Table S1. *Chemical properties of IDE activators.* ClogP, calculated molar refractivity index (CMR) and topological polar surface area (tPSA) values of rat IDE activators were assessed using ChemBioDraw Software (CambrigeSoft, Cambridge, MA). Compounds are identified as in Figure 2. Values for compounds **1, 3** and **6** were obtained by excluding the associated counter ions.

Compound	Molecular weight	CLogP	CMR	tPSA
1	249	-2.474	6.70	57.20
2	288	1.776	7.94	52.35
3	472	-6.042	11.77	179.58
5	296	3.380	7.56	88.04
6	263	3.674	7.65	20.31
7	271	3.921	7.29	58.89
8	188	1.573	5.47	63.84

Figure S1. *Correlation between Abz fluorescence and NitroY concentration*. Fluorescence output was independently measured for free Abz and a 1:1 mixture of Abz and NitroY over a range of concentrations (0-250 μM) in 0.1 M KPi buffer, pH 7.6. The observed fluorescence for free Abz was plotted (GraphPad Prism 4.0) and data points fit to a polynomial function ($y = -0.0628x^2 + 107.09x + 1E\text{-}12$; $R^2 = 1.0000$). The data for the Abz-NitroY mixture was fit to a non-linear, 4-parameter logistic equation ($y = -0.1853x^2 + 98.631x + 232.93$; $R^2 = 0.9989$). These curves were used to determine correction factors that were applied under conditions where different substrate concentrations were employed (e.g. kinetic and dose response experiments; Table 2 and Figure 2, respectively). At each particular substrate concentration evaluated, the fluorescence data obtained was corrected by multiplying against the observed ratio of Abz/Abz-NitroY at that same concentration. The corrected data was then used for calculations of IDE activity.

