Supplementary Material

Bioguided identification of polymethoxyflavones as novel vascular $Ca_V1.2$ channel blockers

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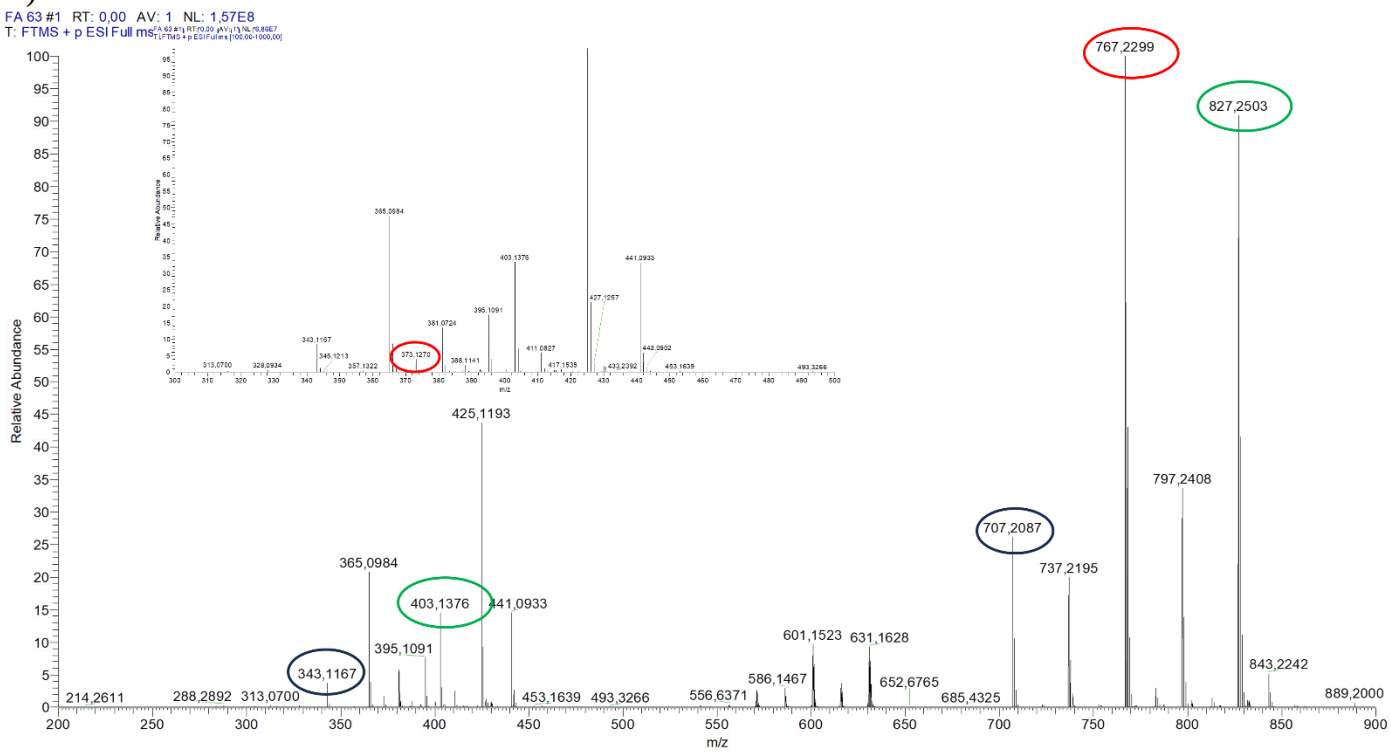
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Figure S1: HRMS spectrum of **M3** fraction : **A)** range 200-900 and **B)** range 300-500

A)



B)

