Electronic Supplementary Material (ESI) for RSC Advances.

Quinoline-triazole hybrids inhibit falcipain-2 and arrest the development of *Plasmodium falciparum* at the trophozoite stage

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Spectral data of the synthesized compounds

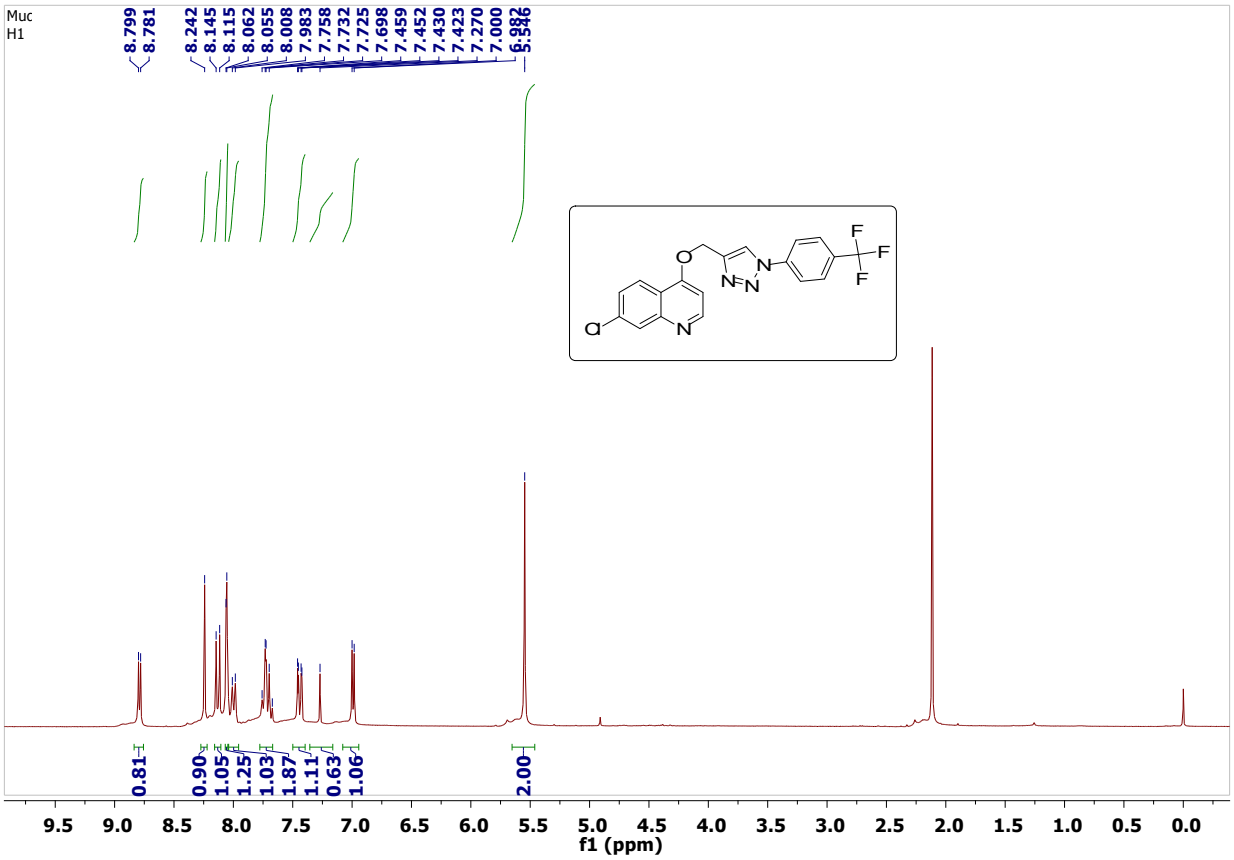


Figure S1: ^{1}H NMR spectrum of Molecule (T1)

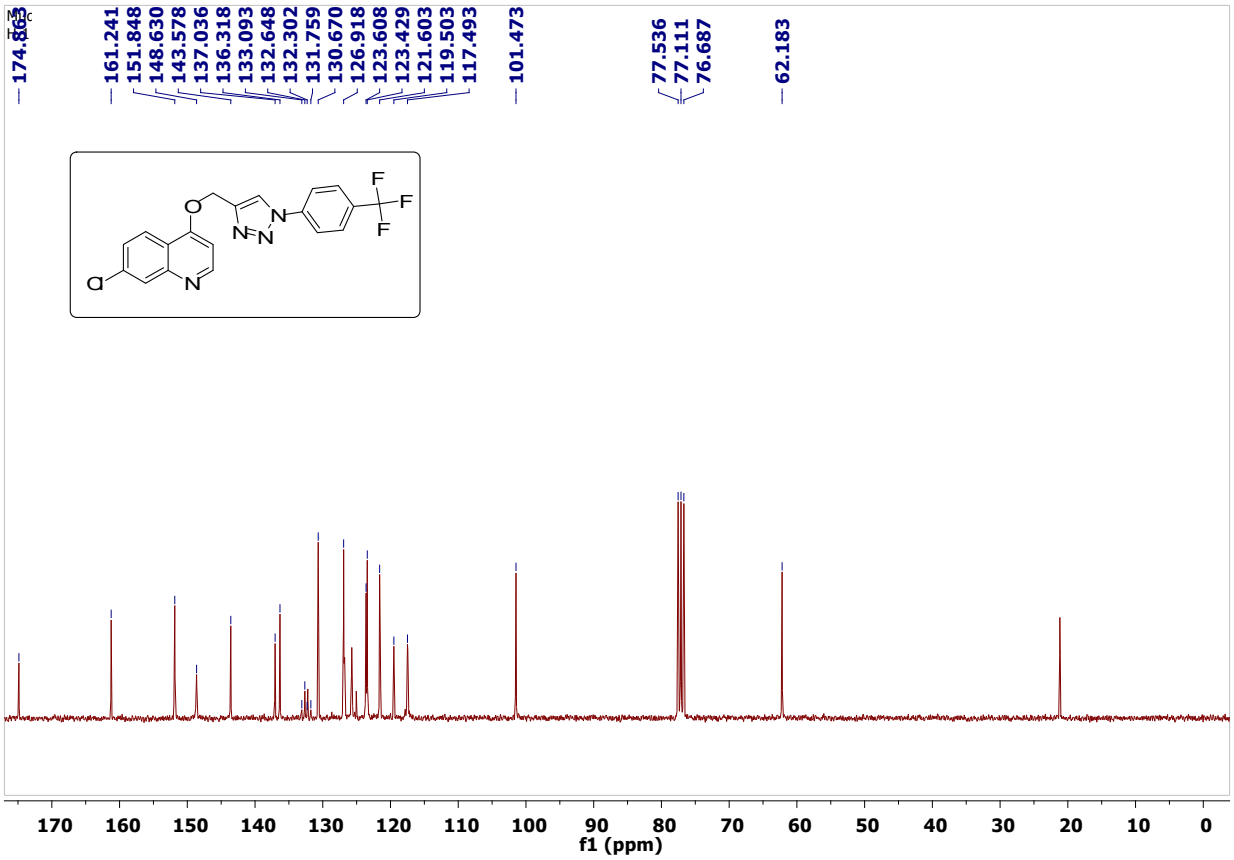


Figure S2: ^{13}C NMR spectrum of Molecule (T1)

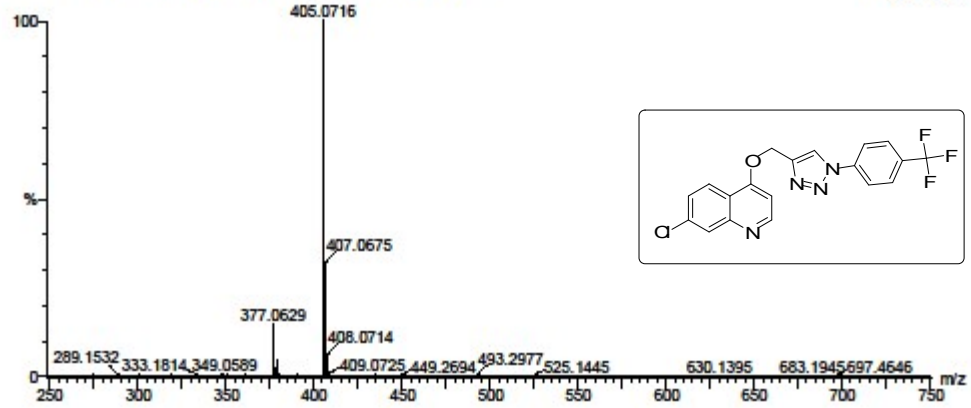
Elemental Composition Report Page 1

Single Mass Analysis

Tolerance = 50.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
62 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 17-20 H: 10-15 N: 0-4 O: 0-1 F: 0-3 Cl: 0-1

Sample Name : C1 INDIAN INSTITUTE OF TECHNOLOGY XEVO G2-XS QTOF
Test Name : HRMS-1 ROPAR
101117-C1-- 2 (0.045) AM (Tbp,4, Ar,10000.0,0.00,0.00); Cm (2:8) 1: TOF MS ES+
3.24e+007



Minimum:				-1.5				
Maximum:		5.0	50.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
405.0716	405.0730	-1.4	-3.5	13.5	536.4	n/a	n/a	C19 H13 N4 O F3 Cl

Figure S3: Mass spectrum of Molecule (T1)

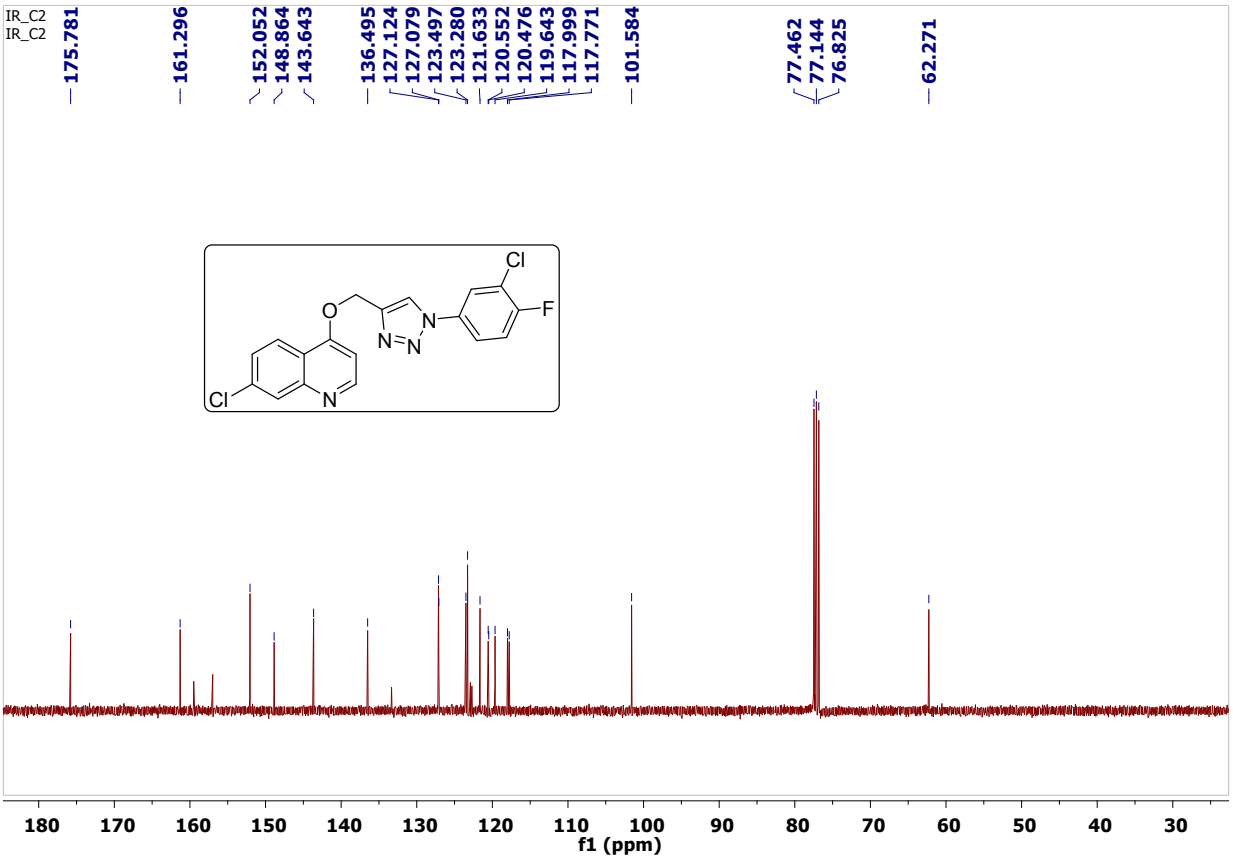


Figure S4: ^{13}C NMR spectrum of Molecule (T2)

