SUPPLEMENTARY MATERIAL

Design of hybrid quinoline-chalcone compounds against *Leishmania amazonensis* based on computational techniques: 2D- and 3D-QSAR with experimental validation

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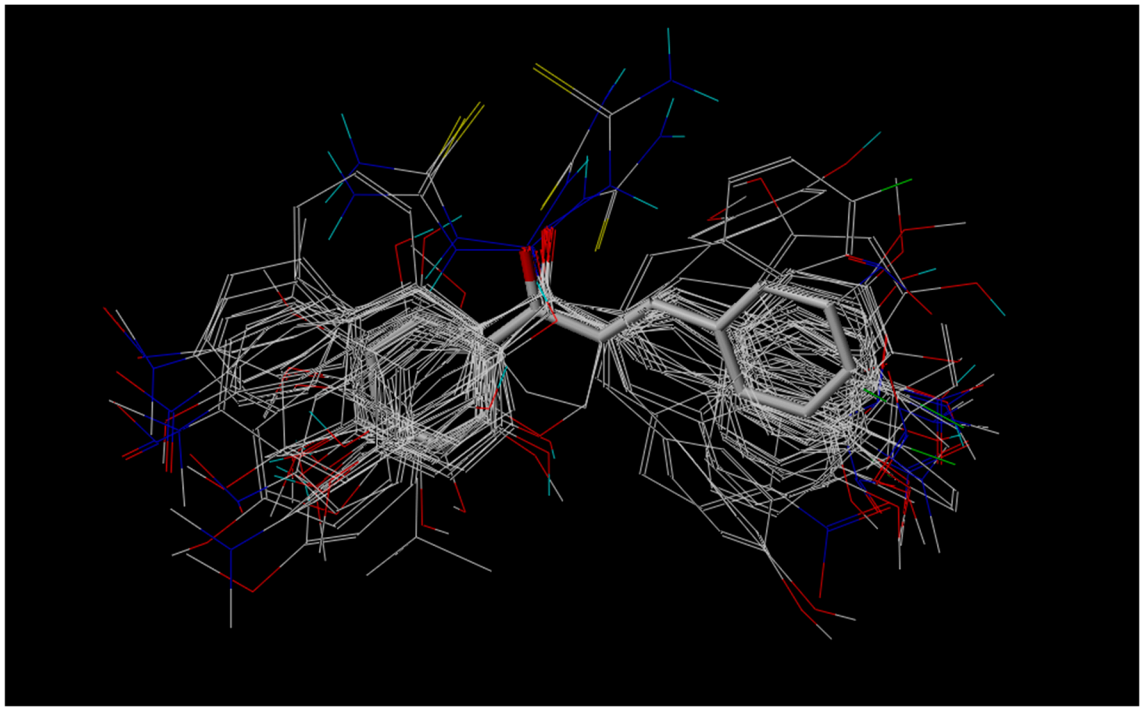
1. Theoretical Models



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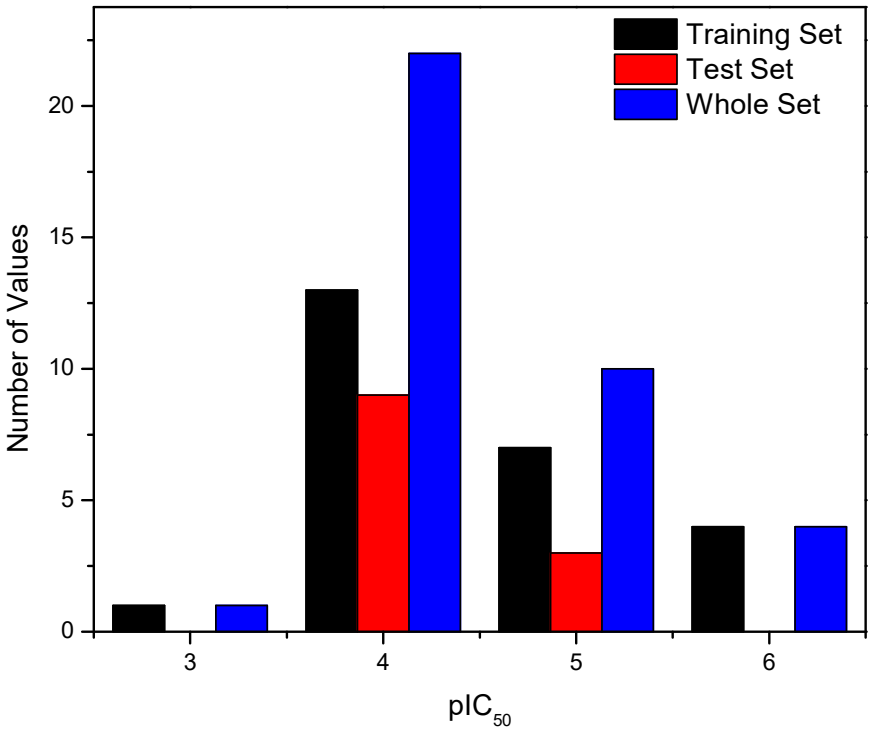

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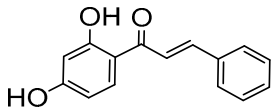
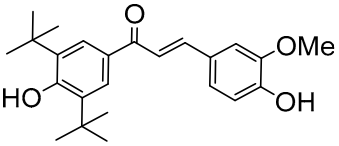
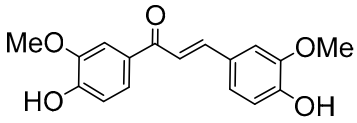
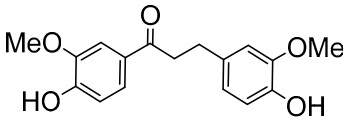
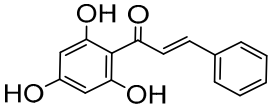
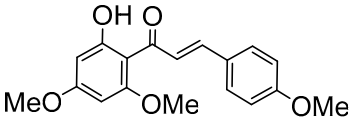
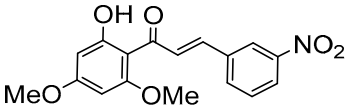
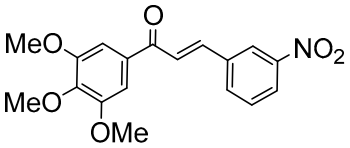
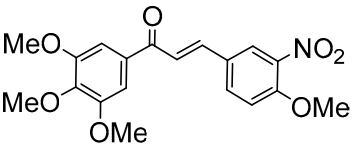
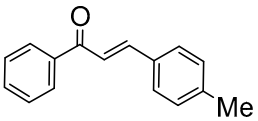
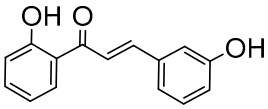
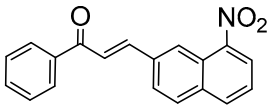
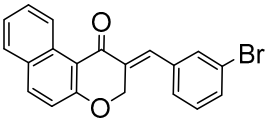
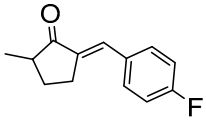
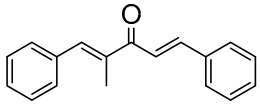
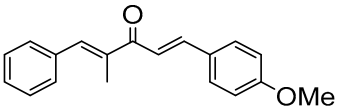
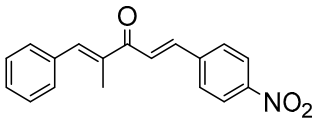
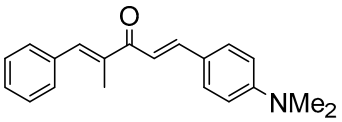
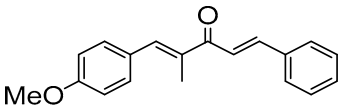
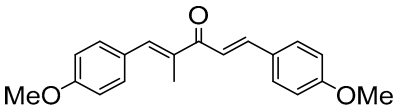
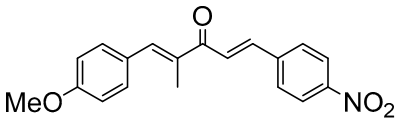
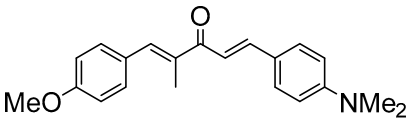
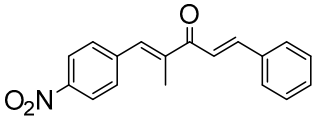
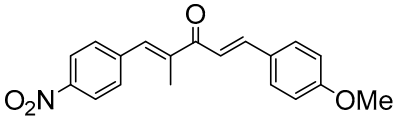
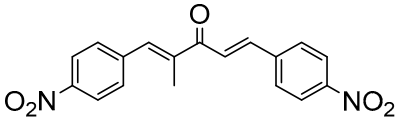
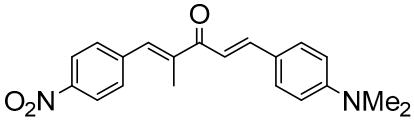
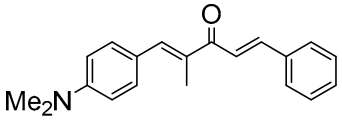
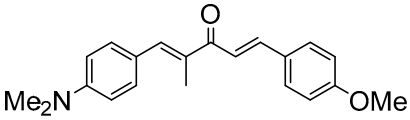
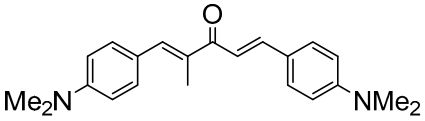
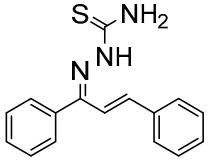
 001 IC_{50}= 0.4x10^{-6} M pIC_{50}= 6.3979 M [1]	 002 IC_{50}= 6.9x10^{-6} M pIC_{50}= 5.1612 M [2]	 003 IC_{50}= 20.5x10^{-6} M pIC_{50}= 4.6882 M [2]
 004 IC_{50}= 16.5x10^{-6} M pIC_{50}= 4.7825 M [2]	 005 IC_{50}= 3.83x10^{-6} M pIC_{50}= 5.4168 M [3]	 006 IC_{50}= 7.60x10^{-6} M pIC_{50}= 5.1192 M [3]
 007 IC_{50}= 0.45x10^{-6} M pIC_{50}= 6.3468 M [3]	 008 IC_{50}= 0.26x10^{-6} M pIC_{50}= 6.585 M [3]	 009 IC_{50}= 2.46x10^{-6} M pIC_{50}= 5.6091 M [3]
 010 IC_{50}= 14.4x10^{-6} M pIC_{50}= 4.8416 M [3]	 011 IC_{50}= 0.83x10^{-6} M pIC_{50}= 6.0809 M [3]	 012 IC_{50}= 1.74x10^{-6} M pIC_{50}= 5.7595 M [3]
 013 IC_{50}= 4.08x10^{-6} M pIC_{50}= 5.3893 M [3]	 014 IC_{50}= 8.59x10^{-6} M pIC_{50}= 5.066 M [3]	 015 IC_{50}= 15.3x10^{-6} M pIC_{50}= 4.8153 M [4]
 016 IC_{50}= 20.4x10^{-6} M pIC_{50}= 4.6904 M [4]	 017 IC_{50}= 11.6x10^{-6} M pIC_{50}= 4.9355 M [4]	 018 IC_{50}= 20.0x10^{-6} M pIC_{50}= 4.699 M [4]

