Supporting Information

Cytochrome c-Urea Functionalized Dipeptide Conjugate: An Efficient HBD framework, to Synthesize 4*H*-Pyrans *via* One-Pot Multicomponent Reaction

Sanjeev Saini[a], Mayank[a], Navneet Kaur[b*], Narinder Singh[a*]

[a] Department of Chemistry, Indian Institute of Technology Ropar, Punjab 140001, India

[b] Department of Chemistry, Panjab University, Chandigarh 160014, India

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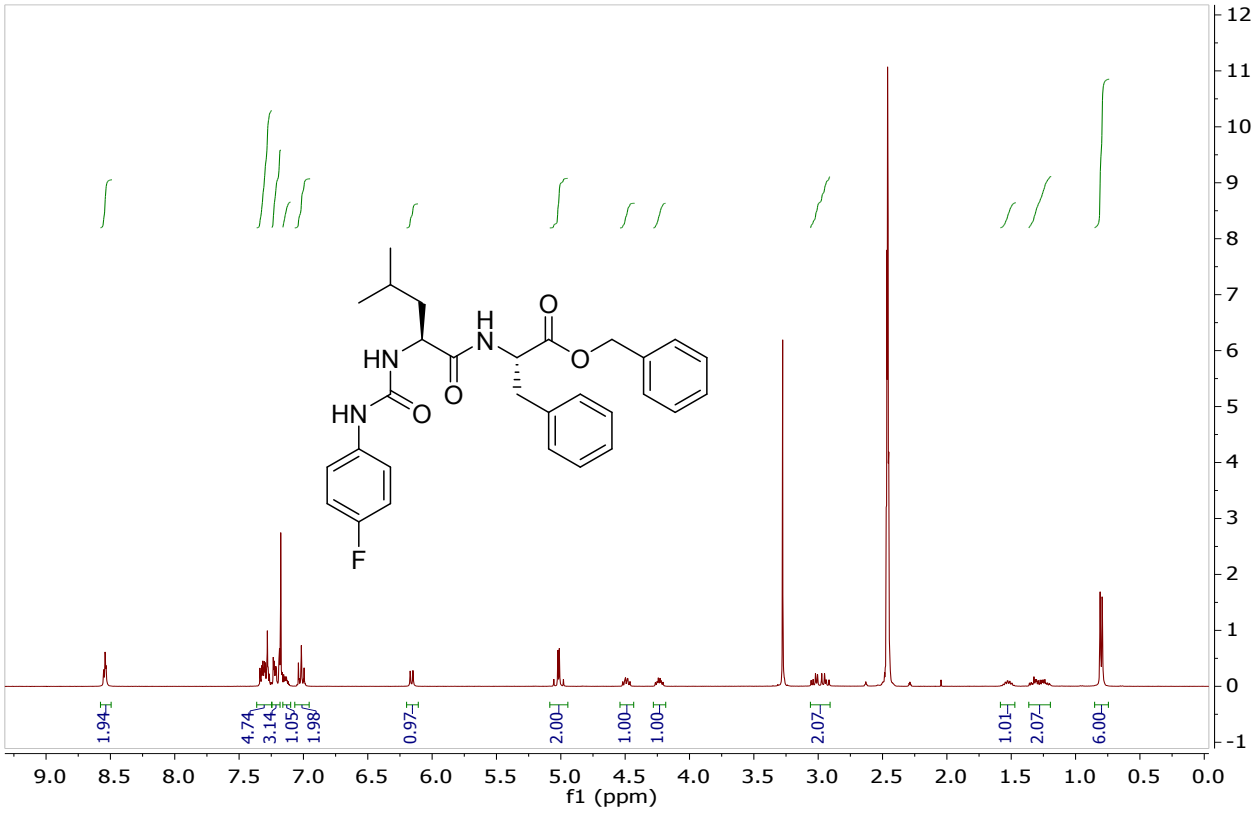


Figure SF1: ^{1}H NMR ($CDCl_3$+DMSO- d_6) spectra of SS1.

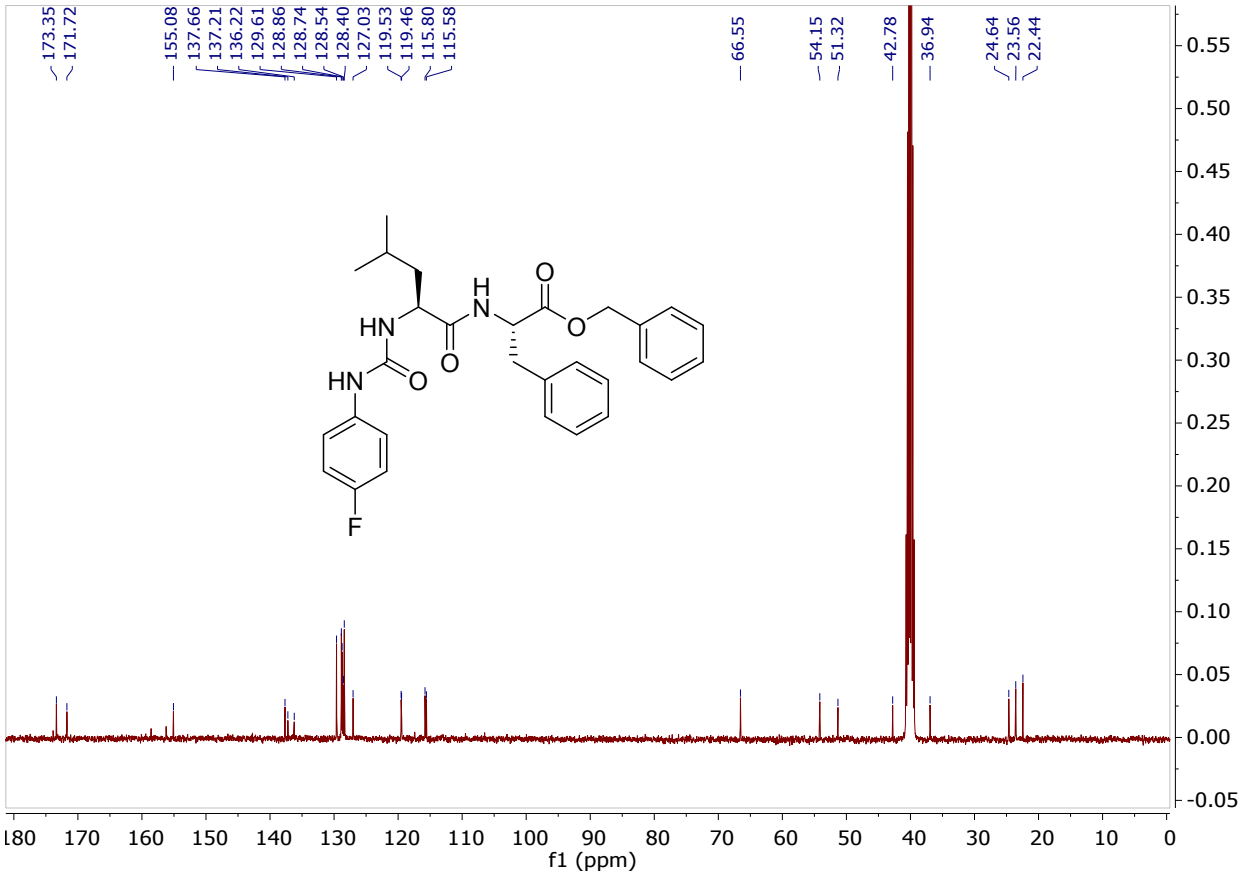
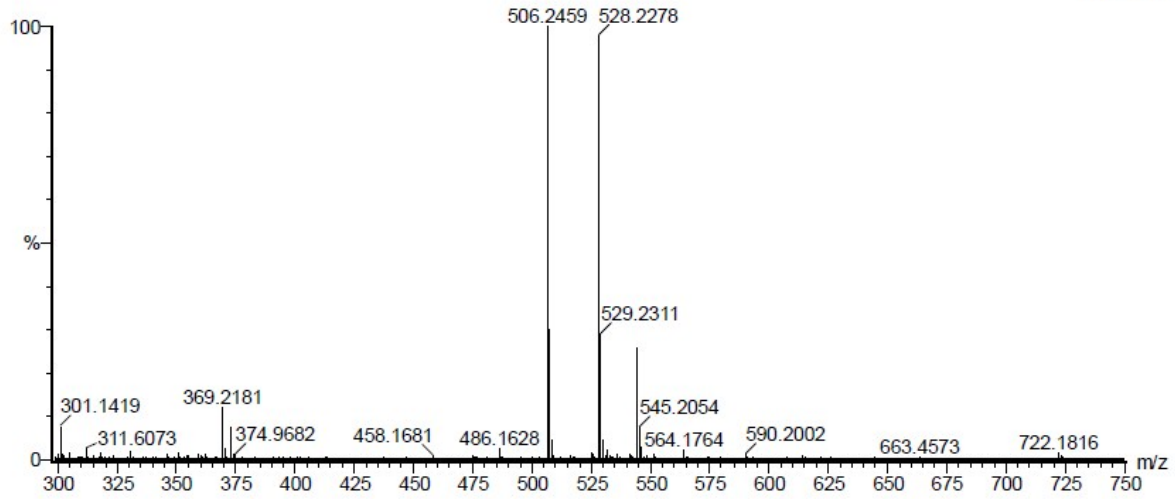


Figure SF2: ^{13}C NMR spectra of SS1.

Monoisotopic Mass, Even Electron Ions
36 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 25-30 H: 25-35 N: 0-3 O: 0-4 F: 0-3

Sample Name : SS-DPD I.I.T.ROPAR XEVO G2-XS QTOF
Test Name : HRMS-1
261018-SS-DPD 7 (0.088) AM2 (Ar,19000.0,0.00,0.00); Cm (6:7) 1: TOF MS ES+
3.47e+006



Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
506.2459	506.2455	0.4	0.8	14.5	430.5	n/a	n/a	C29 H33 N3 O4 F

Figure SF3: HRMS data of SS1.

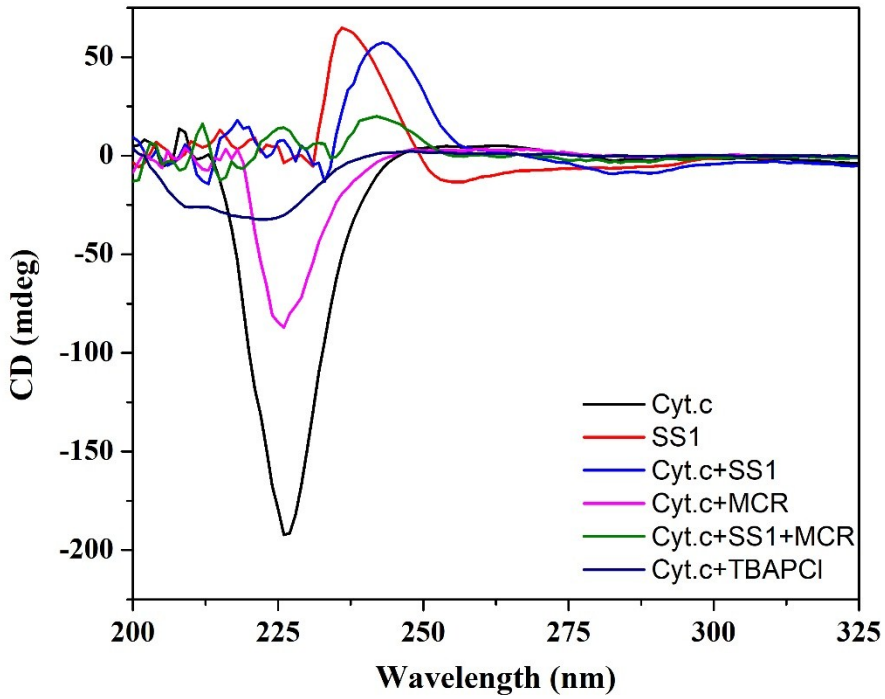


Figure SF4: Circular Dichroism studies of Cytochrome c with SS1 and multicomponent reactants.

