Electronic Supplementary Material (ESI) for RSC Medicinal Chemistry.

Supplementary Materials

Table S1. Data collection and refinement statistics of the ternary complexes of *Pf*DHFR-TS V1/S.

	FB8	**FB6**
PDB ID code	8YQ8	8YQ9
Data collection		
Wavelength (Å)	1.5418	1.5418
Space group	$P2_12_12_1$	$P2_12_12_1$
Molecules/ASU	2	2
Unit-Cell Parameters		
a b c (Å)	57.763 156.41 165.065	58.064 156.496 164.865
$\alpha\ \beta\ \gamma$ (deg)	90 90 90	90 90 90
Resolution[a] (Å)	26.1–2.1 (2.2–2.1)	24.55–2.4 (2.5–2.4)
Completeness (%)	99.7 (100)	99.5 (100.0)
Redundancy	5.9 (4.9)	5.9 (5.6)
$\langle I/\sigma(I)\rangle$	13.5 (2.4)	9.1 (2.0)
CC(1/2)	0.998 (0.915)	0.995 (0.873)
Wilson B-factor	26.8	30.84
R_{merge}[b]	0.077 (0.479)	0.127 (0.483)
Refinement		
R_{work}/R_{free}[c]	0.1945 / 0.2404	0.217 / 0.2909
Average B-factors (Å^2)		
Chains A, B		
Protein	32.2, 38.9	37.8, 47.8
Drg	36.5, 66.9	33.3, 63.5
NDP	28.5, 64.0	38.0, 83.5
UMP	35.0, 40.1	73.4, 83.6
GOL	-	43.5, 40.5
Water	35.5	33.5
R.m.s. deviation		
Bond lengths (Å)	0.0092	0.0087
Bond angles (°)	1.8340	1.8186
Ramachadran Plot		
favored (%)	97.6	96.4
allowed (%)	2.4	3.6
outlier (%)	-	-

[a]Values in parentheses are for the highest-resolution shell.
[b]$R_{merge} = \Sigma_{hkl}\Sigma_i|I_i(hkl) - \langle I(hkl)\rangle|/\Sigma_{hkl}\Sigma_i I_i(hkl)$, where $I_i(hkl)$ is the intensity of an individual reflection and $\langle I(hkl)\rangle$ is the mean intensity of symmetry-equivalent reflections.
[c]$R_{work} = \Sigma_{hkl}||F_{obs}| - |F_{calc}||/\Sigma_{hkl}|F_{obs}|$, where F_{obs} and F_{calc} are the observed and calculated structure-factor amplitudes, respectively. R_{free} was calculated in the same manner as R_{work} but using only a 5% unrefined subset of the reflection data.

Table S2. Docking scores obtained for the lead compounds against QM and WT *Pf*DHFR and *Hs*DHFR.

	Docking score (kcal/mol)		
Compound	QM *Pf*DHFR	WT *Pf*DHFR	*Hs*DHFR
FB1	-11.24	-10.33	-9.12
FB2	-10.51	-11.0	-7.34
FB3	-9.37	-8.88	-8.69
FB4	-10.27	-10.37	-7.71
FB5	-9.83	-9.00	-5.79
FB6	-9.913	-9.88	-6.53
FB7	-9.97	-7.52	-5.69
FB8	-9.69	-11.33	-7.47

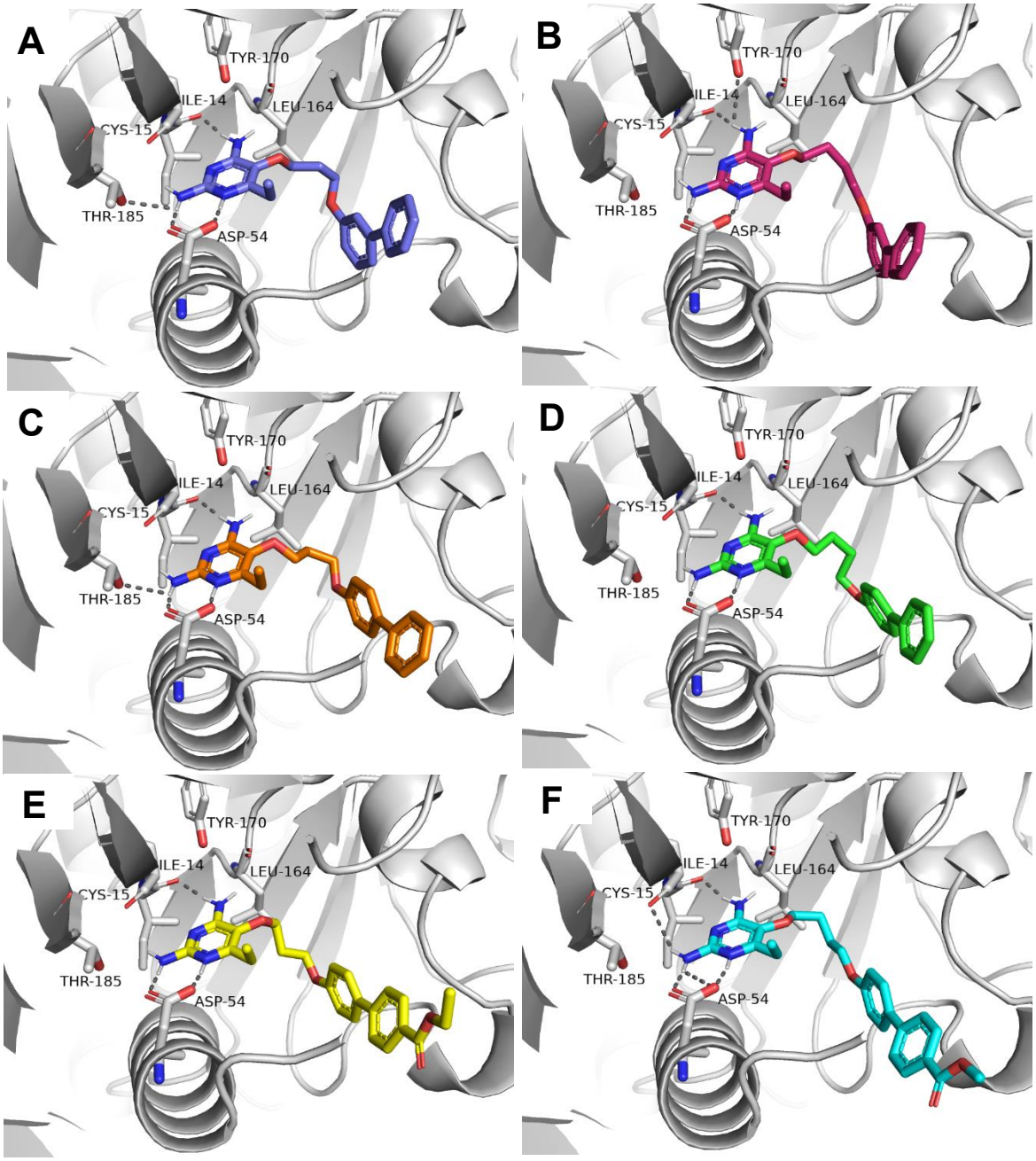

Figure S1. Individual molecular docking poses obtained for lead compounds in QM *Pf*DHFR. (A) FB1, (B) FB2, (C) FB3, (D) FB4, (E) FB5, (F) FB7.

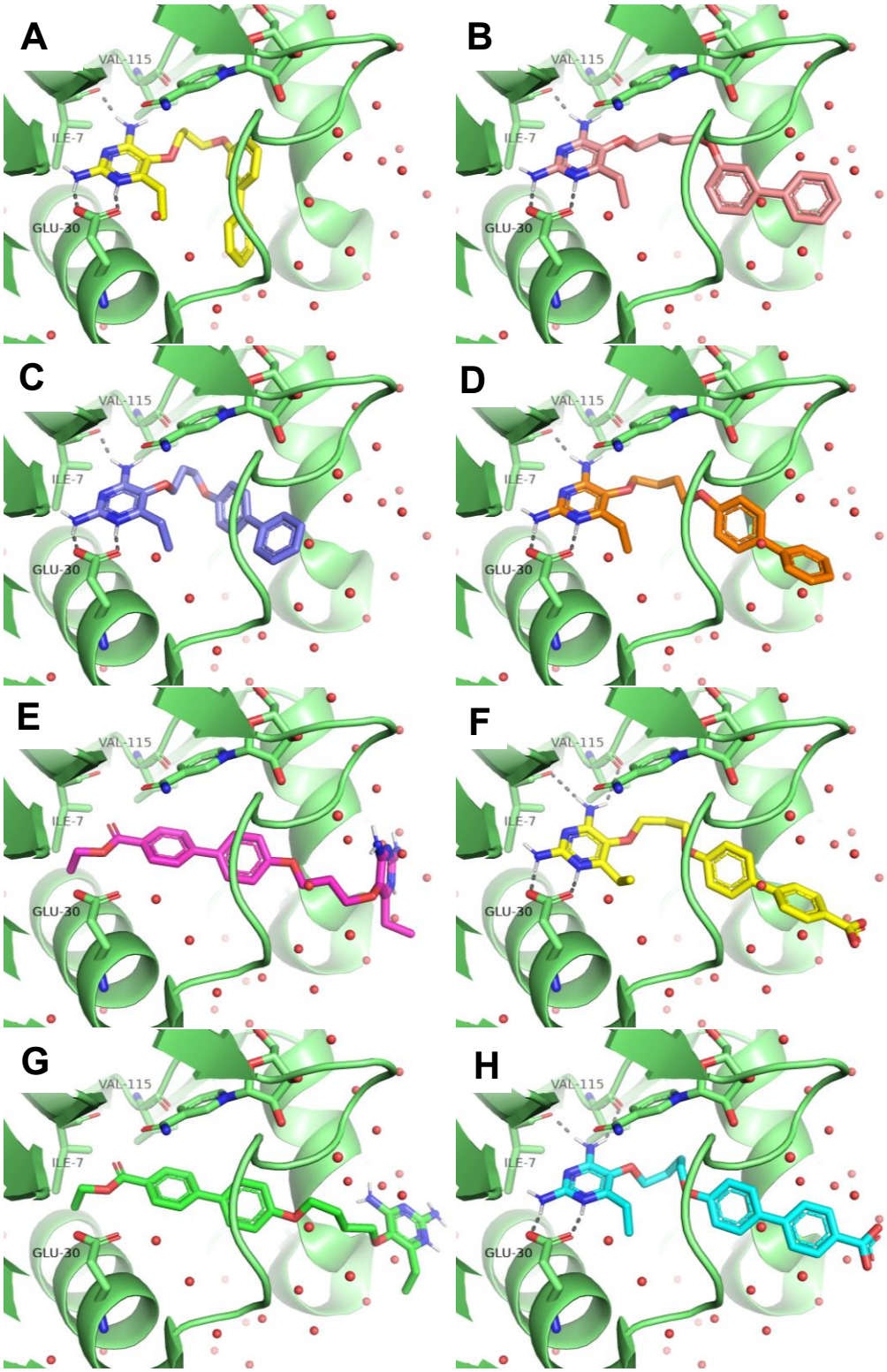

Figure S2. Individual molecular docking poses obtained for lead compounds in *Hs*DHFR. (A) FB1, (B) FB2, (C) FB3, (D) FB4, (E) FB5, (F) FB6, (G) FB7, (H) FB8.

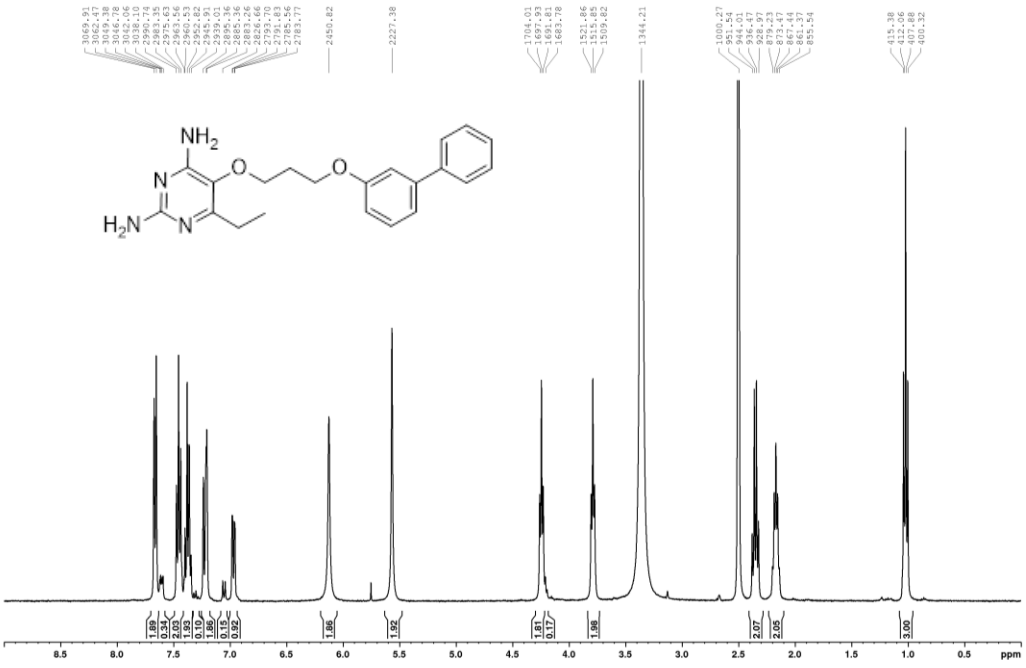

Figure S3. ^{1}H NMR spectrum of compound 14.