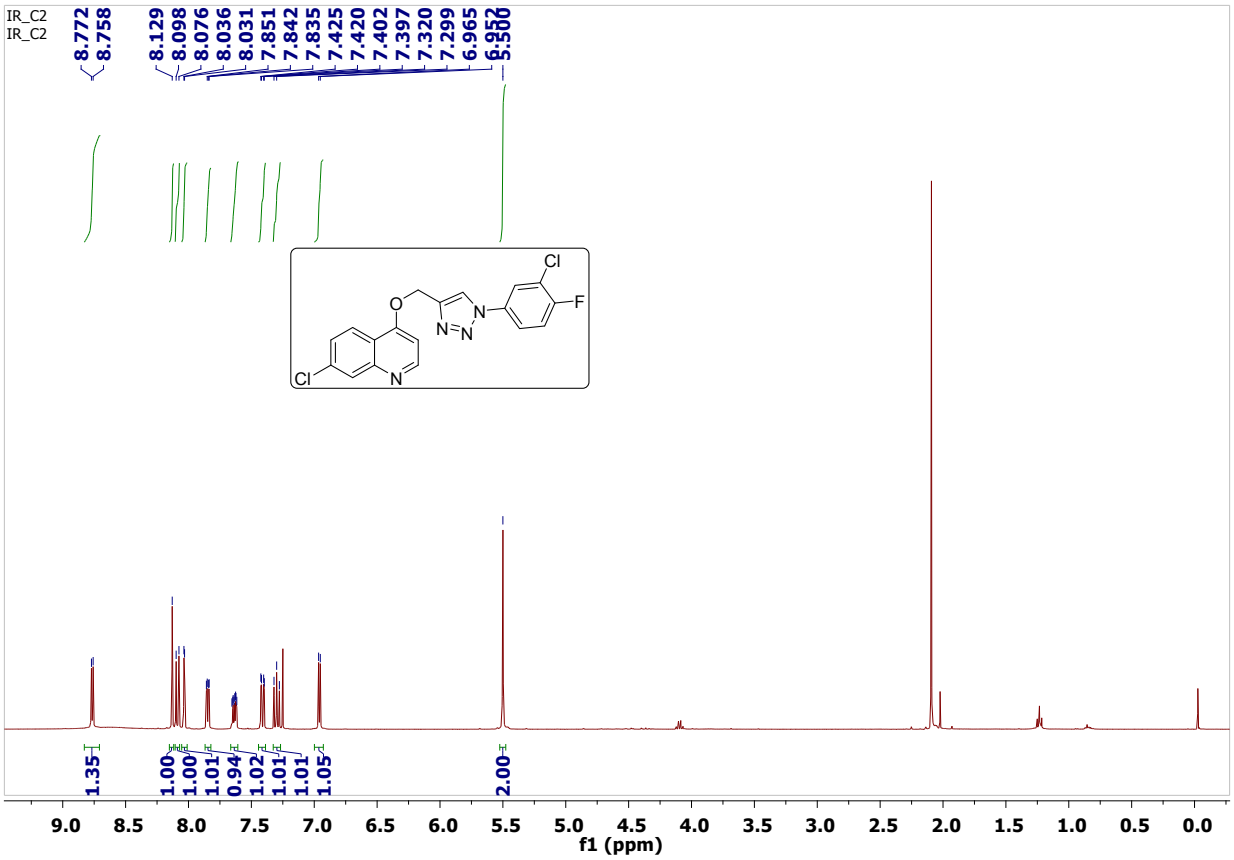


Figure S5: ^{1}H NMR spectrum of Molecule (T2)

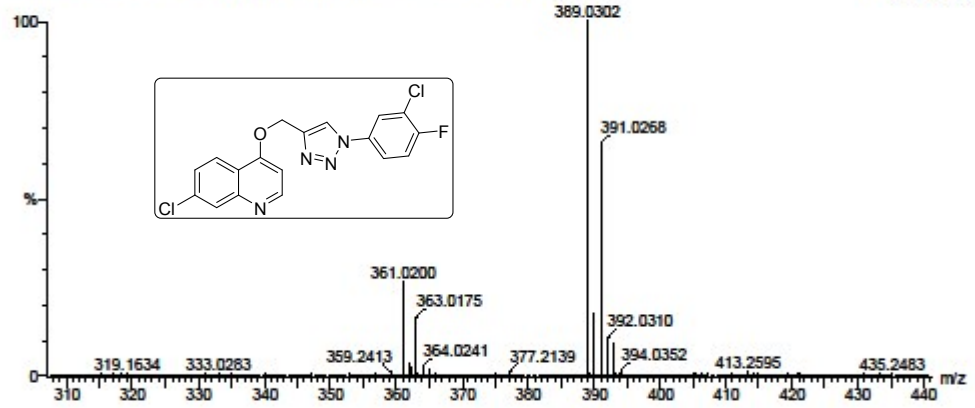
Elemental Composition Report Page 1

Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
39 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 11-16 N: 0-4 O: 0-1 F: 0-1 Cl: 0-2

Sample Name : 07-03-340-C2
Test Name : HRMS-1 ROPAR
141117-07-03-340-C2_- 8 (0.097) AM (Top,4, Ar,10000.0,0.00,0.00); Cm (8)

XEVO G2-XS QTOF
1: TOF MS ES+
1.02e+006



Minimum:				-1.5				
Maximum:		5.0	20.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
389.0302	389.0372	-7.0	-18.0	13.5	418.3	n/a	n/a	C18 H12 N4 O F Cl2

Figure S6: Mass spectrum of Molecule (T2)

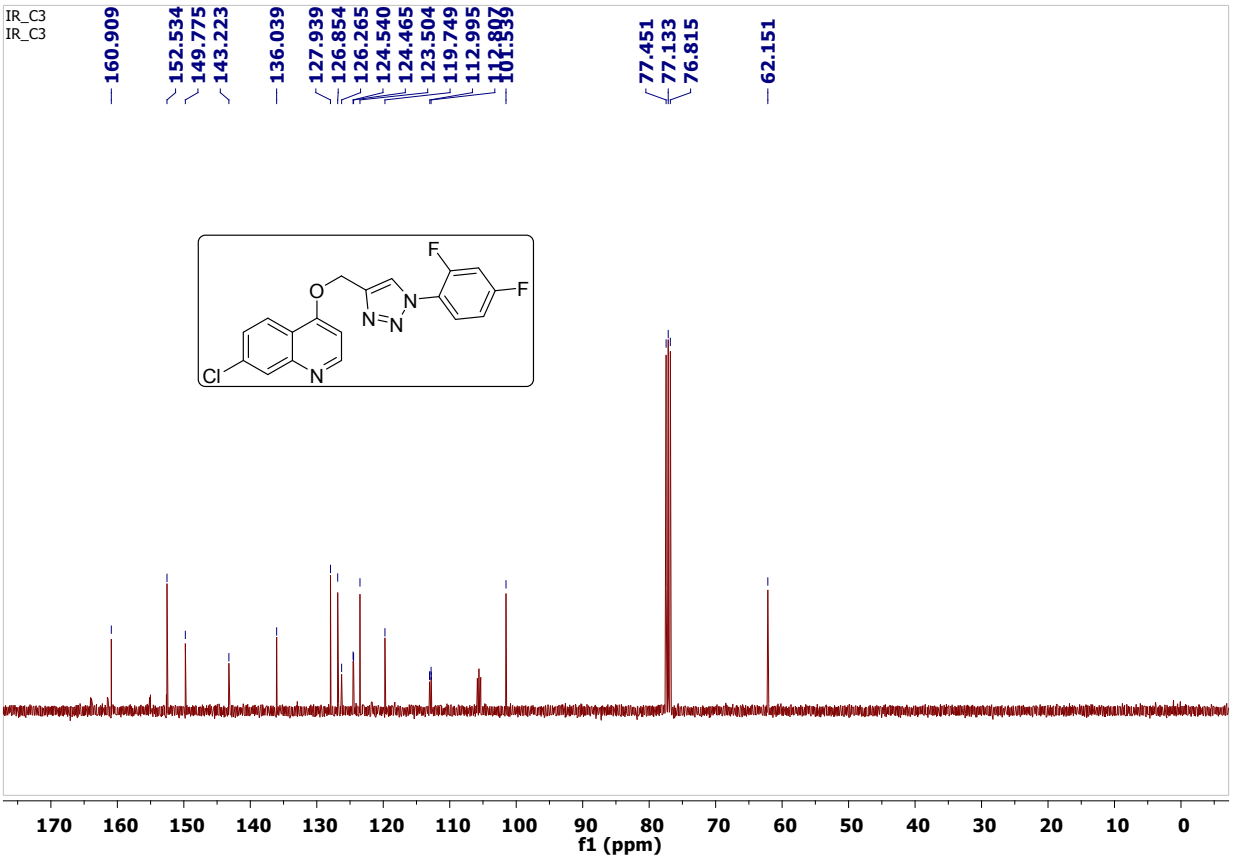


Figure S7: ^{13}C NMR spectrum of Molecule (T3)

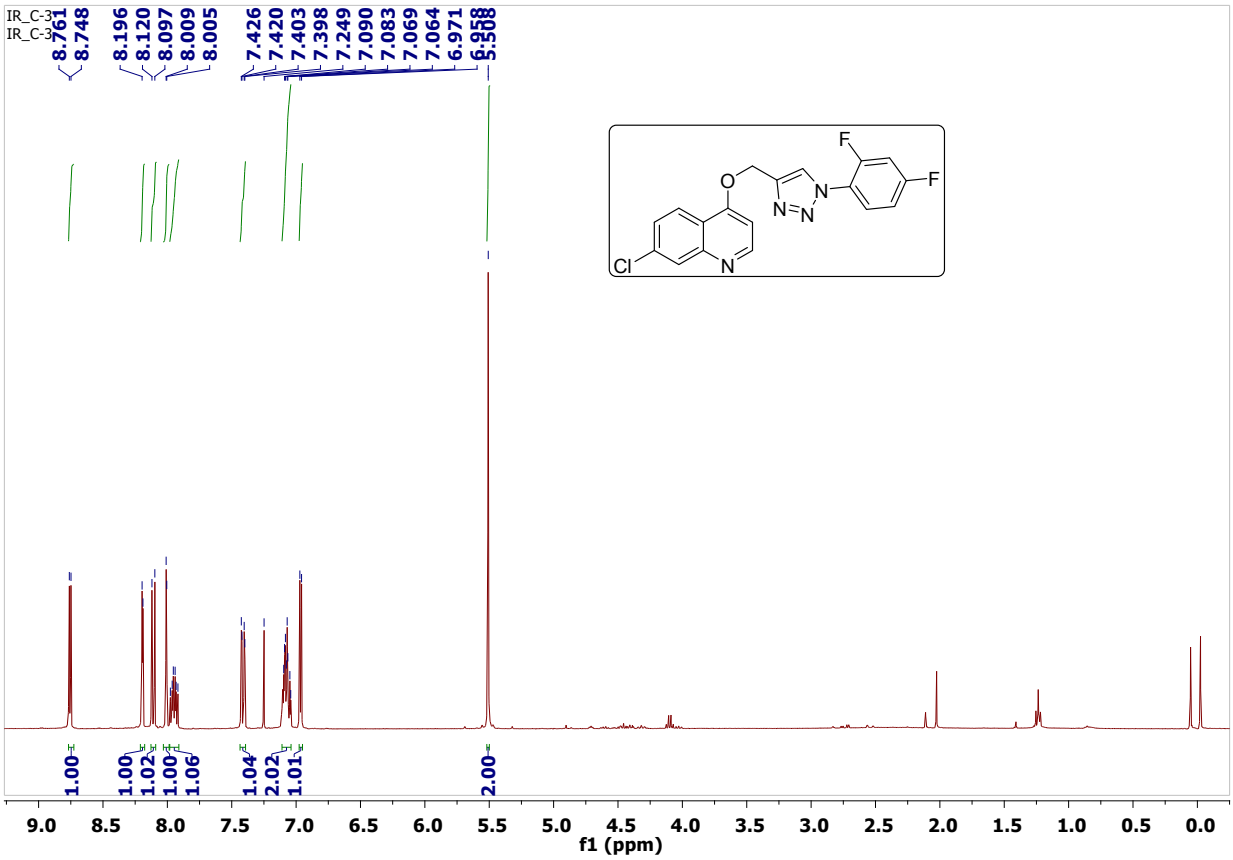


Figure S8: ^{1}H NMR spectrum of Molecule (T3)

