$_3$]$^+$.

Nervous system (N)

Herein, the pharmaceuticals studied were tramadol, 4-aminoantipyrine, 4-acetamidoantipyrine, paracetamol, carbamazepine, carbamazepine 10,11-epoxide, topiramate, gabapentin, levetiracetam, pregabalin, levodopa, rasagiline, diazepam, clomethiazole, scopolamine, fluoxetine, citalopram, escitalopram, trazodone, venlafaxine, caffeine, donepezil and memantine. Tramadol is an opioid pain medication that gave a full scan spectrum with a protonated ion at m/z 264 [M+H]$^+$. Using 9 V as C.V., it produced two fragment ions at m/z 246 [C$_{16}$H$_{24}$NO]$^+$ and at m/z 58 [C$_3$H$_8$N]$^+$ with with 10 eV and 17 eV as C.E., respectively. Similar results were reported by Gurke et al. who developed a SPE-HPLC-MS/MS method for the determination of the most prescribed pharmaceuticals and their related metabolites in urban sewage samples in Germany, and reported the analyse of tramadol using the transition 264>58 as mentioned before (Gurke et al., 2015). On the other hand, the full scan spectrum of 4-aminoantipyrine showed a protonated molecule at m/z 204 [M+H]$^+$ with 20 V of C.V., and the two fragment ions with the highest intensity were at m/z 94 [C$_6$H$_8$N]$^+$ and at m/z 56 [C$_3$H$_6$N]$^+$. Another pharmaceutical included in this group is paracetamol that gave a full scan spectrum with a protonated molecule at m/z 152 [M+H]$^+$. Using 32 V of C.V., the most intense product ions were obtained at m/z 110 [C$_6$H$_8$NO]$^+$ corresponding to the loss of C$_2$H$_3$O at 20 eV of C.E., and at m/z 93 [C$_6$H$_5$O]$^+$ formed by the loss of C$_2$H$_4$NO at 22 eV of C.E. In positive ionization, similar results were reported by Kafeenah et al. who analysed multi-class pharmaceutical residues in tap water and hospital residues, and proposed the same protonated molecule and was in accordance with one product ion at m/z 110 (Kafeenah et al., 2018), and also, García-Galán et al., who developed an analytical method to analyse pharmaceuticals and metabolites in wastewaters and surface waters, reported another product ion at m/z 65 corresponding to the loss of a COCH$_3$ molecule (García-Galán et al., 2016). Whereas, Baena-Nogueras et al., who developed and validated an analytical method for the determination of 83 pharmaceuticals in aqueous samples (Baena-Nogueras et al., 2016), and Paíga et al., who developed a multi-residue method for the analysis of 33 human and veterinary pharmaceuticals, and some of their metabolites in drinking water, surface water and wastewater (Paíga et al., 2017), reported the molecular ion in negative ionization at m/z 150 [M-H]$^-$ and two product ions at m/z 108 and at m/z 106.

Carbamazepine is used in the treatment of epilepsy and neuropathic pain, it was analysed showing a protonated molecule at m/z 237 [M+H]$^+$ and two product ions at m/z 194 [C$_{14}$H$_{12}$N]$^+$ and at m/z 179 [C$_{14}$H$_{11}$]$^+$. The highest intensity of the C.V. was acquired at 30 V, for the C.E. were at 20 eV and 36 eV respectively for each product ion. Similar results were reported for the analysis of micropollutants in unfiltered wastewater and freshwater by LC-MS/MS, acquiring the same protonated ion and showing the fragment ion at m/z 194 (Asimakopoulos et al., 2017). One metabolite of this drug, carbamazepine 10,11-epoxide, was selected to be analysed providing a precursor ion at m/z 253 [M+H]$^+$. Using 29 V of C.V., the two product ions with the highest intensity were at m/z 236 [C$_{15}$H$_{10}$NO$_2$]$^+$ and at m/z 210 [C$_{14}$H$_{10}$NO]$^+$ corresponding to the loss of a amine molecule and a amide molecule, respectively. This metabolite was acquired by García-Galán et al., who developed a method to analyse pharmaceuticals and metabolites in wastewaters and surface waters with LC-LC-MS/MS, and reported the same protonated ion and different fragment ions at m/z 180 and at m/z 210 (García-Galán et al., 2016).

Another pharmaceutical is topiramate, used to treat epilepsy and prevent migraines. It gave a full scan spectrum with a protonated ion at m/z 340 [M+H]$^+$ with a C.V. of 18 V, and two fragment ions at m/z 264 [C$_9$H$_{14}$NO$_6$S]$^+$ and at m/z 127 [C$_7$H$_{11}$O$_2$]$^+$. Gabapentin showed the protonated molecule at m/z 172 [M+H]$^+$ with the highest intensity at 27 V of C.V. Using this precursor ion, gabapentin exhibited at m/z 154 [C$_9$H$_{16}$NO]$^+$ the most intense fragment ion used for confirmation purpose, which corresponds to the loss of a water molecule, and at m/z 137 [C$_9$H$_{14}$O]$^+$ associated with the fragmentation of the water molecule and an amine group, used for quantification purpose. Gurke et al., who developed a SPE-HPLC-MS/MS method for the determination of the most

prescribed pharmaceuticals and their related metabolites in urban sewage samples in Germany, reported similar results for the pharmaceutical topiramate as one fragment ion is in common corresponding to the ion at m/z 264 and also, different transition corresponding to 357>282; for gabapentin the same transitions were reported 172>154 and 172>137 (Gurke et al., 2015). Another pharmaceutical included in this group is levetiracetam, which is an anticonvulsant medication used as a treatment for specific types of epilepsy. Levetiracetam gave an intense protonated ion at m/z 171 [M+H]$^+$ and the fragment ions used for quantification and confirmation purposes at m/z 154 [$C_8H_{12}NO_2$]$^+$, which corresponds to the loss of an amine, and at m/z 126 [$C_7H_{12}NO$]$^+$.

Pregabalin is a medication used to treat epilepsy, by LC-MS/MS this pharmaceutical formed the protonated molecule at m/z 160 [M+H]$^+$. The ion products generated were at m/z 142 [$C_8H_{14}O_2$]$^+$ corresponding to the loss of an amine molecule and at m/z 84 [C_6H_{12}]$^+$ formed by the loss of COOH-CH$_3$ and amine molecules. Several studies have already determinate this pharmaceuticals family such as Gómez-Canela et al. (Gómez-Canela et al., 2019), Asimakopoulos et al. (Asimakopoulos et al., 2017) or Gurke et al. (Gurke et al., 2015). Another pharmaceutical from this group is levodopa, which exhibited a molecular ion at m/z 198 [M+H]$^+$. Using 45 V as C.V., the two fragment ions with the highest intensity were at m/z 152 [$C_8H_{10}NO_2$]$^+$ and at m/z 107 [$C_6H_5O_2$]$^+$. Vilhena et al. developed a new HILIC-MS/MS method for the analysis of carbidopa, levodopa and its metabolites in human plasma; reporting the same protonated ions for levodopa and deuterated levodopa, and different transitions as 198>181 for levodopa confirmation purposes (Vilhena et al., 2014). Rasagiline showed the protonated molecule at m/z 172 [M+H]$^+$ in its full scan spectrum, which also reported two fragment at m/z 117 [C_9H_9]$^+$ and at m/z 91 [C_7H_7]$^+$. The fragment ion at m/z 117 is formed by the loss of a C_3H_4N molecule and the ion at m/z 91 corresponds to the loss of two carbon atoms from the opening of the ring of five carbon atoms. Similar transitions were reported by Ma et al. who determined rasagiline in human plasma (Ma et al., 2008). Diazepam binds the benzodiazepine site on the GABA$_A$ receptor via the constituent chlorine atom, and lead to central nervous system depression. It gave a full scan spectrum with a protonated molecule at m/z 285 [M+H]$^+$ and the formation of two intense product ions at m/z 193 [$C_9H_6ClN_2O$]$^+$ and at m/z 154. The following transitions were used for quantification and confirmation purposes. These transitions were in accordance with the ones reported by Nödler et al. (Nödler et al., 2010) and García-Galán et al. (García-Galán et al., 2016) among others. Clomethiazole acts like a sedative, hypnotic, muscle relaxant and anticonvulsant; by analysing this compound in LC-MS/MS, it gave a full scan spectrum with a precursor ion at m/z 162 [M+H]$^+$. The corresponding product ions generated were at m/z 126 [C_6H_8NS]$^+$, formed by the loss of a chloride molecule, and at m/z 112 [C_5H_6NS]$^+$. Gómez-Canela et al. optimized the protonated molecule of clomethiazole and reported the same product ions by LC-MS/MS (Gómez-Canela et al., 2019). When scopolamine was analysed by LC-MS/MS, the highest intense ion was acquired at m/z 304 [M+H]$^+$ with 27 V as C.V. Using this voltage, was reported the fragment ions at m/z 156 and at m/z 138 [$C_8H_{12}NO$]$^+$. Similar transitions were reported by Björnstad et al., who developed a multi-component LC-MS/MS method for detection of ten plant-derived psychoactive substances in urine (Björnstad et al., 2009).