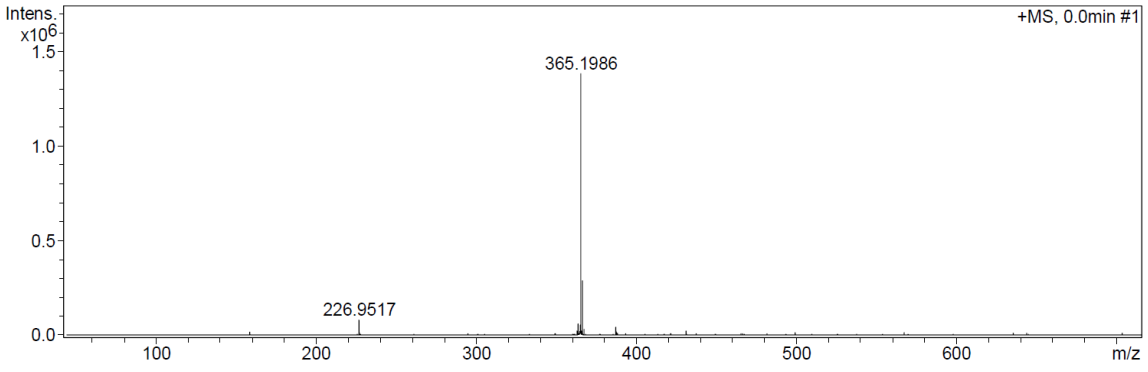

Figure S4. HRMS spectrum of compound 14.

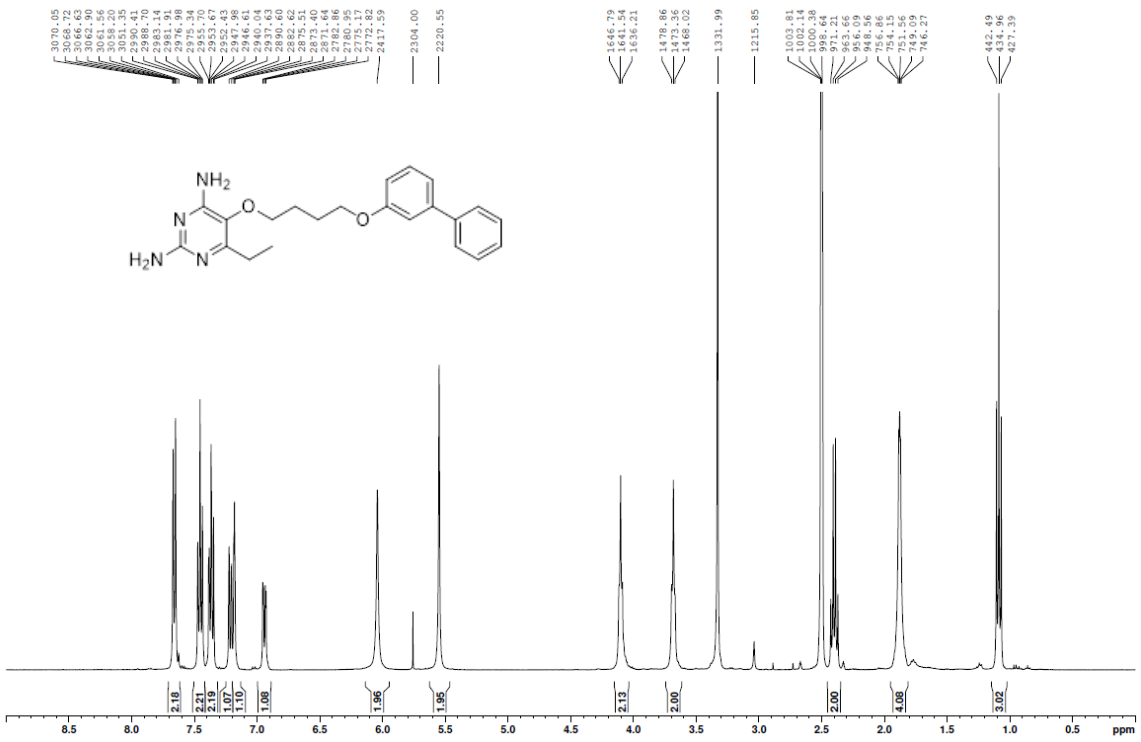

Figure S5. ^{1}H NMR spectrum of compound 15.

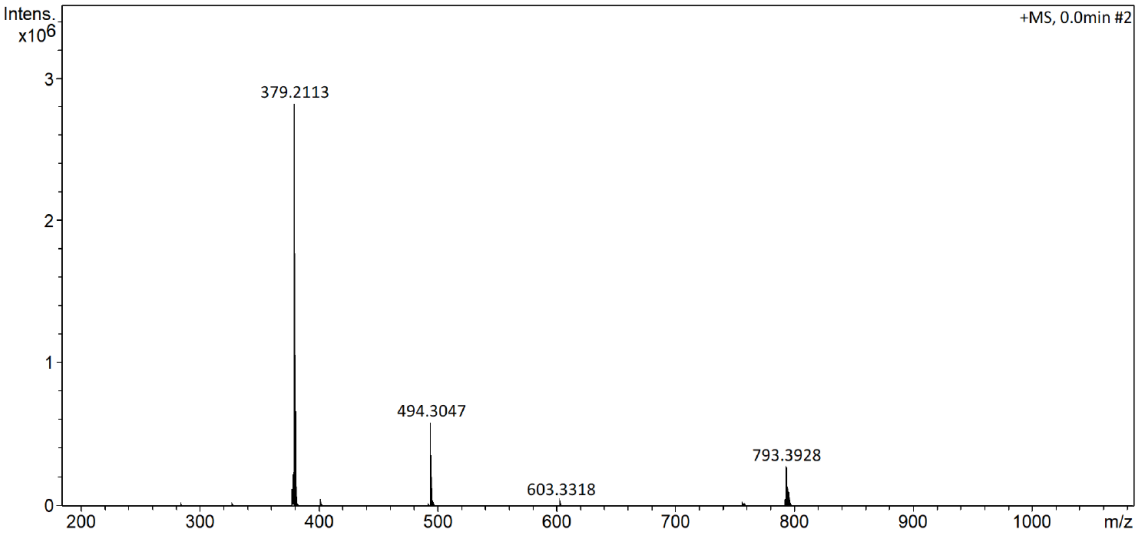

Figure S6. HRMS spectrum of compound 15.

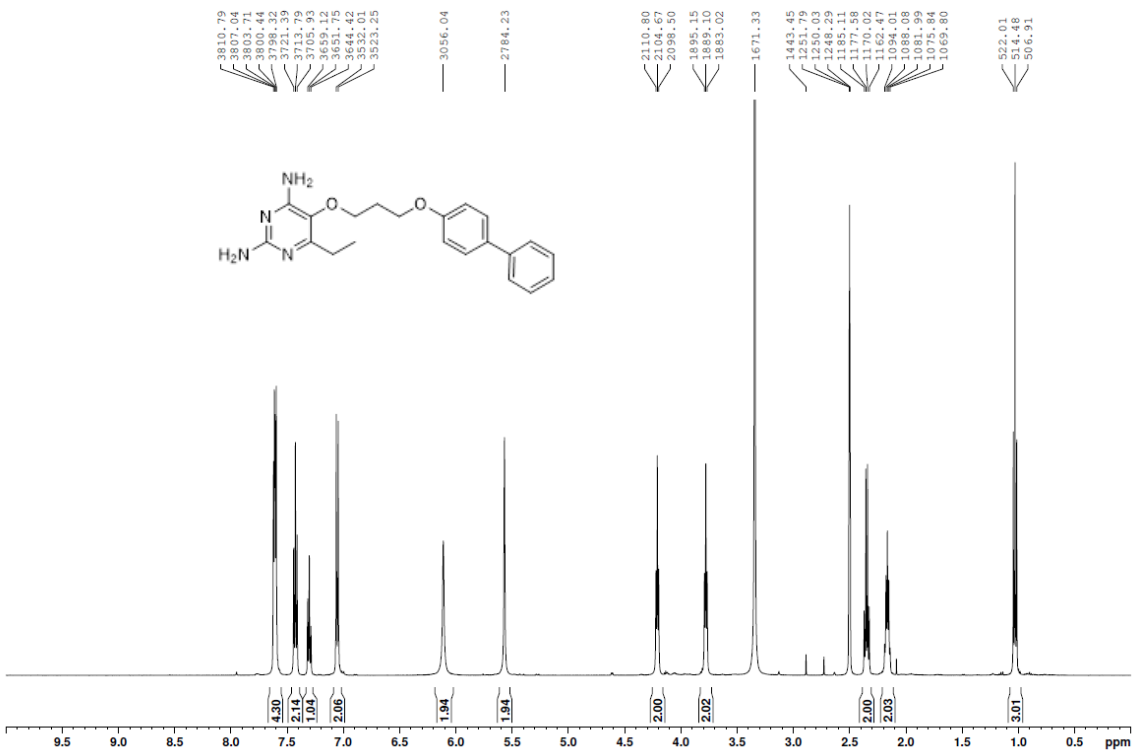

Figure S7. ^{1}H NMR spectrum of compound 16.

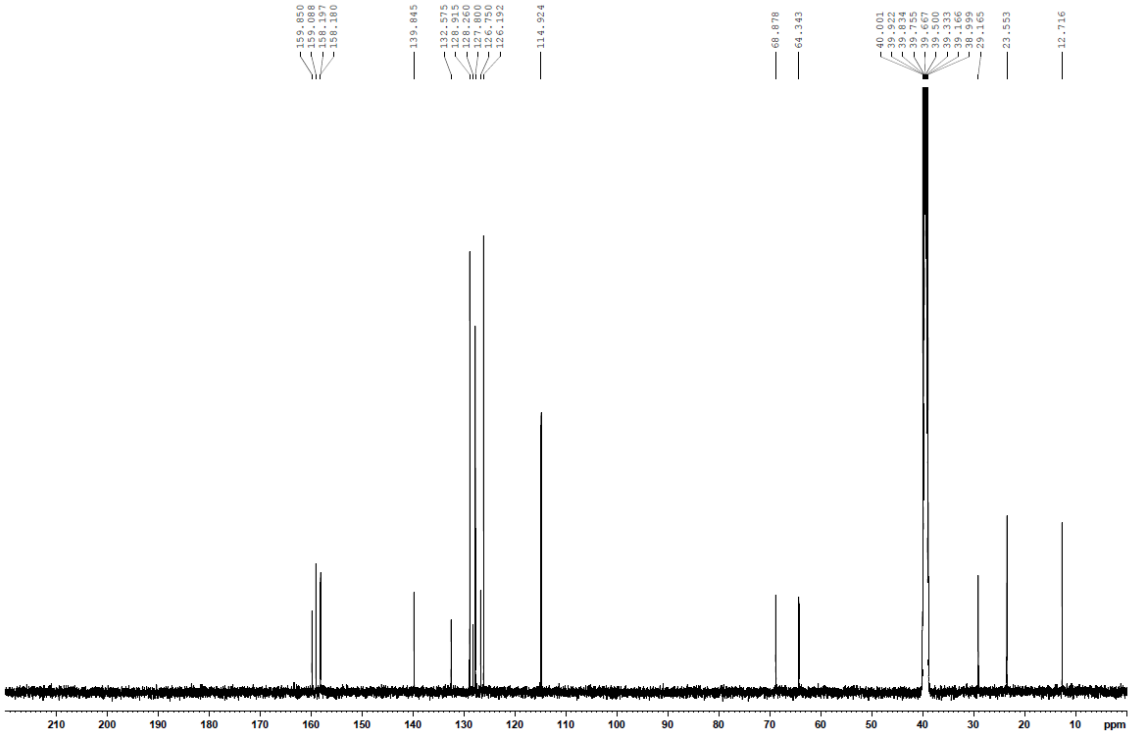

Figure S8. ^{13}C NMR spectrum of compound 16.

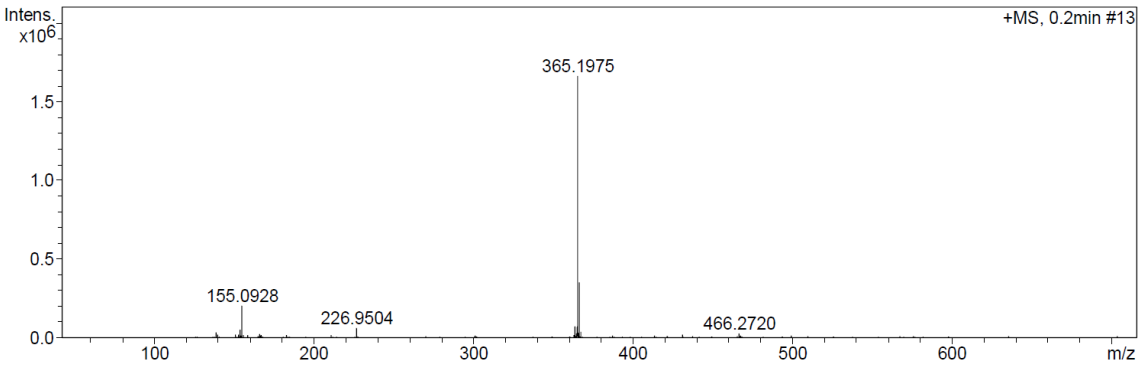

Figure S9. HRMS spectrum of compound 16.