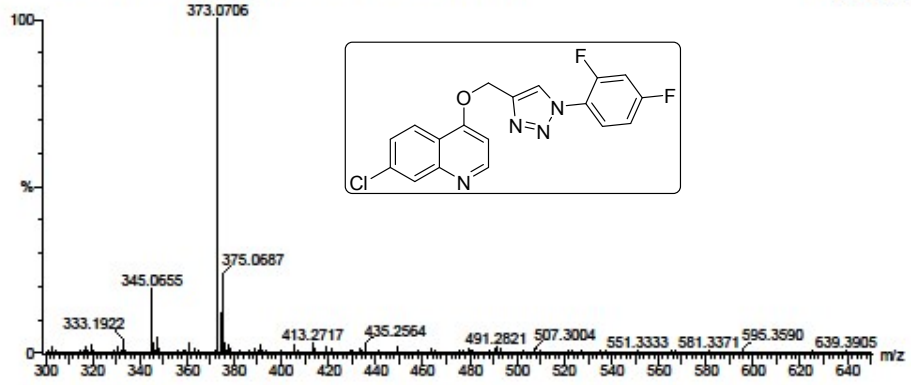
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
34 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 10-15 N: 0-4 O: 0-1 F: 0-2 Cl: 0-1

Sample Name : 07-03-312-C3
Test Name : HRMS-1 ROPAR
031117-07-03-312-C3_ 9 (0.117) AM2 (Ar,13000.0,0.00,0.00); Cm (9:12-17:24)

XEVO G2-XS QTOF
1: TOF MS ES+
6.48e+005



Minimum:				-1.5				
Maximum:		5.0	20.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
373.0706	373.0668	3.8	10.2	13.5	379.6	n/a	n/a	C18 H12 N4 O F2 Cl

Figure S9: Mass spectrum of Molecule (T3)

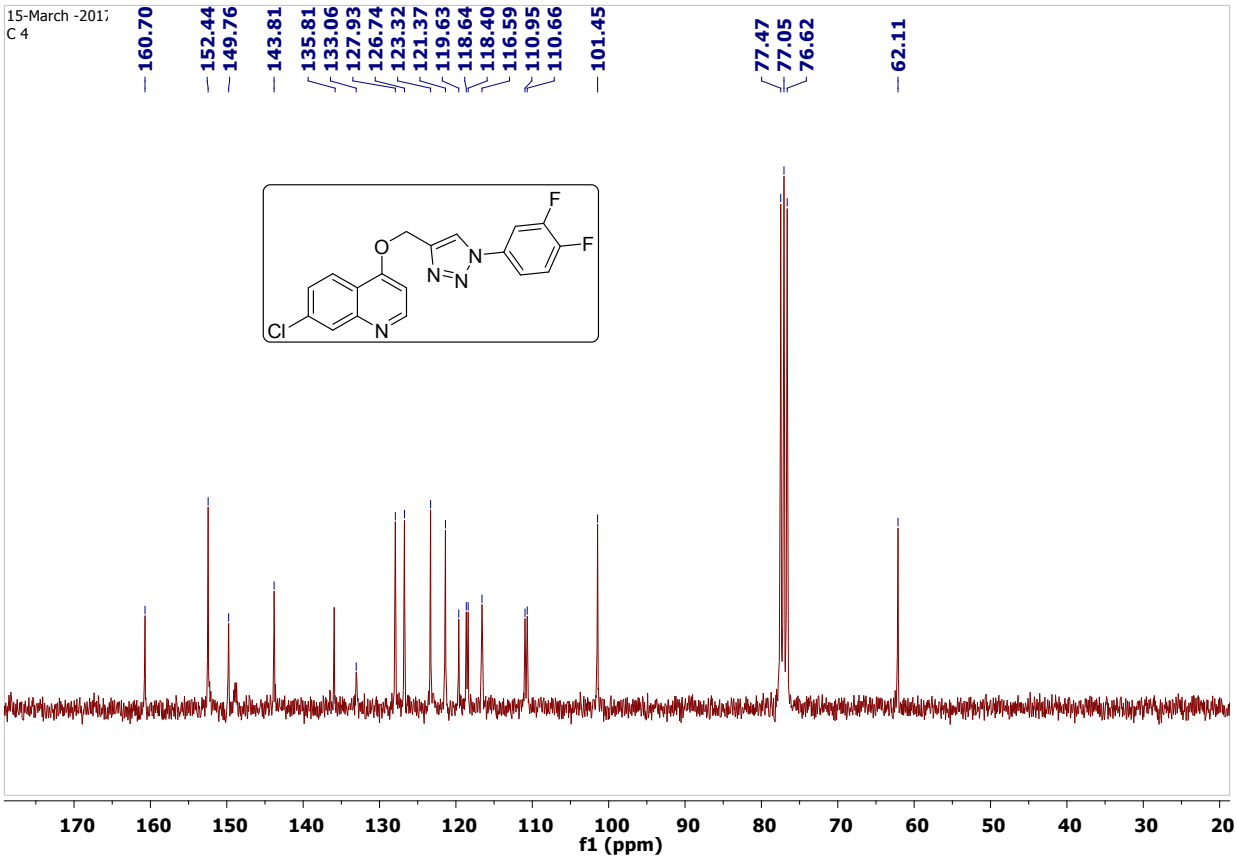


Figure S10: ^{13}C NMR spectrum of Molecule (T4)

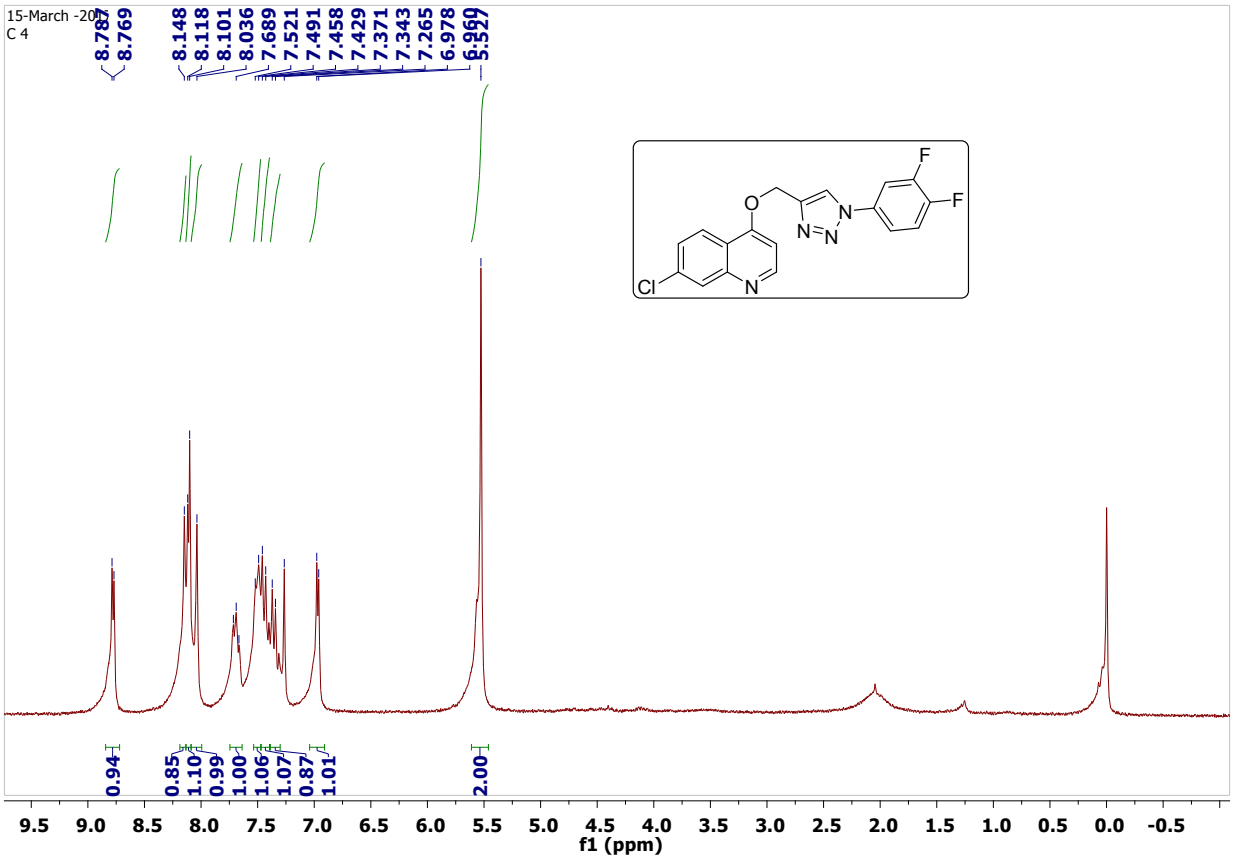


Figure S11: ^{1}H NMR spectrum of Molecule (T4)

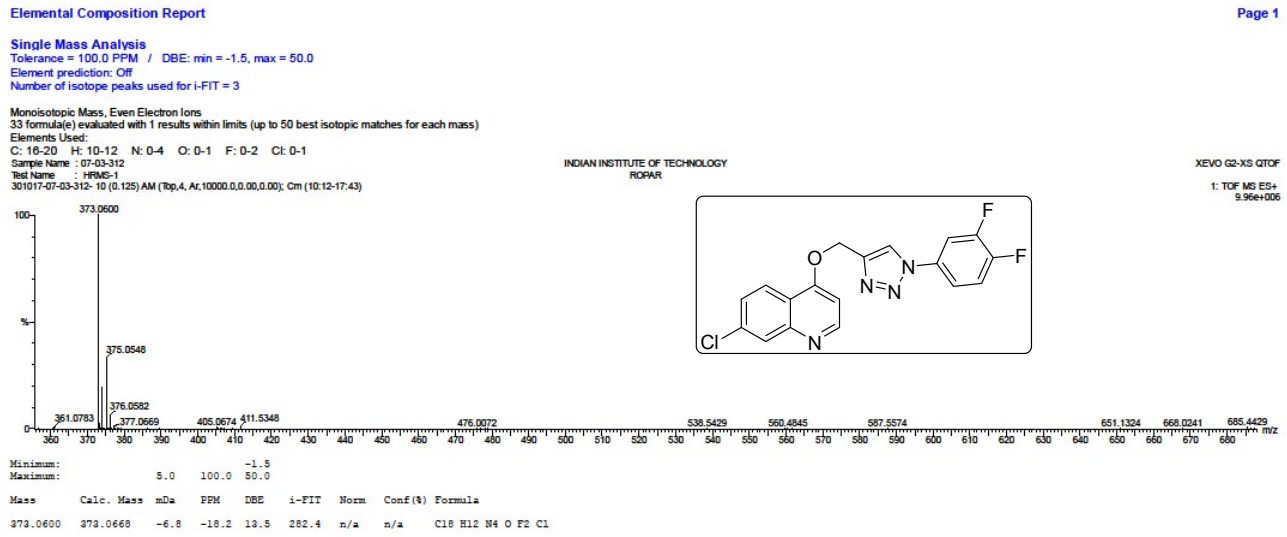


Figure S12: Mass spectrum of Molecule (T4)