Fluoxetine is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class, and its full scan spectrum provided a protonated ion at m/z 310 [M+H]$^+$. From this molecular ion, two product ions were acquired at m/z 148 [$C_{10}H_{14}N$]$^+$ and at m/z 44 [C_2H_6N]$^+$. Other pharmaceuticals classified as SSRIs are citalopram and escitalopram, and also used as antidepressants. Citalopram is a racemic mixture, whereas escitalopram is its S-enantiomer. Both pharmaceuticals have the same molecular weight and were protonated reporting a precursor ion at m/z 325 [M+H]$^+$, and also, two fragment ions at m/z 262 [$C_{18}H_{16}NO$]$^+$ and at m/z 109 [C_7H_6F]$^+$. Trazodone is an antidepressant medication that produced a protonated molecule ion at m/z 372 [M+H]$^+$. Its product ions were at m/z 148 [$C_7H_6N_3O$]$^+$ formed by the loss of a $C_{10}H_{12}N_2Cl$ molecule, and at m/z 176 [$C_9H_{10}N_3O$]$^+$ corresponding to the loss of a C_2H_4 molecule. Whereas another antidepressant medication of the serotonin-norepinephrine reuptake inhibitor class is venlafaxine, it gave full scan spectrum showing a protonated molecule at m/z 278 [M+H]$^+$. Using 47 V as C.V., two product ions were reported at m/z 121 [C_8H_8O]$^+$ and at m/z 58 [C_3H_8N]$^+$. All the previous pharmaceuticals

and metabolite were simultaneously analysed in blood through LC-MS/MS, acquiring similar transitions for each one (Sempio et al., 2014).

Caffeine showed the protonated molecule at m/z 195 [M+H]$^+$ in its full scan spectrum. One product ion from this precursor showed the loss of C_2H_3NO at m/z 138 [$C_6H_8N_3O$]$^+$, whereas the second product ion was formed at m/z 110 [$C_5H_7N_3$]$^+$ formed by the loss of a CO. This stimulant was analysed in some studies providing similar results as the following transitions 195>138 and 195>110 (Althakafy et al., 2017)(Asimakopoulos et al., 2017). Donepezil is a medication used to improve cognition and behaviour of people with Alzeheimer, analysing this drug by LC-MS/MS the compound formed the protonated molecule at m/z 381 [M+H]$^+$. Moreover, from the precursor ion followed the formation of the fragment ions at m/z 243 [$C_{16}H_{21}NO$]$^+$ that corresponds to the loss of a $C_8H_8O_2$ molecule and at m/z 91 [C_7H_7]$^+$. The SRM transitions 380>91 and 380>243 were chosen for quantification and confirmation purposes. Another medication used to treat Alzeheimer's disease is memantine that it gave a full scan spectrum providing a protonated molecule at m/z 180 [M+H]$^+$. Using 30 V as C.V., two fragment ions were acquired at m/z 163 [$C_{12}H_{19}$]$^+$ and at m/z 107. Both pharmaceuticals were chosen to be in the multi-residue method for scrutinizing psychotropic compounds in natural water by Brieudes et al. who reported the same transitions (Brieudes et al., 2017).

Respiratory system (R)

Herein, the pharmaceuticals studied were dichlorobenzyl alcohol, amylmetacresol, budesonide, fluticasone propionate, tiotropium bromide, acetylcysteine, dextromethorphan, cloperastine and chlorpheniramine Dichlorobenzyl alcohol is an antiseptic that showed a protonated molecule at m/z 159 [M-H_2O+H]$^+$, corresponding to the loss of a water molecule. From this protonated ion, the highest intense fragment ions were at m/z 123 [C_7H_5Cl]$^+$ acquired at 19 eV of C.E. and at m/z 89 [C_7H_5]$^+$ with 30 eV. The product ions were formed by the loss of one and two chloride molecules respectively. Otherwise, amylmetacresol is another antiseptic medication used to treat infections of the mouth and throat. It gave a protonated ion at m/z 179 [M+H]$^+$, generating two intense product ions at m/z 109 [C_8H_{13}]$^+$ formed by the loss of C_4H_6O molecule, and at m/z 71 [C_5H_{11}]$^+$ both with 8 eV of C.E.

Budesonide is a pharmaceutical of the corticosteroid type that gave the protonated ion at m/z 431 [M+H]$^+$ at 29 V of C.V. From this precursor, two product ions were formed at m/z 147 [$C_{10}H_{11}O$]$^+$ and at m/z 73 [C_4H_9O]$^+$ both at 30 eV, these fragments were used for quantification and confirmation purposes. Fluticasone propionate was analysed by LC-MS/MS producing the protonated molecule at m/z 501 [M+H]$^+$. From this precursor ion and using 58 V as C.V., two fragment ions were produced at m/z 313 with 12 eV of C.E. and at m/z 293 [$C_{17}H_{19}F_2O_2$]$^+$ with 18 eV. These pharmaceuticals were included in the determination of 160 drugs in urine and blood of livestock and poultry by UHPLC-MS/MS carried out by Qie et al., who reported the protonated ions and product ions (Qie et al., 2019).

Tiotropium bromide full scan spectrum showed the protonated molecule at m/z 393 [M+H]$^+$ corresponding to the initial loss of a water molecule and a bromine molecule as its molecular weight is 472 g·mol^{-1}. It formed two intense product ions at m/z 170 [$C_9H_{16}NO_2$]$^+$ that corresponds to the loss of $C_{10}H_7O_2S_2$ molecule and at m/z 152 [$C_9H_{14}NO$]$^+$ formed by the loss of an oxygen moiety from the other product ion. Acetylcysteine solution is a mucolytic that showed the intense protonated molecule at m/z 164 [M+H]$^+$ at 24 V. The product ion from this precursor ion were reported at m/z 122 [$C_3H_2O_3$]$^+$ corresponding to the loss of an acetyl moiety and at m/z 76 [C_2H_5NS]$^+$, used for quantification and confirmation purposes, respectively. It also belongs to this class dextromethorphan that is a medication used as a cough medicine. It showed the protonated molecule at m/z 272 [M+H]$^+$, corresponding to the loss of a water and bromide molecule, with the formation of two intense product ions at m/z 171 for confirmation purposes and the second product ion at m/z 147 for quantification purposes. Ferrer et Thurman developed an analytical method of 100 pharmaceuticals and their degradates in water samples by LC/Q-TOF-MS reporting in some compounds till four fragment ions, for the dextromethorphan three product ions were acquired at m/z 213, at m/z 171 and at m/z 147 (Ferrer and Thurman, 2012).