 019 IC_{50}= 22.3x10^{-6} M pIC_{50}= 4.6517 M [4]	 020 IC_{50}= 21.8x10^{-6} M pIC_{50}= 4.6615 M [4]
 021 IC_{50}= 14.8x10^{-6} M pIC_{50}= 4.8297 M [4]	 022 IC_{50}= 18.0x10^{-6} M pIC_{50}= 4.7447 M [4]
 023 IC_{50}= 13.4x10^{-6} M pIC_{50}= 4.8729 M [4]	 024 IC_{50}= 15.5x10^{-6} M pIC_{50}= 4.8097 M [4]
 025 IC_{50}= 3.4x10^{-6} M pIC_{50}= 5.4685 M [4]	 026 IC_{50}= 12.0x10^{-6} M pIC_{50}= 4.9208 M [4]
 027 IC_{50}= 21.5 x10^{-6} M pIC_{50}= 4.6676 M [4]	 028 IC_{50}= 20.1x10^{-6} M pIC_{50}= 4.6968 M [4]
 029 IC_{50}= 20.5x10^{-6} M pIC_{50}= 4.6882 M [4]	 030 IC_{50}= 14.68x10^{-6} M pIC_{50}= 4.8333 M [5]

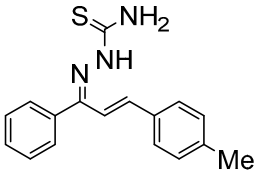
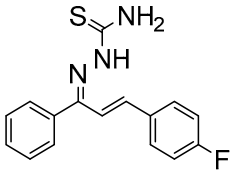
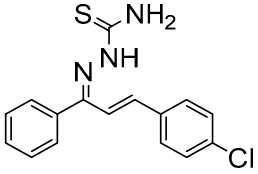
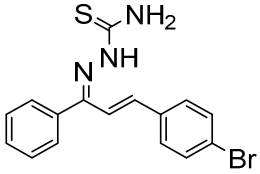
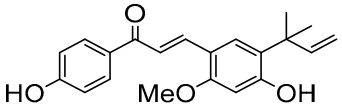
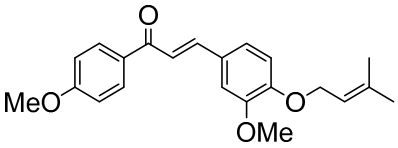
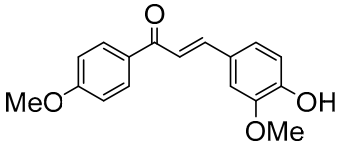
 031 IC_{50}= 14.80x10^{-6} M pIC_{50}= 4.8297 M [5]	 032 IC_{50}= 13.09x10^{-6} M pIC_{50}= 4.8831 M [5]
 033 IC_{50}= 5.22x10^{-6} M pIC_{50}= 5.2823 M [5]	 034 IC_{50}= 12.52x10^{-6} M pIC_{50}= 4.9024 M [5]
 035 IC_{50}= 3.38x10^{-6} M pIC_{50}= 5.4711 M [6]	 036 IC_{50}= 67.16x10^{-6} M pIC_{50}= 4.1729 M [6]
 037 IC_{50}= 287.26x10^{-6} M pIC_{50}= 3.5417 M [6]	

Table S2: Field combination of CoMSIA models of *Leishmania amazonensis* inhibitors

CoMSIA	q^2	N	SEP	SEE	r^2	F	Field Contribution				
							S	E	H	D	A
S	0.749	15	0.567	0.004	1.000	55754.2	1.000				
E	0.451	5	0.576	0.070	0.992	460.3		1.000			
H	0.384	3	0.581	0.166	0.950	132.1			1.000		
D	-0.165	1	0.763	0.576	0.336	11.6				1.000	
A	-0.006	1	0.709	0.546	0.403	15.5					1.000
SE	0.699	11	0.516	0.001	1.000	549047	0.477	0.523			
SEH	0.634	10	0.548	0.001	1.000	1280000	0.327	0.374	0.298		
SEHD	0.539	6	0.542	0.034	0.998	1634.5	0.276	0.274	0.216	0.234	
SEHA	0.586	11	0.605	0.001	1.000	2040000	0.298	0.336	0.264		0.102
SED	0.576	7	0.535	0.023	0.999	3064.3	0.362	0.350		0.283	
SEA	0.633	6	0.484	0.027	0.999	2547.8	0.419	0.448			0.133
SEDA	0.550	7	0.551	0.027	0.999	2276.4	0.344	0.333		0.249	0.074
SH	0.608	2	0.453	0.230	0.899	98	0.538		0.462		
SD	0.629	6	0.486	0.101	0.984	185	0.613			0.387	
SA	0.664	2	0.421	0.167	0.915	129.8	0.775				0.225
SHD	0.540	4	0.514	0.112	0.978	222.8	0.402		0.314	0.285	
SHA	0.582	3	0.478	0.153	0.957	156.8	0.469		0.394		0.137
SDA	0.588	6	0.513	0.112	0.980	149.6	0.570			0.333	0.097
SHDA	0.507	4	0.532	0.114	0.977	216.5	0.374		0.293	0.248	0.085
EH	0.492	11	0.670	0.001	1.000	1820000		0.543	0.457		
ED	0.275	6	0.680	0.049	0.996	785.4		0.612		0.388	
EA	0.396	5	0.604	0.057	0.995	691.6		0.757			0.243
EHD	0.355	6	0.641	0.036	0.998	1451.3		0.394	0.331	0.275	
EHA	0.439	14	0.803	0.000	1.000	6730000		0.462	0.390		0.148
EDA	0.268	7	0.703	0.049	0.997	692.7		0.552		0.319	0.129
EHDA	0.337	6	0.651	0.038	0.998	1309.4		0.364	0.305	0.238	0.093
HD	0.221	7	0.726	0.065	0.994	383.5			0.653	0.347	
HA	0.393	3	0.576	0.14.0	0.964	187.8			0.744		0.256
HDA	0.181	7	0.744	0.072	0.992	311.8			0.576	0.292	0.132
DA	-0.082	1	0.735	0.520	0.459	19.5				0.689	0.311
ALL	0.518	6	0.554	0.034	0.998	1686.6	0.262	0.259	0.206	0.207	0.066

q^2 = the square of the LOO cross-validation (CV) coefficient; N = the optimum number of components; SEP = standard error of prediction; SEE is the standard error of estimation of non CV analysis; r^2_{ncv} is the square of the non CV coefficient; F is the F-test value; S. E. H. D and A are the steric. electrostatic. hydrophobic. hydrogen-bond donor. and hydrogen-bond acceptor contributions respectively.