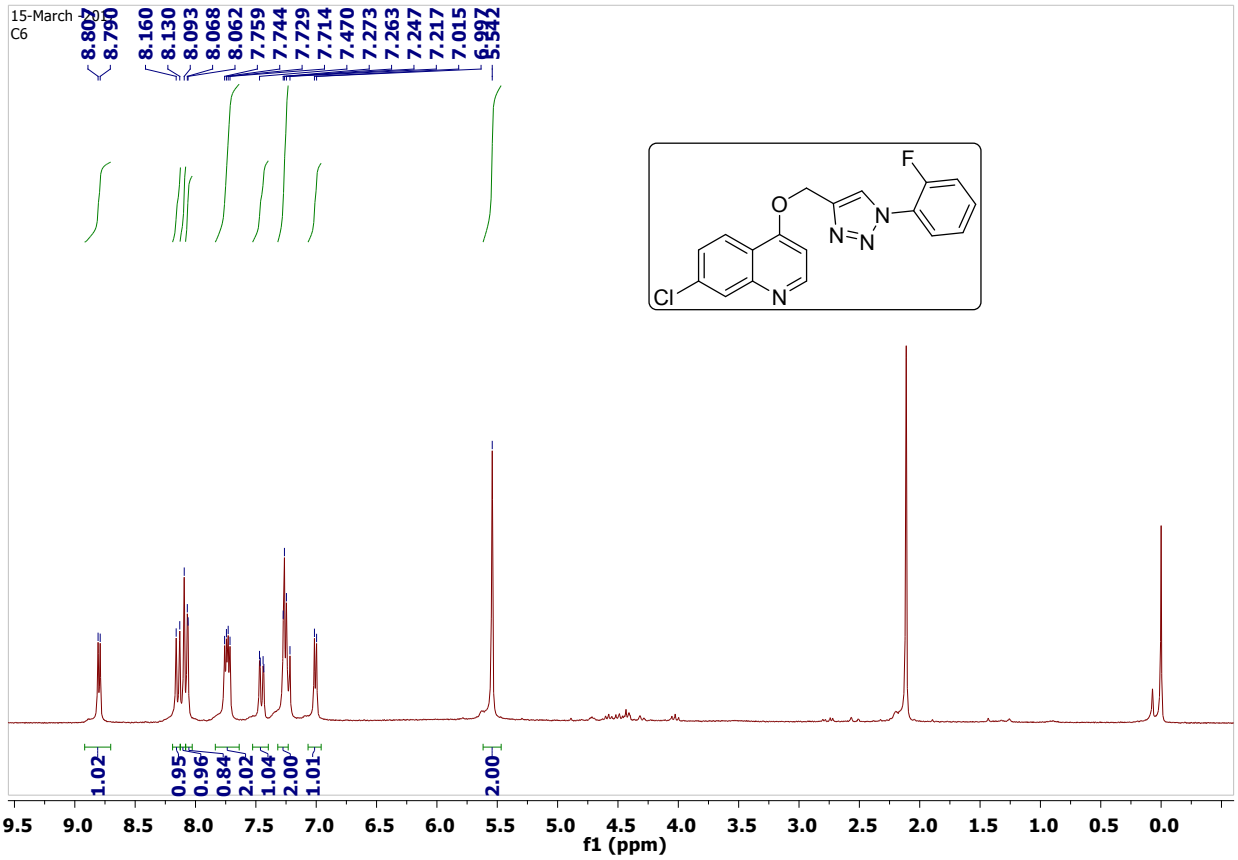


Figure S13: ^{1}H NMR spectrum of Molecule (T5)

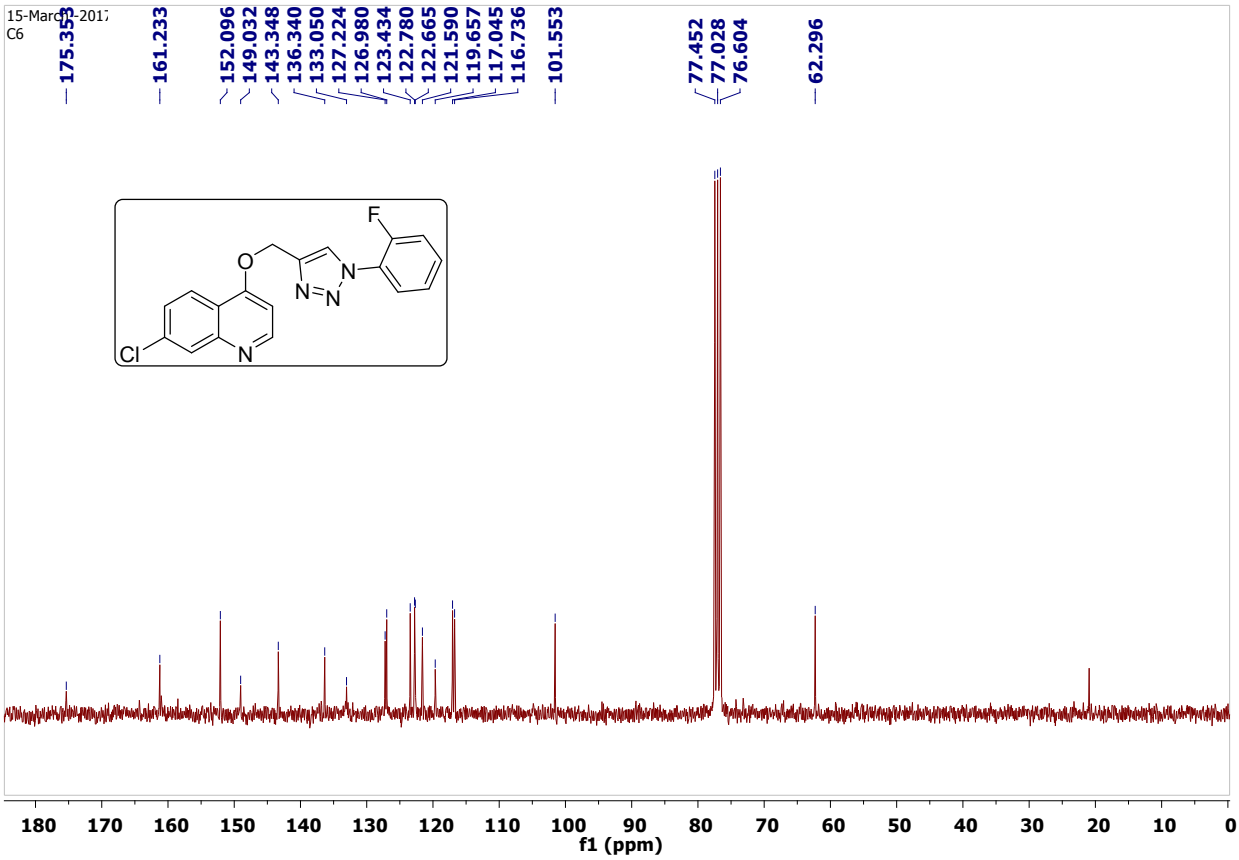


Figure S14: ^{13}C NMR spectrum of Molecule (T5)

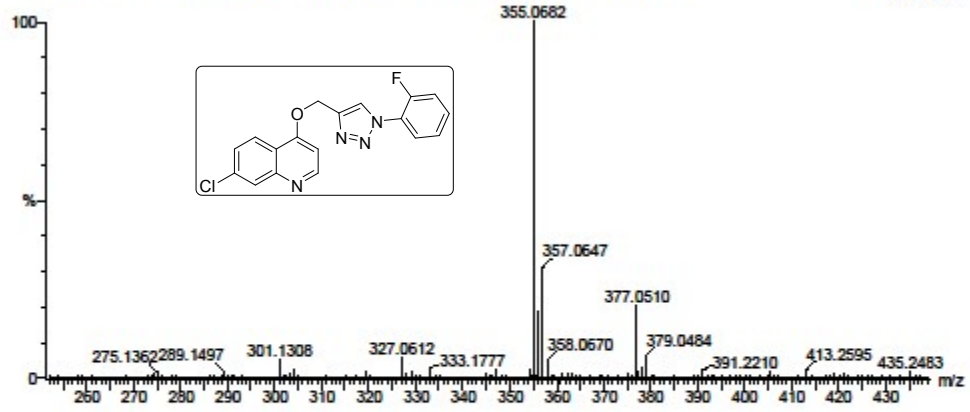
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
19 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 11-16 N: 0-4 O: 0-1 F: 0-1 Cl: 0-1

Sample Name : 07-03-340-C5
Test Name : HRMS-1 ROPAR
141117-07-03-340-C5_ - 10 (0.125) AM (Top,4, Ar,10000.0,0.00,0.00); Sm (SG, 2x5.00); Cm (8:16)

XEVO G2-XS QTOF
1: TOF MS ES+
1.46e+007



Minimum:				-1.5				
Maximum:		5.0	50.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
355.0682	355.0762	-8.0	-22.5	13.5	557.9	n/a	n/a	C18 H13 N4 O F Cl

Figure S15: Mass spectrum of Molecule (T5)

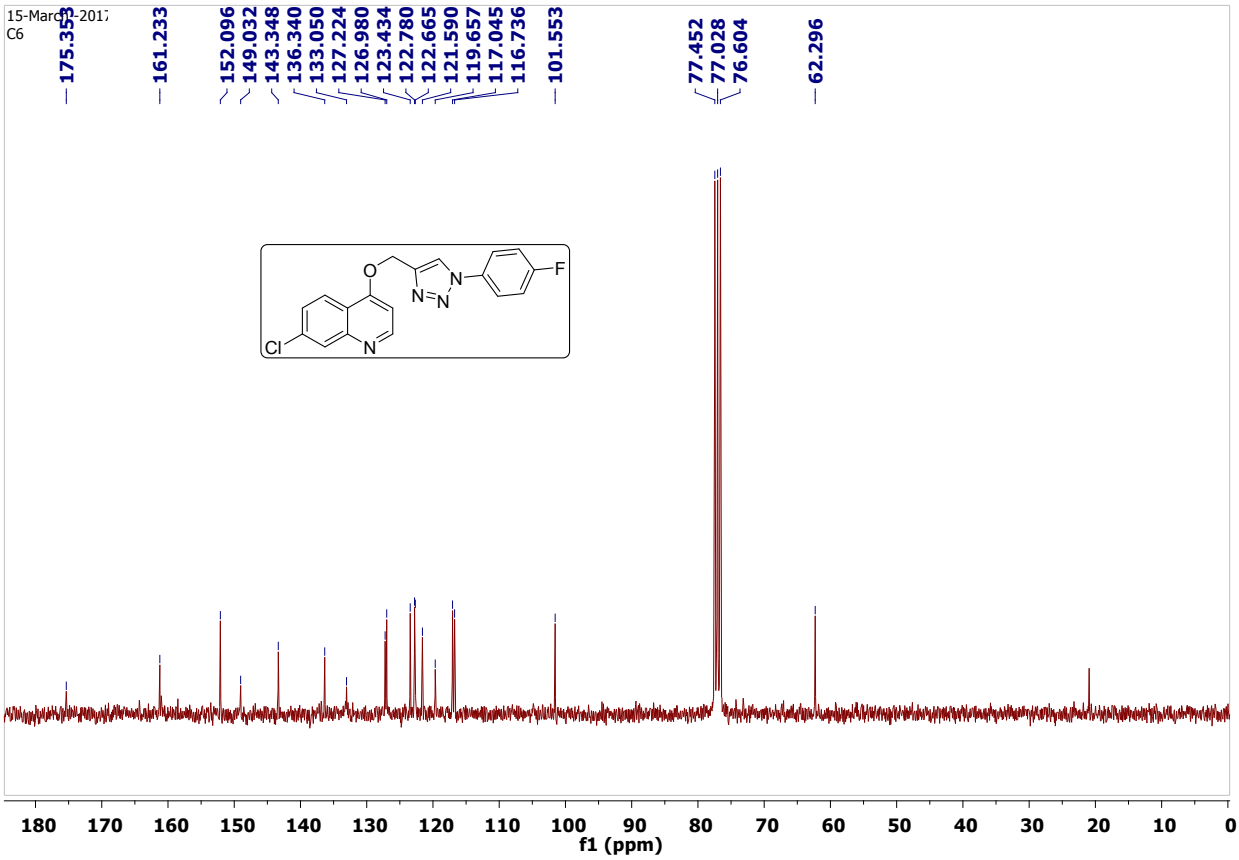


Figure S16: ^{13}C NMR spectrum of Molecule (T6)