Otherwise, cloperastine gave a full scan spectrum with an intense protonated molecule at m/z 331 [M+H]$^+$ corresponding to the loss of a chloride molecule. Using 42 V of CV, it produced the two main fragments at m/z 203 [$C_{13}H_{12}Cl$]$^+$ which corresponds to the loss of a $C_7H_{14}NO$ group and at m/z 166 [$C_{13}H_{10}$]$^+$ corresponding to the loss of chloride molecule from the m/z 203. Finally, another drug belonging to this group is chlorpheniramine, which is a first-generation alkylamine antihistamine. It gave a full mass spectrum with a precursor ion at m/z 275 [M+H]$^+$. MS/MS spectra of this precursor ion provided the fragment ions at m/z 230 [$C_{14}H_{13}ClN$]$^+$ at 18 eV of C.E. and at m/z 167 [$C_9H_{10}NCl$]$^+$ at 43 eV. In a previous study, Gómez-Canela et al. studied these pharmaceuticals by LC-MS/MS and reported the same transitions for both compounds (Gómez-Canela et al., 2019).

Table S3. MS/MS fragmentation of the pharmaceuticals ordered following de ATC code for the pharmaceuticals; and including their metabolites, transformation product and internal standard (*).

Acetylsalicylic acid	Salicylic acid *	Aspirin-d₃

Ranitidine	Omeprazole	Pantoprazole

Esomeprazole

Vildagliptin	Amiodarone
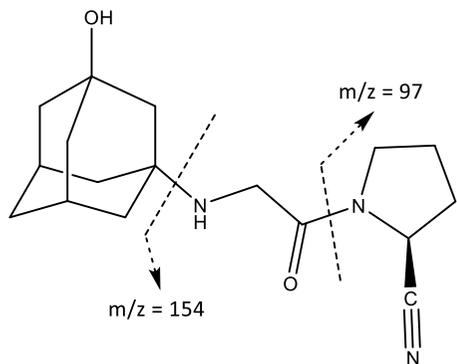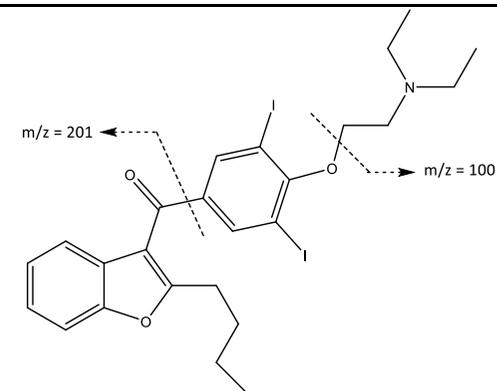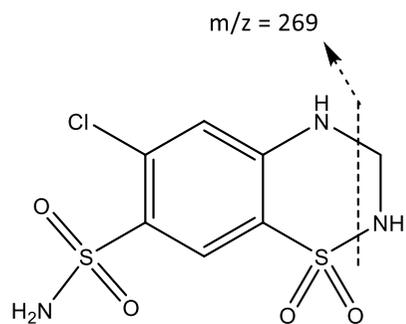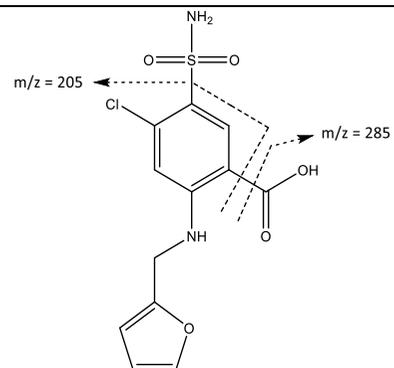
Hydrochlorothiazide	Furosemide	Pentoxifylline
Lidocaine	Lidocaine-d$_{10}$	Propranolol

m/z = 97

m/z = 154

m/z = 201

m/z = 100

m/z = 269

m/z = 205

m/z = 285

m/z = 181

m/z = 138
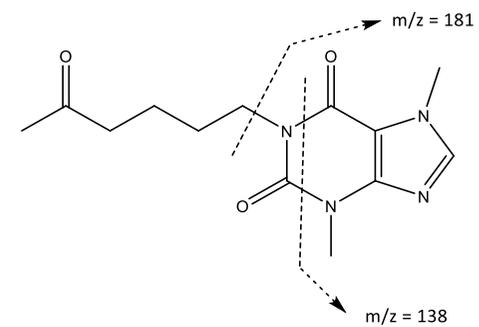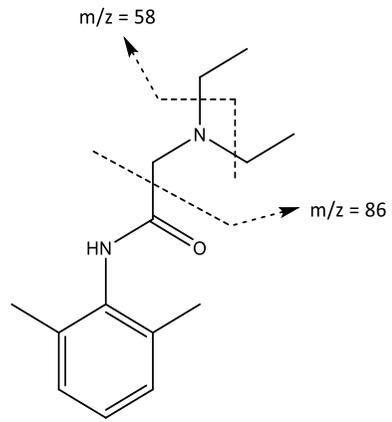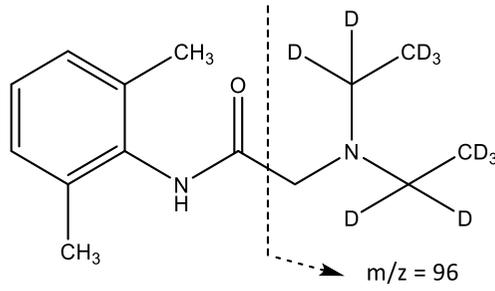
| Propranolol-d7 | Atenolol | Atenolol-d7 |