Table S3: Experimental and predicted pIC_{50} and residual values for analyzed compounds according to CoMSIA-SA.

Compound	pIC_{50}		
	Experimental	Calculated	Residual
1	6.398	6.306	0.092
2	5.161	5.025	0.136
3[t]	4.688	4.632	0.056
4	4.783	5.018	-0.235
5	5.417	5.329	0.088
6	5.119	5.07	0.049
7	6.347	6.339	0.008
8	6.585	6.418	0.167
9	5.609	5.592	0.017
10	4.842	5.145	-0.303
11	6.081	6.063	0.018
12[t]	5.759	5.033	0.727
13	5.389	5.228	0.161
14	5.066	4.852	0.214
15	4.815	4.876	-0.061
16[t]	4.69	4.661	0.029
17	4.936	4.784	0.152
18[t]	4.699	4.687	0.012
19	4.652	4.618	0.034
20[t]	4.662	4.682	-0.021
21[t]	4.83	4.839	-0.009
22	4.745	4.85	-0.105
23	4.873	5.054	-0.181
24	4.81	4.936	-0.126
25[t]	5.469	4.827	0.642
26[t]	4.921	4.668	0.253
27	4.668	4.561	0.107
28[t]	4.697	4.775	-0.078
29	4.688	4.438	0.25
30	4.833	4.475	0.358
31[t]	4.83	5.215	-0.385
32	4.883	5.191	-0.308
33[t]	5.282	5.311	-0.029
34[t]	4.902	4.925	-0.023
35	5.471	5.741	-0.27
36	4.173	3.993	0.18
37	3.542	3.986	-0.444

[t]= Test set

Table S4: *Y*-randomization test for CoMSIA-SA model

Iteration	q^2	N	r^2_{ncv}	Iteration	q^2	N	r^2_{ncv}
Random 1	-0.531	1	0.259	Random 6	-0.301	2	0.736
Random 2	-0.821	1	0.369	Random 7	-0.118	4	0.909
Random 3	0.068	2	0.681	Random 8	-0.458	1	0.353
Random 4	-0.128	3	0.813	Random 9	-0.806	1	0.393
Random 5	-0.887	1	0.416	Random 10	-0.32	1	0.34

Table S5. Summary of external validation parameters for CoMSIA-SA.

Condition	Parameters	Threshold value	CoMSIA
1	q^2	>0.5	0.664
2	r^2_{test}	>0.6	0.915
3a	r^2_0	Close to value of r^2_{test}	0.967
3b	r'^2_0	Close to value of r^2_{test}	0.962
4a	k	0.85 < k < 1.15	1.002
4b	k'	0.85 < k′ < 1.15	0.998
5a	$(r^2 - r^2_0)/r^2$	<0.1	0.051
5b	$(r^2 - r'^2_0)/r^2$	<0.1	0.051
6	$\lvert r^2_0 - r'^2_0 \rvert$	<0.3	0.005
7	r^2_m	>0.5	0.706

q^2 and r^2_{test} are the same parameters as listed in Table S2; r_0^2 and k are the correlation coefficient between the actual and predicted activities for test set and the respective slope of regression; and $r_0'^2$ and k′ are the correlation coefficient between the predicted and actual activities for test set and the respective slope of regression. r^2_m was defined in equation 4.

Table S6: 2D-QSAR results based on electronic descriptors.

Compound	LUMO	$LUMO^2$	ω	$ω^2$	pIC_{50} (M)		Residual
					Experimental	Calculated	
1	-2.195	4.817	4.411	19.456	6.398	5.563	0.835
2[t]	-1.744	3.042	3.503	12.268	5.161	4.377	0.784
3	-1.718	2.953	3.464	11.999	4.688	4.384	0.304
4	-1.299	1.688	2.795	7.81	4.783	4.788	-0.005
5[t]	-2.333	5.442	4.75	22.561	5.417	5.972	-0.555
6[t]	-1.737	3.019	3.49	12.18	5.119	4.366	0.754
7	-2.603	6.776	5.435	29.541	6.347	6.391	-0.044
8	-2.682	7.194	5.604	31.405	6.585	6.487	0.098
9	-2.355	5.544	4.768	22.735	5.609	6.022	-0.413
10	-1.897	3.598	3.808	14.502	4.842	4.762	0.08
11	-2.296	5.272	4.647	21.592	6.081	5.87	0.211
12[t]	-2.785	7.758	5.827	33.957	5.76	6.579	-0.819
13	-2.264	5.126	4.582	20.991	5.389	5.788	-0.398
14	-1.871	3.501	3.762	14.149	5.066	4.716	0.35
15[t]	-2.127	4.522	4.258	18.128	4.815	5.338	-0.522
16	-1.962	3.851	3.926	15.412	4.69	4.884	-0.194
17[t]	-2.965	8.794	6.402	40.984	4.936	5.764	-0.828
18	-1.752	3.068	3.504	12.278	4.699	4.334	0.365
19[t]	-2.018	4.073	4.049	16.392	4.652	5.064	-0.412
20	-1.858	3.453	3.717	13.813	4.662	4.605	0.057
21	-2.885	8.323	6.422	41.245	4.83	4.828	0.002
22[t]	-1.644	2.704	3.29	10.827	4.745	4.068	0.676
23[o]	-2.762	7.628	5.729	32.825	4.873	6.706	-1.833
24[o]	-2.663	7.093	5.622	31.608	4.81	6.304	-1.494
25[t]	-3.263	10.647	7.043	49.606	5.469	5.471	-0.003
26[o]	-2.529	6.396	5.498	30.227	4.921	5.88	-0.959
27[t]	-1.856	3.446	3.735	13.95	4.668	4.691	-0.024
28	-1.704	2.904	3.41	11.627	4.697	4.214	0.482
29	-1.509	2.278	3.027	9.164	4.688	3.789	0.899
30[t]	-1.927	3.714	3.868	14.958	4.833	4.835	-0.002
31[t]	-1.848	3.417	3.701	13.695	4.83	4.595	0.235
32[t]	-1.965	3.861	3.948	15.588	4.883	4.949	-0.066
33[t]	-2.104	4.428	4.266	18.199	5.282	5.402	-0.119
34	-2.107	4.441	4.274	18.264	4.902	5.406	-0.504
35[o]	-1.601	2.564	3.235	10.465	5.471	4.147	1.324
36[t]	-1.837	3.374	3.676	13.514	4.173	4.56	-0.387
37[t]	-1.78	3.17	3.565	12.708	3.542	4.422	-0.88