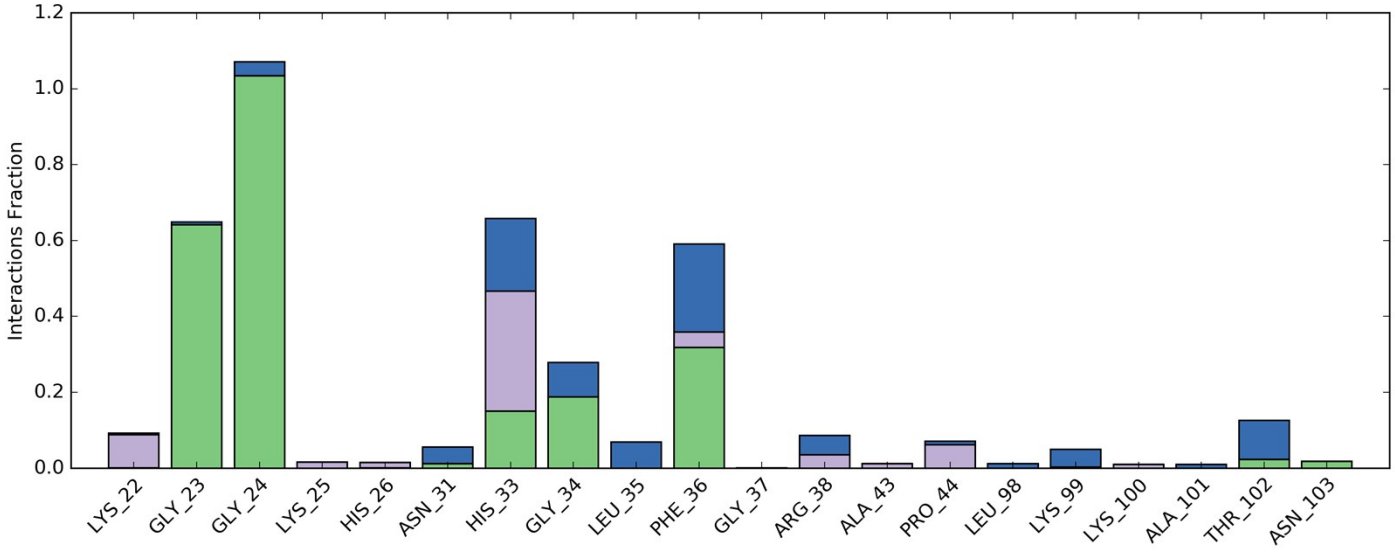


Figure SF5: Cytochrome c – Dipeptide SS1 interaction diagram.

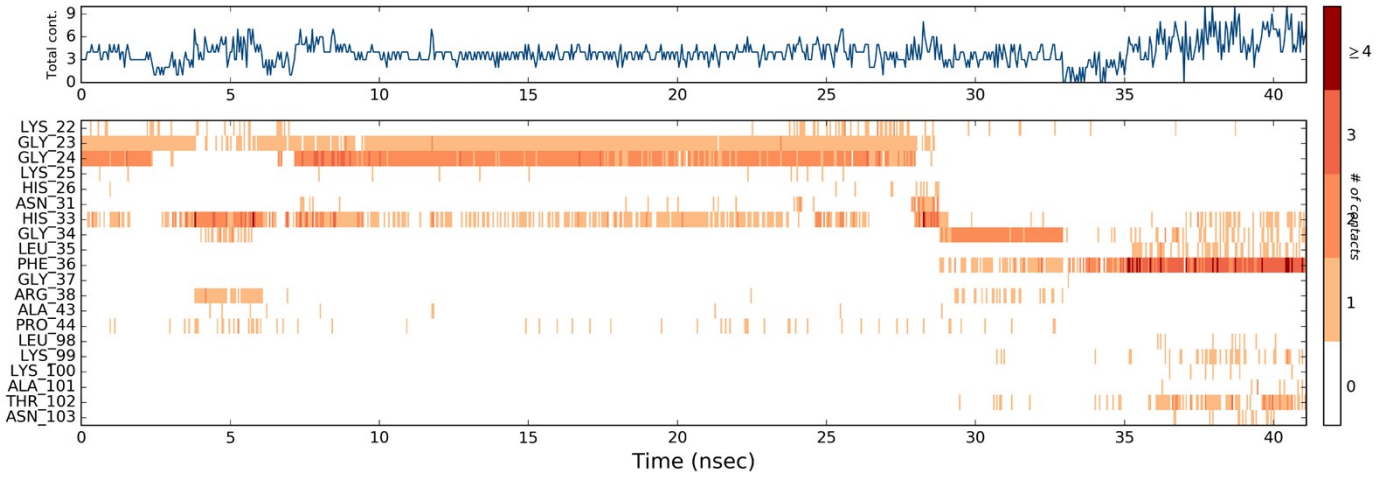


Figure SF6: Protein-Ligand Contacts timeline for SS1 bounded to Cytochrome c obtained from MD Simulation studies.

^{1}H NMR of 4H-Pyran derivatives

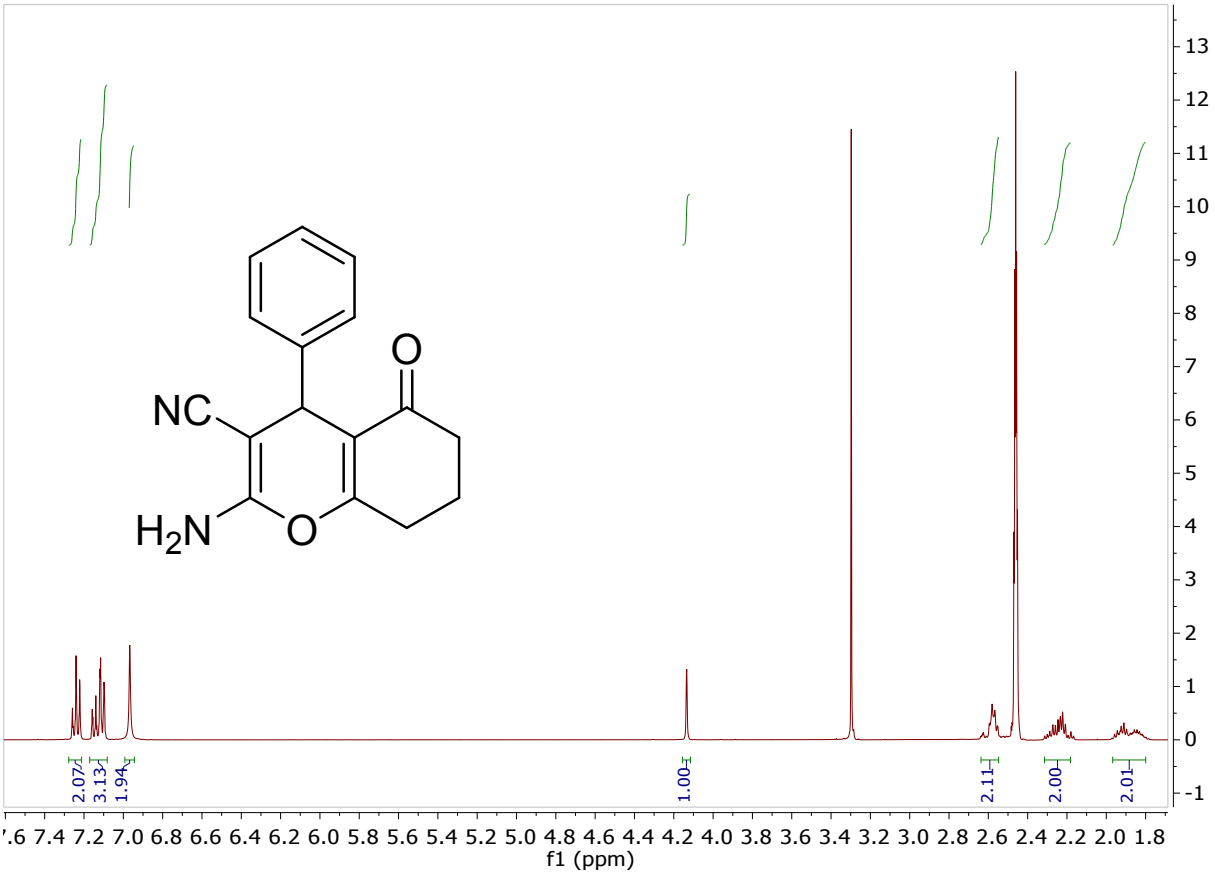


Figure SF7: ^{1}H NMR of **S1**.

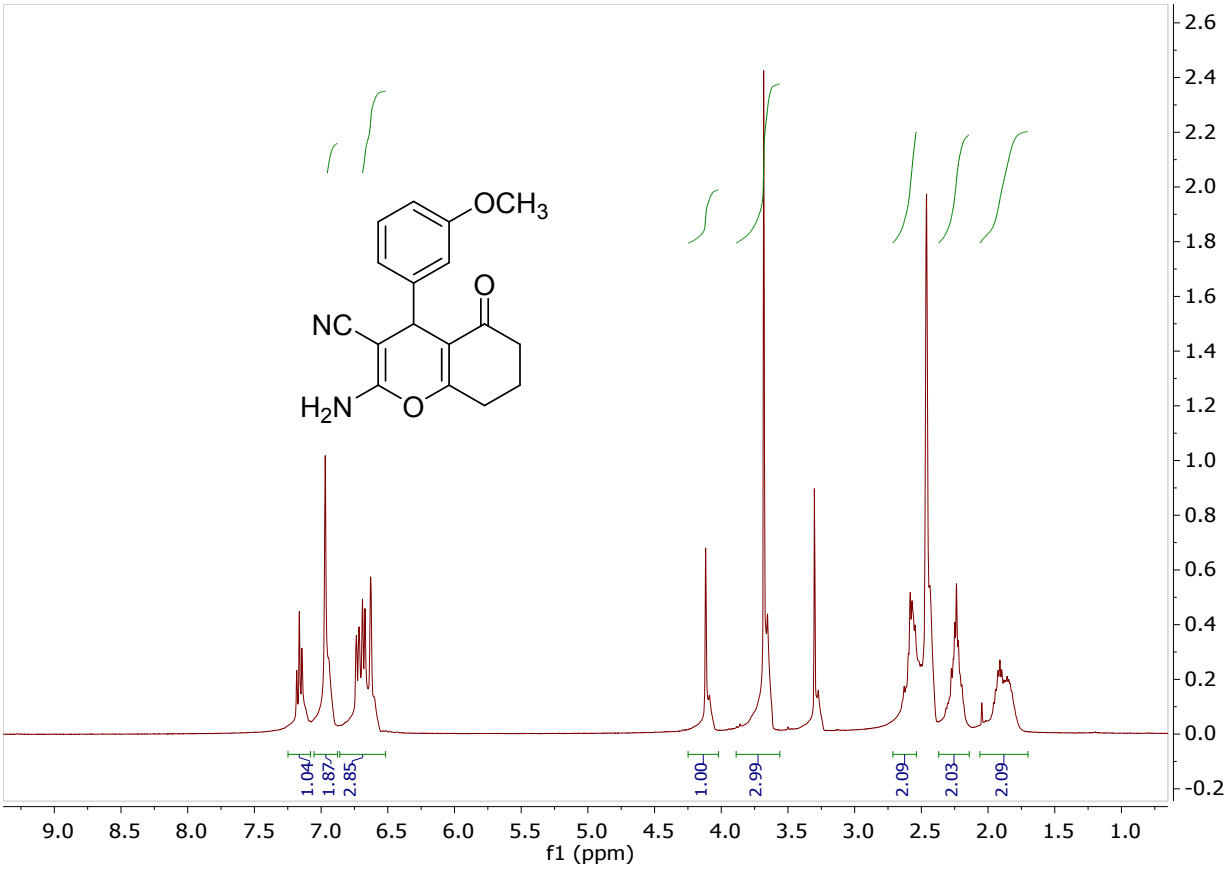


Figure SF8: ^{1}H NMR of **S2**.