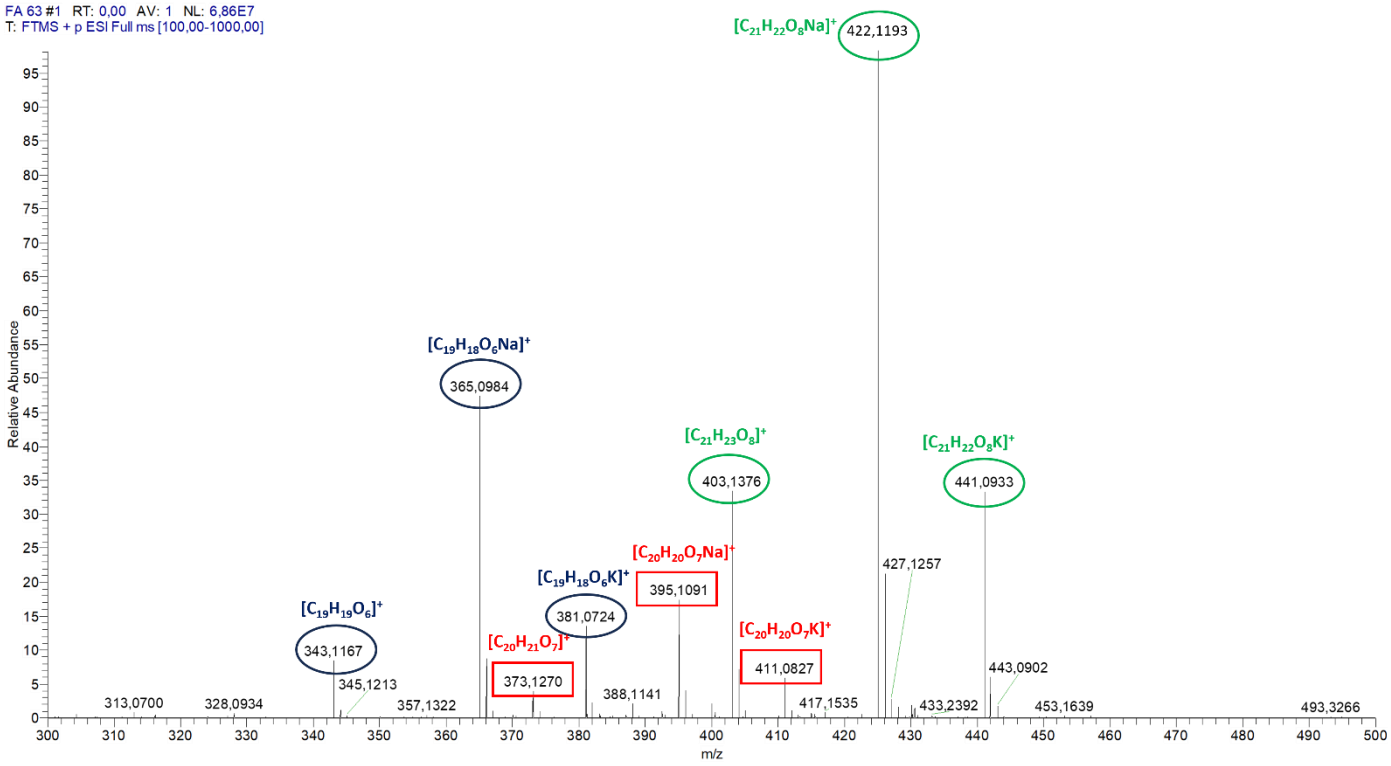


Figure S2: ^{1}H NMR (400 MHz, $CDCl_3$) of **M3**

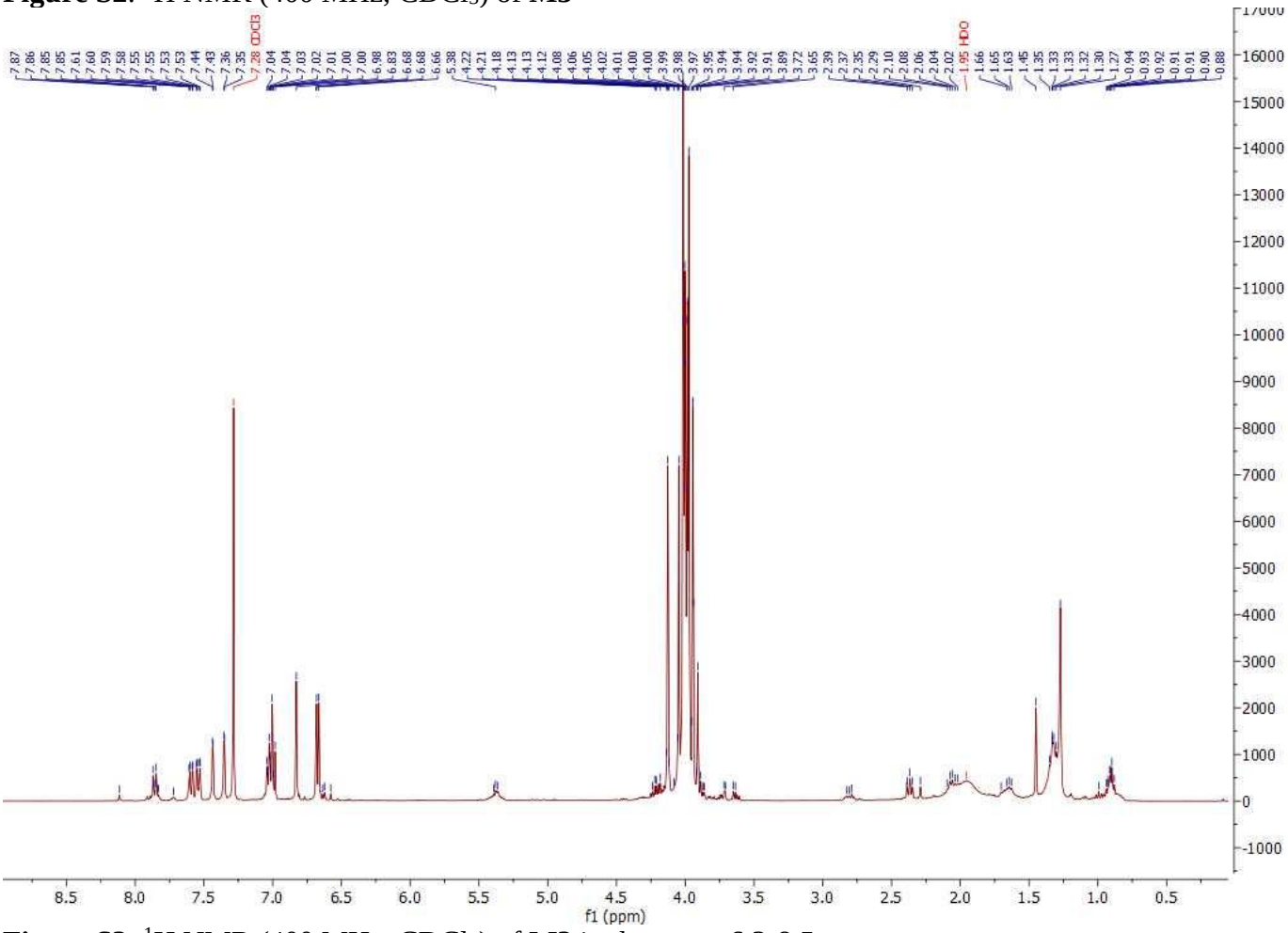


Figure S3: ^{1}H NMR (400 MHz, $CDCl_3$) of **M3** in the range 6.3-8.5 ppm.