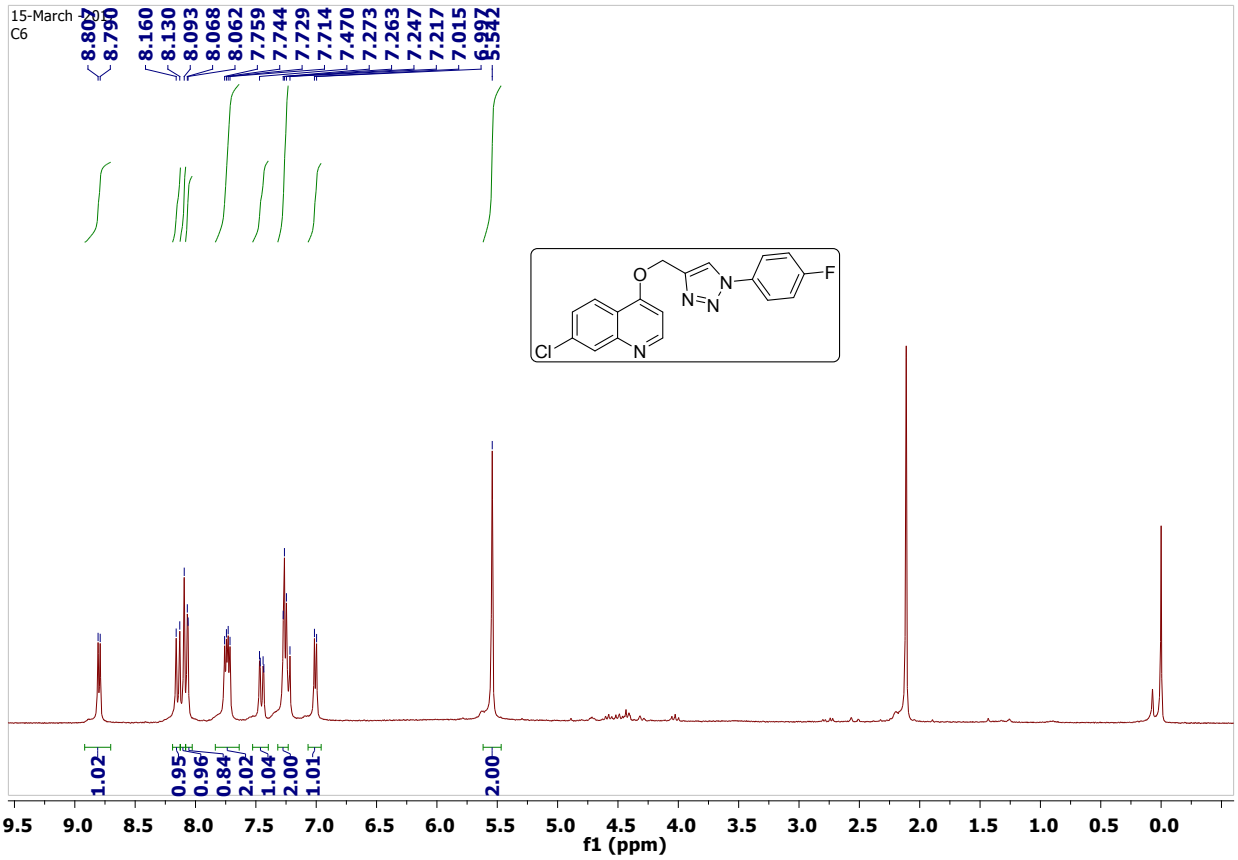


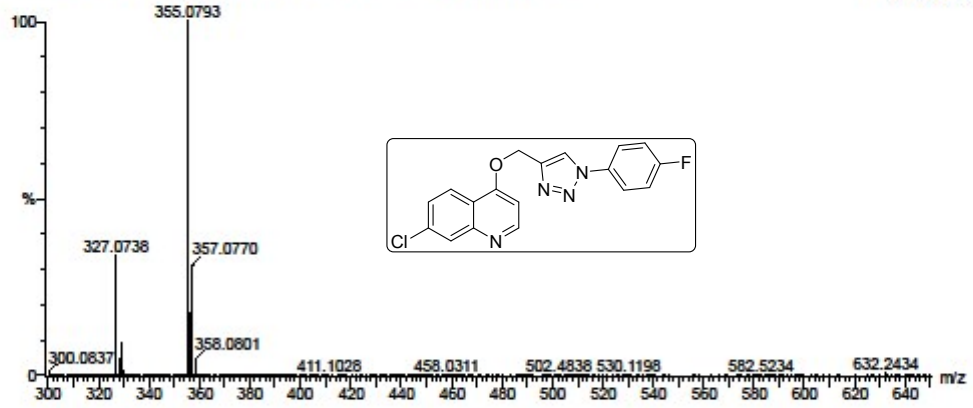
Figure S17: ^{13}C NMR spectrum of Molecule (T6)

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
19 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 10-15 N: 0-4 O: 0-1 F: 0-1 Cl: 0-1

Sample Name : 07-03-312-C6 XEVO G2-XS QTOF
Test Name : HRMS-1 ROPAR
031117-07-03-312-C6- 11 (0.134) AM2 (Ar,13000.0,0.00,0.00); Cm (11:13-20:52) 1: TOF MS ES+
3.09e+006



Minimum:				-1.5				
Maximum:		5.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
355.0793	355.0762	3.1	8.7	13.5	86.4	n/a	n/a	C18 H13 N4 O F Cl

Figure S18: Mass spectrum of Molecule (T6)

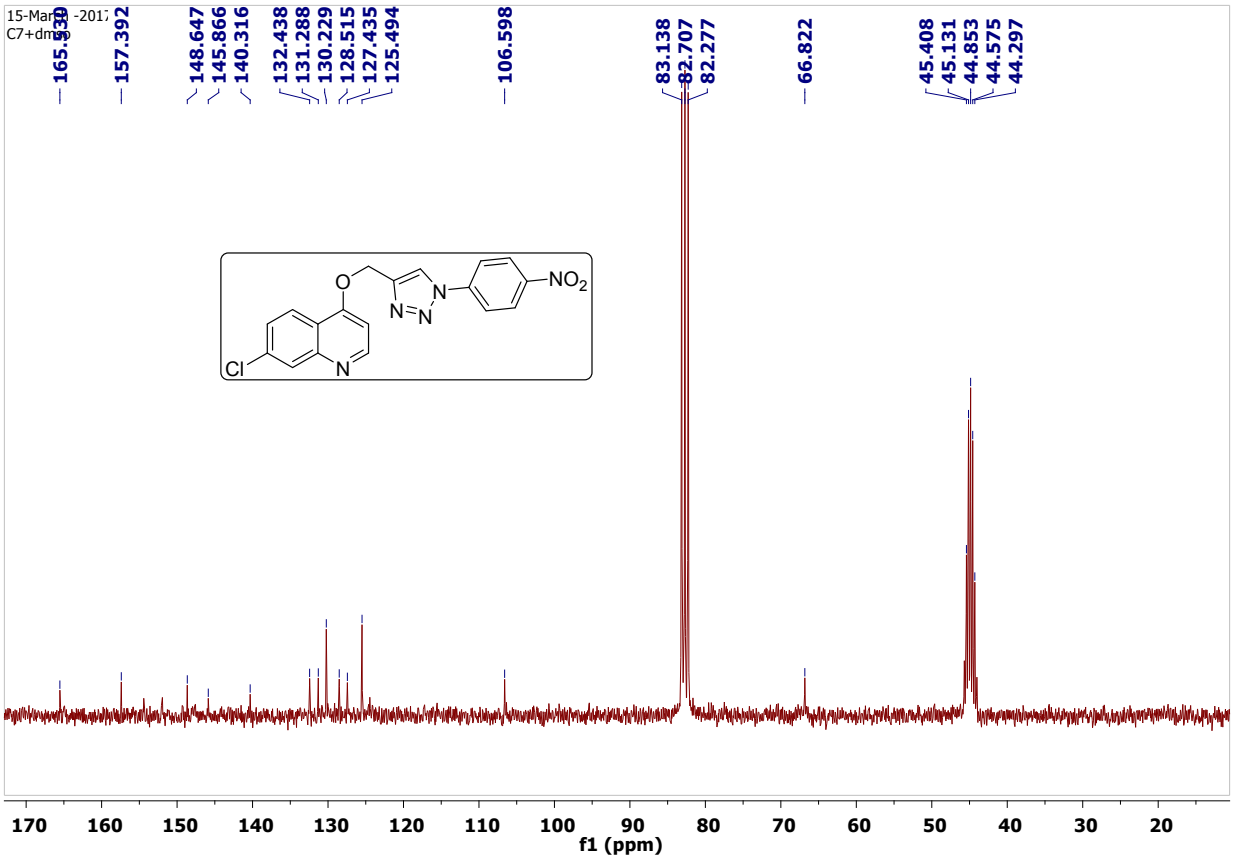


Figure S19: ^{13}C NMR spectrum of Molecule (T7)

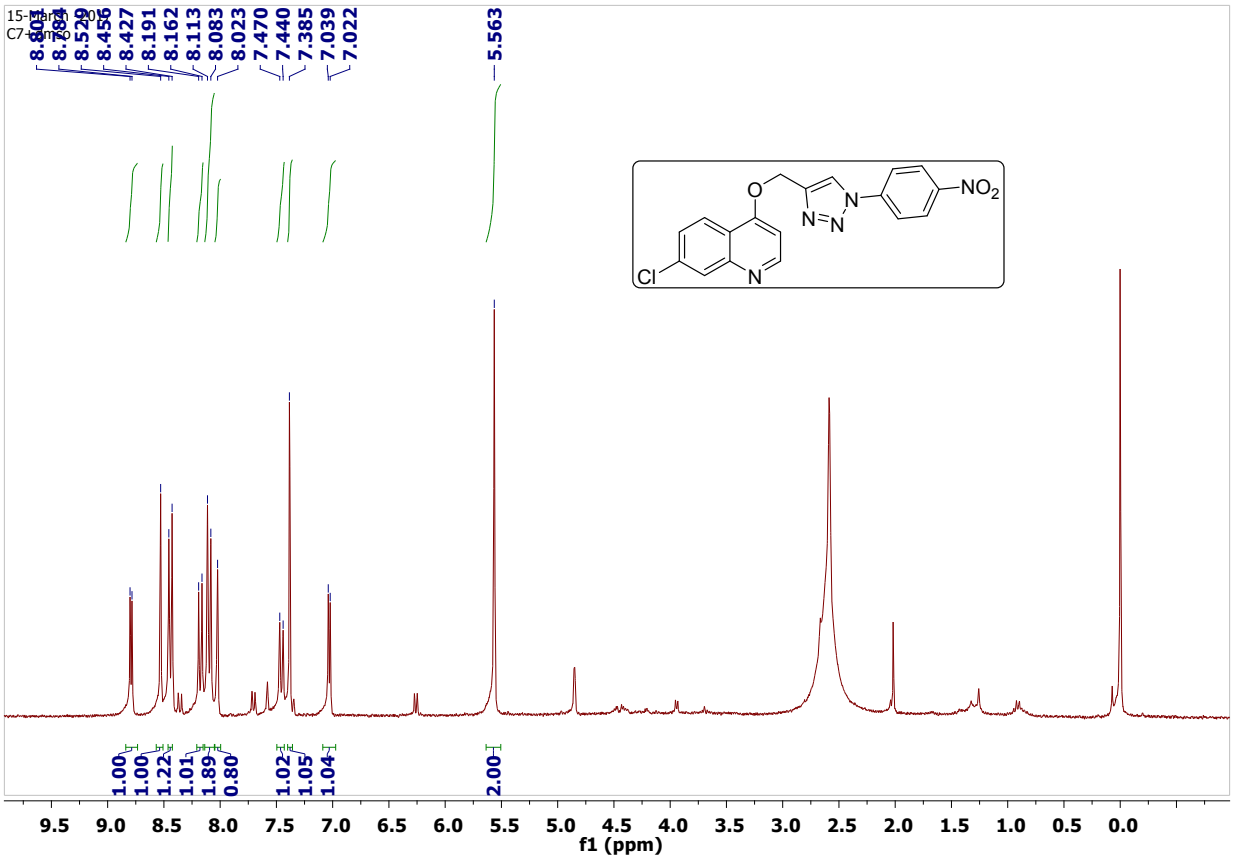


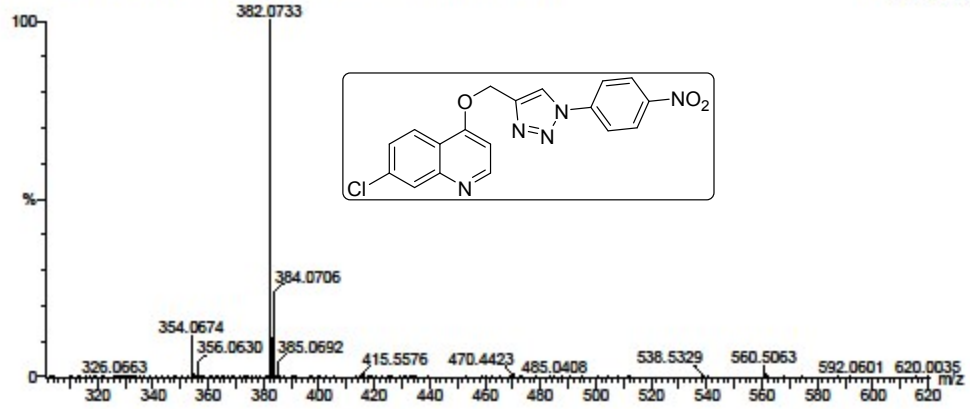
Figure S20: ^{1}H NMR spectrum of Molecule (T7)