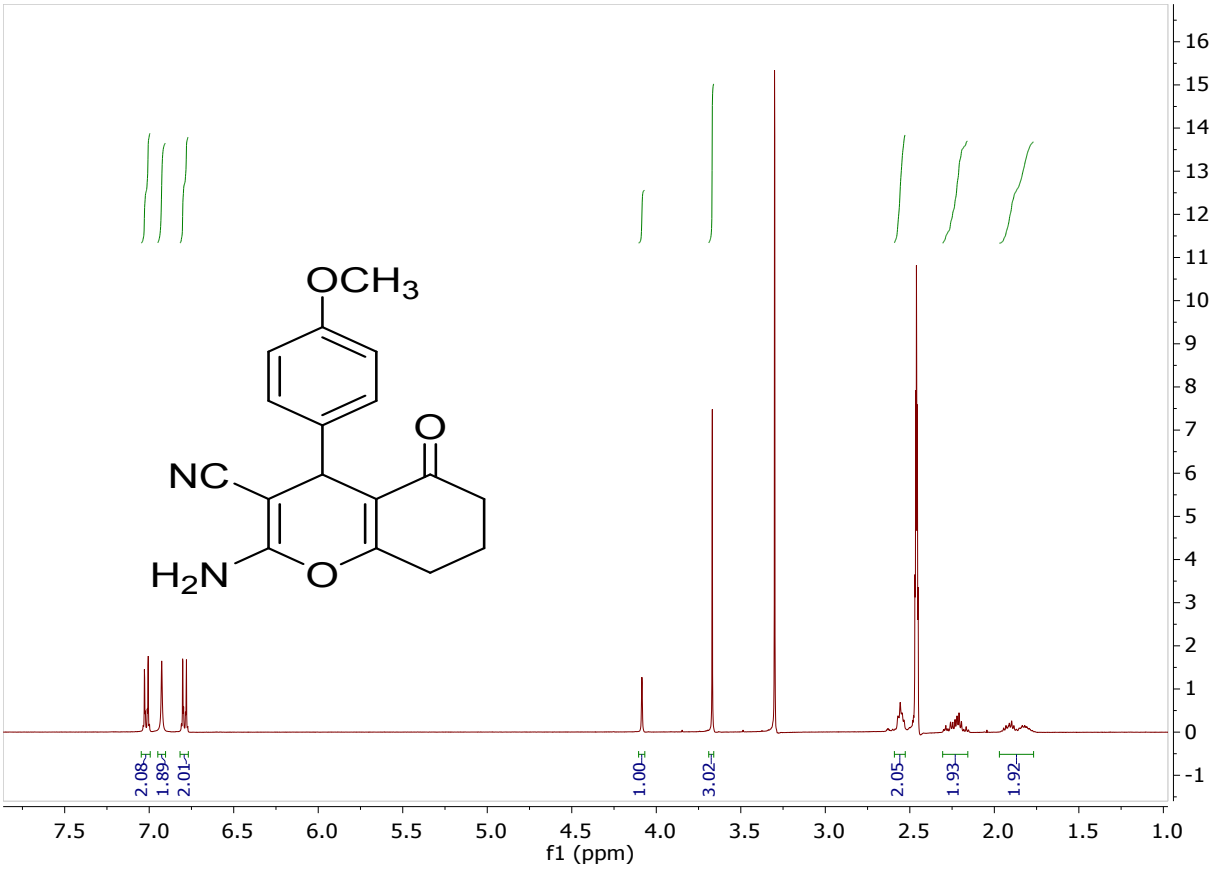


Figure SF9: ^{1}H NMR of **S3**.

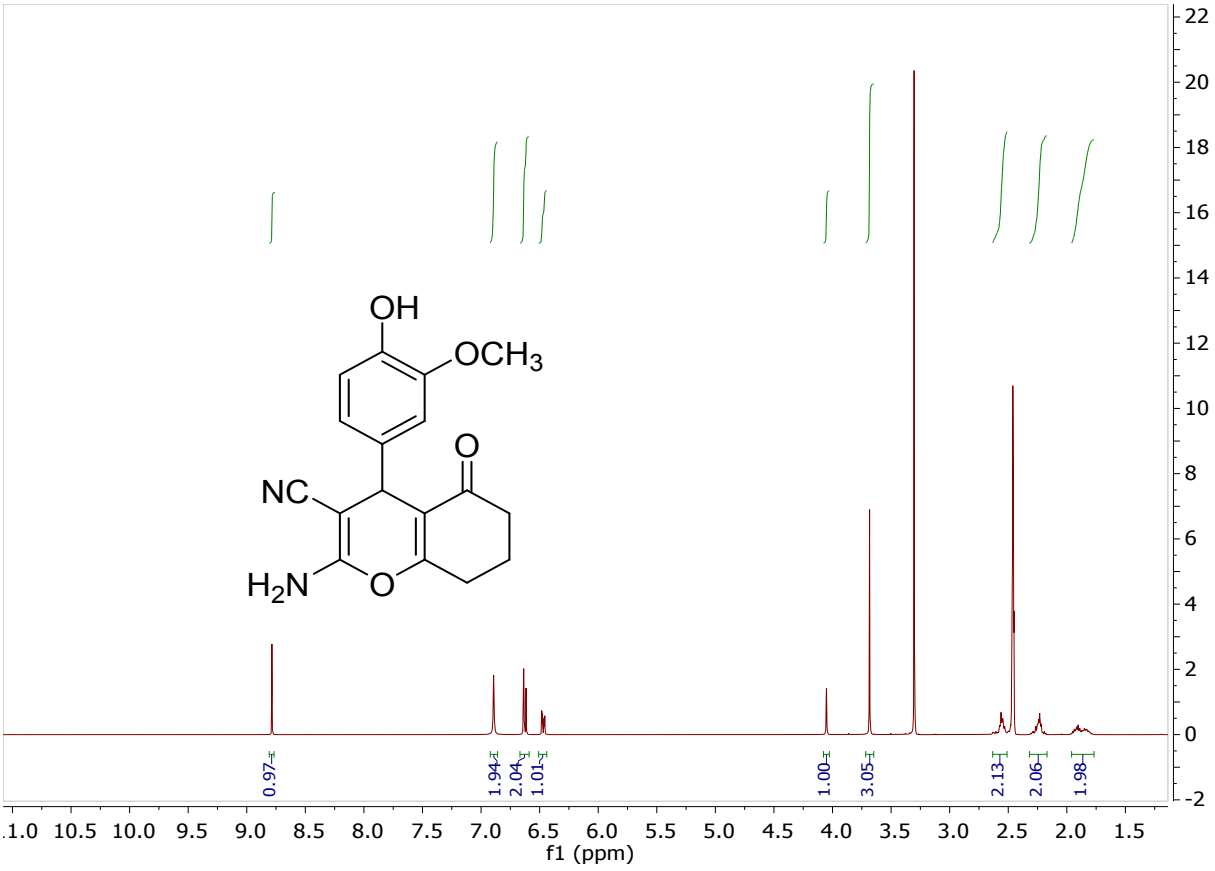


Figure SF10: ^{1}H NMR of **S4**.

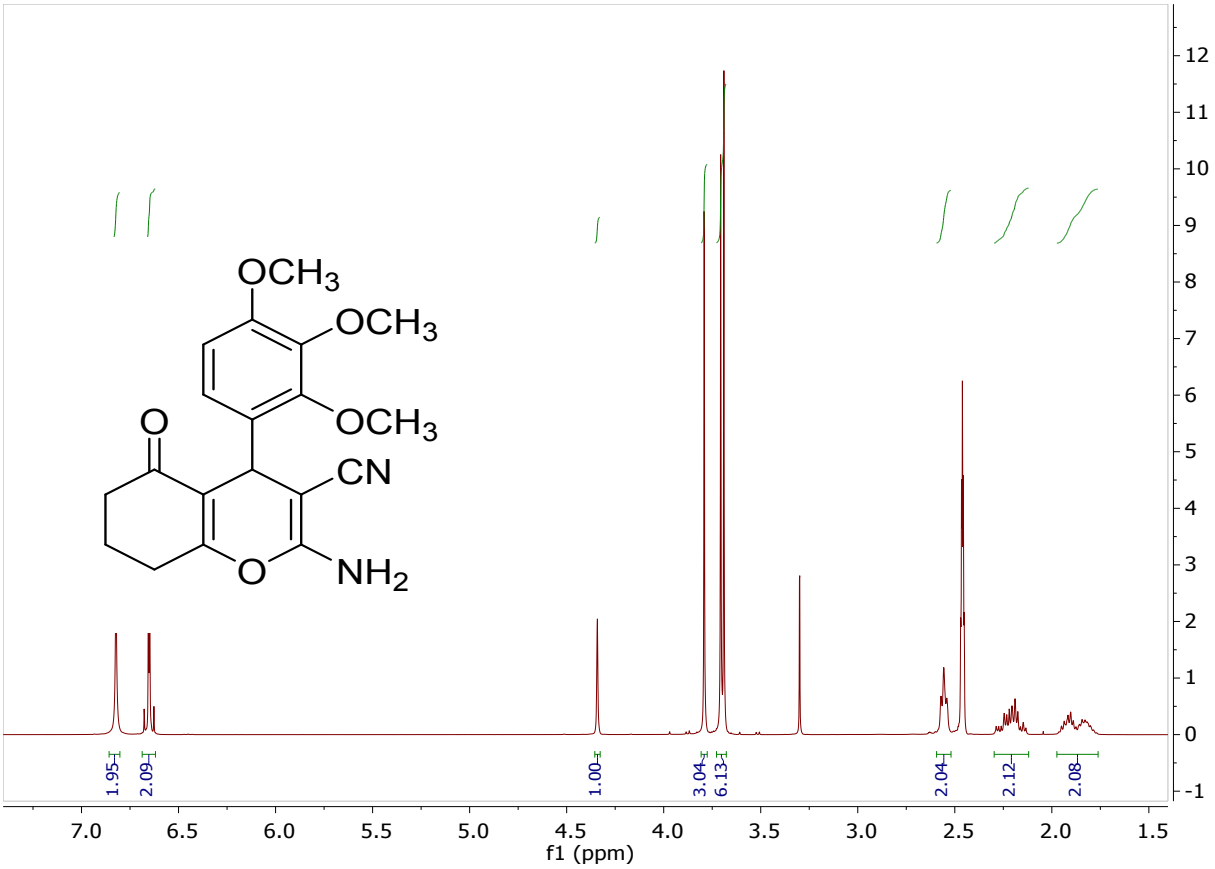


Figure SF11: ^{1}H NMR of **S5**.

