
Activity of GPCR-targeted drugs influenced by human gut microbiota metabolism

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1. Human gut microbiome selection for drug metabolism *in vitro* screening

Table S1. Information for bacterial collection that comprises 30 strains, including thirteen Firmicutes (blue), thirteen Bacteroidetes (orange), three Actinobacteria (green), and one Proteobacteria (black). The term "mix ratio" denotes the initial proportion of each bacterium within the bacterial community mixture used in this study.

Strain codes	Taxa	Phylum	Mix Ratio
ATCC15579	<i>Clostridium sporogenes</i>	Firmicutes	1
AV03	<i>Clotridium scindens</i>	Firmicutes	2
AV11	<i>Blautia luti</i>	Firmicutes	1
D36	<i>Streptococcus parasanguinis</i>	Firmicutes	1
D49	<i>Eubacterium callanderi</i>	Firmicutes	1
D51	<i>Eubacterium bifforme</i>	Firmicutes	2
D53	<i>Dorea longicatena</i>	Firmicutes	1
D57	<i>Ruminococcus faecis</i>	Firmicutes	1
D58	<i>Ruminococcus gnavus</i>	Firmicutes	1
D65	<i>Blautia producta</i>	Firmicutes	2
D67	<i>Coprococcus eutactus</i>	Firmicutes	2
D87	<i>Enterococcus faecium</i>	Firmicutes	1
D88	<i>Blautia hansenii</i>	Firmicutes	2
AV01	<i>Bacteroides caccae</i>	Bacteroidetes	1
AV02	<i>Phocaeicola vulgatus</i>	Bacteroidetes	1
AV09	<i>Phocaeicola dorei</i>	Bacteroidetes	1
AV14	<i>Bacteroides uniformis</i>	Bacteroidetes	1
AV15	<i>Bacteroides eggerthii</i>	Bacteroidetes	1
AV18	<i>Bacteroides fragilis</i>	Bacteroidetes	1
D12	<i>Bacteroides faecis</i>	Bacteroidetes	1
D19	<i>Bacteroides ovatus</i>	Bacteroidetes	1
D21	<i>Bacteroides stercoris</i>	Bacteroidetes	1
D22	<i>Bacteroides salyersiae</i>	Bacteroidetes	1
D23	<i>Parabacteroides merdae</i>	Bacteroidetes	1
D24	<i>Parabacteroides distasonis</i>	Bacteroidetes	1
D85	<i>Bacteroides thetaiotaomicron</i>	Bacteroidetes	1
AV12	<i>Collinsella aerofaciens</i>	Actinobacteria	1
D04	<i>Bifidobacterium adolscentis</i>	Actinobacteria	1
D09	<i>Eggerthella lenta</i>	Actinobacteria	1
D82	<i>Morganella morganii</i>	Proteobacteria	0.2
Firmicutes: 13			
Bacteroidetes: 13			
Actinobacteria: 3			
Proteobacteria: 1			
Total: 30			

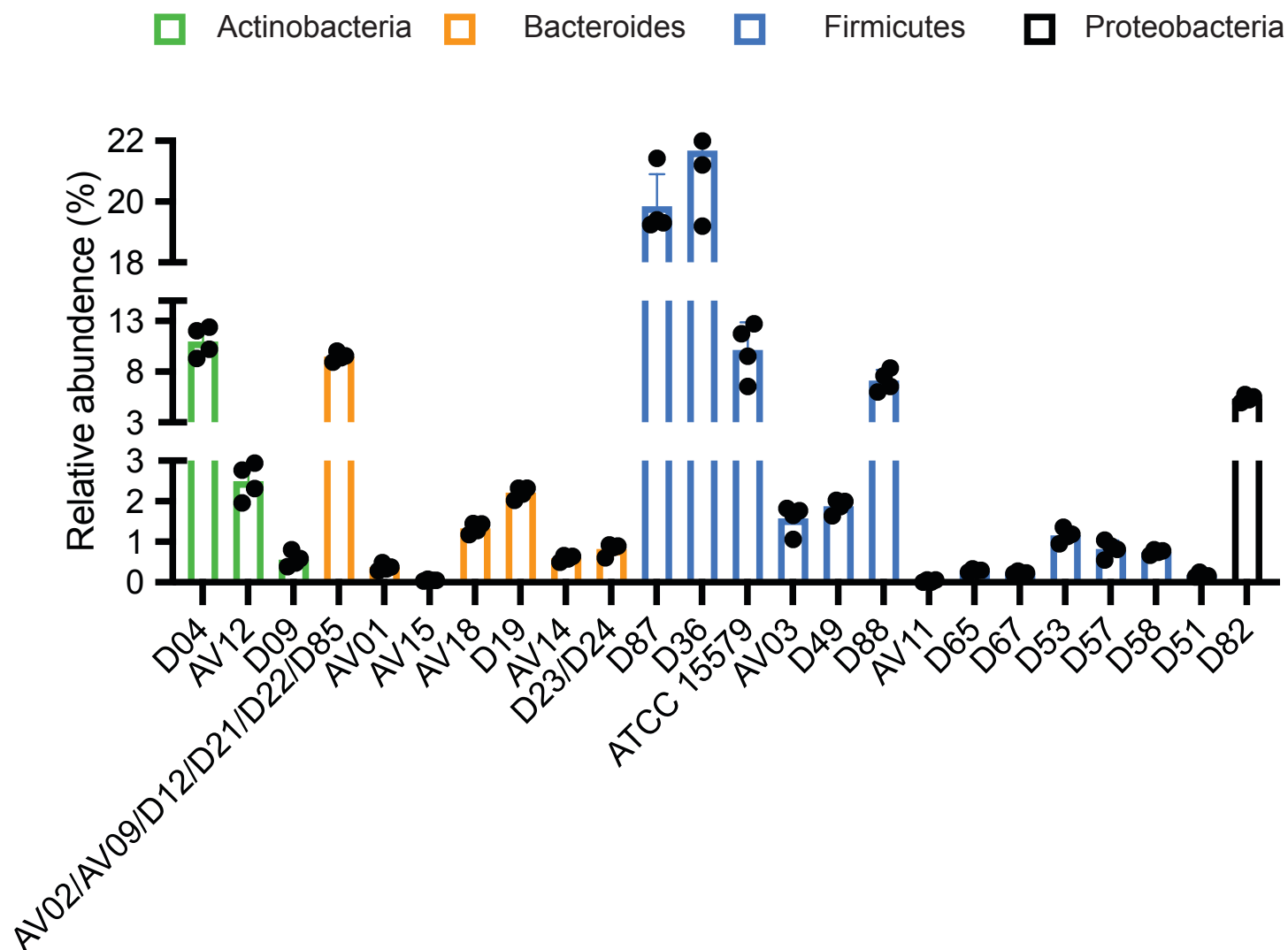
Table S2. Rationale for selecting bacteria for *Bac-Mix* in drug metabolism *in vitro* screening.

Strain codes	Taxa	Note
ATCC15579	<i>Clostridium sporogenes</i>	Reported significant drug metabolism ¹ and amino acid metabolism ²
AV03	<i>Clotridium scindens</i>	Reported significant drug metabolism (dexamethasone metabolism) ³
AV11	<i>Blautia luti</i>	Reported moderate drug metabolism ³ , increase diversity ⁴ 1/15/25 8:34:00 PM
D36	<i>Streptococcus parasanguinis</i>	Increase diversity ⁵
D49	<i>Eubacterium callanderi</i>	Increase diversity ⁶
D51	<i>Eubacterium biforme</i>	Reported significant drug metabolism ³
D53	<i>Dorea longicatena</i>	Increase diversity ⁷
D57	<i>Ruminococcus faecis</i>	Increase diversity ⁸
D58	<i>Ruminococcus gnavus</i>	Increase diversity ⁹
D65	<i>Blautia producta</i>	Increase diversity ⁴
D67	<i>Coprococcus eutactus</i>	Increase diversity ¹⁰
D87	<i>Enterococcus faecium</i>	Increase diversity ¹¹
D88	<i>Blautia hansenii</i>	Reported significant drug metabolism ³
AV01	<i>Bacteroides caccae</i>	Reported moderate drug metabolism ³ , increase diversity ¹²
AV02	<i>Phocaeicola vulgatus</i>	Reported significant drug metabolism ³
AV09	<i>Phocaeicola dorei</i>	Reported significant drug metabolism ³
AV14	<i>Bacteroides uniformis</i>	Reported significant drug metabolism ³
AV15	<i>Bacteroides eggerthii</i>	Reported significant drug metabolism ³
AV18	<i>Bacteroides fragilis</i>	Reported significant drug metabolism ³
D12	<i>Bacteroides faecis</i>	Increase diversity ¹³
D19	<i>Bacteroides ovatus</i>	Reported significant drug metabolism ³
D21	<i>Bacteroides stercoris</i>	Reported significant drug metabolism ³
D22	<i>Bacteroides salyersiae</i>	Increase diversity ¹³
D23	<i>Parabacteroides merdae</i>	Reported significant drug metabolism ³
D24	<i>Parabacteroides distasonis</i>	Reported significant drug metabolism ³
D85	<i>Bacteroides thetaiotaomicron</i>	Reported significant drug metabolism ³
AV12	<i>Collinsella aerofaciens</i>	Increase diversity ¹⁴
D04	<i>Bifidobacterium adolescentis</i>	Increase diversity ¹⁵
D09	<i>Eggerthella lenta</i>	Reported significant xenobiotic metabolism ¹⁶
D82	<i>Morganella morganii</i>	Reported significant amino acid metabolism, diverse metabolism impact on host physiology ^{17–19}

Table S3. Raw data of the relative abundance of each bacterium in the *Bac-Mix* culture broth after 48 hours of cultivation. The relative abundance of each bacterium was determined by 16S rRNA sequencing, and the experiment was conducted in quadruplicates.

	1	2	3	4	Strain codes
k__Bacteria;p__Actinobacteria;c__Actinobacteria;o__Bifidobacteriales;f__Bifidobacteriaceae;g__Bifidobacterium;s__adolescentis	9.321073	10.20793	12.04846	12.4147	D04
k__Bacteria;p__Actinobacteria;c__Coriobacteriia;o__Coriobacteriales;f__Coriobacteriaceae;g__Collinsella;s__aerofaciens	1.954935	2.317084	2.942505	2.770904	AV12
k__Bacteria;p__Actinobacteria;c__Coriobacteriia;o__Coriobacteriales;f__Coriobacteriaceae;g__Eggerthella;s__lenta	0.384577	0.475597	0.583233	0.8024	D09
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Bacteroidaceae;g__Bacteroides;__	10.05078	9.561233	9.395695	8.950131	AV02/AV09/D12/D21/D22/D85
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Bacteroidaceae;g__Bacteroides;s__caccae	0.490583	0.379897	0.334889	0.288714	AV01
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Bacteroidaceae;g__Bacteroides;s__eggerthii	0.049305	0.078299	0.052679	0.029996	AV15
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Bacteroidaceae;g__Bacteroides;s__fragilis	1.4397	1.281791	1.173992	1.447319	AV18
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Bacteroidaceae;g__Bacteroides;s__ovatus	2.176807	2.021286	2.325406	2.324709	D19
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Bacteroidaceae;g__Bacteroides;s__uniformis	0.638497	0.661195	0.575707	0.494938	AV14
k__Bacteria;p__Bacteroidetes;c__Bacteroidia;o__Bacteroidales;f__Porphyromonadaceae;g__Parabacteroides;s__	0.919535	0.898994	0.857917	0.607424	D23/D24
k__Bacteria;p__Firmicutes;c__Bacilli;o__Lactobacillales;f__Enterococcaceae;g__Enterococcus;__	19.24613	19.40376	19.30689	21.42857	D87
k__Bacteria;p__Firmicutes;c__Bacilli;o__Lactobacillales;f__Streptococcaceae;g__Streptococcus;s__	21.20353	19.18917	21.99729	24.32321	D36
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Clostridiaceae;__	11.75673	12.71641	9.531156	6.554181	ATCC 15579
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Clostridiaceae;g__Clostridium;s__	1.765112	1.824087	1.651866	1.061117	AV03
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Eubacteriaceae;g__Pseudoramibacter_Eubacterium;s__	1.64185	2.024186	1.866346	1.991001	D49
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;__	7.595405	8.349042	6.562312	6.014248	D88
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Blautia;s__	0	0.0609	0	0.056243	AV11
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Blautia;s__producta	0.246524	0.327698	0.289735	0.299963	D65
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Coprococcus;s__eutactus	0.231733	0.229098	0.278447	0.217473	D67
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__Dorea;s__longicatena	1.183315	1.36299	1.128838	0.948631	D53
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__[Ruminococcus];s__	1.037866	0.811994	0.895545	0.551181	D57
k__Bacteria;p__Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;g__[Ruminococcus];s__gnavus	0.774085	0.736595	0.801475	0.663667	D58
k__Bacteria;p__Firmicutes;c__Erysipelotrichi;o__Erysipelotrichales;f__Erysipelotrichaceae;g__[Eubacterium];s__biforme	0.135588	0.150799	0.1618	0.247469	D51
k__Bacteria;p__Proteobacteria;c__Gammaproteobacteria;o__Enterobacteriales;f__Enterobacteriaceae;g__Morganella;s__morganii	5.756336	4.929965	5.237809	5.511811	D82

Fig. S1. Bar graph showing the relative abundance of each bacterium in the *Bac-Mix* culture broth after 48 hours of cultivation. Strains AV02, AV09, D12, D21, D22, and D85 are grouped together as they cannot be distinguished based on 16S rRNA sequencing. The experiment was conducted in quadruplicates. n = 3 biological replicates. Data represent mean $\pm$ s.d.



2. Comparative metabolomics section

Table S4. Molecular feature (MOF) list for GSK1292263 metabolism by bacterial community. The identification of false positives was detailed in the method section. Individual peaks were manually verified. UP: upregulation; mzmed: the median of the peaks' m/z values; rtmed: the median of the peaks' retention times.

fold	log ₂ fold	pvalue	UP	mzmed	rtmed	-log ₁₀ pvalue	note
231.6313	7.855687	0.000857	UP	482.1716	8.344758	3.066857572	Sodium adduct
92.78836	6.535872	0.00065	UP	460.1893	8.344758	3.187406595	Hit
87.96443	6.458848	0.000771	UP	483.1744	8.34435	3.113001711	Isotope
86.38813	6.432761	5.77E-05	UP	118.1208	10.66202	4.239059574	False positive
81.45945	6.34801	0.000234	UP	459.1981	6.66155	3.630526157	Hit
73.29139	6.195572	0.000271	UP	460.2017	6.66155	3.567808183	Isotope
73.03467	6.19051	0.009996	UP	391.1269	6.661533	2.000168432	Mass fragment
69.11173	6.110859	0.000699	UP	461.1925	8.344758	3.155671703	Isotope
67.18745	6.07012	0.000294	UP	461.2011	6.661517	3.531652724	Isotope
65.52386	6.033948	0.004073	UP	373.1168	6.66985	2.39010546	Mass fragment
47.07146	5.556781	0.001445	UP	225.1482	12.15258	2.840255964	False positive
29.21756	4.868764	0.000381	UP	462.2029	6.661517	3.418753969	Isotope
16.06327	4.005693	2E-05	UP	211.0857	10.16859	4.69820811	False positive

Table S5. MOF list for ozanimod metabolism by bacterial community. The identification of false positives was detailed in the method section. Individual peaks were manually verified. UP: upregulation; mzmed: the median of the peaks' m/z values; rtmed: the median of the peaks' retention times.

fold	log ₂ fold	pvalue	up/down	mzmed	rtmed	-log ₁₀ pval	Note
351.7536	8.458421	0.002165	UP	186.1854	10.13874	2.664442506	False positive
278.2959	8.120476	0.000194	UP	170.0595	8.076783	3.712802479	False positive
213.7038	7.739468	0.000977	UP	190.0862	8.314033	3.010312342	False positive
178.389	7.478883	0.00011	UP	336.6975	5.4484	3.958610616	False positive
173.7596	7.440949	0.004131	UP	172.1691	9.382292	2.383949169	False positive
104.3528	6.705325	0.007081	UP	407.2085	6.327617	2.149930684	Hit
92.92426	6.537983	0.005784	UP	146.0226	6.317083	2.237787845	Mass fragment
80.90025	6.338072	0.000799	UP	130.0647	8.308117	3.097581983	False positive
74.91032	6.227093	0.000772	UP	611.3443	5.582467	3.112455967	False positive
64.26828	6.006035	0.000533	UP	672.3918	5.44825	3.273609787	False positive
48.23853	5.592114	0.000367	UP	673.3934	5.4336	3.435410375	False positive
46.09677	5.526594	0.00195	UP	130.0496	3.001783	2.710072925	False positive
45.33856	5.502667	0.000178	UP	651.3492	5.31385	3.749721368	False positive
42.42868	5.406968	0.000777	UP	549.2659	5.09535	3.109776887	False positive
40.05478	5.323902	0.004544	UP	408.1916	6.943117	2.342571567	Hit
37.75278	5.238511	9.46E-05	UP	337.1984	5.4484	4.024312761	False positive
35.56692	5.152464	0.006405	UP	346.1541	6.333583	2.193480372	Mass fragment
34.38636	5.103764	0.000274	UP	144.0806	5.649433	3.561645095	False positive
33.85208	5.081173	0.004283	UP	154.0974	3.443175	2.368260234	False positive
31.92316	4.996532	0.001055	UP	642.31	5.06185	2.976946663	False positive
25.82023	4.69043	0.000581	UP	708.4321	5.507783	3.235656712	False positive
25.21436	4.656174	0.000106	UP	145.0834	5.649508	3.973960144	False positive
24.17331	4.595343	0.000944	UP	709.4251	5.4835	3.025175147	False positive
22.20615	4.472888	0.000203	UP	413.7301	5.499458	3.691793955	False positive
21.86244	4.450382	0.001223	UP	132.0662	3.717883	2.912620309	False positive
21.00763	4.392842	0.001341	UP	912.5213	6.433167	2.872485314	False positive
19.05705	4.252253	0.000421	UP	709.4382	5.516125	3.375347393	False positive
17.35655	4.117408	0.002025	UP	751.3696	6.247425	2.693507947	False positive
16.97596	4.085421	0.001445	UP	190.107	3.643033	2.840251659	False positive
16.73535	4.064827	0.00183	UP	168.1131	3.634633	2.737619196	False positive
16.35378	4.031552	0.000887	UP	326.7214	5.316867	3.052096341	False positive

Table S6. MOF list for ponesimod metabolism by bacterial community. The identification of false positives was detailed in the method section. Individual peaks were manually verified. UP: upregulation; mzmed: the median of the peaks' m/z values; rtmed: the median of the peaks' retention times.

fold	log ₂ fold	pvalue	updown	mzmed	rtmed	-log ₁₀ pvalue	note
17294.7	14.07804	6.73279E-05	UP	465.1439	9.398117	4.171804997	Isotope
13223.81	13.69085	1.57468E-05	UP	465.1437	9.069183	4.802806884	Isotope
11706.94	13.51508	1.74314E-05	UP	464.1491	9.069183	4.758667534	Isotope
11560.23	13.49688	1.19221E-05	UP	466.1471	9.069183	4.923648543	Isotope
11041.53	13.43065	4.64351E-05	UP	466.1473	9.398117	4.333153285	Isotope
9724.876	13.24746	7.14964E-05	UP	463.1457	9.398833	4.145715753	Hit
7811.669	12.93142	1.24557E-05	UP	463.1453	9.066633	4.90463185	Hit
3066.216	11.58224	5.89735E-05	UP	464.1493	9.398117	4.229342867	Isotope
2751.563	11.42604	1.24344E-05	UP	467.1442	9.069183	4.90537537	Isotope
2622.961	11.35698	7.50859E-05	UP	467.1444	9.398117	4.12444151	Isotope
2099.862	11.03608	7.99827E-06	UP	609.3623	6.634533	5.097004166	False positive
801.6043	9.646746	0.00116965	UP	600.2385	5.732367	2.931944091	False positive
518.8789	9.019254	0.000748583	UP	453.3067	9.34885	3.125760276	False positive
465.0629	8.861282	0.002424722	UP	739.8372	5.115142	2.615338077	False positive
408.1934	8.673109	7.74405E-05	UP	611.3666	6.634533	4.111031852	False positive
355.0953	8.472062	0.00193457	UP	531.228	5.3523	2.713415543	False positive
152.2769	7.250553	1.25783E-06	UP	225.1478	12.16425	5.900378783	False positive
74.92988	6.227469	0.000190122	UP	186.1821	10.24579	3.720967941	False positive
70.81621	6.146008	0.000435985	UP	822.4652	6.085267	3.360528038	False positive
64.52691	6.011829	0.000575314	UP	131.1432	2.920817	3.24009528	False positive
64.50256	6.011284	1.44434E-06	UP	429.1859	8.298133	5.840331088	Hit
52.05183	5.701877	0.000189265	UP	220.1662	10.17002	3.722929317	False positive
49.50732	5.62957	6.0302E-05	UP	429.1823	8.626383	4.219668062	Hit
40.23892	5.33052	3.09727E-05	UP	120.0508	5.802017	4.509020361	False positive
31.06612	4.95727	0.000109109	UP	270.1443	8.586417	3.962139277	False positive
29.84618	4.899474	2.96585E-05	UP	496.2787	5.98525	4.527850288	False positive
27.8189	4.797993	0.000482609	UP	203.1144	7.564683	3.316404589	False positive
25.41939	4.667857	7.00446E-05	UP	866.5069	5.683892	4.154625601	False positive
22.23969	4.475065	8.36839E-05	UP	154.0945	3.2706	4.077357964	False positive
21.6318	4.435082	0.000897009	UP	145.0806	7.557925	3.04720303	False positive
20.48701	4.356638	0.000932327	UP	231.1448	8.692	3.030431922	False positive
19.72364	4.301854	0.000128024	UP	190.1041	3.4459	3.892709188	False positive
19.49027	4.284682	0.001858044	UP	144.0773	7.55115	2.730943969	False positive
16.76557	4.067429	8.22449E-08	UP	892.4651	4.616367	7.084890894	False positive
16.49641	4.04408	0.000209782	UP	640.2988	5.435567	3.678231951	False positive

Table S7. MOF list for SB756050 metabolism by bacterial community. The identification of false positives was detailed in the method section. Individual peaks were manually verified. UP: upregulation; mzmed: the median of the peaks' m/z values; rtmed: the median of the peaks' retention times.

fold	log ₂ fold	pvalue	updown	mzmed	rtmed	-log ₁₀ pvalue	note
1810.399	10.82209	0.000114	UP	473.1051	8.779375	3.943036476	Hit
1694.035	10.72625	0.001501	UP	495.0868	8.779067	2.823541559	Sodium adduct
1391.883	10.44282	0.000336	UP	474.108	8.779067	3.47384707	Isotope
871.2826	9.766997	0.000309	UP	445.0735	7.729717	3.509752695	Hit
771.7063	9.591908	0.000637	UP	490.1315	8.779067	3.196137687	Isotope
634.6606	9.309842	0.002781	UP	476.1157	8.229667	2.555799351	Isotope
362.6767	8.50254	0.001905	UP	459.0893	8.229692	2.720066747	Hit
335.7562	8.39127	0.001698	UP	578.1838	8.779067	2.769969814	False positive
328.1679	8.35829	2.95E-05	UP	475.1032	8.779067	4.529865043	Isotope
259.6149	8.02023	0.001467	UP	460.0923	8.229667	2.833606325	Isotope
161.5597	7.335923	0.006469	UP	967.1835	8.779067	2.189175171	False positive
150.2494	7.231215	0.000673	UP	995.2149	9.378917	3.172040255	False positive
111.9398	6.806579	0.001109	UP	564.1683	8.230392	2.955183696	False positive
103.4463	6.692738	0.000693	UP	504.1471	8.779067	3.159421562	False positive
74.78484	6.224674	0.002414	UP	579.1869	8.779067	2.617260484	Isotope
72.89618	6.187771	0.001032	UP	509.1024	9.390433	2.986466379	Sodium adduct
62.71013	5.970627	0.005501	UP	520.1425	8.779067	2.259567846	False positive
45.13699	5.496238	0.001395	UP	417.1774	5.755183	2.85545765	False positive
42.81157	5.419929	0.001114	UP	487.1206	9.390992	2.953073971	Hit
41.26846	5.366968	0.000675	UP	488.1235	9.382733	3.170744874	Isotope
38.81383	5.278499	0.001971	UP	504.147	9.391067	2.705389868	False positive
33.98858	5.086978	0.000756	UP	188.0575	5.452333	3.121250315	False positive
32.28513	5.012798	9.82E-05	UP	127.0501	4.37925	4.008032626	False positive
30.23929	4.918352	0.00074	UP	592.1997	9.399325	3.130757775	False positive
29.81622	4.898025	0.002197	UP	534.1592	9.390433	2.658110202	False positive
29.3014	4.872898	0.000457	UP	518.1627	9.395583	3.340110178	False positive
27.27505	4.76951	0.000331	UP	593.2025	9.395733	3.479921712	False positive
26.114	4.706752	0.000337	UP	489.1204	9.395342	3.472288726	Isotope
26.00729	4.700844	0.00036	UP	505.1498	8.779067	3.443702506	Isotope
24.68693	4.625676	0.00049	UP	519.1656	9.378917	3.309605328	False positive
24.38739	4.608063	0.000756	UP	620.1947	9.395975	3.121699618	False positive
22.74847	4.507698	0.00051	UP	287.1061	8.779067	3.292306243	Mass fragment
20.35046	4.34699	0.000379	UP	574.2255	9.395583	3.421300167	False positive
19.56696	4.290347	0.000177	UP	471.3376	4.6951	3.752525916	False positive
18.14666	4.181632	0.004426	UP	225.1486	12.45583	2.353950636	False positive
18.06768	4.175339	0.000794	UP	255.2028	4.312133	3.099976553	False positive
17.6635	4.142699	0.000681	UP	195.1448	3.496233	3.166798825	False positive
17.6366	4.1405	0.000435	UP	594.1991	9.395342	3.361485672	False positive
16.97669	4.085484	5.47E-05	UP	106.0864	6.962617	4.261689251	False positive
16.45742	4.040666	0.000266	UP	866.4985	5.996283	3.574823142	False positive

Table S8. MOF list for trimebutine metabolism by bacterial community. The identification of false positives was detailed in the method section. Individual peaks were manually verified. UP: upregulation; mzmed: the median of the peaks' m/z values; rtmed: the median of the peaks' retention times.

fold	log ₂ fold	pvalue	updown	mzmed	rtmed	-log ₁₀ pval	note
5209.131	12.34683	0.001656831	UP	167.031	6.41755	2.78072187	Mass fragment
1336.61	10.38436	2.4415E-07	UP	181.046	6.67575	6.612342493	Mass fragment
1268.504	10.30891	5.90558E-05	UP	822.4668	6.1201	4.228737508	False positive
581.5771	9.183827	1.2538E-06	UP	329.0703	6.67105	5.901773408	False positive
581.2151	9.182928	4.15922E-05	UP	374.1947	6.681517	4.380988318	Hit
544.1947	9.087979	2.58455E-07	UP	329.136	6.680483	6.5876144	Mass fragment
534.5443	9.062166	0.000130895	UP	610.3664	6.64855	3.883077319	False positive
534.0013	9.0607	0.002168664	UP	453.3051	9.368683	2.66380776	False positive
354.2733	8.468719	1.83303E-05	UP	330.0743	6.671033	4.736830757	False positive
324.5686	8.34238	0.001129503	UP	315.1213	6.41755	2.947112543	Mass fragment
197.3141	7.62435	3.88302E-05	UP	375.1991	6.681517	4.410829999	Isotope
144.238	7.172307	0.00940429	UP	209.058	3.8398	2.026673992	False positive
121.5589	6.925511	3.07929E-05	UP	330.1402	6.682458	4.511549831	Isotope
120.2803	6.910257	4.47186E-06	UP	225.1472	12.18447	5.349512205	False positive
72.15727	6.173073	0.001157686	UP	168.0339	6.41685	2.936409118	Isotope
60.814	5.926332	6.1349E-05	UP	140.0436	6.681517	4.212192402	Mass fragment
59.41931	5.89286	3.38612E-06	UP	821.4662	6.119917	5.470298099	False positive
58.23169	5.863733	0.000126833	UP	611.3669	6.656267	3.896766804	False positive
45.76779	5.516261	4.62734E-08	UP	182.0502	6.6834	7.334669041	Isotope
43.56254	5.445016	0.000318228	UP	126.027	6.418825	3.497261676	Mass fragment
43.55447	5.444749	0.004174368	UP	186.1815	10.25248	2.379409263	False positive
36.37773	5.184983	9.70706E-05	UP	131.0825	6.681517	4.012912143	Mass fragment
35.71557	5.158481	0.001952302	UP	168.0651	3.490067	2.709452948	False positive
35.20489	5.137704	1.9014E-05	UP	866.5062	5.713717	4.720926941	False positive
32.25519	5.011459	0.002120652	UP	220.1658	10.18578	2.673530505	False positive
30.68979	4.939687	0.004929615	UP	867.4912	5.738367	2.307186968	False positive
25.23646	4.657438	2.53547E-05	UP	331.1421	6.681	4.595941526	Isotope
24.9265	4.639609	3.06297E-05	UP	496.2783	6.003817	4.513857174	False positive
20.29698	4.343193	0.001040279	UP	867.5039	5.455367	2.982850003	False positive
20.26239	4.340733	0.001535065	UP	316.1243	6.402383	2.813873179	Isotope
20.23341	4.338668	0.000192332	UP	203.1135	7.55385	3.715947919	False positive
19.6671	4.297712	0.000220608	UP	190.1057	3.439983	3.656377831	False positive
17.68191	4.144202	0.00047092	UP	866.499	6.136492	3.327052696	False positive
17.4426	4.124543	0.000452278	UP	158.0634	3.540033	3.344594483	False positive

Table S9. MOF list for trimethobenzamide metabolism by bacterial community. The identification of false positives was detailed in the method section. Individual peaks were manually verified. UP: upregulation; mzmed: the median of the peaks' m/z values; rtmed: the median of the peaks' retention times.

fold	log ₂ fold	pvalue	updown	mzmed	rtmed	-log ₁₀ pval	note
144.3315	7.173242	2.5108E-05	UP	272.2719	9.91115	4.600188598	False positive
98.85942	6.627307	0.003556727	UP	453.3088	9.6613	2.448949482	False positive
66.8217	6.062245	0.008446586	UP	786.5958	11.51326	2.073318811	False positive
64.88705	6.019859	0.008008553	UP	785.5926	11.51327	2.096445952	False positive
54.68292	5.773018	4.58598E-05	UP	261.0907	5.8725	4.338567643	False positive
42.72273	5.416932	0.007540369	UP	129.0658	4.003283	2.122607397	False positive
41.5321	5.376155	0.003882272	UP	312.2898	9.6613	2.410914019	False positive
38.06628	5.250442	0.004339942	UP	807.5744	11.51327	2.362516105	False positive
35.05174	5.131414	0.004094287	UP	302.3052	11.68017	2.38782173	False positive
29.28415	4.872048	0.001162135	UP	186.1853	10.54536	2.934743448	False positive
28.74204	4.84509	0.001109868	UP	187.1887	10.54543	2.954728761	False positive
27.4732	4.779953	0.000837679	UP	225.1484	12.46453	3.076922146	False positive
27.27484	4.769499	2.47164E-05	UP	467.3247	10.62878	4.607015597	False positive
25.06701	4.647718	1.88698E-05	UP	182.0494	8.876467	4.724231823	False positive
25.06672	4.647701	0.007259842	UP	242.1505	4.871183	2.139072825	False positive
21.13775	4.40175	0.000942412	UP	254.1543	10.46195	3.025759067	False positive
19.55563	4.289512	0.000237832	UP	361.1762	5.456033	3.623729548	Hit
19.40128	4.27808	0.000946348	UP	220.1697	10.47866	3.023949004	False positive
18.08939	4.177072	4.23257E-05	UP	270.1898	3.335817	4.373395745	False positive
18.04442	4.173481	0.000222245	UP	170.06	10.59537	3.65316785	False positive
17.72505	4.147718	7.44448E-06	UP	347.1613	5.037867	5.128165607	Hit
16.72027	4.063526	1.23157E-06	UP	494.3409	6.006017	5.909541258	False positive

Table S10. MOF list for iloperidone metabolism by bacterial community. The identification of false positives was detailed in the method section. Individual peaks were manually verified. UP: upregulation; mzmed: the median of the peaks' m/z values; rtmed: the median of the peaks' retention times.

fold	log2fold	pvalue	updown	mzmed	rtmed	neg log10(p-value)	Notes
20.4806141	4.35618707	2.0393E-06	UP	654.4505484	5.467966667	5.690518833	False positive
19.7071085	4.30064421	2.03527E-05	UP	619.7841396	4.260708333	4.691377084	False positive
311.819748	8.28456849	2.23475E-05	UP	431.1582685	7.559691667	4.650771177	False positive
132.255373	7.04718252	8.0054E-05	UP	431.206983	7.639525	4.096617108	Isotope
26.130129	4.70764234	8.16394E-05	UP	444.2056429	7.668	4.088100031	False positive
95.6710467	6.58001048	8.93156E-05	UP	430.2054669	7.612183333	4.049072697	Hit
19.7771704	4.30576413	9.46846E-05	UP	620.7873463	4.250966667	4.023720703	False positive
35.742346	5.15956243	0.000119377	UP	444.1638124	7.745333333	3.923077893	Hit
231.042427	7.85201399	0.000135828	UP	432.2185836	7.3362	3.867011278	Hit
80.0377821	6.32260928	0.000206442	UP	433.2216481	7.3362	3.685202611	Isotope
20.0290698	4.32402351	0.000254301	UP	1239.5622	4.23705	3.594651143	False positive
84.3219177	6.39783577	0.000310871	UP	432.2088355	7.640866667	3.507419579	False positive
19.5797146	4.29128783	0.000340316	UP	273.1055355	6.487333333	3.46811813	False positive
16.0410327	4.00369512	0.000350702	UP	1238.559544	4.235825	3.455061941	False positive
21.6454641	4.43599283	0.000415087	UP	264.1394203	7.634058333	3.381860942	False positive
29.3509112	4.87533339	0.000442344	UP	563.2924469	5.869766667	3.354240063	False positive
63.9824147	5.99960354	0.000599504	UP	562.2899767	5.869766667	3.222207561	False positive
36.7470899	5.1995581	0.000894106	UP	201.0521504	3.334666667	3.048611155	False positive
33.8881538	5.08270914	0.001020816	UP	236.1081649	7.634058333	2.991052697	False positive
174.906022	7.45043615	0.001132754	UP	72.05285397	3.351266667	2.945864231	False positive
182.011149	7.50788302	0.00145775	UP	461.3296625	2.81875	2.836316829	False positive
24.2095988	4.59750726	0.001648211	UP	433.1696702	7.576308333	2.782987108	False positive
24.8639661	4.63598454	0.002104601	UP	118.064951	8.018066667	2.676830283	False positive
16.8416676	4.07396309	0.002324072	UP	561.6564997	4.667116667	2.633750425	False positive
17.5181174	4.13077583	0.002417728	UP	190.1070851	3.418733333	2.616592572	False positive
23.4867569	4.55377561	0.005539692	UP	200.1282068	6.355808333	2.256514373	False positive
40.241185	5.33060088	0.005805269	UP	453.3078409	9.7515	2.236177679	False positive
43.6761039	5.44877226	0.006278524	UP	485.7585774	3.97105	2.202142447	False positive

Table S11. MOF list for iloperidone metabolism by *Morganella morganii* D82. Ilo-430 (m/z = 430.2070) is below the strict fold change cutoff (≥ 16 fold), with an 11-fold upregulation. UP: upregulation; mzmed: the median of the peaks' m/z values; rtmed: the median of the peaks' retention times.

fold	log ₂ fold	pvalue	updown	mzmed	rtmed	-log ₁₀ pval	note
16.07314	4.00658	5.07E-05	UP	231.059	9.5953	4.295029	False positive
33.88136	5.08242	0.000151	UP	144.0814	7.828533	3.819913	False positive
22.6397	4.500783	0.000221	UP	145.0837	7.828533	3.655872	False positive
41.93144	5.38996	0.001351	UP	508.2329	7.578517	2.869237	False positive
17.62254	4.13935	0.001426	UP	131.1248	7.186825	2.845984	False positive
120.2736	6.910177	0.001523	UP	507.2309	7.578517	2.817251	False positive
17.84826	4.157711	0.001872	UP	146.0602	7.761867	2.727639	False positive
695.9533	9.442847	0.004379	UP	493.2443	7.6952	2.358632	Isotope
36444.01	15.15339	0.004383	UP	491.2372	7.6952	2.358203	Hit
4365.425	12.09191	0.004896	UP	492.2401	7.6952	2.310198	Isotope
21.15554	4.402964	0.005318	UP	164.1074	7.478517	2.274249	False positive
54.65599	5.772308	0.00554	UP	453.1825	10.76203	2.256525	False positive
17.60261	4.137718	0.006216	UP	431.2082	7.36185	2.206505	False positive
90.26909	6.49616	0.006529	UP	466.2938	11.12873	2.185121	False positive
1684.536	10.71814	0.006956	UP	477.2216	7.528533	2.157617	Hit
18.34382	4.197223	0.007032	UP	432.2103	7.361858	2.152918	False positive
76.07156	6.249285	0.007213	UP	478.2235	7.536858	2.141864	Isotope
10.89819	3.446016	0.00585	UP	430.2070	7.345183	2.232864	Hit

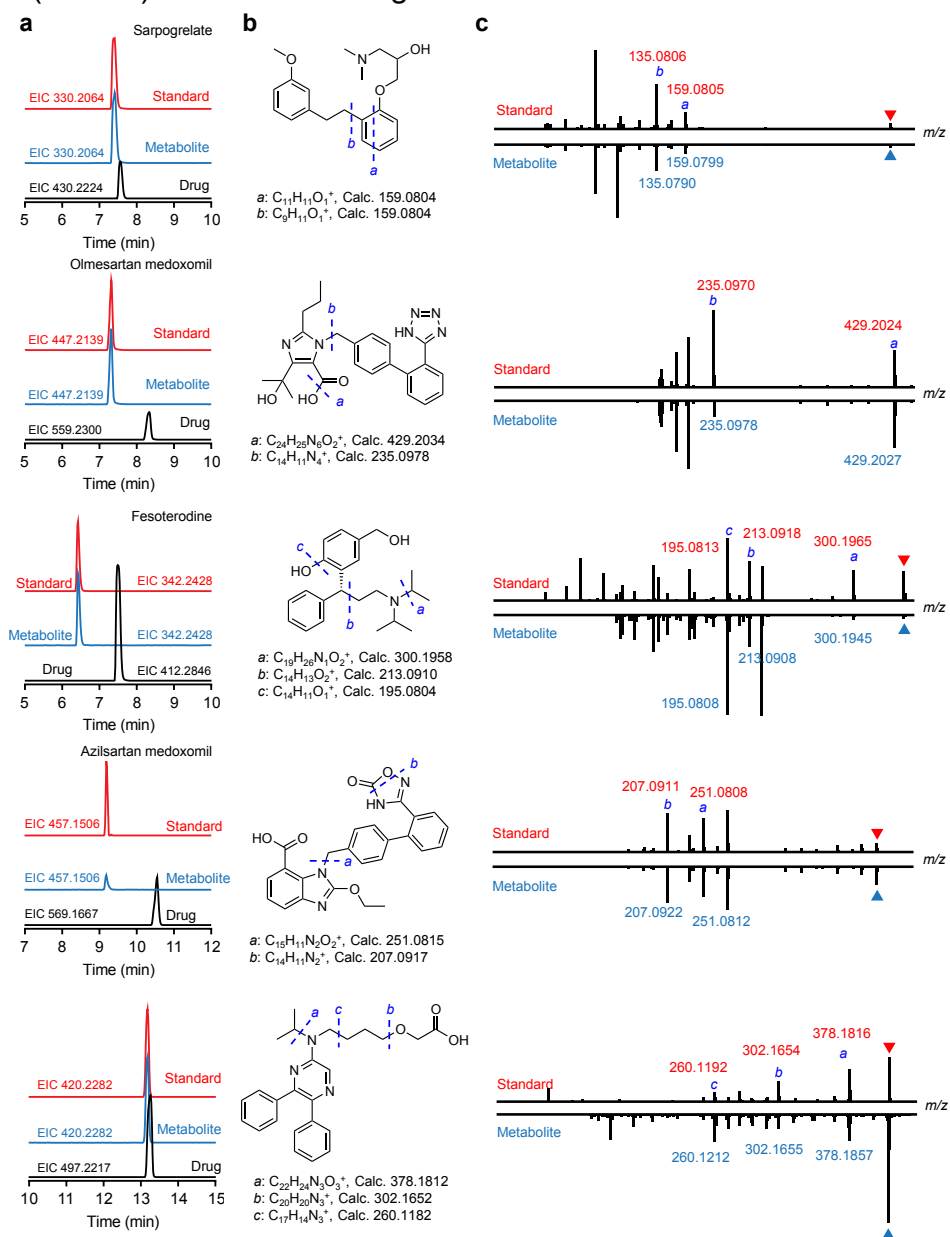
3. Structure elucidation section

3.1 Structure elucidation of metabolites from prodrug metabolism by MS² analyses and chemical standard comparisons.

The chemical transformation through ester/amide hydrolysis was employed to characterize the metabolites of five prodrugs (sarpogrelate, olmesartan medoxomil, fesoterodine, azilsartan medoxomil, and selexipag), as detailed in the method section. A comparison of retention times (t_R) revealed that the metabolites of all five prodrugs exhibited identical retention times to standards (Supplementary Fig. S2a). Furthermore, the confirmation of metabolite identity was reinforced through direct MS/MS comparison with the corresponding standards. Detailed information regarding the selected fragments for this comparison can be found in Supplementary Fig. S2. The comparison between MS/MS spectra revealed similar fragmentation patterns between the metabolites and the corresponding standards.

For sarpogrelate metabolite, two fragments were identified: $C_{11}H_{11}O_1^+$ ($m/z_{calc.}$ 159.0804) and $C_9H_{11}O_1^+$ ($m/z_{calc.}$ 135.0804). Specifically, for the standard, $m/z_{obs.}$ 159.0805; $m/z_{obs.}$ 135.0806, and for the metabolite, $m/z_{obs.}$ 159.0799; $m/z_{obs.}$ 135.0790. Regarding olmesartan medoxomil metabolite, two fragments were successfully identified: $C_{24}H_{25}N_6O_2^+$ ($m/z_{calc.}$ 429.2034) and $C_{14}H_{11}N_4^+$ ($m/z_{calc.}$ 235.0978). For the standard, the observed m/z values were 429.2024 and 235.0970. For the metabolite, the observed m/z values were 429.2027 and 235.0978. In fesoterodine metabolite analysis, three fragments were identified: $C_{19}H_{26}N_1O_2^+$ ($m/z_{calc.}$ 300.1958), $C_{14}H_{13}O_2^+$ ($m/z_{calc.}$ 213.0910) and $C_{14}H_{11}O_1^+$ ($m/z_{calc.}$ 195.0804). Observed fragments showed minor deviations. Standard: $m/z_{obs.}$ 300.1965; $m/z_{obs.}$ 213.0918; $m/z_{obs.}$ 195.0813. Metabolite: $m/z_{obs.}$ 300.1945; $m/z_{obs.}$ 213.0908; $m/z_{obs.}$ 195.0808. In the analysis of azilsartan medoxomil metabolite, two distinct fragments were identified: $C_{15}H_{11}N_2O_2^+$ (with a calculated m/z of 251.0815) and $C_{14}H_{11}N_2^+$ (with a calculated m/z of 207.0917). The observed fragments displayed slight variations as follows: In the standard case, the m/z was observed to be 251.0808 and 207.0911. For the metabolite, the observed m/z values were 251.0812 and 207.0922. In the investigation of selexipag metabolite, the analysis revealed the presence of three distinctive fragments, $C_{22}H_{24}N_3O_3^+$ with a calculated m/z of 378.1812, $C_{20}H_{20}N_3^+$ with a calculated m/z of 302.1652, and $C_{17}H_{14}N_3^+$ with a calculated m/z of 260.1182. The observed fragments displayed minor deviations from their calculated values. In the standard reference scenario, the m/z values were measured at 378.1816, 302.1654, and 260.1192, respectively. In the case of the metabolite, the observed m/z values were 378.1857, 302.1655, and 260.1212.

Fig. S2. Structural characterization of drug metabolites generated from pro-drug hydrolysis through the human gut bacterial collection. (a) EIC comparison of standards and drug metabolites. Black traces: EICs (± 20 ppm) of drug standards. $[M+H]^+$, m/z 430.2224 for sarpogrelate; $[M+H]^+$, m/z 559.2300 for olmesartan medoxomil; $[M+H]^+$, m/z 412.2846 for fesoterodine; $[M+H]^+$, m/z 569.1667 for azilsartan medoxomil; $[M+H]^+$, m/z 497.2217 for selezipag. Blue traces indicate EICs (± 20 ppm) of drug metabolites, while red traces represent synthetic/commercial standards. $[M+H]^+$, m/z 330.2064 for sarpogrelate metabolite; $[M+H]^+$, m/z 447.2139 for olmesartan medoxomil metabolite; $[M+H]^+$, m/z 342.2428 for fesoterodine metabolite; $[M+H]^+$, m/z 457.1506 for azilsartan medoxomil metabolites; $[M+H]^+$, m/z 420.2282 for selezipag metabolite. (b) MS/MS fragment annotation. (c) MS/MS comparison between standards (top) and drug metabolites (bottom) with selected fragments.



3.2 Structural elucidation of metabolites from six previously undocumented bacterial biotransformations in drug metabolism using MS/MS analysis.

After identifying the MOFs through selection, we conducted targeted MS/MS analyses to obtain additional structural information for all MOFs associated with the six drugs (SB756050, ozanimod, GSK1292263, ponesimod, trimethobenzamide, and trimebutine). Due to either the insufficient intensity of metabolites or the co-elution of metabolites with media components or bacterial metabolites, we selectively determined only those MOFs that could provide reliable data for structure elucidation. The determined metabolites are listed (Supplementary Fig. S3). We utilized the Spectral Identification of Research Compounds by Unified Structure (SIRIUS)²⁰ to assist in supporting molecular formulas of the major MOFs (Supplementary Table S12). Based on the determined molecular formulae, we were able to identify several patterns, as described in the main content.

Fig. S3. Mass differences corresponding to six drugs and their structural modification

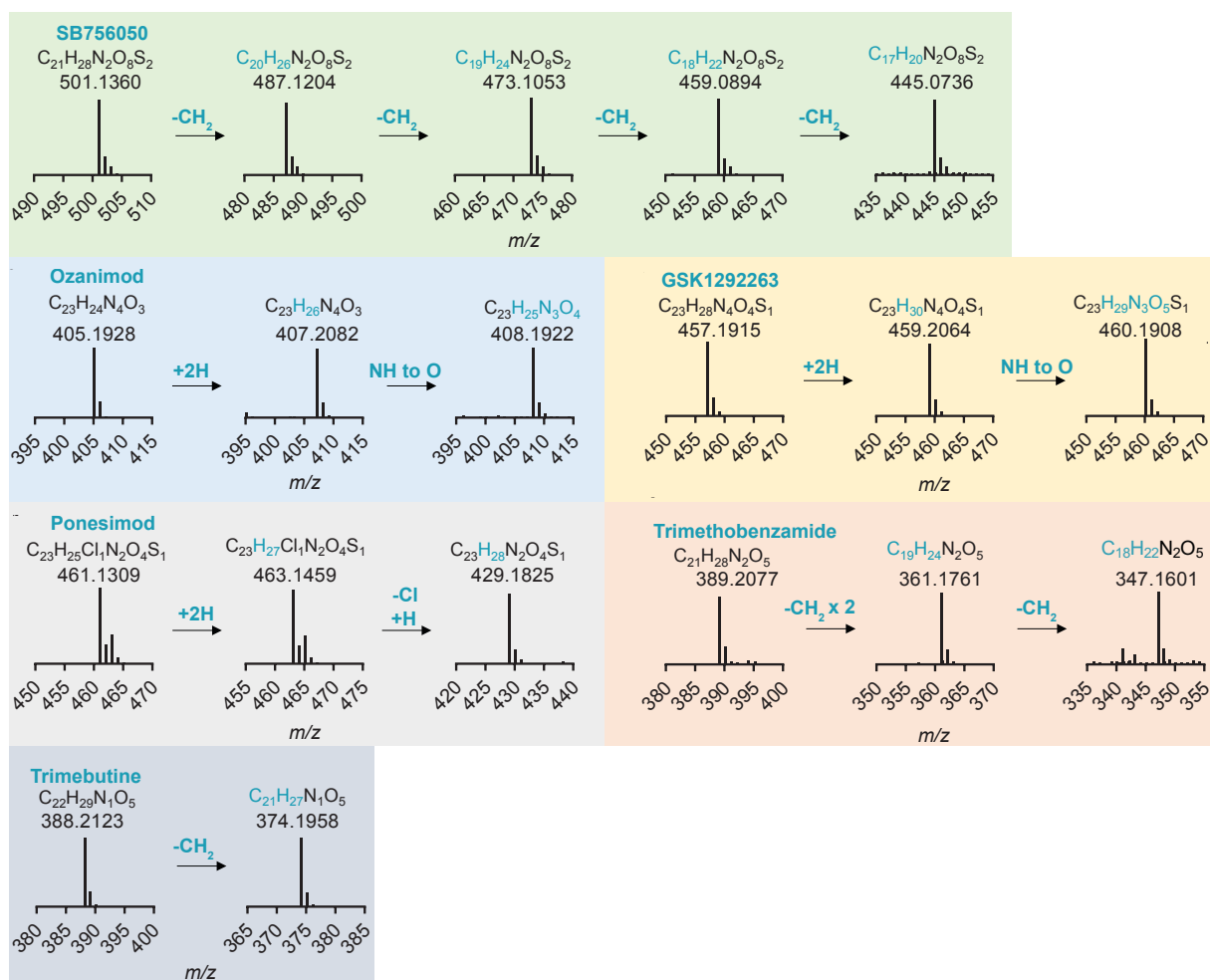


Table S12. Molecular formula determination of MOFs obtained from drug metabolism.

Drug	MOFs	Molecular formula	Notes
SB756050	487.1204	C ₂₀ H ₂₆ N ₂ O ₈ S ₂	SIRIUS MS ² analysis
	473.1053	C ₁₉ H ₂₄ N ₂ O ₈ S ₂	SIRIUS MS ² analysis
	459.0894	C ₁₈ H ₂₂ N ₂ O ₈ S ₂	SIRIUS MS ² analysis
	445.0736	C ₁₇ H ₂₀ N ₂ O ₈ S ₂	MS-based prediction
Ozanimod	407.2082	C ₂₃ H ₂₆ N ₄ O ₃	SIRIUS MS ² analysis
	408.1922	C ₂₃ H ₂₅ N ₃ O ₄	SIRIUS MS ² analysis
GSK1292263	459.2064	C ₂₃ H ₃₀ N ₄ O ₄ S	SIRIUS MS ² analysis
	460.1908	C ₂₃ H ₂₉ N ₃ O ₅ S	SIRIUS MS ² analysis
Ponesimod	463.1459	C ₂₃ H ₂₇ ClN ₂ O ₄ S	SIRIUS MS ² analysis
	463.1459	C ₂₃ H ₂₇ ClN ₂ O ₄ S	SIRIUS MS ² analysis
	429.1825	C ₂₃ H ₂₈ N ₂ O ₄ S	Predicted based on
	429.1825	C ₂₃ H ₂₈ N ₂ O ₄ S	MS isotope pattern
Trimethobenzamide	361.1761	C ₁₉ H ₂₄ N ₂ O ₅	SIRIUS MS ² analysis
	347.1601	C ₁₈ H ₂₂ N ₂ O ₅	SIRIUS MS ² analysis
Trimebutine	374.1958	C ₂₁ H ₂₇ NO ₅	MS-based prediction

HRMS analyses support predictions of the molecular structures of metabolites but do not offer complete structural determination. In the case of trimebutine, for instance, demethylation could occur at the *N*-dimethyl motif, resulting in the generation of reported host kidney elimination products nortrimebutine and *N*-didesmethyltrimebutine^{21–23}. Alternatively, *O*-demethylation at the *O*-methyl group could take place. Regarding ponesimod metabolism, hydrogenation may take place at the imine or double bond, leading to the formation of amine or thiazol-2-imine, respectively. Moreover, the hydrogenation of ilo-430 presented two potential positions for ketone reduction. By comparing parent drug with drug metabolites and through the assistance of SIRIUS, analysis of the tandem mass spectra of the drug metabolites allowed the annotation of drug metabolite fragments. By analyzing the SIRIUS-annotated fragments, it is possible to probe for shared fragments, thereby facilitating identification of specific positional modifications. The fundamental principles of MS/MS-based structural elucidation were outlined in the main content.

With the assistance of SIRIUS, the assignments for the MS/MS spectra are depicted in Supplementary Figs. S4-S24. For the structural elucidation of demethylation products derived from SB756050, trimebutine, and trimethobenzamide metabolism, although multiple metabolites were observed, we focused our characterization efforts on one specific metabolite. This decision was based on the following considerations: In the case of trimethobenzamide and trimebutine metabolism, *O*-methyl demethylation events were found to occur at the aromatic rings instead of the *N*-methyl groups, as further described below. However, determining the precise demethylation positions proved challenging. Additionally, the series demethylation of the *O*-methyl groups could be represented by the methylation of a single *O*-methyl moiety. As a result, for each drug, we chose one metabolite for which a detailed MS/MS-based structural elucidation is provided in the main content (Fig. 3c, trimethobenzamide-361, SB-473, and trimebutine-374).

All four demethylation products of SB756050 were identified, with one *O*-demethylation product being the predominant drug metabolite (Extended data Fig. 5c). In the case of trimebutine, only one *O*-demethylation product was detected (Extended data Fig. 5g), but the specific position of the demethylation could not be determined. For

trimethobenzamide, all aromatic O-demethylation products were detected (Extended data Fig. 5d), while the mono-O-demethylation product was not observed. We found positive mass differences of +2.0 Da (+2H) between ponesimod and two metabolites (Extended Data Fig. 5b). Two ponesimod metabolites containing the reduced imine motif were identified with a 1:1 ratio (Extended Data Fig. 5b), which suggests the existence of possible diastereomers (Extended data Fig. 9). Additionally, their dehalogenation (-Cl, Extended data Fig. 9) products were observed (Extended Data Fig. 5b).

For example, we observed mass losses of CH₂ in the metabolites derived from SB756050, trimebutine, and trimethobenzamide, supporting demethylation (-CH₂, Fig. 3b). Increases of 2.0150 Da and 2.9993 Da were also observed for both GSK1292263 and ozanimod (Fig. 3b), supporting that the metabolites could be *seco*-1,2,4-oxadiazole products formed through 1,2,4-oxadiazole reduction, followed by hydrolysis of the imine to the resulting ketone. Additionally, we found positive mass differences of +2.0150 Da (+2H) between ponesimod and two metabolites supporting a hydrogenation event. Finally, the loss of 33.9634 Da corresponds to the removal of chlorine and the addition of a proton. This, along with the loss of the characteristic isotope pattern of the chlorine substituent in ponesimod, confirms the drug's dehalogenation (Supplementary Fig. S22c).

Figure S4. Fragmentation tree that contains the key observed MS/MS fragments of SB756050 (m/z 501.1348) as revealed by SIRIUS. A representative charge state is shown.

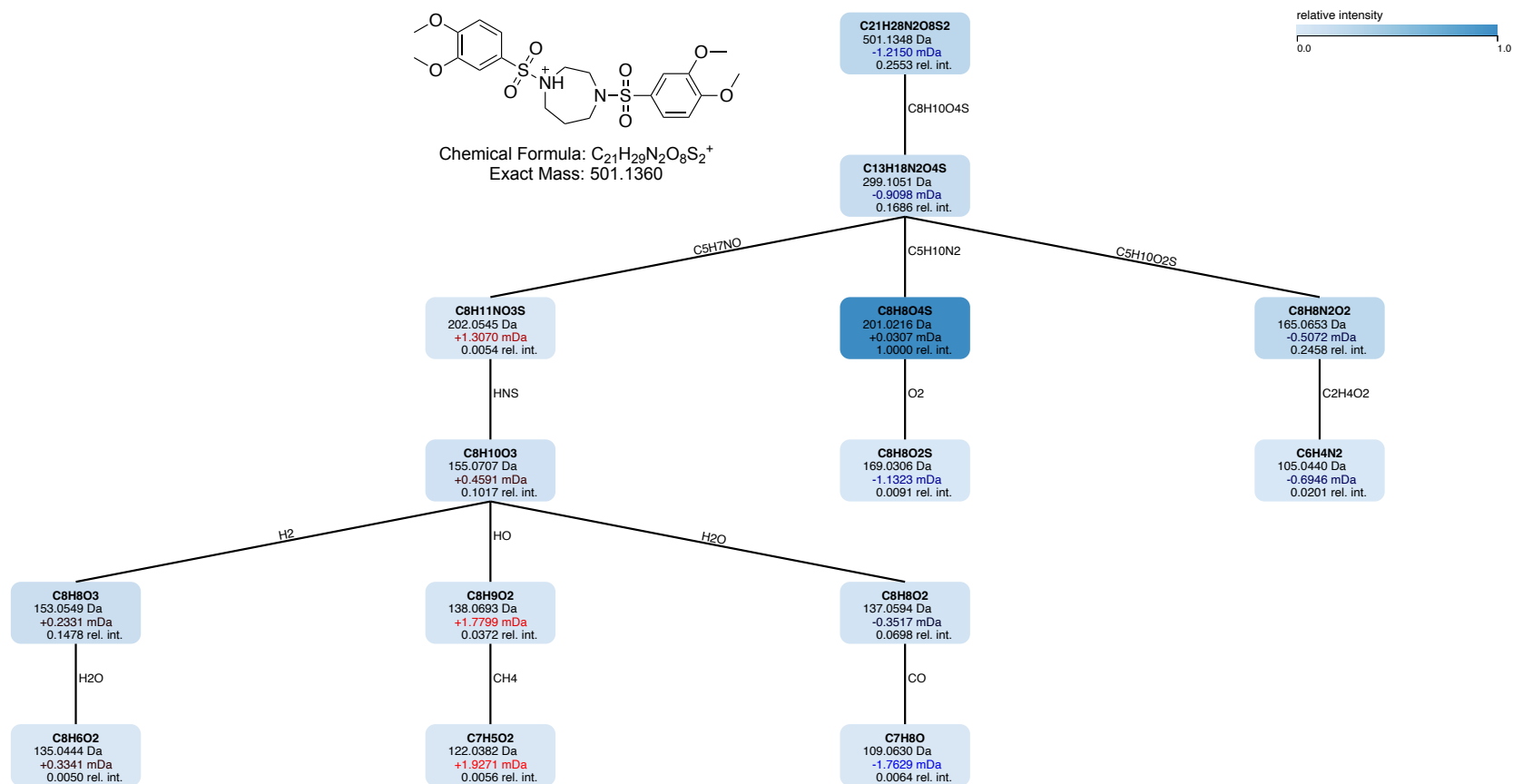


Figure S5. Fragmentation tree that contains the key observed MS/MS fragments of a SB756050 metabolite (SB-487, m/z 487.1193) as revealed by SIRIUS. A representative charge state is shown. The chemical structure shown represents only one possible structure with O-demethylation event(s), as the exact position(s) of demethylation could not be determined by MS/MS analysis.

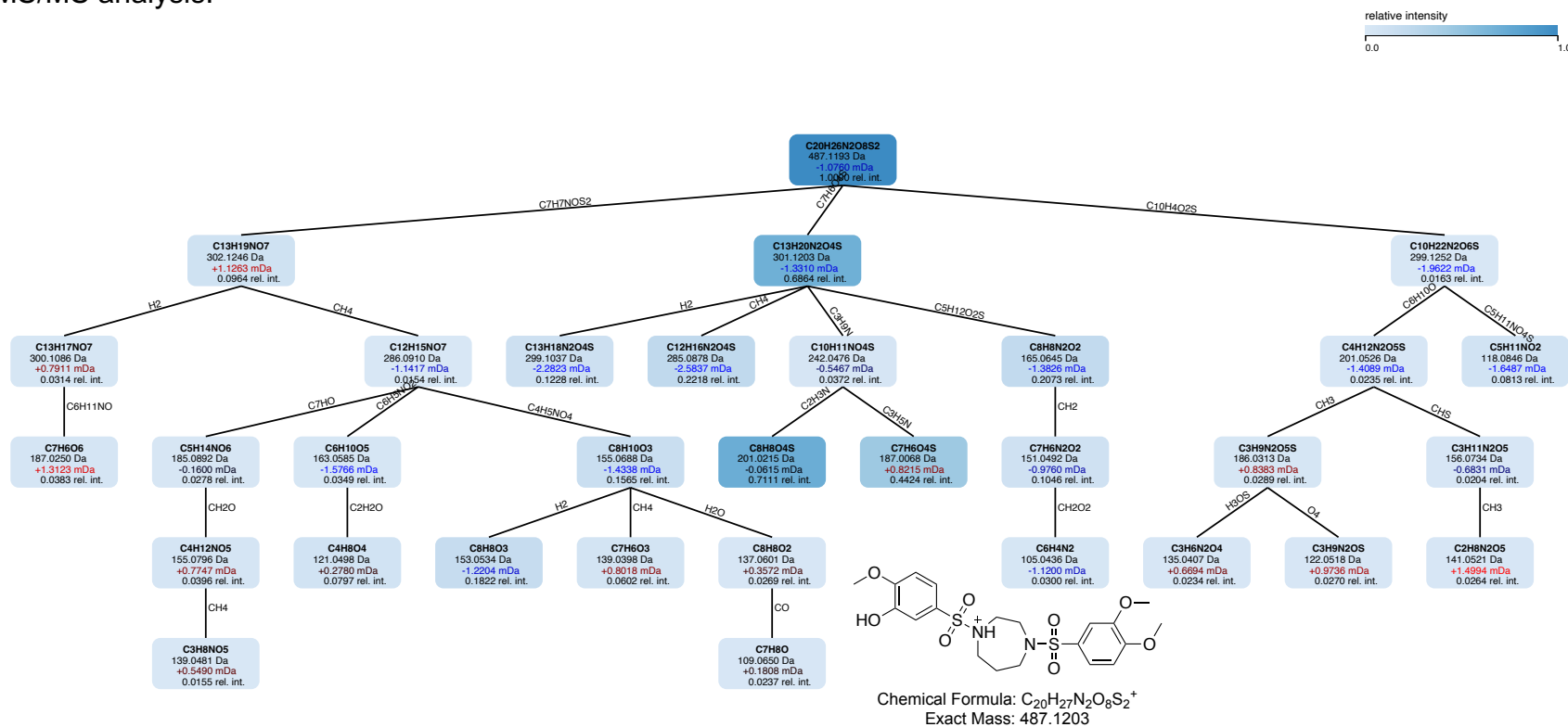
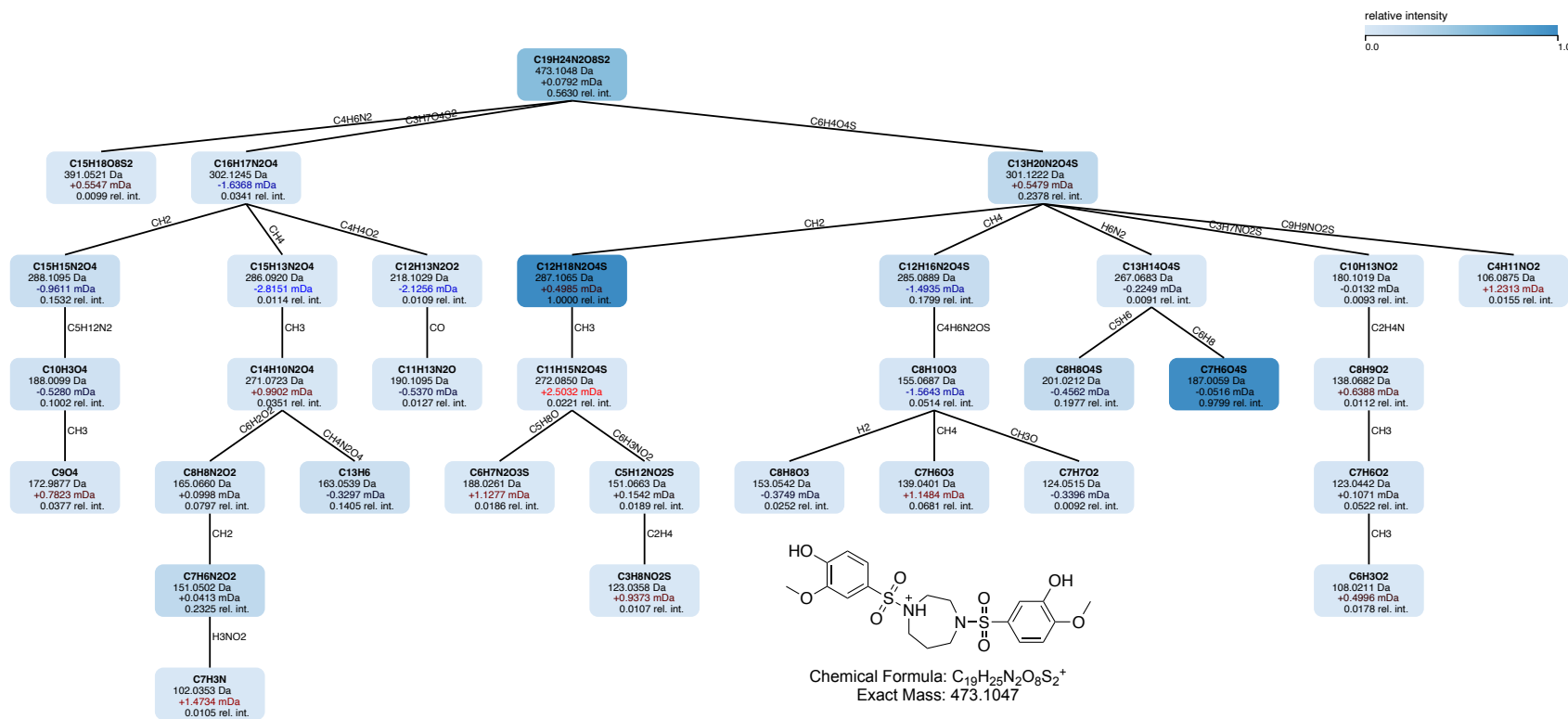


Figure S6. Fragmentation tree that contains the key observed MS/MS fragments of a SB756050 metabolite (SB-473, m/z 473.1048) as revealed by SIRIUS. A representative charge state is shown. The chemical structure shown represents only one possible structure with *O*-demethylation event(s), as the exact position(s) of demethylation could not be determined by MS/MS analysis.



Chemical Formula: $C_{18}H_{23}N_2O_8S_2^+$
Exact Mass: 459.0890

relative intensity

0.0 1.0

C18H22N2O8S2
459.0876 Da
-1.4261 mDa
0.0108 rel. int.

C6H4O4S

C12H18N2O4S
287.1066 Da
+0.6254 mDa
1.0000 rel. int.

CH2 CH3 C5H10N2OS

C11H16N2O4S
273.0902 Da
-0.1086 mDa
0.9155 rel. int.

C11H15N2O4S
272.0826 Da
+0.1170 mDa
0.0155 rel. int.

C7H8O3
141.0566 Da
+1.9926 mDa
0.0446 rel. int.

C2H6O2 C4H10N2 C4O4S

C9H10N2O2S
211.0539 Da
+0.2853 mDa
0.0190 rel. int.

C7H6O4S
187.0065 Da
+0.5537 mDa
0.7141 rel. int.

C7H16N2
129.1389 Da
+0.3082 mDa
0.0135 rel. int.

H2O CH4O

C7H6O2
123.0445 Da
+0.3953 mDa
0.1243 rel. int.

C6H4O2
109.0302 Da
+1.7784 mDa
0.0310 rel. int.

C2H4S C3H6S OS C2H4 CH3

C7H6N2O2
151.0513 Da
+1.0517 mDa
0.7620 rel. int.

C6H4N2O2
137.0336 Da
-0.9397 mDa
0.1306 rel. int.

C7H6O3
139.0393 Da
+0.2938 mDa
0.2989 rel. int.

C5H12N2
101.1069 Da
-0.4331 mDa
0.0554 rel. int.

C6H3O2
108.0197 Da
-0.8927 mDa
0.0302 rel. int.

CO

C6H6N2O
123.0571 Da
+1.8437 mDa
0.0274 rel. int.

Figure S8. Proposed annotation of key observed MS/MS fragments SB756050 (m/z 501.1360). Representative charge states are shown. Fragment A: $m/z_{\text{calcd.}}$ 299.1060, $m/z_{\text{obs.}}$ 299.1067; Fragment B: $m/z_{\text{calcd.}}$ 201.0216, $m/z_{\text{obs.}}$ 201.0212.

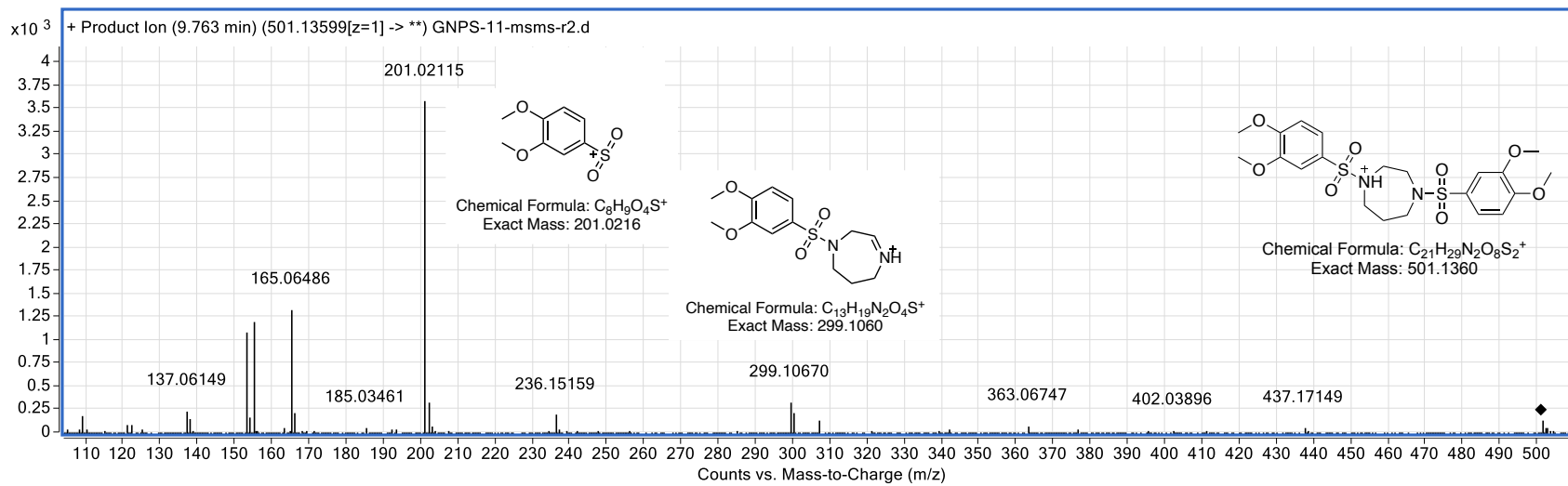


Figure S9. Proposed annotation of key observed MS/MS fragments of a SB756050 metabolite (SB-487, m/z 487.1203). Representative charge states are shown. Fragment A: $m/z_{\text{calcd.}}$ 301.1217, $m/z_{\text{obs.}}$ 301.1194; Fragment B: $m/z_{\text{calcd.}}$ 285.0904, $m/z_{\text{obs.}}$ 285.0910; Fragment C: $m/z_{\text{calcd.}}$ 201.0216, $m/z_{\text{obs.}}$ 201.0200; Fragment D: $m/z_{\text{calcd.}}$ 187.0060, $m/z_{\text{obs.}}$ 187.0061. The chemical structure of SB-487 shown represents only one possible structure with O-demethylation event(s), as the exact position(s) of demethylation could not be determined by MS/MS analysis.

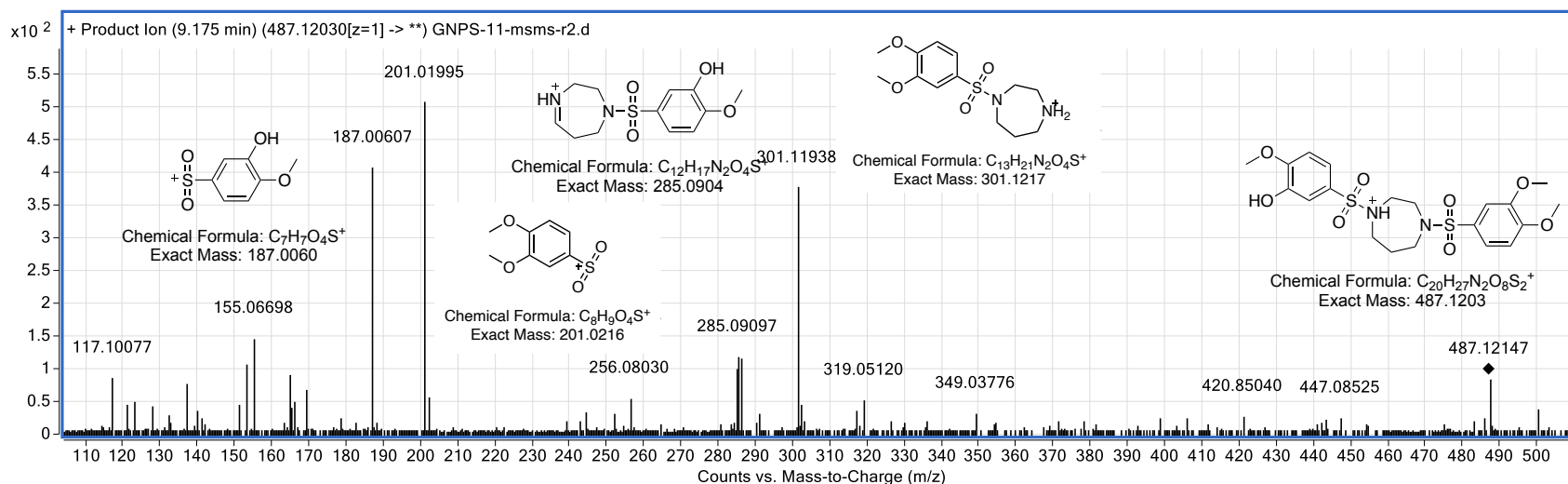


Figure S10. Proposed annotation of key observed MS/MS fragments of a SB756050 metabolite (SB-473, m/z 473.1047). Representative charge states are shown. Fragment A: $m/z_{\text{calcd.}}$ 301.1217, $m/z_{\text{obs.}}$ 301.1222; Fragment B: $m/z_{\text{calcd.}}$ 287.1060, $m/z_{\text{obs.}}$ 287.1065; Fragment C: $m/z_{\text{calcd.}}$ 187.0060, $m/z_{\text{obs.}}$ 187.0059. The chemical structure of SB-473 shown represents only one possible structure with O-demethylation event(s), as the exact position(s) of demethylation could not be determined by MS/MS analysis.

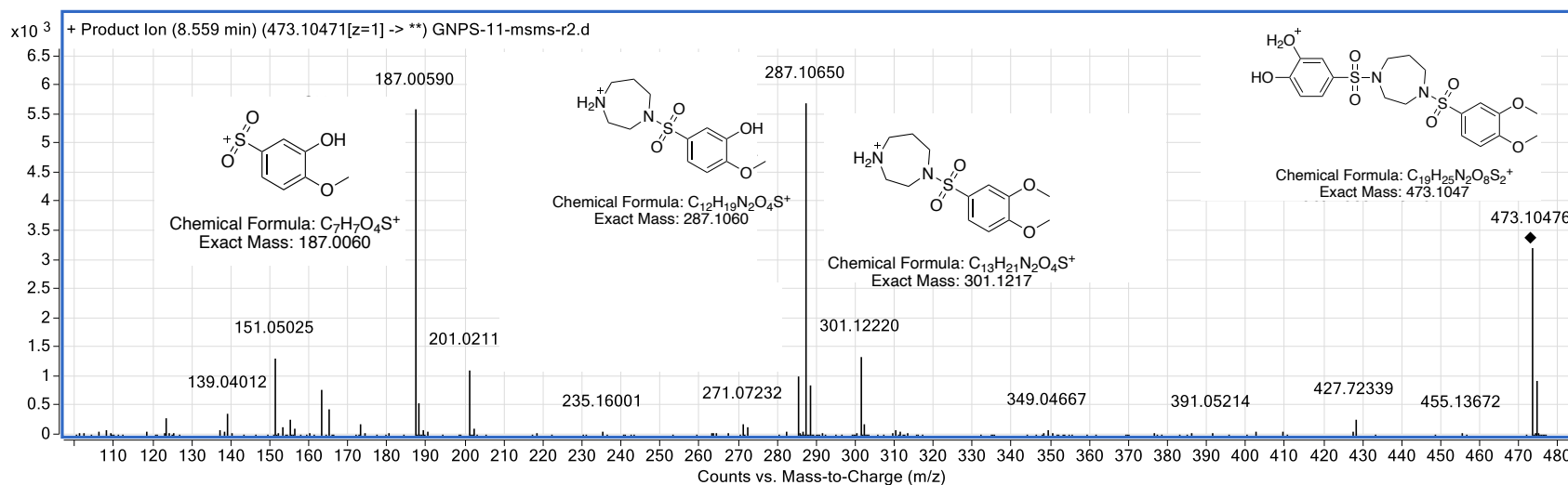


Figure S11. Proposed annotation of key observed MS/MS fragments of a SB756050 metabolite (SB-459, m/z 459.0890). Representative charge states are shown. Fragment A: $m/z_{\text{calcd.}}$ 287.1060, $m/z_{\text{obs.}}$ 287.1062; Fragment B: $m/z_{\text{calcd.}}$ 273.0904, $m/z_{\text{obs.}}$ 273.0903; Fragment C: $m/z_{\text{calcd.}}$ 187.0060, $m/z_{\text{obs.}}$ 187.0057. The chemical structure of SB-459 shown represents only one possible structure with *O*-demethylation event(s), as the exact position(s) of demethylation could not be determined by MS/MS analysis.

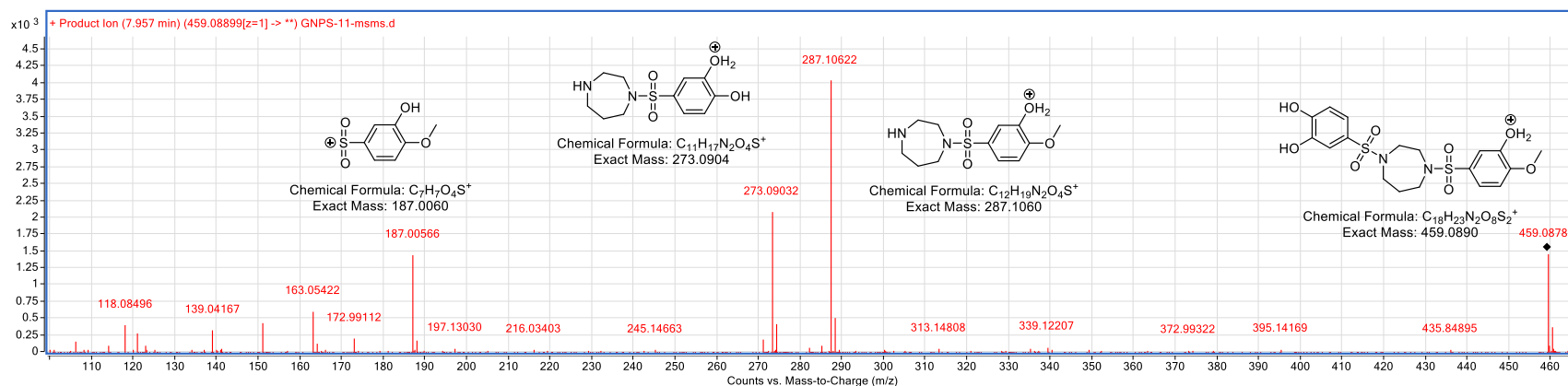


Figure S12. Proposed annotation of key observed MS/MS fragments of a SB756050 metabolite (SB-445, m/z 445.0725). Representative charge states are shown. Fragment A: $m/z_{\text{calcd.}}$ 273.0904, $m/z_{\text{obs.}}$ 273.0879; Fragment B: $m/z_{\text{calcd.}}$ 172.9903, $m/z_{\text{obs.}}$ 172.9892. The chemical structure of SB-445 shown represents only one possible structure with O-demethylation event(s), as the exact position(s) of demethylation could not be determined by MS/MS analysis.

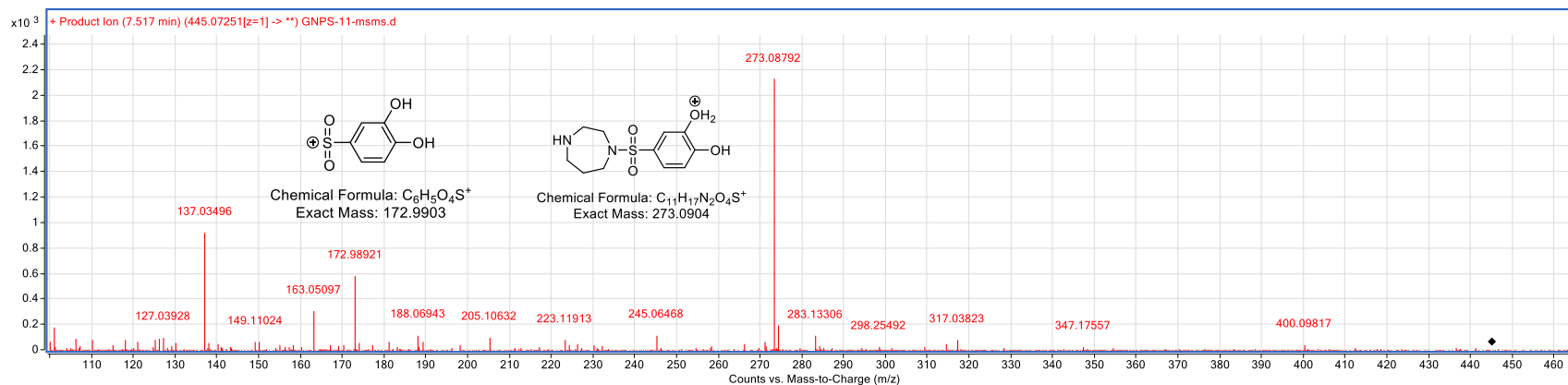


Figure S13. Fragmentation tree that contains the selected observed MS/MS fragments of an ozanimod metabolite (ozanimod-407, m/z 407.2067) as revealed by SIRIUS. A representative charge state is shown.

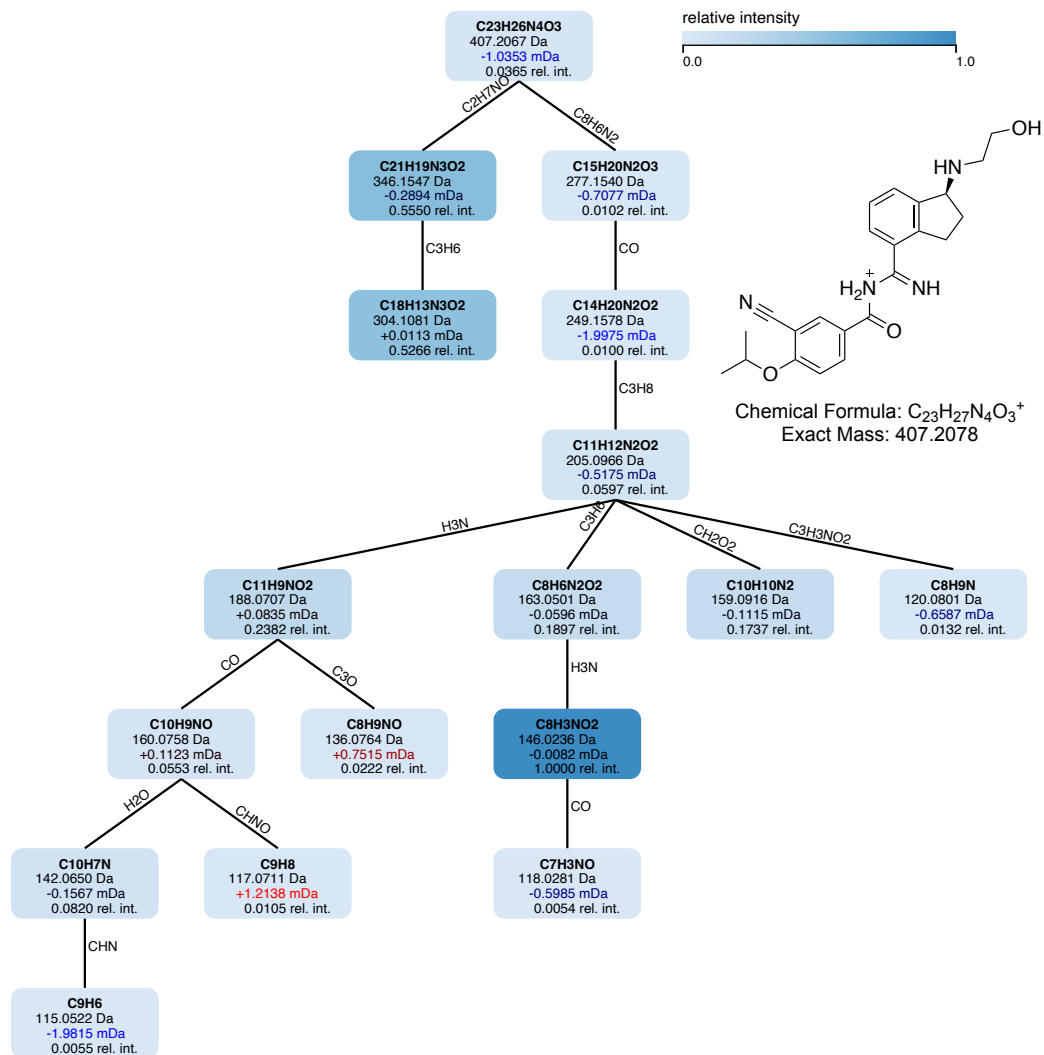


Figure S14. Fragmentation tree that contains the selected observed MS/MS fragments of an ozanimod metabolite (ozanimod-408, m/z 408.1935) as revealed by SIRIUS. A representative charge state is shown.

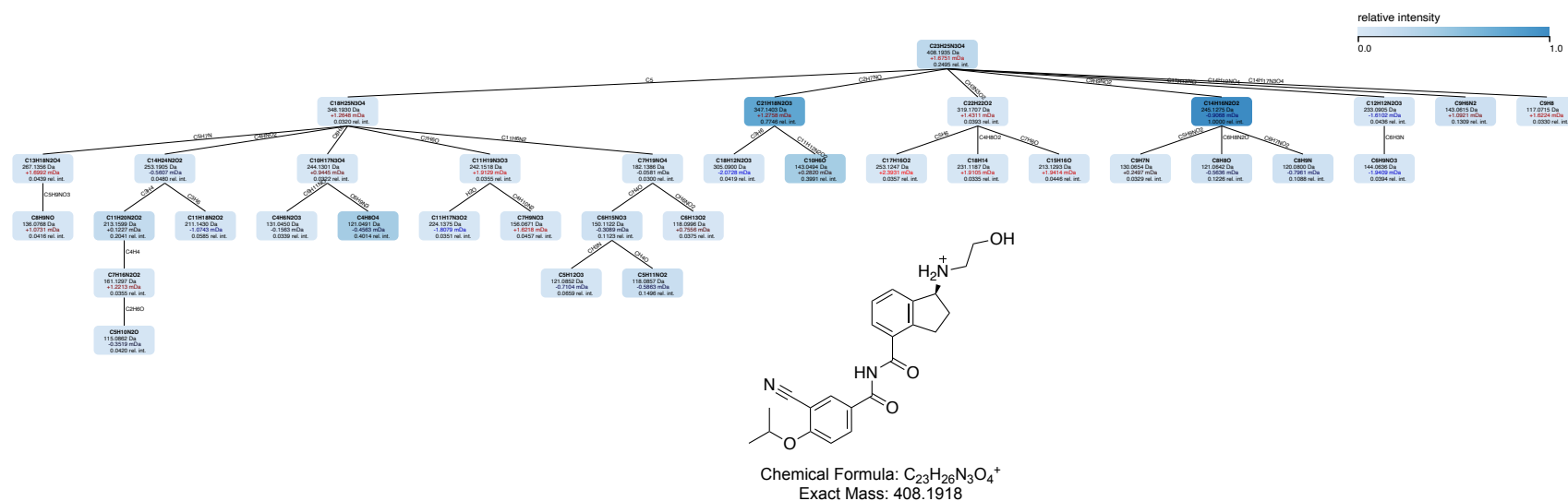


Figure S15. Proposed annotation of selected observed MS/MS fragments of an ozanimod product (ozanimod-407, m/z 407.2077). Representative charge states are shown. Fragment A: $m/z_{\text{calcd.}}$ 346.1550, $m/z_{\text{obs.}}$ 346.1548; Fragment B: $m/z_{\text{calcd.}}$ 304.1081, $m/z_{\text{obs.}}$ 304.1084.

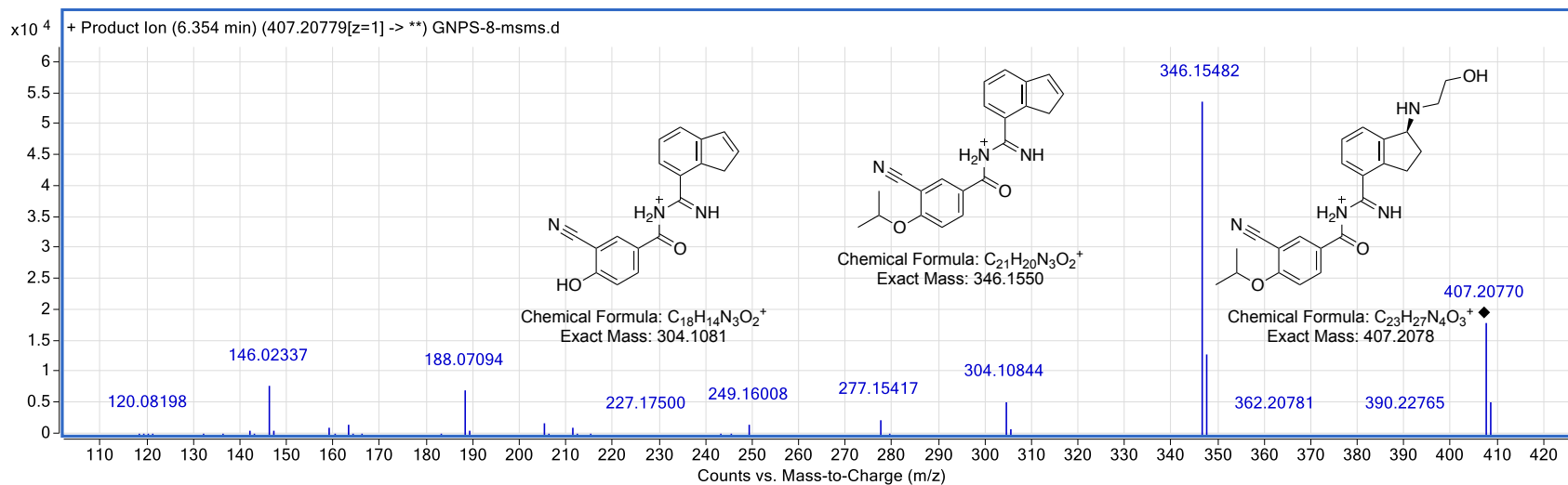


Figure S16. Proposed annotation of selected observed MS/MS fragments of an ozanimod product (ozanimod-408, m/z 408.1935). Representative charge states are shown. Fragment A: $m/z_{\text{calcd.}}$ 347.1390, $m/z_{\text{obs.}}$ 347.1403; Fragment B: $m/z_{\text{calcd.}}$ 305.0921, $m/z_{\text{obs.}}$ 305.0900; Fragment C: $m/z_{\text{calcd.}}$ 143.0491, $m/z_{\text{obs.}}$ 143.0494.

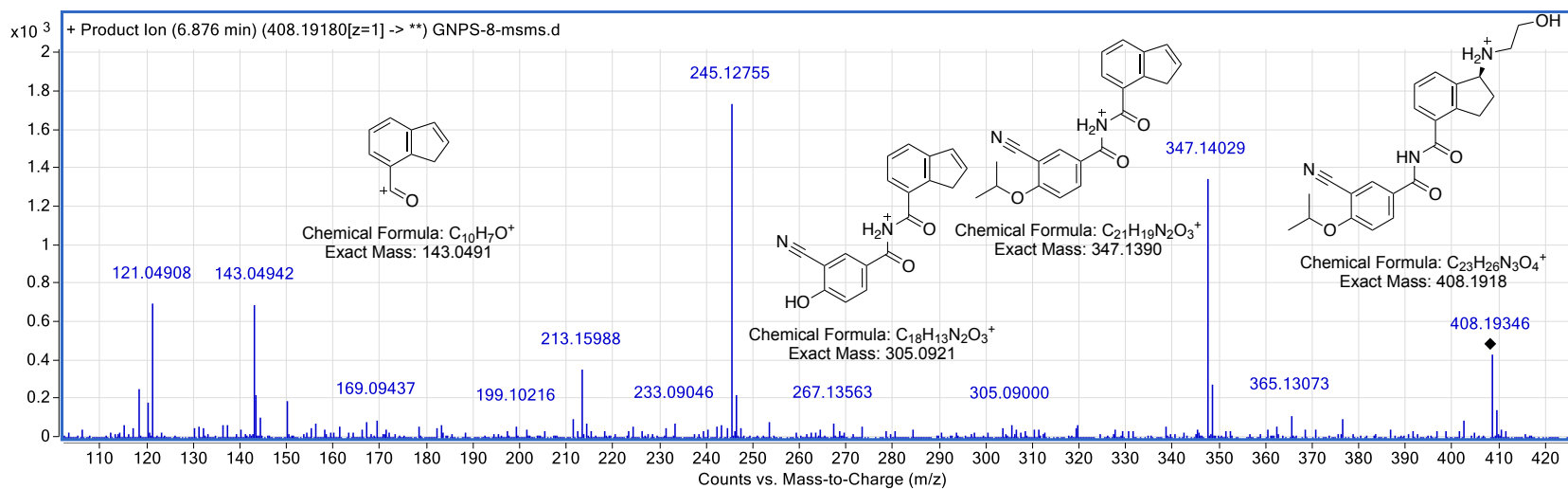
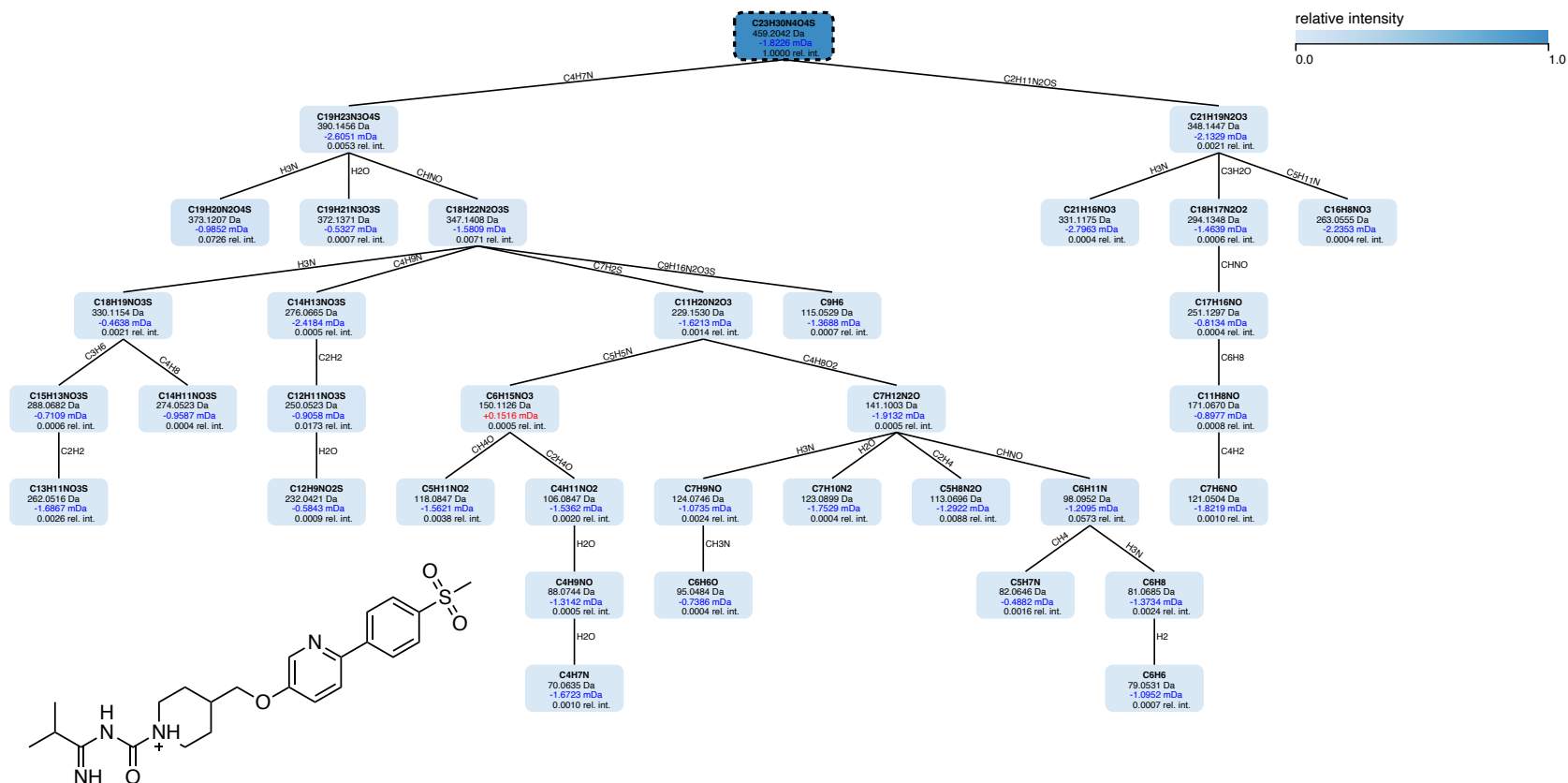


Figure S17. Fragmentation tree that contains the MS/MS fragments of a GSK1292263 product (GSK-459, *m/z* 459.2042) as revealed by SIRIUS. A representative charge state is shown.



Chemical Formula: $C_{23}H_{31}N_4O_4S^+$
Exact Mass: 459.2061

Figure S18. Fragmentation tree that contains the MS/MS fragments of a GSK1292263 product (GSK-460, m/z 460.1891) as revealed by SIRIUS. A representative charge state is shown.

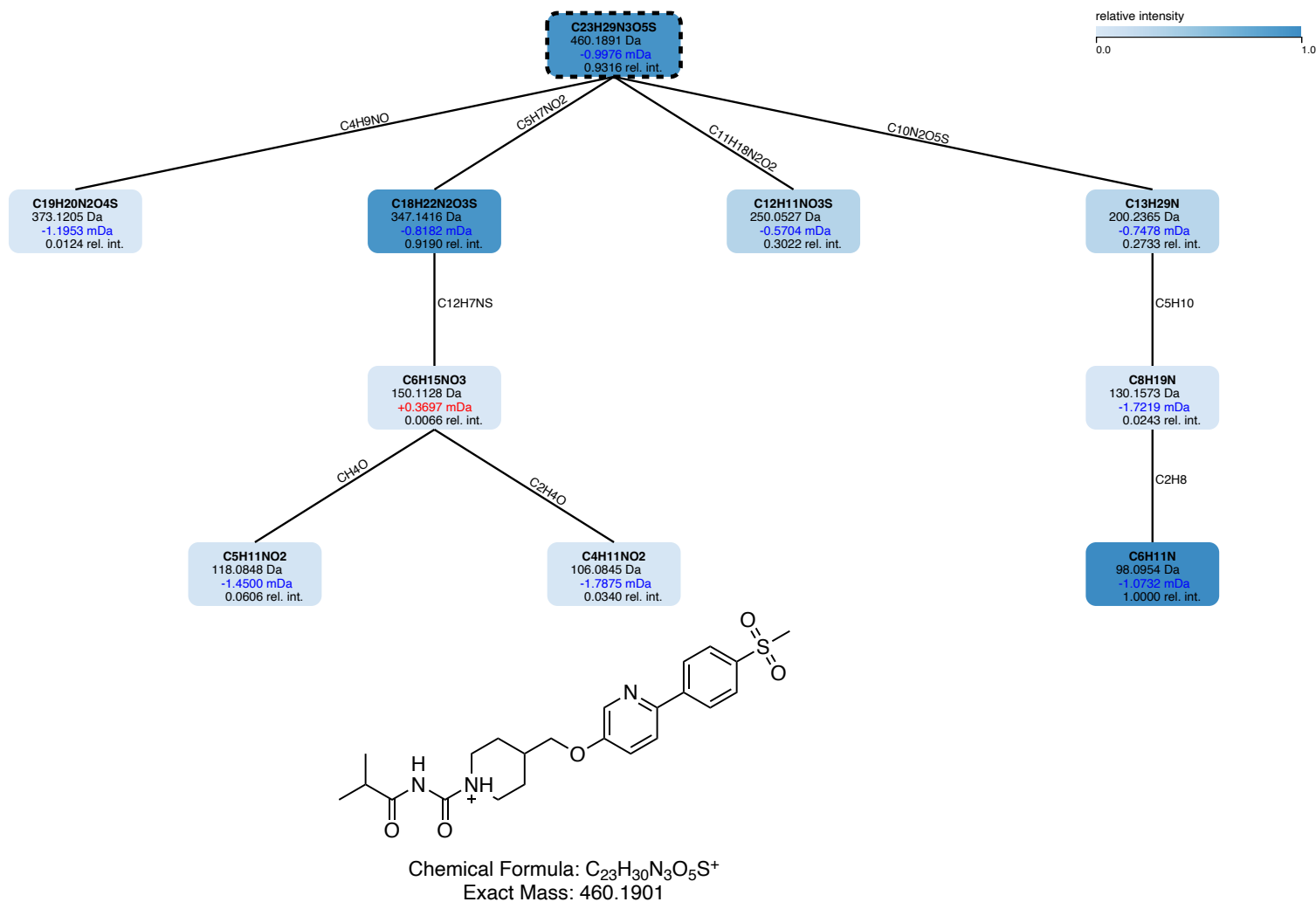


Figure S19. Proposed annotation of selected observed MS/MS fragments of a GSK1292263 product (GSK-459, m/z 459.2063). Representative charge states are shown. Fragment A: $m/z_{\text{calcd.}}$ 373.1217, $m/z_{\text{obs.}}$ 373.1204; Fragment B: $m/z_{\text{calcd.}}$ 250.0532, $m/z_{\text{obs.}}$ 250.0523; Fragment C: $m/z_{\text{calcd.}}$ 113.0709, $m/z_{\text{obs.}}$ 113.0697.

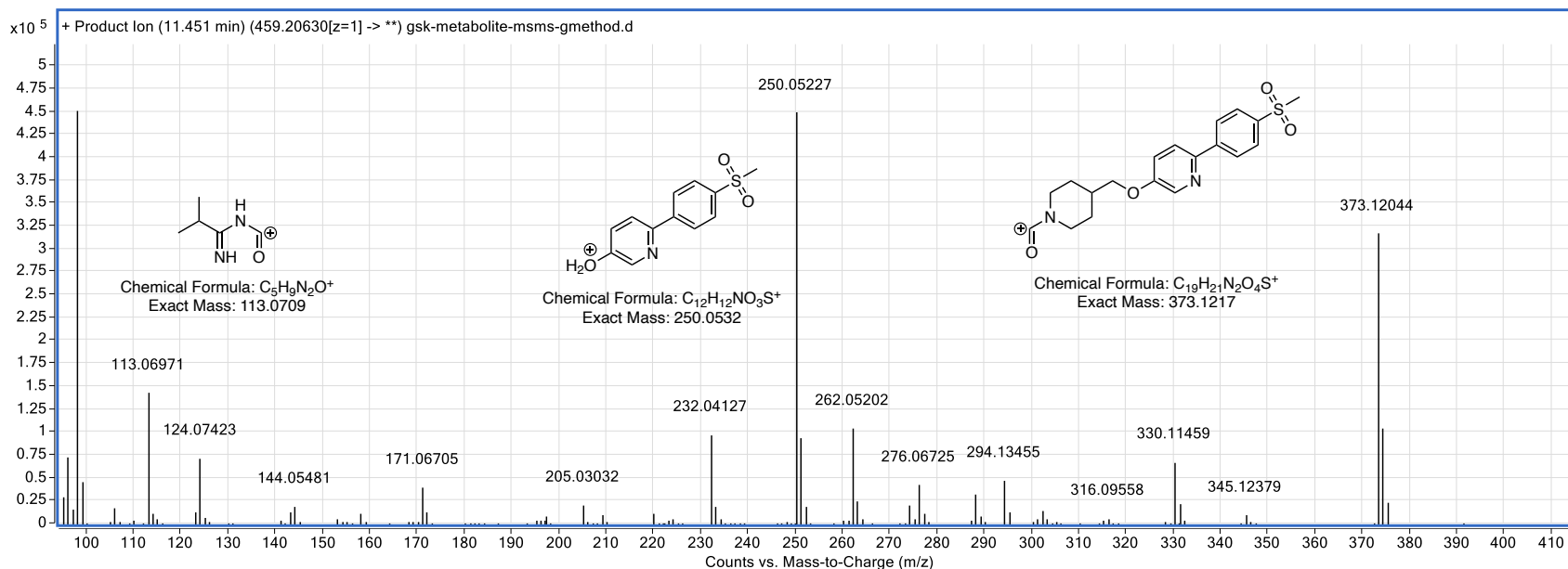


Figure S20. Proposed annotation of selected observed MS/MS fragments of a GSK1292263 product (GSK-460, m/z 460.1892). Representative charge states are shown. Fragment A: $m/z_{\text{calcd.}}$ 373.1217, $m/z_{\text{obs.}}$ 373.1205; Fragment B: $m/z_{\text{calcd.}}$ 347.1424, $m/z_{\text{obs.}}$ 347.1416; Fragment C: $m/z_{\text{calcd.}}$ 250.0532, $m/z_{\text{obs.}}$ 250.0527; Fragment D: $m/z_{\text{calcd.}}$ 88.0757, $m/z_{\text{obs.}}$ 88.0726.

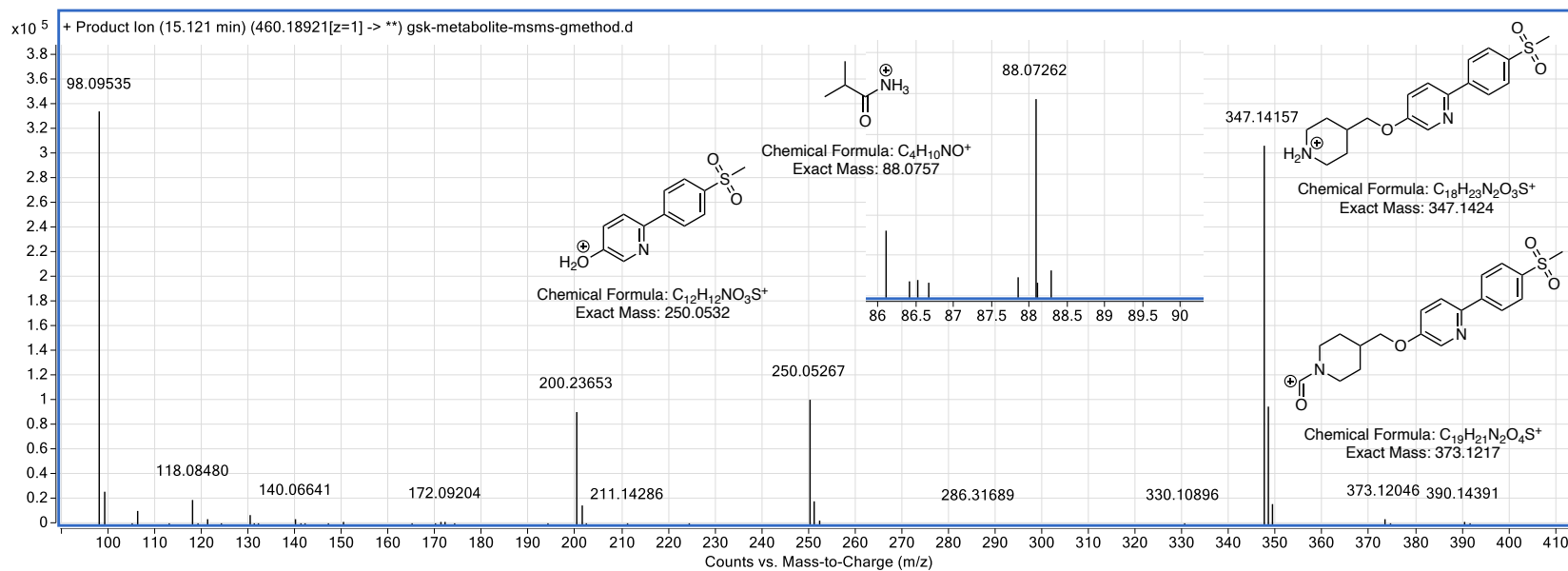


Figure S22. Structure elucidation of metabolite from ponesimod metabolism by MS/MS analysis. Comprehensive structural elucidation requires further NMR analysis. Representative charge states are illustrated. (a) Proposed annotation of selected observed MS/MS fragments of ponesimod (m/z 461.1293). Fragment A: $m/z_{\text{calcd.}}$ 419.0827, $m/z_{\text{obs.}}$ 419.0827; Fragment B: $m/z_{\text{calcd.}}$ 345.0459, $m/z_{\text{obs.}}$ 345.0467. (b) Proposed annotation of selected observed MS/MS fragments of a ponesimod product (ponesimod-463, m/z 463.1458). Fragment A: $m/z_{\text{calcd.}}$ 347.0616, $m/z_{\text{obs.}}$ 347.0624; Fragment B: $m/z_{\text{calcd.}}$ 288.0786, $m/z_{\text{obs.}}$ 288.0786. Proposed imine reduction of ponesimod revealed via MS/MS analysis. (c) Mass spectrum of a dehalogenation product (ponesimod-429) of ponesimod, with calculated m/z at 429.1843 and observed m/z at 429.1825. Structure determination was based on MS isotope pattern analysis, with the absence of signatures associated with chlorine-containing compounds. The proposed imine reduction position was proposed based on the MS² major ion products of ponesimod-463. However, further NMR characterization is required to confirm this prediction.

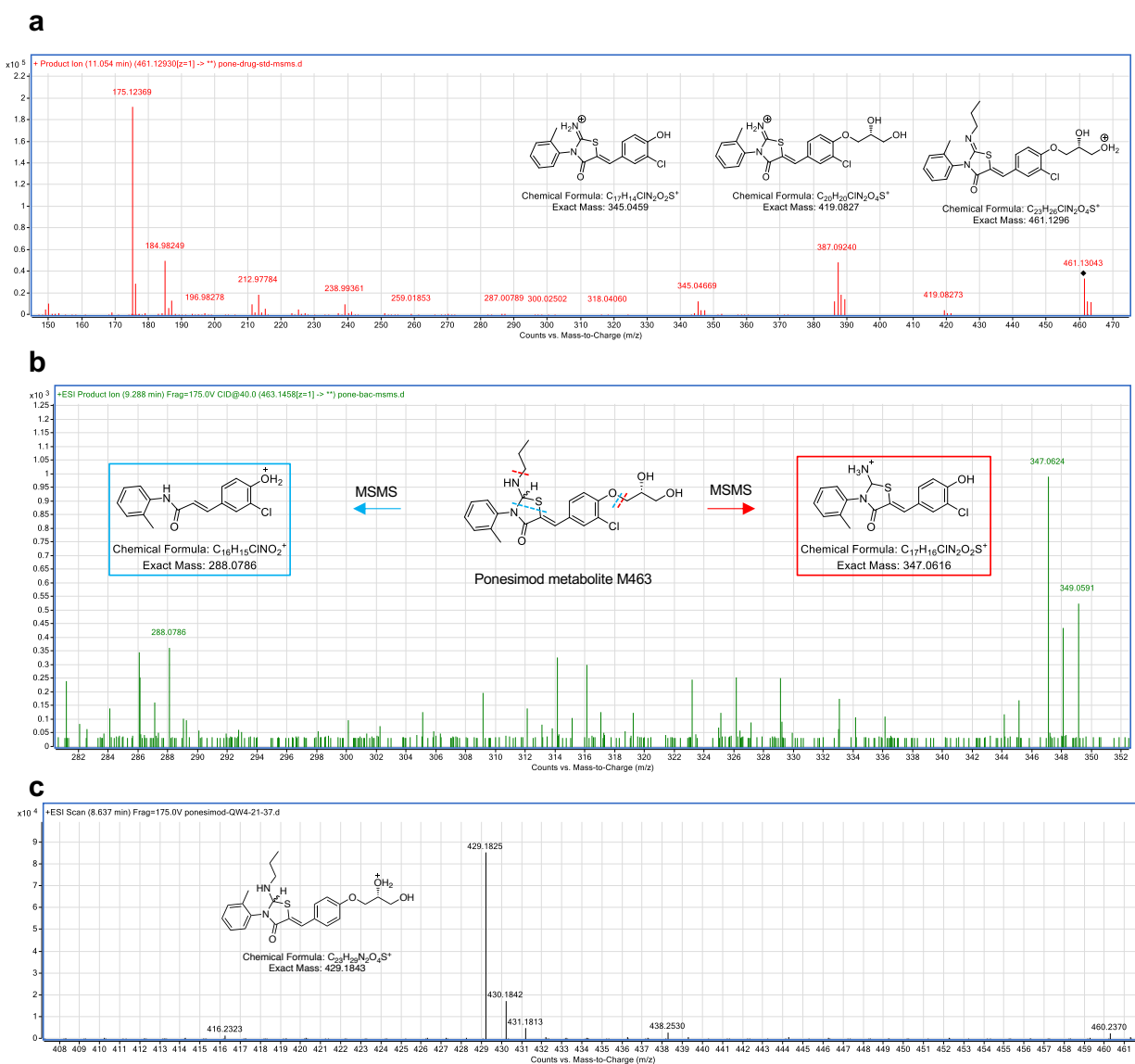


Figure S23. Structure elucidation of metabolite from trimebutine metabolism by MS/MS analysis. Comprehensive structural elucidation requires further NMR analysis. The position of O-demethylation is not determined. Representative charge states are illustrated. **(a)** Proposed annotation of selected observed MS/MS fragments of trimebutine (m/z 388.2123). Fragment A: $m/z_{\text{calcd.}}$ 195.0652, $m/z_{\text{obs.}}$ 195.0642; Fragment B: $m/z_{\text{calcd.}}$ 131.0855, $m/z_{\text{obs.}}$ 131.0859. **(b)** Proposed annotation of selected observed MS/MS fragments of a trimebutine product (trimebutine-374, m/z 374.1962). Fragment A: $m/z_{\text{calcd.}}$ 181.0495, $m/z_{\text{obs.}}$ 181.0479; Fragment B: $m/z_{\text{calcd.}}$ 155.0703, $m/z_{\text{obs.}}$ 155.0681. Fragment C: $m/z_{\text{calcd.}}$ 131.0855, $m/z_{\text{obs.}}$ 131.0854.

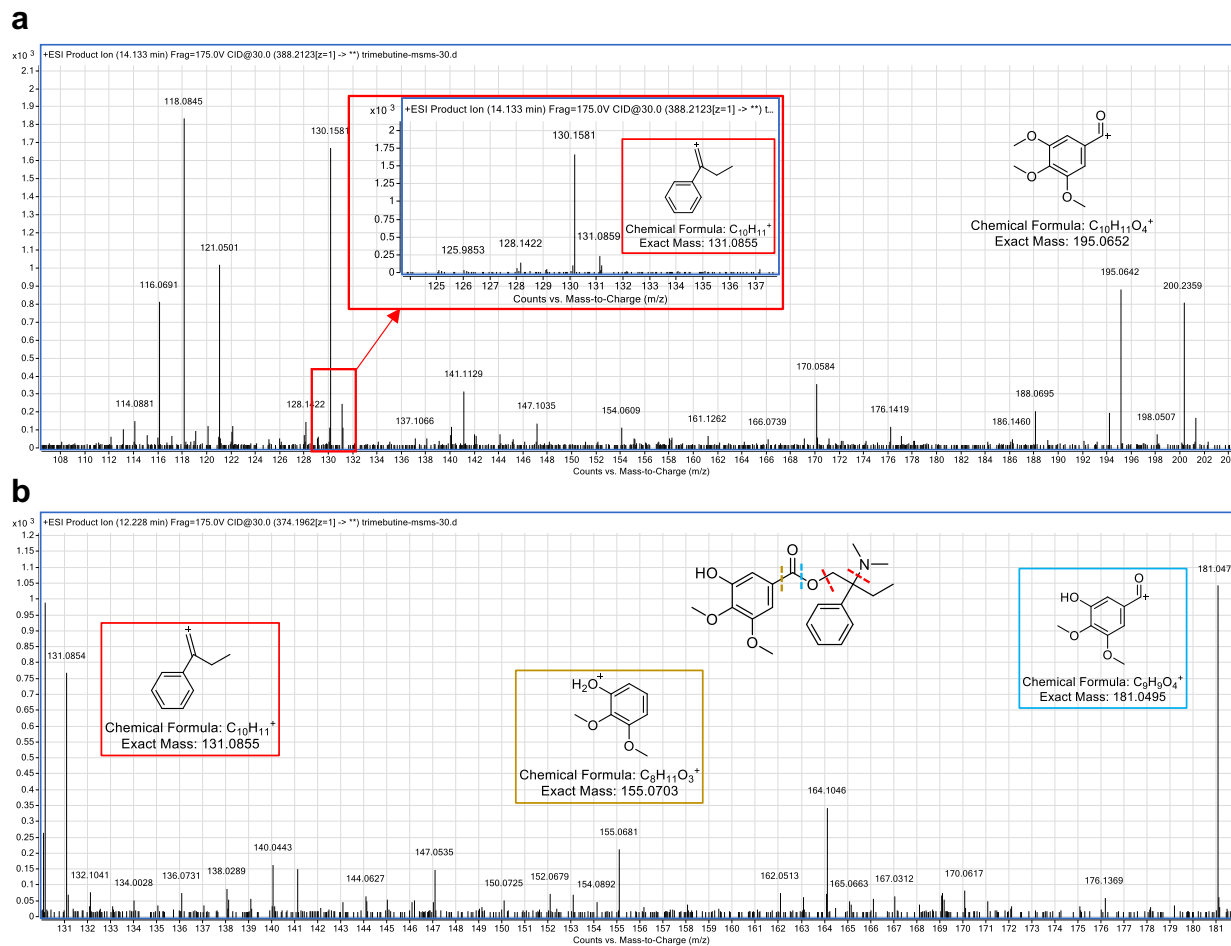


Figure S24. Structure elucidation of metabolite from trimethobenzamide metabolism by MS/MS analysis. Comprehensive structural elucidation requires further NMR analysis. The position of O-demethylation for each metabolite is not determined. Representative charge states are illustrated. (a) Proposed annotation of selected observed MS/MS fragments of trimethobenzamide (m/z 389.2096). Fragment A: $m/z_{\text{calcd.}}$ 195.0652, $m/z_{\text{obs.}}$ 195.0637. (b) Proposed annotation of selected observed MS/MS fragments of a trimebutine product (trimethobenzamide-375, m/z 375.1910). Fragment A: $m/z_{\text{calcd.}}$ 181.0495, $m/z_{\text{obs.}}$ 181.0500. (c) Proposed annotation of selected observed MS/MS fragments of a trimebutine product (trimethobenzamide-361, m/z 361.1753). Fragment A: $m/z_{\text{calcd.}}$ 272.0917, $m/z_{\text{obs.}}$ 272.0896. Fragment B: $m/z_{\text{calcd.}}$ 167.0339, $m/z_{\text{obs.}}$ 167.0336. (d) Proposed annotation of selected observed MS/MS fragments of a trimebutine product (trimethobenzamide-347, m/z 347.1601). Fragment A: $m/z_{\text{calcd.}}$ 153.0182, $m/z_{\text{obs.}}$ 153.0185. Fragment B: $m/z_{\text{calcd.}}$ 125.0233, $m/z_{\text{obs.}}$ 125.0221.

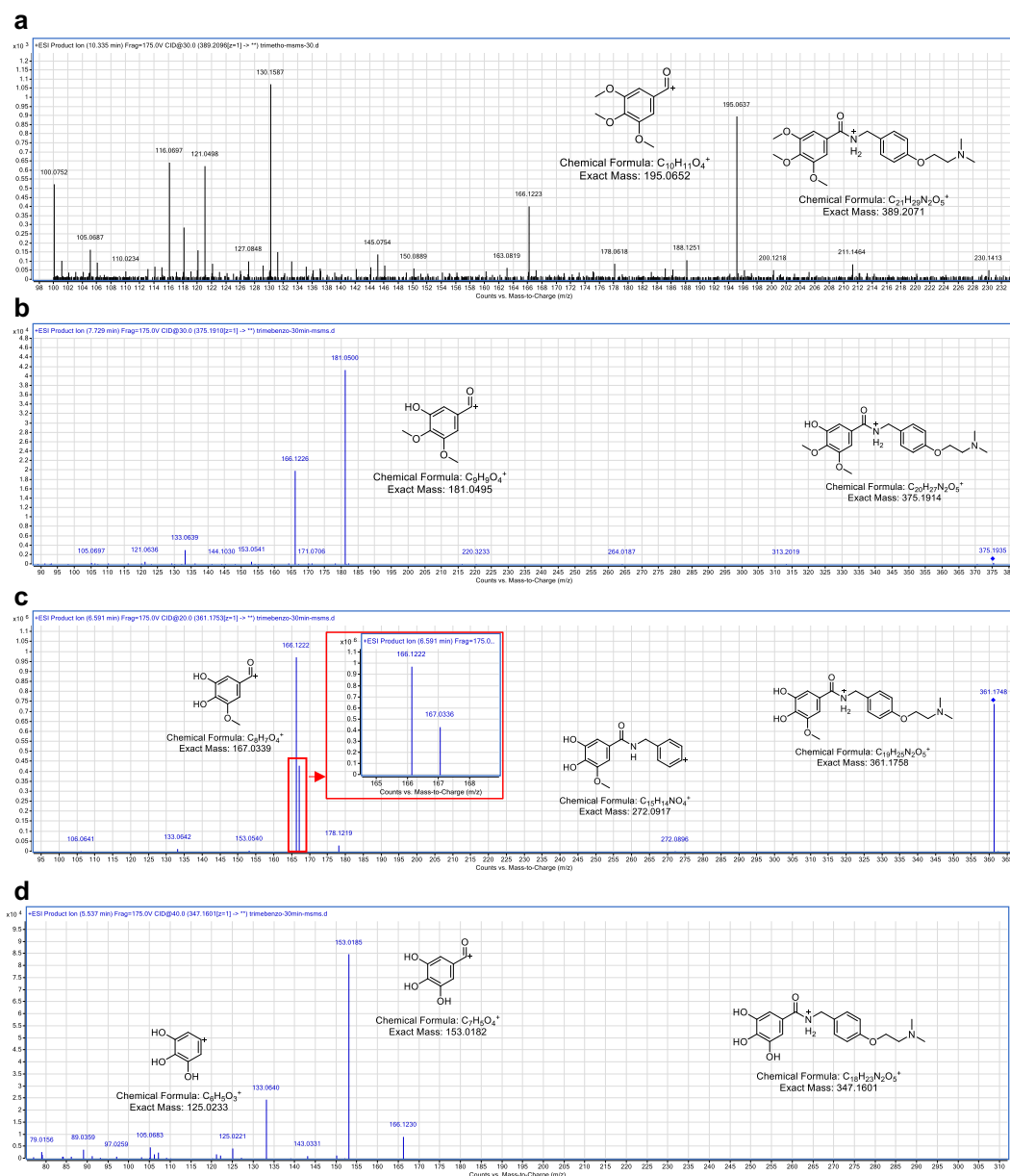


Fig. S25. LC-MS analysis of GSK1292263 reaction products. (a) UV-254 nm chromatography of GSK1292263 reaction products, showing a major peak of GSK1292263 product (GSK-459). (b) Mass spectrum of major peak in panel a, with a pseudo peak at m/z 459.2. (c) Chemical transformation yield. EICs for GSK-459 (top, 1.08×10^8) and residual parent drug GSK1292263 (bottom, peak area: 70199.8). (d) HR-ESI-MS of GSK-459, $m/z_{\text{calcd.}}$ 459.2061, $m/z_{\text{obs.}}$ 459.2049. Representative charge states are shown.

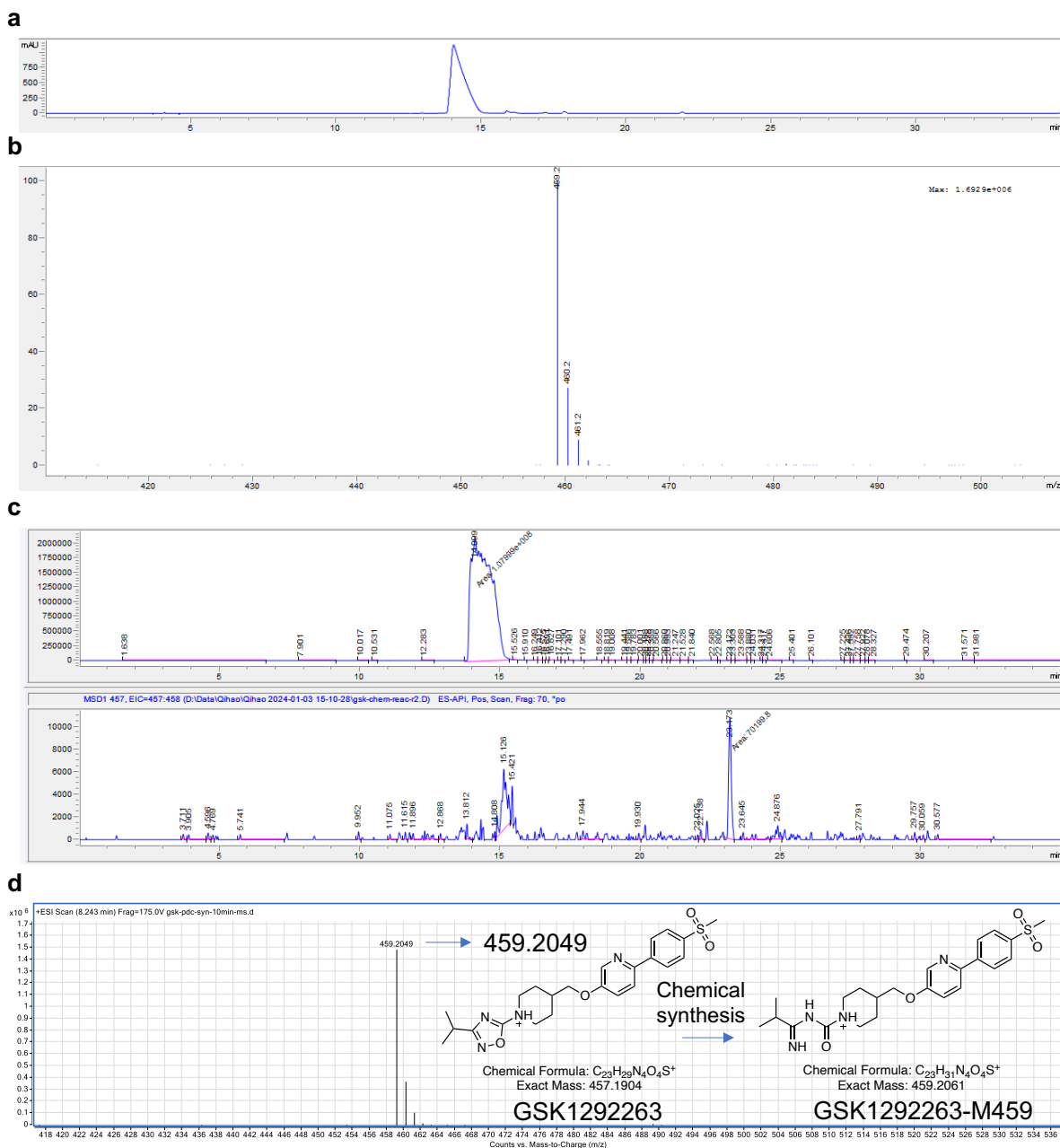


Table S13. ^1H and ^{13}C NMR data for synthetic GSK-459 in $\text{DMSO}-d_6$ (600 MHz for ^1H , 150 MHz for ^{13}C). The carbon chemical shifts were determined by HSQC and HMBC analyses.

Position	δ_{C} , type	δ_{H} , (J in Hz)
1	140.3, qC	-
2	128.0 ^a , CH	7.99 ^a , d (8.4)
3	126.9 ^a , CH	8.28 ^a , d (8.4)
4	143.8, qC	-
5	126.9 ^a , CH	8.28 ^a , d (8.4)
6	128.0 ^a , CH	7.99 ^a , d (8.4)
7	44.0, CH_3	3.25, s
8	146.7, qC	-
9	122.0, CH	8.04, d (9.0)
10	122.0, CH	7.53, dd (9.0, 3.0)
11	155.5, qC	-
12	138.5, CH	8.43, d (3.0)
13	72.3, CH_2	3.99, d (6.0)
14	35.7, CH	1.98, m
15	29.0 ^a , CH_2	1.17 ^a , m; 1.76 ^a , m
16	41.5, CH_2	4.32, d (12.6); 2.61, t (12.6)
17	29.0 ^a , CH_2	1.17 ^a , m; 1.76 ^a , m
18	44.6, CH_2	4.73, d (12.6); 2.80, t (12.6)
19	n.d.	-
20	174.2, qC	-
21	35.5, CH	2.37, m
22	20.9 ^a , CH_3	1.08 ^a , d (7.2)
23	20.9 ^a , CH_3	1.08 ^a , d (7.2)

^aoverlapped signals; n.d. not detected.

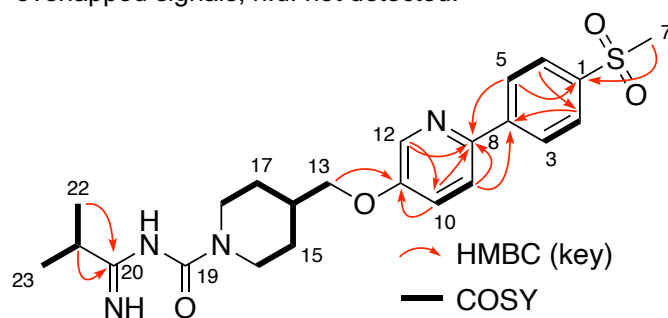


Fig. S26. ^1H NMR spectrum of synthetic GSK-459.

GSK-Prod_PROTON_01

GSK-Prod

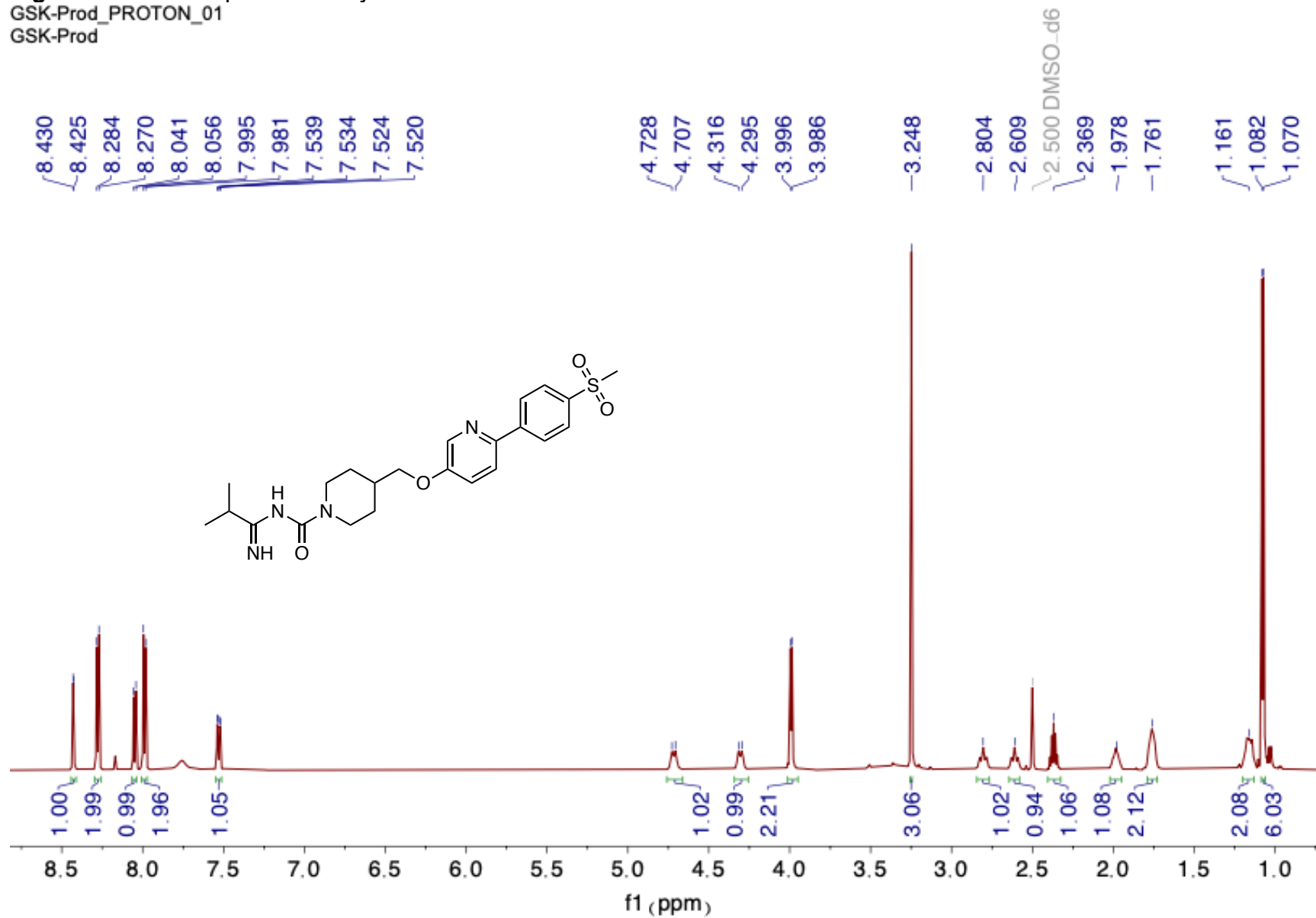


Fig. S27. COSY spectrum of synthetic GSK-459.

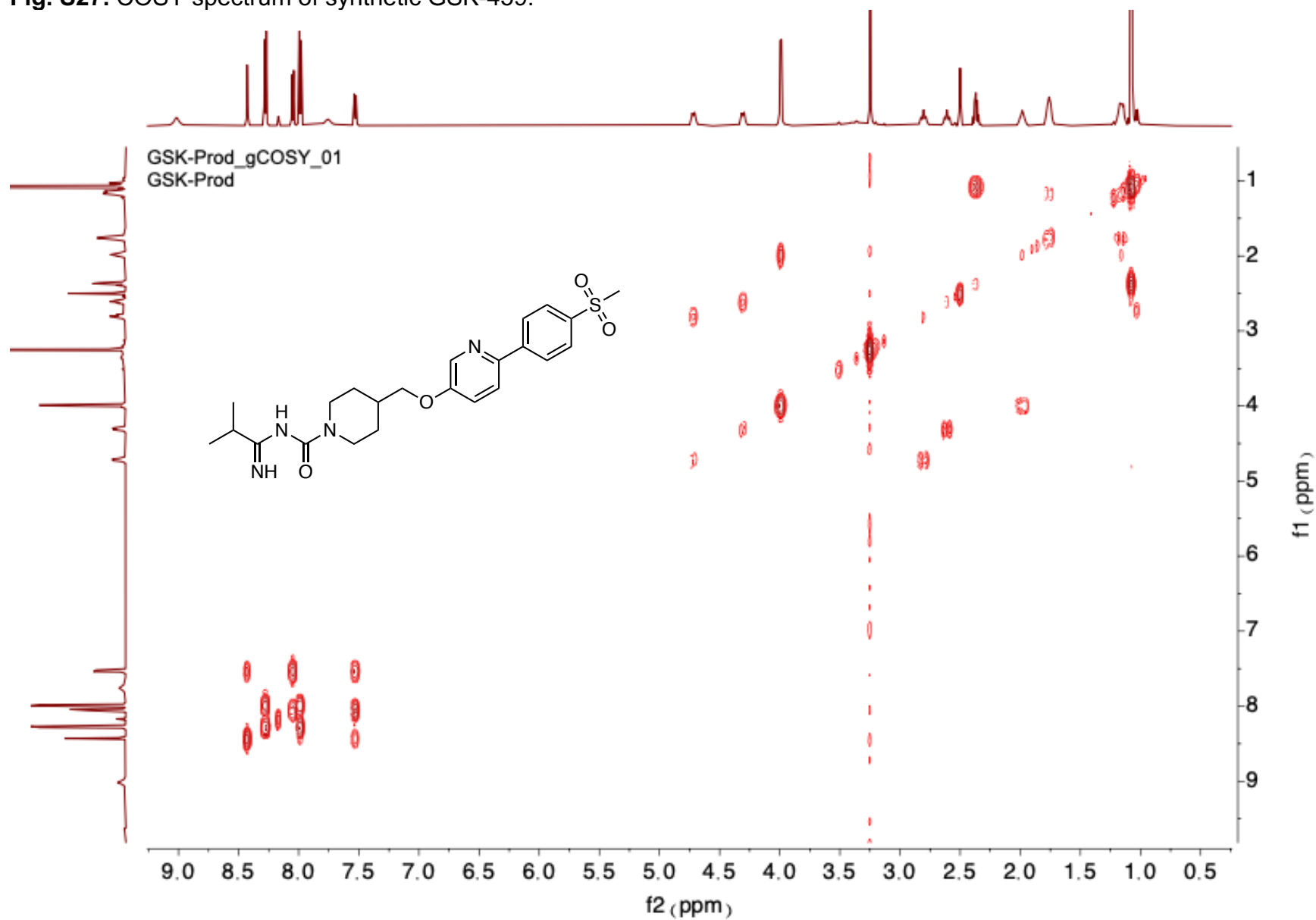


Fig. S28. HSQC spectrum of synthetic GSK-459.

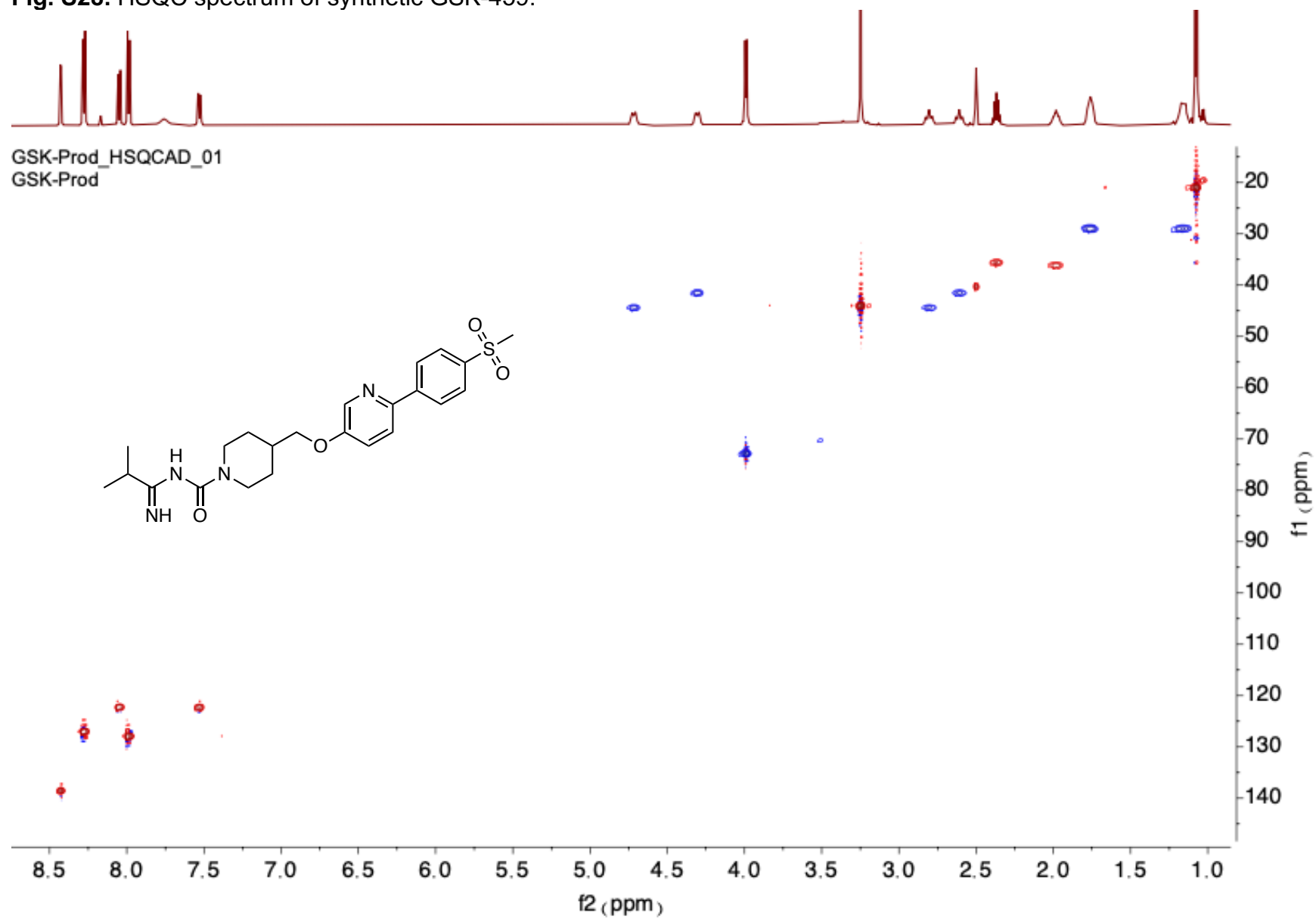
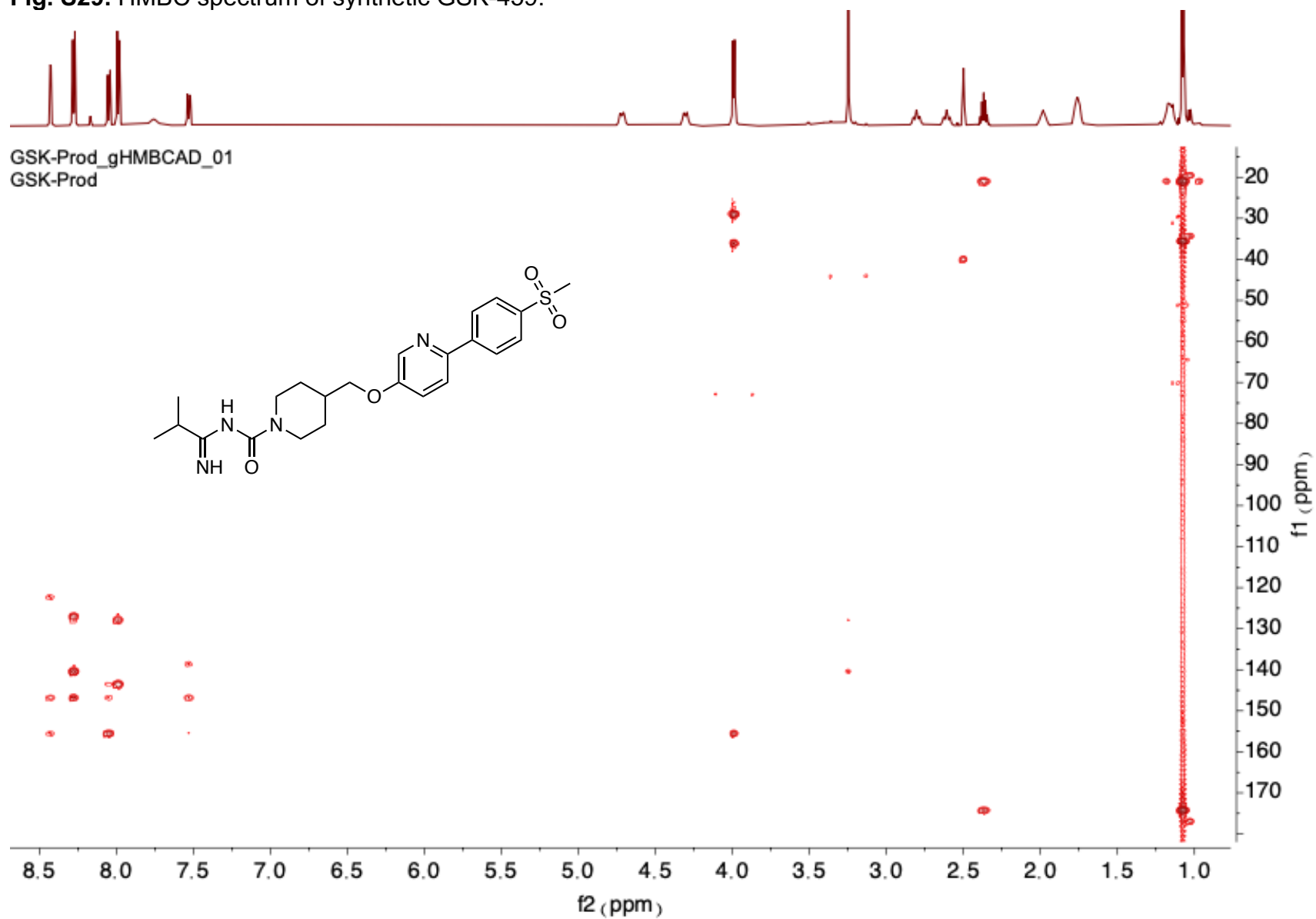


Fig. S29. HMBC spectrum of synthetic GSK-459.



3.3 Structural elucidation of iloperidone and risperidone metabolites

Ilo-430 was isolated as white powder. The molecular formula of ilo-430 was determined by HR-ESI-MS $\{[M+H]^+ m/z = 430.2025$ (calcd. for $C_{24}H_{29}FNO_5^+$ 430.2024)}. The chemical modification was determined by MS/MS analysis and the key HMBC correlations from H-8 (δ_H 3.74, m) to C-6 (δ_C 117.8) and C-7 (δ_C 205.4). Ilo-444 was isolated as brown solid. Its molecular formula was determined to be $C_{24}H_{26}FNO_4S$ on the basis of the HR-ESI-MS ions at m/z 444.1637 $[M+H]^+$ (calcd. 444.1639). The partial structures (parts A and C) were identified by comparing the NMR data to those of ilo-430, and also by interpreting key HMBC correlations. Part B, featuring a thiophene motif, was recognized using SMART NMR spectral comparisons as outlined in the main text. Its presence was further validated through COSY correlations between H₂-11 (δ_H 2.93, m) and H₂-12 (δ_H 3.25, m), H-8 (δ_H 7.43, d, $J = 4.5$) and H-9 (δ_H 7.07, d, $J = 4.5$), in addition to key HMBC correlations from H₂-11 to C-7 (δ_C 135.2)/C-9 (δ_C 127.4)/C-10 (δ_C 133.4) and from H-9 to C-7/C-10. The linkage of these three parts was confirmed through HMBC correlations, from H₂-13 (δ_H 3.23, m) to C-12 (δ_C 47.7) and from H-5 (δ_H 7.19, m) to C-7.

Both molecular formulae of ilo-491 and ilo-493 were determined by HR-ESI-MS $\{[M+H]^+ m/z = 491.2341$ for ilo491, calcd. for $C_{29}H_{32}FN_2O_4^+$ 491.2341; $[M+H]^+ m/z = 493.2499$ for ilo493, calcd. for $C_{29}H_{34}FN_2O_4^+$ 493.2497}. Similar to the ilo-444 case, ilo-491 exhibited the identical partial structures (parts A and C) in comparison to iloperidone. The unique 6/5/6 ring systems were unambiguously characterized through careful interpretation of COSY and HMBC correlations. First, COSY correlations of H₂-11 (δ_H 2.78, m)/H₂-12 (δ_H 1.80, m)/H₂-13 (δ_H 1.92, m)/H₂-14 (δ_H 3.64, m; δ_H 3.89, m) and HMBC correlations from H₂-11/H₂-14 to C-10 (δ_C 142.8) established the constructed piperidine-like six-membered ring system. Subsequently, using SMARTNMR analysis, the distinctive chemical shift observed for C-17 (δ_H 8.66, s, δ_C 156.6) was interpreted as indicative of an imine motif, akin to what was demonstrated in our previously reported indolimine-214 metabolite from *M. organii* (with an imine signal δ_H 8.42, δ_C 155.2). The HMBC correlations from H-17 to C-8 (δ_C 115.0)/C-9 (δ_C 111.4)/C-16 (δ_C 48.2) further established the structural arrangement of part B as shown in Fig. 6e. Finally, the 6/5/6 ring system was established via C-9 and C-10 connection, as well as through C-7 and C-8/N-1 connection, respectively, giving rise to a pyrrole-like motif (Fig. 6e). This assignment was further confirmed by HMBC correlation from H-17 to C-10, H₂-15 (δ_H 2.78, m; δ_H 2.87, m) to C-7 (δ_C 127.4)/C-8 and H₂-11 to C-9. Finally, the linkage of three parts were connected, through HMBC correlations from H₂-18 (δ_H 4.03, t, $J = 5.0$) to C-16, from H-17 to C-18 (δ_C 57.1) and from H-5 (δ_H 7.15, m) to C-7. The structure of ilo-493 showed high similarity to ilo-491 with the only difference being the reduction of the imine motif as evidenced by the HMBC correlations from H₂-17 (δ_H 4.12, m; δ_H 4.67, m) to C-8 (δ_C 110.4)/C-9 (δ_C 104.4)/C-16 (δ_C 52.1). The chemical structure of ilo-477 was predicted through a combination of MS/MS analysis, comparisons with the structurally related metabolites, biosynthetic analysis, and (isotopic) precursor feeding experiments, which are discussed in the main text.

We conducted a study on the biotransformation of human gut microbiota with risperidone, an analog of iloperidone. After examining our drug metabolism screening data, we performed EIC for two potential metabolites of risperidone: a ring-opened product with m/z 414.2187 and a thiophene-incorporated product with m/z 428.1803. Both metabolites were detected in the bacterial culture undergoing risperidone metabolism,

while no detection was observed in the 3K control, supporting an analogous metabolism to that of iloperidone.

Fig. S30. MSMS spectrum of iloperidone for molecular networking generation. The spectrum was generated by using SIRIUS from the raw data.

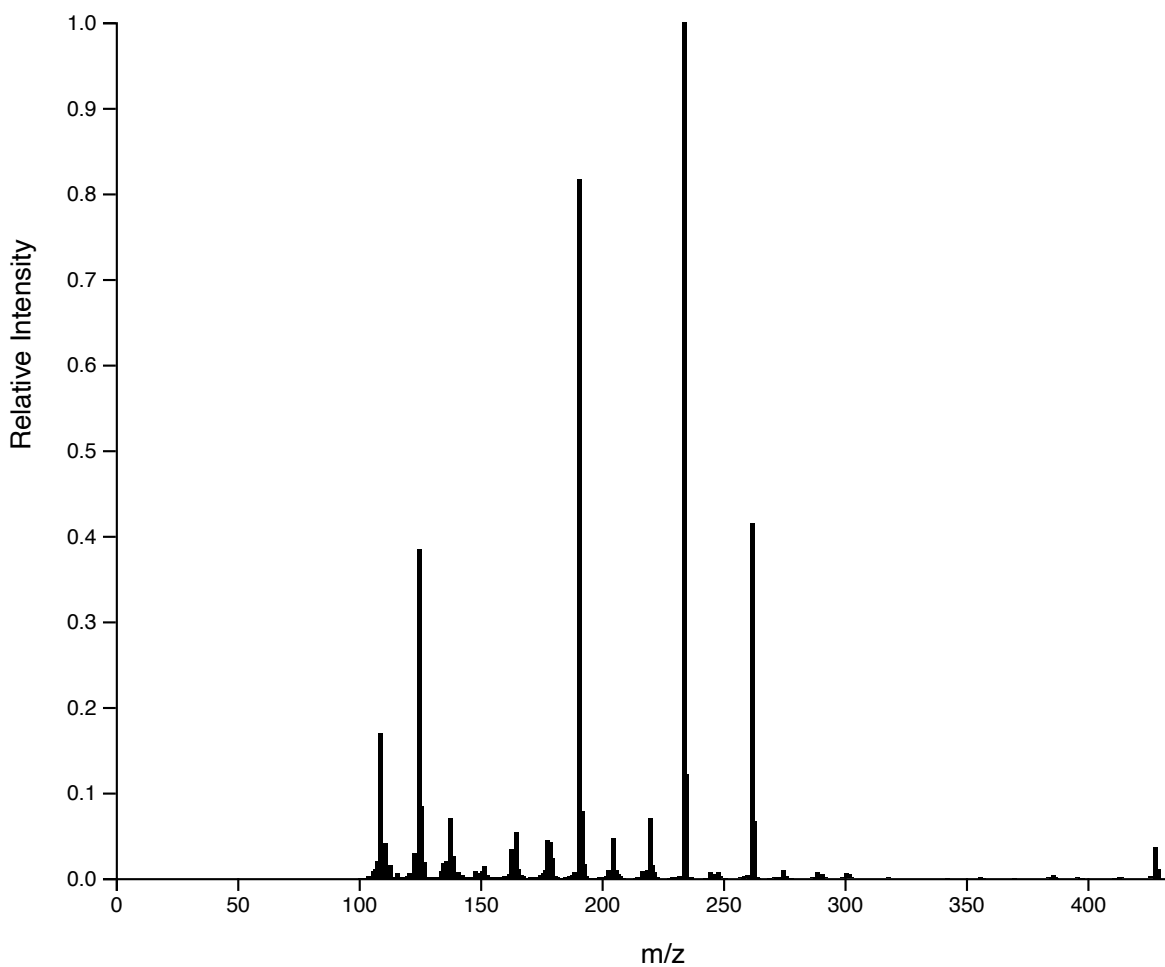


Fig. S31. MSMS spectrum of ilo-430 for molecular networking generation. The spectrum was generated by using SIRIUS from the raw data.

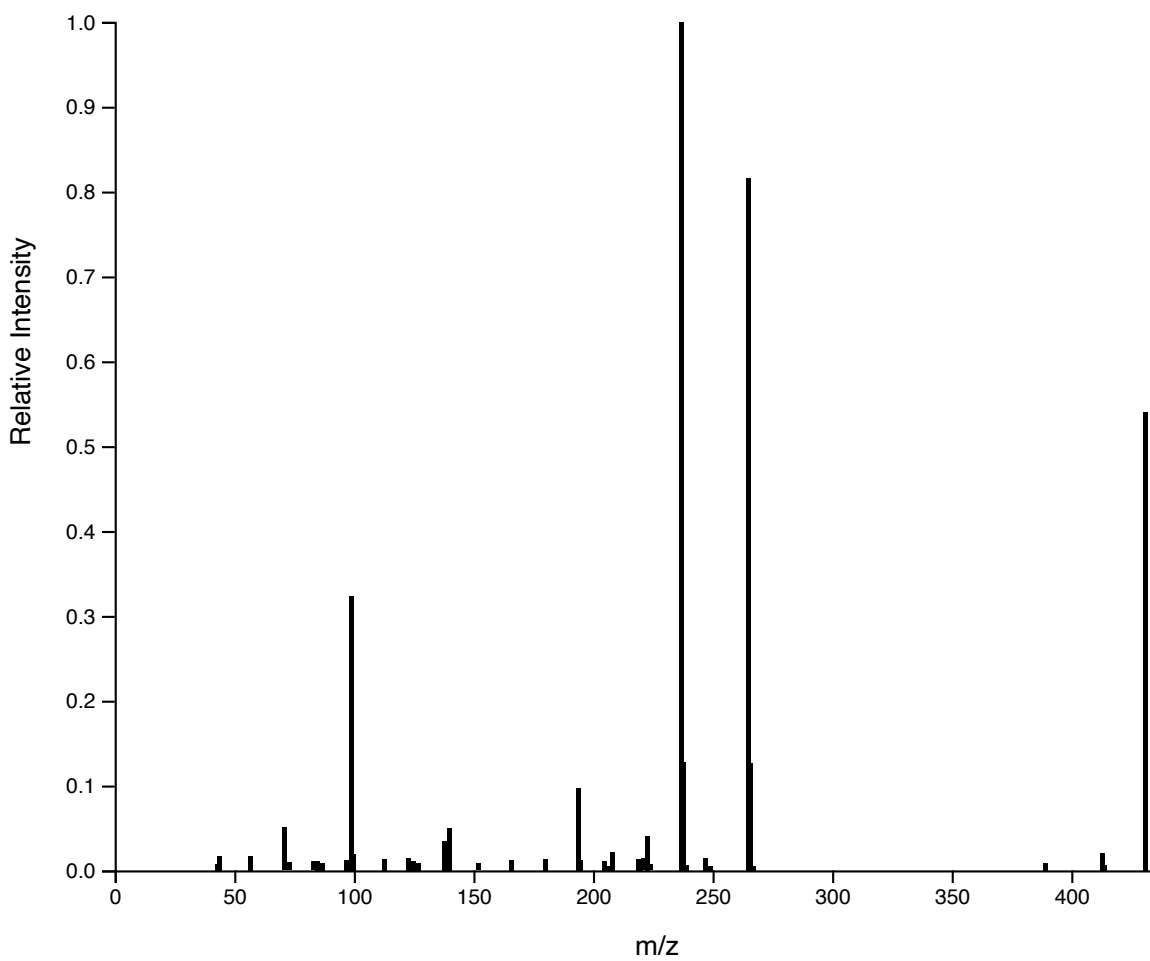


Fig. S32. MSMS spectrum of ilo-432 for molecular networking generation. The spectrum was generated by using SIRIUS from the raw data.