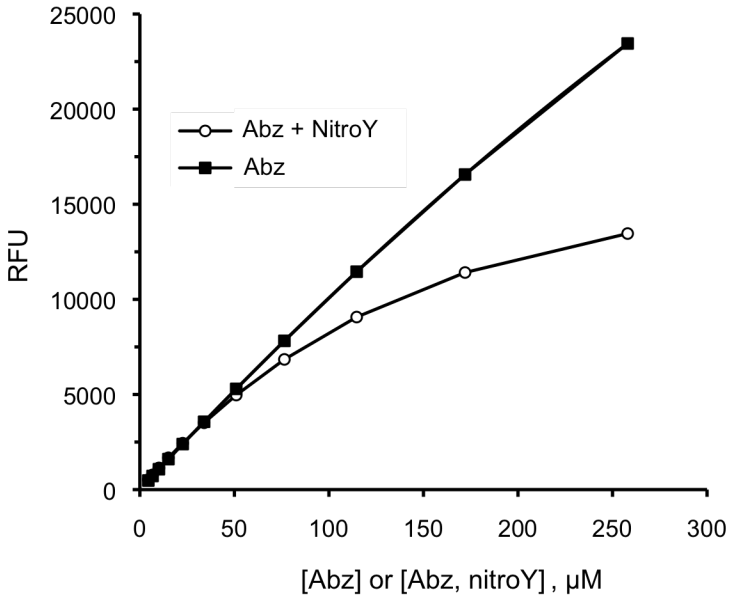
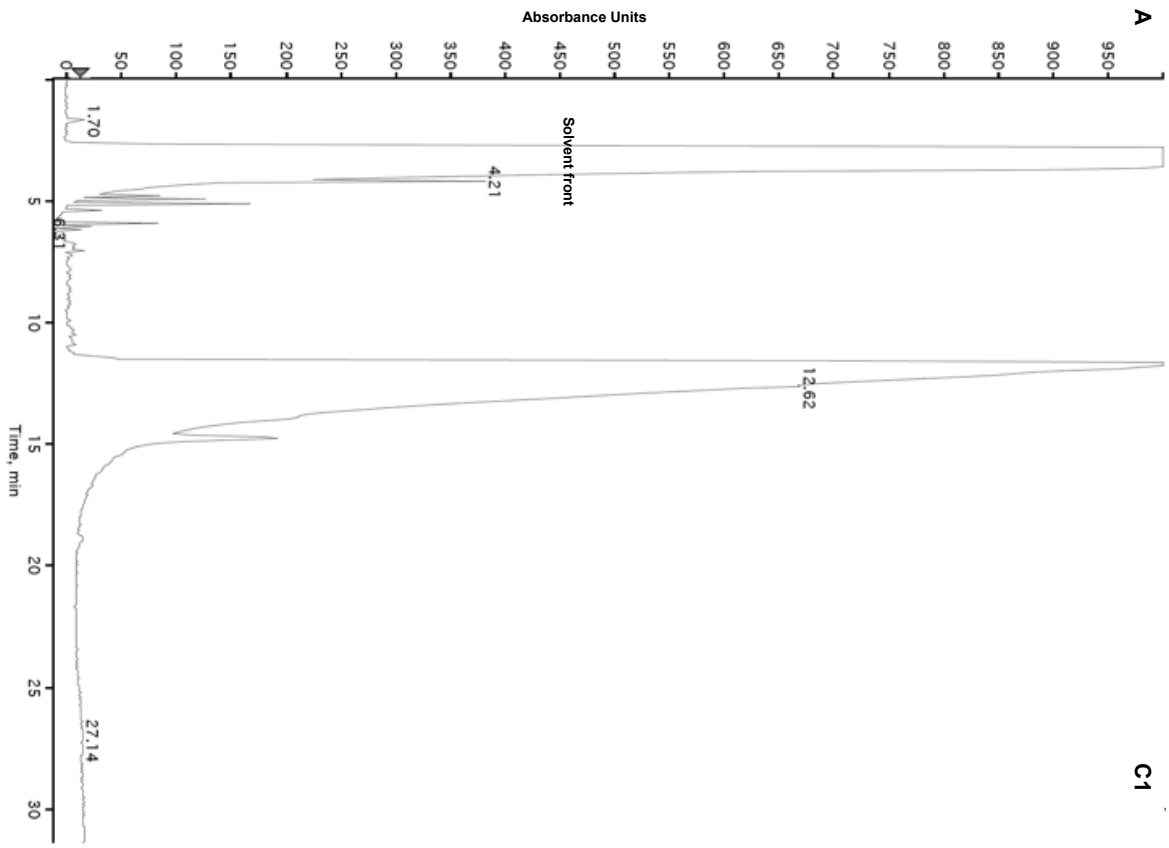
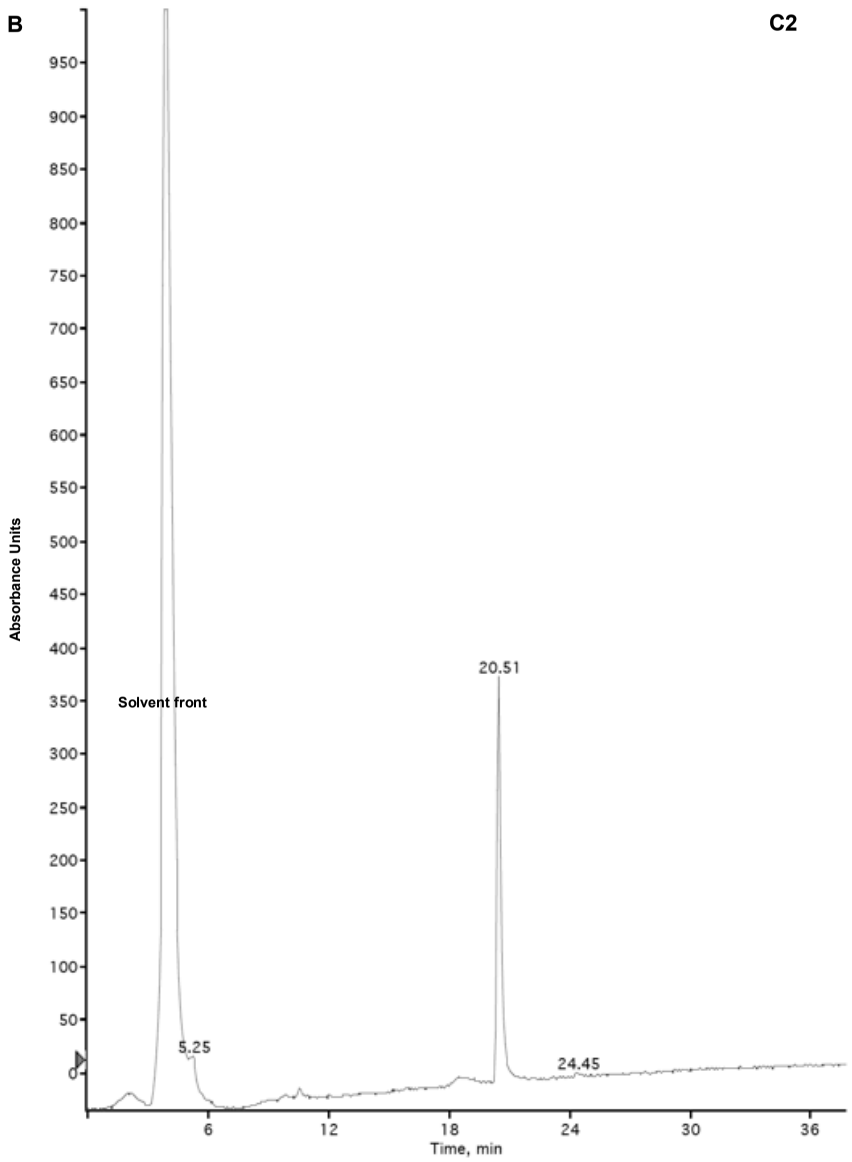