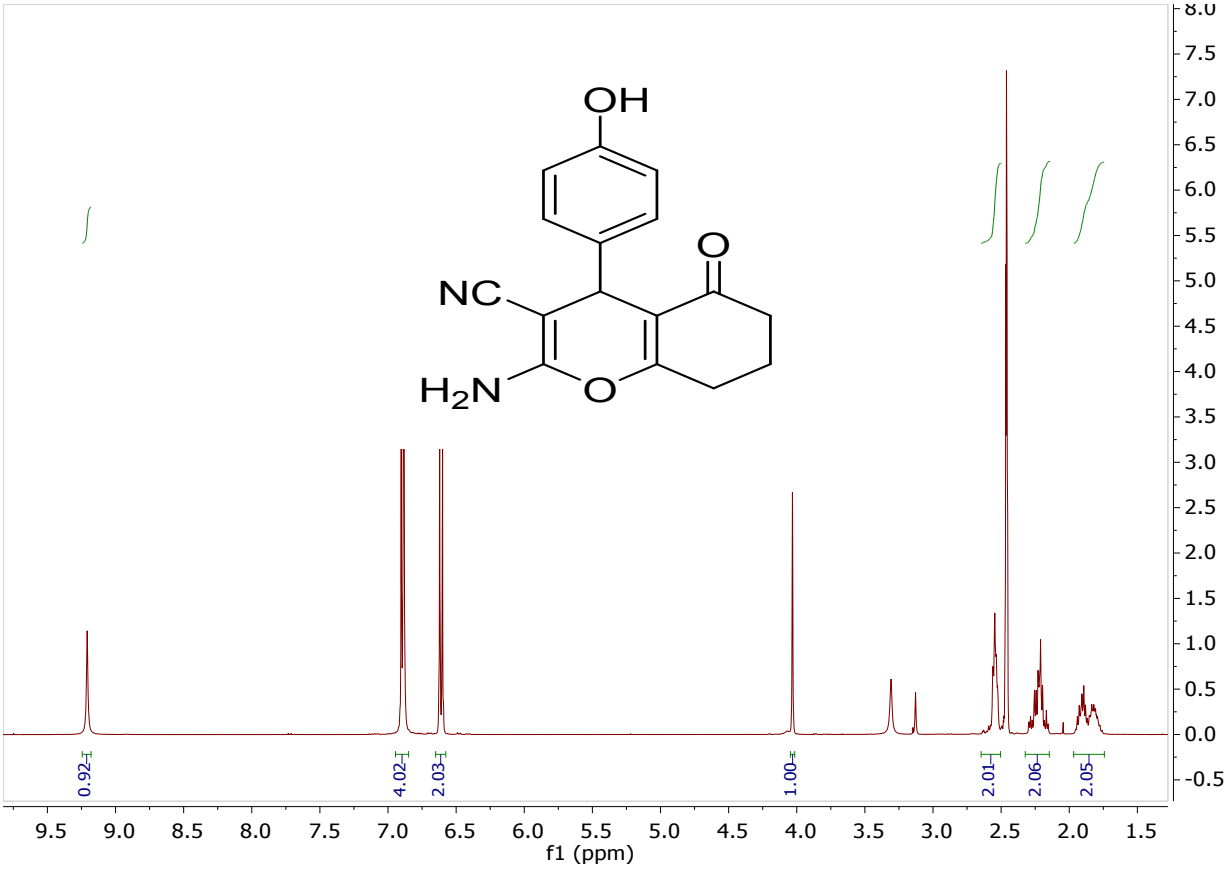


Figure SF12: ^{1}H NMR of **S6**.

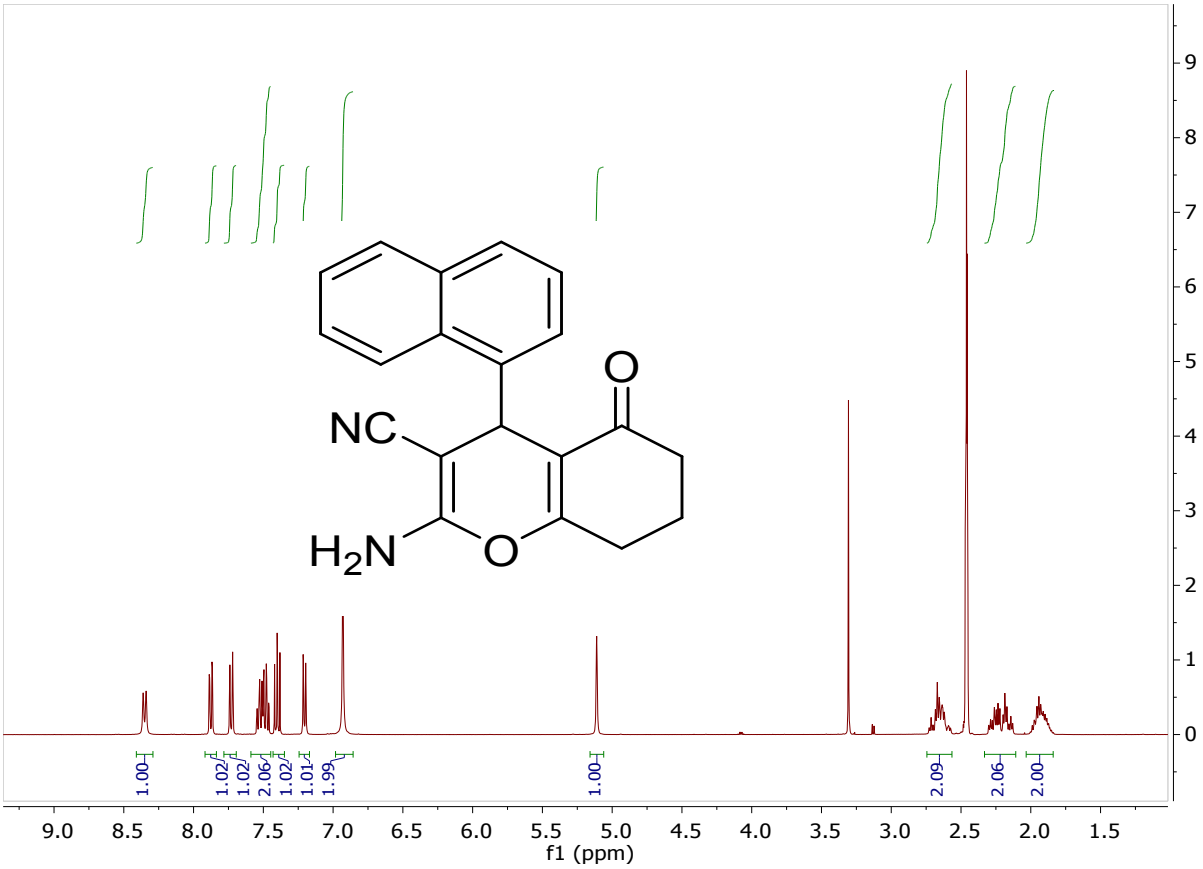


Figure SF13: ^{1}H NMR of **S7**.

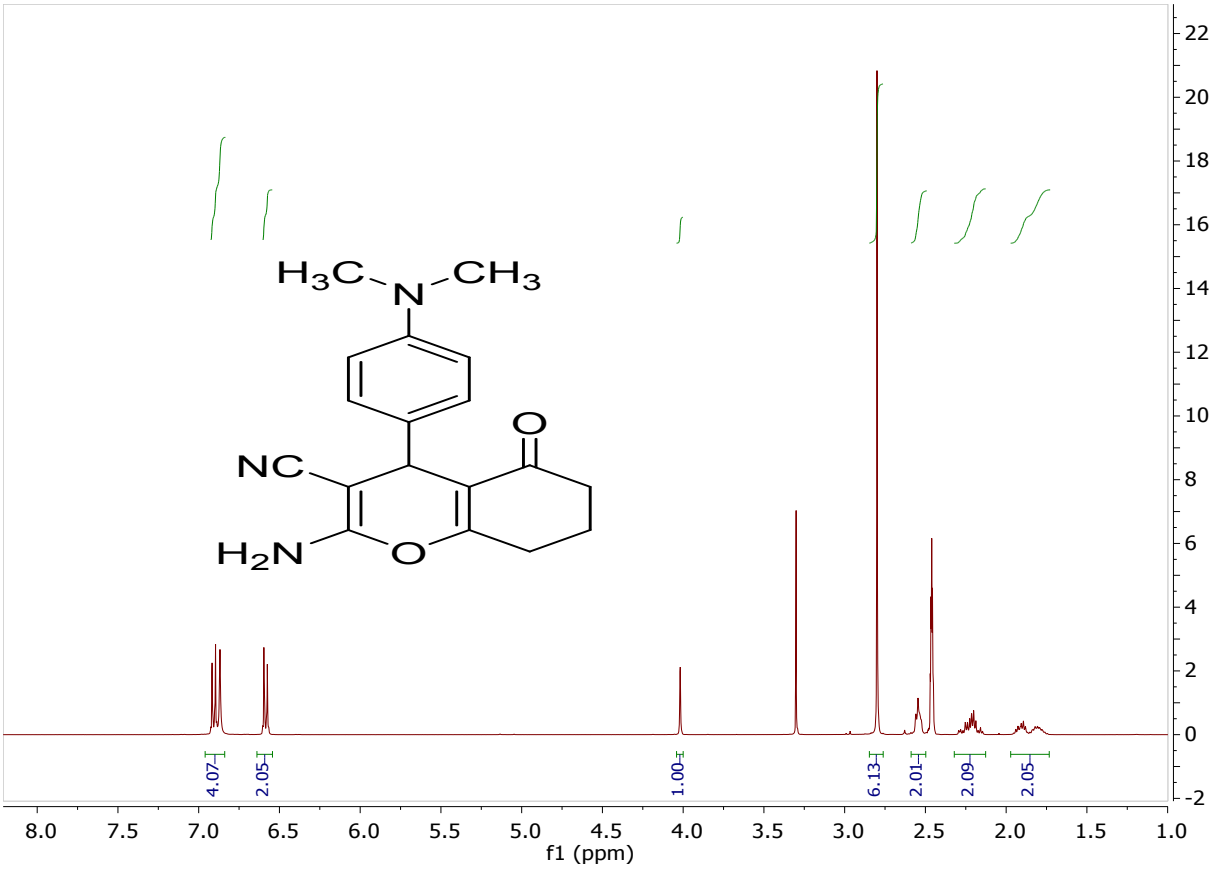


Figure SF14: ^{1}H NMR of **S8**.

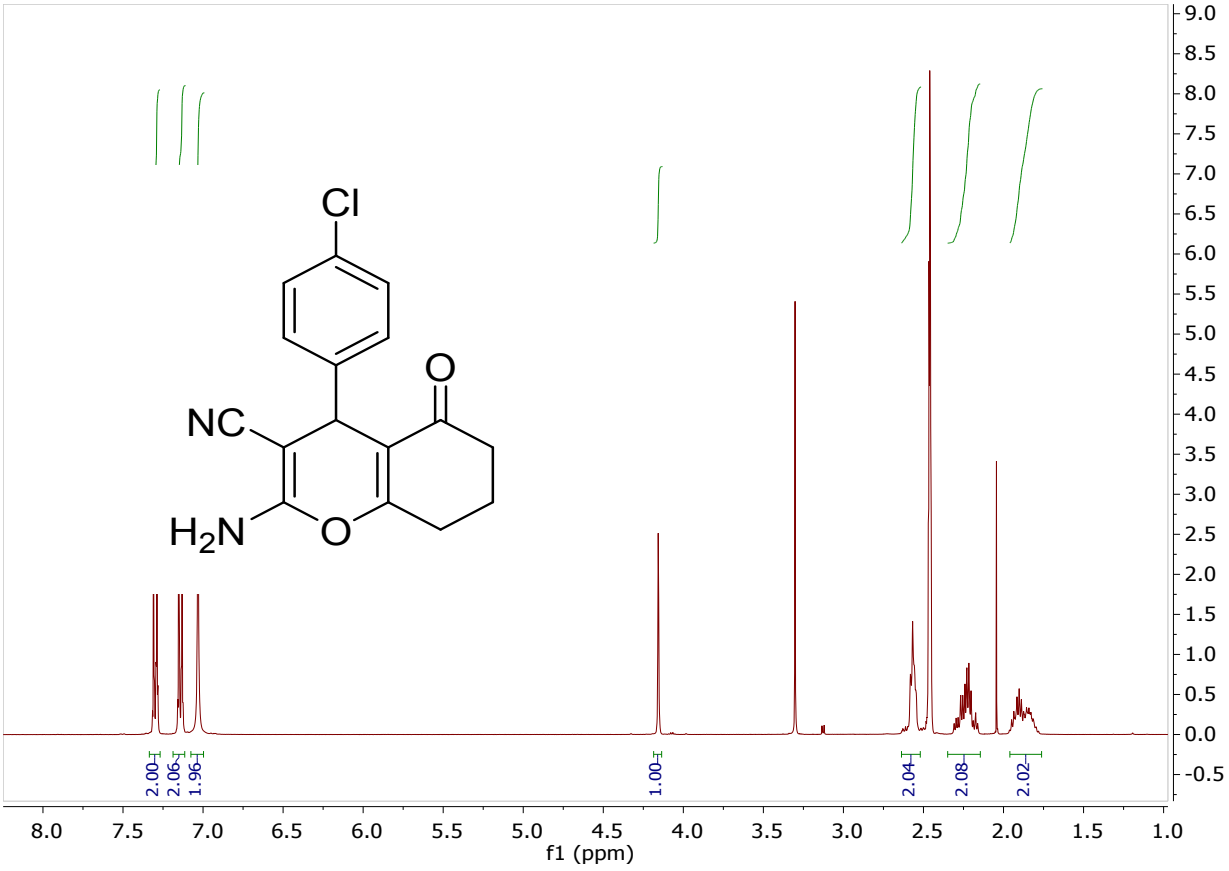


Figure SF15: ^{1}H NMR of **S9**.