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 25.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
39 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 12-17 N: 0-5 O: 0-3 Cl: 0-2

Sample Name : 07-03-C-10 INDIAN INSTITUTE OF TECHNOLOGY XEVO G2-XS QTOF
Test Name : HRMS-1 ROPAR
201117-07-03-C-10 17 (0.197) AM2 (Ar,15000.0,0.00,0.00); Cm (17:20-23:43) 1: TOF MS ES+
1.01e+006



Minimum:				-1.5				
Maximum:		5.0	25.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
382.0733	382.0707	2.6	6.8	14.5	75.4	n/a	n/a	C18 H13 N5 O3 Cl

Figure S21: Mass spectrum of Molecule (T7)

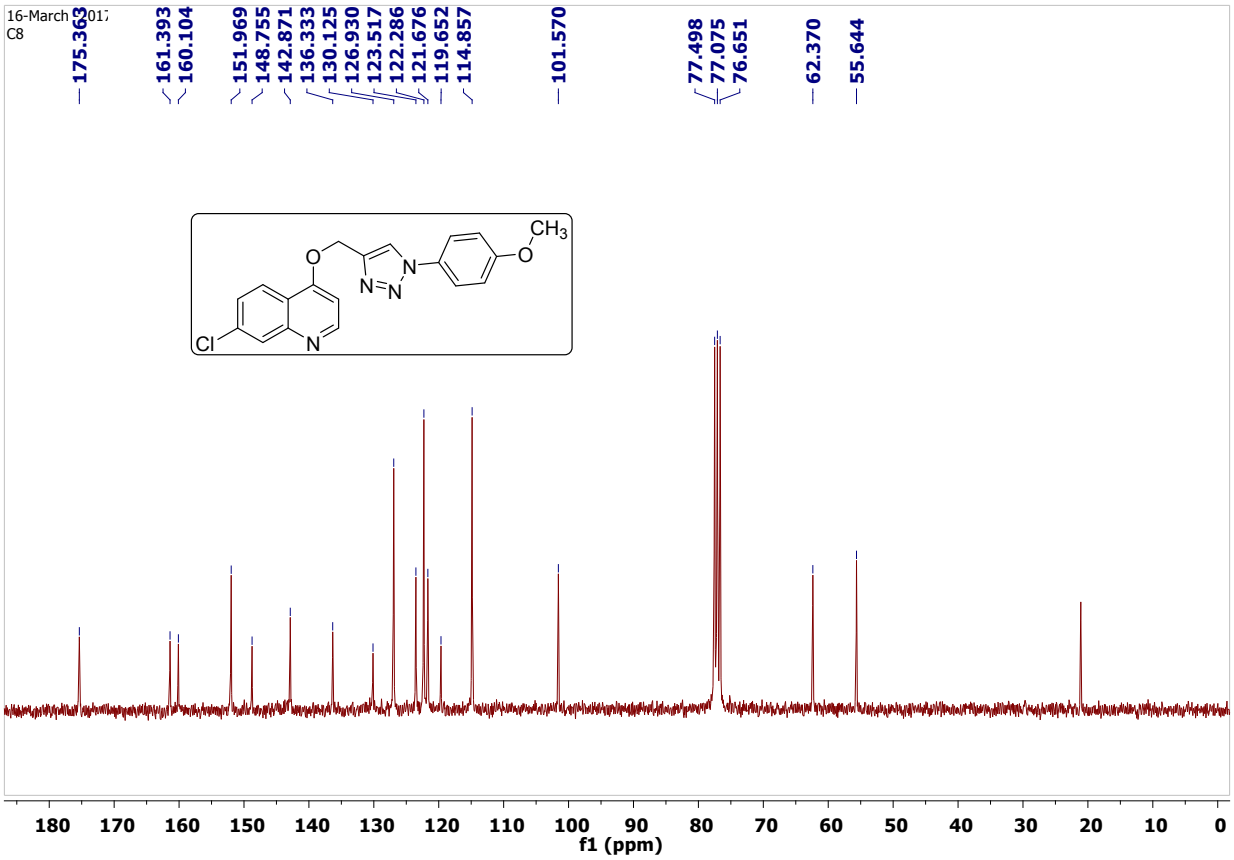


Figure S22: ^{13}C NMR spectrum of Molecule (T8)

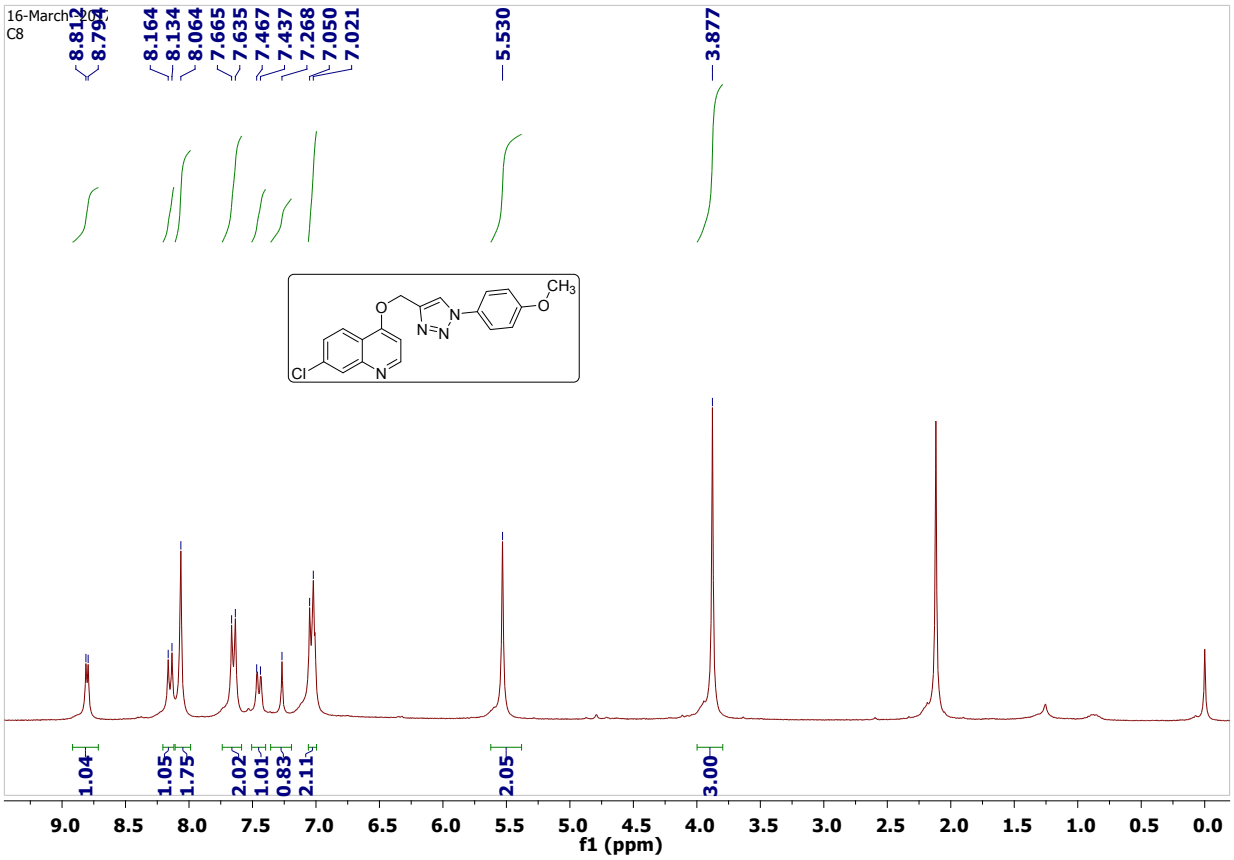


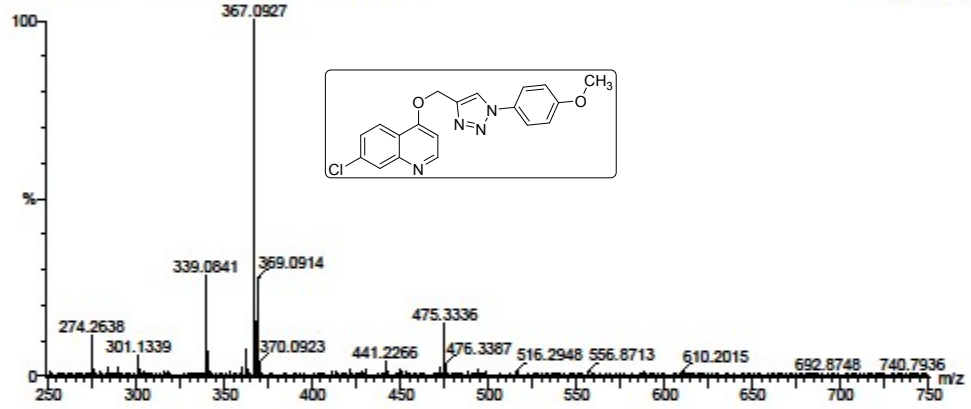
Figure S23: ^{1}H NMR spectrum of Molecule (T8)

Elemental Composition Report Page 1

Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
32 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 12-16 N: 0-4 O: 0-2 S: 0-1 Cl: 0-1

Sample Name : C8 INDIAN INSTITUTE OF TECHNOLOGY XEVO G2-XS QTOF
Test Name : HRMS-1 ROPAR
101117-C8 7 (0.088) AM2 (Ar,13000.0,0.00,0.00); Cm (7) 1: TOF MS ES+
1.32e+005



Minimum:				-1.5				
Maximum:		5.0	20.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
367.0927	367.0962	-3.5	-9.5	13.5	245.6	n/a	n/a	C19 H16 N4 O2 Cl

Figure S24: Mass spectrum of Molecule (T8)