| Verapamil | Enalapril | Enalaprilat * |
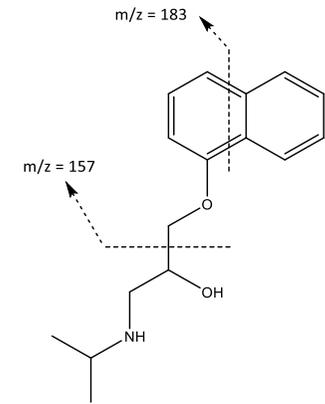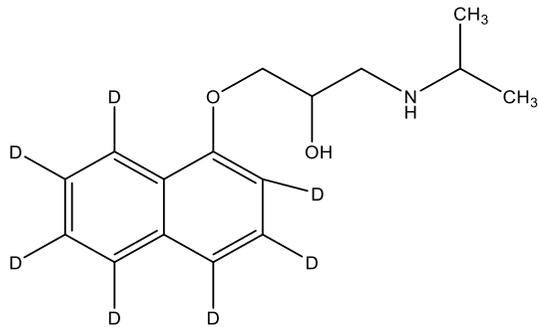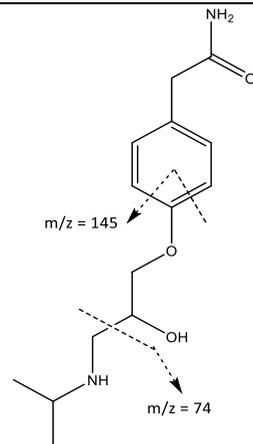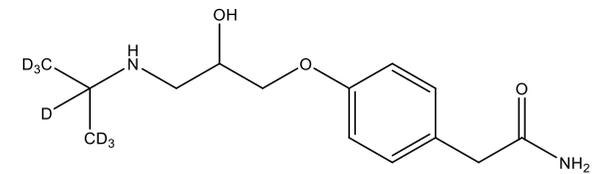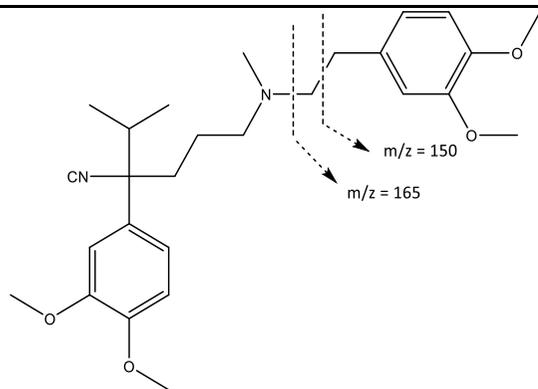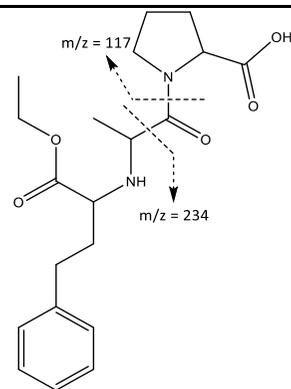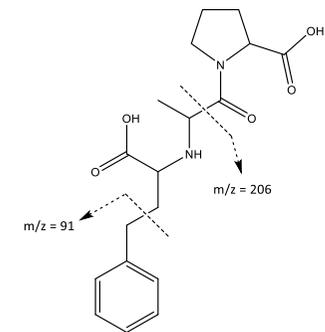
Losartan   Valsartan   Simvastatin
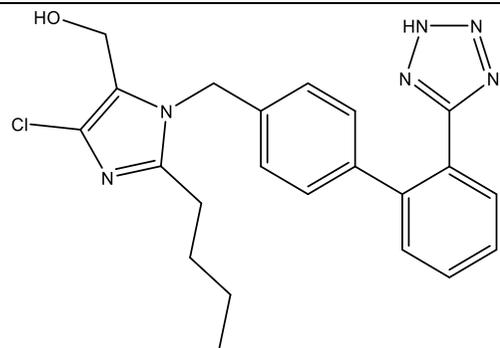
Rosuvastatin   Ezetimibe   (Dutasteride)
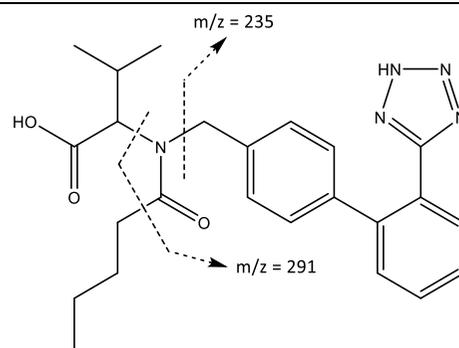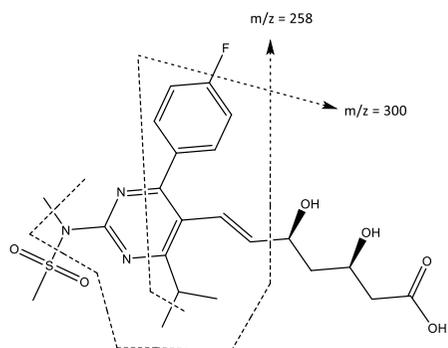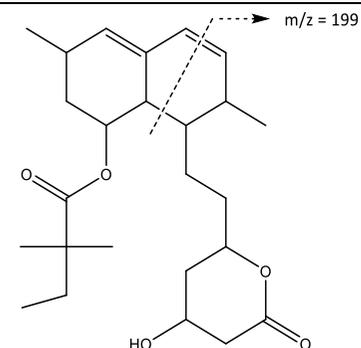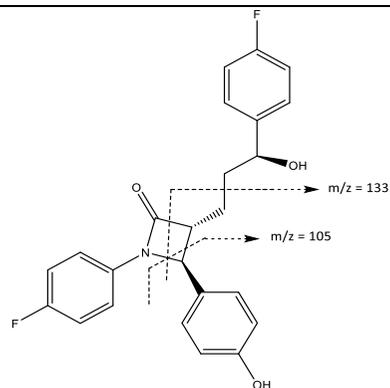
Estrone   Cyproterone   Dutasteride
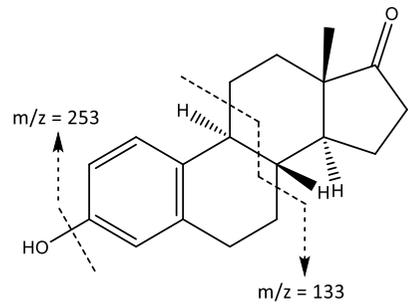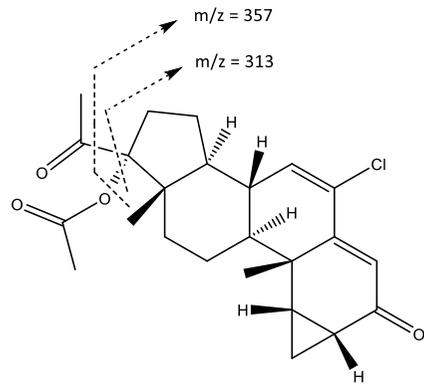
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m/z = 133	m/z = 313	m/z = 69
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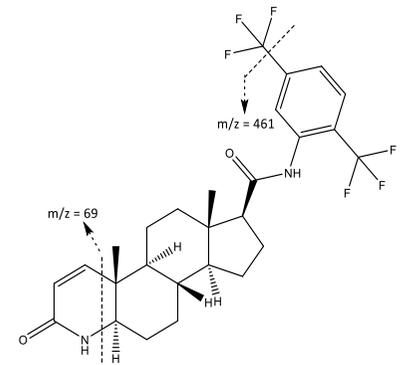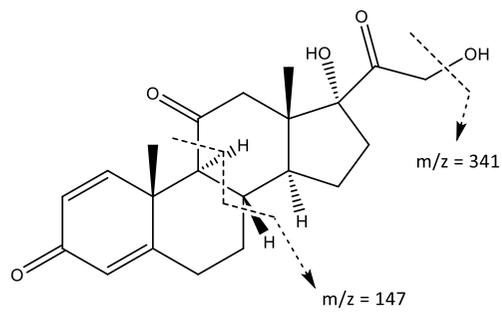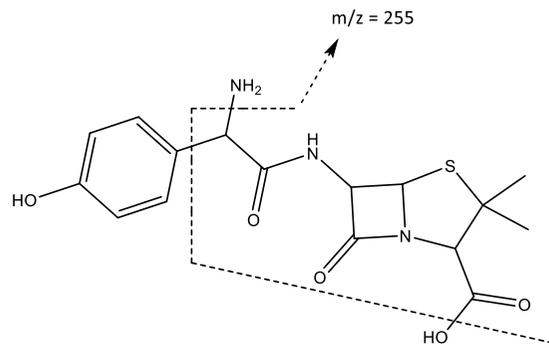
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m/z = 147		m/z = 156
Sulfamethoxazole	N⁴-acetylsulfamethoxazole *	Sulfadiazine