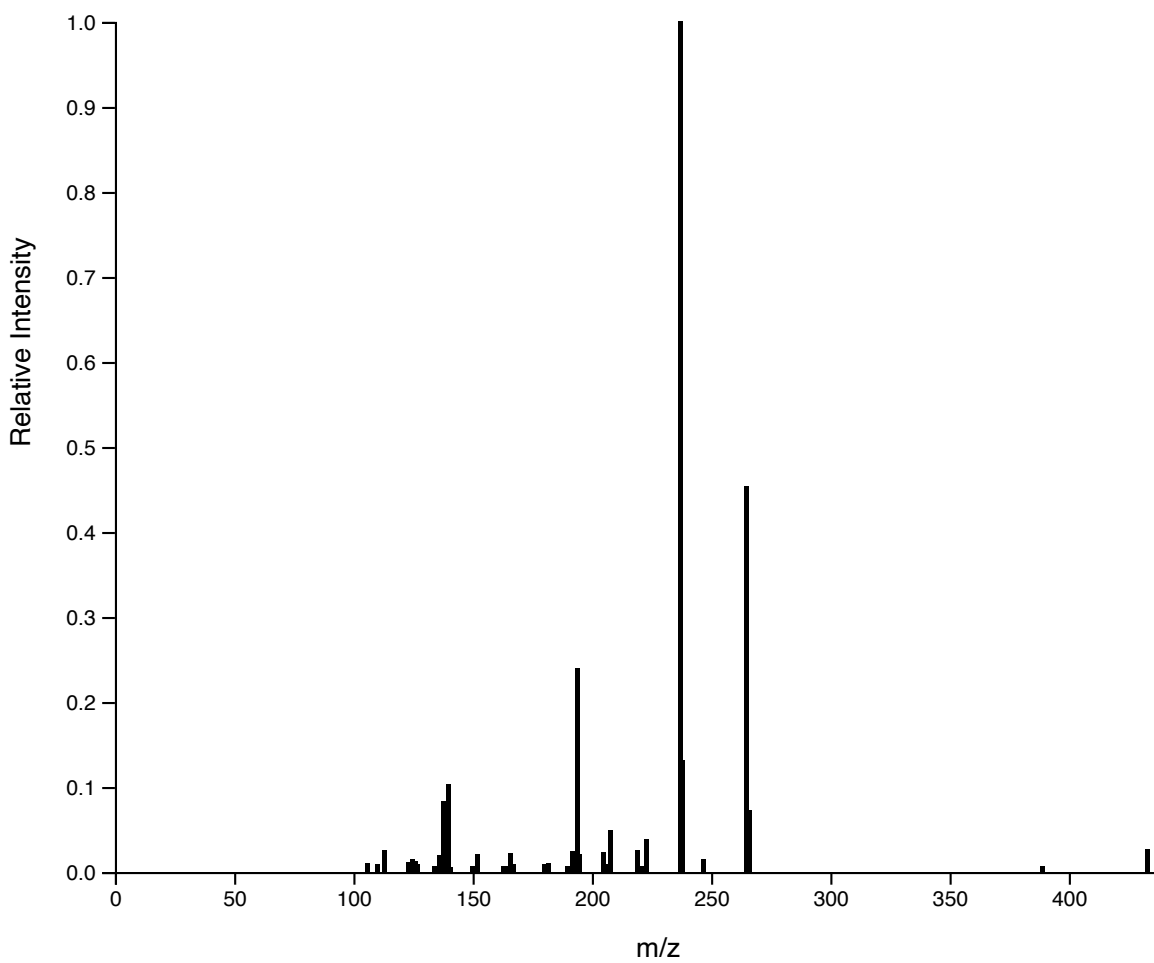


Fig. S33. MSMS spectrum of ilo-444 for molecular networking generation. The spectrum was generated by using SIRIUS from the raw data.

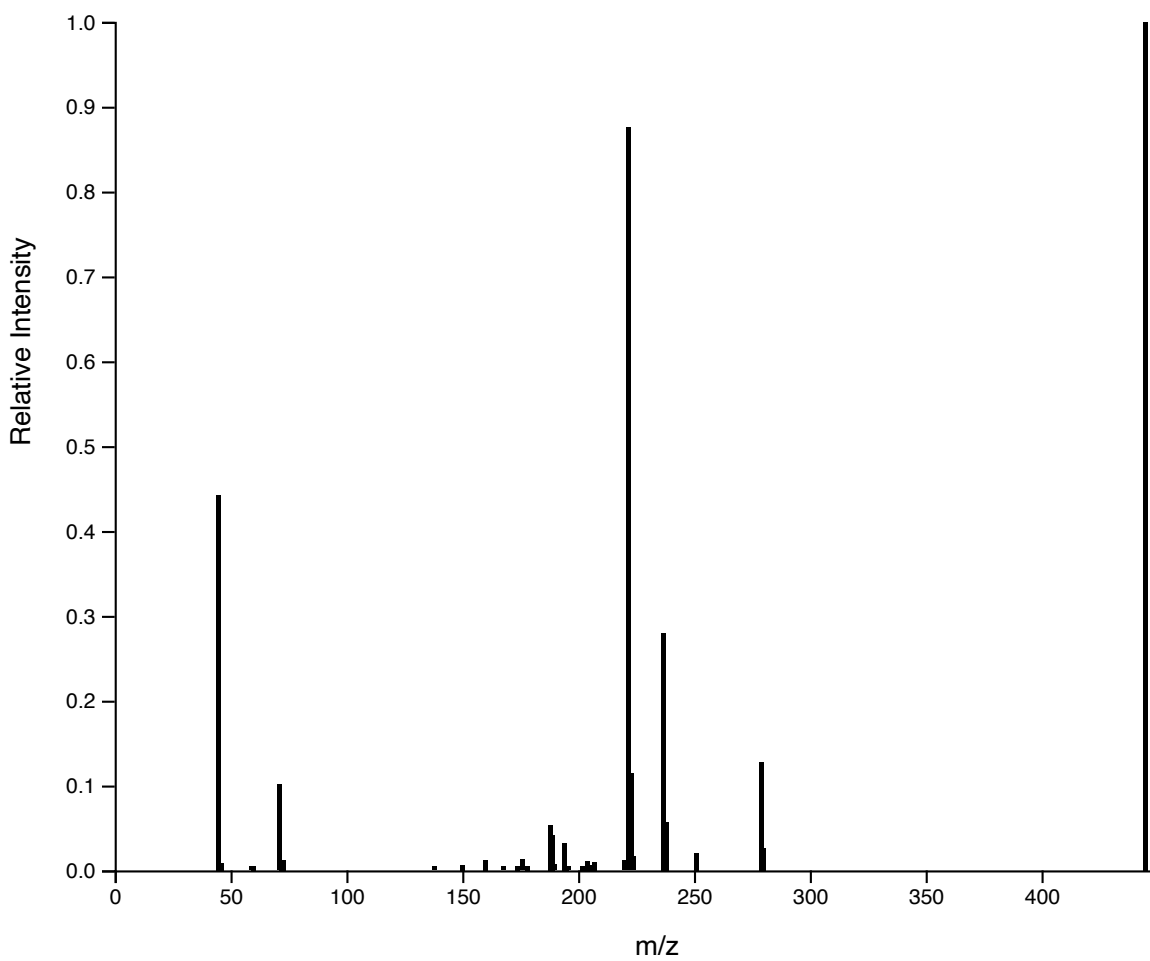


Fig. S34. MSMS spectrum of ilo-477 for molecular networking generation. The spectrum was generated by using SIRIUS from the raw data.

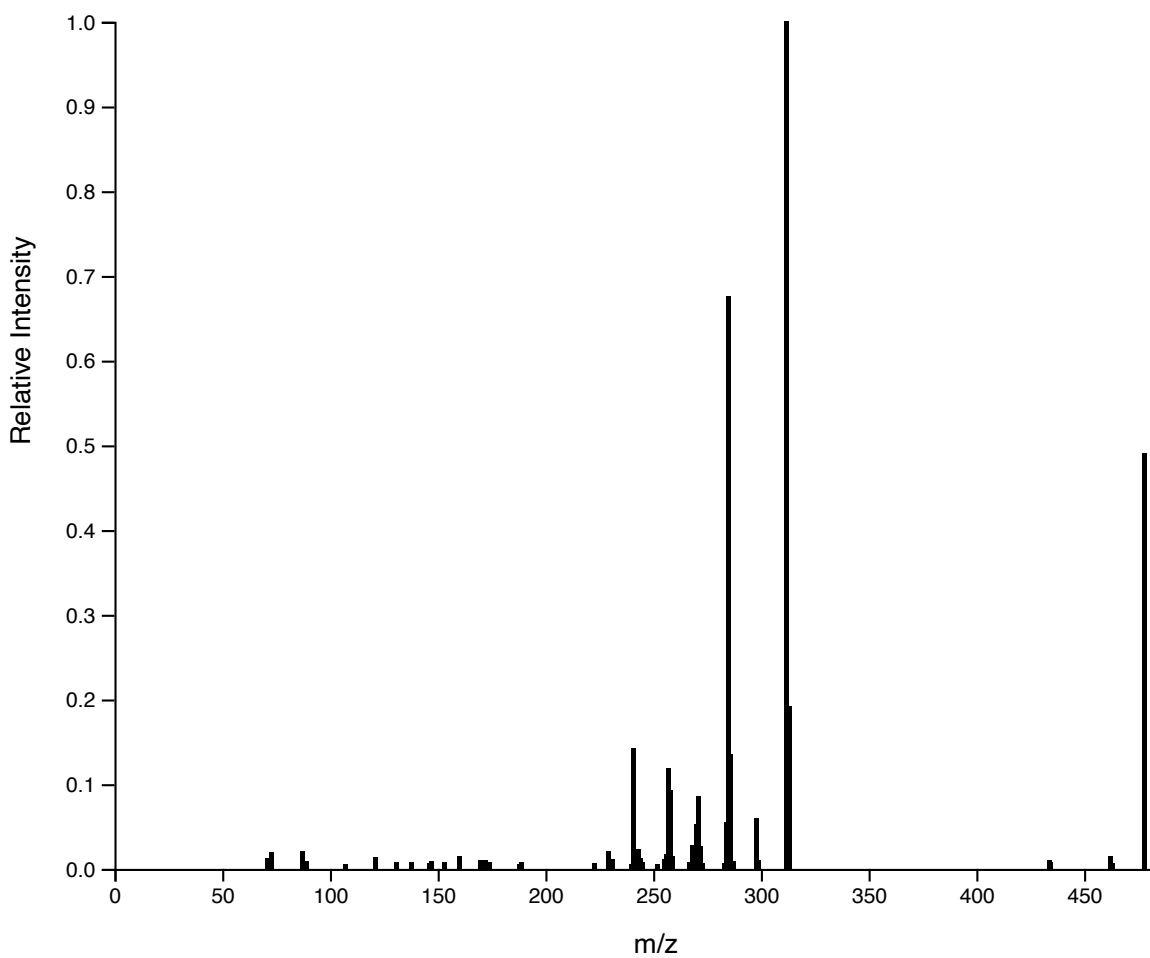


Fig. S35. MSMS spectrum of ilo-491 for molecular networking generation. The spectrum was generated by using SIRIUS from the raw data.

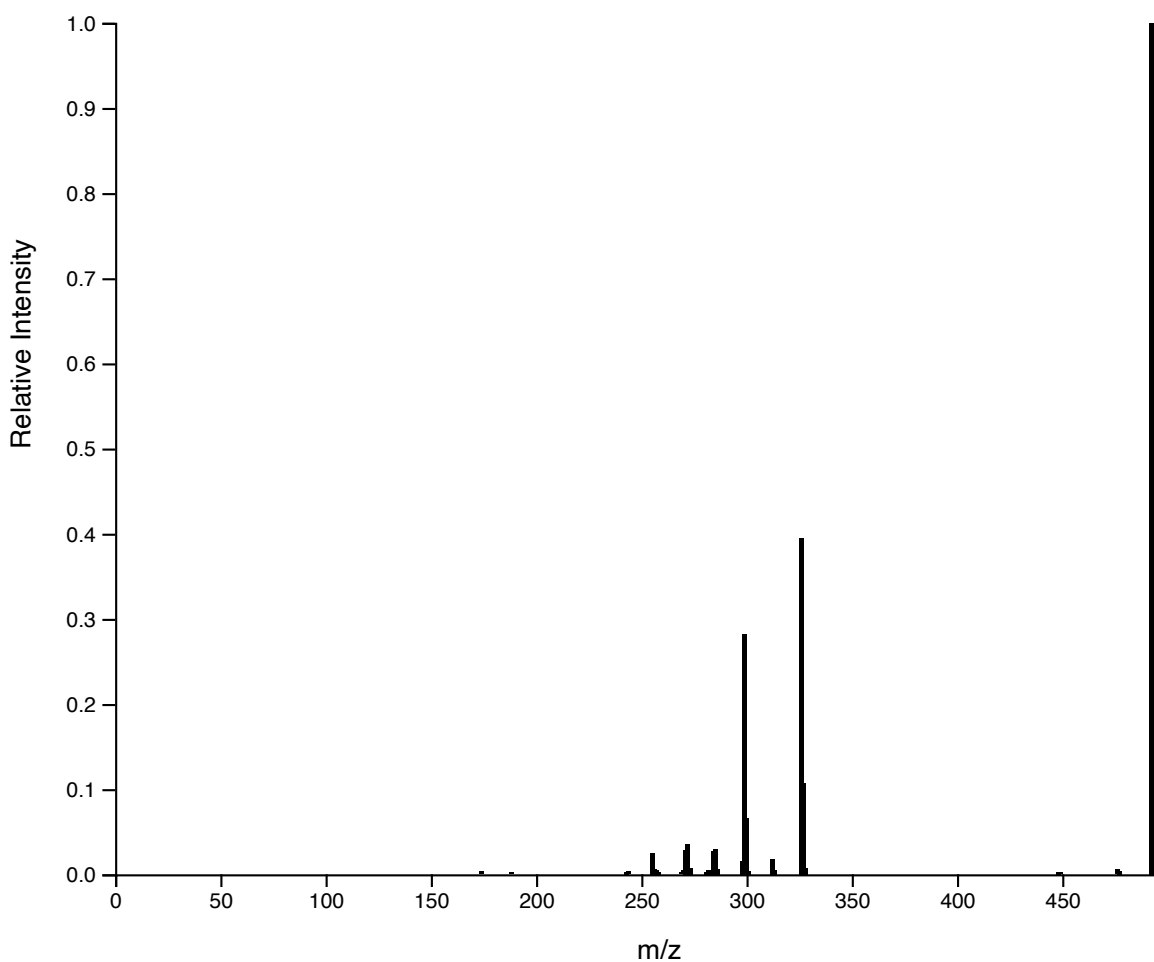


Fig. S36. MSMS spectrum of ilo-493 for molecular networking generation. The spectrum was generated by using SIRIUS from the raw data.

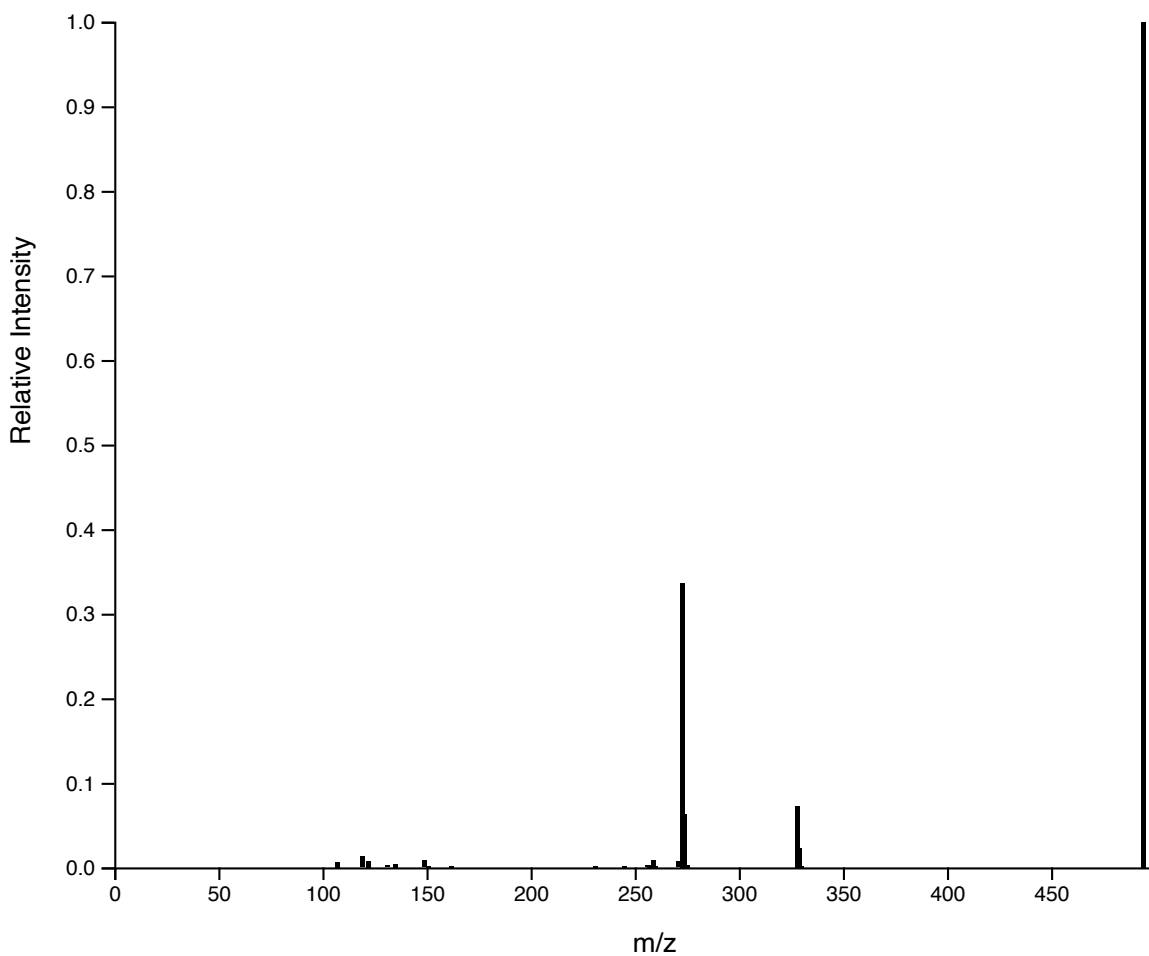


Table S14. Similarity calculation between features in iloperidone metabolism, including all similarity scores. Similarity scores greater than 0.45 are highlighted in green. Molecular networking illustrates connections with similarity scores above 0.45 (depicted by blue solid lines) and below 0.45 (represented by grey dotted lines).

	iloperidone	ilo432	ilo430	ilo444	ilo477	ilo491
iloperidone						
ilo432	0.013626380154164508_18					
ilo430	0.7005933398904745_18	0.8661577165039489_23				
ilo444	0.06985662208171561_5	0.19709143607178703_7	0.45963793934788555_9			
ilo477	0.3508874233593815_14	0.009262546052923426_4	0.645315881811257_15	0.32827050609193975_10		
ilo491	0.164600486663403_8	0.020414438098669052_1	0.5711836913251318_7	0.649978842237033_5	0.7415983762475662_12	
ilo493	0.041807172528933734_3	0.021595463156700134_1	0.3905697889858857_3	0.6623768032004591_4	0.4284981780219823_5	0.8780642438214272_5

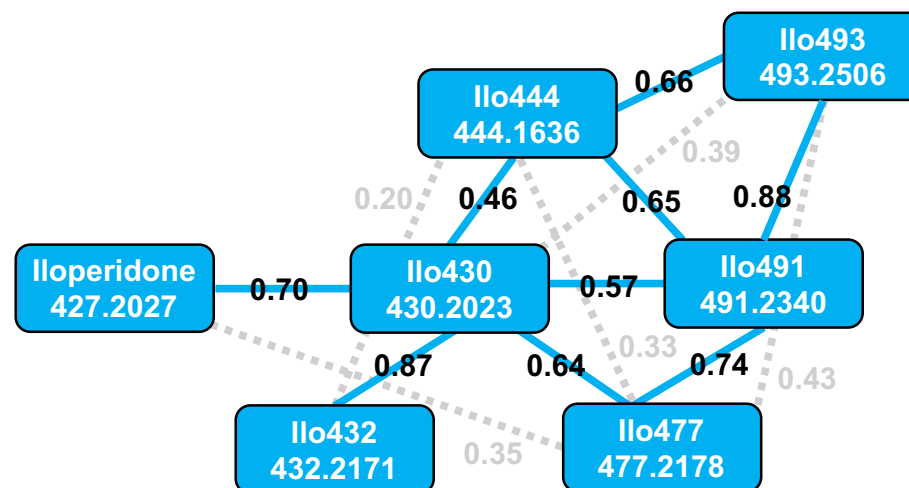
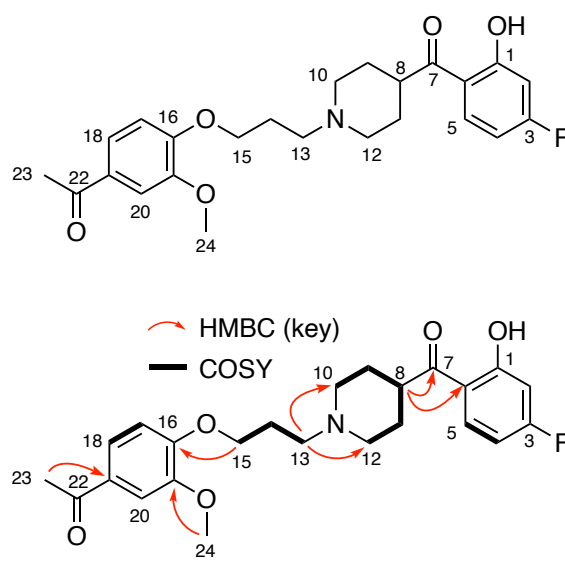


Fig. S37. Similarity calculation for iloperidone and all the detected metabolites. The numbers next to the lines indicate the similarity scores between two MOFs.

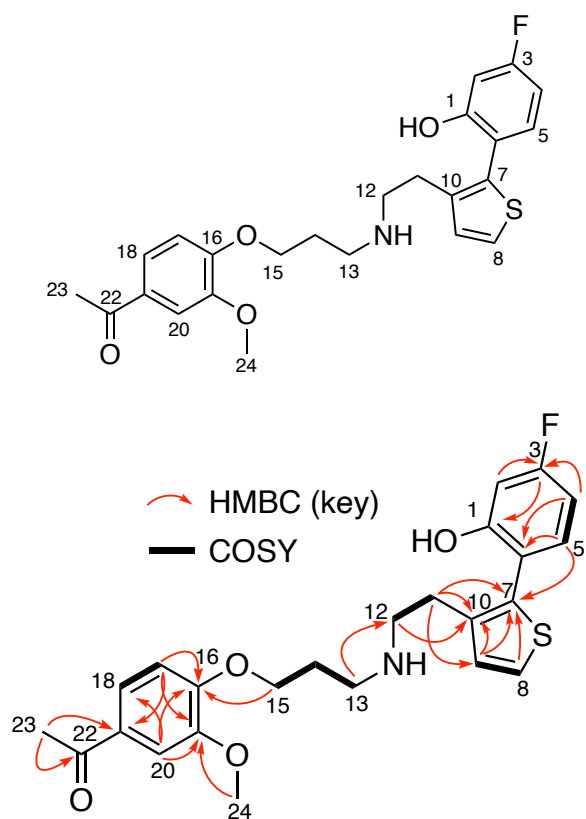
Table S15. ^1H and ^{13}C NMR data for ilo-430 in CD_3OD (600 MHz for ^1H). The carbon chemical shifts were determined by HSQC and HMBC analyses.



Position	δ_{C} , type	δ_{H} , (J in Hz)
1	165.9, qC	—
2	104.7, CH	6.85, s ^a
3	162.8, qC	—
4	107.6, CH	6.84, m ^a
5	133.8, CH	7.99, m ^a
6	117.8, qC	—
7	205.4, qC	—
8	41.8, CH	3.74, m
9	26.1, CH ₂	1.82, m; 2.07, m
10	57.1, CH ₂	3.09, m; 3.65, m
11	26.1, CH ₂	1.82, m; 2.07, m
12	57.1, CH ₂	3.09, m; 3.65, m
13	54.2, CH ₂	3.28, m
14	23.8, CH ₂	2.20, m
15	66.7, CH ₂	4.16, t (5.0)
16	152.2, qC	—
17	112.4, CH	7.09, d (7.0)
18	123.4, CH	7.63, dd (7.0, 1.5)
19	130.7, qC	—
20	110.7, CH	7.47, d (1.5)
21	149.0, qC	—
22	196.8, qC	—
23	27.4, CH ₃	2.53, s
24	55.7, CH ₃	3.75, s

^aoverlapped signals.

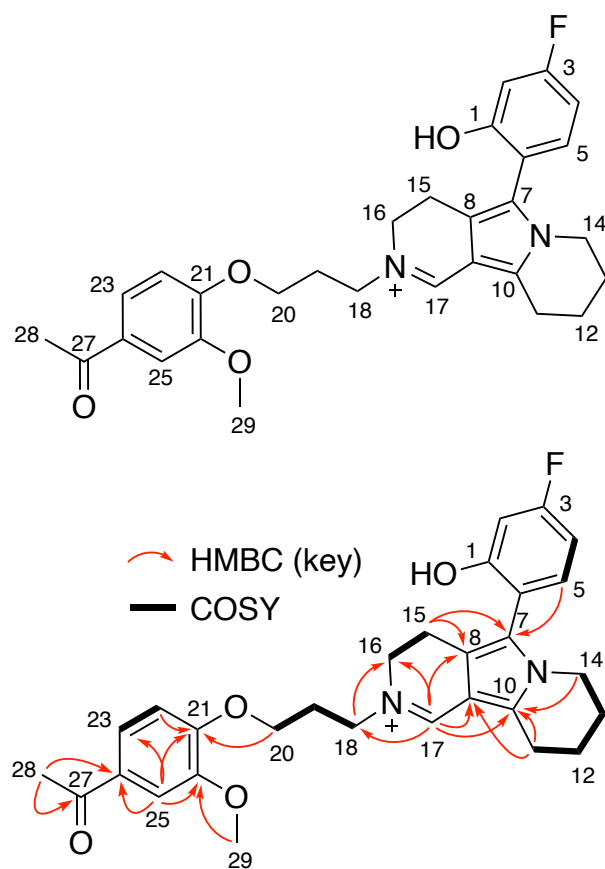
Table S16. ^1H and ^{13}C NMR data for ilo-444 in CD_3OD (600 MHz for ^1H). The carbon chemical shifts were determined by HSQC and HMBC analyses.



Position	δ_{C} , type	δ_{H} , (J in Hz)
1	164.5, qC	—
2	106.0, CH	6.62, s
3	162.8, qC	—
4	102.7, CH	6.64, m ^a
5	133.2, CH	7.19, m ^a
6	156.6, qC	—
7	135.2, qC	—
8	125.2, CH	7.43, d (4.5)
9	127.4, CH	7.07, d (4.5)
10	133.4, qC	—
11	25.7, CH_2	2.93, m
12	47.7, CH_2	3.25, m
13	46.2, CH_2	3.23, m
14	25.3, CH_2	2.19, m
15	67.1, CH_2	4.21, t (4.5)
16	152.1, qC	—
17	111.4, CH	7.04, d (7.0)
18	123.3, CH	7.68, dd (7.0, 1.5)
19	130.8, qC	—
20	110.0, CH	7.54, s
21	149.0, qC	—
22	197.9, qC	—
23	24.9, CH_3	2.57, s
24	55.0, CH_3	3.82, s

^aoverlapped signals.

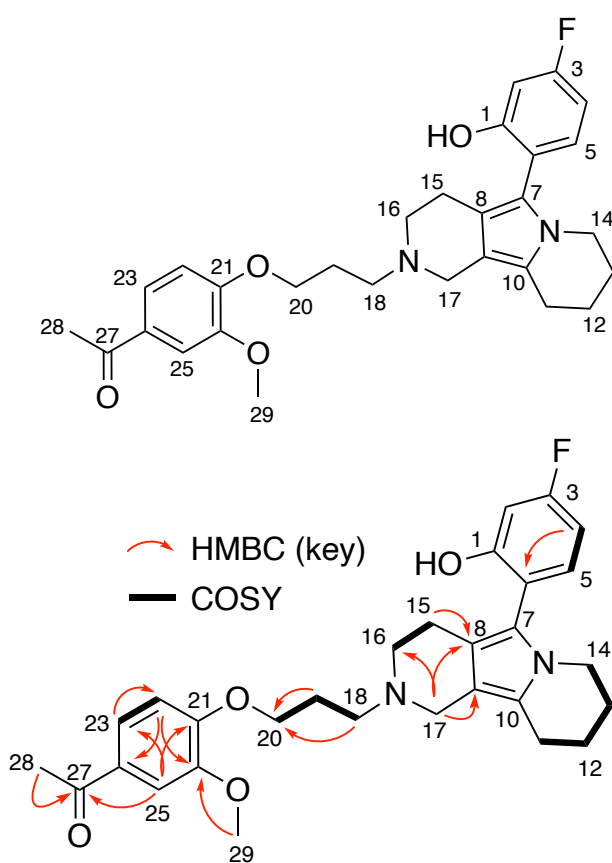
Table S17. ^1H and ^{13}C NMR data for ilo-491 in CD_3OD (600 MHz for ^1H). The carbon chemical shifts were determined by HSQC and HMBC analyses.



Position	δ_{C} , type	δ_{H} , (J in Hz)
1	165.2, qC	–
2	106.4, CH	6.69, s
3	163.4, qC	–
4	102.6, CH	6.68, d (7.5)
5	133.0, CH	7.15, m ^a
6	157.6, qC	–
7	127.4, qC	–
8	115.0, qC	–
9	111.4, qC	–
10	142.8, qC	–
11	21.1, CH_2	2.78, m
12	18.5, CH_2	1.80, m
13	22.2, CH_2	1.92, m
14	43.8, CH_2	3.64, m; 3.89, m ^a
15	18.9, CH_2	2.78, m; 2.87, m ^a
16	48.2, CH_2	3.92, m
17	156.6, CH	8.66, s
18	57.1, CH_2	4.03, t (5.0)
19	26.2, CH_2	2.35, m
20	66.3, CH_2	4.29, m
21	152.3, qC	–
22	111.3, CH	7.05, d (7.0)
23	123.2, CH	7.65, dd (7.0, 1.5)
24	130.8, qC	–
25	109.7, CH	7.47, d (1.5)
26	149.1, qC	–
27	198.1, qC	–
28	25.0, CH_3	2.56, s
29	54.6, CH_3	3.70, s

^aoverlapped signals.

Table S18. ^1H and ^{13}C NMR data for ilo-493 in CD_3OD (600 MHz for ^1H). The carbon chemical shifts were determined by HSQC and HMBC analyses.



Position	δ_{C} , type	δ_{H} , (J in Hz)
1	— ^b	—
2	105.8, CH	6.68, s
3	— ^b	—
4	102.5, CH	6.68, m ^a
5	133.0, CH	7.13, m ^a
6	157.3, qC	—
7	— ^b	—
8	110.4, qC	—
9	104.4, qC	—
10	— ^b	—
11	21.3, CH ₂	2.71, m
12	20.4, CH ₂	1.85, m
13	23.3, CH ₂	1.90, m
14	43.3, CH ₂	3.69, m; 3.81, m
15	23.4, CH ₂	2.41, m
16	52.1, CH ₂	3.33, m; 3.81, m
17	50.1, CH ₂	4.12, m; 4.67, m
18	54.6, CH ₂	3.57, m ^a
19	23.5, CH ₂	2.40, m
20	67.3, CH ₂	4.33, m
21	152.0, qC	—
22	111.0, CH	7.07, m
23	123.2, CH	7.68, m
24	130.8, qC	—
25	109.9, CH	7.51, m
26	149.0, qC	—
27	198.0, qC	—
28	25.1, CH ₃	2.56, s
29	54.6, CH ₃	3.62, s

^aoverlapped signals.

Fig. S38. ^1H NMR spectrum of ilo-430.

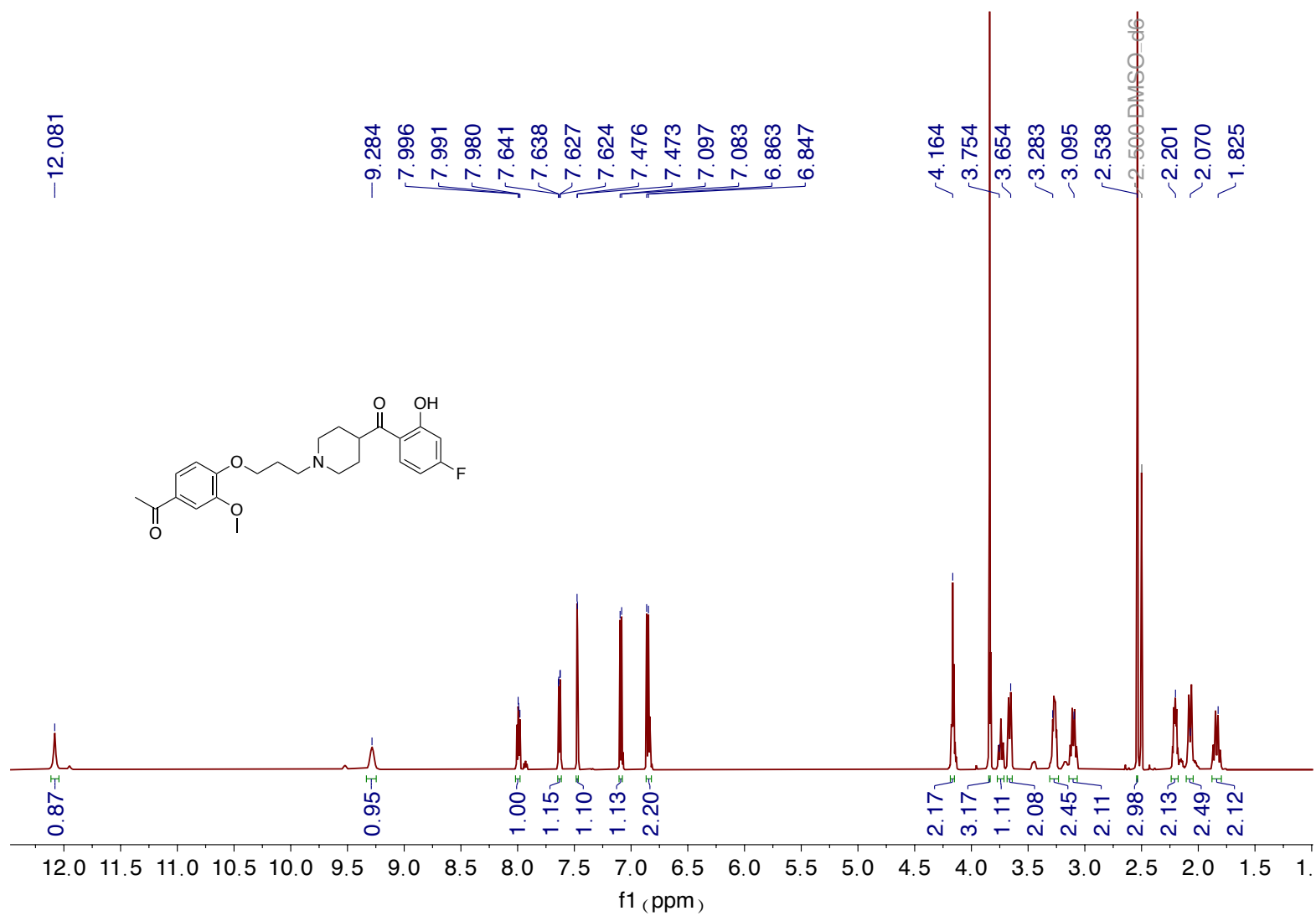


Fig. S39. ^1H - ^1H COSY spectrum of ilo-430.

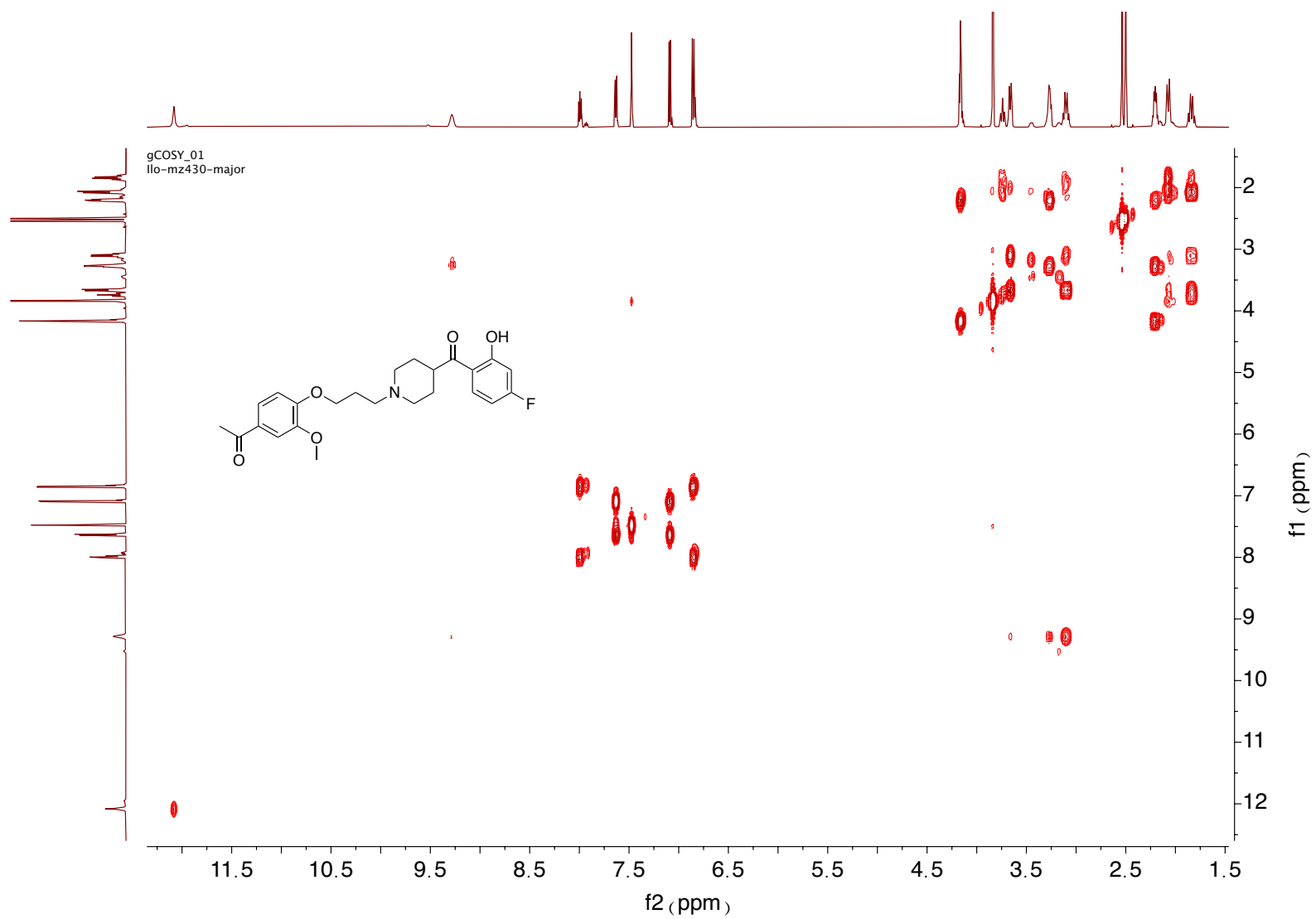


Fig. S40. HSQC spectrum of ilo-430.

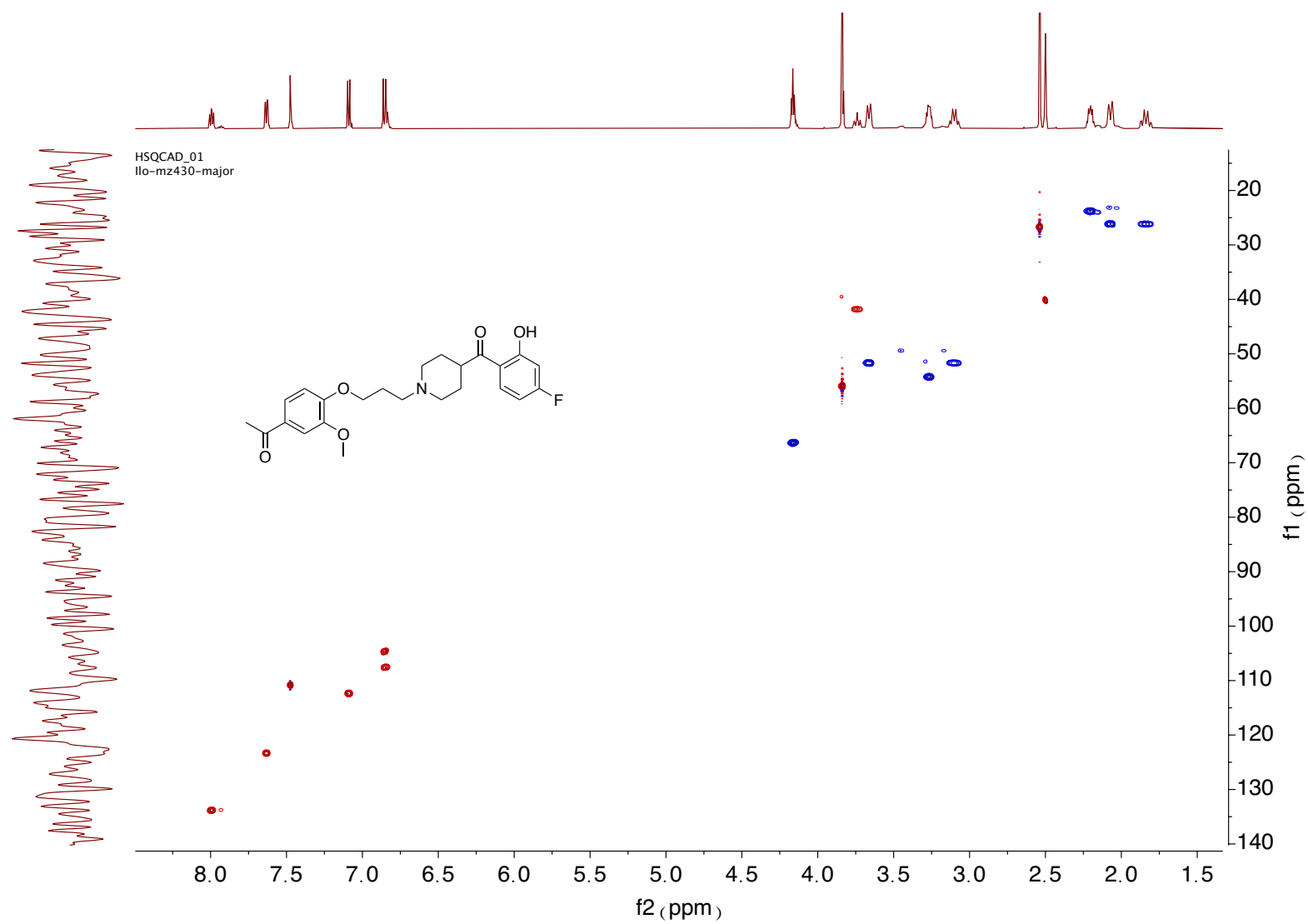


Fig. S41. HMBC spectrum of ilo-430.

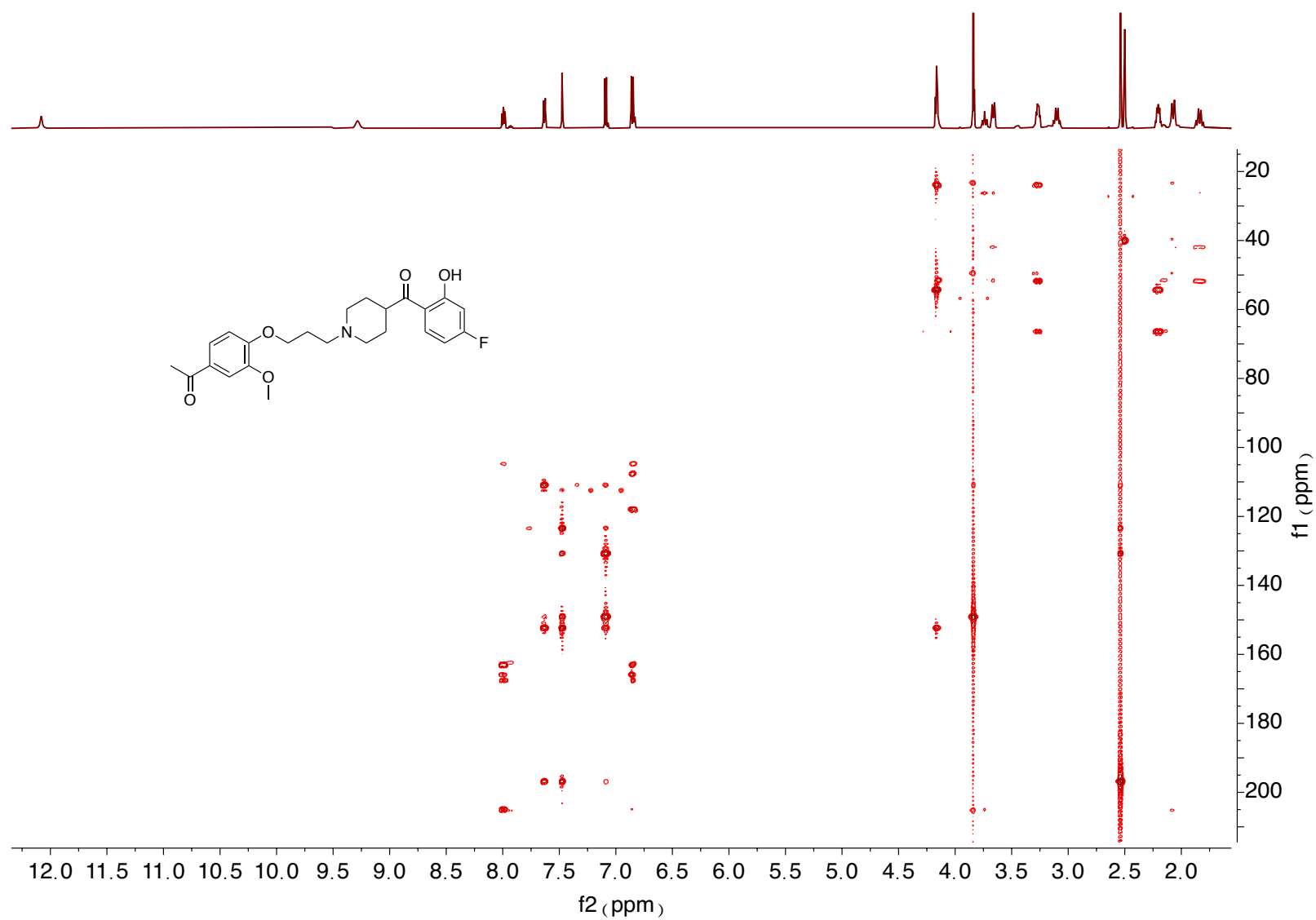


Fig. S42. ^1H NMR spectrum of ilo-444.

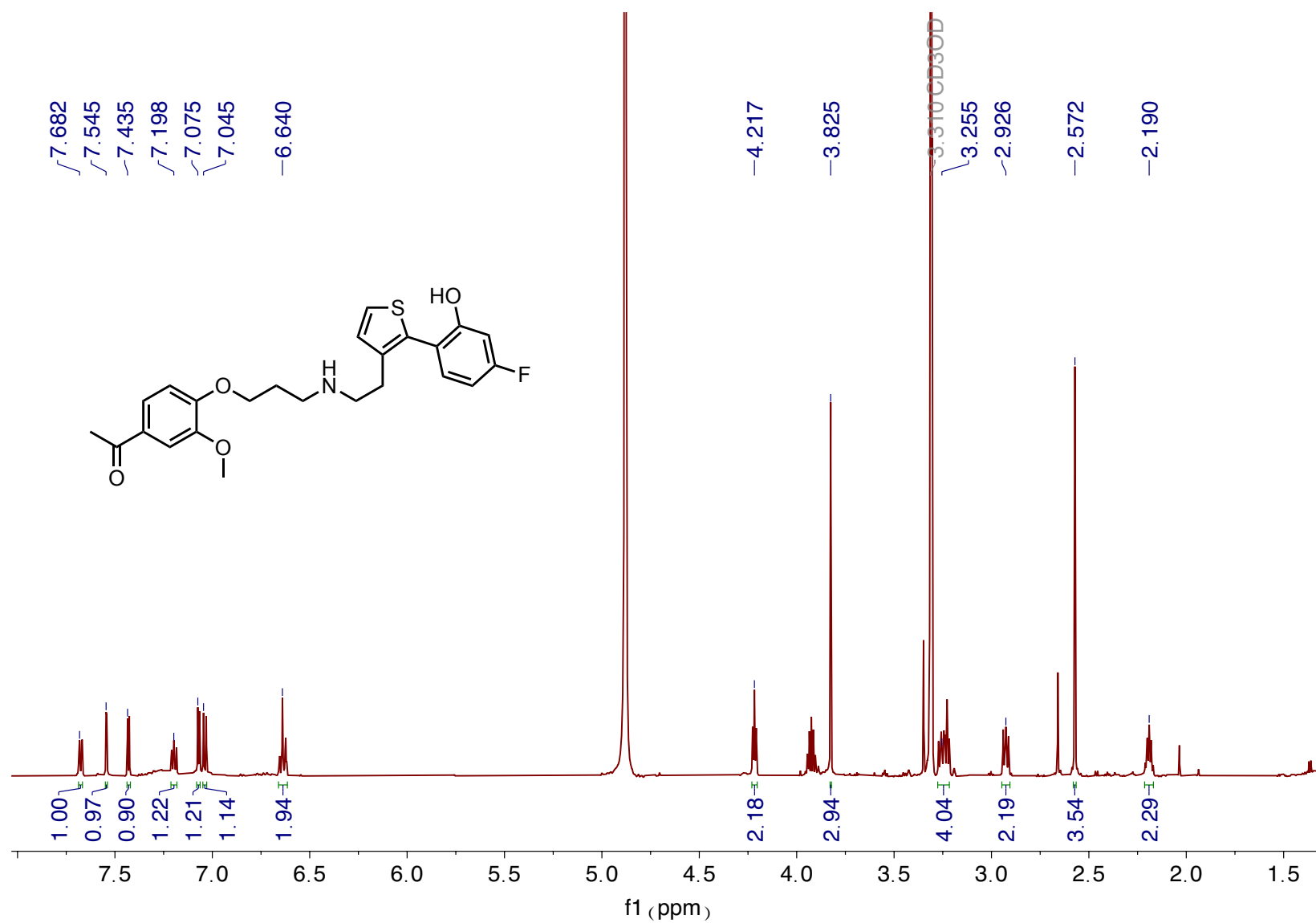


Fig. S43. ^1H - ^1H COSY spectrum of ilo-444.

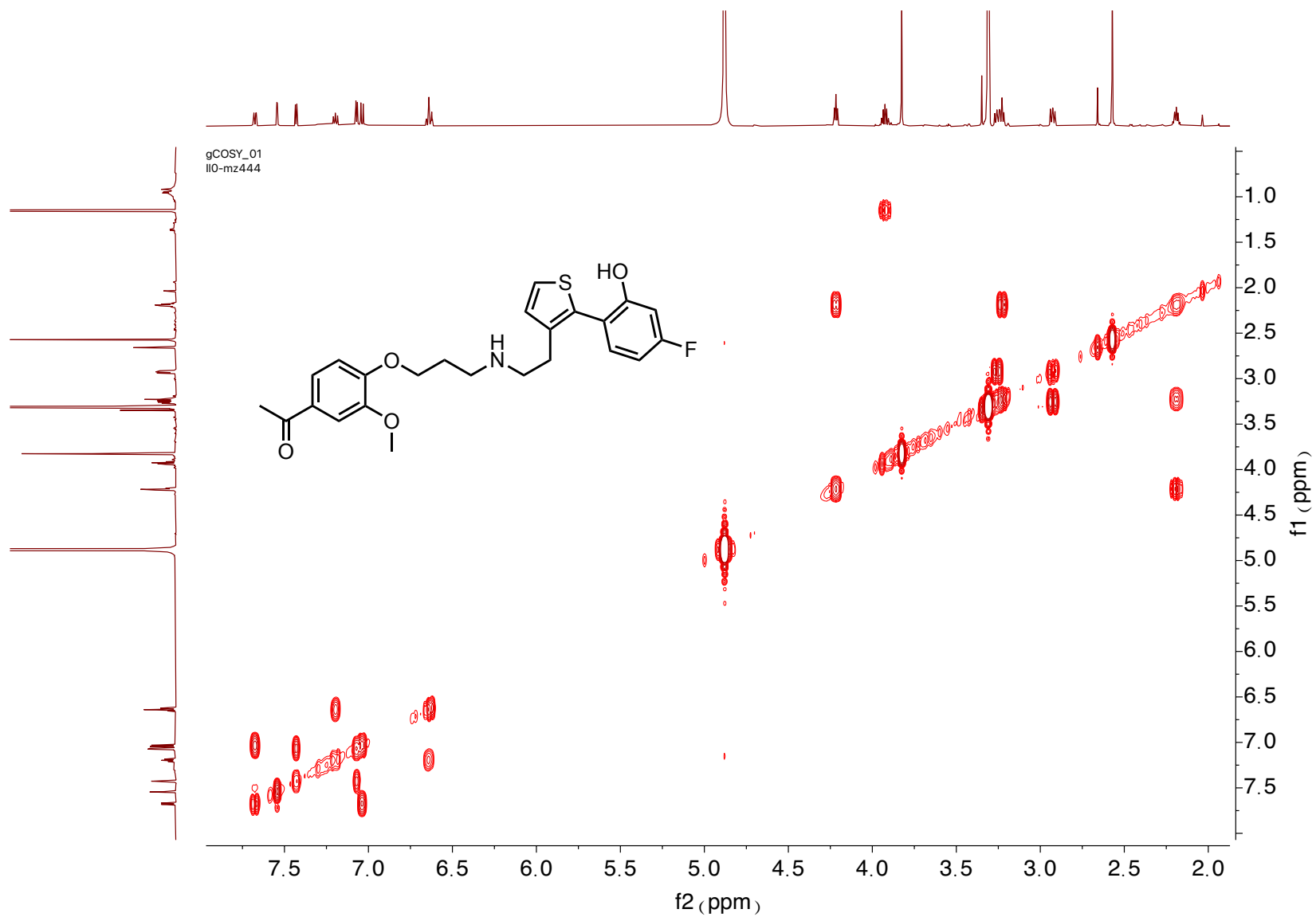


Fig. S44. HSQC spectrum of ilo-444.

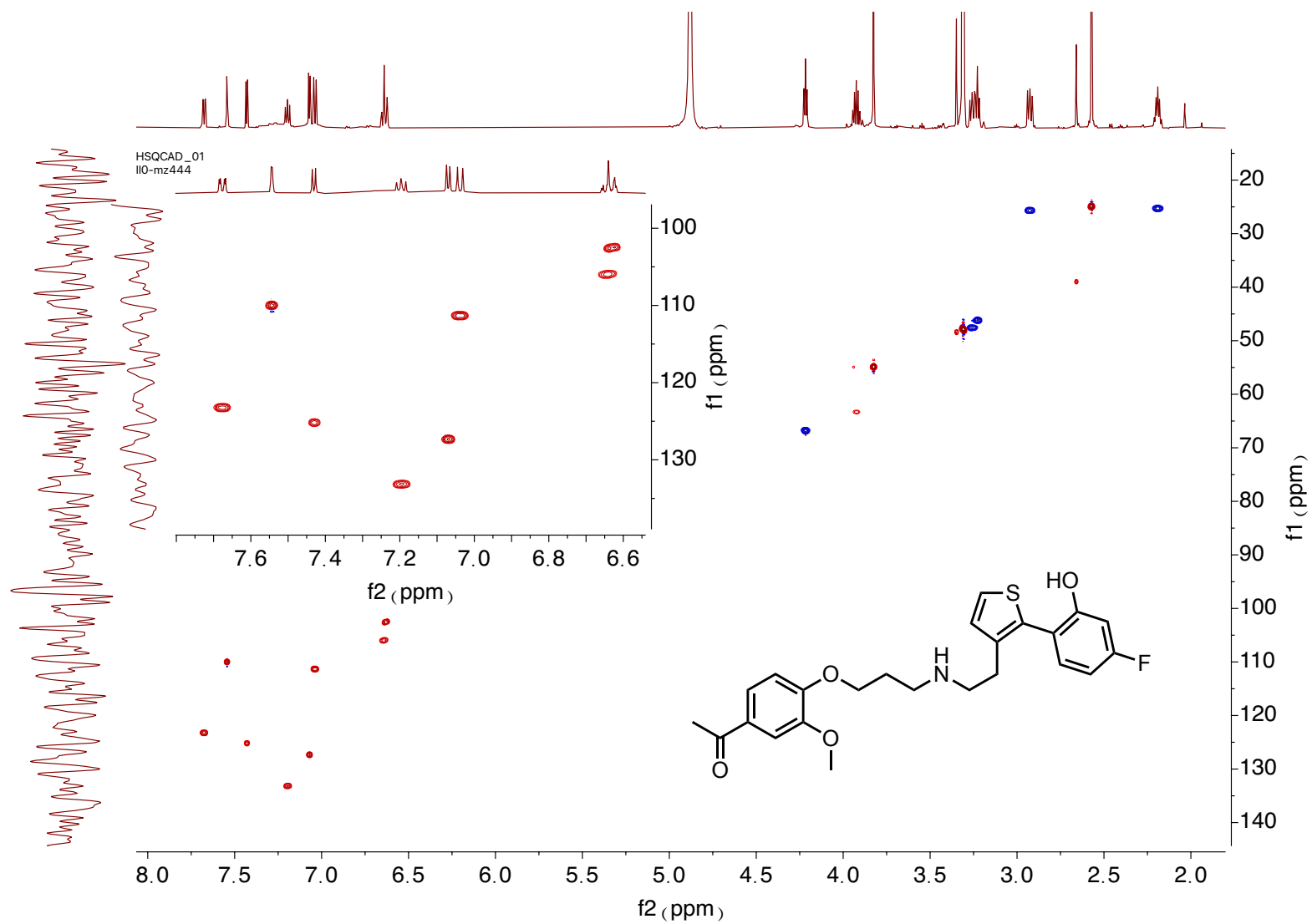


Fig. S45. HMBC spectrum of ilo-444.

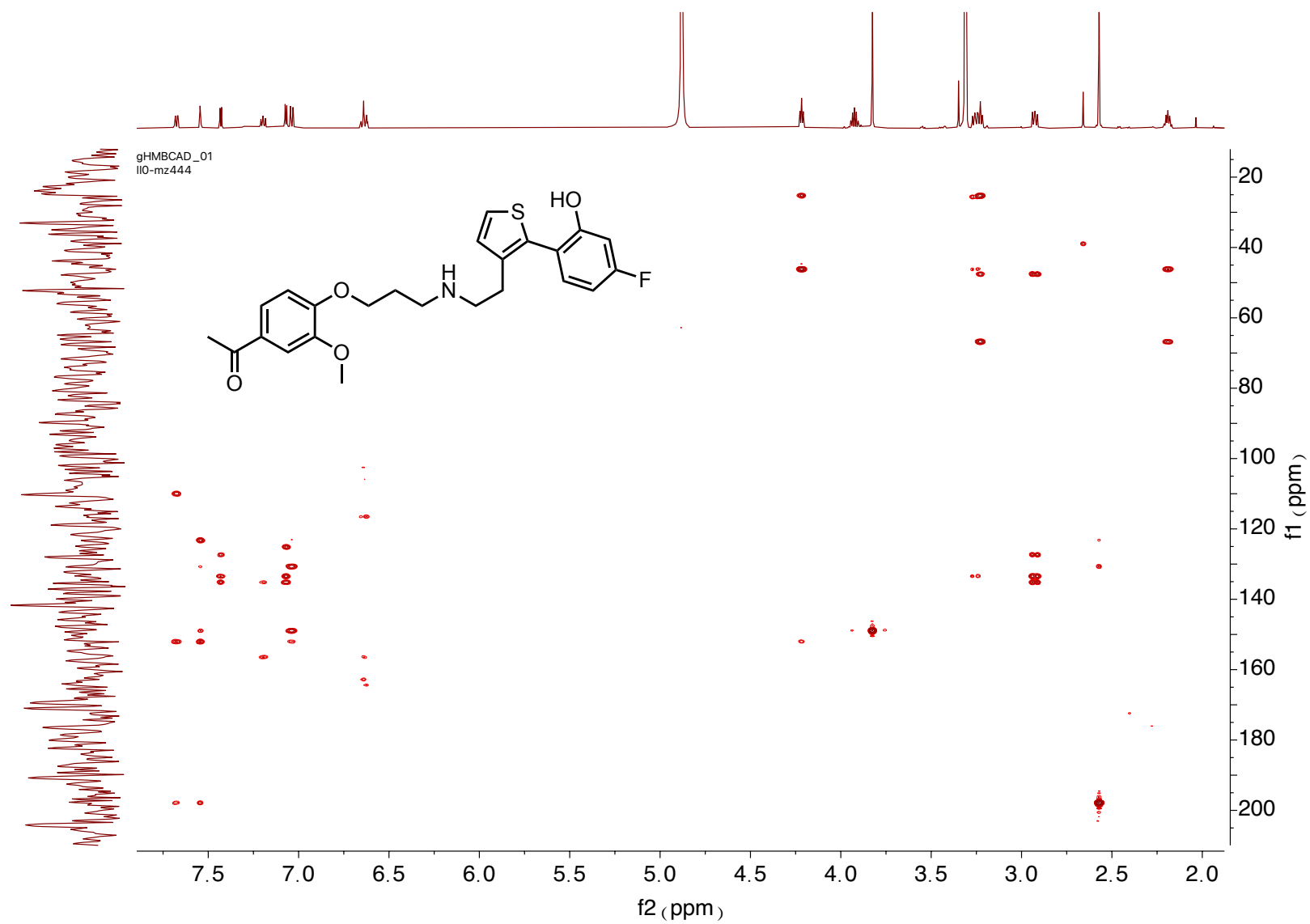


Fig. S46. ^1H NMR spectrum of ilo-491.

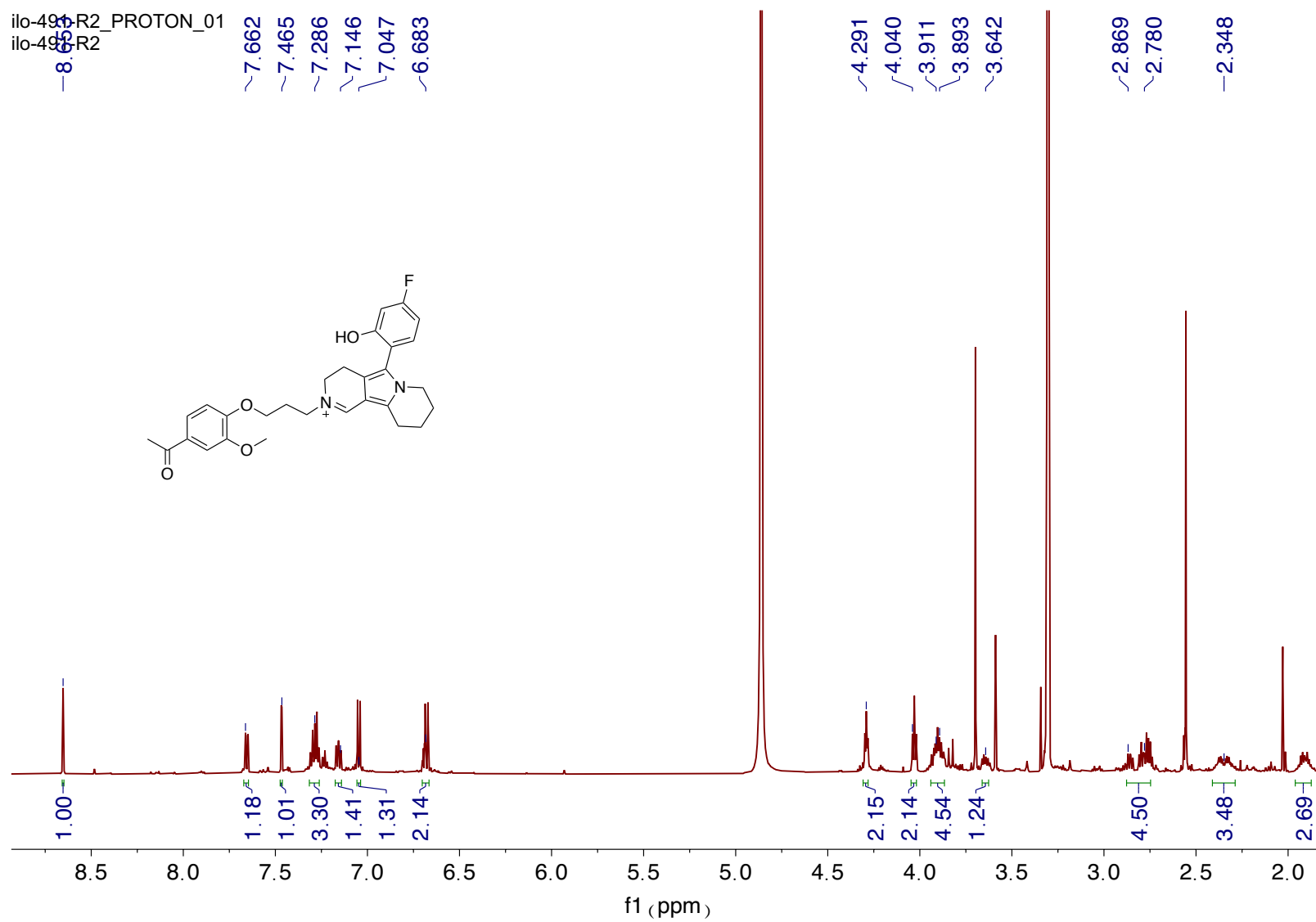


Fig. S47. ^1H - ^1H COSY spectrum of ilo-491.

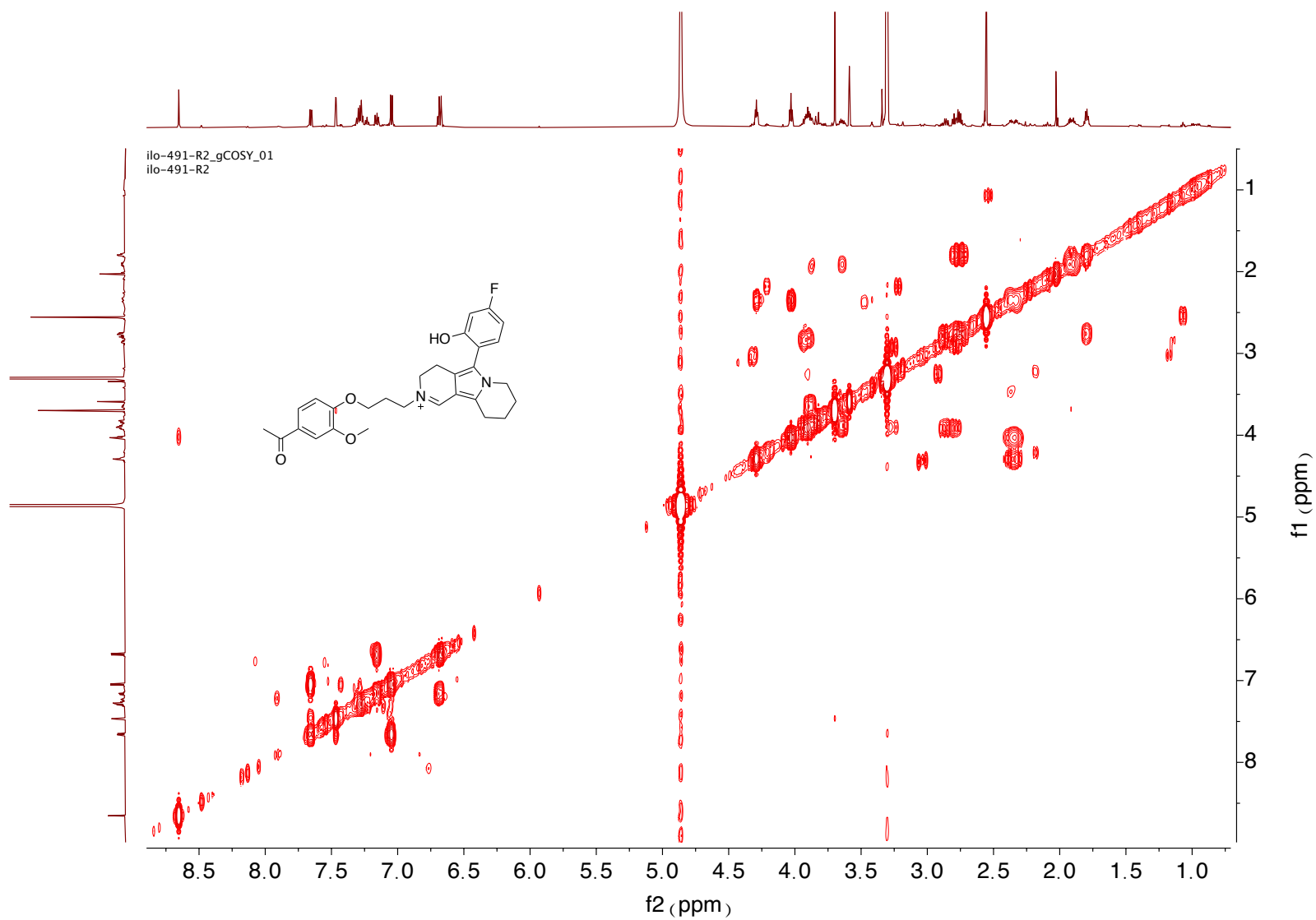


Fig. S48. HSQC spectrum of ilo-491.

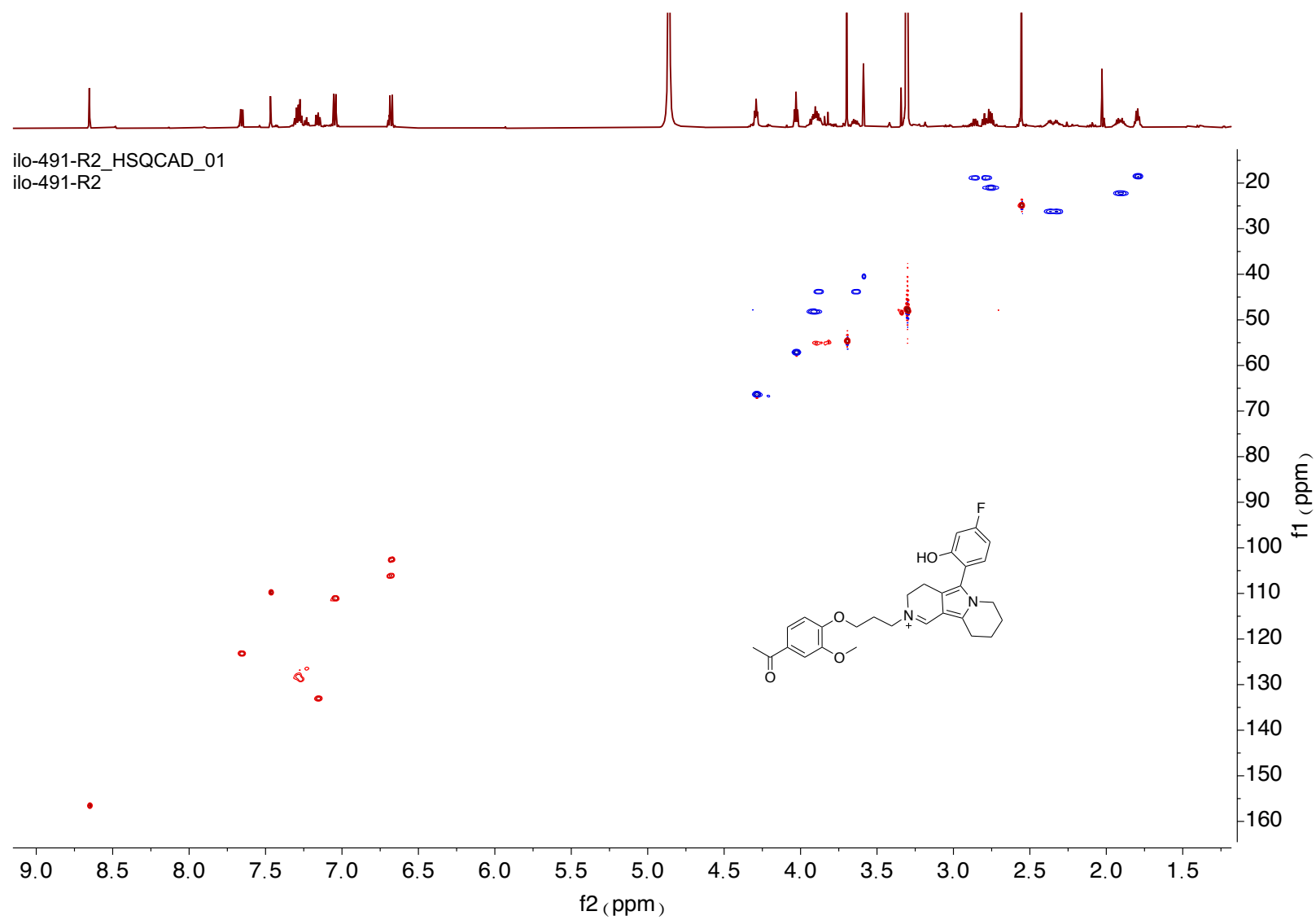


Fig. S49. HMBC spectrum of ilo-491.

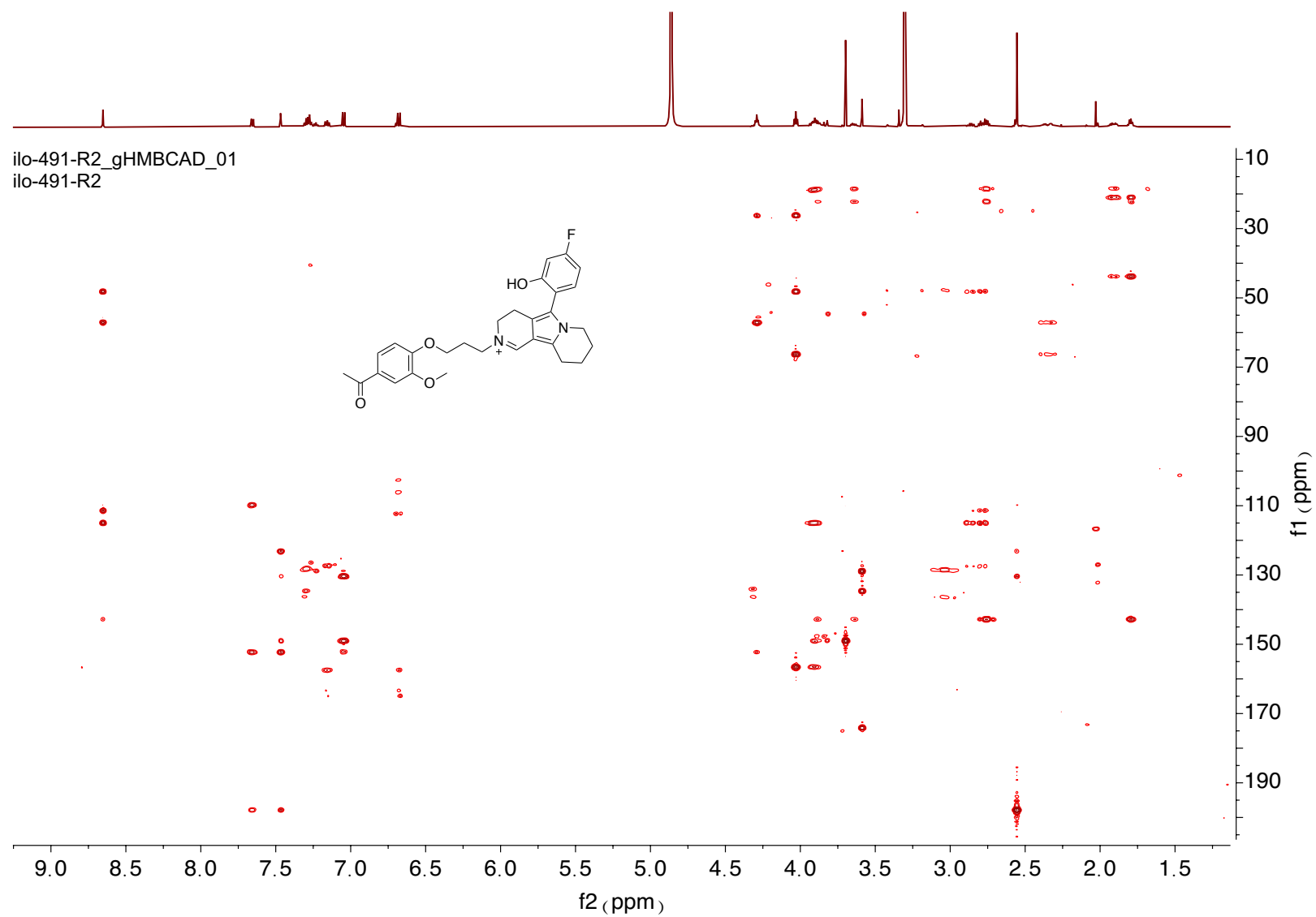


Fig. S50. ^1H NMR spectrum of ilo-493.

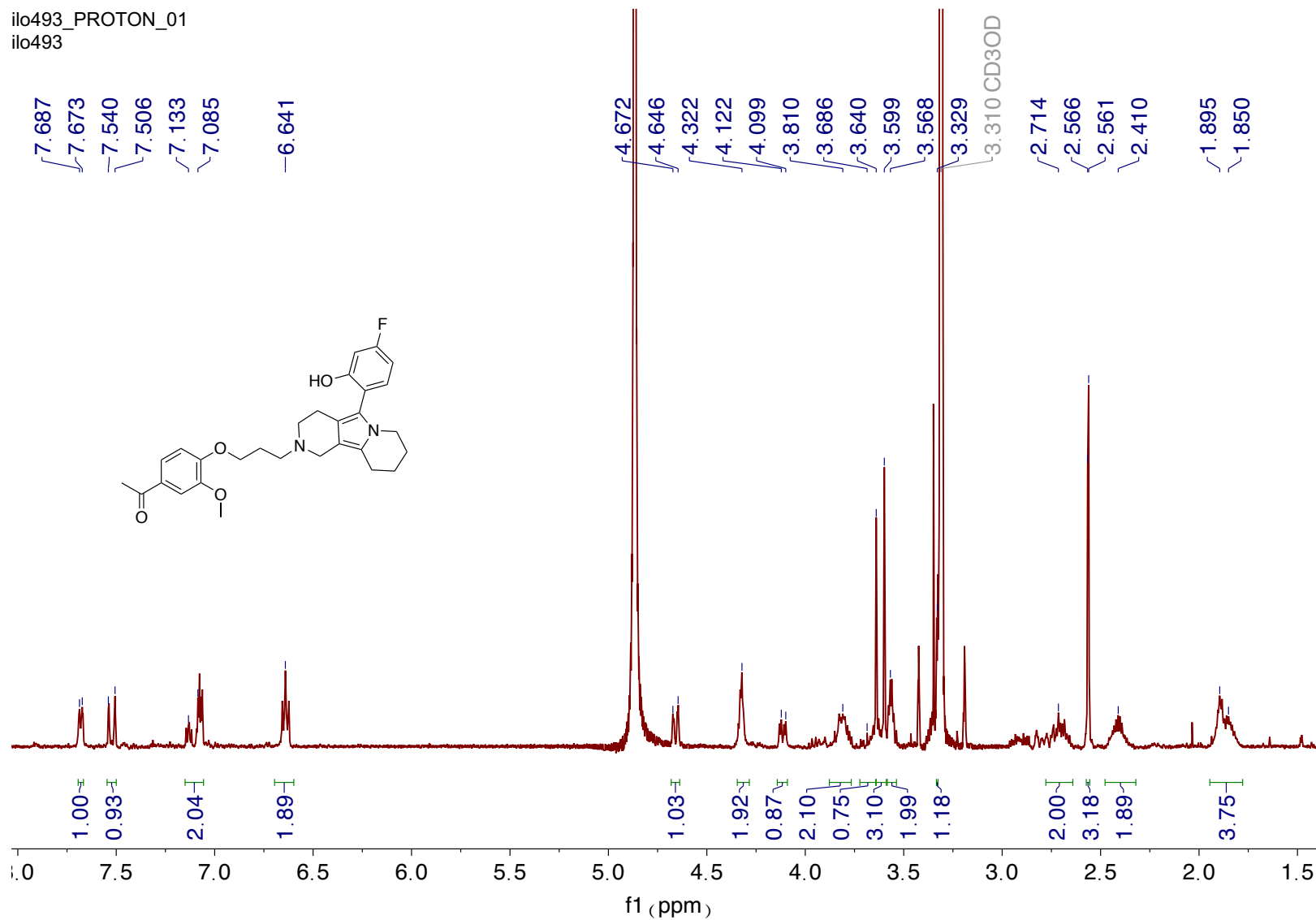


Fig. S51. ^1H - ^1H COSY spectrum of ilo-493.

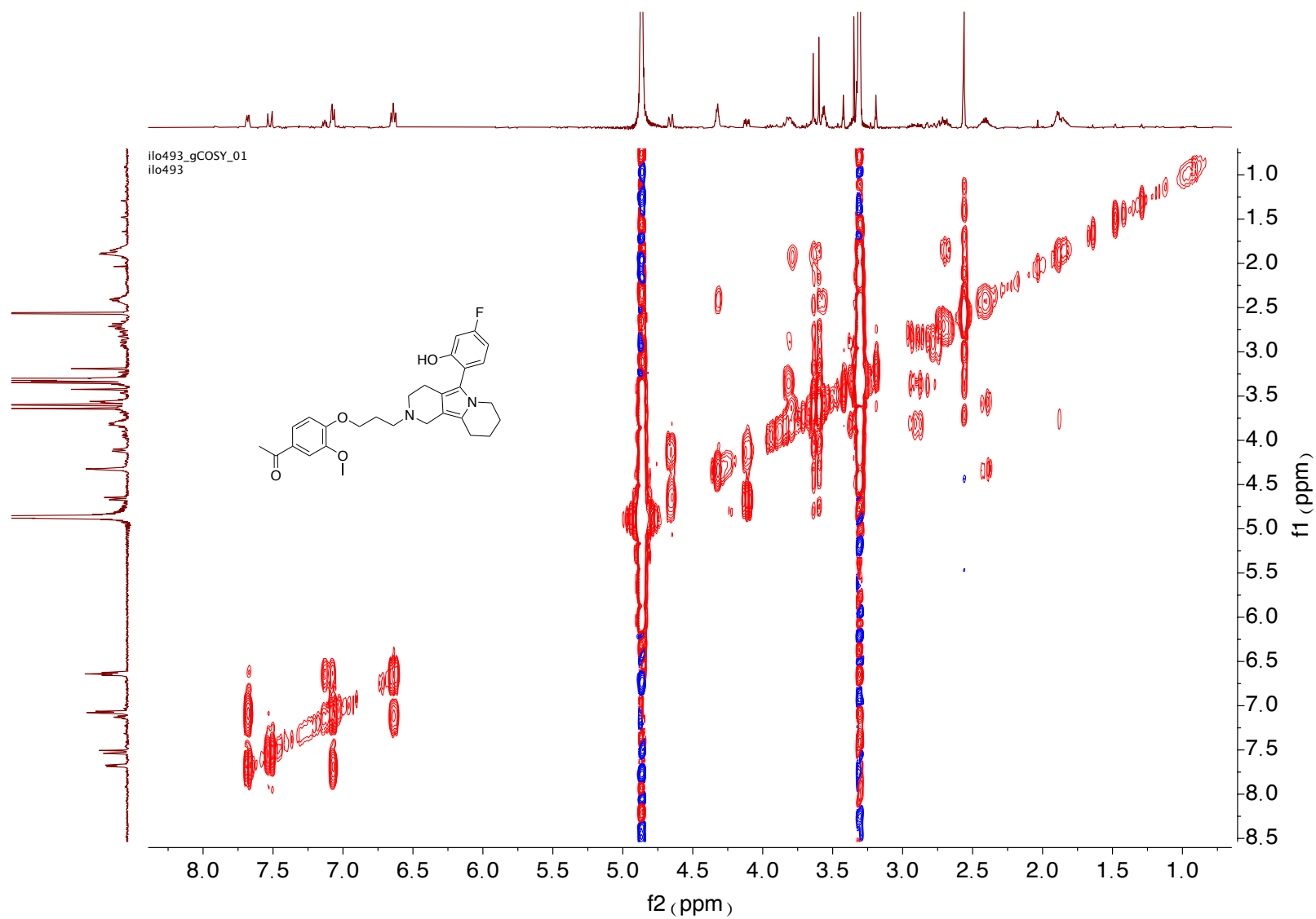


Fig. S52. HSQC spectrum of ilo-493.

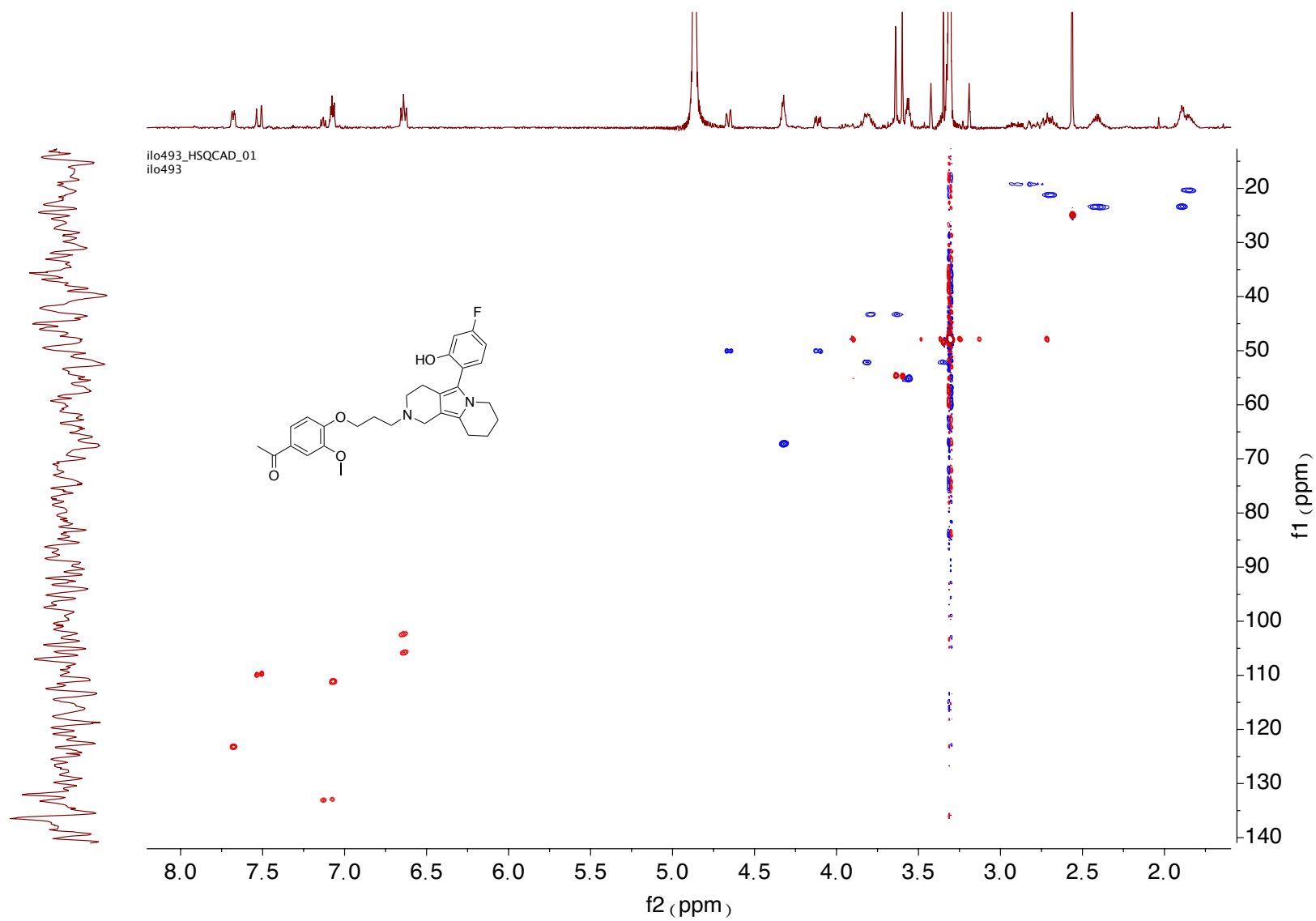


Fig. S53. HMBC spectrum of ilo-493.

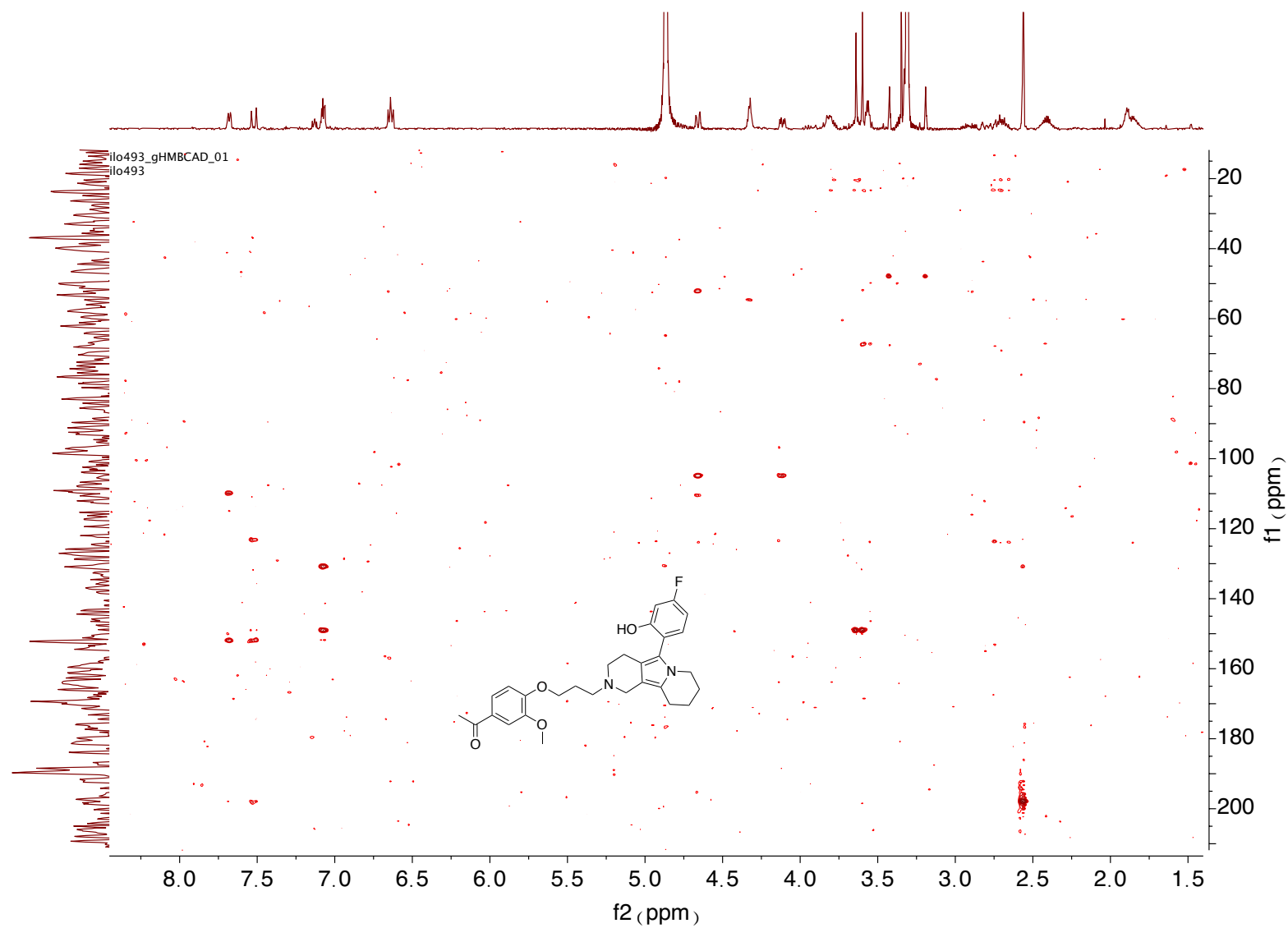


Fig. S54. HR-ESI-MS of ilo-430. Ilo-430 $m/z_{\text{calcd.}}$ 430.2024, $m/z_{\text{obs.}}$ 430.2025.

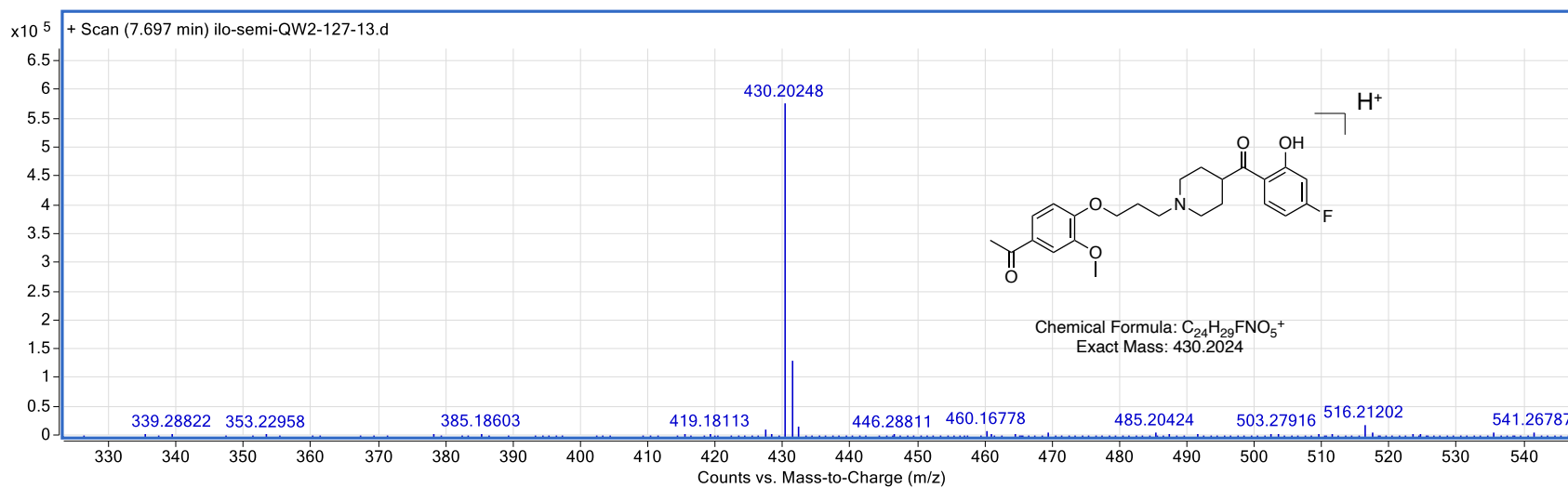


Fig. S55. HR-ESI-MS of ilo-432. Ilo-432, $m/z_{\text{calcd.}}$ 432.2181, $m/z_{\text{obs.}}$ 432.2188.

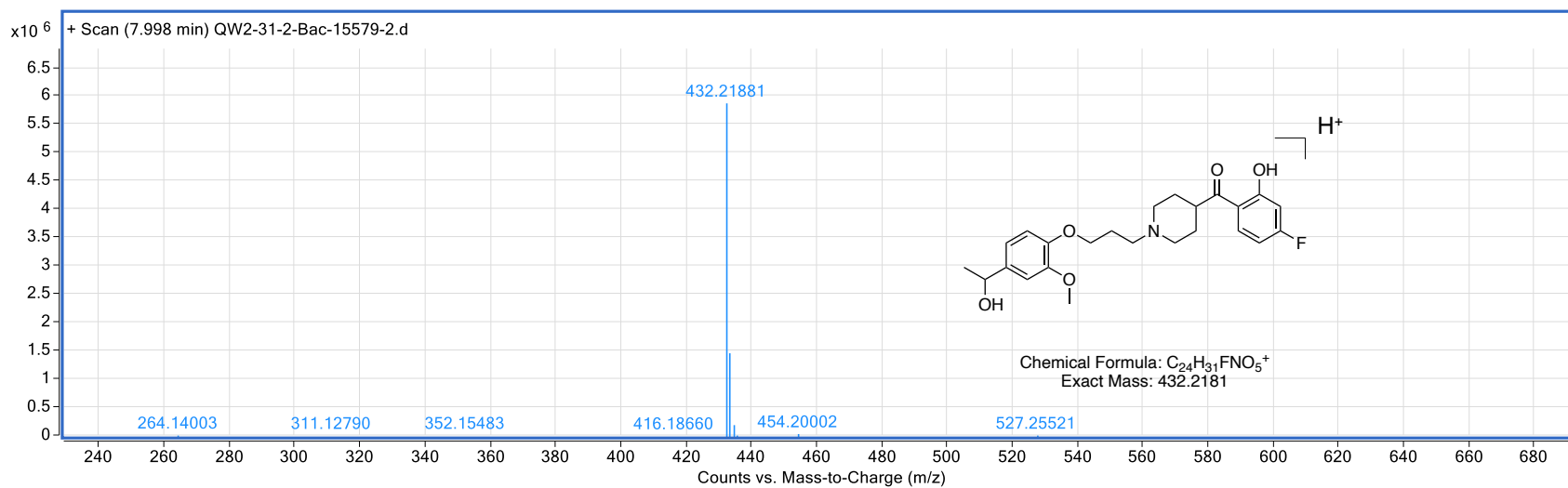


Fig. S56. HR-ESI-MS of ilo-444. Ilo-444, $m/z_{\text{calcd.}}$ 444.1639, $m/z_{\text{obs.}}$ 444.1637.

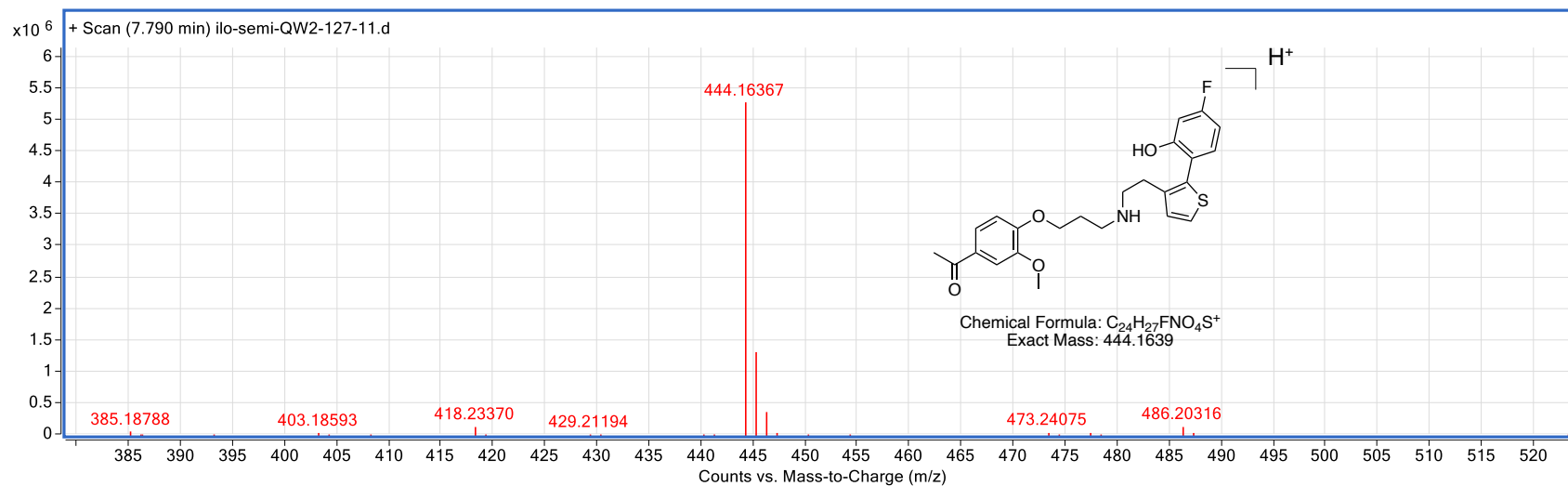


Fig. S57. HR-ESI-MS of ilo-491. Ilo-491, $m/z_{\text{calcd.}}$ 491.2341, $m/z_{\text{obs.}}$ 491.2341.

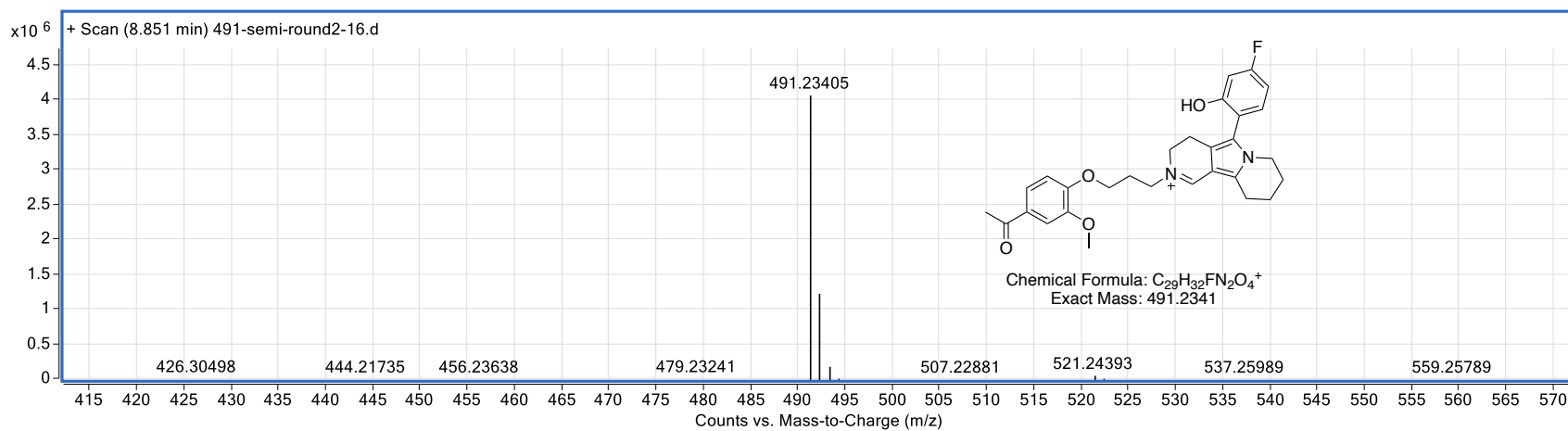


Fig. S58. HR-ESI-MS of ilo-477. Ilo-477, $m/z_{\text{calcd.}}$ 477.2184, $m/z_{\text{obs.}}$ 477.2189.

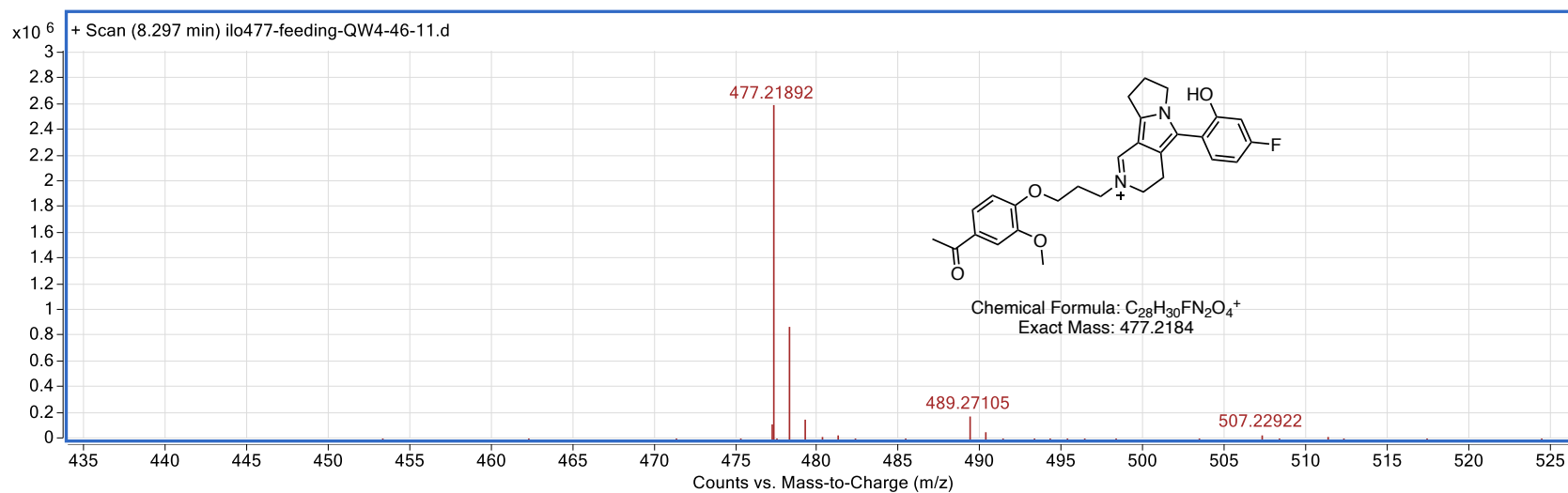


Fig. S59. HR-ESI-MS of ilo-493. Ilo-493, $m/z_{\text{calcd.}}$ 493.2497, $m/z_{\text{obs.}}$ 493.2499.

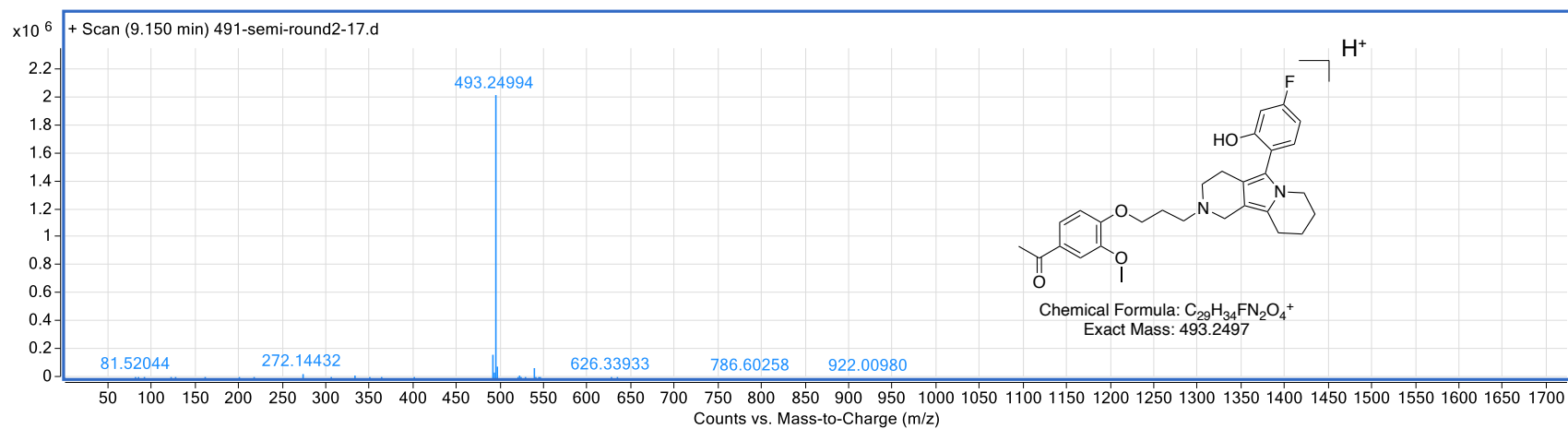


Fig. S60. Proposed HR-ESI-MS² fragmentation of ilo-430. Fragment A: $m/z_{\text{calcd.}}$ 264.1394, $m/z_{\text{obs.}}$ 264.1395; Fragment B: $m/z_{\text{calcd.}}$ 236.1081, $m/z_{\text{obs.}}$ 236.1085; Fragment C: $m/z_{\text{calcd.}}$ 222.0925, $m/z_{\text{obs.}}$ 222.0920; Fragment D: $m/z_{\text{calcd.}}$ 193.0659, $m/z_{\text{obs.}}$ 193.0660; Fragment E: $m/z_{\text{calcd.}}$ 139.0190, $m/z_{\text{obs.}}$ 139.0186.

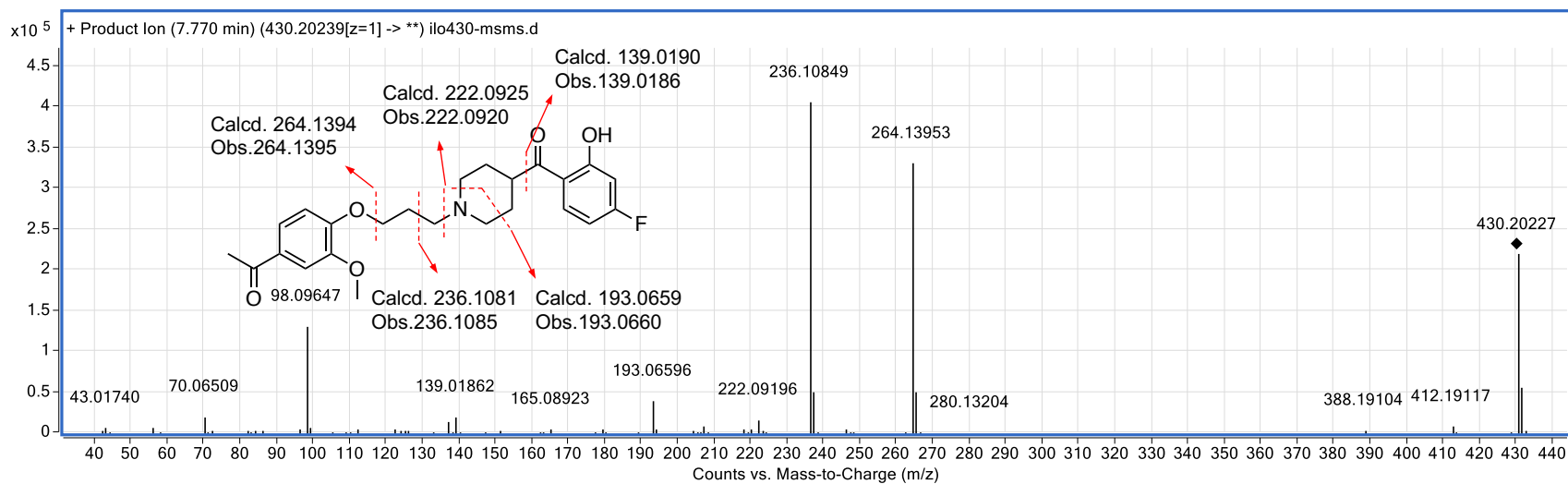


Fig. S61. Proposed HR-ESI-MS² fragmentation of ilo-432. Fragment A: $m/z_{\text{calcd.}}$ 264.1394, $m/z_{\text{obs.}}$ 264.1394; Fragment B: $m/z_{\text{calcd.}}$ 236.1081, $m/z_{\text{obs.}}$ 236.1083; Fragment C: $m/z_{\text{calcd.}}$ 222.0925, $m/z_{\text{obs.}}$ 222.0926; Fragment D: $m/z_{\text{calcd.}}$ 193.0659, $m/z_{\text{obs.}}$ 193.0659.

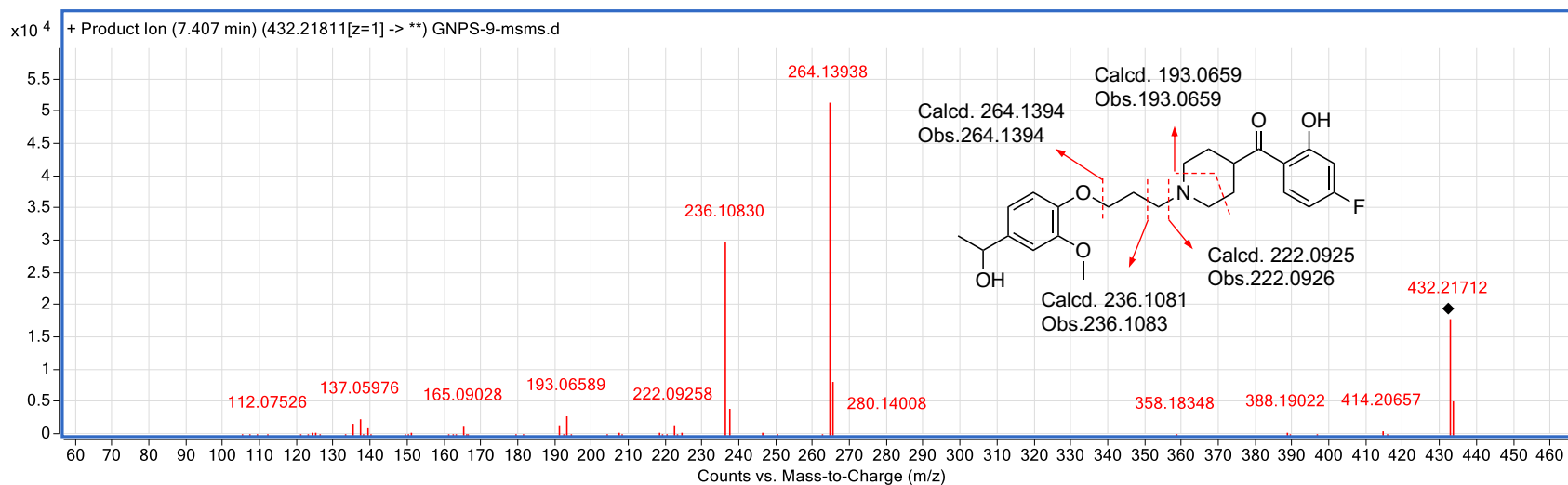


Fig. S62. Proposed HR-ESI-MS² fragmentation of ilo-444. Fragment A: $m/z_{\text{calcd.}}$ 278.1009, $m/z_{\text{obs.}}$ 278.1001; Fragment B: $m/z_{\text{calcd.}}$ 221.0431, $m/z_{\text{obs.}}$ 221.0430; Fragment C: $m/z_{\text{calcd.}}$ 203.0325, $m/z_{\text{obs.}}$ 203.0321.

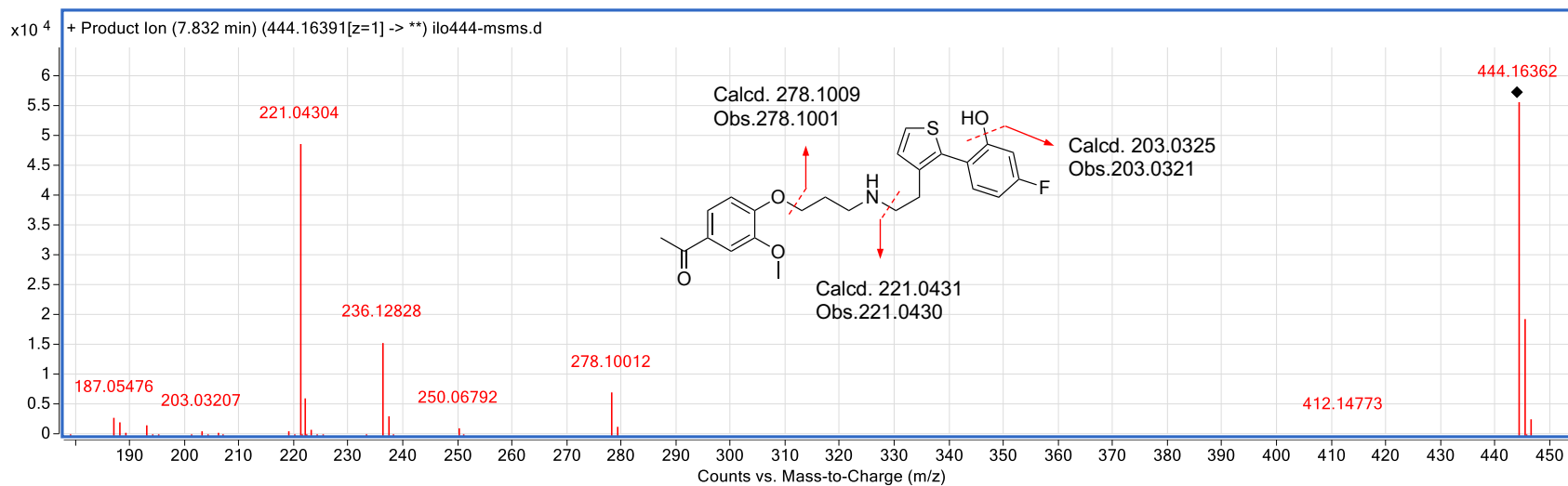


Fig. S63. Proposed HR-ESI-MS² fragmentation of ilo-491. Fragment A: $m/z_{\text{calcd.}}$ 475.2028, $m/z_{\text{obs.}}$ 475.2002; Fragment B: $m/z_{\text{calcd.}}$ 447.2078, $m/z_{\text{obs.}}$ 447.2079; Fragment C: $m/z_{\text{calcd.}}$ 325.1711, $m/z_{\text{obs.}}$ 325.1714; Fragment D: $m/z_{\text{calcd.}}$ 311.1554, $m/z_{\text{obs.}}$ 311.1550.

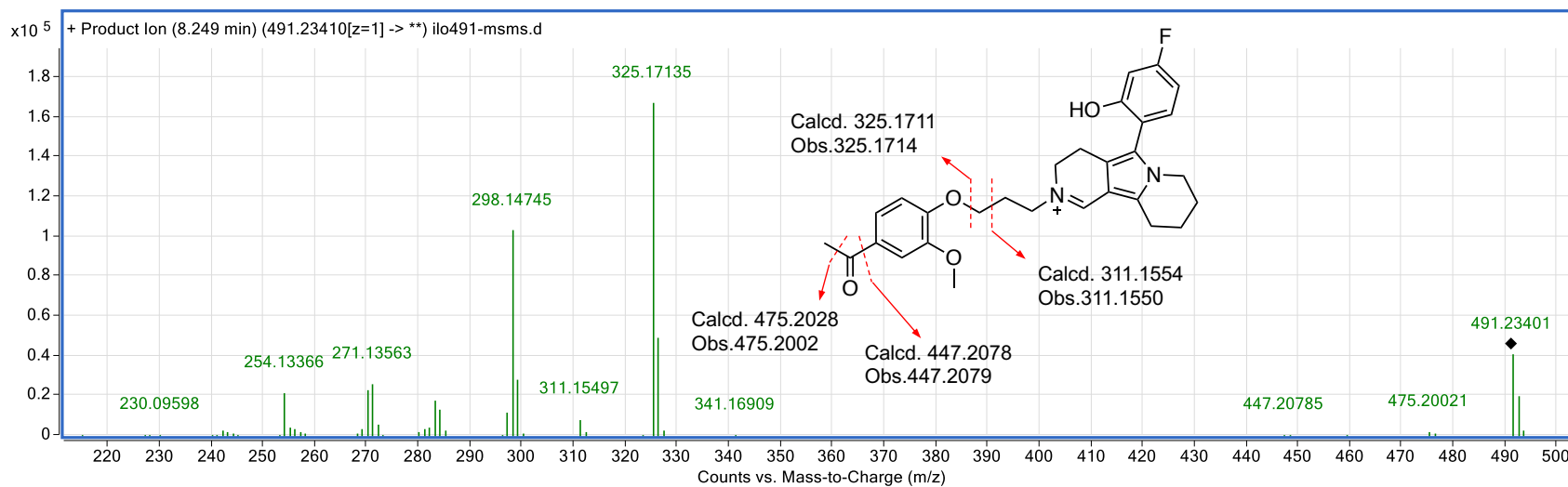


Fig. S64. Proposed HR-ESI-MS² fragmentation of ilo-493. Fragment A: $m/z_{\text{calcd.}}$ 327.1867, $m/z_{\text{obs.}}$ 327.1871; Fragment B: $m/z_{\text{calcd.}}$ 272.1445, $m/z_{\text{obs.}}$ 272.1454; Fragment C: $m/z_{\text{calcd.}}$ 258.1289, $m/z_{\text{obs.}}$ 258.1285; Fragment D: $m/z_{\text{calcd.}}$ 230.0976, $m/z_{\text{obs.}}$ 230.0986; Fragment E: $m/z_{\text{calcd.}}$ 189.0710, $m/z_{\text{obs.}}$ 189.0717.

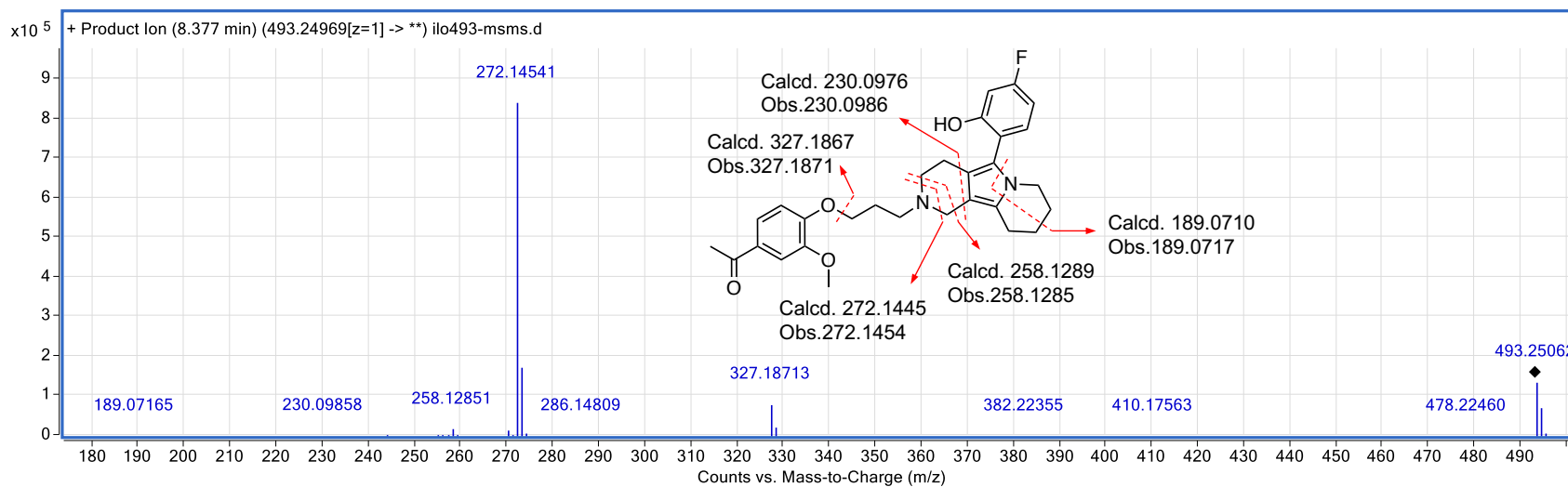


Fig. S65. Proposed HR-ESI-MS² fragmentation of ilo-477. Fragment A: $m/z_{\text{calcd.}}$ 461.1871, $m/z_{\text{obs.}}$ 461.1880; Fragment B: $m/z_{\text{calcd.}}$ 311.1554, $m/z_{\text{obs.}}$ 311.1542; Fragment C: $m/z_{\text{calcd.}}$ 240.1179, $m/z_{\text{obs.}}$ 240.1179.

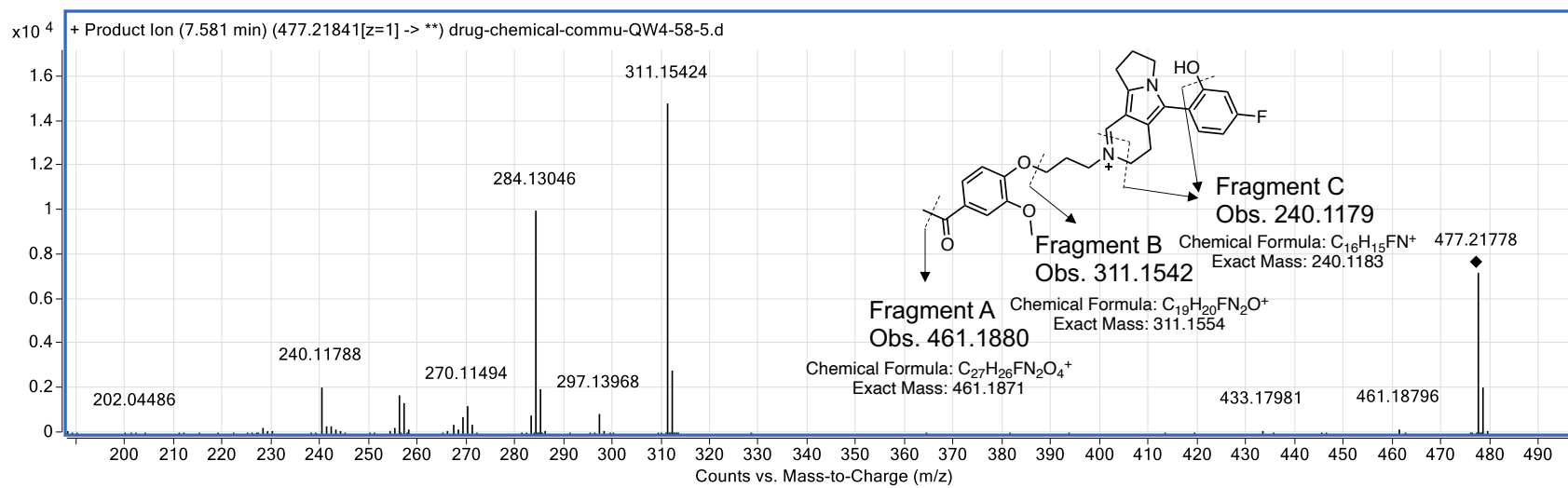


Fig. S66. Fragmentation tree that contains the selected observed MS/MS fragments of ilo-430 (*m/z* 430.2008) as revealed by SIRIUS. A representative charge state is shown.

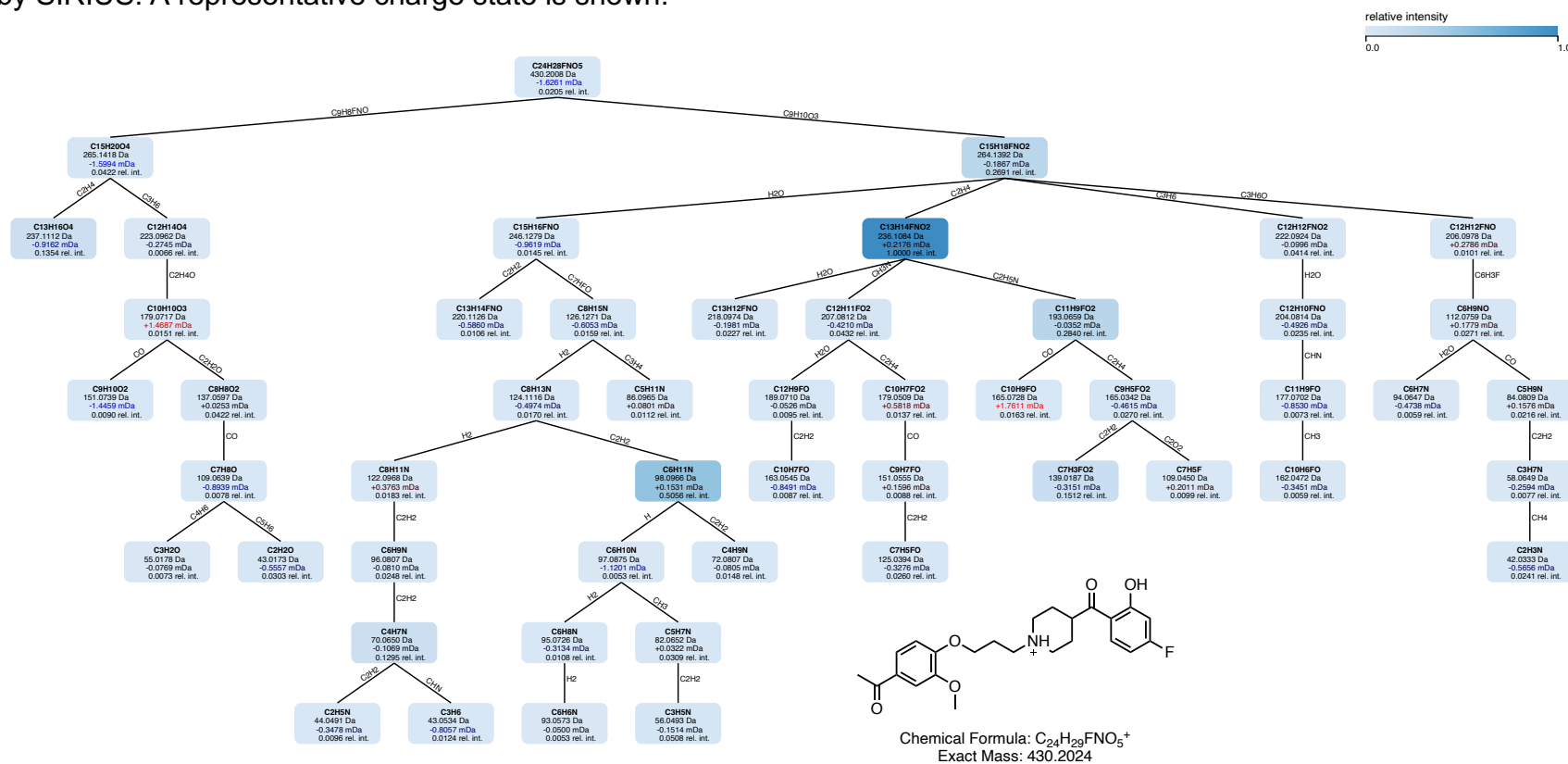


Fig. S67. Fragmentation tree that contains the selected observed MS/MS fragments of ilo-444 (m/z 444.1636) as revealed by SIRIUS. A representative charge state is shown.

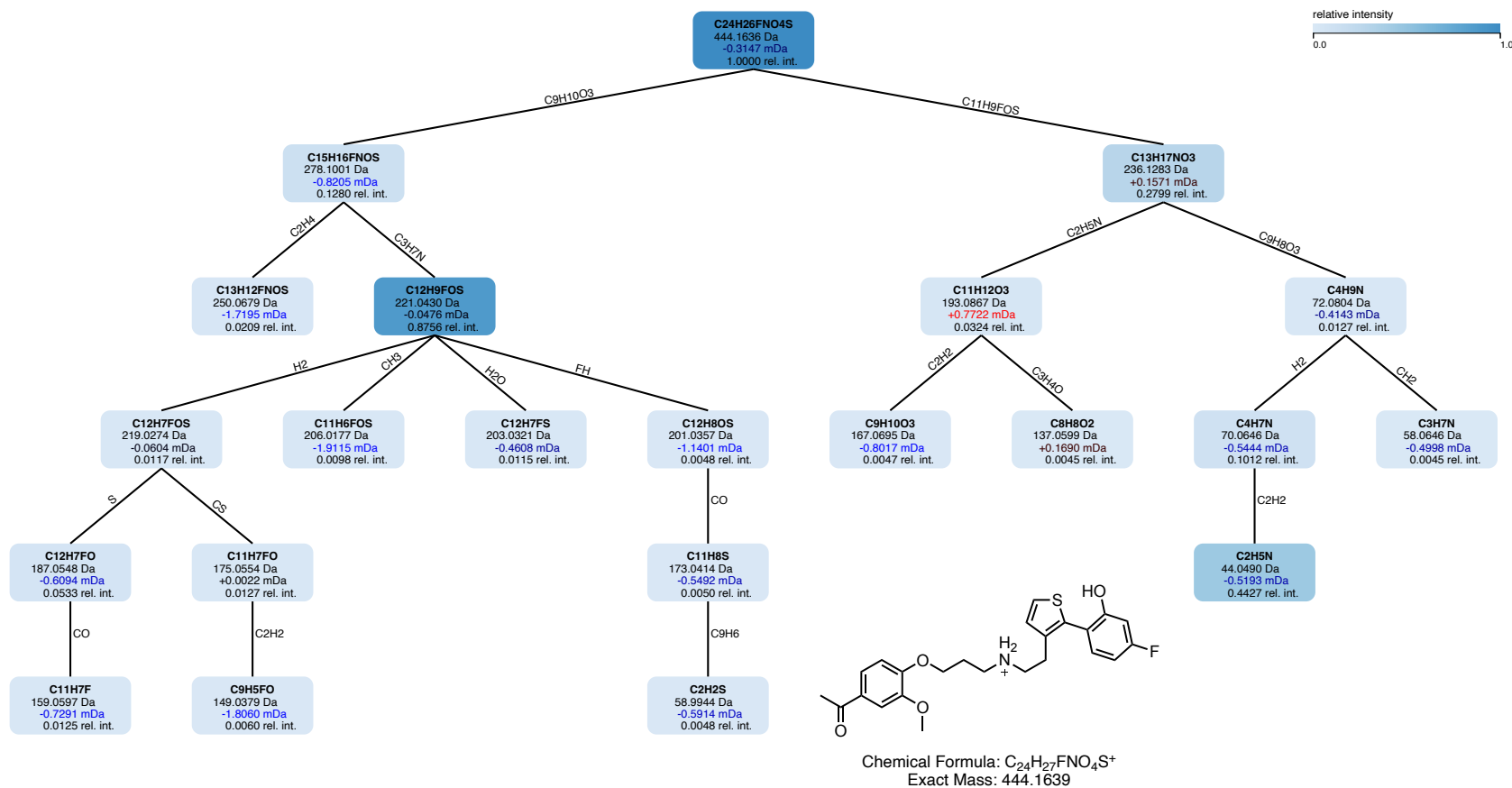


Fig. S68. Fragmentation tree that contains the selected observed MS/MS fragments of ilo-491 (m/z 491.2343) as revealed by SIRIUS.

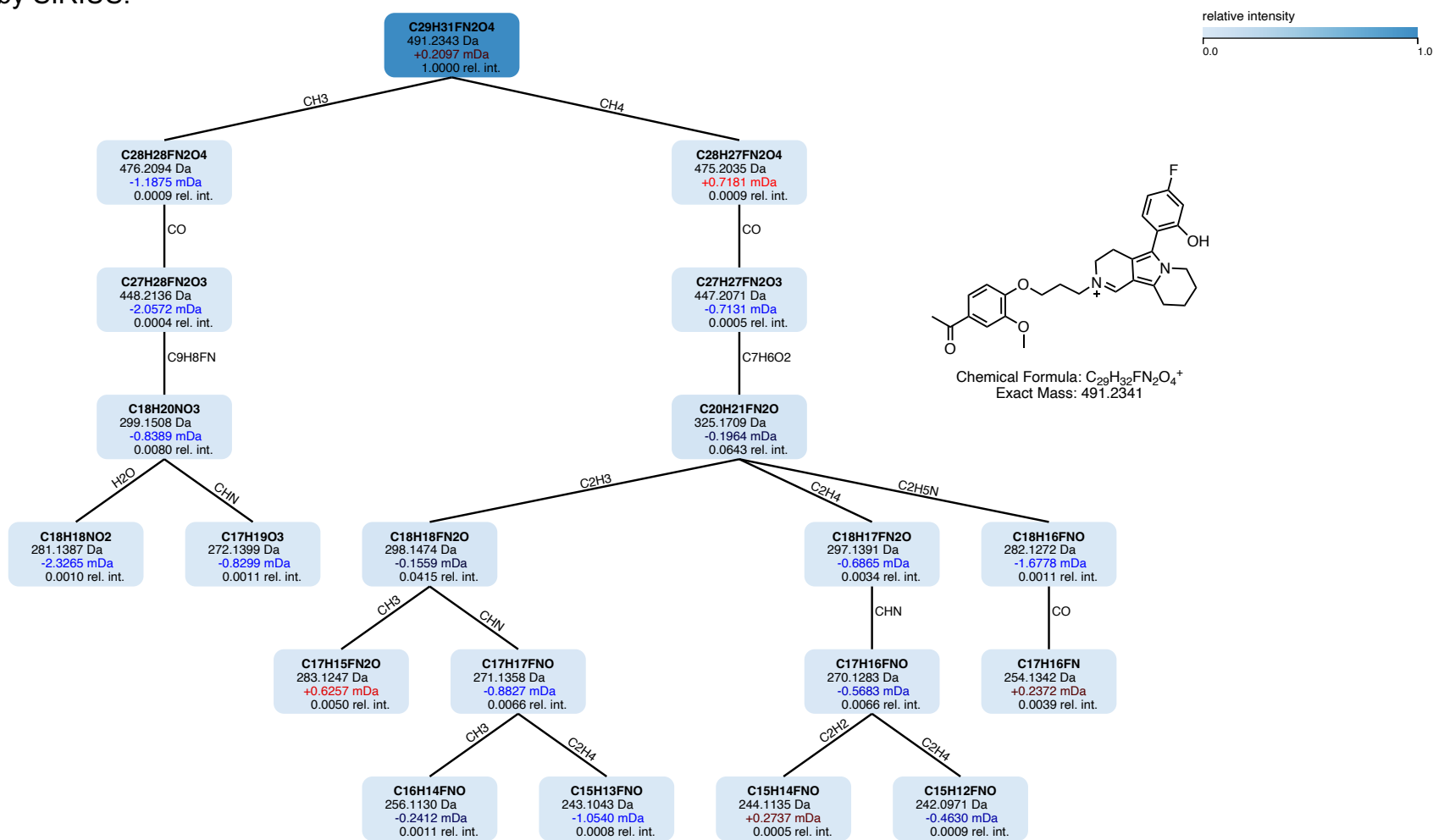


Fig. S69. Fragmentation tree that contains the selected observed MS/MS fragments of ilo-493 (m/z 493.2489) as revealed by SIRIUS. A representative charge state is shown.

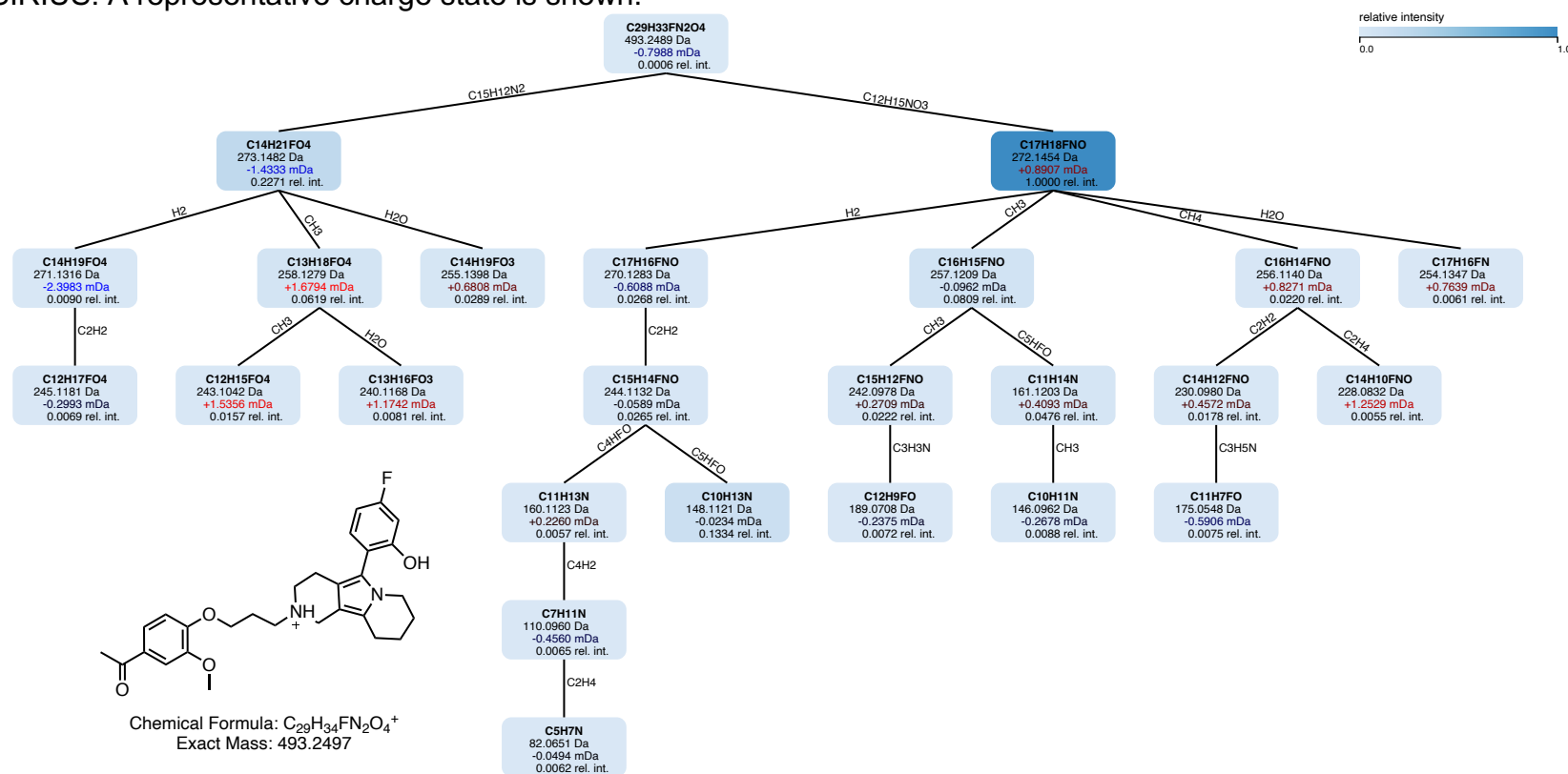


Fig. S70. Fragmentation tree that contains the selected observed MS/MS fragments of ilo-477 (m/z 477.2184) as revealed by SIRIUS.

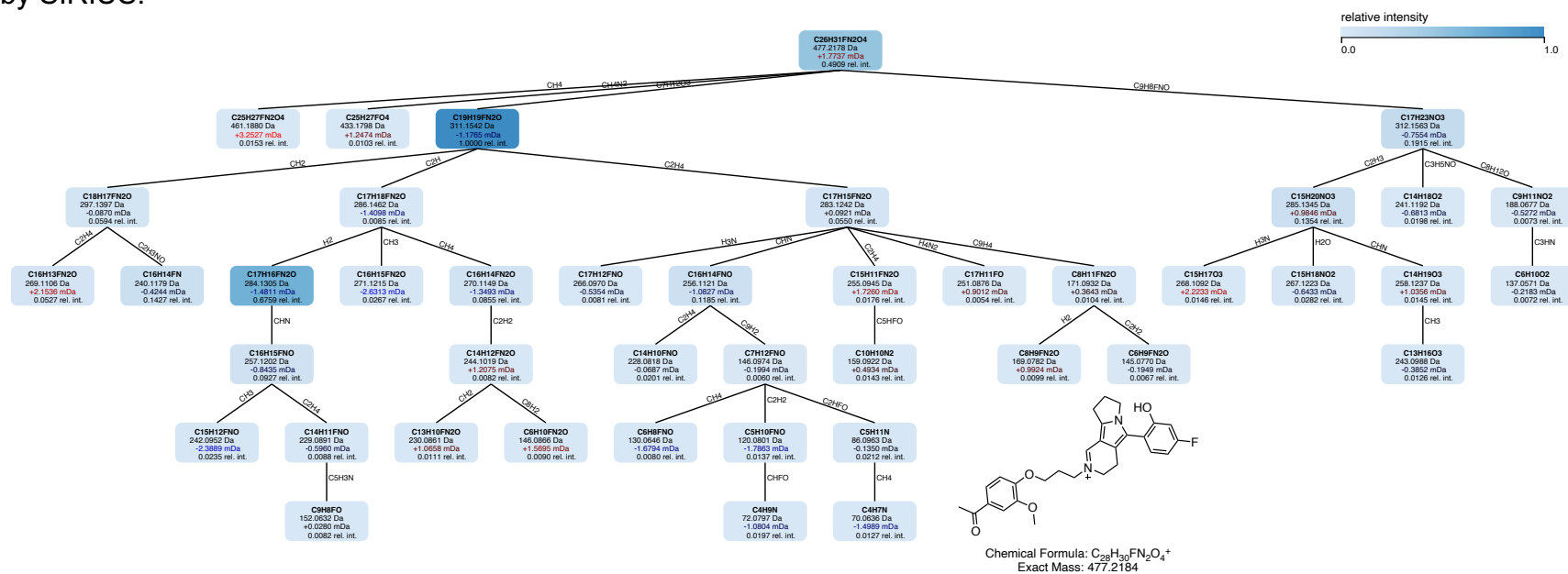
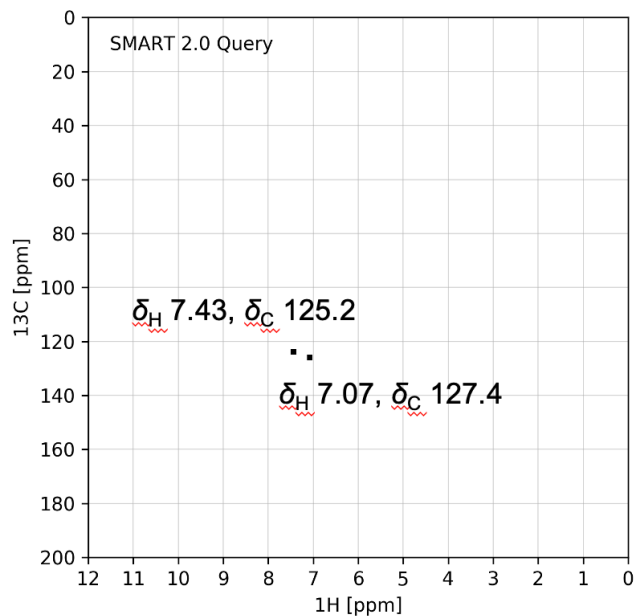


Fig. S71. SMARTNMR spectral comparisons for ilo-444. Two unassigned peaks (δ_H 7.43, δ_C 125.2 and δ_H 7.07, δ_C 127.4) were then input into the SMART peak entry, which is available at <https://smart.ucsd.edu>.



Name	Structure	Cosine score	MW	Source	External
MLS000554076-01!Dilantin		0.988228926848916	274.1	ACD_Labs	
thiophene		0.9871782897435196	84	Jeol	



Fig. S72. Incorporation of four deuterated protons from L-lysine-d₄ supplement (2 mg/mL) into ilo-491 (top, $m/z_{\text{calcd.}}$ 459.2592, $m/z_{\text{obs.}}$ 459.2607 and L-lysine supplement (2 mg/mL) into ilo-491 (bottom, $m/z_{\text{calcd.}}$ 491.2341, $m/z_{\text{obs.}}$ 491.2342).

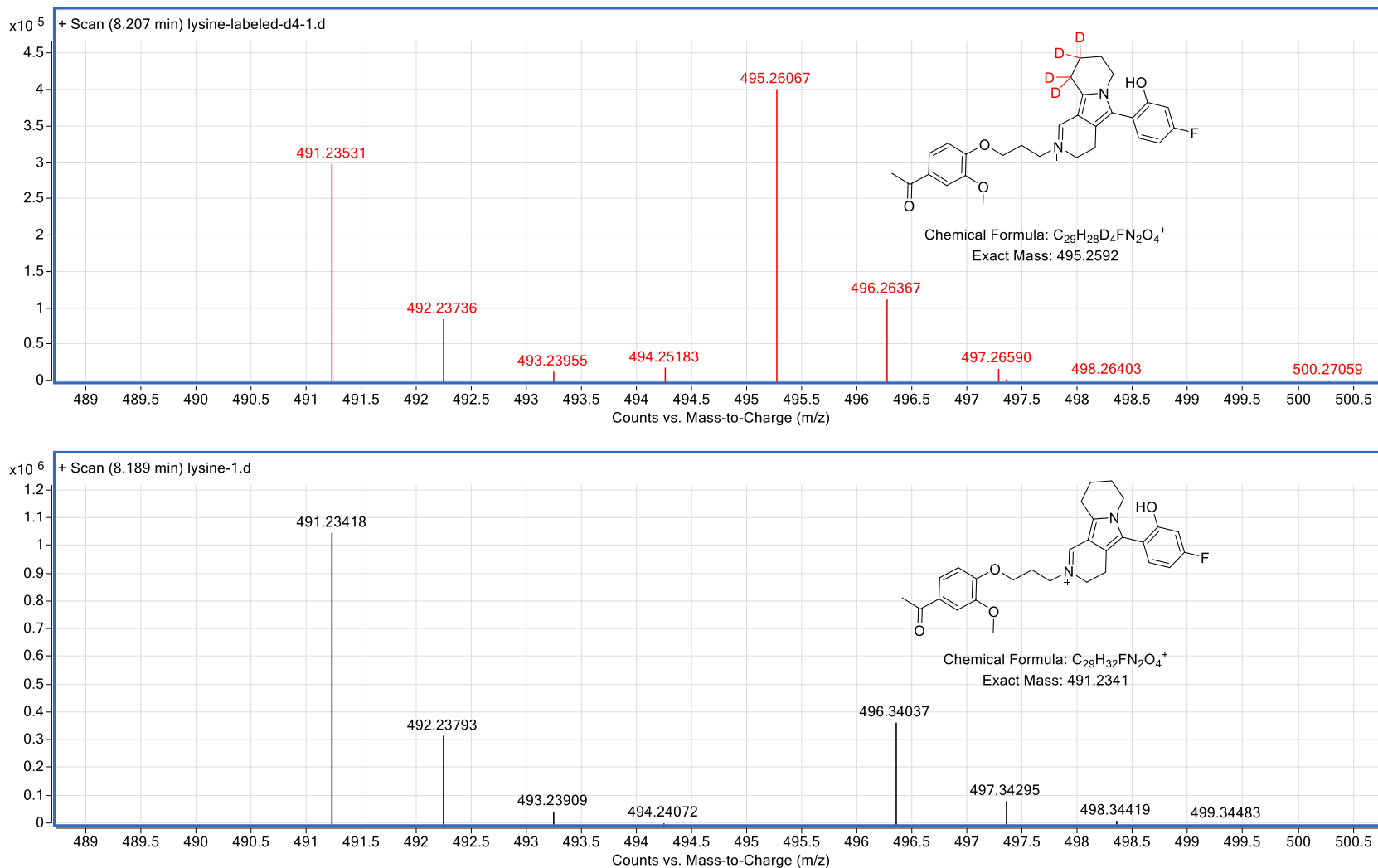


Fig. S73. MS² analysis of the incorporation of four deuterated protons in fragment A of ilo-491. Fragment A from L-lysine-d₄ supplement (top, $m/z_{\text{calcd.}}$ 329.1962, $m/z_{\text{obs.}}$ 329.1950 and L-lysine supplement (bottom, $m/z_{\text{calcd.}}$ 325.1711, $m/z_{\text{obs.}}$ 325.1706). Representative charge states are shown.

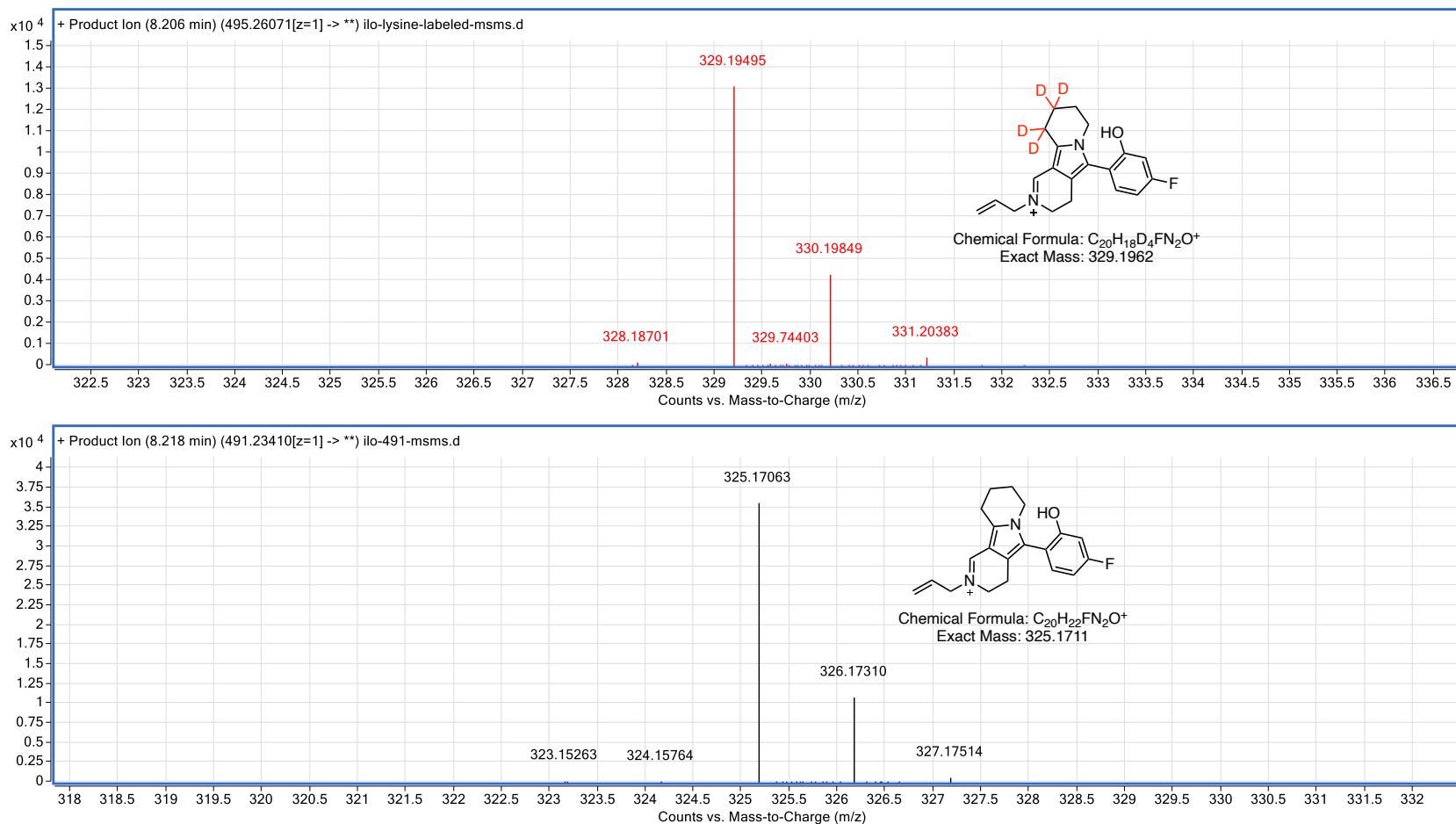


Fig. S74. MS² analysis of the incorporation of four deuterated protons in fragment B of ilo-491. Fragment B from L-lysine supplement (top, $m/z_{\text{calcd.}}$ 270.1289, $m/z_{\text{obs.}}$ 270.1272 and L-lysine-d₄ supplement (bottom, $m/z_{\text{calcd.}}$ 274.1540, $m/z_{\text{obs.}}$ 274.1537). Representative charge states are shown.

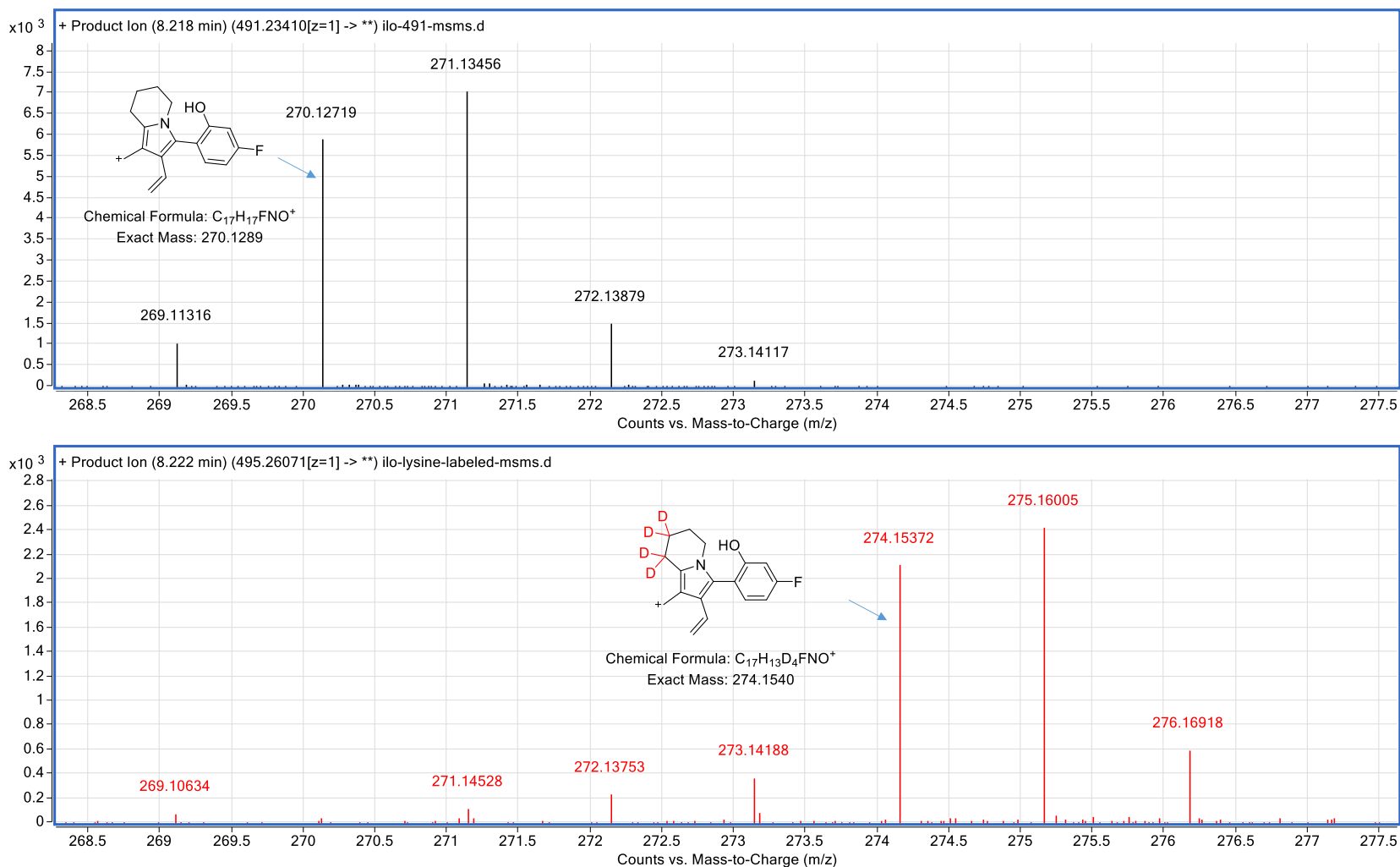


Fig. S75. MS² analysis of the incorporation of four deuterated protons in fragment C of ilo-491. Fragment C from L-lysine supplement (top, $m/z_{\text{calcd.}}$ 254.1340, $m/z_{\text{obs.}}$ 254.1325 and L-lysine-d₄ supplement (bottom, $m/z_{\text{calcd.}}$ 258.1591, $m/z_{\text{obs.}}$ 258.1581). Representative charge states are shown.