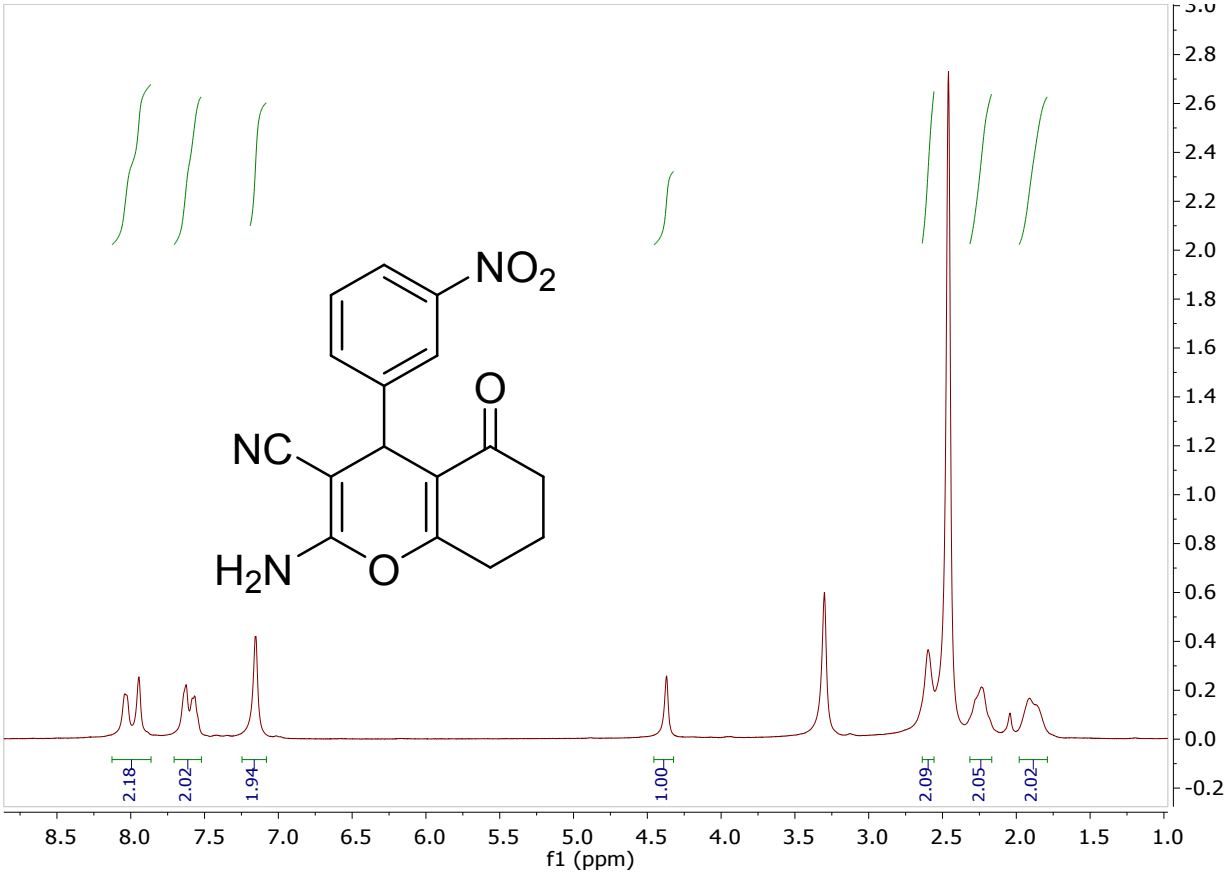


Figure SF16: ^{1}H NMR of **S10**.

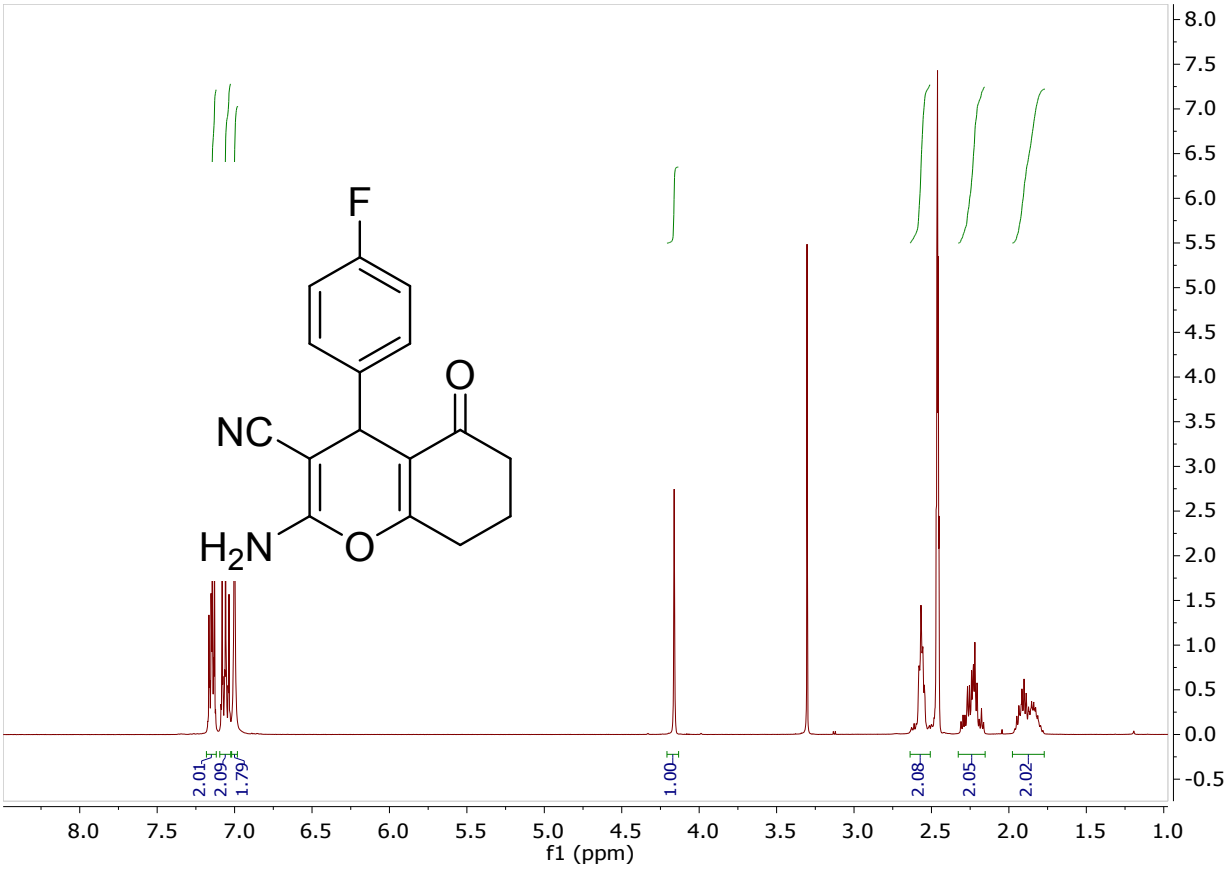


Figure SF17: ^{1}H NMR of **S11**.

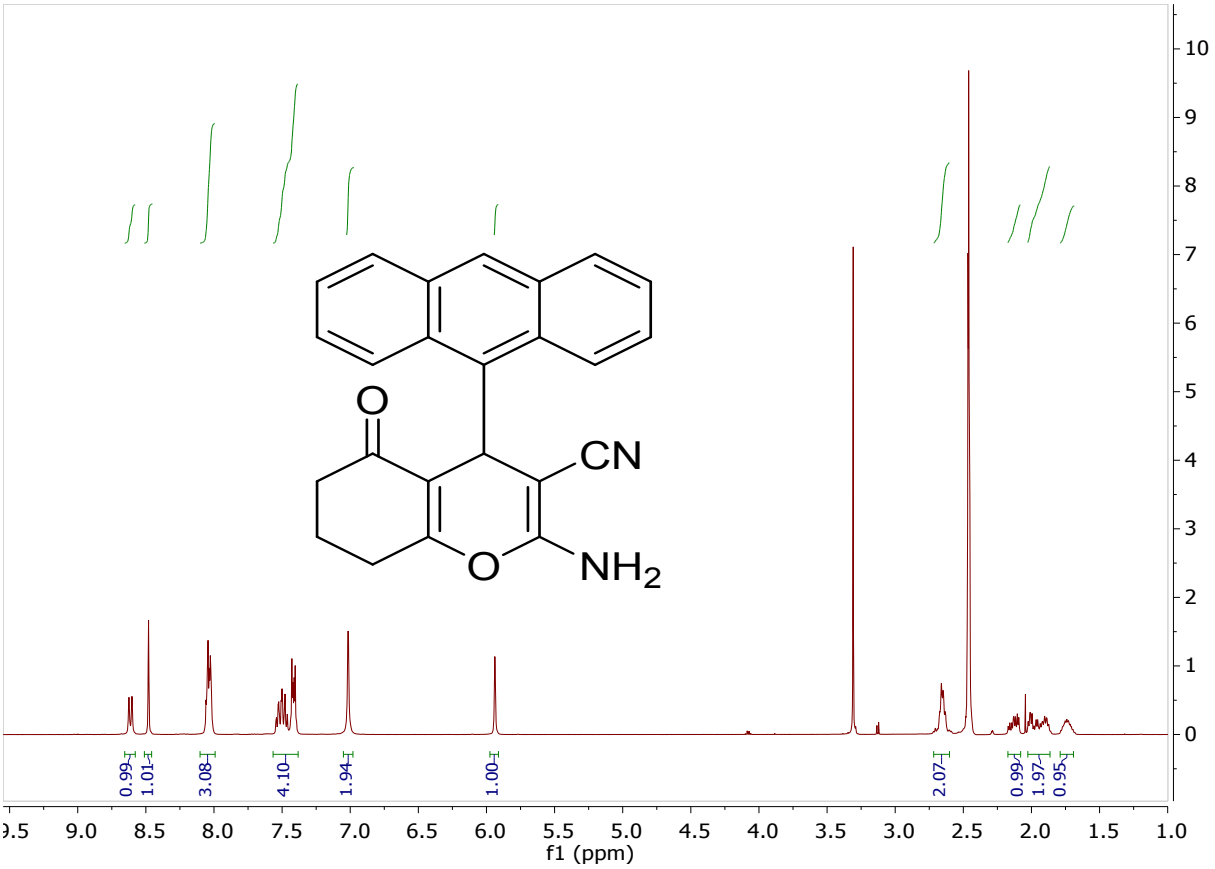
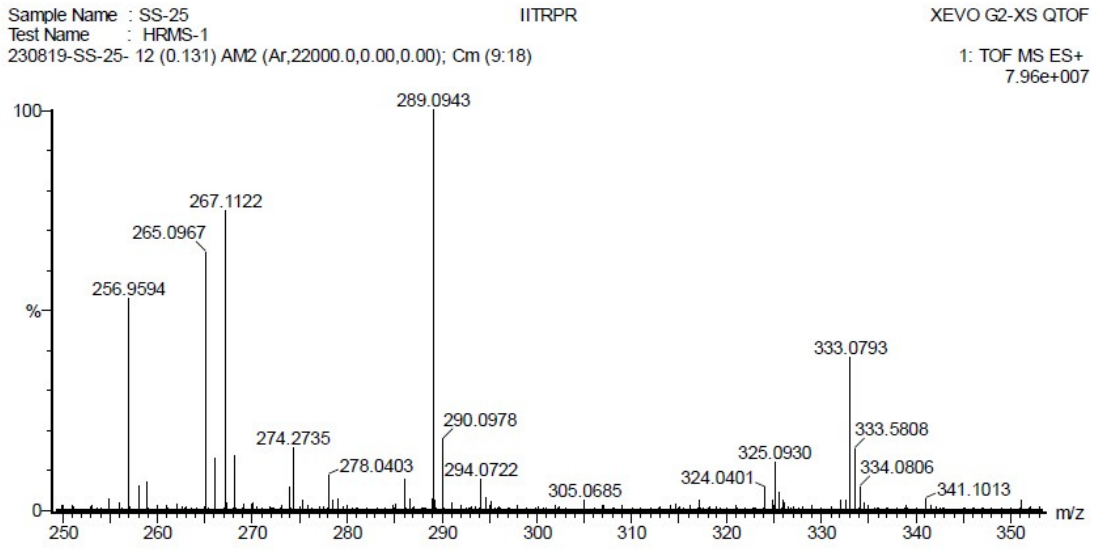