[t]= test set; [0]= outlier compound

2. *L. amazonensis* inhibition growth

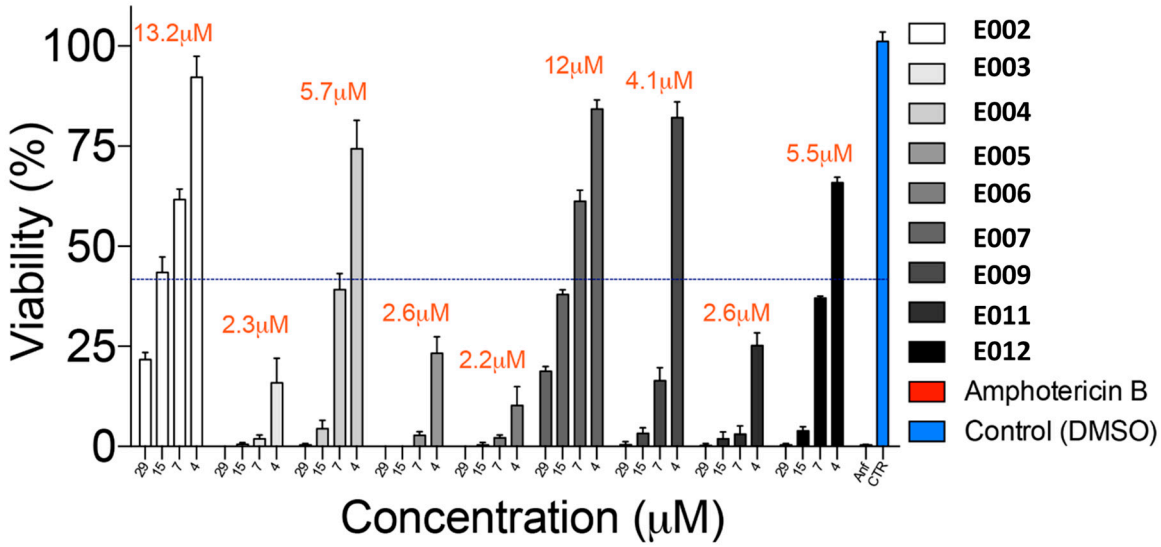
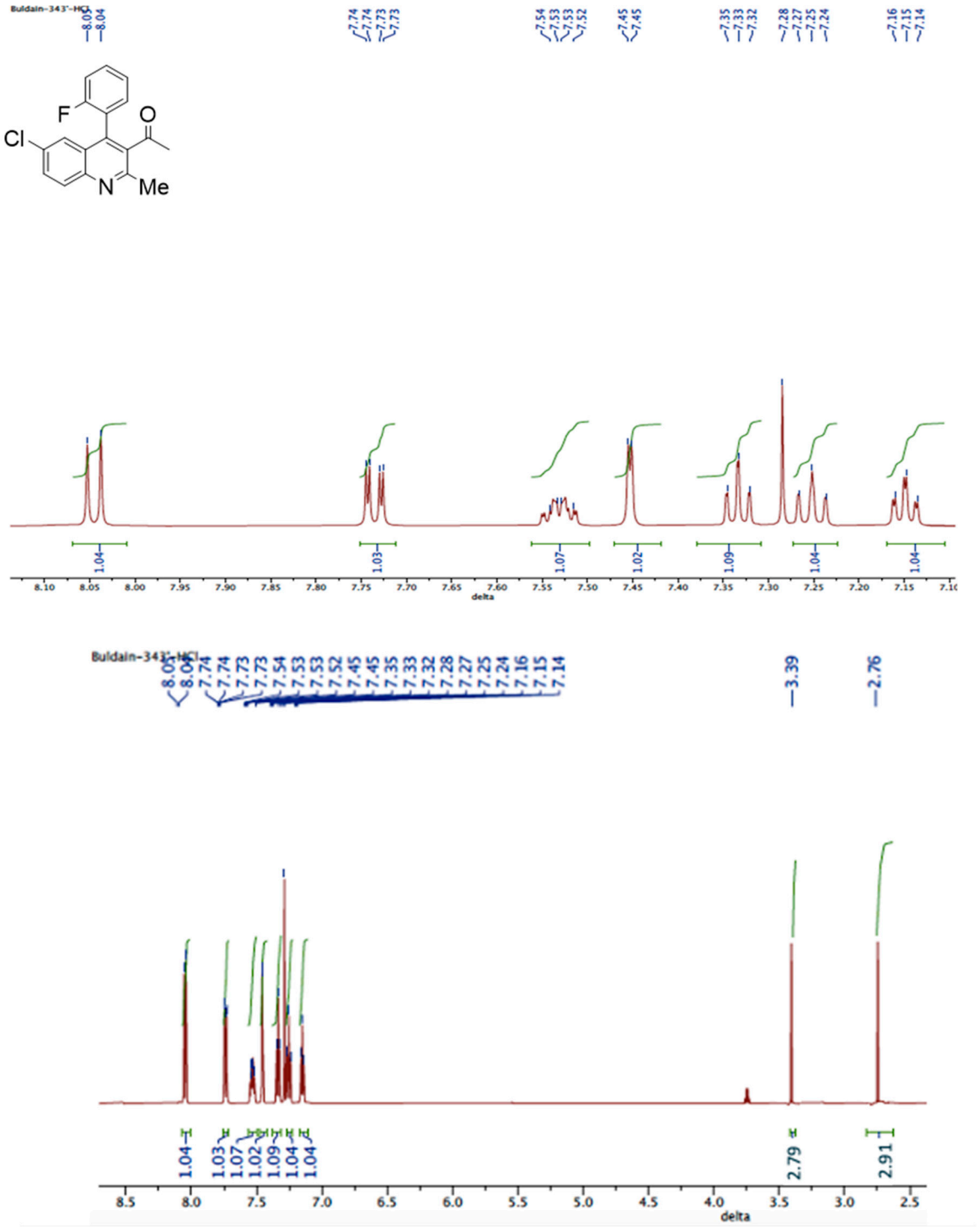


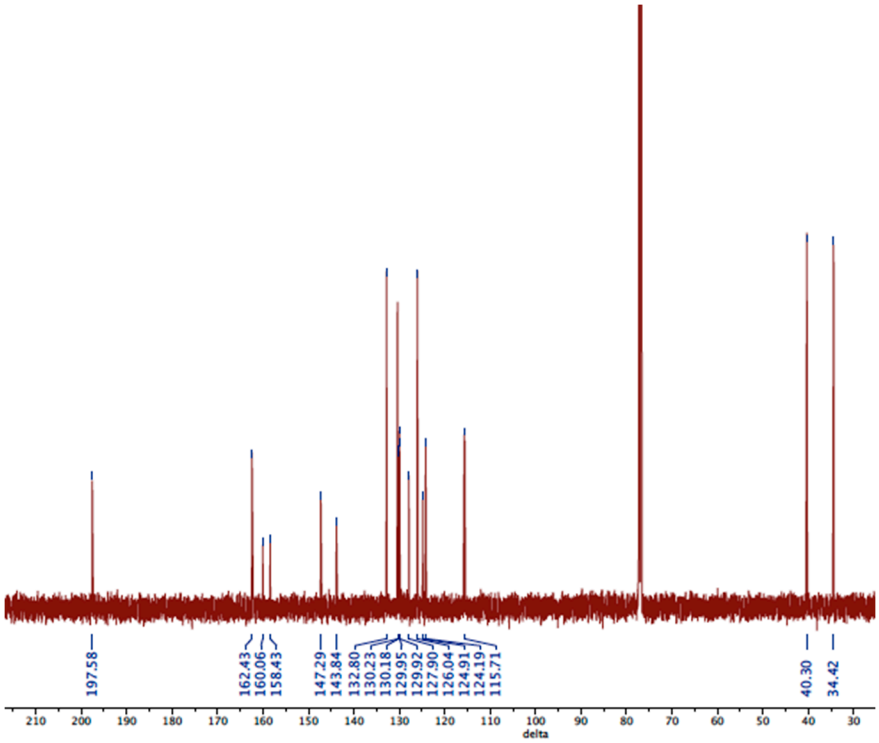
Figure S3: Dose-response graph of the active compounds

3. Chemistry

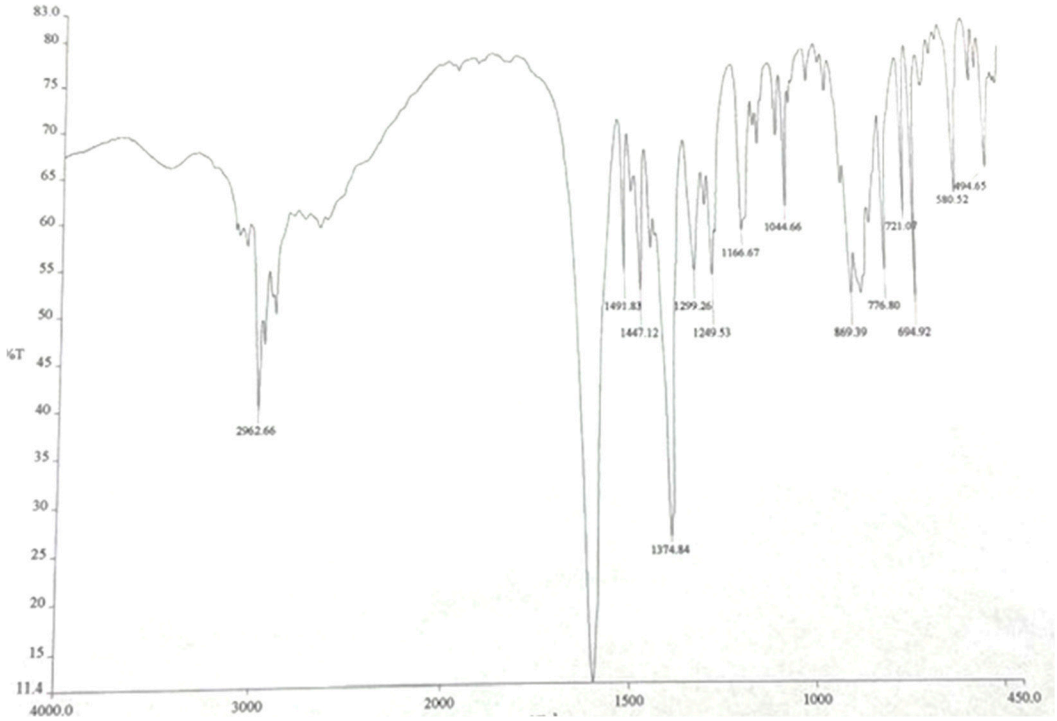
Spectrum S1: ^{1}H-NMR ($CDCl_3$). 1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)ethan-1-one **(III)**