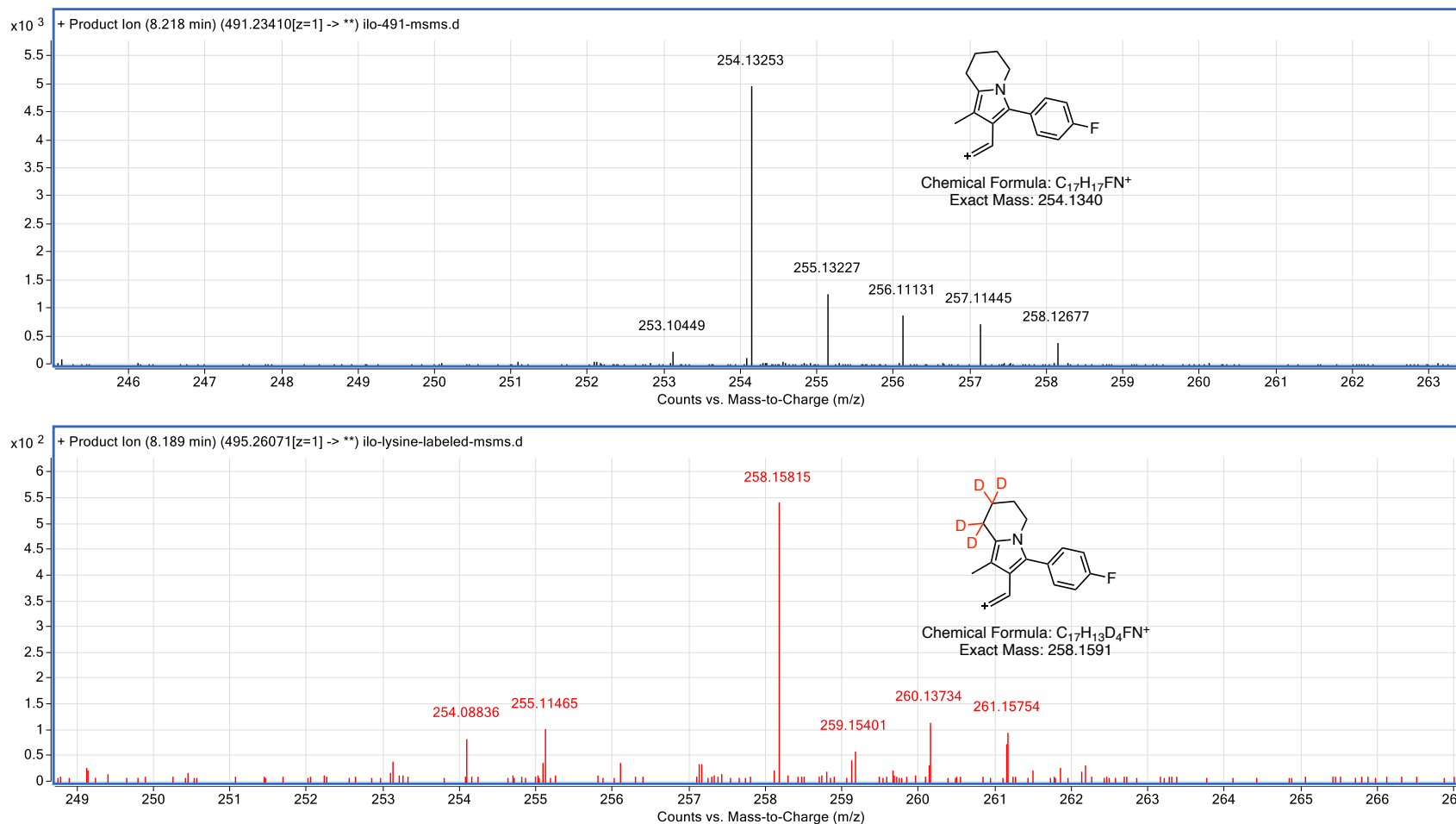


Fig. S76. Incorporation of four ^{13}C atoms from L-ornithine- $^{13}\text{C}_5$ supplement (2 mg/mL) into ilo-477. Ilo-477 from L-ornithine supplement (top, $m/z_{\text{calcd.}}$ 477.2184, $m/z_{\text{obs.}}$ 477.2187 and L-ornithine- $^{13}\text{C}_5$ supplement (bottom, $m/z_{\text{calcd.}}$ 481.2318, $m/z_{\text{obs.}}$ 481.2317).

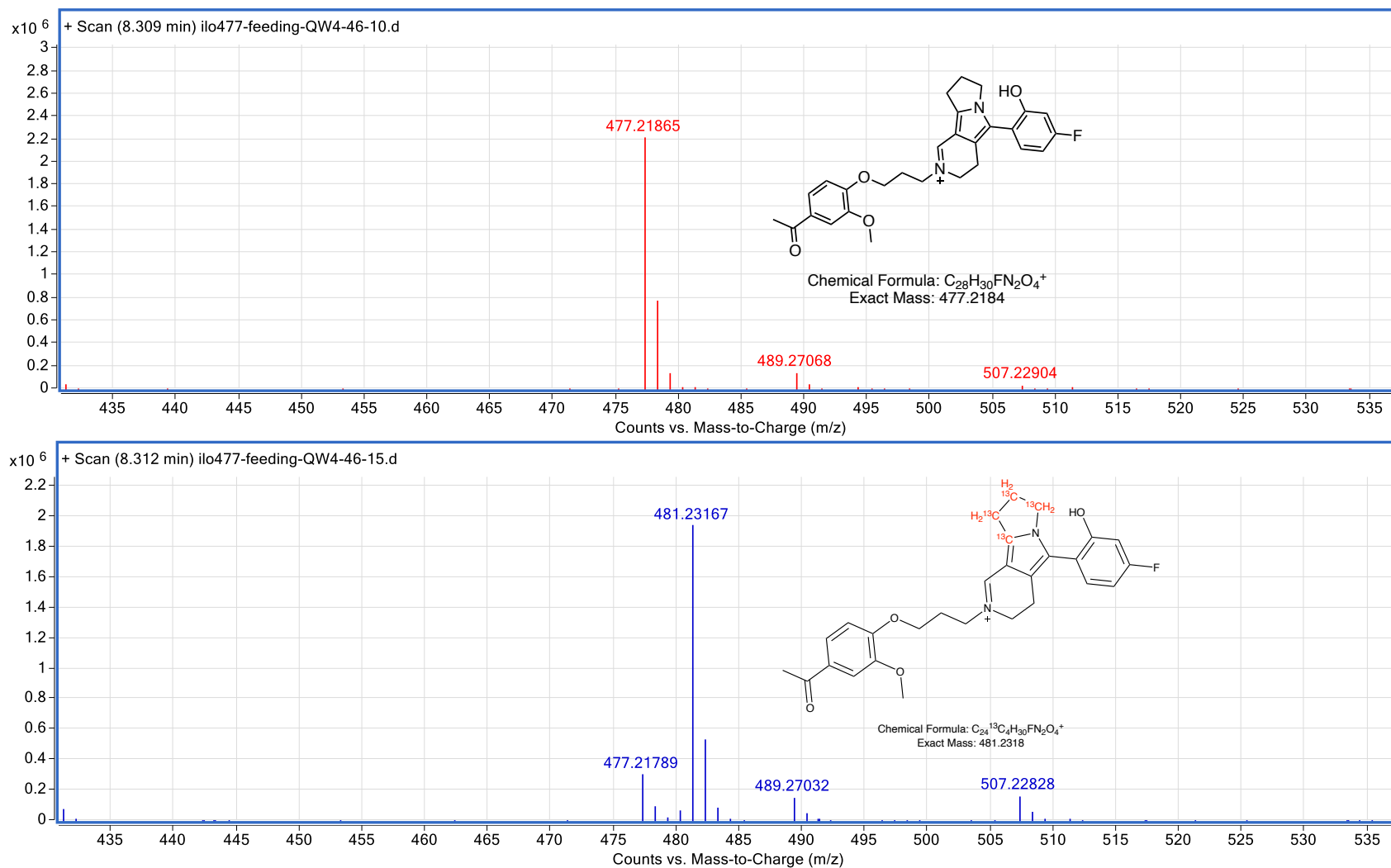


Fig. S77. MS² analysis of the incorporation of four ¹³C atoms from L-ornithine-¹³C₅ supplement (2 mg/mL) in three fragments of ilo-477. Top, L-ornithine supplement: Fragment A: $m/z_{\text{calcd.}}$ 461.1871, $m/z_{\text{obs.}}$ 461.1880; Fragment B: $m/z_{\text{calcd.}}$ 311.1554, $m/z_{\text{obs.}}$ 311.1542; Fragment C: $m/z_{\text{calcd.}}$ 240.1183, $m/z_{\text{obs.}}$ 240.1179. Bottom, L-ornithine-¹³C₅ supplement: Fragment A: $m/z_{\text{calcd.}}$ 465.2005, $m/z_{\text{obs.}}$ 465.1975; Fragment B: $m/z_{\text{calcd.}}$ 315.1688, $m/z_{\text{obs.}}$ 315.1673; Fragment C: $m/z_{\text{calcd.}}$ 244.1317, $m/z_{\text{obs.}}$ 244.1296.

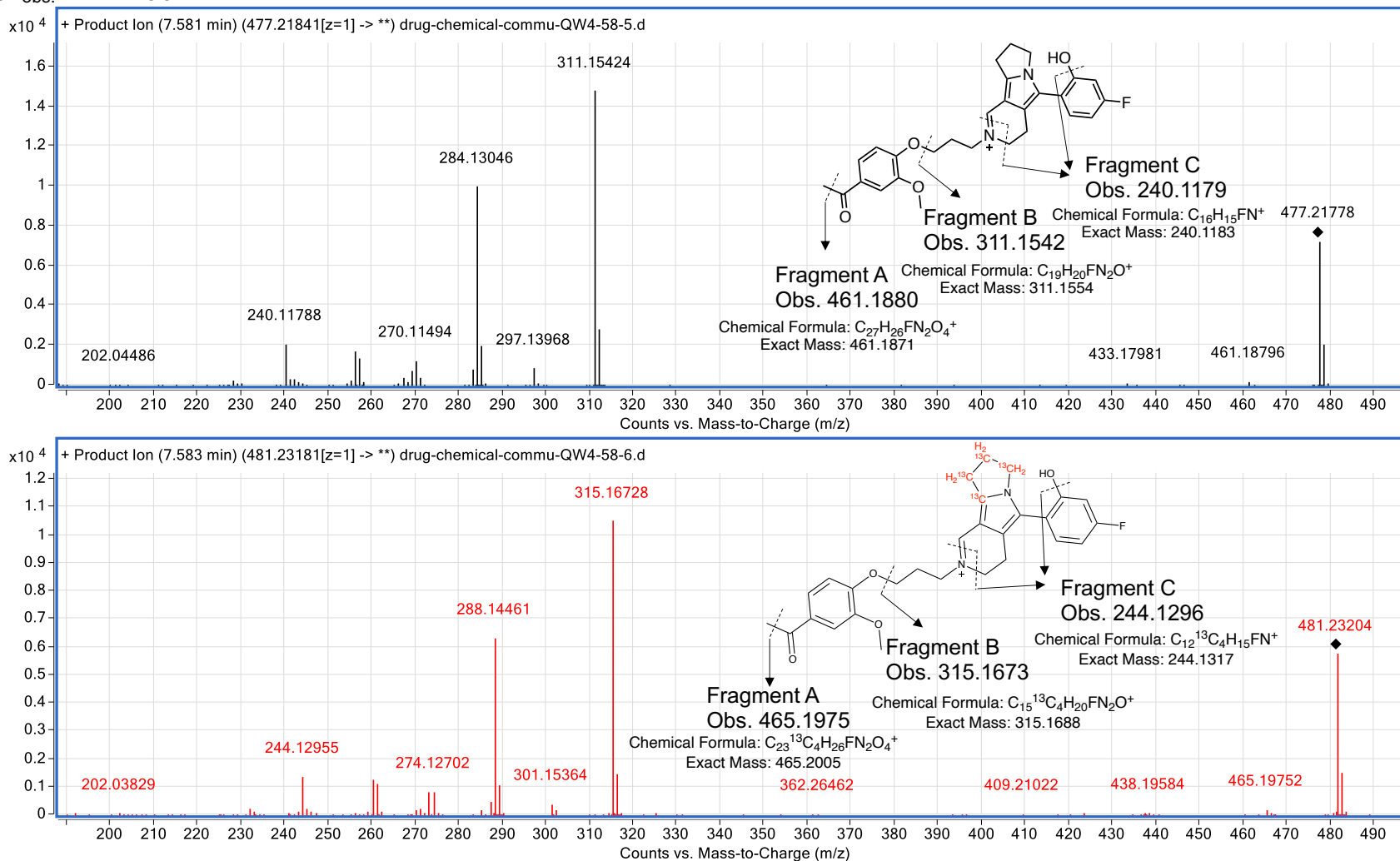
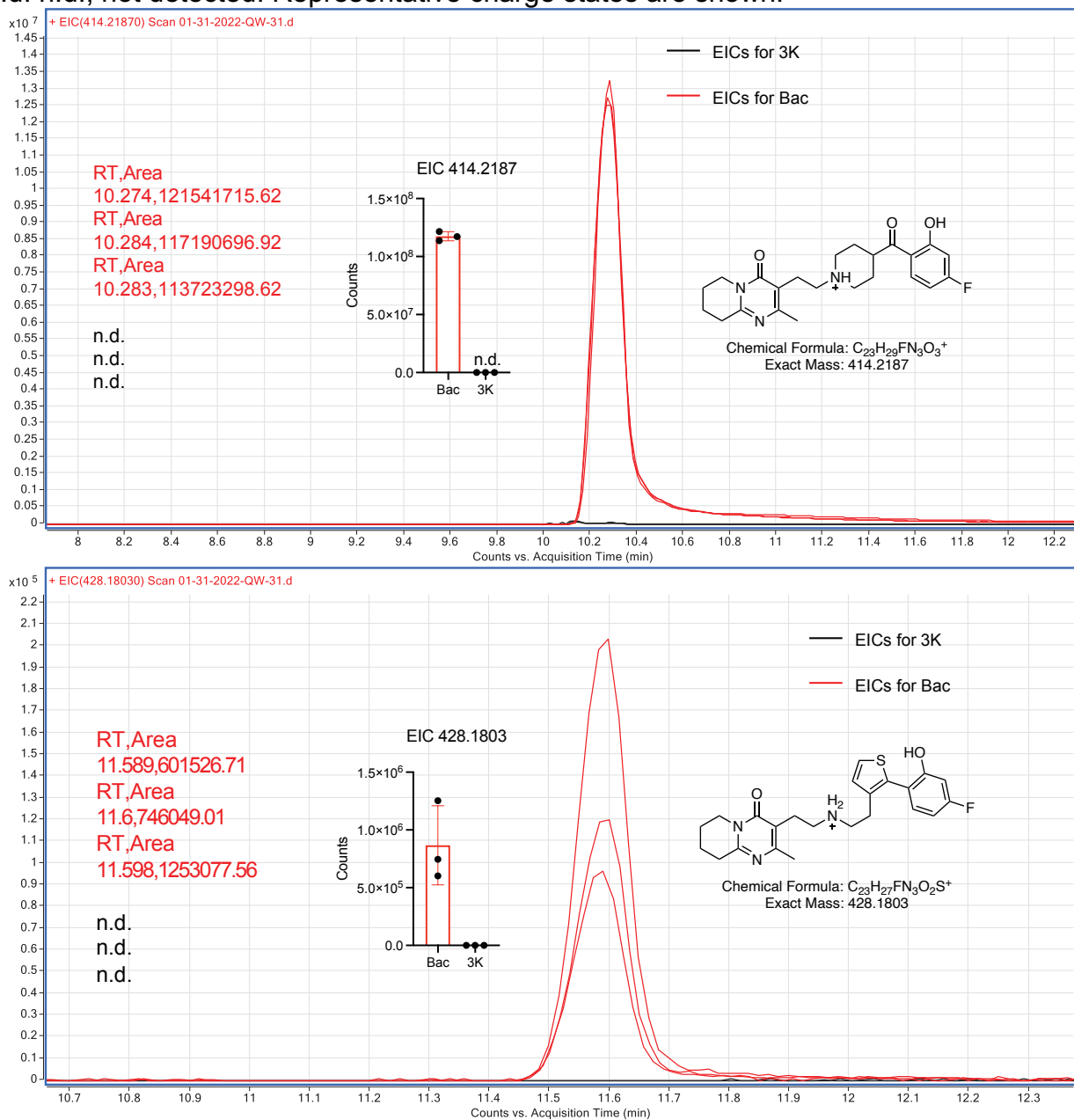


Fig. S78. Comparing Bac⁺ (Bac) and Bac⁻ with a MWCO 3K cutoff (3K) for the enzymatic-dependent detection of two MOFs (*m/z* 414.2187, top panel and *m/z* 428.1803, bottom panel) from risperidone metabolism; *n* = 3 biological replicates. Data represent mean $\pm$ s.d. n.d., not detected. Representative charge states are shown.



4. Mono-culture bacterial drug metabolism studies

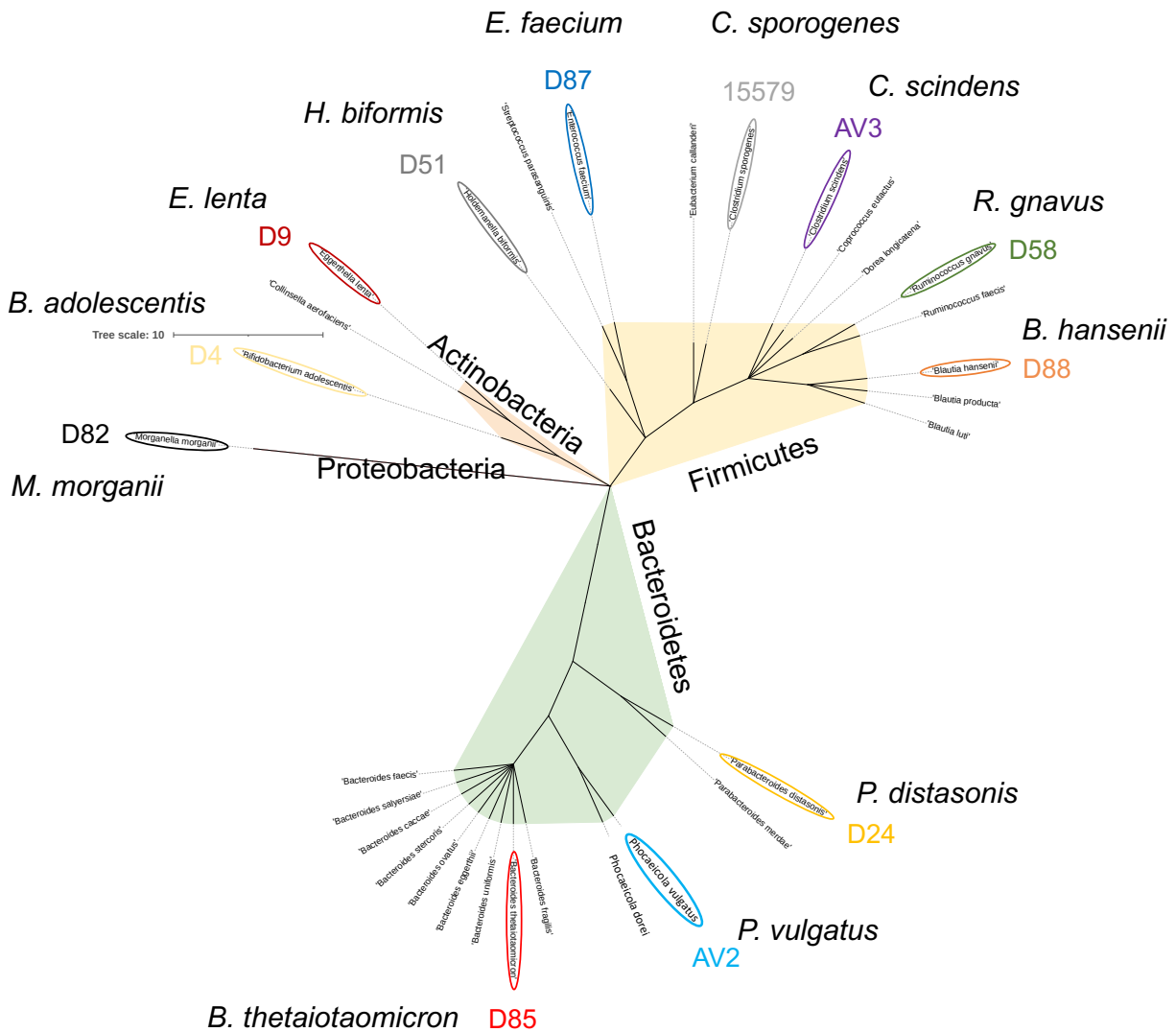


Fig. S79. Selection of 12 isolates from a bacterial collection (30 isolates) representing their corresponding clades for the mono-culture bacterial drug metabolism screening.

Fig. S80. Mapping iloperidone metabolism by individual bacterial isolates. (a) The consumption levels of iloperidone by 12 bacterial strains were evaluated. Enzyme/cell-free control was applied to eliminate the influence of spontaneous degradation in our analysis. n = 3 biological replicates. (b) Comparison of ilo-430 production among 12 bacterial strains. n = 3 biological replicates. (c) Comparison of ilo-491 production among 12 bacterial strains. Only *M. morganii* D82 showed robust ilo-491 production compared to the other strains. n = 3 biological replicates.

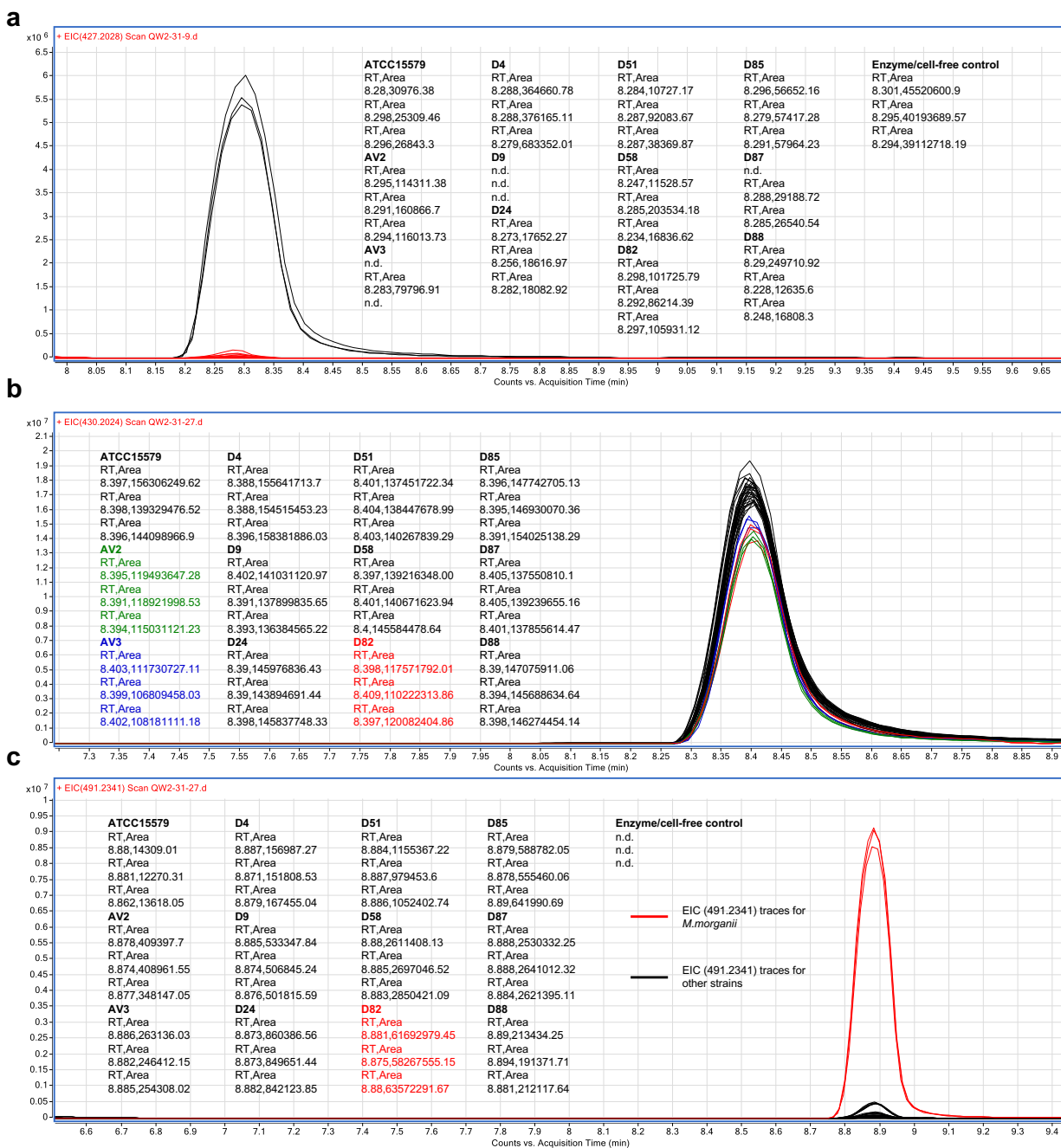


Fig. S81. Weak O-demethylation activity in selected 12 bacterial isolates toward three drugs in mono-culture conditions. Compared to the remaining parent drug in the culture broth, which showed high intensity (black traces with approximately 10^6 to 10^7 intensity), only trace amounts of the corresponding O-demethylation products (red traces with 10^3 to 10^5 intensity) were detected, indicating weak biotransformation by the selected 12 strains. Black traces represent EICs for remaining parent drugs of trimebutine (a), trimethobenzamide (b), and SB756050 (c) after bacterium-drug interaction, while red traces correspond to EICs for their respective major products. The positions for O-demethylation in the trimebutine and trimethobenzamide metabolomes are not determined, while O-demethylation position in SB756050 was determined by 2D NMR (Supplementary Figs. S258-S261). n = 3 biological replicates. Representative charge states are shown.

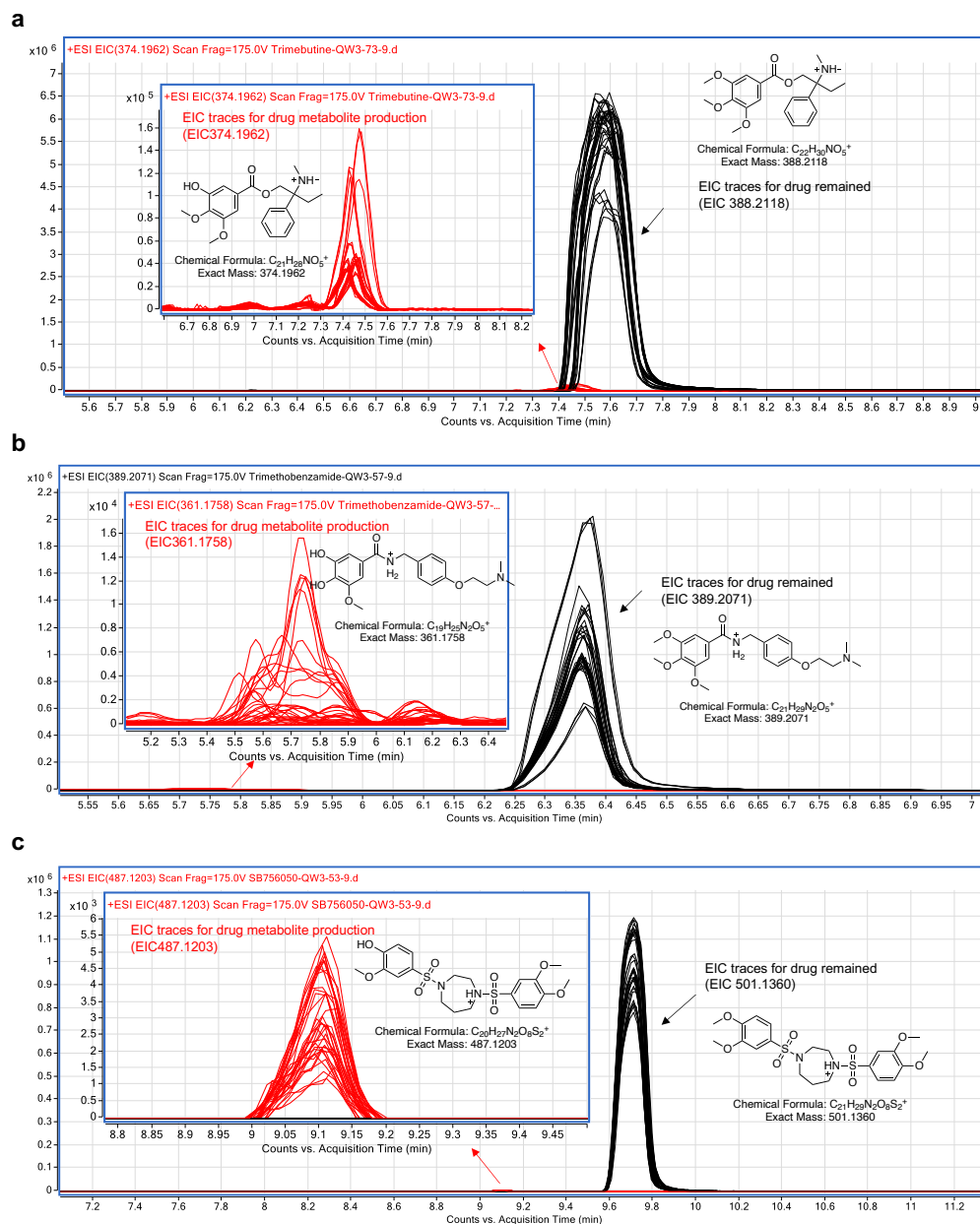
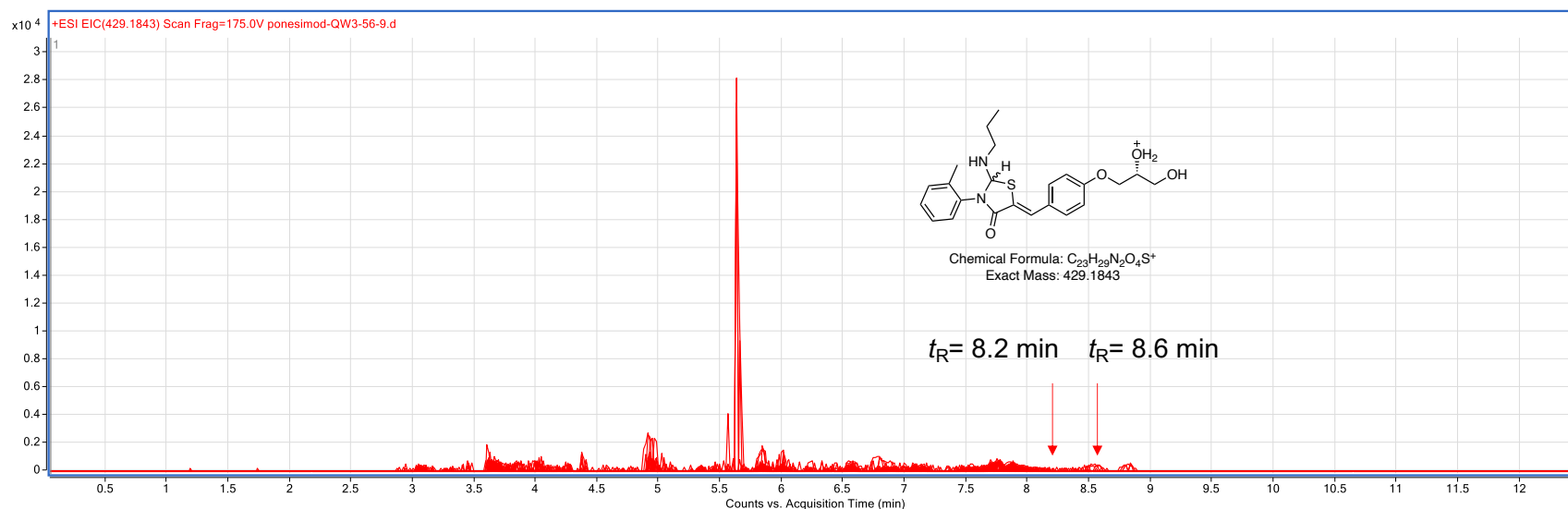


Fig. S82 Absence of dechlorination activity in selected 12 bacterial isolates toward ponosimod in mono-culture conditions. The highlighted retention times of two dehalogenated products ($t_R=8.2$ min and 8.6 min, Extended data Fig. 5b) are shown; however, no products were observed under the mono-culture conditions. $n = 3$ biological replicates. A representative charge state is shown. The proposed structure with imine reduction position was proposed based on the MS² major ion products of ponosimod-463. However, further NMR characterization is required to confirm this prediction.



5. Drug metabolism *in vitro* screening

Table S19. Information (names, structures, and consumption rates) of drugs examined in this study.

Drug	Smiles	Drug consumed (%)
Umeclidinium (bromide)	<chem>OC(C12CC[N+](CC2)(CCOCC3=CC=CC=C3)CC1)(C4=CC=CC=C4)C5=CC=CC=C5.[Br-]</chem>	3.947232141
Clonidine (hydrochloride)	<chem>C1C1=C(C(NC2=NCCN2)C(C1)=CC=C1.Cl</chem>	7.72673374
Tozadenant	<chem>O=C(NC1=NC2=C(C=C(C(N3CCOCC3)=C2S1)OC)N4CCC(O)(C4)C</chem>	0.09864213
Naftopidil	<chem>OC(CN1CCN(C(C=CC=C2)=C2OC)CC1)COC3=CC=CC4=CC=CC=C34</chem>	-10.09309697
Loratadine	<chem>O=C(N1CC(C(C1)=C2C3=CC=C(C1)C=C3CC4=CC=CN=C42)OCC</chem>	-27.97847833
Progylumide	<chem>O=C(O)CCC(NC(C1=CC=CC=C1)=O)C(N(CCC)CCC)=O</chem>	0.593258982
Volinanserin	<chem>FC1=CC=C(C(CCN2CCC([C@@]([H])(O)C3=CC=CC(OC)=C3OC)CC2)C=C1</chem>	-7.521755916
MK-0557	<chem>O=C([C@H]1CC[C@@]([C2=C3C=CN=C2](OC3=O)CC1)NC4=NN(C5=CC=CC=C5F)C=C4</chem>	-11.49128904
Setipiprant	<chem>O=C(O)CN1C2=C(CN(C(C3=C4C=CC=CC4=CC=C3)=O)CC2)C5=C1C=CC(F)=C5</chem>	12.50793511
Mavoxikafor (trihydrochloride)	<chem>[H]Cl.[H]Cl.[H]Cl.NCCCCN(C1=NC2=CC=CC=C2N1)[C@@H]3C4=NC=CC=C4CCC3</chem>	44.10074513
Timapiprant	<chem>O=C(O)CN1C(C(C)=C(C2=NC3=CC=CC=C3C=C2)C4=C1C=CC(F)=C4</chem>	-12.77466601
Ozanimod	<chem>N#CC1=CC(C2=NC(C3=CC=CC4=C3CC(C)[C@@H]4NCCO)=NO2)=CC=C1OC(C)C</chem>	100
Fasiglifam	<chem>CC1=C(C(C)=CC(C(OCCS(C)=O)=O)=C1)C2=CC(COC3=CC=C4[C@@H](COC4=C3)CC(O)=O)=CC=C2</chem>	44.30918157
Lumateperone (Tosylate)	<chem>O=C(C1=CC=C(F)C=C1)CCCNC2C[C@@]([N3CCN(C)C4=C3C5=CC=C4]([H])([C@@]5([H])C2.O=S(C6=CC=C(C)C=C6)(O)=O</chem>	8.53685893
Imavanserin tartrate	<chem>O=C(NCC1=CC=C(OC(C)C)C=C1)N(C2C=CC=C(F)C=C2)C3CCN(C)CC3.O=C(O)[C@H](O)[C@@H](O)C(O)=O.O=C(NCC4=CC=C(C(OC(C)C)C=C4)N(C5=CC=C(F)C=C5)C6CCN(C)CC6</chem>	9.762526729
Imaradenant	<chem>CC1=CC=C(C(=N1)C)C2=C(N(C=N2)N)C3=CC=C(C=C3)F</chem>	36.7616883
Zafirlukast	<chem>O=C(OC1CCCC1)NC2=CC3=C(N(C)C=C3CC4=CC=C(C)NS(=O)(C5=CC=CC=C5C)=O)=O)C=C4OC(C)C=C2</chem>	33.1371126
Ponesimod	<chem>O=C1N(C2=CC=CC=C2C)C(S(C1=C(C)C3=CC=C(C)OC(C)[H](O)CO)C(C1)=C3)=N/CCC</chem>	97.06977075
Molindone (hydrochloride)	<chem>O=C1C2=C(N(C)C=C2CC)CCC1CN3COCOC3.[H]Cl</chem>	-18.89159636
Telcagepant	<chem>O=C1NC2=C(N1C3CCN(C)N(C)[C@@H]4CC[C@@H](C5=CC=CC(F)=C5F)CN(C(F)(F)F)C4=O)=O)CC3)C=CC=N2</chem>	11.87907808
Trimethobenzamide hydrochloride	<chem>O=C(NCC1=CC=C(C(OC(C)C)C=C1)C2=C(C)C(OC)=C(C)OC(C)OC)=C2.Cl</chem>	89.56939711
Adoprazine	<chem>FC1=CC=C(C(C2=CN=CC(CN3CCN(C4=C5COCOC5=CC=C4)CC3)=C2)C=C1</chem>	-1.440194803
Nicergoline	<chem>CO[C@@]([C@@]([H])([H])C2)(C(C)[C@@H](COC(C3=CN=CC(Br)=C3)=O)CN1)C4=C5C2=CN(C)C5=CC=C4</chem>	26.39794401
Aprepitant	<chem>O=C1NC(CN2[C@H]([C@@H]([C@@H](O[C@H](C3=CC(C(F)(F)F)=CC(C(F)(F)F)=C3)O)CC2)C4=CC=C(C(F)C=C4)=NN1</chem>	35.41589981
Bambuterol hydrochloride	<chem>OC(C1=CC(OC(N(C)C)=O)=CC(OC(N(C)C)=O)=C1)CNC(C)(C)C.[H]Cl</chem>	6.110025144
Filorexant	<chem>CC1=CC(C(N2C[C@H](COC3=CC=C(F)C=N3)CC[C@H]2C)=O)C(C4=NC=CC=N4)C=C1</chem>	6.669851115
Pavinetant	<chem>CC(C)[H](NC(C1=C(C=CC=C2)C2=NC(C3=CC=CC=C3)=C1NS(C)(=O)=O)=O)C4=CC=CC=C4</chem>	9.491447203
Cisapride	<chem>O=C(N(C)[C@@H]1[C@H](OC)CN(CCCOC2=CC=C(F)C=C2)CC1)C3=CC(C)=C(N)C=C3OC</chem>	-2.434106731
Clopidogrel (hydrogen sulfate)	<chem>C1C1=C([C@H](C)(OC)=O)N2CCC3=C(C=CS3)C2)C=CC=C1.O=S(O)(O)=O</chem>	13.85627424
Basimglurant	<chem>CC1=C(C#CC2=CC(C1)=NC=C2)N=C(C)N1C3=CC=C(F)C=C3</chem>	20.42356677
Sitaxsentan (sodium)	<chem>O=S([N-]C1=C(C(C)=NO1)Cl)(C2=C(C)SC=C2)C(C3=C(C=C4OCOC4=C3)C)=O.[Na+]</chem>	Not applicable
Zuclopenthixol	<chem>OCCN1CCN(C(C)C=C2C3=C(C)SC4=C2C=CC=C4)C=CC(C1)=C3)CC1</chem>	37.10809071
Doxazosin (mesylate)	<chem>O=C(N1CCN(C2=NC(N)=C3=C(C(OC(C)OC)=CC3=N2)CC1)O4OC5=CC=CC=C5OC4.CS(=O)(O)=O</chem>	17.2009597
Sparsentan	<chem>O=S(C1=CC=CC=C1C2=CC=C(C(CN3C(CCCC)=NC4(CCCC4)C3=O)C=C2COC(C)NC5=NOC(C)=C5C)=O</chem>	11.39416966
E7046	<chem>O=C(O)C1=CC=C([C@@H](NC(C2=C(C)OC3=CC=CC(C(F)(F)F)=C3)N(C)N=C2C(F)F)=O)C)C=C1</chem>	16.96404559
Fesoterodine (fumarate)	<chem>CCC1=CC([C@H](CCN(C(C)C)C(C)C)C2=CC=CC=C2)=C(C=C1)OC(C)C(C)=O.O=C(/C=C/C(O)=O)=O</chem>	100
Candesartan Cilexetil	<chem>O=C(C1=C2C(N(C)OC)N2CC3=CC=C(C4=CC=CC=C4C5=NNN=N5)C=C3)=CC=C1)OC(OC6CCCC6)=O)C</chem>	35.96329576
Piribedil	<chem>C1(N2CCN(C3=CC=C(C(OC4)C4=C3)CC2)=NC=CC=N1</chem>	-10.6041707
Avosentan	<chem>COC1=C(OC(C)NS(C2=NC=C(C=C2)C)(=O)=O)NC(C3=CC=NC=C3)=N4)C4OC)C=CC=C1</chem>	9.554514481
Pardoprunox (hydrochloride)	<chem>O=C1OC2=C(N3CCN(C)CC3)C=CC=C2N1.[H]Cl</chem>	62.68797755
PF-04418948	<chem>O=C(C1(COC2=CC=C3C=C(C)OC)C=C3C2)CN(C(C4=CC=C(F)C=C4)=O)C1)O</chem>	6.998017881
Famotidine	<chem>N=C(NS(=O)(N)=O)CCSCC1=CSC(NC(N)=N)=N1</chem>	18.11759013
Homatropine (Bromide)	<chem>O=C(C(C1=CC=CC=C1)O)O[C@H]2C[C@@H](CC3)N(C)[C@@H]3C.Br</chem>	6.759134862
Acrivastine	<chem>O=C(O)C=C(C1=NC(C)C(C2=CC=C(C)C=C2)=C(CN3CCCC3)=CC=C1</chem>	3.050364013
Sograzepide	<chem>O=C(NC1=CC=CC(NC)=C1)N(C)[C@H]2C(N(C)C(C)C(C)=O)C3=CC=CC=C3(C4=NC=CC=C4)=N2)=O</chem>	-13.01124922
Buspirone (hydrochloride)	<chem>O=C(N(CCCCN1CCN(C2=NC=CC=N2)CC1)C(C3)=O)CC4CCCC4.[H]Cl</chem>	-25.85947461
Sertindole	<chem>FC1=CC=C(N2C3=CC=C(C1)C=C3C(C4CCN(CCN5COCN5=O)CC4)=C2)C=C1</chem>	1.891010515
Thioridazine (hydrochloride)	<chem>CSC(C=C1N2CCC3N(C)CCCC3)=CC=C1SC4=C2C=CC=C4.[H]Cl</chem>	5.712041984
Ambrisentan	<chem>O=C([C@H](C(OC)C1=CC=CC=C1)C2=CC=CC=C2)OC3=NC(C)=CC(C)=N3)O</chem>	6.853886477
Vicrivirod (maleate)	<chem>CC1(N2C[C@H](C)N([C@H](C3=CC=C(C(F)(F)F)C=C3)COC)CC2)CCN(C(C4=C(C)C=NC=N4C)=O)CC1.O=C(O)C=C(C)O)=O</chem>	2.040695639
Blonsaserin	<chem>FC1=CC=C(C(C2=C(C)CCCCC3)C3=NC(C4NCCN(C)CC4)=C2)C=C1</chem>	-1.898471022
Fezolinetant	<chem>O=C(N1[C@H](C)C2=NN=C(C3=NC(C)=NS3)N2CC1)C4=CC=C(F)C=C4</chem>	0.926935463
Cyclobenzaprine (hydrochloride)	<chem>CN(C)CC(C=C1C2=CC=CC=C2C3=CC=CC=C13)Cl</chem>	-5.741593231
Loxapine (succinate)	<chem>O=C(O)CC(C)O.O.CN1CCN(C2=NC3=CC=CC=C3OC4=CC=C(C1)C=C24)CC1</chem>	-4.24085505
Tolterodine (tartrate)	<chem>OC1=CC=C(C=C1)[C@H]([C@H](CCN(C)C(C)C(C)C)C2=CC=CC=C2)C.O=C([C@H]([C@H](C)O)=O)O)O</chem>	1.263253779
Chlorprothixene	<chem>CN(C)CC(C=C1C2=C(C)SC3=C1C=CC=C3)C=C(C1)C=C2</chem>	8.854968333
Pindolol	<chem>OC(CN(C)C)COC1=CC=CC=C1C=CN2</chem>	-31.09225333
GSK1292263	<chem>CC(C1=NO(C)N2CCC(C2)COC3=CC=C(C=C3)C4=CC=C(C=C4)S(C)(=O)=O)=N1)C</chem>	100
Velneperit	<chem>FC(F)(F)C1=CN=C(NC([C@H]2CC[C@H](NS(=O)(=O)C(C)C)=O)CC2)=O)C=C1</chem>	8.275588556
Iloperidone	<chem>CC(C1=CC=C(C)OCCCN2CCC(C3=NOCC4=C3C=CC(F)=C4)CC2(C)OC)=C1=O</chem>	87.01298494
Ketanserin (tartrate)	<chem>O=C(C1=CC=CC=C1N2)N(CCN3CCC(C(C4=CC=C(F)C=C4)=O)CC3)C2=O.O=C(O)[C@H](O)[C@@H](O)C(O)=O</chem>	-30.74232335
SB756050	<chem>O=S(N1CCN(S(=O)(C2=CC=CC(C)OC)C(C)C)=O)CCC1)(C3=CC=CC(C)OC(C)C)=O</chem>	91.98354195

BI-671800	O=C(O)CC1=C(N(C)C)N=C(C)C2=CC=C(NC(C3=CC=C(C(F)F)C=C3)=O)C=C2)N=C1N(C)C	4.152300425
Metoprolol (Succinate)	OC(CNC(C)C)COC1=CC=C(C(COC)C)=C1.OC(CNC(C)C)COC2=CC=C(C(COC)C)=C2.OC(CCC(O)=O)=O	-18.14872624
Mirabegron	O=C(NC1=CC=C(C)CCN[C@H](O)C2=CC=CC=C2)C=C1)CC3=CSC(N)=N3	-1.380734737
Brexiprazole	O=C1NC2=C(C=C)C(OC(CCN3CCN(C4=C(C=CS)C5=CC=C4)CC3)=C2)C=C1	0.480725102
Fimasartan	O=C1N(C)(CCCC)=NC(C)=C1CC(N(C)C)=S)CC2=CC=C(C3=C(C4=NN=NN4)C=CC=C3)C=C2	3.254902022
Camical	O=C(N1CCC(NC2=CC=CC(F)=C2)CC1)CC3=CC=C(C)CN4C[C@H](C)NCC4)C=C3	8.115229661
(R)-Elagolix	FC1=C(C2=C(C)N)CC3=C(C(F)F)C=CC=C3F)C(N(C)C@H(C4=CC=CC=C4))([H])NCCC(O)=O)C2=O)=O)C=CC=C1OC	-20.88887914
Selexipag	O=C(NS(O)(C)=O)C=OCCCCCN(C1=NC(C2=CC=CC=C2)=C(C3=CC=CC=C3)N=C1)C(C)C	81.26423639
Valsartan	CC(C)[C@H](C)(O)=O)N(C(CCCC)=O)CC1=CC=C(C2=CC=CC=C2C3=NNN=N3)C=C1	10.6936578
Balovaptan	CN1CC2=NN=C([C@H]3CC[C@H](OC4=NC=CC=C4)CC3)[N@]2[C@]5=CC=C(C)C=C5C1	-13.3913558
Glycopyrrolate	C[N+](C)CC(C)OC(C)(O)(C2CCCC2)C3=CC=CC=C3)O)CC1.[Br-]	-15.46635769
Trospium (chloride)	[H][C@]12CC[C@]([C]C@H)(OC(C(C3=CC=CC=C3)O)C4=CC=CC=C4)=O)C2)([H])[N+](C)CCCC5.[Cl-]	-1.348219171
Lafutidine	O=C(NC/C=C)COC1=NC=CC(CN2CCCC2)=C1)CS(CCC3=CC=C3)=O	-15.43278348
Ketotifen (fumarate)	O=C(C1=C/2C=C)CC3=CC=CC=C3C2=C4CCN(C)CC4.O=C(O)/C=C/C(O)=O	-17.76462848
Telmisartan	O=C(C1=CC=CC=C1C2=CC=C(C)N3C4=C(C)C5=NC6=CC=CC=C6N5C)=CC(C)=C4N=C3CCC)C=C2)O	0.007712891
Relugolix	O=C(NOC)NC1=CC=C(C)S2)=C(CN(C)C)C(C)N3C4=NN=C(C)C=C4)=O)C2N(C)CC5=C(F)C=CC=C5F)C3=O)C=C1	10.58000439
Tolvaptan	O=C(C1=CC=CC=C1C)NC2=CC=C(C)C=C2)C(N3CCCC(C4=C(C)C)=CC=C43)O)=O	-6.5554149
Cariprazine (hydrochloride)	O=C(N[C@H]1CC[C@H](CCN2CCN(C3=CC=CC(C)C=C3)CC2)CC1)N(C)C.[H]Cl	1.740963301
Setipitline (maleate)	CN1CC(C(C=C=CC=C2)=CC23)=C(C(C1)C4=C3C=CC=C4.O=C(O)/C=C(C)C)=O	-5.174259857
Ranitidine (hydrochloride)	CN(C)NCCSCC1=CC=C(CN(C)C)O1=C(N+)([O-])=O.Cl	25.29234397
GSK163090	O=C1NCCN1C2=CC=CC(CCN3CCN(C4=C5C=CC(C)C)=NC5=CC=C4)CC3)=C2	5.954961445
Atrasentan (hydrochloride)	O=C([C@H]1[C@H](C2=CC=C(C)C)C=C2)N(C)C(N(C)CCCC)CCCC)O)C[C@H]1C3=CC=C(C)C(C4=CC=C4)O.Cl	8.444424461
Risperidone	O=C1C(CCN2CCC(C3=NO4=C3C=CC(F)=C4)CC2)=C(C)N=C5N1CCCC5	35.65552822
Prucalopride	ClC1=C(N)C(CCO2)=C2C(C)N(C3CCN(CCCOC)CC3)=O)=C1	-19.01608679
GSK598809	CC1=C(C2=NN=C(C)CCCN3CC4(C5=CC=C(C(F)F)C=C5F)CC4C3)N2C)OC=N1	6.671073795
Dexpramipexole (dihydrochloride)	NC(S1)=NC2=C1C[C@H](NCCC)CC2.[H]Cl.[H]Cl	-14.06663733
Maraviroc	O=C(C1CCC(F)F)CC1)N(C)C@H(C2=CC=CC=C2)CCN3[C@H]4C[C@H](N5C(C)=NN=C5(C)C)C[C@H]3CC4	-39.47326994
Aripiprazole	O=C1NC2=C(C=C)C(OC(CCN3CCN(C4=C5C=CC(C)C)=C4)CC3)=C2)CC1	7.41784878
Vortioxetine (hydrobromide)	CC1=CC=C(C)S2)=CC=CC=C2N3CCN(C3)C(C)=C1.[Br-]	-2.76605931
Silodosin	O=C(N)C1=CC(C)C@H(C)N(C)CCCC2=CC=CC=C2OCC(F)F)=CC3=C1N(C)CCCCO	-16.4496063
Pericyazine	N#CC(C=C1N2CCCCN3CCC(O)CC3)=CC=C1SC4=C2C=CC=C4	-0.3513776
Olodanrigan	O=C([C@H]1N(C)C(C2=CC=CC=C2)C3=CC=CC=C3)O)CC4=C(C)C(CCC5=CC=CC=C5)=C(C)C(C4)C1)O	12.25448558
Carteolol hydrochloride	O=C1NC2=C(C)C(OC(C)C)CNC(C)(C)C=C2)CC1.Cl	16.30001575
Cetirizine (dihydrochloride)	O=C(O)CCCCN1CCN(C)C2=CC=C(C)C2)C3=CC=CC=C3)CC1.Cl.Cl	1.702251404
Ticagrelor	O(C@H)1C[C@H](O)C[C@H](N2N=NC3=C(N)C(C)C4[C@H](C5=CC=C(F)C(F)=C5)C4)N=C(SCCC)N=C32)C[C@H]1OCCO	24.91692784
Rauwolfscine (hydrochloride)	[H]Cl.[H][C@]12C(NC3=C4C=CC=C3)=C4CCN1C[C@]5([H])CC(C)C@H([O])C@H(C)C(C)=O)C[C@]5(C2)[H]	-31.4326284
Azilsartan (medoximil)	O=C(C1=C2C(N=C(OC)N2CC3=CC=C(C4=CC=CC=C4C5=NC(N)O5)=O)C3)=CC=C1)OCC6=C(C)OC(O6)=O	100
Chlorpheniramine (maleate)	CN(C)CCC(C1=CC=C(C)C)C=C1)C2=CC=CC=N2.O=C(O)/C=C(C)C(O)=O	-22.39978683
Latrepirdine (dihydrochloride)	CN(C1)CCC2=C1C3=C(C)C=CC=C3N2CCC4=CN(C)C(C)C=C4.Cl.Cl	14.46112537
Tasimelteon	[H][C@]1(C2=C3C(C)C(C)=CC=C2)[C@]([C]C(C)C)=O)C1.[H]Cl	5.479157591
Guanfacine (hydrochloride)	O=C(NC(N)=N)CC1=C(C)C=C=C1.Cl.[H]Cl	-9.184059056
Acebutolol (hydrochloride)	CCCC(NC1=CC=C(C)C(C)C)CNC(C)C(C)C(C)=O)=C1.Cl	-35.42126134
Darusentan	COC1=NC([C@H](C)C(O)=O)C(C2=CC=CC=C2)(C3=CC=CC=C3)OC)=NC(OC)=C1	16.38133197
Asenapine (hydrochloride)	[H]Cl.ClC1=CC2=C(C=C1)OC3=C(C=C=C3)[C@]([C4])([H])[C@]2([H])CN4C	-2.470934688
Intepirdine	O=S(C1=CC=CC=C1)(C2=CC(C)C=CC=C3N4CCNCC4)=C3N=C2)=O	-20.54602703
Reparixin (L-lysine salt)	N(C@H)(CCCCN)C(O)=O.CS(O)=O)N(C)[C@H](C1=CC=C(C)C(C)C=C1)C(O)=O	12.76704846
Fevipirant	O=C(O)CC1=C(C)N)CC2=CC=C(S(O)=O)C(O)C=C2(C)F)C3=NC=CC=C31	21.70509597
Ibutamoren (Mesylate)	CC(N)C(N(C)C@H)(C1N1CCC2(CN(C3=C2C=CC=C3)S(O)=O)C(O)CC1)=O)C(C4=CC=CC=C4)=O)C.CS(O)(O)=O	-8.773297397
Rolapitant	C[C@]([C1=C(C)C(F)F)=CC(C(F)F)F=C1])([H])OC[C@]2(C3=CC=CC=C3)CC[C@]([C4=O])(N4)CN2	9.061374069
Olimesartan (medoximil)	O=C(OC(C1=C(C)C(O1)=O)C)C2=C(N=C(N2CC3=CC=C(C3)C4=CC=CC=C4C5=NN=NN5)CCC)C(O)C(C)C	100
Sarpogrelate (hydrochloride)	OC(C1=CC=CC(CCC2=CC=CC=C2OCC(CN(C)C)OC(CCC(O)=O)=O)=O)C1.Cl	85.58035873
Melatonin	CC(NCCC1=CNC2=C1C=C(C)C)C=C2)=O	-3.62112602
Trimebutine (maleate)	O=C(O)/C=C(C)C(O)=O.O=C(OC(C1=CC=CC=C1)(N(C)C)CC)C2=CC(OC)=C(OC)C(OC)=C2	95.08883665
Almorexant	CNC([C@H](C1=CC=CC=C1)N2CCCC3=CC(OC)=C(C)C)C=C3[C@H]2CCC4=CC=C(C(F)F)C=C4)=O	19.44470676
Xanomeline (oxalate)	CN1CCC=C(C2=NSN=C2OCCCCC)C1.O=C(O)C(O)=O	26.43563996
Lofexidine	CC(C1=NCCN1)OC2=C(C)C=C=CC2Cl	37.27975308
Losartan (potassium)	OCC1=C(C)N=C(C)CCCC)N1CC2=CC=C(C3=CC=CC=C3C4=N[N-]N4)C=C2.[K+]	9.572254101
Idolopirdine Hydrochloride	FC1=CC(NC=C2CCNCCC3=CC(OC(C)F)C(F)F)=CC=C3)=C2C=C1.Cl	28.61703672
Carvedilol	OC(CNCCOC1=CC=CC=C1OC)COC2=CC=CC(C3)=C2C4=C3C=CC=C4	14.05065134
Anamorelin (hydrochloride)	[H][C@]([C1=CNC2=CC=CC=C2])(N(C)C(C)N)=O)C(N3CCC[C@]([C]C(N(C)N(C)C)=O)(CC4=CC=CC=C4)C3)=O.[H]Cl	0.323859411
Otilonium (bromide)	O=C(OC(C[N+](C)C(C)C)C1=CC=C(C)C)C2=CC=CC=C2OCCCCCCCC)O)C=C1.[Br-]	46.65724777
Vilazodone (Hydrochloride)	NC(C1=CC2=C(C=C)N3CCN(CCCOC4=CCN5=CC=C(C=C54)C#N)CC3)=C2)O1)=O.[H]Cl	-24.90589023
Oxybutynin (chloride)	O=C(C)C(O)C1=CC=CC=C1)C2CCCC2)OCC#CCN(C)CC.[H]Cl	12
MK-3207 (Hydrochloride)	O=C1C2(NC[C@H](C3=CC(F)=CC(F)=C3)N1CC(NC4=CC=C(C)C[C@H]6(C)NC7=C6C=CC=N7)=O)C5(C=C4)=O)CCCC2.Cl	-30.69066554
Talnetant	OC1=C(C)N(C)C@H(C2=CC=CC=C2)C(C)=O)C3=C(N=C1C4=CC=CC=C4)C=CC=C3	12.36243492

Fig. S83. Bac⁺ vs Bac⁻ (MWCO 3K) of umecclidinium (*m/z* 428.2584) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

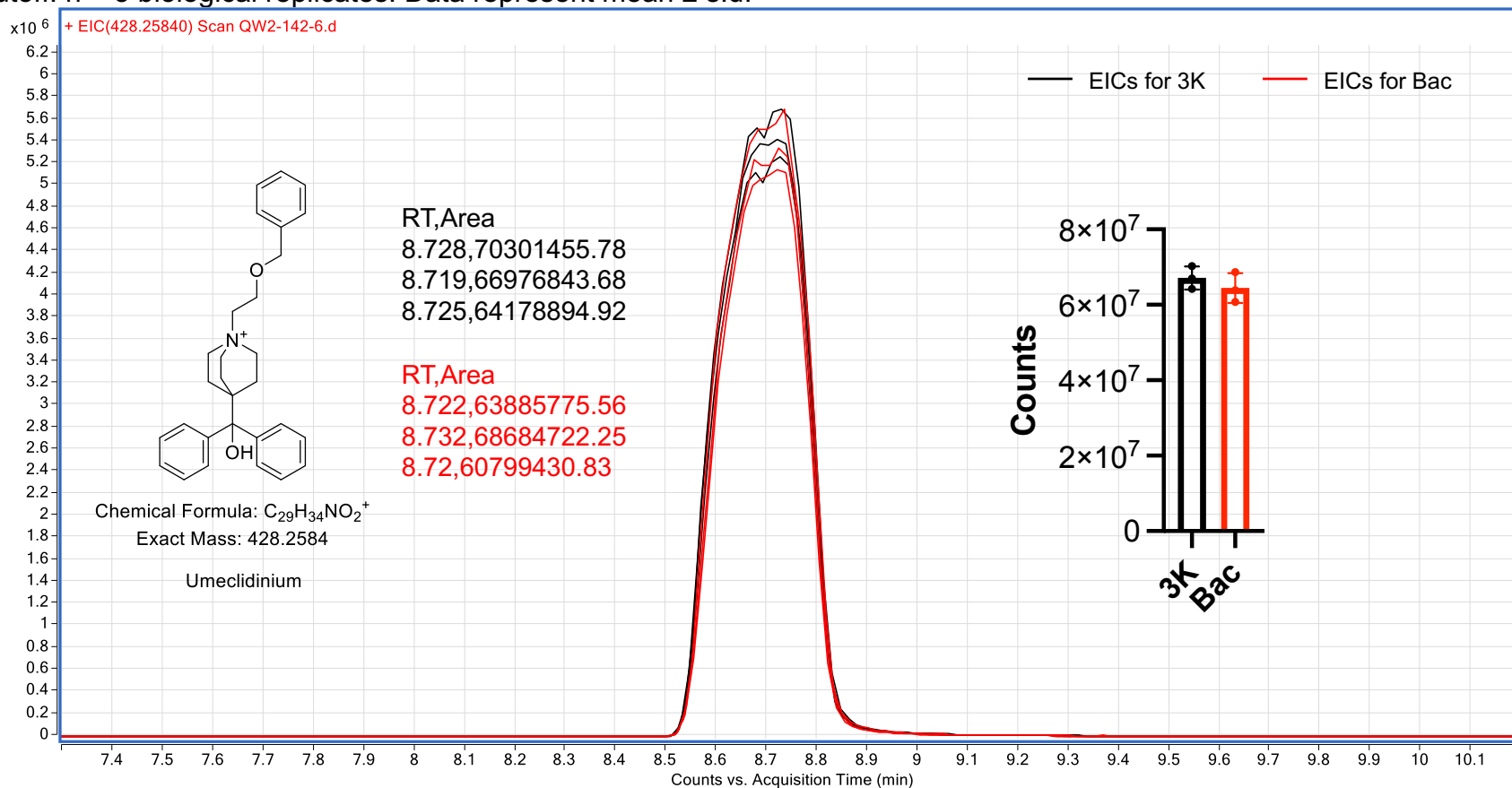


Fig. S84. Bac⁺ vs Bac⁻ (MWCO 3K) of clonidine (*m/z* 230.0246) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

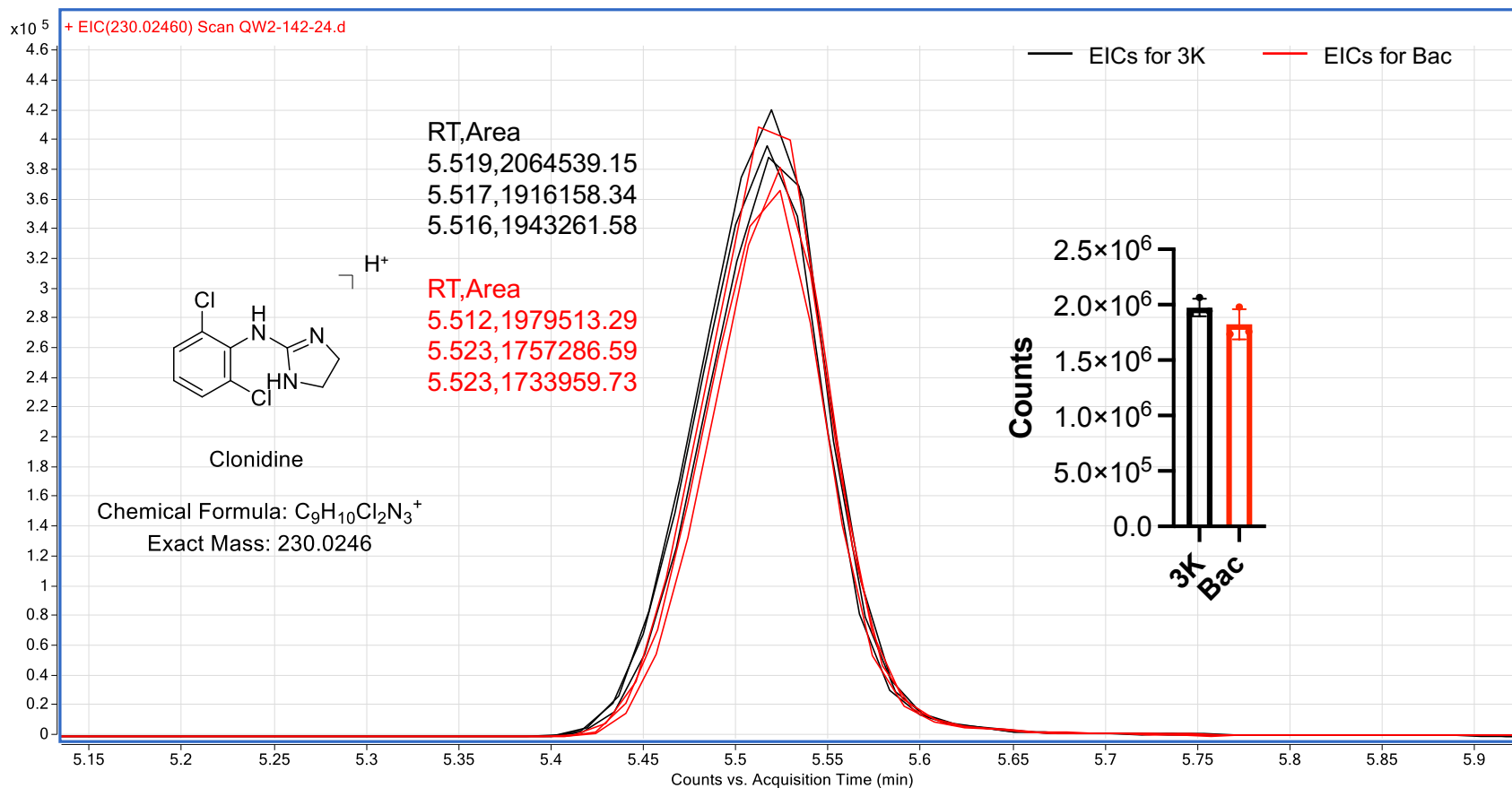


Fig. S85. Bac⁺ vs Bac⁻ (MWCO 3K) of tozadenant (*m/z* 407.1748) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

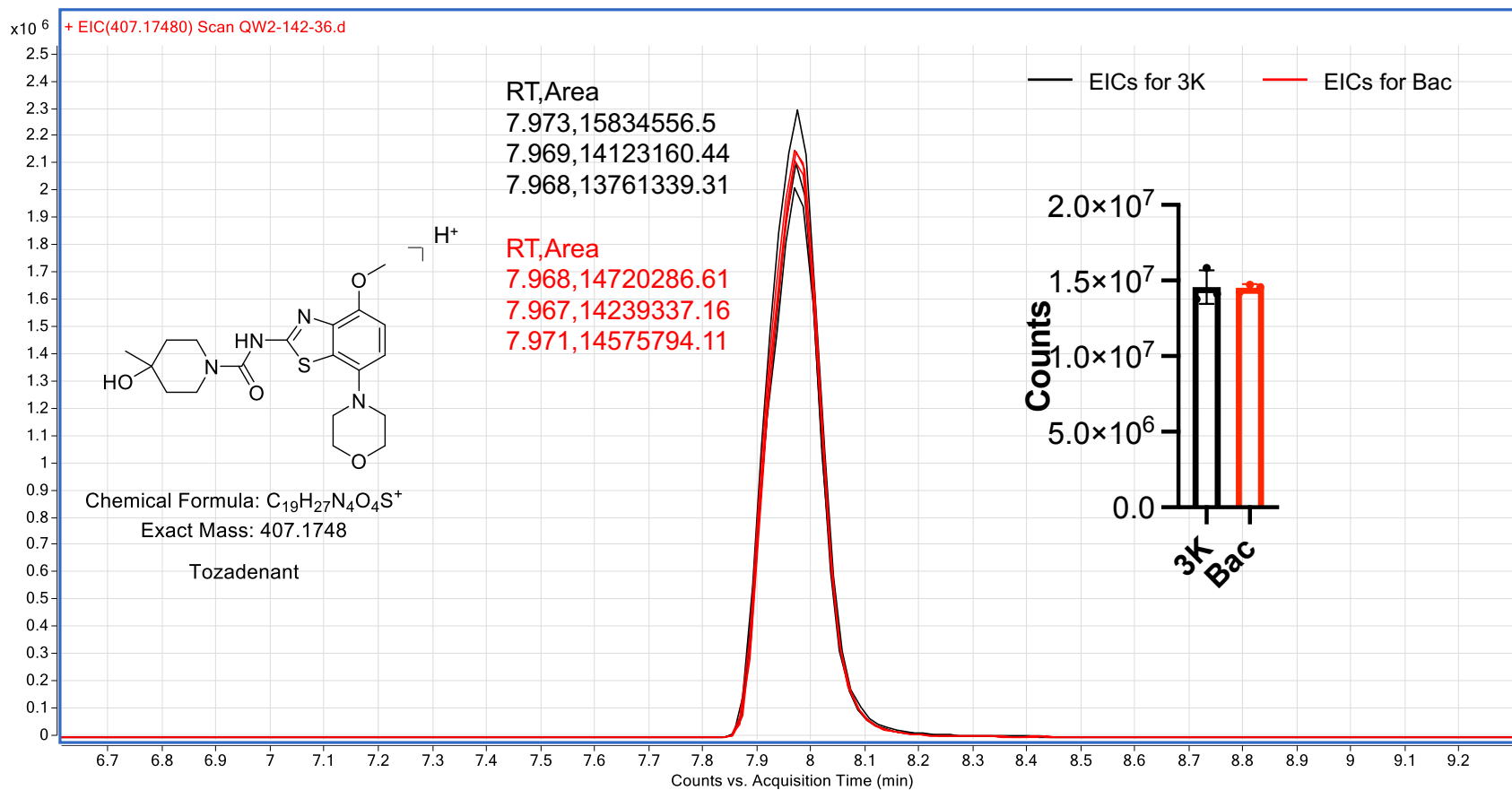


Fig. S86. Bac⁺ vs Bac⁻ (MWCO 3K) of naftopidil (*m/z* 393.2173) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

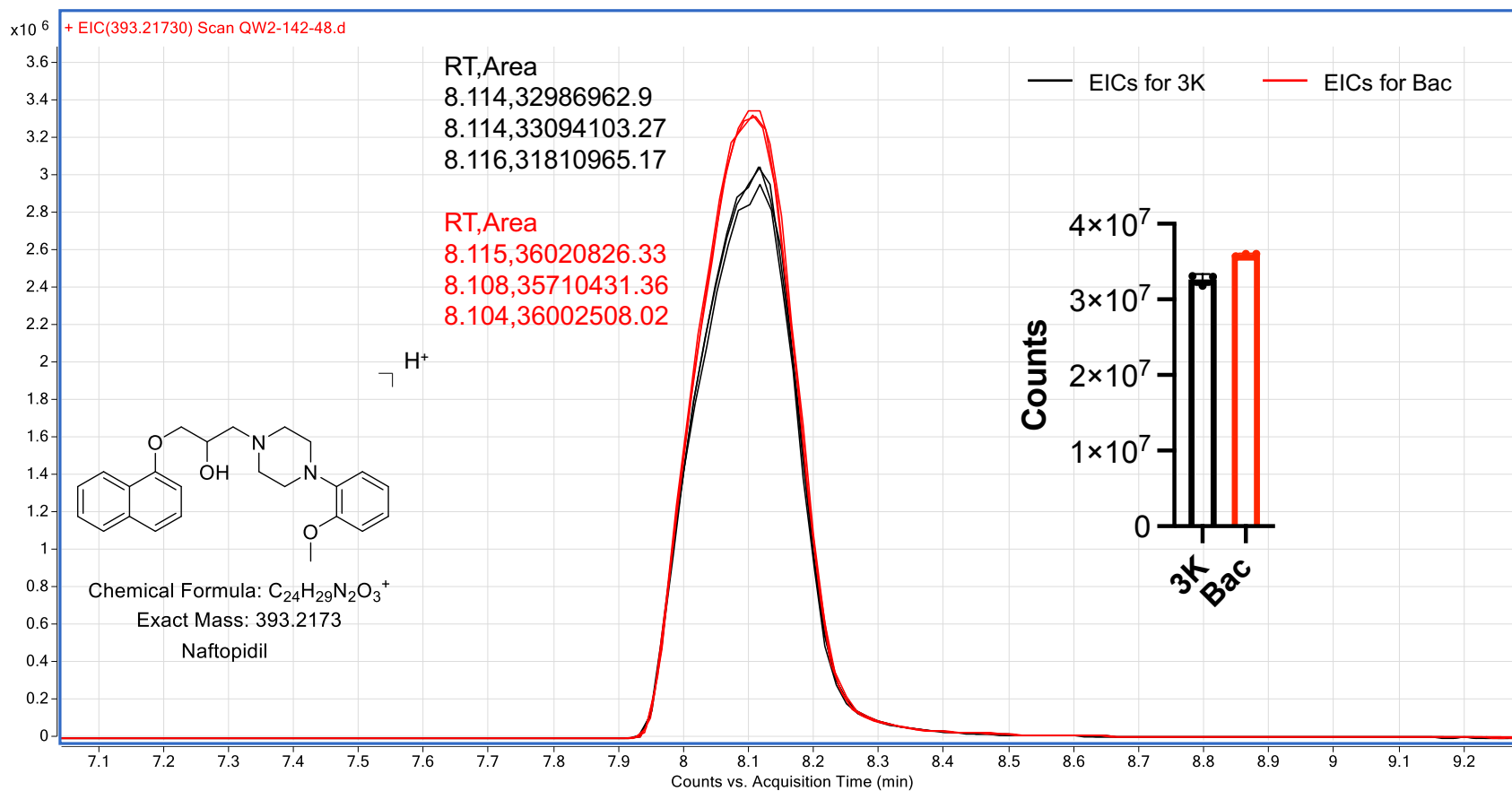


Fig. S87. Bac⁺ vs Bac⁻ (MWCO 3K) of loratadine (*m/z* 383.1521) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean $\pm$ s.d.

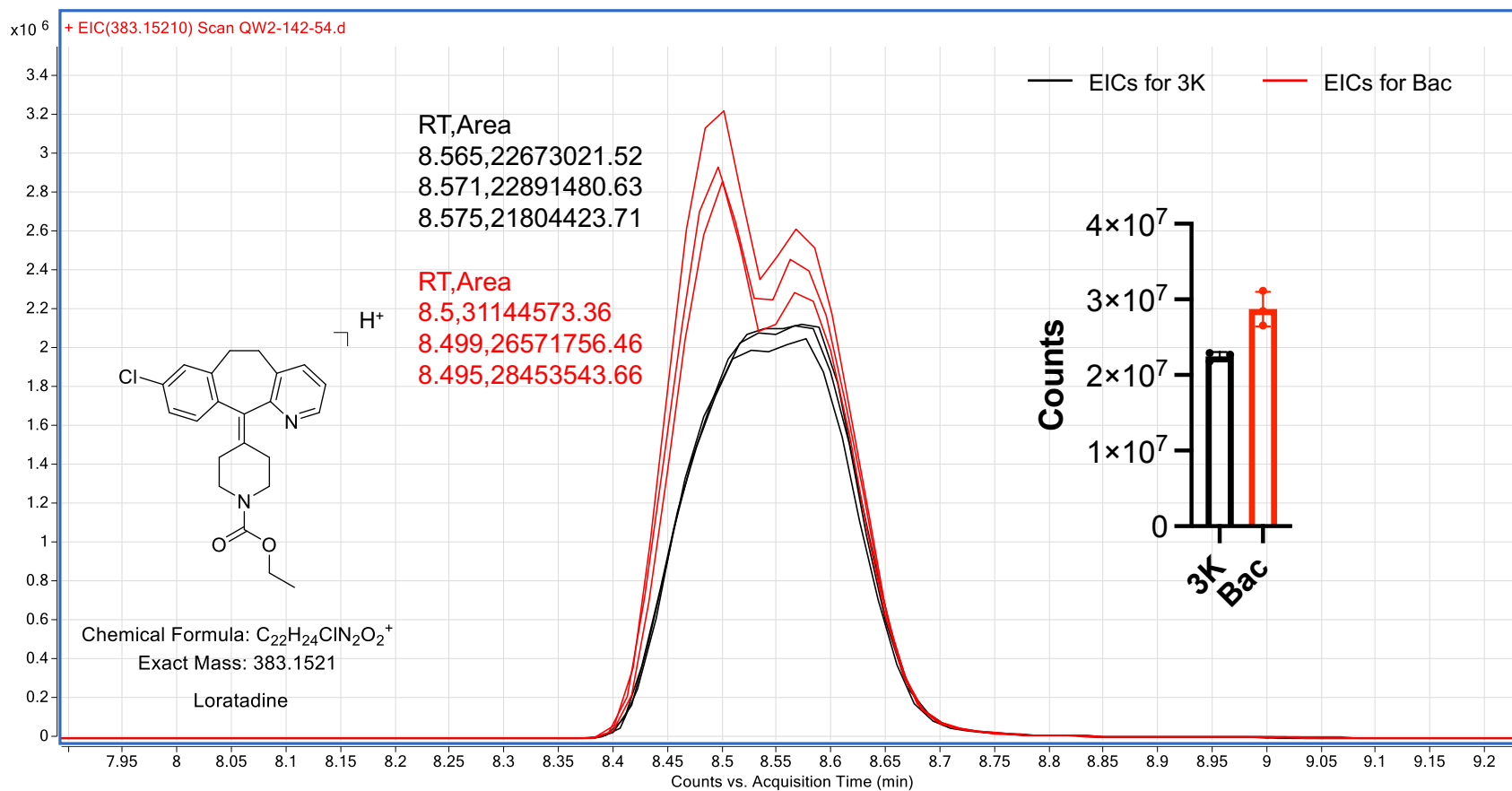


Fig. S88. Bac⁺ vs Bac⁻ (MWCO 3K) of proglumide (*m/z* 335.1965) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

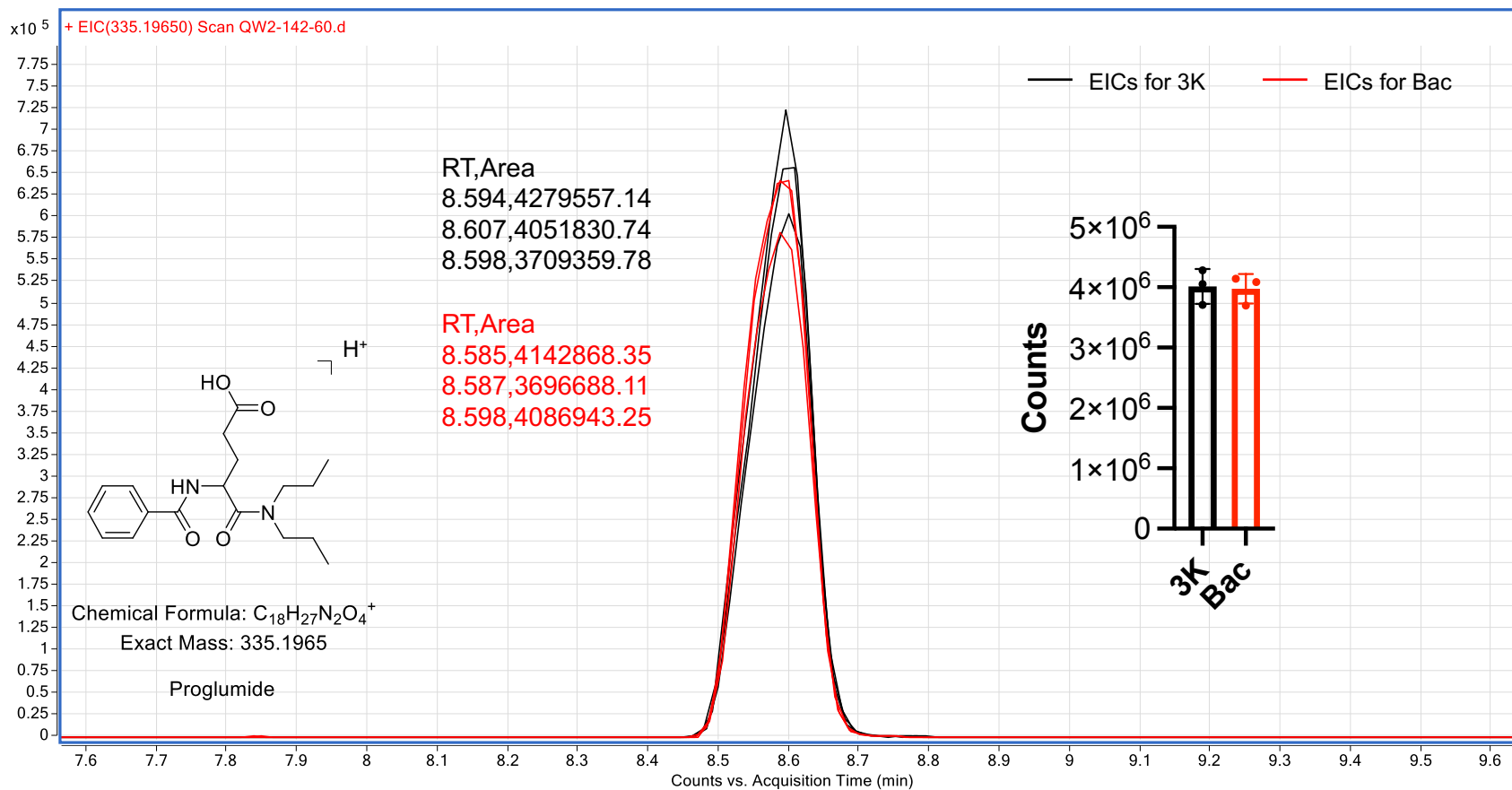


Fig. S89. Bac⁺ vs Bac⁻ (MWCO 3K) of volinanserin (*m/z* 374.2126) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

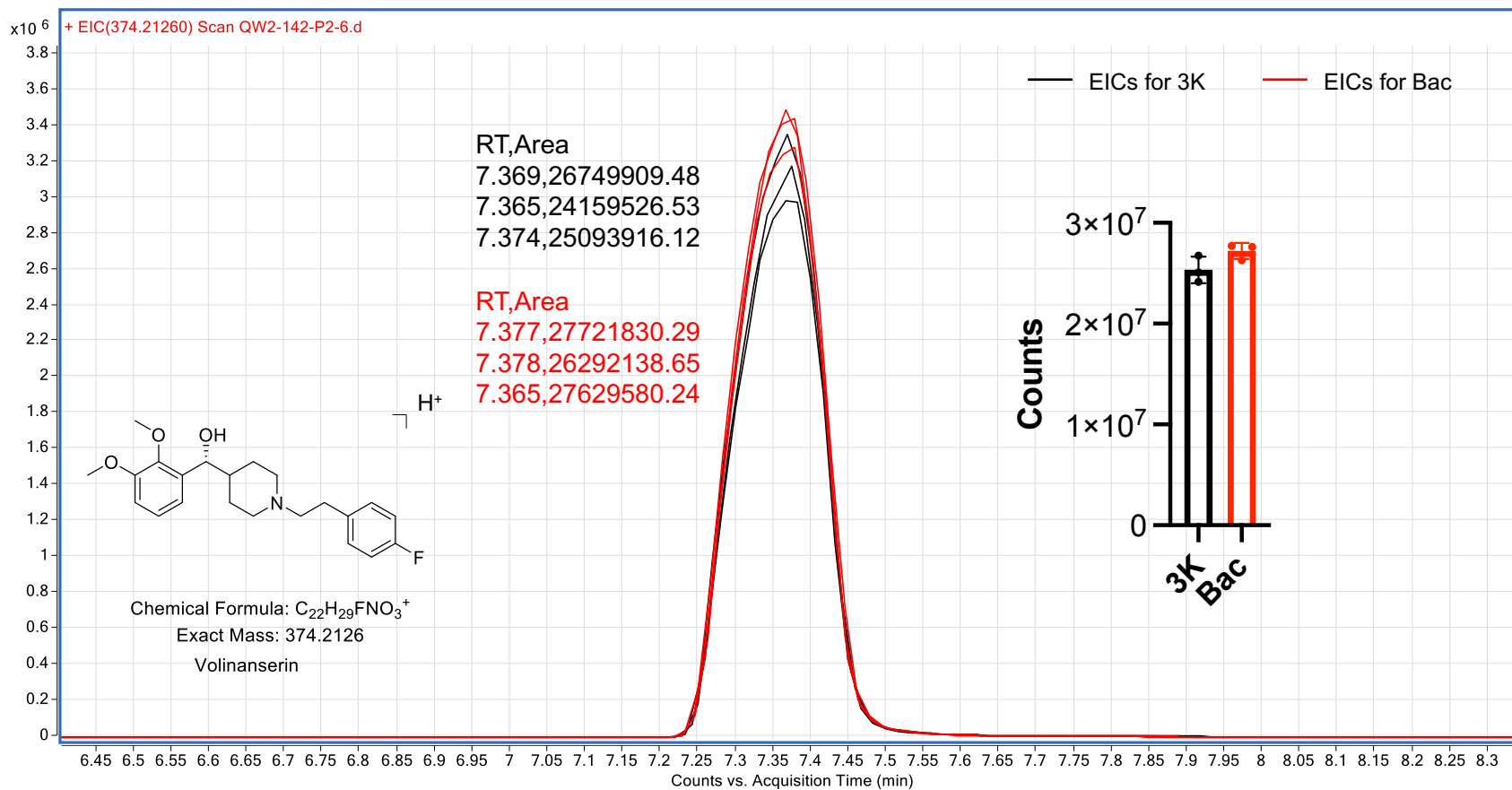


Fig. S90. Bac⁺ vs Bac⁻ (MWCO 3K) of MK-0557 (*m/z* 407.1514) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

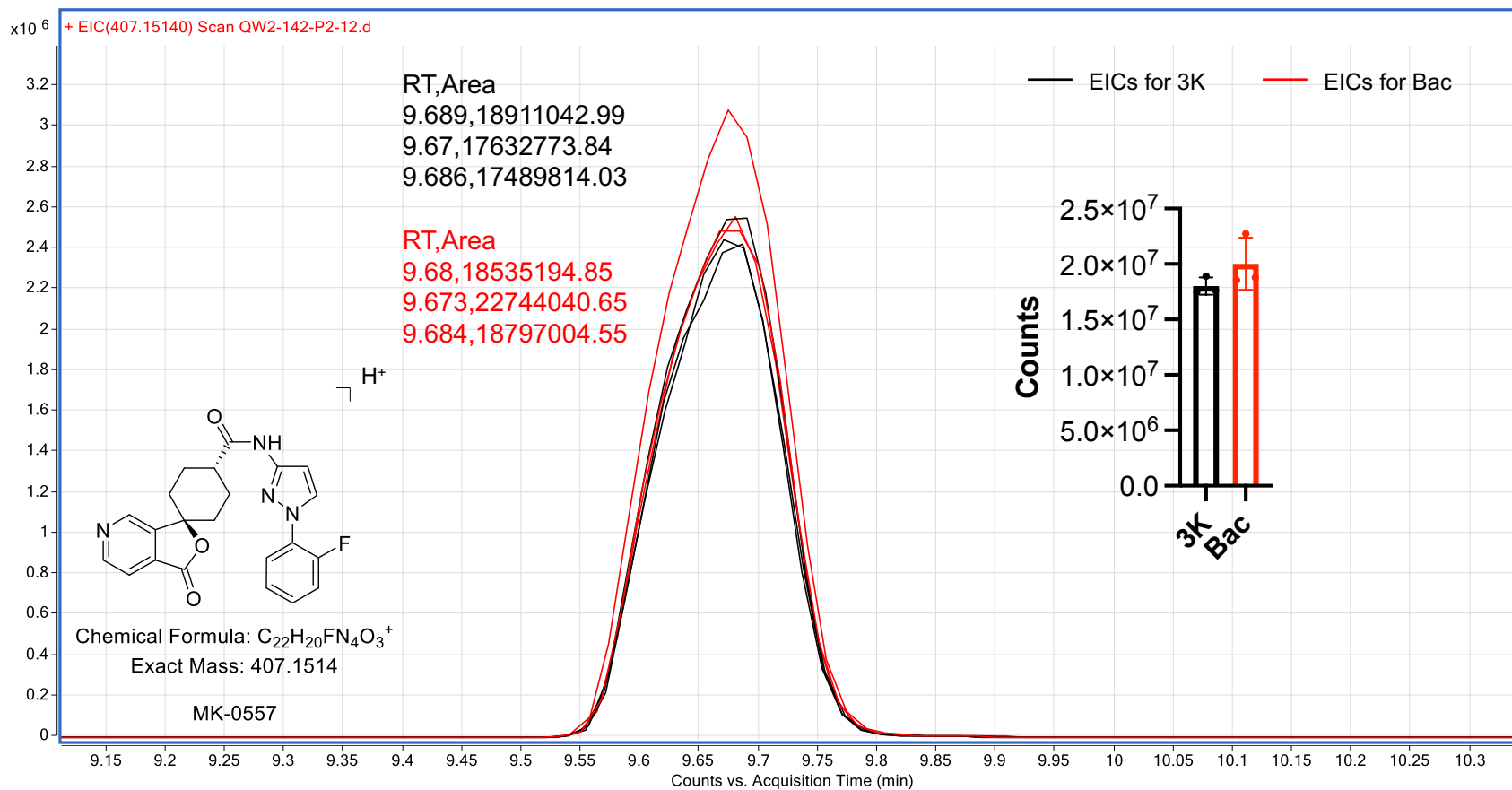


Fig. S91. Bac⁺ vs Bac⁻ (MWCO 3K) of setipiprant (*m/z* 403.1452) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

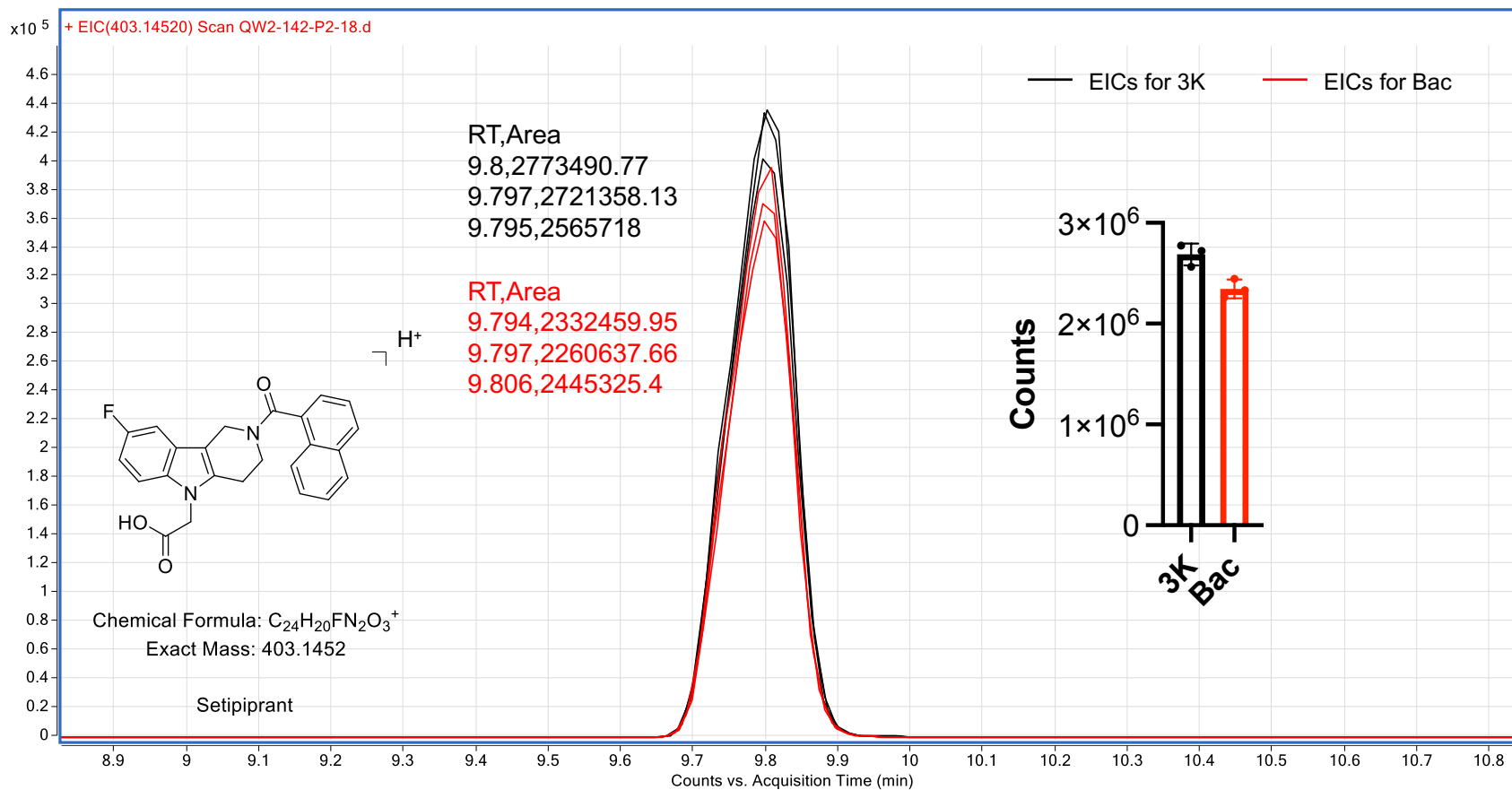


Fig. S92. Bac⁺ vs Bac⁻ (MWCO 3K) of mavorixafor (*m/z* 350.2339) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

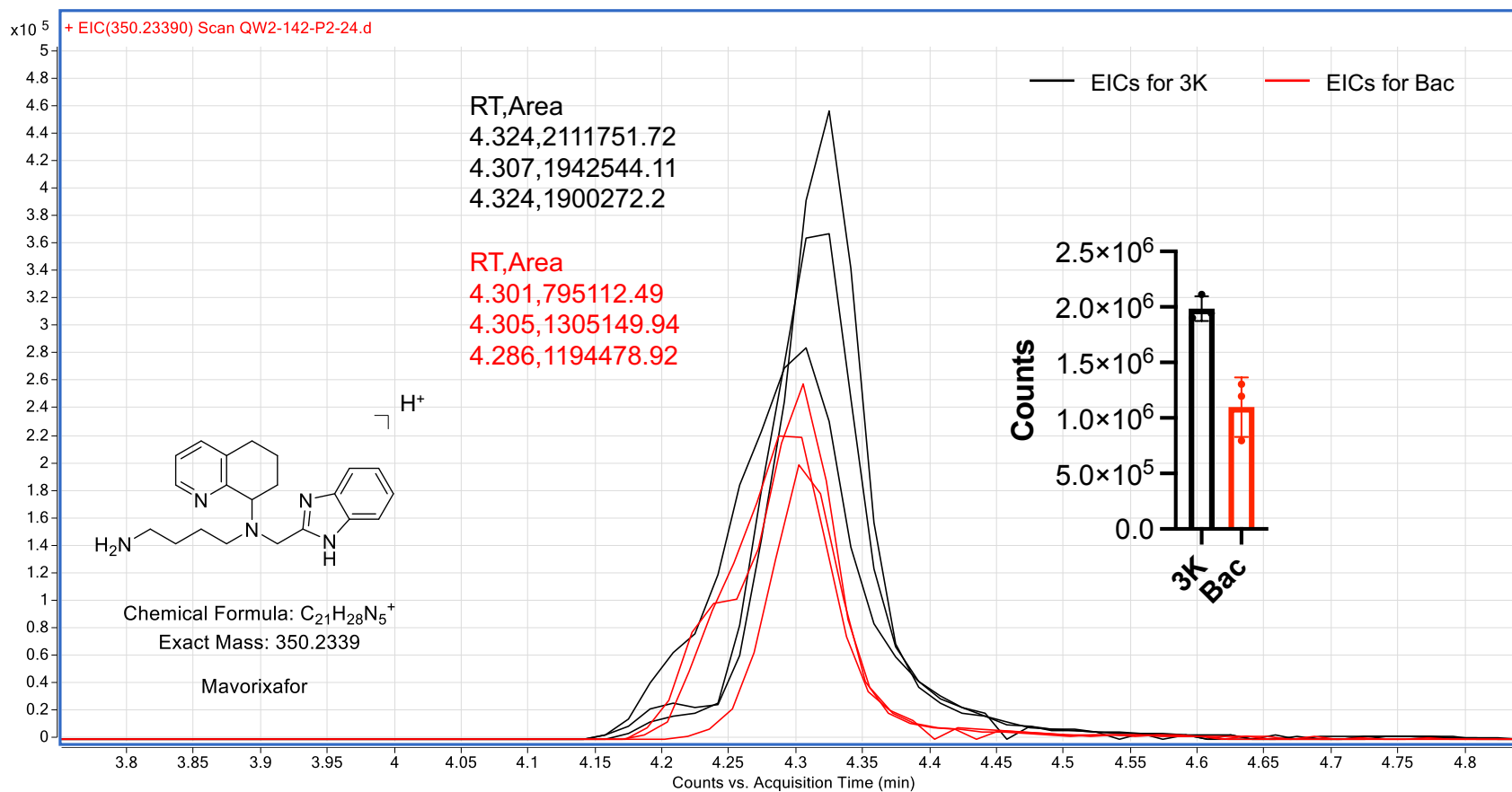


Fig. S93. Bac⁺ vs Bac⁻ (MWCO 3K) of timapiprant (*m/z* 349.1347) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

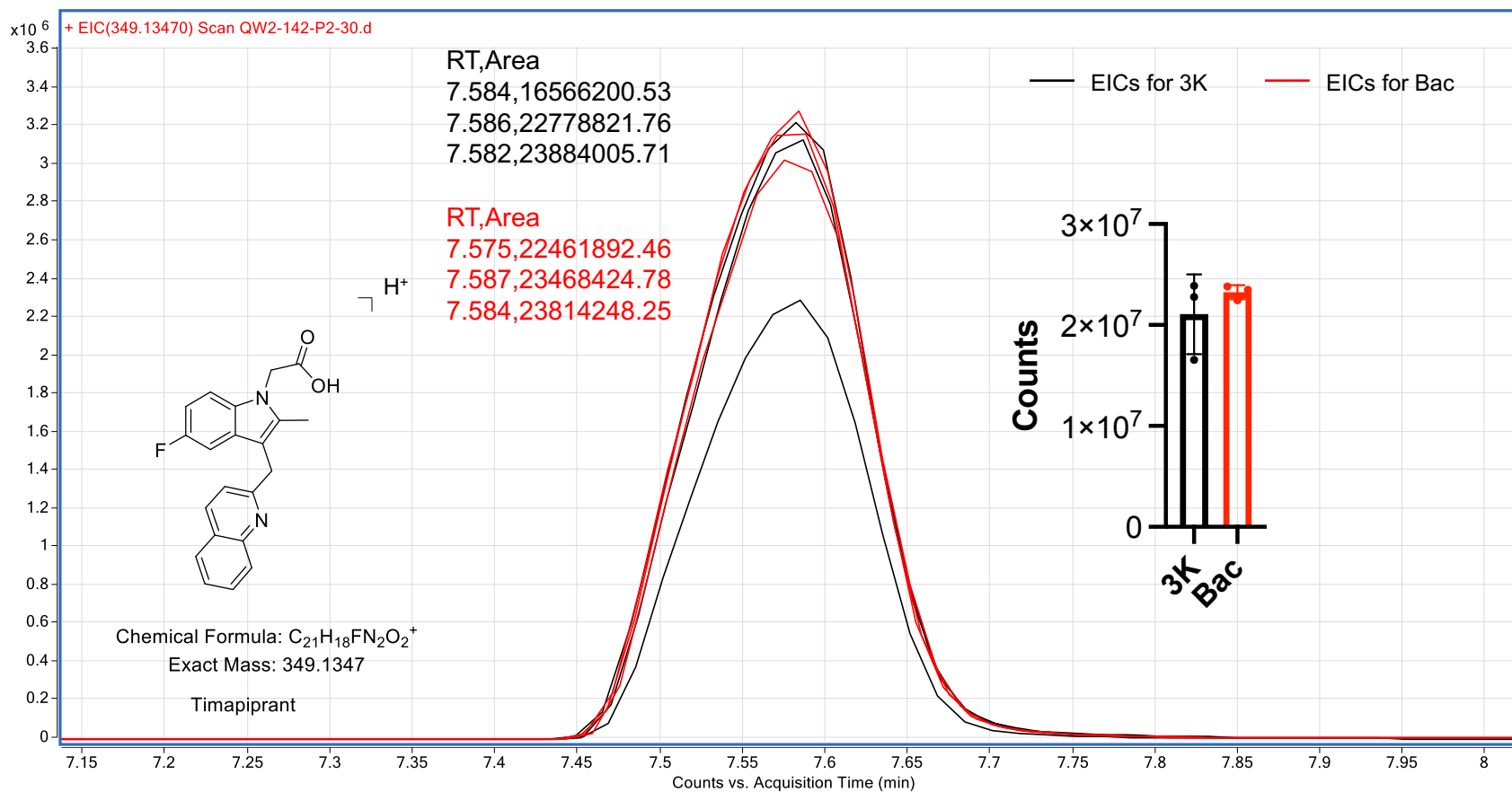


Fig. S94. Bac⁺ vs Bac⁻ (MWCO 3K) of ozanimod (*m/z* 405.1921) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

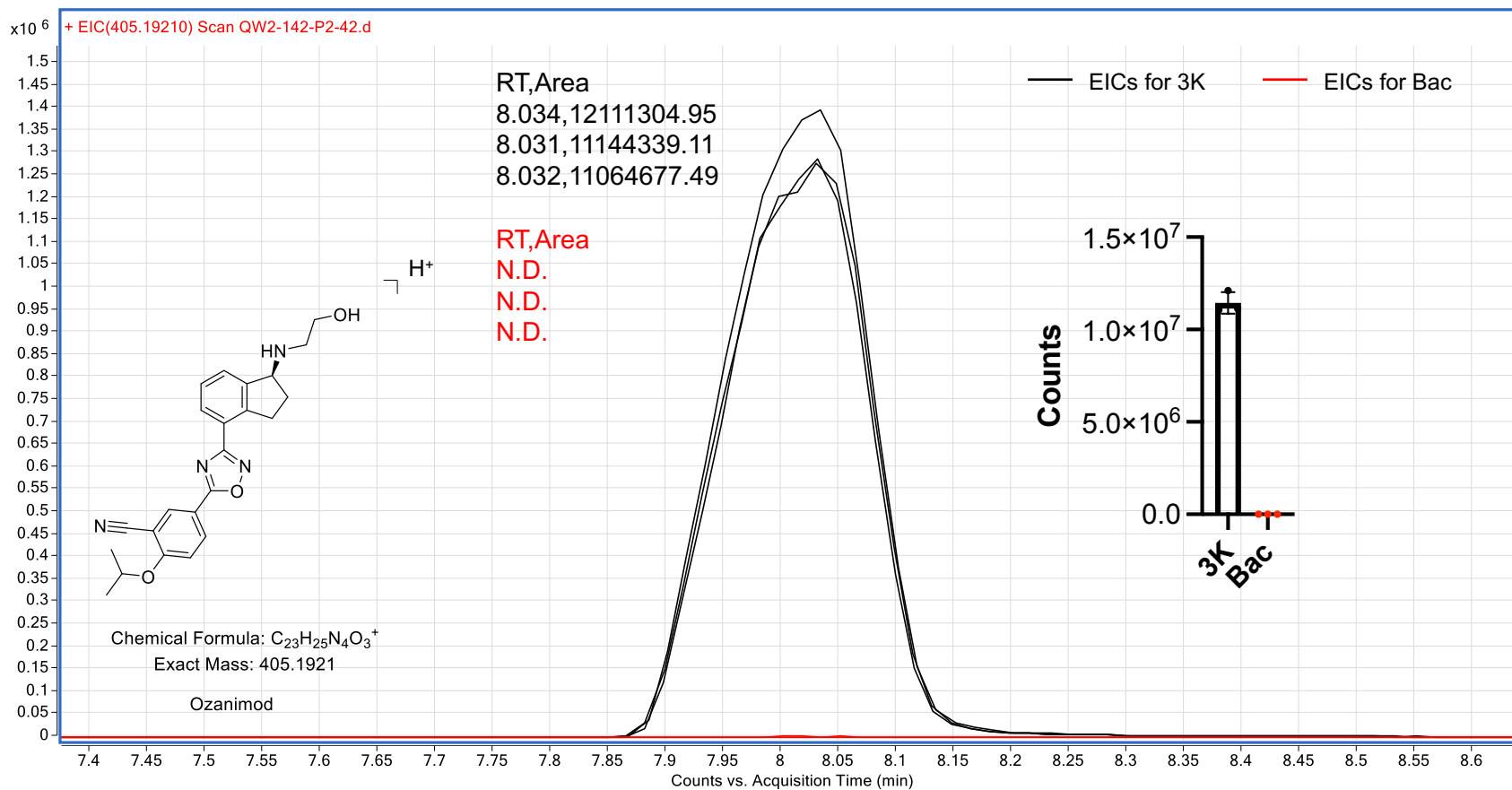


Fig. S95. Bac⁺ vs Bac⁻ (MWCO 3K) of fasiglifam (*m/z* 525.1942) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

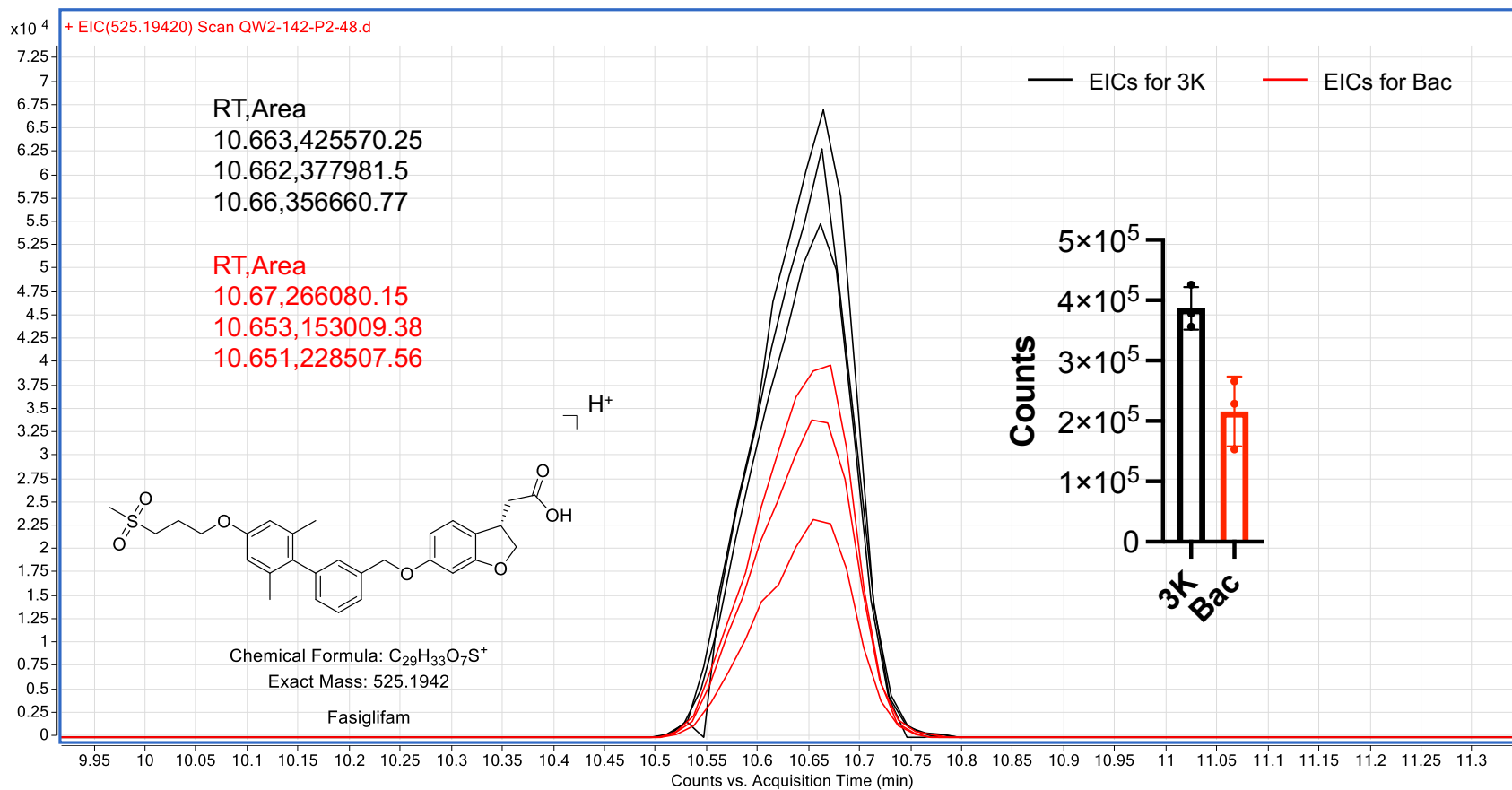


Fig. S96. Bac⁺ vs Bac⁻ (MWCO 3K) of lumateperone (*m/z* 394.2289) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

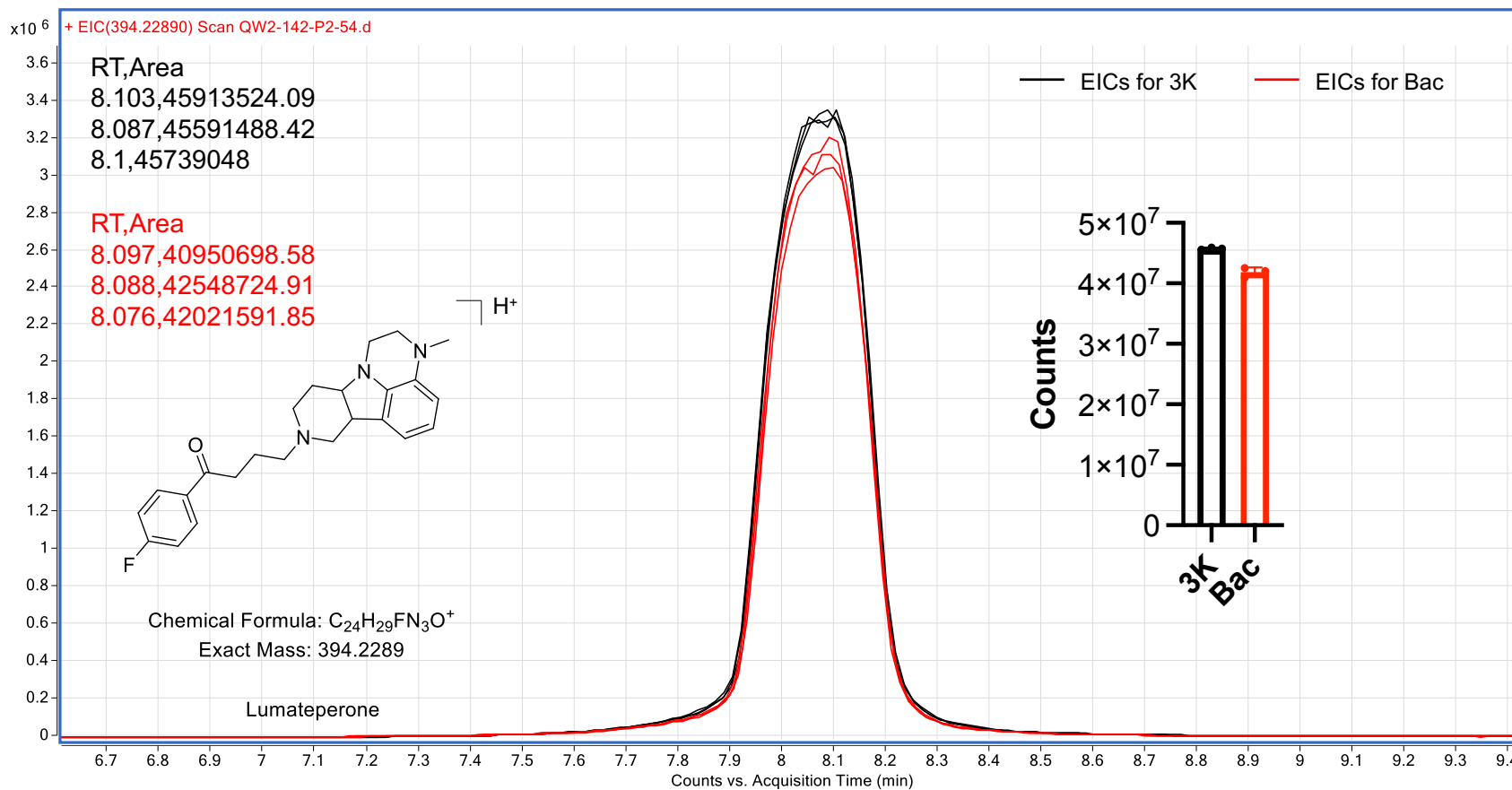


Fig. S97. Bac⁺ vs Bac⁻ (MWCO 3K) of pimavanserin (*m/z* 428.2708) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

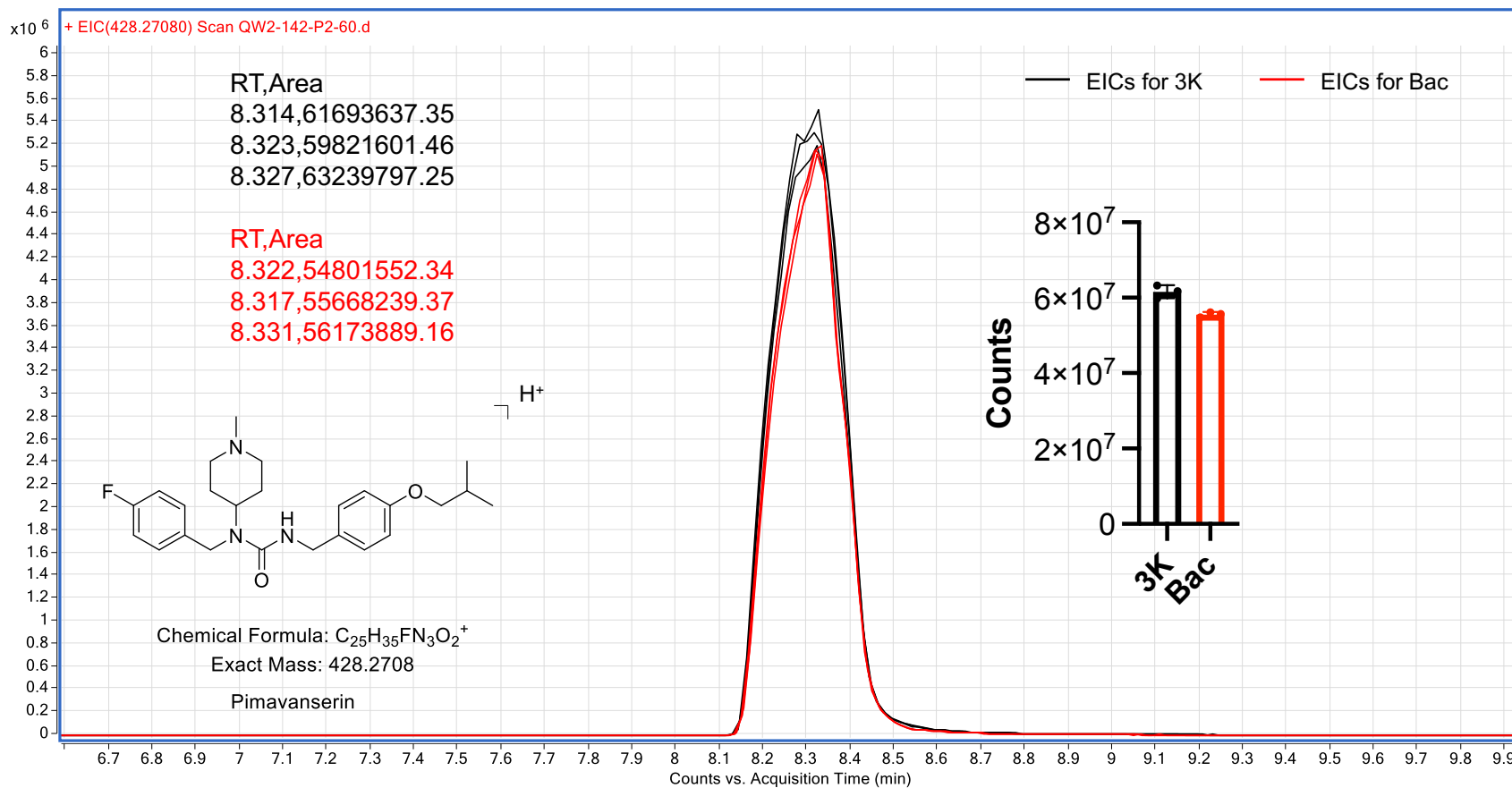


Fig. S98. Bac⁺ vs Bac⁻ (MWCO 3K) of imaradenant (*m/z* 316.0760) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

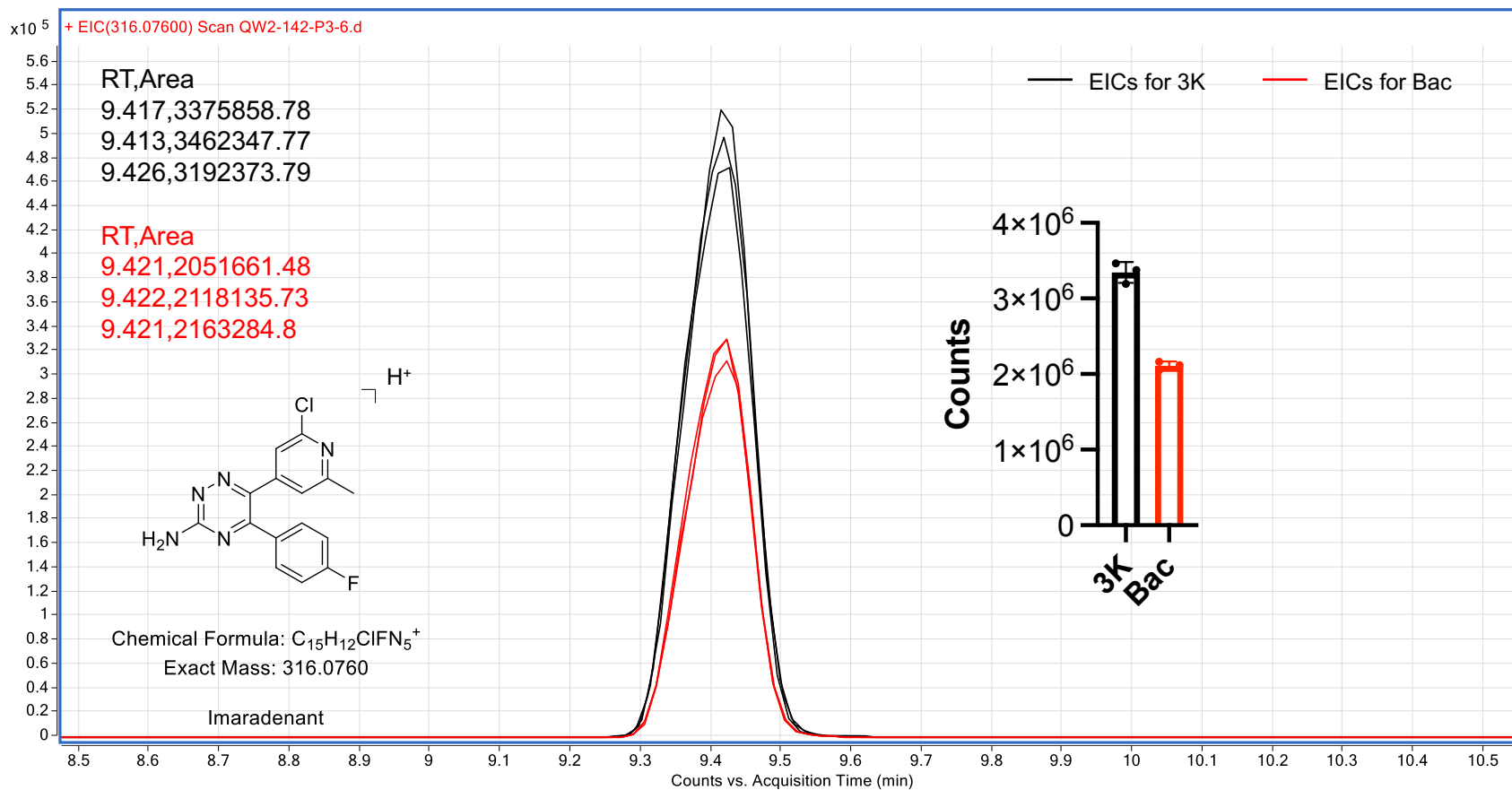


Fig. S99. Bac⁺ vs Bac⁻ (MWCO 3K) of zafirlukast (*m/z* 576.2163) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

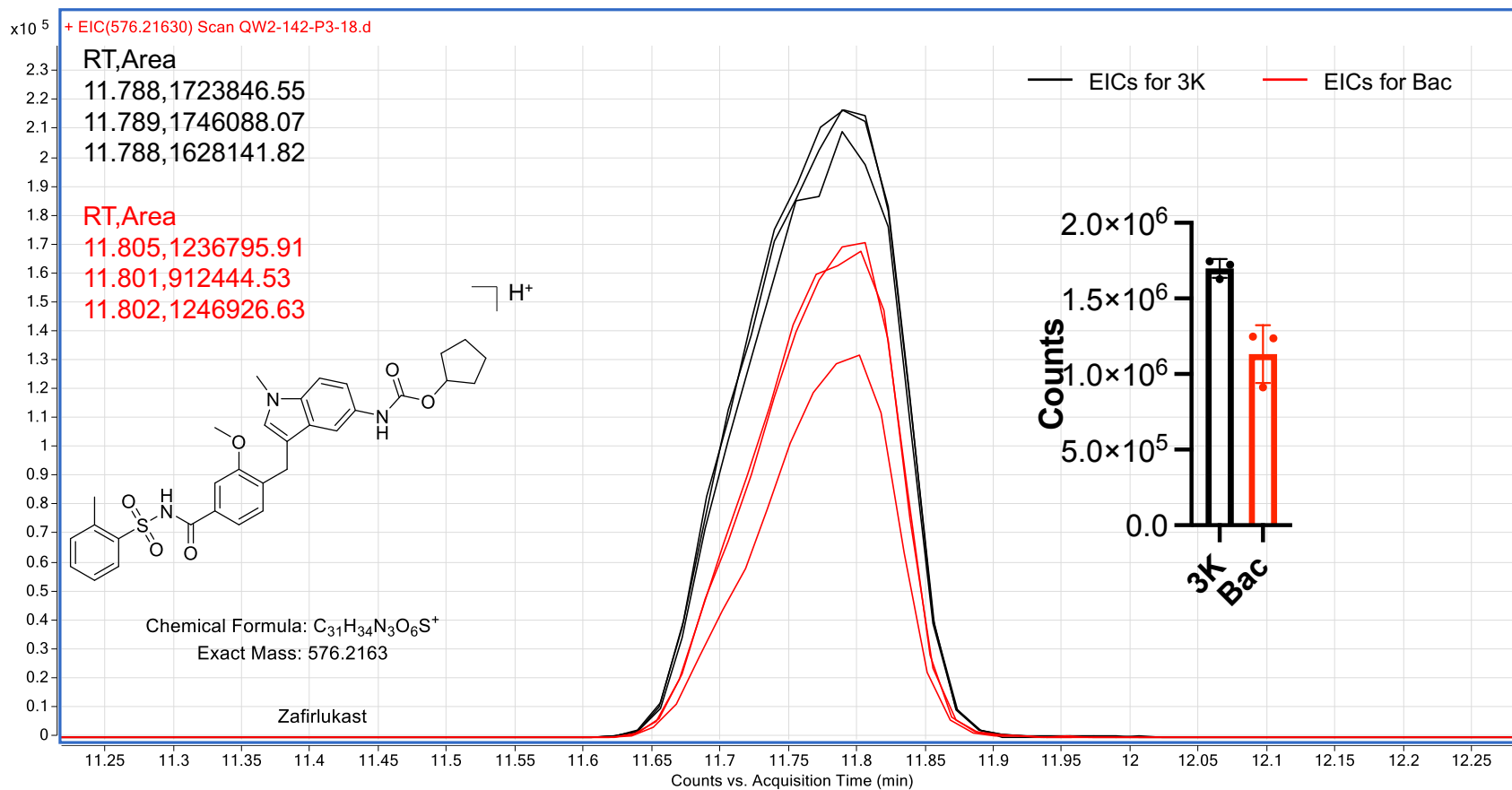


Fig. S100. Bac⁺ vs Bac⁻ (MWCO 3K) of ponesimod (*m/z* 461.1296) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

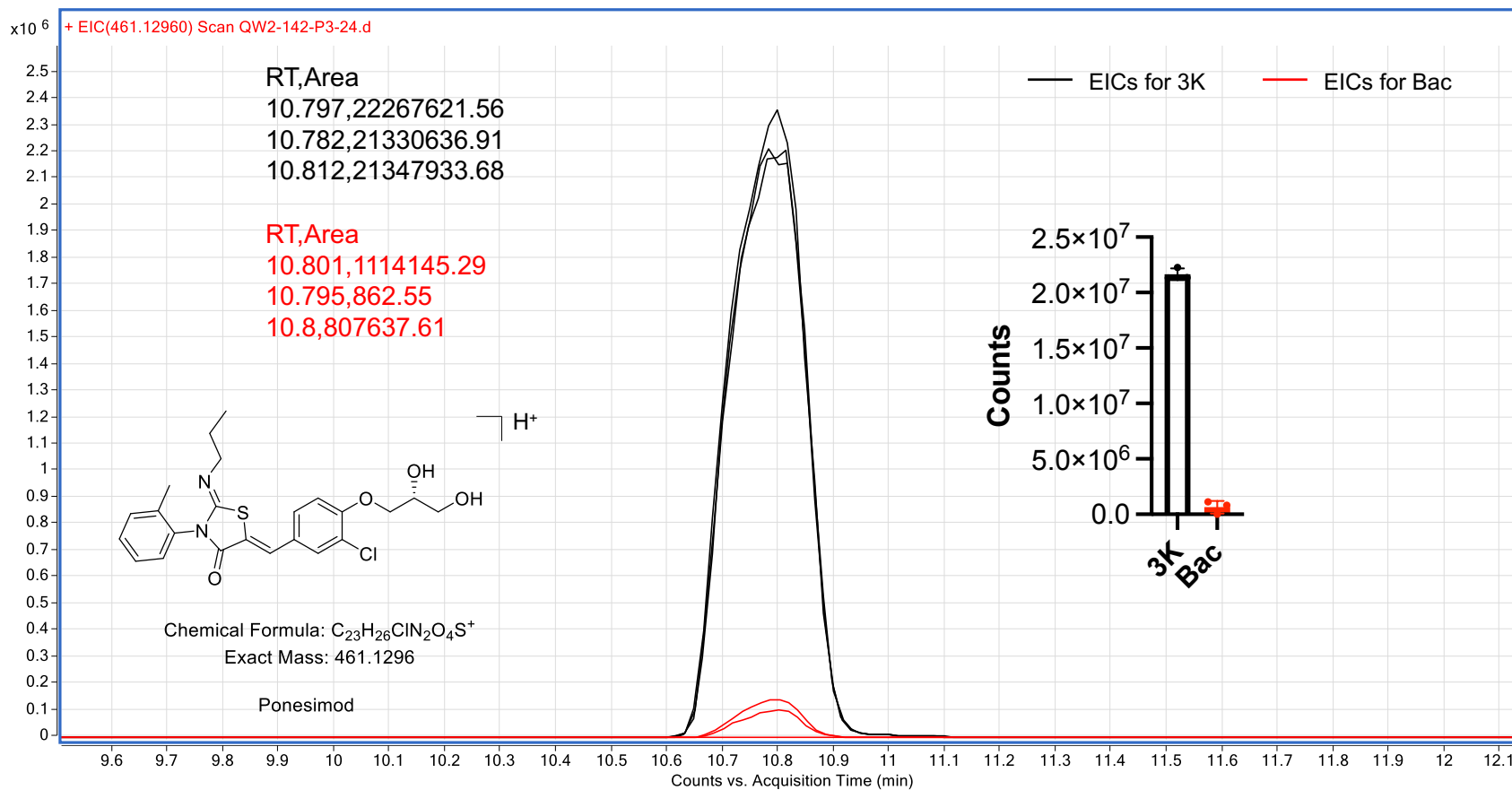


Fig. S101. Bac⁺ vs Bac⁻ (MWCO 3K) of molindone (*m/z* 277.1911) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

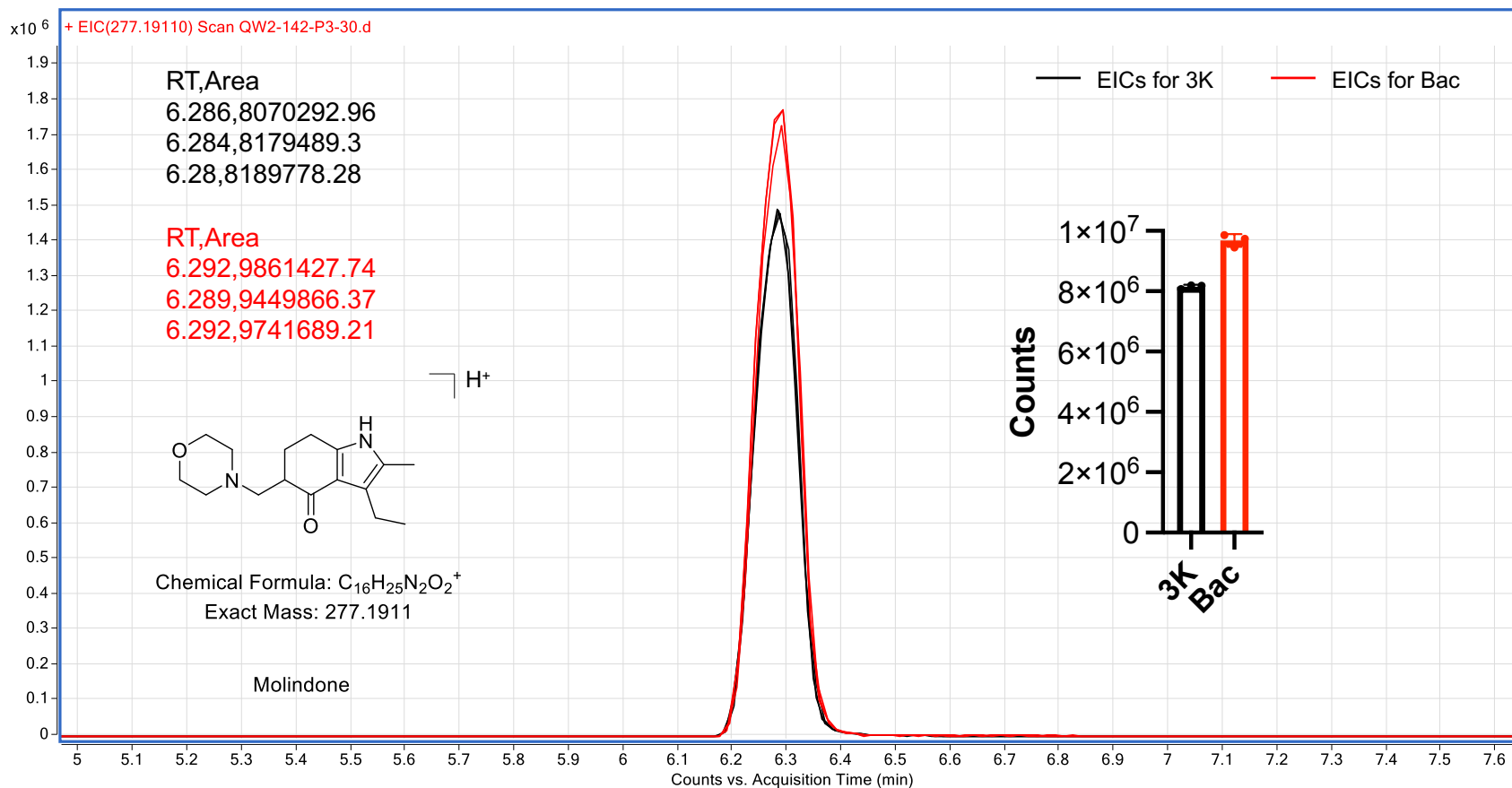


Fig. S102. Bac⁺ vs Bac⁻ (MWCO 3K) of telcagepant (*m/z* 567.2138) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

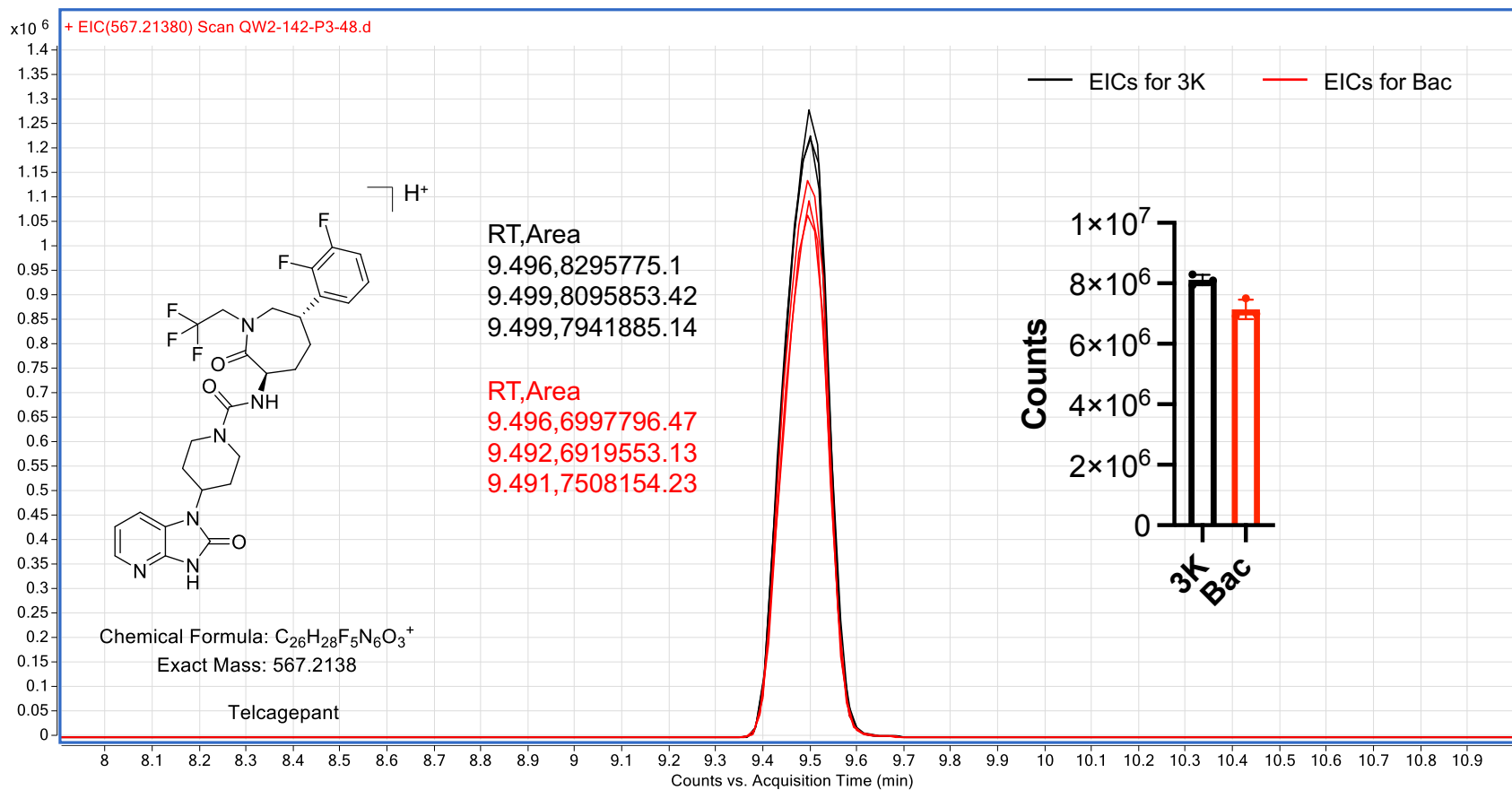


Fig. S103. Bac⁺ vs Bac⁻ (MWCO 3K) of trimethobenzamide (*m/z* 389.2071) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

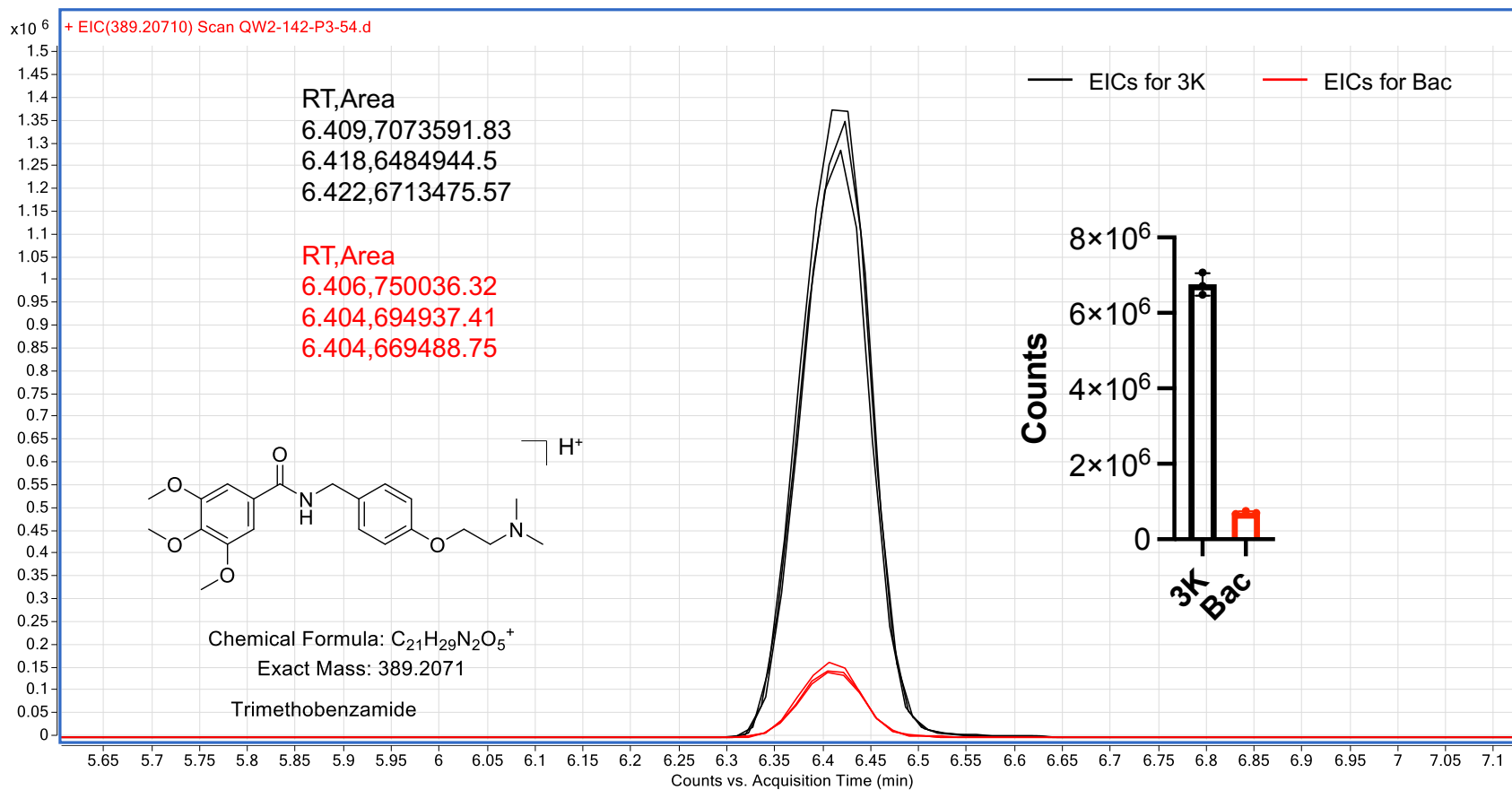


Fig. S104. Bac⁺ vs Bac⁻ (MWCO 3K) of adoprazine (*m/z* 406.1925) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

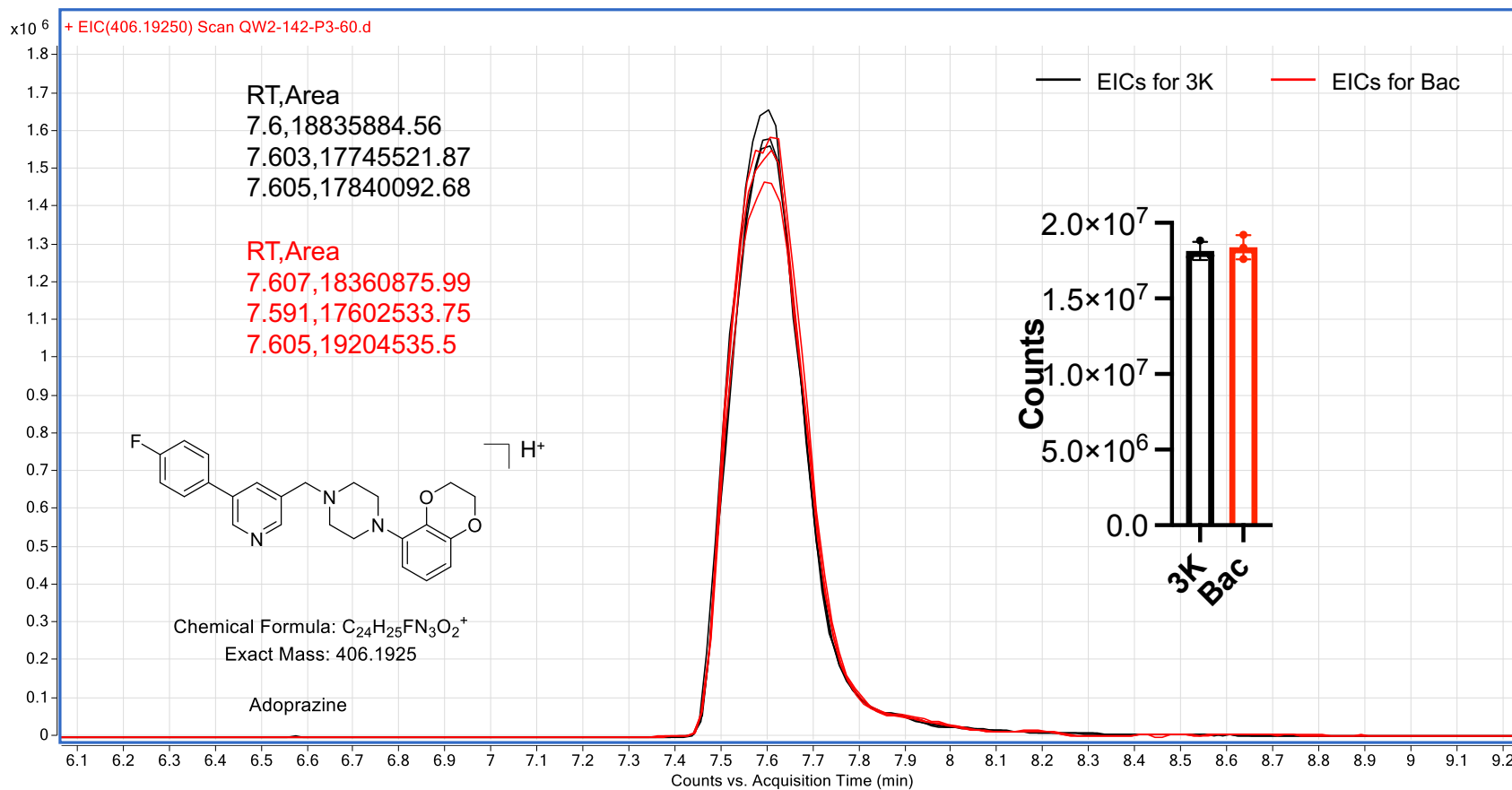


Fig. S105. Bac⁺ vs Bac⁻ (MWCO 3K) of nicergoline (*m/z* 484.1230) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

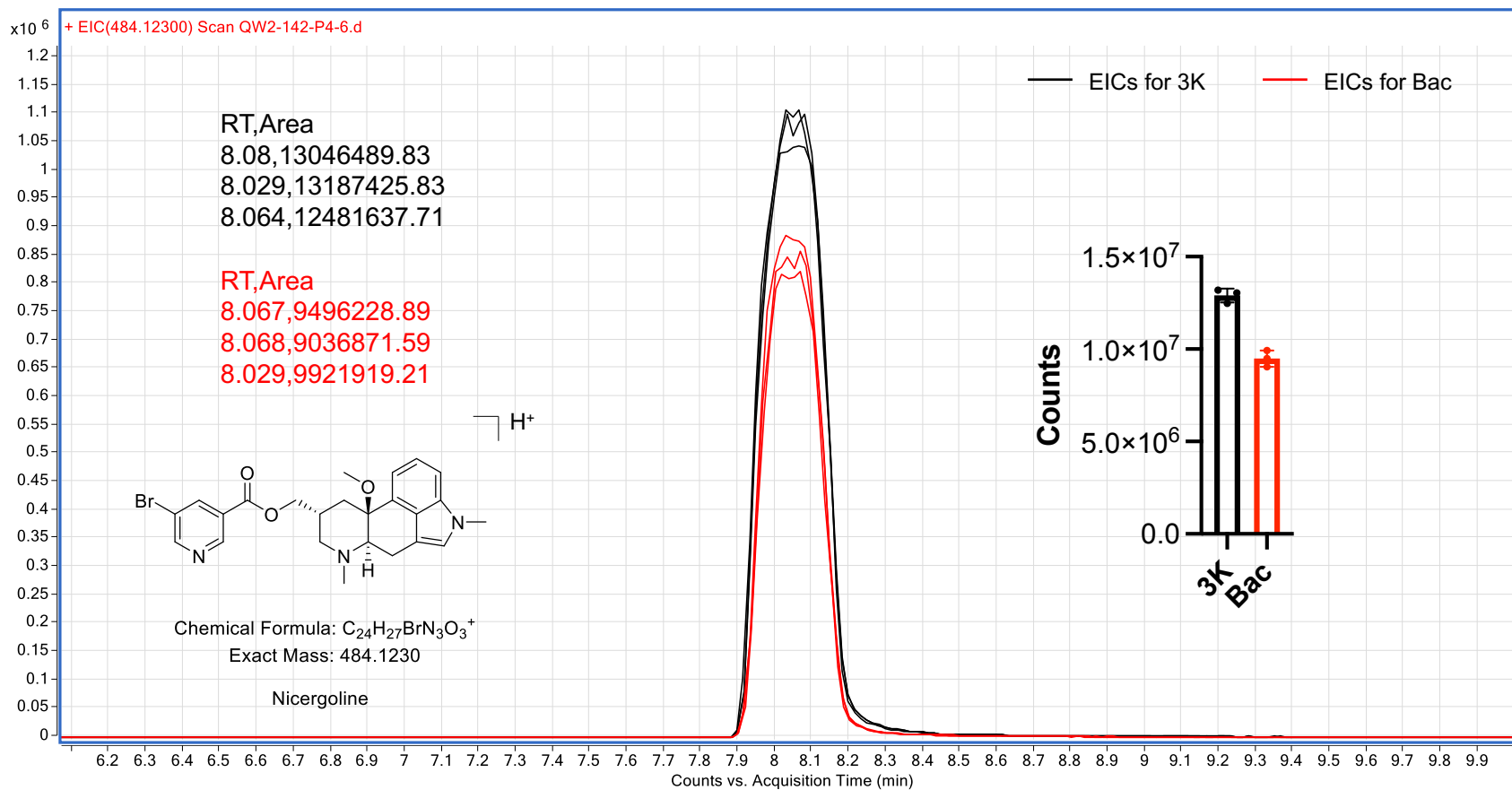


Fig. S106. Bac⁺ vs Bac⁻ (MWCO 3K) of aprepitant (*m/z* 535.1575) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

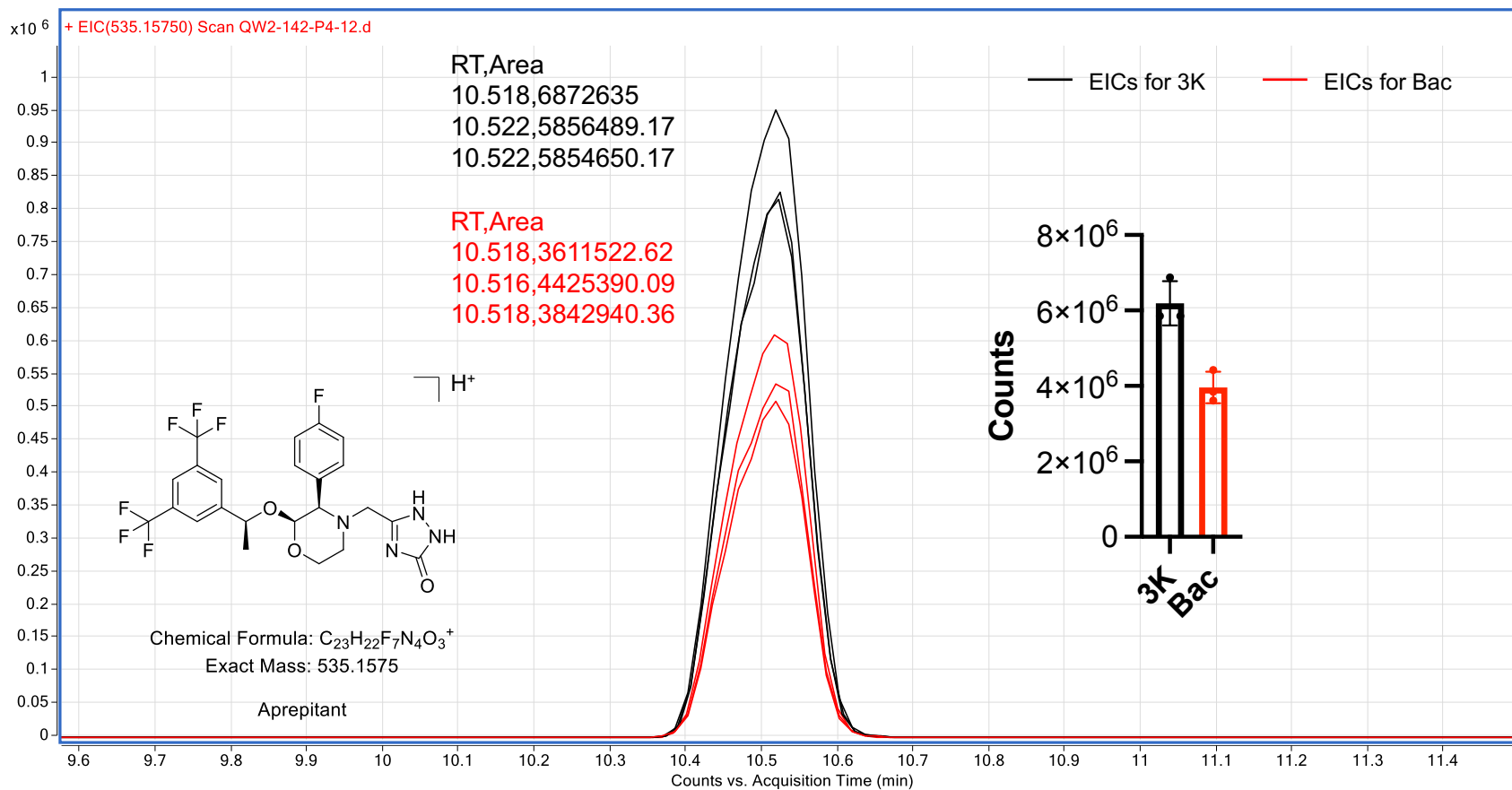


Fig. S107. Bac⁺ vs Bac⁻ (MWCO 3K) of bambuterol (*m/z* 368.2180) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

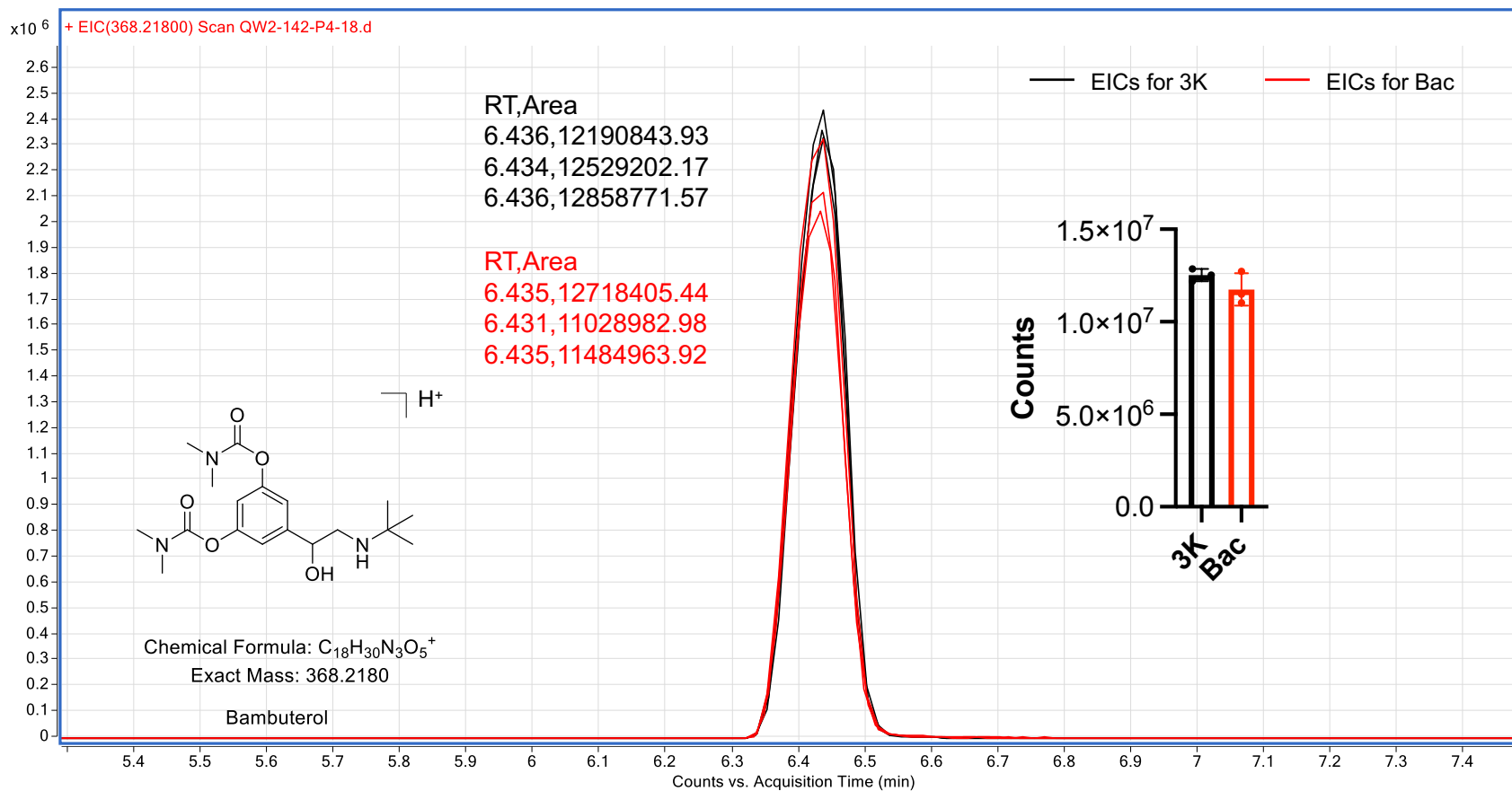


Fig. S108. Bac⁺ vs Bac⁻ (MWCO 3K) of filorexant (*m/z* 421.2034) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

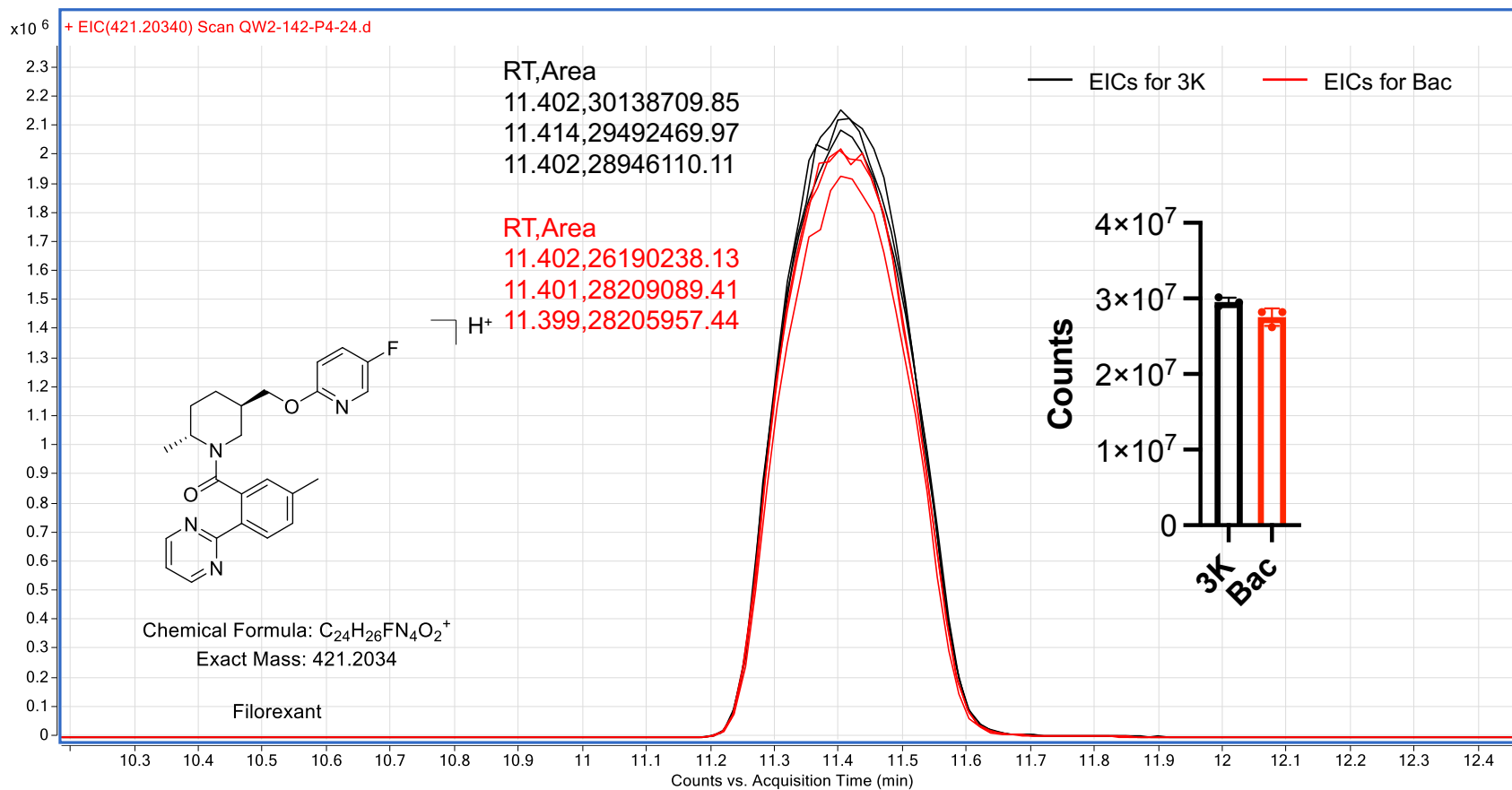


Fig. S109. Bac⁺ vs Bac⁻ (MWCO 3K) of pavinetante (*m/z* 460.1689) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean $\pm$ s.d.