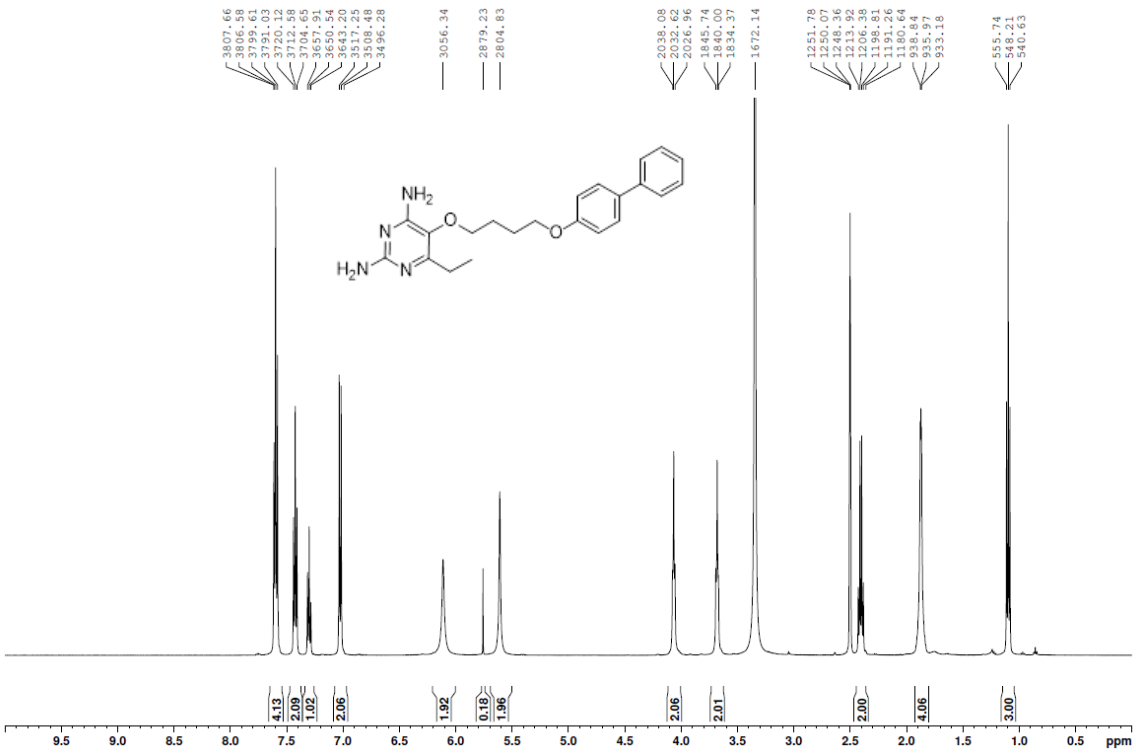

Figure S10. ^{1}H NMR spectrum of compound 17.

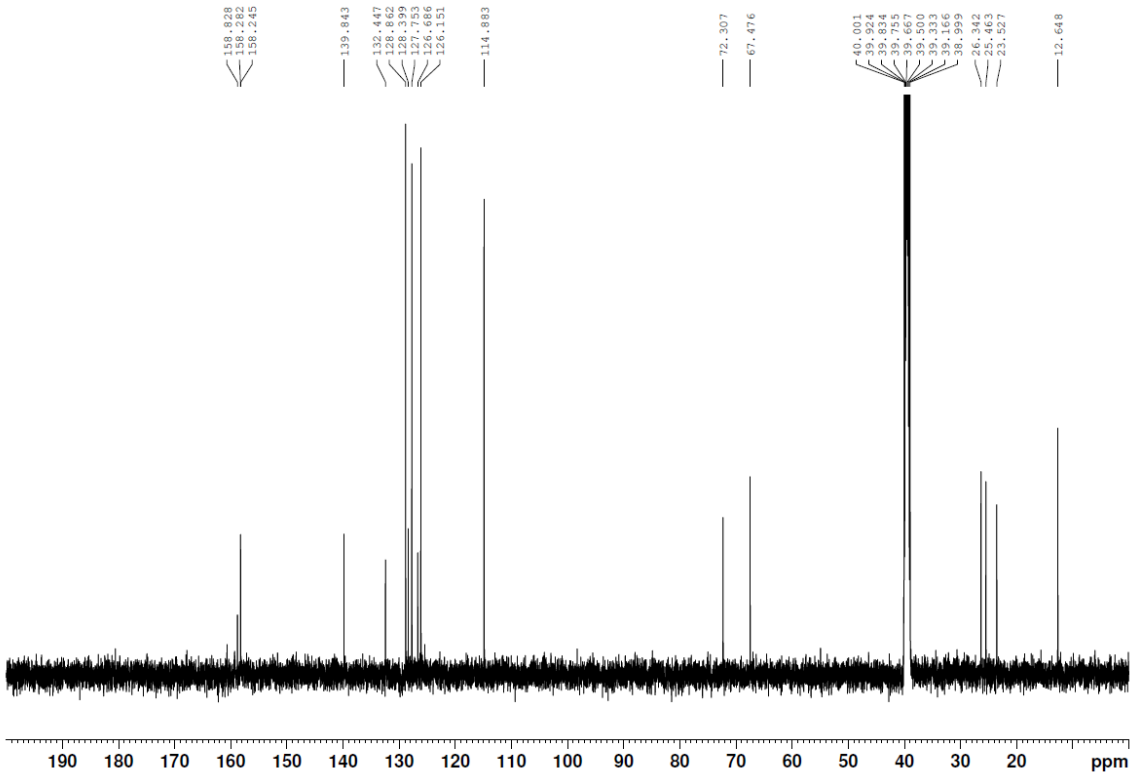

Figure S11. ^{13}C NMR spectrum of compound 17.

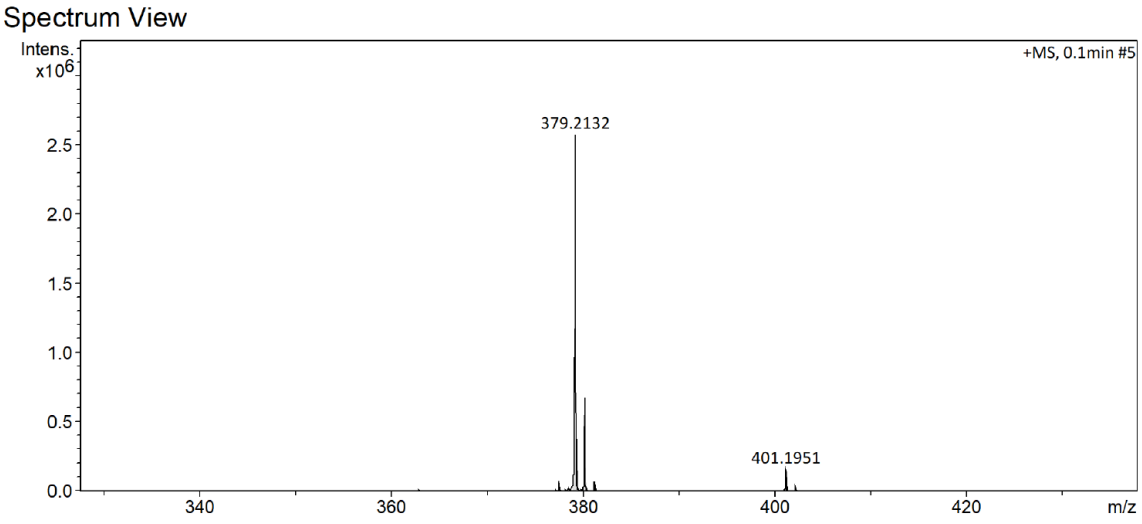

Figure S12. HRMS spectrum of compound 17.

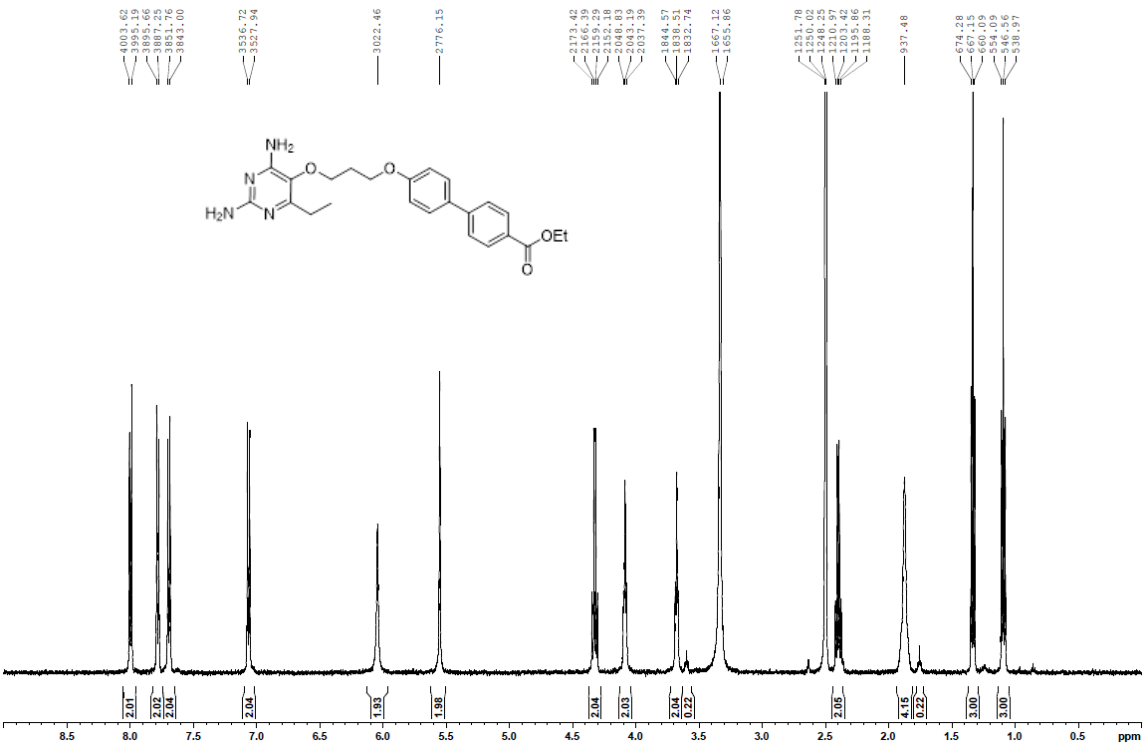

Figure S13. ^{1}H NMR spectrum of compound 18.

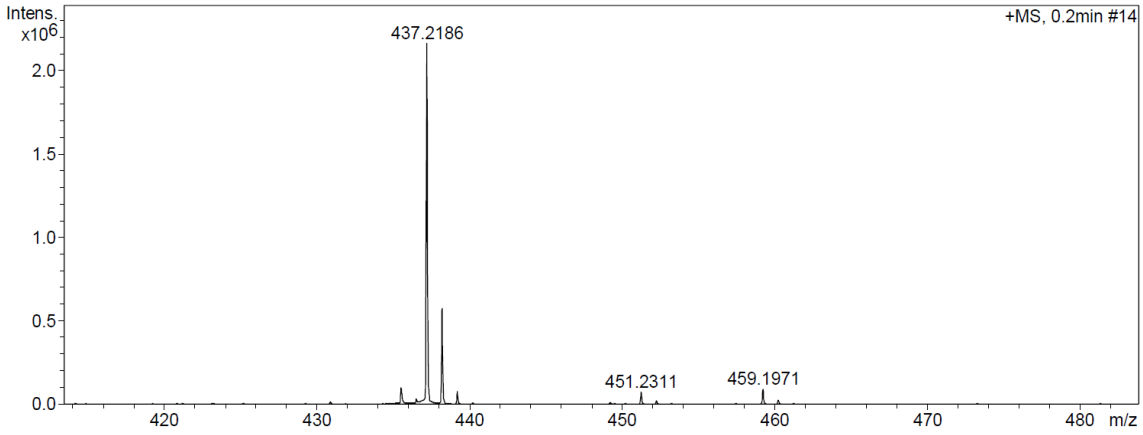

Figure S14. HRMS spectrum of compound 18.

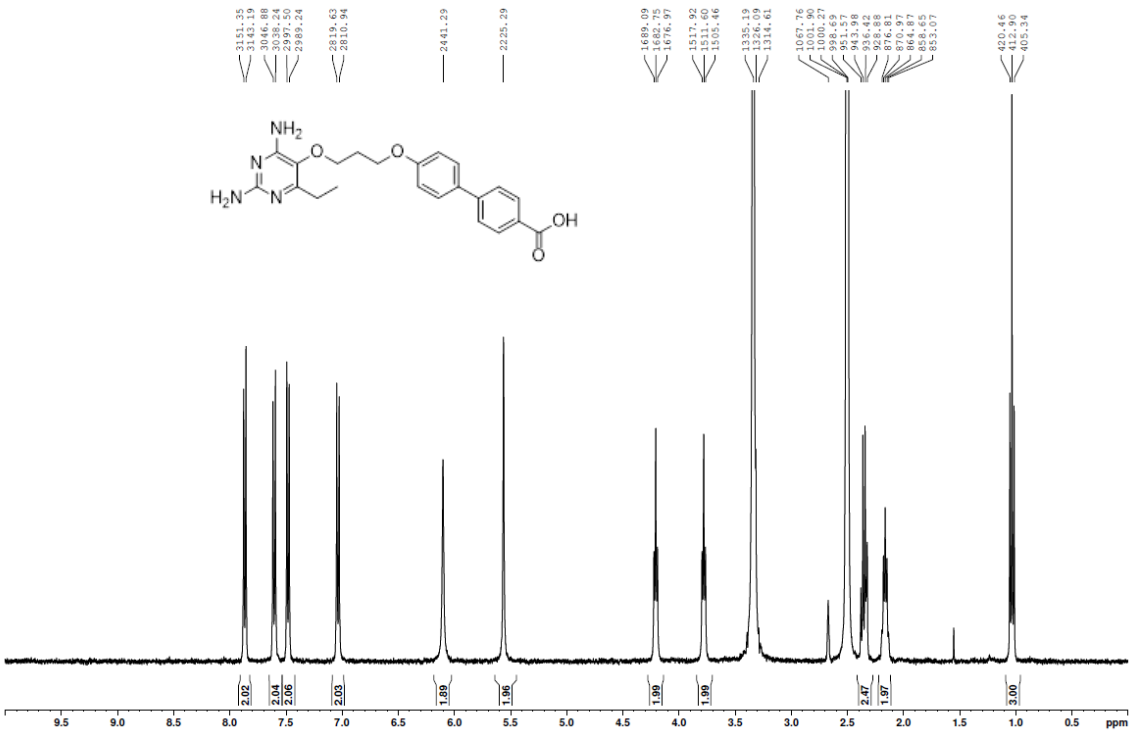

Figure S15. ^{1}H NMR spectrum of compound 19.