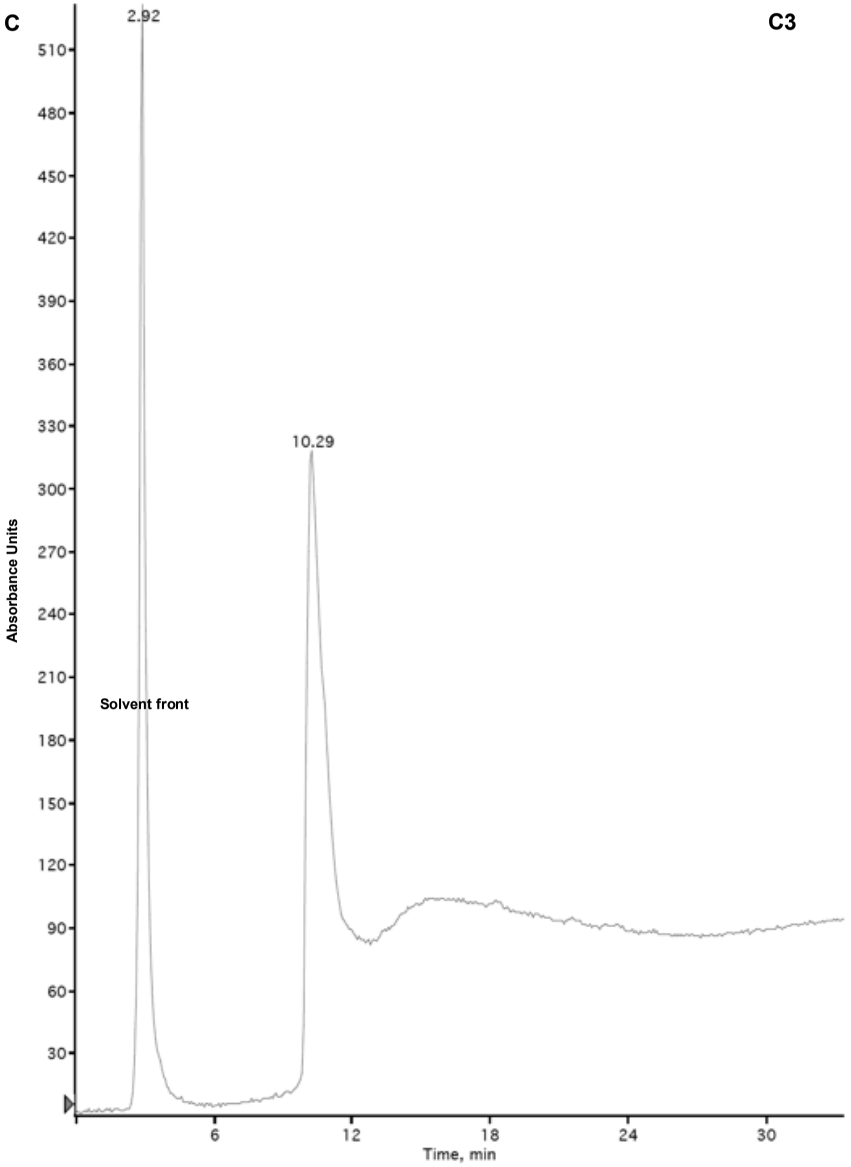
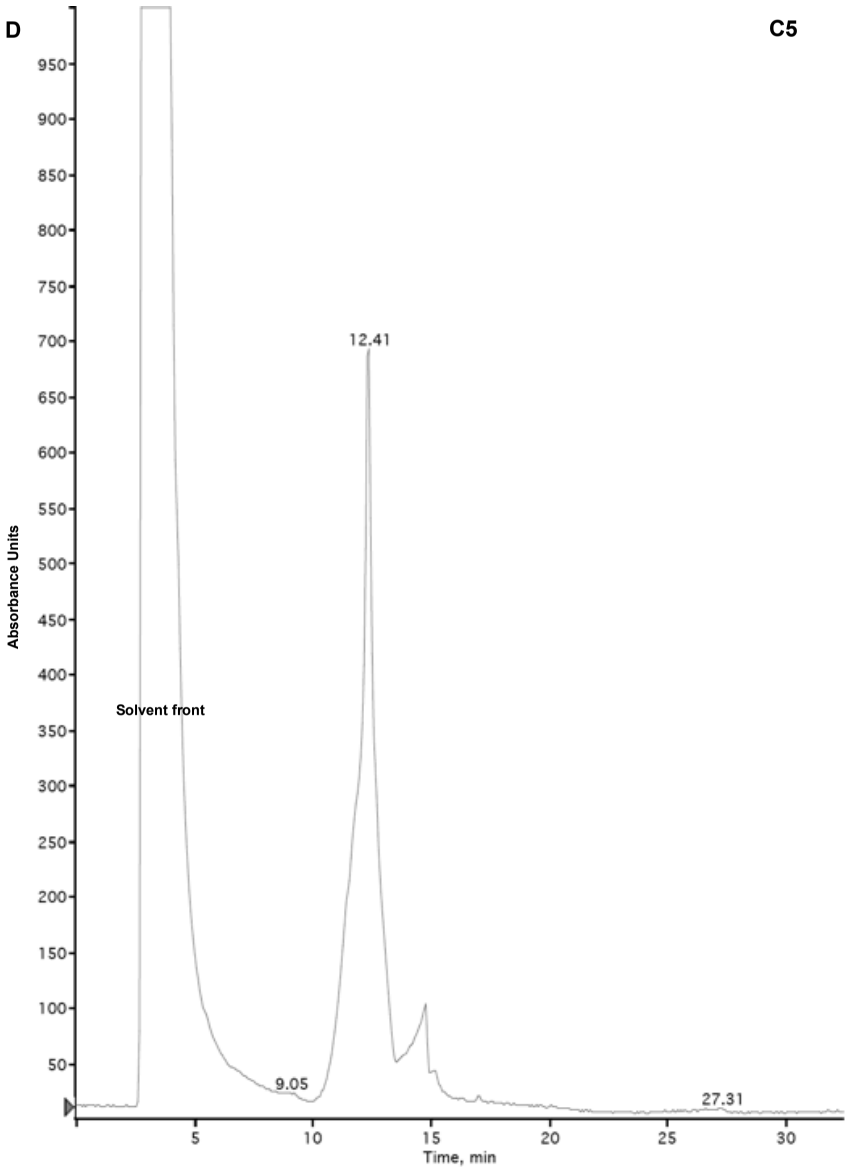