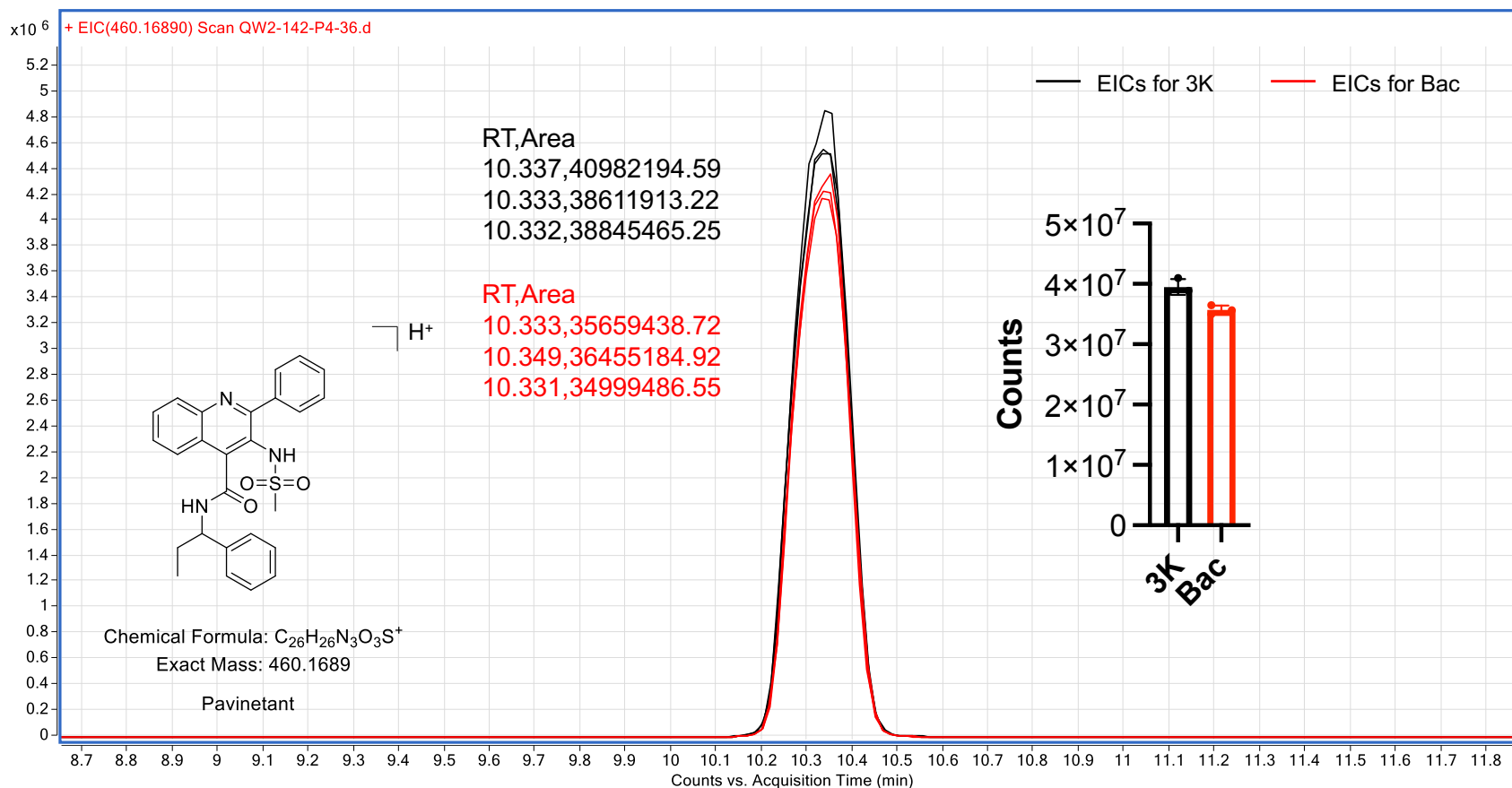


Fig. S110. Bac⁺ vs Bac⁻ (MWCO 3K) of cisapride (*m/z* 466.1903) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

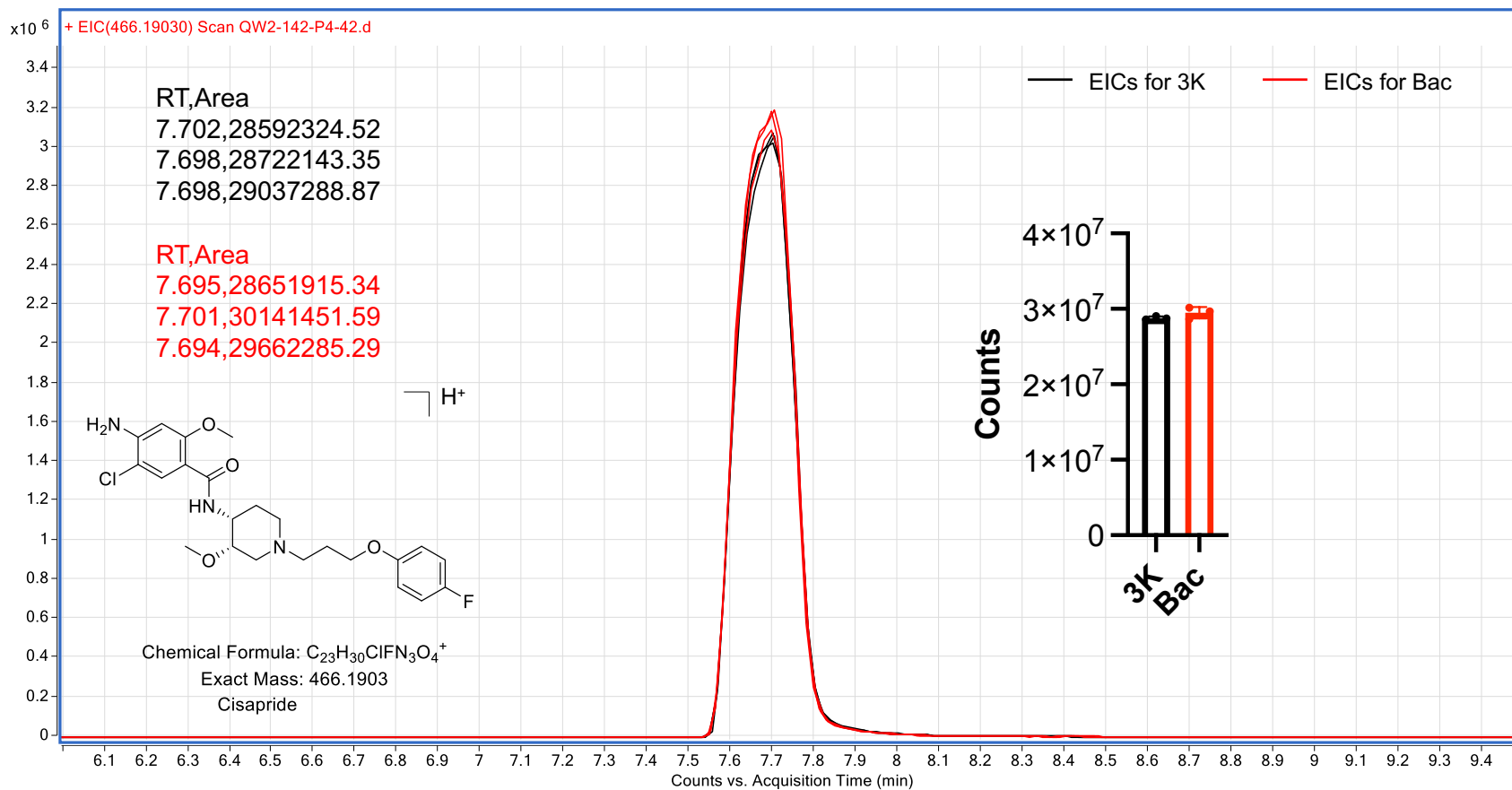


Fig. S111. Bac⁺ vs Bac⁻ (MWCO 3K) of clopidogrel (*m/z* 322.0663) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

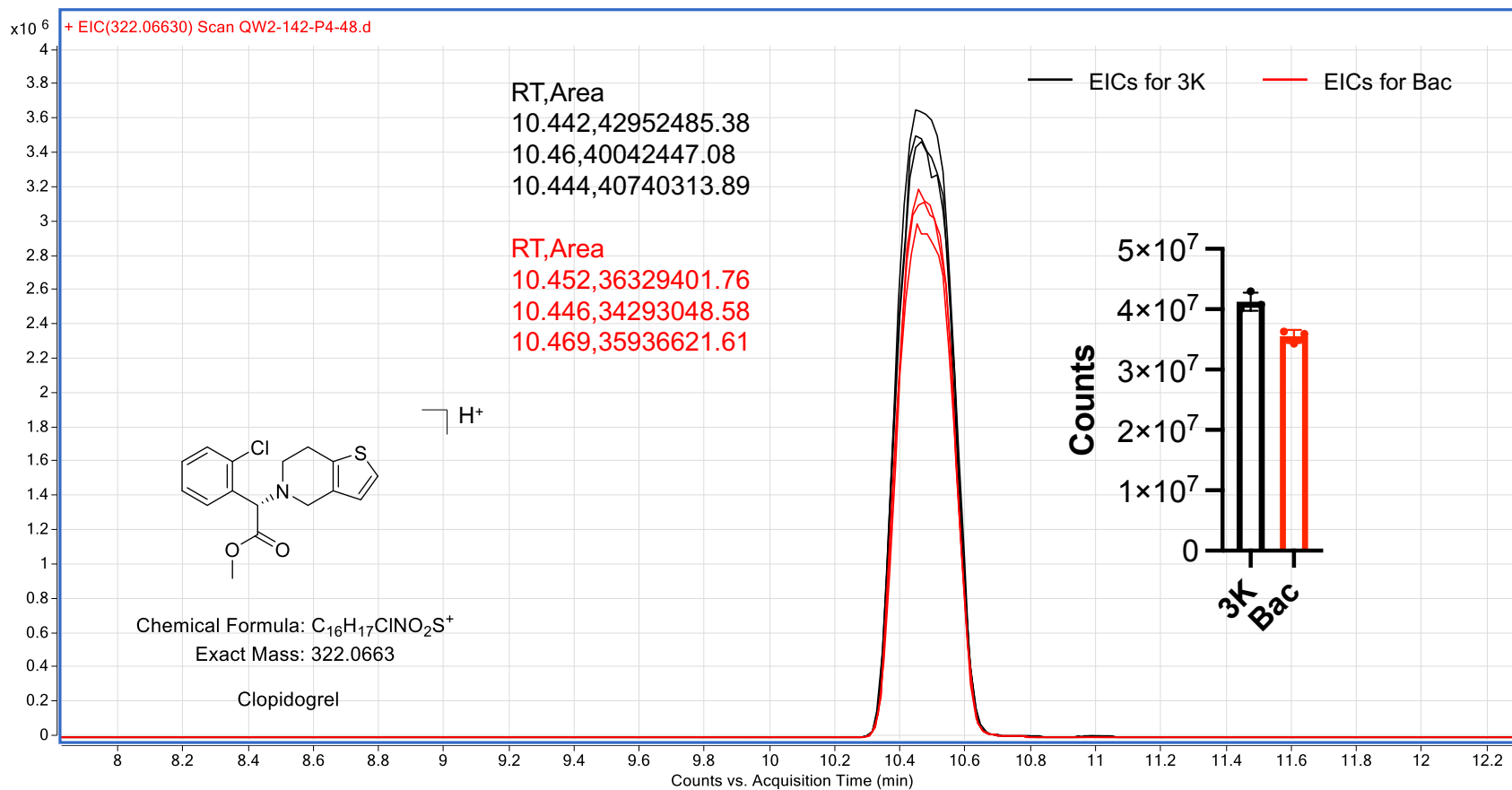


Fig. S112. Bac⁺ vs Bac⁻ (MWCO 3K) of basimglurant (*m/z* 326.0855) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

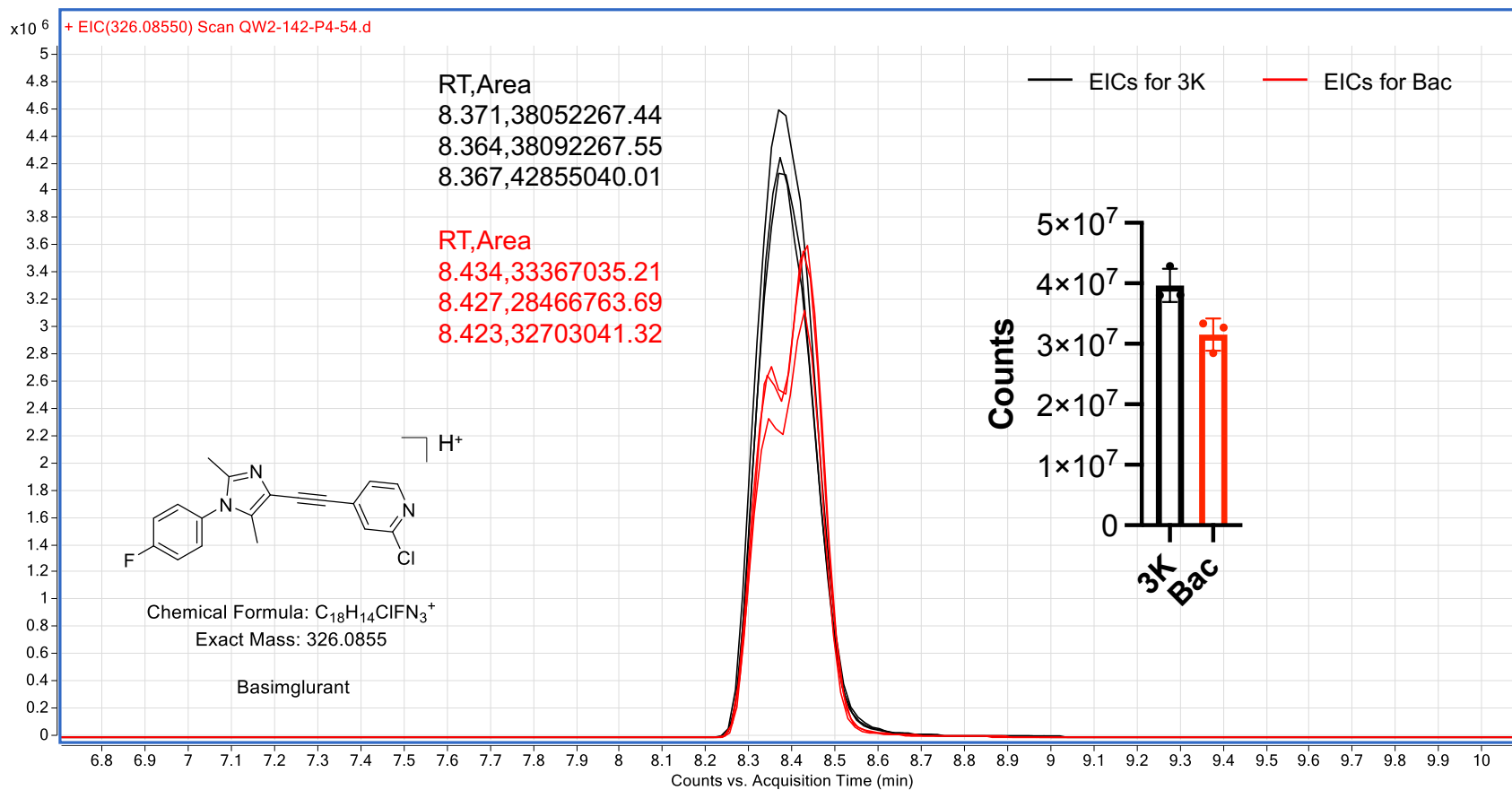


Fig. S113. Bac⁺ vs Bac⁻ (MWCO 3K) of sitaxsentan (*m/z* 455.0133) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

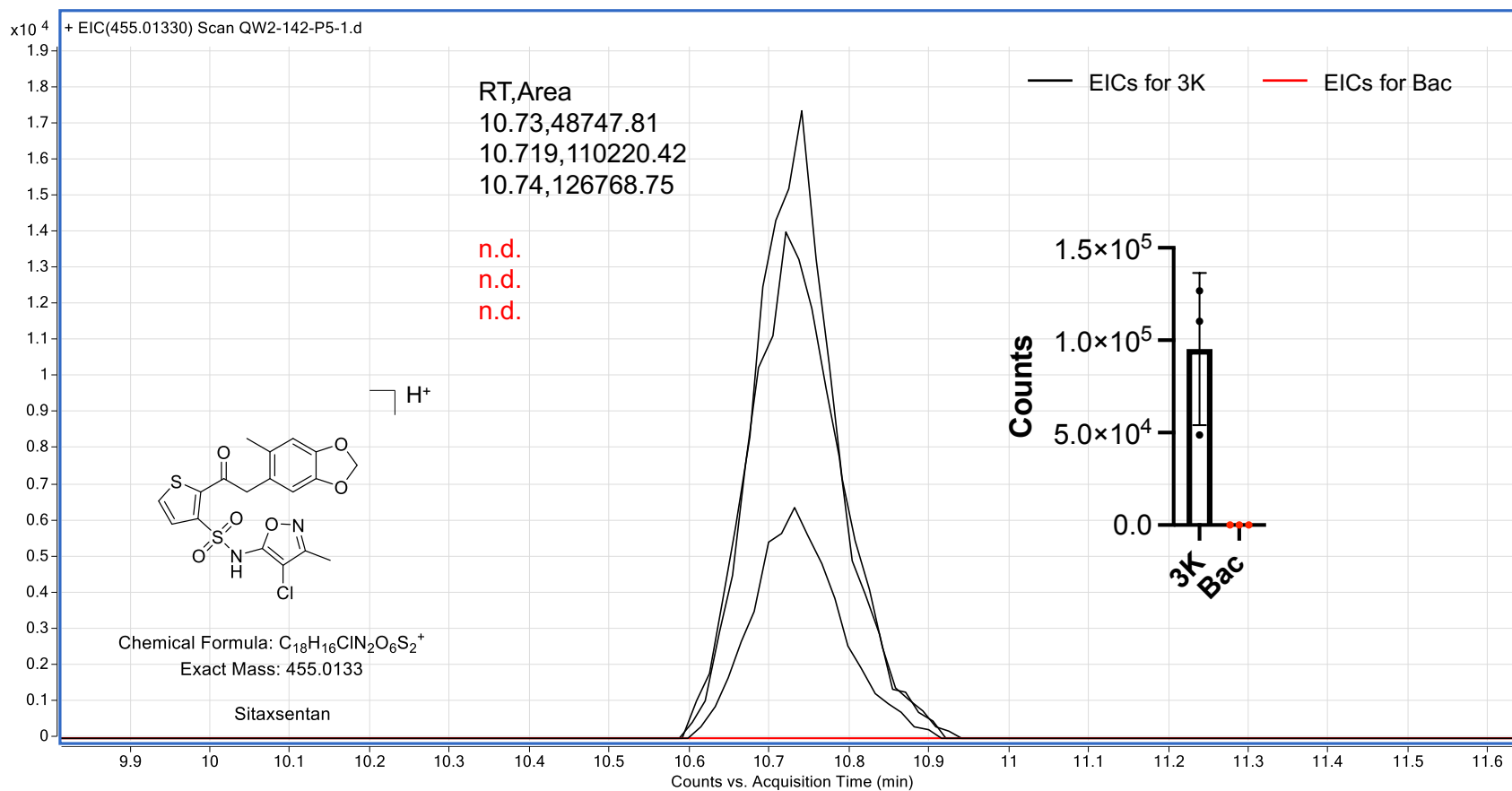


Fig. S114. Bac⁺ vs Bac⁻ (MWCO 3K) of zuclopenthixol (*m/z* 401.1449) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

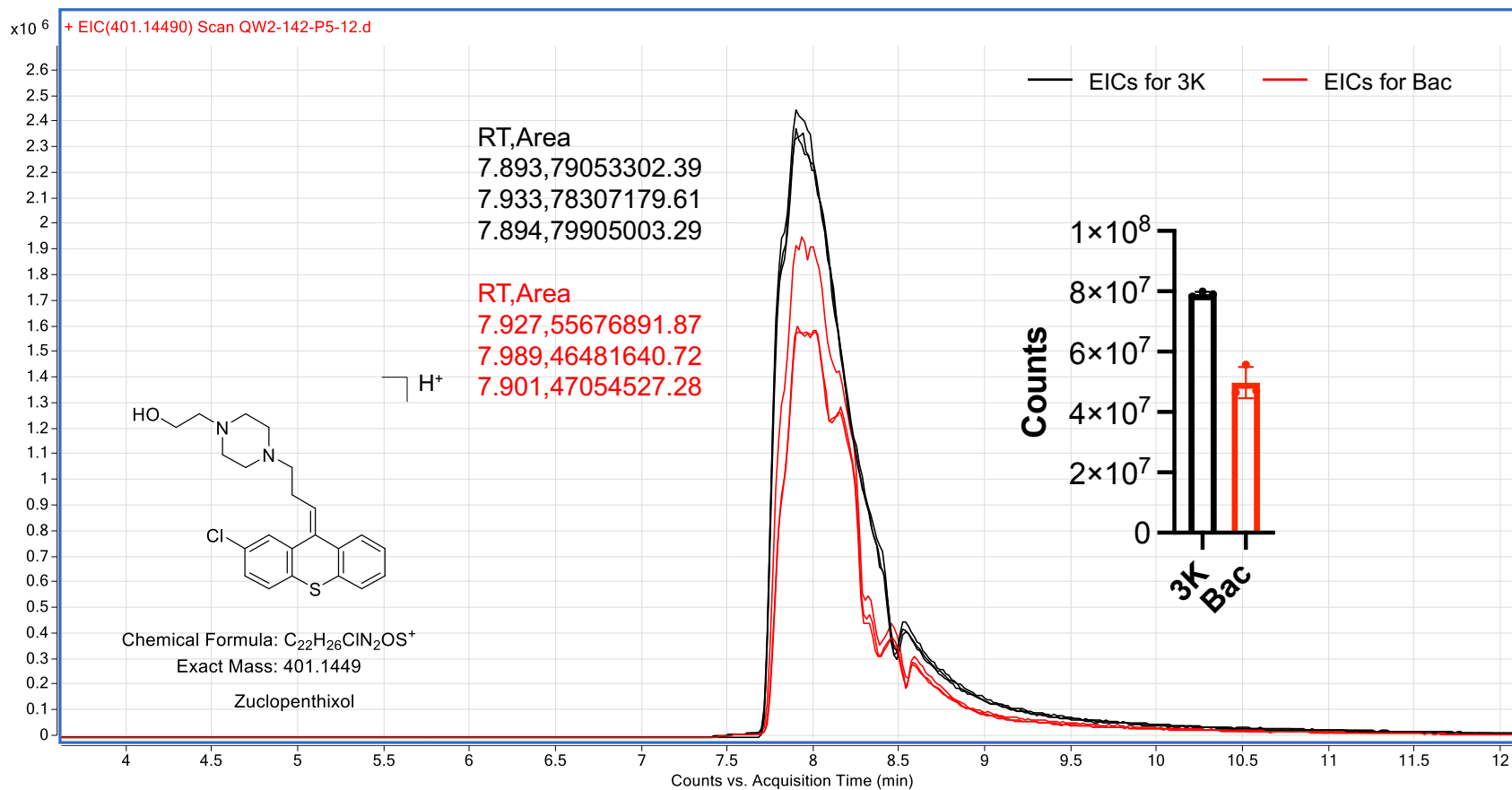


Fig. S115. Bac⁺ vs Bac⁻ (MWCO 3K) of doxazosin (*m/z* 452.1928) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

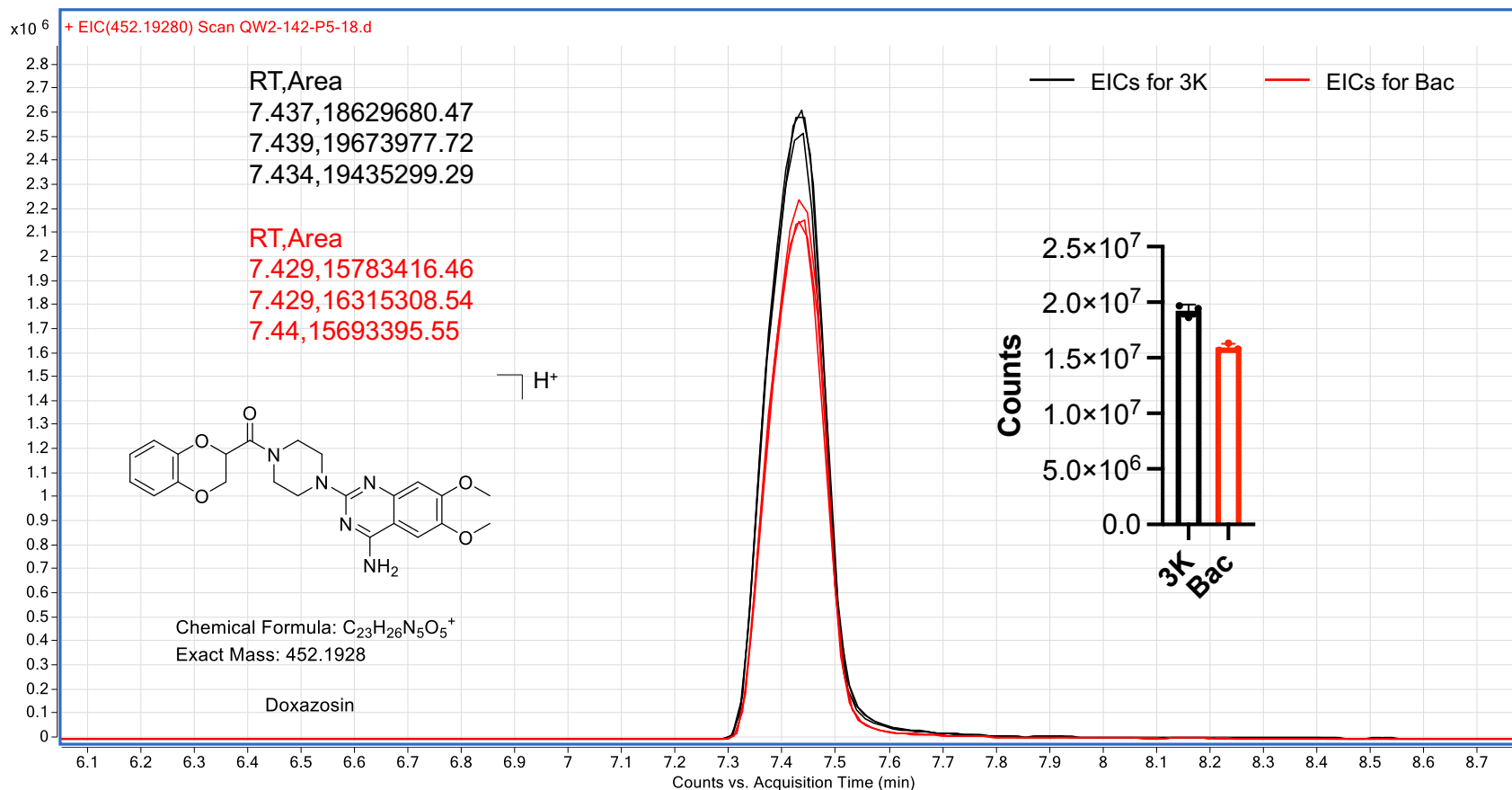


Fig. S116. Bac⁺ vs Bac⁻ (MWCO 3K) of sparsentan (*m/z* 593.2792) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean $\pm$ s.d.

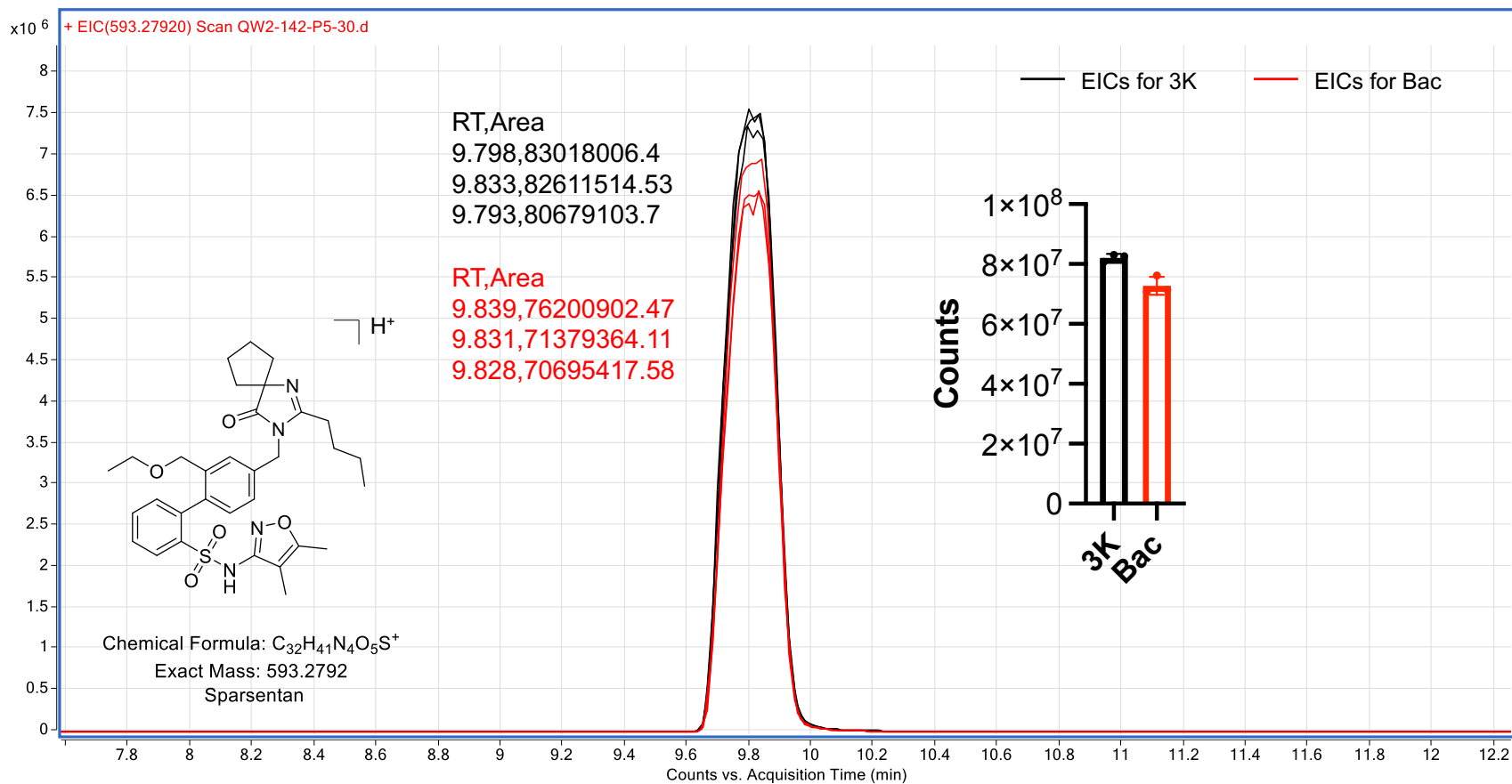


Fig. S117. Bac⁺ vs Bac⁻ (MWCO 3K) of E7046 (*m/z* 484.1290) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

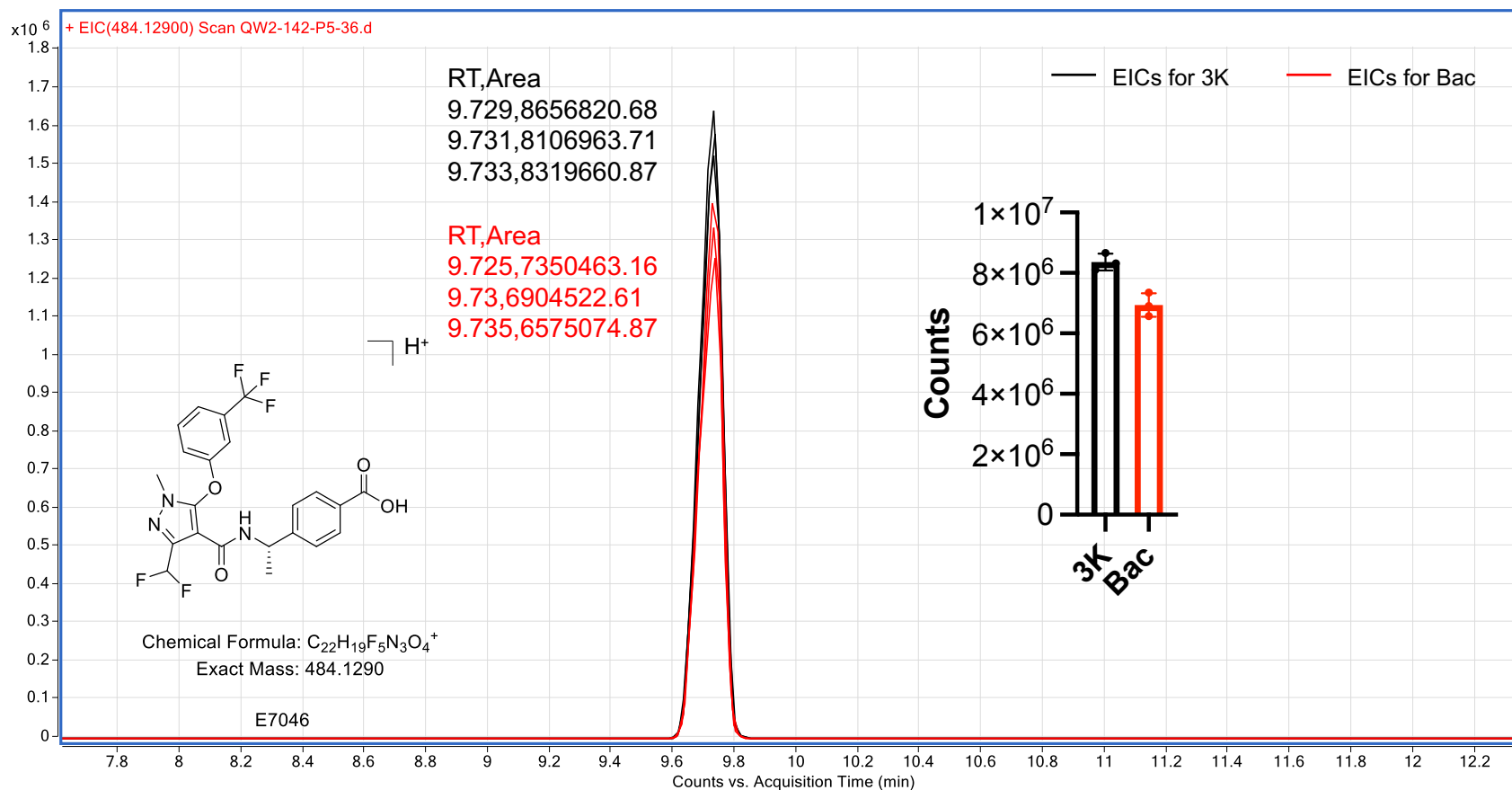


Fig. S118. Bac⁺ vs Bac⁻ (MWCO 3K) of fesoterodine (*m/z* 412.2846) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

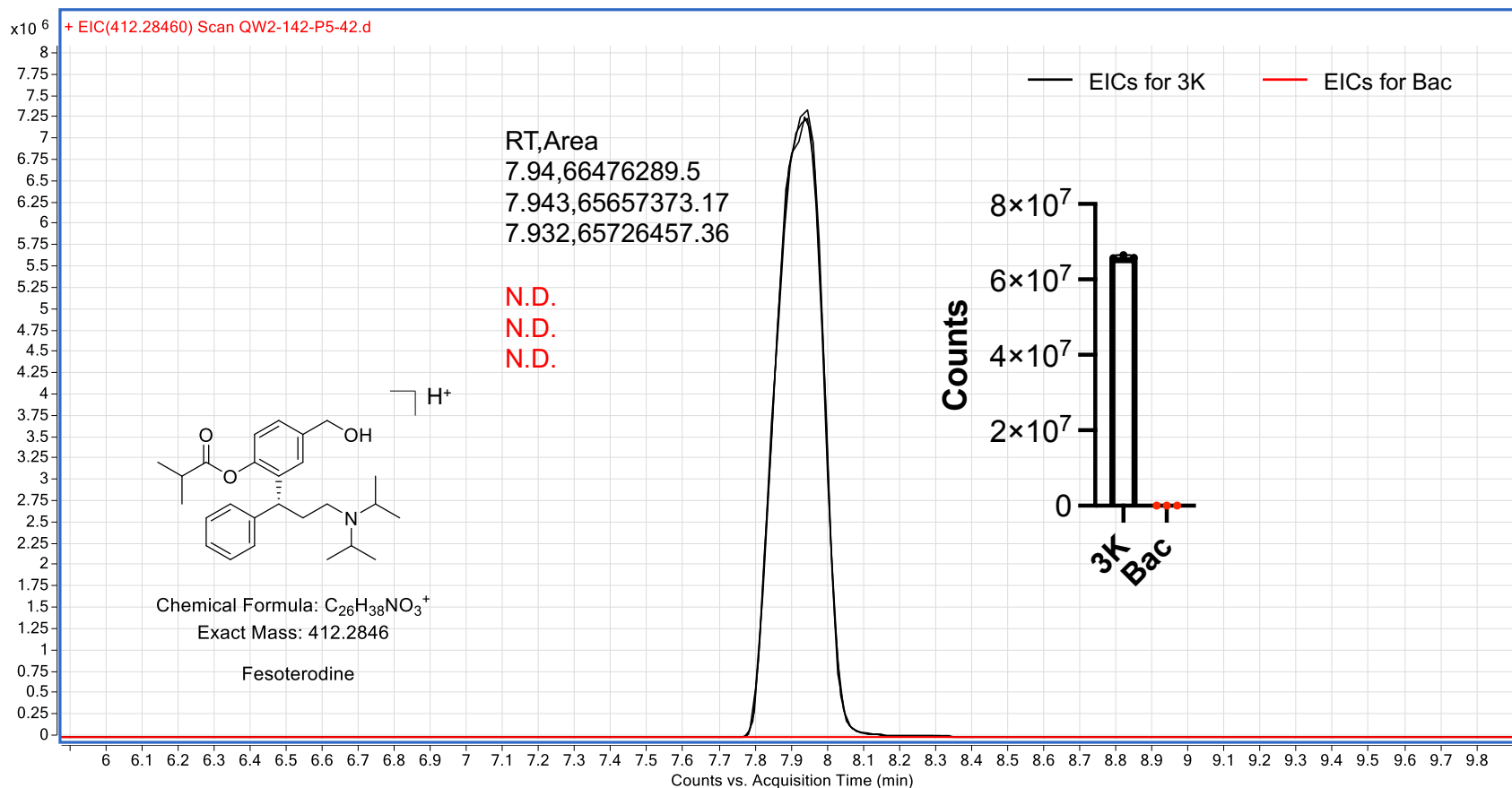


Fig. S119. Bac⁺ vs Bac⁻ (MWCO 3K) of candesartan cilexetil (*m/z* 611.2613) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

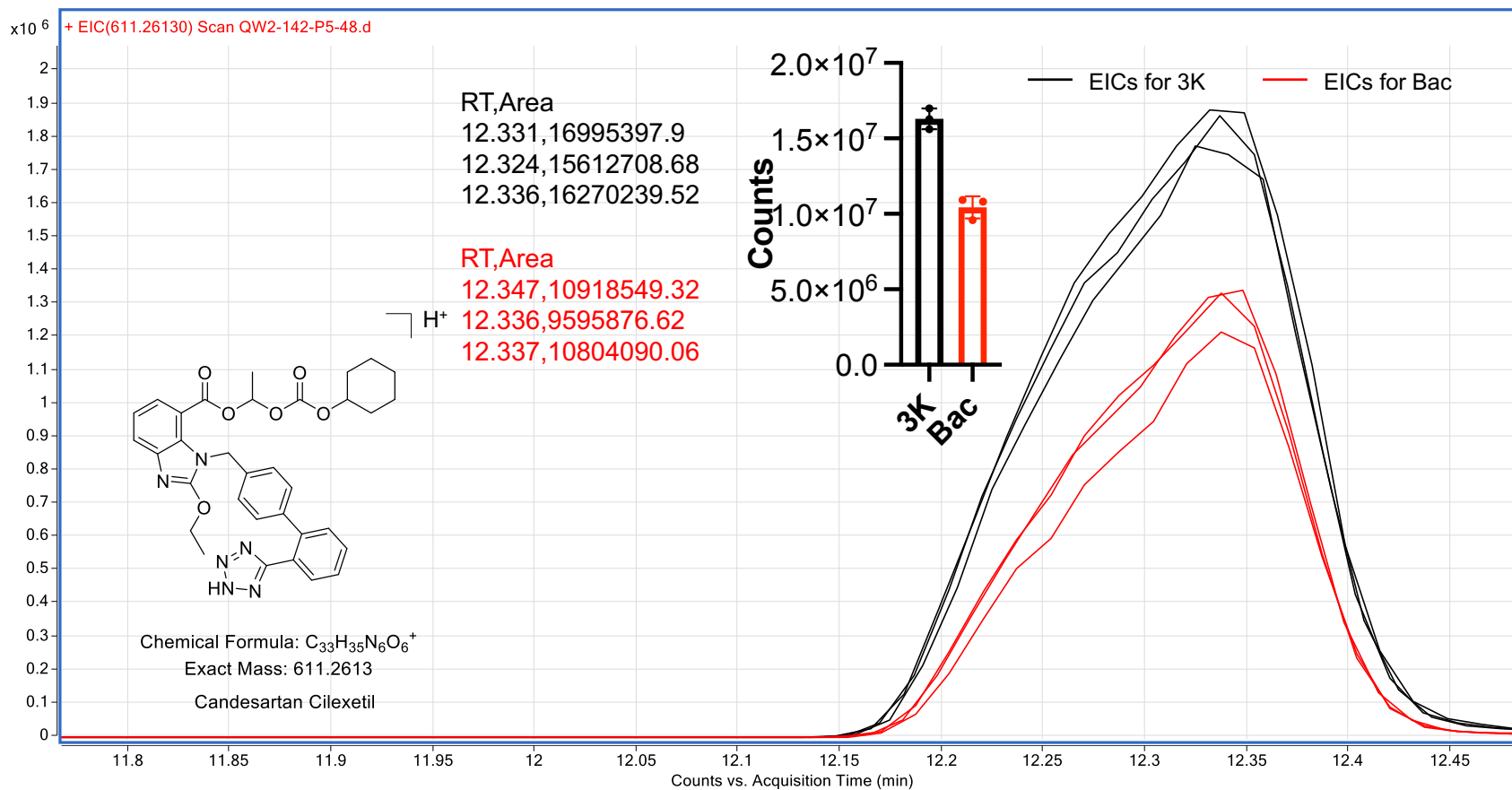


Fig. S120. Bac⁺ vs Bac⁻ (MWCO 3K) of piribedil (*m/z* 299.1503) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

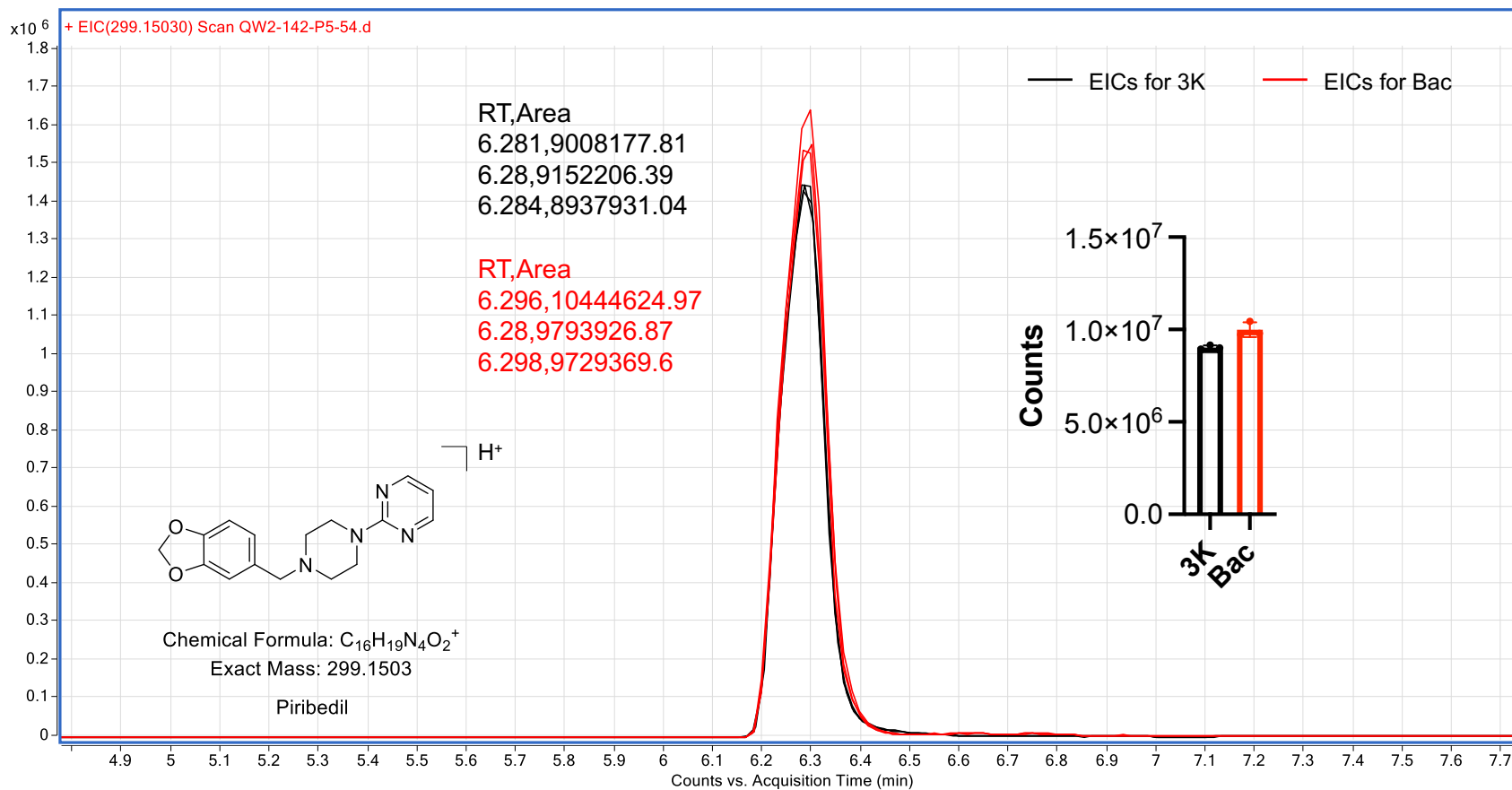


Fig. S121. Bac⁺ vs Bac⁻ (MWCO 3K) of avosentan (*m/z* 480.1336) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

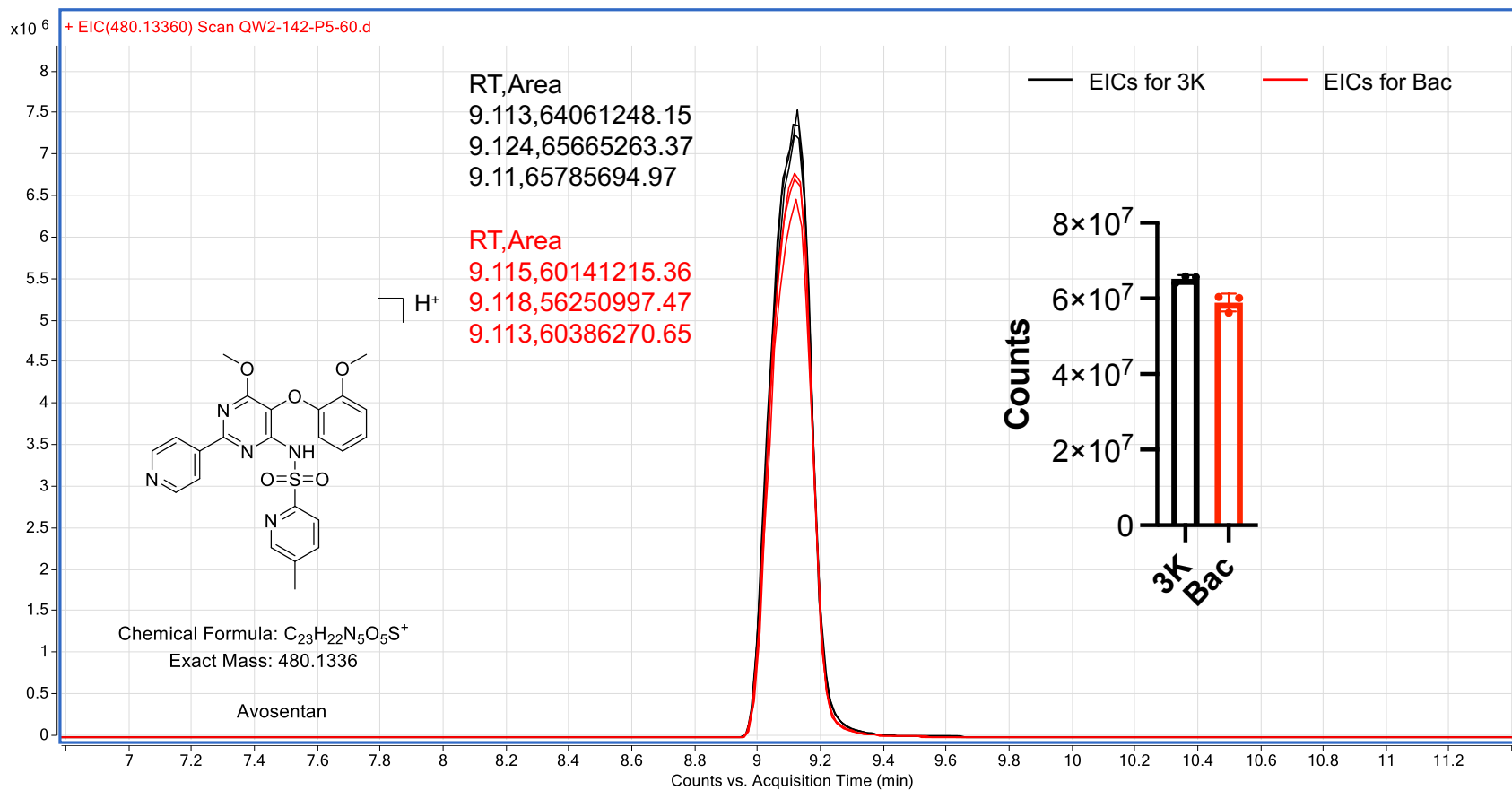


Fig. S122. Bac⁺ vs Bac⁻ (MWCO 3K) of pardoprinox (*m/z* 234.1237) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean $\pm$ s.d.

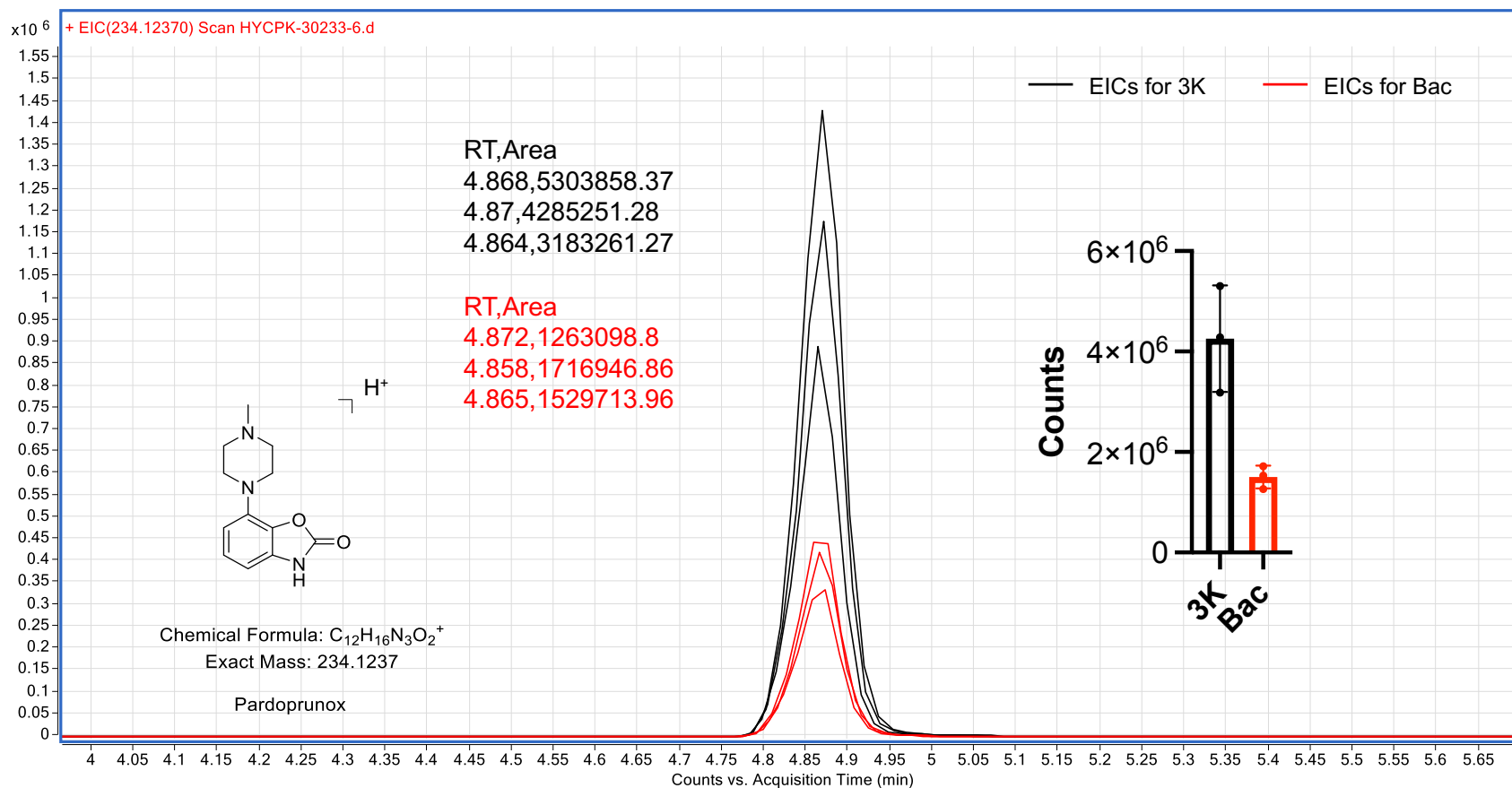


Fig. S123. Bac⁺ vs Bac⁻ (MWCO 3K) of PF-04418948 (*m/z* 410.1398) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

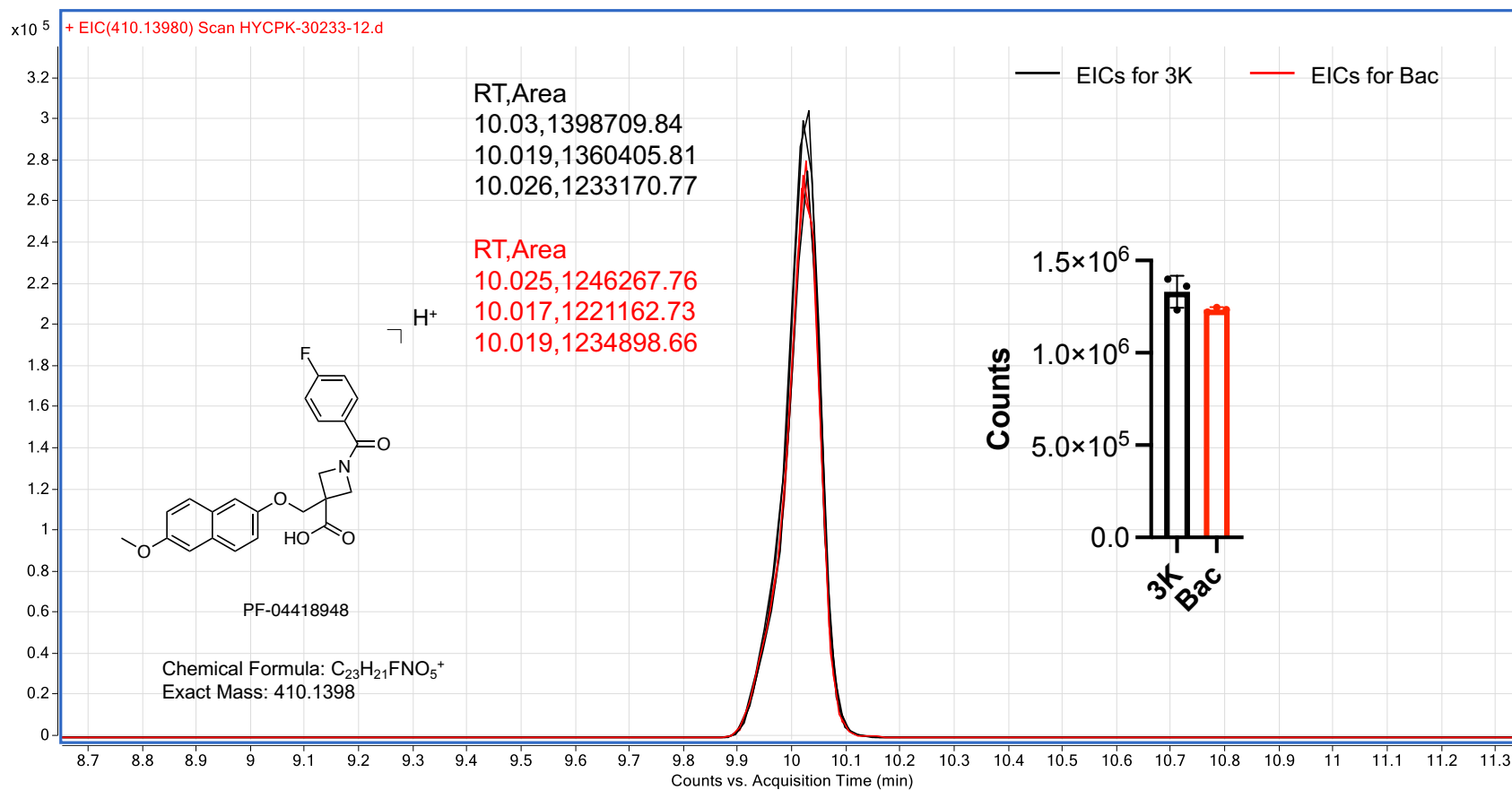


Fig. S124. Bac⁺ vs Bac⁻ (MWCO 3K) of famotidine (*m/z* 338.0522) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

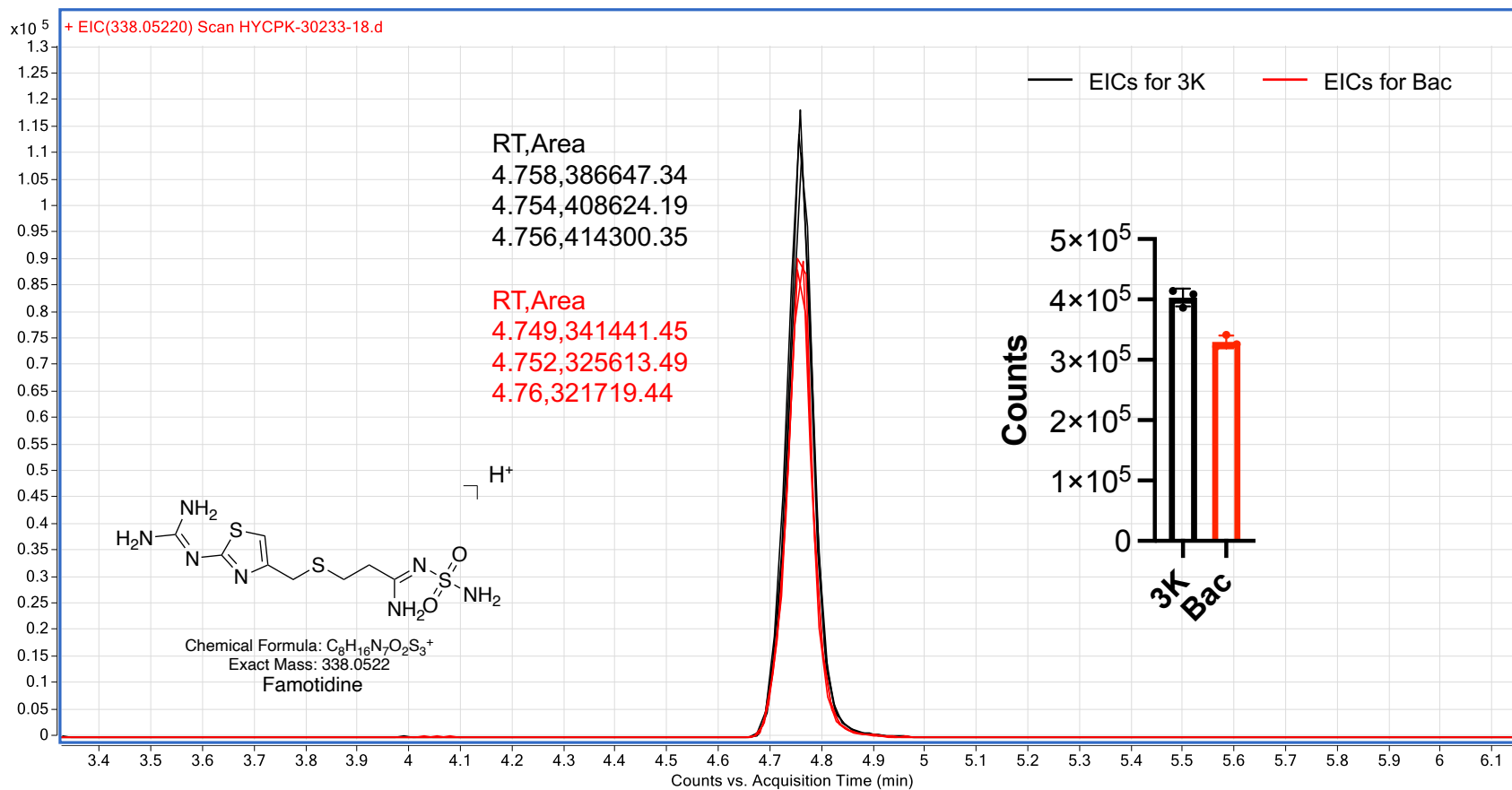


Fig. S125. Bac⁺ vs Bac⁻ (MWCO 3K) of homatropine (*m/z* 276.1594) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

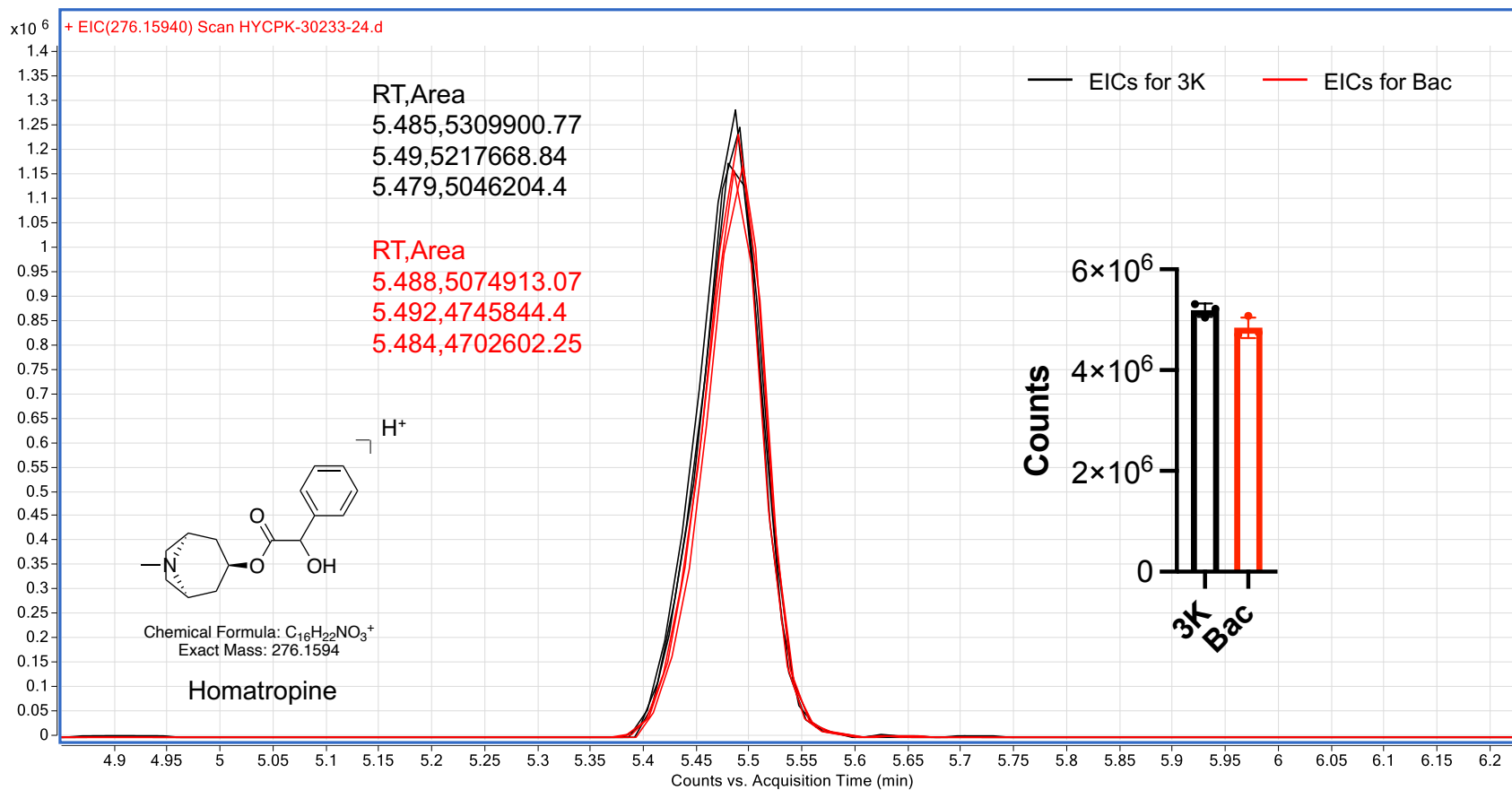


Fig. S126. Bac⁺ vs Bac⁻ (MWCO 3K) of acrivastine (*m/z* 349.1911) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

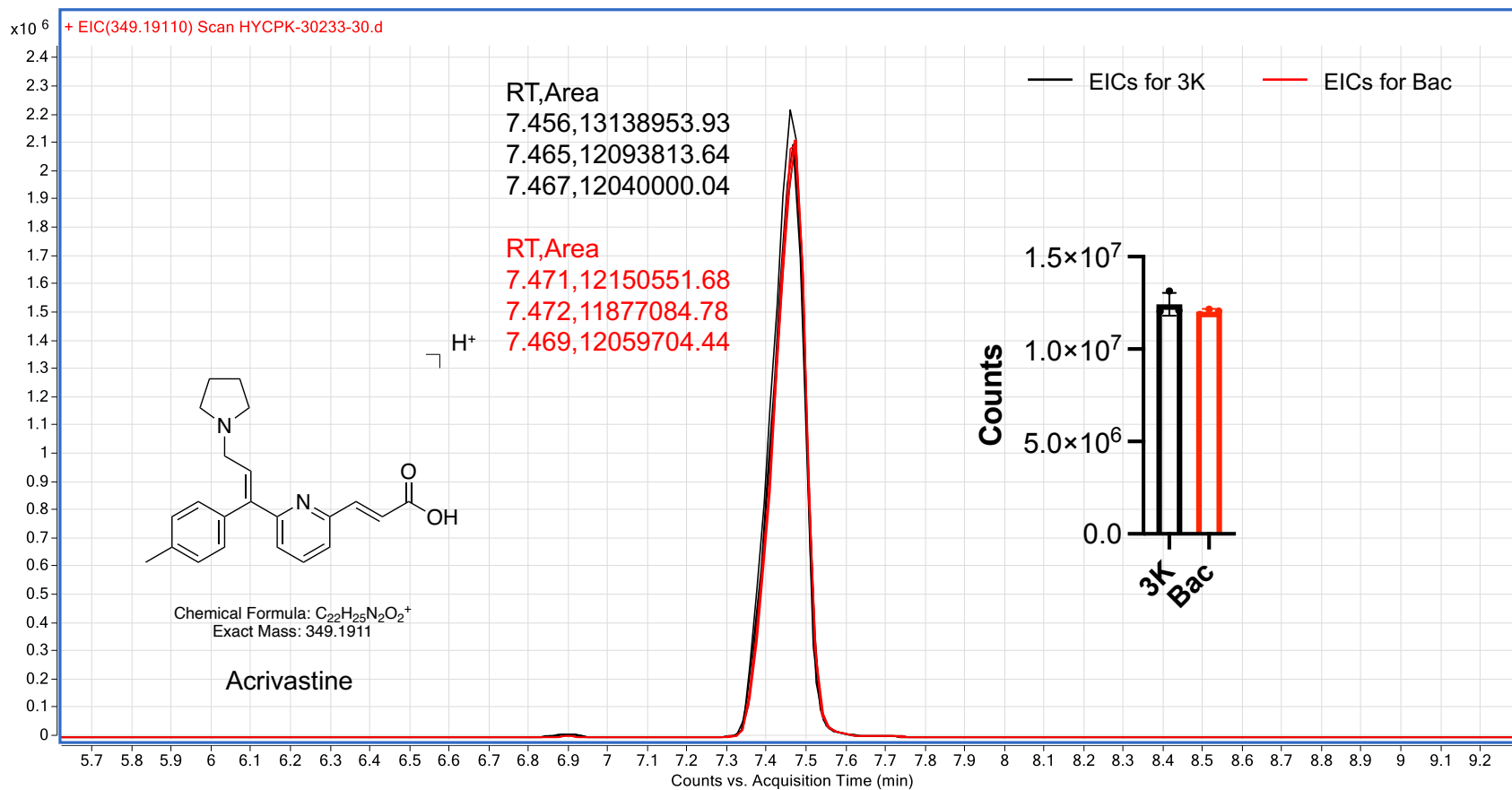


Fig. S127. Bac⁺ vs Bac⁻ (MWCO 3K) of sograzepide (*m/z* 499.2452) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

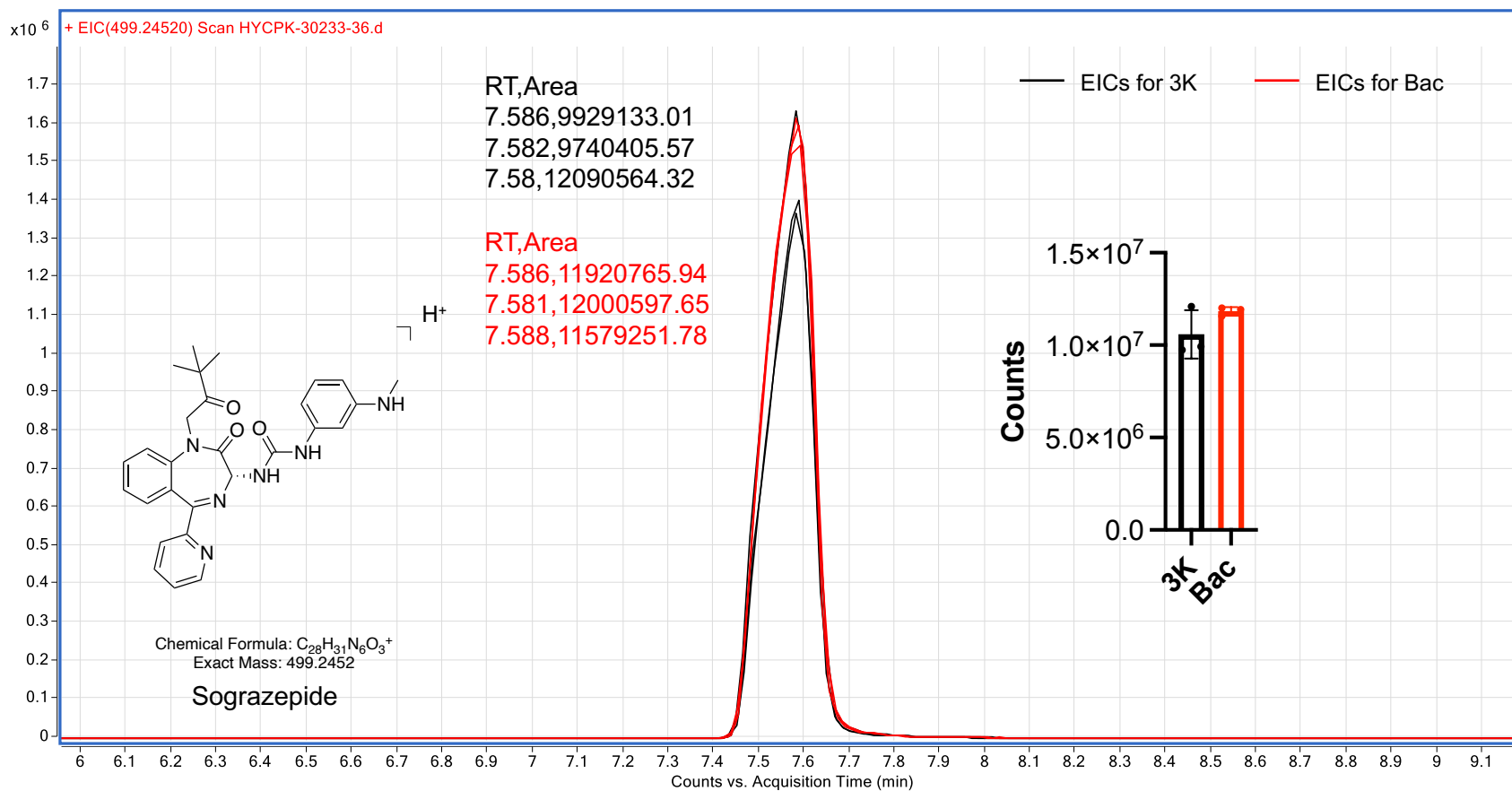


Fig. S128. Bac⁺ vs Bac⁻ (MWCO 3K) of fluspirone (*m/z* 386.2551) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

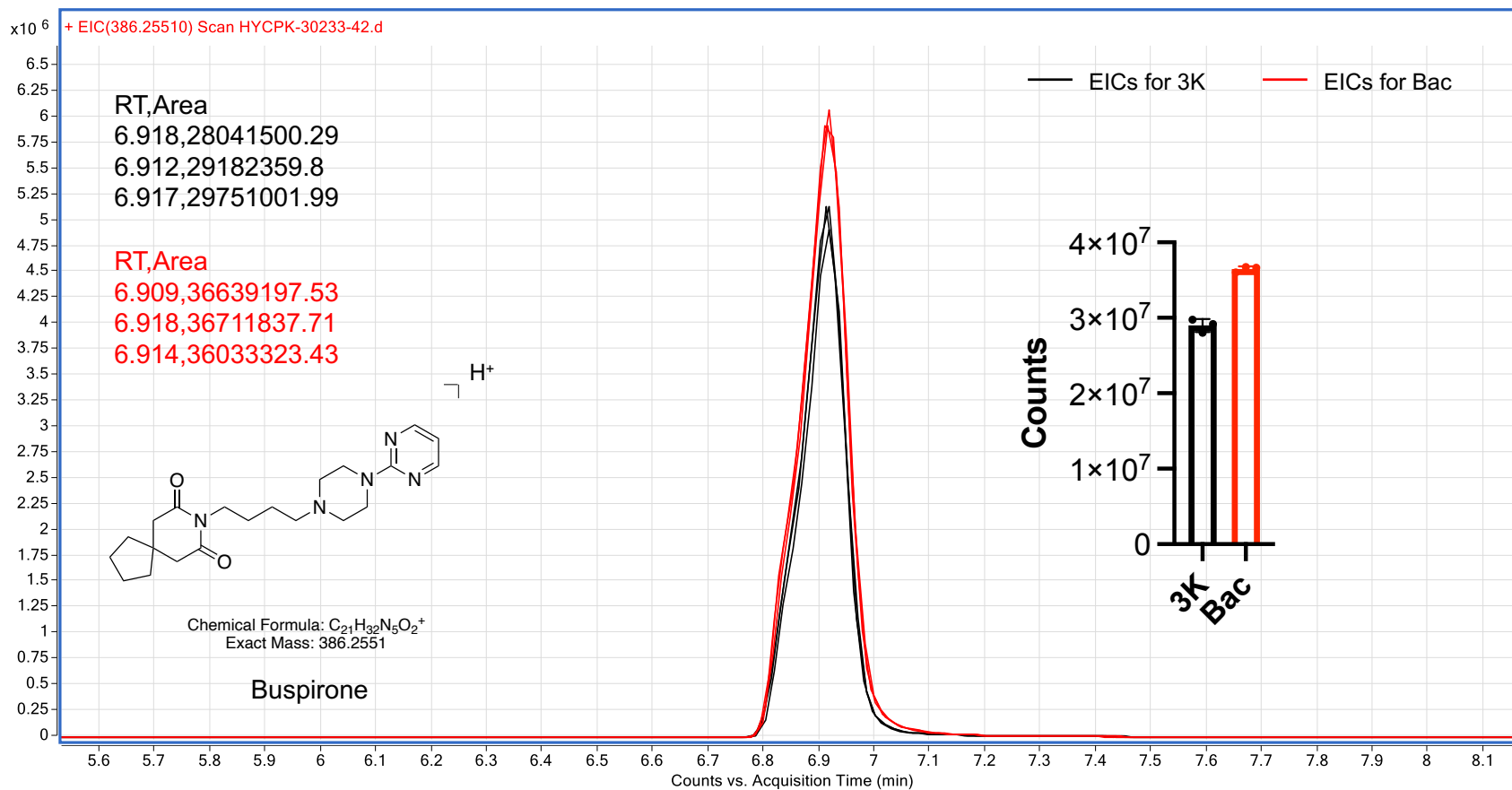


Fig. S129. Bac⁺ vs Bac⁻ (MWCO 3K) of sertindole (*m/z* 441.1852) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

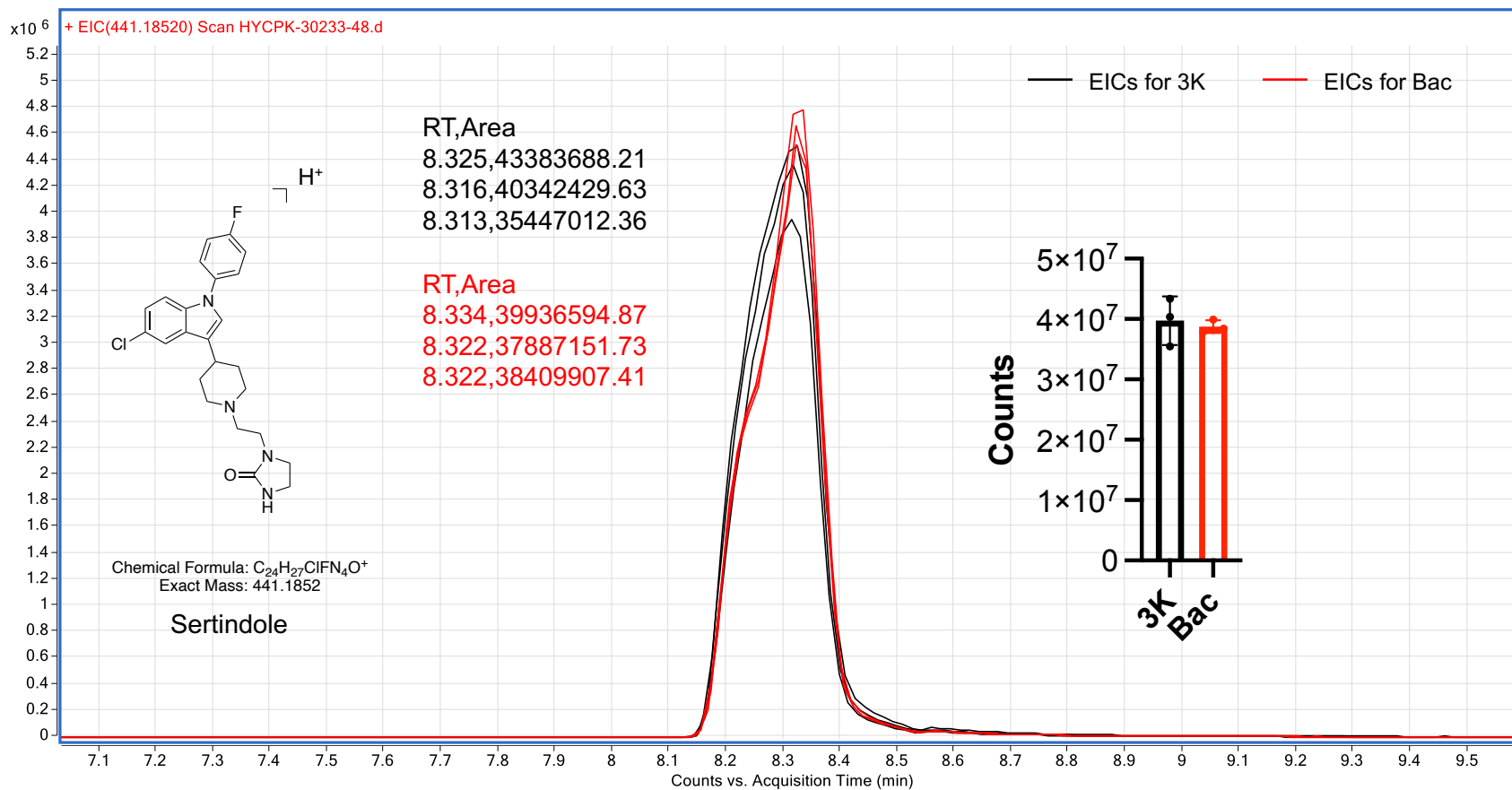


Fig. S130. Bac⁺ vs Bac⁻ (MWCO 3K) of thiorisazine (*m/z* 371.1610) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

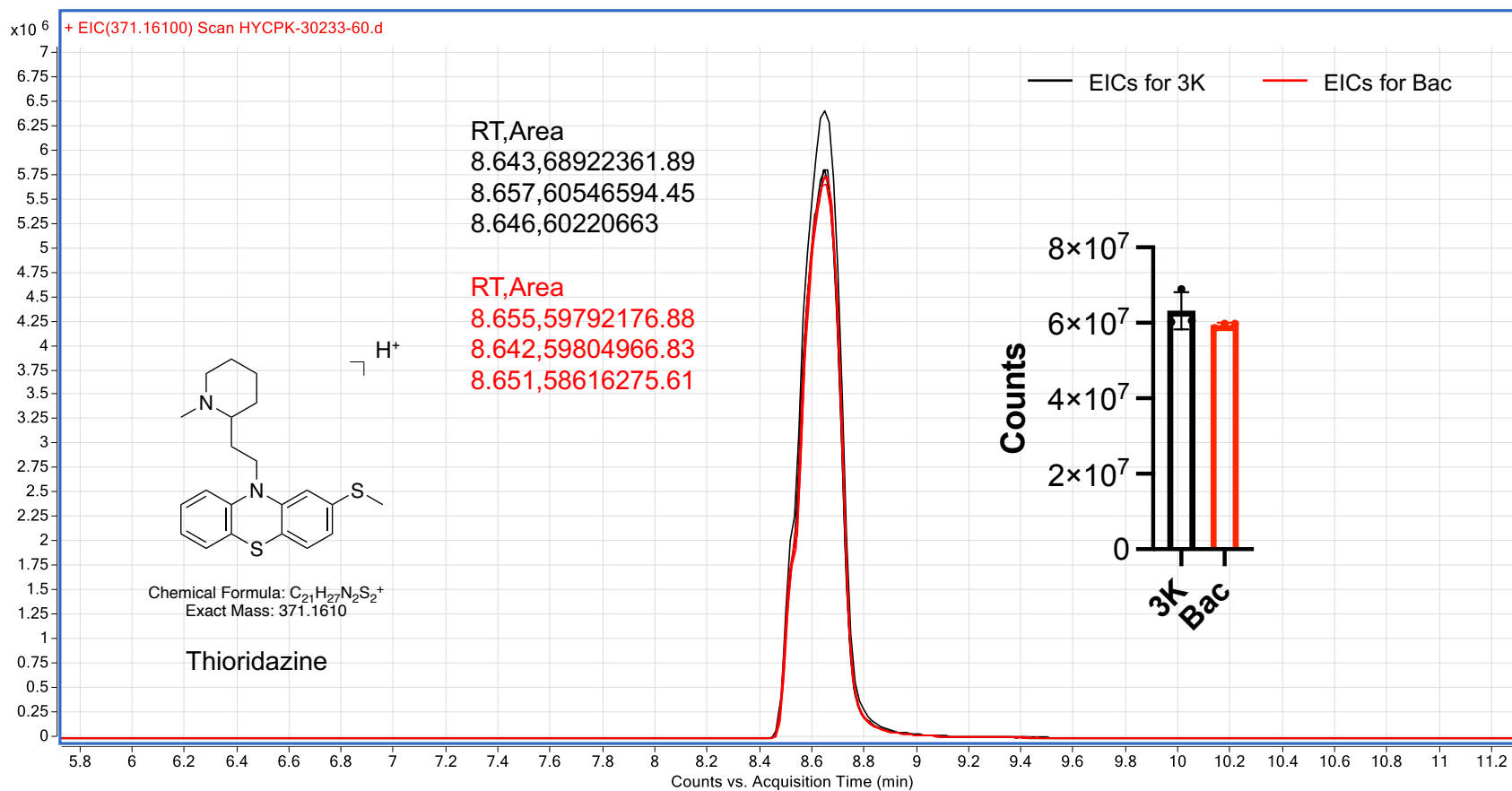


Fig. S131. Bac⁺ vs Bac⁻ (MWCO 3K) of ambrisentan (*m/z* 379.1652) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

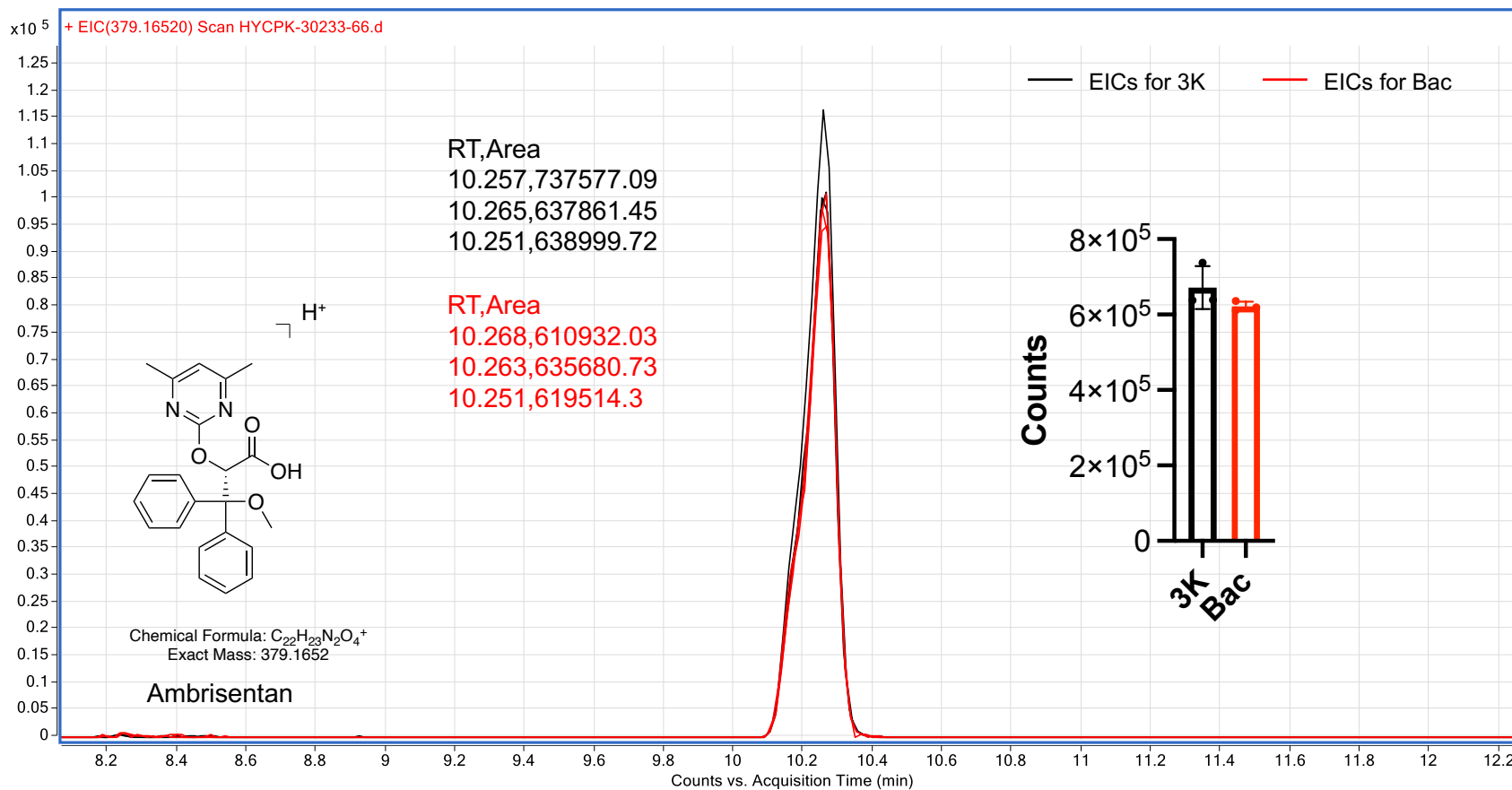


Fig. S132. Bac⁺ vs Bac⁻ (MWCO 3K) of vicriviroc (*m/z* 534.3050) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

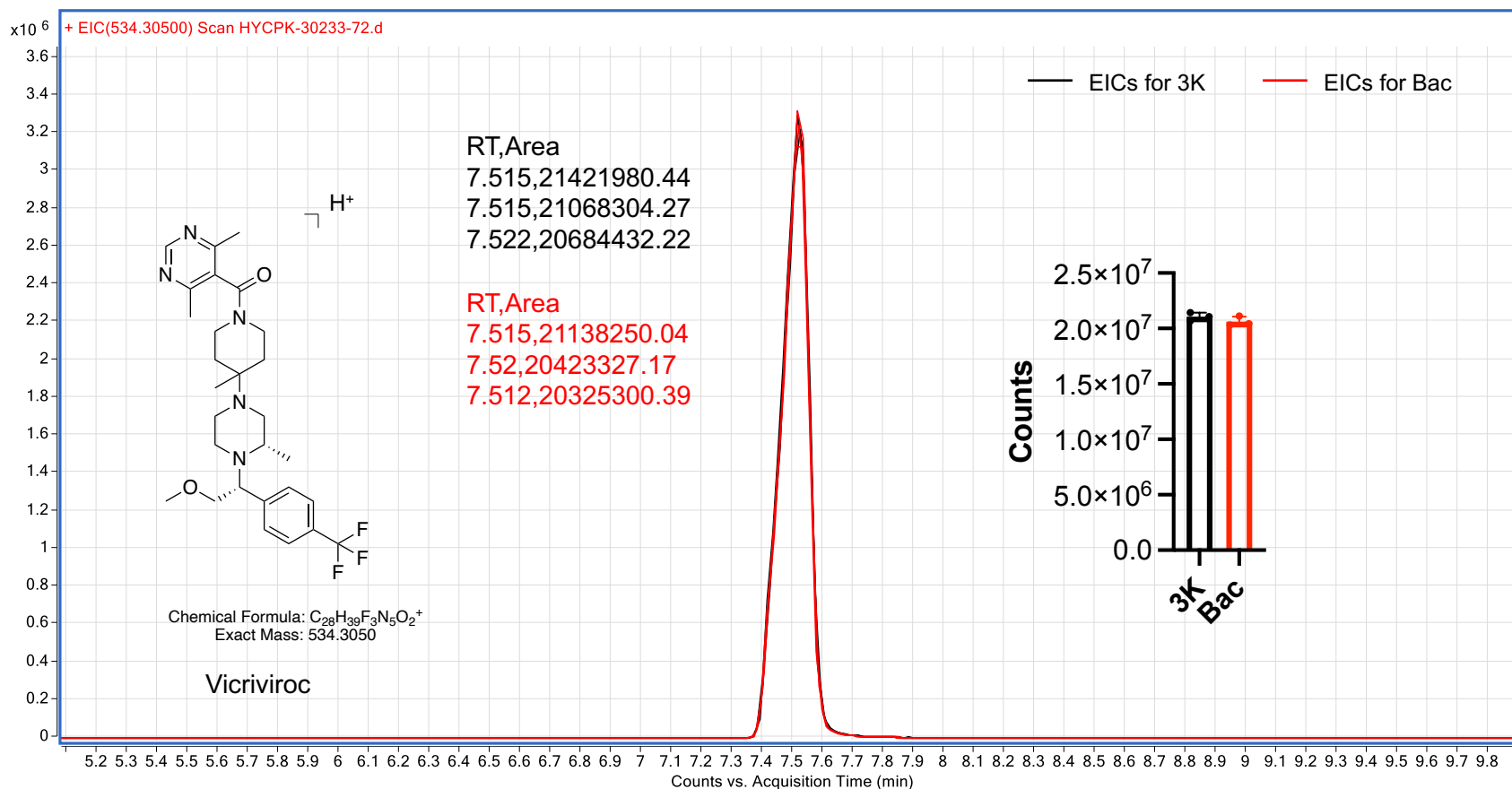


Fig. S133. Bac⁺ vs Bac⁻ (MWCO 3K) of blonanserin (*m/z* 368.2497) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

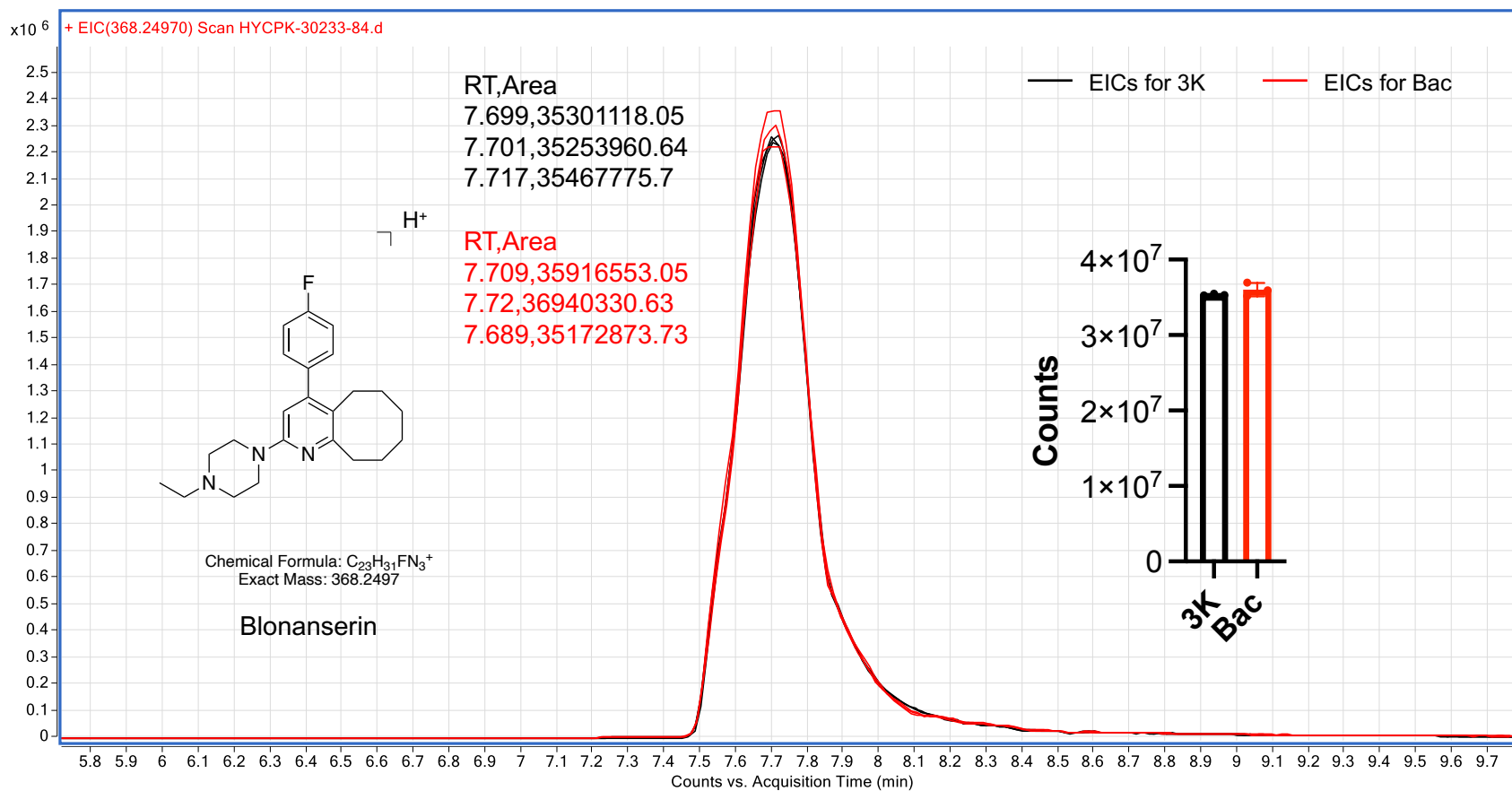


Fig. S134. Bac⁺ vs Bac⁻ (MWCO 3K) of fezolinetant (*m/z* 359.1085) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

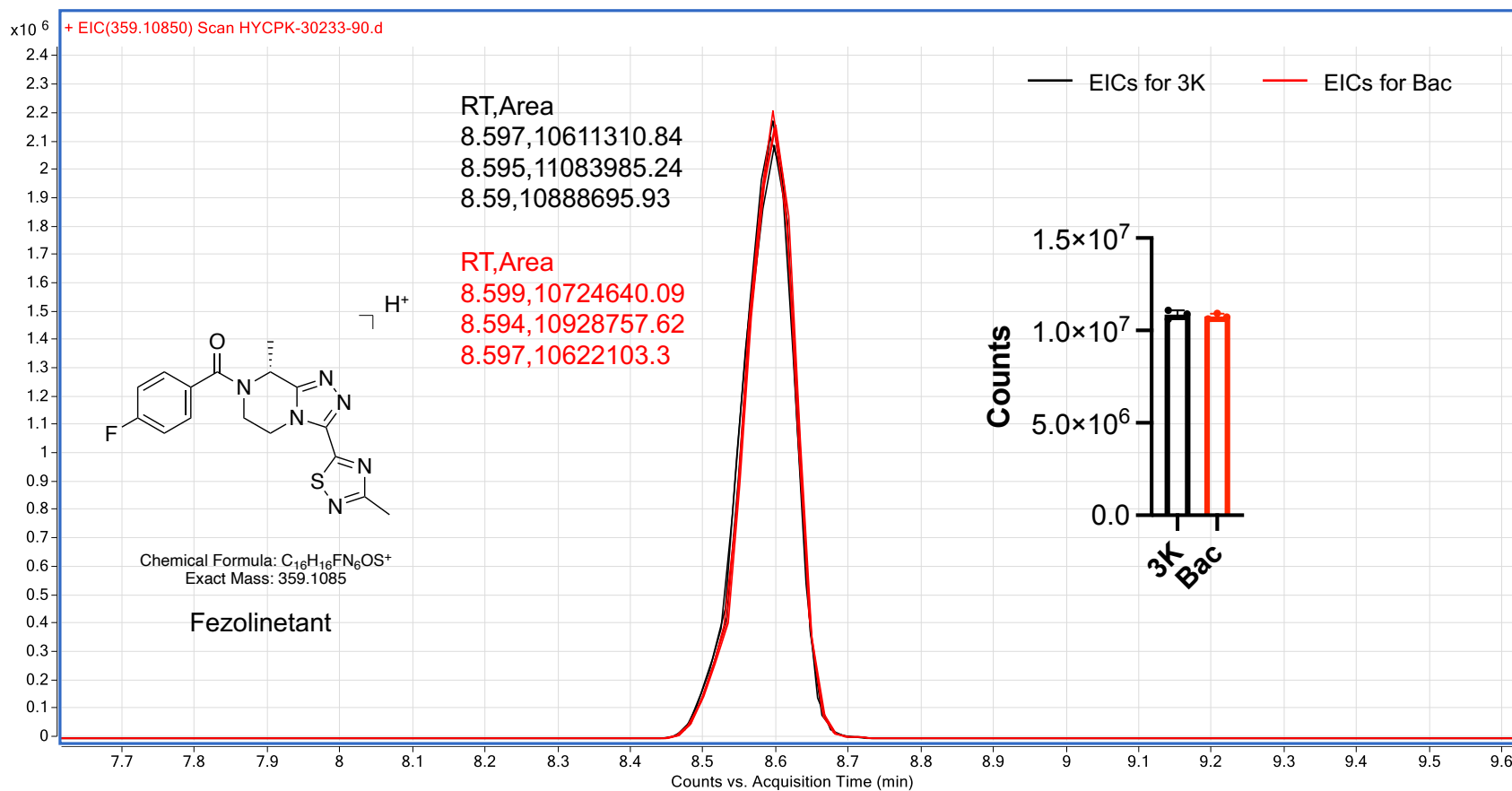


Fig. S135. Bac⁺ vs Bac⁻ (MWCO 3K) of cyclobenzaprine (*m/z* 276.1747) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

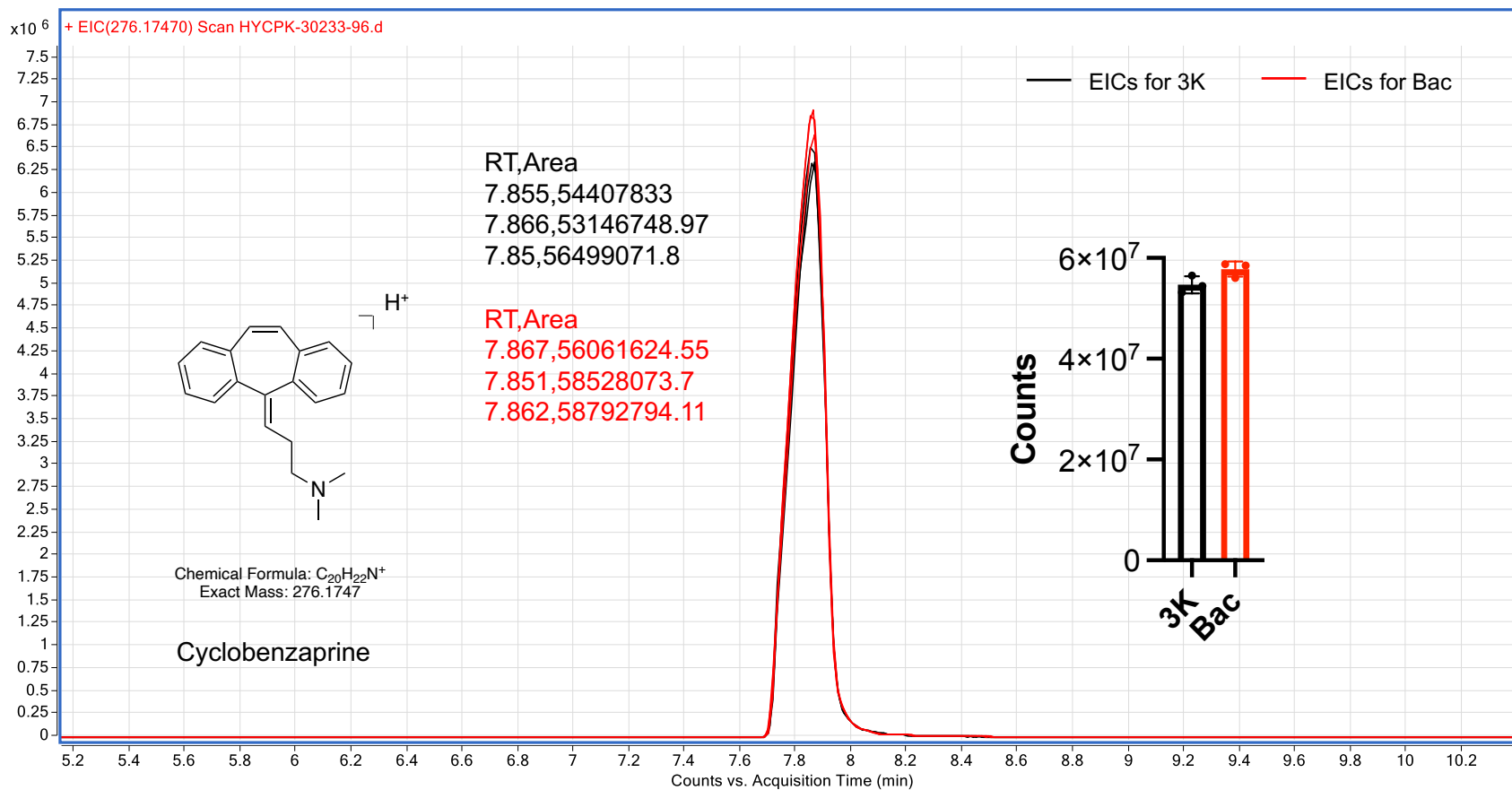


Fig. S136. Bac⁺ vs Bac⁻ (MWCO 3K) of loxapine (*m/z* 328.1211) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

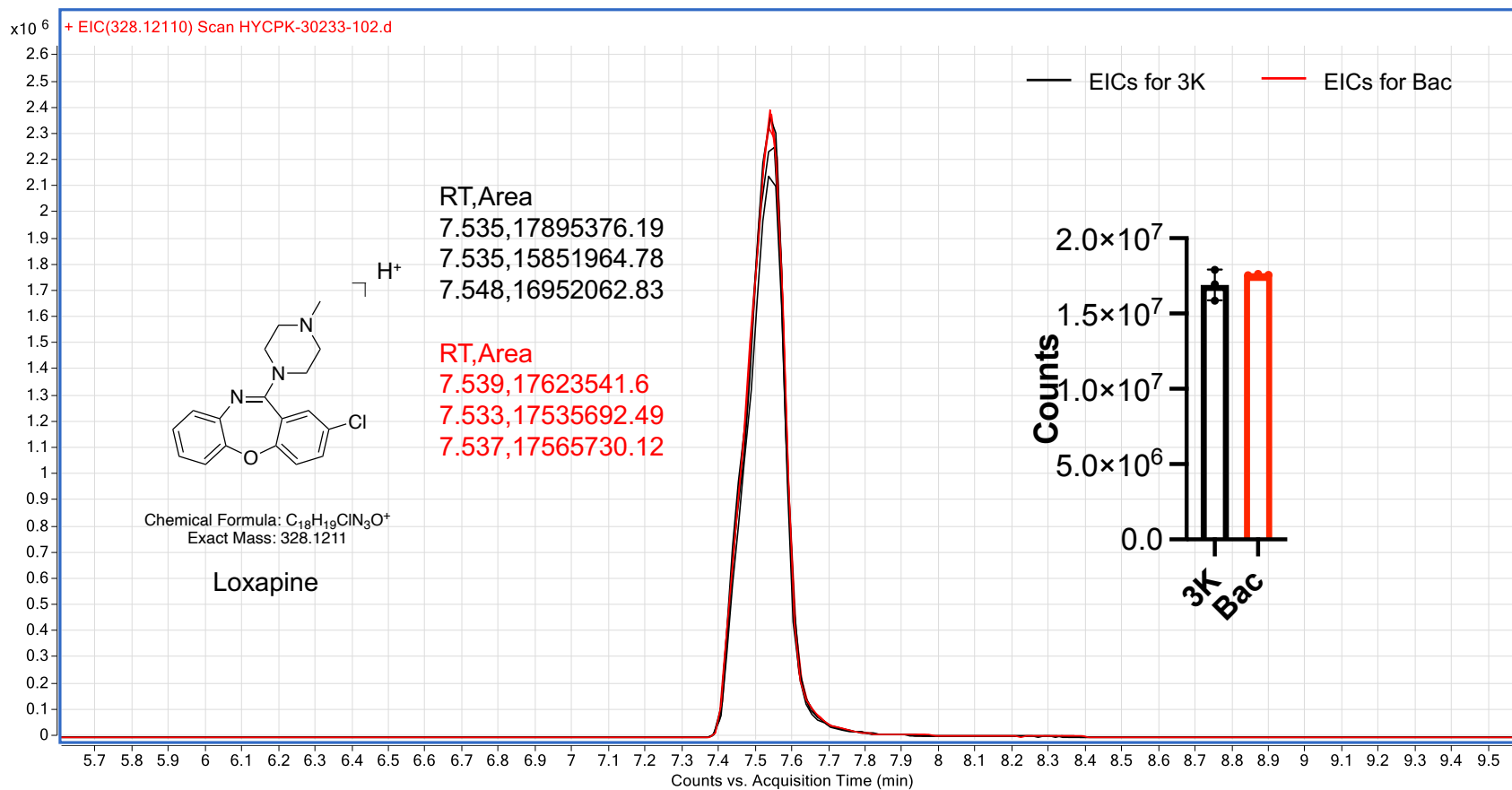


Fig. S137. Bac⁺ vs Bac⁻ (MWCO 3K) of tolterodine (*m/z* 3326.2478) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

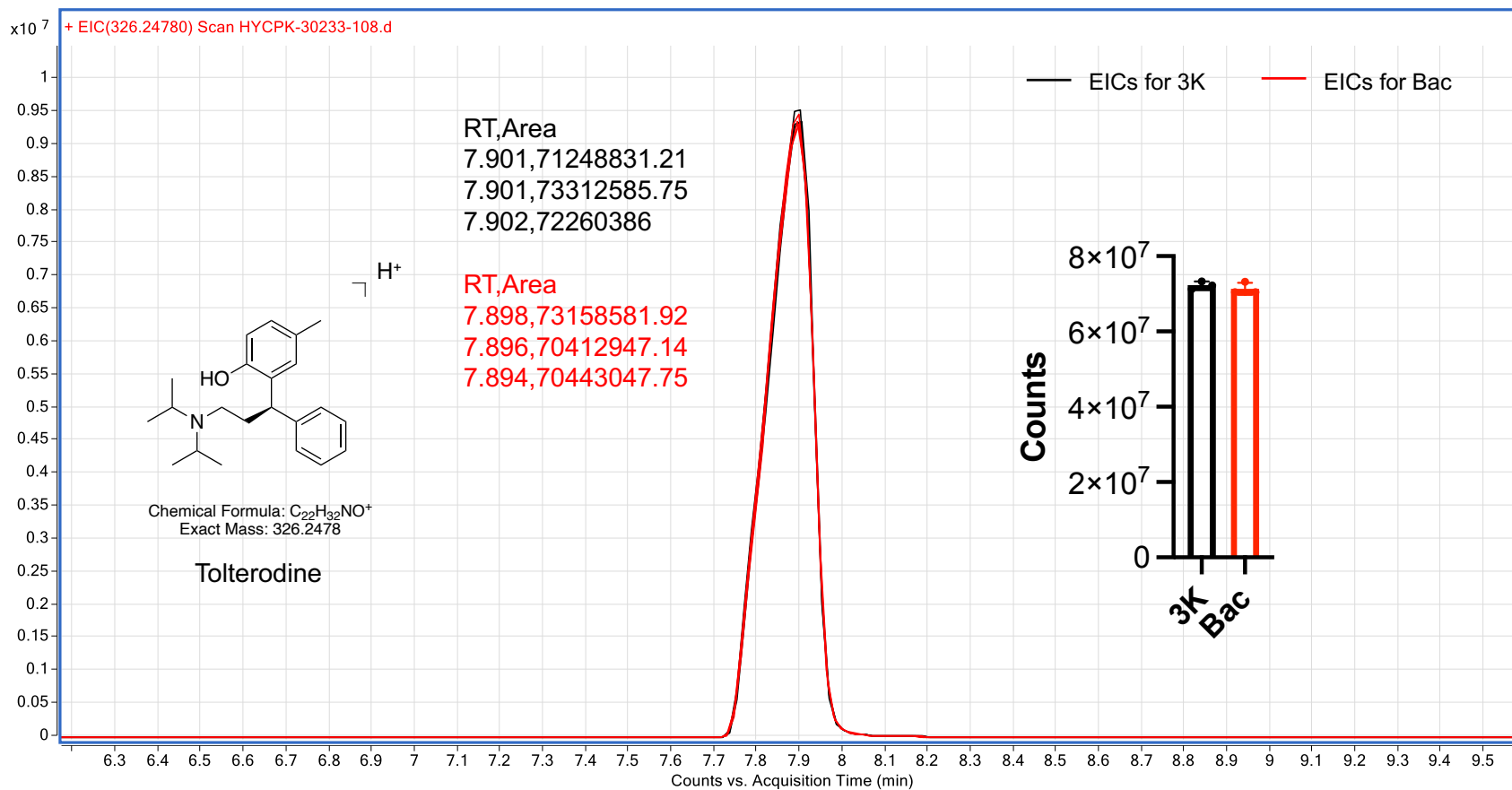


Fig. S138. Bac⁺ vs Bac⁻ (MWCO 3K) of chlorprothixene (*m/z* 316.0921) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

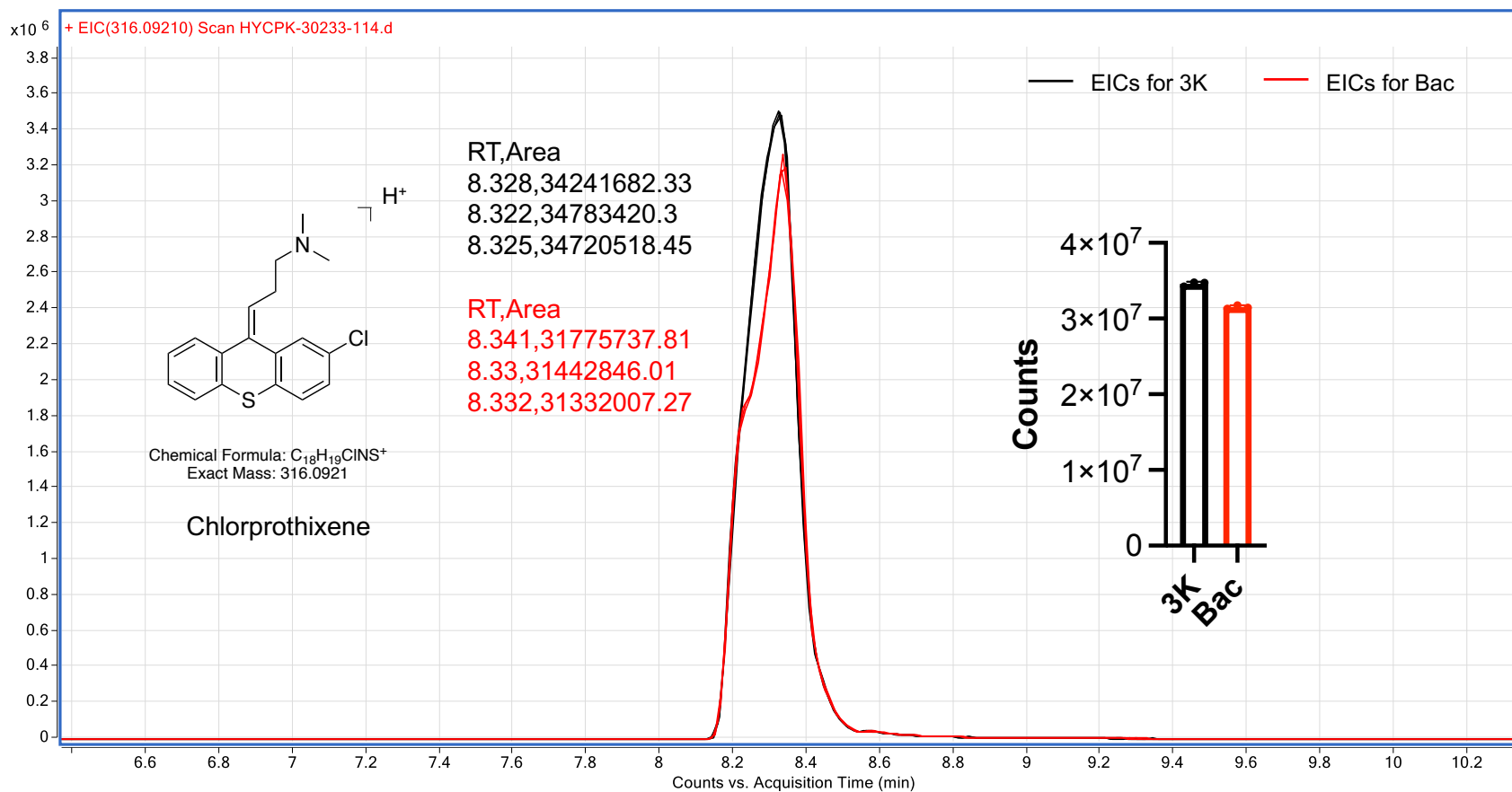


Fig. S139. Bac⁺ vs Bac⁻ (MWCO 3K) of pindolol (*m/z* 249.1598) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

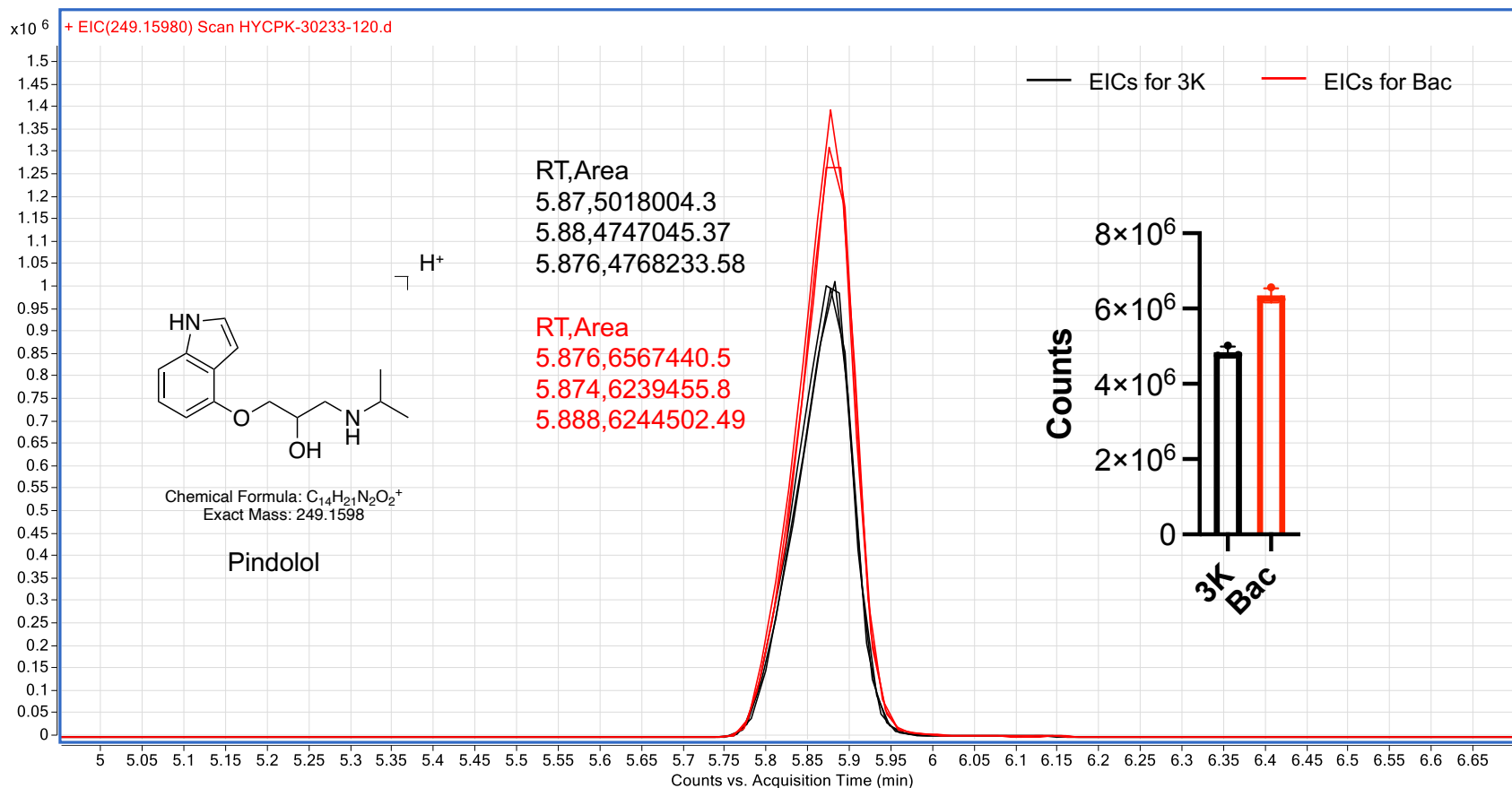


Fig. S140. Bac⁺ vs Bac⁻ (MWCO 3K) of GSK1292263 (*m/z* 457.1904) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

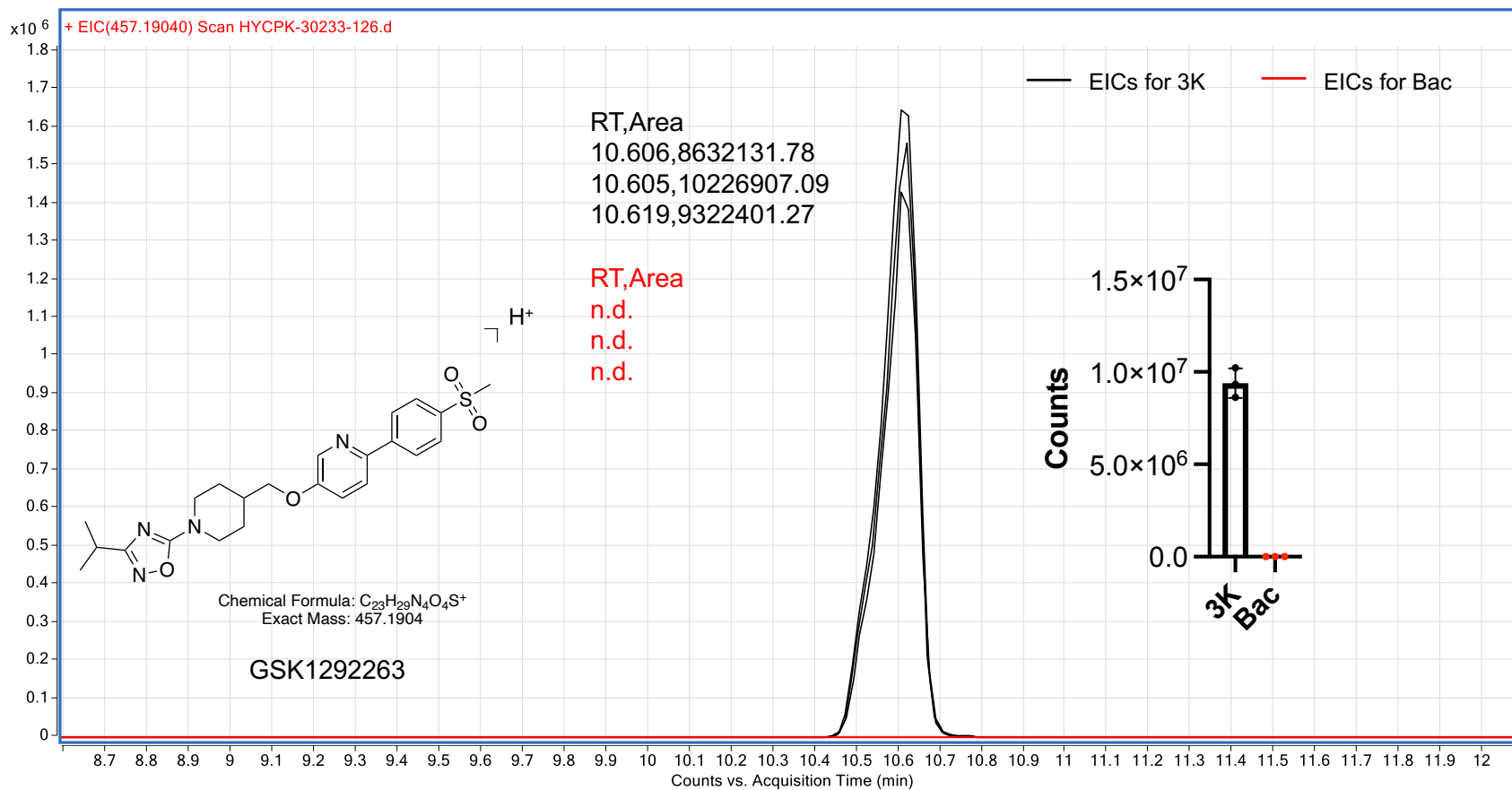


Fig. S141. Bac⁺ vs Bac⁻ (MWCO 3K) of velneperit (*m/z* 408.1563) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

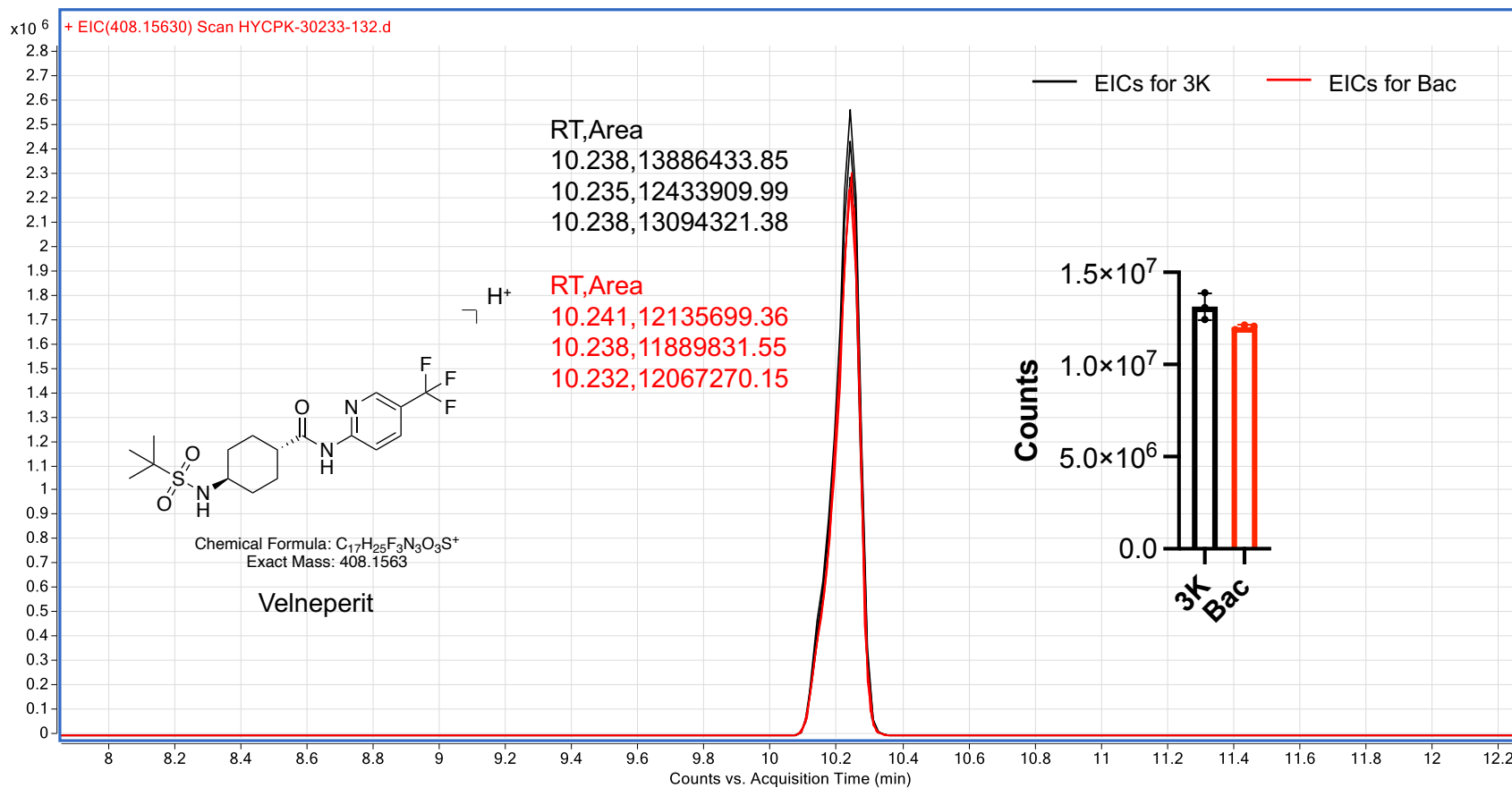


Fig. S142. Bac⁺ vs Bac⁻ (MWCO 3K) of iloperidone (*m/z* 427.2028) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

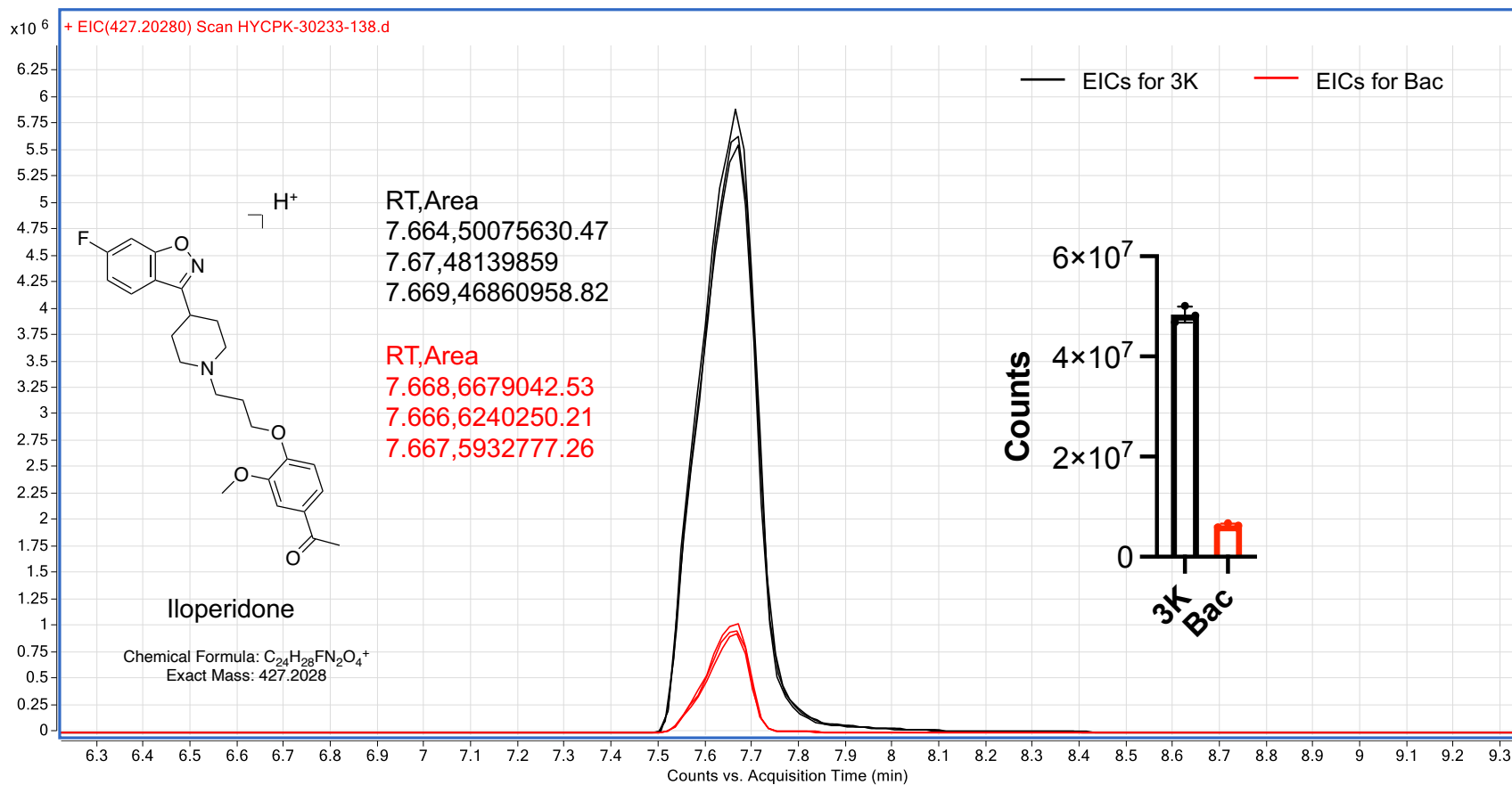


Fig. S143. Bac⁺ vs Bac⁻ (MWCO 3K) of ketanserin (*m/z* 396.1718) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

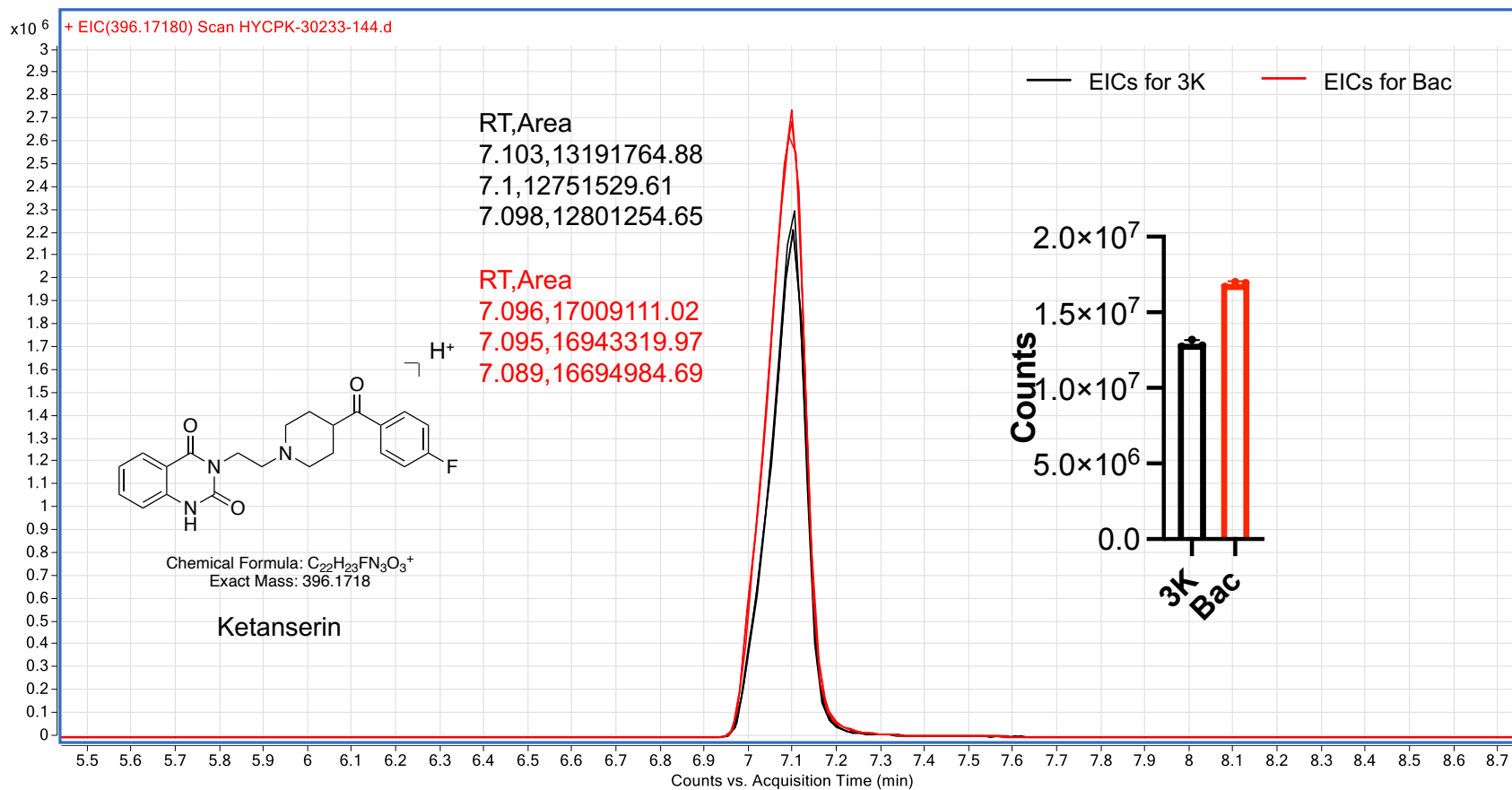


Fig. S144. Bac⁺ vs Bac⁻ (MWCO 3K) of SB756050 (*m/z* 501.1360) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

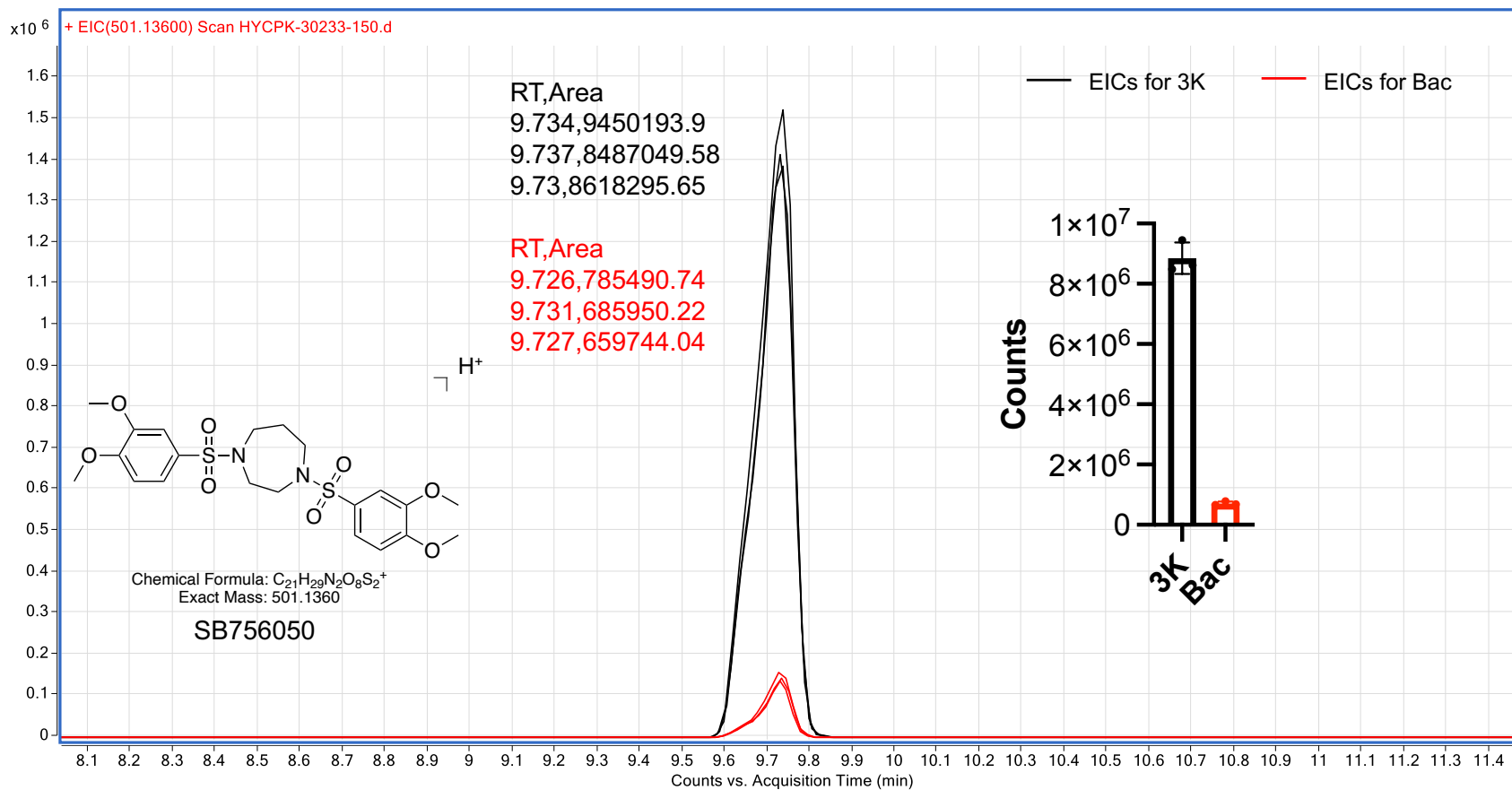


Fig. S145. Bac⁺ vs Bac⁻ (MWCO 3K) of BI-671800 (*m/z* 502.2061) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

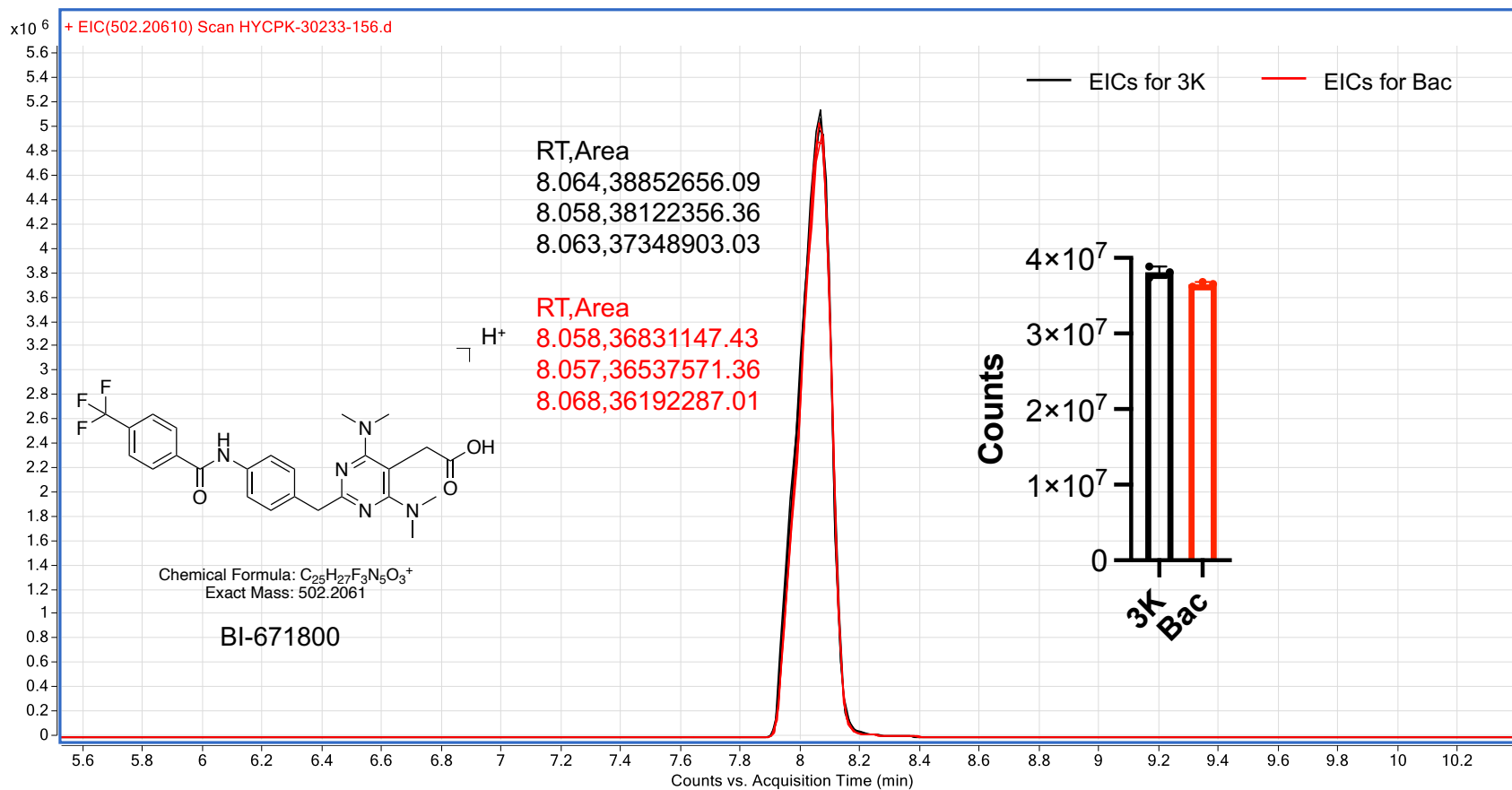


Fig. S146. Bac⁺ vs Bac⁻ (MWCO 3K) of metoprolol (*m/z* 268.1907) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

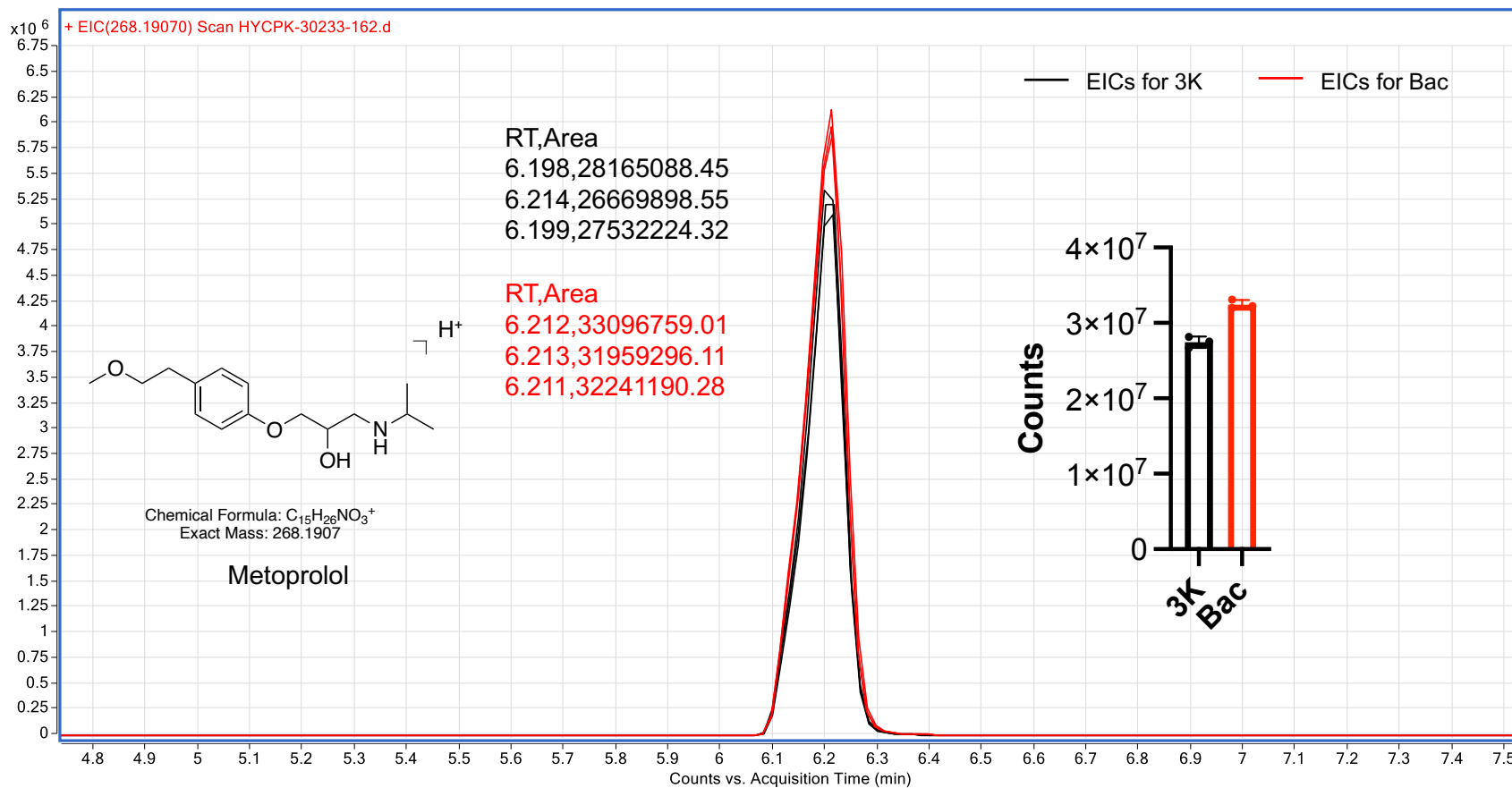


Fig. S147. Bac⁺ vs Bac⁻ (MWCO 3K) of mirabegron (*m/z* 397.1693) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

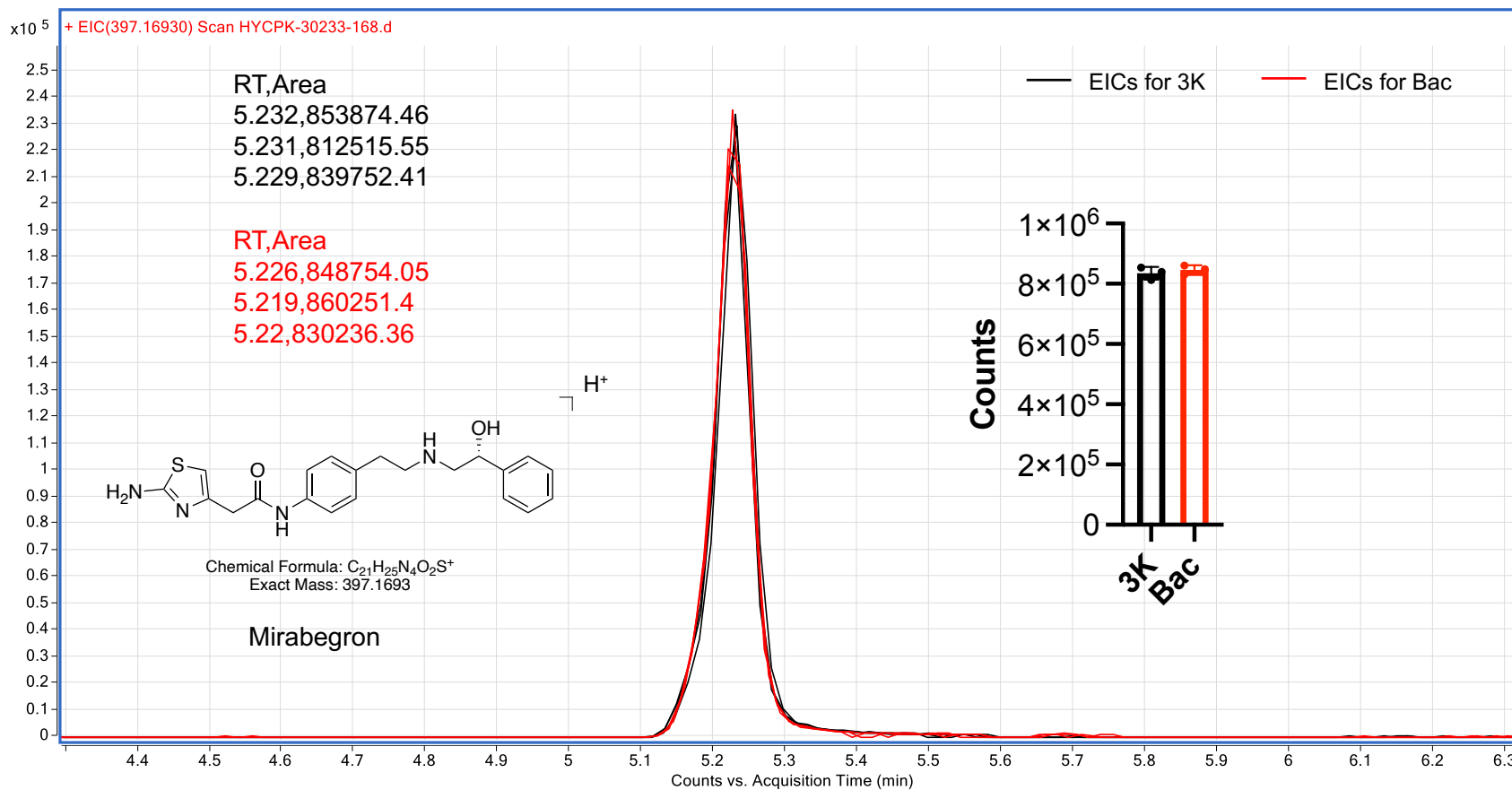


Fig. S148. Bac⁺ vs Bac⁻ (MWCO 3K) of brexpiprazole (*m/z* 434.1897) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

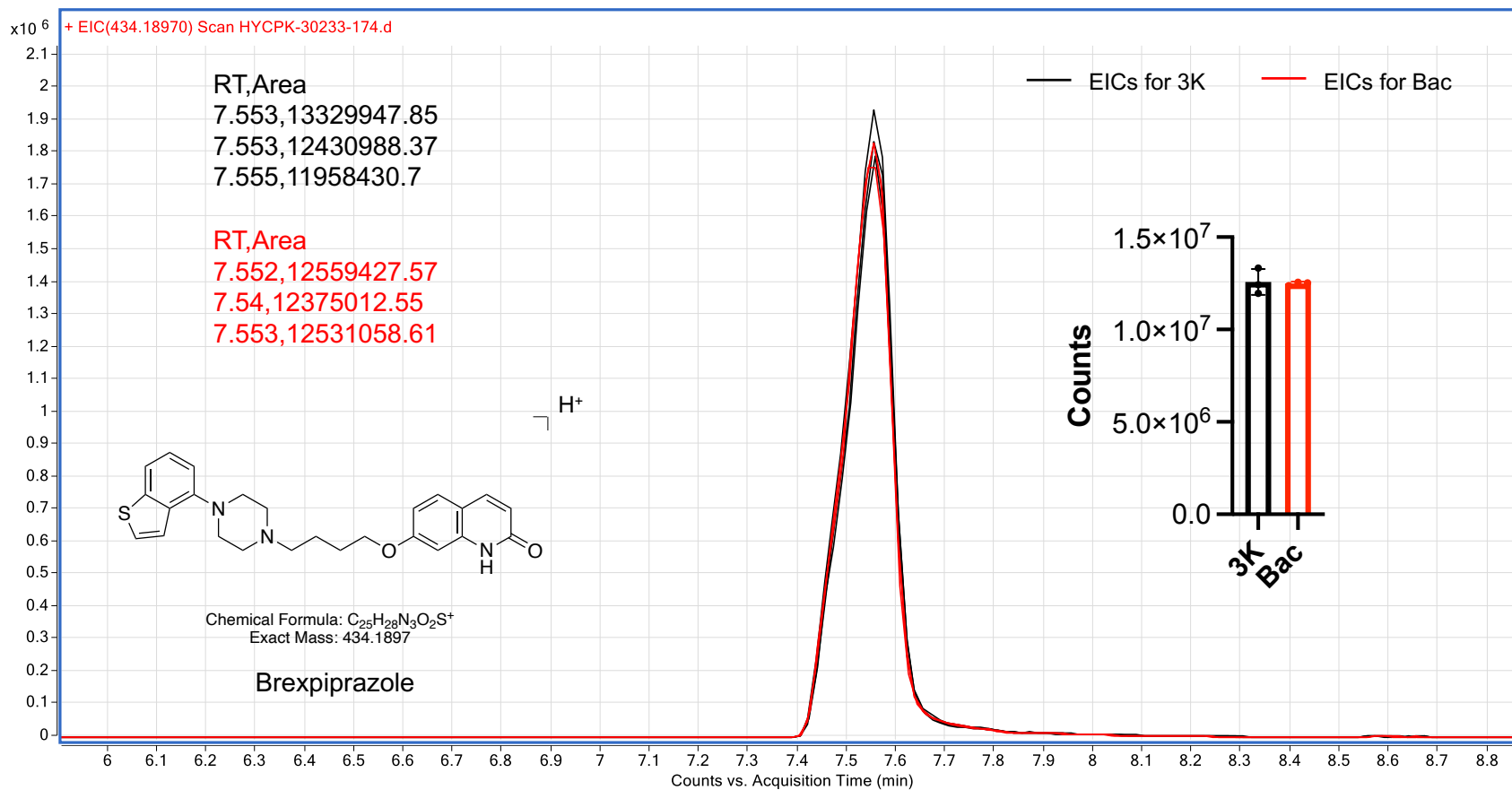


Fig. S149. Bac⁺ vs Bac⁻ (MWCO 3K) of fimasartan (*m/z* 502.2348) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