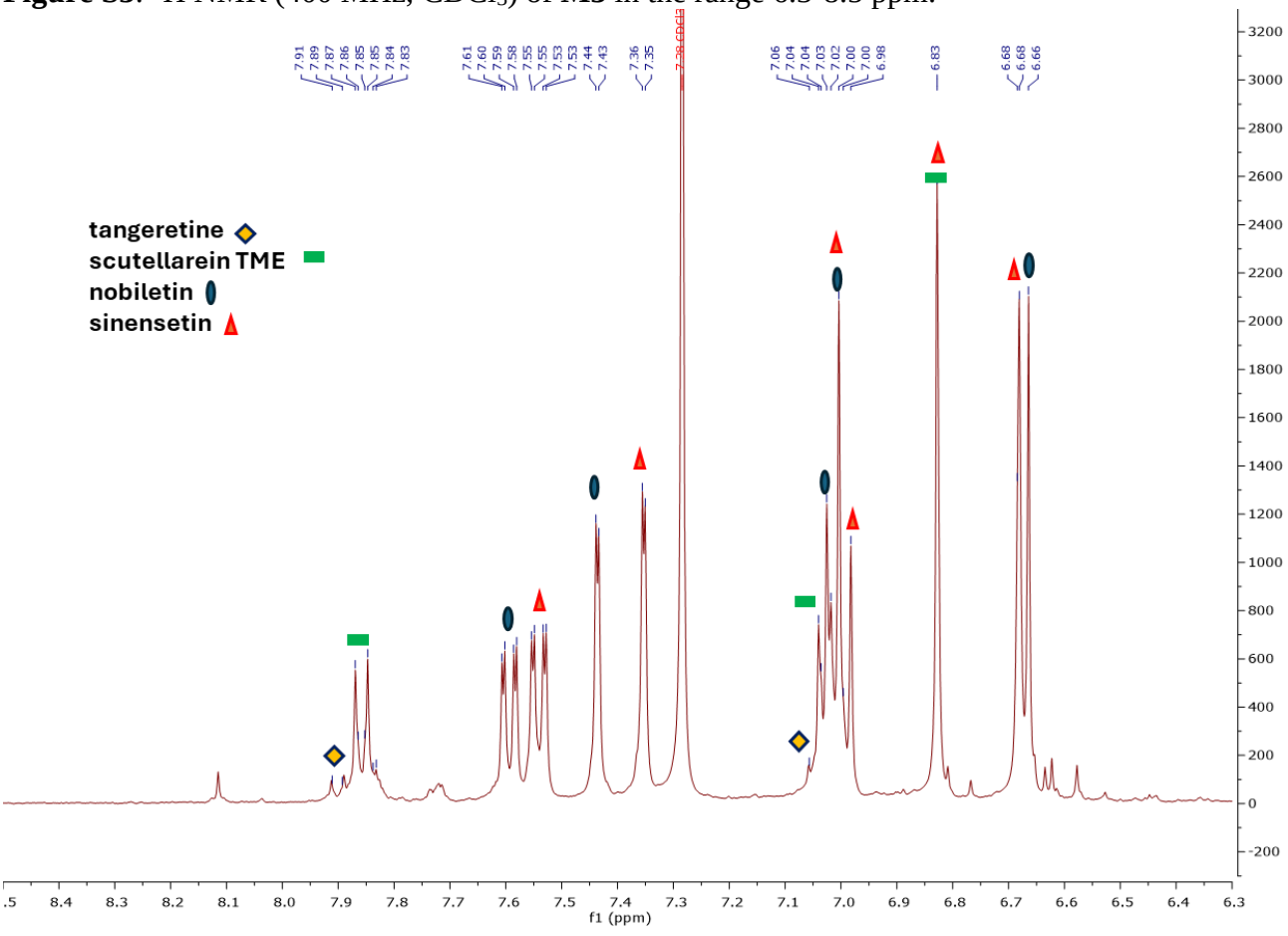


Figure S4: ^{1}H NMR (400 MHz, $CDCl_3$) of **M3** in the range 3.8-4.3 ppm

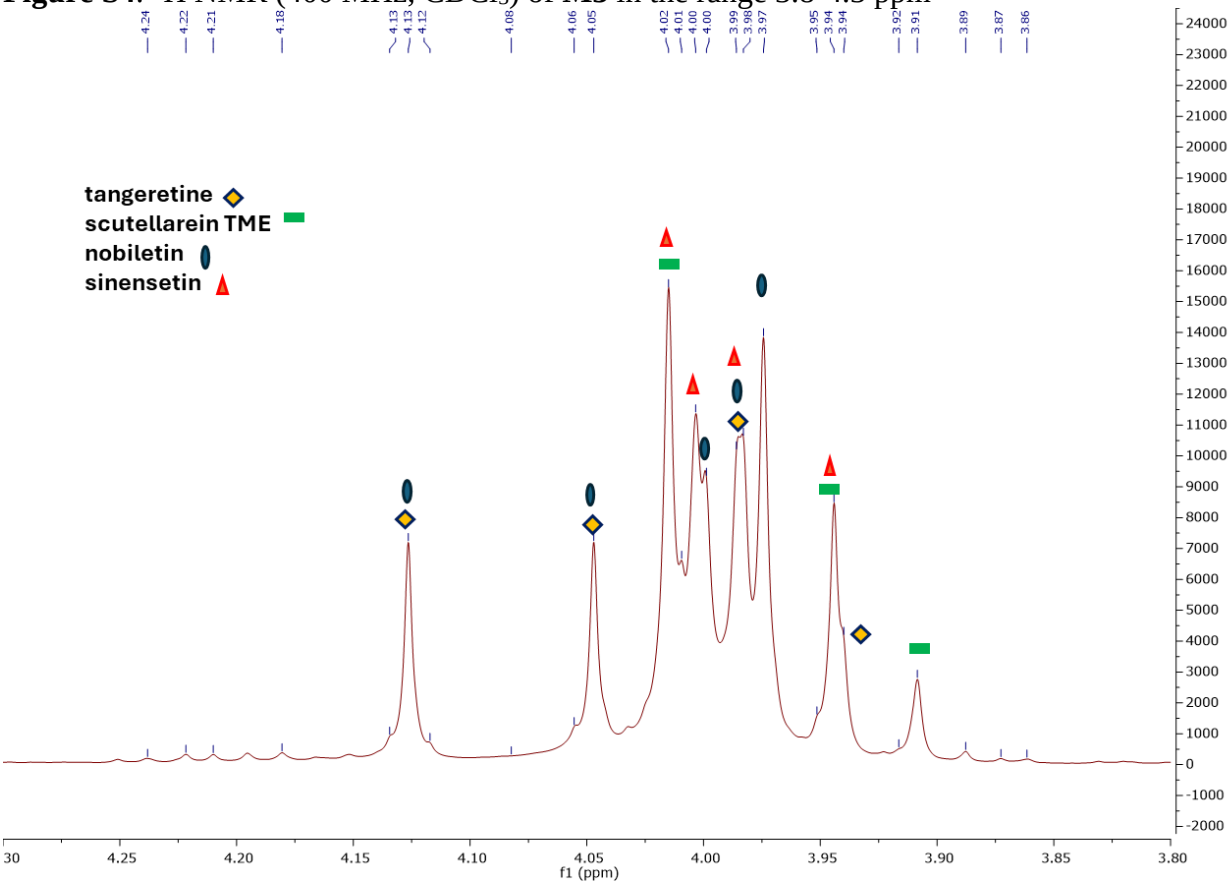


Figure S5: ^{1}H NMR (400 MHz, $CDCl_3$) of **M4**