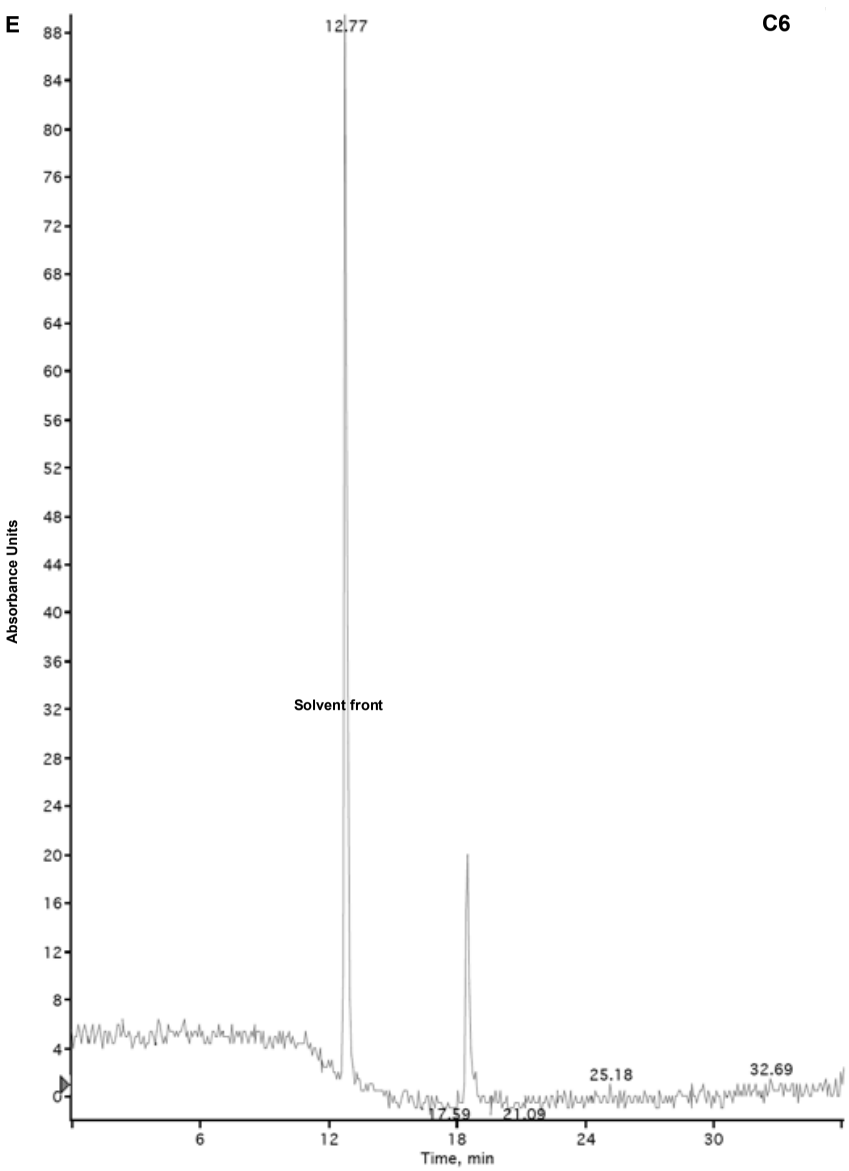
Figure S2. *Purity assessment of activators using HPLC*. Activators were analyzed using C-4 or C-18 columns (Thermo Electron Corp, MA, USA) and absorbance measured at 214 nm (compounds **1, 2,** and **3**), 319 nm (compound **5**), 310 nm (compound **6** and **7**), and 220 nm (compound **8**). The initial peak in each chromatogram represents the solvent front.