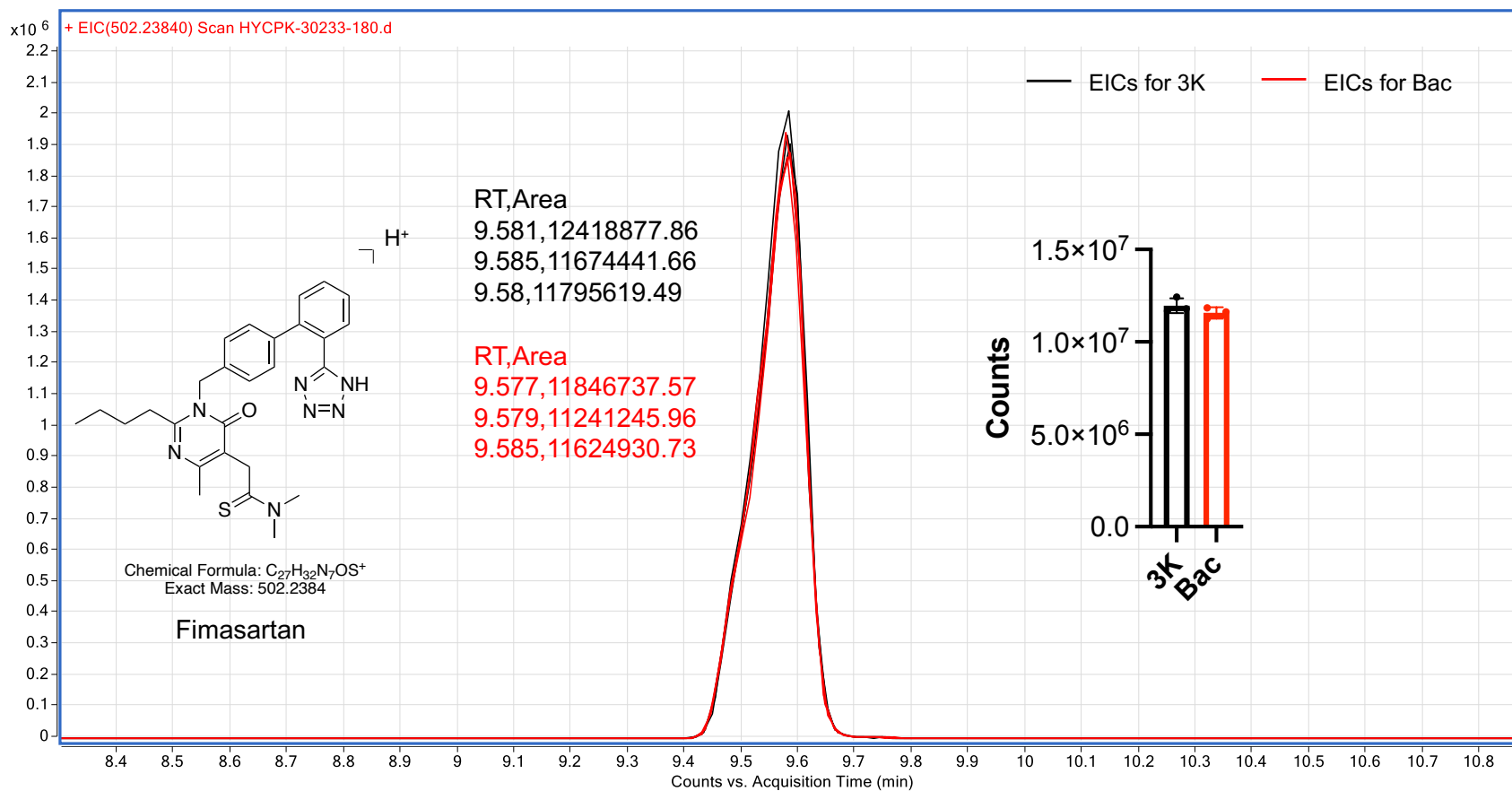


Fig. S150. Bac⁺ vs Bac⁻ (MWCO 3K) of camicalinal (*m/z* 425.2711) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

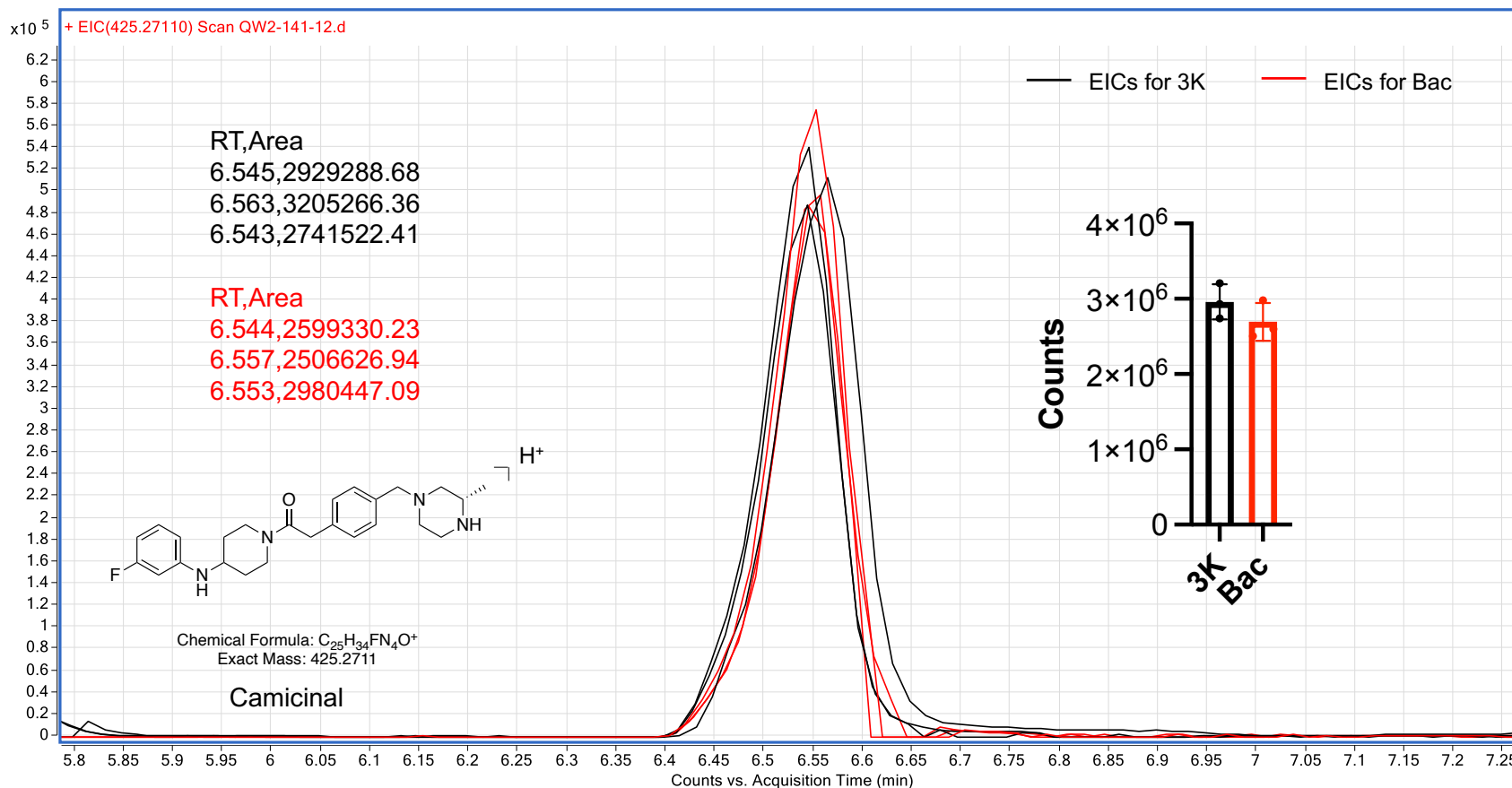


Fig. S151. Bac⁺ vs Bac⁻ (MWCO 3K) of (*R*)-elagolix (*m/z* 632.2178) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

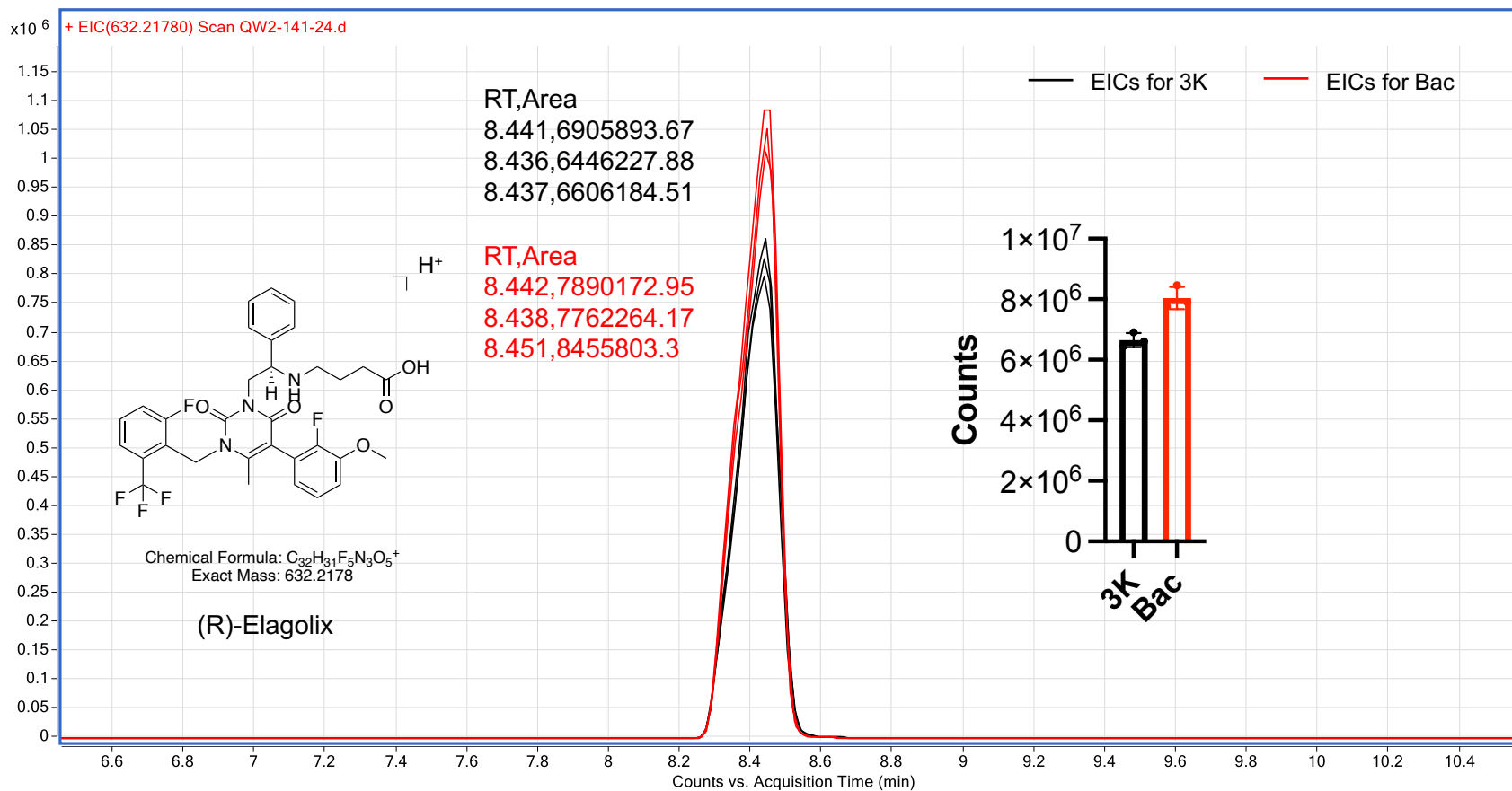


Fig. S152. Bac⁺ vs Bac⁻ (MWCO 3K) of selezipag (*m/z* 497.2217) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

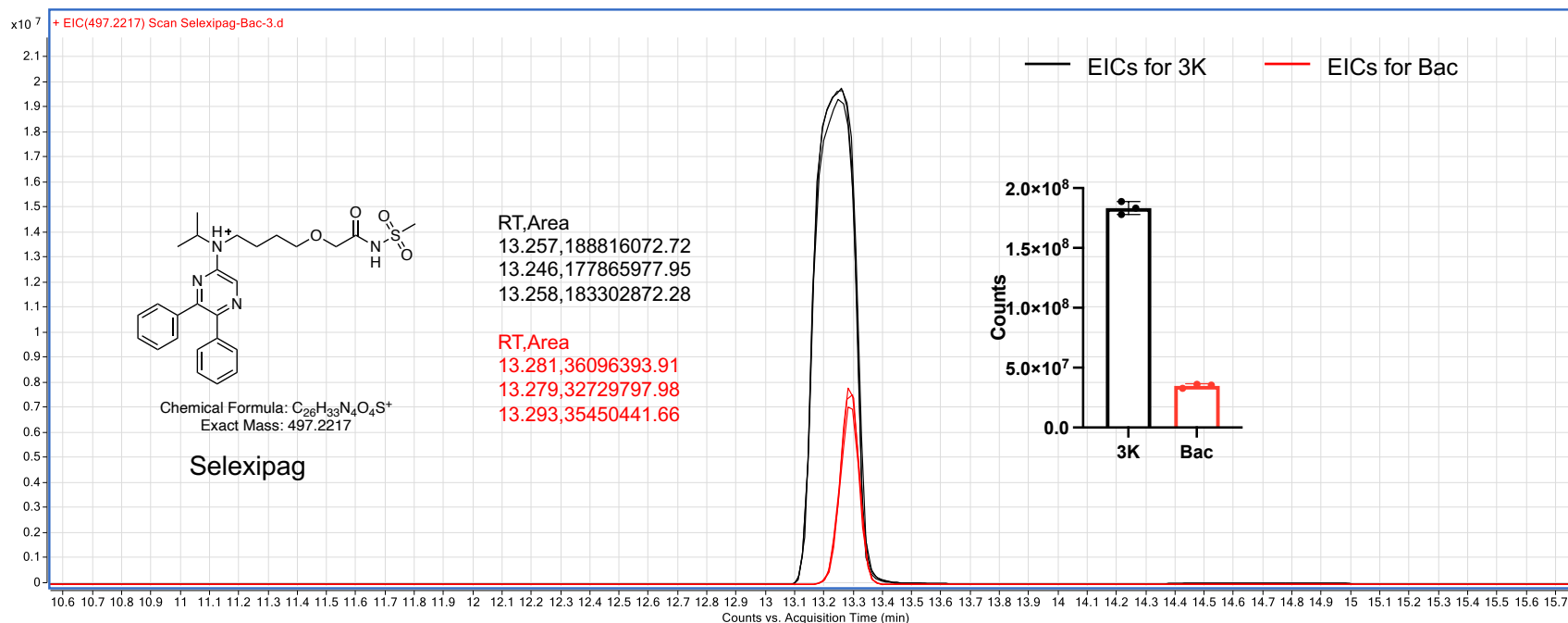


Fig. S153. Bac⁺ vs Bac⁻ (MWCO 3K) of valsartan (*m/z* 436.2343) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

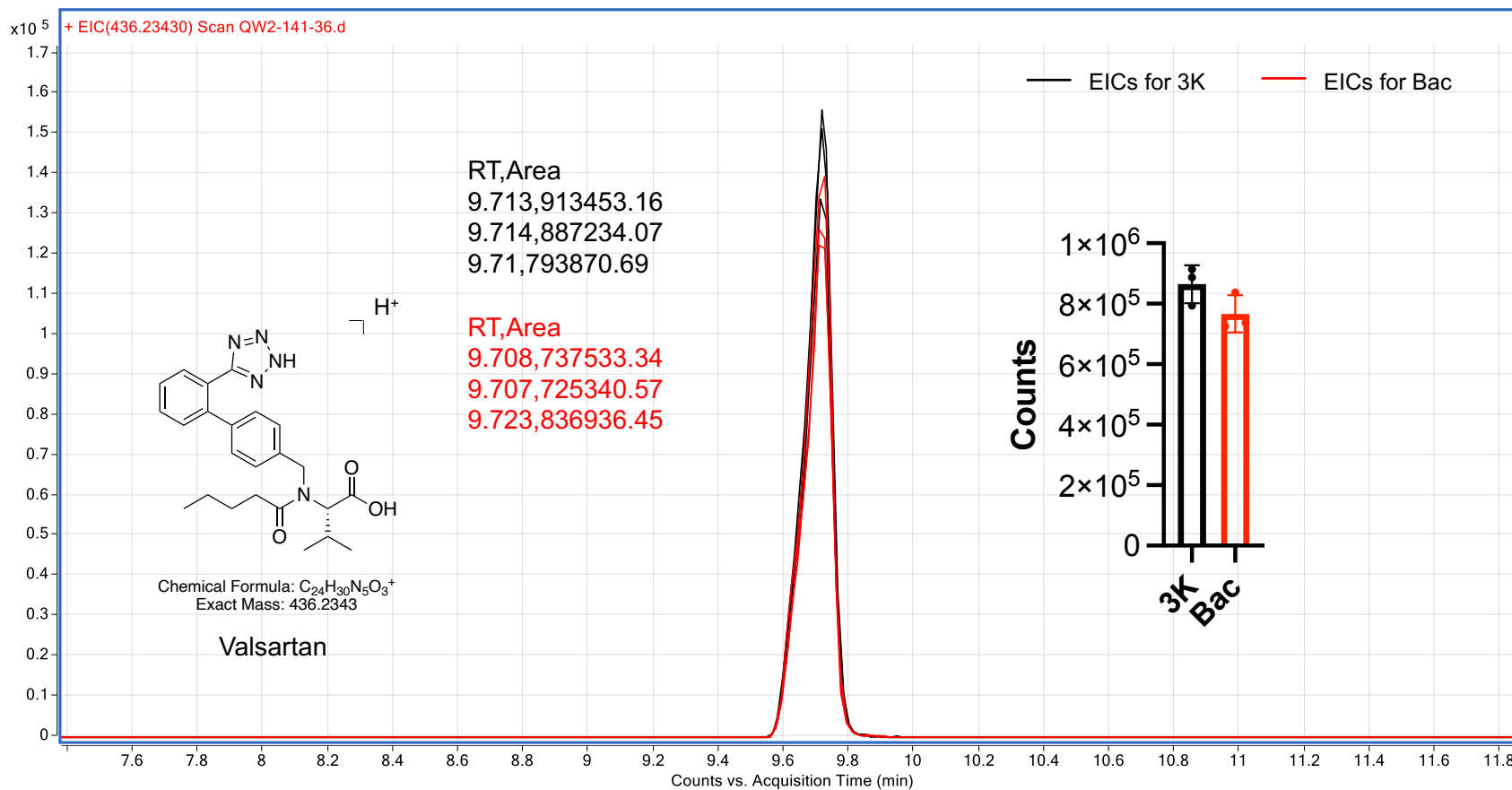


Fig. S154. Bac⁺ vs Bac⁻ (MWCO 3K) of balovaptan (*m/z* 410.1742) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

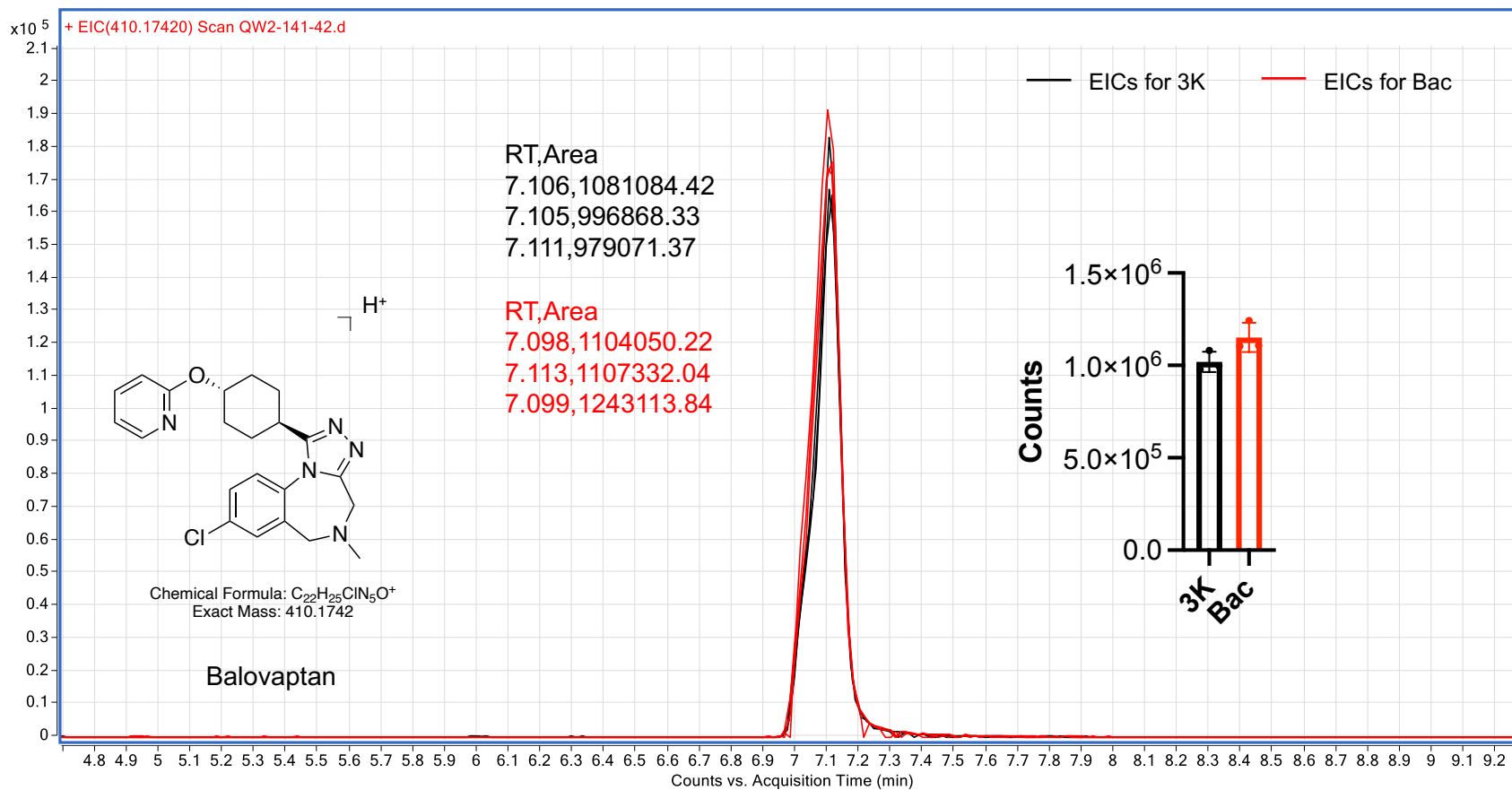


Fig. S155. Bac⁺ vs Bac⁻ (MWCO 3K) of glycopyrrolate (*m/z* 318.2064) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

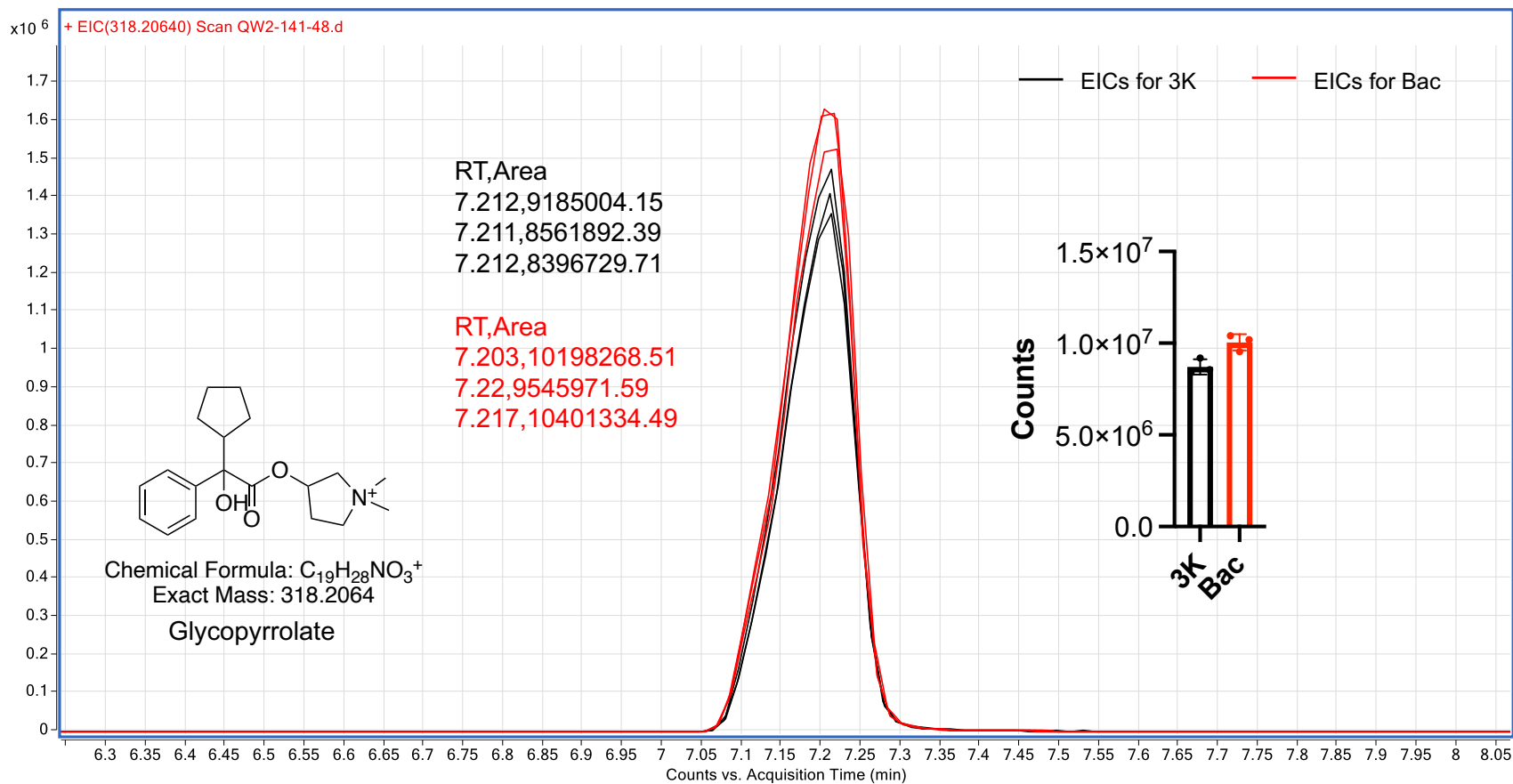


Fig. S156. Bac⁺ vs Bac⁻ (MWCO 3K) of trospium (*m/z* 392.2220) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

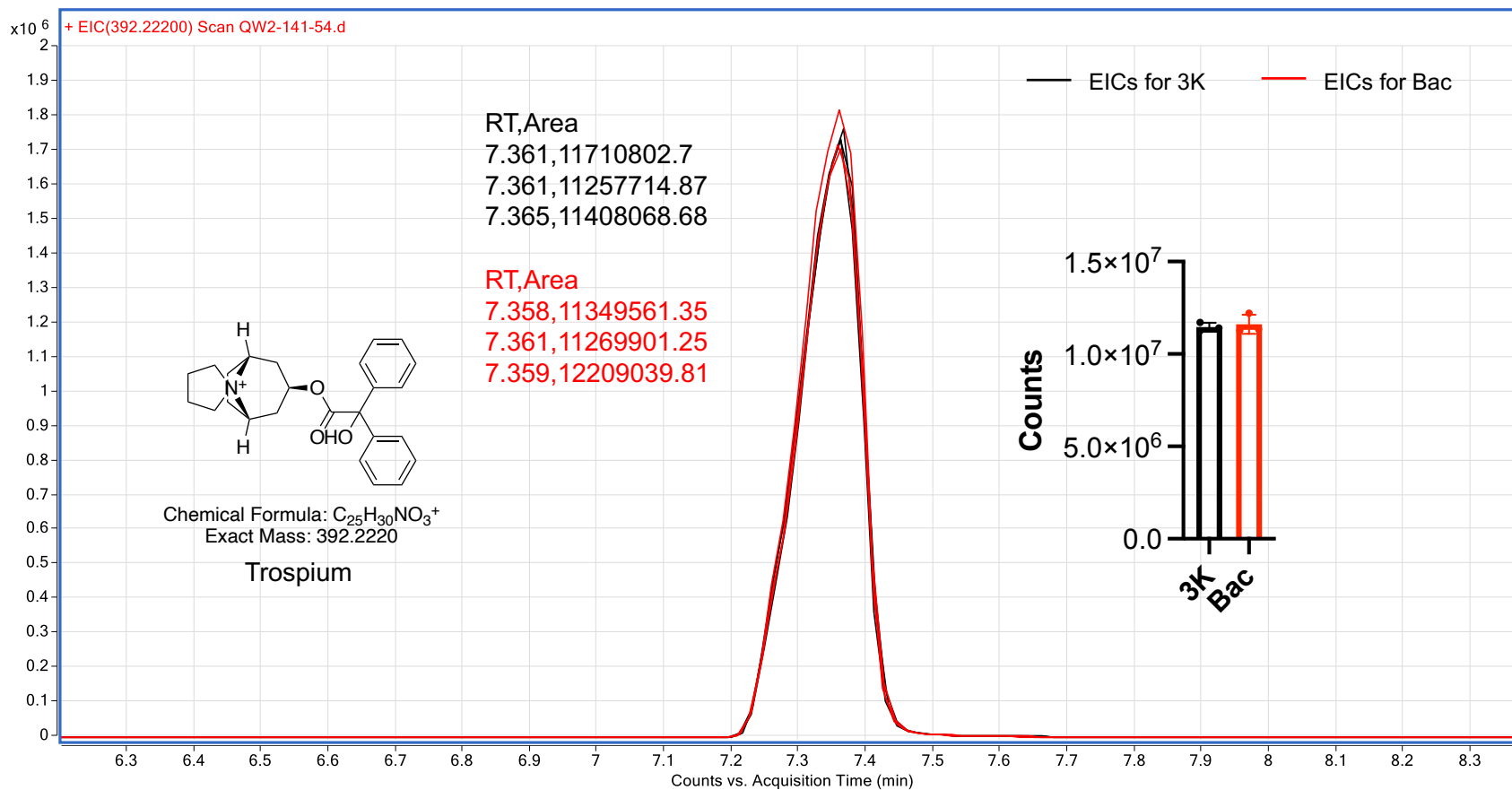


Fig. S157. Bac⁺ vs Bac⁻ (MWCO 3K) of lafutidine (*m/z* 432.1952) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

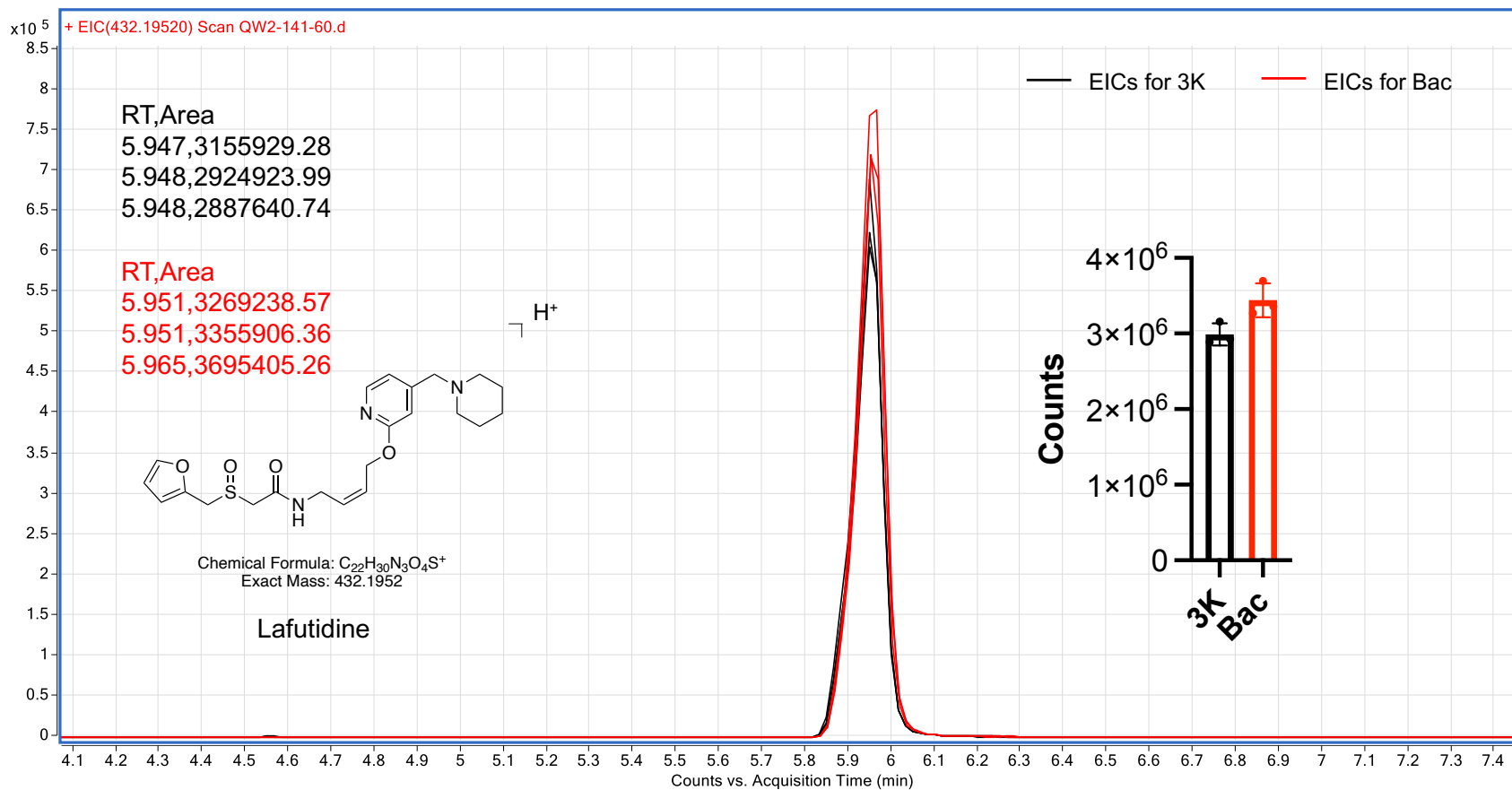


Fig. S158. Bac⁺ vs Bac⁻ (MWCO 3K) of ketotifen (*m/z* 310.1260) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

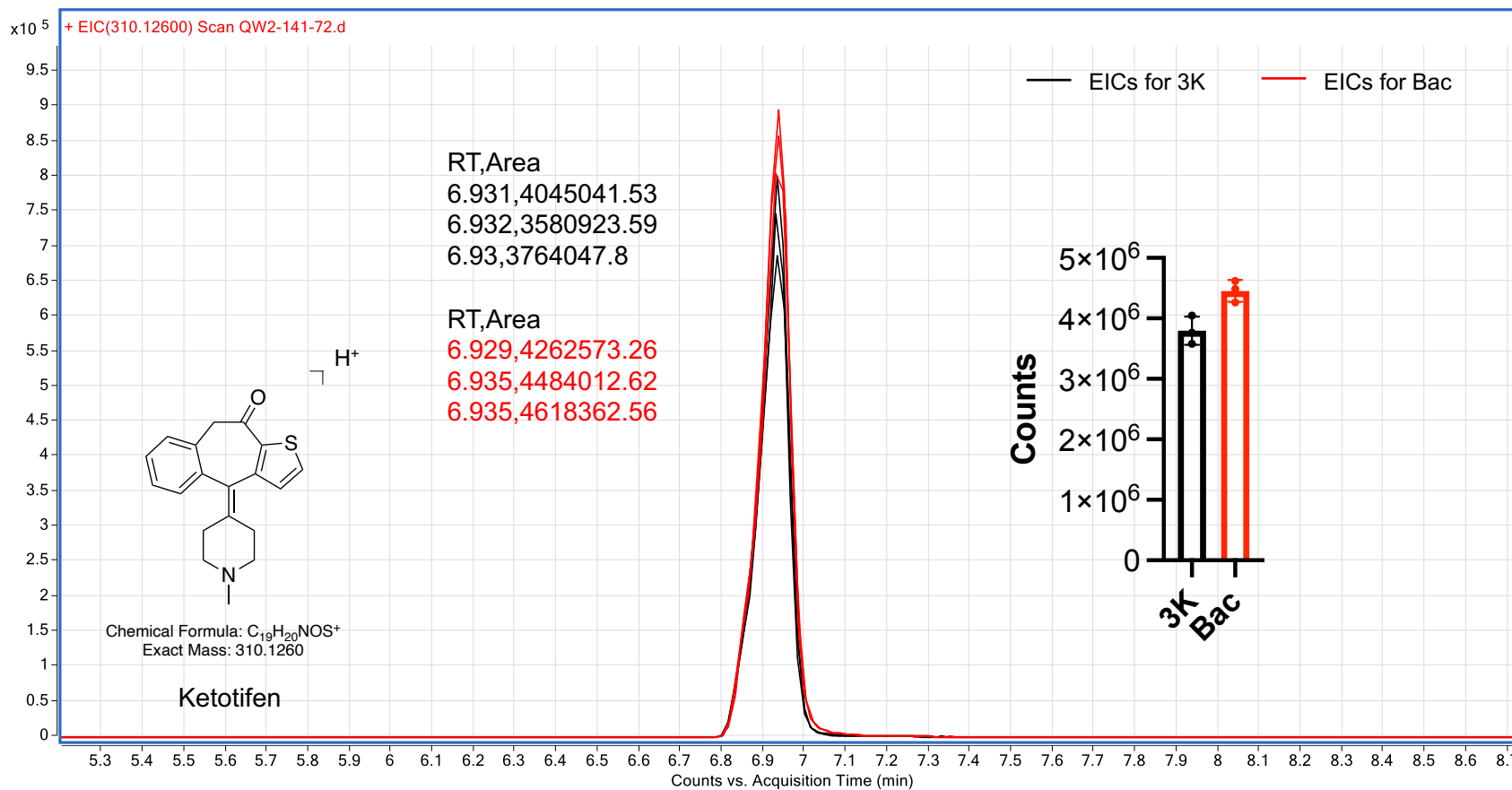


Fig. S159. Bac⁺ vs Bac⁻ (MWCO 3K) of telmisartan (*m/z* 515.2442) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

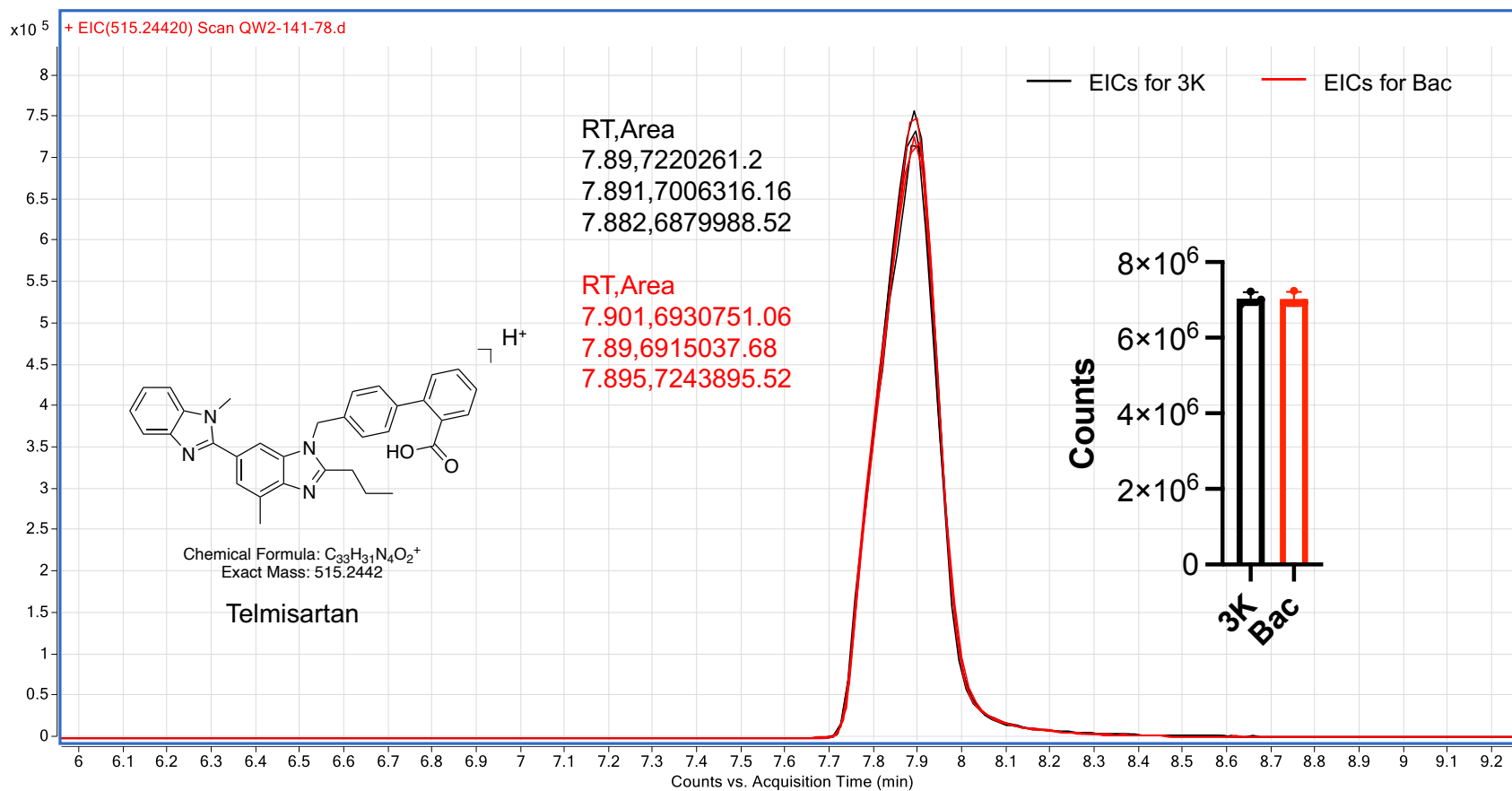


Fig. S160. Bac⁺ vs Bac⁻ (MWCO 3K) of relugolix (*m/z* 624.1835) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

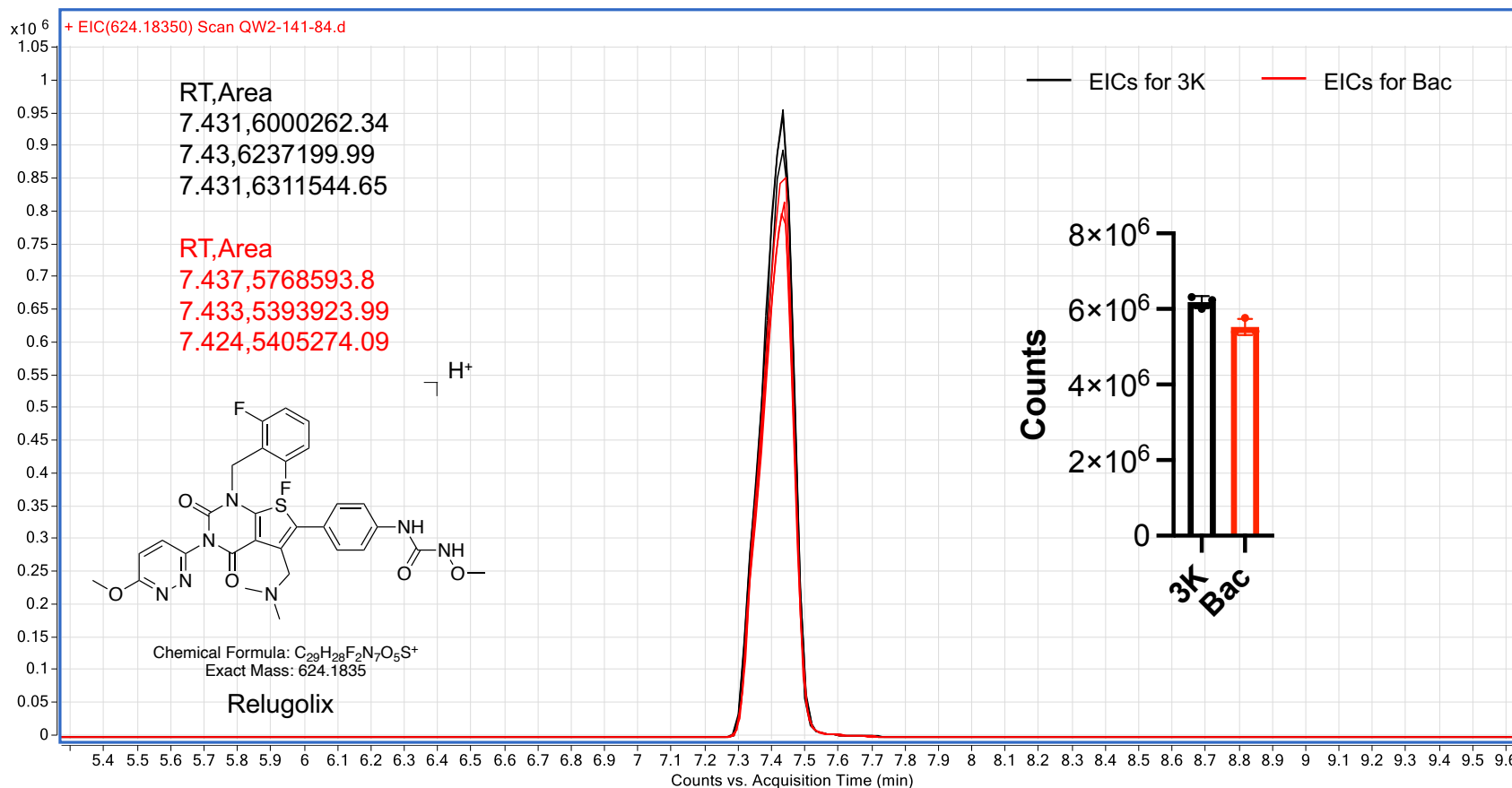


Fig. S161. Bac⁺ vs Bac⁻ (MWCO 3K) of tolvaptan (*m/z* 449.1626) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

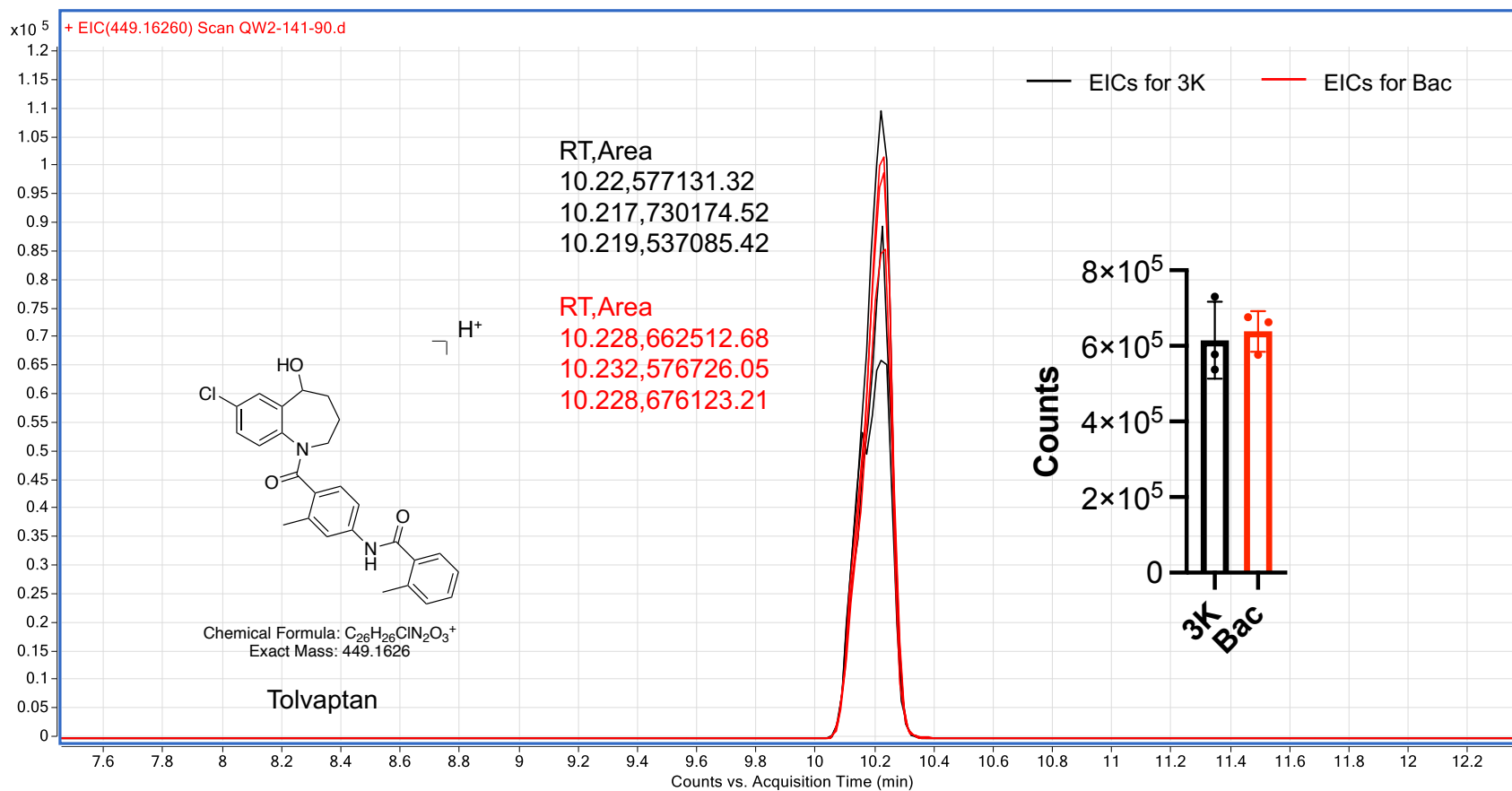


Fig. S162. Bac⁺ vs Bac⁻ (MWCO 3K) of cariprazine (*m/z* 427.2026) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

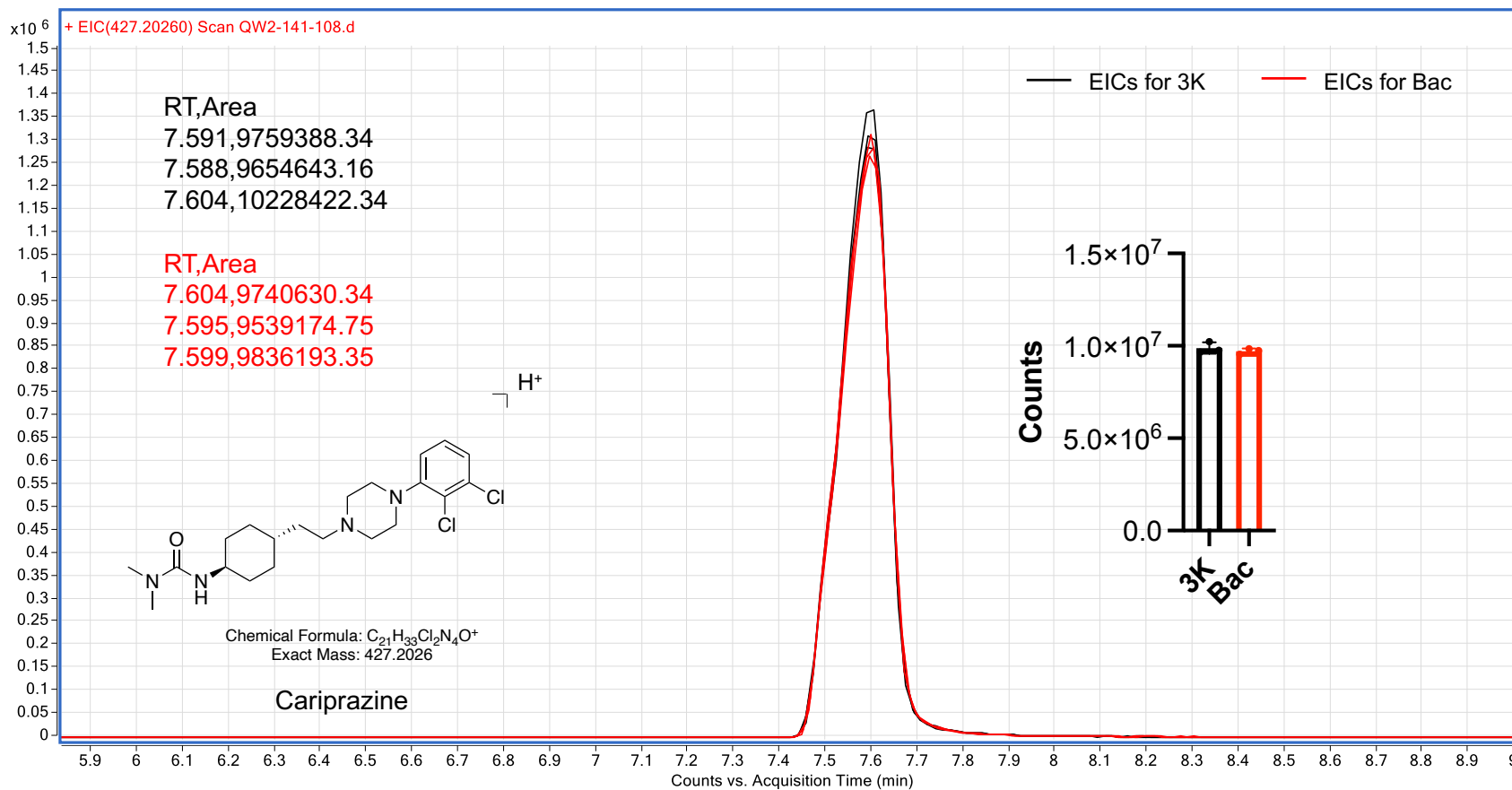


Fig. S163. Bac⁺ vs Bac⁻ (MWCO 3K) of setiptiline (*m/z* 262.1590) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

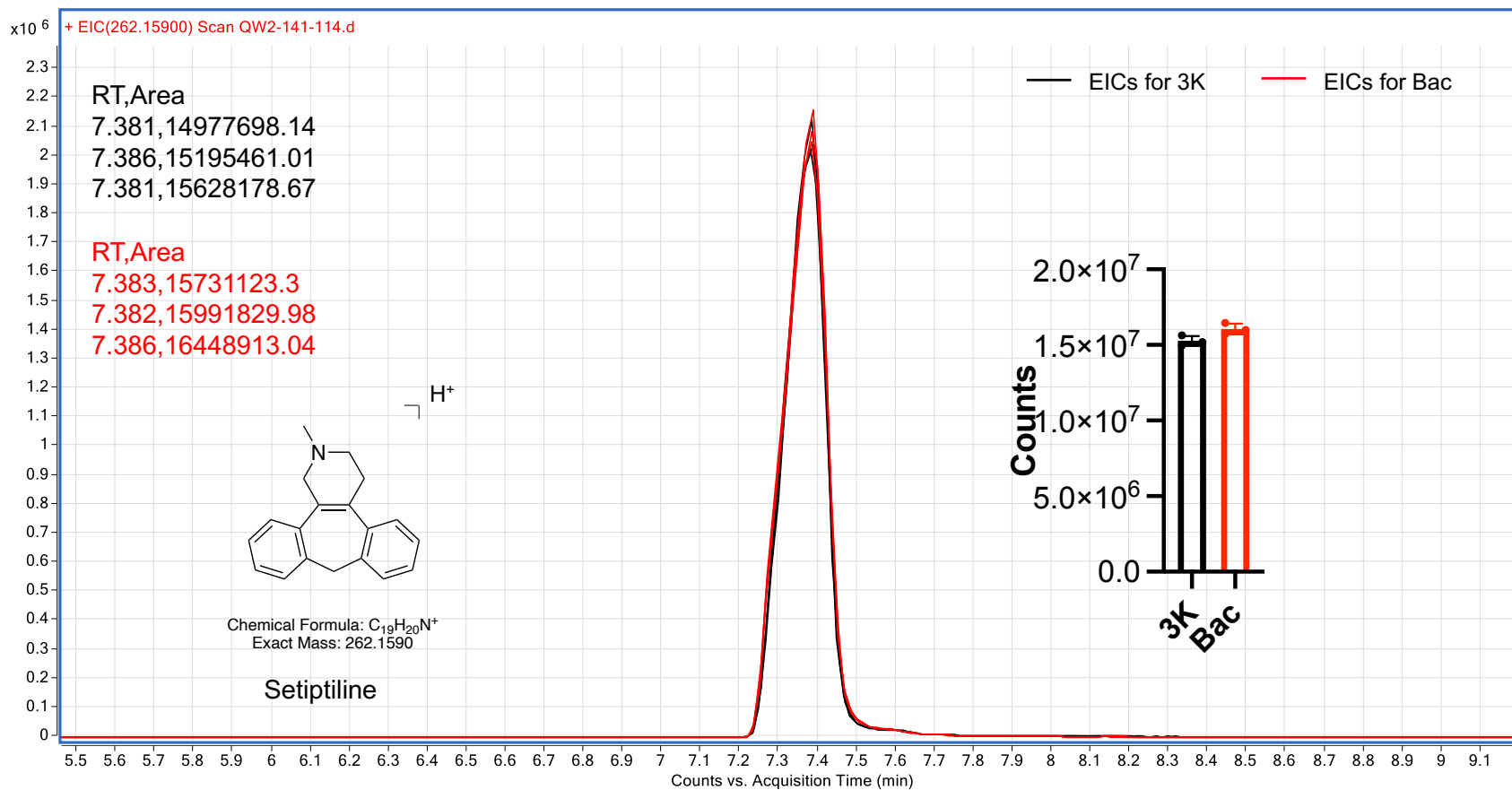


Fig. S164. Bac⁺ vs Bac⁻ (MWCO 3K) of ranitidine (*m/z* 315.1485) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

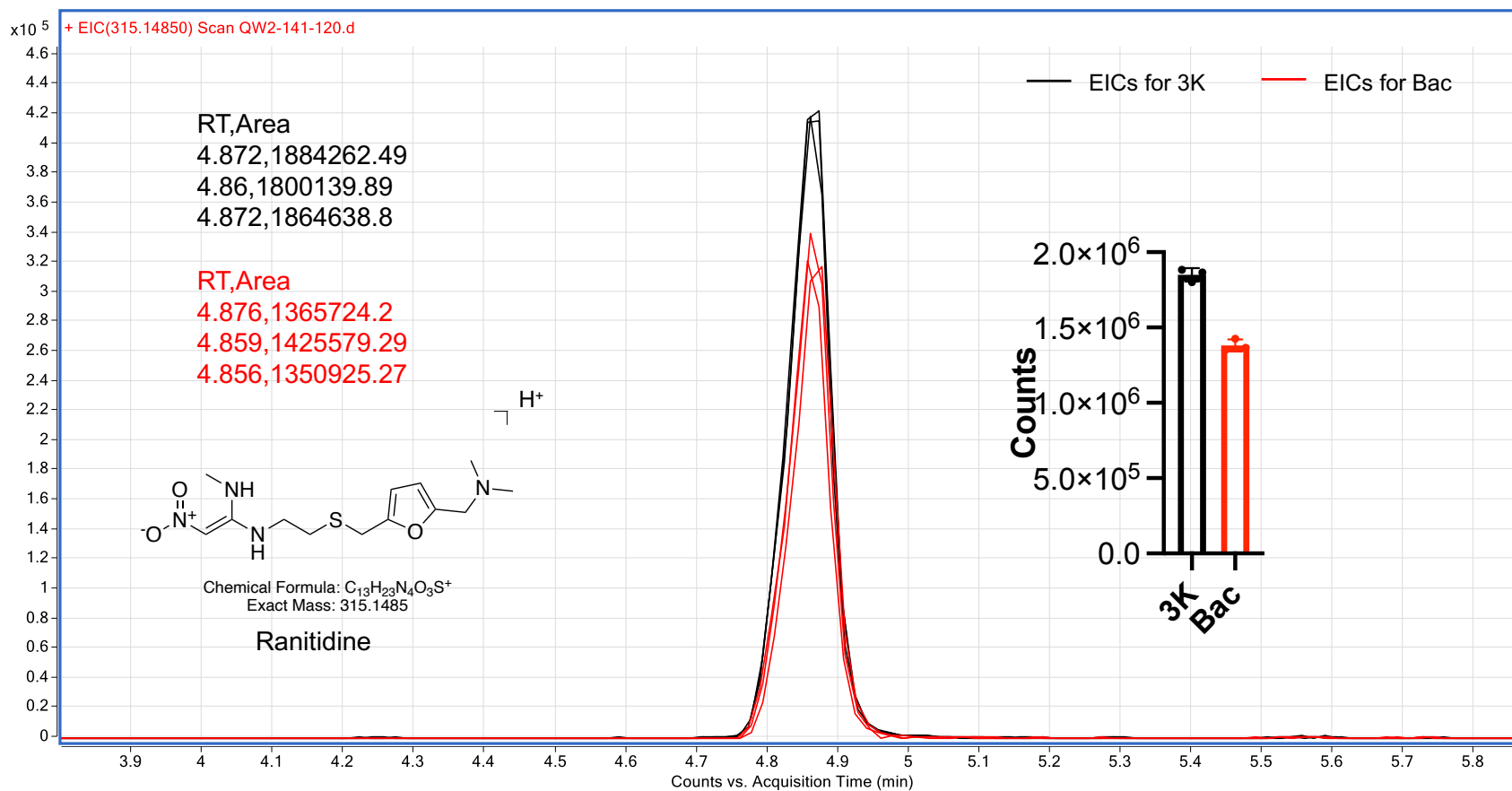


Fig. S165. Bac⁺ vs Bac⁻ (MWCO 3K) of GSK163090 (*m/z* 416.2445) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

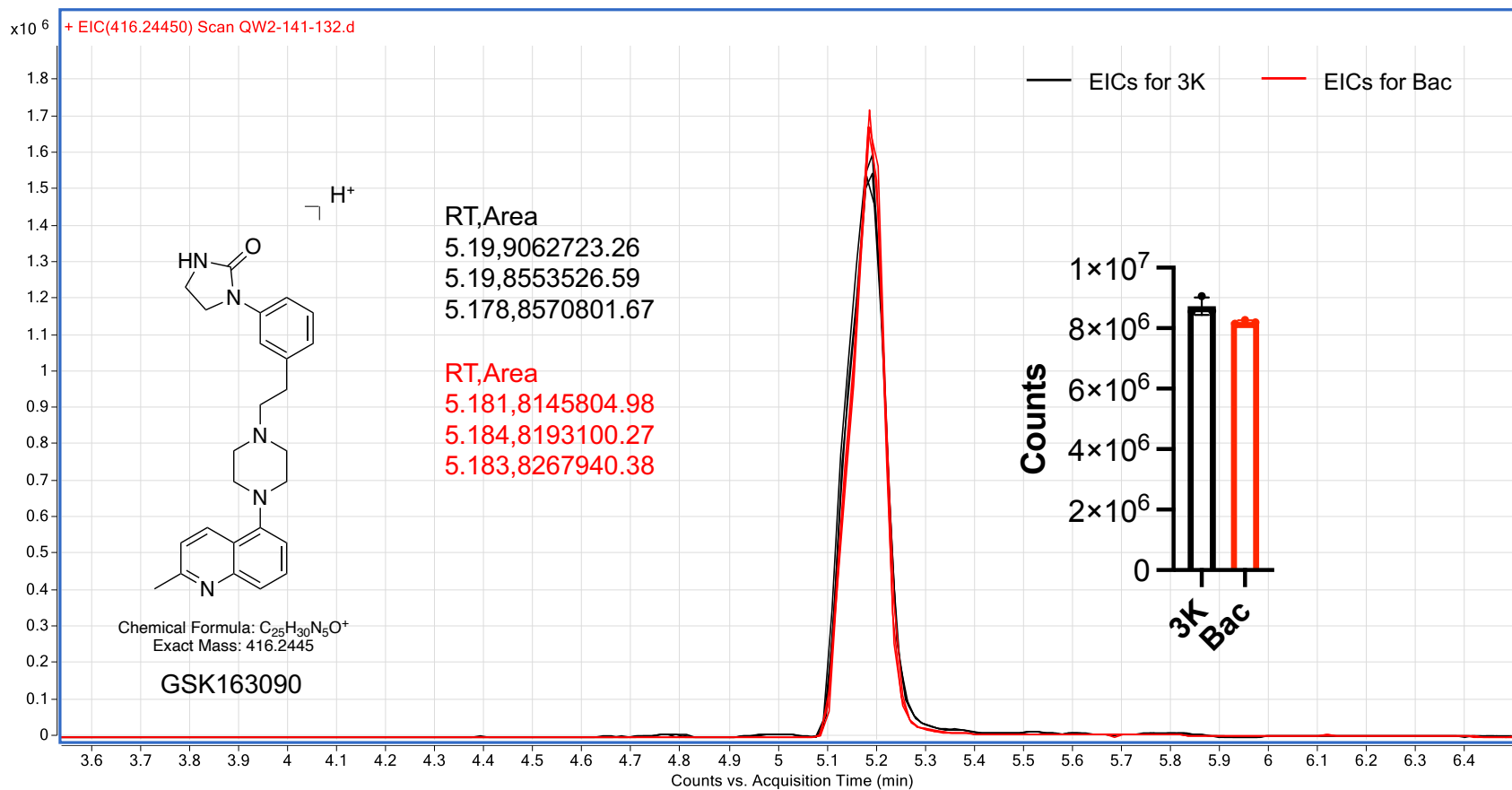


Fig. S166. Bac⁺ vs Bac⁻ (MWCO 3K) of atrasentan (*m/z* 511.2803) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

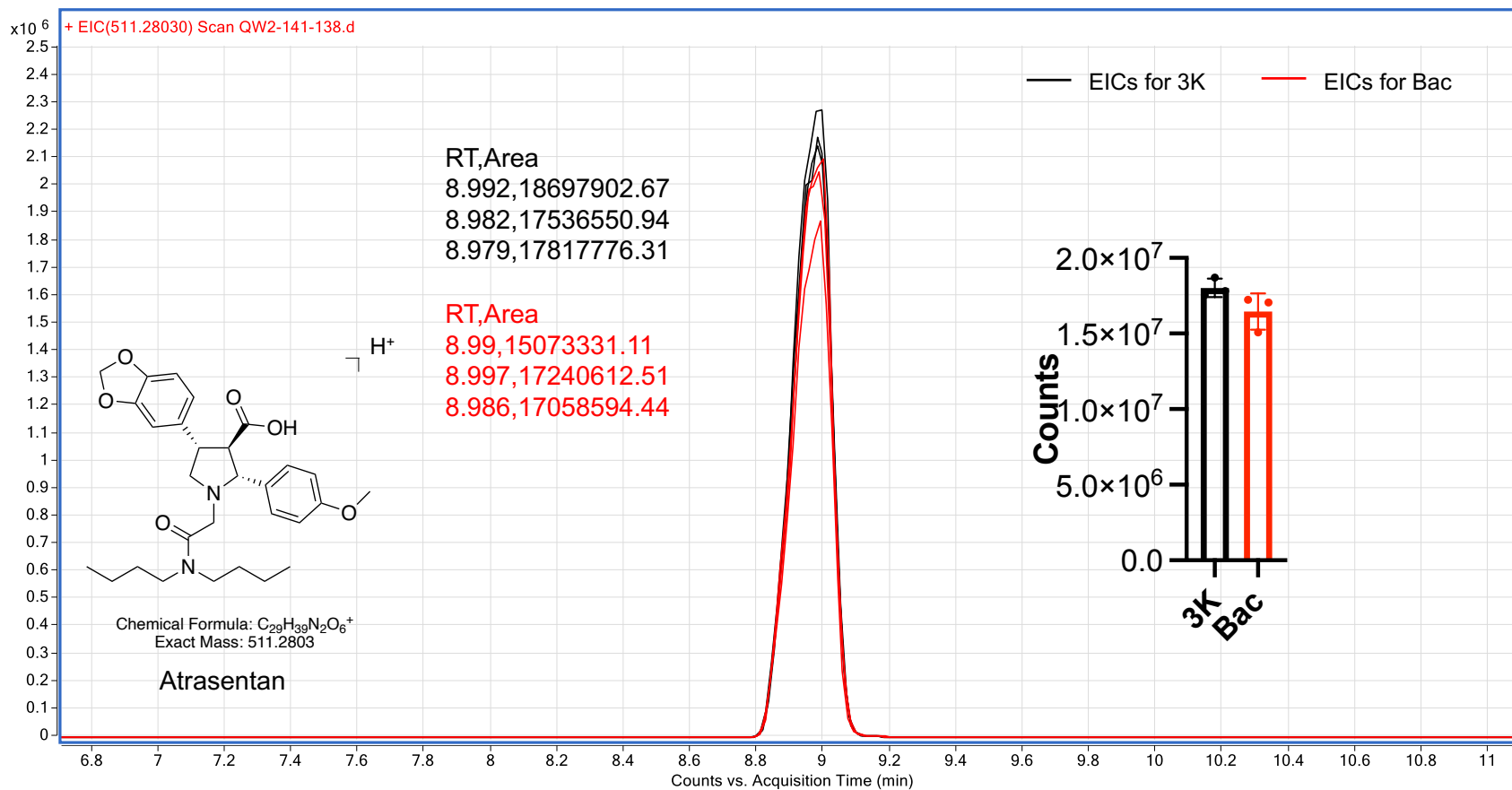


Fig. S167. Bac⁺ vs Bac⁻ (MWCO 3K) of risperidone (*m/z* 411.2191) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

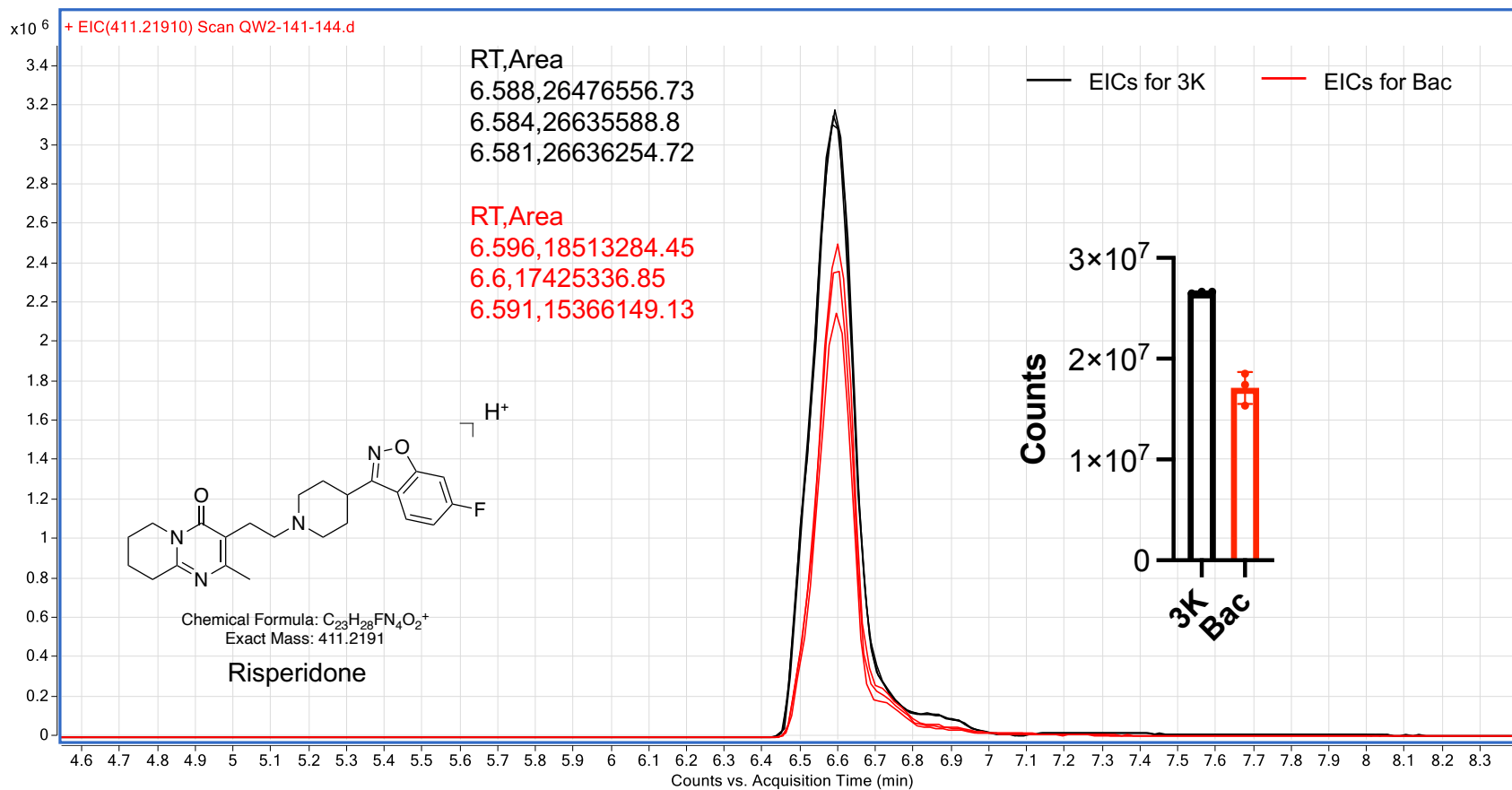


Fig. S168. Bac⁺ vs Bac⁻ (MWCO 3K) of prucalopride (*m/z* 368.1735) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

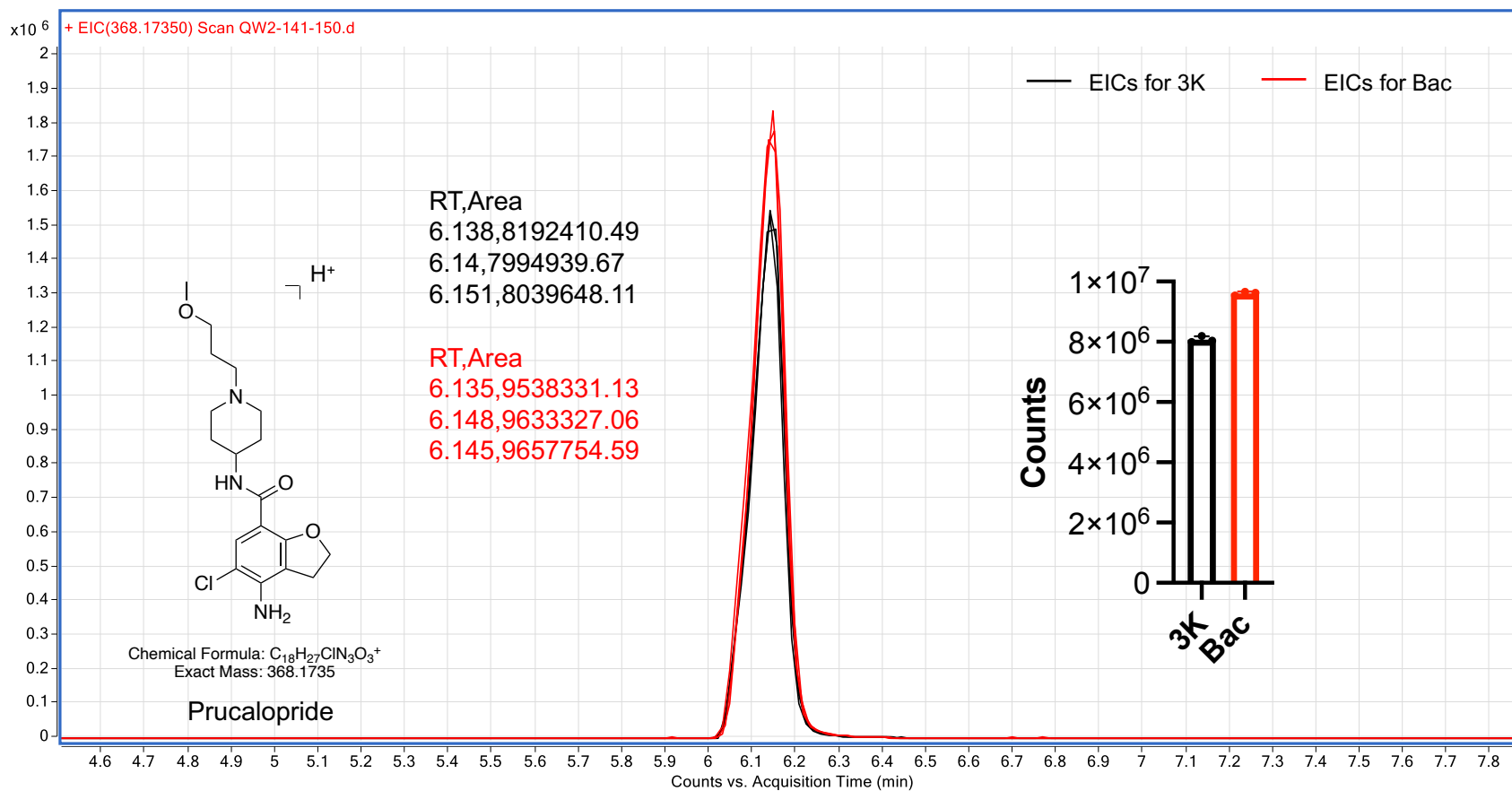


Fig. S169. Bac⁺ vs Bac⁻ (MWCO 3K) of GSK598809 (*m/z* 482.1632) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

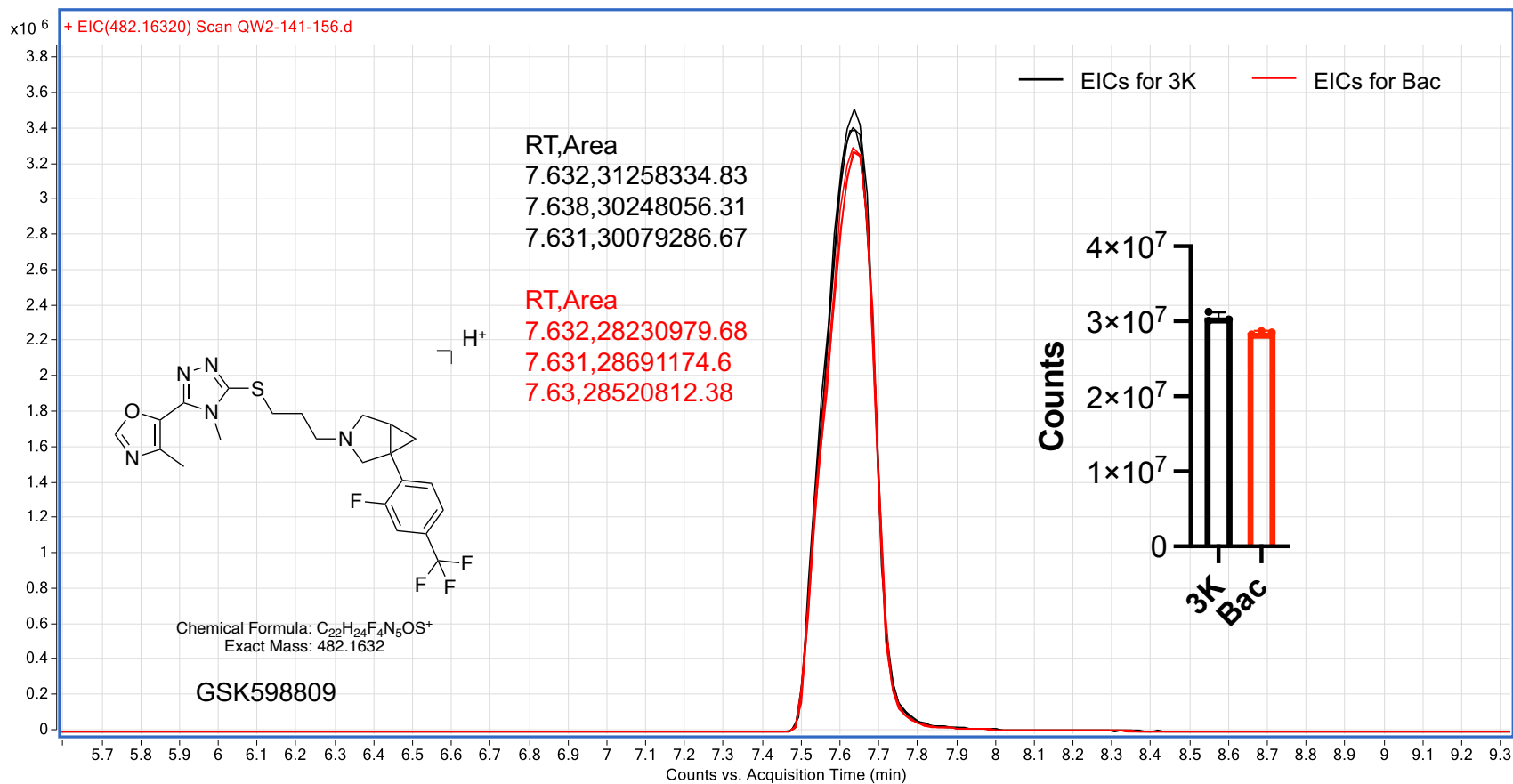


Fig. S170. Bac⁺ vs Bac⁻ (MWCO 3K) of dexpramipexole (*m/z* 212.1216) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

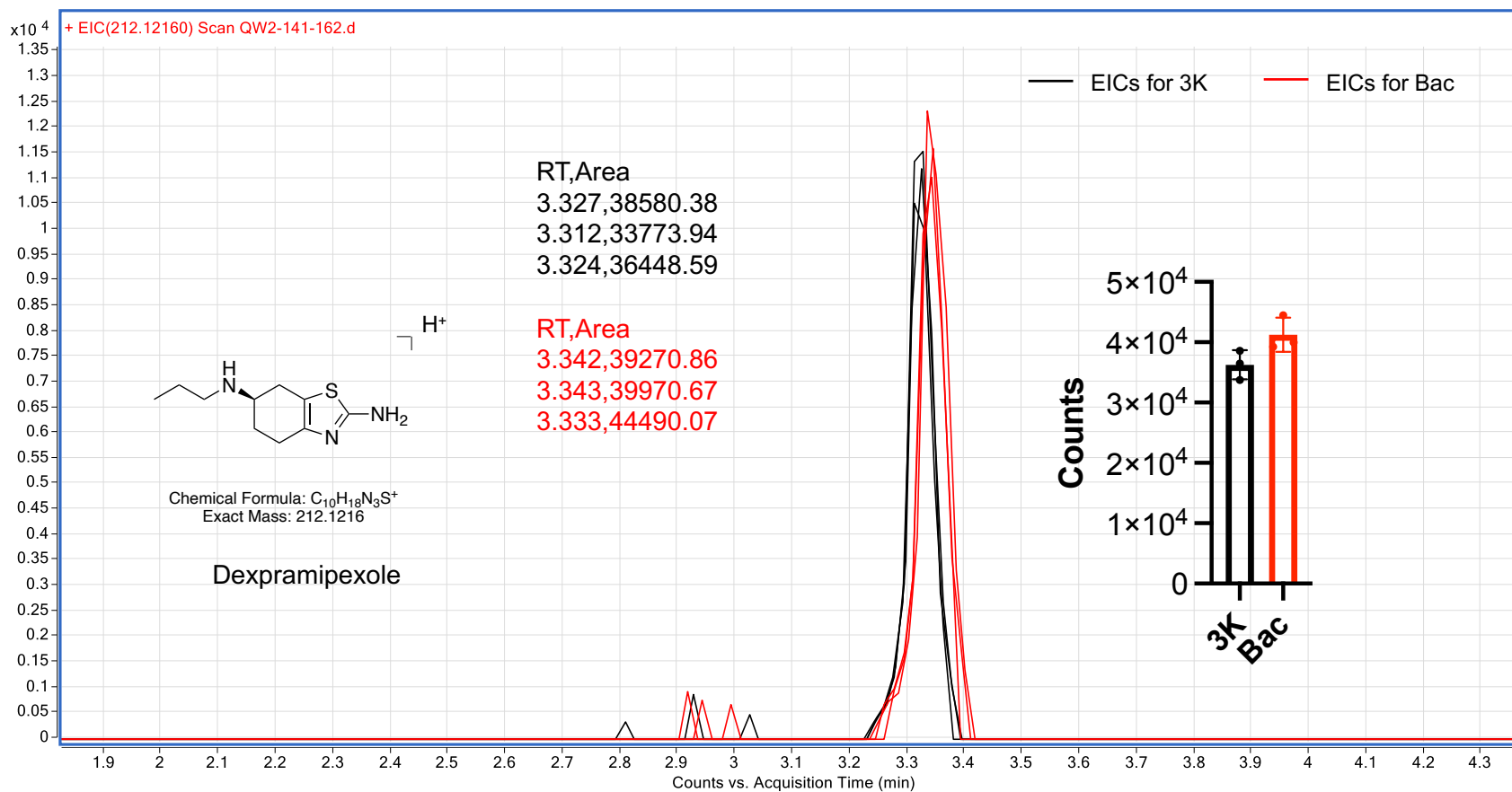


Fig. S171. Bac⁺ vs Bac⁻ (MWCO 3K) of maraviroc (*m/z* 514.3352) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

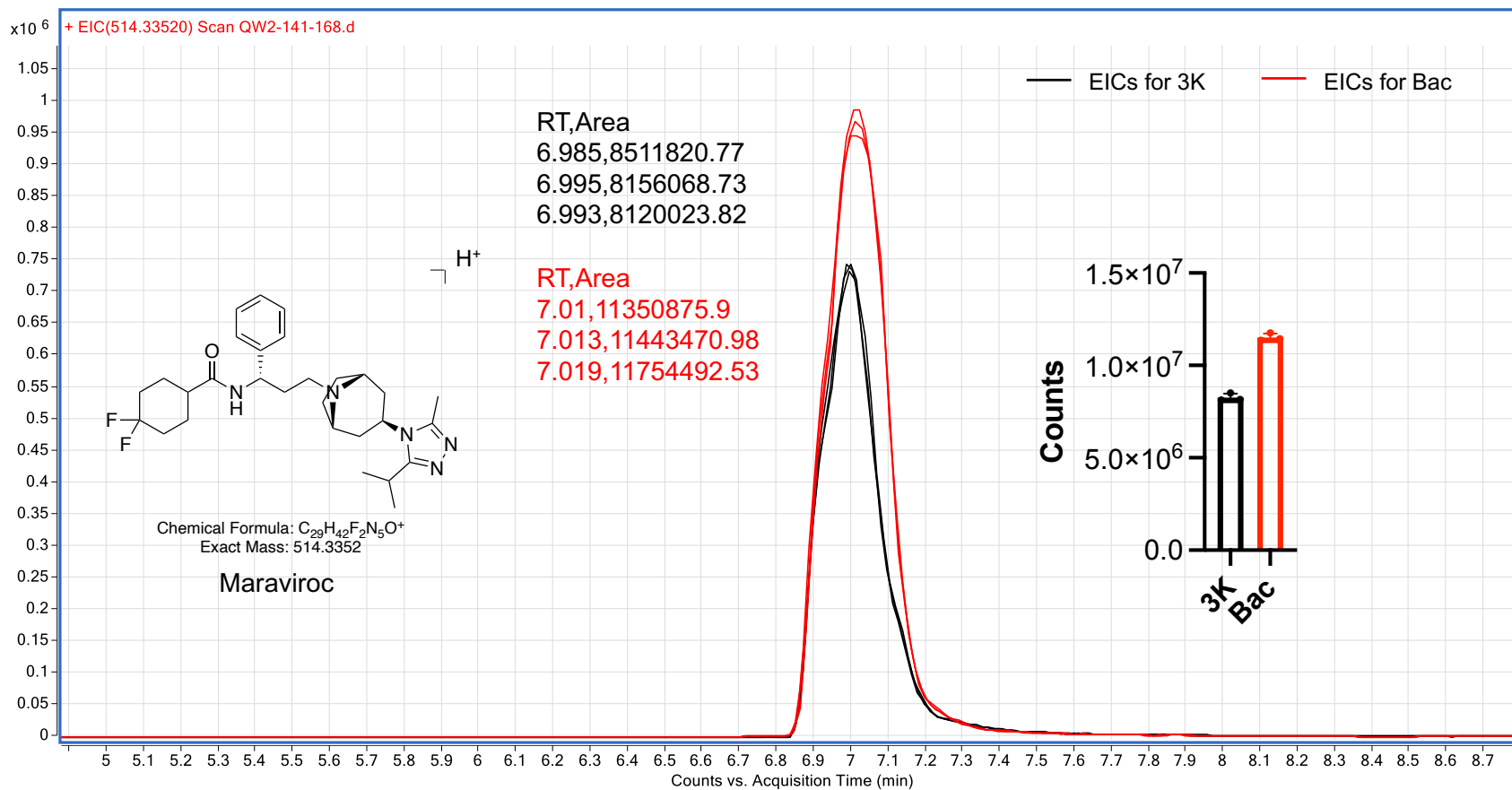


Fig. S172. Bac⁺ vs Bac⁻ (MWCO 3K) of aripiprazole (*m/z* 448.1553) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

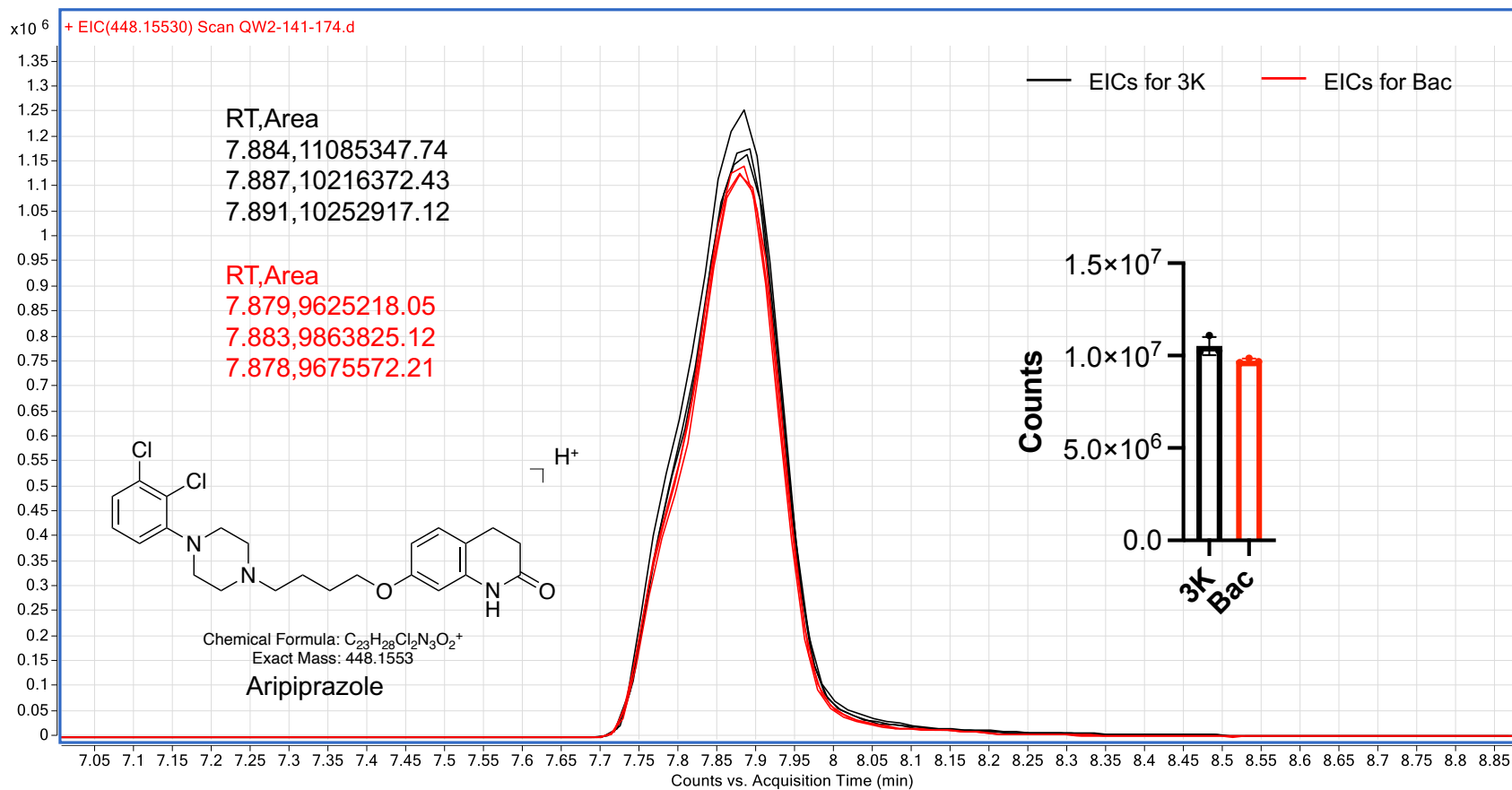


Fig. S173. Bac⁺ vs Bac⁻ (MWCO 3K) of vortioxetine (*m/z* 299.1576) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

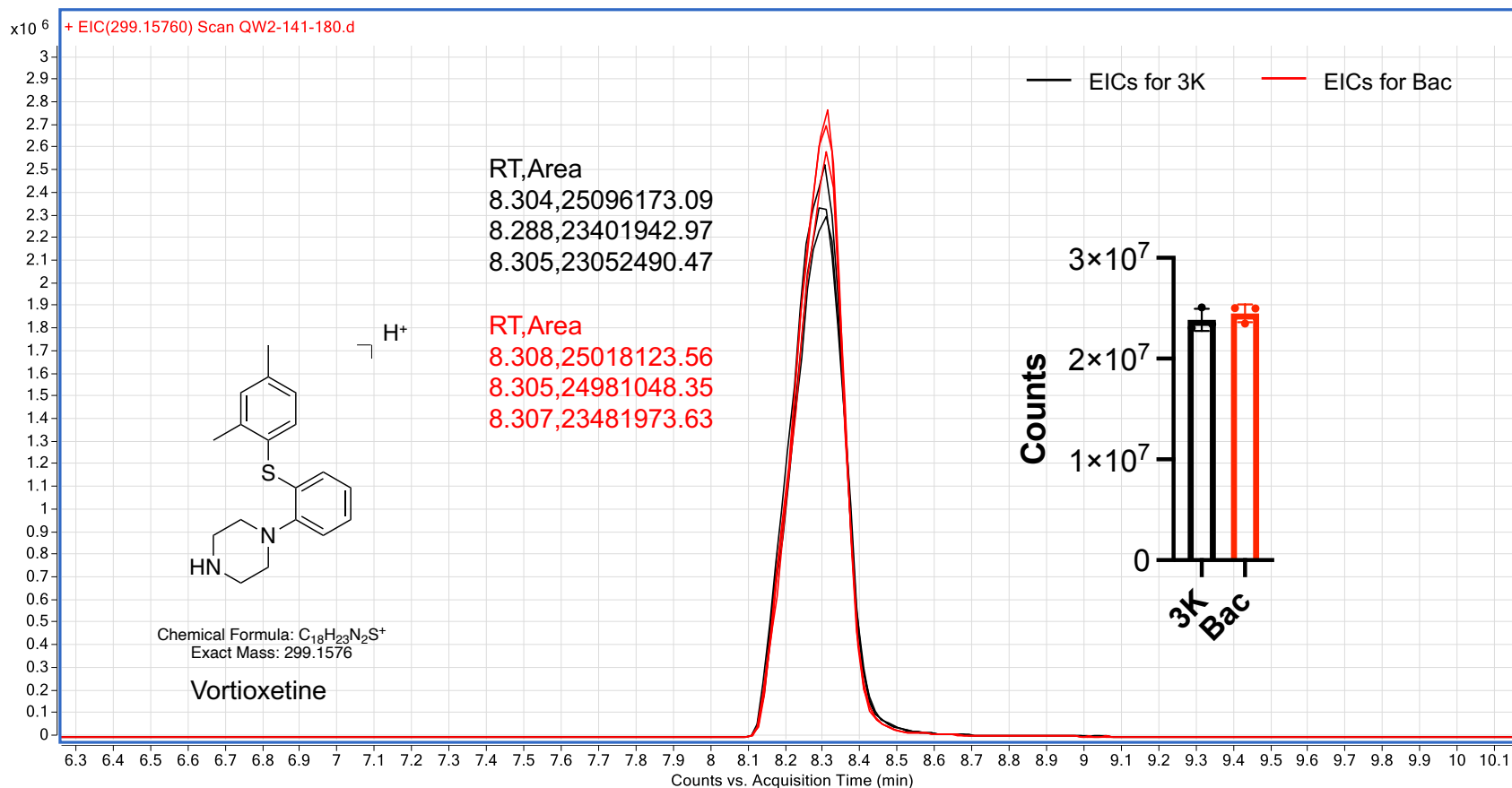


Fig. S174. Bac⁺ vs Bac⁻ (MWCO 3K) of silodosin (*m/z* 496.2418) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

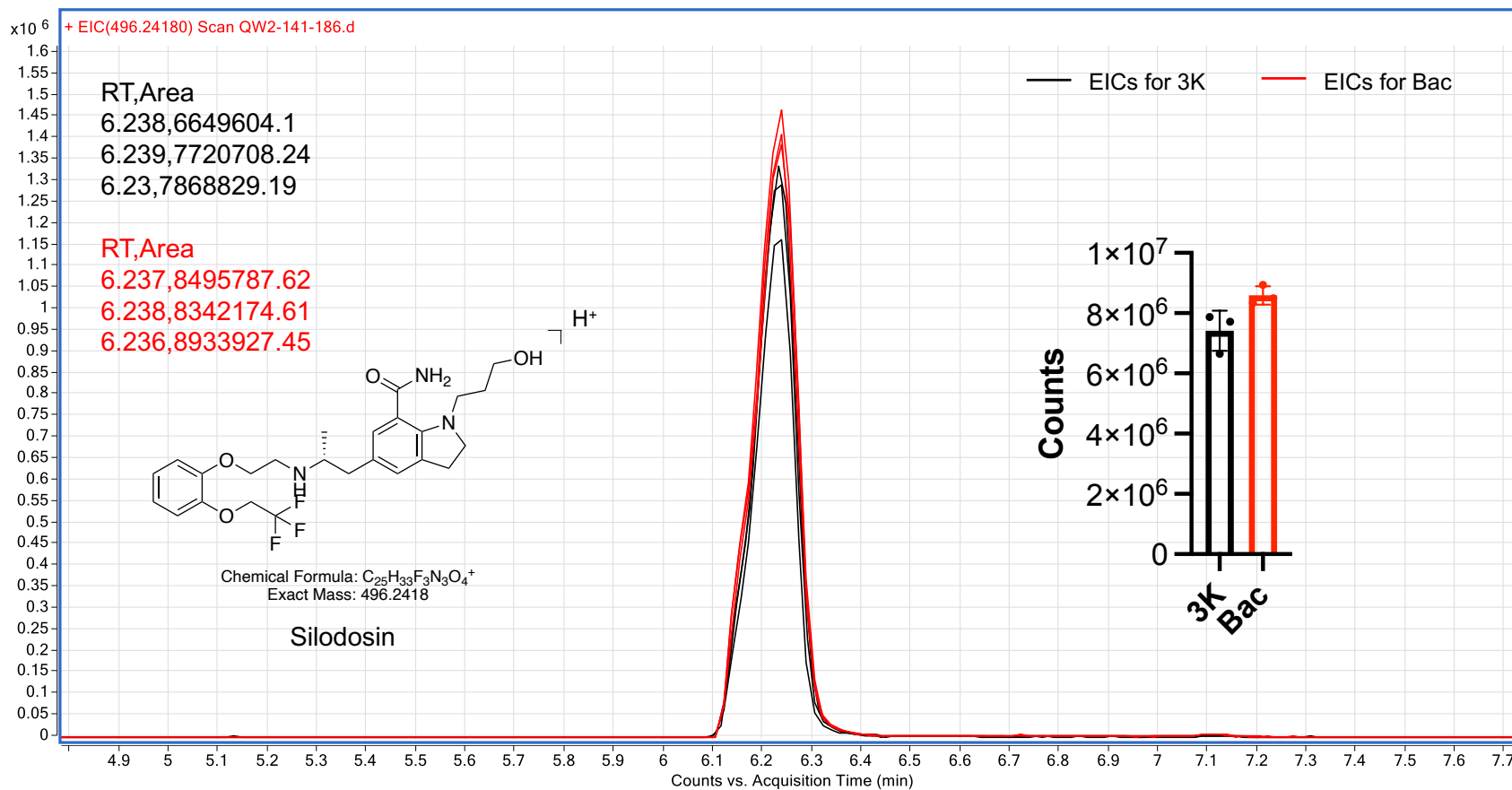


Fig. S175. Bac⁺ vs Bac⁻ (MWCO 3K) of pericyazine (*m/z* 366.1635) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

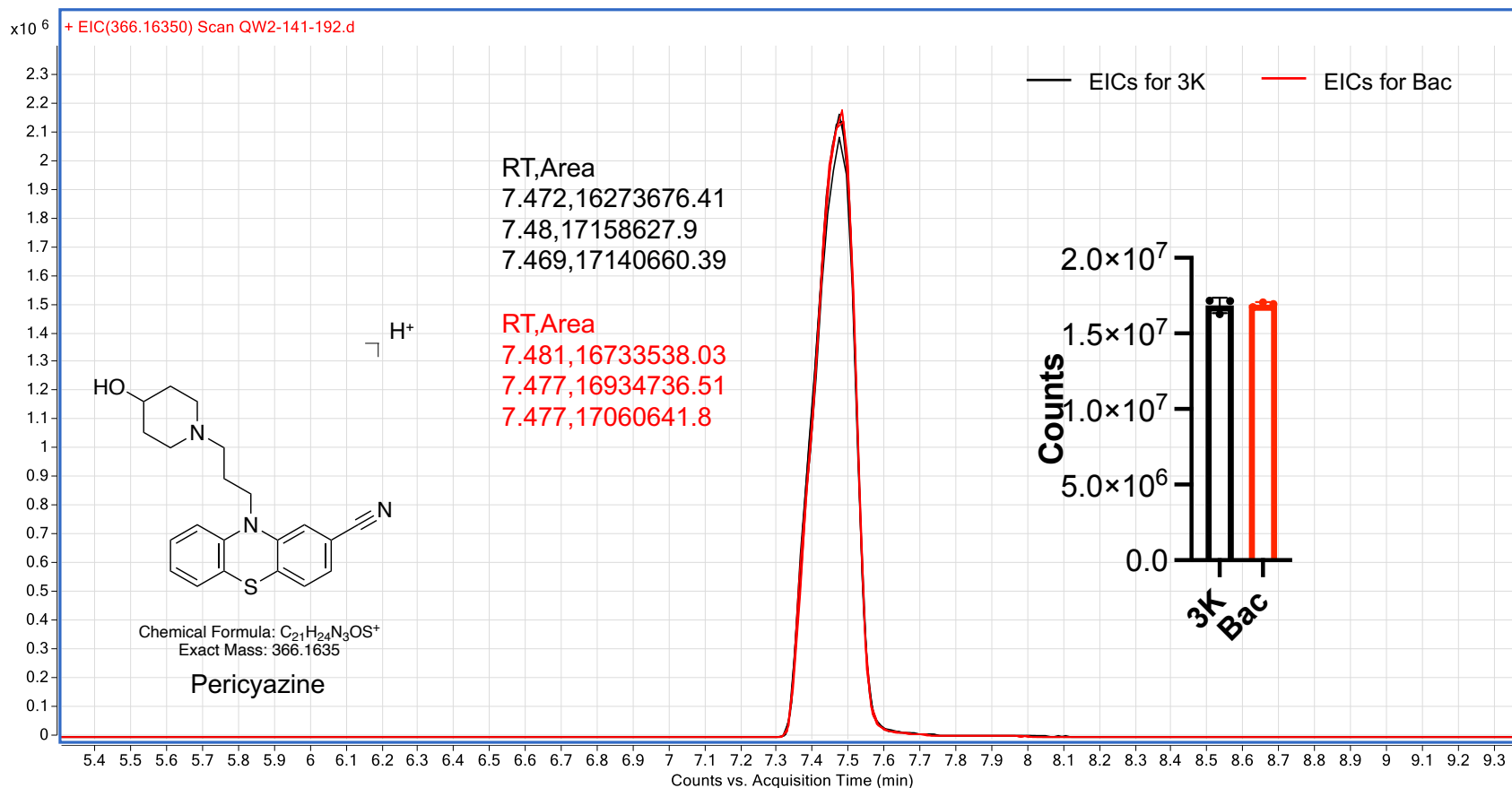


Fig. S176. Bac⁺ vs Bac⁻ (MWCO 3K) of olodanrigan (*m/z* 508.2118) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean $\pm$ s.d.

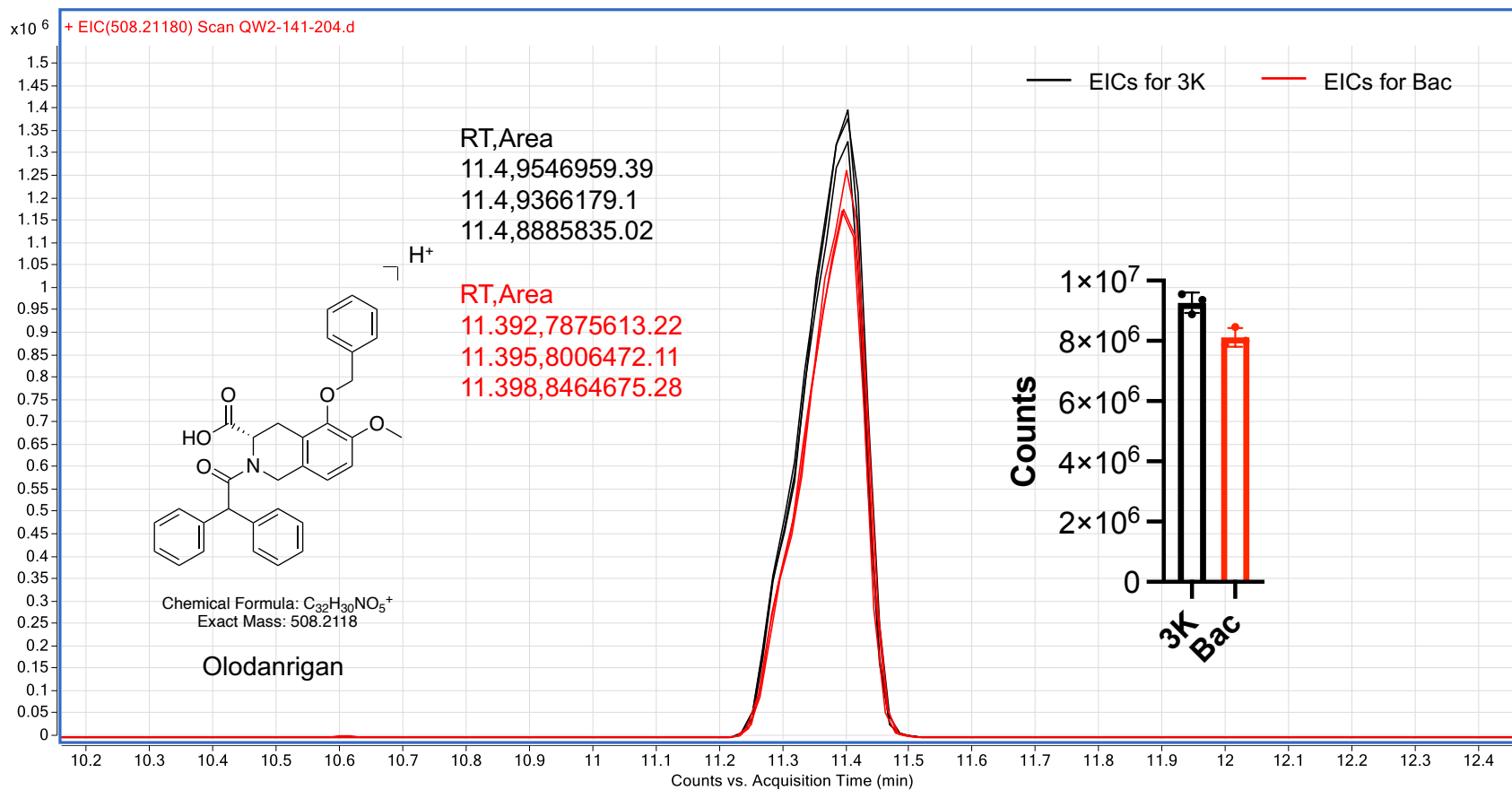


Fig. S177. Bac⁺ vs Bac⁻ (MWCO 3K) of carteolol (*m/z* 293.1860) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

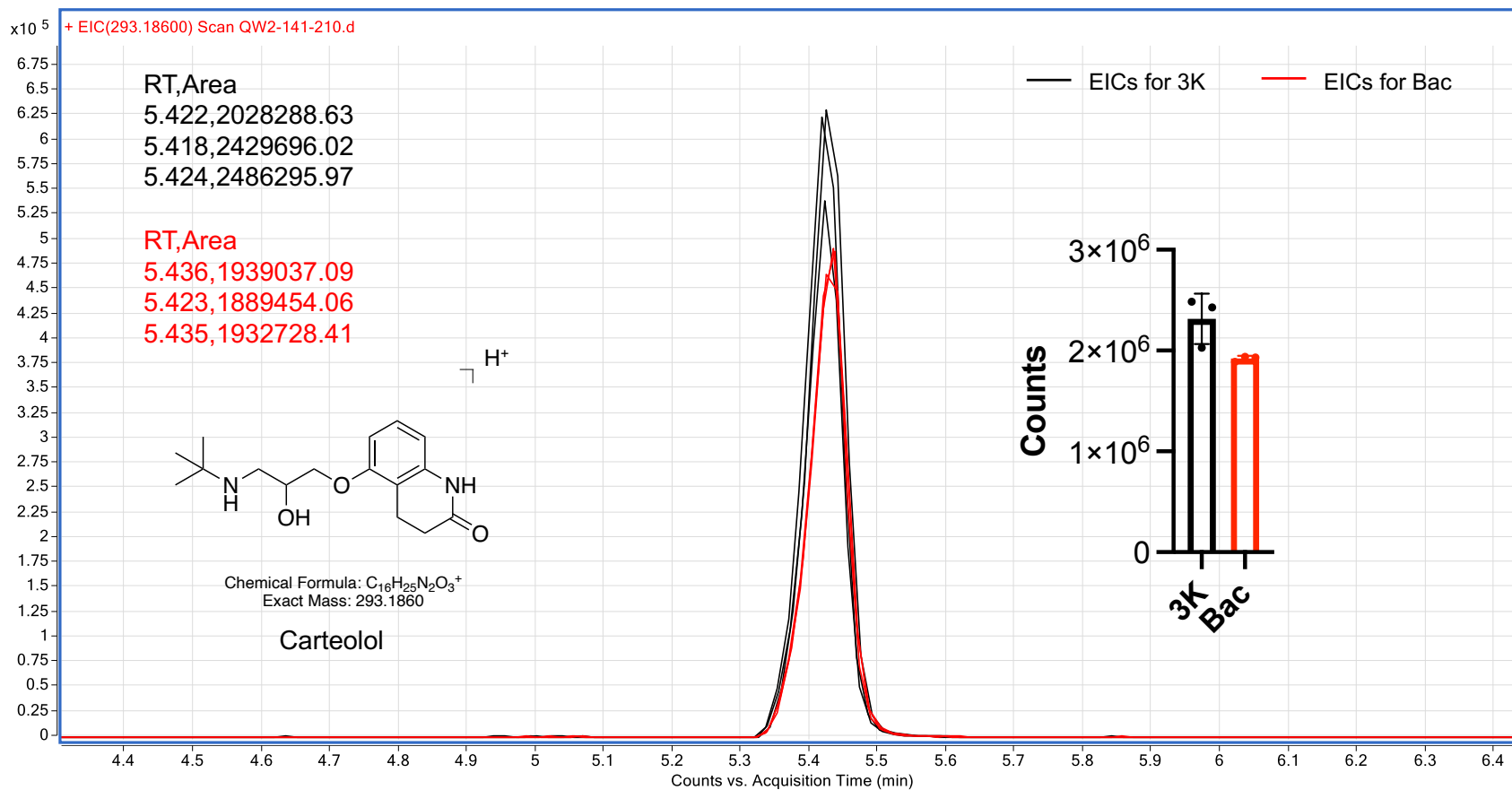


Fig. S178. Bac⁺ vs Bac⁻ (MWCO 3K) of cetirizine (*m/z* 389.1626) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

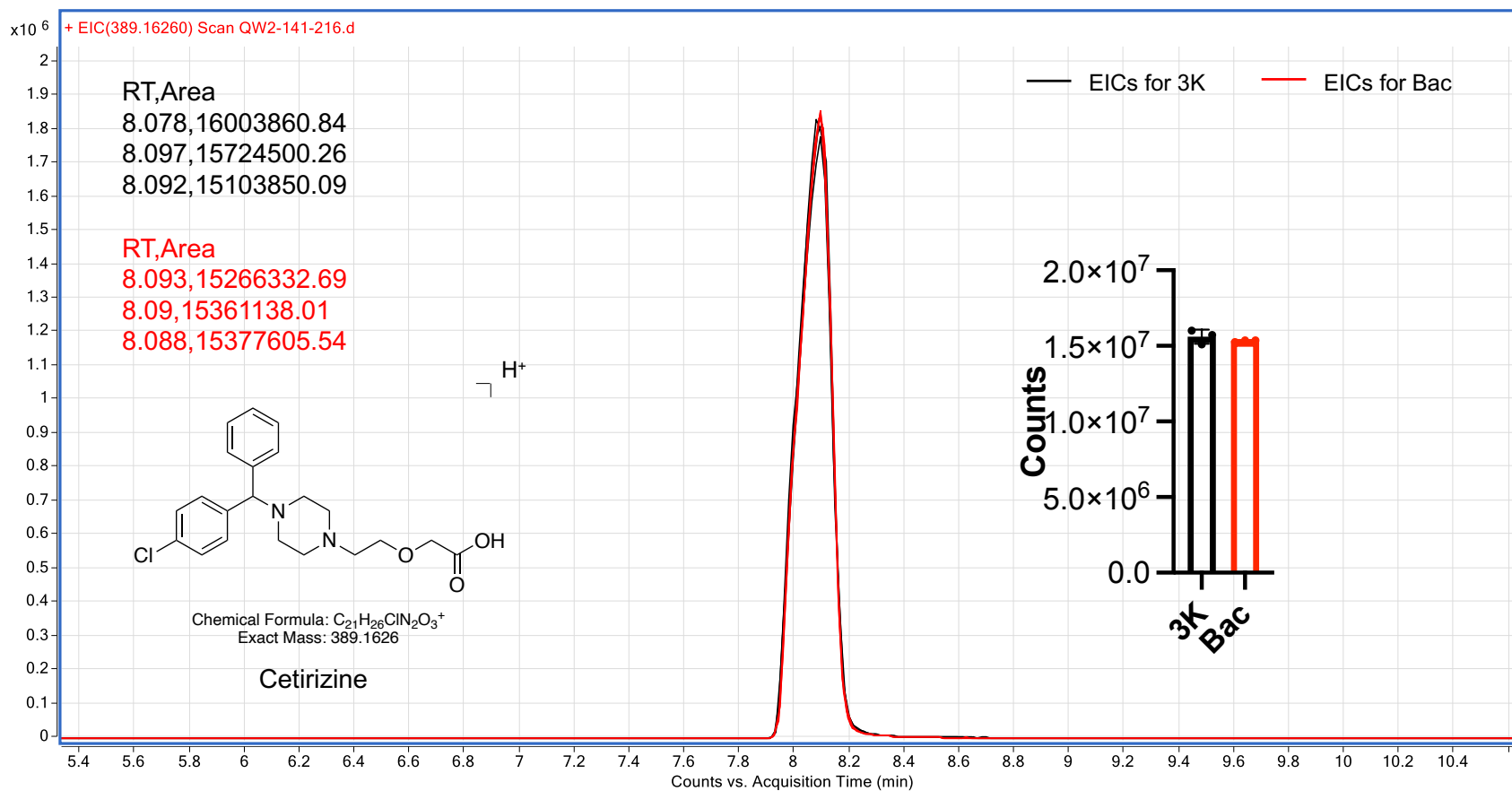


Fig. S179. Bac⁺ vs Bac⁻ (MWCO 3K) of ticagrelor (*m/z* 523.1934) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

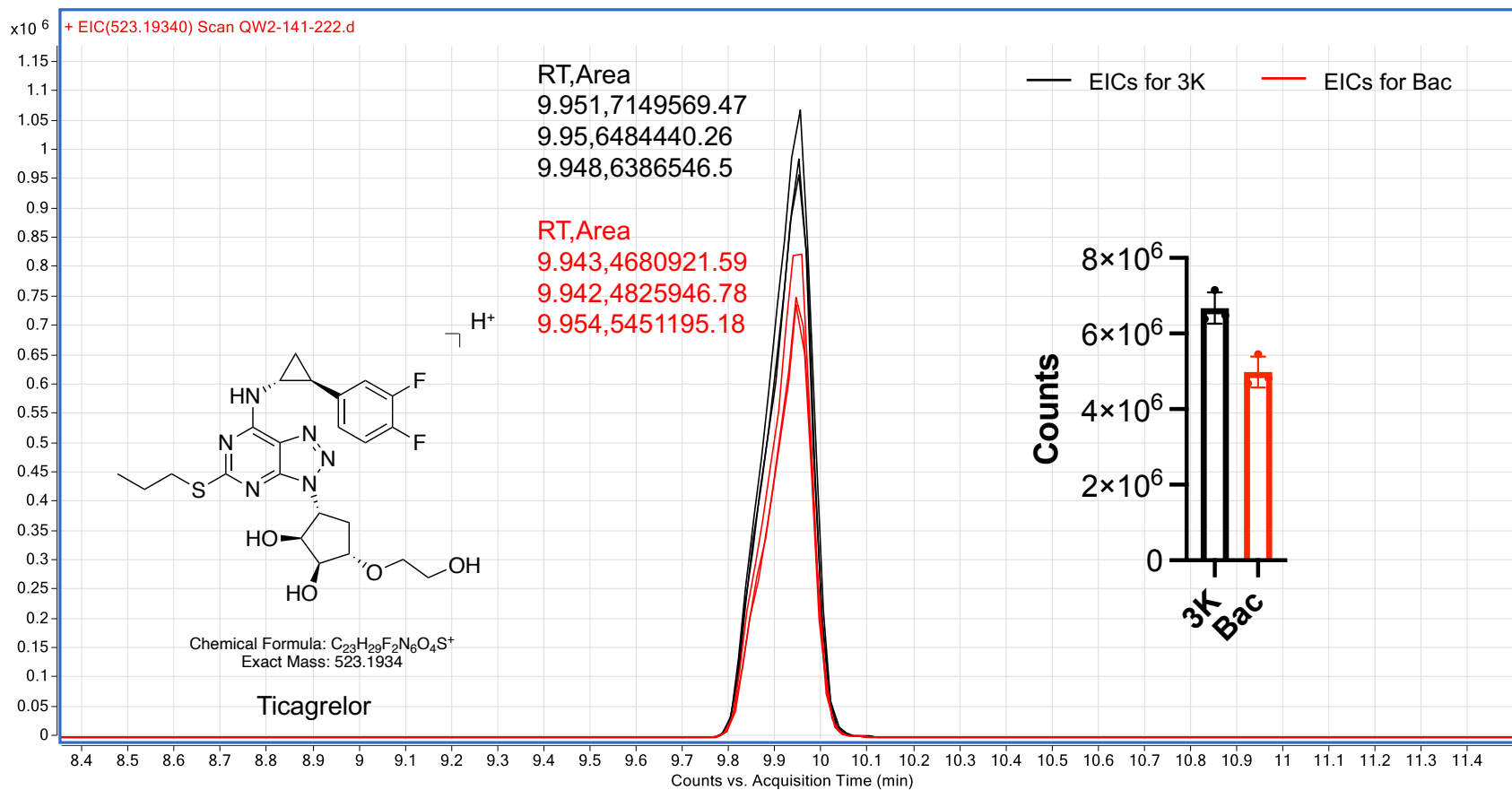


Fig. S180. Bac⁺ vs Bac⁻ (MWCO 3K) of rauwolscine (*m/z* 355.2016) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

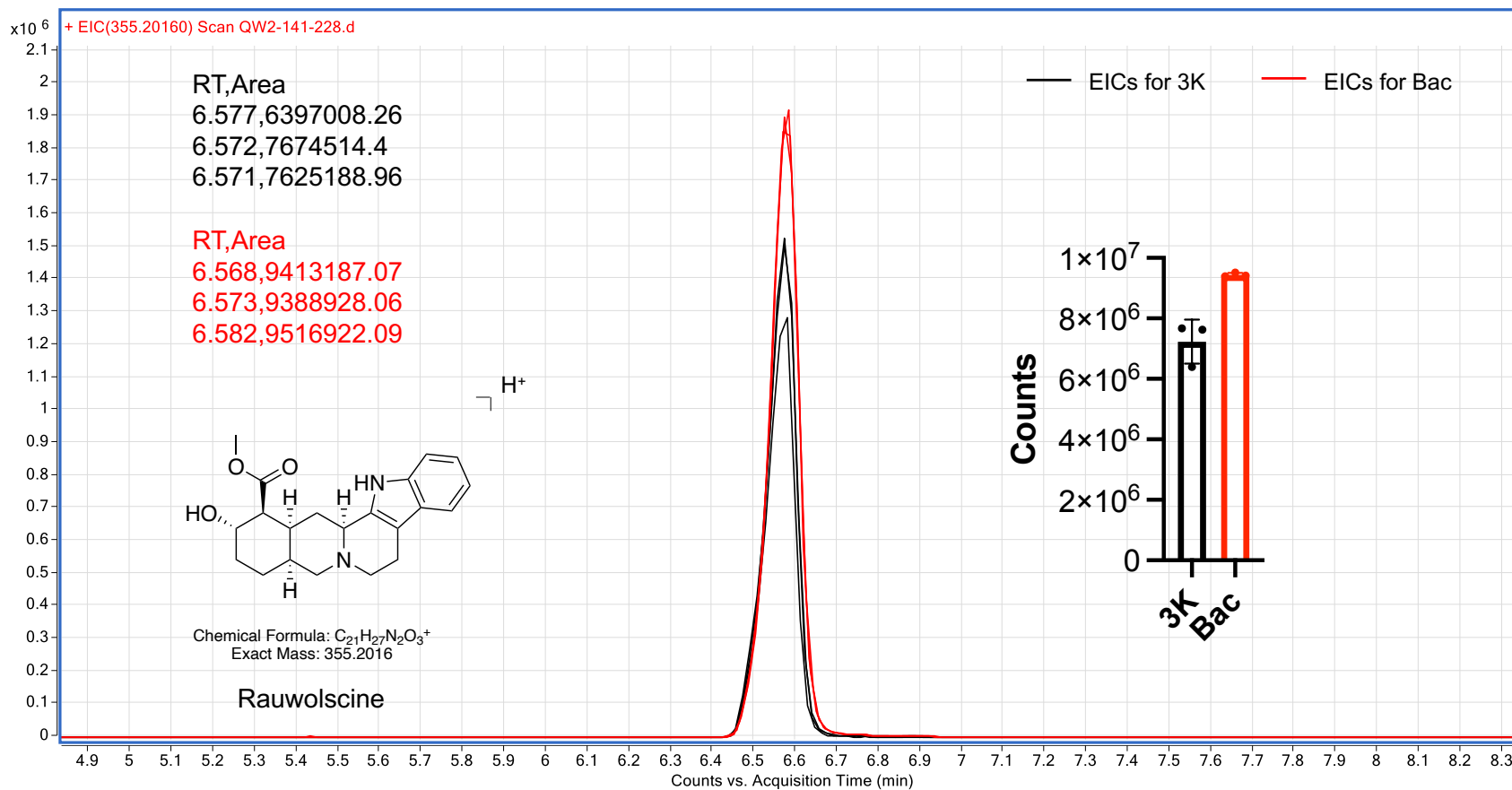


Fig. S181. Bac⁺ vs Bac⁻ (MWCO 3K) of azilsartan medoxomil (*m/z* 569.1667) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

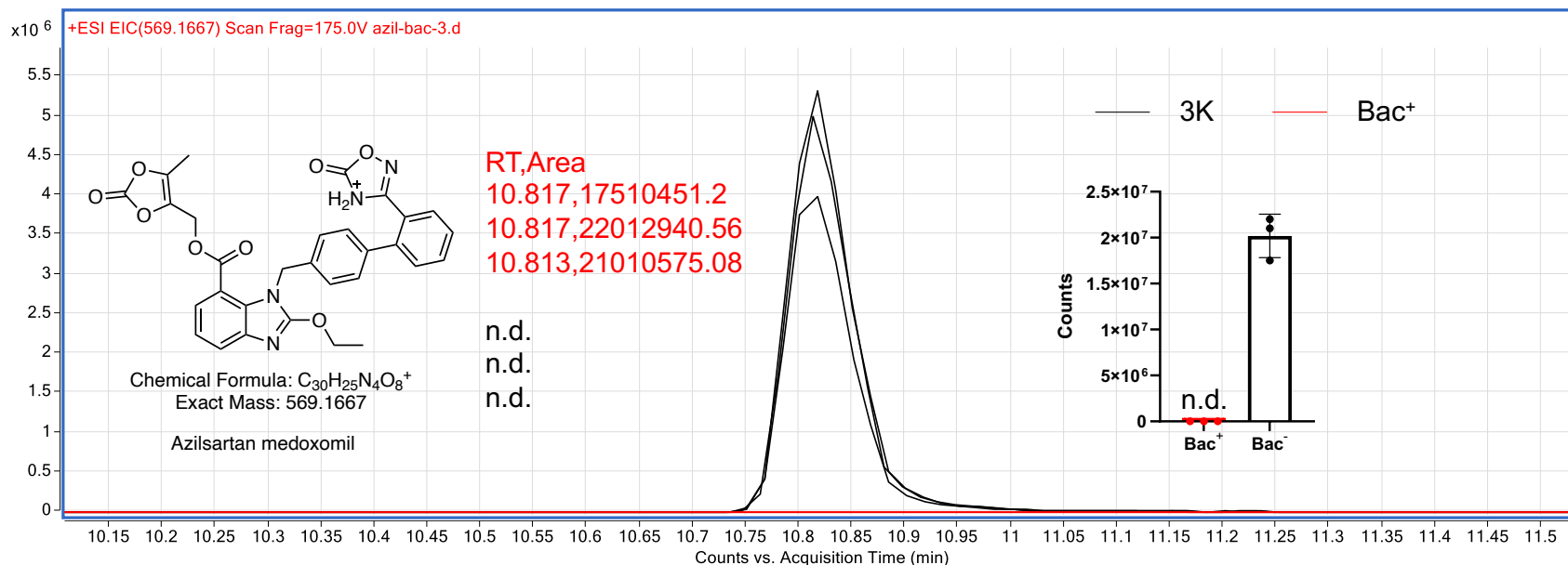


Fig. S182. Bac⁺ vs Bac⁻ (MWCO 3K) of chlorpheniramine (*m/z* 275.1310) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

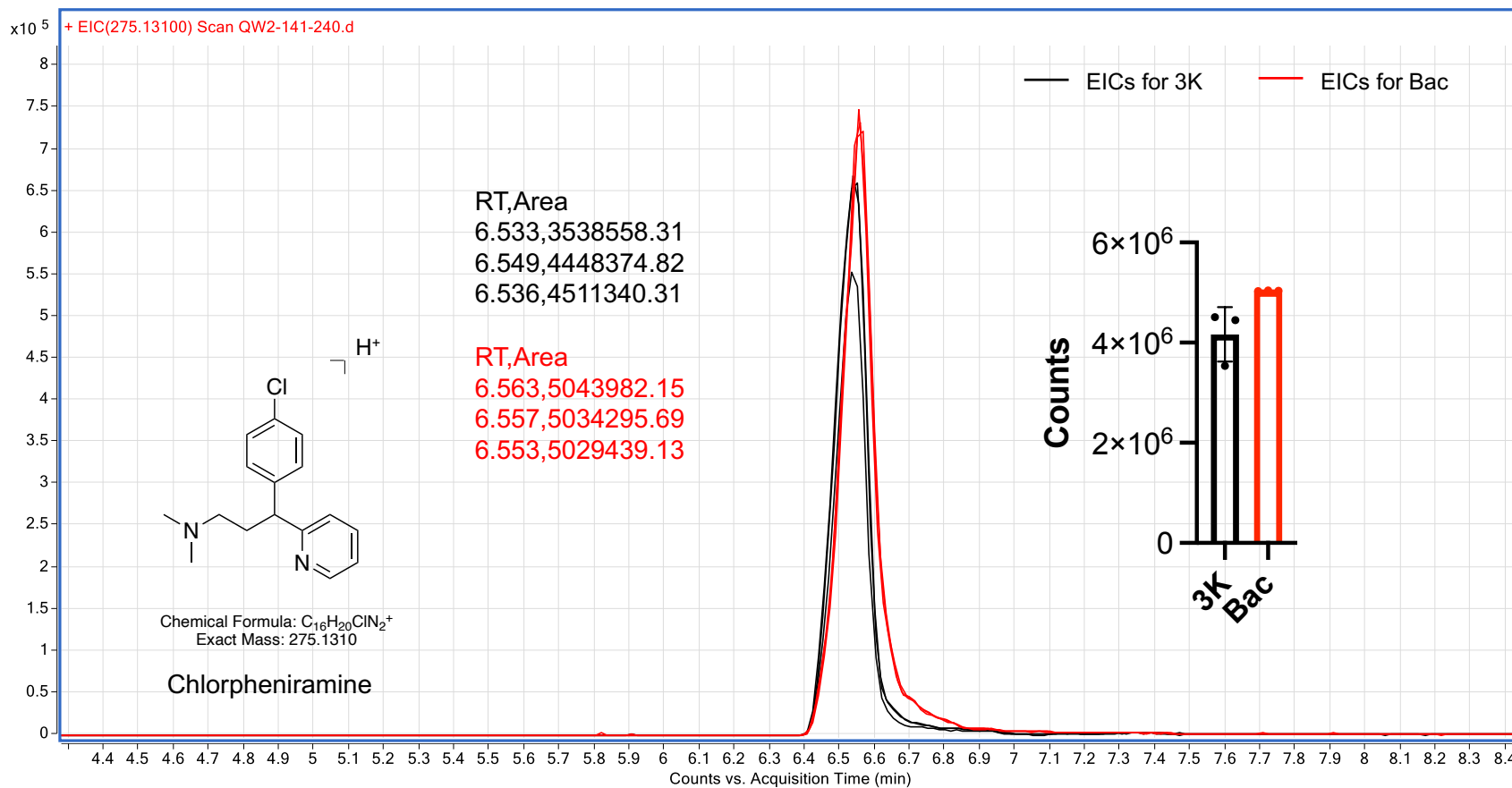


Fig. S183. Bac⁺ vs Bac⁻ (MWCO 3K) of latrepirdine (*m/z* 320.2121) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

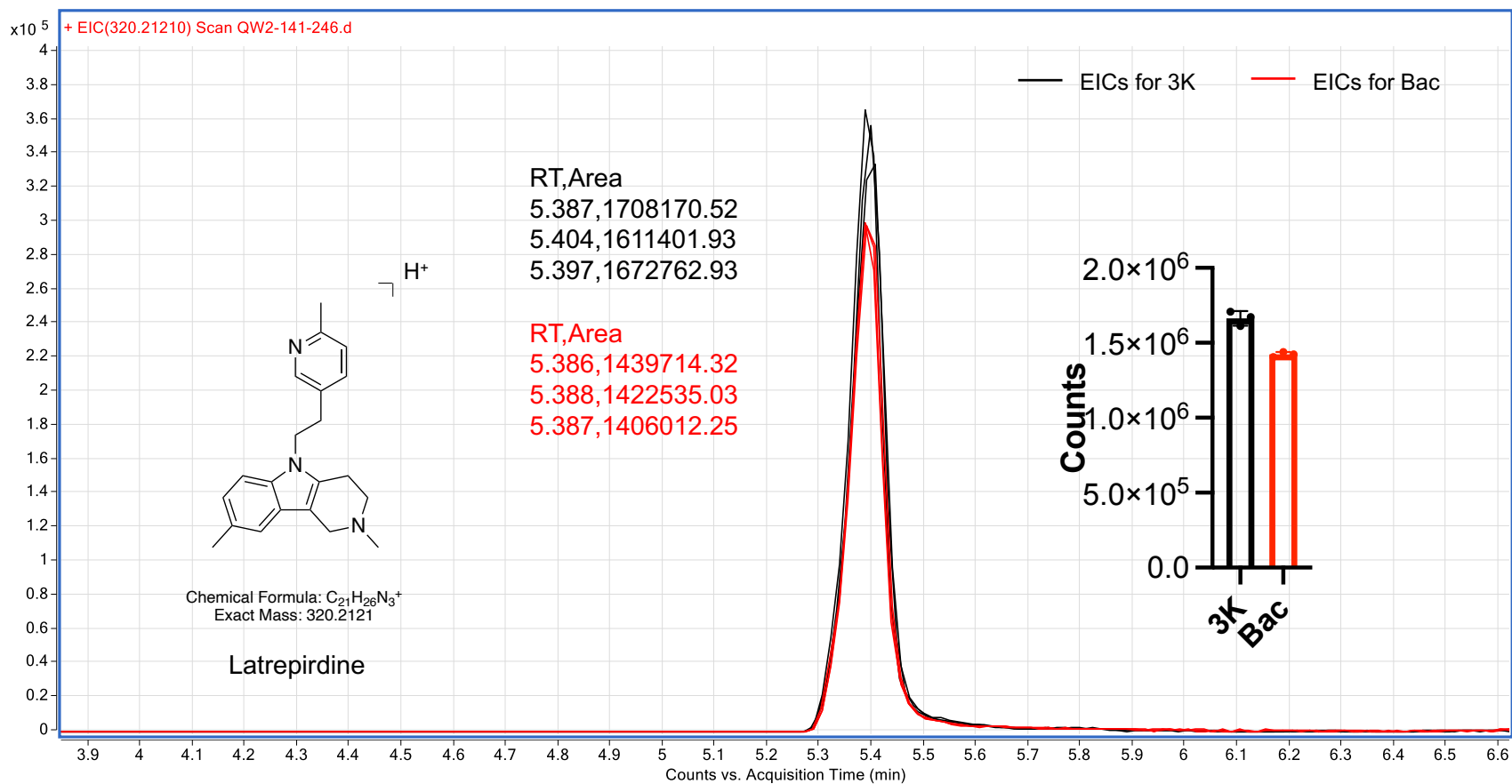


Fig. S184. Bac⁺ vs Bac⁻ (MWCO 3K) of tasimelteon (*m/z* 246.1489) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

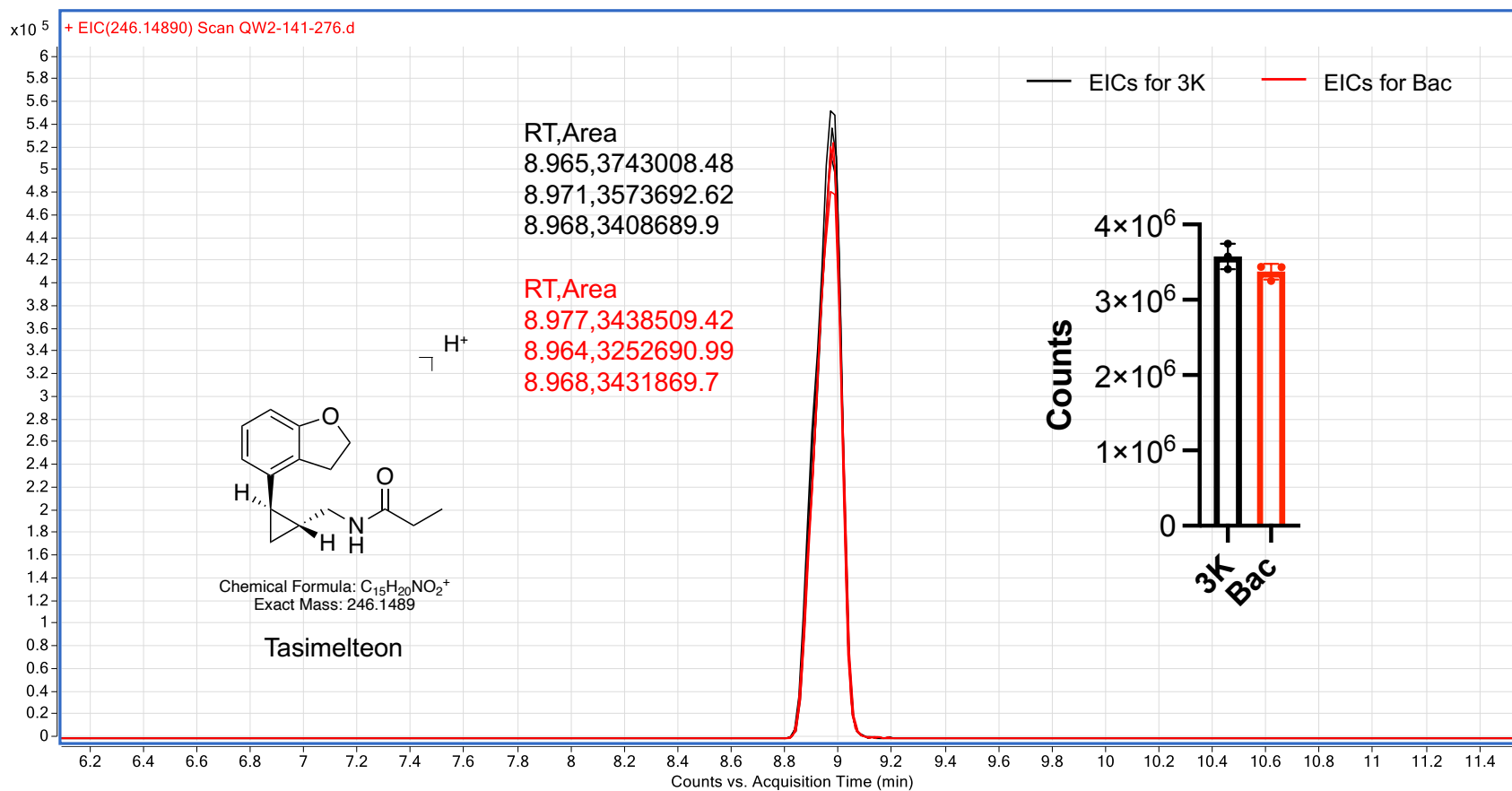


Fig. S185. Bac⁺ vs Bac⁻ (MWCO 3K) of guanfacine (*m/z* 246.0195) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

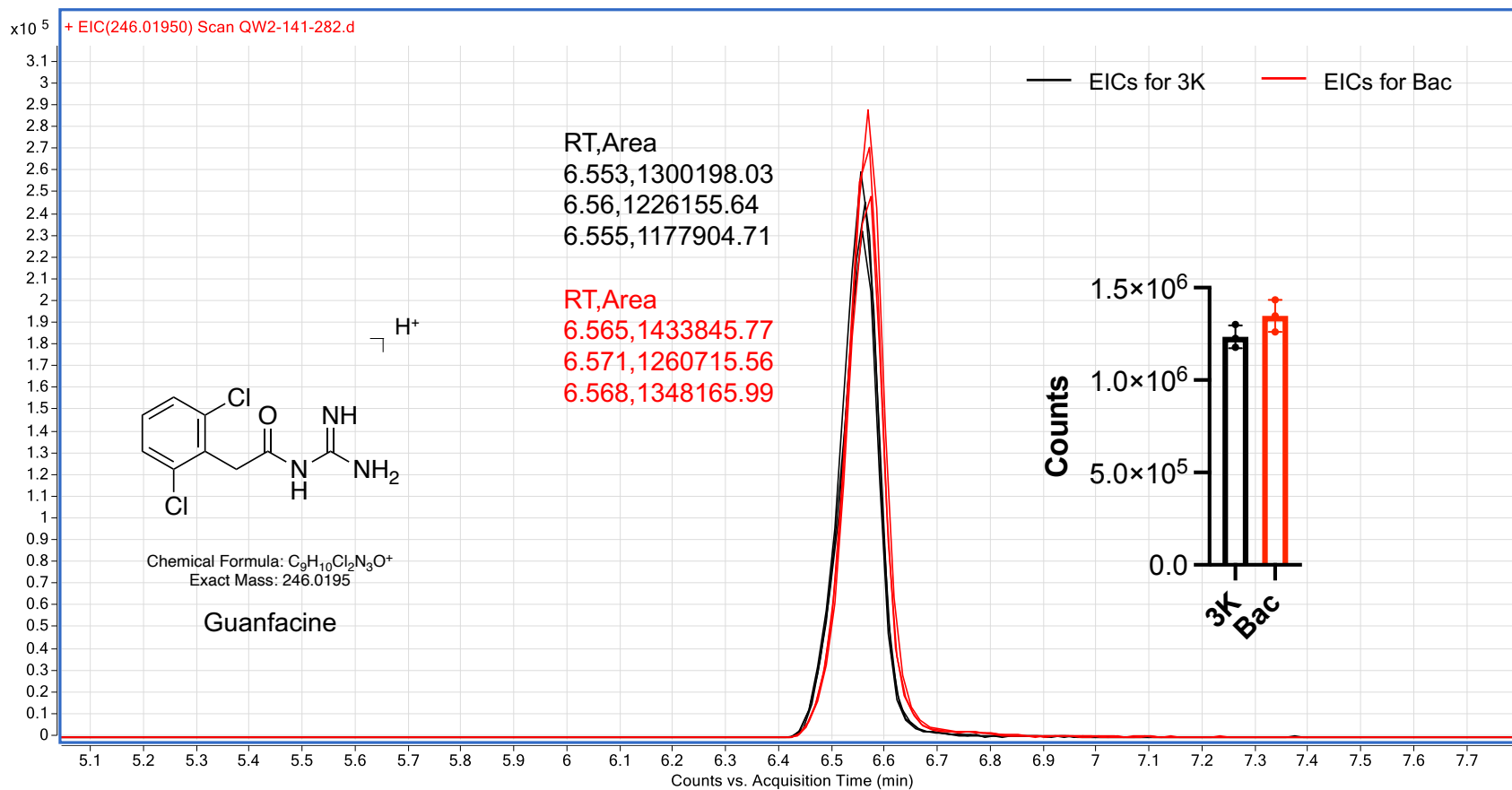


Fig. S186. Bac⁺ vs Bac⁻ (MWCO 3K) of acebutolol (*m/z* 337.2122) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean $\pm$ s.d.

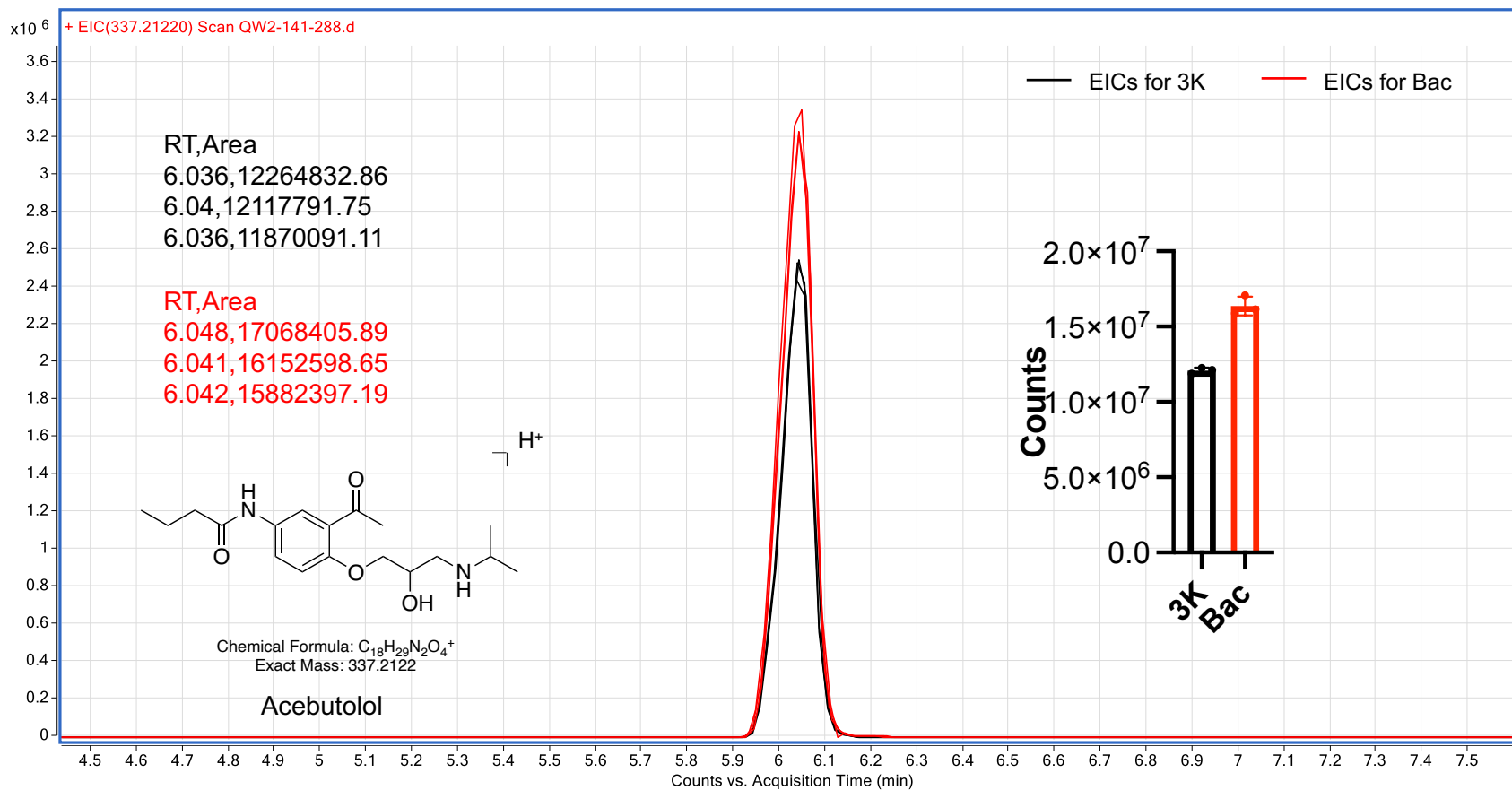


Fig. S187. Bac⁺ vs Bac⁻ (MWCO 3K) of darusentan (*m/z* 411.1551) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

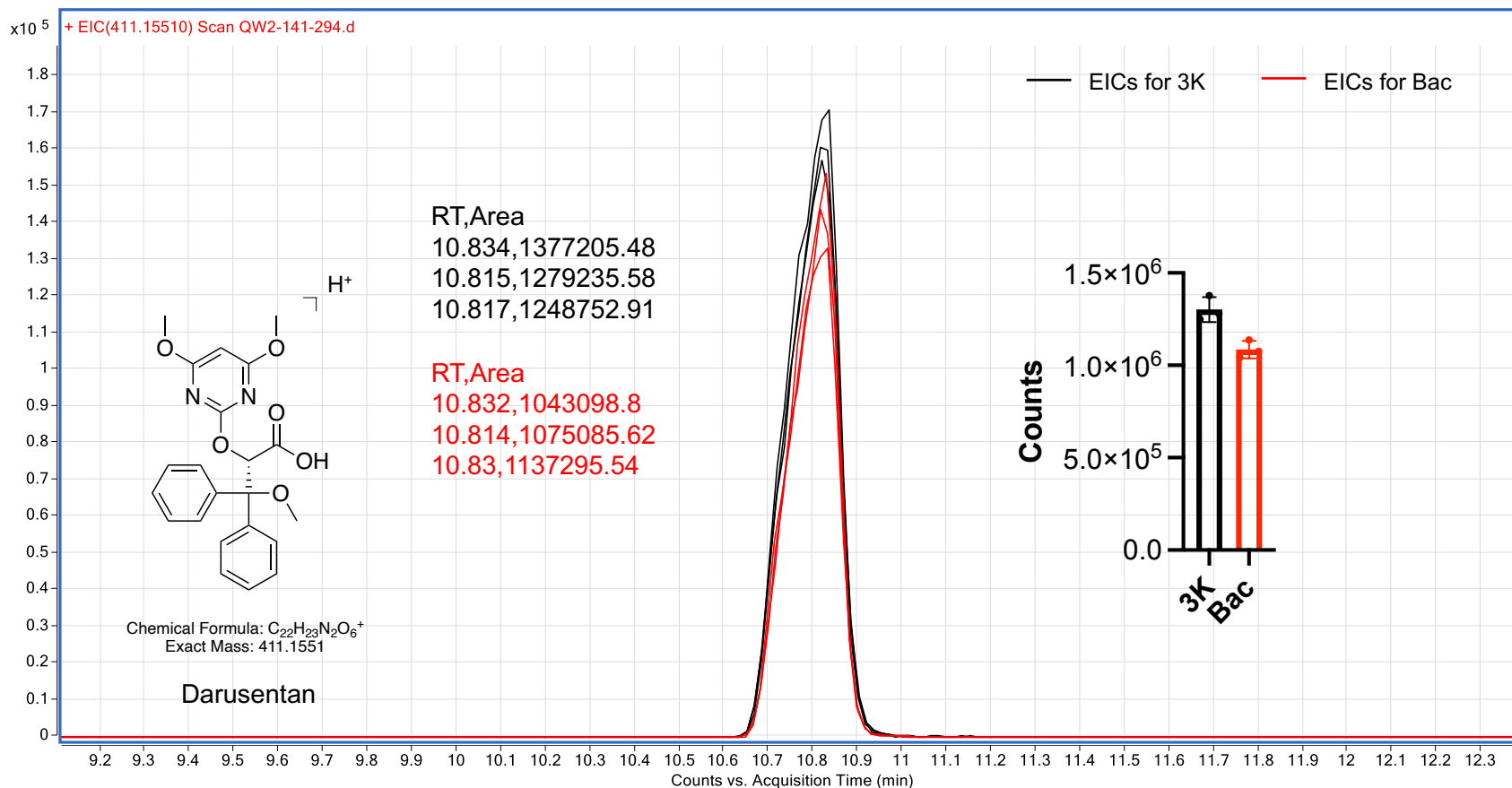


Fig. S188. Bac⁺ vs Bac⁻ (MWCO 3K) of asenapine (*m/z* 286.0993) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

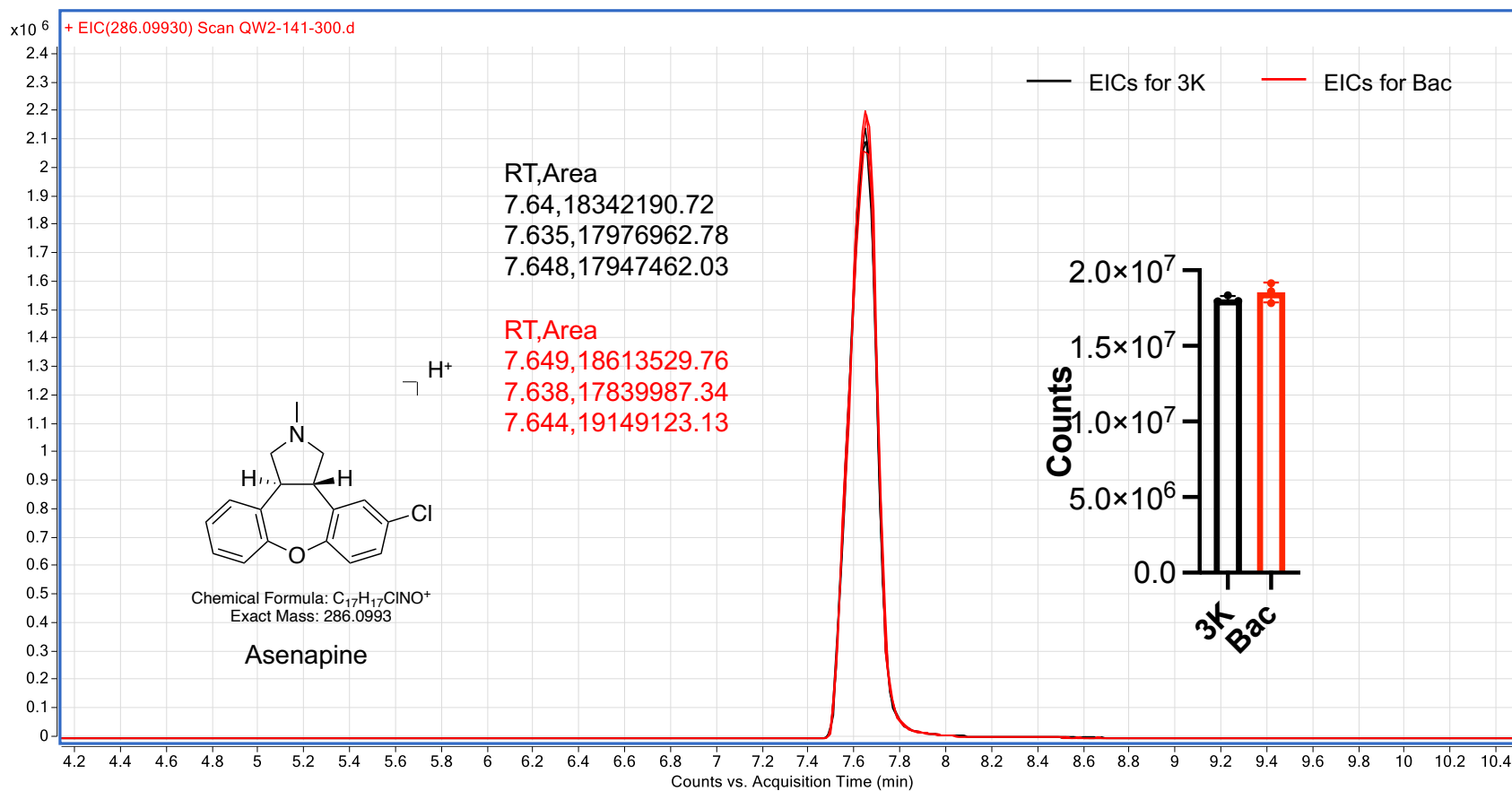


Fig. S189. Bac⁺ vs Bac⁻ (MWCO 3K) of intepirdine (*m/z* 354.1271) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean $\pm$ s.d.