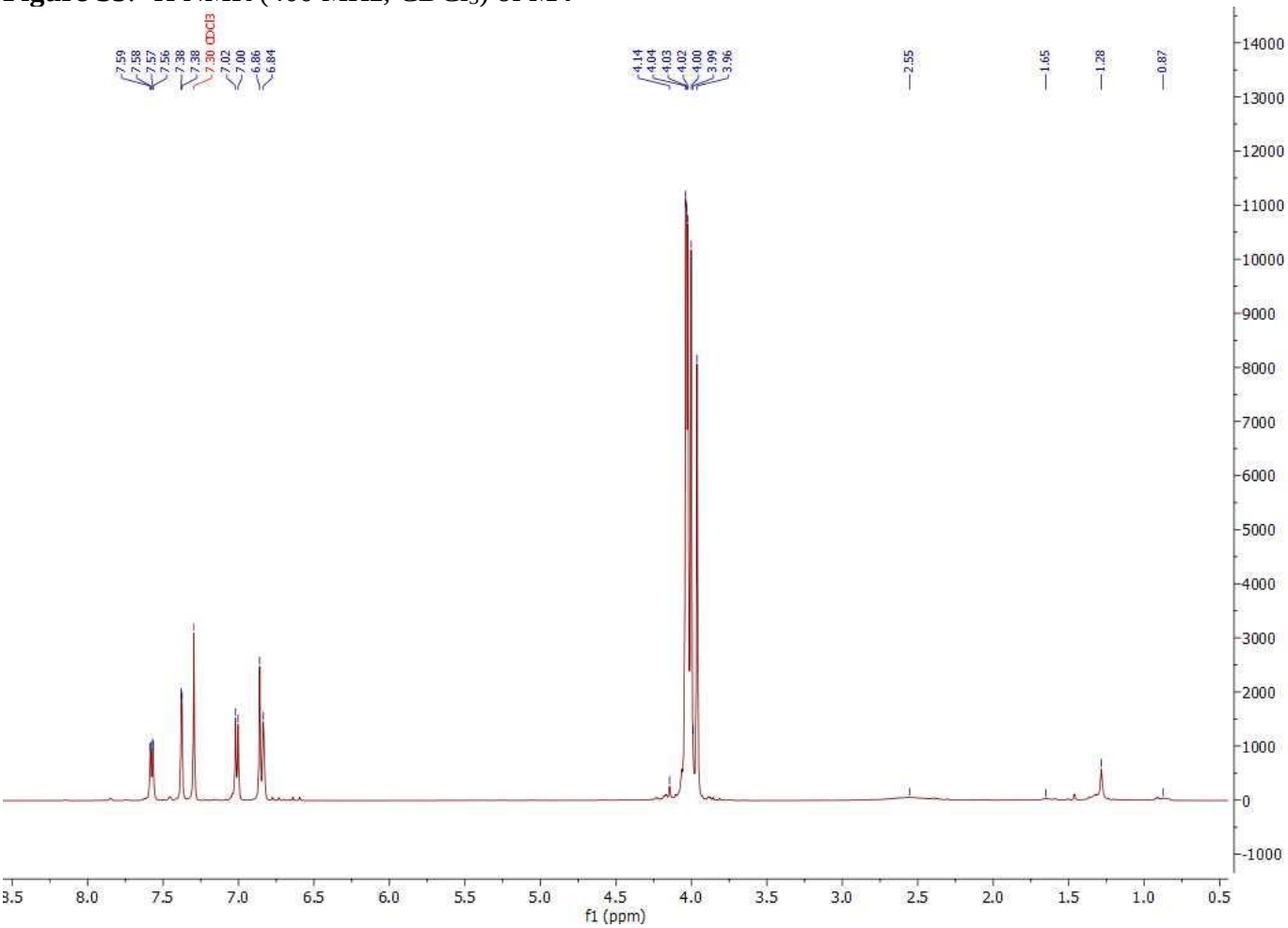
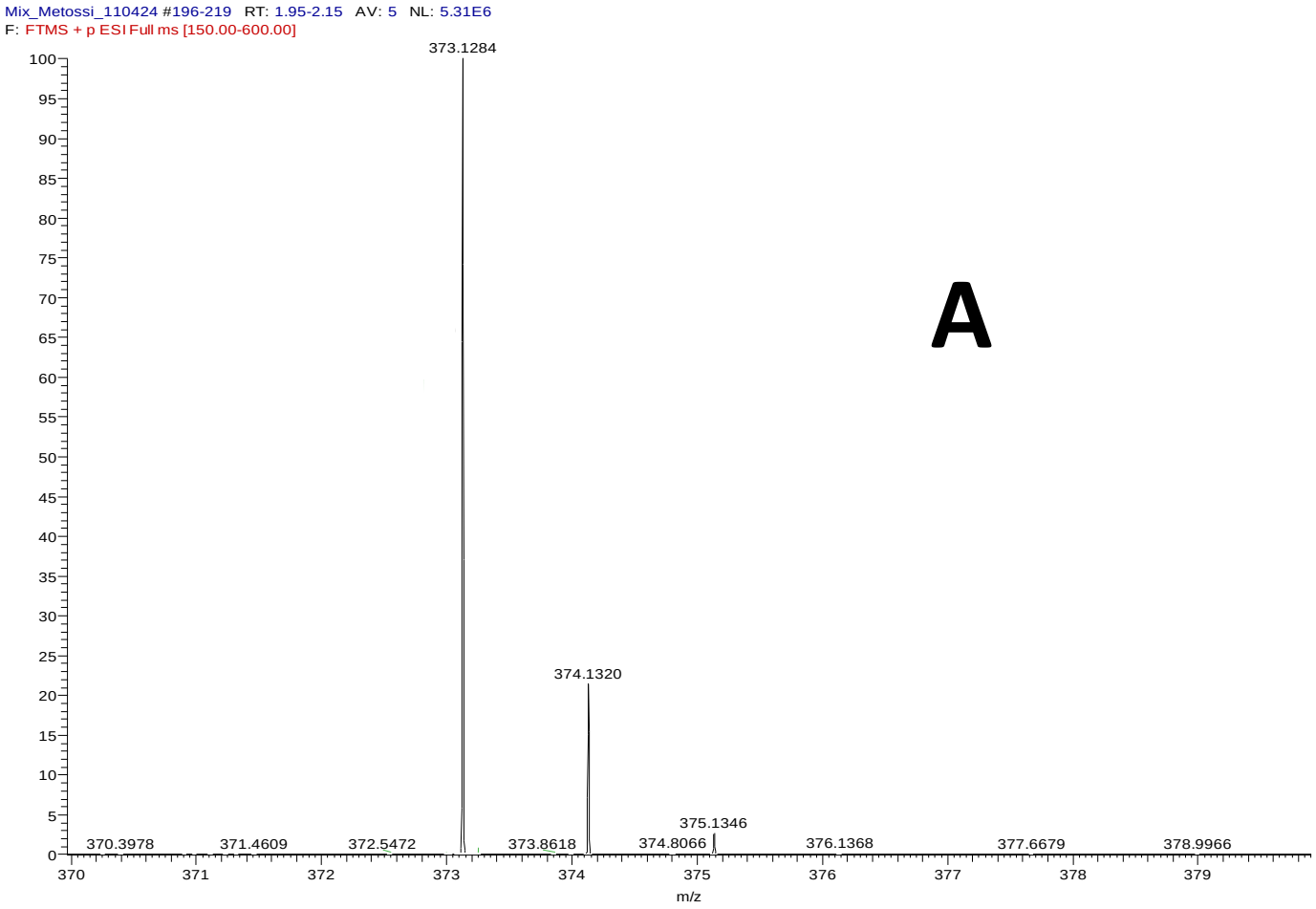
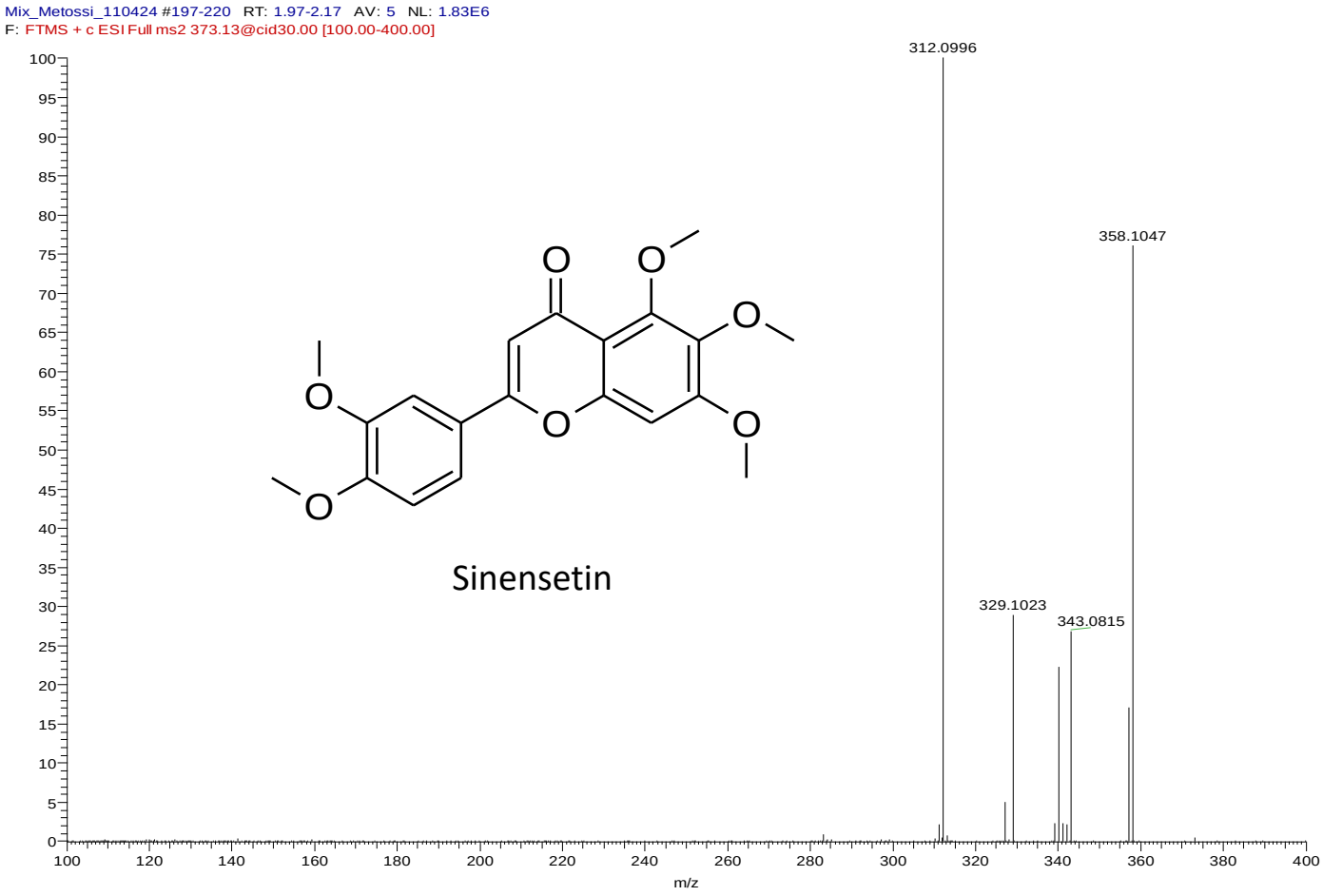
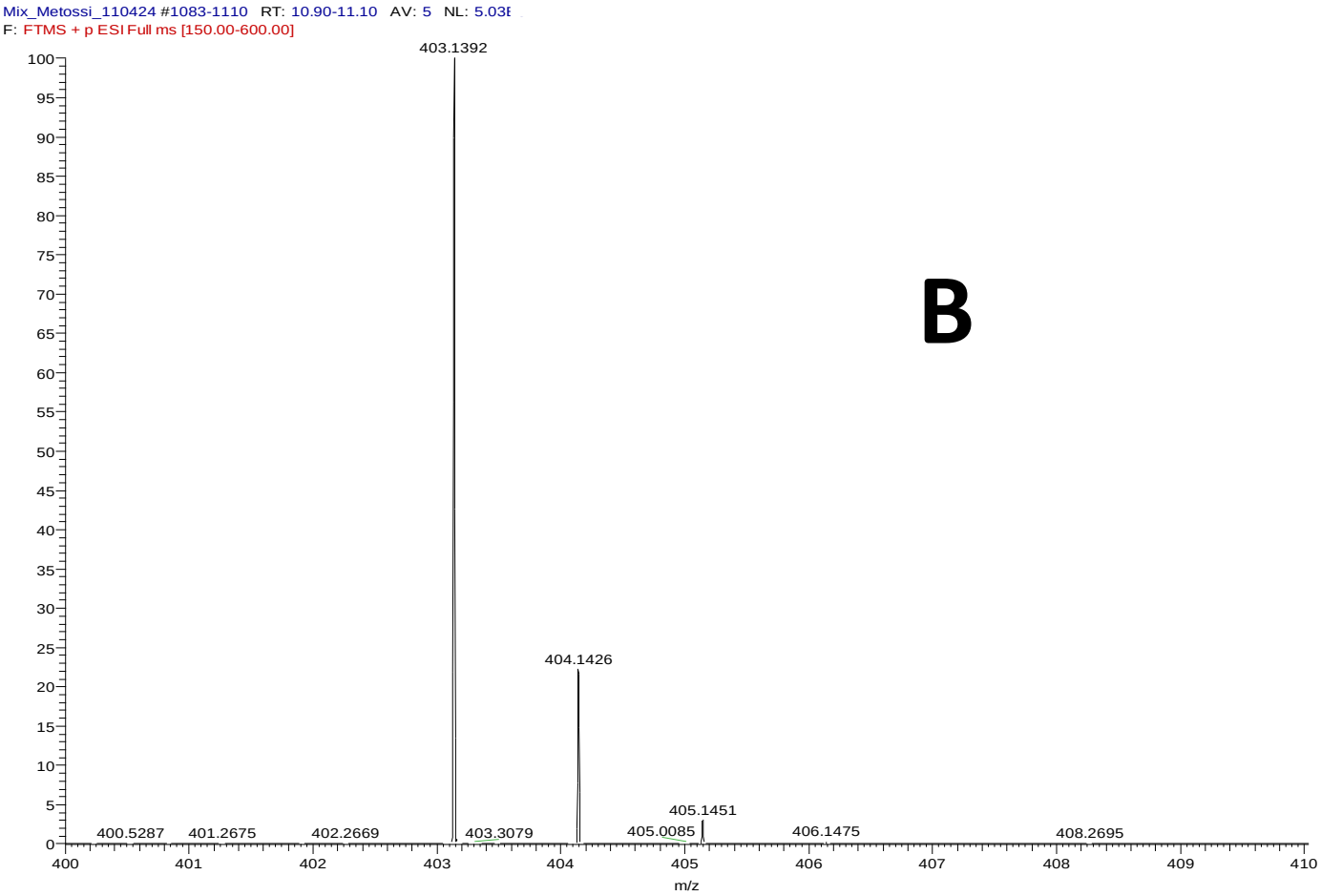