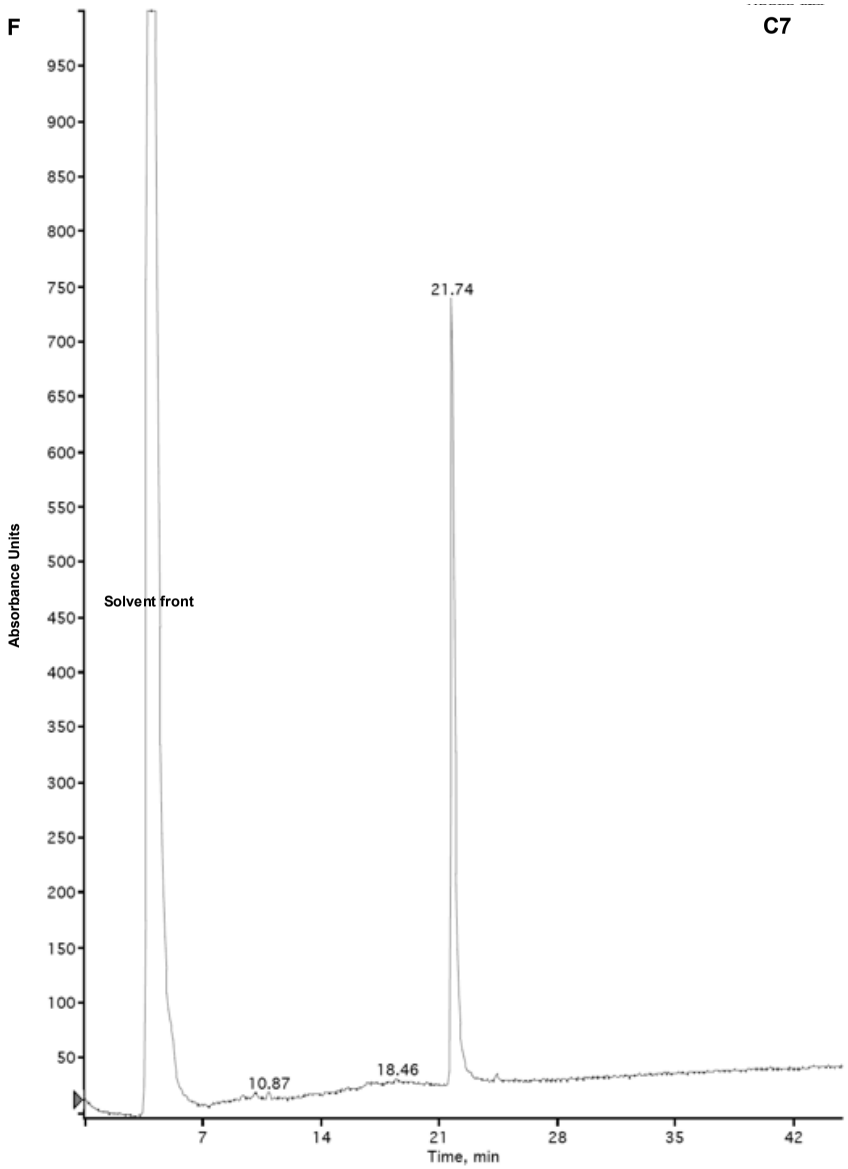

B
C2
Absorbance Units
Solvent front
20.51
5.25
24.45
Time, min


C
C3
2.92
10.29
Absorbance Units
Solvent front
Time, min


D
C5
Absorbance Units
Time, min
Solvent front
12.41
9.05
27.31


E
C6
Absorbance Units
Time, min
Solvent front
12.77
17.59