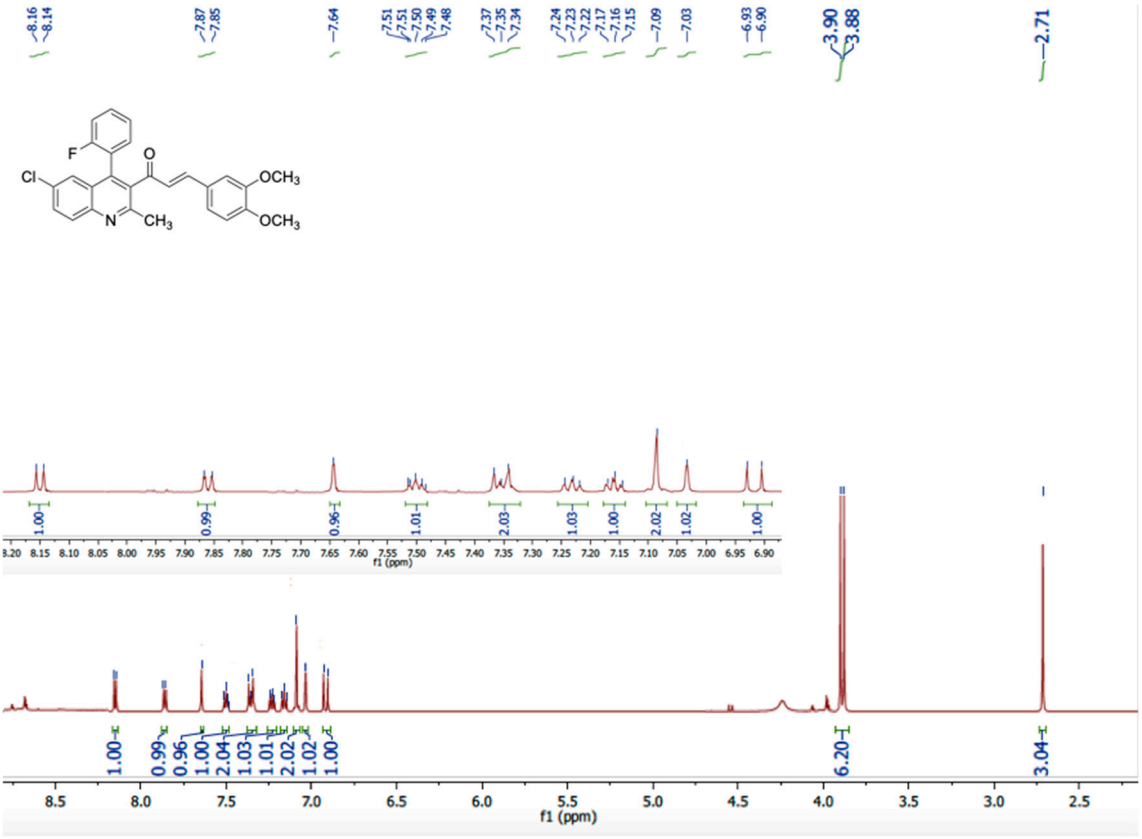
Spectrum S2: ^{13}C-NMR ($CDCl_3$). 1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)ethan-1-one **(III)**



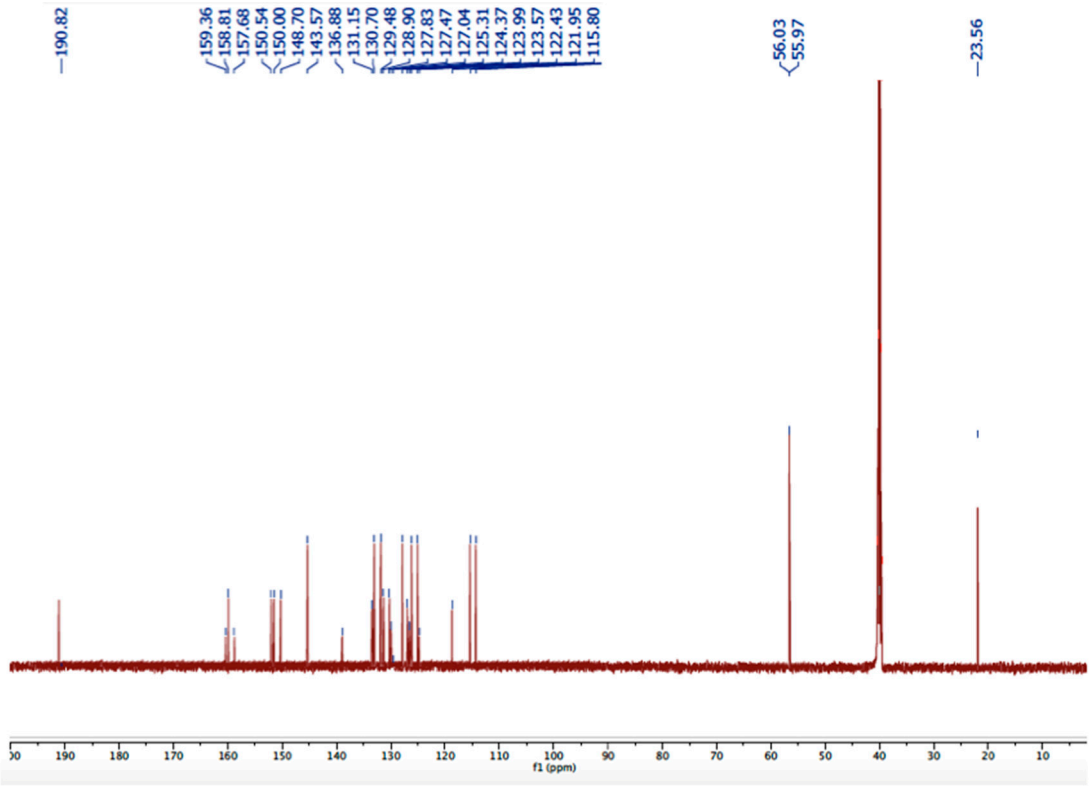
Spectrum S3: IR (KBr). 1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)ethan-1-one **(III)**



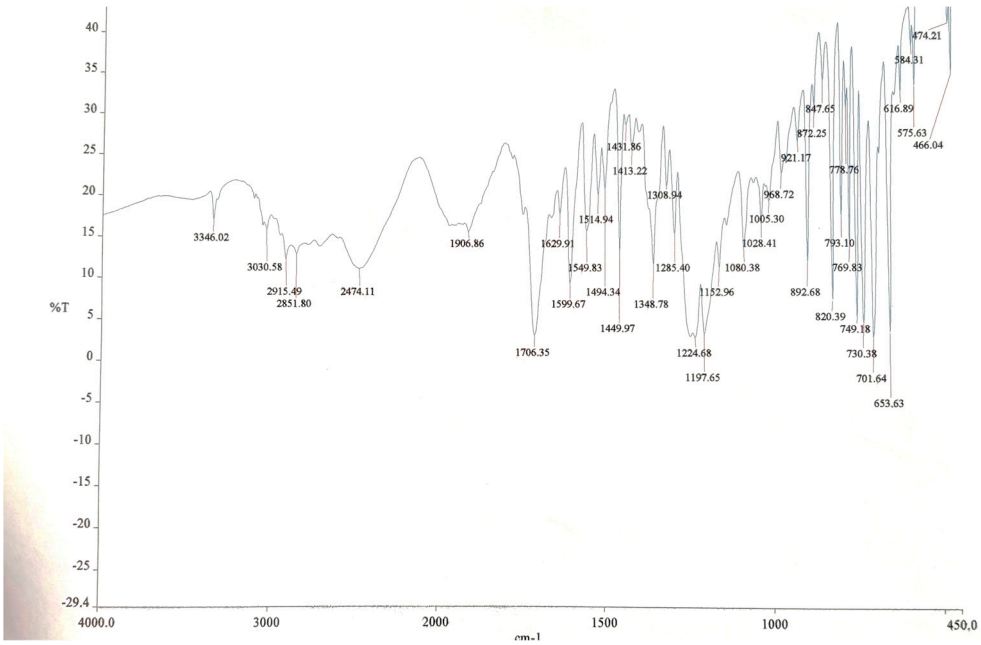
Spectrum S4: ^{1}H-NMR (DMSO-d_6). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4-dimetoxyphenyl)prop-2-en-1-one **(E001)**