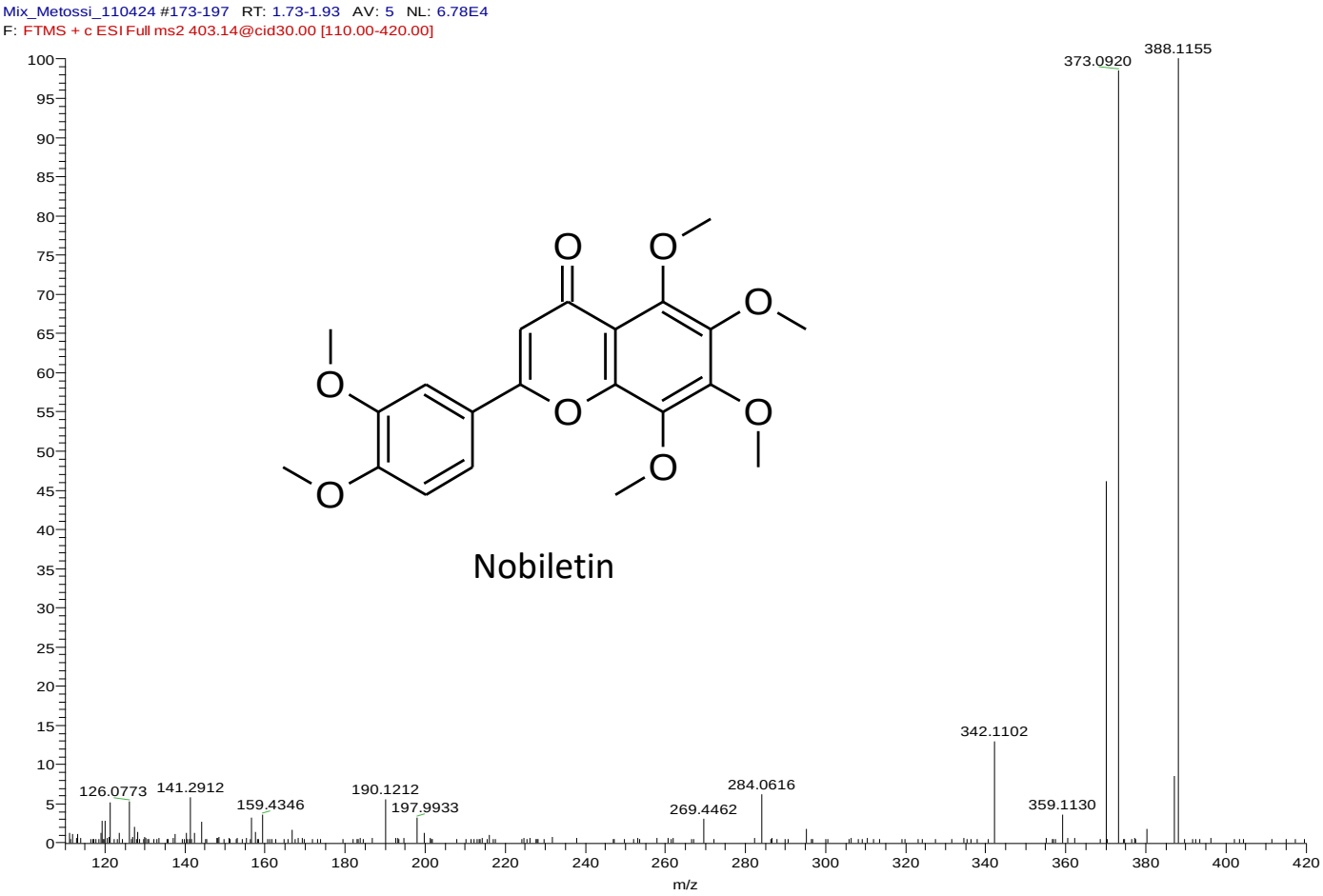
Figure S6: LC-HRMS and LC-HRMS/MS spectra of the four major components of the **M3** fraction: A) sinensetin, B) nobiletin, C) scutellareine tetramethyl ether, D) tangeretin



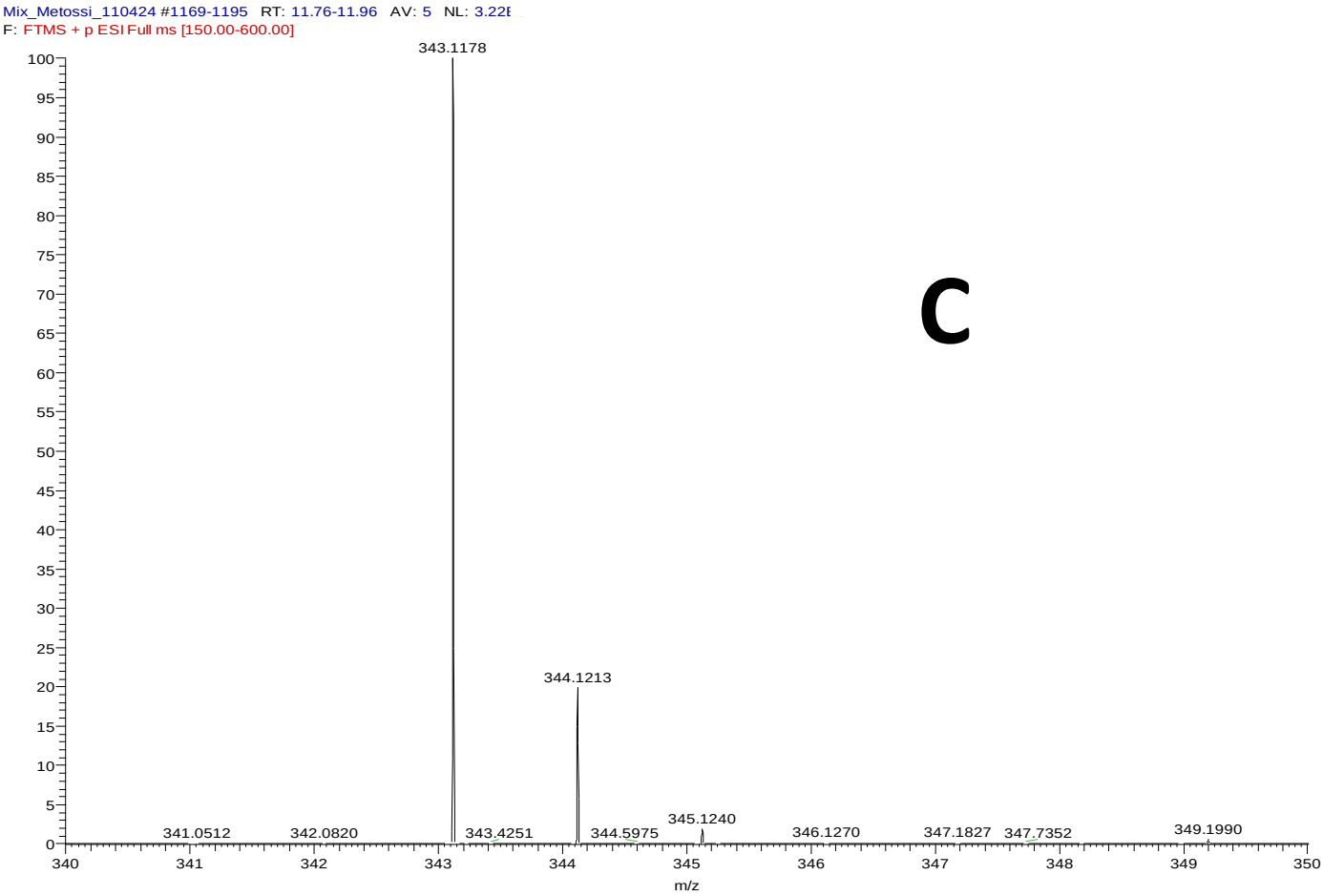



Mix_Metossi_110424 #1083-1110 RT: 10.90-11.10 AV: 5 NL: 5.03E
F: FTMS + p ESI Full ms [150.00-600.00]
403.1392
404.1426
405.1451
400.5287
401.2675
402.2669
403.3079
405.0085
406.1475
408.2695
m/z