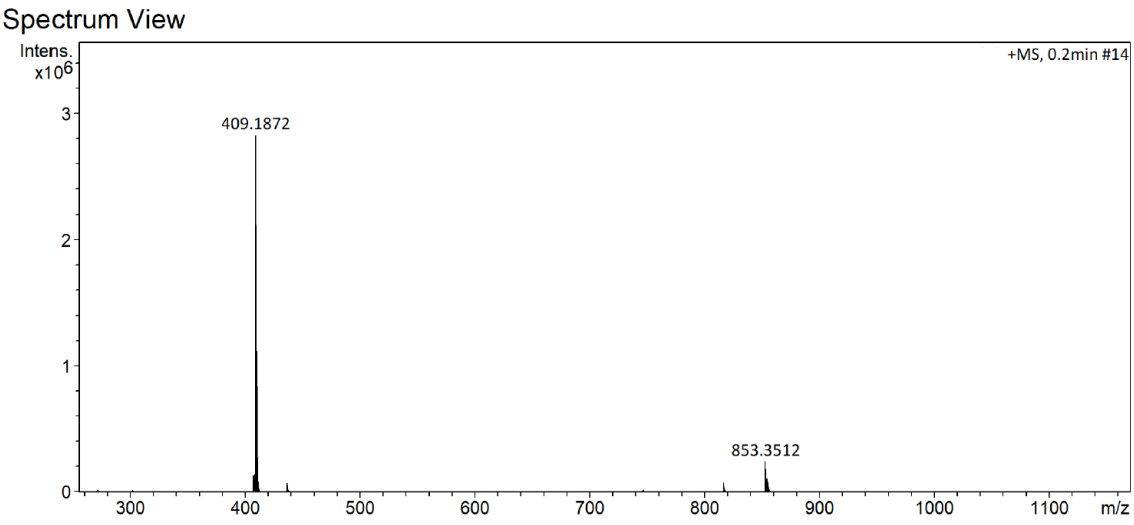

Figure S16. HRMS spectrum of compound 19.

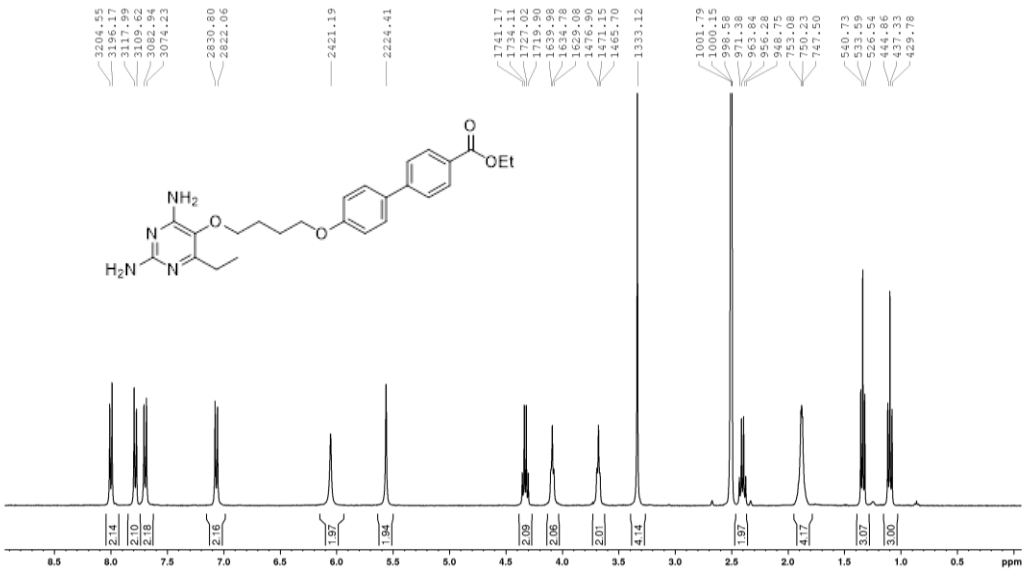

Figure S17. ^{1}H NMR spectrum of compound 20.

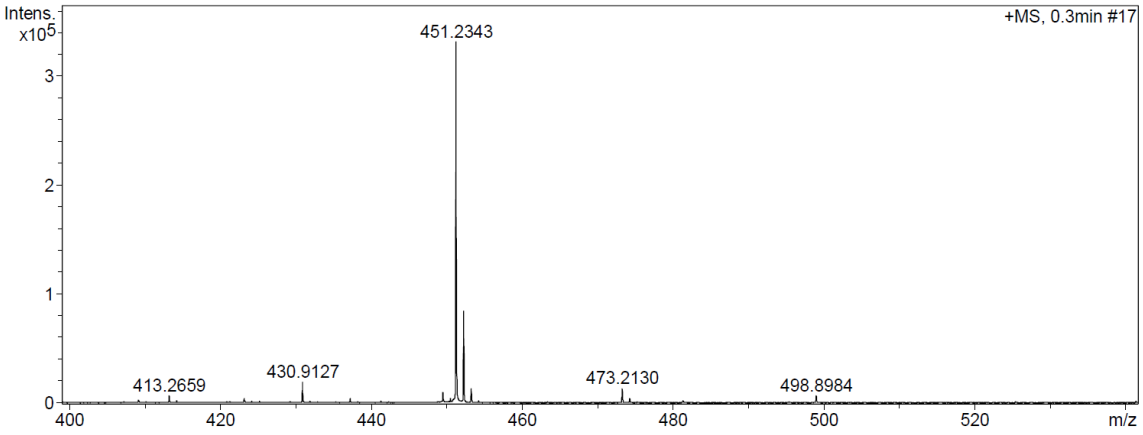

Figure S18. HRMS spectrum of compound 20.

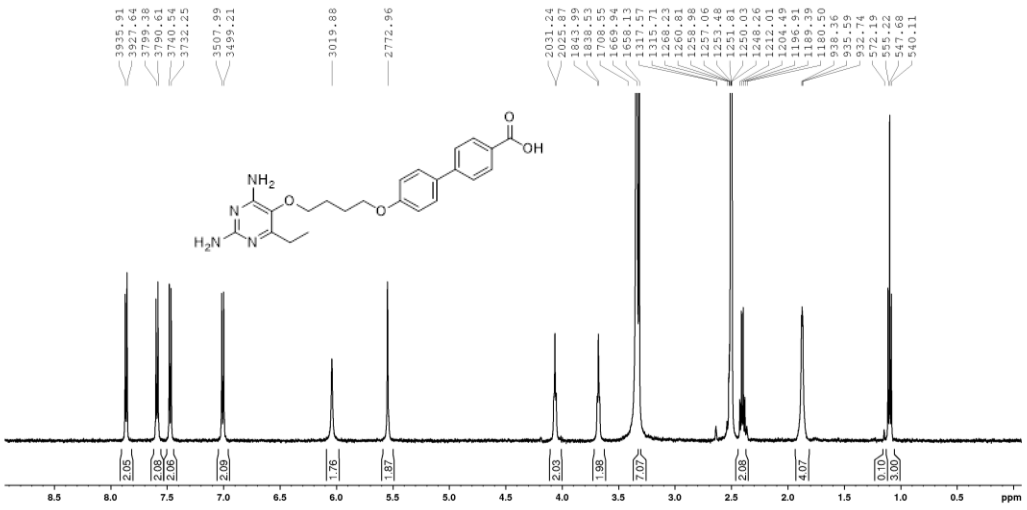

Figure S19. ^{1}H NMR spectrum of compound 21.

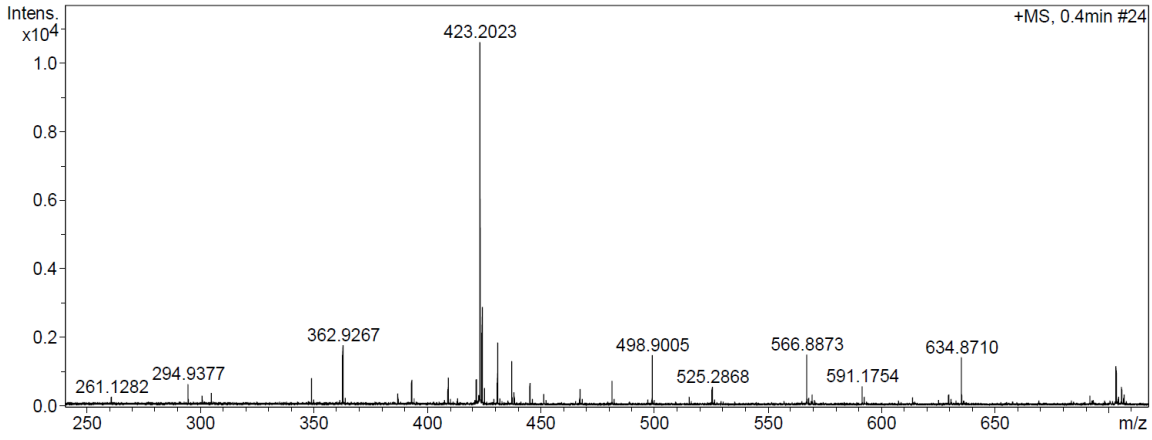

Figure S20. HRMS spectrum of compound 21.

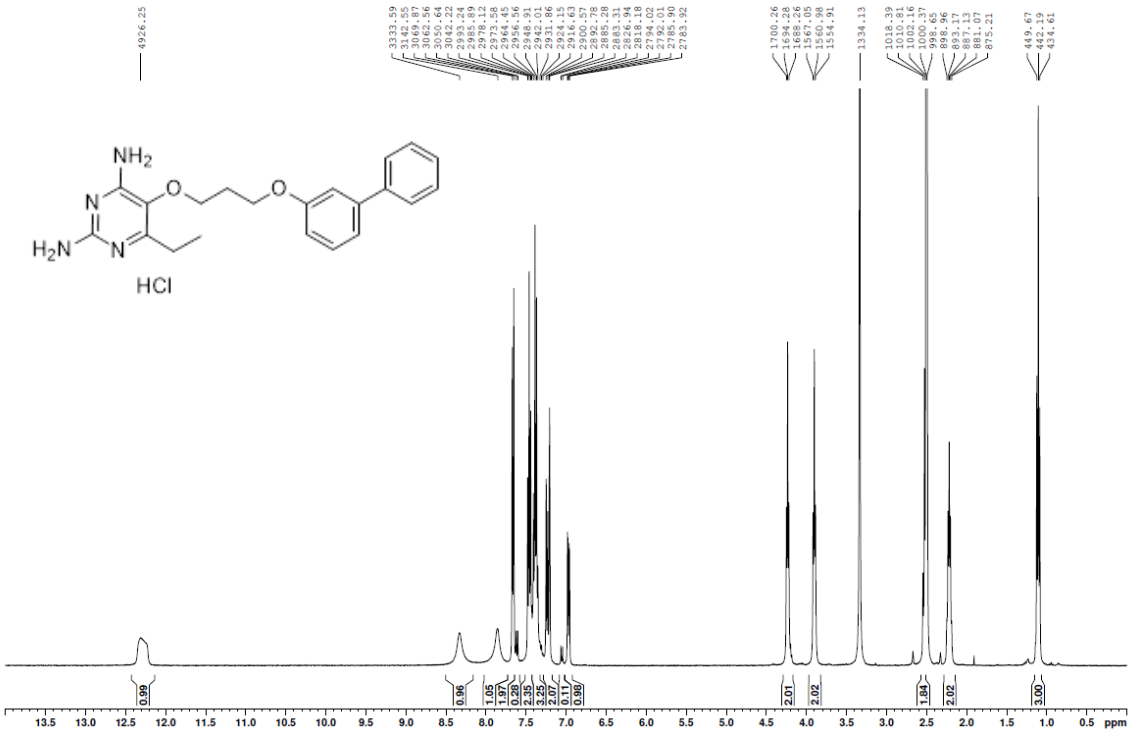

Figure S21. ^{1}H NMR spectrum of compound FB1.