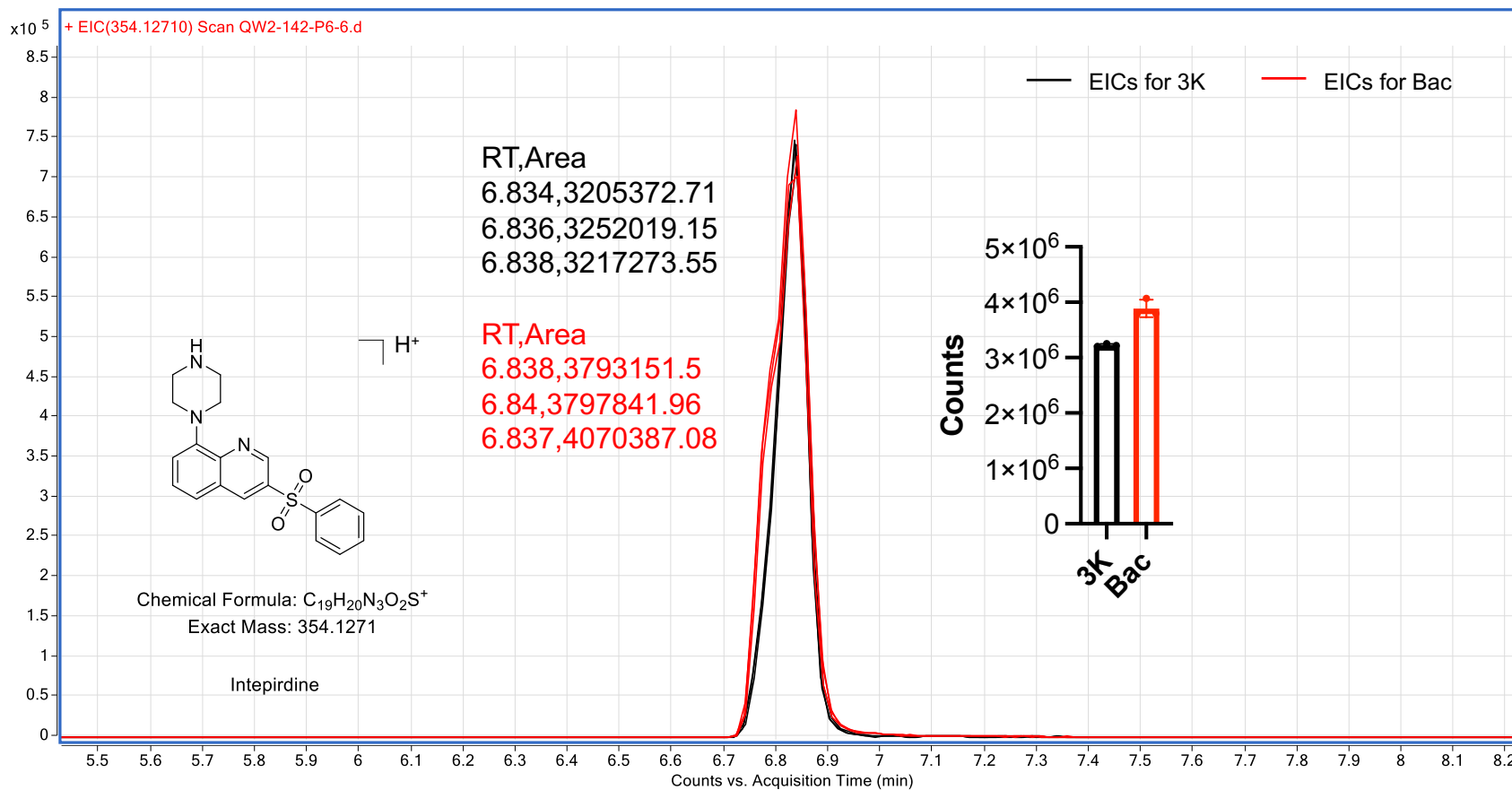


Fig. S190. Bac⁺ vs Bac⁻ (MWCO 3K) of reparixin (*m/z* 284.1315) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

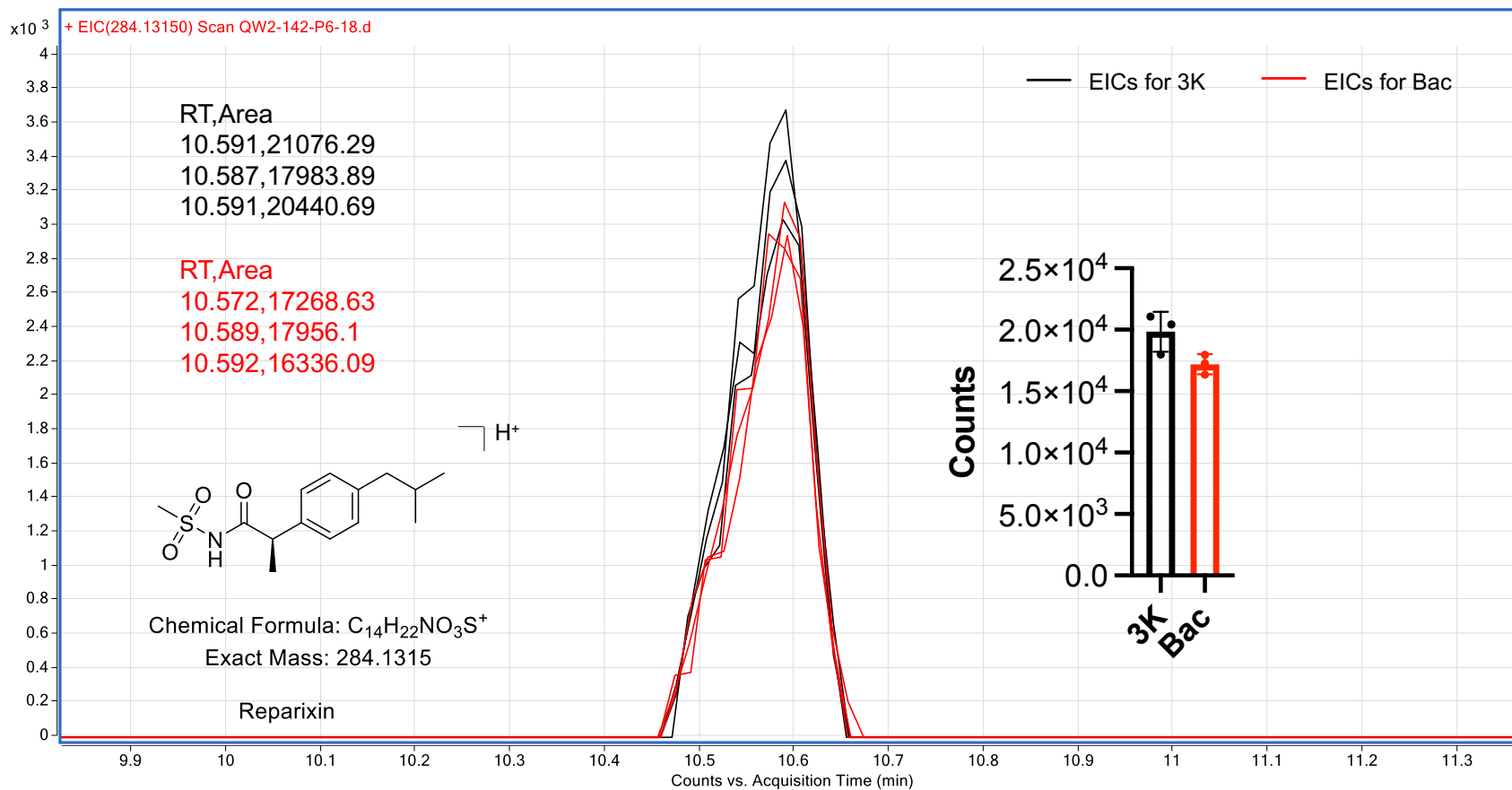


Fig. S191. Bac⁺ vs Bac⁻ (MWCO 3K) of fevipiprant (*m/z* 427.0934) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

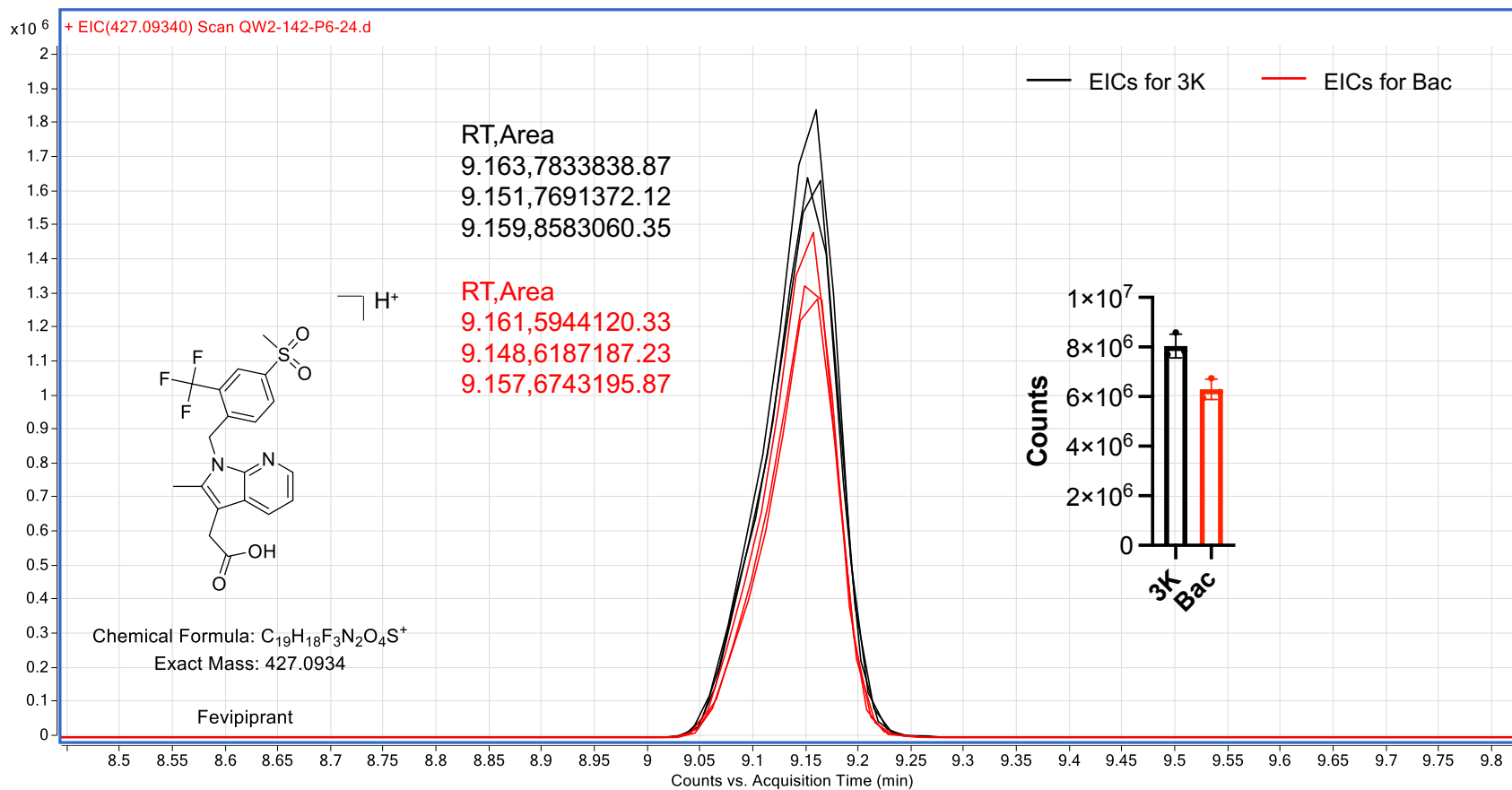


Fig. S192. Bac⁺ vs Bac⁻ (MWCO 3K) of ibutamoren (*m/z* 529.2479) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

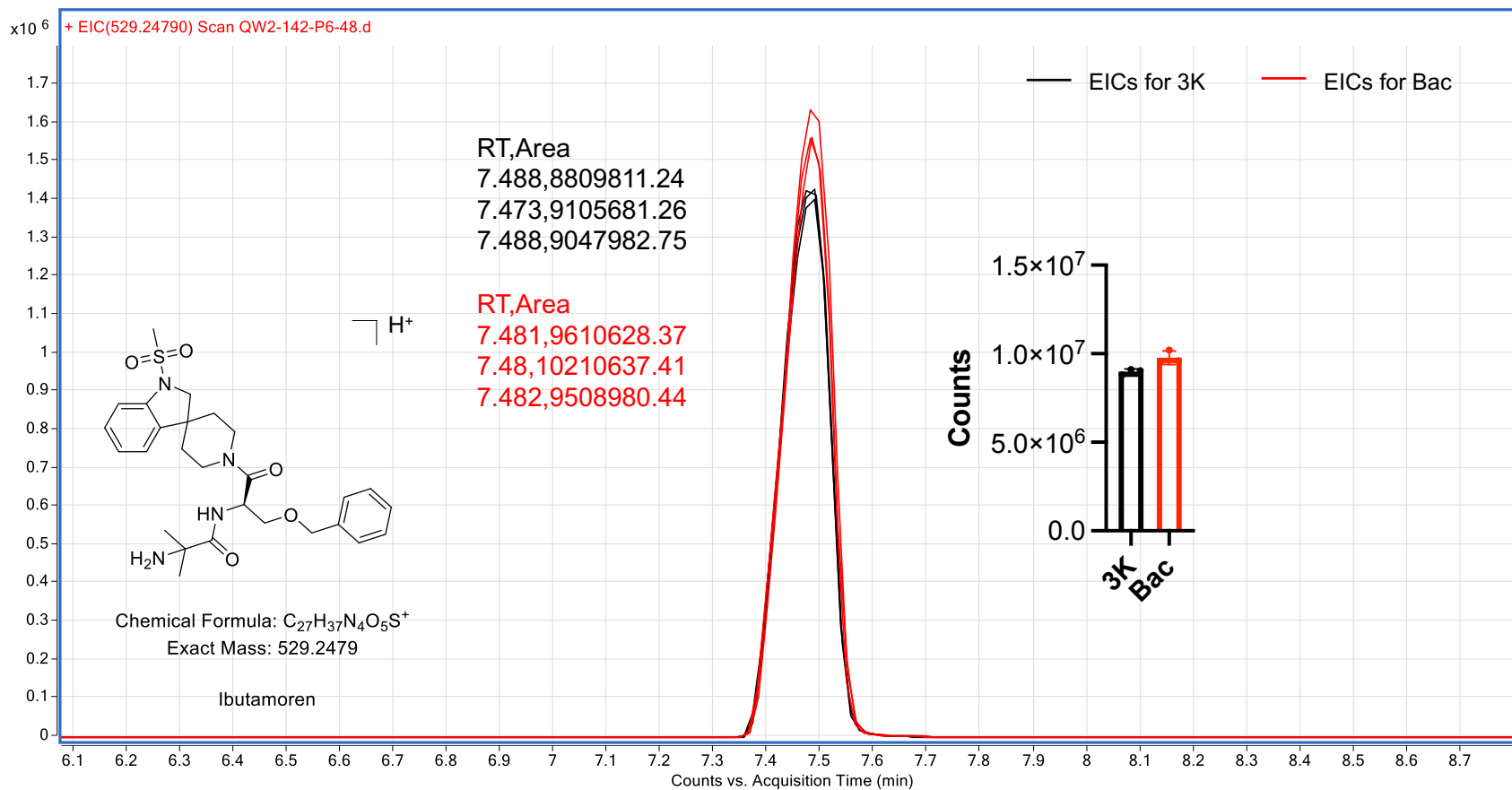


Fig. S193. Bac⁺ vs Bac⁻ (MWCO 3K) of rolapitant (*m/z* 501.1971) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

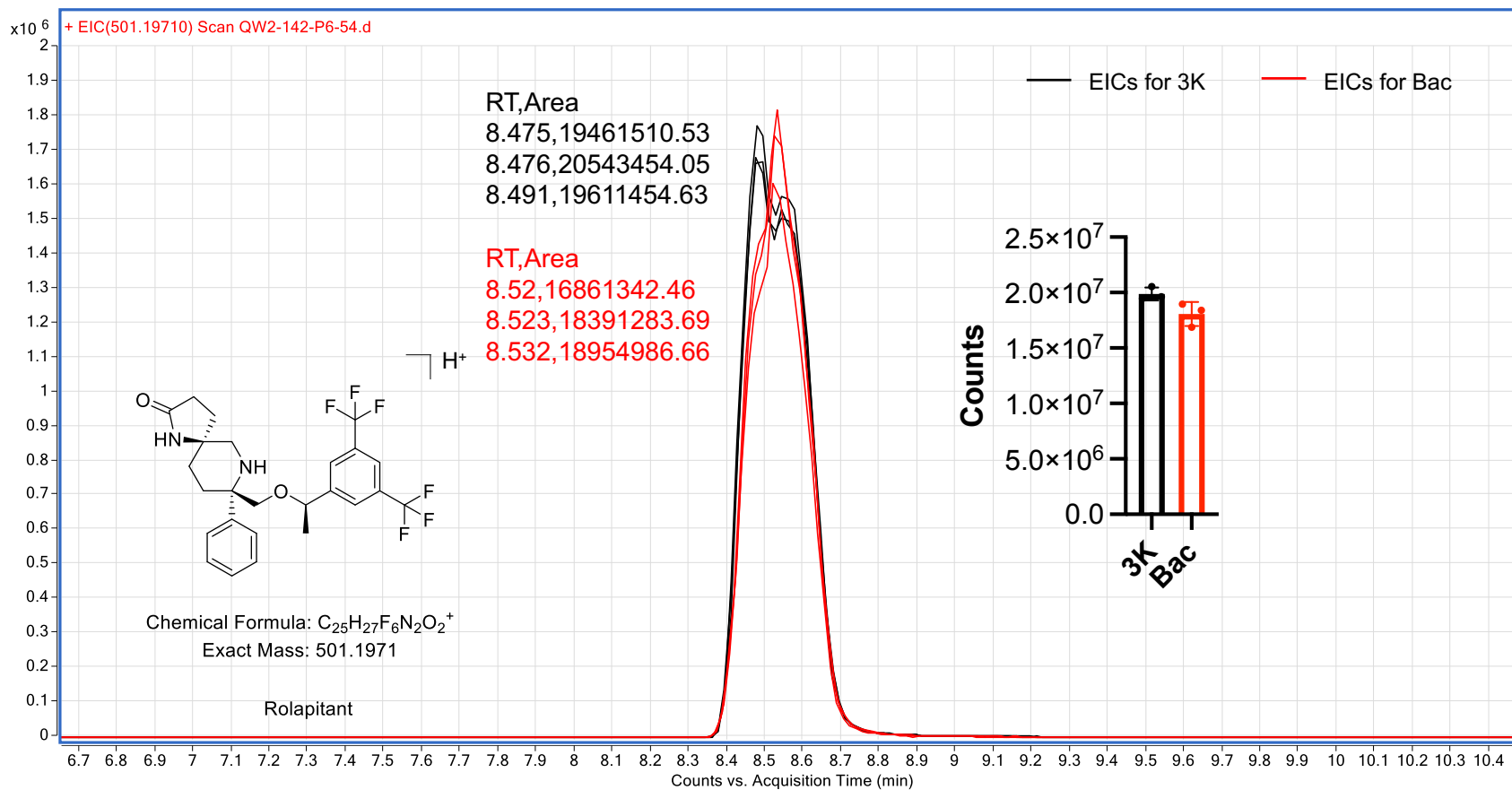


Fig. S194. Bac⁺ vs Bac⁻ (MWCO 3K) of Olmesartan medoxomil (*m/z* 559.2300) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

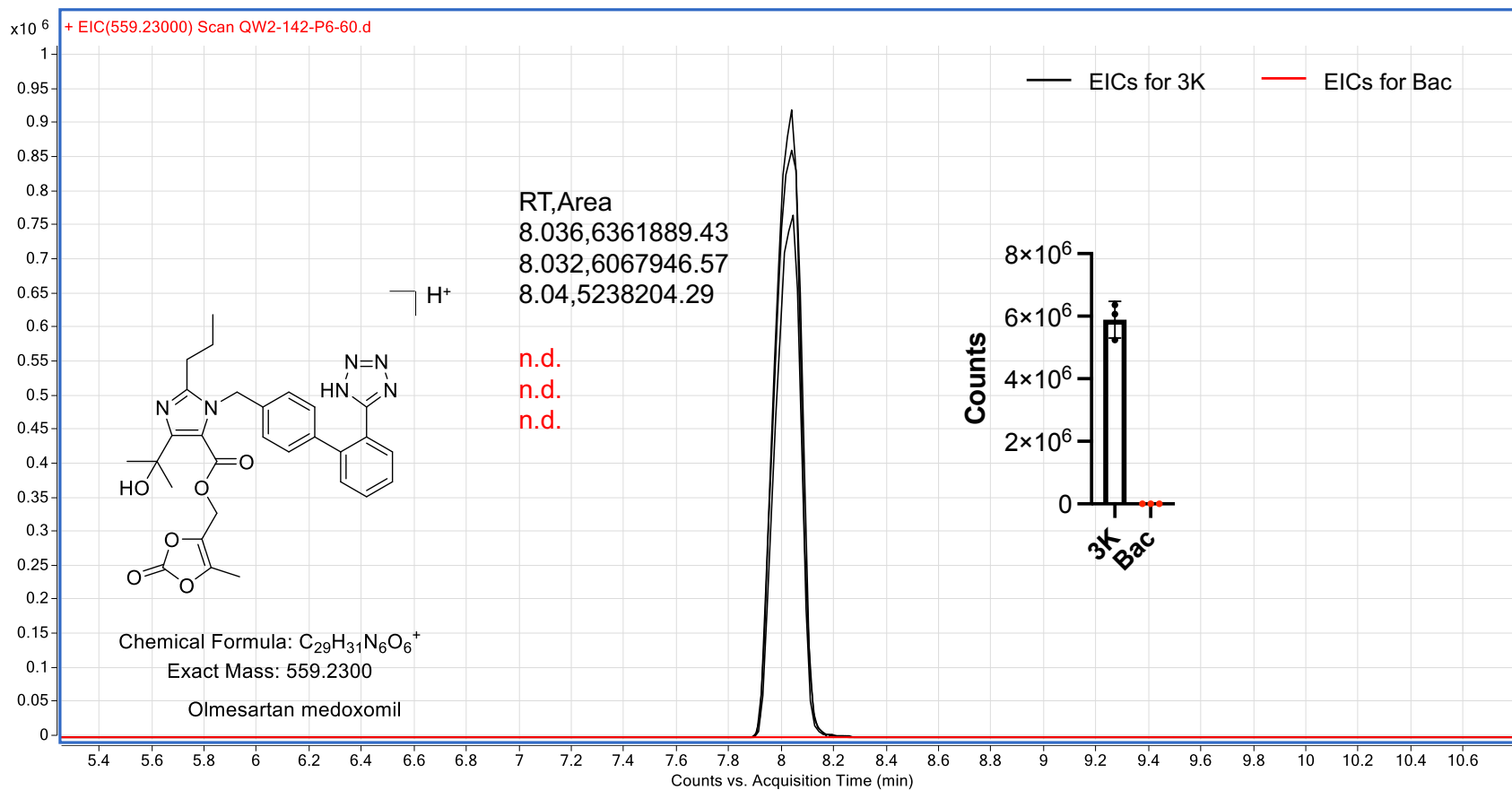


Fig. S195. Bac⁺ vs Bac⁻ (MWCO 3K) of sarpogrelate (*m/z* 430.2224) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

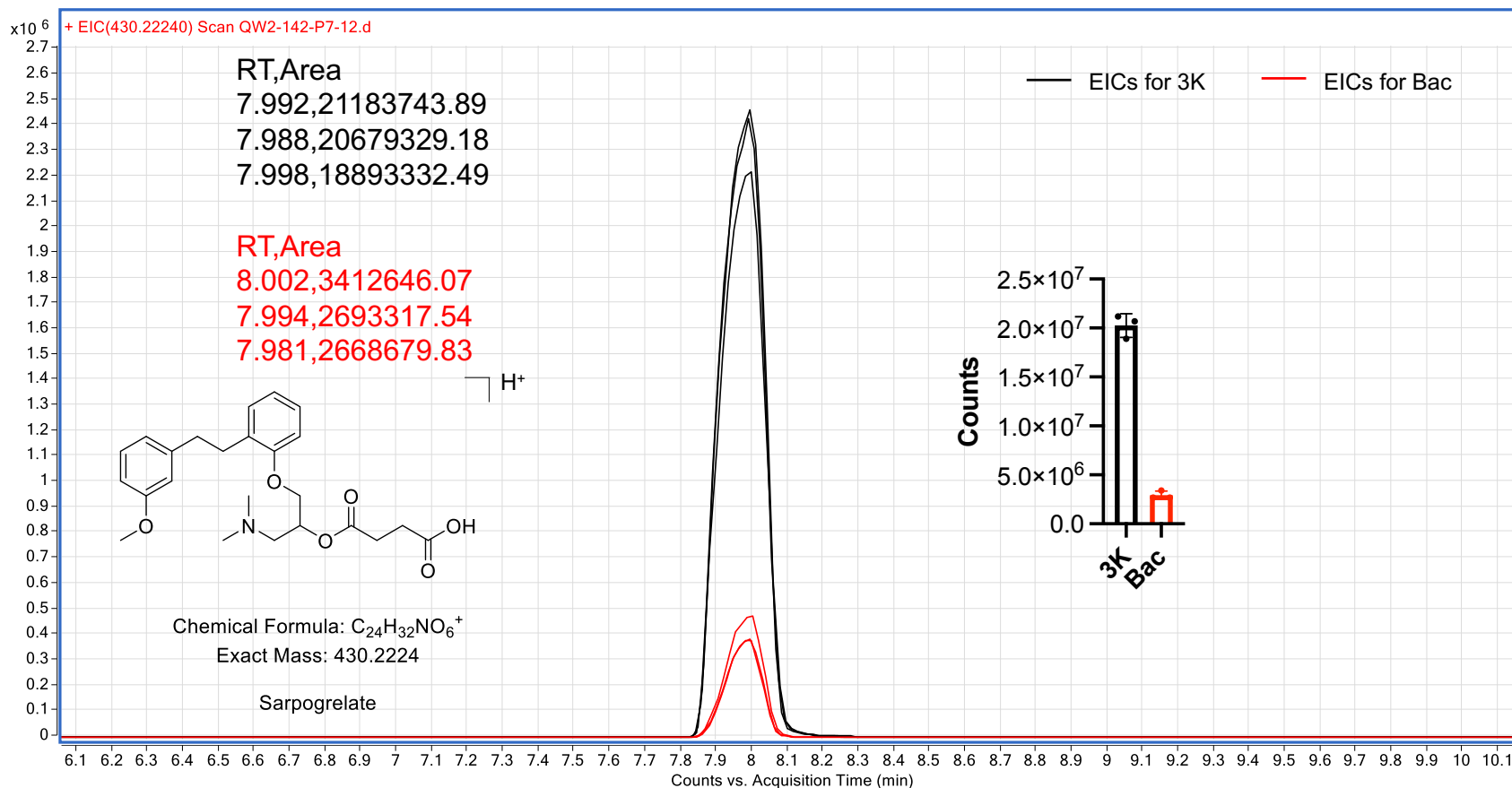


Fig. S196. Bac⁺ vs Bac⁻ (MWCO 3K) of melatonin (*m/z* 233.1285) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

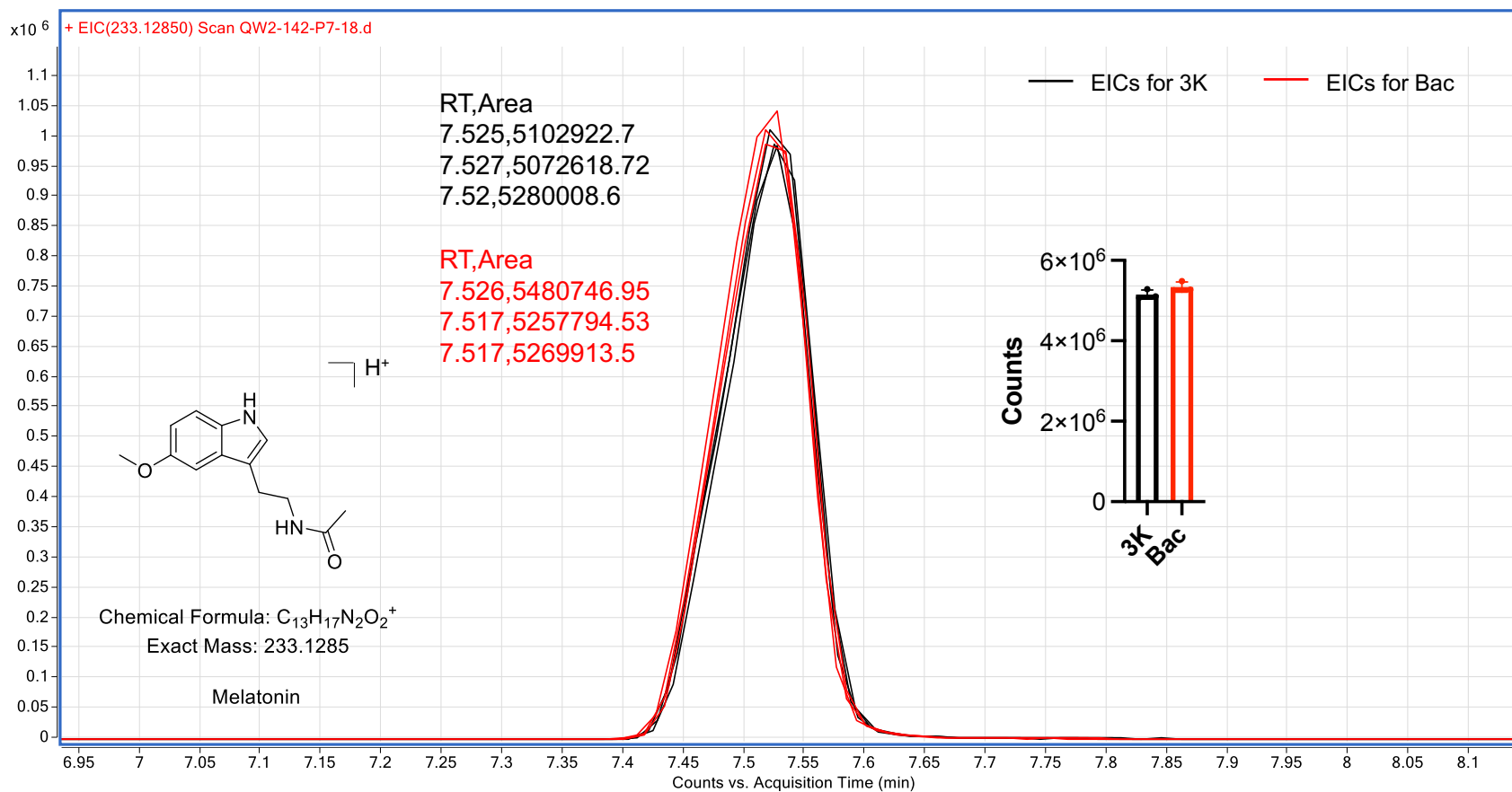


Fig. S197. Bac⁺ vs Bac⁻ (MWCO 3K) of trimebutine (*m/z* 388.2118) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

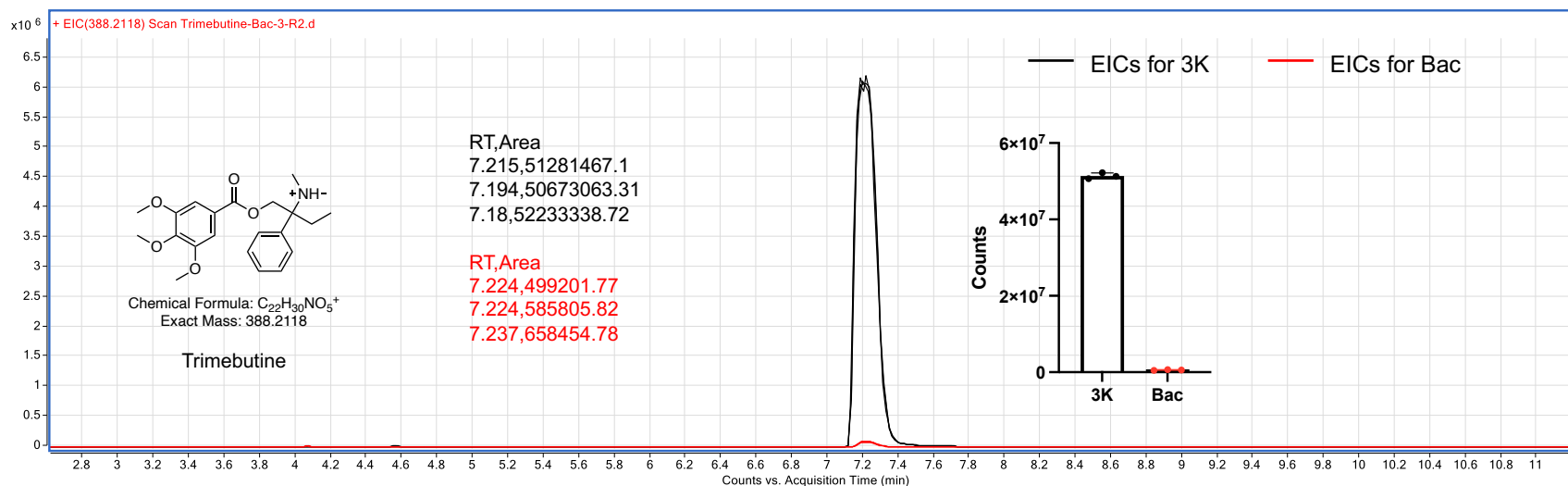


Fig. S198. Bac⁺ vs Bac⁻ (MWCO 3K) of almorexant (*m/z* 513.2360) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

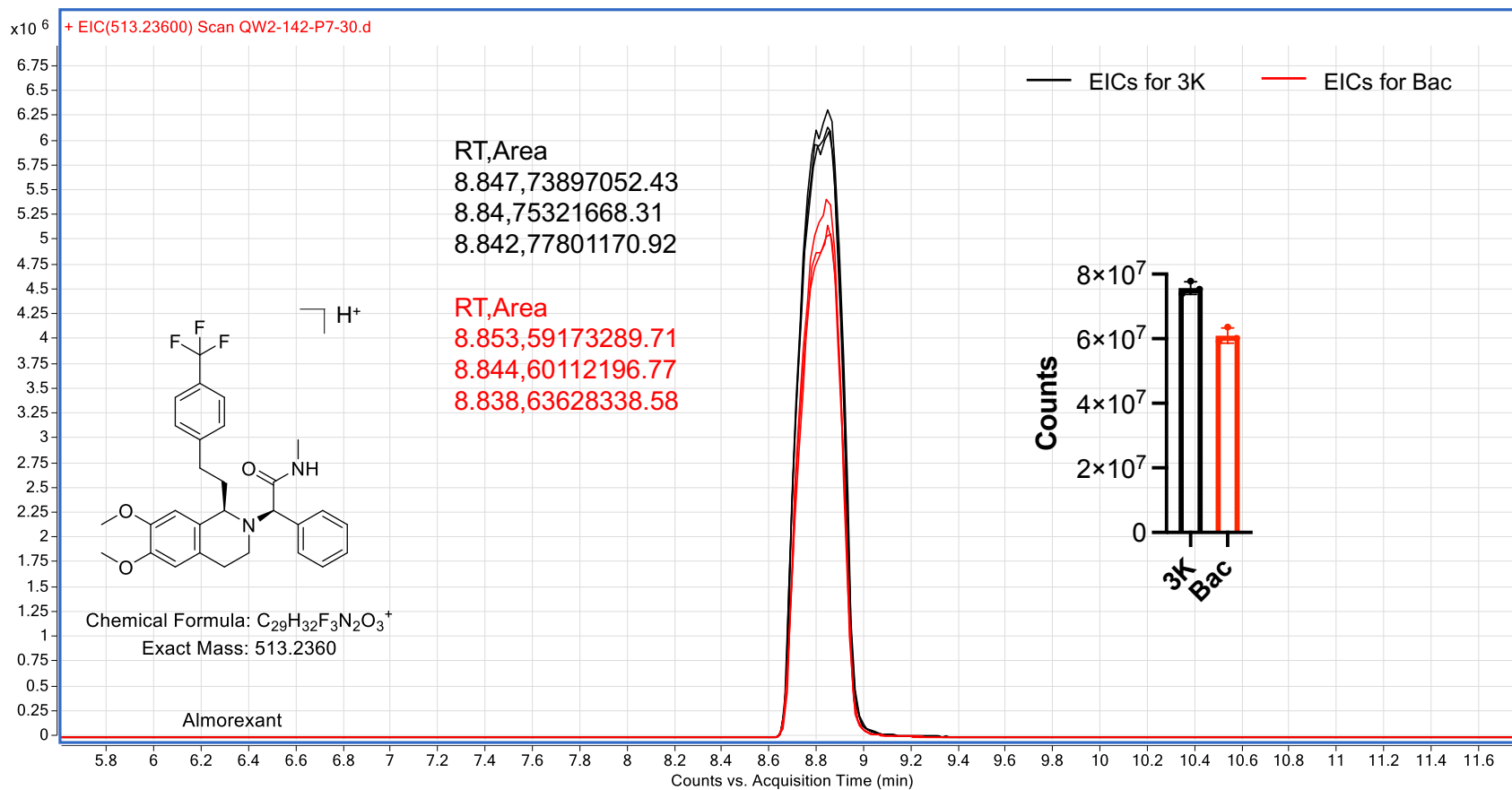


Fig. S199. Bac⁺ vs Bac⁻ (MWCO 3K) of xanomeline (*m/z* 282.1635) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean ± s.d.

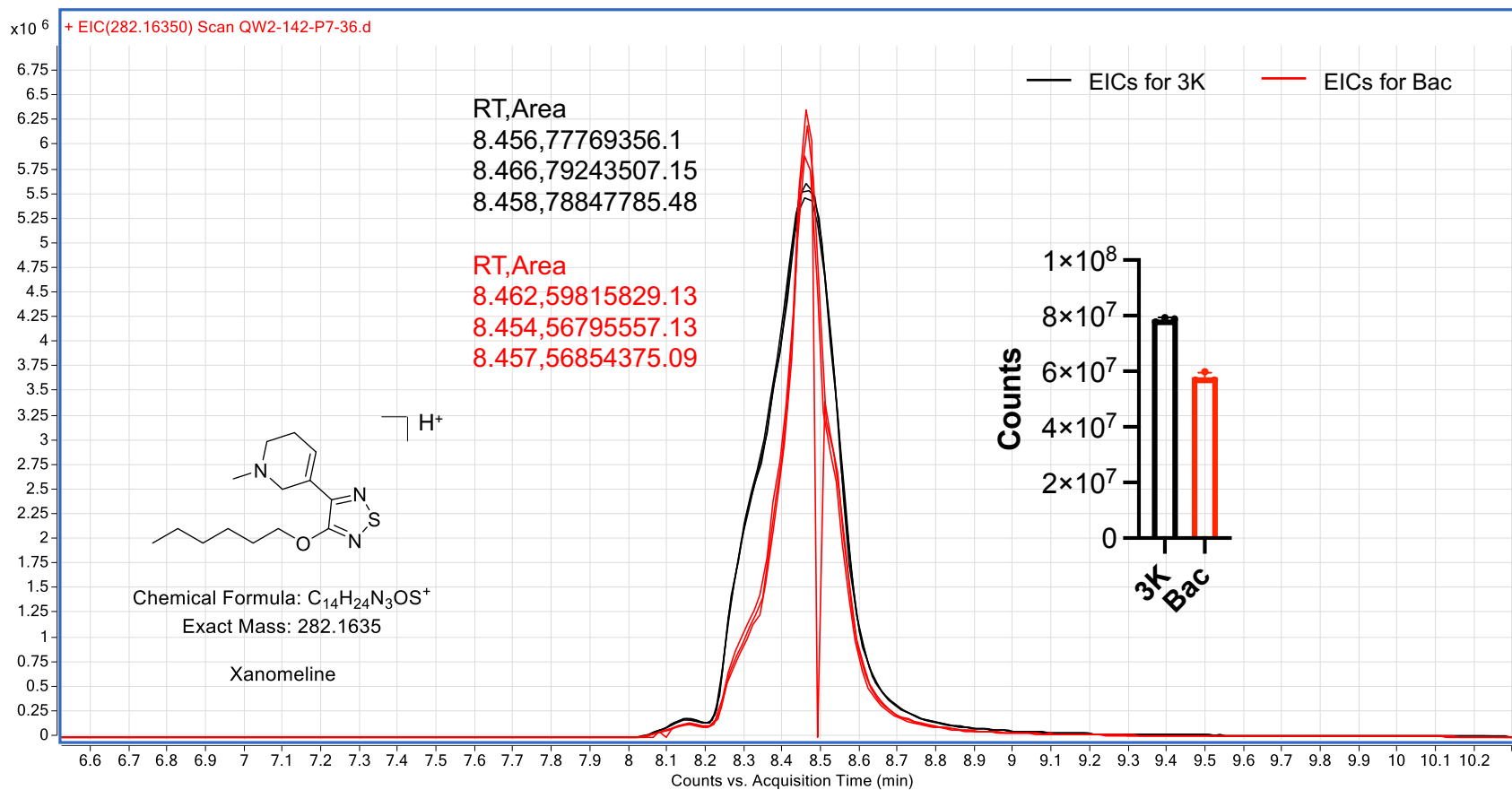


Fig. S200. Bac⁺ vs Bac⁻ (MWCO 3K) of lofexidine (*m/z* 259.0399) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

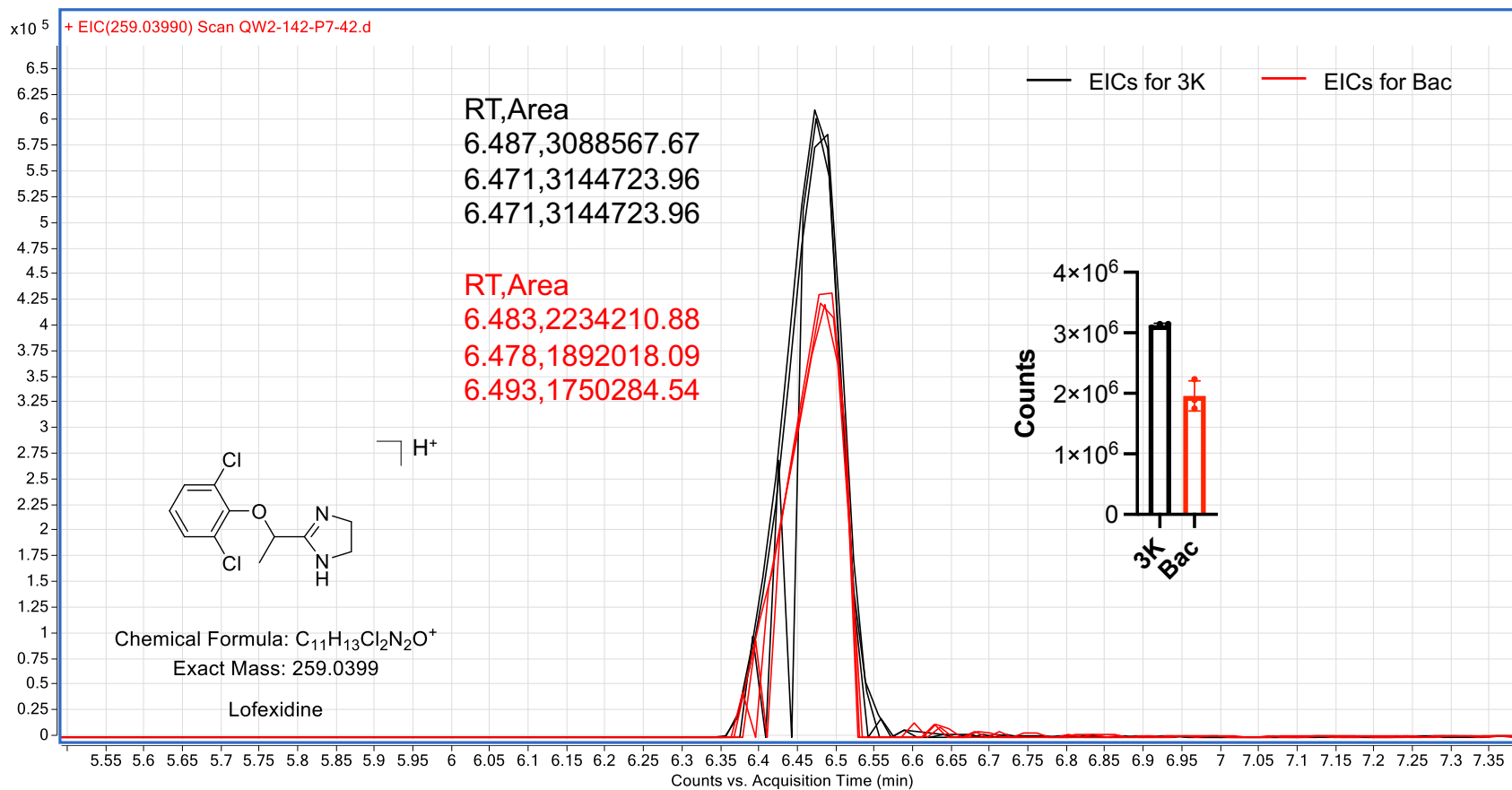


Fig. S201. Bac⁺ vs Bac⁻ (MWCO 3K) of losartan (*m/z* 423.1695) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

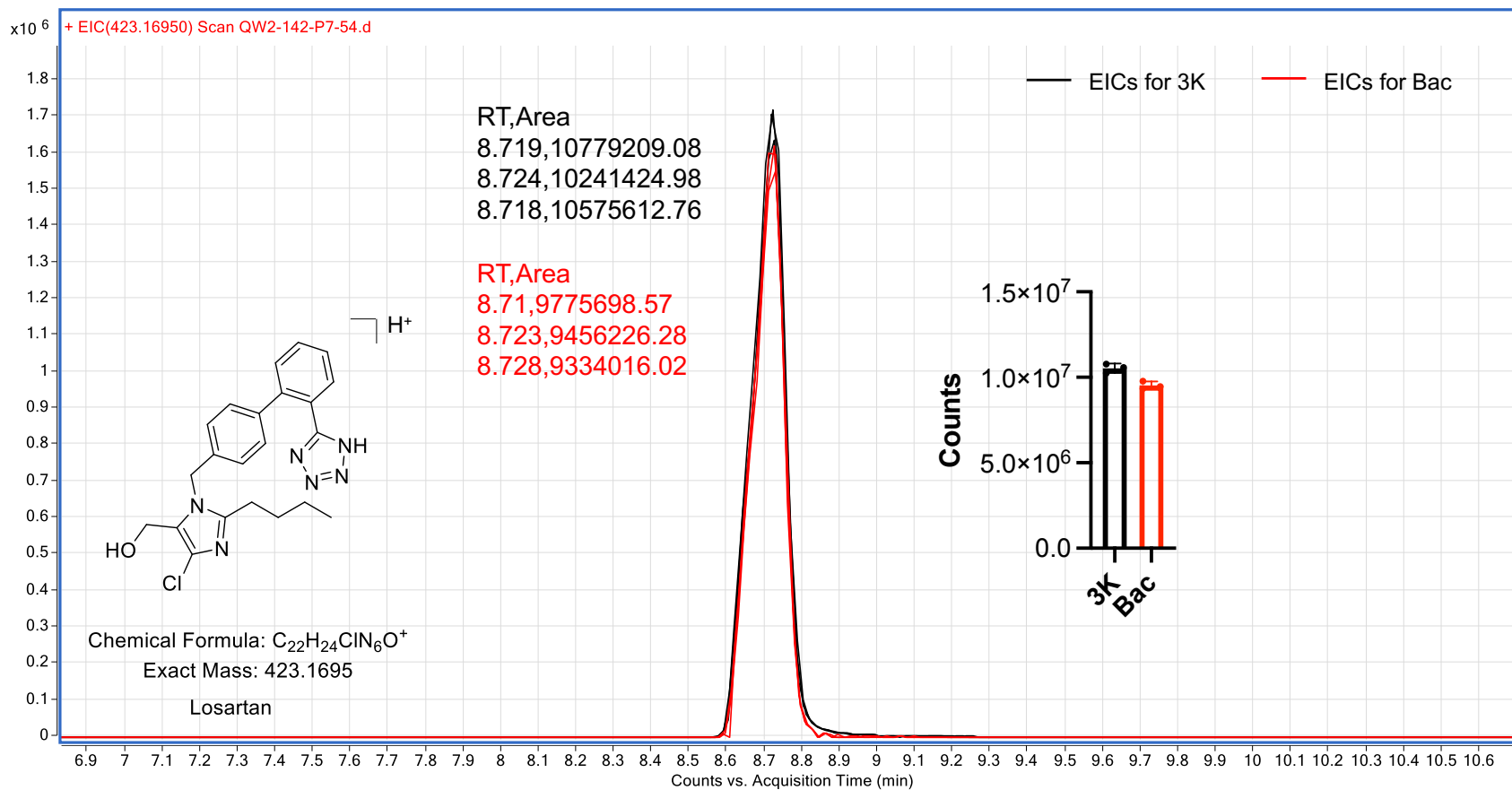


Fig. S202. Bac⁺ vs Bac⁻ (MWCO 3K) of idalopirdine (*m/z* 399.1490) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

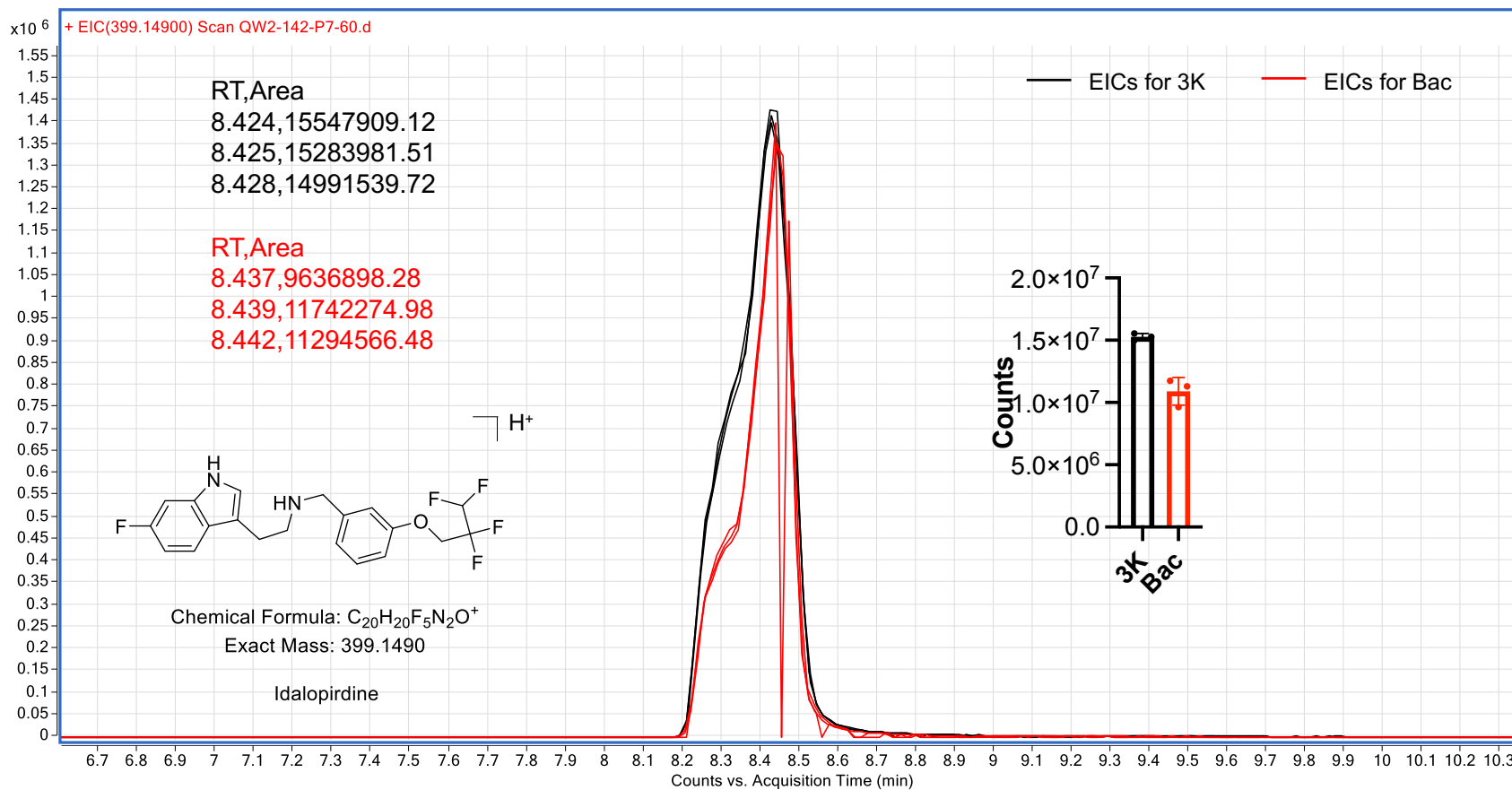


Fig. S203. Bac⁺ vs Bac⁻ (MWCO 3K) of carvedilol (*m/z* 407.1965) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

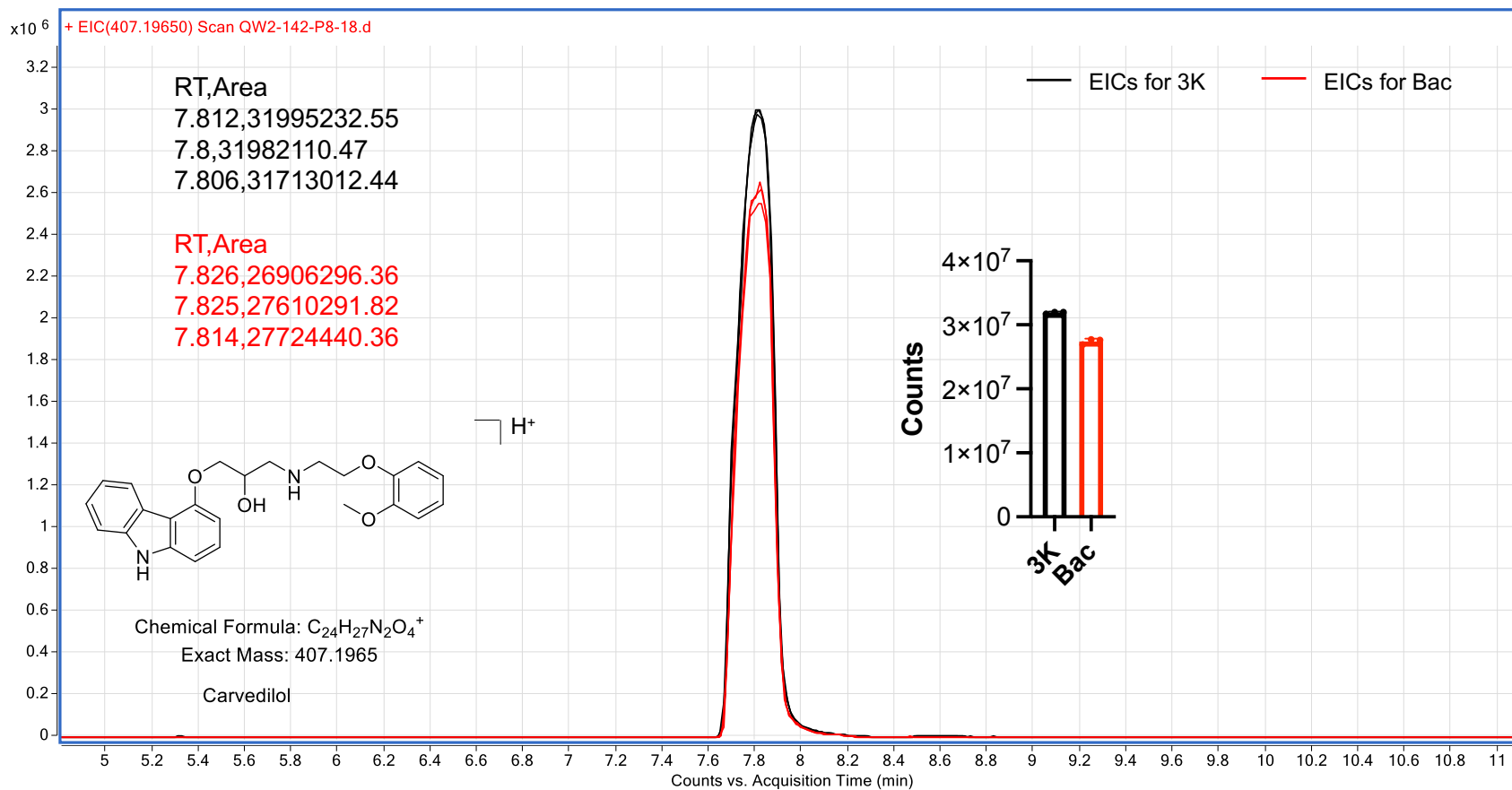


Fig. S204. Bac⁺ vs Bac⁻ (MWCO 3K) of anamorelin (*m/z* 547.3391) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. *n* = 3 biological replicates. Data represent mean $\pm$ s.d.

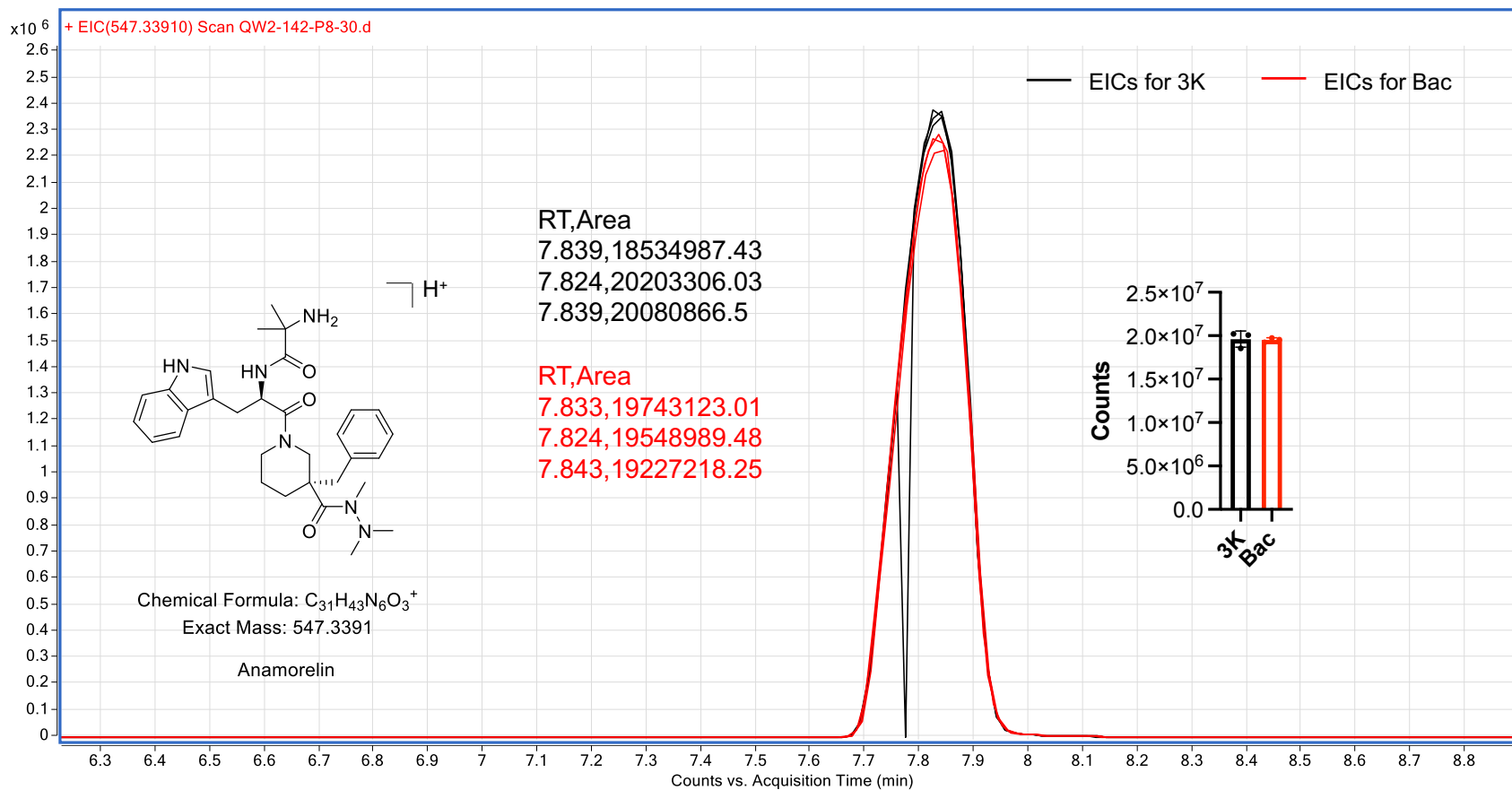


Fig. S205. Bac⁺ vs Bac⁻ (MWCO 3K) of otilonium (*m/z* 483.3217) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

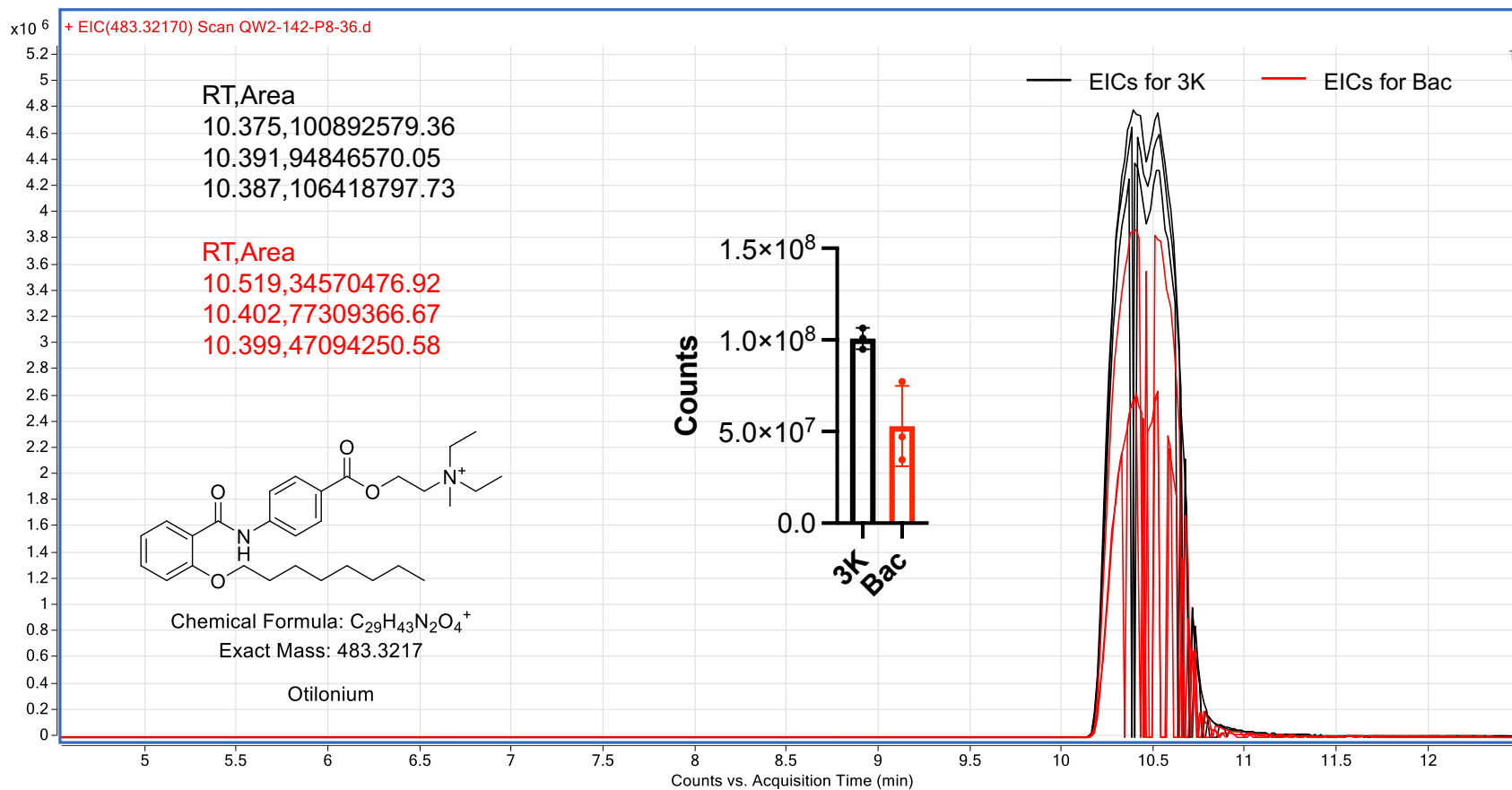


Fig. S206. Bac⁺ vs Bac⁻ (MWCO 3K) of vilazodone (*m/z* 442.2238) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

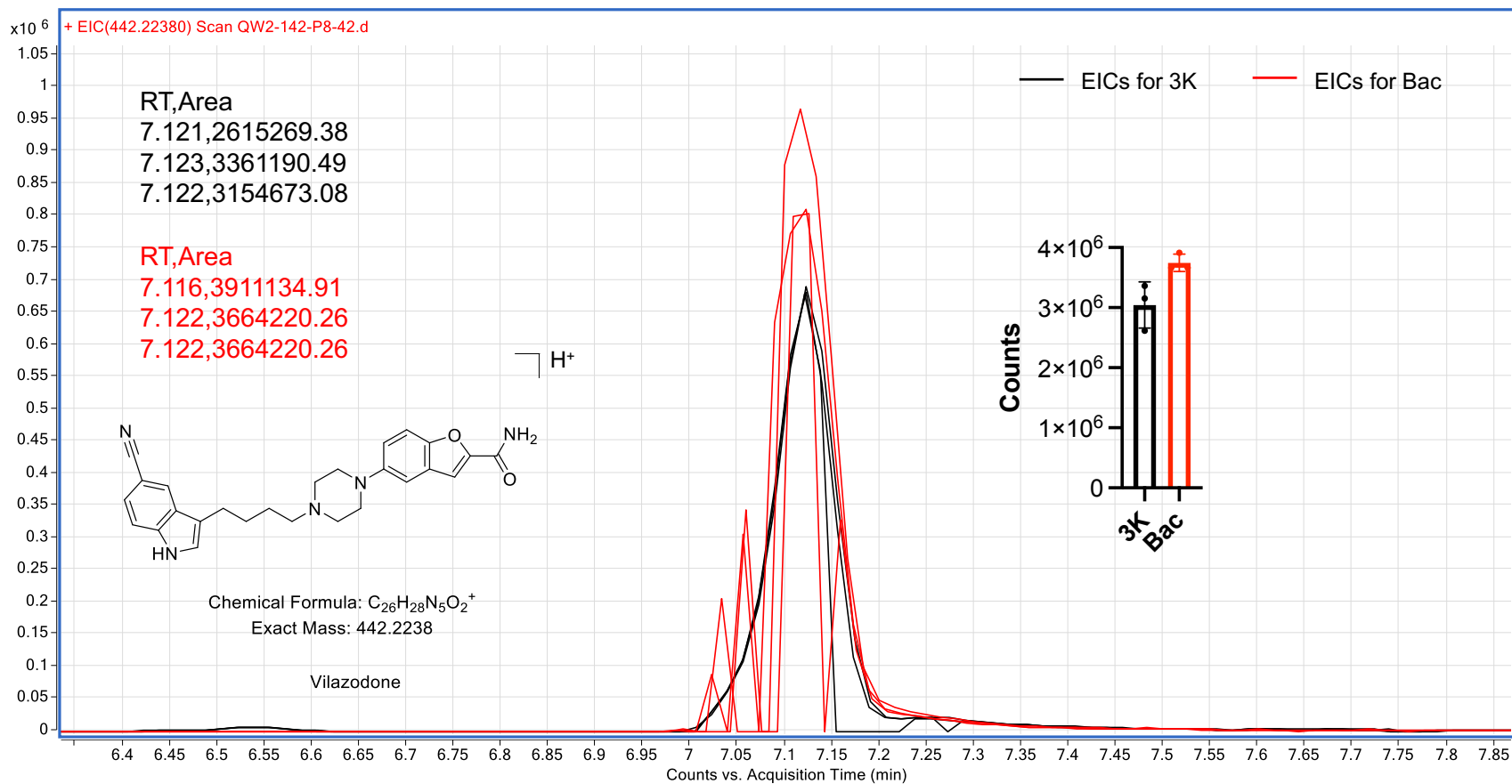


Fig. S207. Bac⁺ vs Bac⁻ (MWCO 3K) of oxybutynin (*m/z* 358.2377) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

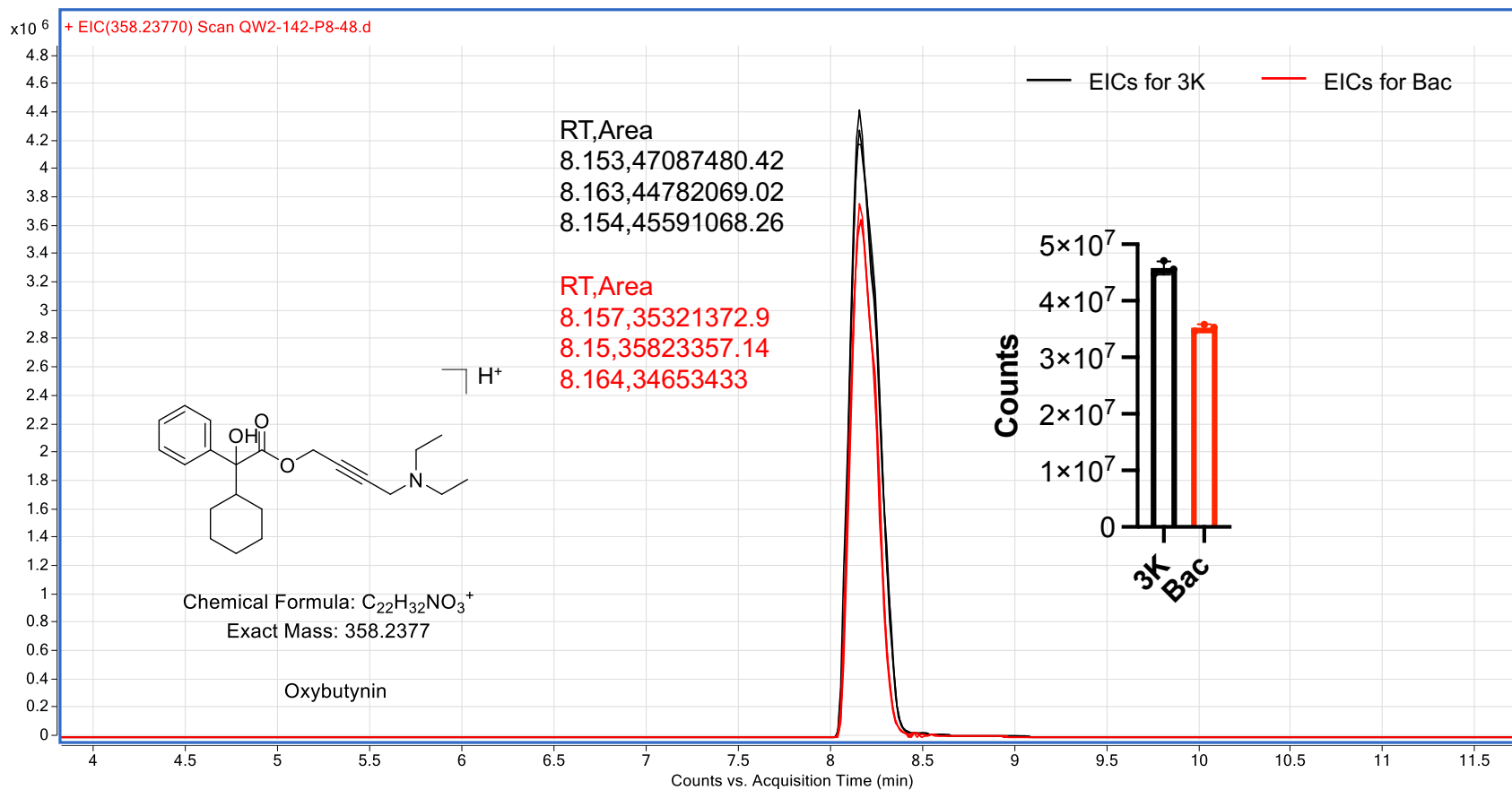


Fig. S208. Bac⁺ vs Bac⁻ (MWCO 3K) of MK-3207 (*m/z* 558.2311) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

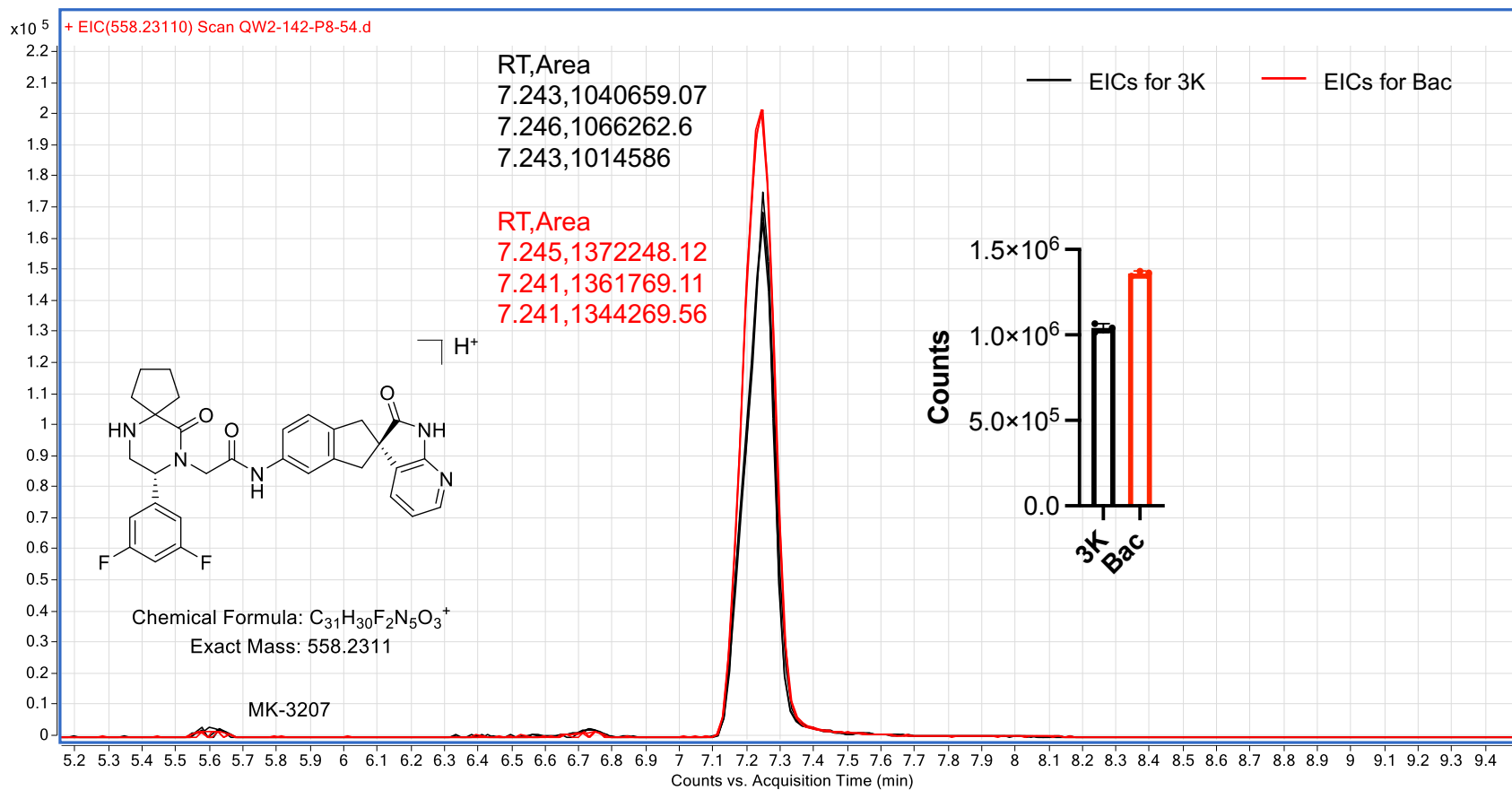


Fig. S209. Bac⁺ vs Bac⁻ (MWCO 3K) of talnetant (*m/z* 383.1754) in drug metabolism screening. Bac⁺: Drug metabolism with bacterial community. Bac⁻: Drug metabolism with cell/enzyme-free supernatant obtained from 3K molecular weight cutoff. n = 3 biological replicates. Data represent mean ± s.d.

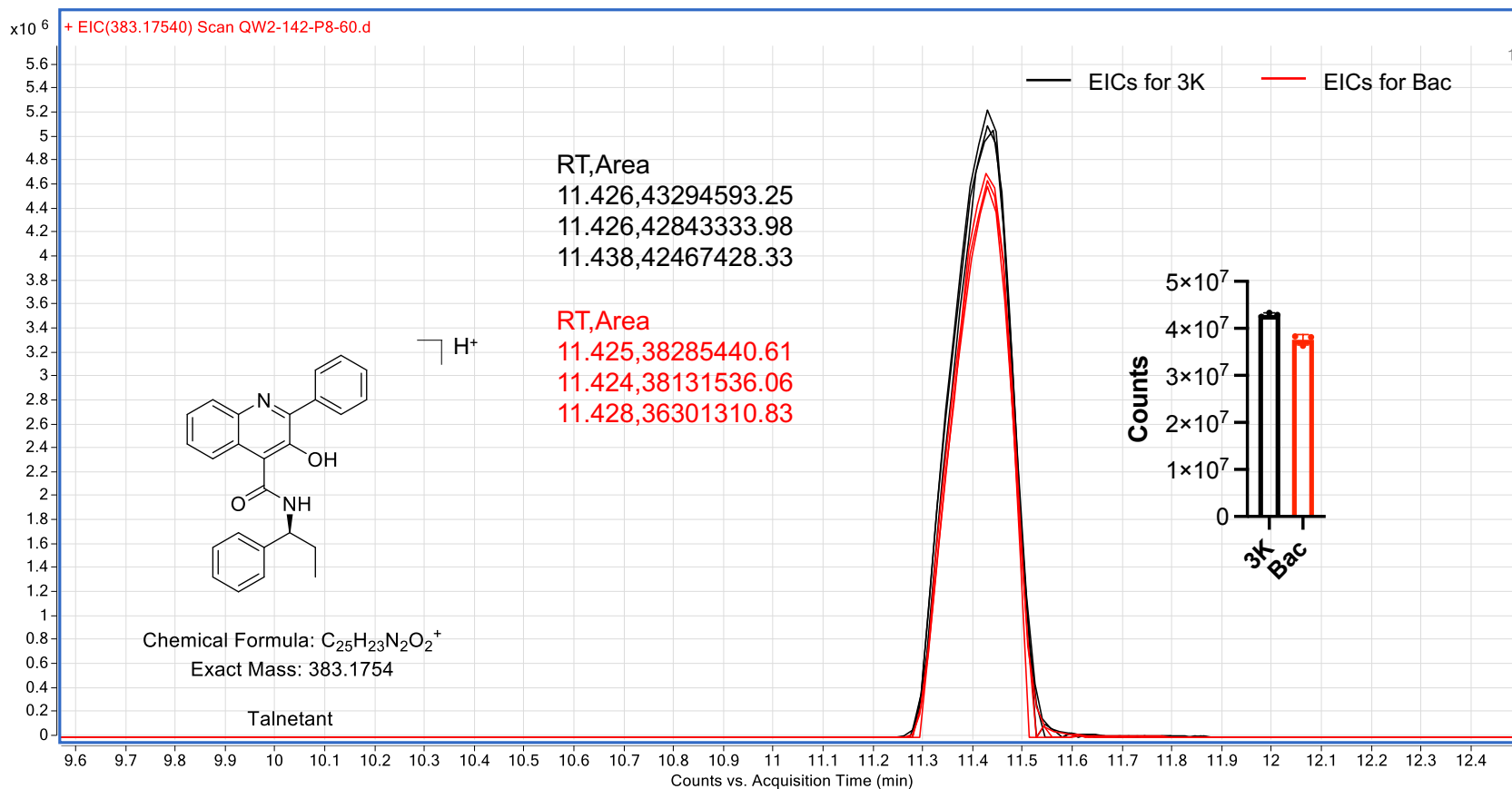


Table S20. Information of the 346 commercially available GPCR drugs in Drugbank.

No.	Name	SMILES
1	Levosulpiride	O=C(NC)C@H1N1(C)CCC1C2=CC(S(=O)N)=CC=C2OC
2	Ketanserin (tartrate)	O=C(C1=CC=CC=C1N2)N(CCN3CC(C)C4=CC=C(F)C=C4)=O)CC3C2=O. O=C(O)C@H1(O)C(O)C=O
3	Silodosin	O=C(N)C1=CC(C)C@H1(C)NCCC2=CC=CC=C2OC(F)(F)F)=CC3=C1N(C)CCCO
4	Balovaptan	CN1CC2=NN=C(C)[C@H]3C(C)C@H1(OC4=NC=CC=C4)CC3)N@2(C)C@5=CC=C(C)C=C=C5C1
5	Biperiden (Hydrochloride)	O=C(C1CC2=C(C1C2)CCN3CCCC3)C4=CC=CC=C4.[H]Cl
6	Aripiprazole	O=C1NC2=C(C=C)CC(C)C3C(C)C4=CC=CC(C1)=C4(O)C3)=C2)JC1
7	Atrasentan (hydrochloride)	O=C([C@H]1[C@H](C2=CC=C(C)(C)C=C2)N(C)CC(N)CCCC)CCCC=O)C(C@H)1C3=CC=C(C)C(O)C4=C3)O.Cl
8	Triptelenamine (hydrochloride)	CN(C)CCN(C)C1=CC=CC=C1C2=NC=CC=C2.[H]Cl
9	Aprocitentan	O=S(N)NC1=N=NC=NC(OC(C)C2=NC=C(Br)C=N2)=C1C3=CC=C(Br)C=C3=O
10	USL311	O=C(C1=N(C)N2CCN(C)CCN(C)C)CC3)CC2)=CC=C1)NC4=CC=NC=C4
11	Fezolinetant	O=C(N1(C)C@H1(C)C2=NN=C(C)C=N(C)CC(N)N2CC1)C4=CC=C(F)C=C4
12	Vorapaxar	O=C(O)C@H1(C)C@22([H])(C)C@11([H])C@H1(C)C=C(NC=C(C)C3)C4=CC=CC(F)=C4)C@11(C5)([H])(C)C@H1(C)C@H15N(C)CC=O
13	Latrepirdine (dihydrochloride)	CN(C)CC2=C1C3=CC(C)C=C3N2CCOC4=CN(C)C(O)C=C4.Cl.Cl
14	Pardoprunox (hydrochloride)	O=C1OC2=C(N3CCN(C)C)C3=C=CC=C2N1.[H]Cl
15	Diphylline	O=C(N1(C)N(C)C2=C(C)CC(O)CO)C=N2)C1=O
16	Asenapine (hydrochloride)	[H]Cl.Cl.C1=CC2=C(C=C1)OC3=C(C=CC=C3)C@1(C4)([H])(C@2([H])CN4C
17	Telmisartan	O=C(C1=CC=CC=C1C2=CC=C(C)CN3C4=CC(C5=NO6=CC=CC=C6N5C)=CC(C)C=C4N=C3CCC)C=C2)O
18	Vabicaserin hydrochloride	[H]([C@H]12C3=CC=CC4=C3N(C)CCN4)C(C)C@11([H])CCC2.Cl
19	Betahistine (dihydrochloride)	CNCCC1=CC=CC=N1.Cl.Cl
20	SB756050	O=S(N1CCN(S)=O)C2=CC=C(C)C(O)C(C)=O)CCC1(C3=CC=C(C)C(O)C(C)=C3)=O
21	Blonanserin	FC1=CC=C(C)C2=C(C)CCCCC3C3=NC(N4CCN(C)CC4)=C2)C=C1
22	Cariprazine (hydrochloride)	O=C(N(C)C@H11C(C)C@H1(CN2CCN(C3=CC=CC(C1)=C3(C)CC2)CC1)N(C)C.[H]Cl
23	PRX-08066	N#CC1=CC(C)CN2CCC(NC3=C(C)C(C)S4)C4=NC=N3)CC2=CC=C1F
24	Chlorprothixene	CN(C)CC/C=C1C2=C(SC3=C1C=CC=C3)C=CC(O)C=C2
25	Cyclobenzaprine (hydrochloride)	CN(C)CC/C=C1C2=CC=CC=C2C=CC3=CC=CC=C13.Cl
26	Capadenoson	N#CC1=C(C)C2=CC=C(C)CC(O)C=C2)C(C)N(C)C(C)C3=CC=C(C)C4=CC=C(C)C=C4)N3)N=C1N
27	Velneripit	F(C)(F)C1=CN=C(N)C([C@H]2C[C@H]1N(S(=O)C)(C)C(C)=O)CC2=O)C=C1
28	(S)-Timolol (Maleate)	O(C@H)(COC1=N=SN=C1N2CCOC2)N(C)C(C)C=C=O)C=C(C)C(O)=O
29	Deoxycholic acid sodium salt	C(C)C@11([C@H]2([H])(C@H)(C)CCC(O)C)C@11([H])(C)C@2([H])(C@H)(C)C@H13([H])(C@H)4(C)C@H1(O)C3)C([H])(C@H)4([H])(C)C@H1O.[Na+]
30	Piclidenoson	O(C)C@H1(C)C@H1(N2C=NC3=C(N)CC=C(C)C(O)C1)=C4)N=CN=C23)O(C)C@H1(C)N(C)=O)C@H1O
31	Cebranopadol	CN(C)C@11(C2=CC=CC=C2)OC(C)C@3(C)C(N)=C(C)CCO3)C5=C4C=C(C)F)=C5)CC1
32	GSK163090	O=C1NCCN1C2=CC=CC(C)CCN3CCN(C4=C5C=C(C)C=C4)C3)=C2
33	Olanzapine	CC1=CC(C)N2CCN(C)CC2)=N3)=C(S1)NC4=C3=CC=C4
34	Ketotifen (fumarate)	O=C(C1=C2/C=C(S1)CC3=CC=CC=C3C2=C4CCN(C)CC4.O=C(O)C/C=C(C)C(O)=O
35	Flavoxate (hydrochloride)	O=C(C1=C2C(C)C(C)=C(C3=CC=CC=C3)O2)=O)CC=C1)OCCN4CCCC4.Cl
36	Cetirizine (dihydrochloride)	O=C(O)OCCCN1CCN(C)C2=CC=C(C)C=C2)C3=CC=CC=C3)CC1.Cl.Cl
37	Bavisan (dihydrochloride hydrate)	O=C(N1CCN(C)CC2)CC1(C)C=C(C)=CC=C3CN4CCOCC4.[H]Cl.[H]Cl.O
38	Ziprasidone (hydrochloride monohydrate)	O=C1C2=CC(C)CCN3CCN(C4=NSC5=C4C=CC=C5)CC3)=C(C)C=C2N1.[H]Cl.O
39	Metoprolol (Succinate)	O(C)CC(C)C(C)CCO1=C=CC(C)CC(C)C=C1.O(C)CC(C)C(C)CCO2=CC=C(C)CC(C)C=C2.O(C)CC(C)C(C)C=C1
40	Chlorpheniramine (maleate)	CN(C)CCC(C1=CC=C(C)C=C1)C2=CC=CC=C2.O=C(O)C=C(C)C(O)=O
41	Pindolol	O(C)CC(C)C(C)CCO1=C=CC=C2)C=C1C=CN2
42	Elagolix sodium	O=C([O-])CCCN(C)C@H1(C1=CC=CC=C1)CN(C)CC2=C(C)C(F)(F)C=C(C)C2)C(C)=C3C4=CC=C(C)C(O)C(C)=C4)O)C3=O.[Na+]
43	Vortioxetine (hydrobromide)	CC1=CC=C(C)C2=CC=CC=C2N3CCN(C)C(C)C=C1.[H]Br
44	Ranitidine (hydrochloride)	CN(C)CCN(C)CC1=CC=C(C)C(C)O1)=C(N)N([O-])=O.Cl
45	Acrivastine	O=C(O)C=C(C)C=N(C)C(C)C2=CC=C(C)C=C2)=C(C)CCN3CCCC3)=CC=C1
46	Trospium (chloride)	[H]([C@H]12CC(C)C@H1(C)C@H1(O)C(C)C3=CC=CC=C4)O)C4=CC=CC=C4)O)C2([H])(N+15CCCC5.[Cl-]
47	Yohimbine (Hydrochloride)	[H]([C@H]12(C)NC3=C4C=CC=C3)=CC4CN1C(C)C@H15(C)C@H1(O)C@H1(C)OC=O)C@H15(C)C@H1([H])(C)C@H1O
48	GSK1292263	CC(C1=NO(C)N2CC(C)CC2)OCC3=CN=C(C)C3)C4=CC=C(C)C=C4)S(C1)=O)=N1)C
49	Quinagolide (hydrochloride)	O=C=C2C(C)C(C)N(C)CC(C)C(C)C@H1(N(C)CC(C)C)C=C(O)C3)([H])(C@H)3([H])C2)=CC=C1.Cl
50	Macitentan	BrC1=CN=C(C)CCOC2=C(C3=CC=C(C)C(C)C3)CC(N)CC(C)=O)=NC=N2)N=C1
51	Ambrisentan	O=C([C@H](C)CC(C)C1=CC=CC=C1)C2=CC=CC=C2)OC3=NC(C)=CC(C)C=C3)O
52	Iloperidone	CC(C1=C=CC(O)CCN2CCC(C3=NO(C4=C3C=CC(F)=C4)CC2)C(O)C1)=O
53	GSK598809	CC1=C(C)C2=NN=C(SCCN3CC4(C5=CC=C(C)C(F)C=C5F)CC4C3)N2C)OC=N1
54	Mirabegron	O=C(NC1=CC=C(C)CCN(C)C@H1(O)C2=CC=CC=C2)C=C1)CC3=CC(C)N=N3
55	Risperidone	O=C1C(C)CCN2CC(C3=NO(C4=C3C=CC(F)=C4)CC2)=C(C)N=C1N5CCCC5
56	Talipexole dihydrochloride	NC1=NC2=C(C)CCN(C)C2=CC=C(S1.Cl.Cl
57	Ipratropium (bromide)	C(N+11([C@H]2C(C)C@H11C(C)CC(O)C(C)C)C2=CC=CC=C3)=O)C2)C(C)C.[Br-]
58	Vipadenant	NC1=NC2=C(N=NN2CC3=CC=C(N)C(C)C)=C3)C(C4=C(C)=CCO4)=N1
59	Darusentan	CCO1=NC(O)C@H1(C)C(O)=O)C(C2=CC=CC=C2)C3=CC=CC=C3)OC)=NC(O)C=C1

161	Lasmiditan (hydrochloride)	<chem>O=C(NC1=NC(C2CCN(C)CC2)=O)=CC=C1)C3=C(F)C=C(F)C=C3F.[H]Cl</chem>
162	(R)-Elagolix	<chem>FC1=C(C2=C(C)N(CC3=C(C(F)(F)F)C=CC=C3F)C(N(C)C@H)(C4=CC=CC=C4)C(=O)C2=O)=O)C=CC=C1OC</chem>
163	Pavinetant	<chem>C[C@H](NC1=C(C=CC=C2)C2=NC(C3=CC=CC=C3)S(=O)(=O)C1=O)C4=CC=CC=C4</chem>
164	Setipiprant	<chem>O=C(O)CN1C2=C(C)C(N(C)C3=C4C=CC=CC4=CC=C3)O(C2)C5=C1C=CC(F)=C5</chem>
165	Ozanimod	<chem>N#CC1=CC(C2=NC(C3=CC=CC4=C3C[C@H]4NCCO)=NO2)=CC=C1OC(C)C</chem>
166	Ibutamoren (Mesylate)	<chem>CC(N)C(N(C@H)(C1NCCC2(CN(C3=C2C=CC=C3)S(=O)(=O)C1=O)COC4=CC=CC=C4)O)C.S(=O)(=O)=O</chem>
167	Diphenylpyraline (hydrochloride)	<chem>CN1CC(C)C(C2=CC=CC=C2)C3=CC=CC=C3)C1.[H]Cl</chem>
168	Adoprazine	<chem>FC1=CC=C(C2=CN=CC(C3CCN(C4=C5OCCOC5=CC=C4)CC3)=C2)C=C1</chem>
169	MK-0557	<chem>O=C([C@H]1CC[C@H](C2=C3C=CN=C2)(OC3=O)CC1)NC4=NN(C5=CC=CC=C5F)C=C4</chem>
170	Terfenadine	<chem>O(C1=CC=C(C(C)C)C=C1)CCCN2CCC(C3=CC=CC=C3)O(C4=CC=CC=C4)CC2</chem>
171	Anamorelin (hydrochloride)	<chem>[H]Cl.CC1=CC=CC=C(C2=CC=CC=C2)1(NC(C)C(C)C(N)=O)C(N3CC(C)C@H)(C(N(C)N(C)C)=O)C4=CC=CC=C4)C3=O.[H]Cl</chem>
172	Taranabant	<chem>C1C1=CC=C(C(C)C@H)(C2=CC=CC(C#N)=C2)(C@H)(NC(C)C(C)OC3=CC=C(C(N3)C(F)(F)F)C)C1C=C1</chem>
173	Almorexant	<chem>CNC([C@H](C1=CC=CC=C1)N2CCC3=CC(OC)=C(C)C)C=C3(C@H)2CC4=CC=C(C(F)(F)F)C=C4)=O</chem>
174	Flopropione	<chem>CCC(C1=C(O)C=C(O)C=C1O)=O</chem>
175	Ponesimod	<chem>O=C1N(C2=CC=CC=C2)C(S1C1=C(C)C3=CC=C(C)O(C@H)(O)CO)C(C1)=C3=N'CCC</chem>
176	MBX-2982	<chem>CCC1=CN(C)N2CCC(C3=NC(COC4=CC=CC=C4)N5N=NN=C5)C=C4=CC3)CC2)N=C1</chem>
177	GW842166X	<chem>OC1=CC(C1)=C(NC2=NC=C(C)C(NC3CCOC3)C=O)C(C(F)F)=N2)C=C1</chem>
178	AZD1981	<chem>O=C(O)CN1C(C)=C(SC2=CC=C(C)C=C2)C3=C1C=CC=C3NC(C)=O</chem>
179	Fevipiprant	<chem>O=C(O)CC1=C(C)N(CC2=CC=C(S1=O)(C)=O)C=C2C(F)(F)F)C3=NC=CC=C31</chem>
180	Grapiprant	<chem>O=S(C1=CC=C(C)C=C1)(NC(NCOC2=CC=C(C)N3C(C)C=C4(C)N=C4C)C=C2)=O)=O</chem>
181	lumateperone (Tosylate)	<chem>O=C(C1=CC=C(C(F)C=C1)CCCN2CC(C)C@H)(N3CCN(C)C4=C3C5=CC=C4)([H])(C@H)5([H])C2.O=S(=O)(=O)C(C)C=C(C)C=C(C)C(=O)O)=O</chem>
182	Zuclopenthixol	<chem>CCCN1CCN(CC(C=C2C3=C(C)C(C4=C2C=CC=C4)C=CC(C1)=C3)CC1</chem>
183	Pridopidine	<chem>O=S(C1=CC(C2CCN(C)C)CC2)=CC=C1)C=O</chem>
184	ADL-5859	<chem>OC1=C2C(OC3(C=C2C4=CC=C(C=C4)C(N(C)C)CC)=O)CCNCC3)=CC=C1.O</chem>
185	E7046	<chem>O=C(O)C1=CC=C([C@H](NC(C2=C(C)OC3=CC=CC(C)C(F)(F)F)=C3)N(C)N=C2C(F)F)O)C)C=C1</chem>
186	MSX-122	<chem>C1(CNC2=NC=CC=N2)=CC=C(C)CNC3=NC=CC=N3)C=C1</chem>
187	Adomeglivant	<chem>O=C(O)CCNC1=CC=C([C@H](OC2=CC(C)C=C(C)C(C)C)C=C3)C(C)=C2)CC(C(F)(F)F)C=C1=O</chem>
188	Mavoxifafor (trihydrochloride)	<chem>[H]Cl.[H]Cl.[H]Cl.NC(C)CCN1CC1=NC2=CC=CC=C2N1)(C@H)3C4=NC=CC=C4CC3</chem>
189	Tarafenacin (D-tartrate)	<chem>O=C(O)[C@H]1CN2CCC1C2)N(C3=CC=C(C)F)C3)CC4=CC(F)=C(C)C(F)F)=C4.O[C@H]([C@H](C)O)C(O)C(O)=O</chem>
190	Cenerimod	<chem>O(C[C@H](O)COC1=C(C)C)C=C(C)C2=NO(C)C3=C(C)C4CCCC4=NC(O)C=C3)=N2)C=C1CC</chem>
191	Timapiprant	<chem>O=C(O)CN1C(C)=C(C)CC2=NC3=CC=CC=C3C2)C4=C1C=CC(F)=C4</chem>
192	Elitoprazine (hydrochloride)	<chem>[H]Cl.N1(C2=C3OCCOC3=CC=C2)CCNCC1</chem>
193	Pumosestrag Hydrochloride	<chem>O=C(C1=CC(C)C=CC2)=C2C1=O)N(C@H)3CN4CCC3CC4.[H]Cl</chem>
194	MK-3207 (Hydrochloride)	<chem>O=C1C2(NC(C)C@H)(C3=C(C)F)=CC(F)=C3)N1CN(C4=CC5=C(C)C@H)6(C(NC7=CC=CC=C7)=O)C5)C=C4)=O)CCCC2.Cl</chem>
195	Talnetant	<chem>OC1=C(C)N(C@H)(C2=CC=CC=C2)OC)C3=C1C=CC=CC=C4)C=CC=C3</chem>
196	Avosentan	<chem>COC1=O(C)C(NS(C2=NC=C(C)C=C2)C)=O)=NC(C3=CC=CC=C3)=N4)C4OC(C)C=CC=C1</chem>
197	Cevimeline (hydrochloride hemihydrate)	<chem>C(C@H)1SC(C)C@H)2(CN3CCC2CC3)O1.[H]Cl.[Relative Stereochemistry].[0.5 H2O]</chem>
198	Scopolamine butylbromide	<chem>C[N+](C([C@H]2[C@H]([O3])(C@H)3(C@H)1C(C)C@H)(OC([C@H](C4=CC=CC=C4)CO)=O)C2)CCCC.[Br-]</chem>
199	Vilazodone (Hydrochloride)	<chem>N(C1=CC2=C(C=C(C)N3CCN(C)CC(C4=CC5=CC=C(C=C5)C(N)CC3)=C2)O1)=O.[H]Cl</chem>
200	Alprenolol (hydrochloride)	<chem>OC(COC1=CC=CC=C1CC=C(C)C)C(C)C.[H]Cl</chem>
201	Cisapride	<chem>O=C(N(C)C@H)1(C@H)(OC)CN(CCCOC2=CC=C(C)C=C2)CC1)C3=CC(C1)=C(N)C=C3OC</chem>
202	Volinsanserin	<chem>FC1=CC=C(C)CCN2CCC([C@H]([H])([H])C3=CC=CC=C(C)C=C3)CC2)C=C1</chem>
203	Ramelteon	<chem>O=C(NC(C)C@H)1C2=C(C)C=C3=C2CCOC3)CC1)CC</chem>
204	Telcagepant	<chem>O=C1NC2=C(N1C3CCN(C)N(C@H)4CC(C)C@H(C5=CC=CC(F)=C5F)CN(C)C(F)F)C4=O)=O)CC3)C=CC=N2</chem>
205	MK-7622	<chem>O=C1N([C@H]2[C@H]([O)CCCC2)C=NC3=C1C(C)C4=CC=C(C)N=C4)C5=CC=CC=C5</chem>
206	Intepirdine	<chem>O=S(C1=CC=CC=C1)(C2=CC(C)C=CC=C3N4CCNCC4)=C3N=C2=O</chem>
207	Tozadenant	<chem>O=C(NC1=NC2=C(C=CC(N3CCOCC3)=C2S1)OC(N4CC(C)C)O(C4)C</chem>
208	Rimonabant (Hydrochloride)	<chem>OC1=CC=C(C2=C(C)C(C)N(N3CCOCC3)=O)=NN2C4=CC=C(C)C=C4(C)C=C1.Cl</chem>
209	JDTic (dihydrochloride)	<chem>O=C([C@H]1NCC2=C(C=C(O)=C2)C1)N(C@H)(C(C)C)CN3C(C@H)(C)C@H([C]C@H)(C(C4=CC=CC(O)C4)CC3.[H]Cl.[H]Cl</chem>
210	Xanomeline (oxalate)	<chem>CN1CCO=C(C2=NSN=C2OCCOCC)C1.O=C(O)C(O)=O</chem>
211	AZD4635	<chem>NC1=NC(C2=CC=C(C)C=C2)=C(C3=CC(C1)=NC(C)C=C3)N=N1</chem>
212	Namodenoson	<chem>O(C[C@H]([C@H]1O)([C@H](O)C@H)1(C)NC(C)N2C3=NC(C1)=NC(NC4=C(C)C(=O)C=C4)=C3N=C2</chem>
213	Asimadoline	<chem>O(C[C@H]1CCN(C1)C(C)C@H)(C2=CC=CC=C2)N(C)C(C)C3=CC=CC=C3)C4=CC=CC=C4)=O</chem>
214	Piboserod	<chem>O=C(C1=C(C)OCC(C)N2C3=C1C=CC=C3)NCC4CCN(C)CC(C)CC4</chem>
215	Navarixin	<chem>O=C1C(C)N(C2=CC=C(C)C(N(C)C)=O)=C2O)=C1N(C@H)(C)C3=CC=C(C)C3)C=O</chem>
216	Reparixin (L-lysine salt)	<chem>N(C@H)(CC(C)C)C(O)=O.CS(=O)N(C[C@H](C1=CC=C(C)C(C)C=C1)C)O)=O</chem>
217	Fasiglifam	<chem>CC1=C(C)C=C(C)OCC(CS(C)=O)=C1)C2=CC(C)C3=CC=C4(C@H)(COC4=C3)CC(O)=O)=CC=C2</chem>
218	Sitaxsentan (sodium)	<chem>O=S([N-]C1=C(C)C(NO1)Cl)(C2=C(C)SC=C2)C(C)C3=C(C=C4COC4=C3)C(O)=O.[Na+]</chem>
219	Tulobuterol (hydrochloride)	<chem>CC(C)(NOC(C)C1=CC=CC=C1O)C.Cl</chem>
220	Clonidine (hydrochloride)	<chem>OC1=C(NC2=NCN2)C(C)=CC=C1.Cl</chem>
221	AZD-5069	<chem>O=S(N1CCC1)(NC2=NC(SCC3=CC=CC(F)=C3F)=NC(C)C(C@H)(C)C@H)(O)O)=C2=O</chem>
222	MK 0893	<chem>OC1=CC(C2=NN(C)C3=CC4=C(C=C3)C=C(C)C)C=C4)C@H)(C5=CC=C(C=C5)C(NCCC(O)=O)=O)C(C)C(C)C=C1</chem>
223	Naftopidil	<chem>OC(CN1CCN(C)C=CC=C2)C(C1)COC3=CC=CC4=CC=CC=C34</chem>
224	Piribedil	<chem>C1(N2CCN(C)C3=CC=C(C)C4)C4=C3)CC2)=NC=CC=N1</chem>
225	Pizotifen	<chem>CN1CC(C)C(C1)=C2C3=CC=CC=C3CCC4=C2C=C4</chem>
226	Fesoterodine (fumarate)	<chem>OCC1=CC([C@H](CCN(C)C)C(C)C)C2=CC=CC=C2)=C(C=C1)OC(C)C(C)=O.O(C(C)C(C)O)=O</chem>
227	Sparsentan	<chem>O=S(C1=CC=CC=C1C2=CC=C(C)N3C(C)CCC(C)N4(C)CC(C)C3)=O)C=C2COC(C)N(C5=NO(C)C=C5C)=O</chem>
228	LY2828360	<chem>CN1CCN(C2=C3N=C(C4=CC=CC=C4)N(C5CCOCC5)C3=NC(C)C=N2)CC1</chem>
229	BMS-813160	<chem>CC(N)C@H)1(C@H)(N2C([C@H](NC3=NC=NC4=CC(C)C(C)C)=NN43)CC2)=O)CC(C@H)(NC(C)C)C1=O</chem>
230	Filorexant	<chem>CC1=CC(C)N2C(C)C@H)(COC3=CC=C(C)C(F)C=N3)CC(C@H)2C(O)=C(C4=NC=CC=N4)C=C1</chem>
231	Trimethobenzamide hydrochloride	<chem>O=C(NCC1=CC=C(C)OCCN(C)C=C1)C2=CC(C)C(C)C=C(C)C(C)C(C)C=C2.Cl</chem>
232	Doxofylline	<chem>O=C(N1C)N(C)C2=C(N)CC3OCC3)C=N2)C1=O</chem>
233	Foligluxar (monohydrochloride)	<chem>O/N=C1C=C(C2=CC3=C(C=C3)C=N2)OC4=CC=C(C)CCCN5CCOCC5)C=C14.Cl</chem>
234	Clorprenaline hydrochloride	<chem>O(C)CNC(C)C(C1=CC=CC=C1Cl).[H]Cl</chem>
235	Eletriptan (hydrobromide)	<chem>O=S(CCC1=CC2=O)NC=C2C(C@H)3N(C)C(C)C=C1)(C4=CC=CC=C4)=O.Br</chem>
236	Evocalcet	<chem>O=C(O)CC1=CC=C(C)N2C(C)C@H)(N(C)C@H)(C3=C4C=CC=CC4=CC=C3)C(C)CC2)C=C1</chem>
237	Bilastine	<chem>CC(C)C1=CC=C(C)CCN2CCC(C3=NC4=CC=CC=C4N3CCOCC)CC2)C=C1)C(O)=O</chem>
238	LGD-6972	<chem>O=C(N(CS(=O)(=O)O)O)C1=CC=C(C)C(C@H)(C2=CC=C(C3=CC=C(C(C)C)C=C3)C=C2)C(NC4=CC=C(C5=C(C)C=C(C)C(C5)C=C4)O)C=C1</chem>
239	E6130	<chem>C(C@H)(C1)C@H)(C1)C(NC2CCN(C)C=CC(C)C2)=O)C(C)O)CN1CC4=C(C)C(F)(F)F)C=CC=C4Cl</chem>
240	Aticaprant	<chem>O=C(N)C1=CC=C(C)C2=CC=C(C)N3(C@H)(C4=CC(C)=CC(C)C4)CCC3)C=C2)C(F)=C1</chem>

321	Mebhydrolin (napadisylate)	<chem>O=S(C1=C2C=CC=C(S(=O)(O)=O)C2=CC=C1)(O)=O.CN(C3)CCC(N4CC5=CC=CC=C5)=C3C6=C4C=CC=C6.CN(C7)CCC(N8CC9=CC=CC=C9)=C7C%10=C8C=CC=C%10</chem>
322	Trazodone (hydrochloride)	<chem>O=C1N(CCN2CCN(C3=CC=CC(C)=C3)CC2)N=C4C=CC=CN41.Cl</chem>
323	Clebopride (maleate)	<chem>O=C(O)C(O)CC(O)=O.O=C(NC1CCN(CC2=CC=CC=C2)CC1)C3=CC(C)=C(N)C=C3OC</chem>
324	Bindarit	<chem>CC(OC1=NN(CC2=CC=CC=C2)C3=C1C=CC=C3)(C)C(O)=O</chem>
325	Atenolol	<chem>O=C(N)CC1=CC=C(OC(C)CNC(C)C)C=C1</chem>
326	Doxylamine (succinate)	<chem>O=C(O)CC(O)=O.CC(C1=NC=CC=C1)(C2=CC=CC=C2)OCCN(C)C</chem>
327	Alvimopan (dihydrate)	<chem>OC1=CC=CC([C@@]2(C)[C@@H](C)CN(C[C@@H](CC3=CC=CC=C3)C(NCC(O)=O)CC2)=C1.O.O</chem>
328	Phenoxybenzamine (hydrochloride)	<chem>CC(COC1=CC=CC=C1)N(CCC)CC2=CC=CC=C2.Cl</chem>
329	Carbazochrome (sodium sulfonate)	<chem>O=S(C(C1=C/C2=N/NC(N)=O)N(C)C1=CC2=O)([O-])=O.[Na+]</chem>
330	Tizanidine (hydrochloride)	<chem>ClC1=C(NC2=NCCN2)C3=NSN=C3C=C1.Cl</chem>
331	Fenspiride (Hydrochloride)	<chem>O=C1OC2(CCN(CCC3=CC=CC=C3)CC2)CN1.[H]Cl</chem>
332	Bromocriptine (mesylate)	<chem>[H][C@@]12CC3=C(Br)NC4=CC=CC(C1=C[C@@H](C(N(C@@)5(C)C)C(N6[C@@H](CC(C)C)C(N7CC[C@@]7([C@@]6(O)O5)[H])=O)=O)=O)CN2C)=C43.OS(=O)(C)=O</chem>
333	Setiptiline (maleate)	<chem>CN1CC(C(C=CC=C2)=C2C3)=C(C1)C4=C3C=CC=C4.O=C(O)/C=C/C(O)=O</chem>
334	Chlorcyclizine (hydrochloride)	<chem>Cl(C=C1)=CC=C1C(C2=CC=CC=C2)N3CCN(C)CC3.Cl</chem>
335	Nebivolol (hydrochloride)	<chem>FC1=CC=C2C(C(C)[C@@H](C)CN(C[C@@H](O)[C@@]3([H])CCC(C=C(F)C=C4)=C4O3)([H])O2)=C1.Cl</chem>
336	Perphenazine	<chem>OCCN1CCN(CCCN2C3=C(C=CC=C3)SC4=CC=C(C)C=C24)CC1</chem>
337	Mianserin (hydrochloride)	<chem>CN(C1)CC2N1C3=CC=CC=C3CC4=CC=CC=C24.Cl</chem>
338	Clemastine (fumarate)	<chem>CN1[C@@H](CCO[C@@](C2=CC=CC=C2)(C3=CC=C(C)C=C3)CCC1.O=C(O)/C=C/C(O)=O</chem>
339	Mepyramine maleate	<chem>CN(C)CCN(C1=CC=C(C(O)C=C1)C2=NC=CC=C2.O=C(O)/C=C/C(O)=O</chem>
340	Mozavaptan	<chem>CC1=CC=CC=C1C(NC2=CC=C(C(N3C(C=CC=C4)=C4C(N(C)C)CCC3)=O)C=C2)=O</chem>
341	Naratriptan (hydrochloride)	<chem>O=S(CCC1=CC2=C(NC=C2C3CCN(C)CC3)C=C1)(NC)=O.Cl</chem>
342	Solifenacin (hydrochloride)	<chem>O=C(O)C@H1CN2CCC1CC2)N3[C@H](C4=C(C)CC3)C=CC=C4)C5=CC=CC=C5.Cl</chem>
343	Tegaserod (maleate)	<chem>O=C(O)/C=C/C(O)=O.COC1=CC=C(NC=C2/C=N/NC(NCCCC)=N)C2=C1</chem>
344	Istradefylline	<chem>O=C1C2=C(N=C(/C=C/C3=CC(O)C(O)C=C3)N2O)N(CO)C(N1CC)=O</chem>
345	Dexpramipexole (dihydrochloride)	<chem>NC(S1)=NC2=C1C[C@H](NCCC)CC2.[H]Cl.[H]Cl</chem>
346	Nalfurafine (hydrochloride)	<chem>O[C@@]1(CC[C@@H](N(C)C/C=C/C2=COC=C2)=O)[C@]3([H])OC4=C5O[C@@]63C4=C(C=C5)C[C@@]1([H])N(CC7CC7)CC6.[H]Cl</chem>

6. Time course metabolism study of 12 selected drugs using *Bac-Mix*

Fig. S210. Time course metabolism study of iloperidone using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 427.2028) were determined at various time points (0 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, $n=3$. Data represent mean $\pm$ s.d. RT: retention time; area: peak area.

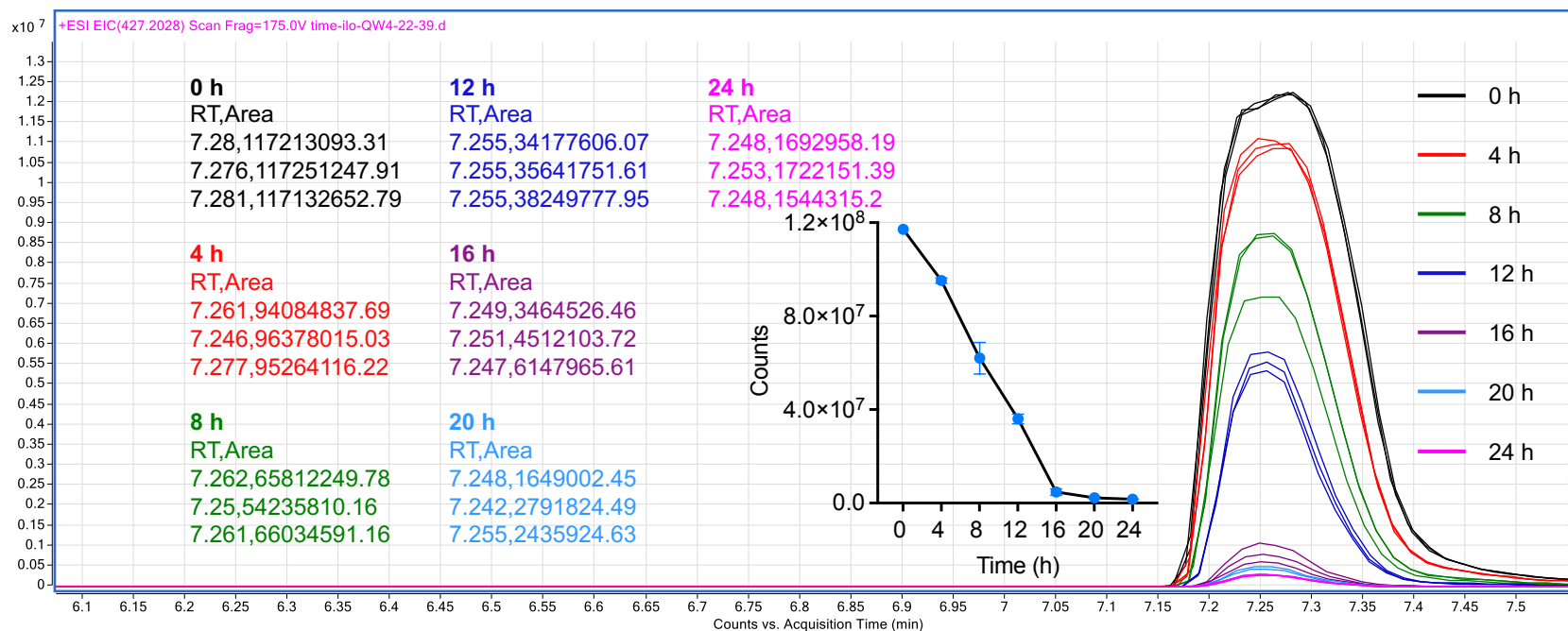


Fig. S211. Time course metabolism study of ponesimod using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 461.1296) were determined at various time points (0 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, $n=3$. Data represent mean $\pm$ s.d. RT: retention time; area: peak area.

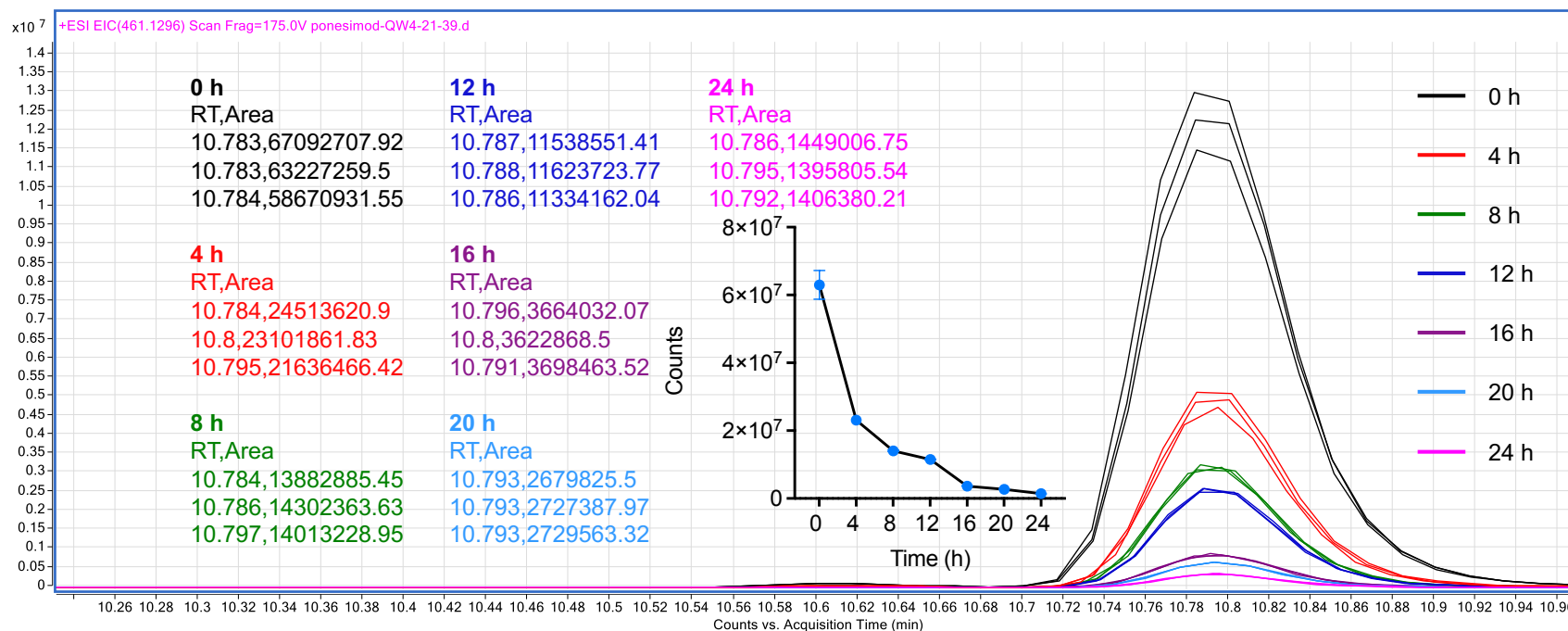


Fig. S212. Time course metabolism study of SB756050 using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 501.1360) were determined at various time points (0 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, $n=3$. Data represent mean $\pm$ s.d. RT: retention time; area: peak area.

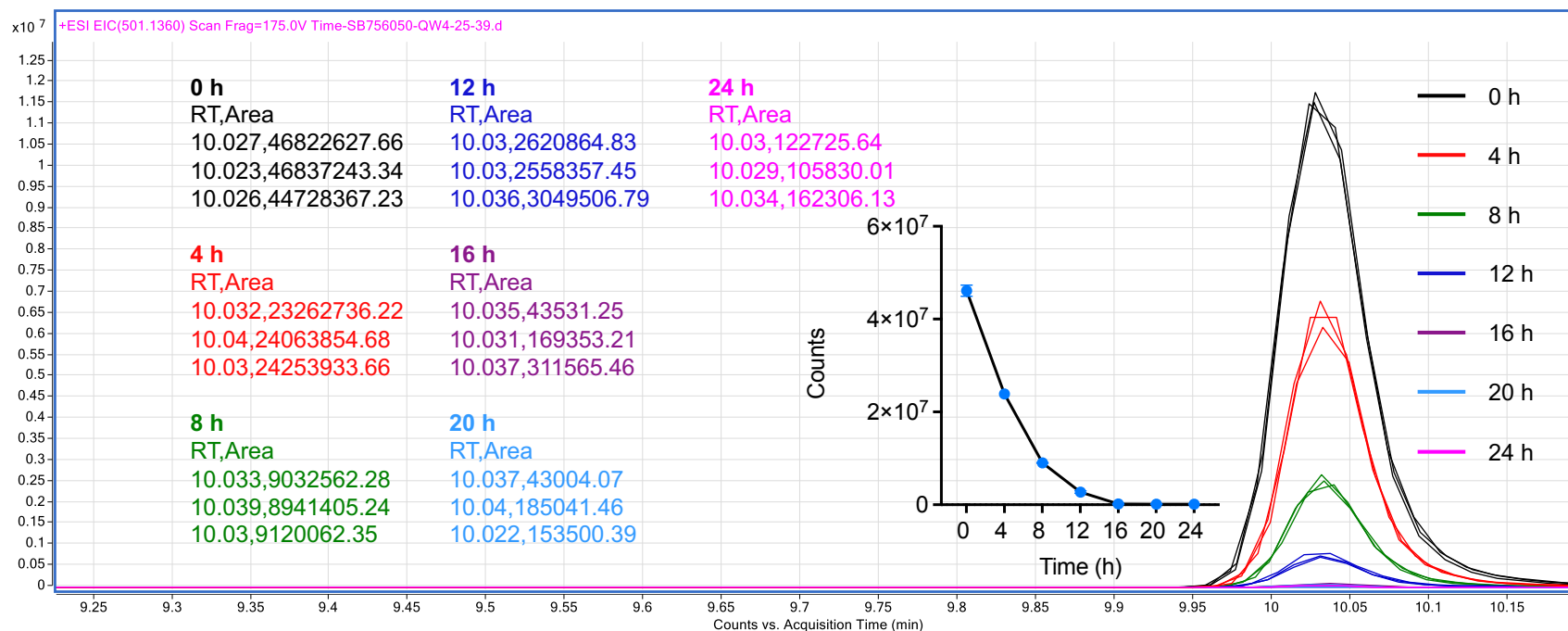


Fig. S213. Time course metabolism study of ozanimod using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 405.1921) were determined at various time points (0 h, 4h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, n=3. Data represent mean $\pm$ s.d. RT: retention time; area: peak area; not detected: n.d.

Fig. S214. Time course metabolism study of fesoterodine using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 412.2846) were determined at various time points (0 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, $n=3$. Data represent mean $\pm$ s.d. RT: retention time; area: peak area.

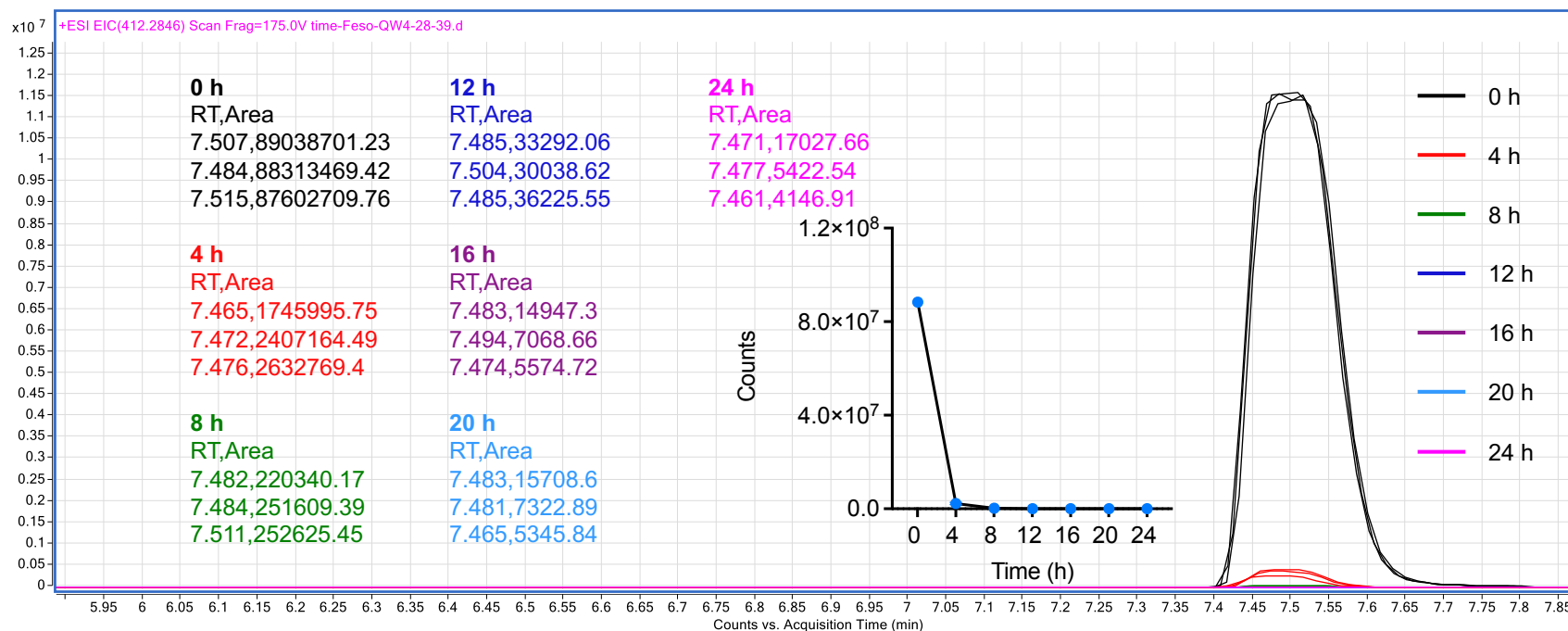


Fig. S215. Time course metabolism study of GSK1292263 using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 457.1904) were determined at various time points (0 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, $n=3$. Data represent mean $\pm$ s.d. RT: retention time; area: peak area; not detected: n.d.

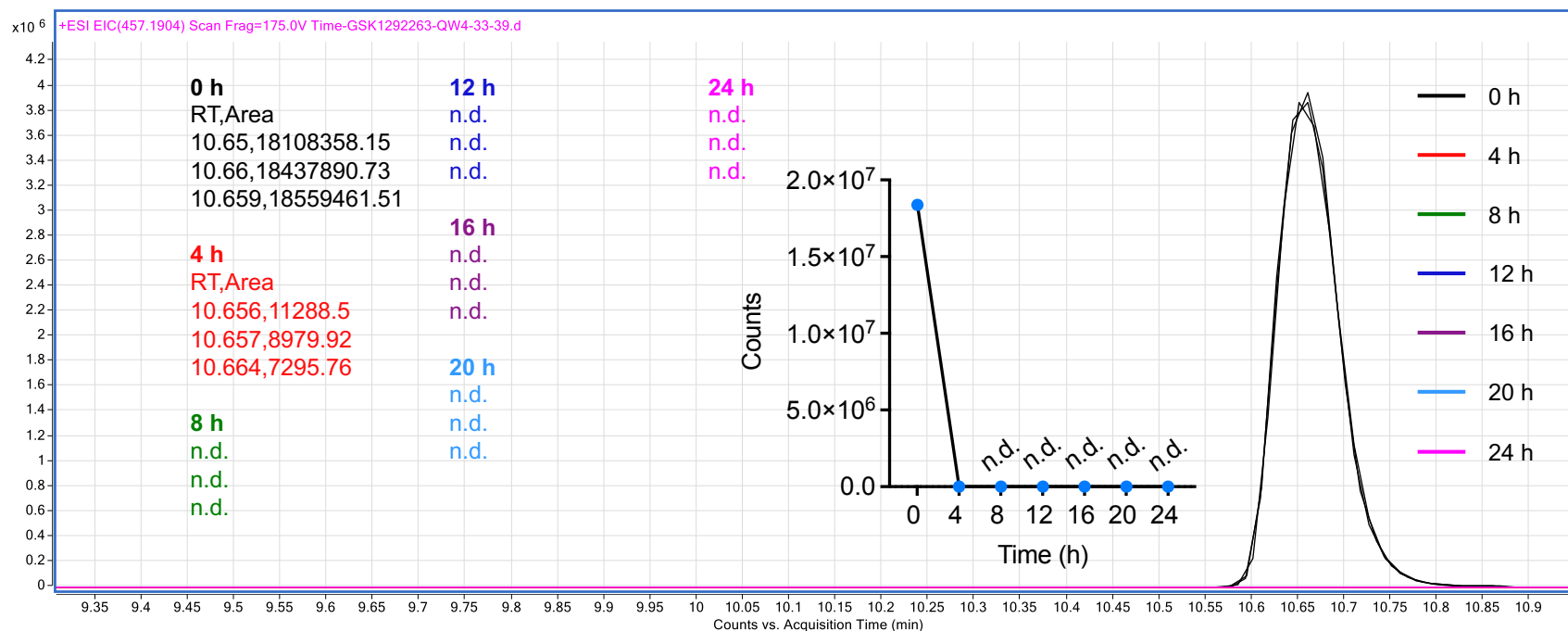


Fig. S216. Time course metabolism study of olmesartan medoxomil using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 559.2300) were determined at various time points (0 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, $n=3$. Data represent mean $\pm$ s.d. RT: retention time; area: peak area; not detected: n.d.

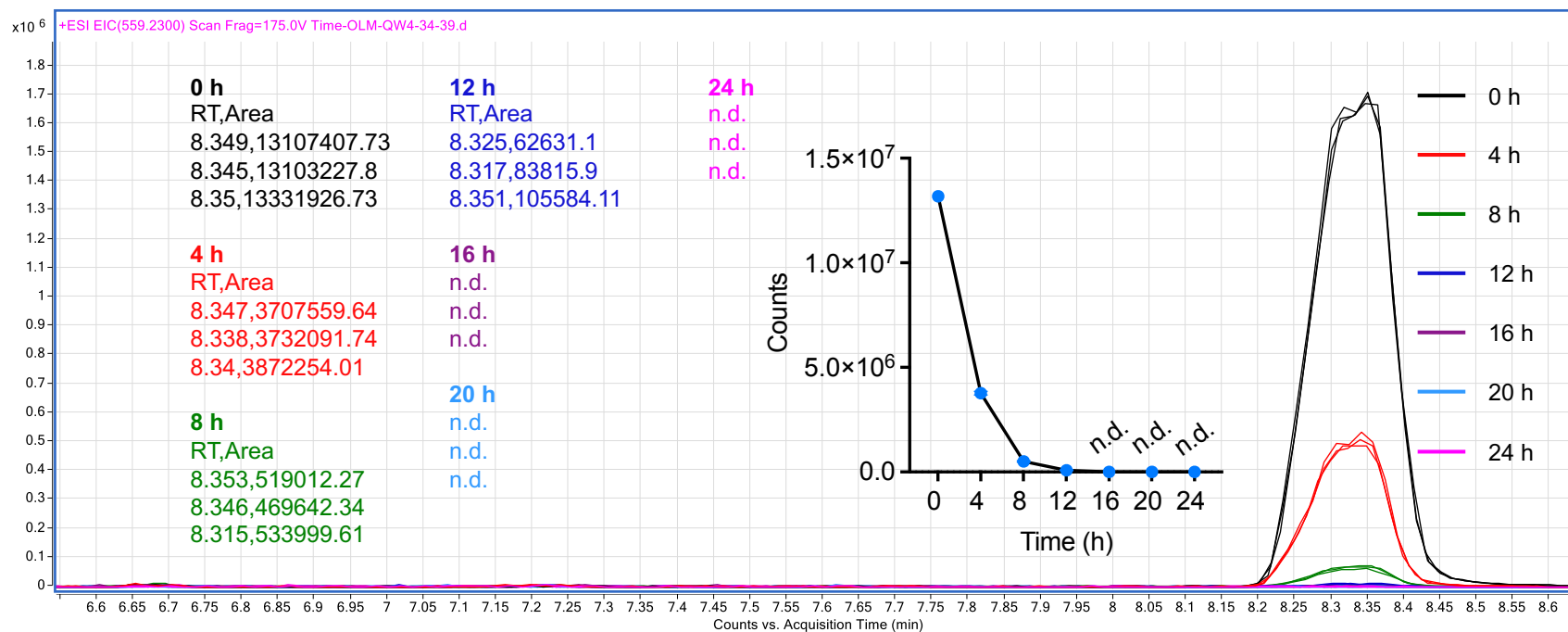


Fig. S217. Time course metabolism study of sarpogrelate using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 430.2224) were determined at various time points (0 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, $n=3$. Data represent mean $\pm$ s.d. RT: retention time; area: peak area.

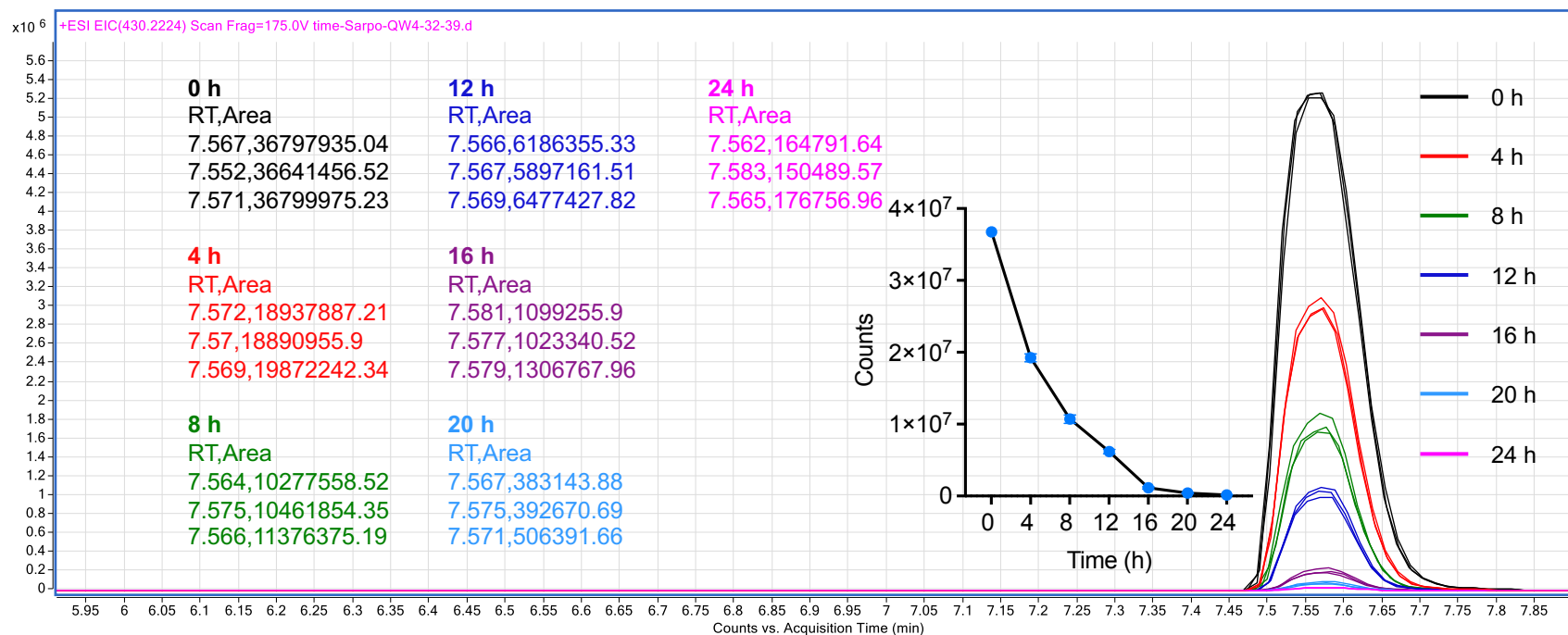


Fig. S218. Time course metabolism study of trimethobenzamide using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 389.2071) were determined at various time points (0 h, 4h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, $n=3$. Data represent mean $\pm$ s.d. RT: retention time; area: peak area; not detected: n.d.

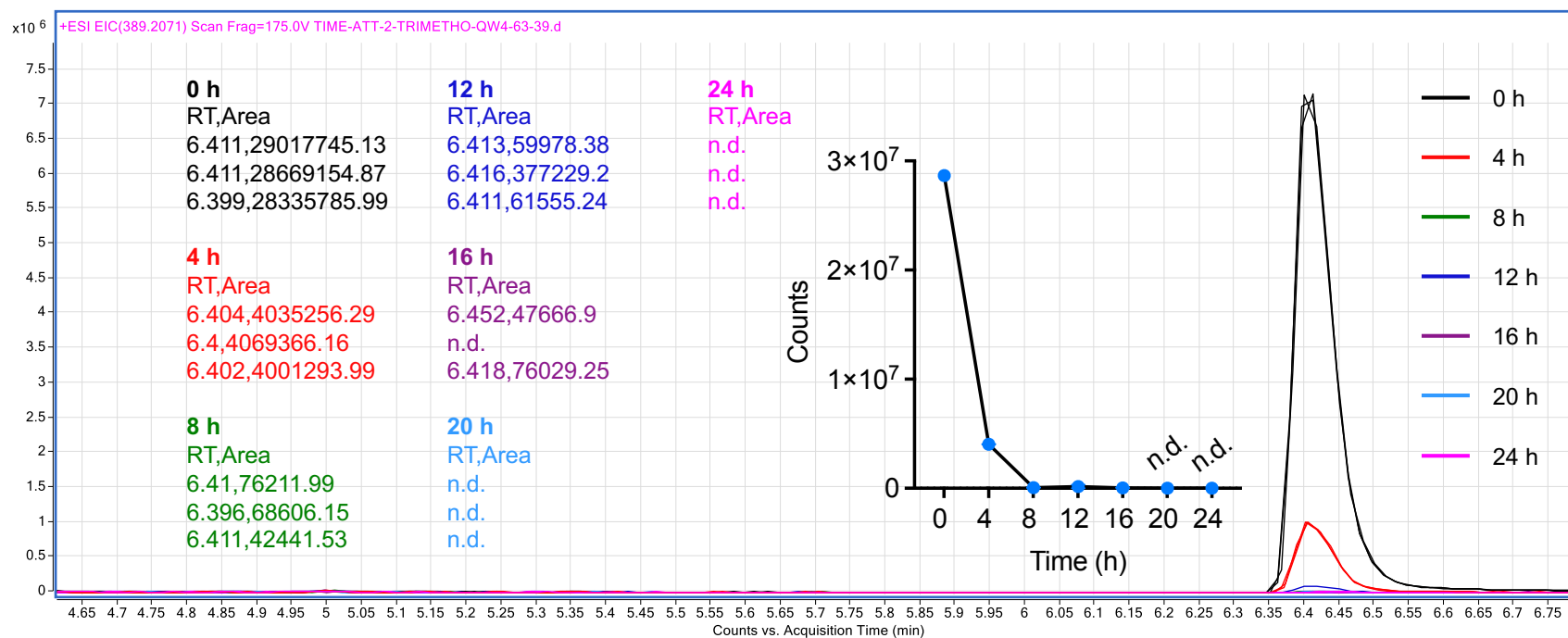


Fig. S219. Time course metabolism study of azilsartan medoxomil using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 569.1667) were determined at various time points (0 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, $n=3$. Data represent mean $\pm$ s.d. RT: retention time; area: peak area; not detected: n.d.

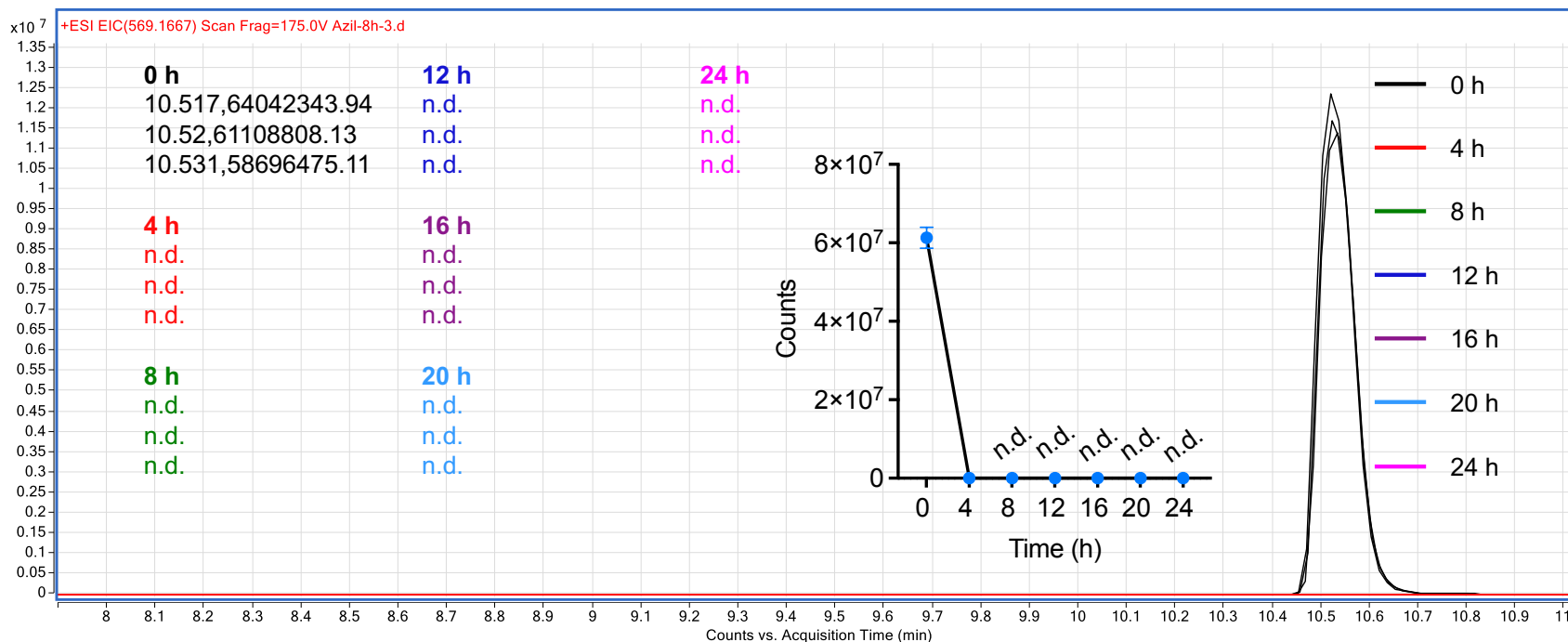


Fig. S220. Time course metabolism study of trimebutine using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 388.2118) were determined at various time points (0 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, $n=3$. Data represent mean $\pm$ s.d. RT: retention time; area: peak area.

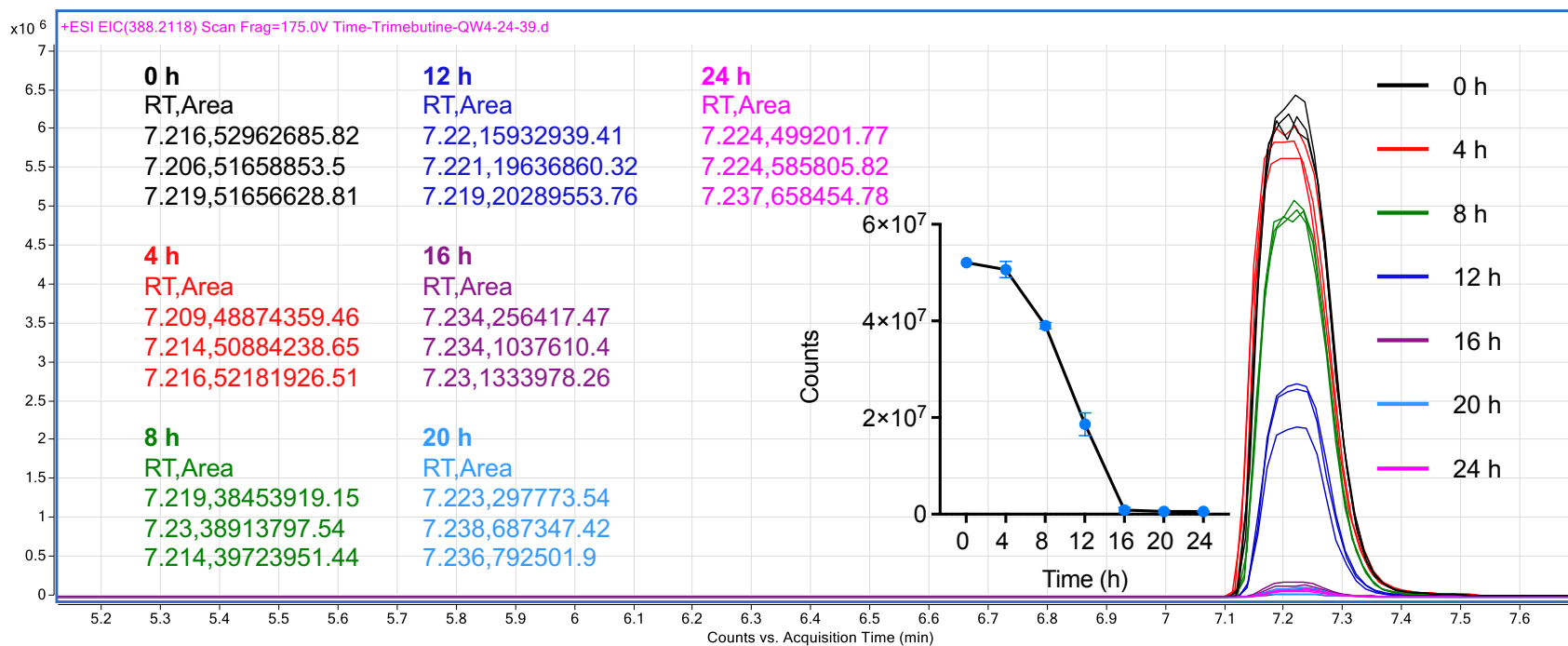
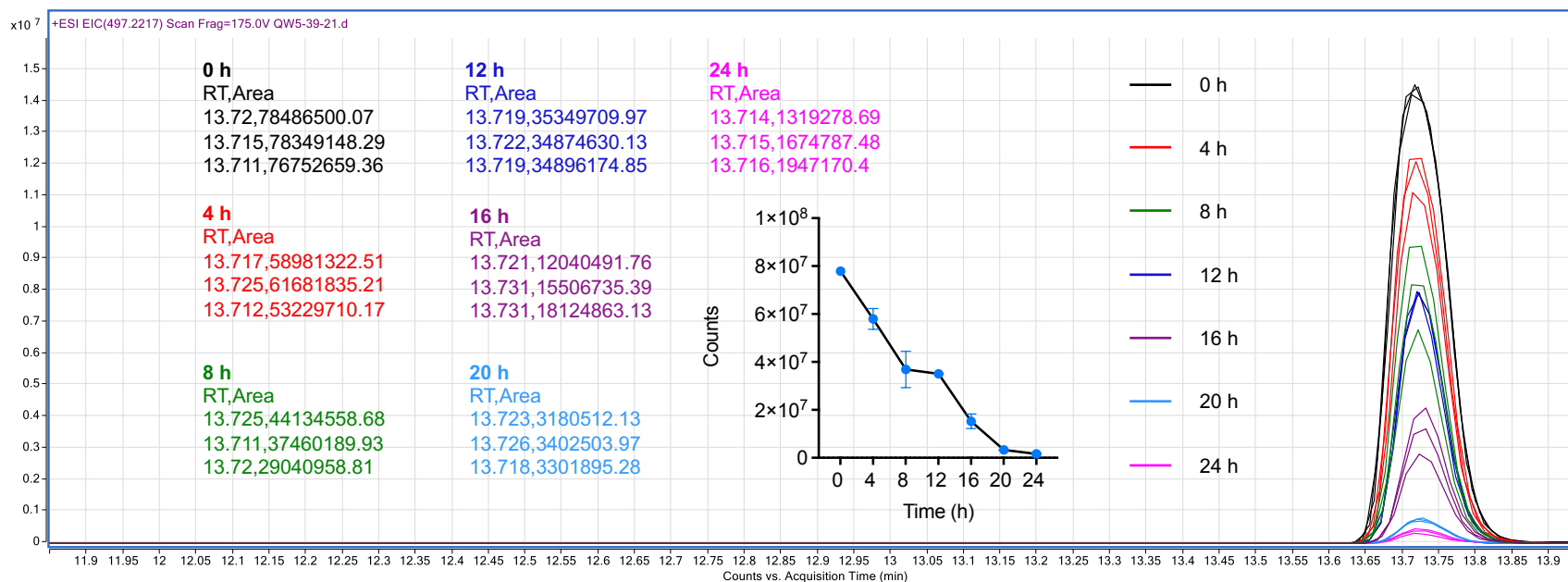


Fig. S221. Time course metabolism study of selezipag using *Bac-Mix*. The EICs (with a ± 20 ppm window) of the parent drug ion (m/z 497.2217) were determined at various time points (0 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h). The experiment was performed in triplicate, $n=3$. Data represent mean $\pm$ s.d. RT: retention time; area: peak area.



7. *In vivo* study of iloperidone in a mouse model

Fig. S222. Detection of iloperidone ($[M+H]^+$, m/z 427.2028) and its metabolite (ilo-430, $[M+H]^+$, m/z 430.2024) in mouse cecum samples colonized by *Bac-Mix* (n=4). A ± 20 ppm window was applied for EIC.

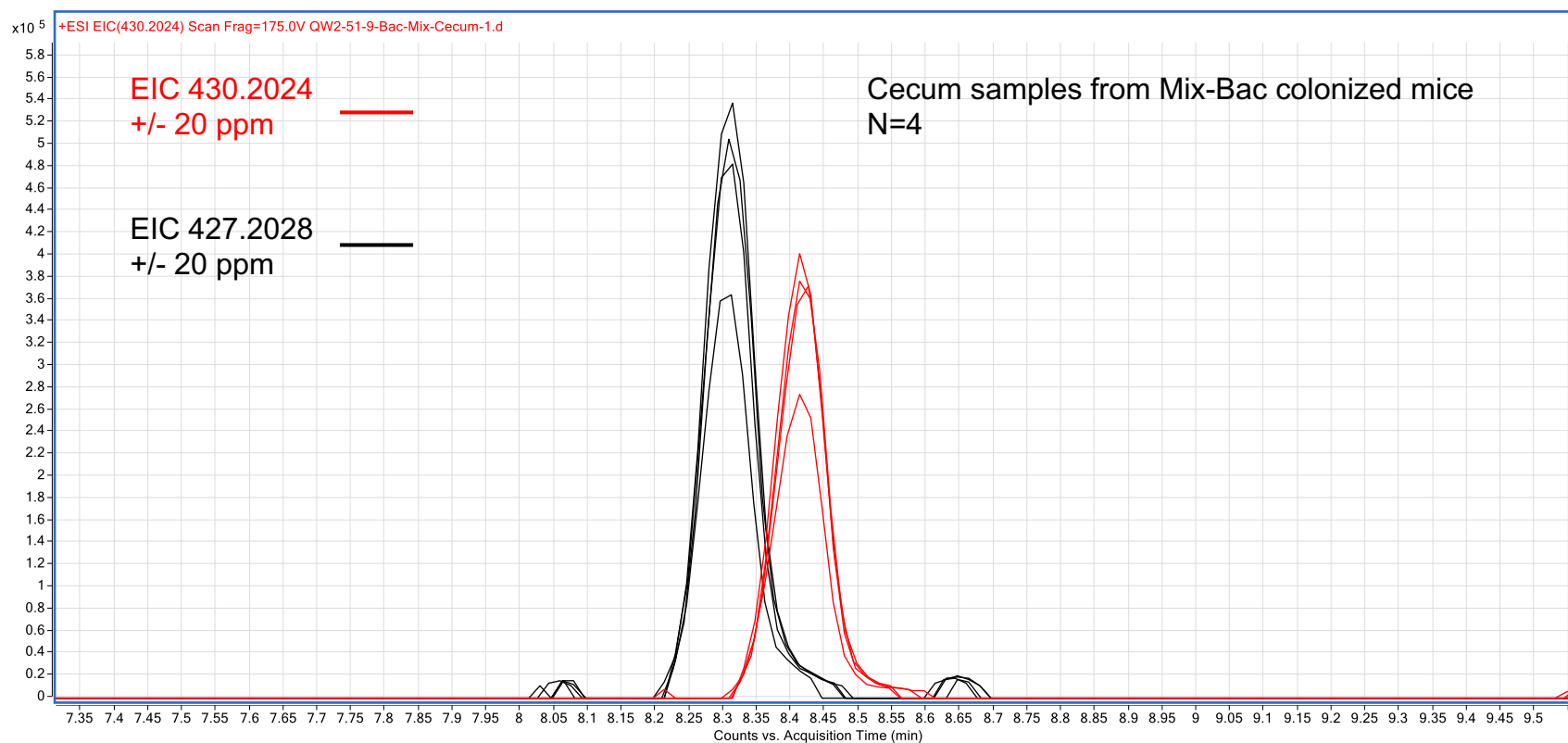


Fig. S223. Detection of iloperidone ($[M+H]^+$, m/z 427.2028) and its metabolite (ilo-430, $[M+H]^+$, m/z 430.2024) in mouse colon samples colonized by *Bac-Mix* ($n=4$). A ± 20 ppm window was applied for EIC.

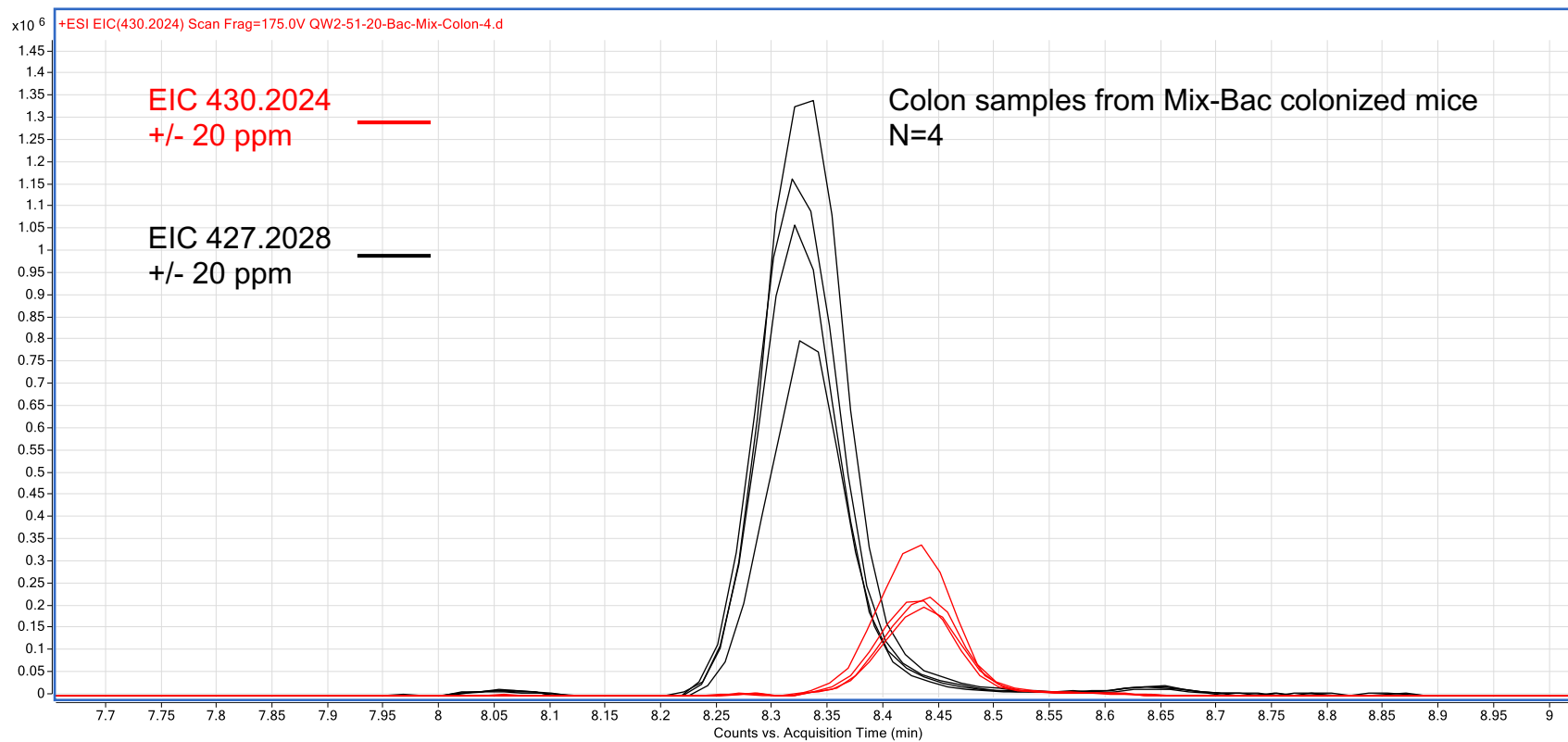


Fig. S224. Detection of iloperidone ($[M+H]^+$, m/z 427.2028) and its metabolite (ilo-430, $[M+H]^+$, m/z 430.2024) in germ-free (GF) mouse fecal samples ($n=3$). A ± 20 ppm window was applied for EIC.

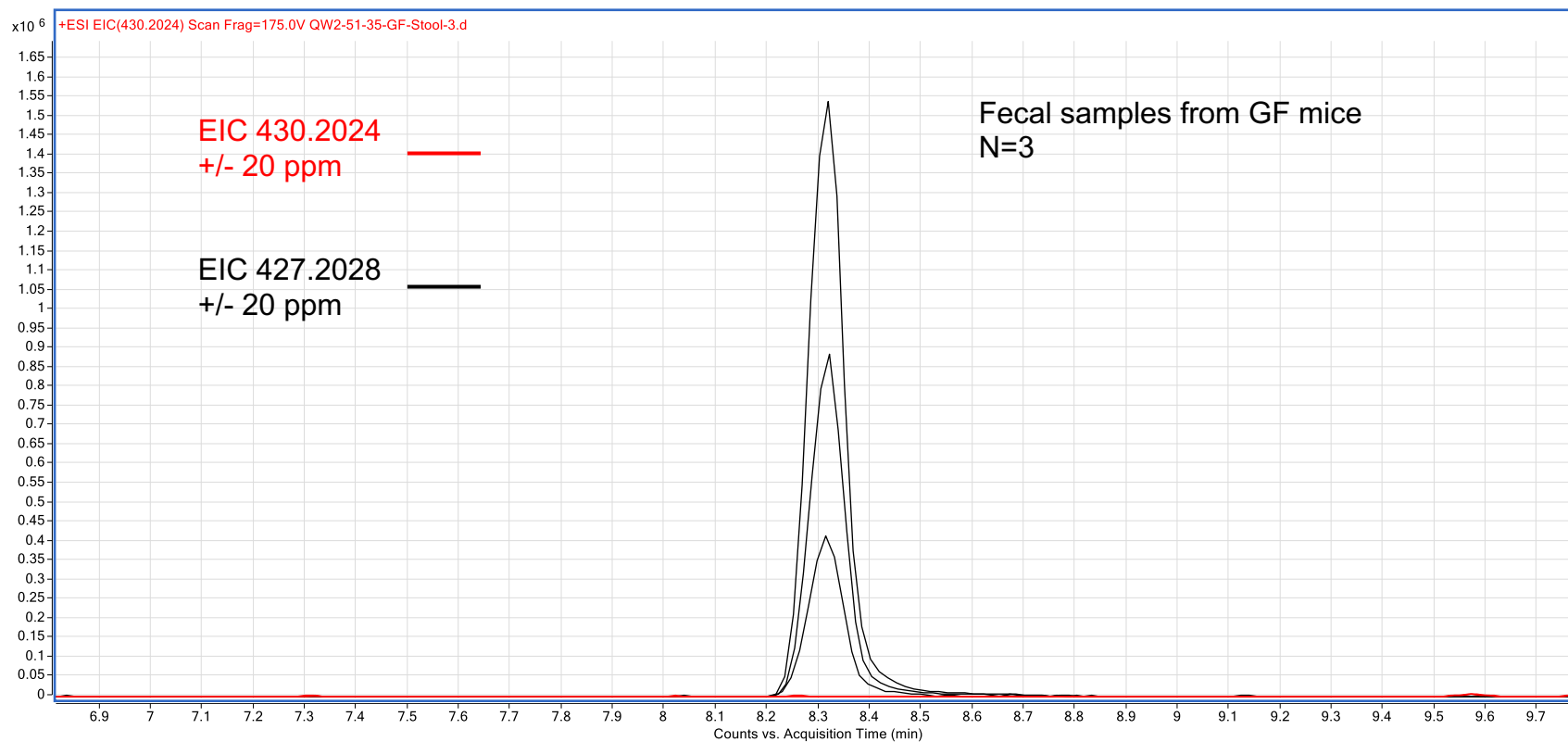


Fig. S225. Detection of iloperidone ($[M+H]^+$, m/z 427.2028) and its metabolite (ilo-430, $[M+H]^+$, m/z 430.2024) in germ-free (GF) mouse cecum samples (n=4). A ± 20 ppm window was applied for EIC.