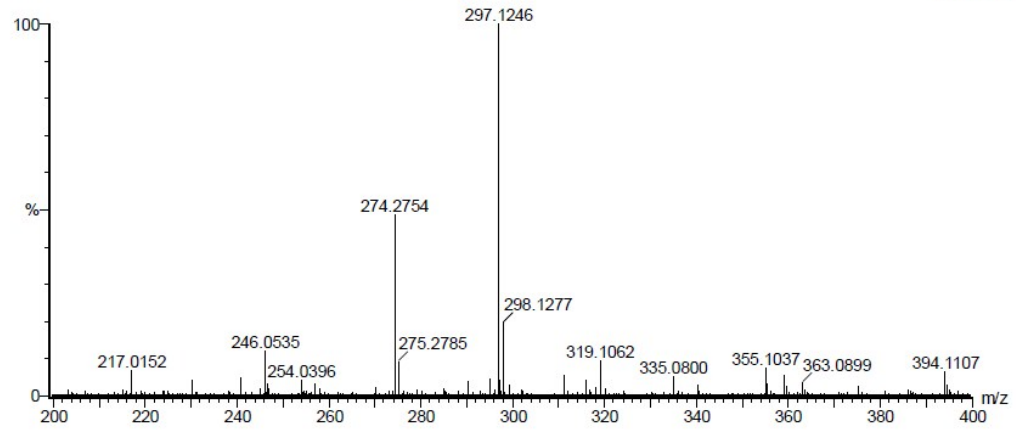
Figure SF18: ^{1}H NMR of **S12**.



Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
289.0943	289.0953	-1.0	-3.5	10.5	1030.2	n/a	n/a	C16 H14 N2 O2 Na

Figure SF19: HRMS data of S1.

Monoisotopic Mass, Even Electron Ions
15 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 9-25 H: 10-30 N: 0-2 O: 1-3

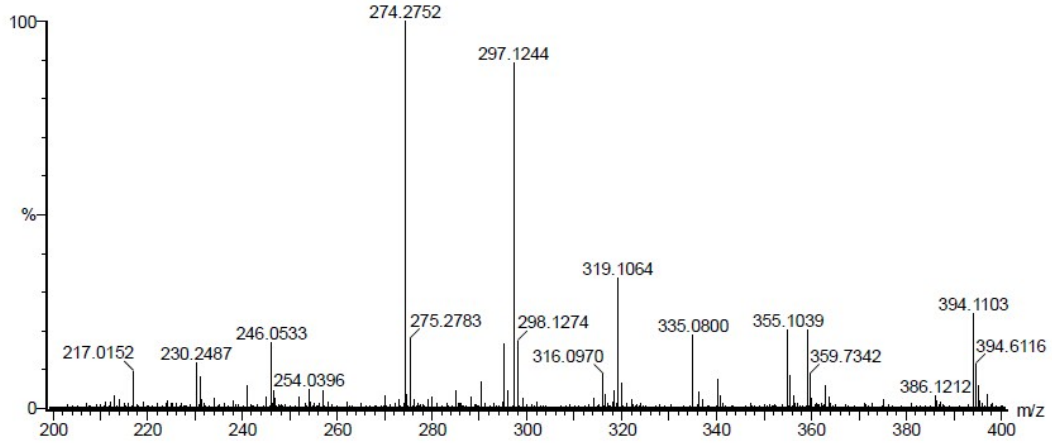


Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
297.1246	297.1239	0.7	2.4	10.5	795.4	n/a	n/a	C17 H17 N2 O3

Figure SF20: HRMS data of S2.

Monoisotopic Mass, Even Electron Ions
15 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 9-25 H: 10-30 N: 0-2 O: 1-3

Sample Name : SS-27 IITRPR XEVO G2-XS QTOF
Test Name : HRMS-1
260719-SS-27- 16 (0.165) AM2 (Ar,22000.0,0.00,0.00); Cm (16:18) 1: TOF MS ES+ 9.80e+006

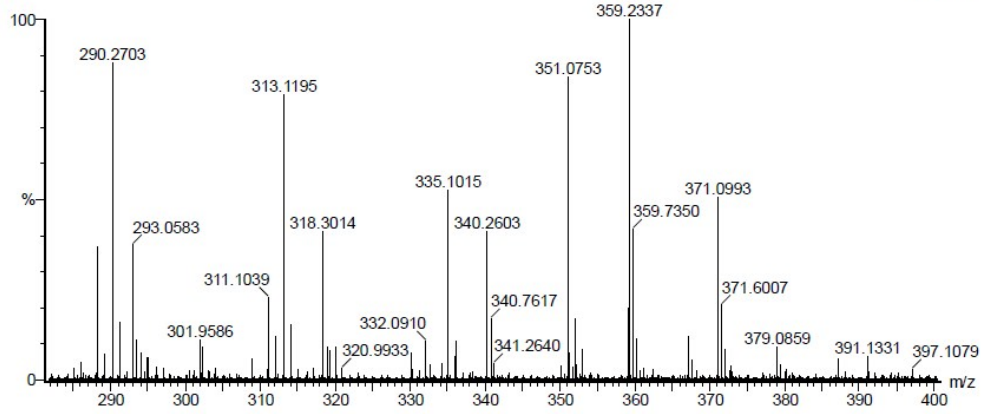


Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
297.1244	297.1239	0.5	1.7	10.5	873.1	n/a	n/a	C17 H17 N2 O3

Figure SF21: HRMS data of S3.

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: 9-25 H: 10-30 N: 0-2 O: 1-4

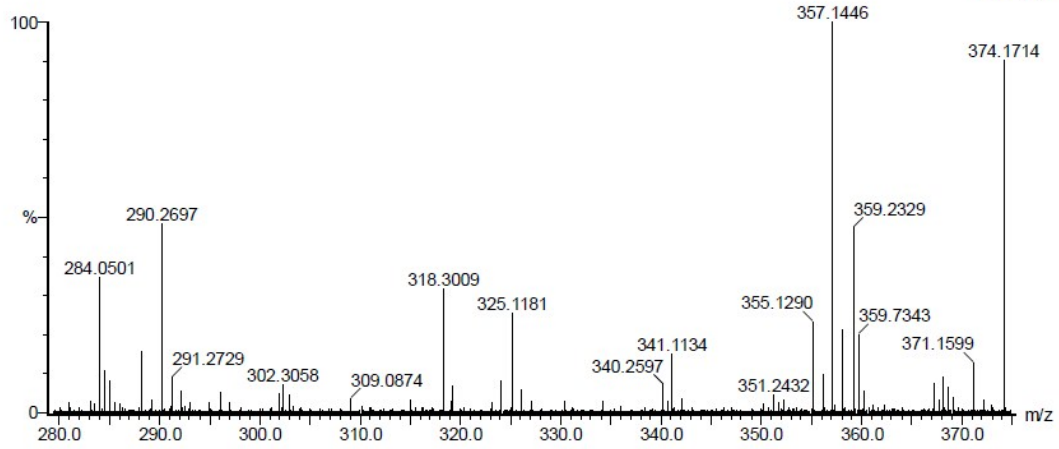
Sample Name : SS-28 IITRPR XEVO G2-XS QTOF
Test Name : HRMS-1
260719-SS-28- 12 (0.131) AM2 (Ar,22000.0,0.00,0.00); Cm (12:20) 1: TOF MS ES+ 5.15e+006



Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
313.1195	313.1188	0.7	2.2	10.5	834.1	n/a	n/a	C17 H17 N2 O4

Figure SF22: HRMS data of S4.

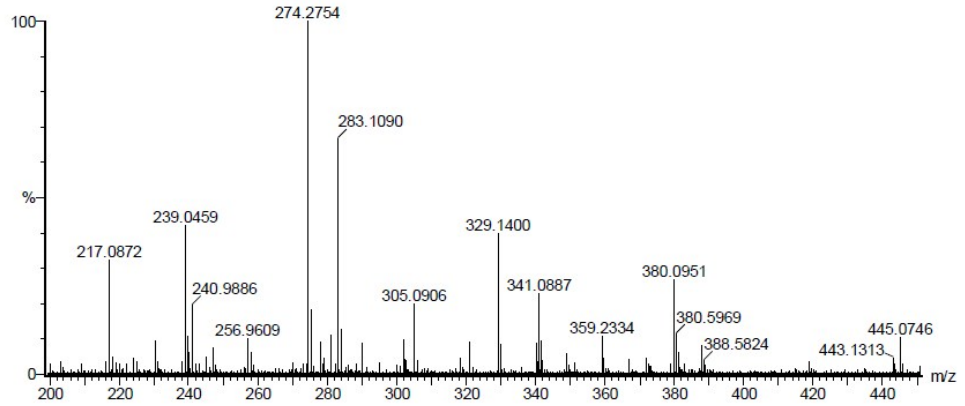
Monoisotopic Mass, Even Electron Ions
22 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 9-25 H: 10-30 N: 0-2 O: 1-5
Sample Name : SS-29 IITRPR XEVO G2-XS QTOF
Test Name : HRMS-1
260719-SS-29- 12 (0.131) AM2 (Ar,22000.0,0.00,0.00); Cm (7:19) 1: TOF MS ES+ 1.31e+007



Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
357.1446	357.1450	-0.4	-1.1	10.5	792.5	n/a	n/a	C19 H21 N2 O5

Figure SF23: HRMS data of S5.

Monoisotopic Mass, Even Electron Ions
25 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 9-25 H: 10-30 N: 0-2 O: 1-5
Sample Name : SS-30 IITRPR XEVO G2-XS QTOF
Test Name : HRMS-1
260719-SS-30 17 (0.174) AM2 (Ar,22000.0,0.00,0.00); Cm (17:22) 1: TOF MS ES+ 6.01e+006

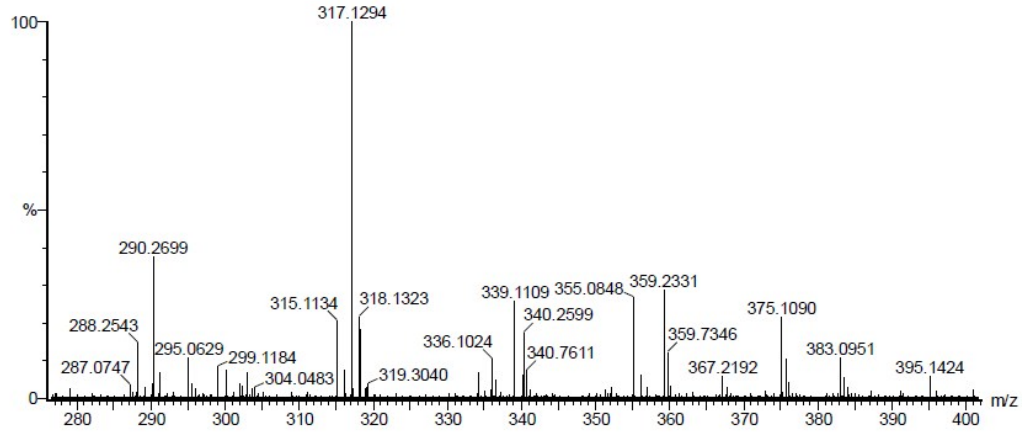


Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
283.1090	283.1083	0.7	2.5	10.5	843.5	n/a	n/a	C16 H15 N2 O3

Figure SF24: HRMS data of S6.