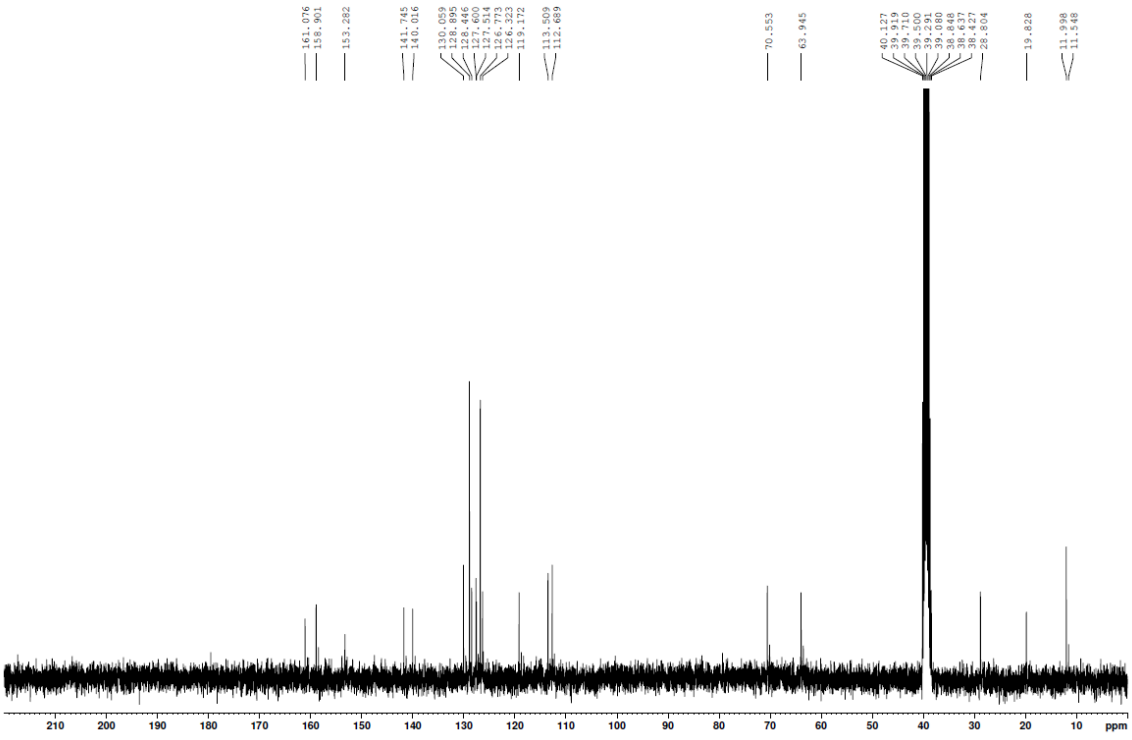

Figure S22. ^{13}C NMR spectrum of compound FB1.

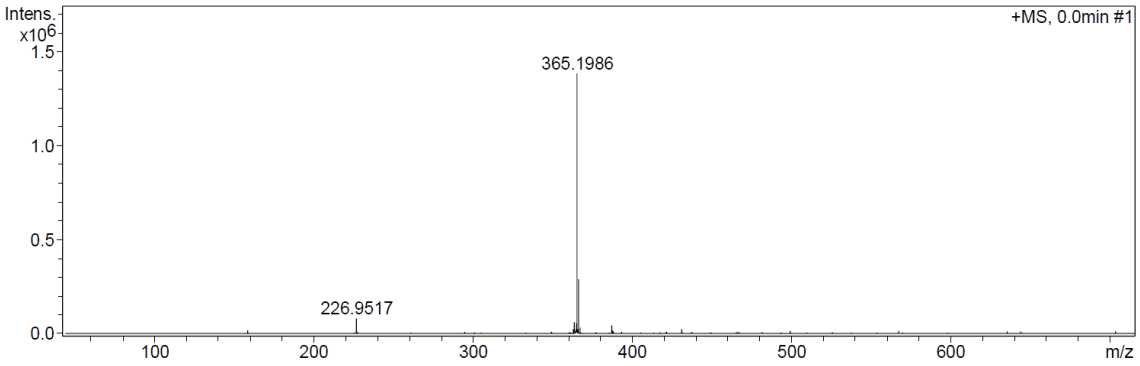

Figure S23. HRMS spectrum of compound FB1.

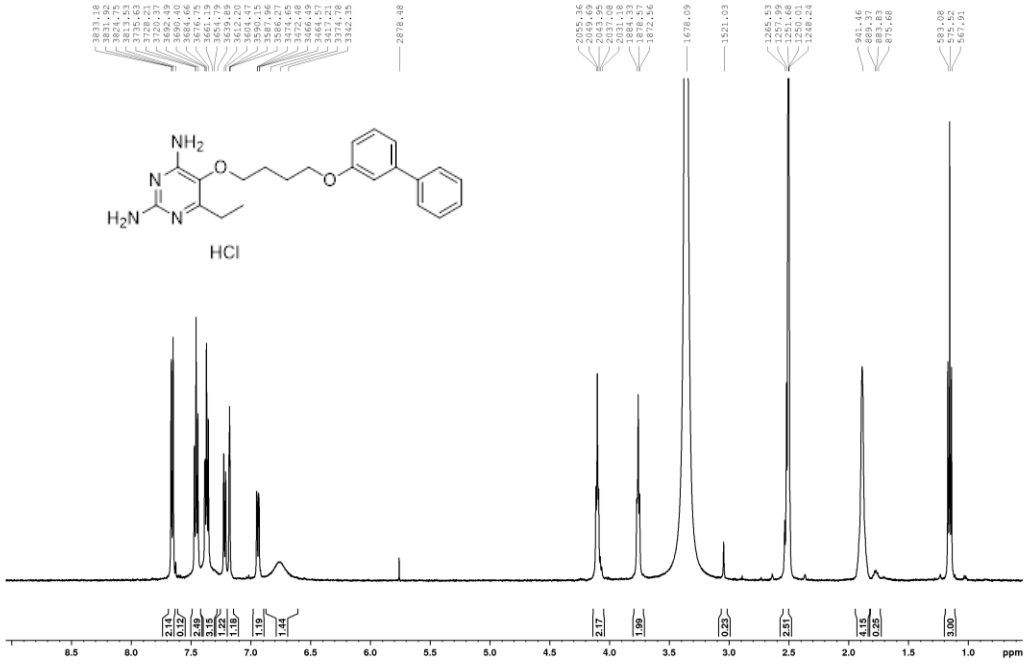

Figure S24. ^{1}H NMR spectrum of compound FB2.

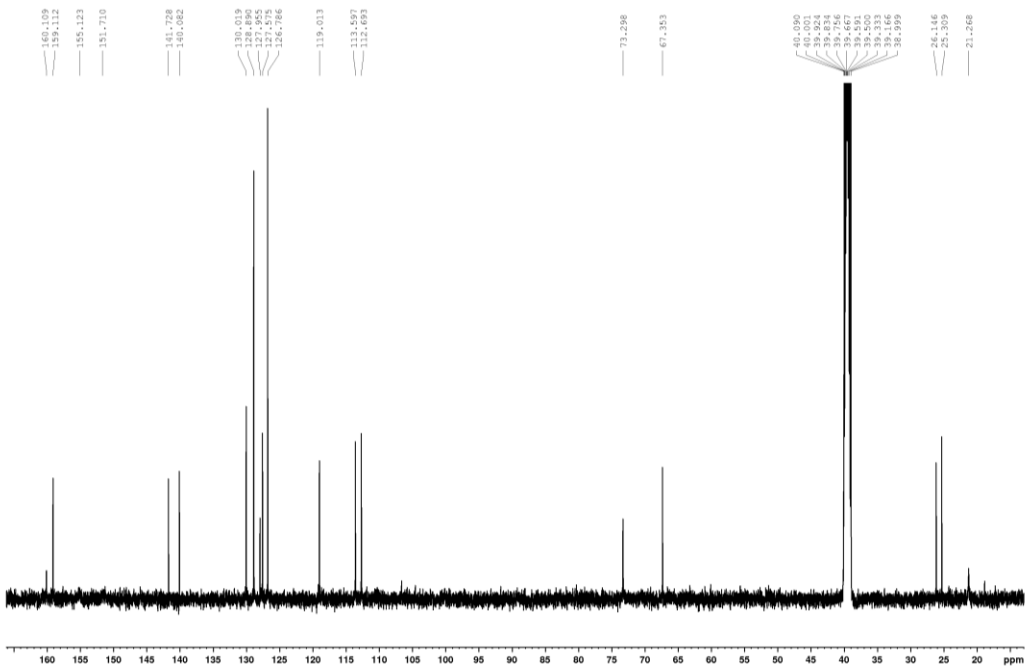

Figure S25. ^{13}C NMR spectrum of compound FB2.

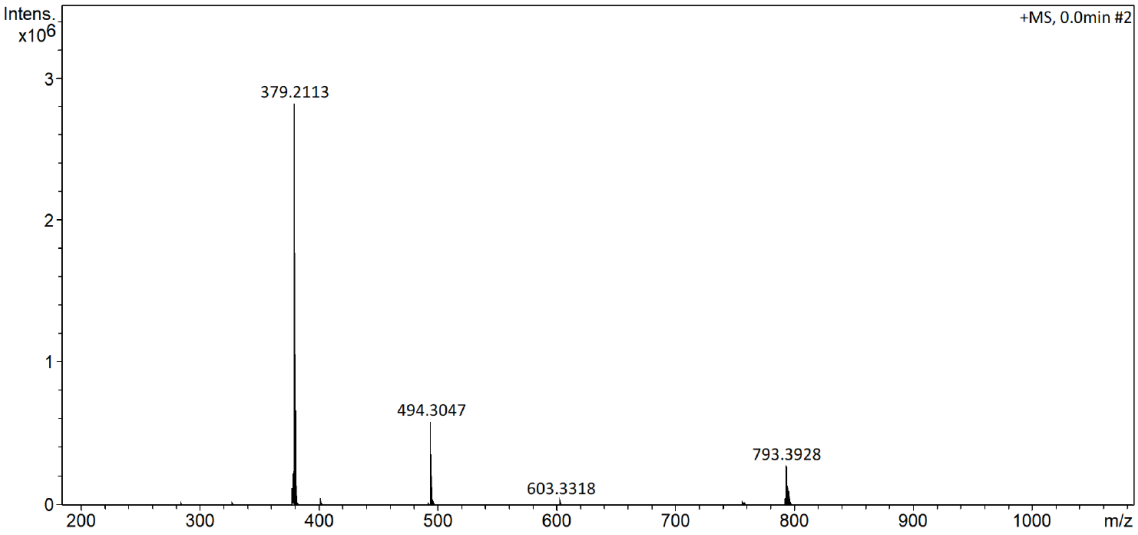

Figure S26. HRMS spectrum of compound FB2.

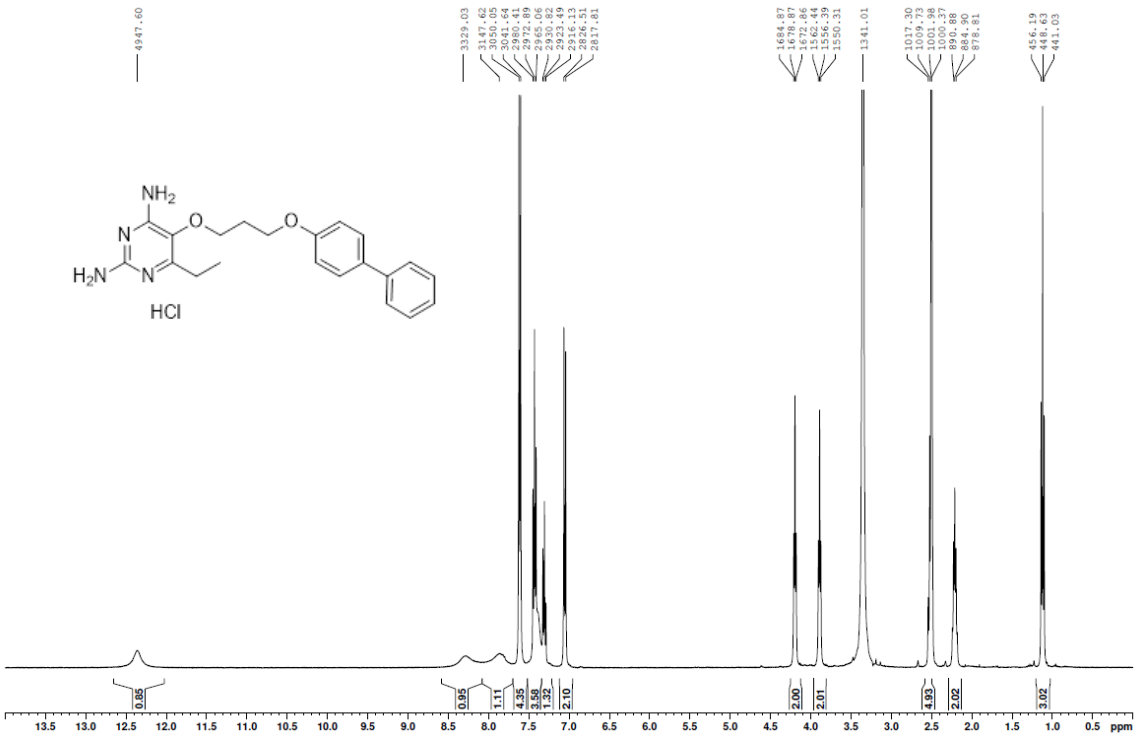

Figure S27. ^{1}H NMR spectrum of compound FB3.