21.09
25.18
32.69

F


C7
Absorbance Units
Solvent front
21.74
10.87
18.46
Time, min

G

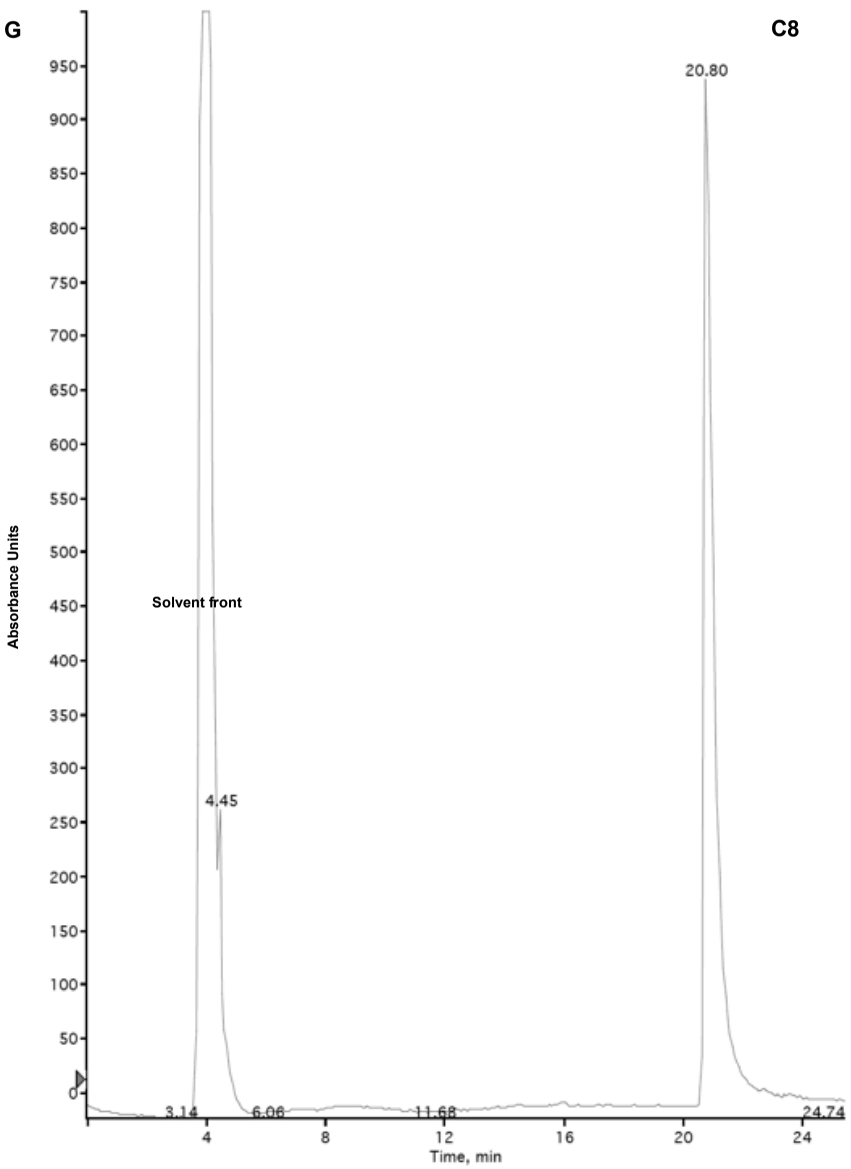
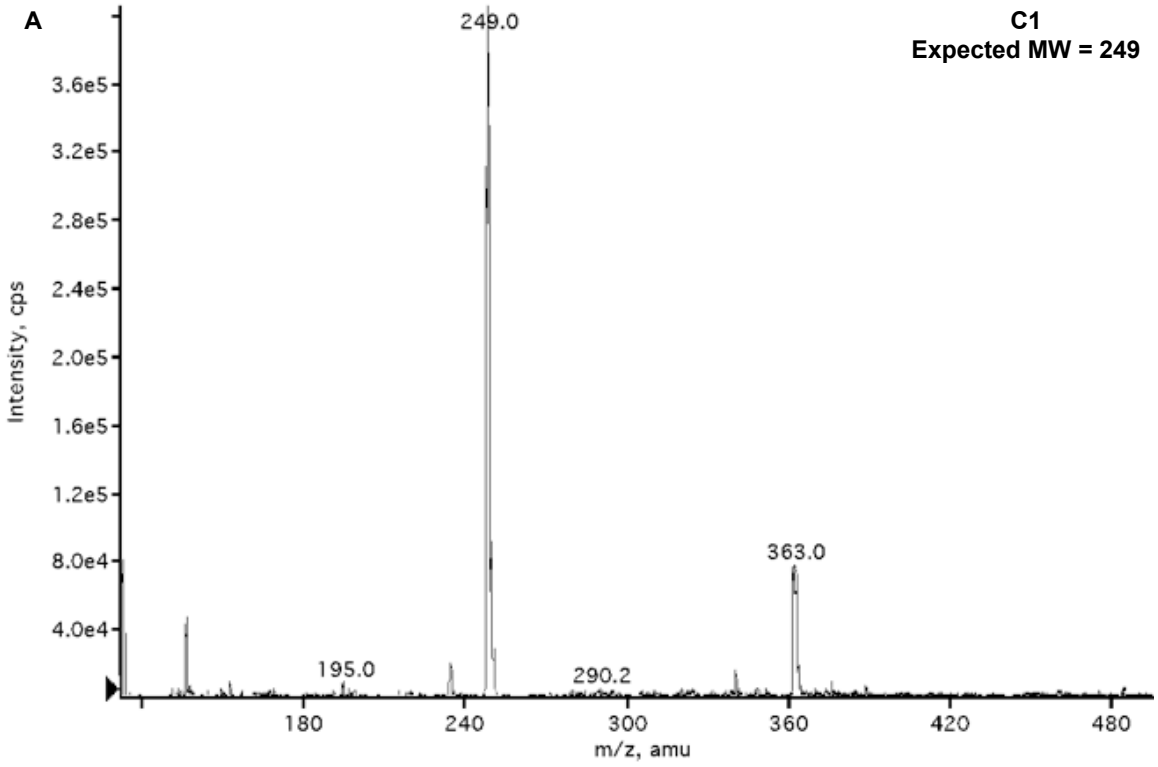
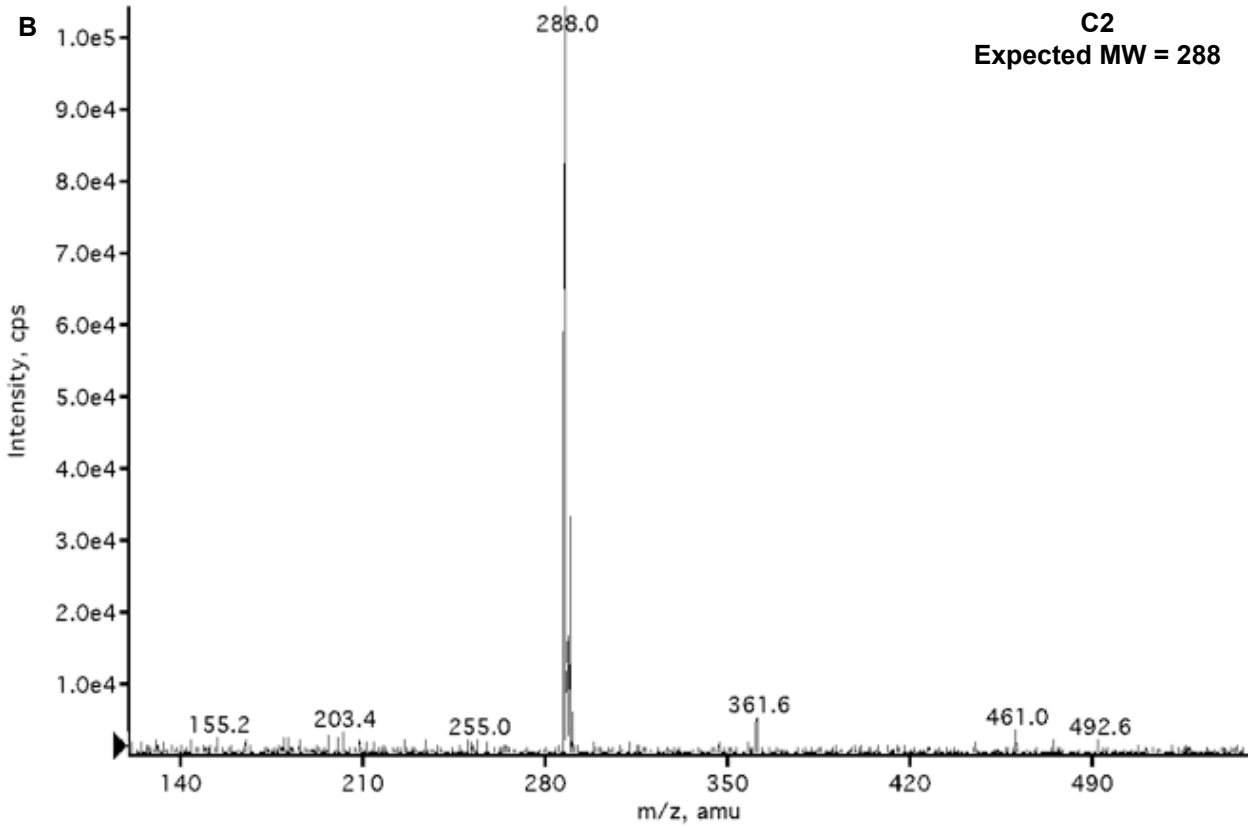
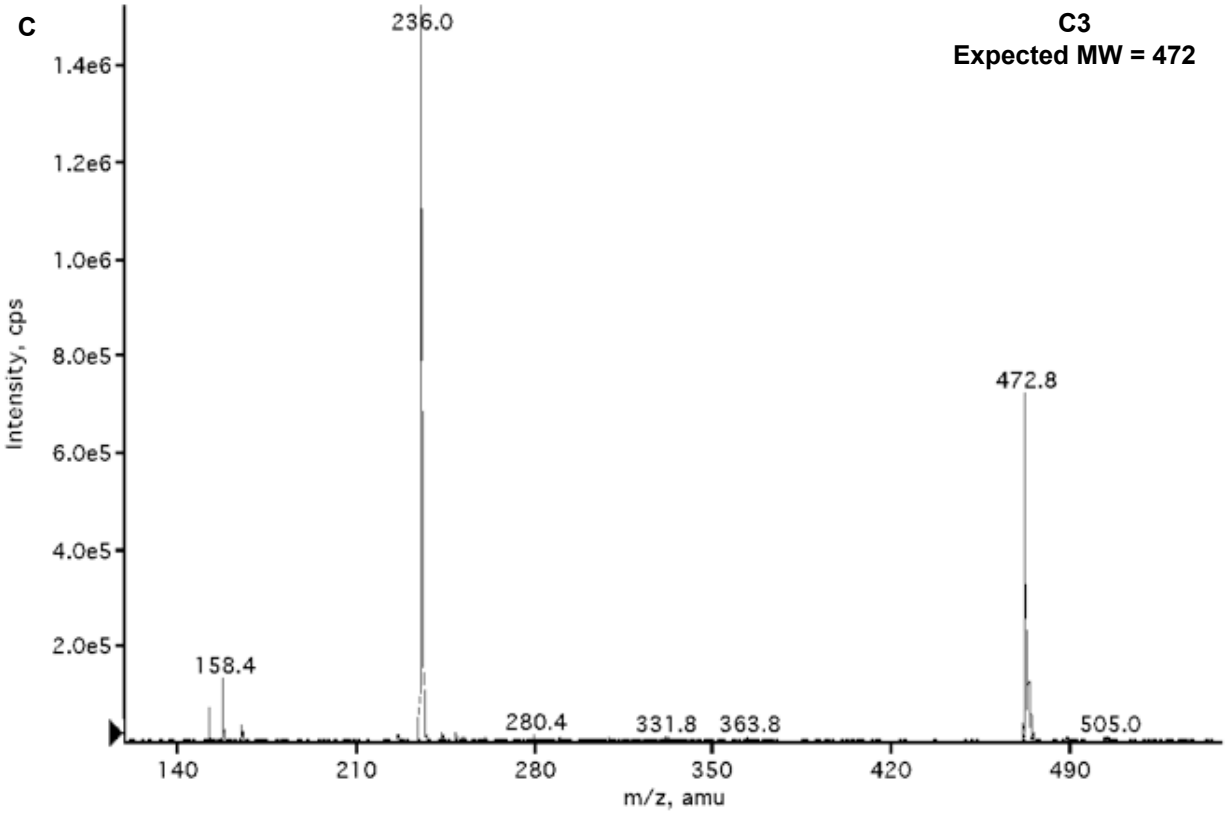
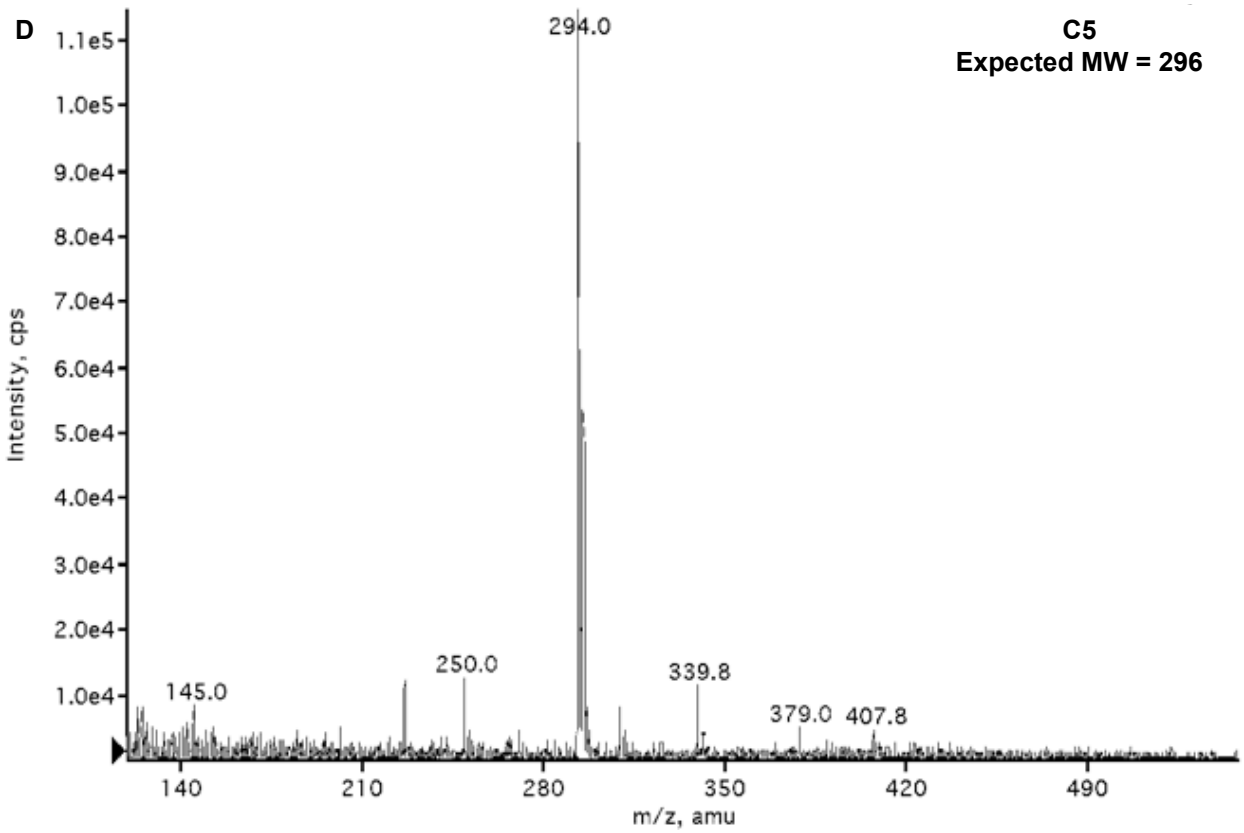