Monoisotopic Mass, Even Electron Ions
24 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 9-25 H: 10-30 N: 0-2 O: 1-5

Sample Name : SS-33 IITRPR XEVO G2-XS QTOF
Test Name : HRMS-1
260719-SS-33 12 (0.131) AM2 (Ar,22000.0,0.00,0.00); Cm (8:20) 1: TOF MS ES+
2.29e+007

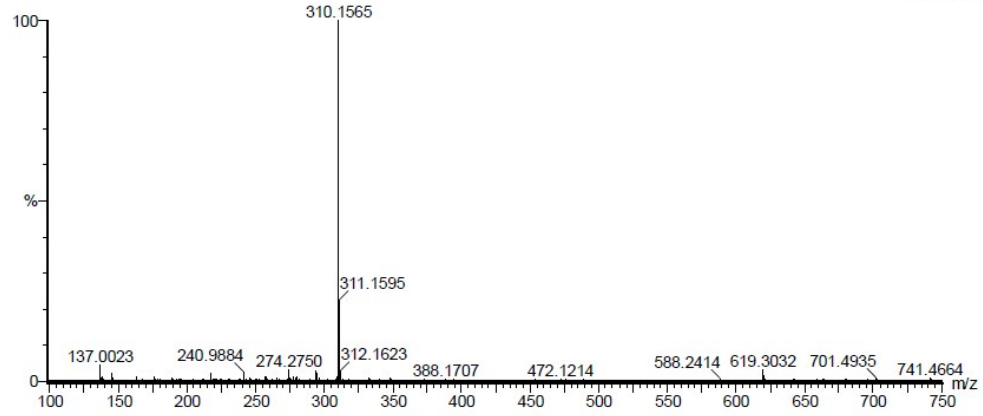


Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
317.1294	317.1290	0.4	1.3	13.5	829.4	n/a	n/a	C20 H17 N2 O2

Figure SF25: HRMS data of S7.

Monoisotopic Mass, Even Electron Ions
61 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 9-20 H: 10-25 N: 0-4 O: 1-5 Na: 0-1

Sample Name : SS-34 IITRPR XEVO G2-XS QTOF
Test Name : HRMS-1
260719-SS-34 19 (0.203) AM2 (Ar,22000.0,0.00,0.00); Cm (19:20) 1: TOF MS ES+
2.16e+007

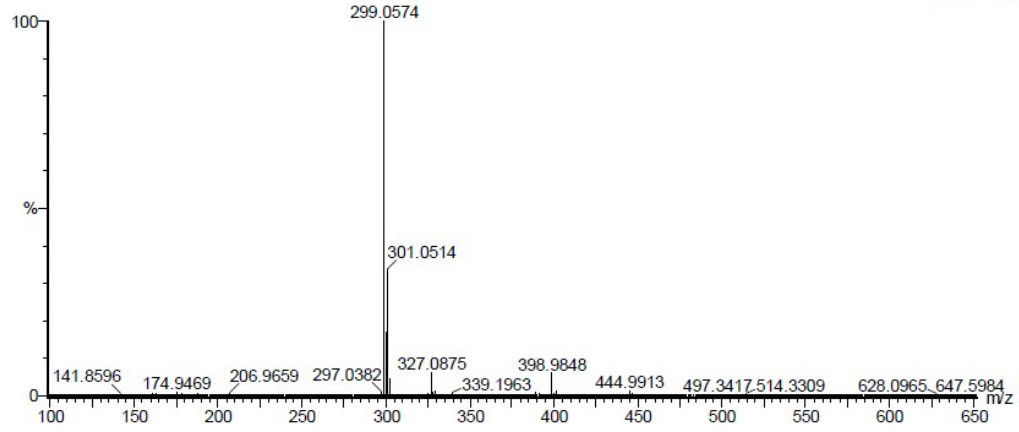


Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
310.1565	310.1556	0.9	2.9	10.5	818.7	n/a	n/a	C18 H20 N3 O2

Figure SF26: HRMS data of S8.

Monoisotopic Mass, Even Electron Ions
29 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 9-25 H: 10-30 N: 0-3 O: 1-2 Cl: 0-1

Sample Name : SS-39-R IITRPR XEVO G2-XS QTOF
Test Name : HRMS-1
091019-SS-39-R_ 16 (0.165) AM (Top,4, Ar,10000.0,0.00,0.00); Cm (16:22) 1: TOF MS ES-
7.35e+006

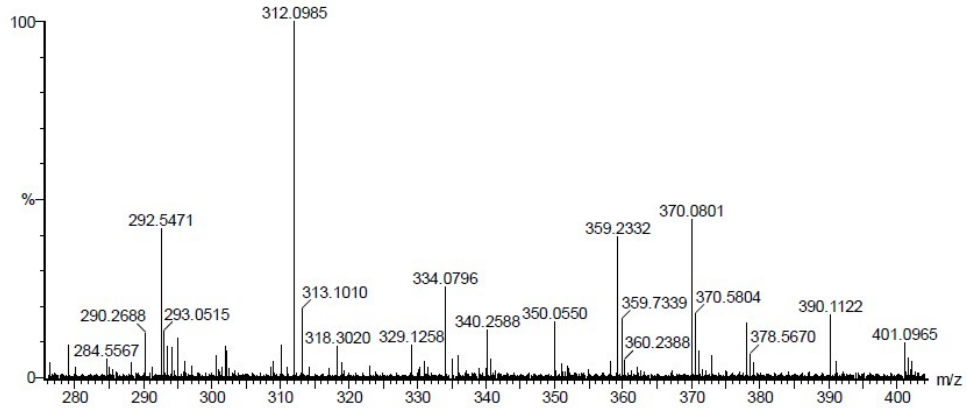


Minimum:				-1.5				
Maximum:		5.0	50.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
299.0574	299.0587	-1.3	-4.3	11.5	375.6	n/a	n/a	C16 H12 N2 O2 Cl

Figure SF27: HRMS data of S9.

Monoisotopic Mass, Even Electron Ions
37 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 9-25 H: 10-30 N: 0-3 O: 1-5

Sample Name : SS-40 IITRPR XEVO G2-XS QTOF
Test Name : HRMS-1
260719-SS-40 17 (0.174) AM (Top,4, Ar,10000.0,0.00,0.00); Cm (17:21) 1: TOF MS ES+
2.94e+006

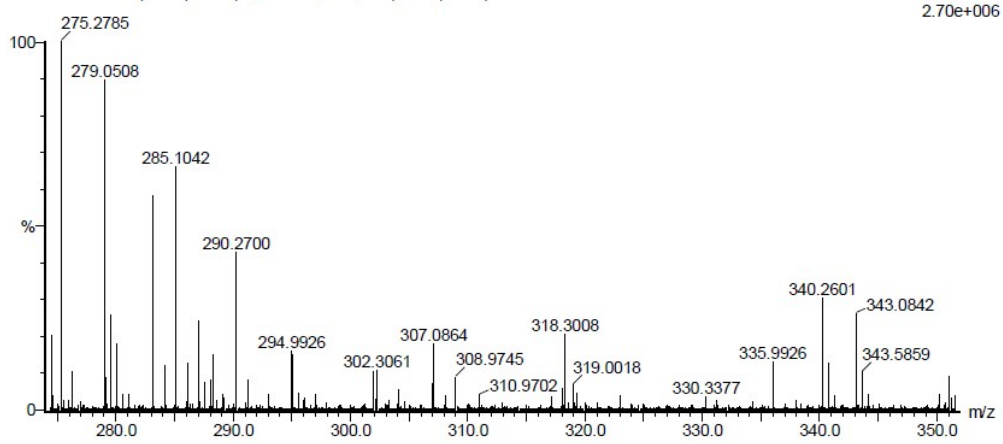


Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
312.0985	312.0984	0.1	0.3	11.5	889.0	n/a	n/a	C16 H14 N3 O4

Figure SF28: HRMS data of S10.

Monoisotopic Mass, Even Electron Ions
61 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 9-18 H: 10-30 N: 0-3 O: 1-5 F: 0-1

Sample Name : SS-42 IITRPR XEVO G2-XS QTOF
Test Name : HRMS-1
260719-SS-42 16 (0.165) AM2 (Ar,22000.0,0.00,0.00); Cm (16:21) 1: TOF MS ES+
2.70e+006



Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
285.1042	285.1039	0.3	1.1	10.5	887.4	n/a	n/a	C16 H14 N2 O2 F

Figure SF29: HRMS data of S11.

Monoisotopic Mass, Even Electron Ions
26 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 9-25 H: 10-30 N: 0-3 O: 1-5

Sample Name : SS-43 IITRPR XEVO G2-XS QTOF
Test Name : HRMS-1
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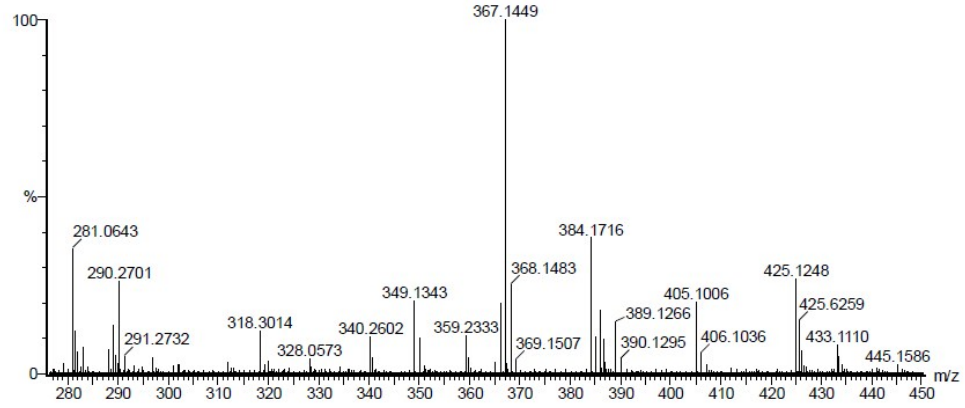
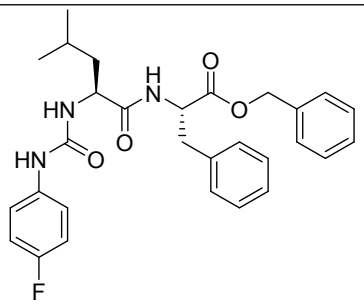
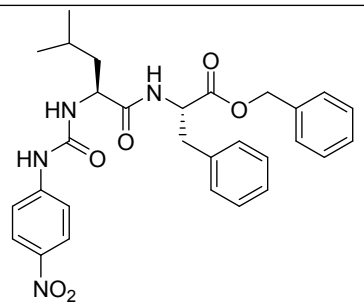
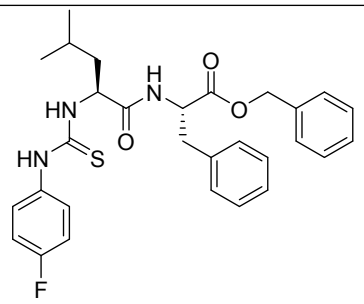
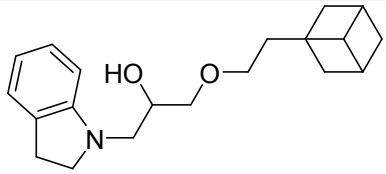
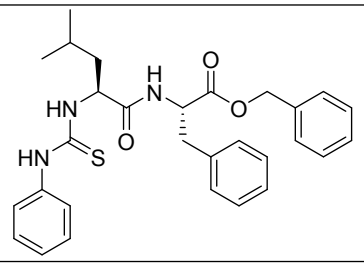
1.11e+007

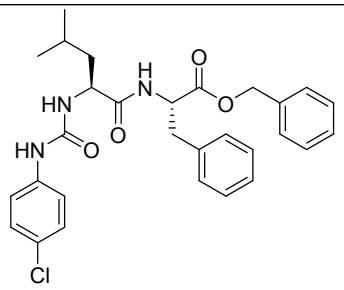
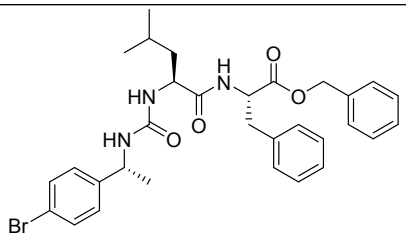
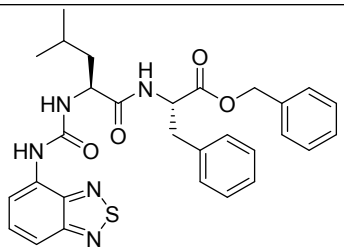
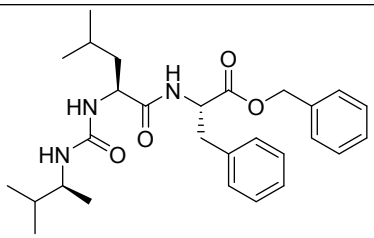
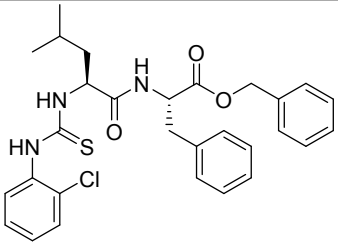


Minimum:				-1.5				
Maximum:		5.0	5.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
367.1449	367.1447	0.2	0.5	16.5	744.7	n/a	n/a	C24 H19 N2 O2

Figure SF30: HRMS data of S12.