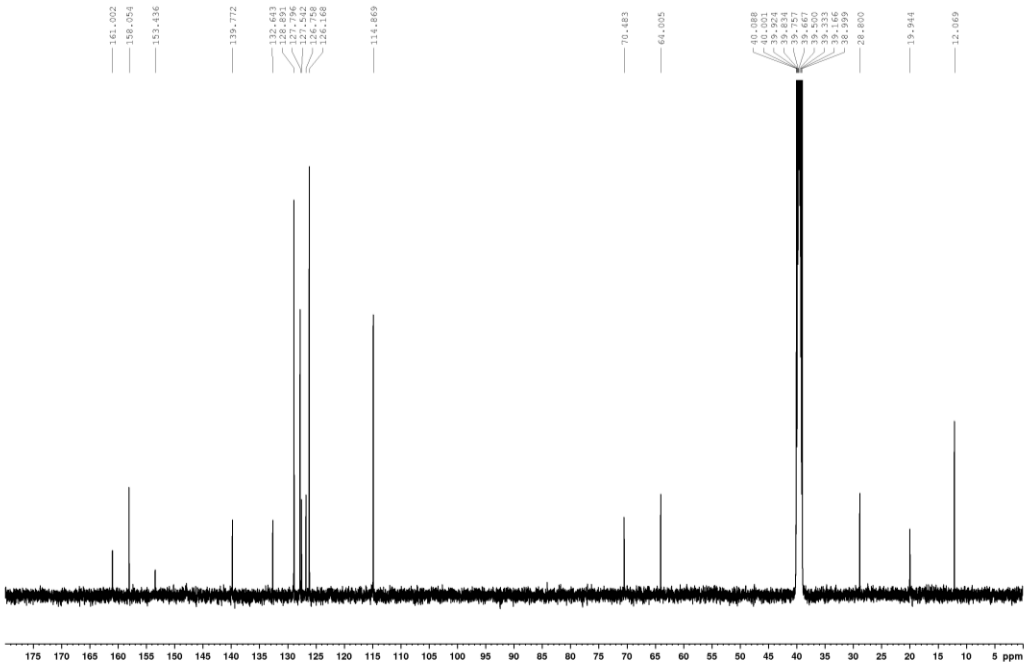

Figure S28. ^{13}C NMR spectrum of compound FB3.

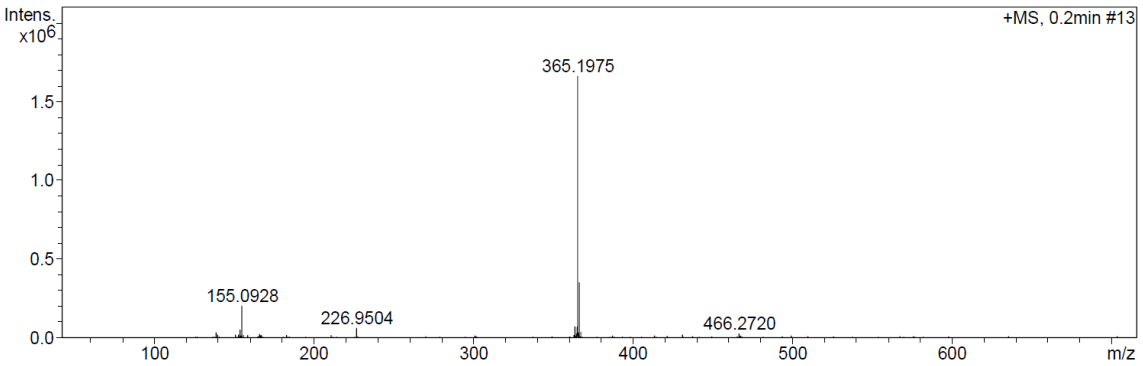

Figure S29. HRMS spectrum of compound FB3.

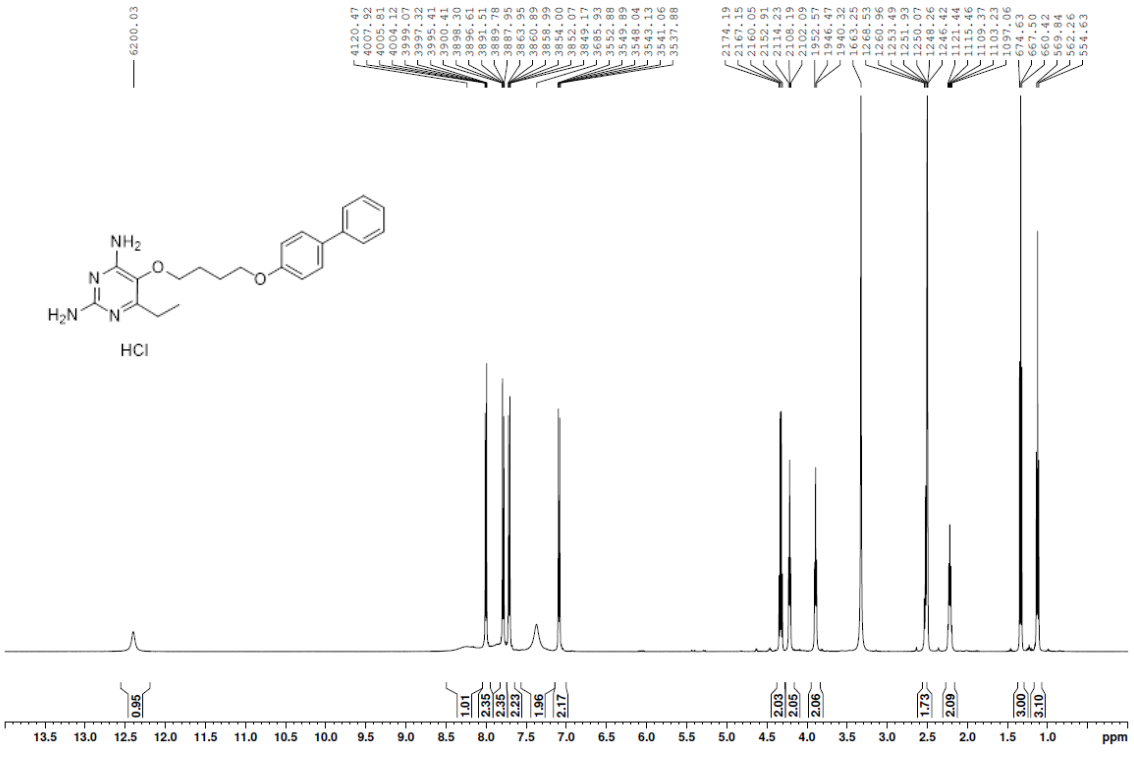

Figure S30. ^{1}H NMR spectrum of compound FB4.

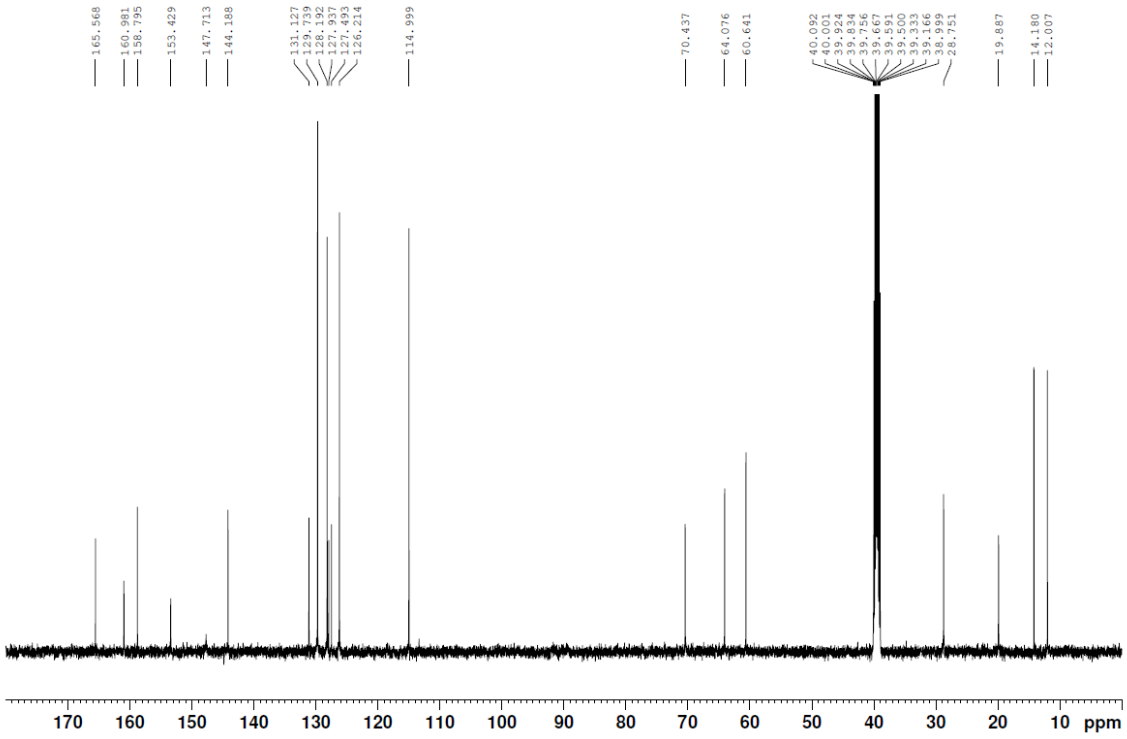

Figure S31. ^{13}C NMR spectrum of compound FB4.

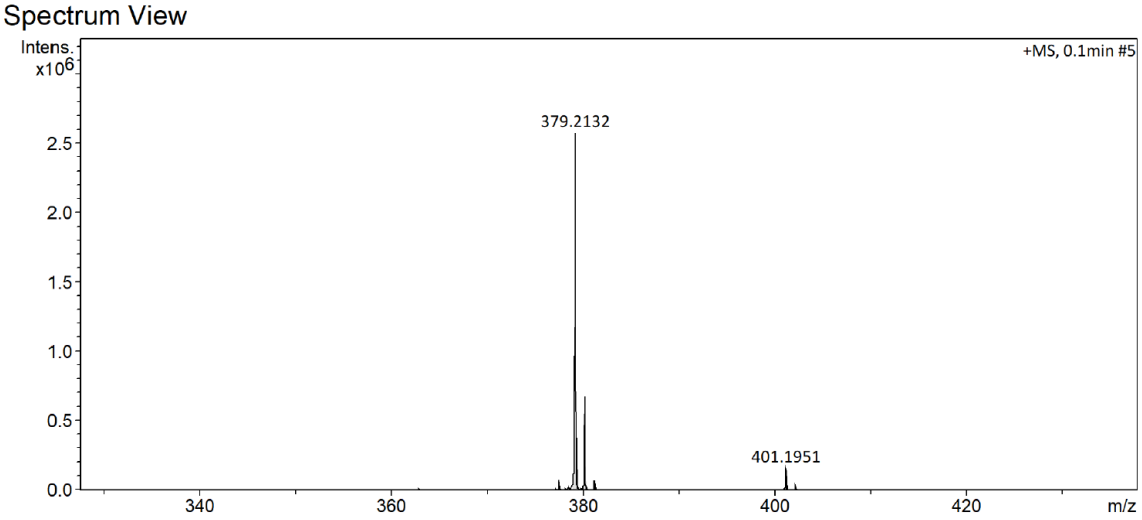

Figure S32. HRMS spectrum of compound FB4.

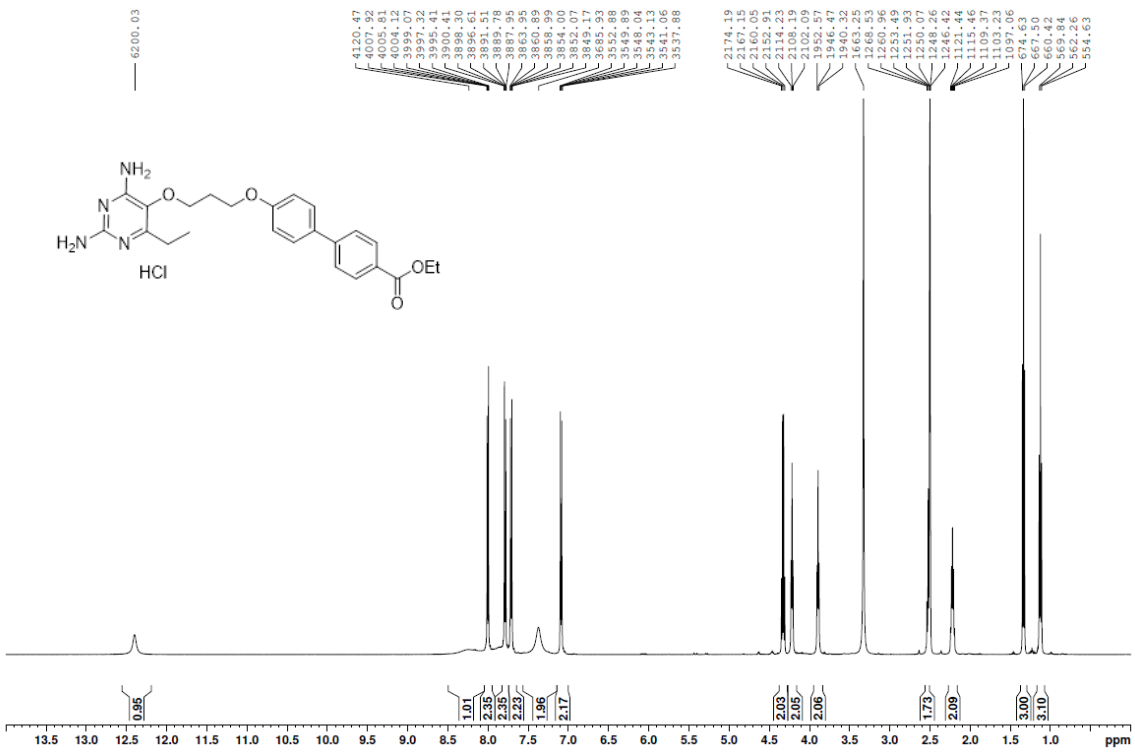

Figure S33. ^{1}H NMR spectrum of compound FB5.