C8
Absorbance Units
Solvent front
20.80
4.45
3.14
6.06
11.68
24.74
Time, min

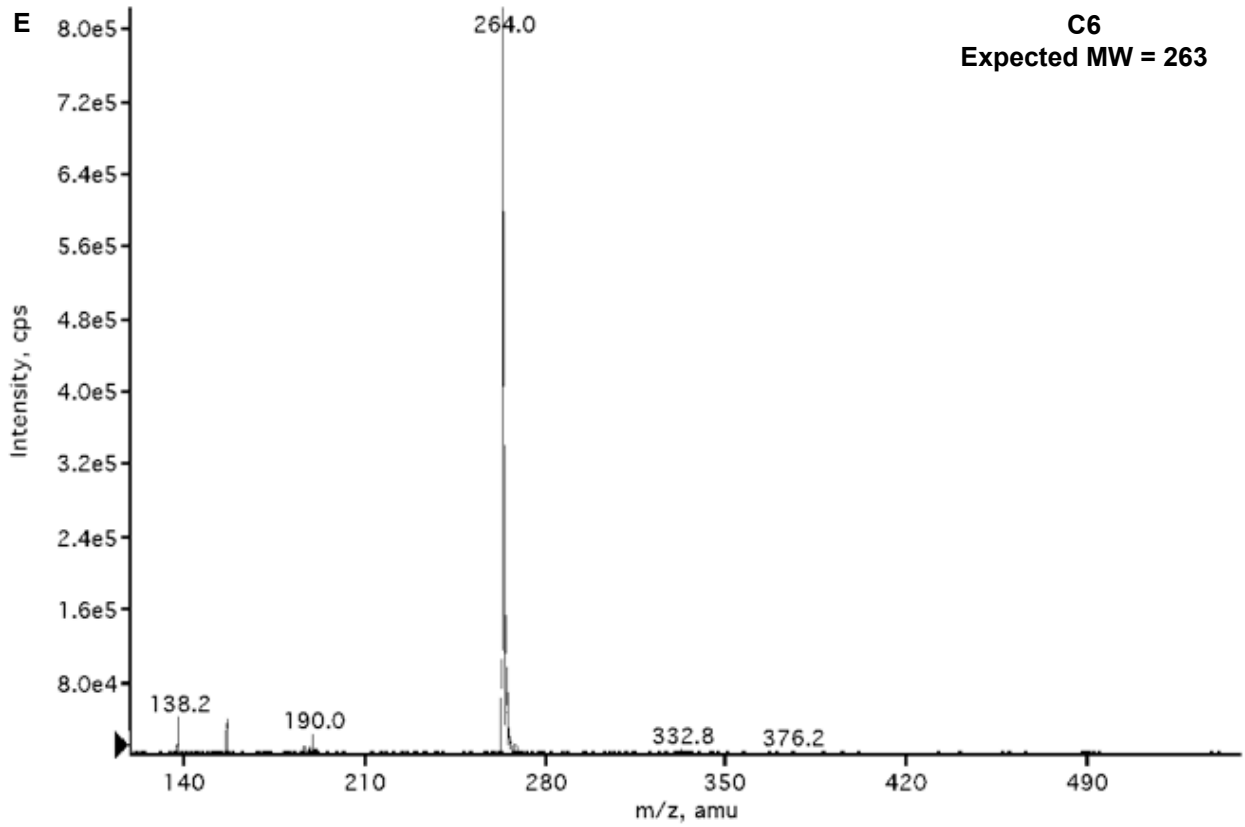
Figure S3. *Purity assessment of activators using MS*. The mass of sample components in peak fractions identified by HPLC (see Figure S2) were determined using mass spectrometry (Perkin Elmer-Sciex API I plus) in negative ion mode for all compounds except **2**, **6** and **7,** which were analyzed in positive ion mode.