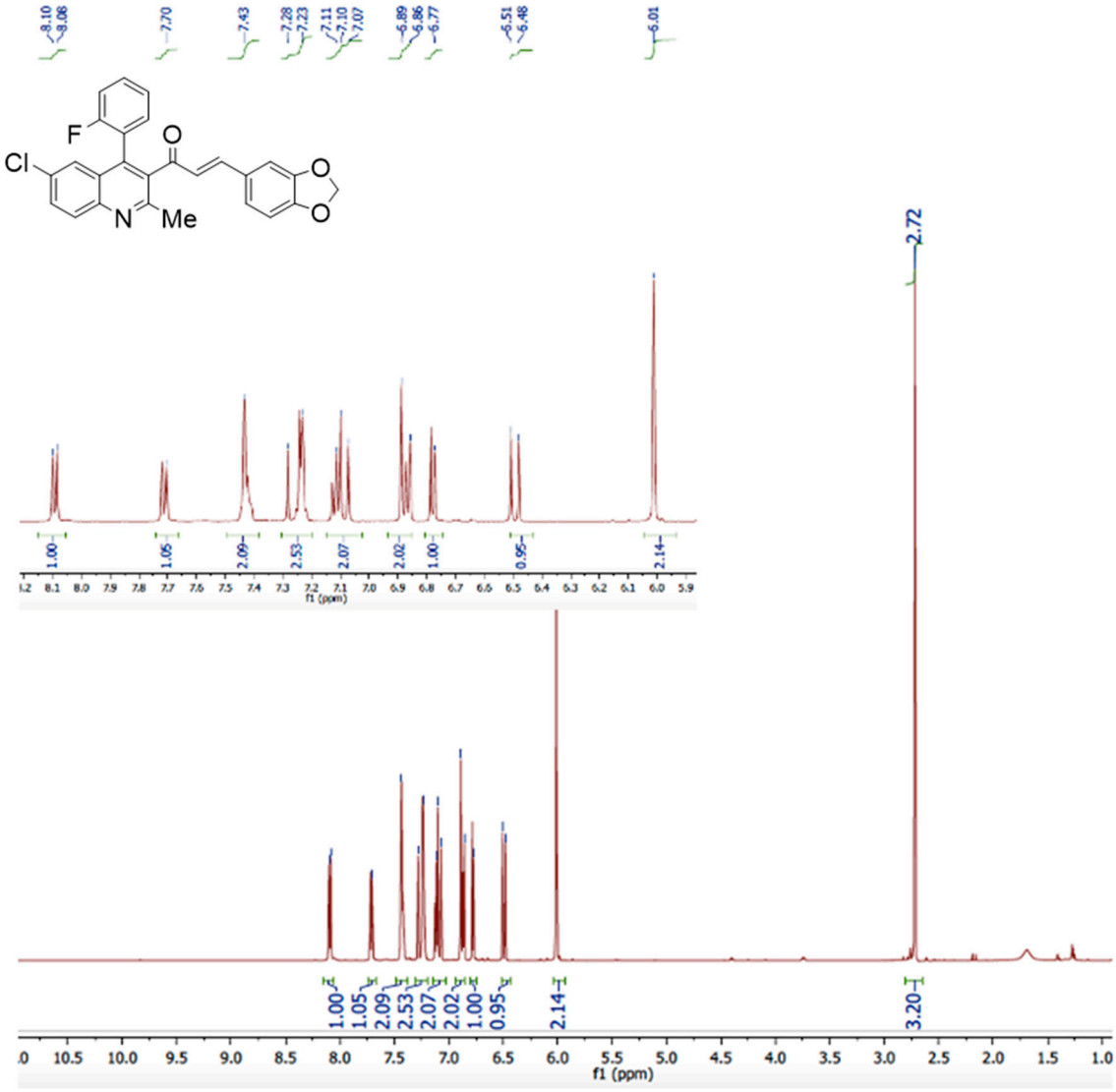
Spectrum S5: ^{13}C-NMR (DMSO-d^6). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4-dimetoxyphenyl)prop-2-en-1-one **(E001)**



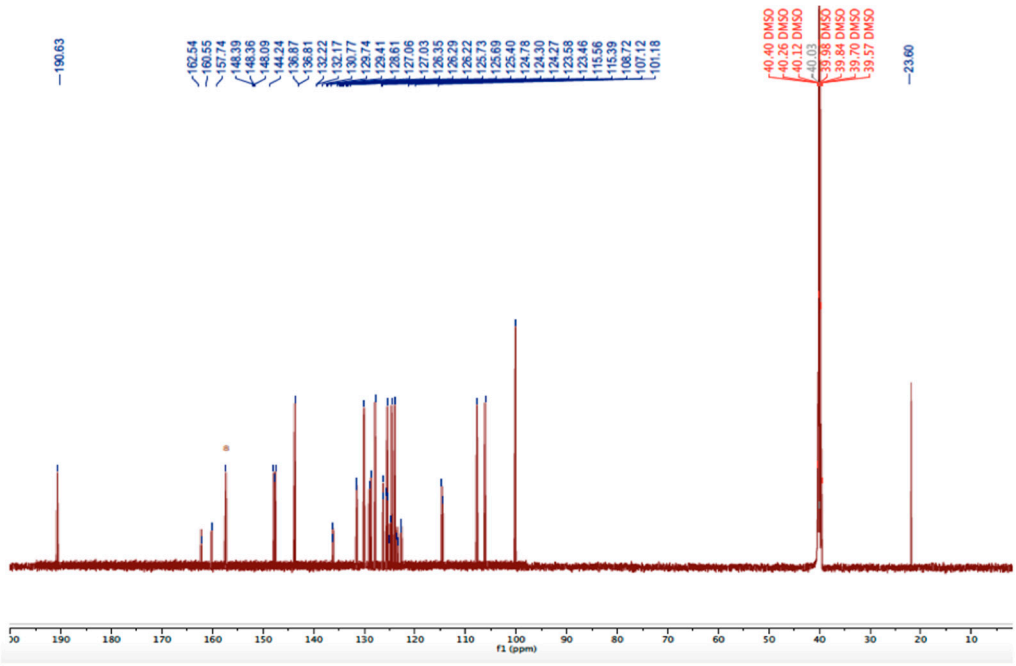
Spectrum S6: IR (KBr). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4-dimetoxyphenyl)prop-2-en-1-one **(E001)**



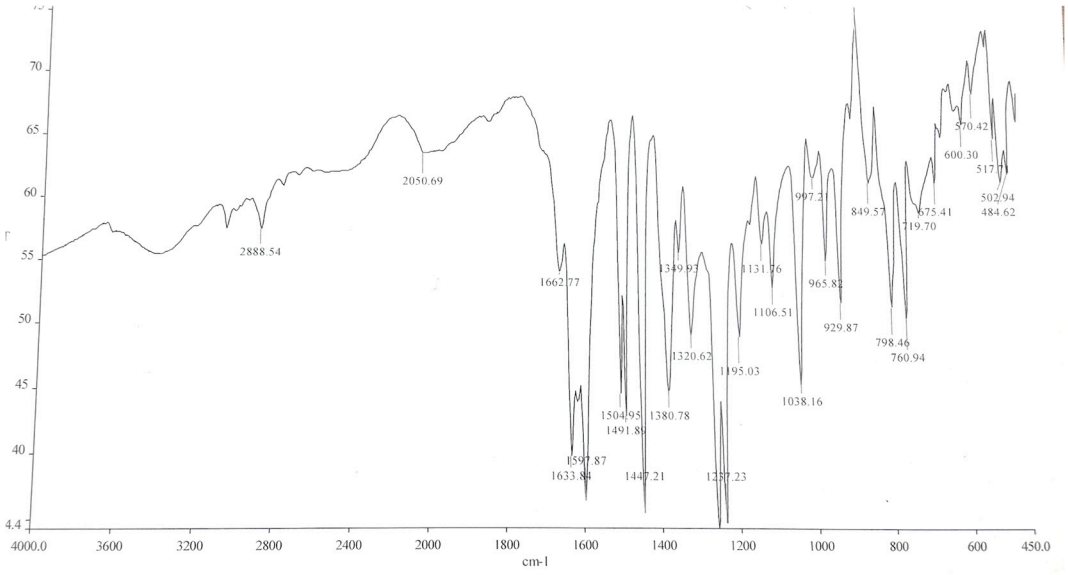
Spectrum S7: ^{1}H-NMR (DMSO-d$_6$). (*E*)-3-(benzo[d][1,3]dioxol-5-yl)1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)prop-2-en-1-one **(E002)**



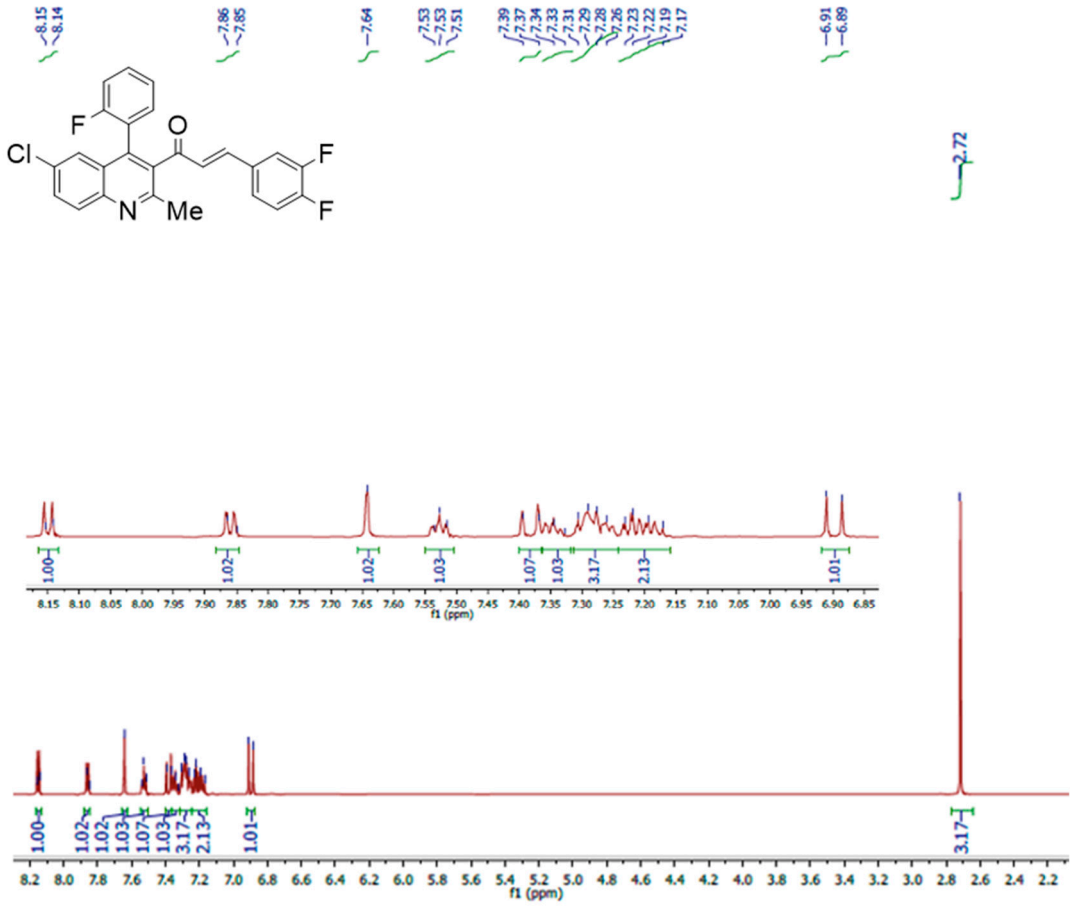
Spectrum S8: ^{13}C-NMR (DMSO-d_6). (*E*)-3-(benzo[d][1,3]dioxol-5-yl)1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)prop-2-en-1-one **(E002)**