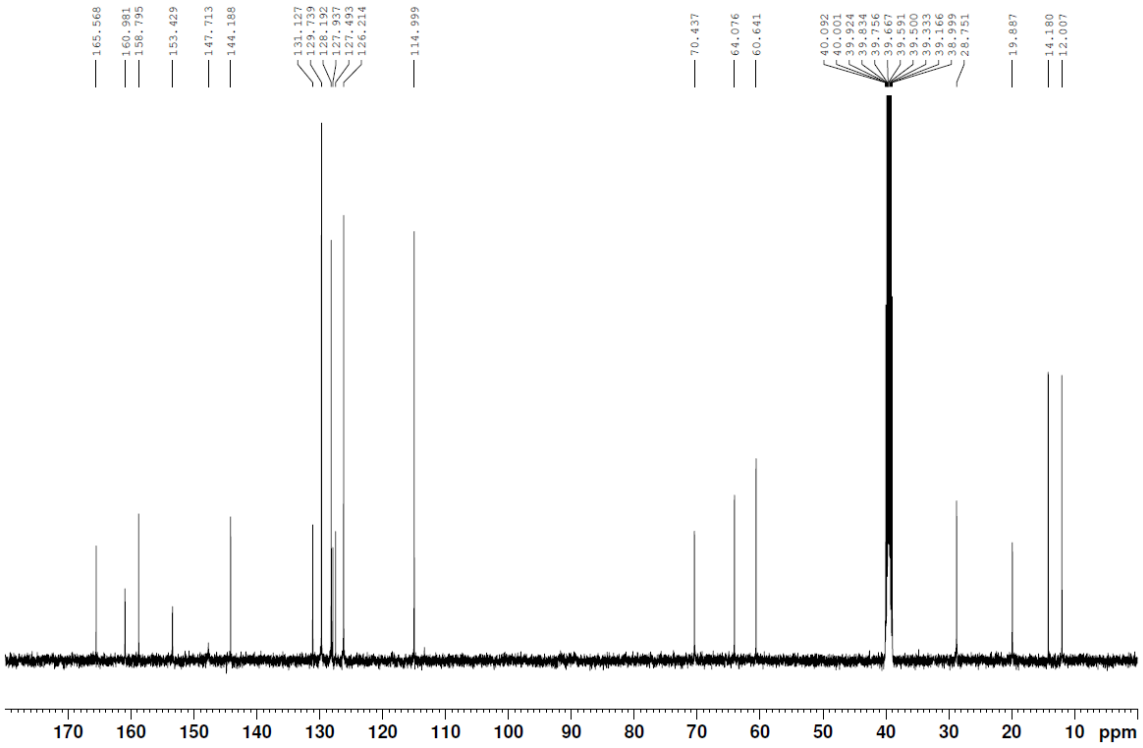

Figure S34. ^{13}C NMR spectrum of compound FB5.

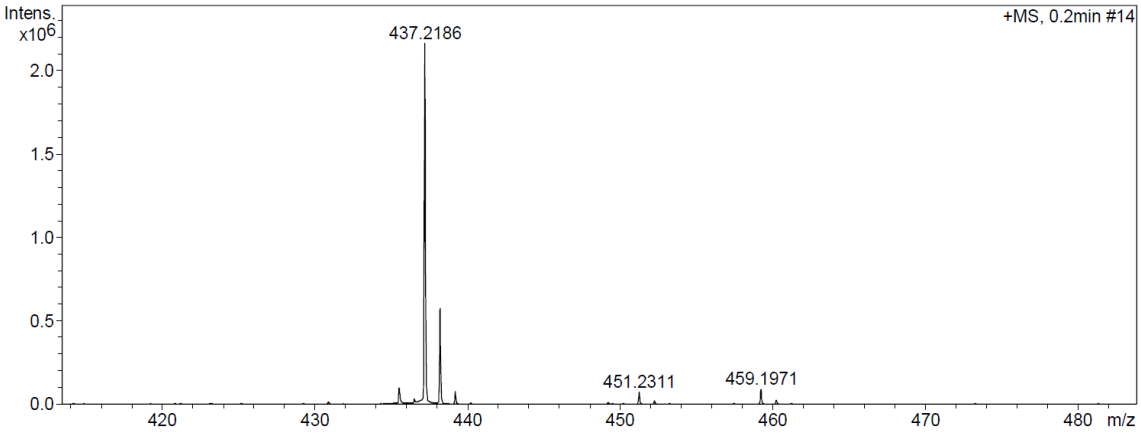

Figure S35. HRMS spectrum of compound FB5.

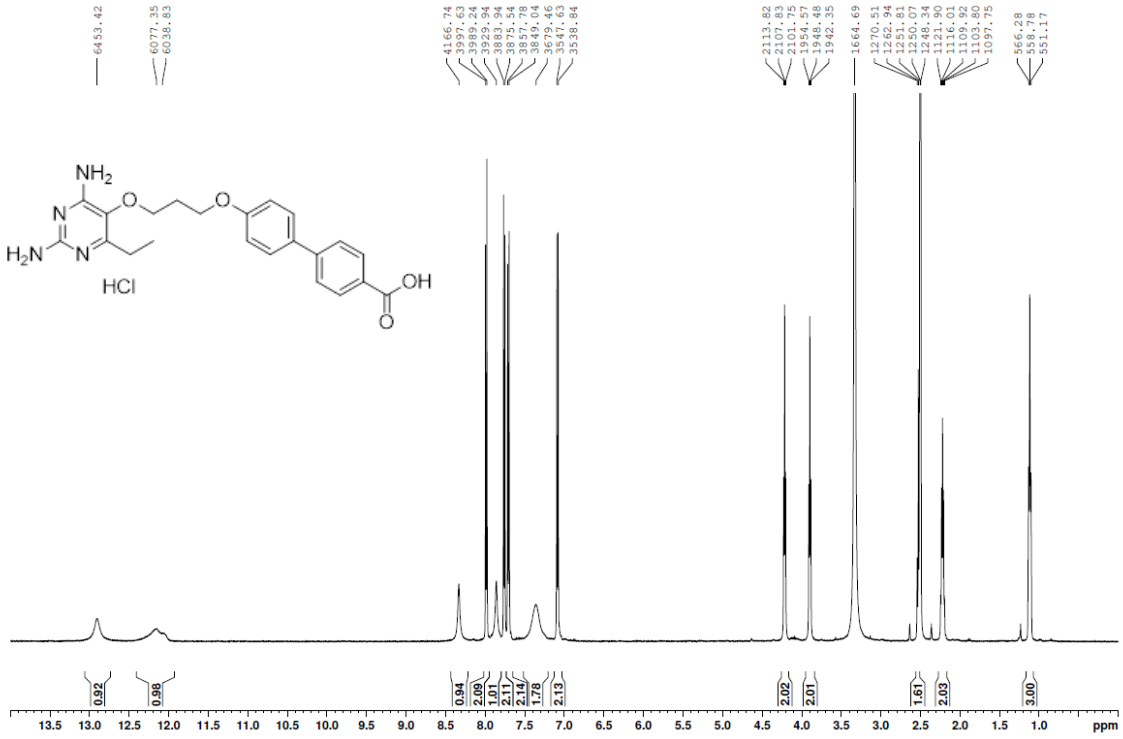

Figure S36. ^{1}H NMR spectrum of compound FB6.

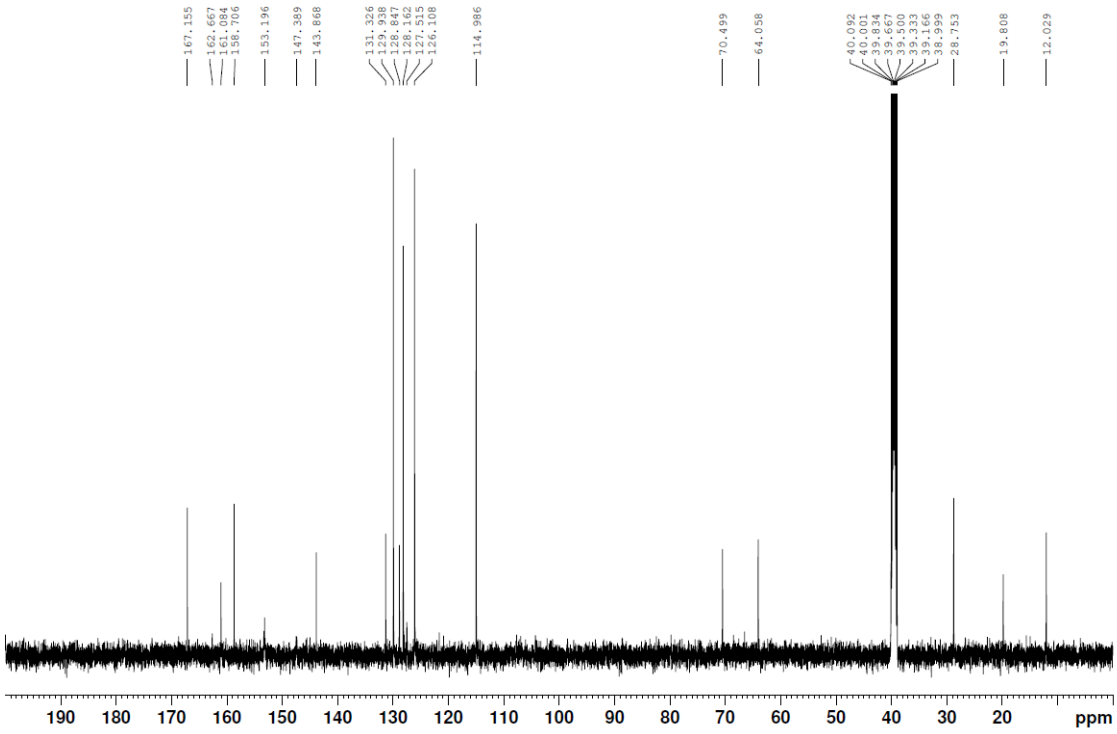

Figure S37. ^{13}C NMR spectrum of compound FB6.

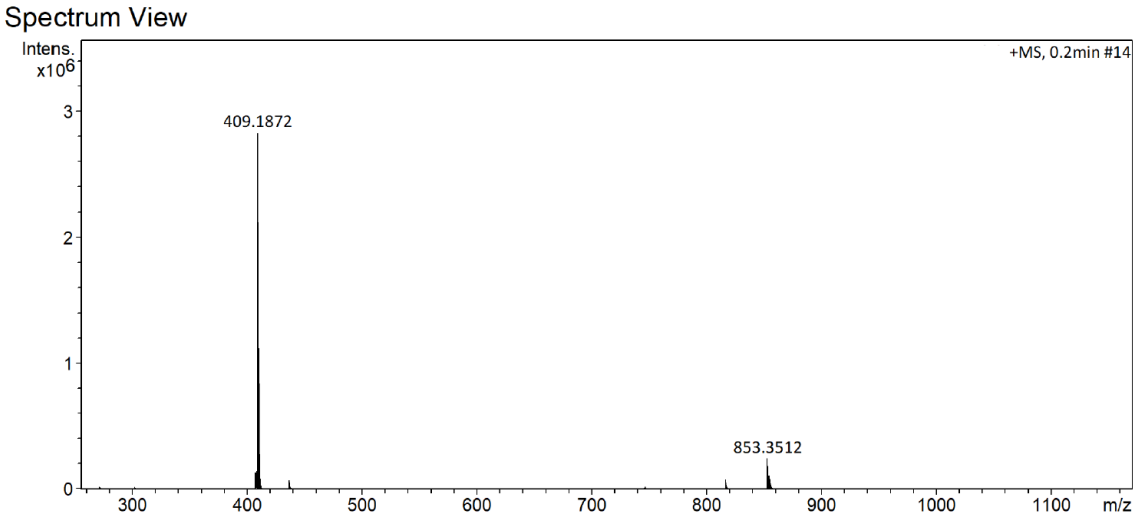

Figure S38. HRMS spectrum of compound FB6.

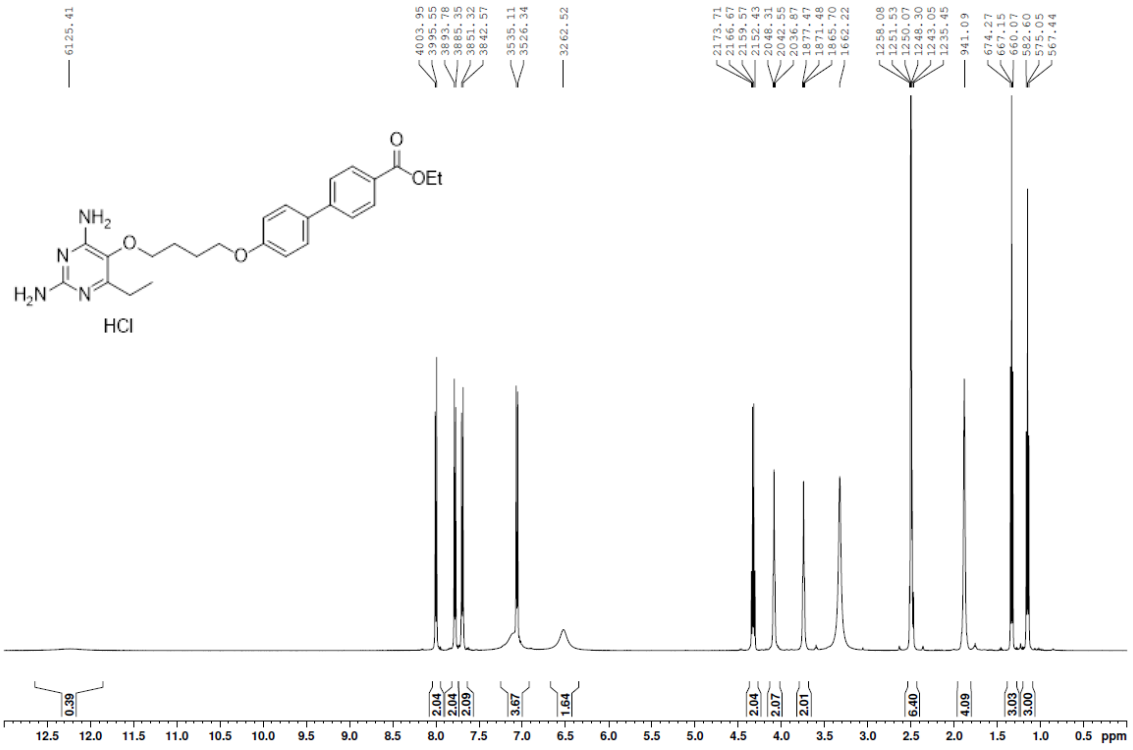

Figure S39. ^{1}H NMR spectrum of compound FB7.