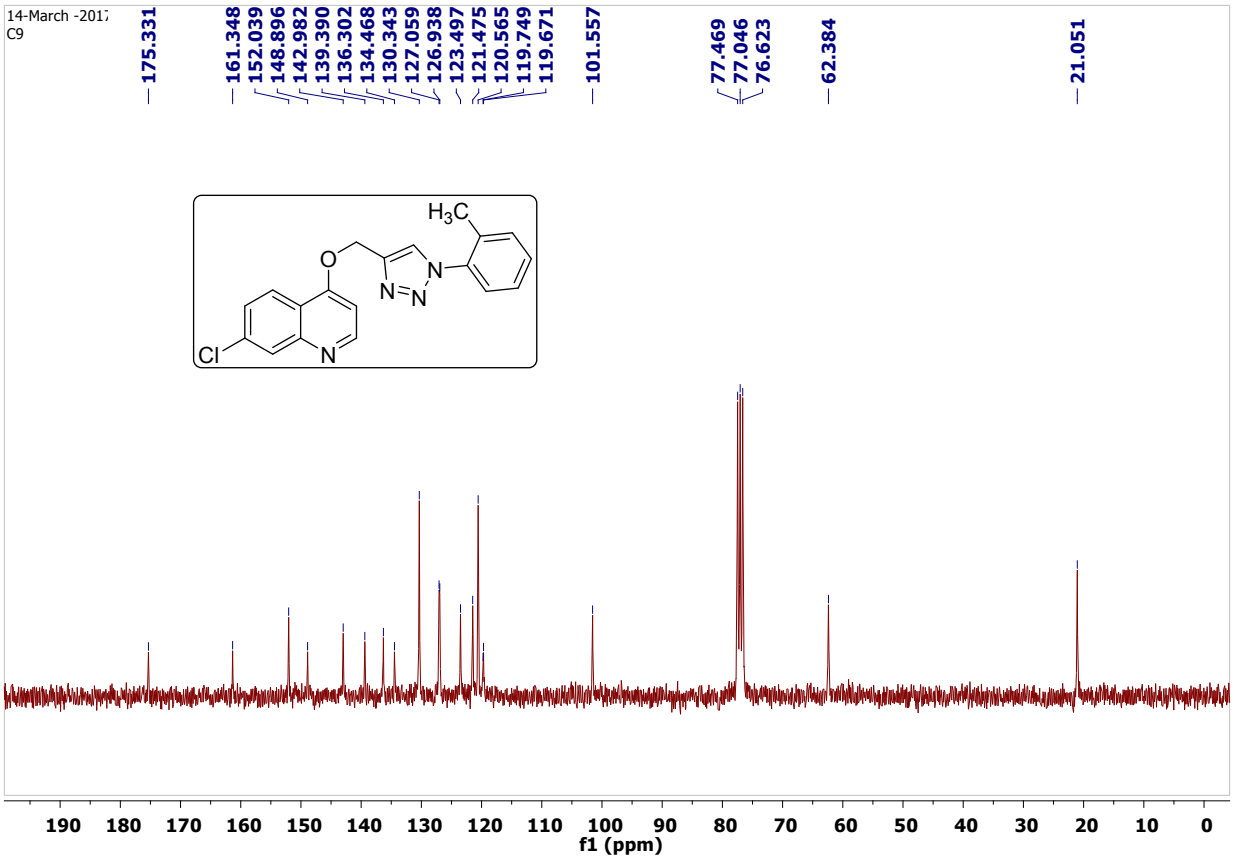


Figure S25: ^{13}C NMR spectrum of Molecule (T9)

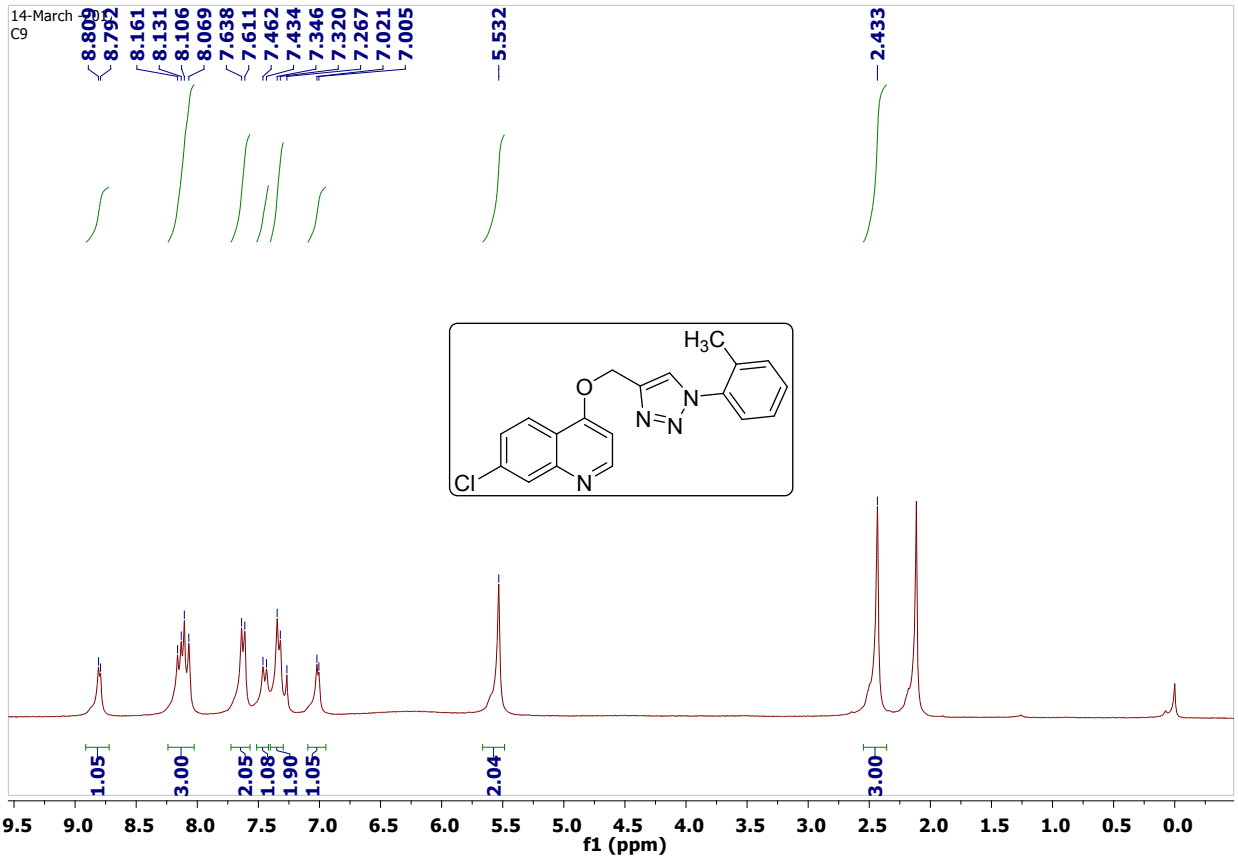


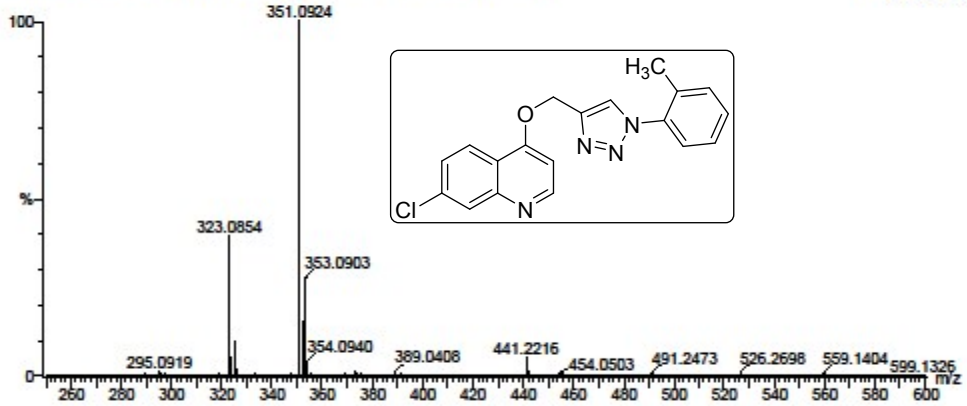
Figure S26: ^{1}H NMR spectrum of Molecule (T9)

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 50.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd and Even Electron Ions
11 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 11-16 N: 0-4 O: 0-1 Cl: 0-1

Sample Name : 07-03-340-C9 XEVO G2-XS QTOF
Test Name : HRMS-1 ROPAR
141117-07-03-340-C9_ 9 (0.117) AM2 (Ar,13000.0,0.00,0.00); Cm (9:13-18:30) 1: TOF MS ES+
1.50e+006



Minimum:				-1.5				
Maximum:		5.0	50.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
351.0924	351.1013	-8.9	-25.3	13.5	257.9	n/a	n/a	C19 H16 N4 O Cl

Figure S27: Mass spectrum of Molecule (T9)

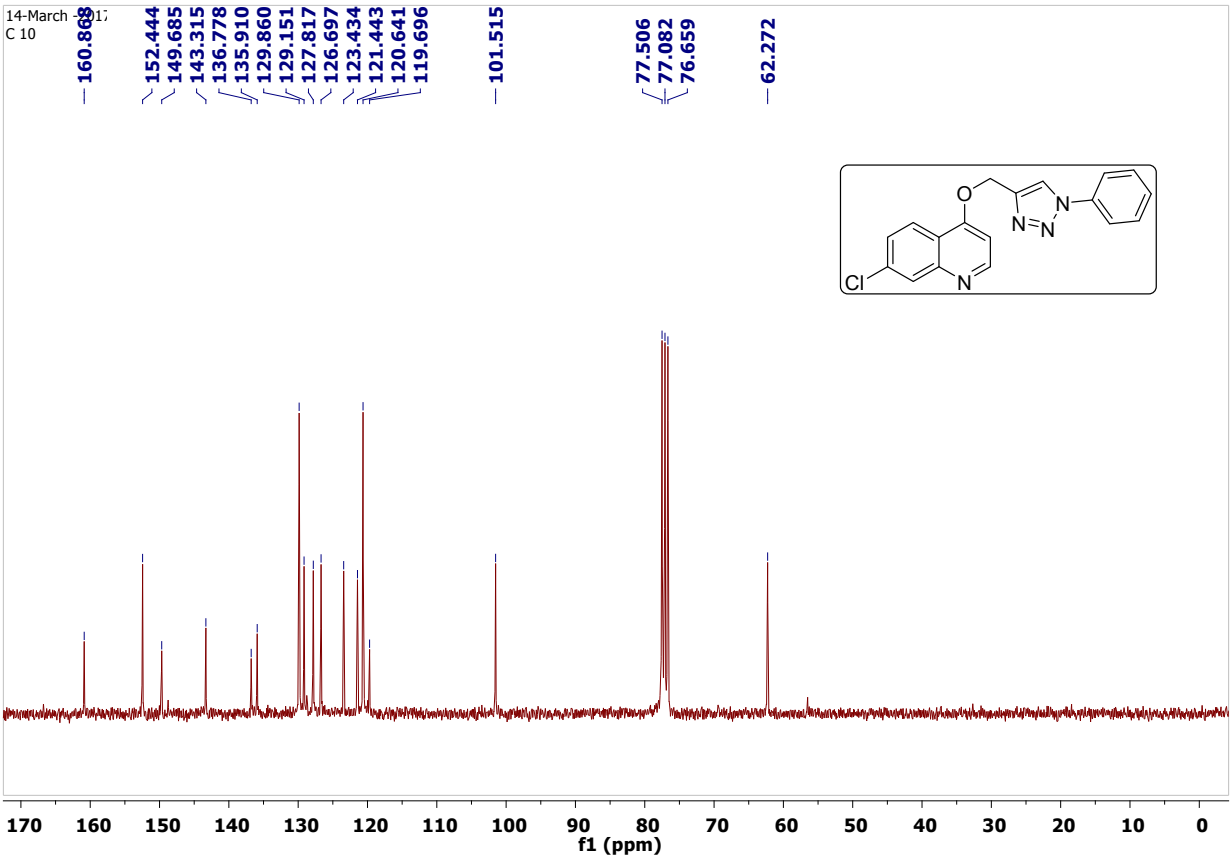


Figure S28: ^{13}C NMR spectrum of Molecule (T10)