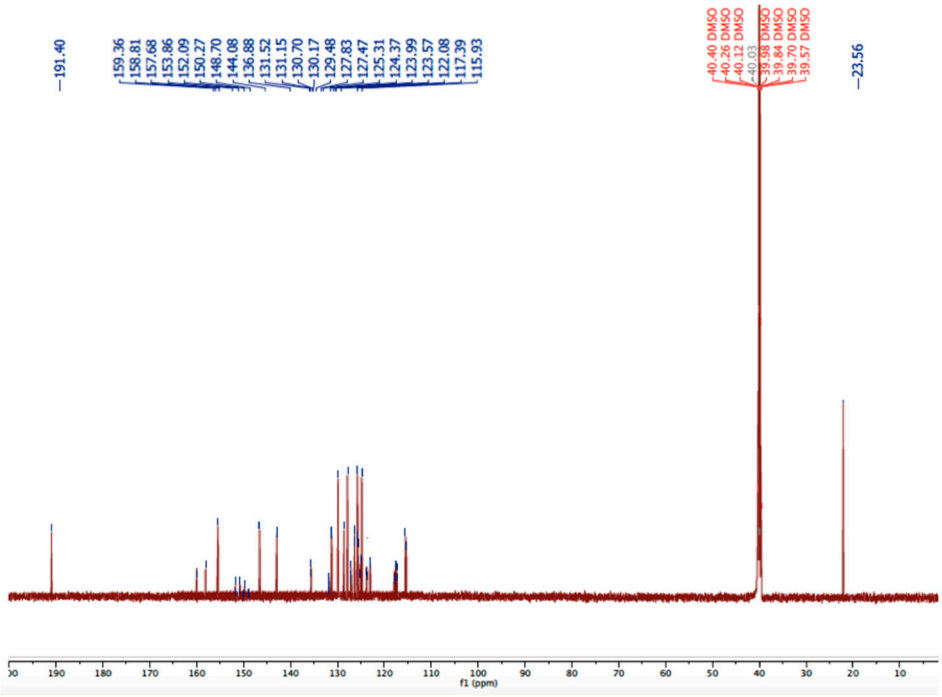
Spectrum S9: IR (KBr). (*E*)-3-(benzo[d][1,3]dioxol-5-yl)1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)prop-2-en-1-one **(E002)**



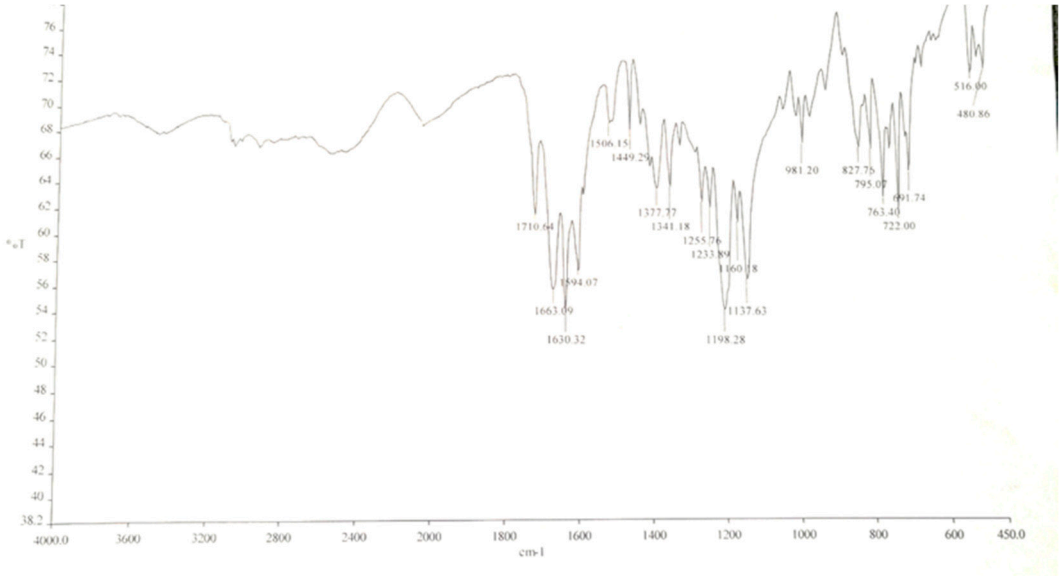
Spectrum S10: ^{1}H-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4-difluorophenyl)prop-2-en-1-one **(E003)**



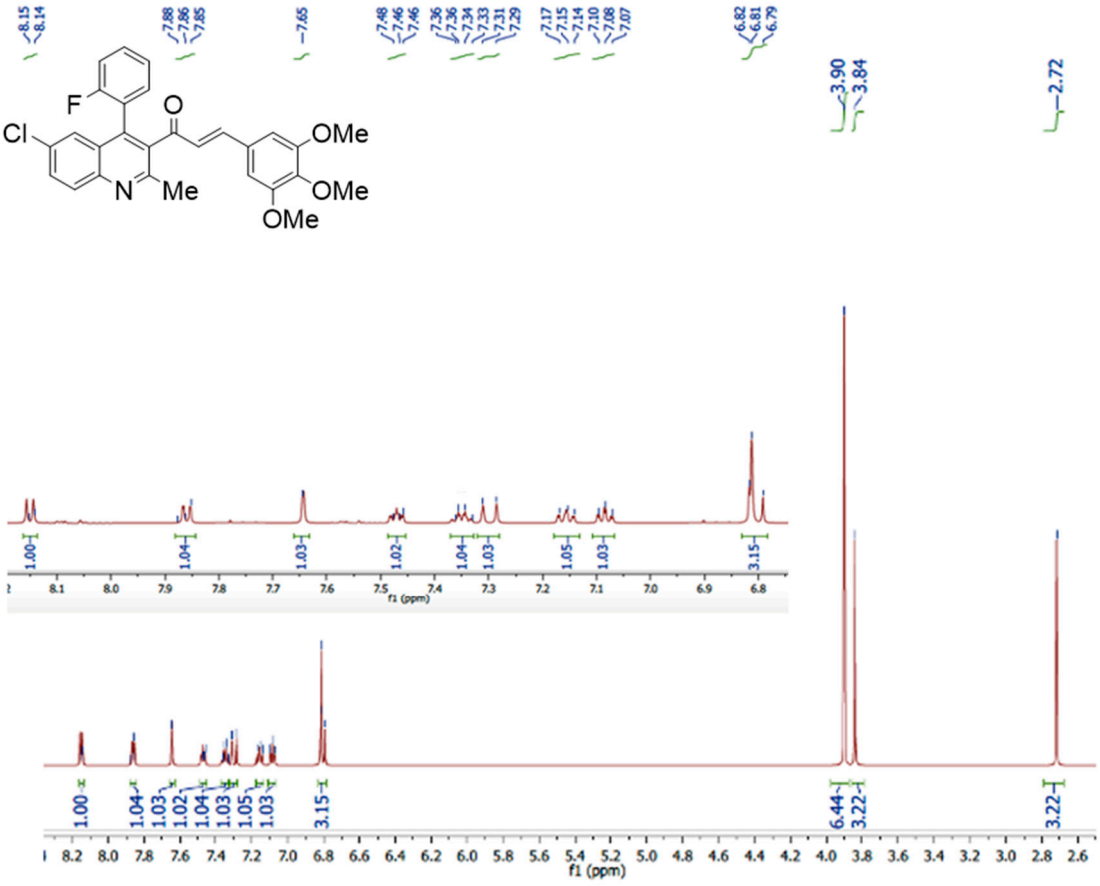
Spectrum S11: ^{13}C-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4-difluorophenyl)prop-2-en-1-one **(E003)**