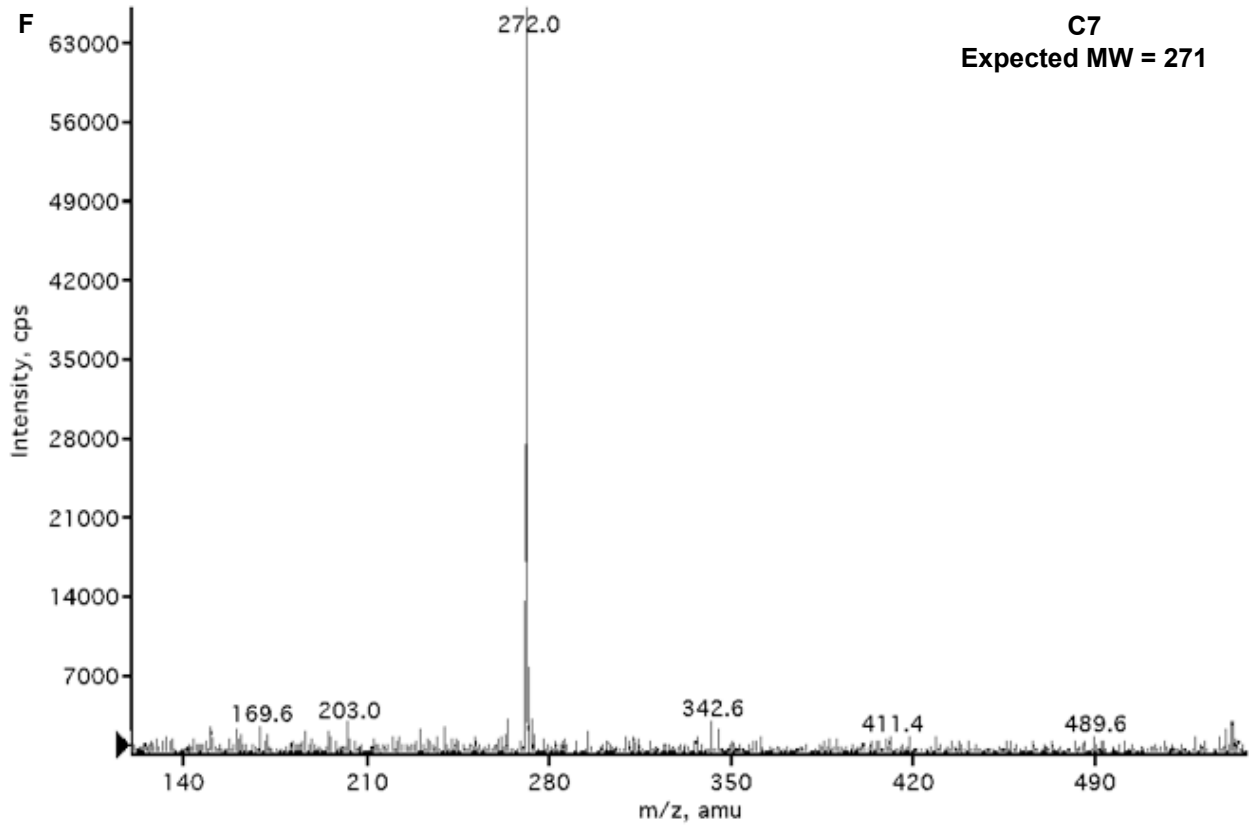

B
C2
Expected MW = 288
288.0
155.2
203.4
255.0
361.6
461.0
492.6
Intensity, cps
m/z, amu


C
C3
Expected MW = 472
236.0
472.8
158.4
280.4
331.8
363.8
505.0
Intensity, cps
m/z, amu


D
C5
Expected MW = 296
294.0
250.0
339.8
145.0
379.0
407.8
Intensity, cps
m/z, amu

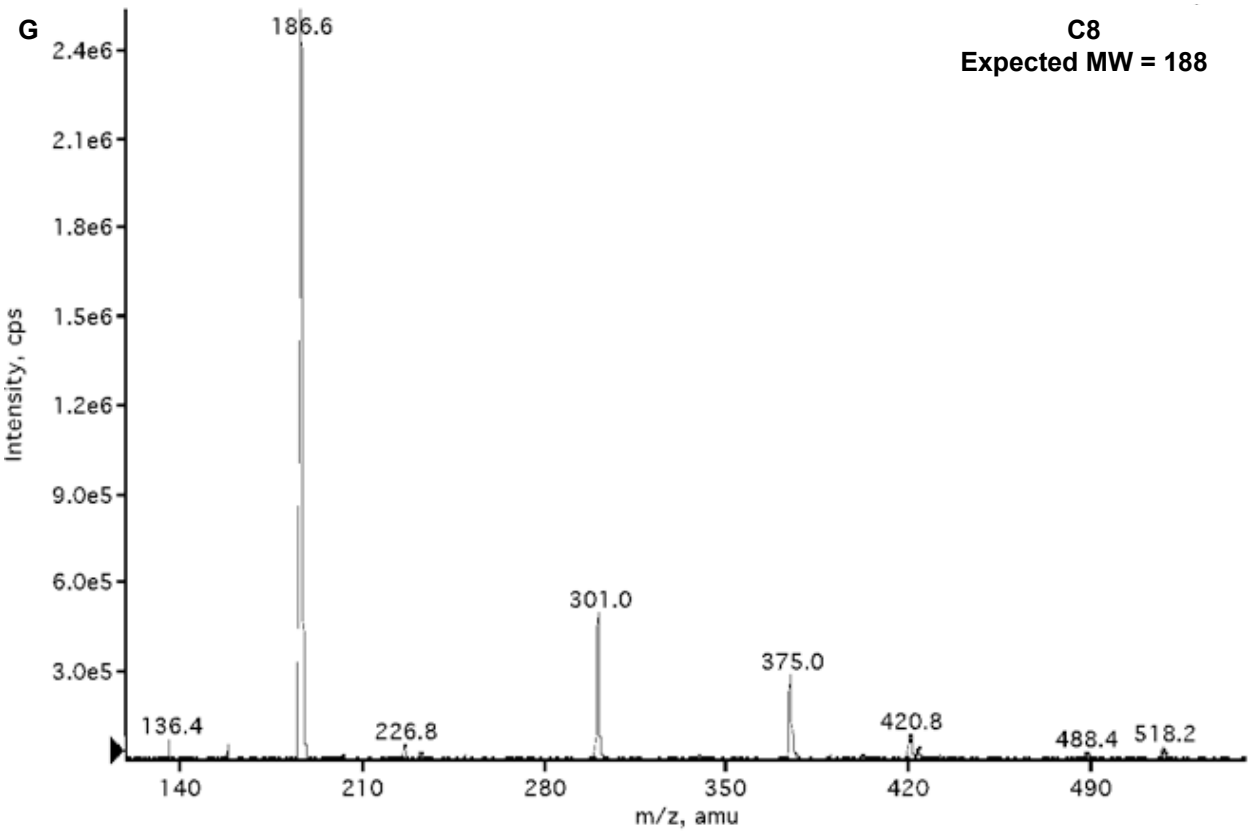

E
C6
Expected MW = 263
264.0
138.2
190.0
332.8
376.2
Intensity, cps
m/z, amu

F



C7
Expected MW = 271

G



C8
Expected MW = 188