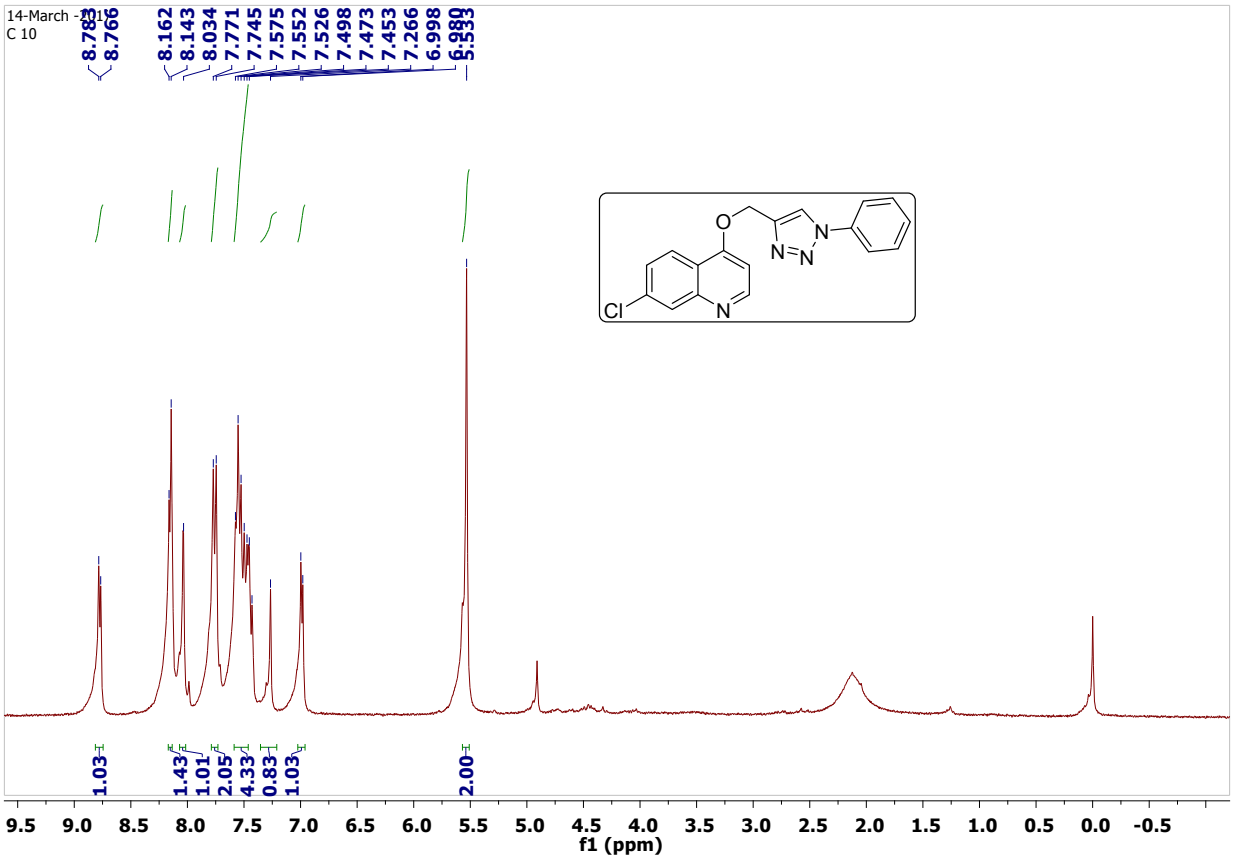


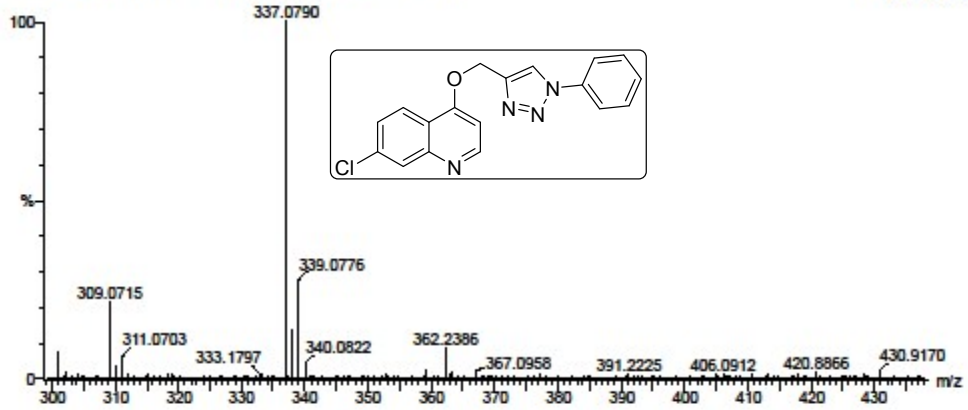
Figure S29: ^{1}H NMR spectrum of Molecule (T10)

Elemental Composition Report Page 1

Single Mass Analysis
Tolerance = 20.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
8 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 15-20 H: 12-16 N: 0-4 O: 0-1 Cl: 0-1

Sample Name : C10 INDIAN INSTITUTE OF TECHNOLOGY XEVO G2-XS QTOF
Test Name : HRMS-1 ROPAR
101117-C10_ 10 (0.125) AM2 (Ar,13000.0,0.00,0.00); Cm (9:14) 1: TOF MS ES+
7.22e+005



Minimum:				-1.5				
Maximum:		5.0	20.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
337.0790	337.0856	-6.6	-19.6	13.5	411.0	n/a	n/a	C18 H14 N4 O Cl

Figure S30: Mass spectrum of Molecule (T10)

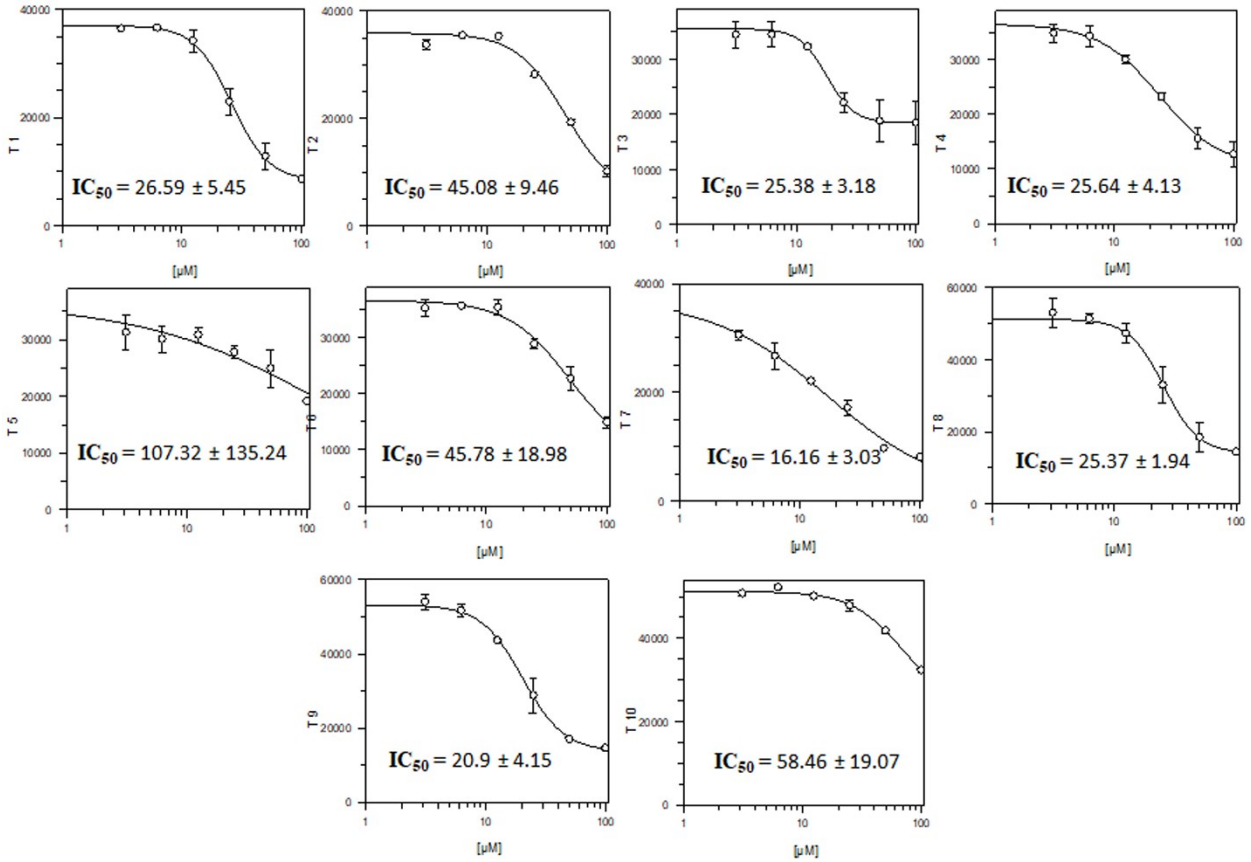


Figure S31: Dose-response curve for Falcipain-2 inhibitions. Release of fluorescence units of fluorogenic substrate (AMC) was measured at different increasing concentrations of the inhibitors. IC_{50} values were determined by using the experimental data with the help of GraFit version 7 software. Error bars represent SD of the results from three different sets of experiments. Y axis of graph represent the arbitrary fluorescence units (AFU) and X axis represent the log(substrate) concentration (µM).

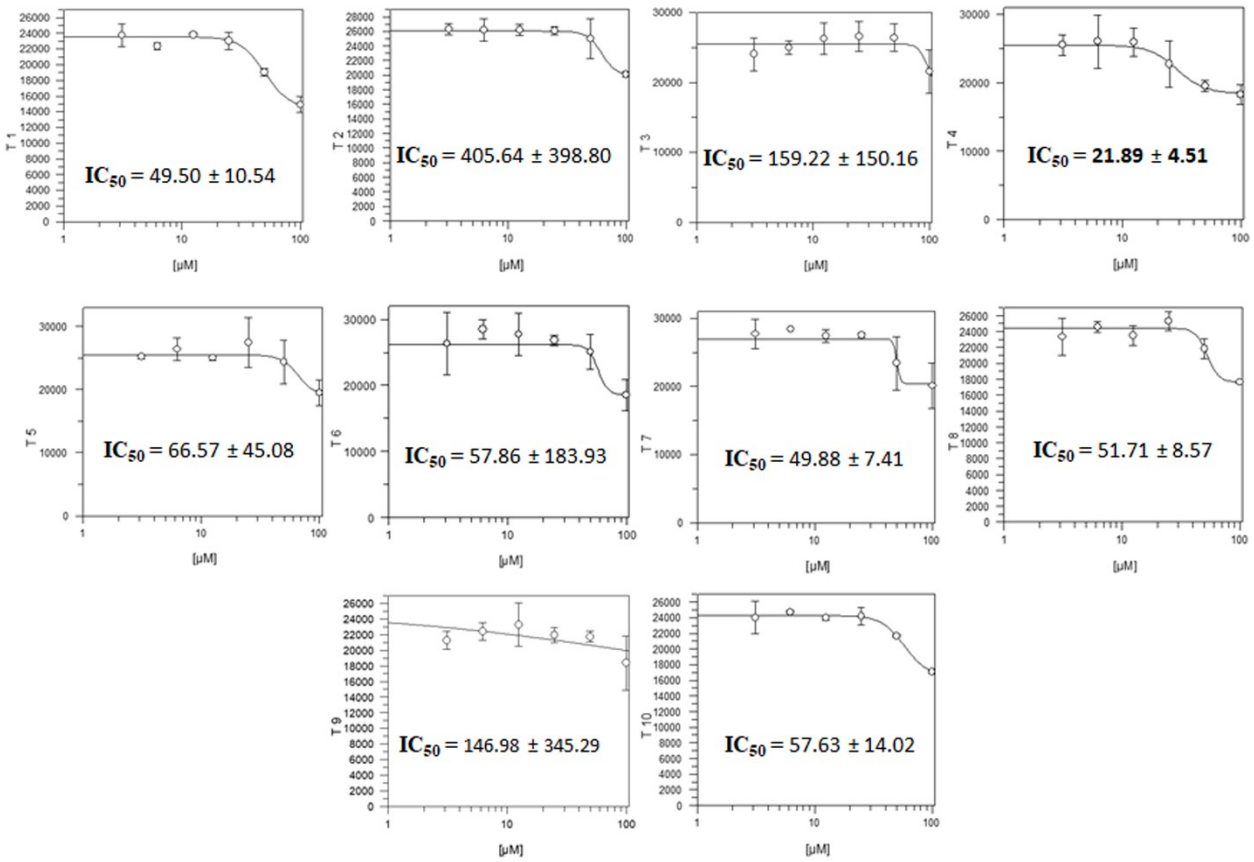


Figure S32: *P. falciparum* 3D7 dose inhibition graph.

Validation of docking results

The Pardock[1] module of Sanjeevini (SCFBIO, IITD) was chosen for docking and scoring resolutions and Auto Dock Vina program[2] (version 1.5.6) was used for validation of the docking results. The results obtained were found from these two docking tools adopt almost identical Pattern. The difference in the binding energies of the respective compounds using both the programs was found in the range of ±1 Kcal/mol. Moreover, the ligands occupied the similar binding pockets by both the docking tools which displays good correlation with the previously reported FP-2 inhibitors.[3–5]

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