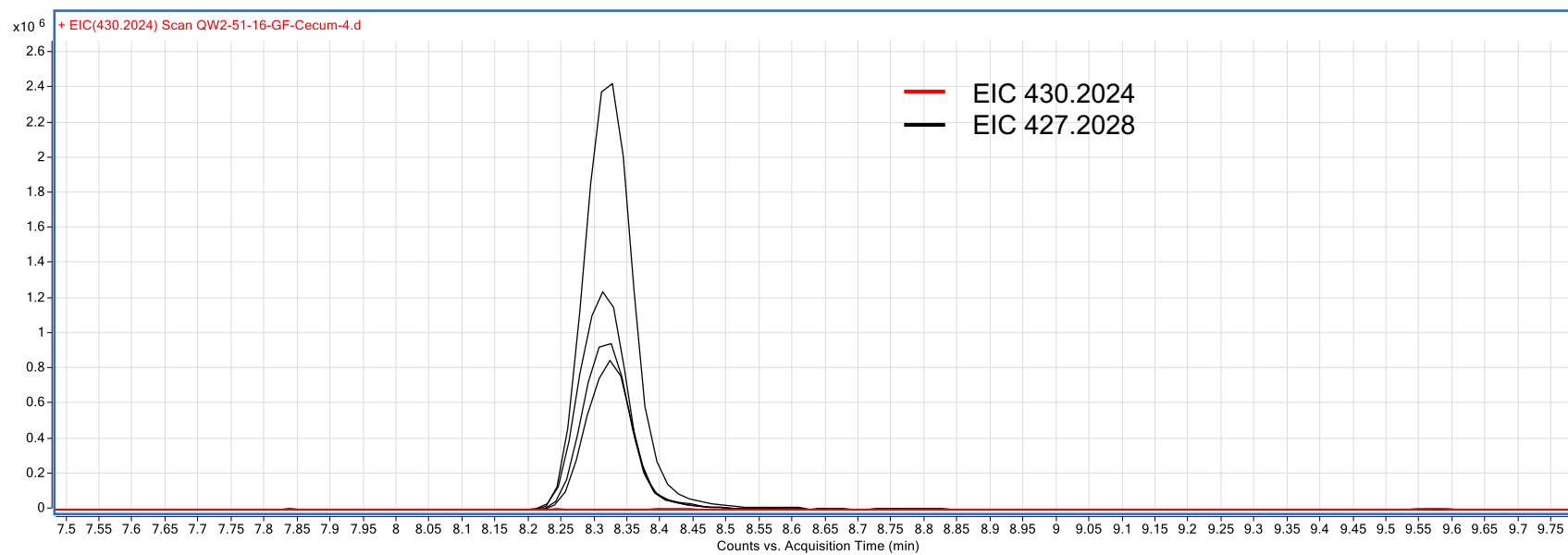


Fig. S226. Detection of iloperidone ($[M+H]^+$, m/z 427.2028) and its metabolite (ilo-430, $[M+H]^+$, m/z 430.2024) in germ-free (GF) mouse colon samples (n=4). A +/- 20 ppm window was applied for EIC.

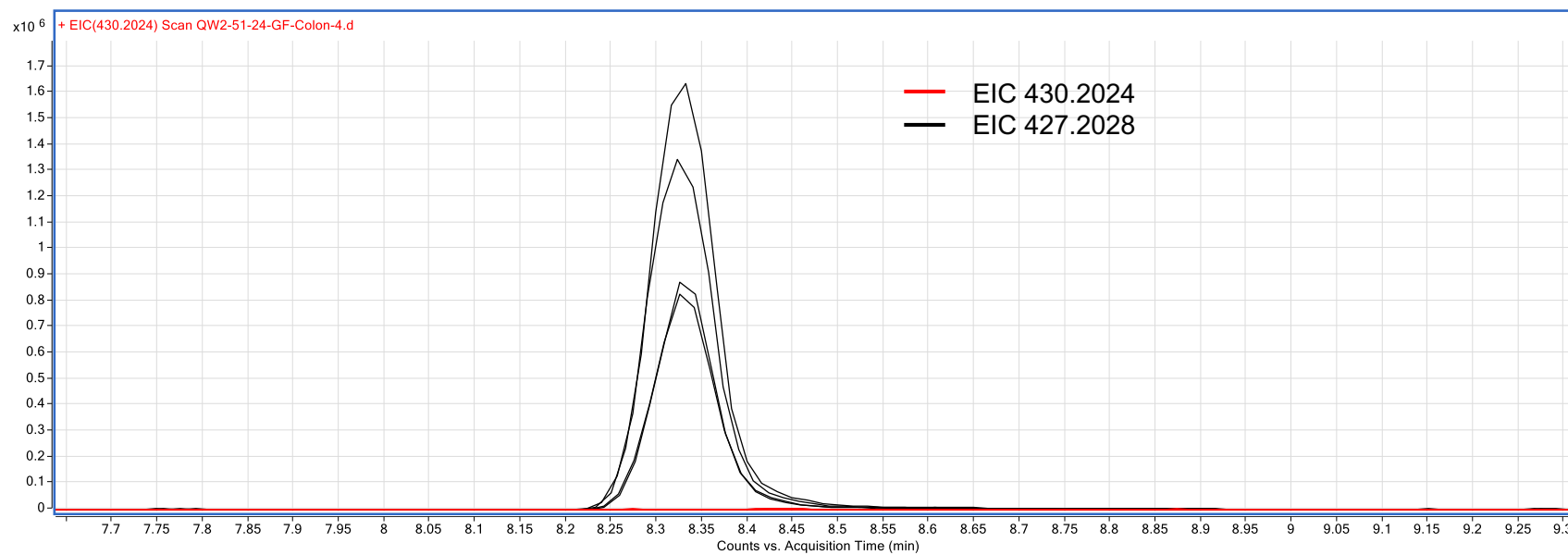


Fig. S227. Comparison of iloperidone metabolite (ilo-430, $[M+H]^+$, m/z 430.2024) levels in germ-free (GF) and *Bac-Mix* colonized mouse cecum samples (n=4). An EIC window of ± 20 ppm was applied. Not detected, n.d.

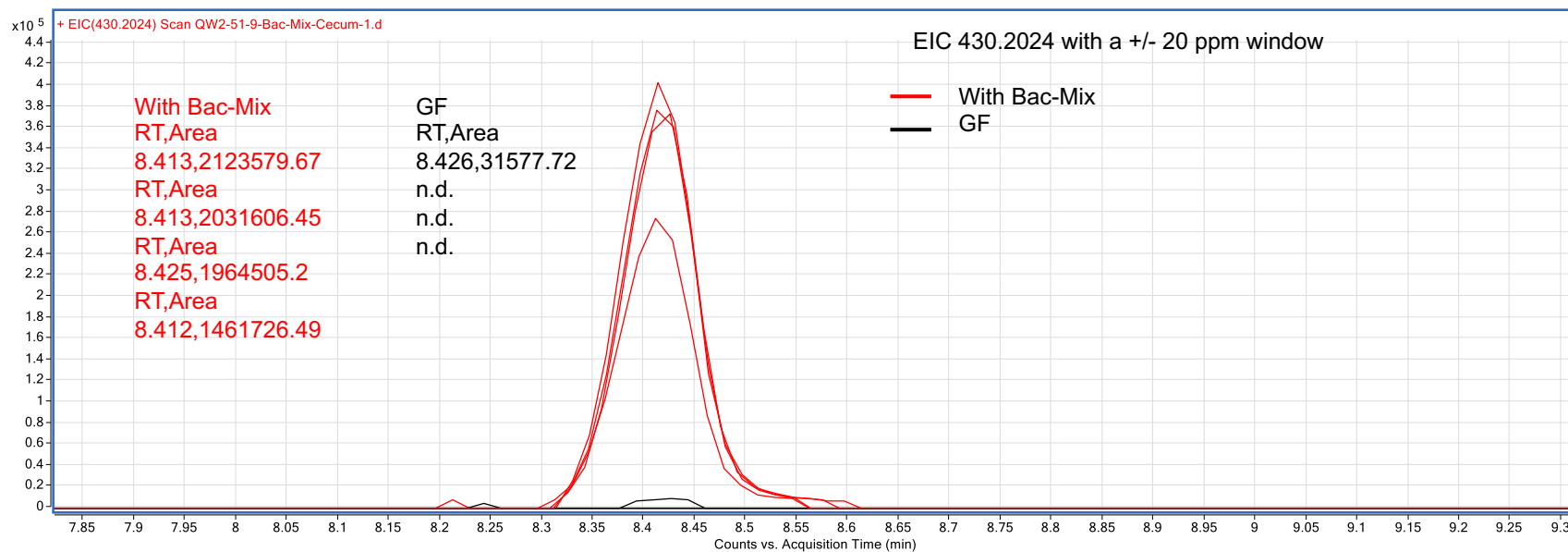


Fig. S228. Comparison of iloperidone metabolite (ilo-432, $[M+H]^+$, m/z 432.2181) levels in germ-free (GF) and *Bac-Mix* colonized mouse cecum samples (n=4). An EIC window of ± 20 ppm was applied. Not detected, n.d.

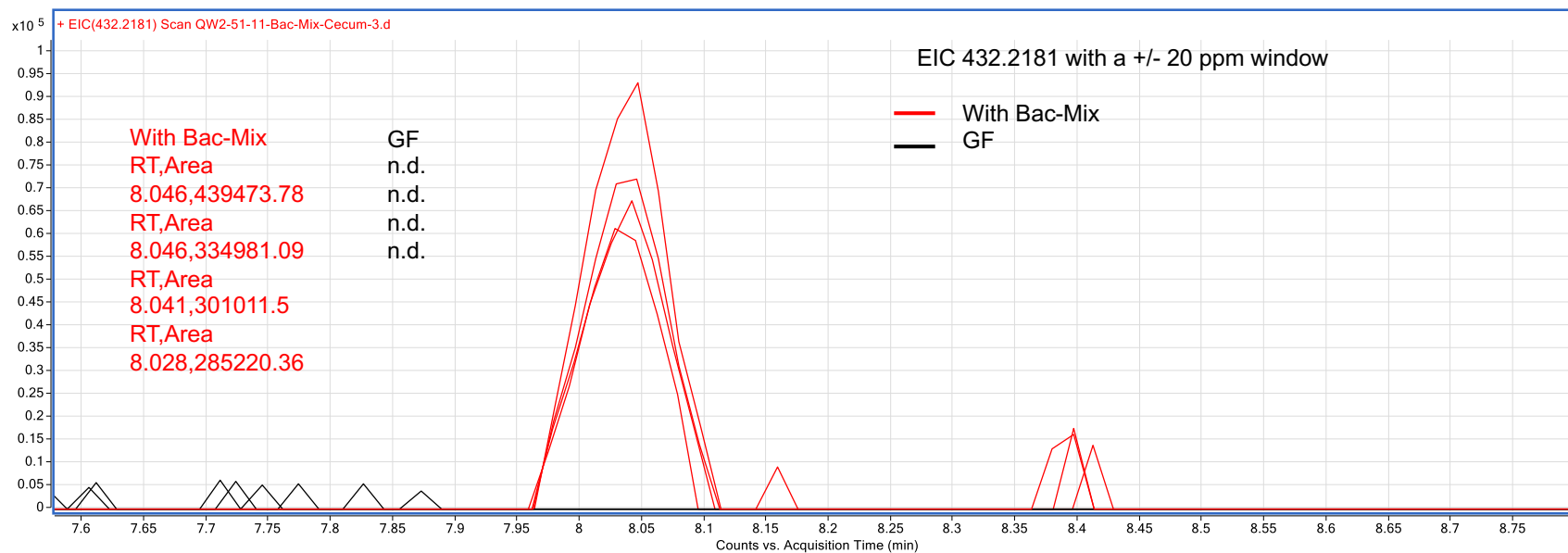


Fig. S229. Comparison of iloperidone metabolite (ilo-430, $[M+H]^+$, m/z 430.2024) levels in germ-free (GF) and *Bac-Mix* colonized mouse colon samples (n=4). An EIC window of ± 20 ppm was applied. Not detected, n.d.

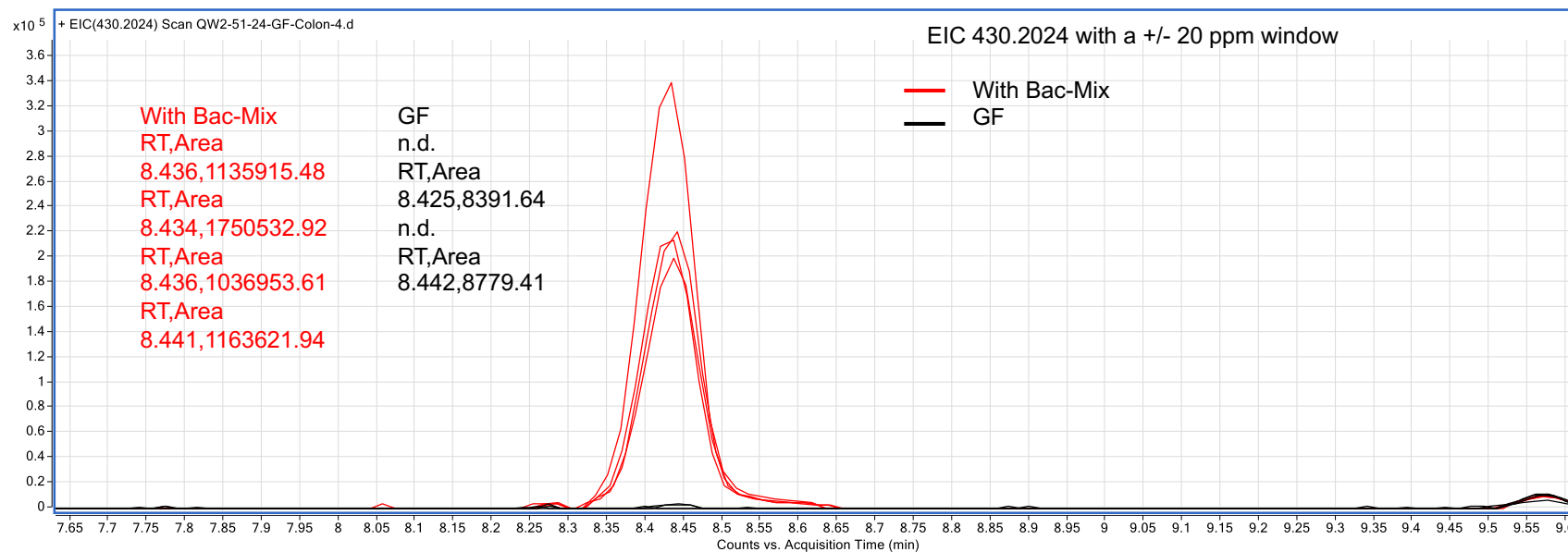


Fig. S230. Comparison of iloperidone metabolite (ilo-432, $[M+H]^+$, m/z 432.2181) levels in germ-free (GF) and *Bac-Mix* colonized mouse colon samples (n=4). An EIC window of ± 20 ppm was applied. Not detected, n.d.

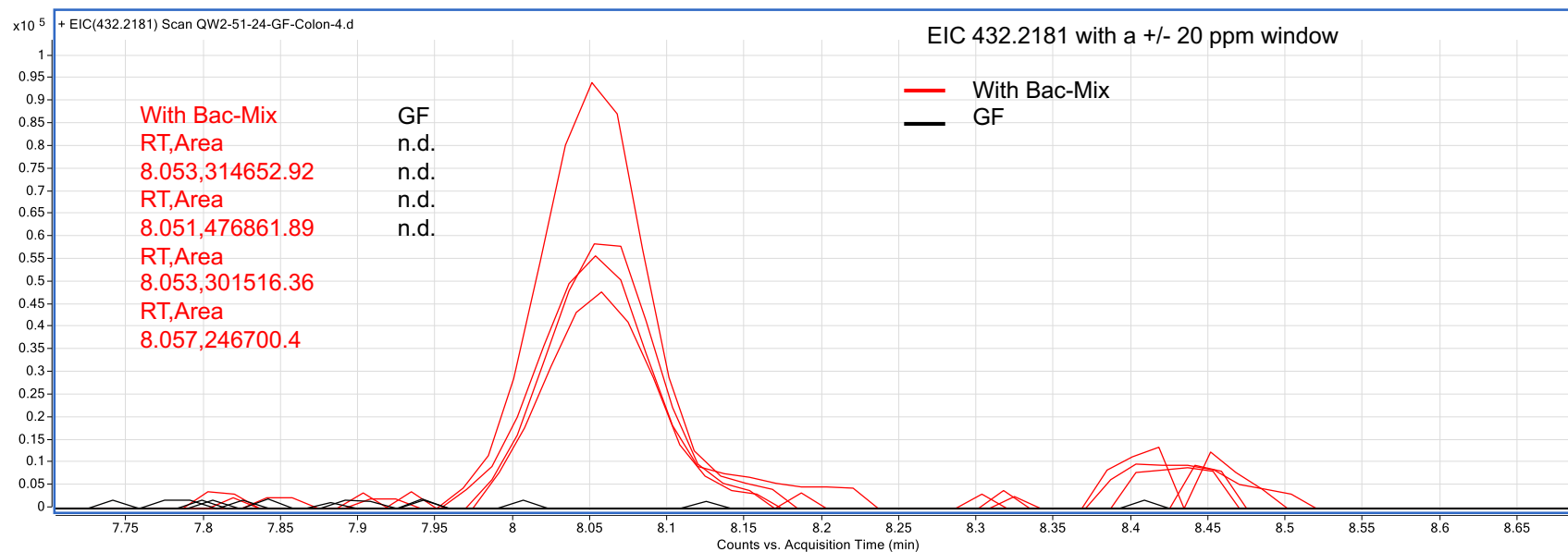


Fig. S231. Comparison of iloperidone metabolite (ilo-430, $[M+H]^+$, m/z 430.2024) levels in germ-free (GF) and *Bac-Mix* colonized mouse small intestine samples (n=4). An EIC window of ± 20 ppm was applied.

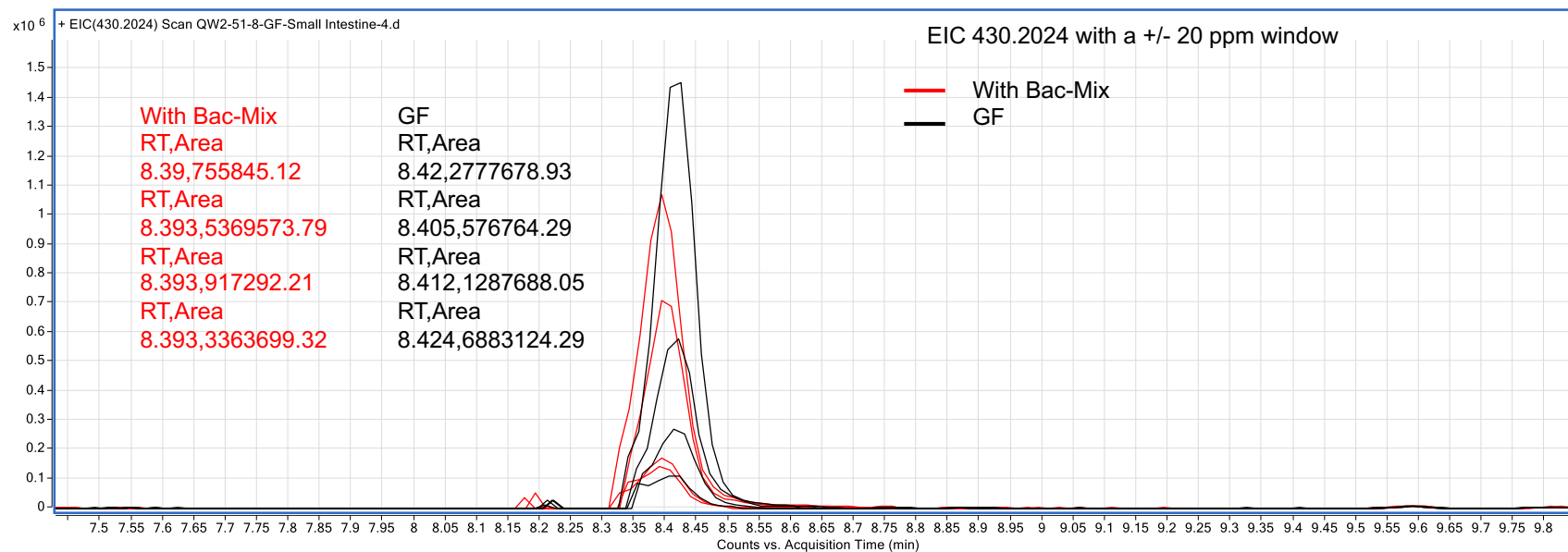


Fig. S232. Comparison of iloperidone metabolite (ilo-432, $[M+H]^+$, m/z 432.2181) levels in germ-free (GF) and *Bac-Mix* colonized mouse small intestine samples (n=4). An EIC window of ± 20 ppm was applied. The blue trace represents the EIC 432.2181 of a sample from the *Bac-Mix* cecum sample, shown as a standard of ilo-432. Samples from the small intestine of *Bac-Mix* and germ-free mice showed no detection of ilo-432. Not detected, n.d.

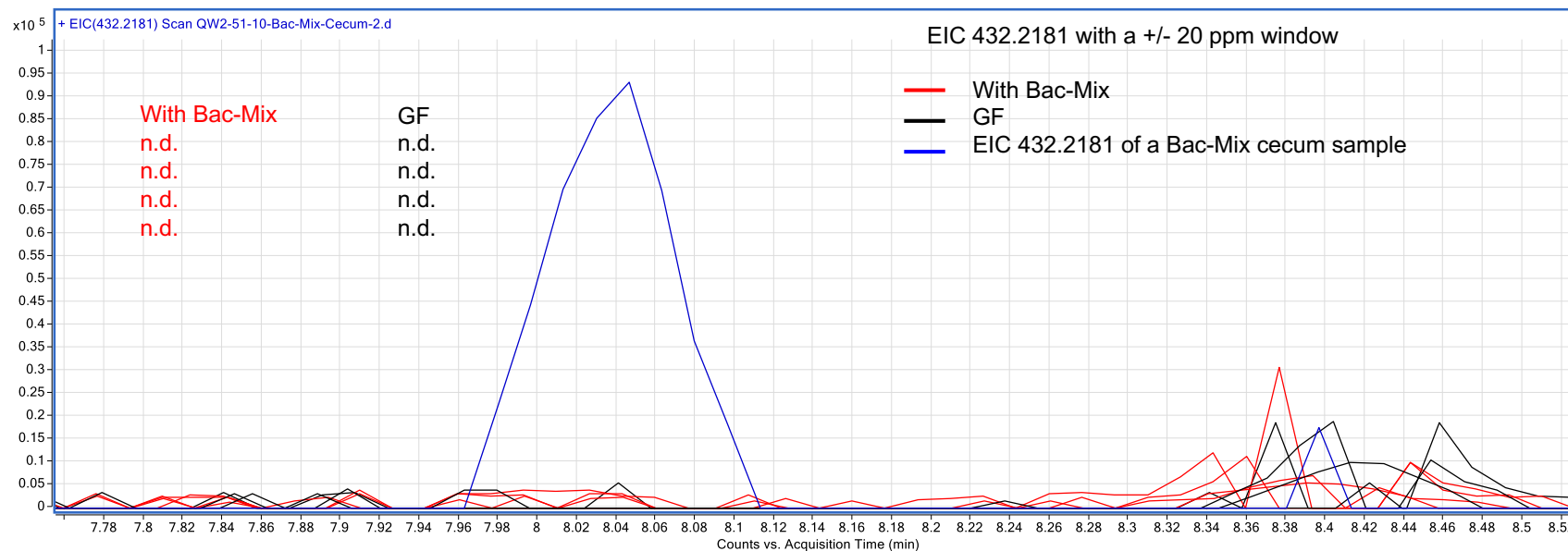


Fig. S233. Detection of iloperidone metabolite ilo-444 ($[M+H]^+$, m/z 444.1639) in *Bac-Mix* colonized mouse samples (n=4). A ± 20 ppm window was applied for EIC. No detection of ilo-444 was observed in the samples from the mouse cecum, colon, or small intestine.

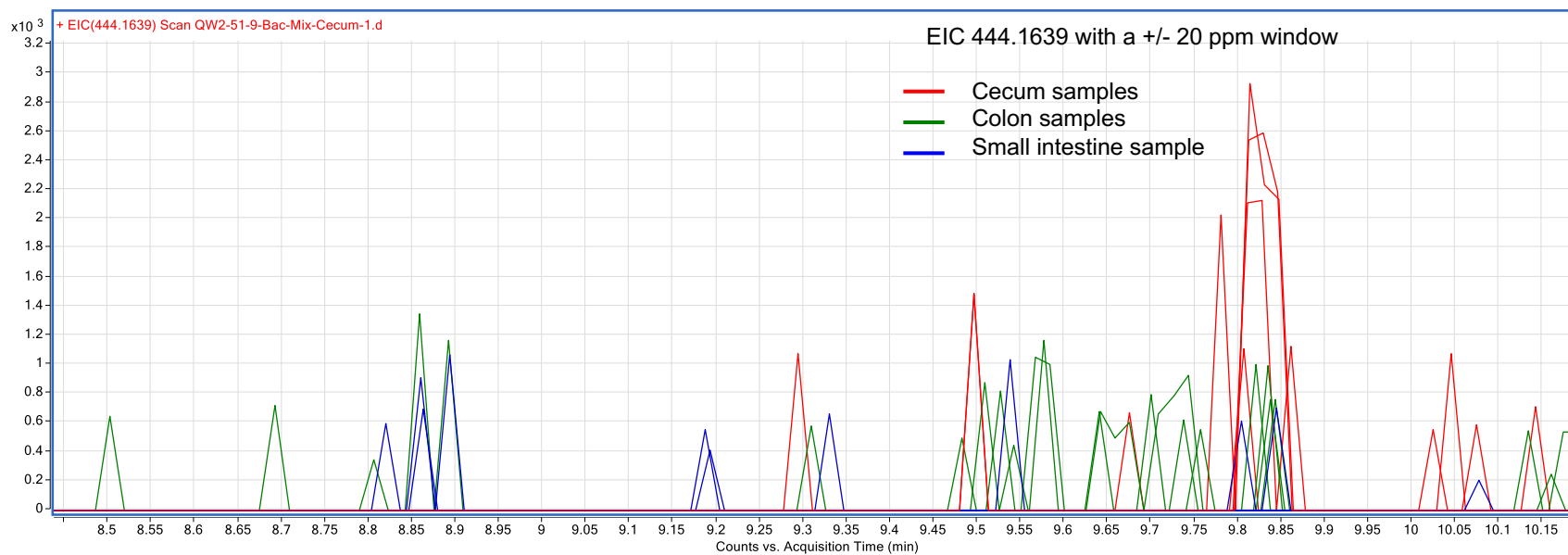


Fig. S234. Detection of iloperidone metabolite ilo-491 ($[M+H]^+$, m/z 491.2341) in *Bac-Mix* colonized mouse samples (n=4). A +/- 20 ppm window was applied for EIC. No detection of ilo-491 was observed in the samples from the mouse cecum, colon, or small intestine.

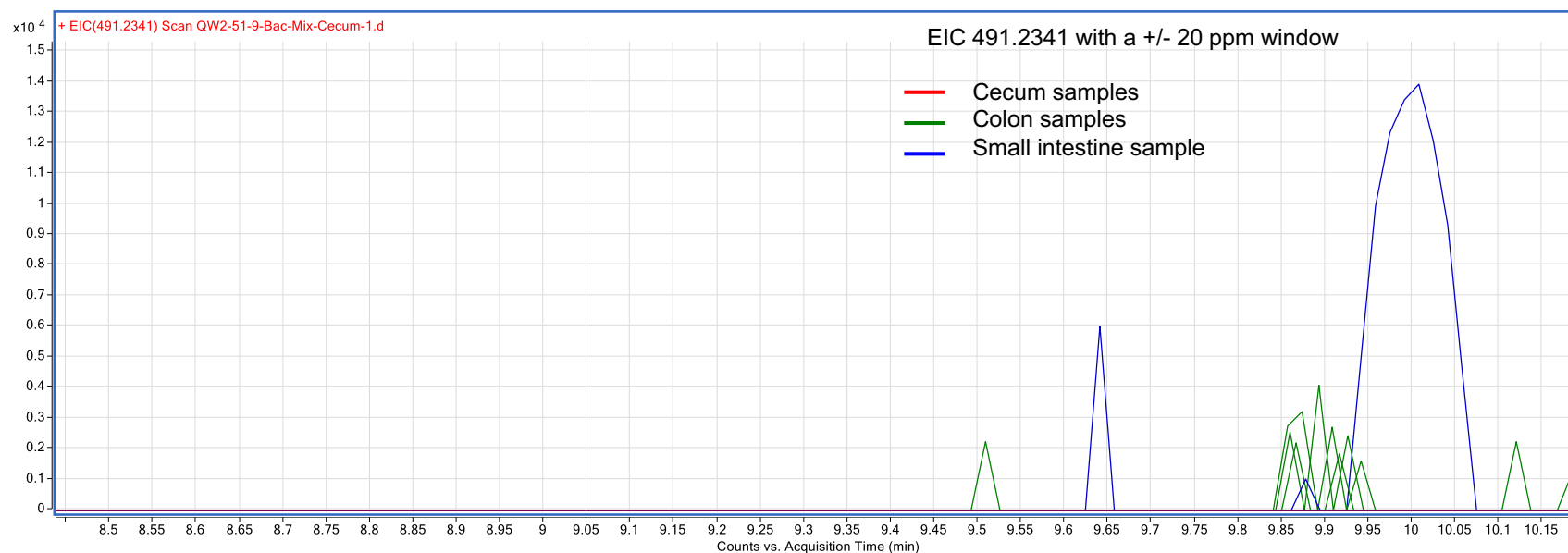


Fig. S235. Detection of iloperidone metabolite ilo-493 ($[M+H]^+$, m/z 493.2497) in *Bac-Mix* colonized mouse samples (n=4). A ± 20 ppm window was applied for EIC. No detection of ilo-493 was observed in the samples from the mouse cecum, colon, or small intestine.

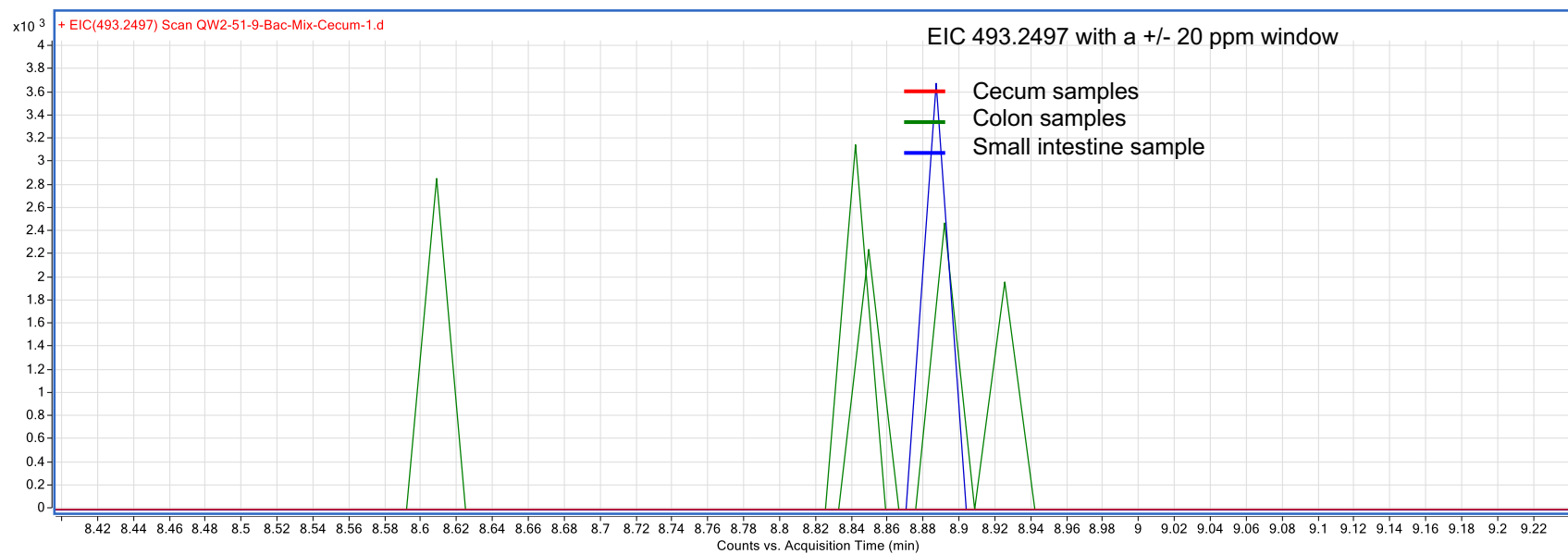


Fig. S236. Detection of iloperidone metabolite ilo-477 ($[M+H]^+$, m/z 477.2184) in *Bac-Mix* colonized mouse samples (n=4). A +/- 20 ppm window was applied for EIC. No detection of ilo-477 was observed in the samples from the mouse cecum, colon, or small intestine.

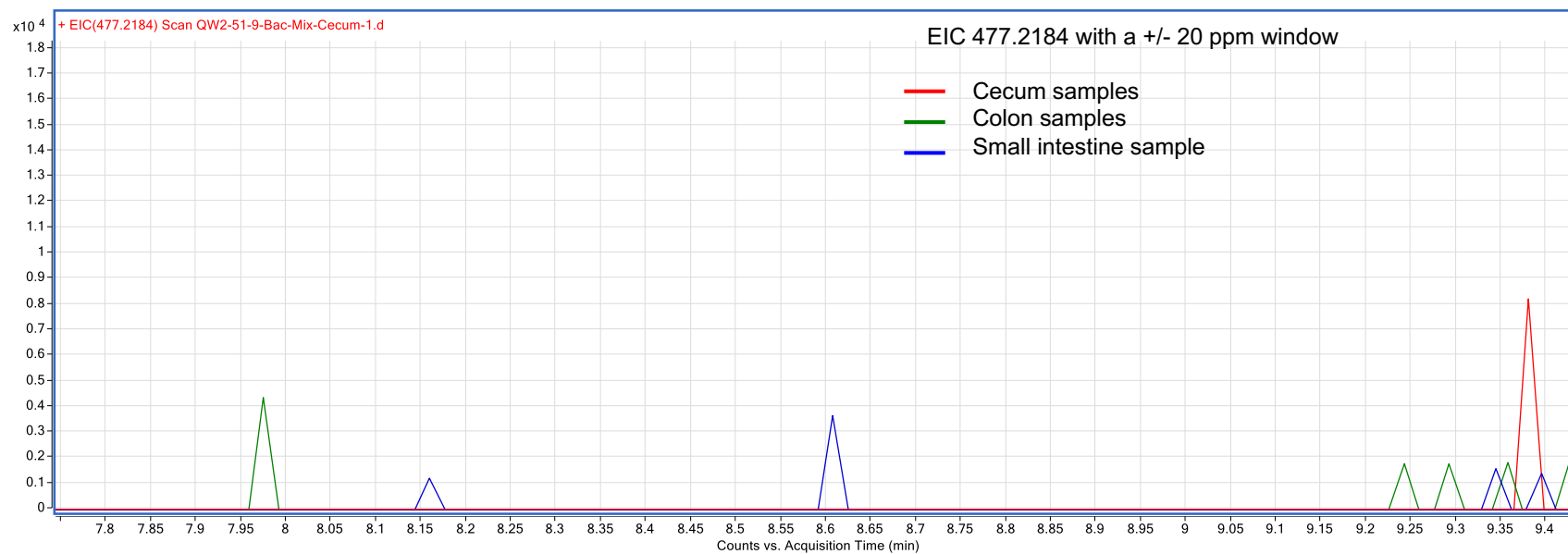


Fig. S237. Detection of iloperidone metabolite ilo-430 ($[M+H]^+$, m/z 430.2024) in conventional mouse fecal samples (n=5). A +/- 20 ppm window was applied for EIC. The EIC trace of ilo-430 standard is color-coded in blue, while the EIC traces for mouse fecal samples are in red. Ilo-430 was detected in only one mouse fecal sample (mouse 1).

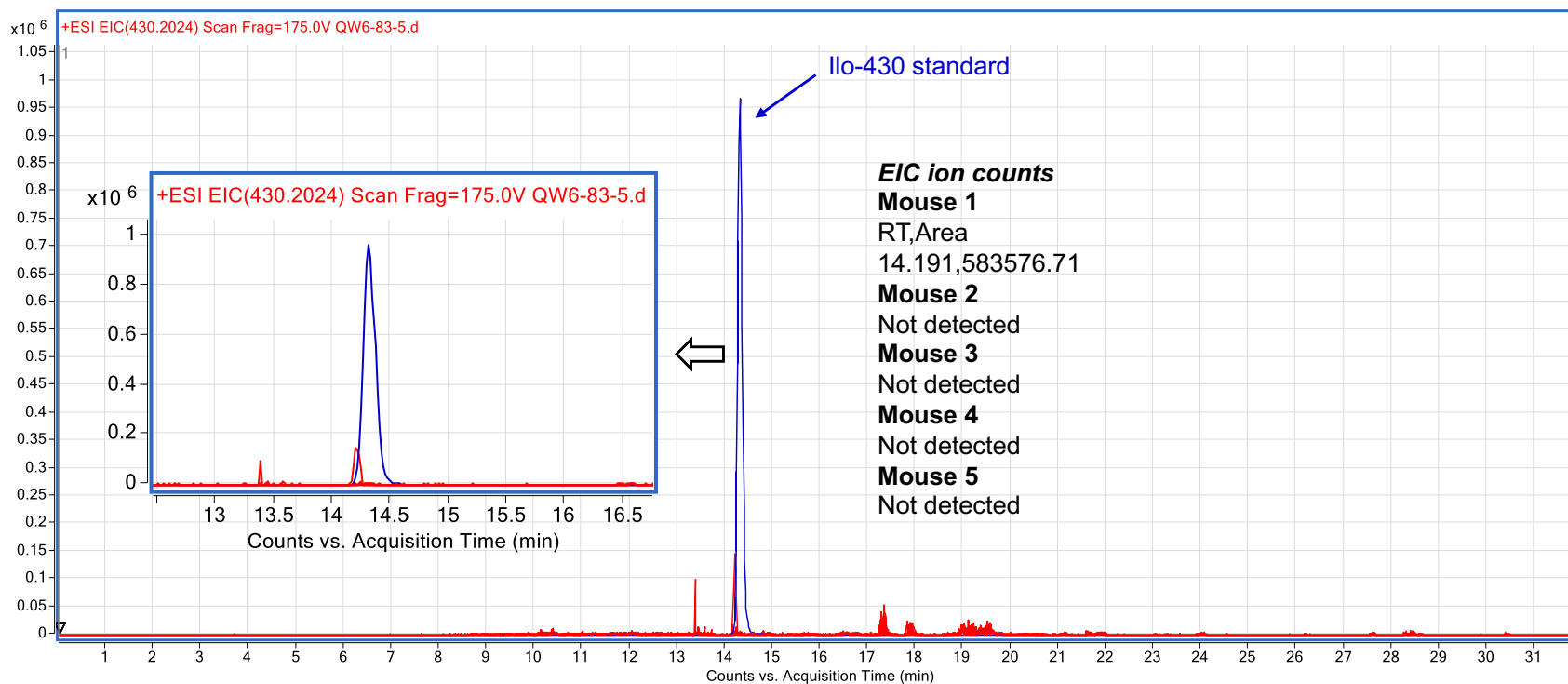


Fig. S238. Detection of iloperidone metabolite ilo-430 ($[M+H]^+$, m/z 430.2024) in conventional mouse cecum samples (n=5). A +/- 20 ppm window was applied for EIC. The EIC trace of ilo-430 standard is color-coded in blue, while the EIC traces for mouse fecal samples are in red. Ilo-430 was detected in four mouse cecum samples, except for mouse 4.

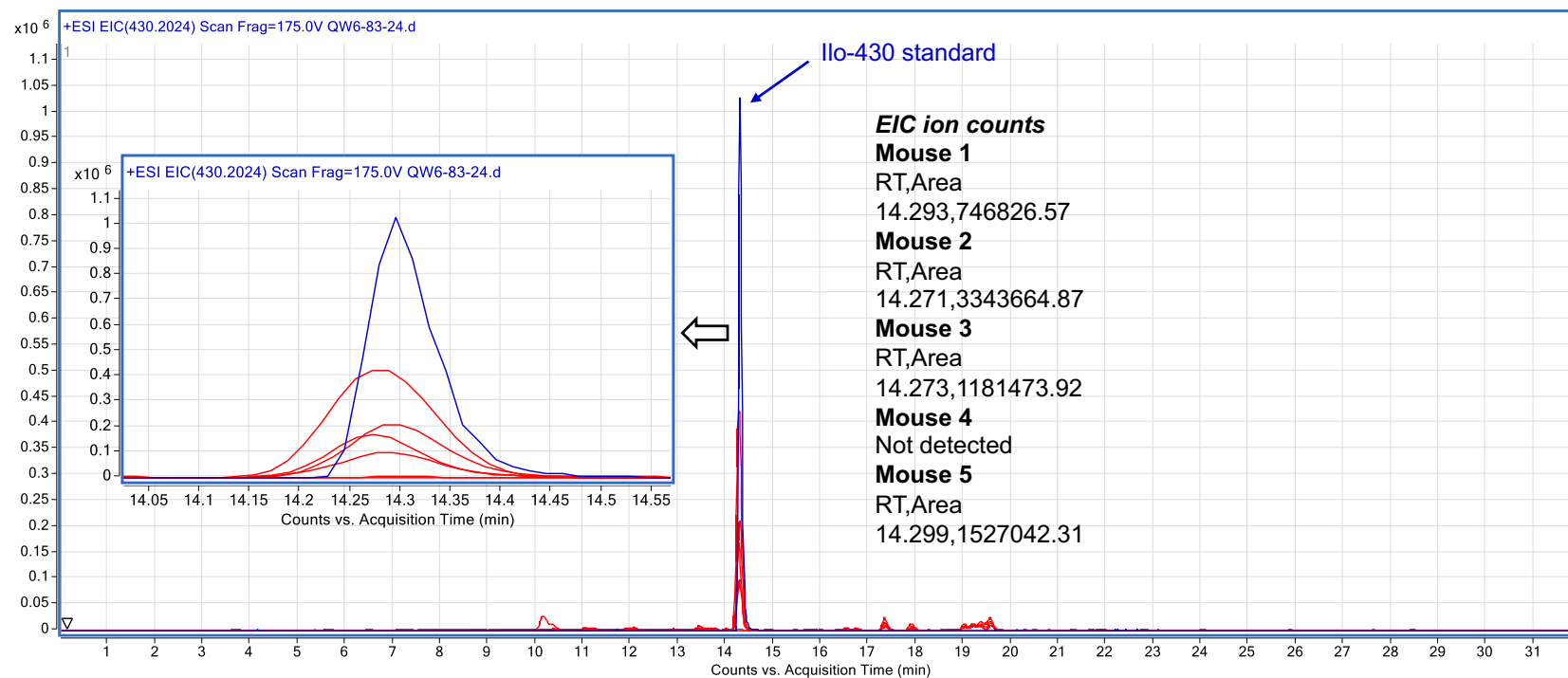


Fig. S239. Detection of iloperidone metabolite ilo-430 ($[M+H]^+$, m/z 430.2024) in conventional mouse colon samples (n=5). A +/- 20 ppm window was applied for EIC. The EIC trace of ilo-430 standard is color-coded in blue, while the EIC traces for mouse fecal samples are in red. Ilo-430 was detected in all five mouse colon samples.

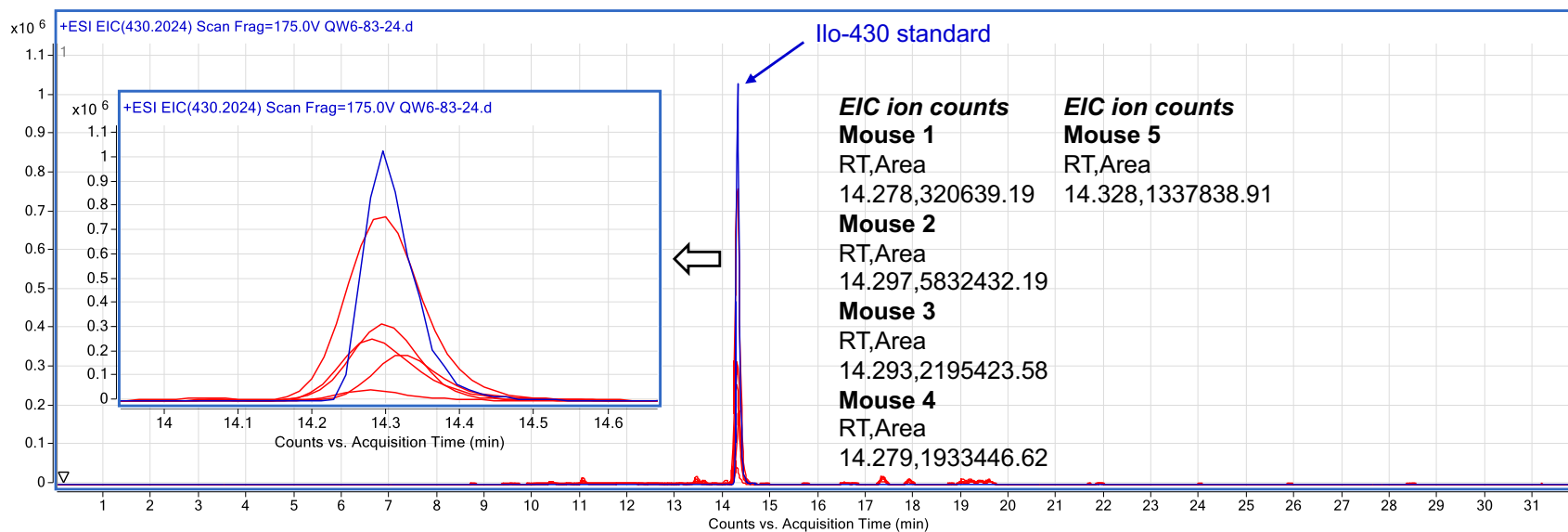
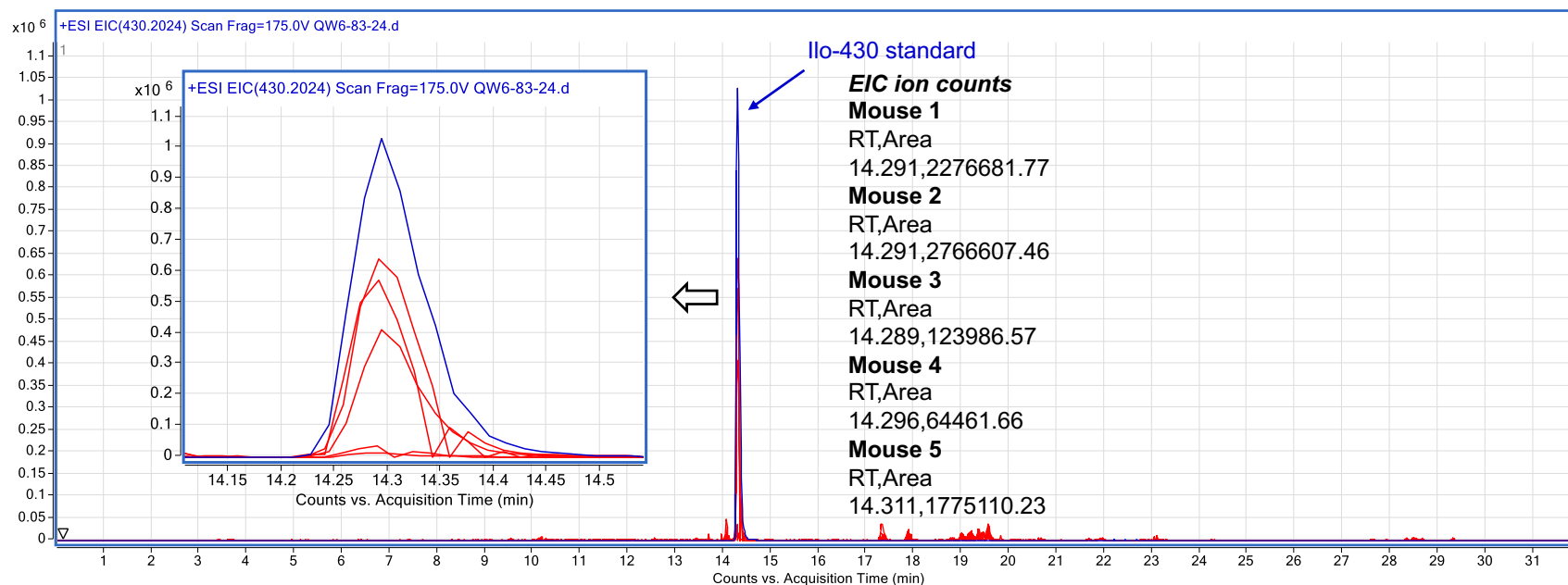


Fig. S240. Detection of iloperidone metabolite ilo-430 ($[M+H]^+$, m/z 430.2024) in conventional mouse small intestine samples ($n=5$). A ± 20 ppm window was applied for EIC. The EIC trace of ilo-430 standard is color-coded in blue, while the EIC traces for mouse fecal samples are in red. Ilo-430 was detected in all five mouse small intestine samples.



8. Investigation of O-demethylation metabolism in drugs containing aryl O-methyl or related functional groups

Fig. S241. Investigation of O-demethylation metabolism in tozadenant. A ± 20 ppm window was applied for the EIC of the predicted demethylated product (m/z 393.1591). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

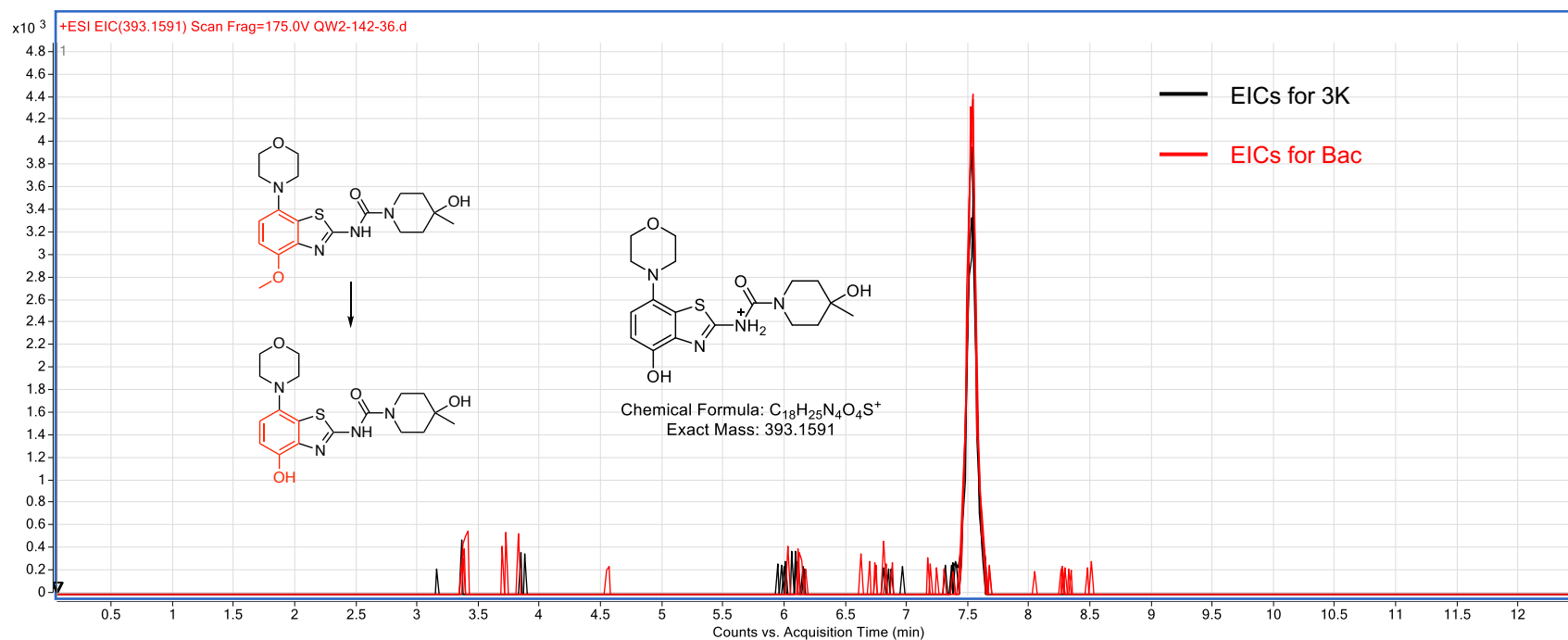


Fig. S242. Investigation of O-demethylation metabolism in naftopidil. A ± 20 ppm window was applied for the EIC of the predicted demethylated product (m/z 379.2016). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

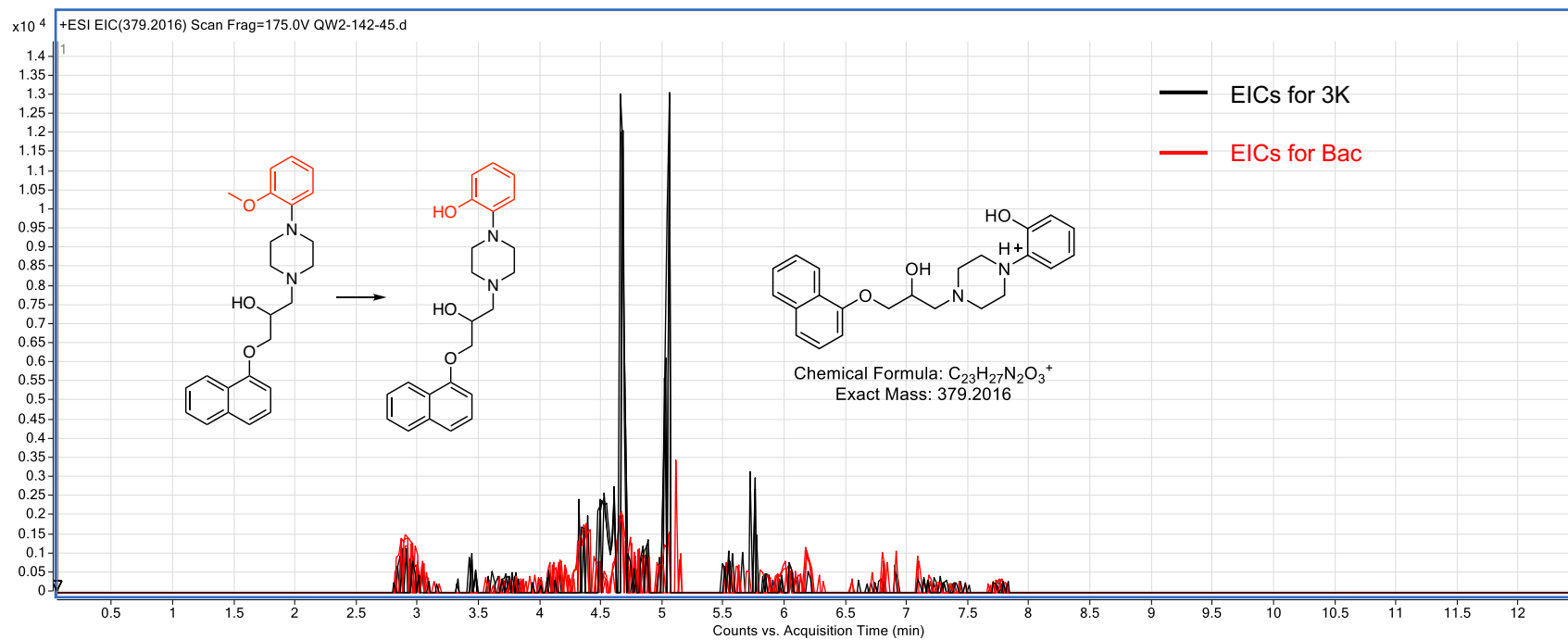


Fig. S243. Investigation of *O*-demethylation metabolism in volinanserin. A ± 20 ppm window was applied for the EIC of the predicted demethylated products (*m/z* 360.1969 and 346.1813). None of the metabolites were detected. Representative charge states are shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. *n* = 3 biological replicates.

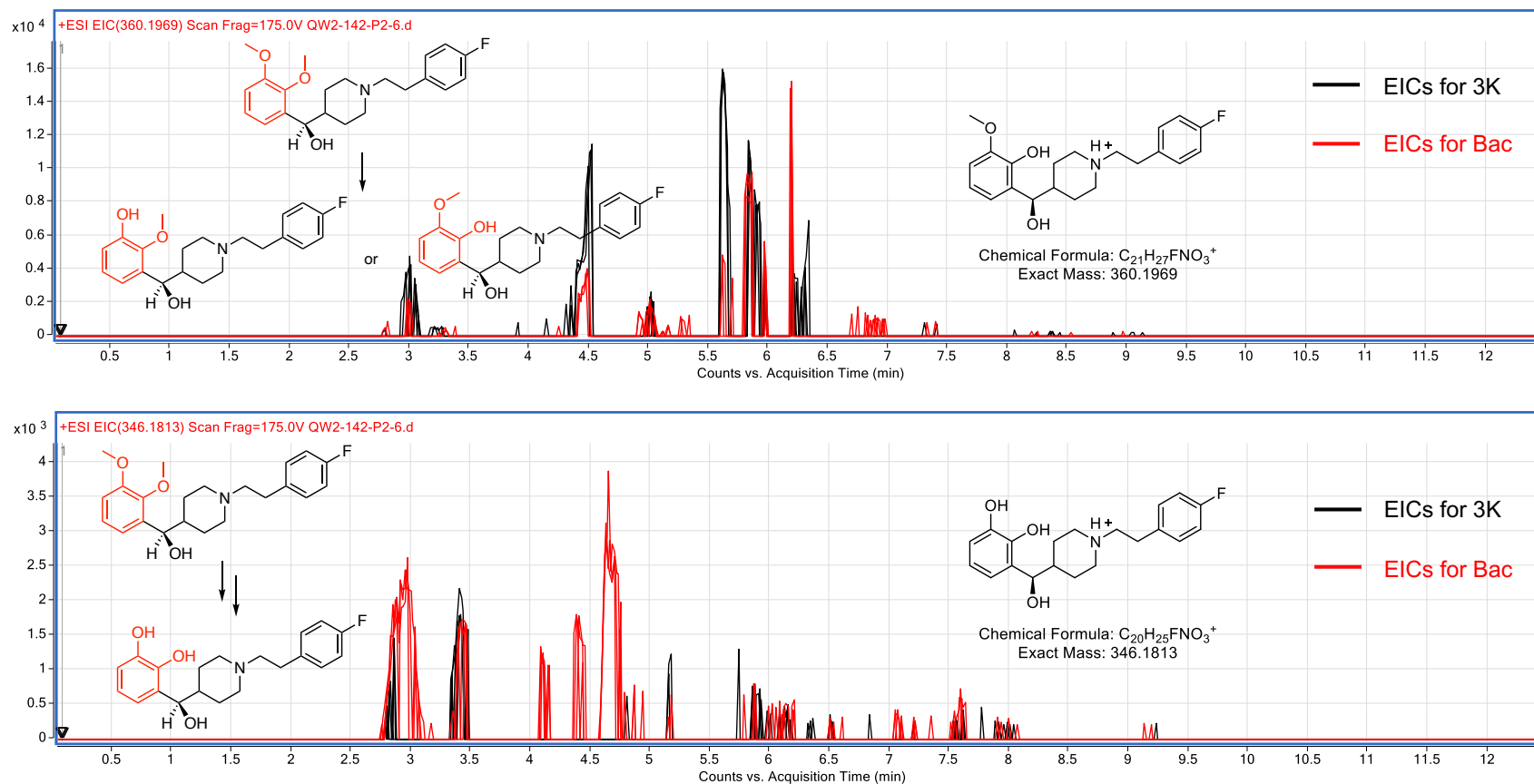


Fig. S244. Investigation of O-demethylation metabolism in zafirlukast. A ± 20 ppm window was applied for the EIC of the predicted demethylated product (m/z 562.2006). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

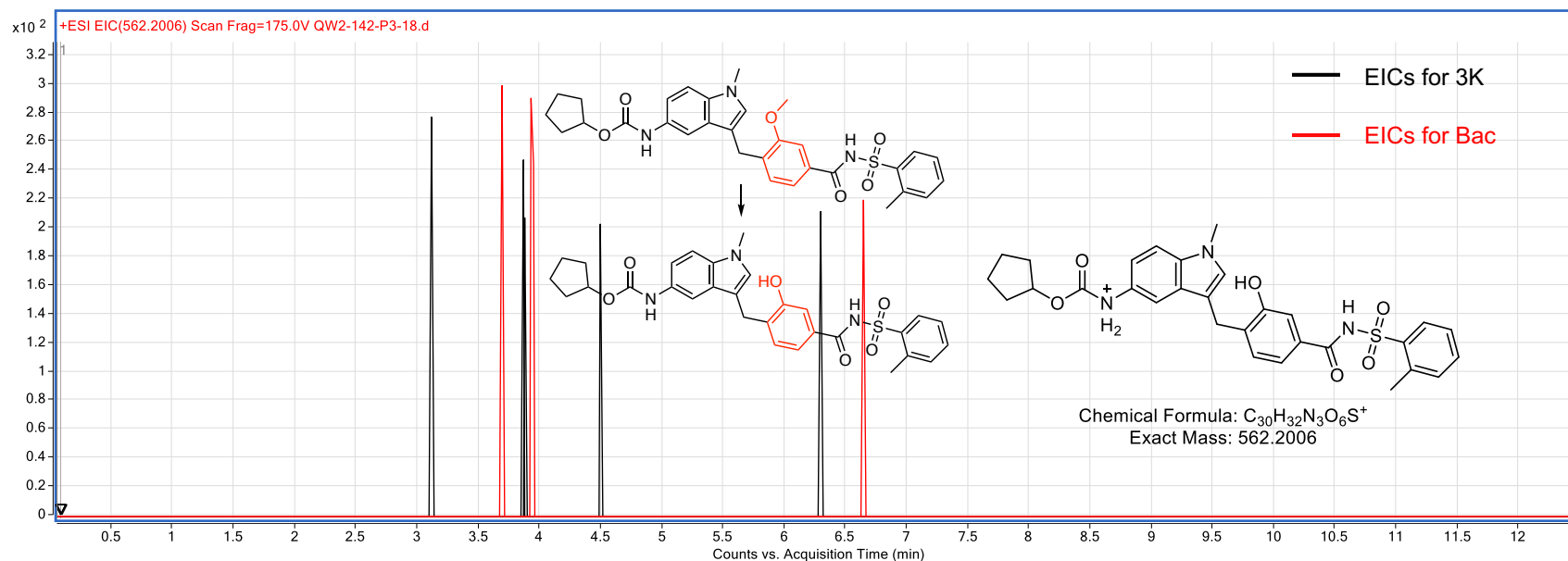


Fig. S245. Investigation of O-demethylation metabolism in cisapride. A ± 20 ppm window was applied for the EIC of the predicted demethylated product (m/z 452.1747). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

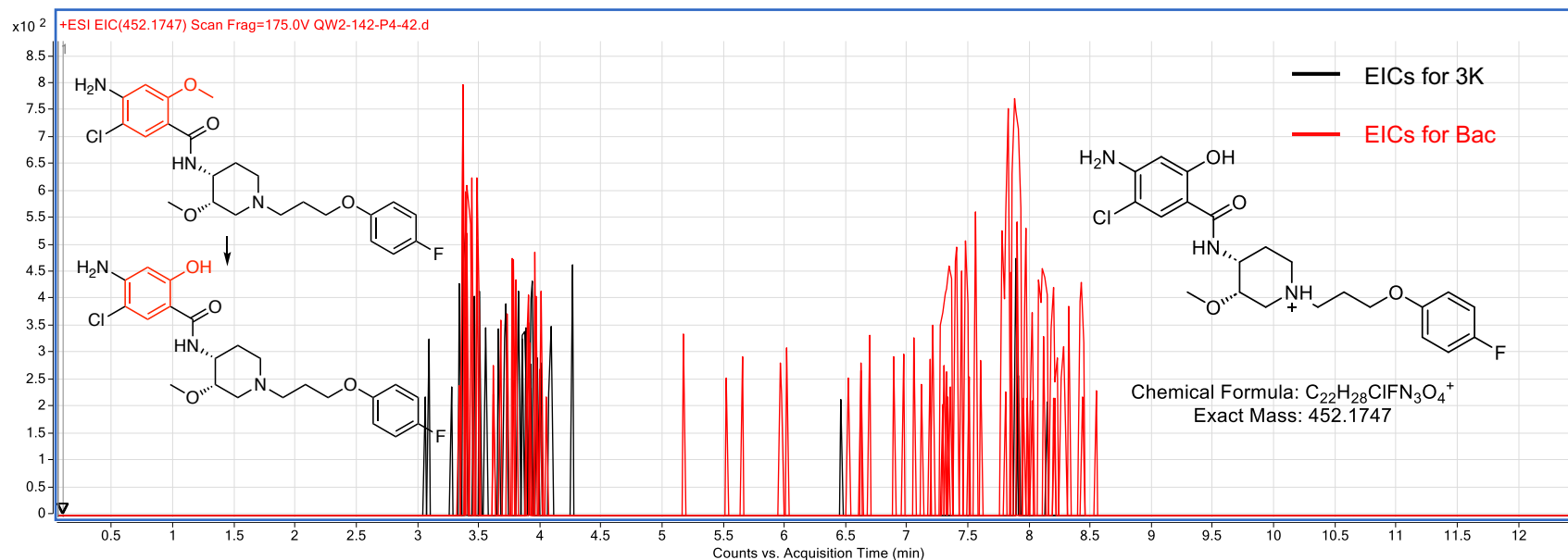


Fig. S246. Investigation of O-demethylation metabolism in doxazosin. A ± 20 ppm window was applied for the EIC of the predicted demethylated products (doxazosin-438, m/z 438.1772 and doxazosin-424 m/z 424.1615). Both predicted metabolites were detected. The production of both metabolites depends on the presence of bacterial cells. The position of mono-demethylation for doxazosin-438 was not determined. Representative charge states are shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K; not detected: n.d. $n = 3$ biological replicates. Data represent mean $\pm$ s.d.

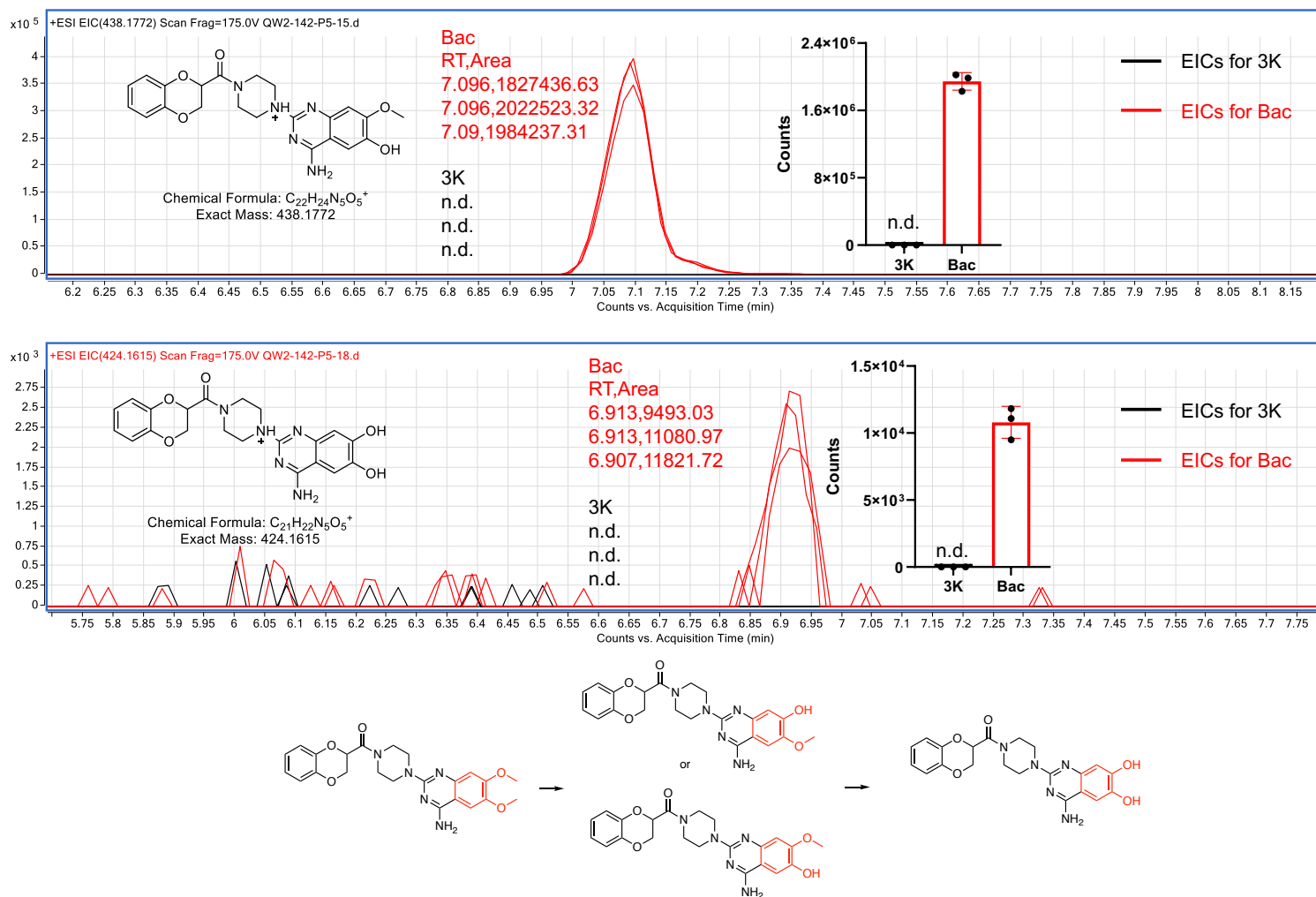


Fig. S247. Proposed HR-ESI-MS² fragmentation of doxazosin. Fragment A: $m/z_{\text{calcd.}}$ 344.1717, $m/z_{\text{obs.}}$ 344.1720; Fragment B: $m/z_{\text{calcd.}}$ 290.1612, $m/z_{\text{obs.}}$ 290.1610; Fragment C: $m/z_{\text{calcd.}}$ 247.1190, $m/z_{\text{obs.}}$ 247.1192; Fragment D: $m/z_{\text{calcd.}}$ 221.1033, $m/z_{\text{obs.}}$ 221.1033. Representative charge states are shown.

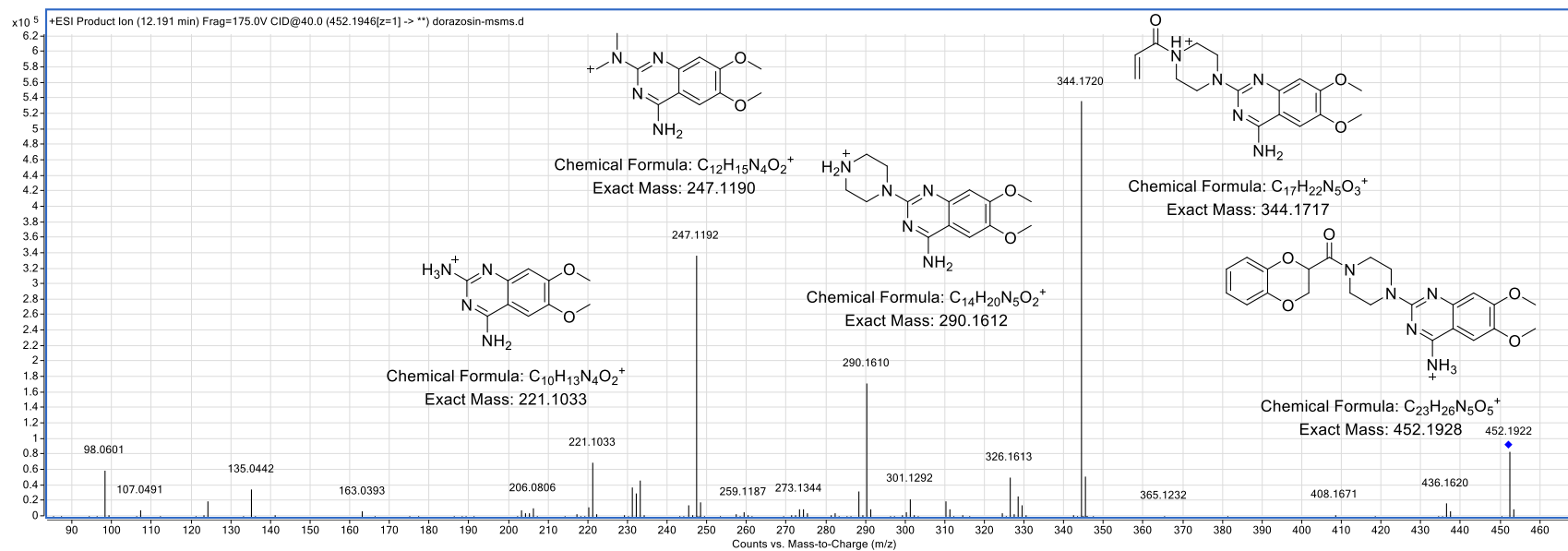


Fig. S248. Proposed HR-ESI-MS² fragmentation of doxazosin metabolite doxazosin-438. To show the proposed MS² patterns, only one of the two possible metabolites with a single O-demethylation is depicted. Fragment A: $m/z_{\text{calcd.}}$ 330.1561, $m/z_{\text{obs.}}$ 330.1562; Fragment B: $m/z_{\text{calcd.}}$ 276.1455, $m/z_{\text{obs.}}$ 276.1454; Fragment C: $m/z_{\text{calcd.}}$ 233.1033, $m/z_{\text{obs.}}$ 233.1031; Fragment D: $m/z_{\text{calcd.}}$ 207.0877, $m/z_{\text{obs.}}$ 207.0878. Representative charge states are shown.

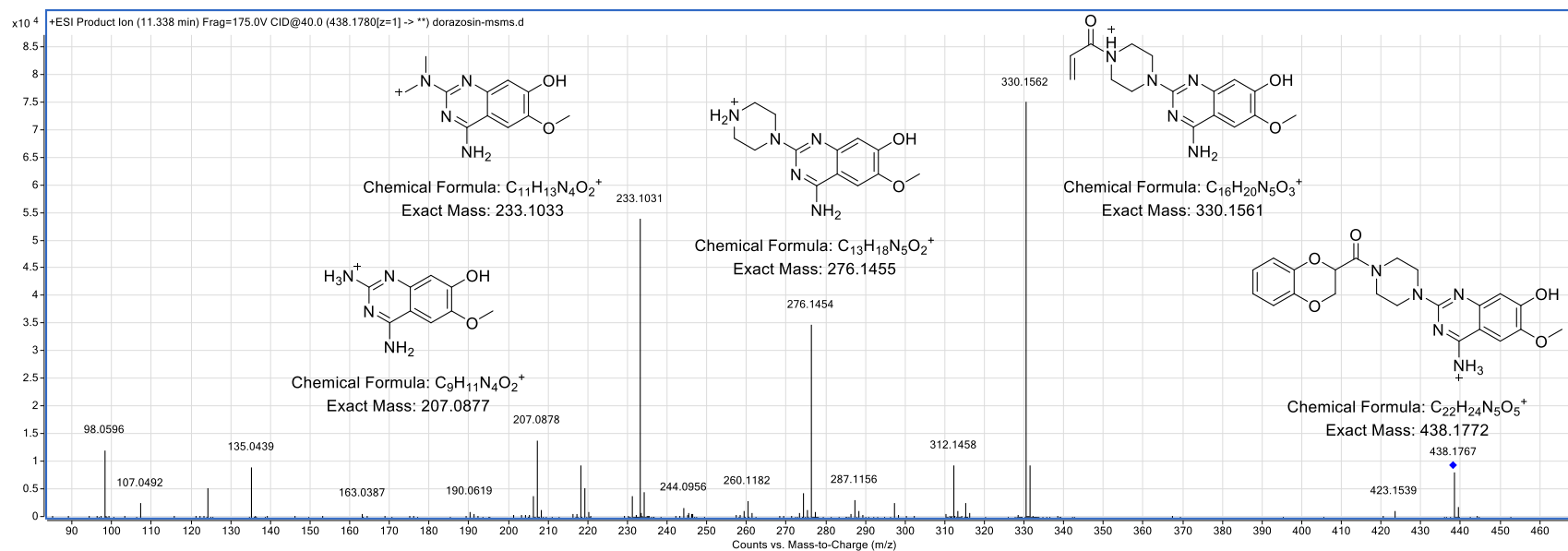


Fig. S249. Proposed HR-ESI-MS² fragmentation of doxazosin metabolite doxazosin-424. Fragment A: $m/z_{\text{calcd.}}$ 316.1404, $m/z_{\text{obs.}}$ 316.1408; Fragment B: $m/z_{\text{calcd.}}$ 262.1299, $m/z_{\text{obs.}}$ 262.1301; Fragment C: $m/z_{\text{calcd.}}$ 219.0877, $m/z_{\text{obs.}}$ 219.0879; Fragment D: $m/z_{\text{calcd.}}$ 193.0720, $m/z_{\text{obs.}}$ 193.0733. Representative charge states are shown.

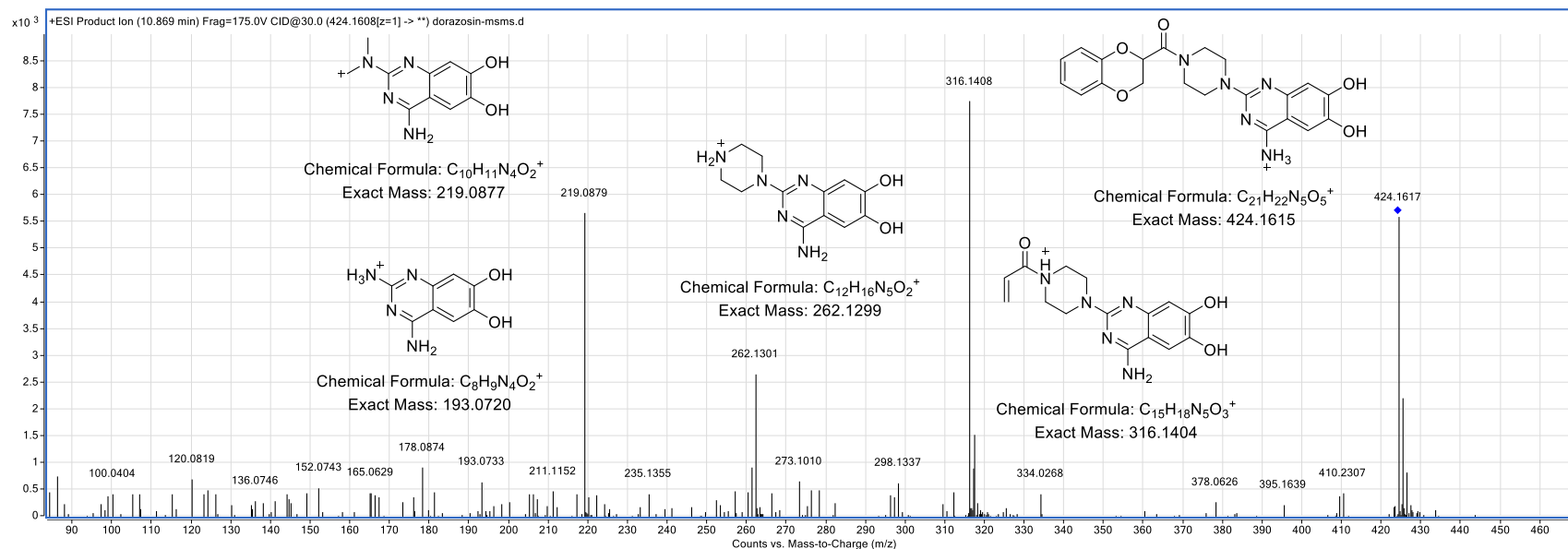


Fig. S250. Investigation of *O*-demethylation metabolism in avosentan. A ± 20 ppm window was applied for the EIC of the predicted demethylated product (m/z 466.1180). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

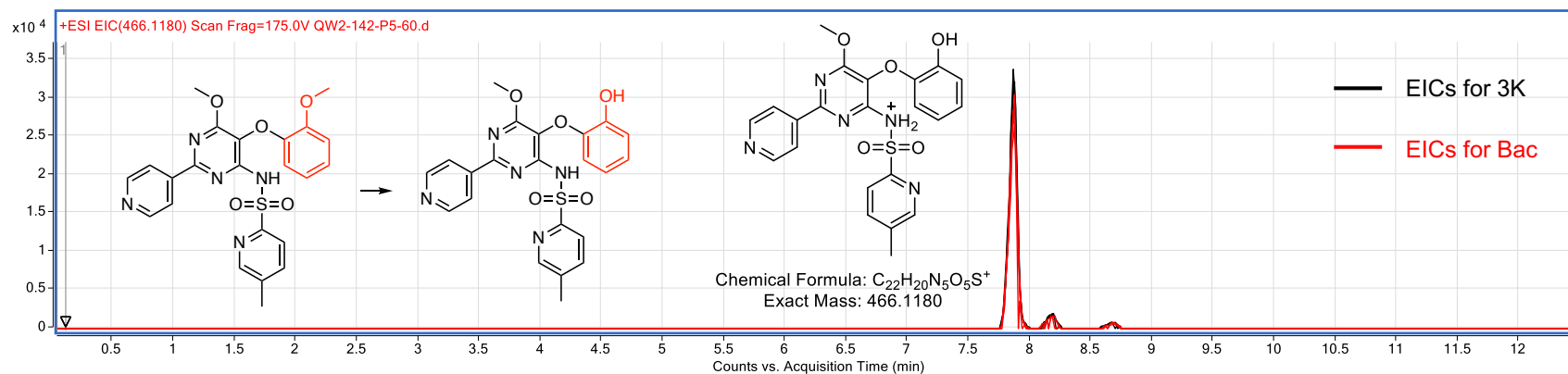


Fig. S251. Investigation of *O*-demethylation metabolism in PF-04418948. A ± 20 ppm window was applied for the EIC of the predicted demethylated product (*m/z* 396.1242). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. *n* = 3 biological replicates.

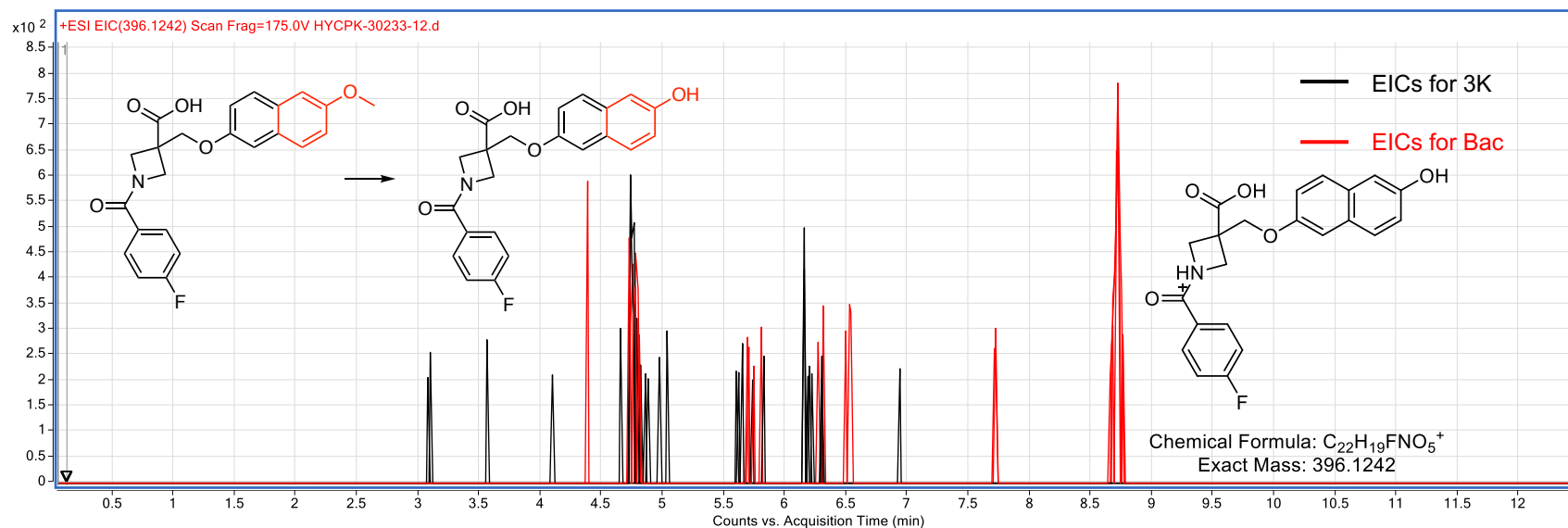


Fig. S252. Investigation of *O*-demethylation metabolism in *R*-elagolix. A ± 20 ppm window was applied for the EIC of the predicted demethylated product (*m/z* 618.2022). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. *n* = 3 biological replicates.

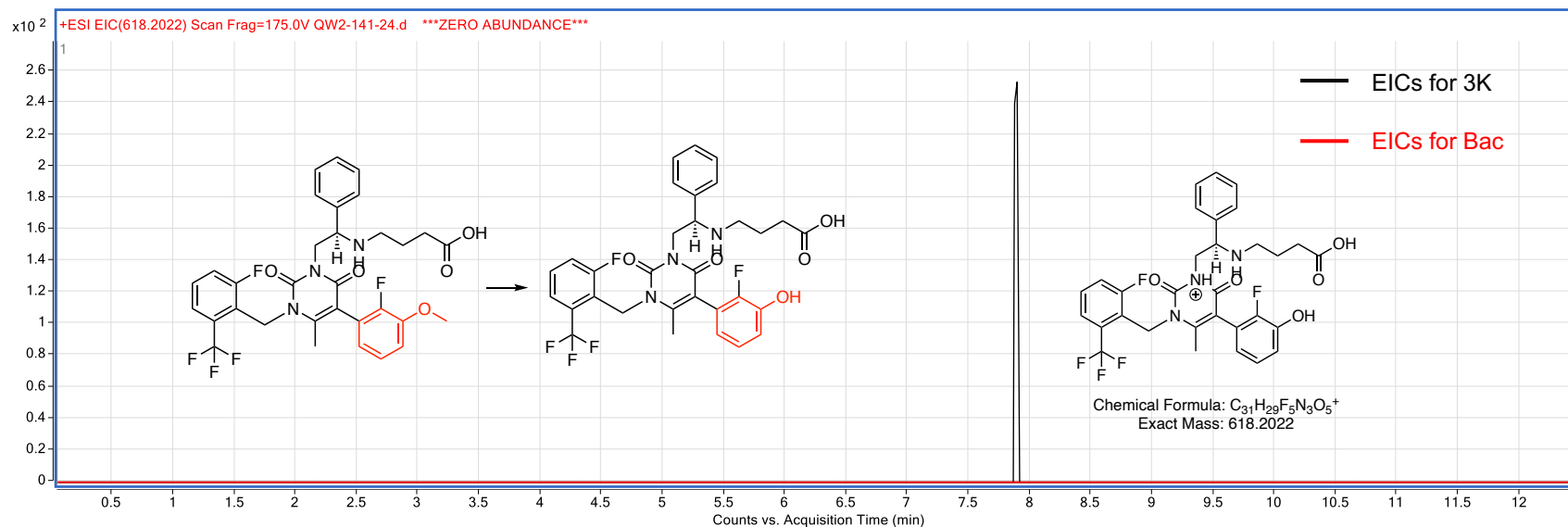


Fig. S253. Investigation of *O*-demethylation metabolism in atrasentan. A ± 20 ppm window was applied for the EIC of the predicted demethylated product (m/z 497.2646). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

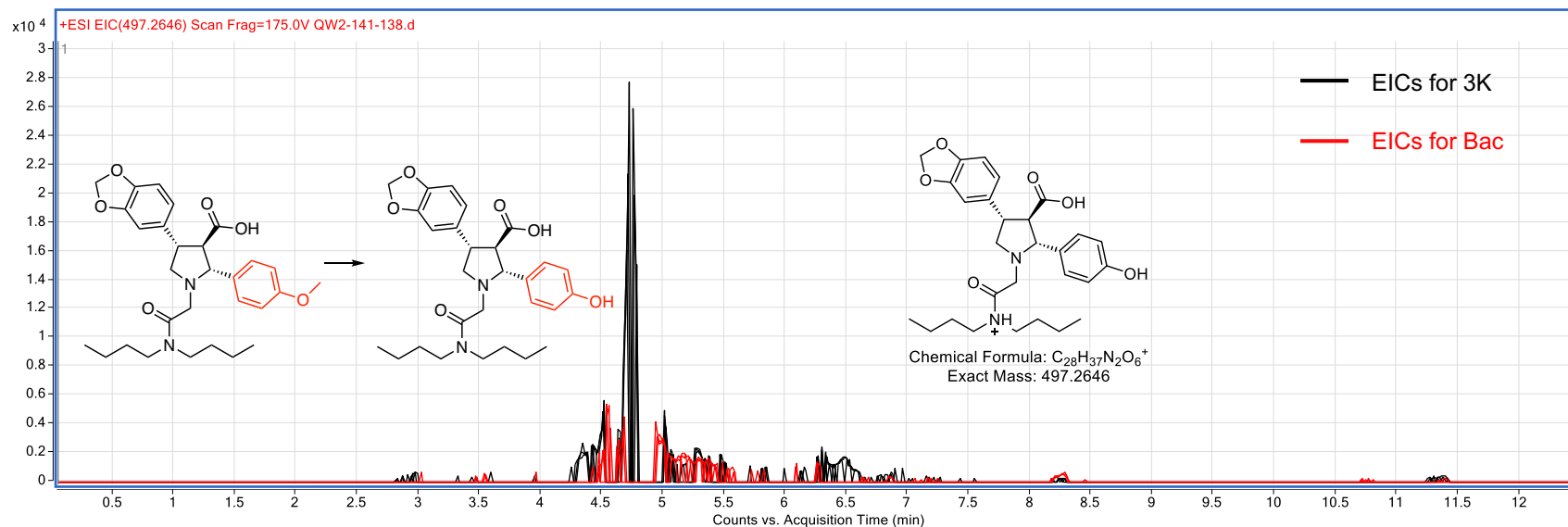


Fig. S254. Investigation of O-demethylation metabolism in olodanrigan. A ± 20 ppm window was applied for the EIC of the predicted demethylated product (m/z 494.1962). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

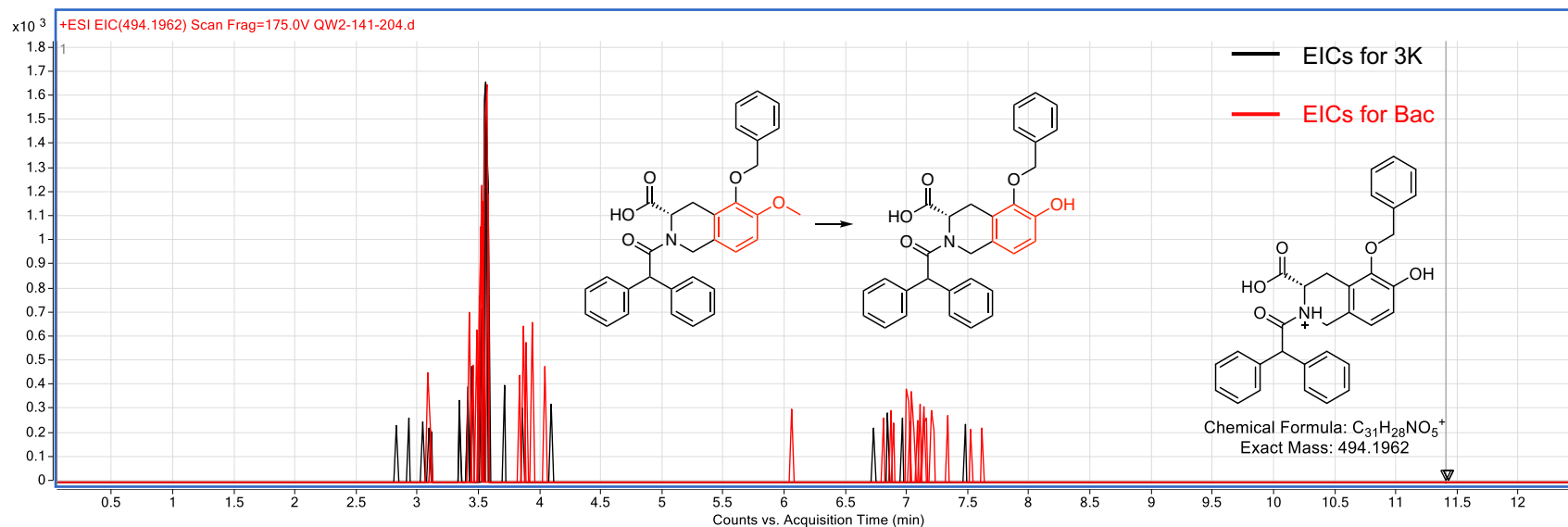


Fig. S255. Investigation of O-demethylation metabolism in melatonin. A ± 20 ppm window was applied for the EIC of the predicted demethylated product (m/z 219.1128). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

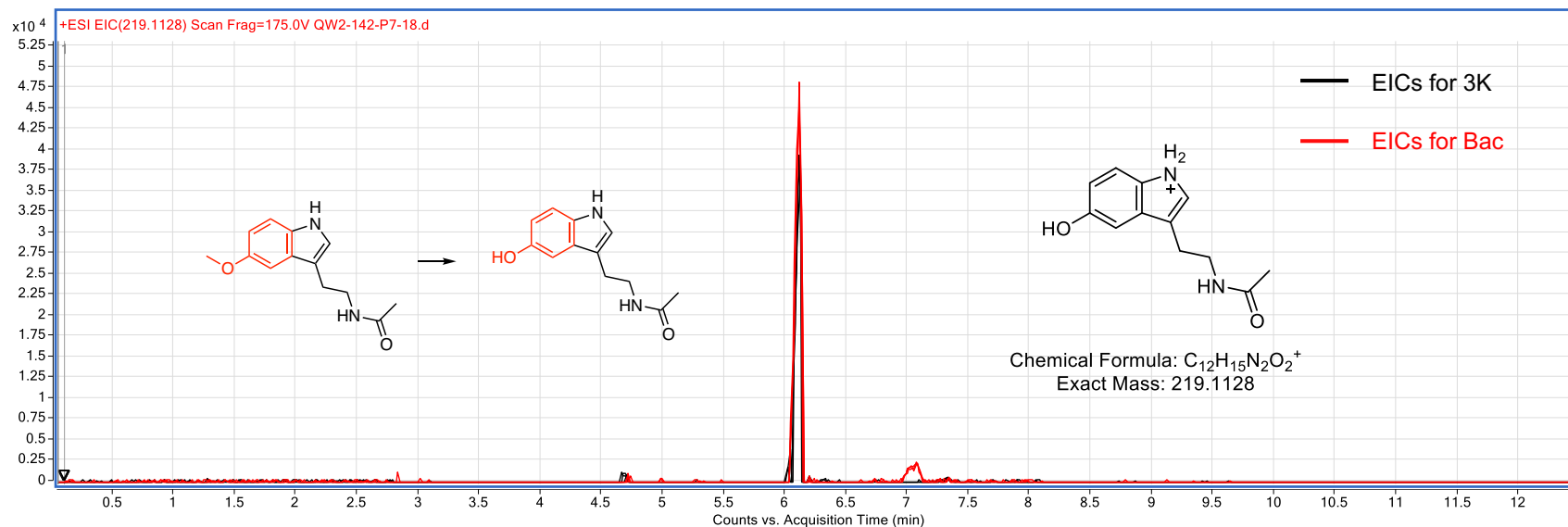


Fig. S256. Investigation of *O*-demethylation metabolism in almorexant. A ± 20 ppm window was applied for the EIC of the predicted demethylated products (m/z 499.2203 and 485.2047). None of the metabolites were detected. Representative charge states are shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

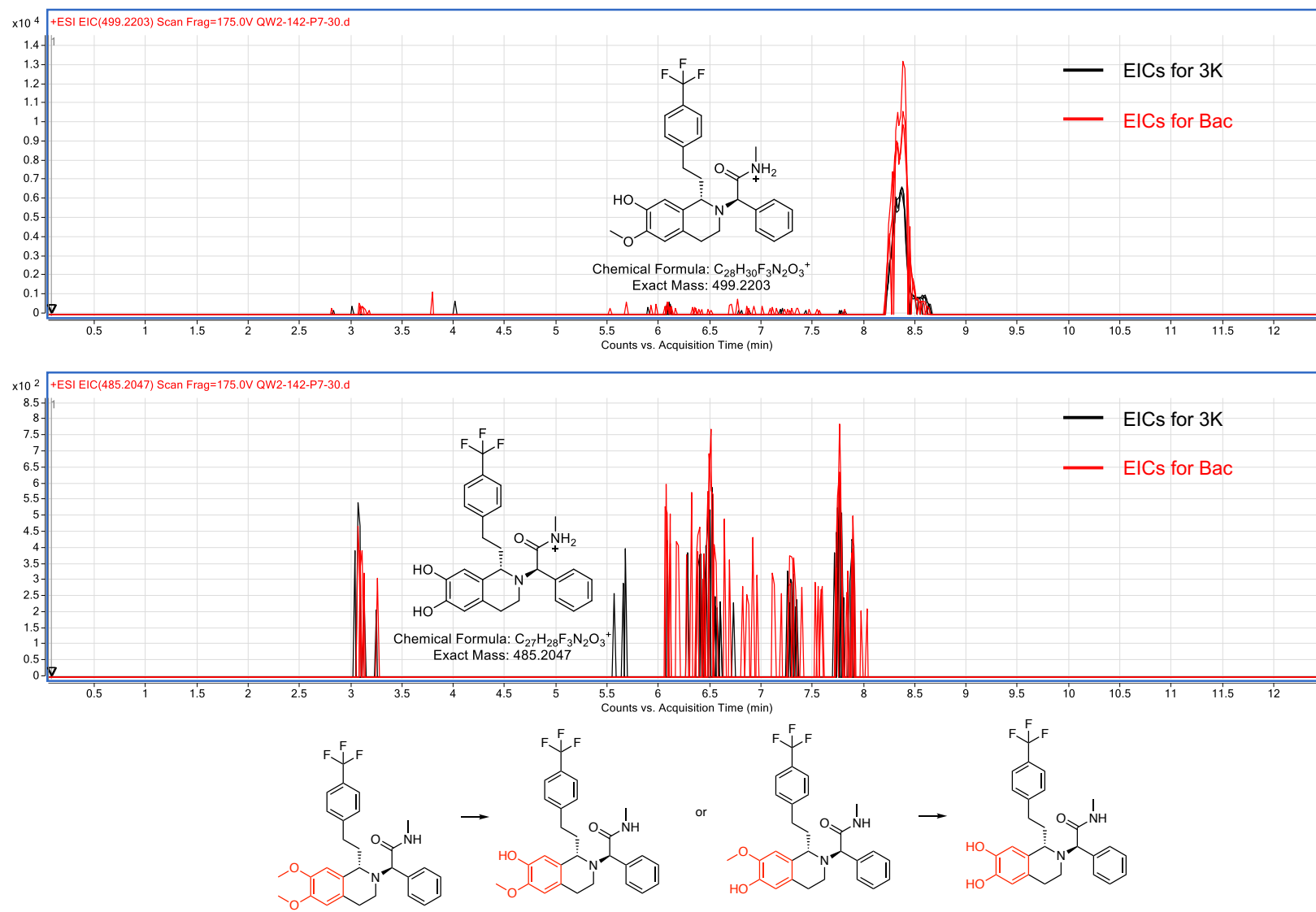


Fig. S257. Investigation of O-demethylation metabolism in carvedilol. A ± 20 ppm window was applied for the EIC of the predicted demethylated product (m/z 393.1809). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

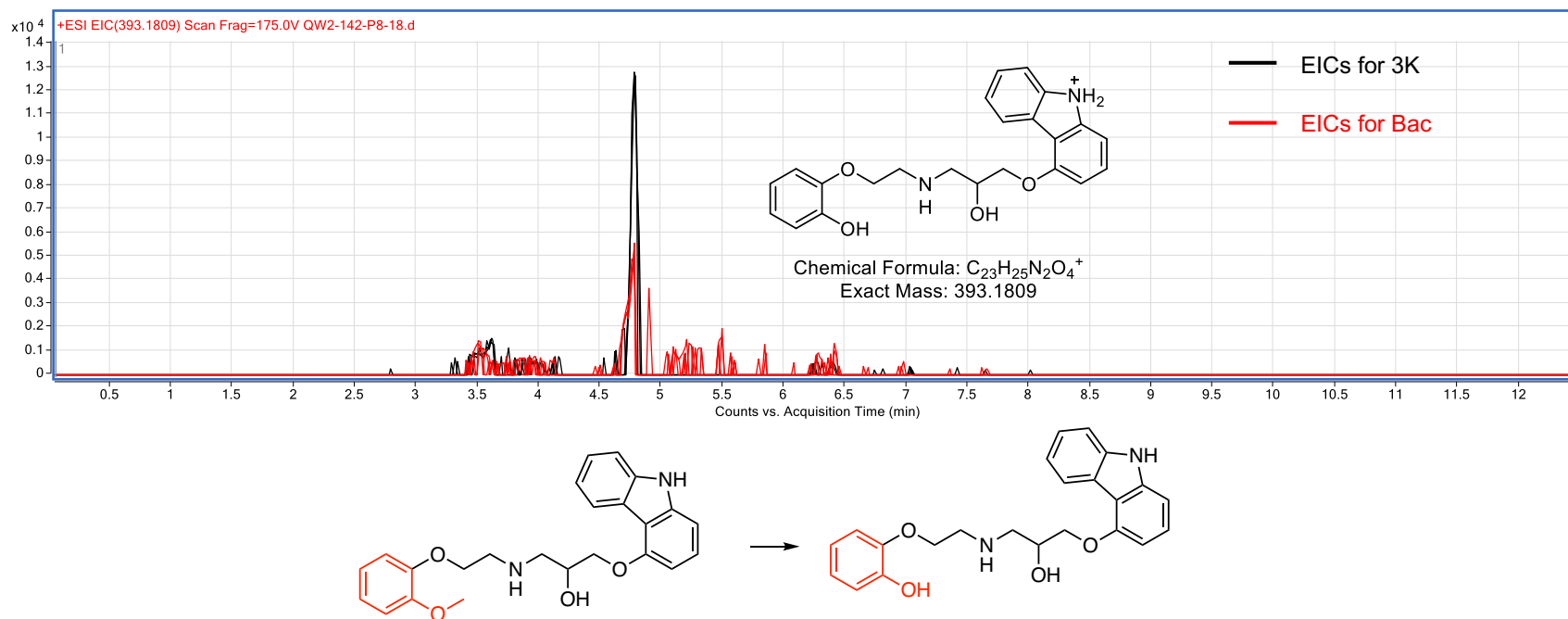


Fig. S258. ^1H NMR spectrum of SB756050 metabolite SB-487. SB-487 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

SB-487_PROTON_01
SB-487

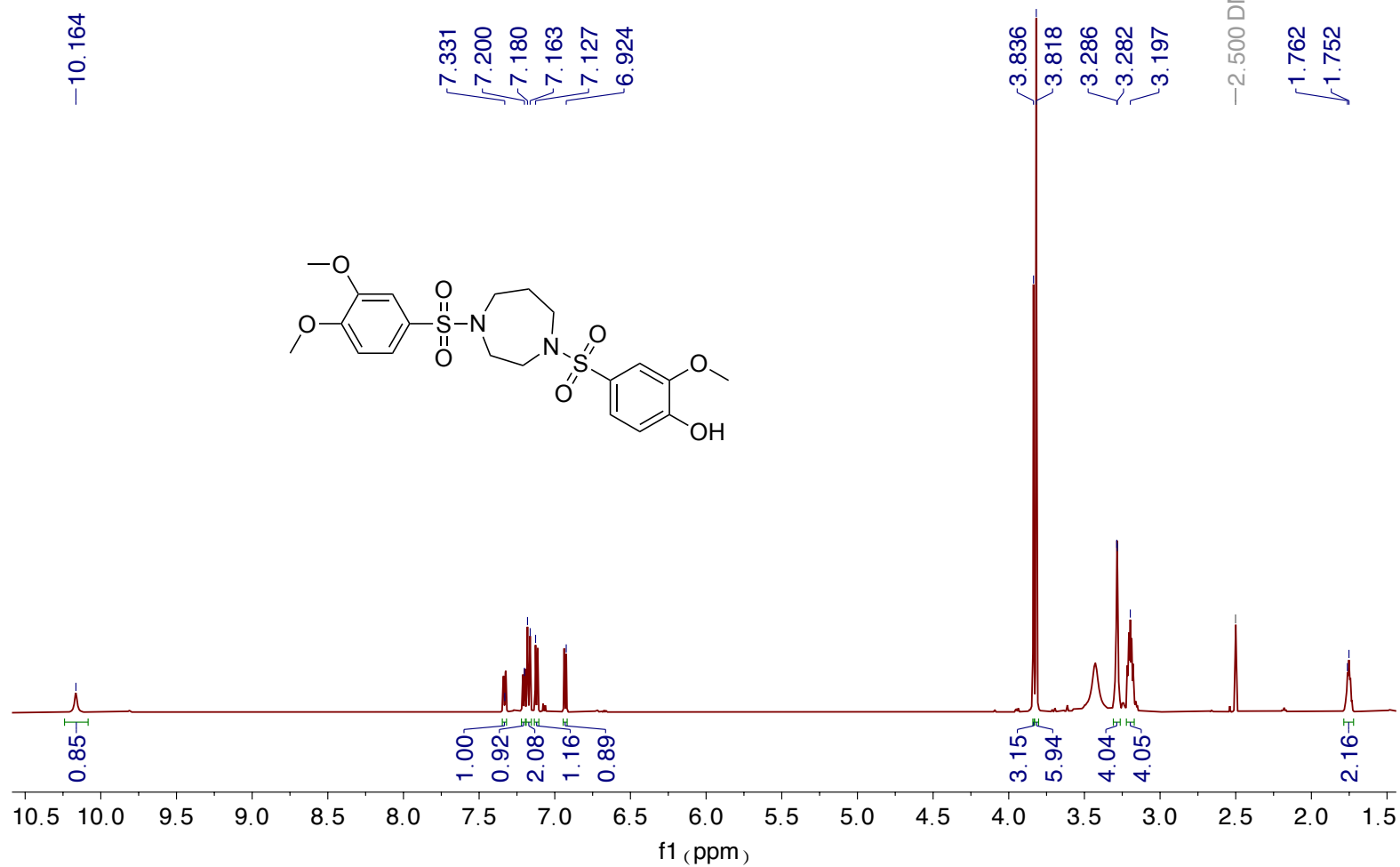


Fig. S259. ^1H - ^1H COSY spectrum of SB756050 metabolite SB-487. SB-487 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

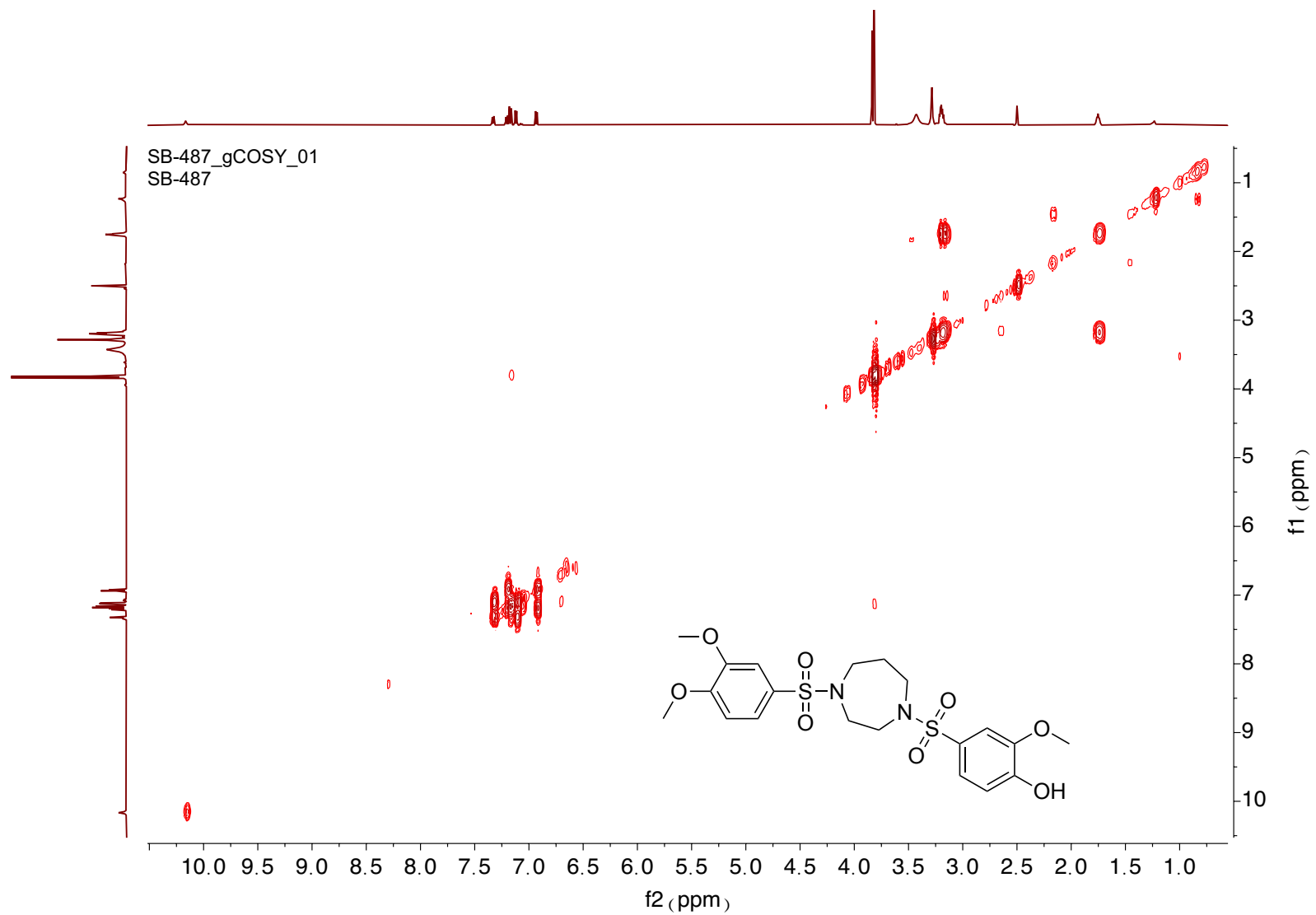


Fig. S260. HSQC spectrum of SB756050 metabolite SB-487. SB-487 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

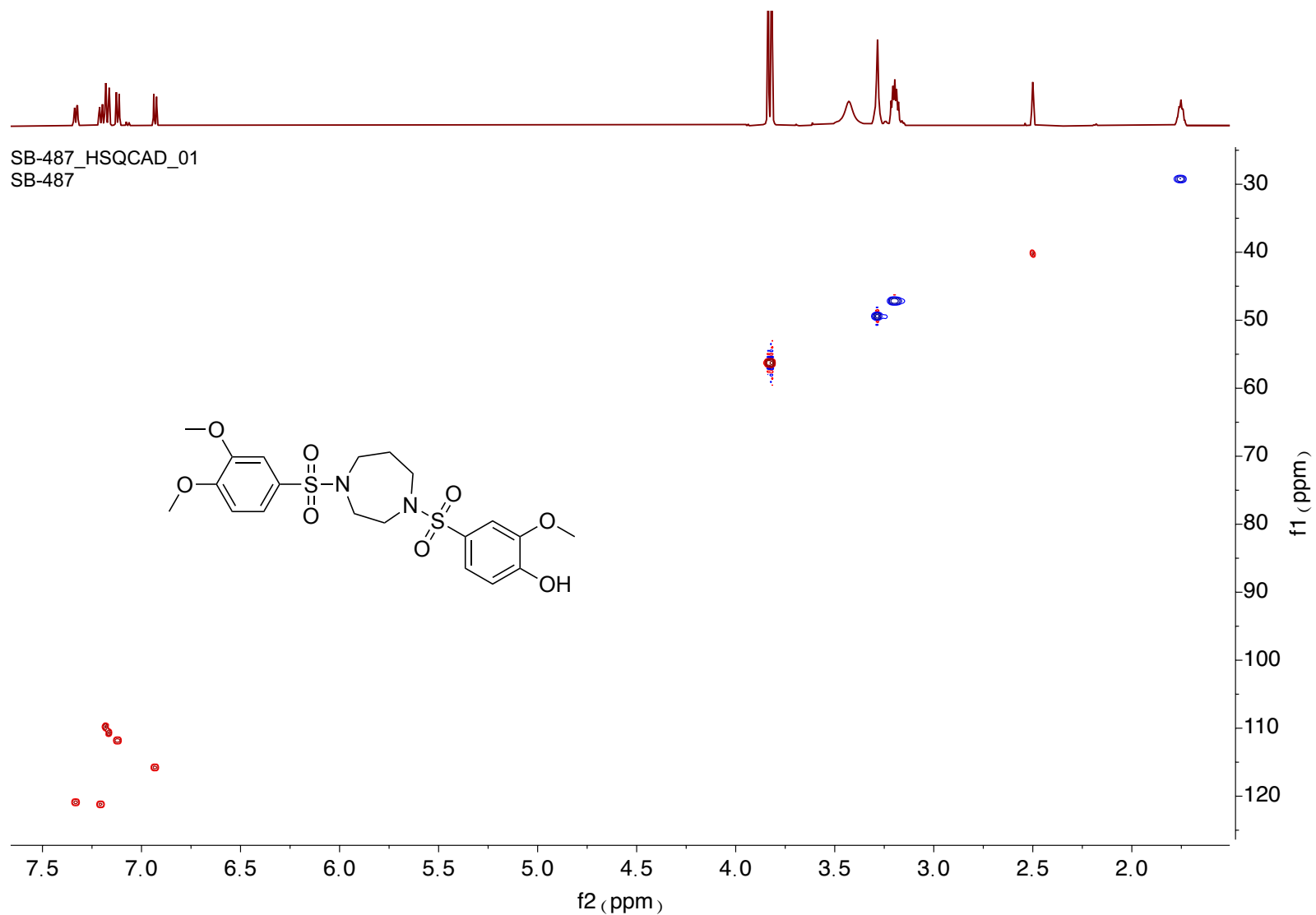


Fig. S261. HMBC spectrum of SB756050 metabolite SB-487. SB-487 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

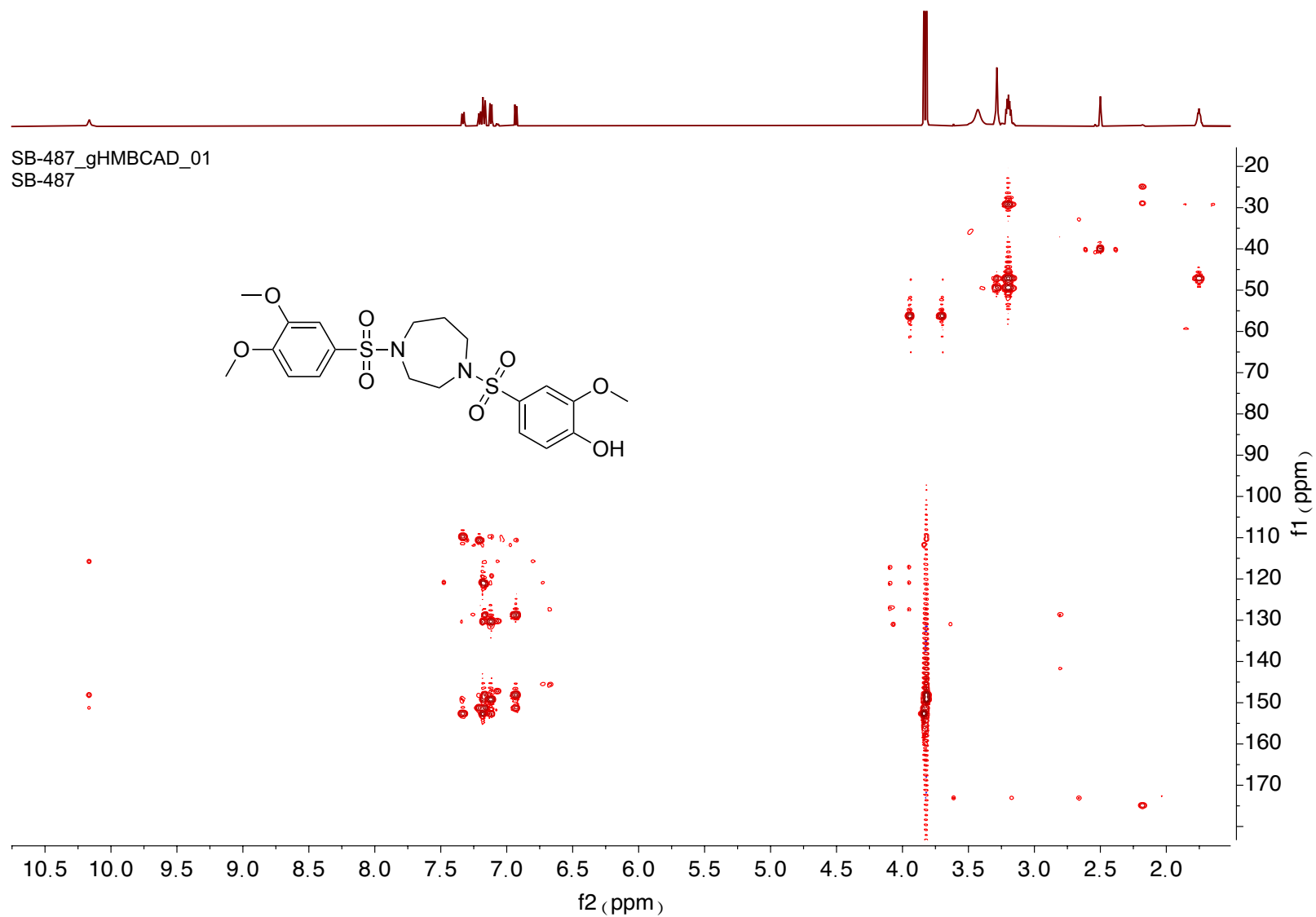


Fig. S262. ^1H NMR spectrum of SB756050 metabolite SB-473. SB-473 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

SB-473_PROTON_01
SB-473

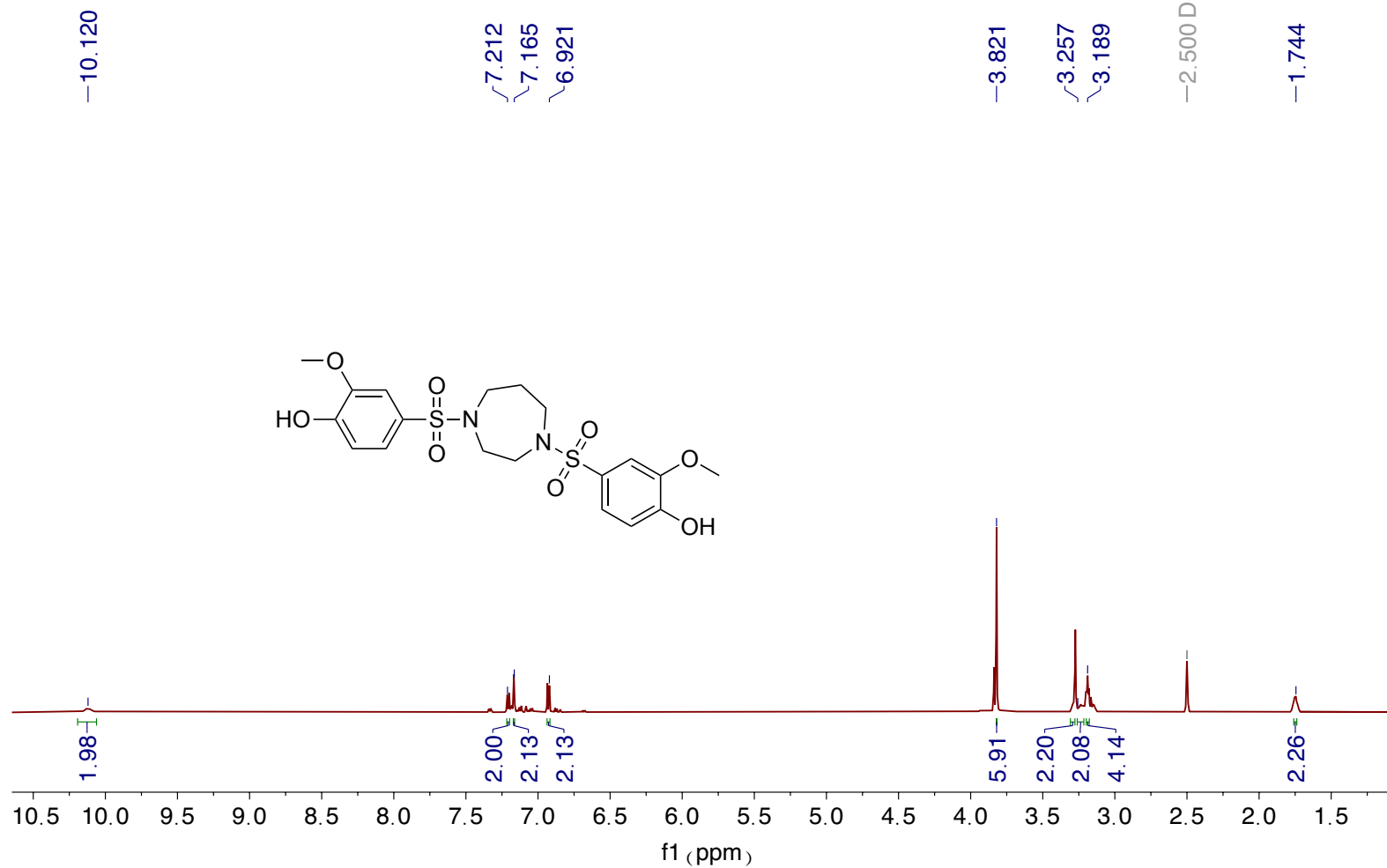


Fig. S263. ^1H - ^1H COSY spectrum of SB756050 metabolite SB-473. SB-473 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

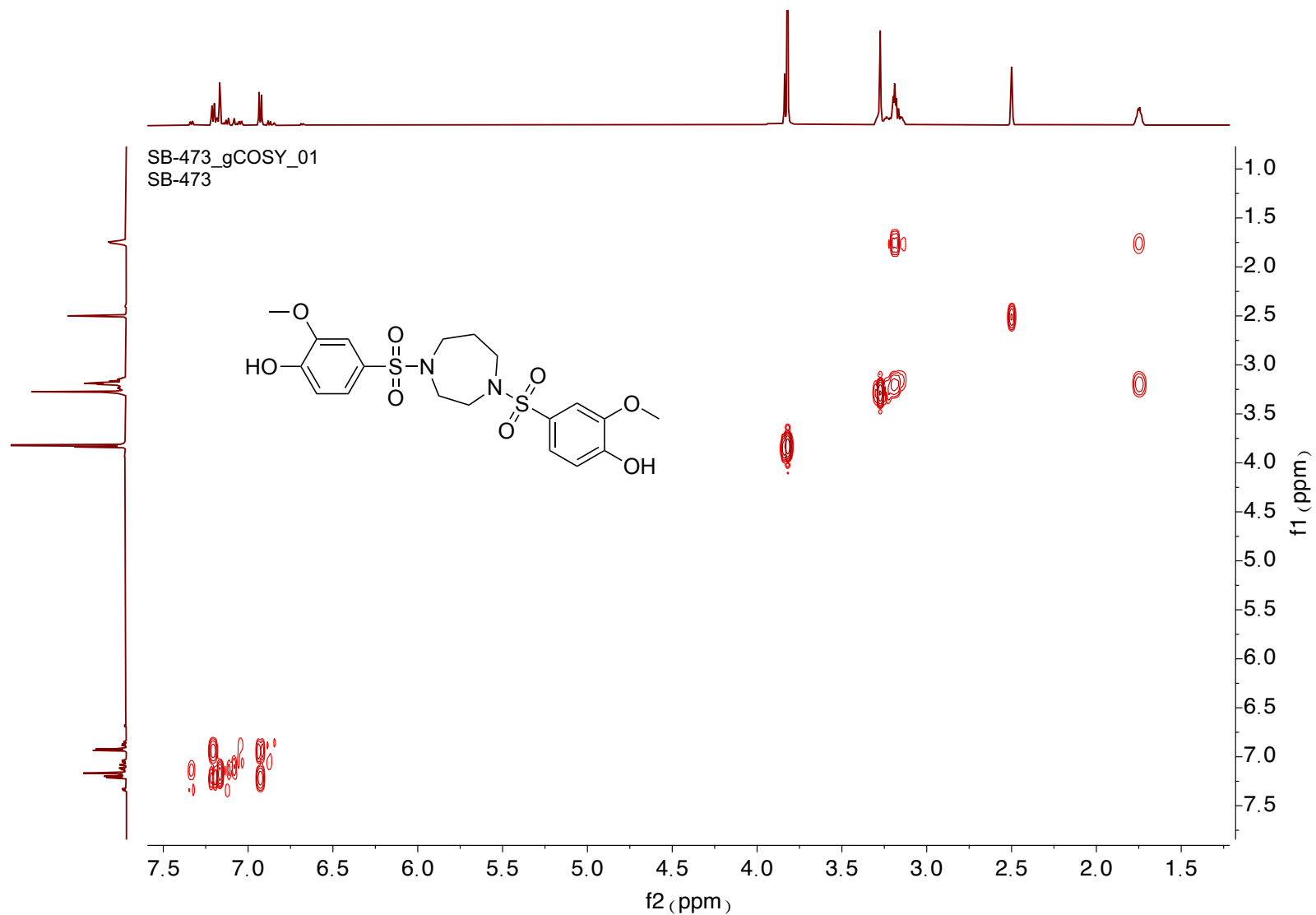


Fig. S264. HSQC spectrum of SB756050 metabolite SB-473. SB-473 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

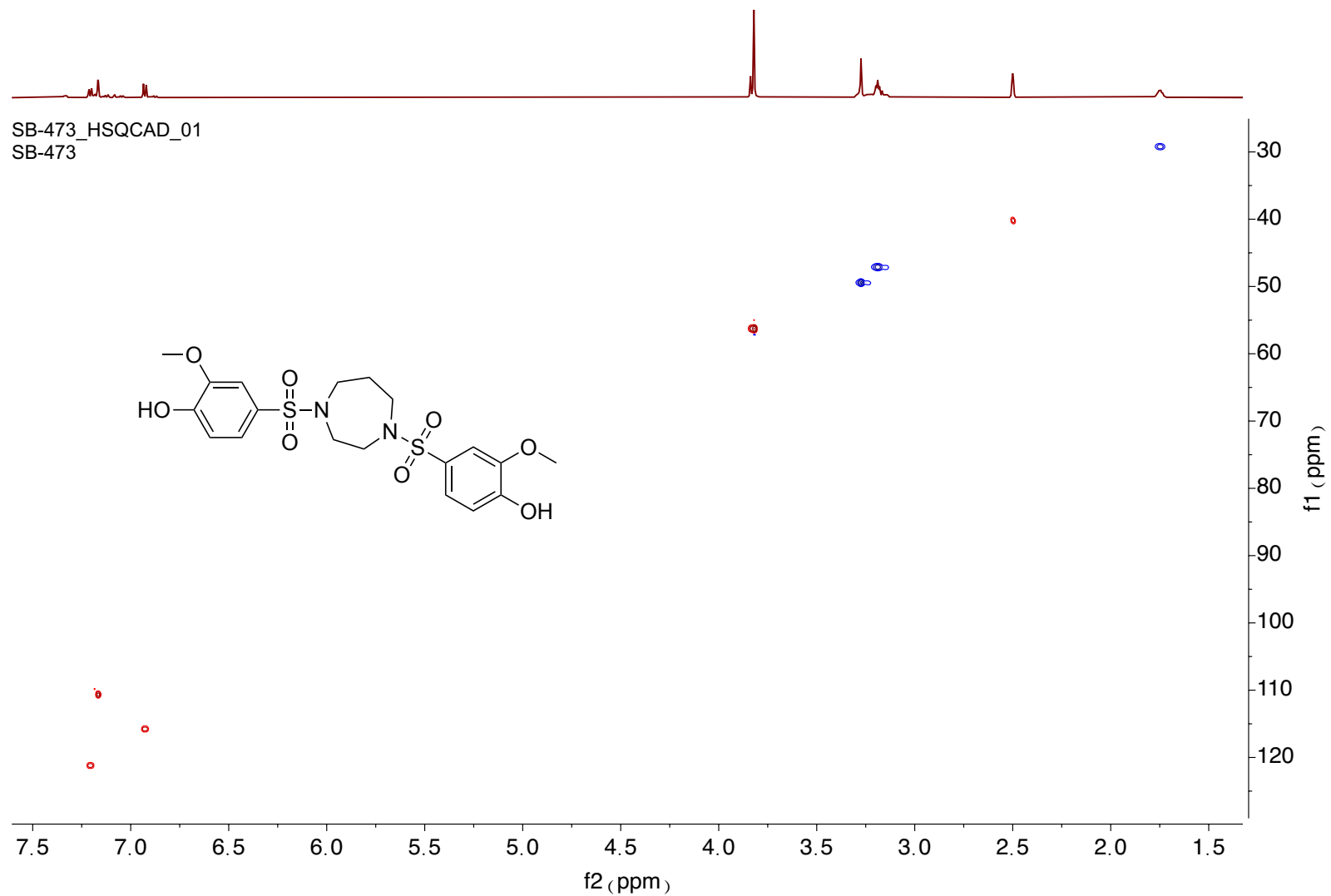


Fig. S265. HMBC spectrum of SB756050 metabolite SB-473. SB-473 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

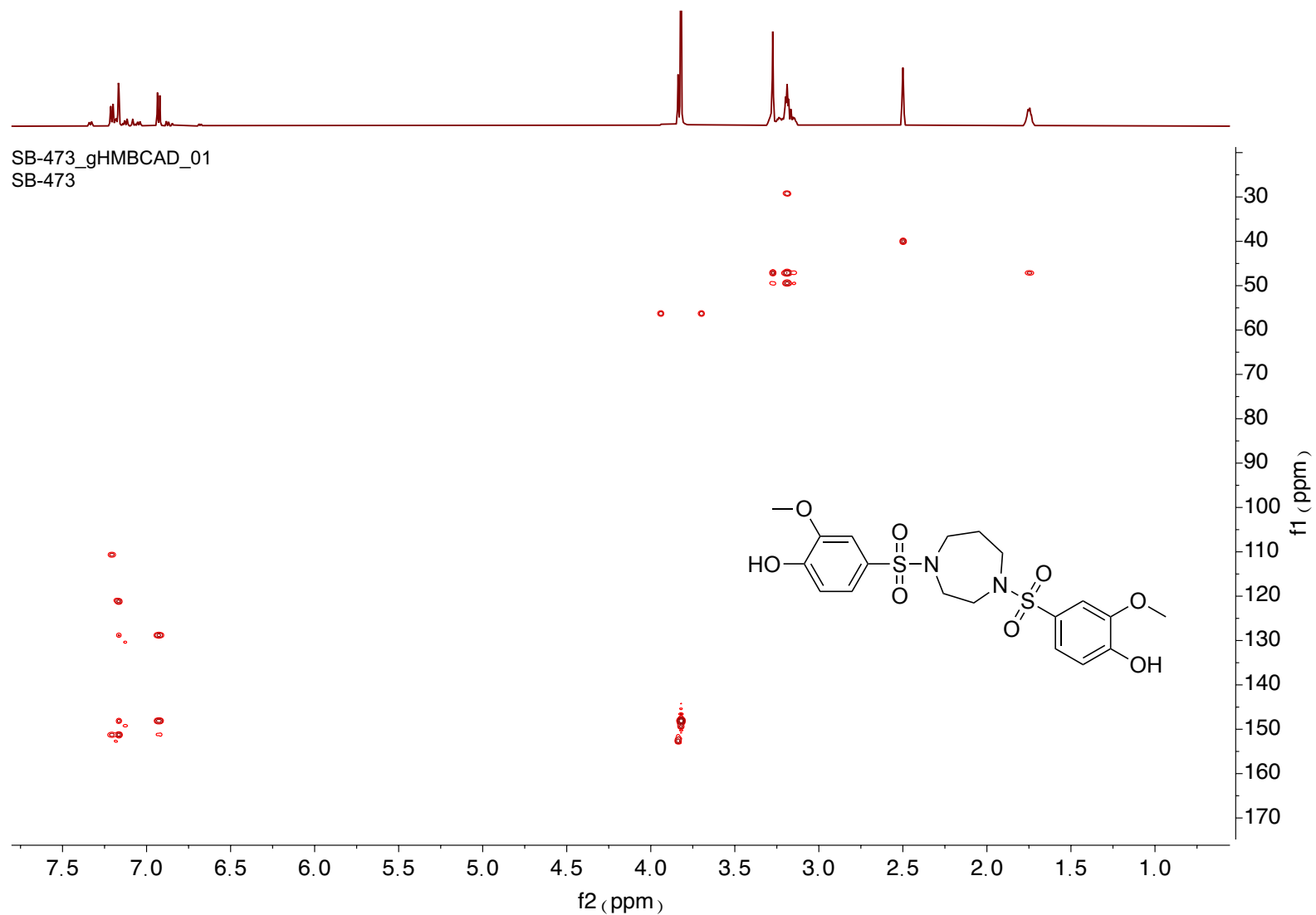


Fig. S266. ^1H NMR spectrum of SB756050 metabolite SB-459. SB-459 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

SB-459_PROTON_01
SB-459

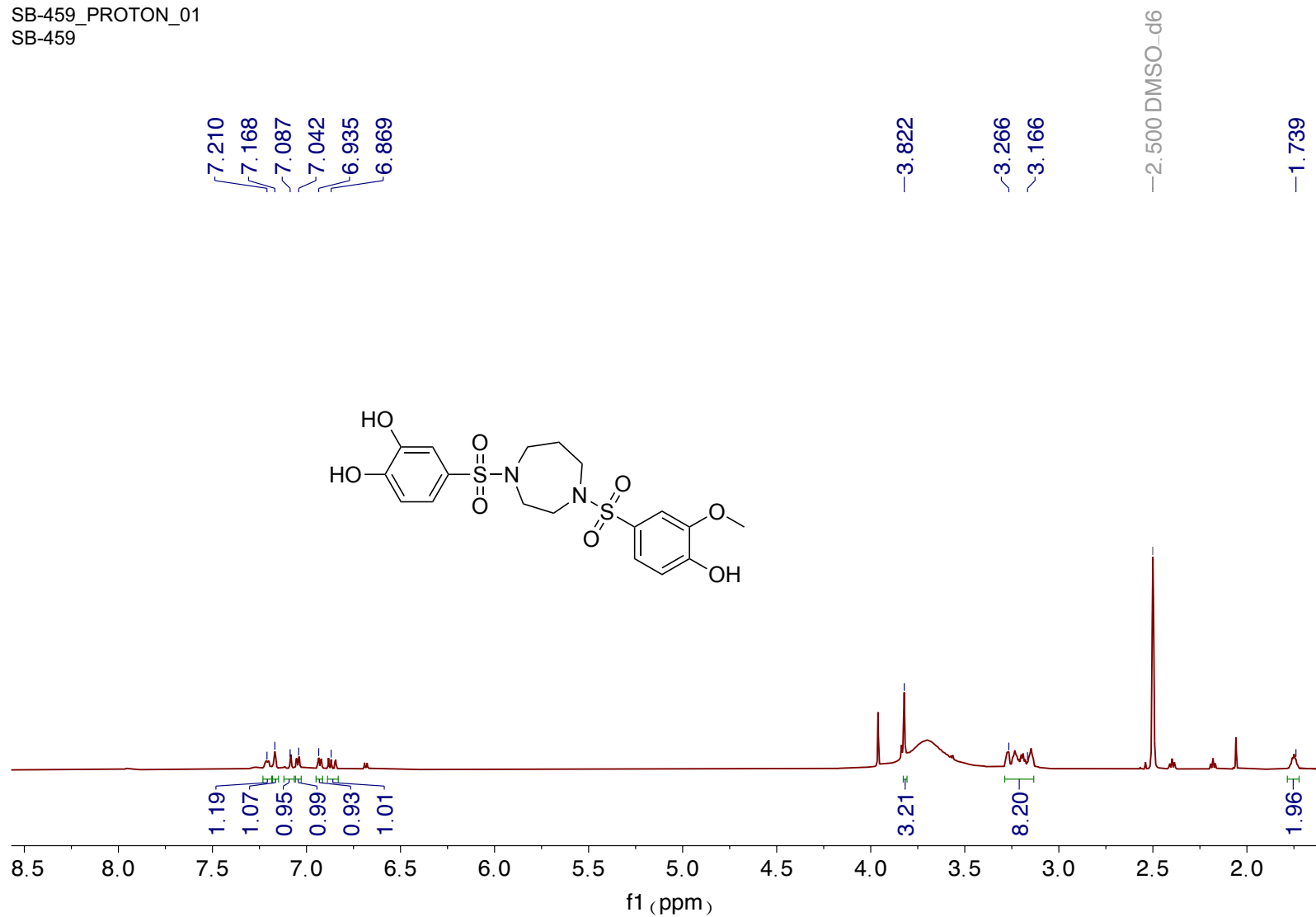


Fig. S267. ^1H - ^1H COSY spectrum of SB756050 metabolite SB-459. SB-459 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

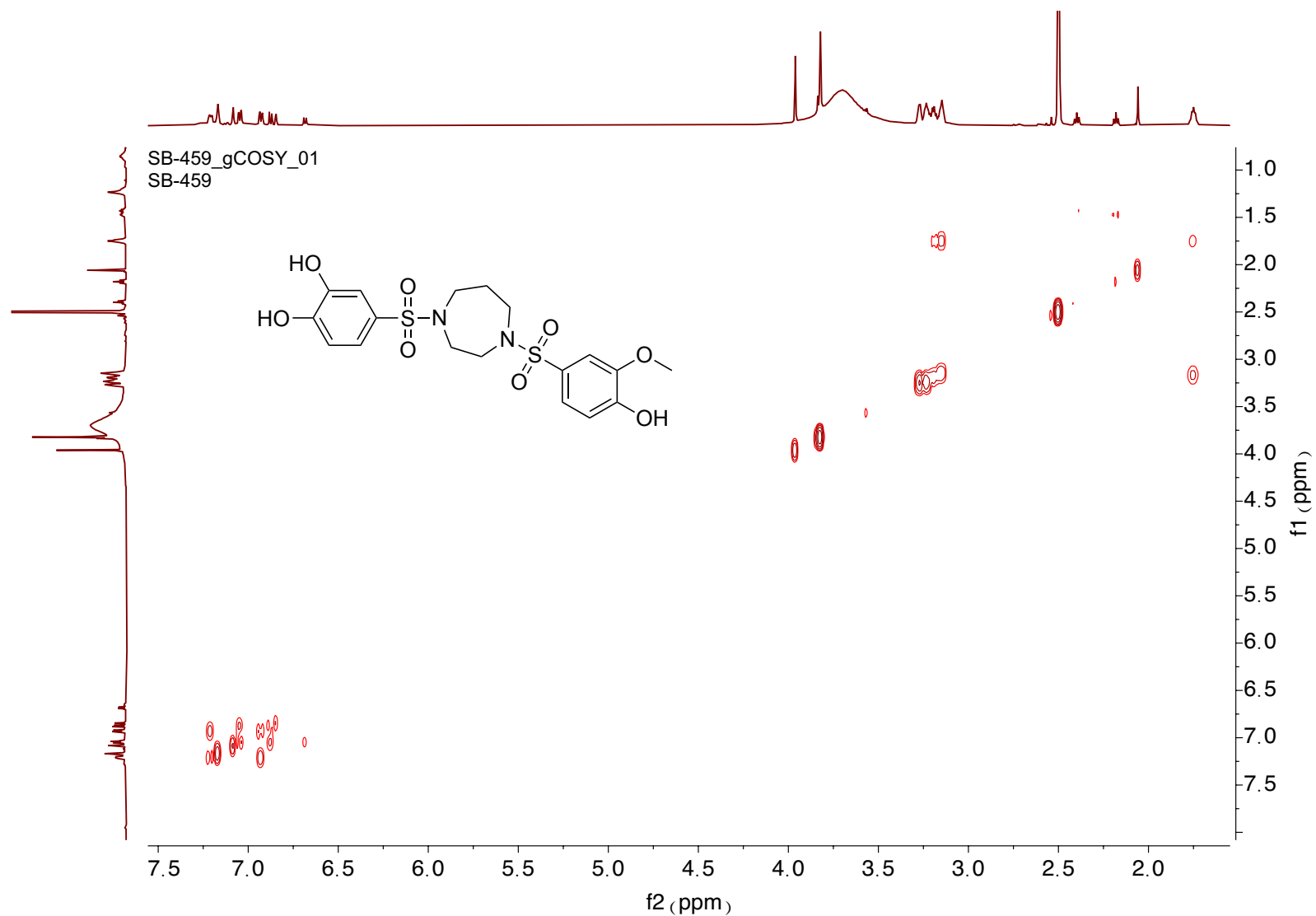


Fig. S268. HSQC spectrum of SB756050 metabolite SB-459. SB-459 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

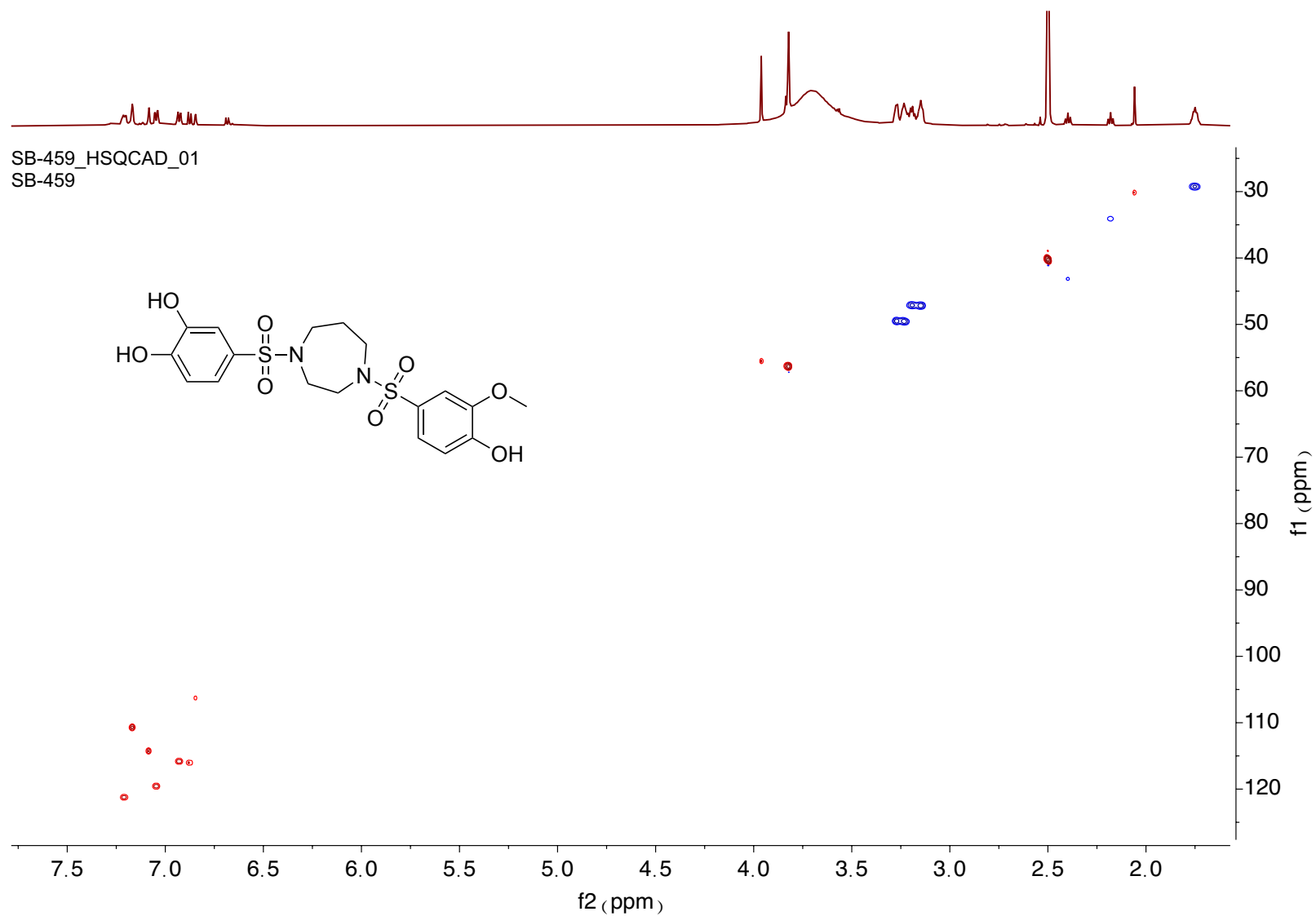


Fig. S269. HMBC spectrum of SB756050 metabolite SB-459. SB-459 was isolated from the SB756050 biotransformation culture using *Bac-Mix*.

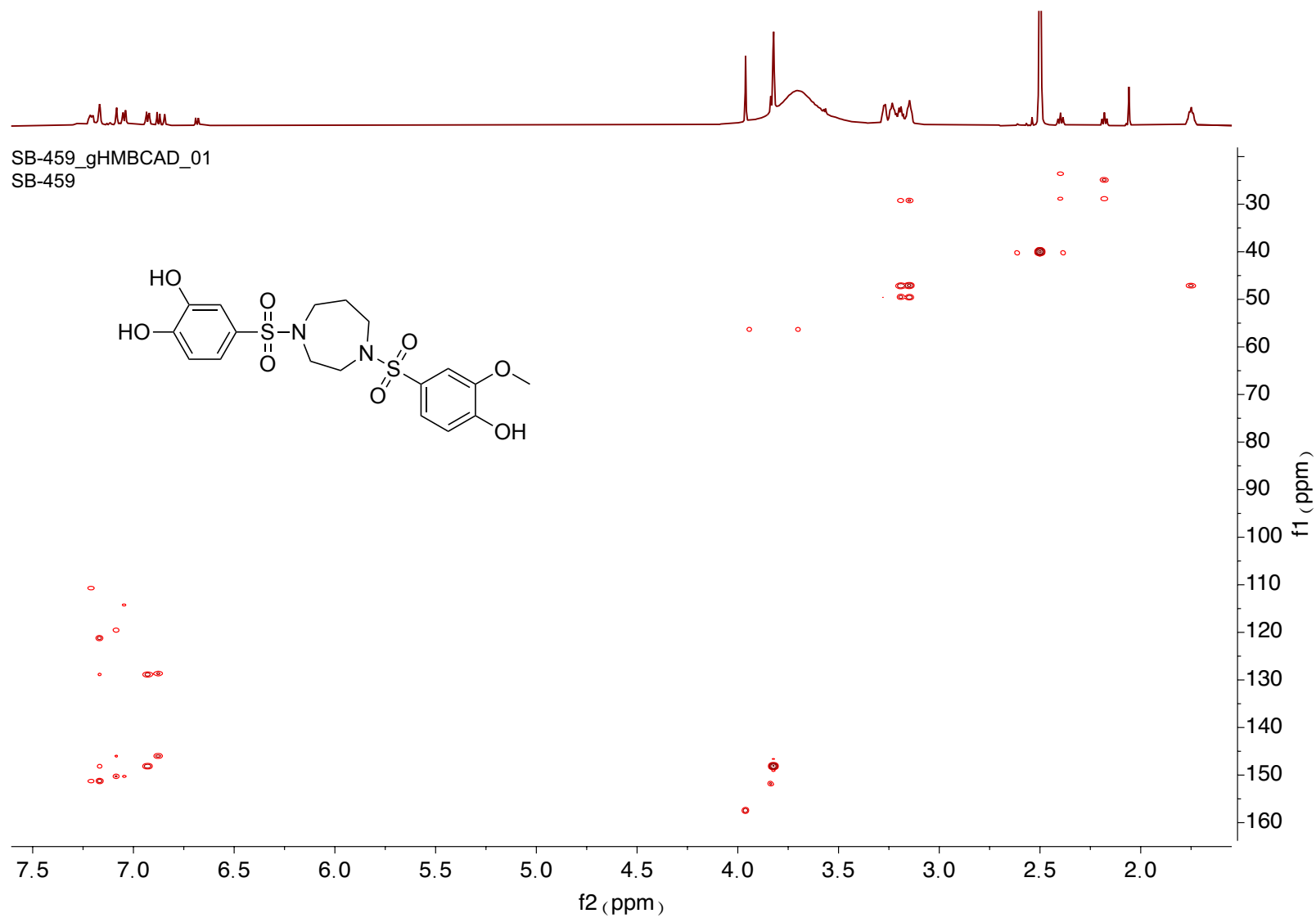


Table S21. ^1H and ^{13}C NMR data for SB-487 in $\text{DMSO}-d_6$ (600 MHz for ^1H). The carbon chemical shifts were determined by HSQC and HMBC analyses.

Position	δ_{C} , type	δ_{H} , (J in Hz)
1	152.8, qC	-
2	149.6, qC	-
3	109.9, CH	7.18, d (2.4)
4	130.5, qC	-
5	121.1, CH	7.33, dd (1.8, 8.4)
6	111.8, CH	7.12, d (8.4)
7	56.3 ^a , CH_3	3.82 ^a , s
8	56.3 ^a , CH_3	3.84, s
9	47.3 ^a , CH_2	3.20 ^a , m
10	29.4, CH_2	1.74, m
11	47.3 ^a , CH_2	3.20 ^a , m
12	49.5 ^a , CH_2	3.28 ^a , brs
13	49.5 ^a , CH_2	3.28 ^a , brs
14	128.8, qC	-
15	121.3, CH	7.20, dd (1.8, 8.4)
16	115.7, CH	6.92, d (8.4)
17	151.4, qC	-
18	148.0, qC	-
19	110.8, CH	7.16, d (1.8)
20	56.3 ^a , CH_3	3.82 ^a , s
OH	-	10.16, brs

^aoverlapped signals.

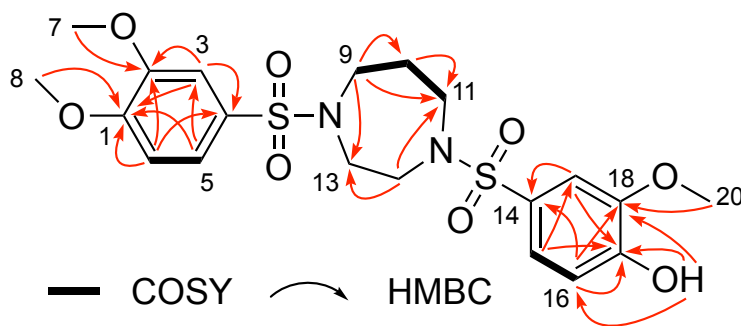


Table S22. ^1H and ^{13}C NMR data for SB-473 in $\text{DMSO-}d_6$ (600 MHz for ^1H). The carbon chemical shifts were determined by HSQC and HMBC analyses.

Position	δ_{C} , type	δ_{H} , (J in Hz)
1	151.3 ^a , qC	-
2	148.1 ^a , qC	-
3	110.7 ^a , CH	7.16 ^a , d (1.8)
4	128.8 ^a , qC	-
5	121.2 ^a , CH	7.21 ^a , dd (1.8, 8.4)
6	115.7 ^a , CH	6.92 ^a , d (8.4)
7	56.3 ^a , CH_3	3.82 ^a , s
8	47.1 ^a , CH_2	3.19 ^a , m
9	29.2, CH_2	1.74, m
10	47.1 ^a , CH_2	3.19 ^a , m
11	49.5 ^a , CH_2	3.26 ^a , brs
12	49.5 ^a , CH_2	3.26 ^a , brs
13	128.8 ^a , qC	-
14	121.2 ^a , CH	7.21 ^a , dd (1.8, 8.4)
15	115.7 ^a , CH	6.92 ^a , d (8.4)
16	151.3 ^a , qC	-
17	148.1 ^a , qC	-
18	110.7 ^a , CH	7.16 ^a , d (1.8)
19	56.3 ^a , CH_3	3.82 ^a , s

^aoverlapped signals.

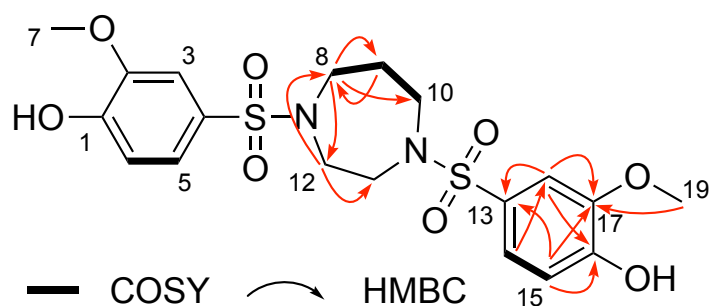


Table S23. ^1H and ^{13}C NMR data for SB-459 in $\text{DMSO}-d_6$ (600 MHz for ^1H). The carbon chemical shifts were determined by HSQC and HMBC analyses.

Position	δ_{C} , type	δ_{H} , (J in Hz)
1	150.3, qC	-
2	146.0, qC	-
3	114.3, CH	7.08, brs
4	128.6, qC	-
5	119.6, CH	7.04, dd (1.8, 8.4)
6	116.0, CH	6.87, d (8.4)
7	47.2 ^a , CH_2	3.17 ^a , m
8	29.3, CH_2	1.74, m
9	47.2 ^a , CH_2	3.17 ^a , m
10	49.5 ^a , CH_2	3.25 ^a , brs
11	49.5 ^a , CH_2	3.25 ^a , brs
12	128.8, qC	-
13	121.3, CH	7.21, m
14	115.8, CH	6.93, m
15	151.3, qC	-
16	148.2, qC	-
17	110.7, CH	7.17, brs
18	56.3, CH_3	3.82, s

^aoverlapped signals.

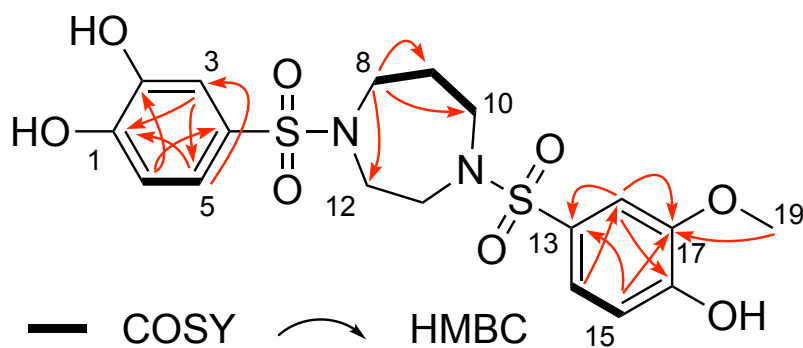


Fig. S270. HR-ESI-MS of purified SB-487. SB-487, $m/z_{\text{calcd.}}$ 487.1202, $m/z_{\text{obs.}}$ 487.1202; A representative charge state is shown.

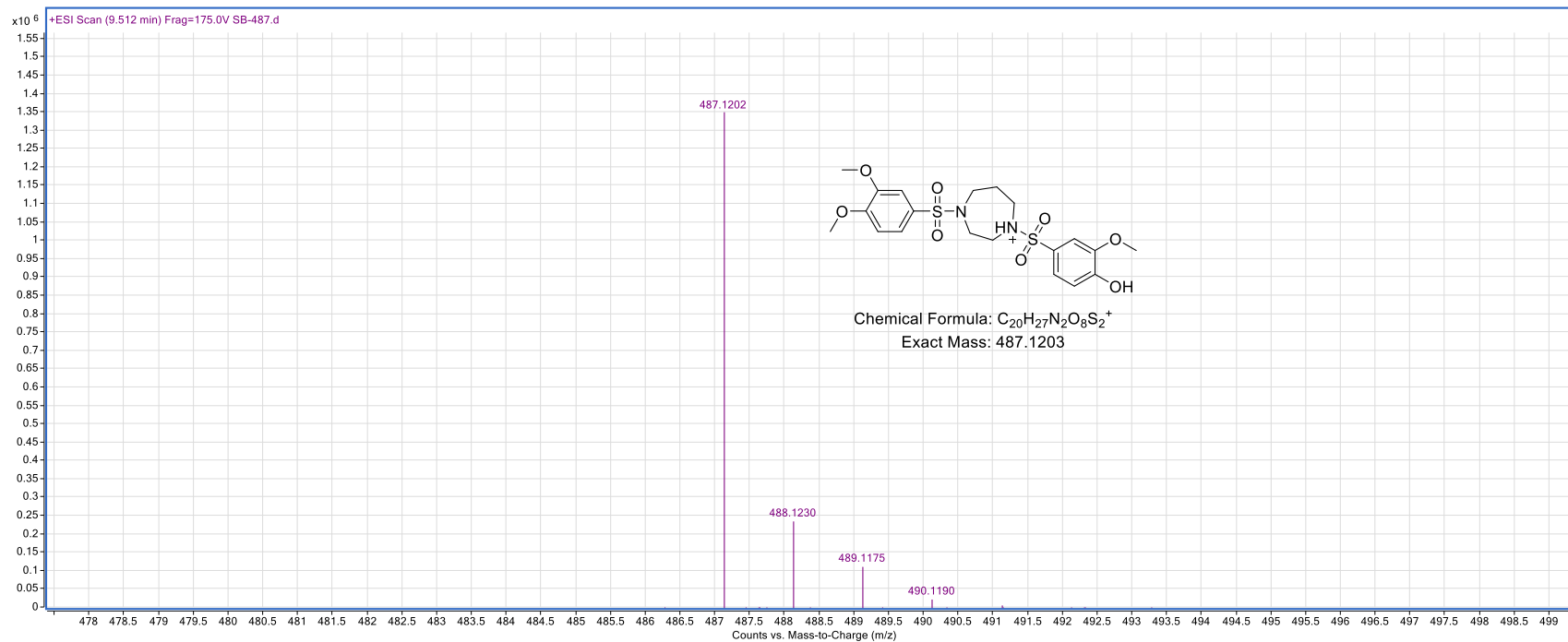


Fig. S271. Proposed HR-ESI-MS² fragmentation of SB-487. Fragment A: $m/z_{\text{calcd.}}$ 301.1217, $m/z_{\text{obs.}}$ 301.1213; Fragment B: $m/z_{\text{calcd.}}$ 285.0904, $m/z_{\text{obs.}}$ 285.0900; Fragment C: $m/z_{\text{calcd.}}$ 201.0216, $m/z_{\text{obs.}}$ 201.0214; Fragment D: $m/z_{\text{calcd.}}$ 187.0060, $m/z_{\text{obs.}}$ 187.0057; Fragment E: $m/z_{\text{calcd.}}$ 137.0597, $m/z_{\text{obs.}}$ 137.0597; Fragment F: $m/z_{\text{calcd.}}$ 123.0441, $m/z_{\text{obs.}}$ 123.0438. Representative charge states are shown.