m/z = 198	m/z = 65	m/z = 96
m/z = 156		m/z = 156
m/z = 92		
Erythromycin	Clarithromycin	Ciprofloxacin
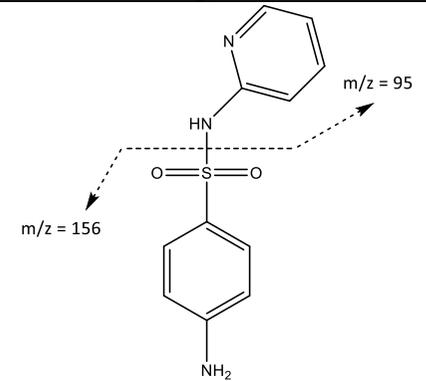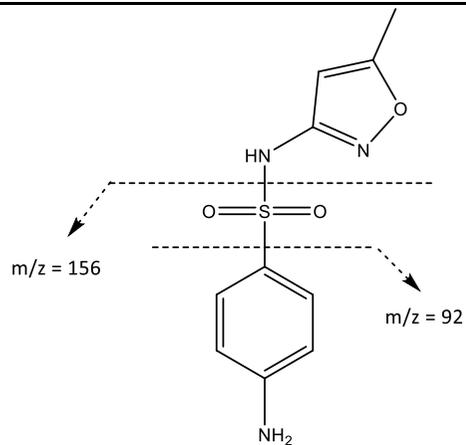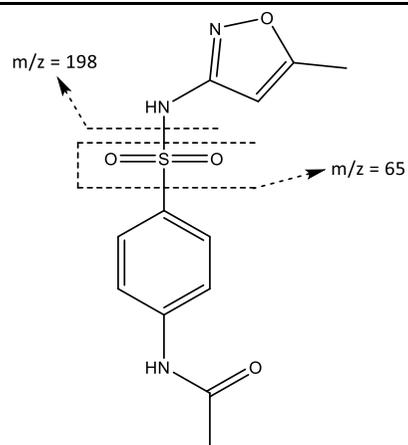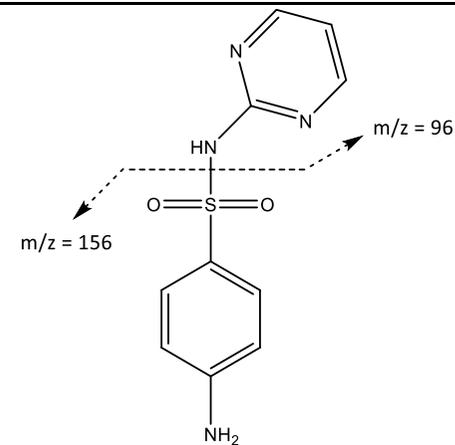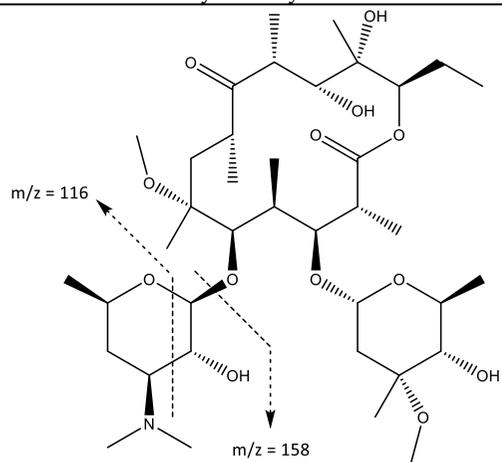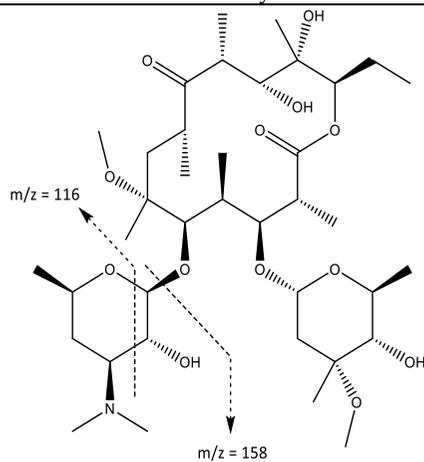
m/z = 116	m/z = 116	m/z = 245
m/z = 158	m/z = 158	m/z = 314
Norfloxacin	Levofloxacin	Cyclophosphamide

m/z = 302	
m/z = 276	m/z = 263
	m/z = 318
	m/z = 140
	m/z = 106

Ifosfamide

m/z = 154

m/z = 78
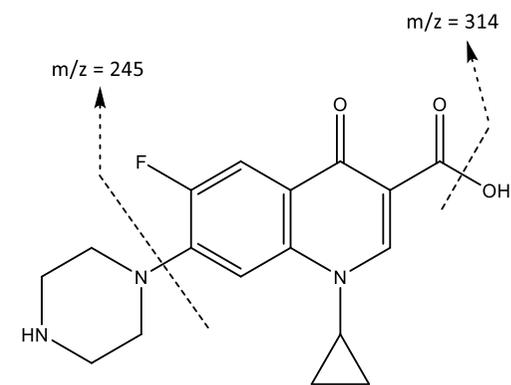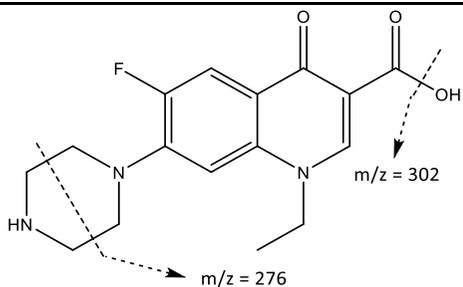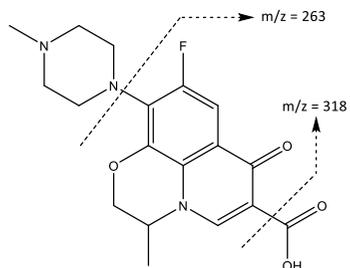
Megestrol	Bicalutamide

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m/z = 217

m/z = 95
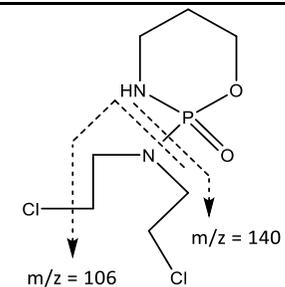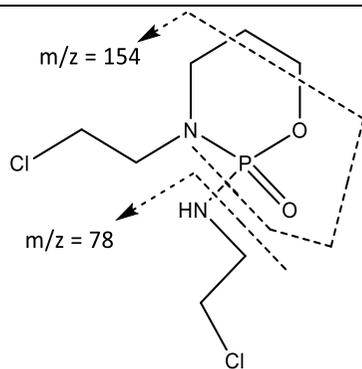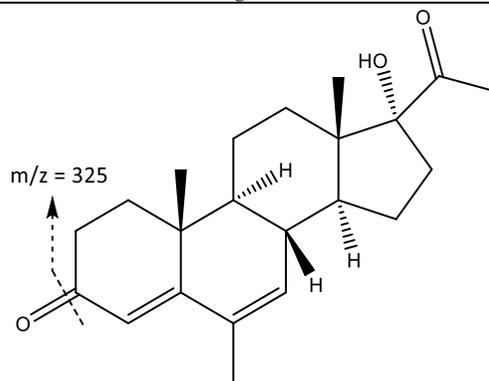
Mycophenolic acid	Diclofenac	N-(2,6-dichlorophenyl)-2-indolinone *
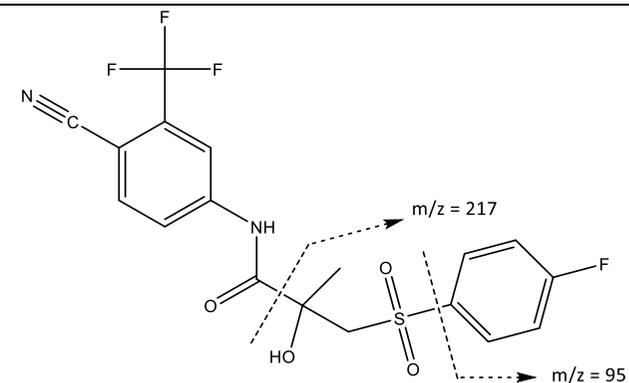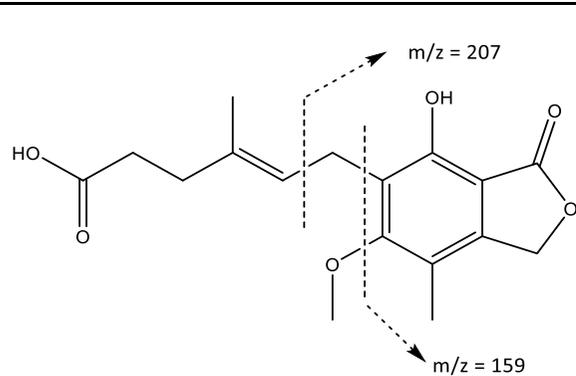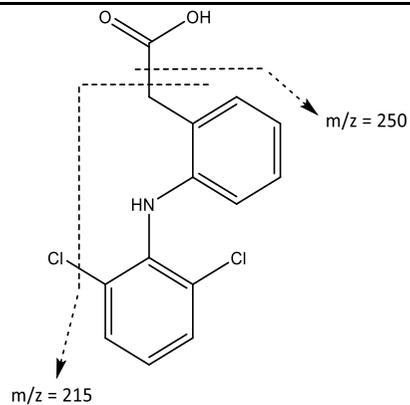
Ibuprofen	1-hydroxy ibuprofen *	2-hydroxy ibuprofen *
Ibuprofen-d₃		Tramadol
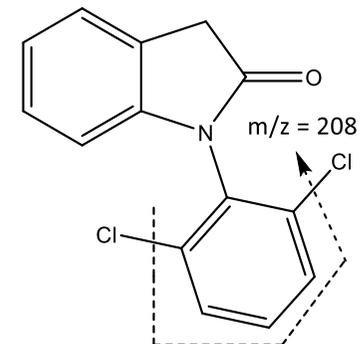
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m/z = 215