Table S1: Possible structure of dipeptide derivatives and their dock score.

S.No.	Code	Chemical structure	Dock score (g)
1.	SS1		-3.70
2.	SS2		-2.87
3.	SS3		-2.72
4.	SS4	 ADDA (Cytochrome c inhibitor)	-2.45
5.	SS5		-3.10

6.	SS6		-2.67
7.	SS7		-3.47
8.	SS8		-3.682
9.	SS9		-3.36
10.	SS10		-3.17

Crystal Data of S10

Table S2 Crystal data and structure refinement.	
Identification code	S-10
Empirical formula	$C_{16}H_{13}N_3O_4$
Formula weight	311.30
Temperature/K	273.15
Crystal system	triclinic
Space group	P-1
a/Å	9.0134(4)
b/Å	9.0528(4)
c/Å	9.6602(5)
α/°	70.923(2)
β/°	76.940(2)
γ/°	75.474(2)
Volume/Å^3	712.15(6)
Z	2
ρ_{calc}g/cm^3	1.4516
μ/mm^{-1}	0.107
F(000)	324.2
Crystal size/mm^3	0.4 × 0.12 × 0.1
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.52 to 56.56
Index ranges	-12 ≤ h ≤ 12, -12 ≤ k ≤ 12, -12 ≤ l ≤ 12
Reflections collected	17207
Independent reflections	3514 [R_{int} = 0.0319, R_{sigma} = 0.0241]
Data/restraints/parameters	3514/0/216
Goodness-of-fit on F^2	1.096
Final R indexes [I>=2σ (I)]	R_1 = 0.0440, wR_2 = 0.1111
Final R indexes [all data]	R_1 = 0.0559, wR_2 = 0.1239
Largest diff. peak/hole / e Å^{-3}	0.26/-0.32

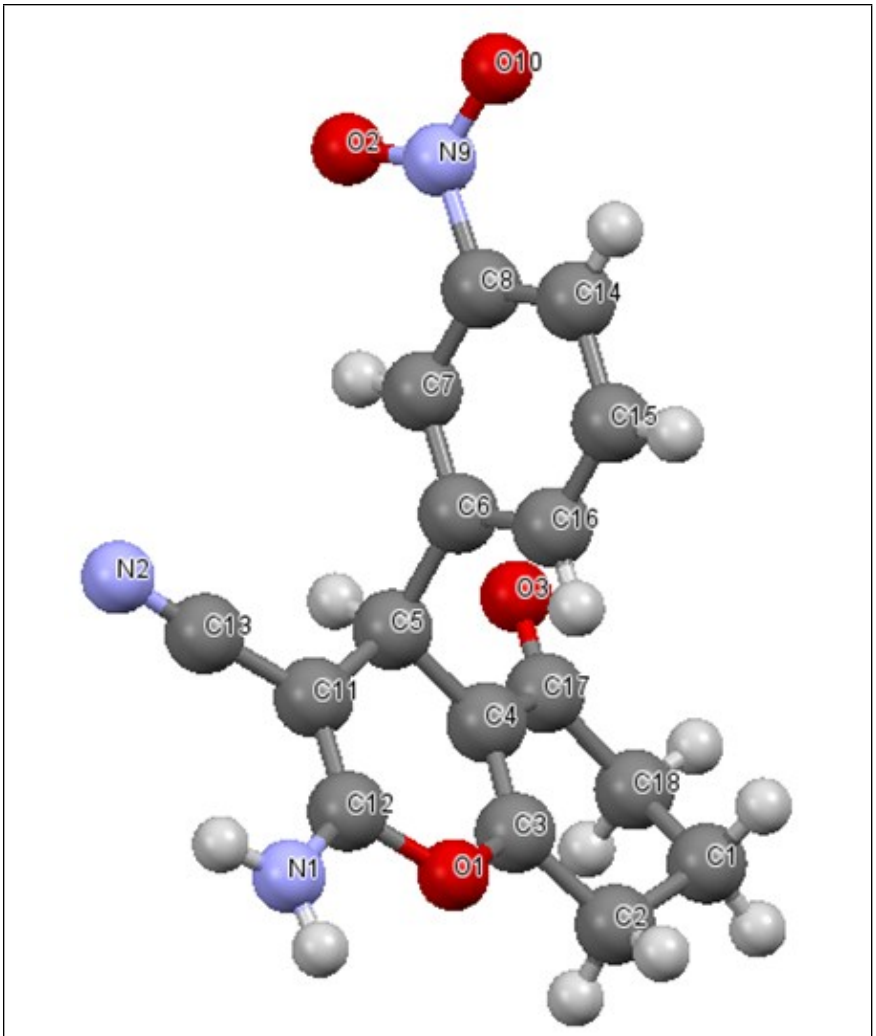


Table S3 Bond Lengths for S10.

Atom	Atom	Length/Å		Atom	Atom	Length/Å
O1	C3	1.3772(16)		C5	C11	1.5141(18)
O1	C12	1.3667(16)		C6	C7	1.3862(18)
O2	N9	1.213(2)		C6	C16	1.390(2)
O3	C17	1.2203(17)		C7	C8	1.383(2)
N1	C12	1.3372(18)		C8	N9	1.4689(19)
N2	C13	1.1440(19)		C8	C14	1.372(2)
C1	C2	1.519(2)		N9	O10	1.2129(19)
C1	C18	1.522(2)		C11	C12	1.3559(18)
C2	C3	1.4880(19)		C11	C13	1.4116(19)
C3	C4	1.3370(18)		C14	C15	1.384(2)
C4	C5	1.5052(18)		C15	C16	1.381(2)
C4	C17	1.4666(18)		C17	C18	1.501(2)
C5	C6	1.5252(19)				

Table S4 Bond Angles for S10.								
Atom	**Atom**	**Atom**	**Angle/°**		**Atom**	**Atom**	**Atom**	**Angle/°**
C12	O1	C3	118.70(10)		C14	C8	N9	118.78(14)
C18	C1	C2	110.62(13)		C8	N9	O2	118.72(14)
C3	C2	C1	111.05(12)		O10	N9	O2	122.56(16)
C2	C3	O1	110.90(11)		O10	N9	C8	118.71(16)
C4	C3	O1	122.83(12)		C12	C11	C5	122.78(12)
C4	C3	C2	126.26(12)		C13	C11	C5	117.28(11)
C5	C4	C3	122.45(12)		C13	C11	C12	119.84(12)
C17	C4	C3	119.07(12)		N1	C12	O1	110.54(12)
C17	C4	C5	118.43(11)		C11	C12	O1	121.68(12)
C6	C5	C4	111.66(11)		C11	C12	N1	127.77(13)
C11	C5	C4	108.69(10)		C11	C13	N2	177.02(16)
C11	C5	C6	110.63(11)		C15	C14	C8	117.67(15)
C7	C6	C5	120.64(12)		C16	C15	C14	120.25(15)
C16	C6	C5	120.81(12)		C15	C16	C6	121.49(15)
C16	C6	C7	118.51(13)		C4	C17	O3	120.73(13)
C8	C7	C6	118.84(14)		C18	C17	O3	121.83(13)
N9	C8	C7	118.00(14)		C18	C17	C4	117.36(12)
C14	C8	C7	123.22(14)		C17	C18	C1	112.87(13)

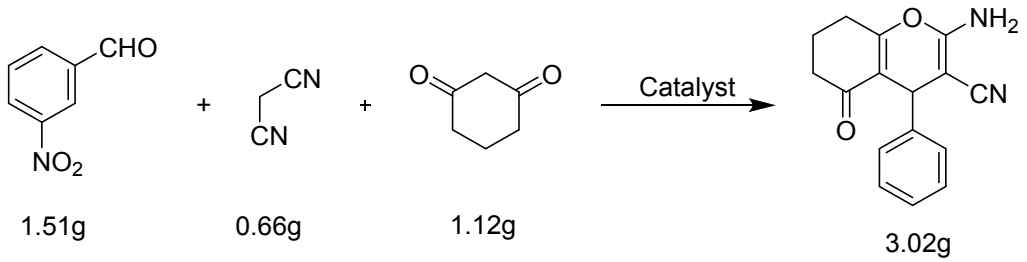
Table S5 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for S10.				
Atom	***x***	***y***	***z***	**U(eq)**
H1c	10964.1(18)	1803.5(19)	4282(2)	51.7(4)
H1d	12661.2(18)	1663.1(19)	3400(2)	51.7(4)
H2a	12109.9(17)	417.8(17)	1926.6(18)	44.9(4)
H2b	11355.9(17)	-425.3(17)	3534.1(18)	44.9(4)
H5	7130.0(15)	3736.9(15)	766.6(15)	34.6(3)
H7	4824.2(16)	5182.7(16)	1805.1(16)	39.9(4)
H14	2943.7(19)	3724(2)	6096.9(19)	55.1(5)
H15	4904(2)	1465(2)	6426.1(19)	60.5(5)
H16	6773.7(18)	1064.7(19)	4457.7(18)	50.1(4)
H18a	11238.3(19)	4295.0(19)	2666(2)	58.8(5)
H18b	11833.8(19)	3583.7(19)	1318(2)	58.8(5)
H1a	8680(20)	-2220(30)	1460(20)	56(6)
H1b	7150(20)	-1430(20)	870(20)	58(6)

Table S6: Eco-Scale calculation for the reaction of 3-nitrobenzaldehyde, 1,3-cyclohexanedione and malononitrile in 10 mol scale.

	detail of parameters	penalty points[a]
1. yield	94%	3
2. cost of reactants to obtain 10 mmol of product		
	3-nitrobenzaldehyde	0
	1,3-cyclohexanedione	0
	malononitrile	0
	Cytochrome c	3
	Leucine Phenyl alanine Phosphate buffer saline	0 0 0
3. safety		
	3-nitrobenzaldehyde	5 (T)
	1,3-cyclohexanedione	5 (T)
	malononitrile	5 (N)
	Cytochrome c	0
	Leucine Phenyl alanine	0 0
	PBS	0
4. technical setup	stirrer	0
5. temperature /time	room temperature, < 1 h	0
	30 min	0
6. work-up and purification		
	solvent added	0
	filtration	0

[a]Total of all penalties is 21. The total score is found to be 79 (100-21), indicating acceptable synthesis.

Table S7. Calculation of E-factor for the reaction of 3-nitrobenzaldehyde, 1,3-cyclohexanedione and malononitrile.



Total amount of reactants: 1.51 g + 1.12 g + 0.66 g = 3.29 g
Amount of final product: 3.02 g
Amount of waste: 3.29 g – 3.02 g = 0.27 g
E-factor = amount of waste/amount of product = 0.27 g/3.02 g = 0.089.

Table S8. Comparison of the synthesis reported in the literature with the present work[14,38].

Entry	Catalyst	medium	Time	Yield (%)
1	Piperidine	water	5h	78
2	L-proline	water	5h	81
3	-----	glycerol	190 min	89
4	mono-6-NH2-β-CD	water	1h	69
5	per-6-NH2-β-CD	DMSO	1h	76
6	per-6-NH2-β-CD	DMF	1h	81
7	per-6-NH2-β-CD	EtOH	1h	86
8	Cyt.c+SS1	PBS	30 min	94 (present work)