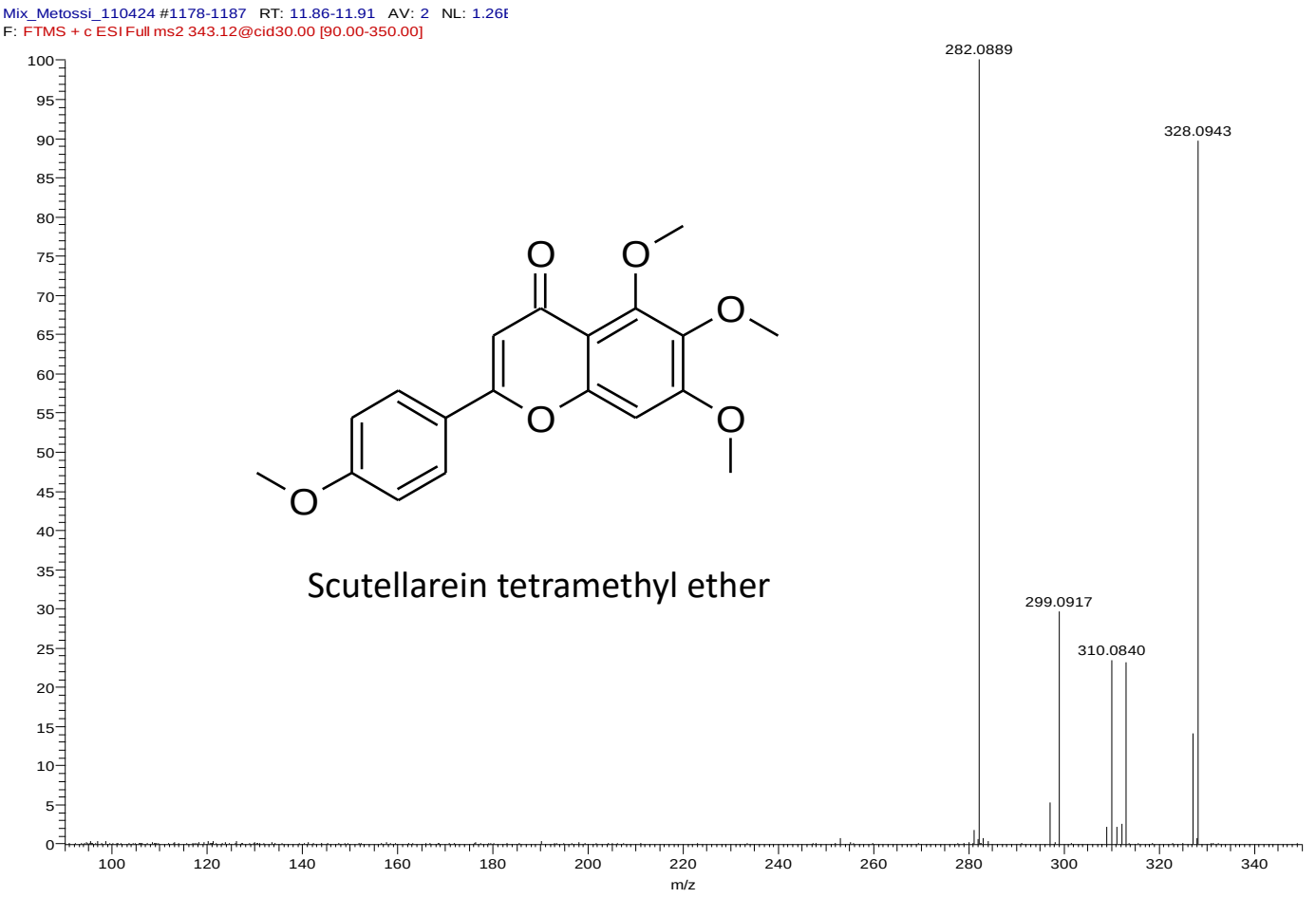
B


Mix_Metossi_110424 #173-197 RT: 1.73-1.93 AV: 5 NL: 6.78E4
F: FTMS + c ESI Full ms2 403.14@cid30.00 [110.00-420.00]
388.1155
373.0920
342.1102
126.0773
141.2912
159.4346
190.1212
197.9933
269.4462
284.0616
359.1130
m/z