m/z = 208

m/z = 119

m/z = 104

m/z = 207

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m/z = 207

m/z = 193

m/z = 108

m/z = 122

CD₃... (CD$_3$)

OH

m/z = 246

HO

m/z = 58

4-aminoantipyrine *

NH$_2$

m/z = 56

m/z = 94
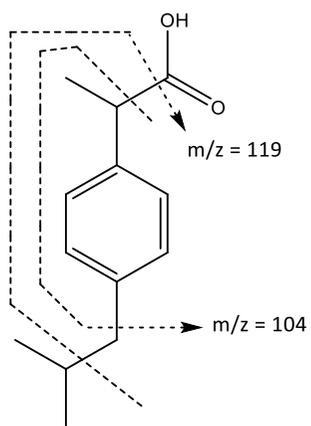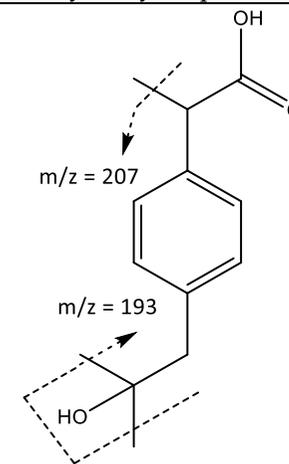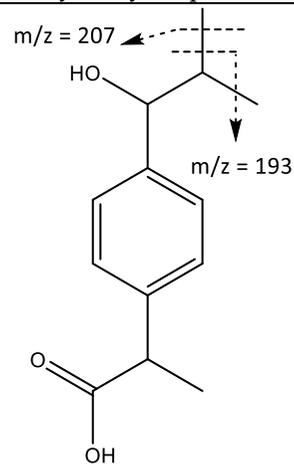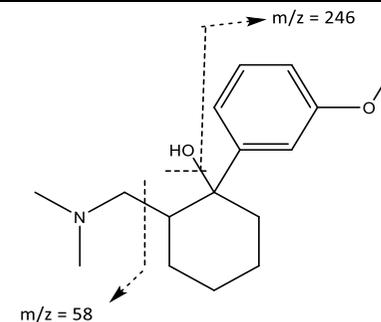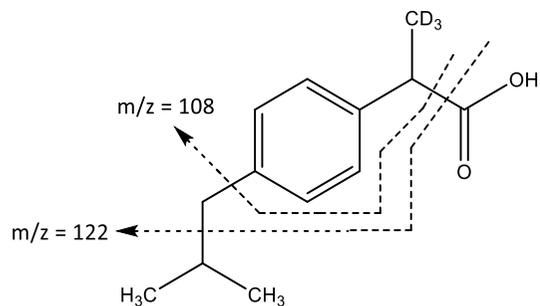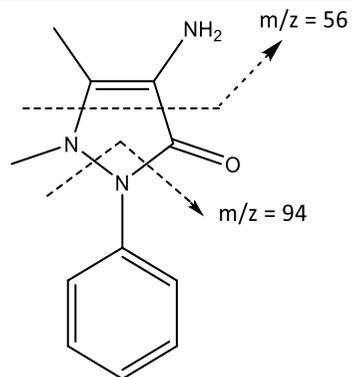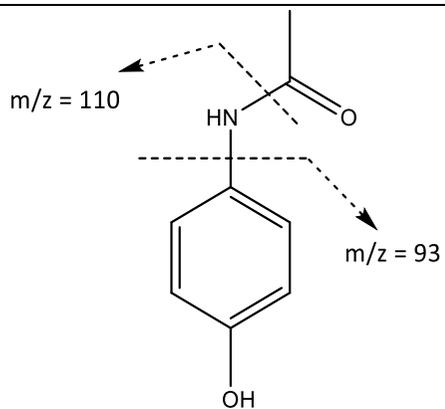
Paracetamol	Acetaminophen-(methyl-d$_3$)	Carbamazepine