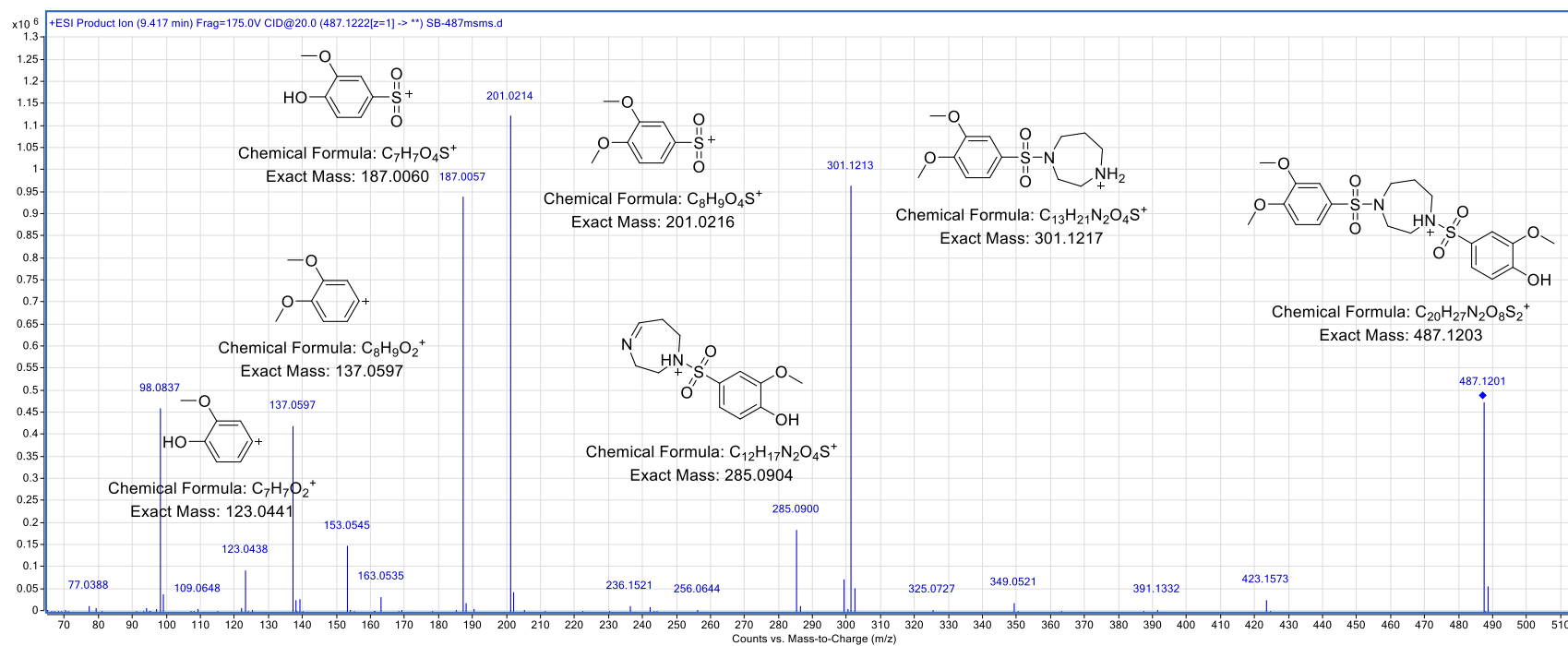


Fig. S272. HR-ESI-MS of purified SB-473. SB-473, $m/z_{\text{calcd.}}$ 473.1047, $m/z_{\text{obs.}}$ 473.1047; A representative charge state is shown.

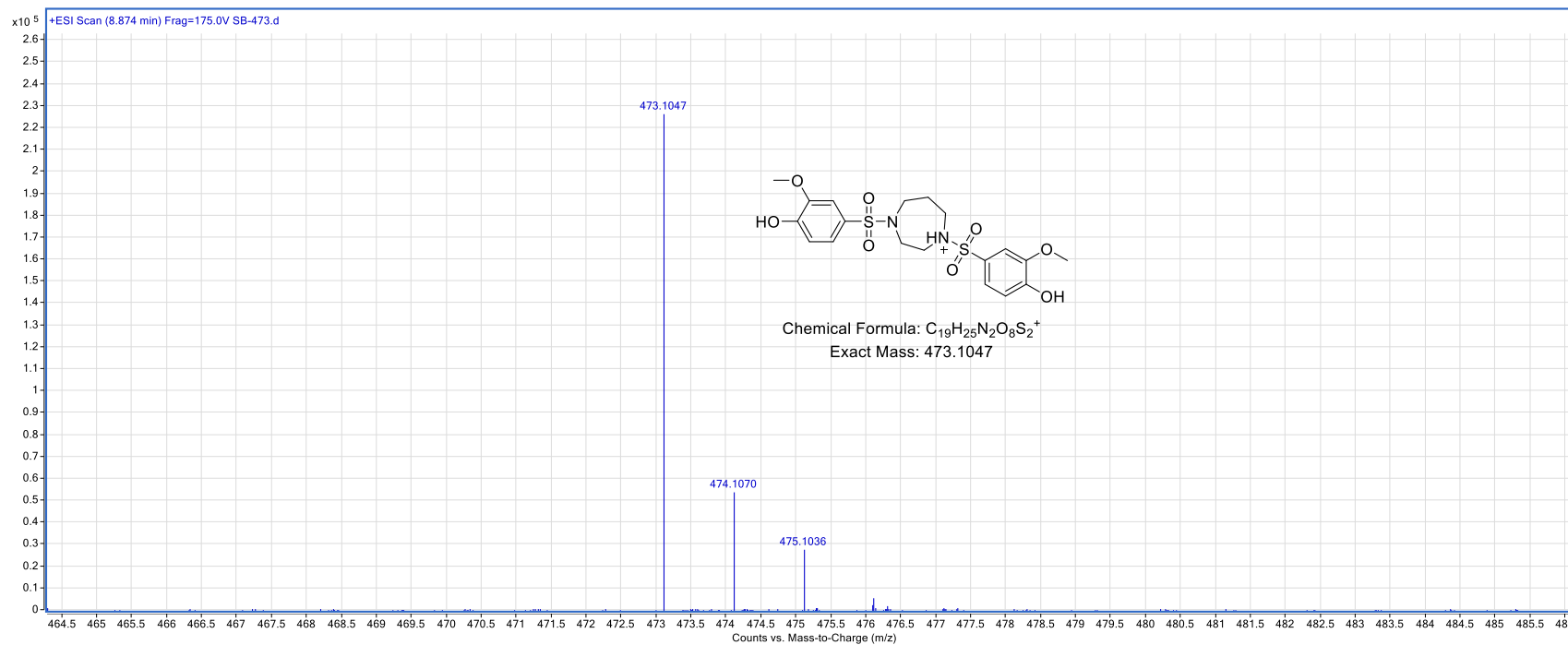


Fig. S273. Proposed HR-ESI-MS² fragmentation of SB-473. Fragment A: $m/z_{\text{calcd.}}$ 287.1060, $m/z_{\text{obs.}}$ 287.1059; Fragment B: $m/z_{\text{calcd.}}$ 187.0060, $m/z_{\text{obs.}}$ 187.0061. Representative charge states are shown.

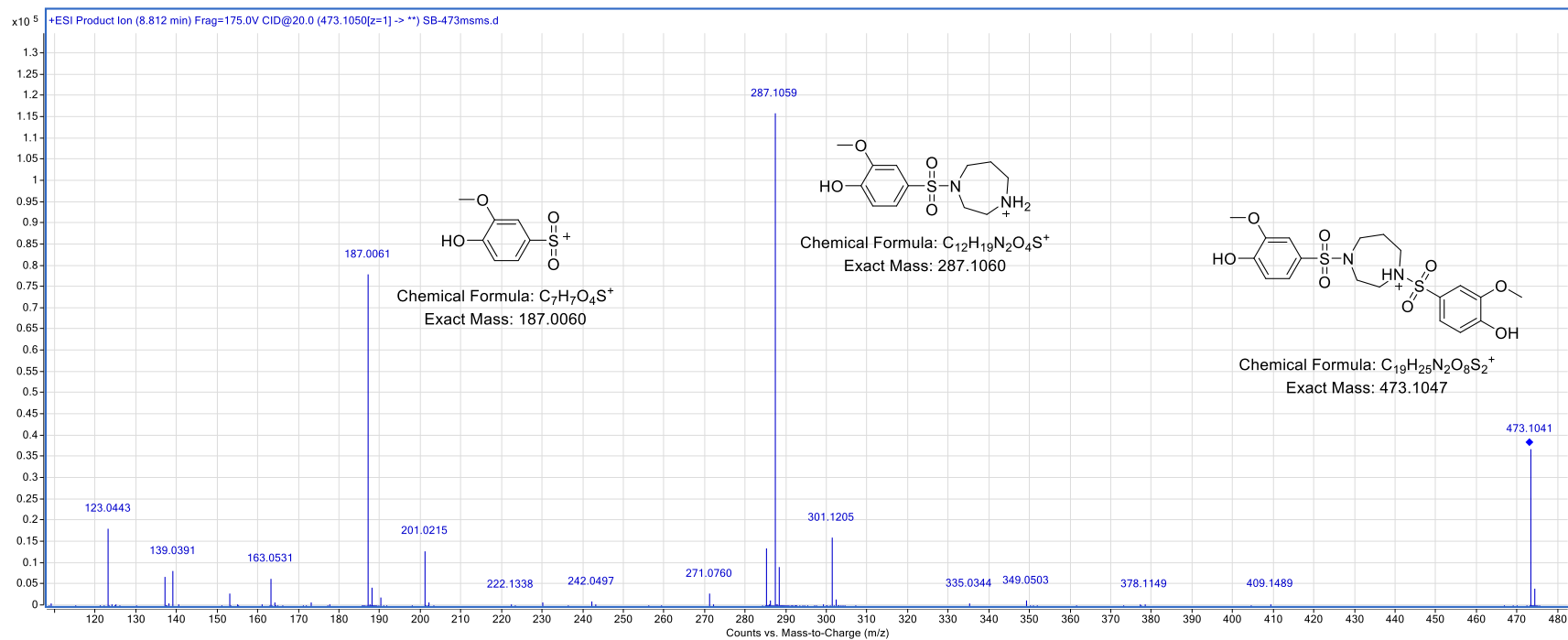


Fig. S274. HR-ESI-MS of purified SB-459. SB-459, $m/z_{\text{calcd.}}$ 459.0890, $m/z_{\text{obs.}}$ 459.0889; A representative charge state is shown.

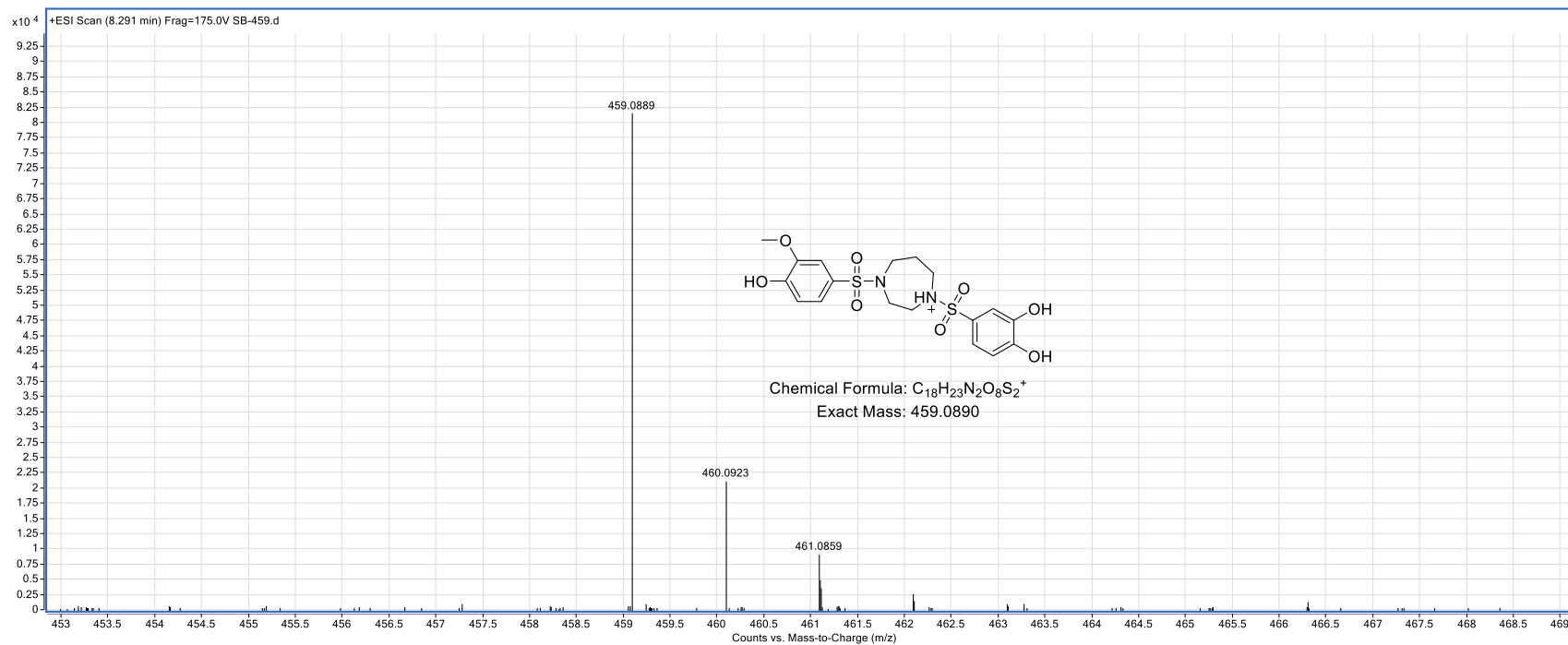


Fig. S275. Proposed HR-ESI-MS² fragmentation of SB-459. Fragment A: $m/z_{\text{calcd.}}$ 287.1060, $m/z_{\text{obs.}}$ 287.1056; Fragment B: $m/z_{\text{calcd.}}$ 273.0904, $m/z_{\text{obs.}}$ 273.0907; Fragment C: $m/z_{\text{calcd.}}$ 187.0060, $m/z_{\text{obs.}}$ 187.0057; Fragment D: $m/z_{\text{calcd.}}$ 172.9903, $m/z_{\text{obs.}}$ 172.9896. Representative charge states are shown.

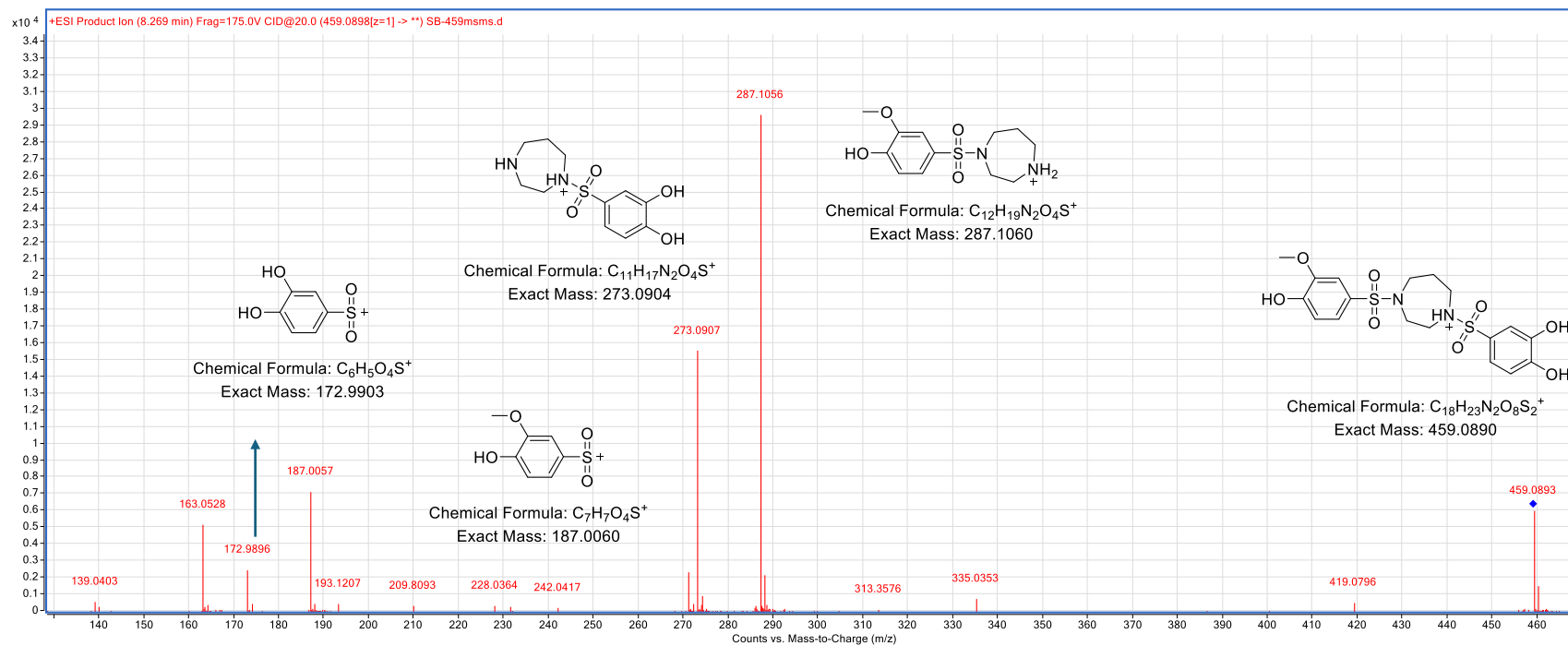
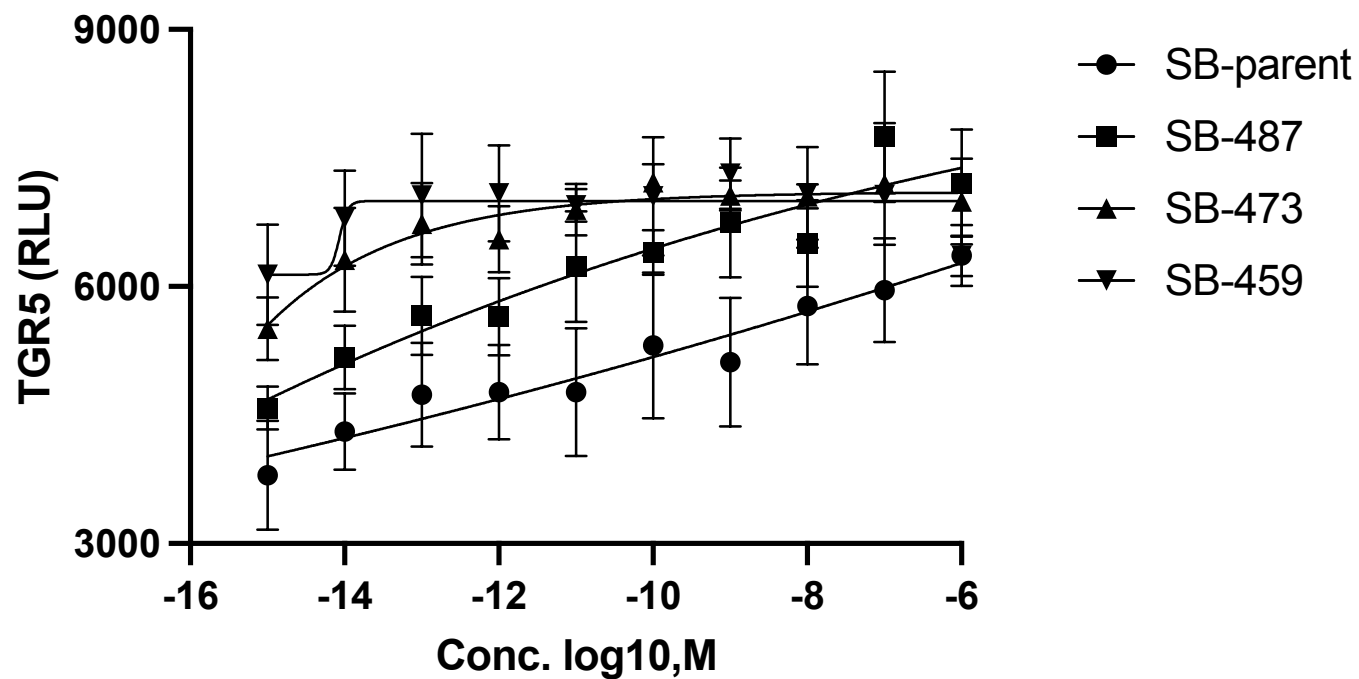


Fig. S276. TGR5 activation activity test of SB756050 and its metabolites by PRESTO-Tango. Three purified metabolites exhibited better TGR5 activation activity compared to SB756050. n = 3 biological replicates. Data represent mean $\pm$ s.d.



9. Investigation of ester cleavage in drugs containing ester groups

Fig. S277. Investigation of ester cleavage in loratadine. A ± 20 ppm window was applied for the EIC of the predicted product (m/z 355.1208). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

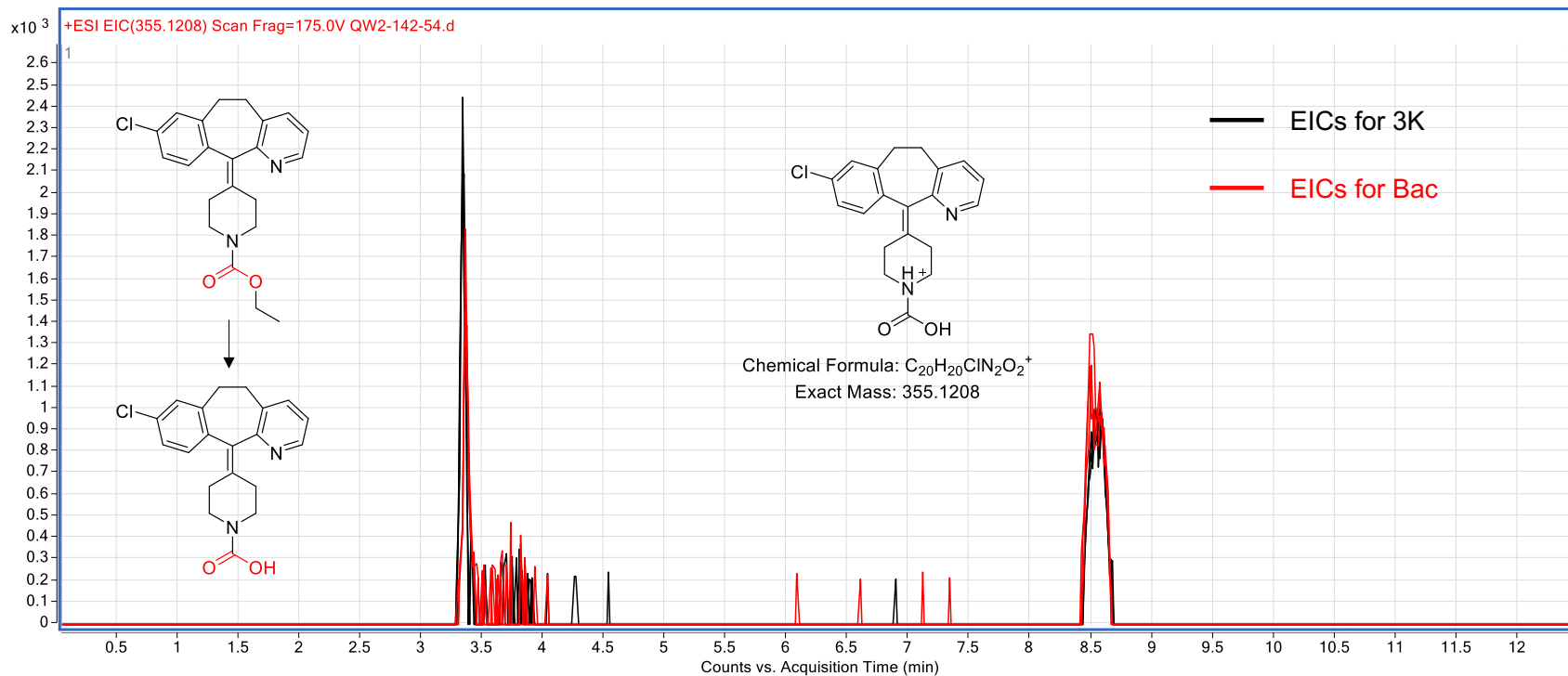


Fig. S278. Investigation of ester cleavage in MK-0557. A ± 20 ppm window was applied for the EIC of the predicted product (MK-425, m/z 425.1620). Although spontaneous degradation occurred in the cell/enzyme-free 3K supernatants, significantly more metabolites accumulated, indicating the contribution of bacterial cell-dependent metabolism. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K; $n = 3$ biological replicates. Data represent mean $\pm$ s.d. $**P = 0.0021$. Statistical significance was determined using two-tailed t-test.

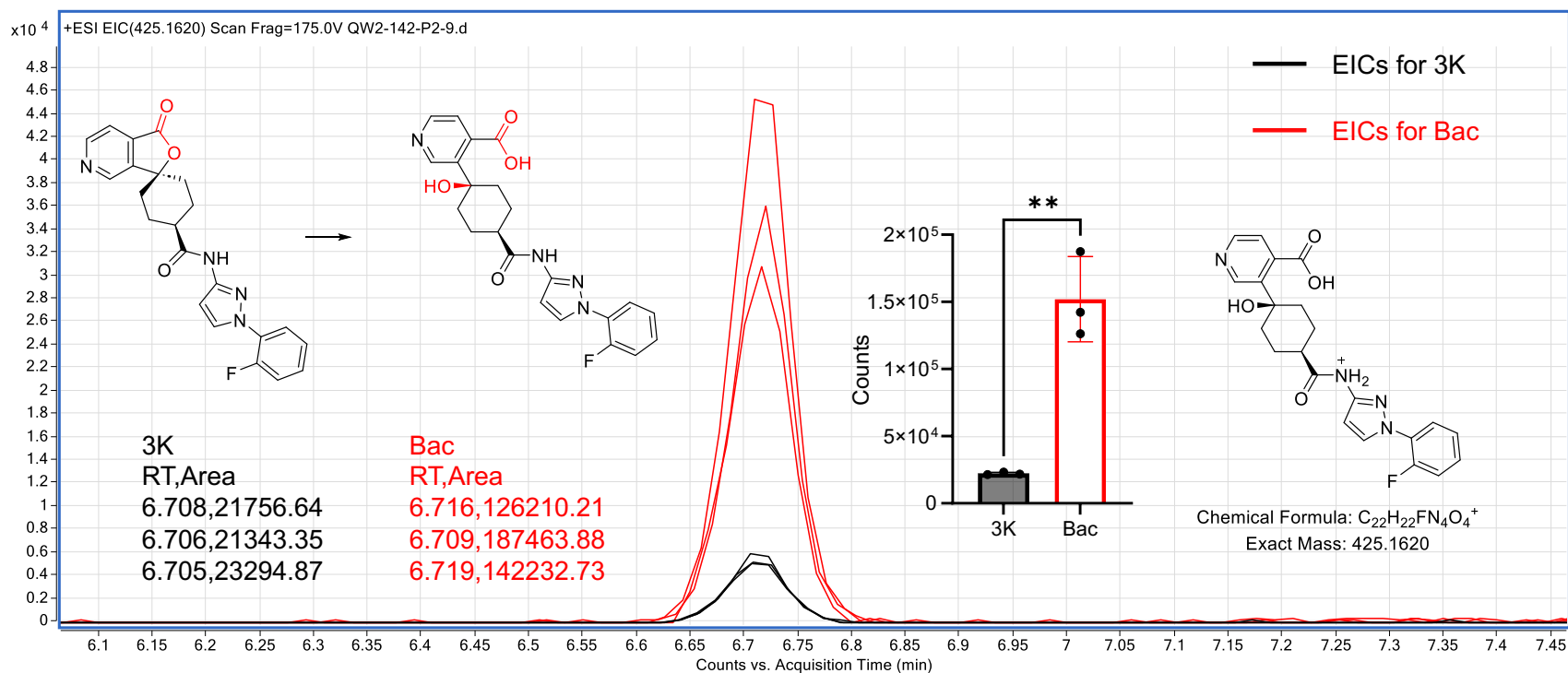


Fig. S279. Investigation of ester cleavage in zafirlukast. A ± 20 ppm window was applied for the EIC of the predicted product (m/z 508.1537). No predicted metabolite was detected. The observed peaks are internal fragments of the parent drug. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

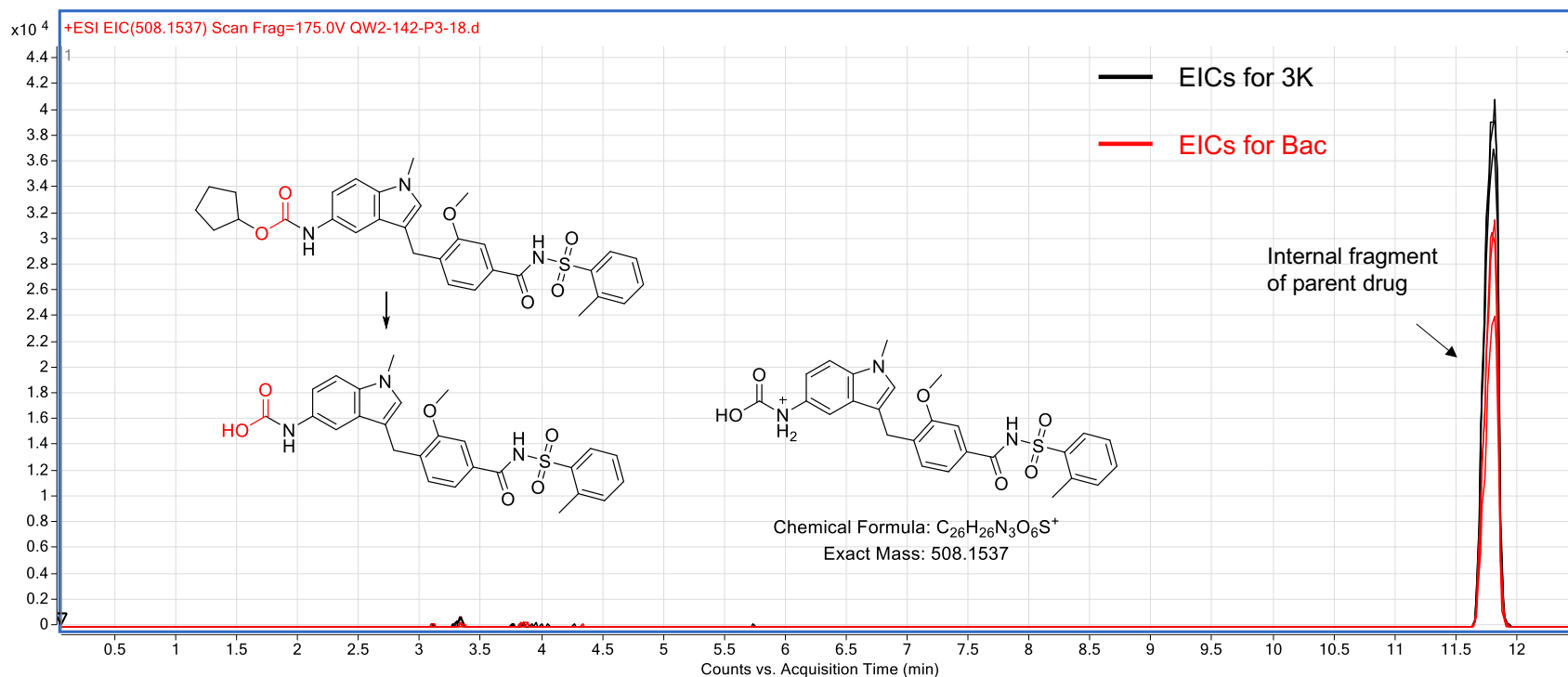


Fig. S280. Investigation of ester cleavage in nicergoline. A ± 20 ppm window was applied for the EIC of the predicted products (nicergoline-301, m/z 301.1911 and nicergoline-201, m/z 201.9498). Although spontaneous degradation occurred in the cell/enzyme-free 3K supernatants, significantly more metabolites accumulated, indicating the contribution of bacterial cell-dependent metabolism. Representative charge states are shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K; $n = 3$ biological replicates. Data represent mean $\pm$ s.d. *** $P = 0.0001$, **** $P < 0.0001$. Statistical significance was determined using two-tailed t-test.

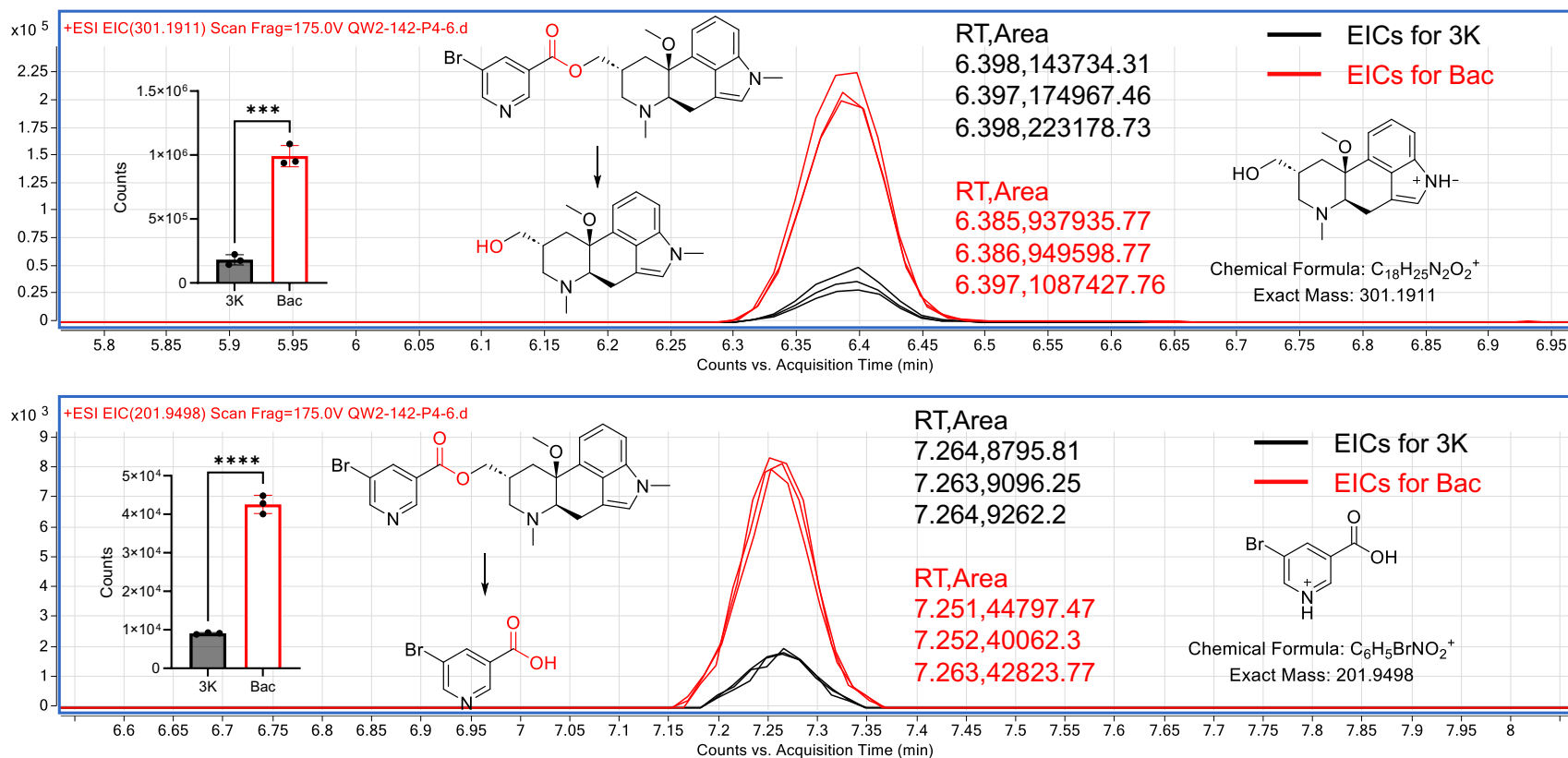


Fig. S281. Investigation of ester cleavage in bambuterol. A ± 20 ppm window was applied for the EIC of the predicted products (m/z 297.1809 and 226.1438). None of the metabolites were detected. Representative charge states are shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

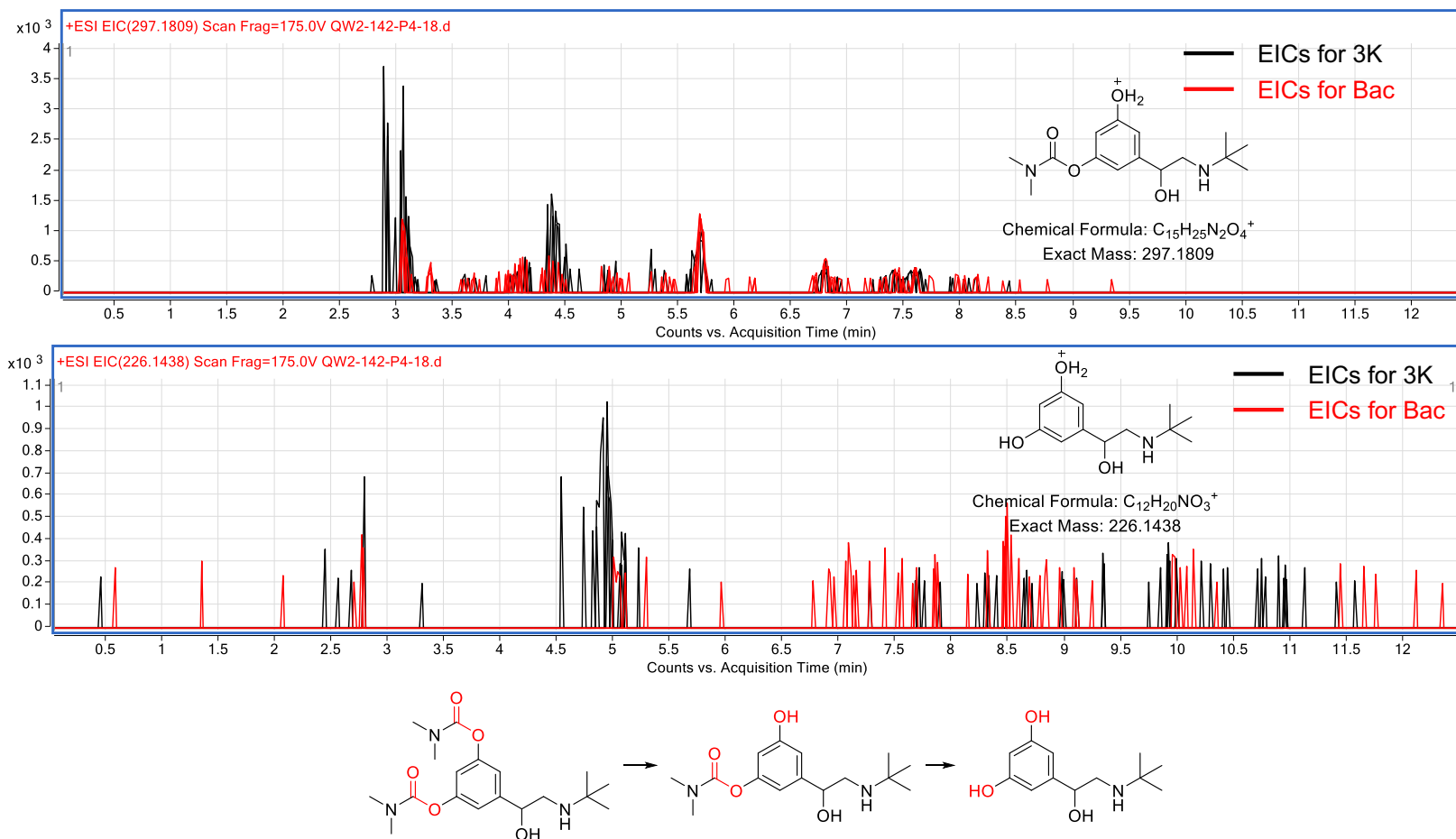


Fig. S282. Investigation of ester cleavage in clopidogrel. A ± 20 ppm window was applied for the EIC of the predicted product (m/z 308.0507). Although spontaneous degradation occurred in the cell/enzyme-free 3K supernatants, significantly more metabolites accumulated, indicating the contribution of bacterial cell-dependent metabolism. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K; $n = 3$ biological replicates. Data represent mean $\pm$ s.d. **** $P < 0.0001$. Statistical significance was determined using two-tailed t-test.

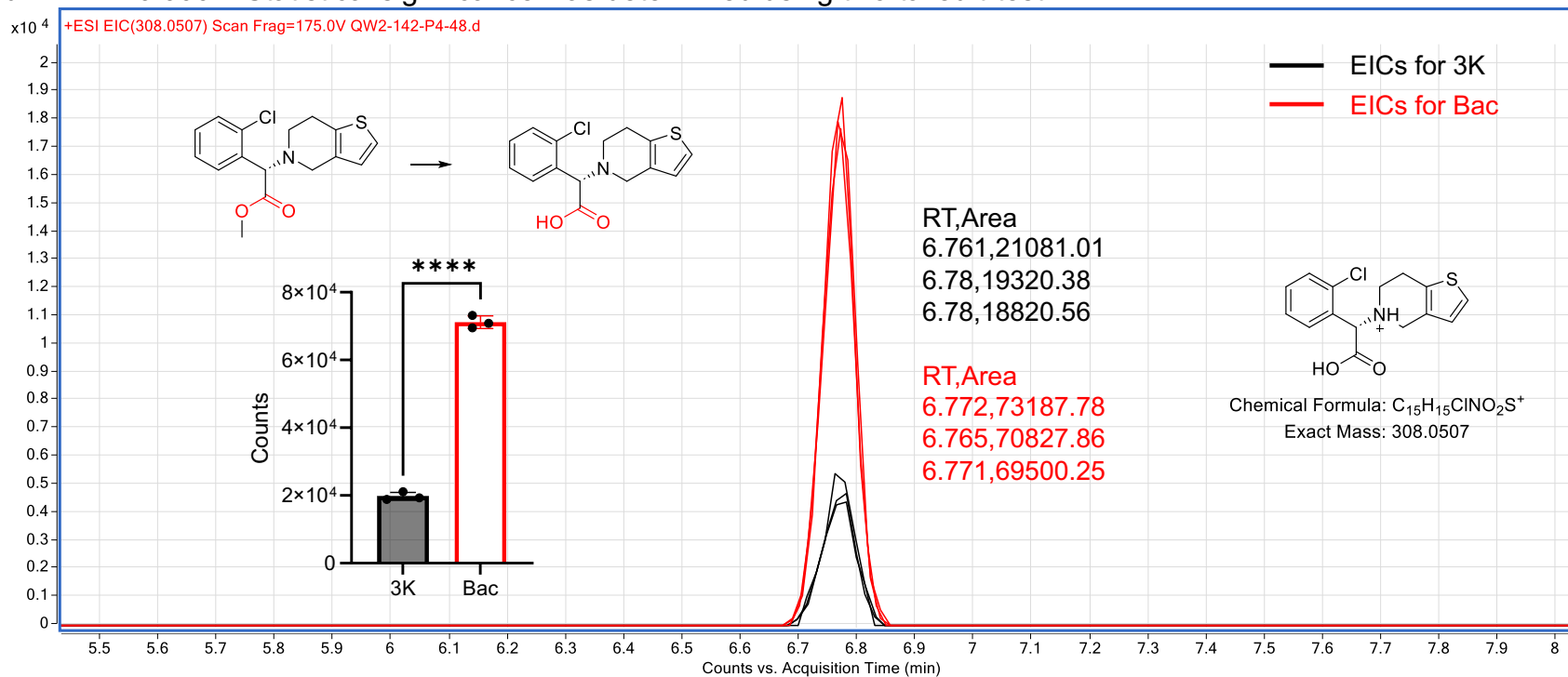


Fig. S283. Investigation of ester cleavage in pardoprunox. A ± 20 ppm window was applied for the EIC of the predicted product (m/z 252.1343). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

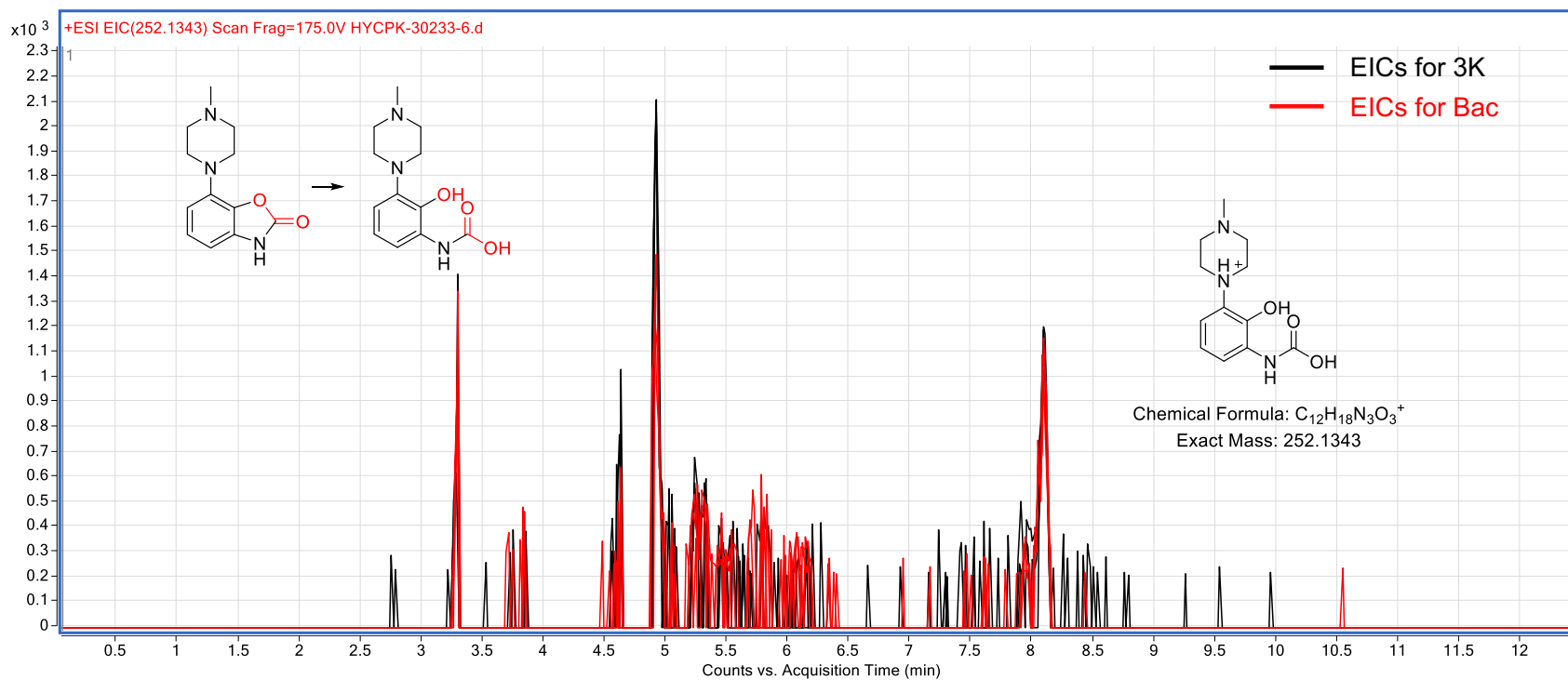


Fig. S284. Investigation of ester cleavage in homatropine. A ± 20 ppm window was applied for the EIC of the predicted products (m/z 153.0546 and 142.1226). None of the metabolites were detected. Representative charge states are shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

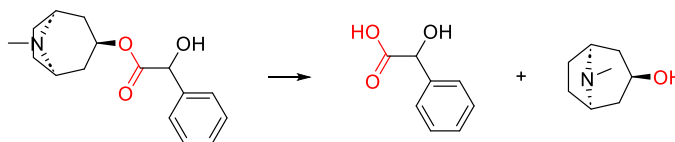
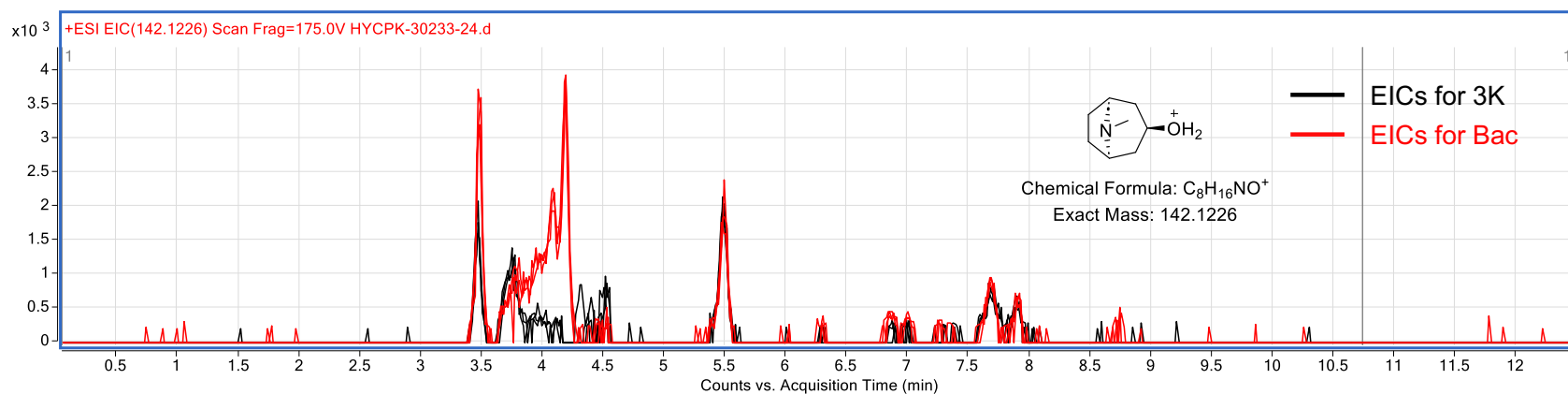
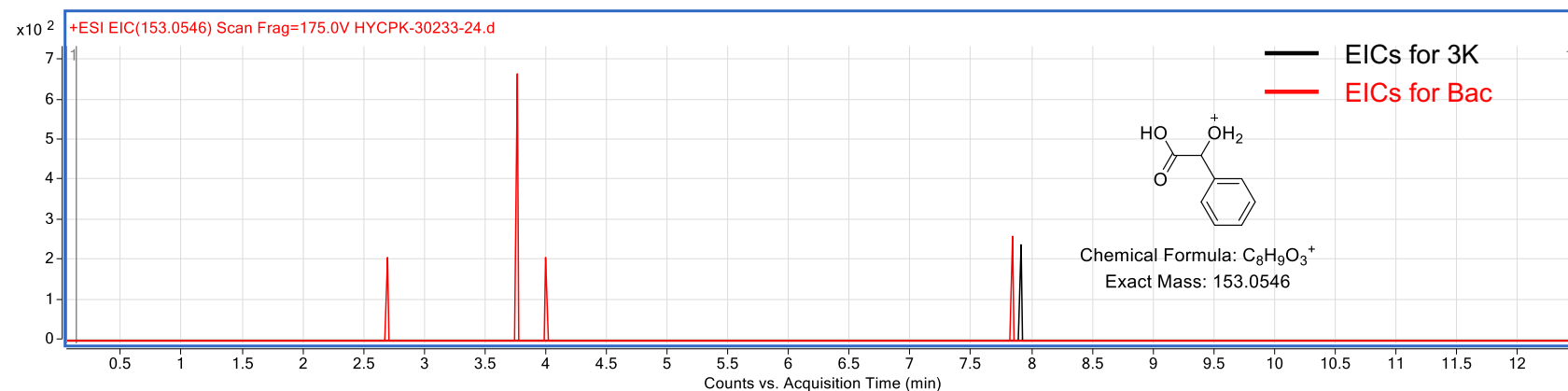


Fig. S285. Investigation of ester cleavage in glycopyrrolate. A ± 20 ppm window was applied for the EIC of the predicted products (m/z 221.1172 and 116.1070). None of the metabolites were detected. Representative charge states are shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

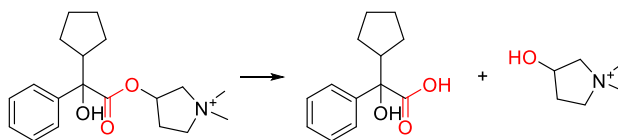
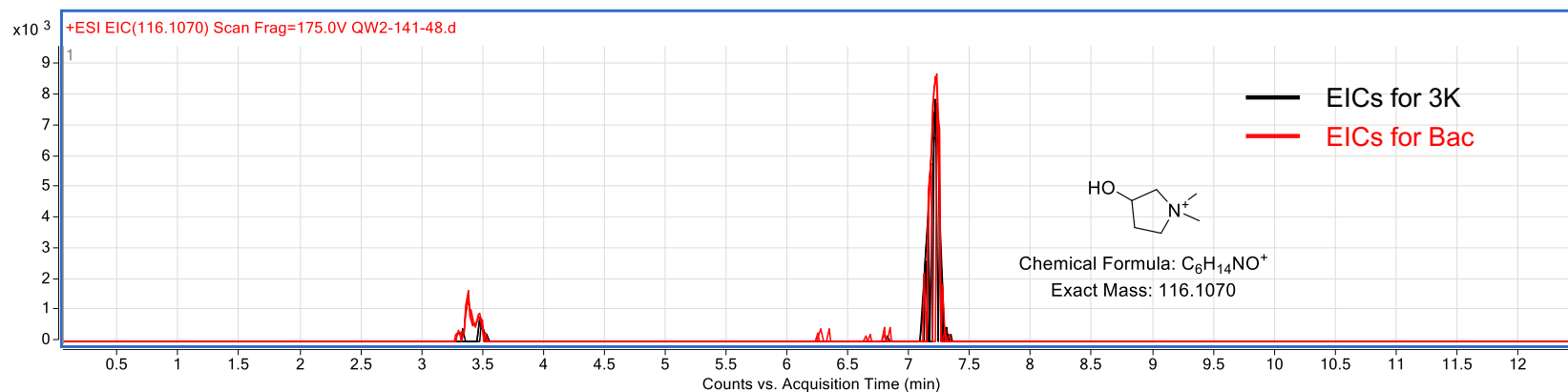
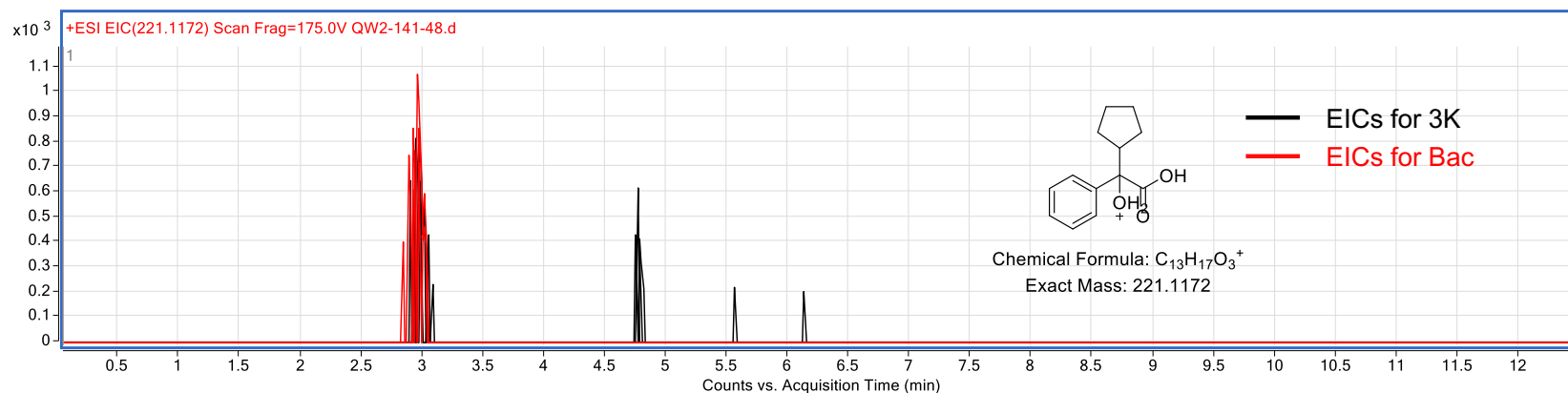


Fig. S286. Investigation of ester cleavage in trospium. A ± 20 ppm window was applied for the EIC of the predicted products (m/z 229.0859 and 182.1539). None of the metabolites were detected. Representative charge states are shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

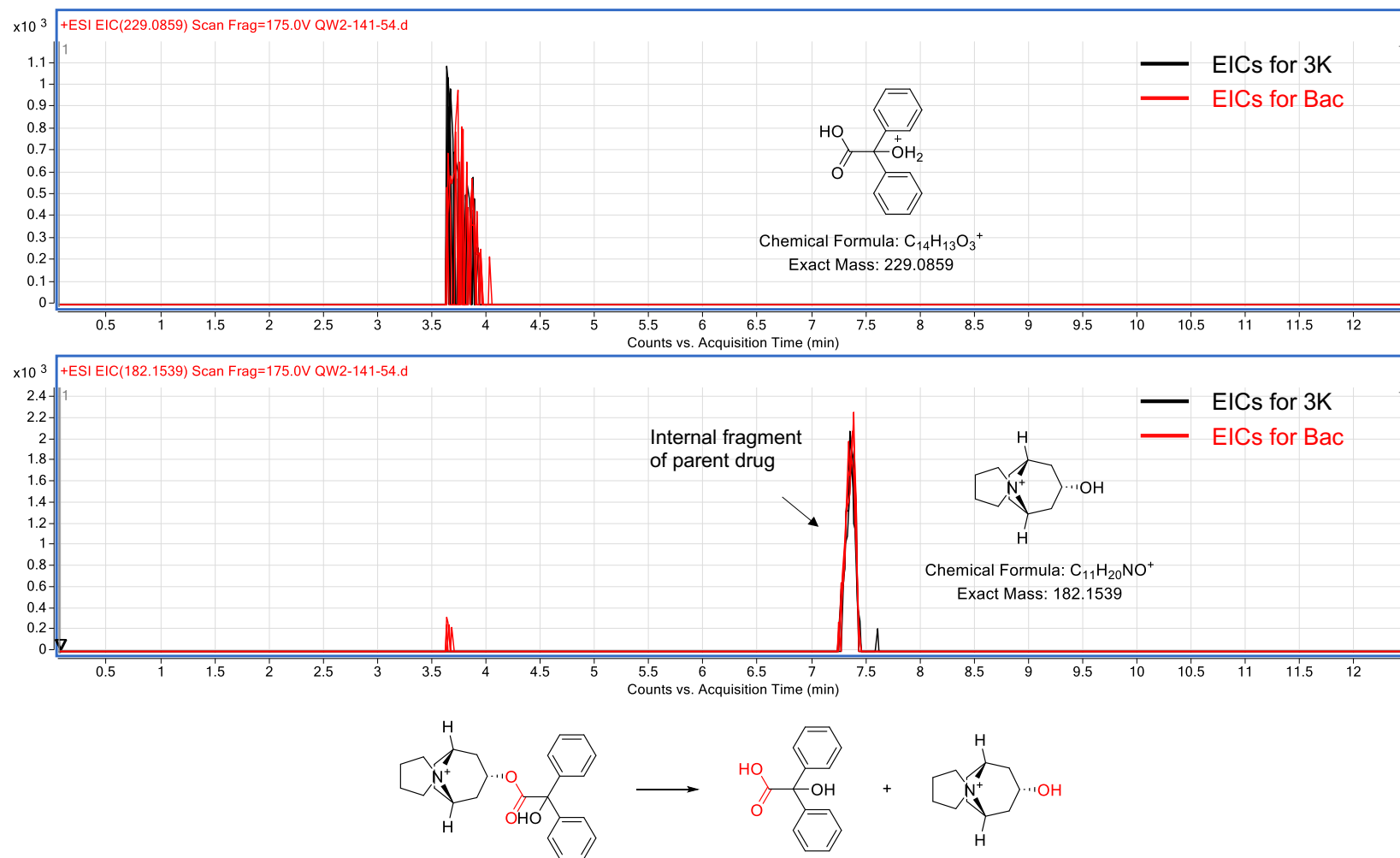


Fig. S287. Investigation of ester cleavage in rauwolscline. A ± 20 ppm window was applied for the EIC of the predicted product (m/z 341.1860). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

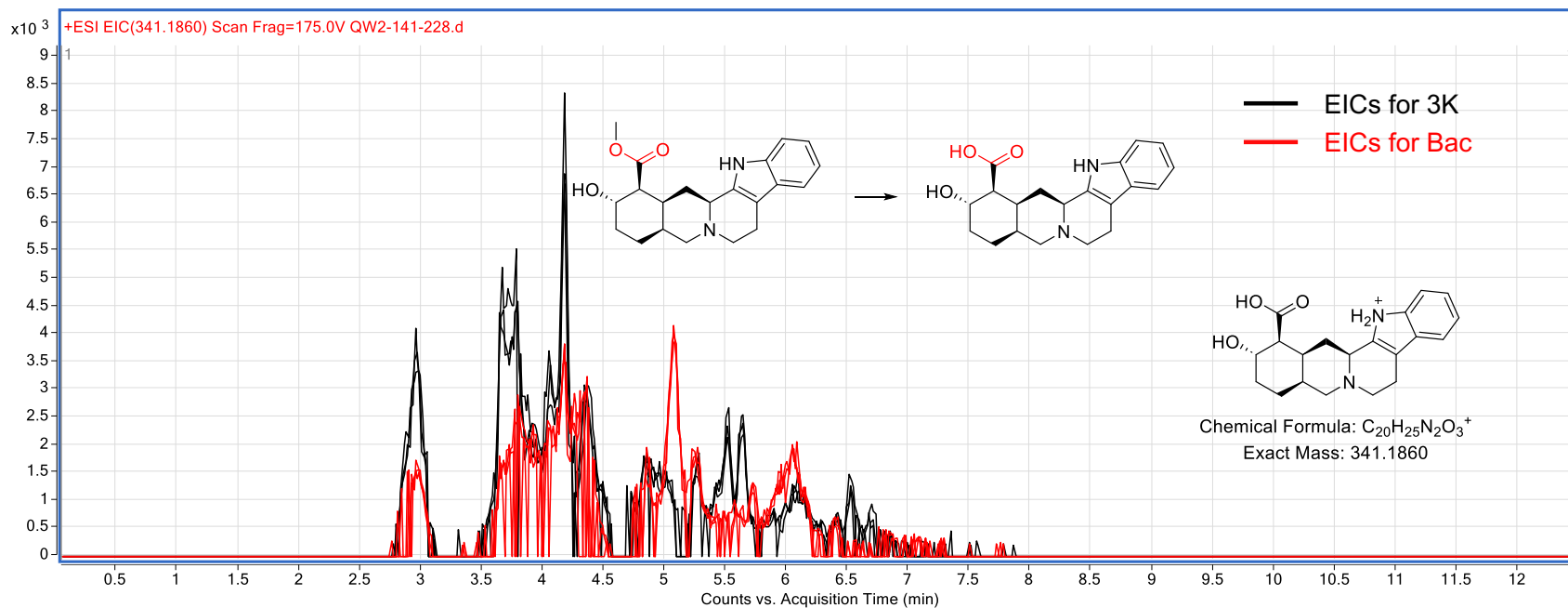


Fig. S288. Investigation of ester cleavage in otilonium. A ± 20 ppm window was applied for the EIC of the predicted product (m/z 370.2013). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

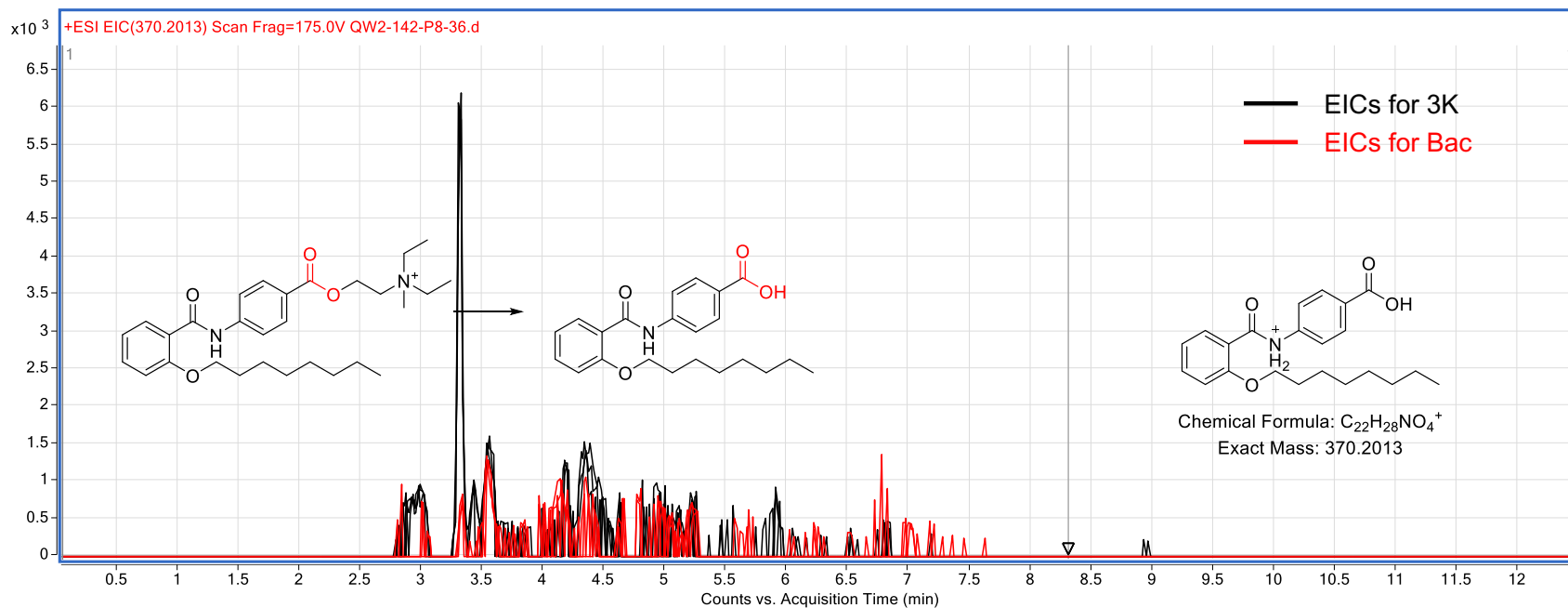


Fig. S289. Investigation of ester cleavage in oxybutynin. A ± 20 ppm window was applied for the EIC of the predicted products (m/z 235.1329 and 142.1226). None of the metabolites were detected. Representative charge states are shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

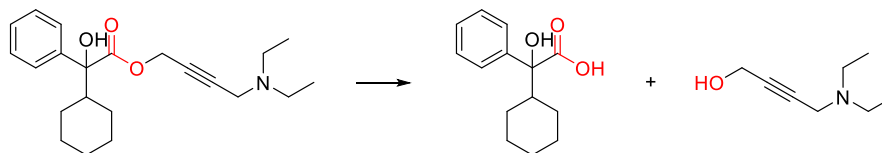
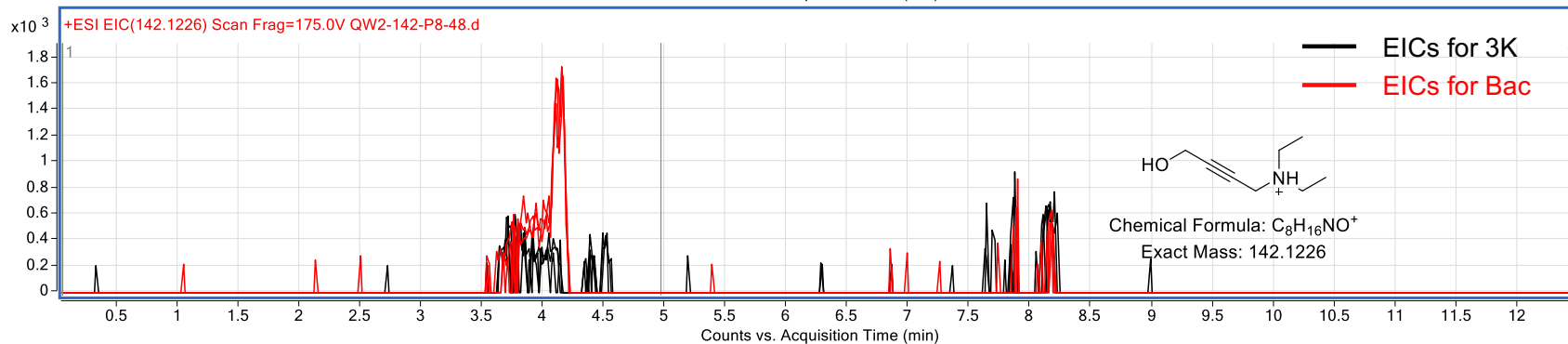
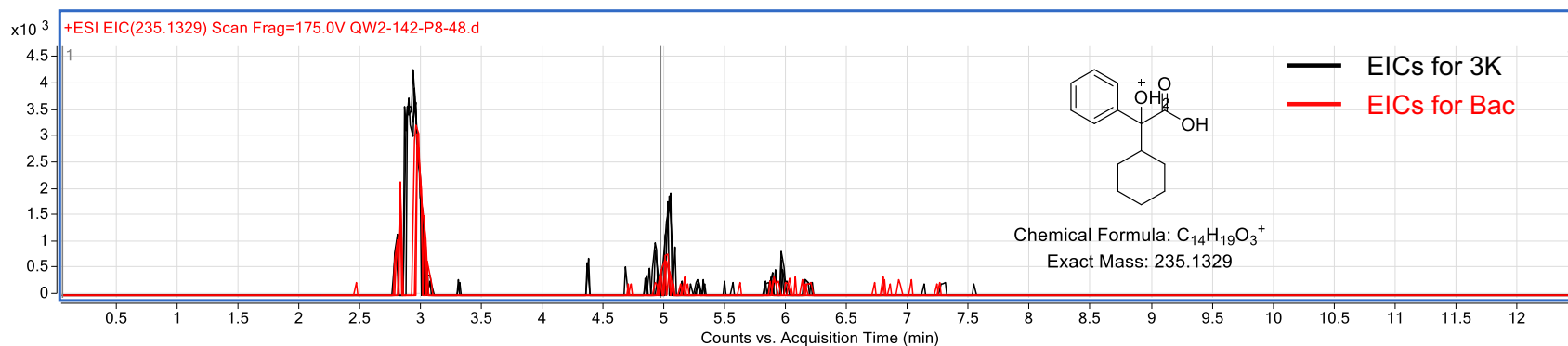


Fig. S290. Investigation of amide cleavage in reparixin. A ± 20 ppm window was applied for the EIC of the predicted product (m/z 207.1380). No predicted metabolite was detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates.

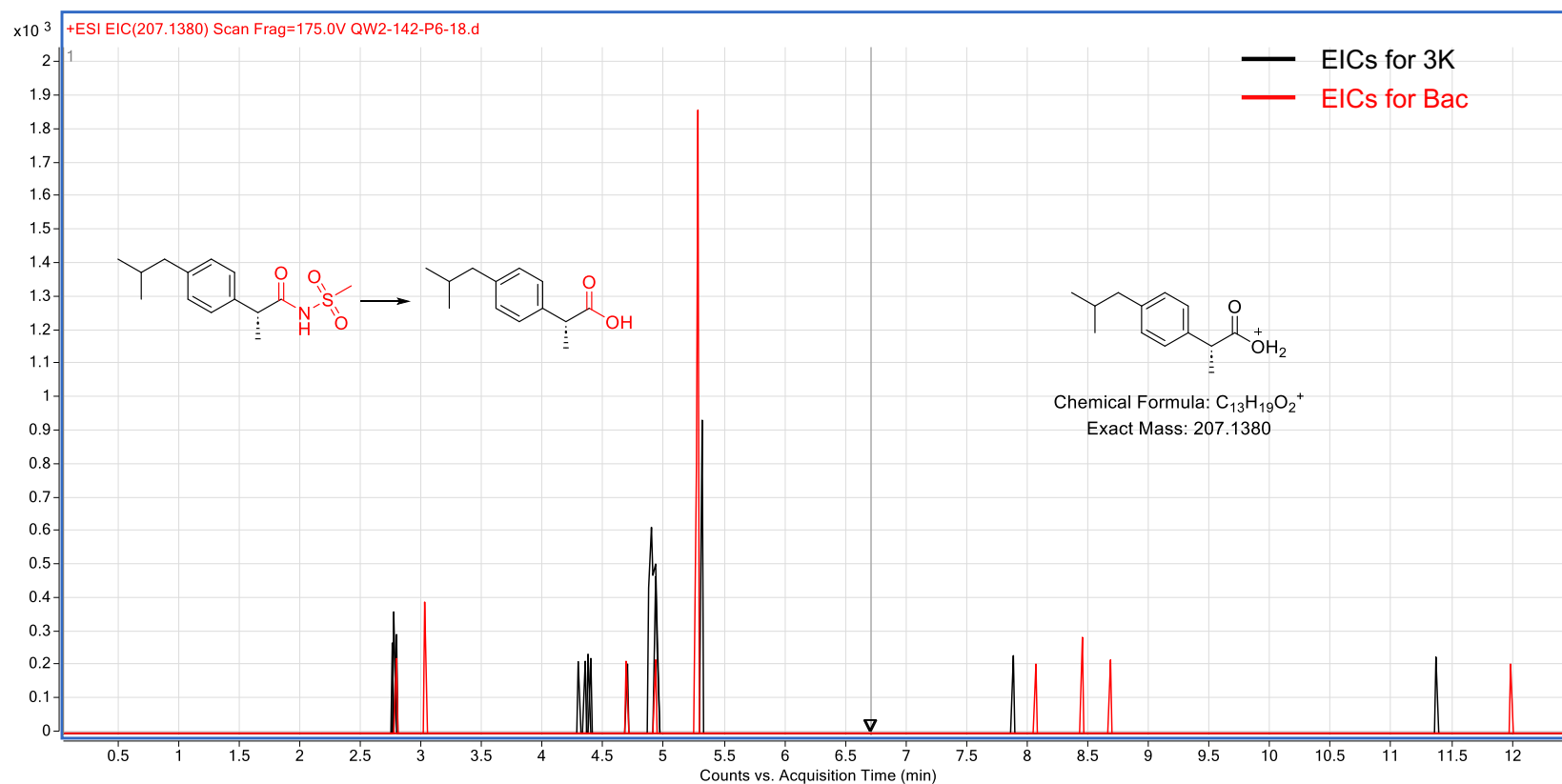
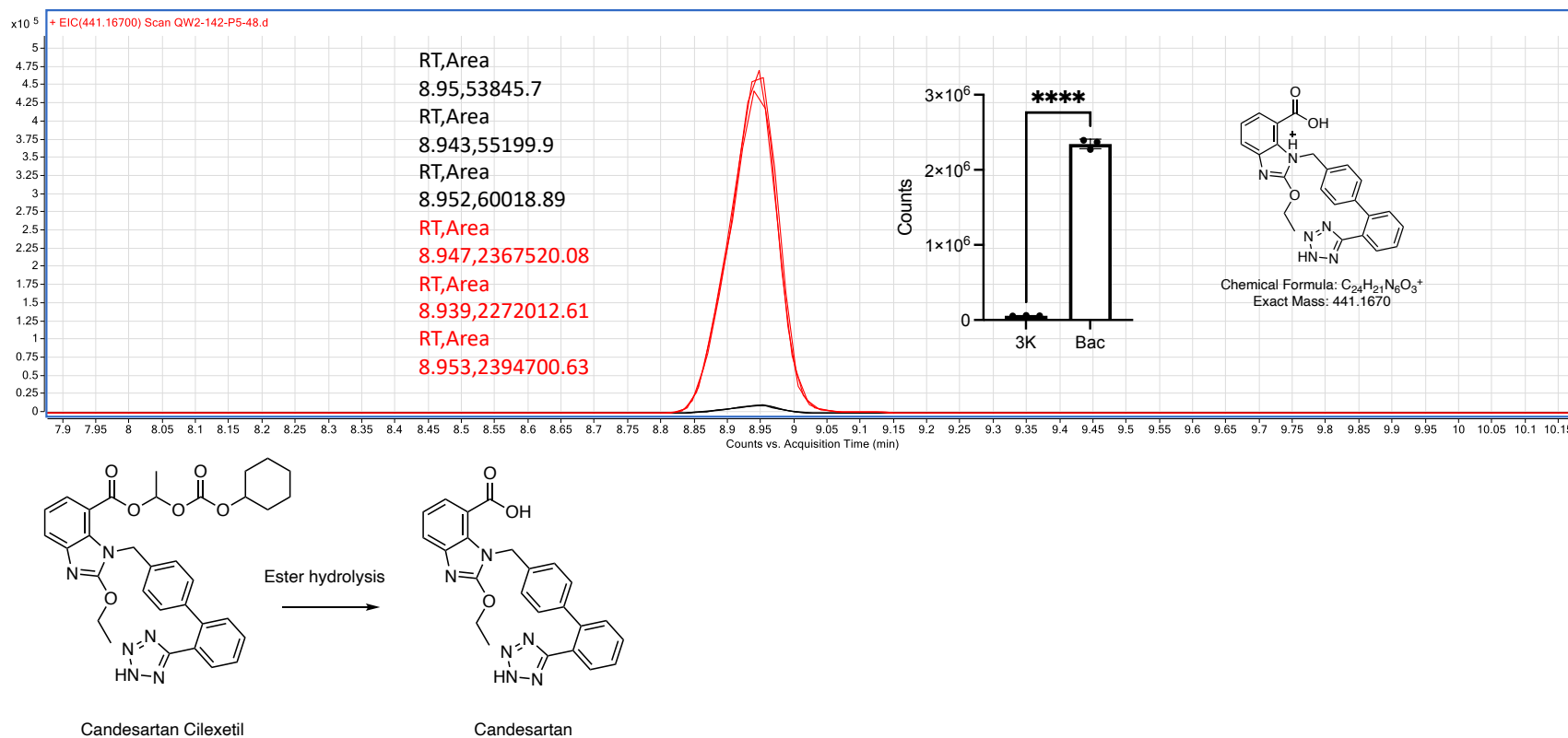


Fig. S291. Comparing Bac⁺ (Bac, red traces) and Bac⁻ (MWCO 3K cutoff, 3K, black traces) for the cell-dependent detection of a MOF (*m/z* 441.1670) from candesartan cilexetil metabolism. A representative charge state is shown. RT: retention time; Area: EIC peak area. *n* = 3 biological replicates. Data represent mean ± s.d. Statistical significance was determined using two-tailed t-test. *****P* < 0.0001.



10. Comparison of drug metabolism by the human host and gut microbiome

Fig. S292. Human gut microbiome-derived metabolism of iloperidone revealed metabolites ilo-430, ilo-444, and ilo-432 from *Bac-Mix*, while ilo-491, ilo-493, and ilo-444 were identified from *M. morganii*.

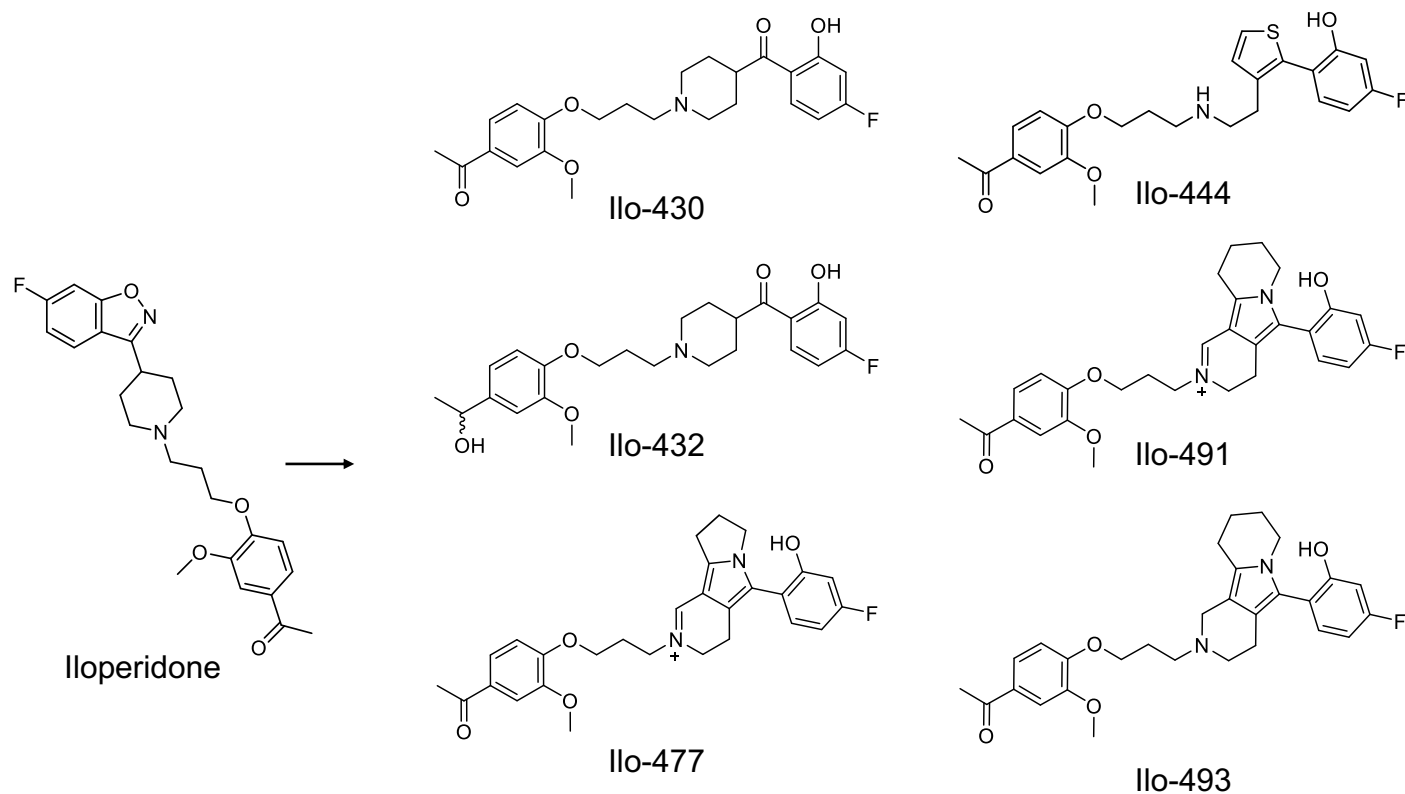
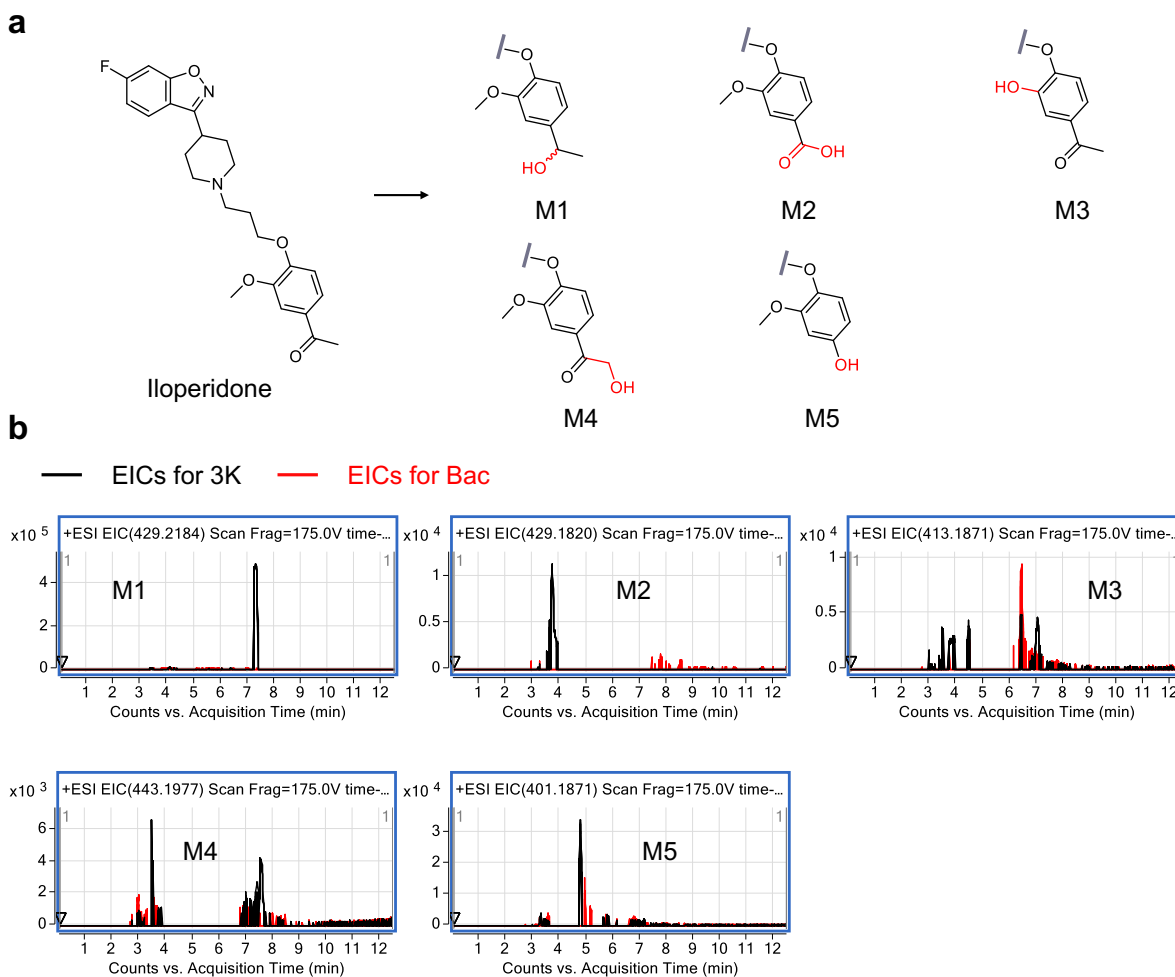


Fig. S293. Summary of iloperidone metabolism by the human host. (a) Chemical structures of iloperidone and its metabolites from human metabolism, which differ from those produced by microbial metabolism. Structures of microbial iloperidone metabolites are detailed in the main text and shown in Extended Data Fig. 8f. (b) Detection of metabolites (M1-M5) of iloperidone in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EICs of the predicted products (m/z 429.2184, 429.1820, 413.1871, 443.1977, and 401.1871). None of the metabolites were detected. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates. (c) Summary of human host metabolism of iloperidone. ^aMolecular formula; ^bMicrobiome-derived metabolism. Information on human drug metabolism was obtained from DrugBank Online²⁴ (<https://go.drugbank.com/>).



Metabolite	Enzyme	m/z	MF ^a	MDM ^b	Activity
M1	Not available	429.2184	C ₂₄ H ₂₉ FN ₂ O ₄	No	Active
M2	Cytochrome P450 2D6	429.1820	C ₂₃ H ₂₅ FN ₂ O ₅	No	Unknown
M3	Cytochrome P450 3A4	413.1871	C ₂₃ H ₂₅ FN ₂ O ₄	No	Unknown
M4	Cytochrome P450 2D6	443.1977	C ₂₄ H ₂₇ FN ₂ O ₅	No	Unknown
M5	Not available	401.1871	C ₂₂ H ₂₅ FN ₂ O ₄	No	Unknown

Fig. S294. Chemical structures of selexipag and its metabolites from human metabolism. Information on human drug metabolism was obtained from DrugBank Online²⁴ (<https://go.drugbank.com/>).

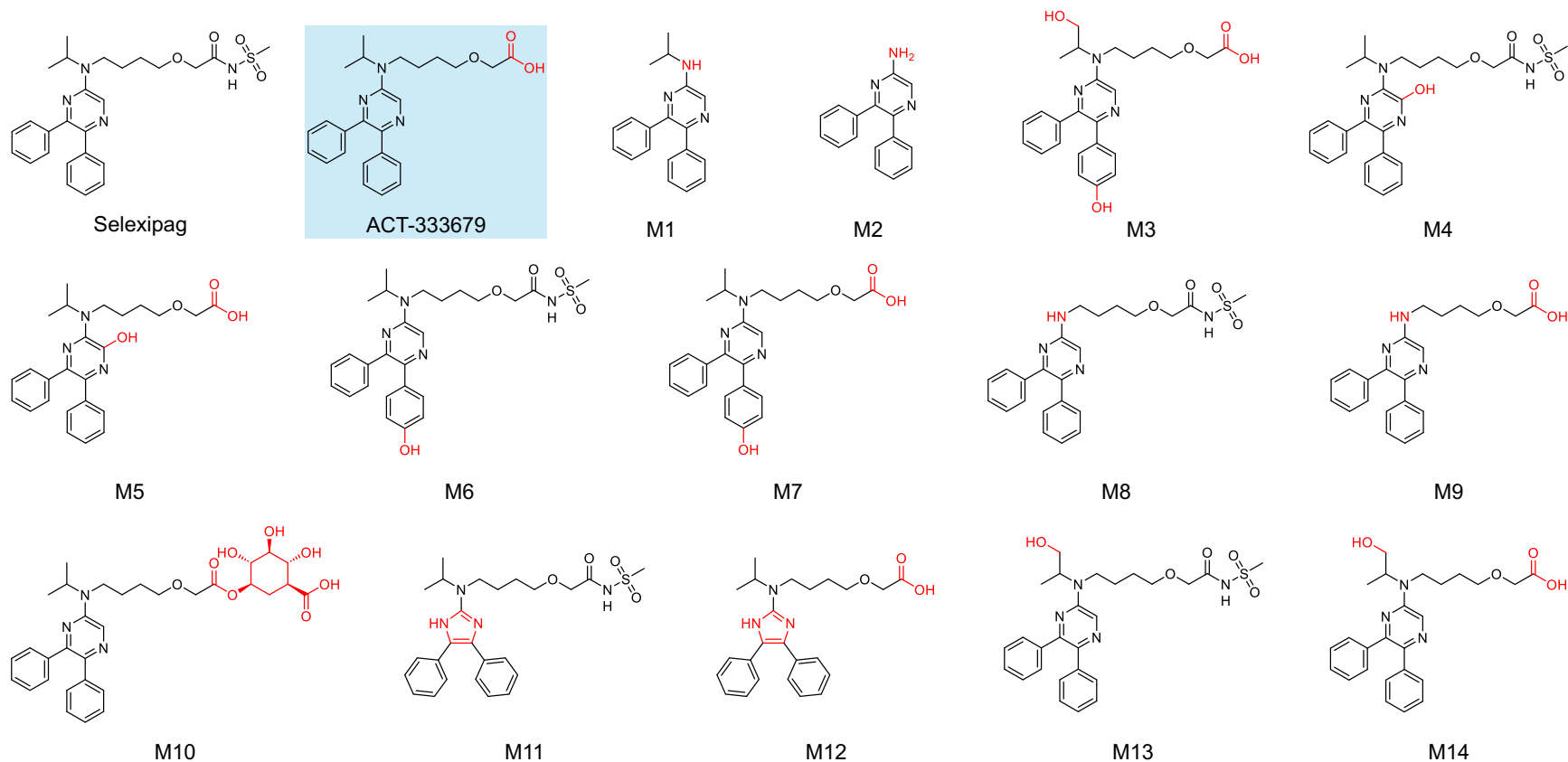


Fig. S295. Detection of metabolites (M1-M14) of selezipag in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EICs of the predicted products. None of the metabolites were detected. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. n = 3 biological replicates.

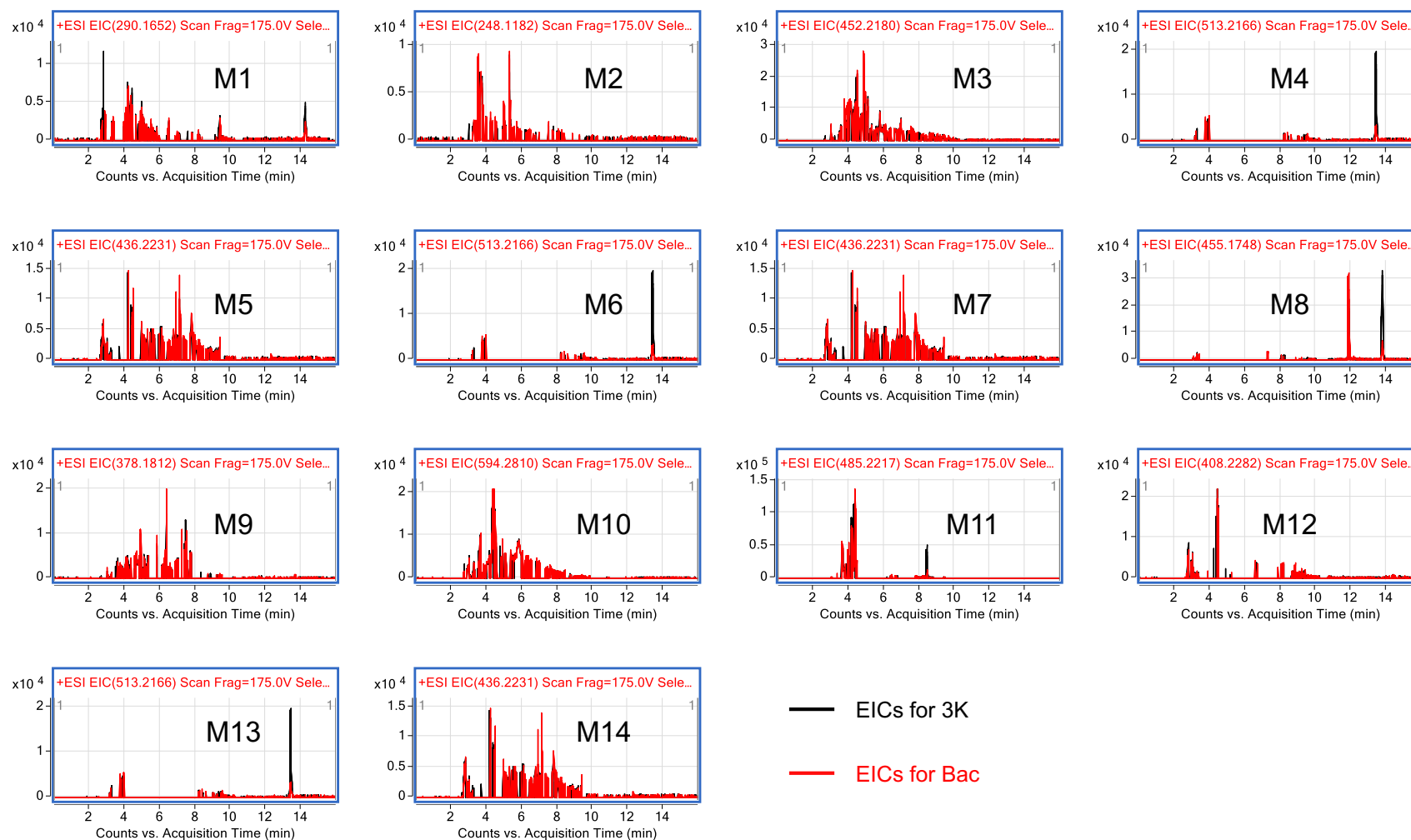
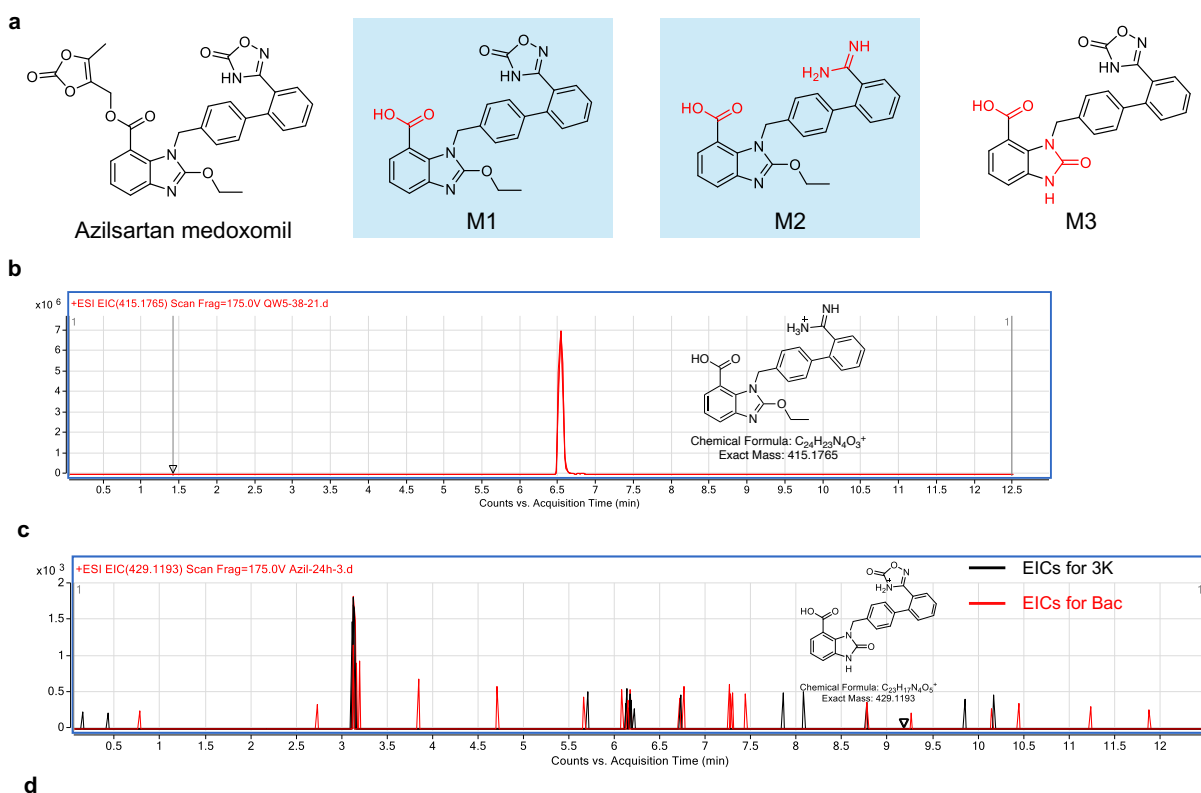


Table S24. Summary of human host metabolism of selexipag. ^aMolecular formula; ^bMicrobiome-derived metabolism. Information on human drug metabolism was obtained from DrugBank Online²⁴ (<https://go.drugbank.com/>). ACT-333679 was detected in human gut microbiome metabolism, as shown in Fig. S2a.

Metabolite	Enzyme	<i>m/z</i>	MF ^a	MDM ^b	Activity
ACT-333679	Liver carboxylesterase 1	420.2282	C ₂₅ H ₂₉ N ₃ O ₃	Yes	Activation
M1	Unknown	290.1652	C ₁₉ H ₁₉ N ₃	No	Unknown
M2	Unknown	248.1182	C ₁₆ H ₁₃ N ₃	No	Unknown
M3	Unknown	452.2180	C ₂₅ H ₂₉ N ₃ O ₅	No	Unknown
M4	Unknown	513.2166	C ₂₆ H ₃₂ N ₄ O ₅ S	No	Unknown
M5	Unknown	436.2231	C ₂₅ H ₂₉ N ₃ O ₄	No	Unknown
M6	Unknown	513.2166	C ₂₆ H ₃₂ N ₄ O ₅ S	No	Unknown
M7	Unknown	436.2231	C ₂₅ H ₂₉ N ₃ O ₄	No	Unknown
M8	Unknown	455.1748	C ₂₃ H ₂₆ N ₄ O ₄ S	No	Unknown
M9	Unknown	378.1812	C ₂₂ H ₂₃ N ₃ O ₃	No	Unknown
M10	UDP-glucuronosyltransferase 1-3 UDP-glucuronosyltransferase 2B7	594.2810	C ₃₂ H ₃₉ N ₃ O ₈	No	Unknown
M11	Unknown	485.2217	C ₂₅ H ₃₂ N ₄ O ₄ S	No	Unknown
M12	Unknown	408.2282	C ₂₄ H ₂₉ N ₃ O ₃	No	Unknown
M13	Unknown	513.2166	C ₂₆ H ₃₂ N ₄ O ₅ S	No	Unknown
M14	Unknown	436.2231	C ₂₅ H ₂₉ N ₃ O ₄	No	Unknown

Fig. S296. Comparison between the human gut microbiome and the human host metabolism of azilsartan medoxomil. (a) Previously reported azilsartan medoxomil metabolism by the human host^{25,26}. The shared metabolites between the host and microbiome, M1 and M2, were highlighted in blue boxes. (b) Detection of azilsartan medoxomil metabolite M2 (azil-415) in azilsartan medoxomil biotransformation with *Bac-Mix*. A representative charge state is shown. For the detection of azilsartan medoxomil metabolite M1 (azil-457), see Supplementary Fig. S2a. n = 3 biological replicates. (c) Detection of metabolites M3 of azilsartan medoxomil in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EIC of the predicted product (m/z 429.1193). Metabolite M3 was not detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. (d) Summary of human host metabolism of azilsartan medoxomil. ^aMolecular formula; ^bMicrobiome-derived metabolism. Information on human drug metabolism was obtained from DrugBank Online²⁴ (<https://go.drugbank.com/>).



Metabolite	Enzyme	m/z	MF ^a	MDM ^b	Activity
M1	Unknown	457.1506	$C_{25}H_{20}N_4O_5$	Yes	Active
M2	Cytochrome P450 2C8 Cytochrome P450 2B6	415.1765	$C_{24}H_{22}N_4O_3$	Yes	Inactive
M3	Cytochrome P450 2C9	429.1193	$C_{23}H_{16}N_4O_5$	No	Unknown

Fig. S297. Comparison between the human gut microbiome and the human host metabolism of fesoterodine. (a) Previously reported fesoterodine metabolism by the human host^{27–30}. (b) Detection of metabolites M1-M4 of fesoterodine in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EIC of the predicted products (m/z 342.2428, 300.1958, 314.1751, and 354.2064). Only metabolite M1 was detected. The detected M2 signals correspond to the internal fragmentation of the parent drug. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates. (c) Summary of human host metabolism of fesoterodine. ^aMolecular formula; ^bMicrobiome-derived metabolism; ^cEnzyme for *N*-dealkylation; ^dEnzyme for oxidation. M1 was detected in human gut microbiome metabolism, as shown in Fig. S2a.

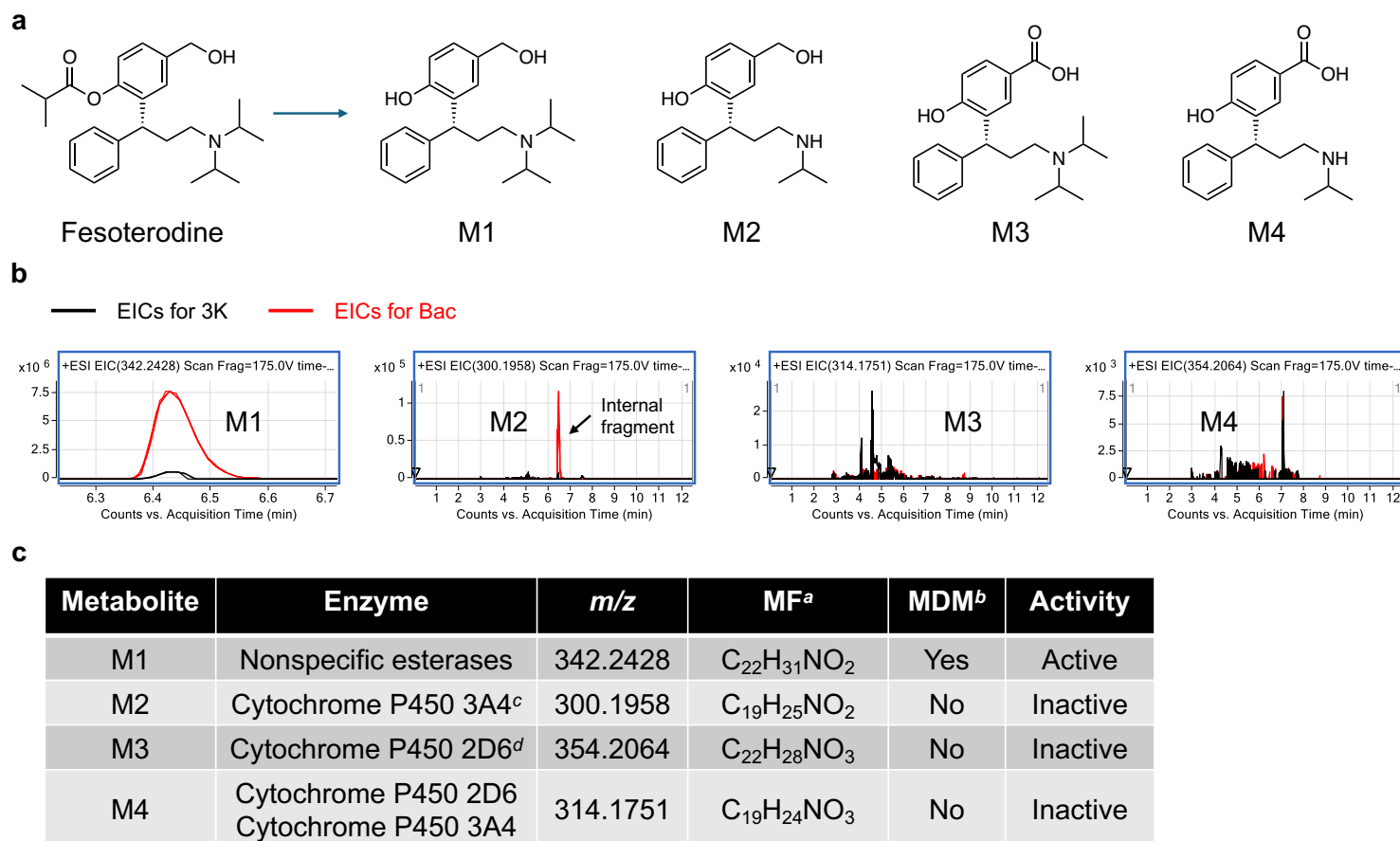


Fig. S298. Comparison between the human gut microbiome and the human host metabolism of ponesimod. (a) Detection of metabolites (M1-M4) of ponesimod in samples of human gut microbiome metabolism. M1 shares the same molecular formula as the microbiome-derived metabolite but potentially has a different chemical structure (Fig. S22). The EIC peaks were identified as metabolites resulting from microbial metabolism. None of the metabolites were detected. n = 3 biological replicates. (b) Detection of metabolite M5 of ponesimod in samples of human gut microbiome metabolism. The chemical structure, highlighted in the red box, is reported as a metabolite from human drug metabolism. Additionally, two other possible structures are suggested as metabolites of microbial metabolism. The characteristic isotope pattern of chlorine further supports the identification of these as ponesimod metabolites. A ± 20 ppm window was applied for the EICs of the predicted products. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. n = 3 biological replicates. (c) Summary of human host metabolism of ponesimod. ^aMolecular formula; ^bMicrobiome-derived metabolism; ^cThe microbial drug metabolite has not been fully confirmed. Information on human drug metabolism was obtained from DrugBank Online²⁴ (<https://go.drugbank.com/>).

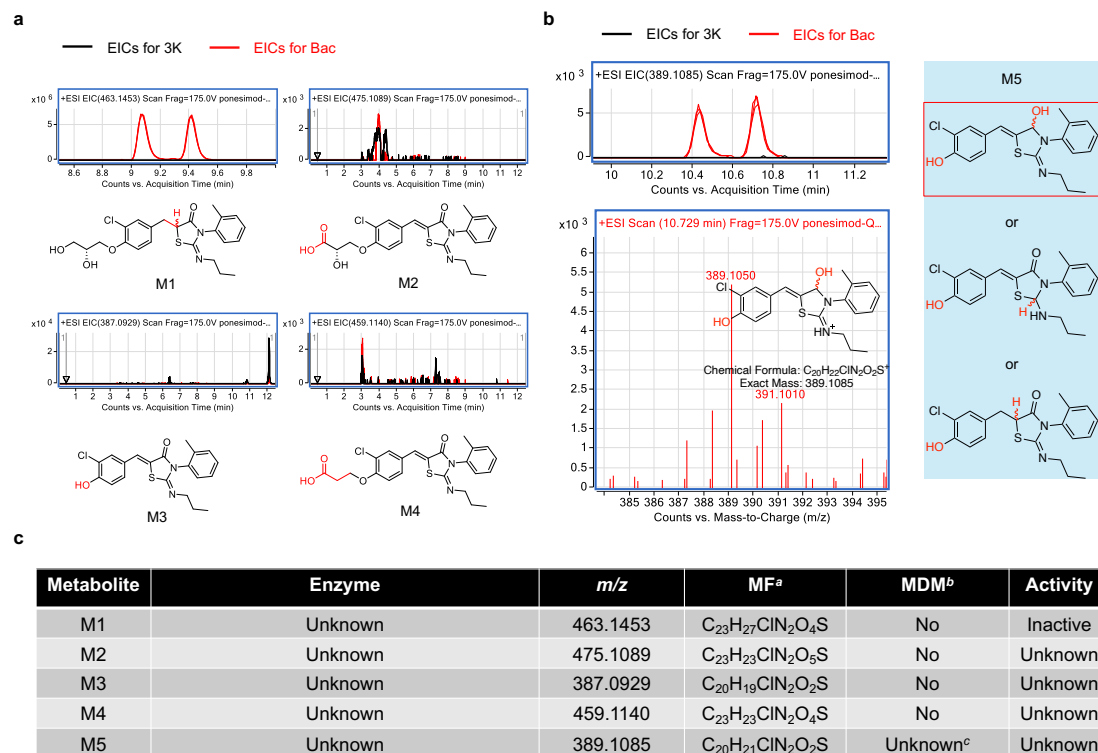
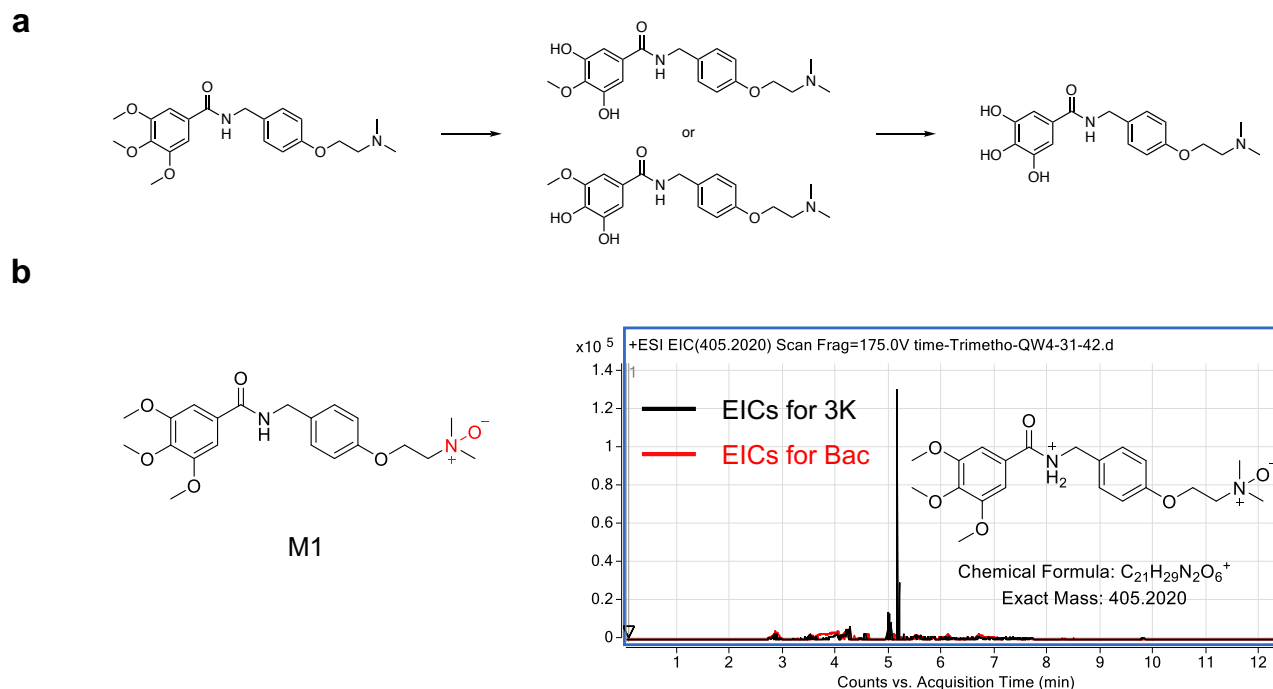


Fig. S299. Comparison between the human gut microbiome and the human host metabolism of trimethobenzamide. (a) Trimethobenzamide metabolism by the human gut microbiome characterized in this study. (b) Detection of metabolite M1 of trimethobenzamide in samples of human gut microbiome metabolism. Metabolite M1 was previously reported as a metabolite from human host metabolism. A ± 20 ppm window was applied for the EIC of the predicted product (m/z 405.2020). Metabolite M1 was not detected. A representative charge state is shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates. (c) Summary of human host metabolism of trimethobenzamide. ^aMolecular formula; ^bMicrobiome-derived metabolism.



Metabolite	Enzyme	m/z	MF ^a	MDM ^b	Activity
M1	Unknown	405.2020	C ₂₁ H ₂₈ N ₂ O ₆	No	Unknown

Fig. S300. Comparison between the human gut microbiome and the human host metabolism of doxazosin. (a) Previously reported doxazosin metabolism by the human host³¹. (b) Doxazosin metabolism by the human gut microbiome characterized in this study (Supplementary Fig. S246). (c) Detection of metabolite M2 of doxazosin in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EIC of the predicted products (m/z 468.1878). Metabolite M2 was not detected. Only one of the two possible structures with one representative oxidation position is depicted. Representative charge states are shown. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates. (d) Summary of human host metabolism of doxazosin. ^aMolecular formula; ^bMicrobiome-derived metabolite.

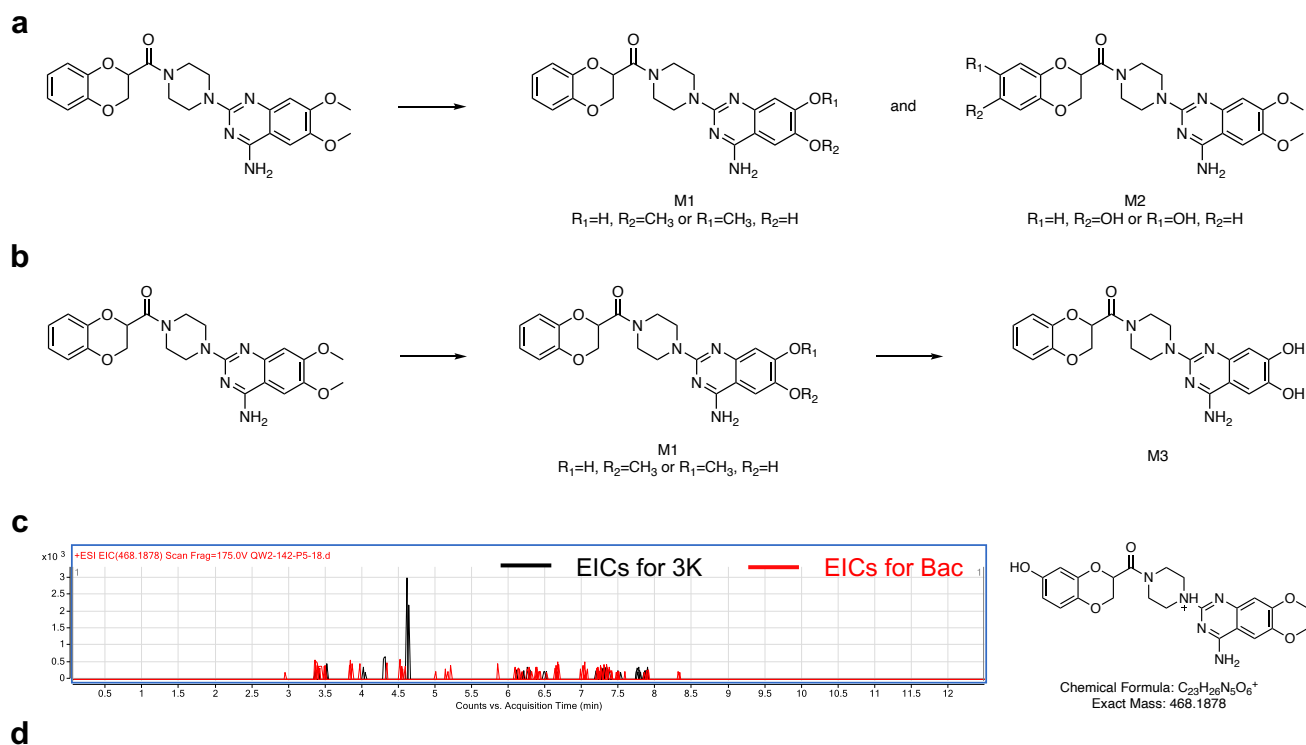


Fig. S301. Comparison between the human gut microbiome and the human host metabolism of trimebutine. (a) Trimebutine metabolism by the human gut microbiome characterized in this study. (b) Previously reported trimebutine metabolism by the human host²¹. (c) Detection of metabolites of trimebutine in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EICs of the predicted products. The EIC peaks (M1 and M2) were identified as drug metabolites resulting from microbial metabolism, which were distinct from human metabolism. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates. (d) Summary of human host metabolism of trimebutine. ^aMolecular formula; ^bMicrobiome-derived metabolism. (e) MS/MS data provided evidence that the demethylation position of the chemical feature at m/z 360.1805 is located on the aromatic O-methyl group. Fragment A: $m/z_{\text{calcd.}}$ 315.1227, $m/z_{\text{obs.}}$ 315.1234; Fragment B: $m/z_{\text{calcd.}}$ 185.0444, $m/z_{\text{obs.}}$ 185.0437; Fragment C: $m/z_{\text{calcd.}}$ 167.0339, $m/z_{\text{obs.}}$ 167.0345.

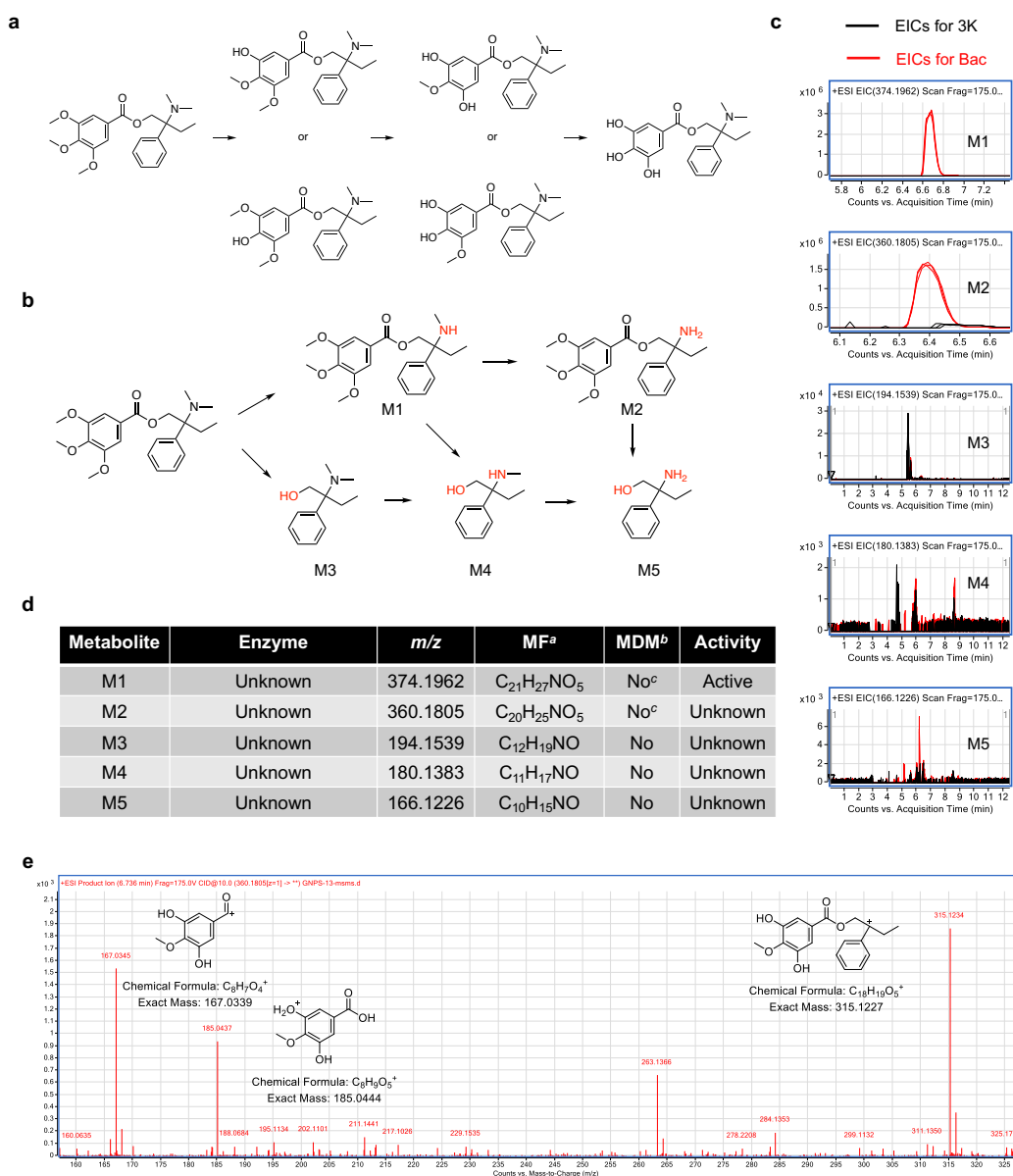


Fig. S302. Comparison between the human gut microbiome and the human host metabolism of risperidone. (b) Risperidone metabolism by the human gut microbiome characterized in this study. (a) Previously reported risperidone metabolism by the human host³². (c) Detection of metabolite M1 of risperidone in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EIC of the predicted products. Metabolite M1 was not detected. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. n = 3 biological replicates. (d) Summary of human host metabolism of risperidone. ^aMolecular formula; ^bMicrobiome-derived metabolism.

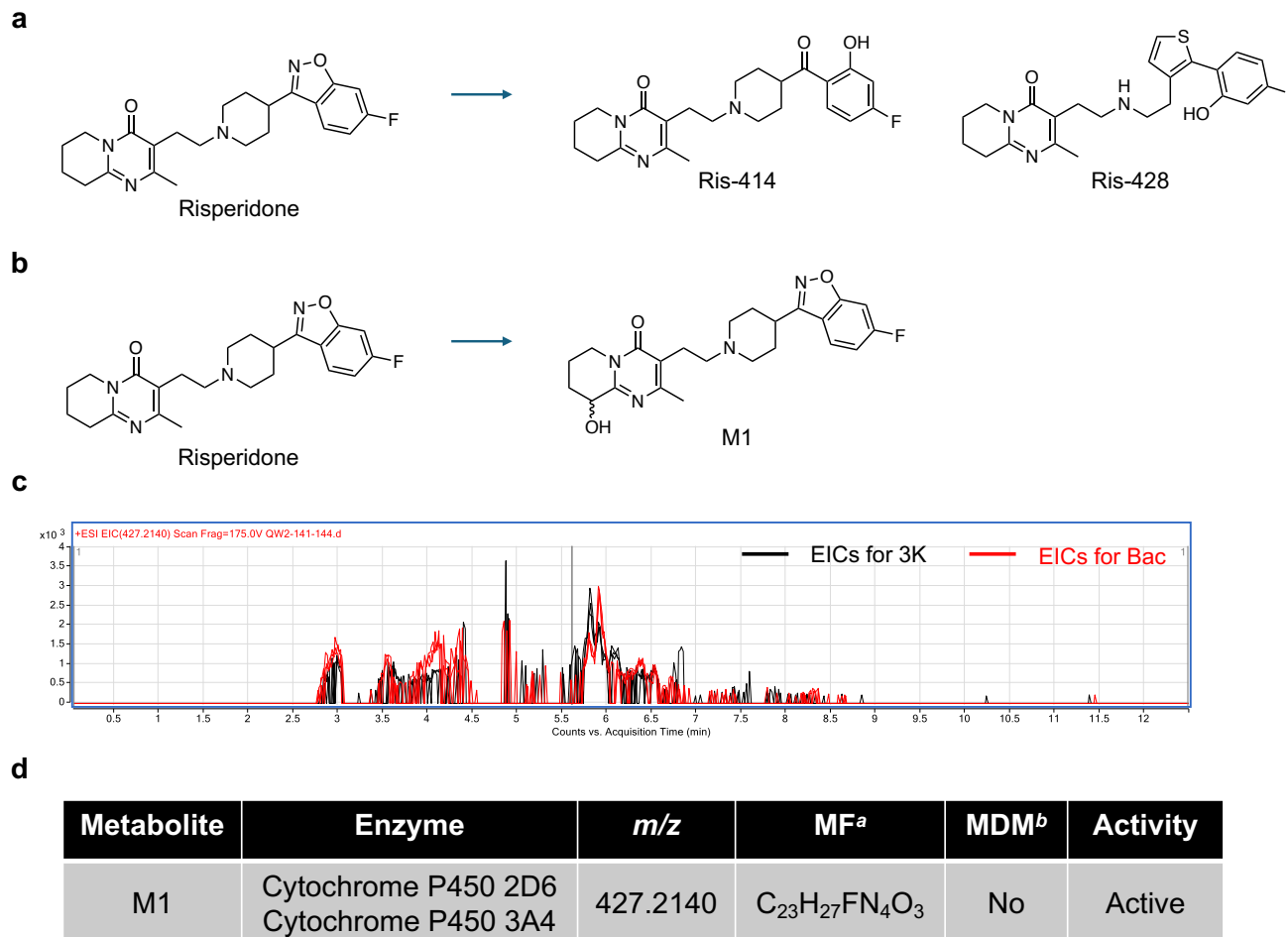


Fig. S303. Comparison between the human gut microbiome and the human host metabolism of candesartan cilexetil. (a) Previously reported candesartan cilexetil metabolism by the human host. Information on human drug metabolism was obtained from DrugBank Online²⁴ (<https://go.drugbank.com/>). The formation of M1 by the human gut microbiome was characterized in this study. (b) Detection of candesartan cilexetil metabolites in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EIC of the predicted products. Only M1 was detected. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. n = 3 biological replicates. (c) Summary of human host metabolism of candesartan cilexetil. ^aMolecular formula; ^bMicrobiome-derived metabolism.

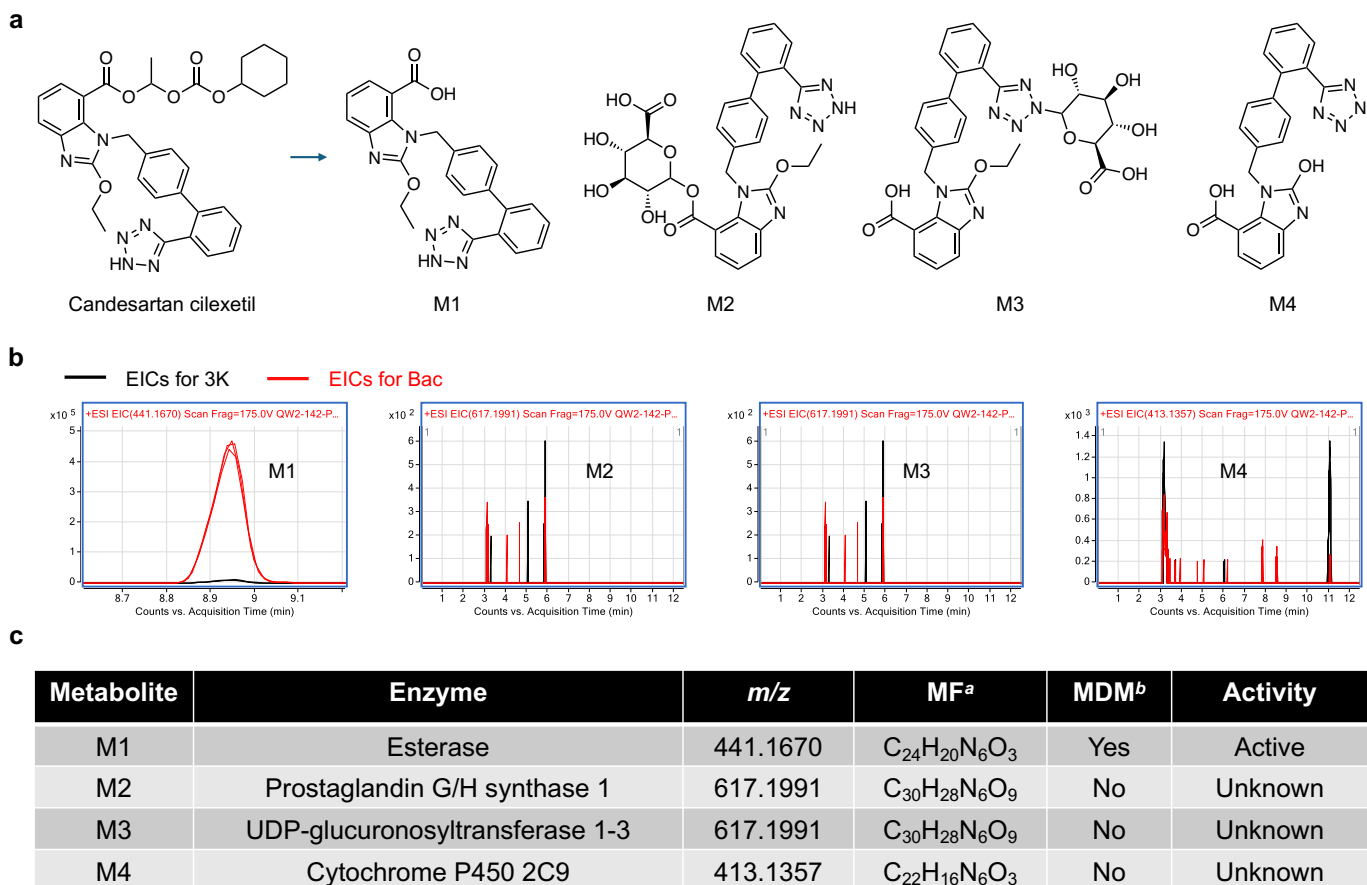


Fig. S304. Comparison between the human gut microbiome and the human host metabolism of nicergoline. (a) Nicergoline metabolism by the human gut microbiome characterized in this study (Fig. S298). M1 was detected in nicergoline metabolism in humans³³. (b) The previously reported *N*-demethylation product by the human host³³. (c) Detection of metabolite M3 of nicergoline in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EIC of the predicted products. Metabolite M3 was not detected. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates. (d) Summary of human host metabolism of nicergoline. ^aMolecular formula; ^bMicrobiome-derived metabolism.

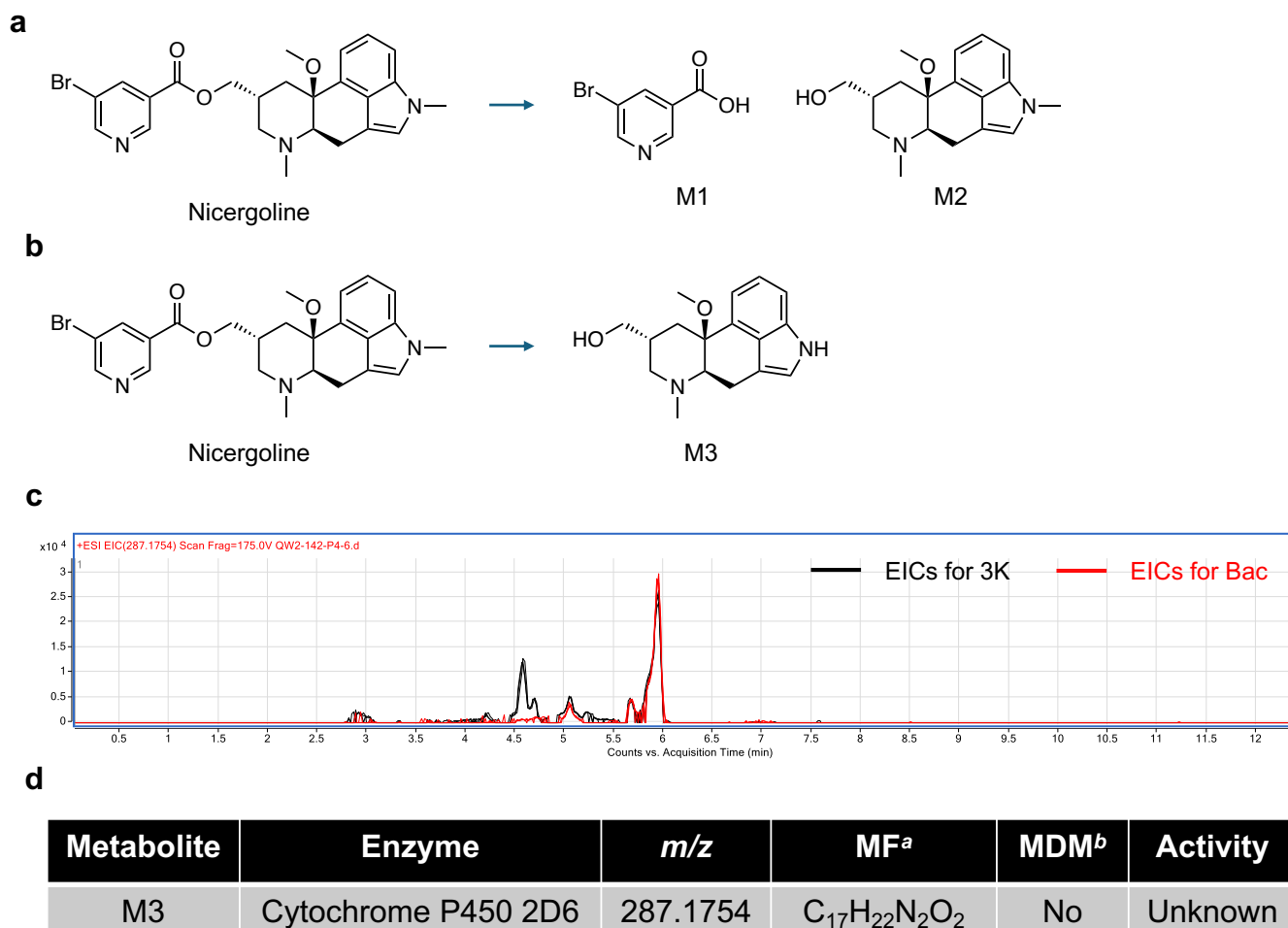


Fig. S305. Comparison between the human gut microbiome and the human host metabolism of clopidogrel. (a) Previously reported clopidogrel metabolism by the human host^{34,35}. Clopidogrel metabolism by the human gut microbiome characterized in this study was highlighted in the blue box. (b) Detection of clopidogrel metabolites in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EIC of the predicted products. Only metabolite M1 was detected. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. $n = 3$ biological replicates. (c) Summary of human host metabolism of clopidogrel. ^aMolecular formula; ^bMicrobiome-derived metabolism.

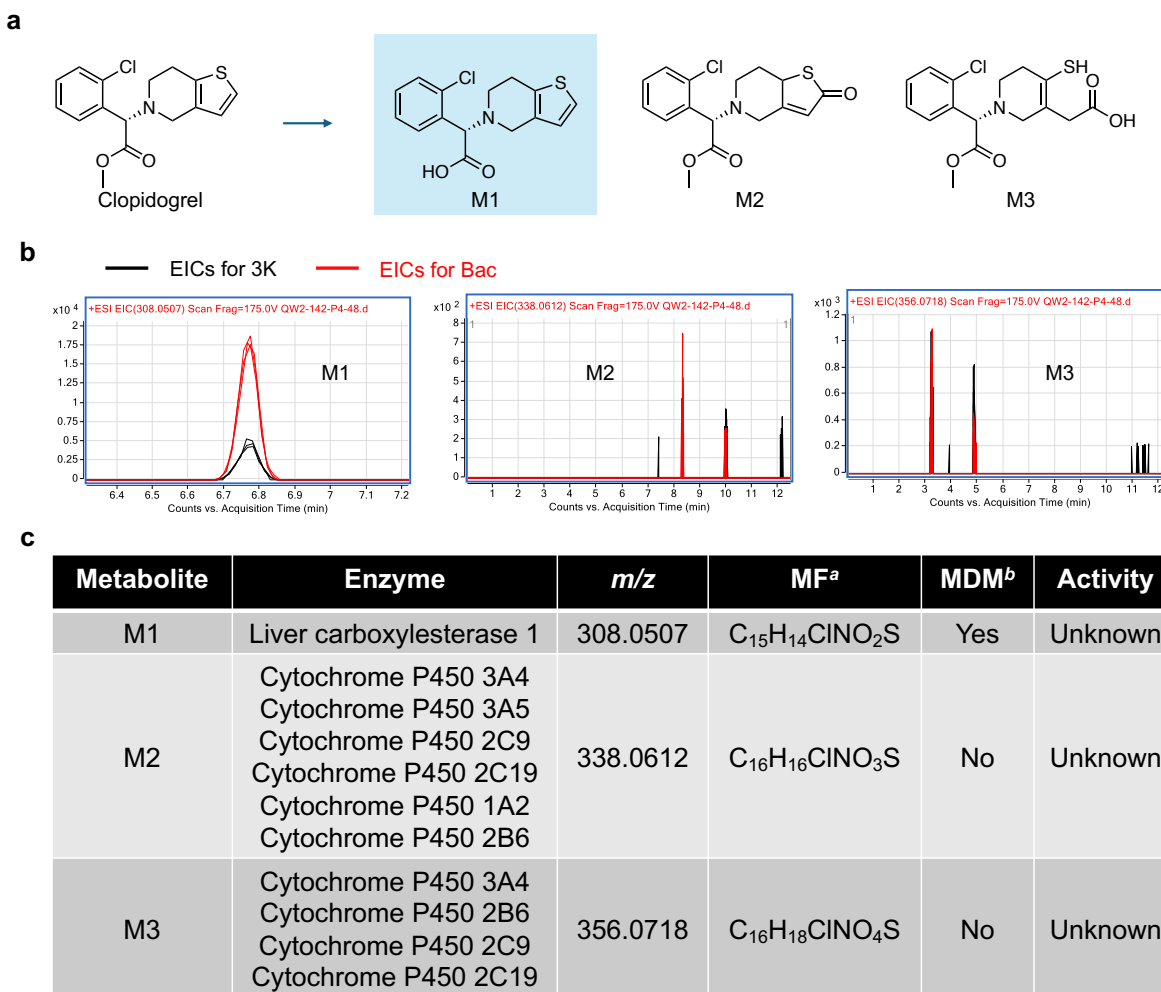


Fig. S306. Comparison between the human gut microbiome and the human host metabolism of ozanimod. (a) Previously reported ozanimod metabolism by the human host³⁶. (b) Metabolites detected in feces. (c) Ozanimod metabolism by the human gut microbiome characterized in this study. (d) Other reported ozanimod metabolites were detected in various biological samples. M12 was found in plasma, urine, and feces. M14 and M15 were identified in urine samples, while M13 was detected in feces samples.

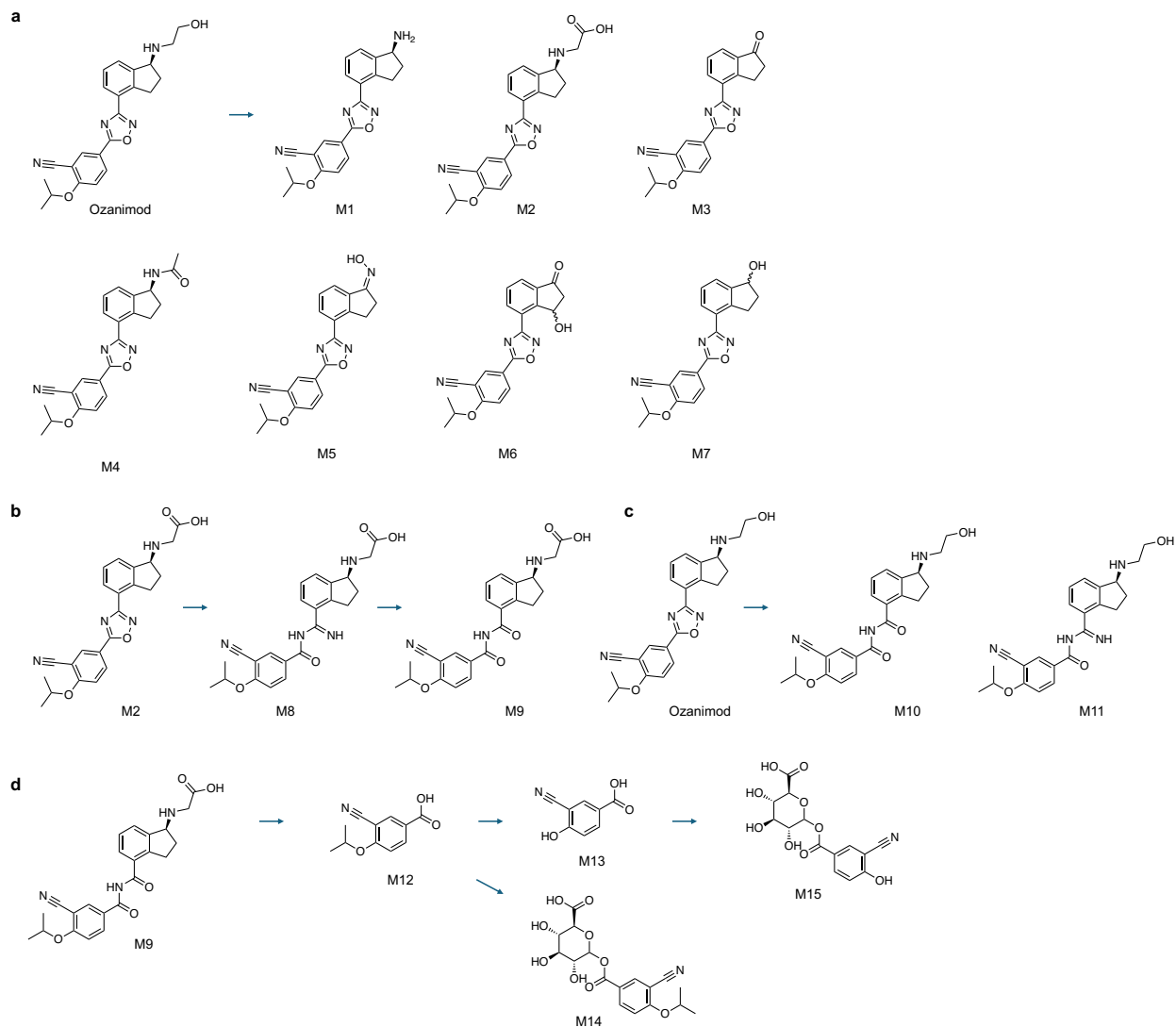


Fig. S307. Detection of ozanimod metabolites in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EIC of the predicted products. Metabolites consistent with M12 and M13 were detected. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. n = 3 biological replicates.

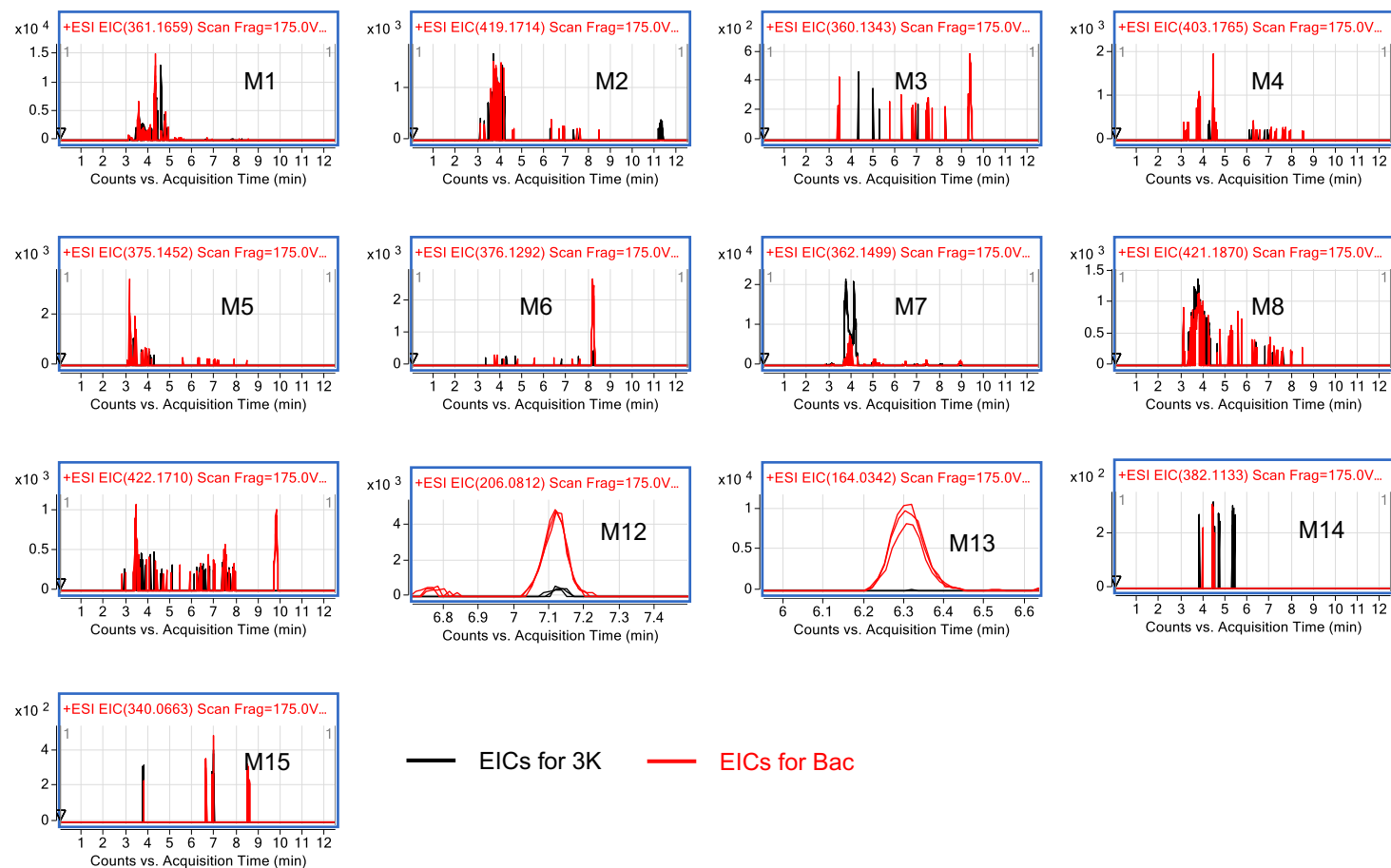
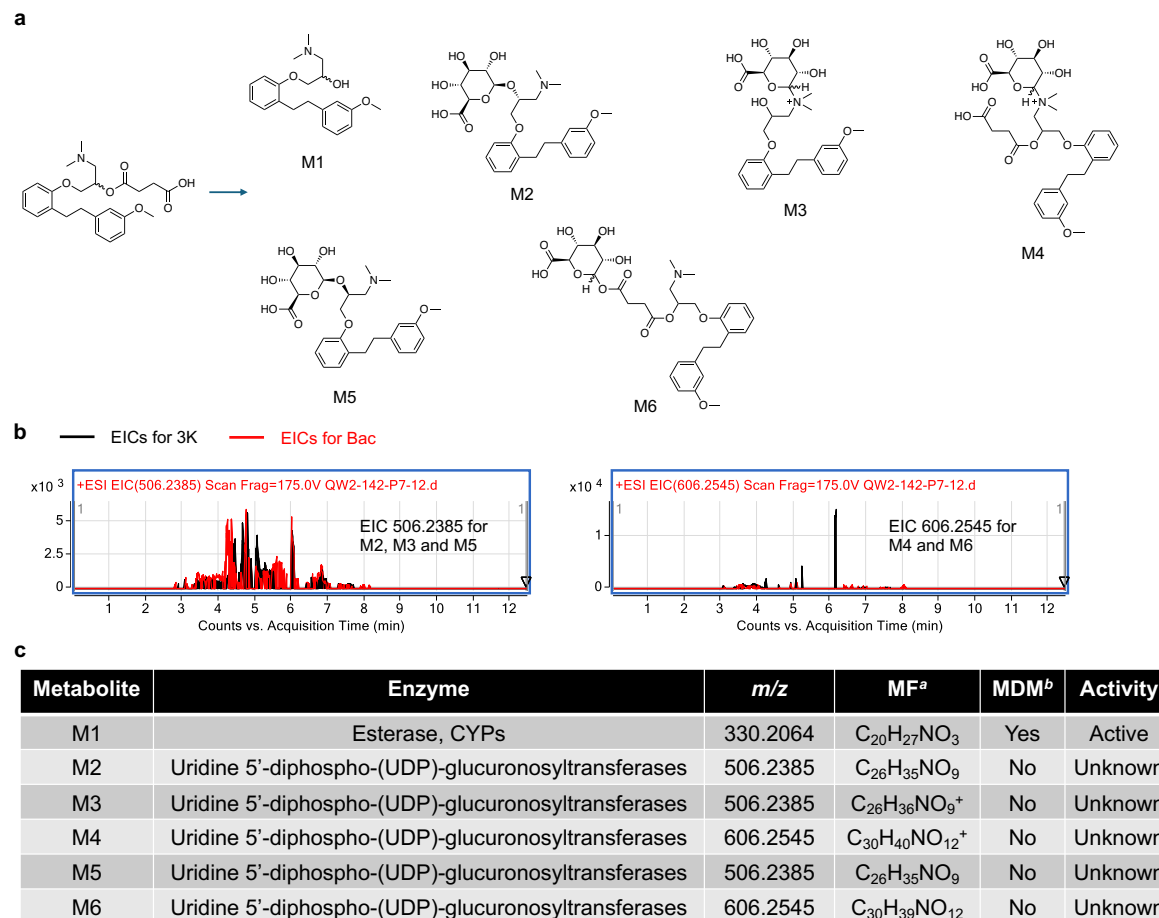


Table S25. Summary of human host metabolism of ozanimod. ^aMolecular formula; ^bMicrobiome-derived metabolism.

Metabolite	Enzyme	<i>m/z</i>	MF ^a	MDM ^b	Activity
M1	Cytochrome P450 3A4 Cytochrome P450 1A1	361.1659	C ₂₁ H ₂₀ N ₄ O ₂	No	Active
M2	Unknown	419.1714	C ₂₃ H ₂₂ N ₄ O ₄	No	Active
M3	Unknown	360.1343	C ₂₁ H ₁₇ N ₃ O ₃	No	Active
M4	<i>N</i> -acetyltransferase 2	403.1765	C ₂₃ H ₂₂ N ₄ O ₃	No	Active
M5	Cytochrome P450 3A4 Cytochrome P450 3A5	375.1452	C ₂₁ H ₁₈ N ₄ O ₃	No	Active
M6	Cytochrome P450 2C8	376.1292	C ₂₁ H ₁₇ N ₃ O ₄	No	Active
M7	Unknown	362.1499	C ₂₁ H ₁₉ N ₃ O ₃	No	Active
M8	Unknown	421.1870	C ₂₃ H ₂₄ N ₄ O ₄	No	Unknown
M9	Unknown	422.1710	C ₂₃ H ₂₃ N ₃ O ₅	No	Unknown
M12	Unknown	206.0812	C ₁₁ H ₁₁ NO ₃	Yes	Unknown
M13	Unknown	164.0342	C ₈ H ₅ NO ₃	Yes	Unknown
M14	Unknown	382.1133	C ₁₇ H ₁₉ NO ₉	No	Unknown
M15	Unknown	340.0663	C ₁₄ H ₁₃ NO ₉	No	Unknown

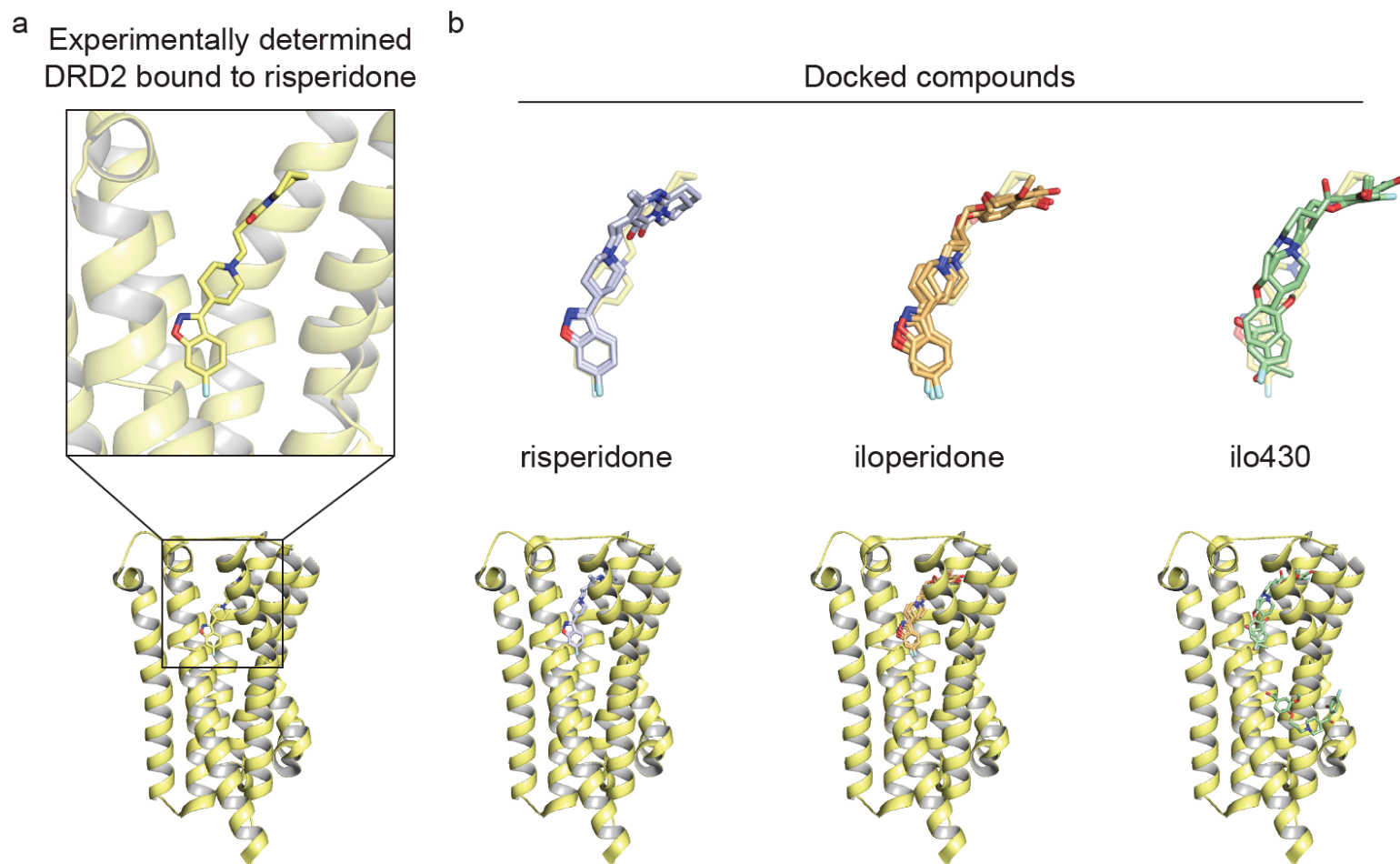
Fig. S308. Comparison between the human gut microbiome and the human host metabolism of sarpogrelate. (a) Previously reported sarpogrelate metabolism by the human host³⁷. This study detected the formation of metabolite M1 in the sarpogrelate metabolism of the human gut microbiome. (b) Detection of metabolites of sarpogrelate in samples of human gut microbiome metabolism. A ± 20 ppm window was applied for the EIC of the predicted products. None of the metabolites were detected. Bac (red traces): *Bac-Mix*; 3K (black traces): MWCO 3K. n = 3 biological replicates. (c) Summary of human host metabolism of sarpogrelate. ^aMolecular formula; ^bMicrobiome-derived metabolism.



11. Molecular docking of risperidone, iloperidone, and ilo-430 with DRD2

The structural basis of DRD2 bound to risperidone has been reported through crystal structure analysis³⁸. The 6-fluoro-benzisoxazole moiety of risperidone extends into a deep hydrophobic binding pocket below the orthosteric site. Additionally, above the orthosteric site, Asp114^{3,32} forms a salt bridge with the tertiary amine of risperidone. Molecular docking of the known DRD2 antagonists risperidone and iloperidone show consistent docking, with the 6-fluoro-benzisoxazole moiety deep within the ligand binding pocket as was previously determined for risperidone. However, ilo-430 was inconsistently docked, including being localized entirely outside of the ligand binding pocket. These findings are in agreement with the conventional reduction mechanism by which most human gut commensals from our representative collection deactivate iloperidone, as well as the atypical metabolism mode mediated by *M. morganii*. While the reductive metabolism of the 1,2,4-oxadiazole had been previously reported in risperidone^{3,39}, this study identifies that iloperidone can undergo a similar metabolism mode followed by subsequent amino acid-derived metabolite functionalization.

Fig. S309. Molecular docking of risperidone, iloperidone, and ilo-430 with DRD2. (a) Experimentally determined structure of DRD2 bound to risperidone. (b) Highest ranking conformation from 4 independent AutoDock Vina runs of risperidone (white), iloperidone (orange), and ilo-430 metabolite (green) docked into DRD2 structure. Experimentally determined risperidone conformation is shown in yellow for reference. Compound conformations within the ligand binding pocket of DRD2 are shown on top, with all conformations, including ilo-430 outside the binding pocket, are shown on the bottom.



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