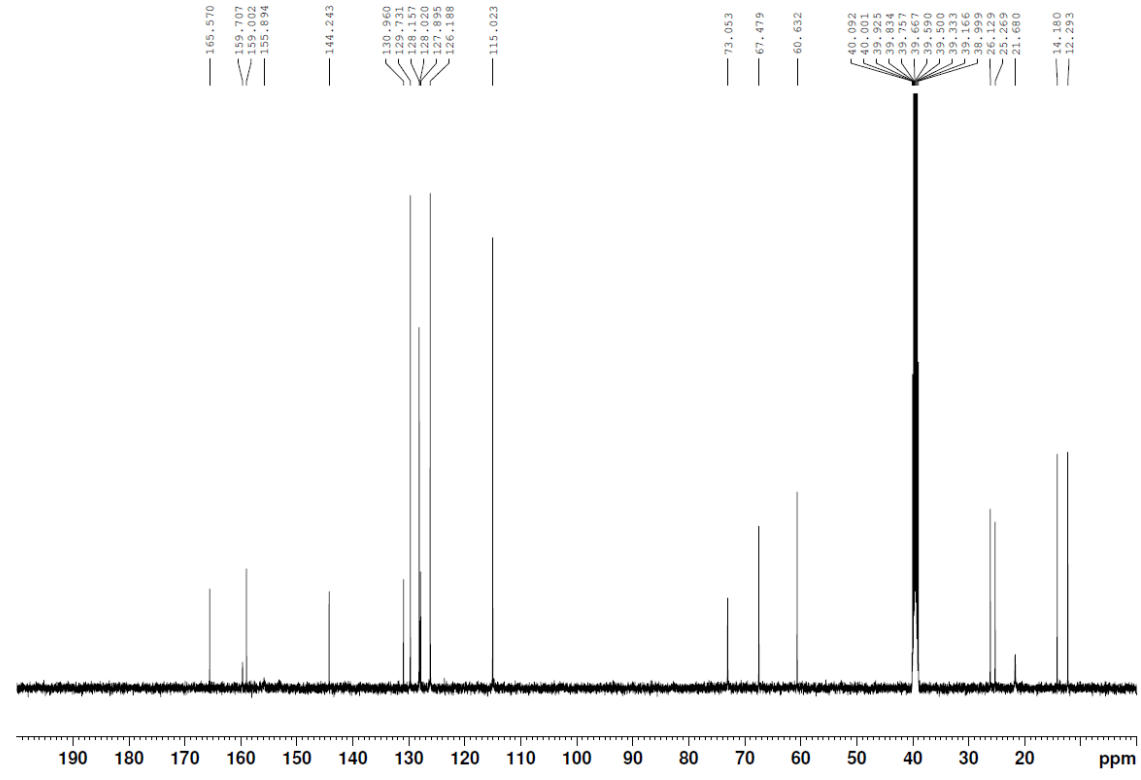

Figure S40. ^{13}C NMR spectrum of compound FB7.

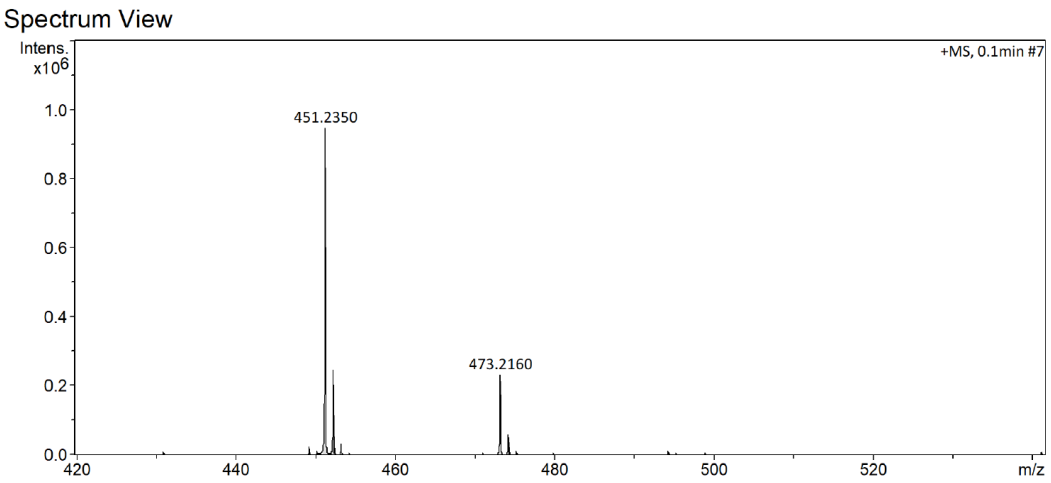

Figure S41. HRMS spectrum of compound FB7.

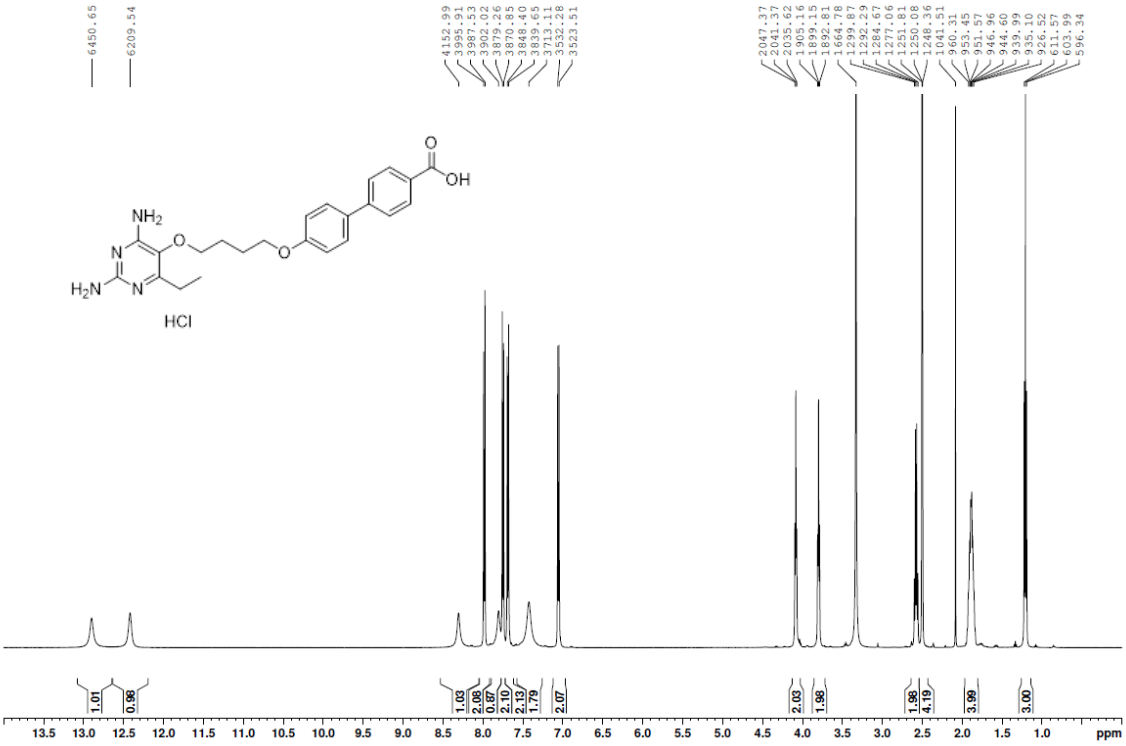

Figure S42. ^{1}H NMR spectrum of compound FB8.

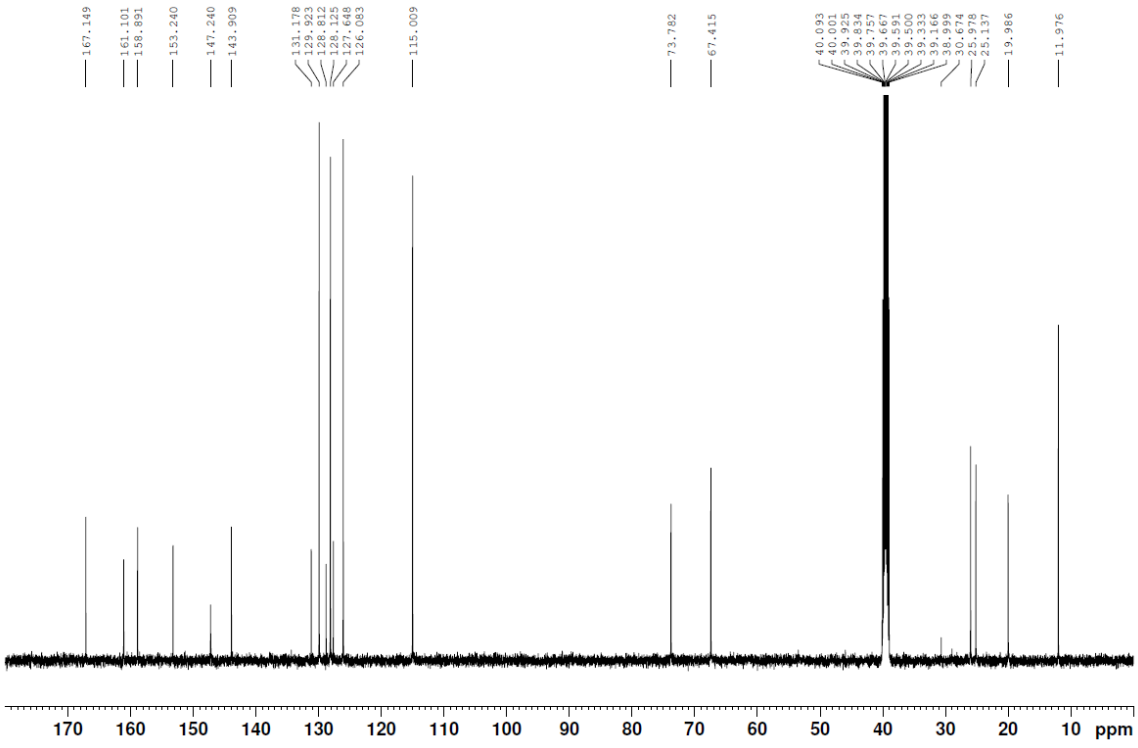

Figure S43. ^{13}C NMR spectrum of compound FB8.

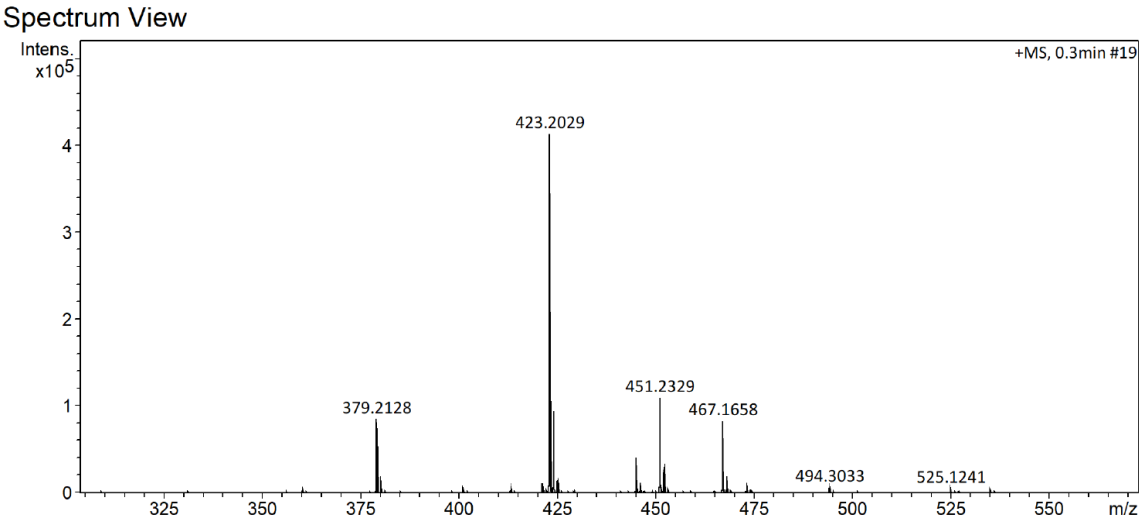

Figure S44. HRMS spectrum of compound FB8.