m/z = 110

m/z = 93

OH

OH

m/z = 110

m/z = 93

m/z = 194

m/z = 179

H$_2$N
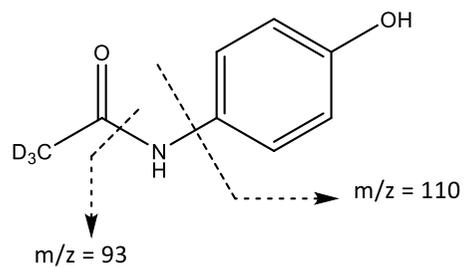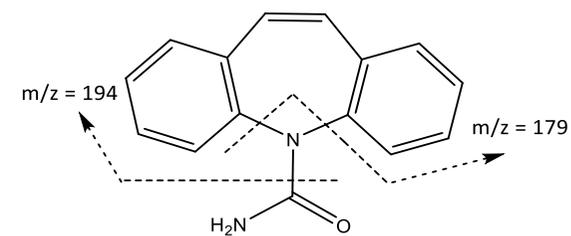
Carbamazepine 10,11-epoxide *	Carbamazepine-^{13}C$_6$	Topiramate
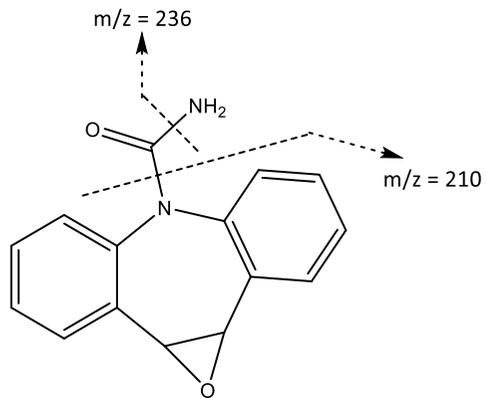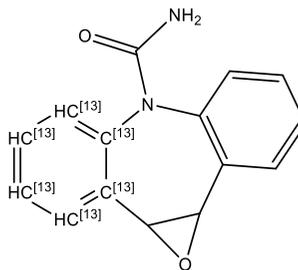
m/z = 236 / m/z = 210		m/z = 264 / m/z = 127
Gabapentin	Gabapentin-$^{13}C_3$	Levetiracetam
m/z = 155 / m/z = 137		m/z = 126 / m/z = 154
Pregabalin	Levodopa	Levodopa-d_3
m/z = 84 / m/z = 143	m/z = 107 / m/z = 152	m/z = 184 / m/z = 155
Rasagiline	Diazepam	Clomethiazole
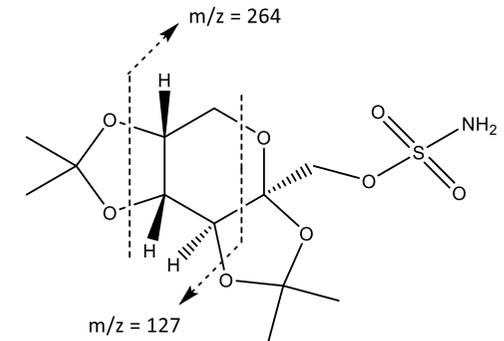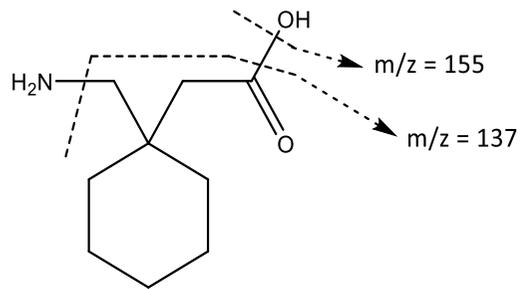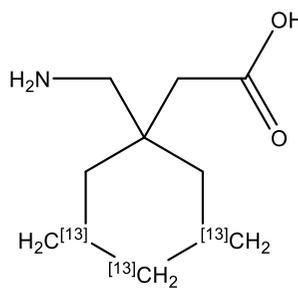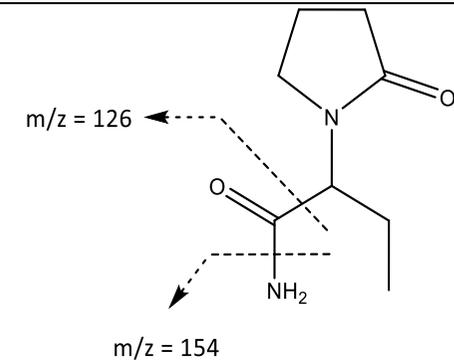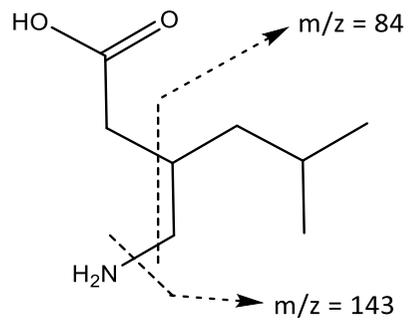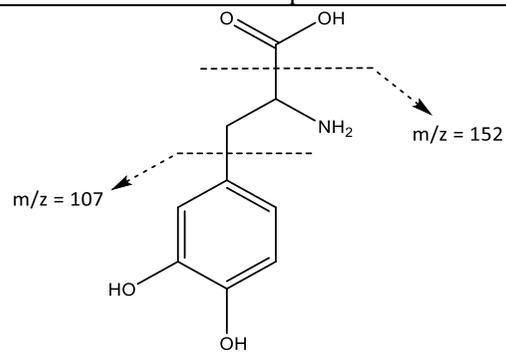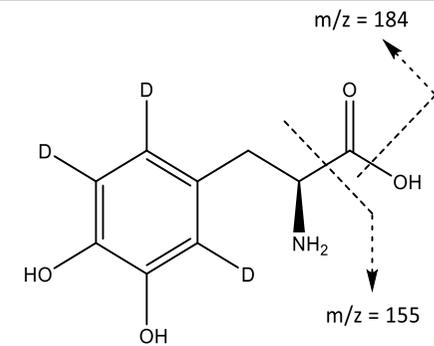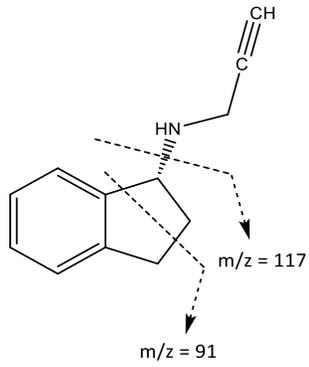
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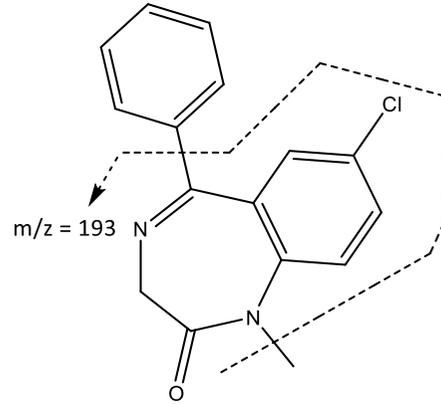
Fluoxetine
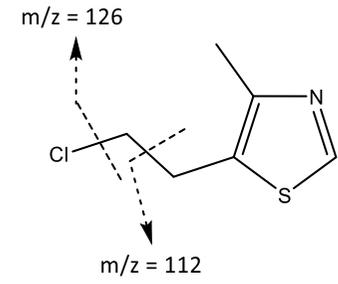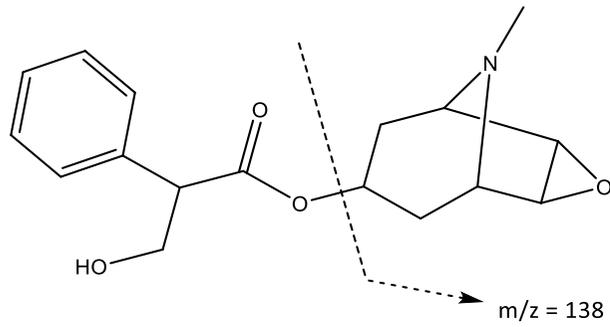
Citalopram