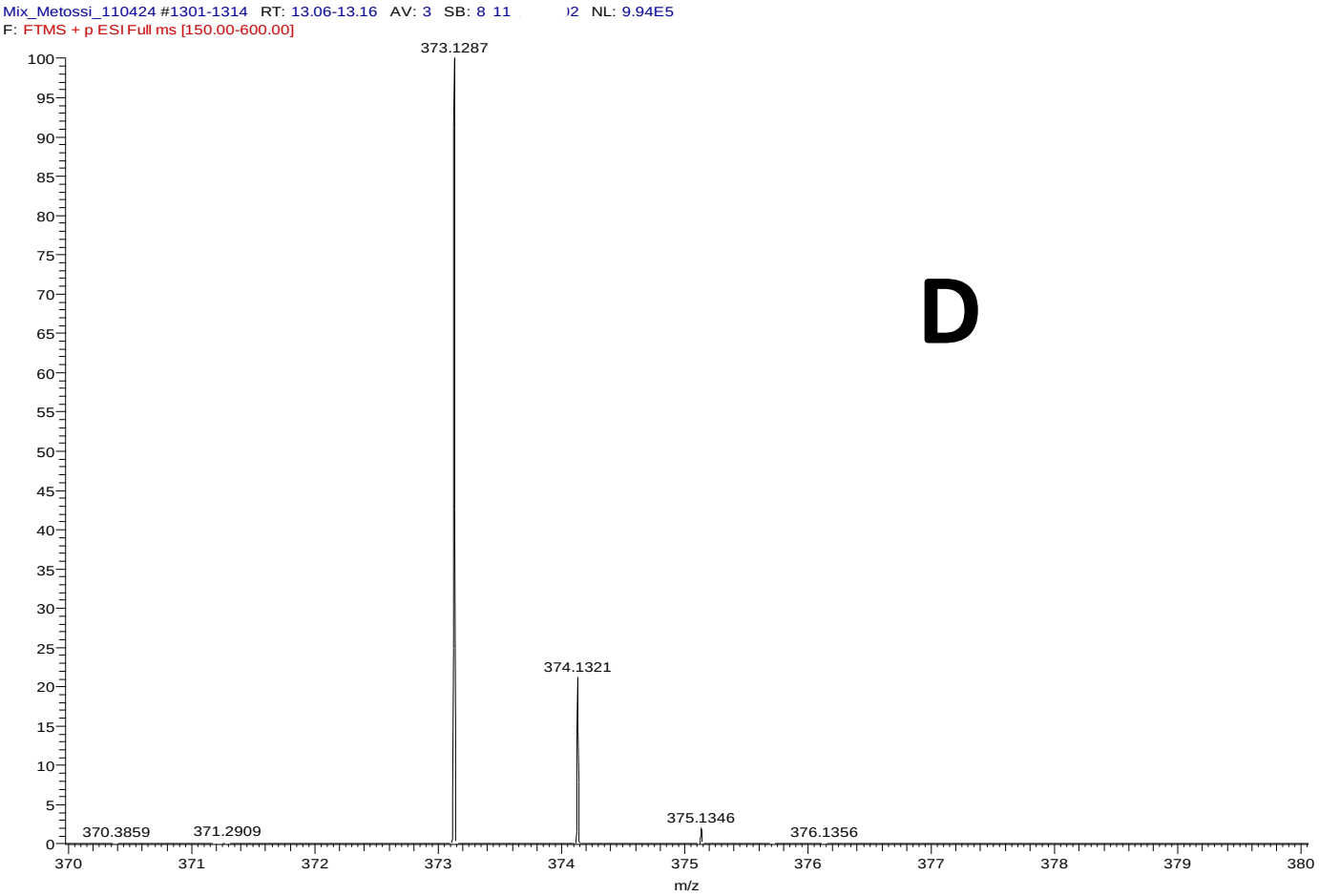
Nobiletin



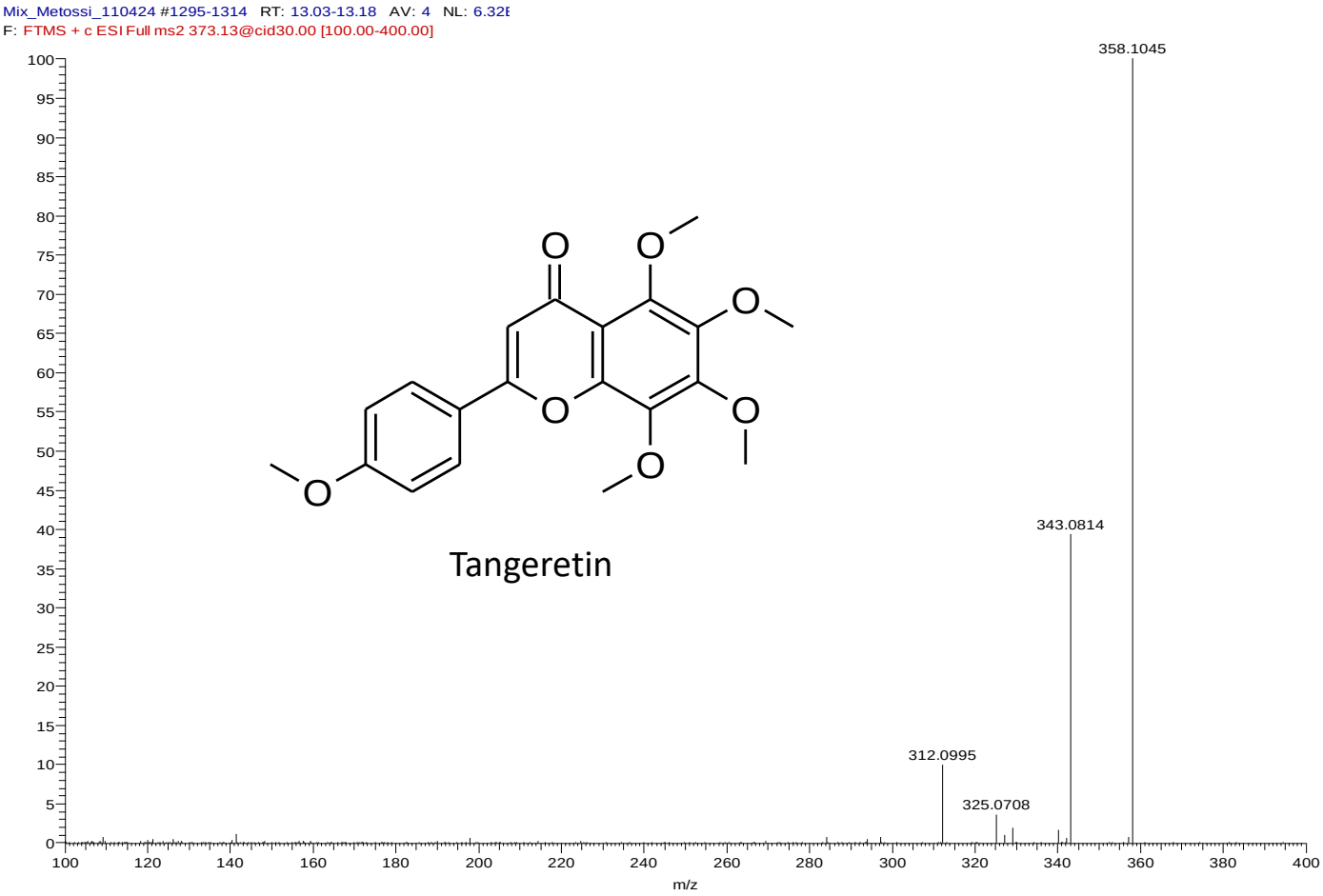
C



Scutellarein tetramethyl ether



D

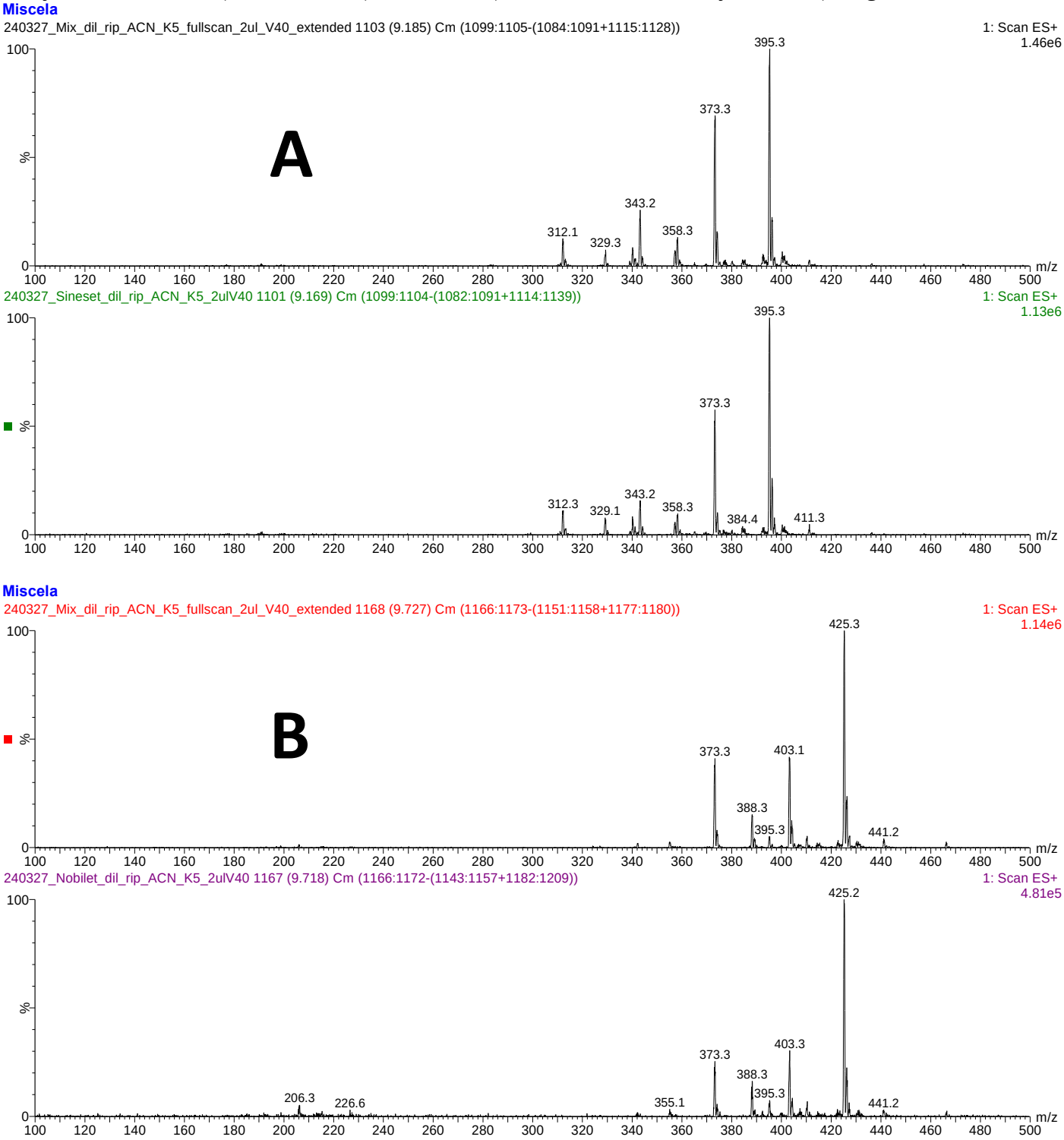


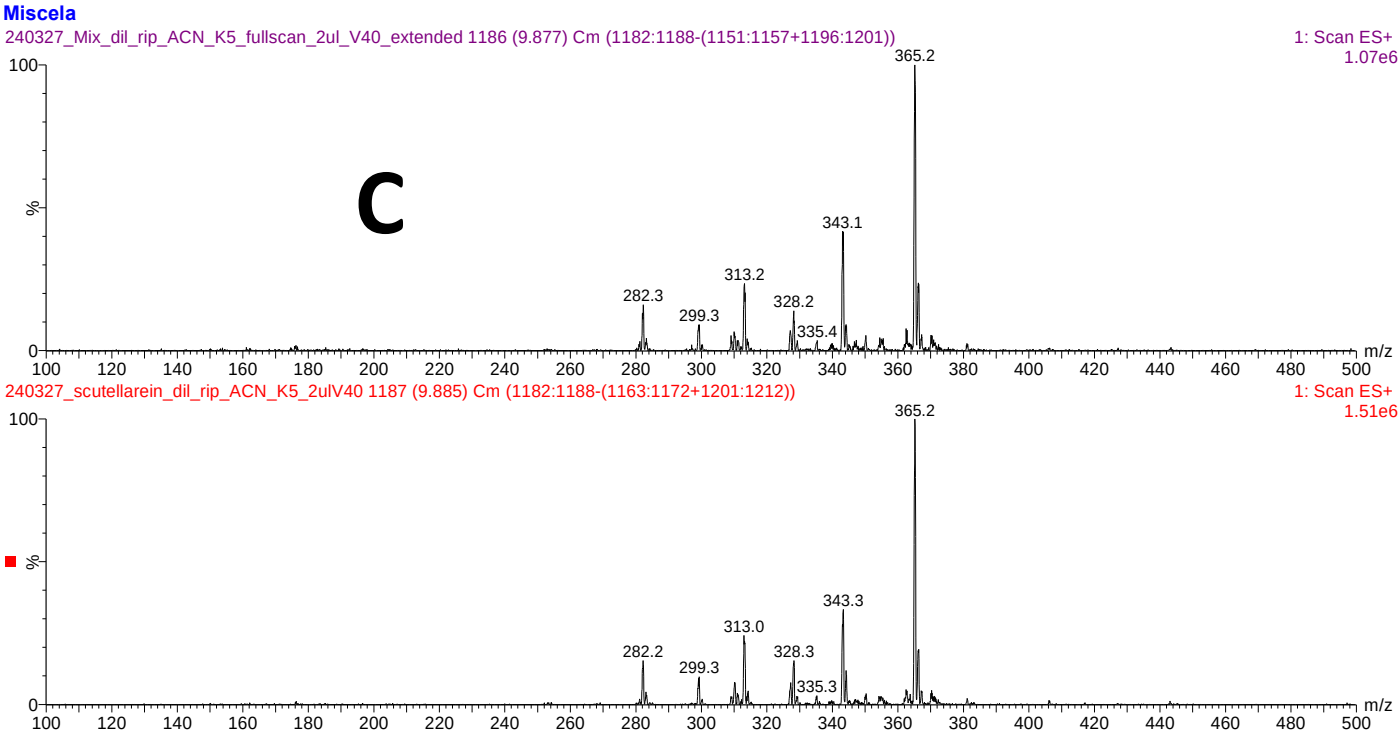
Tangeretin

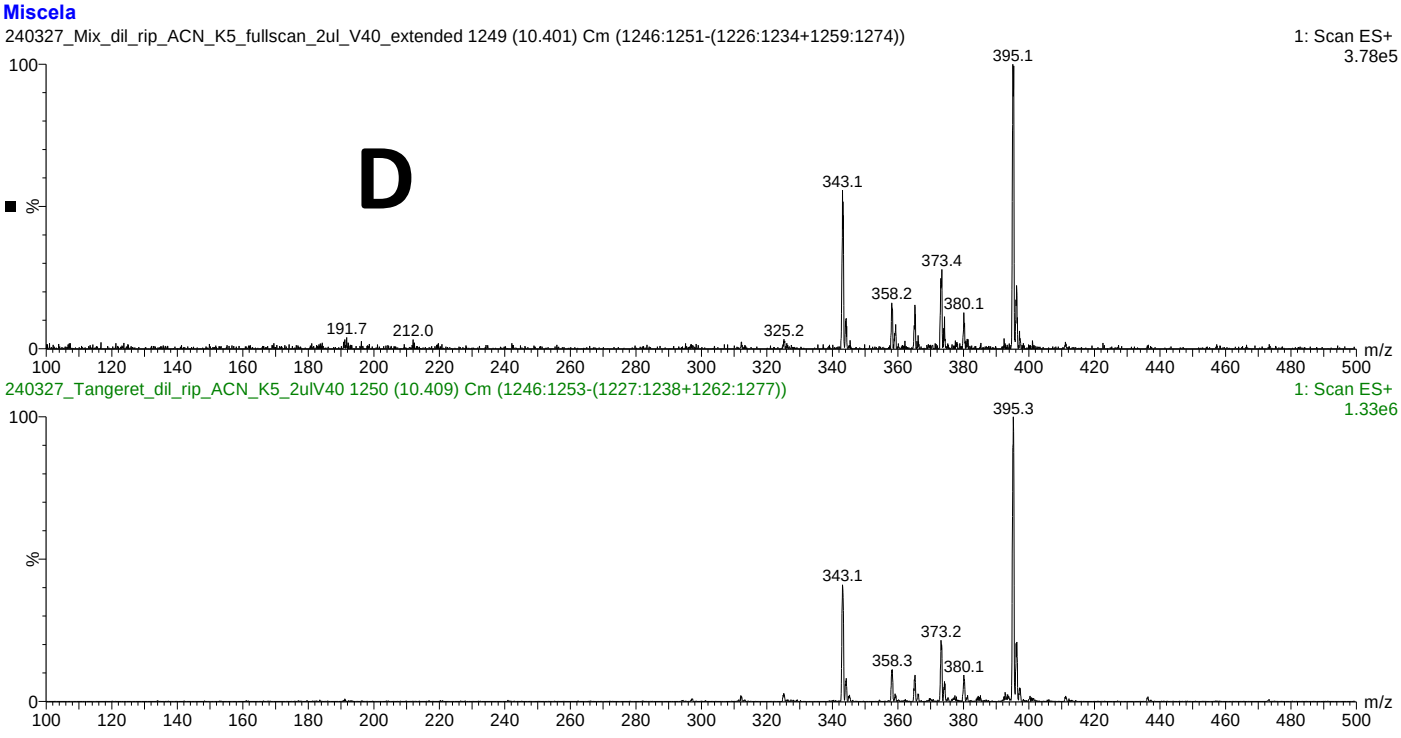
Table **S1.** HRMS (ESI) *m/z* $[M+H]^+$ calculated and found for compounds reported in Figure S6.

Compound	Molecular formula	calcd $[M+H]^+$	Found	MMA (mDa)
sinensetin	$C_{20}H_{20}O_7$	373.1282	373.1284	0.23057
nobiletin	$C_{21}H_{22}O_8$	403.1387	403.1392	0.49591
tangeretin	$C_{20}H_{20}O_7$	373.1282	343.1178	0.23523
scutellarein TME	$C_{19}H_{18}O_6$	343.1176	373.1287	0.50057

Figure S7: in source ESI-CID spectra of four major component of the **M3** mixture compared with separated analytical standards. **A**) sinensetin, **B**) nobiletin, **C**) scutellarein tetramethyl ether, **D**) tangeretin.




Miscela
240327_Mix_dil_rip_ACN_K5_fullscan_2ul_V40_extended 1186 (9.877) Cm (1182:1188-(1151:1157+1196:1201))
1: Scan ES+
1.07e6
C
365.2
343.1
313.2
282.3
328.2
299.3
335.4
240327_scutellarein_dil_rip_ACN_K5_2ulV40 1187 (9.885) Cm (1182:1188-(1163:1172+1201:1212))
1: Scan ES+
1.51e6
365.2
343.3
313.0
282.2
328.3
299.3
335.3
m/z


Miscela
240327_Mix_dil_rip_ACN_K5_fullscan_2ul_V40_extended 1249 (10.401) Cm (1246:1251-(1226:1234+1259:1274))
1: Scan ES+
3.78e5
D
395.1
343.1
373.4
358.2
380.1
191.7
212.0
325.2
240327_Tangeret_dil_rip_ACN_K5_2ulV40 1250 (10.409) Cm (1246:1253-(1227:1238+1262:1277))
1: Scan ES+
1.33e6
395.3
343.1
373.2
358.3
380.1
m/z

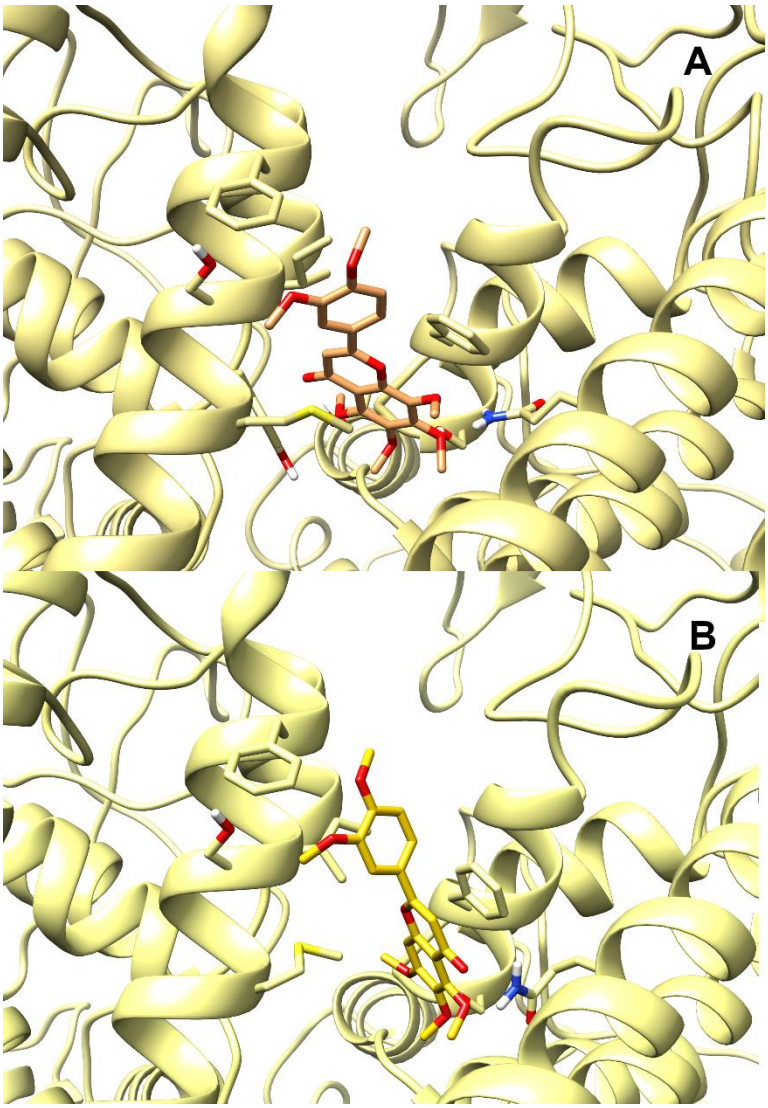


Figure S8. Representative docking poses of nobiletin (coloured in orange, panel A) and sinensetin (coloured in gold, panel B). Protein backbone atoms are represented as ribbons coloured in yellow. according to the side chains. Hydrogen, nitrogen, oxygen, and sulfur atoms are painted white, blue, red, and yellow, respec-tively