Escitalopram
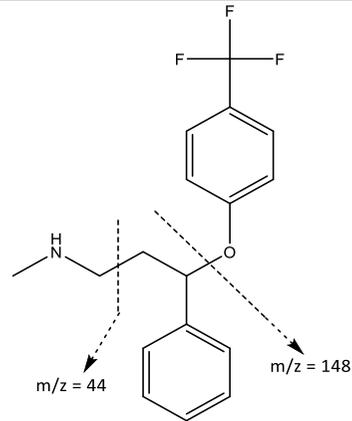
Trazodone
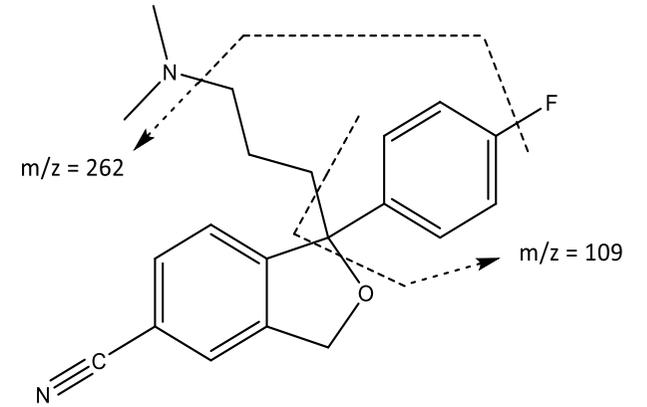
Venlafaxine
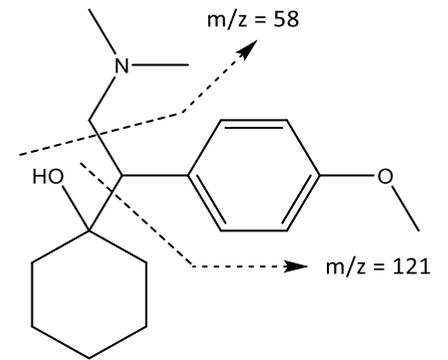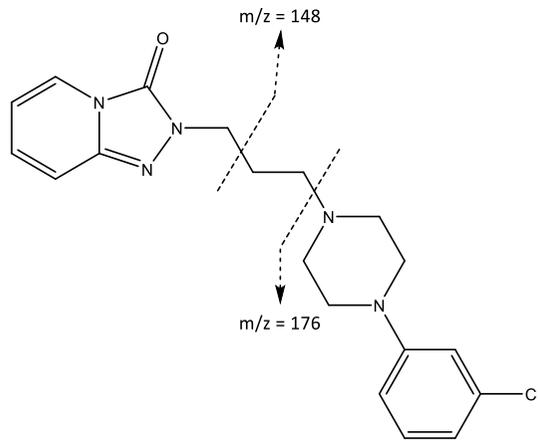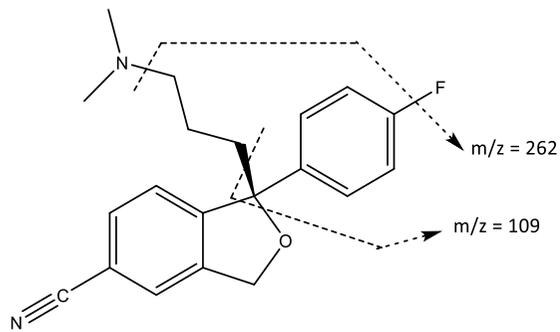
	Caffeine	Donepezil
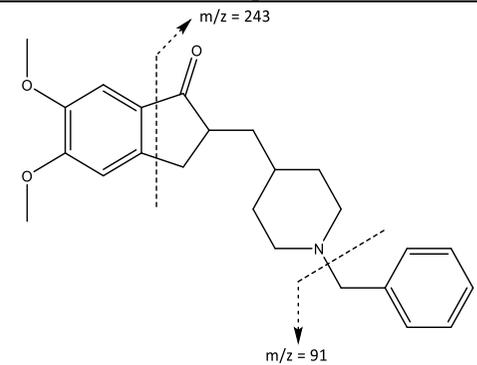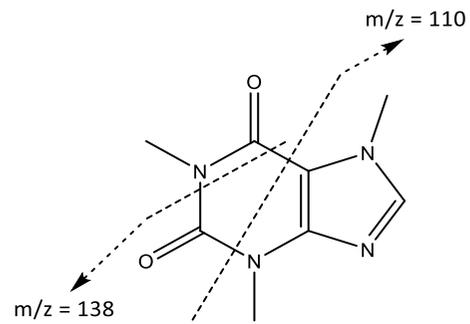
| Memantine | Dichlorobenzyl alcohol | Amylmetacresol |
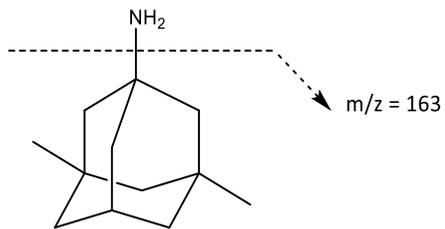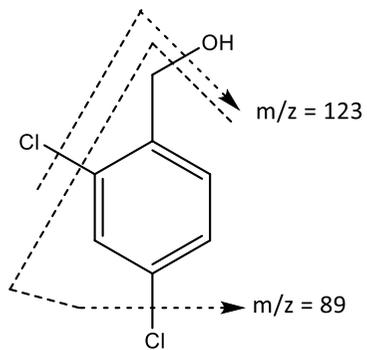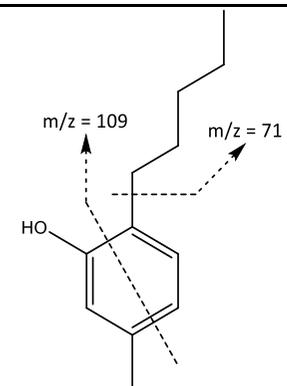
m/z = 163	m/z = 123 m/z = 89	m/z = 109 m/z = 71
Budesonide	Fluticasone	Tiotropium bromide
m/z = 147 m/z = 73	m/z = 293	m/z = 152 Br⁻ m/z = 170
Acetylcysteine	Dextromethorphan	Cloperastine
m/z = 76 m/z = 122	m/z = 171 m/z = 147	m/z = 203 m/z = 166

Chlorpheniramine

m/z = 230

m/z = 167

Cl
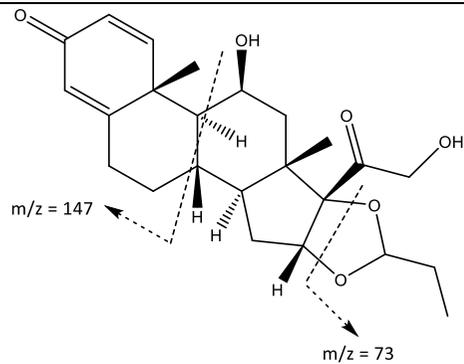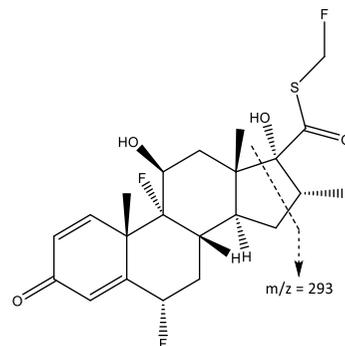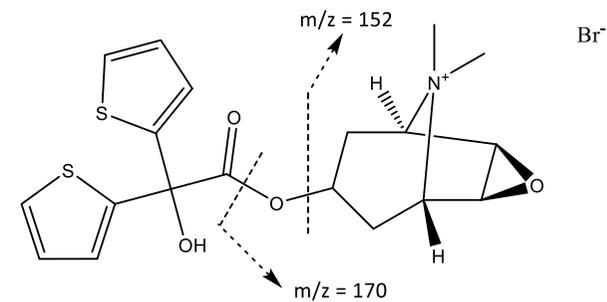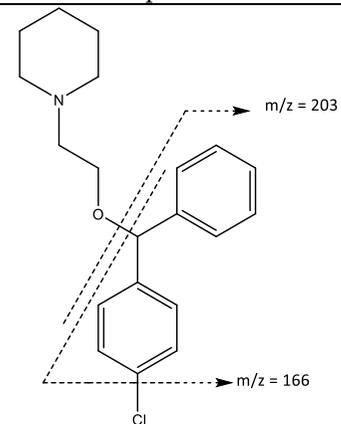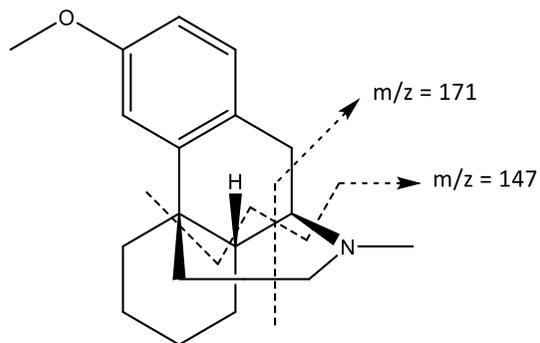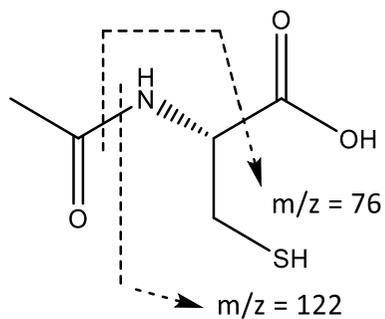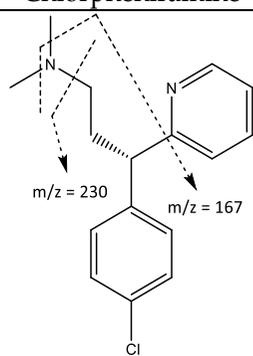
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