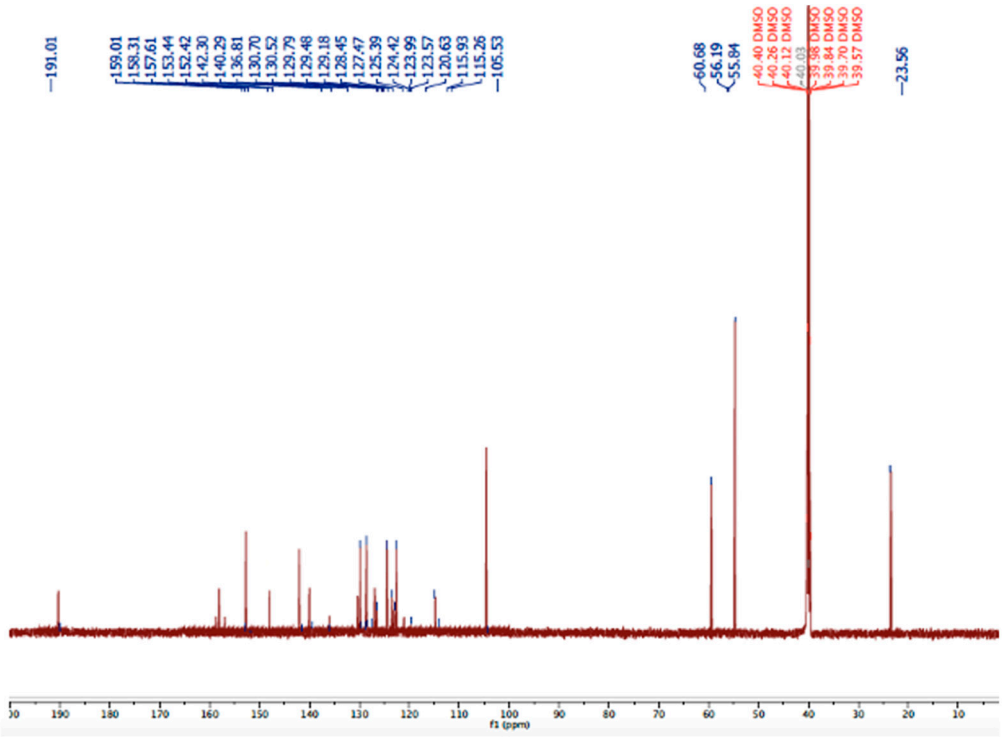
Spectrum S12: IR (KBr). (E)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4-difluorophenyl)prop-2-en-1-one **(E003)**



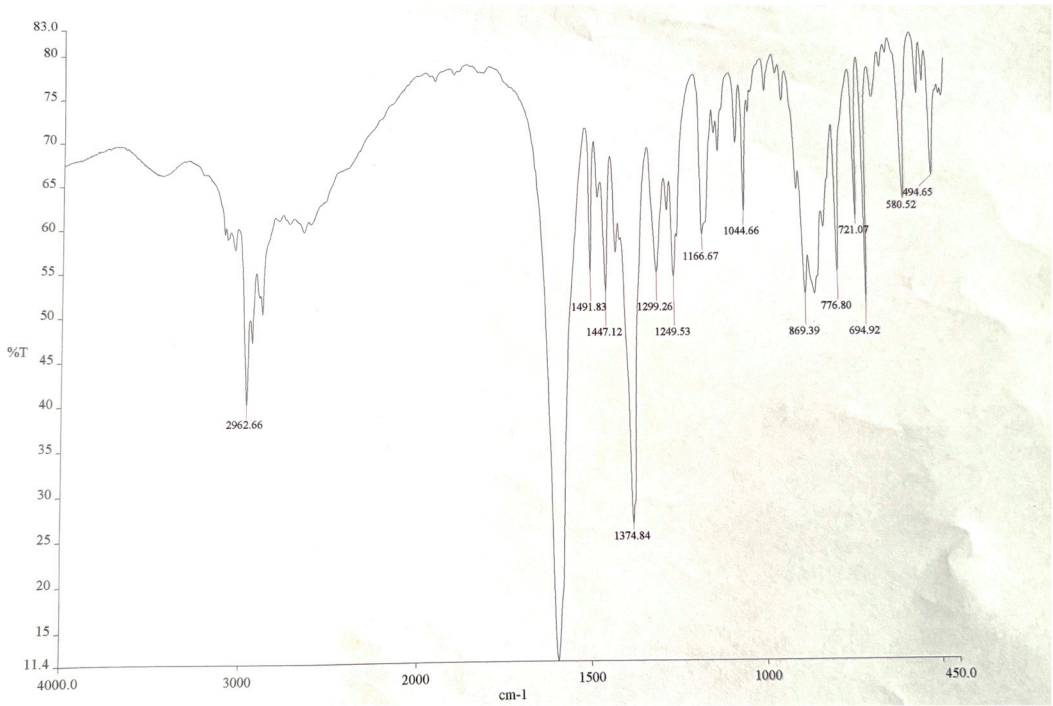
Spectrum S13: ^{1}H-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4,5-trimetoxyphenyl)prop-2-en-1-one **(E004)**



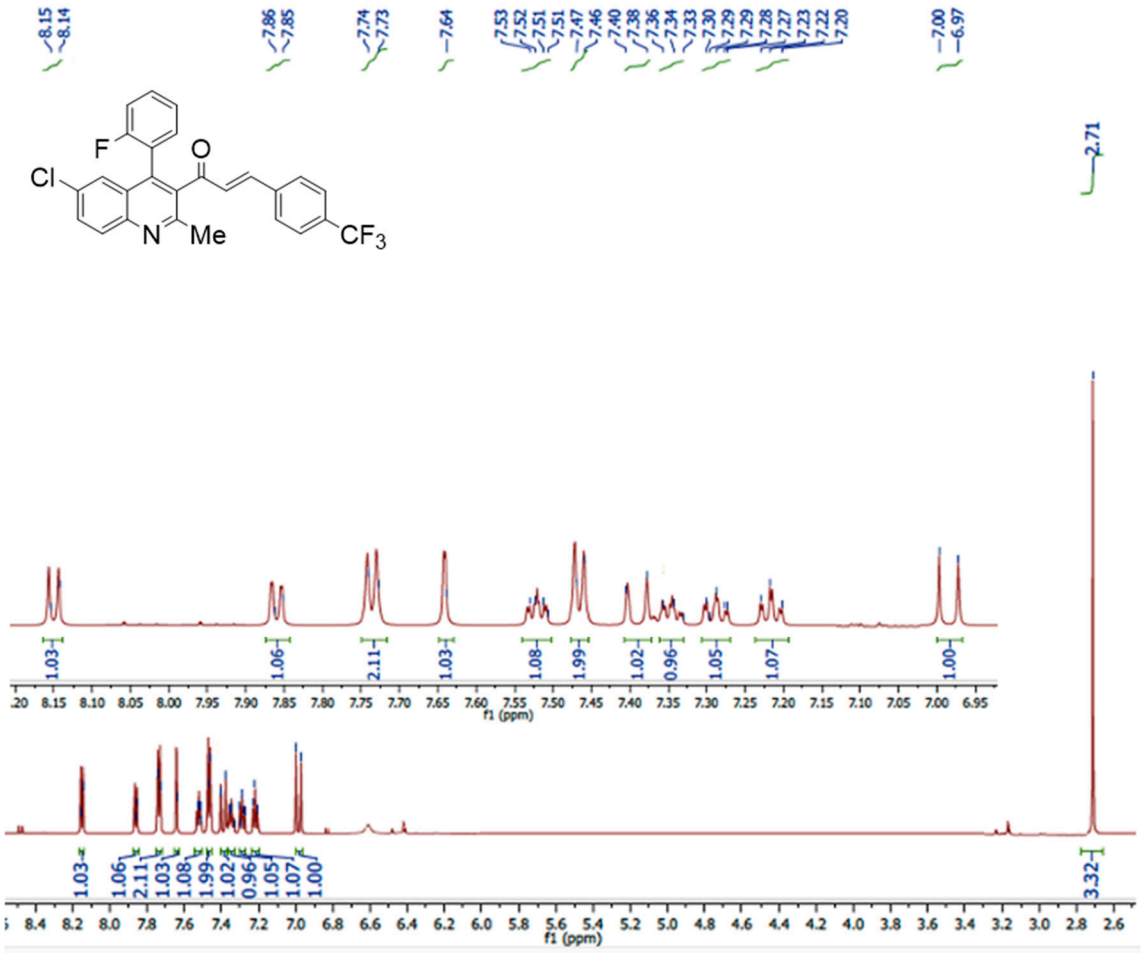
Spectrum S14: ^{13}C-NMR (DMSO-d_6). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4,5-trimetoxyphenyl)prop-2-en-1-one **(E004)**



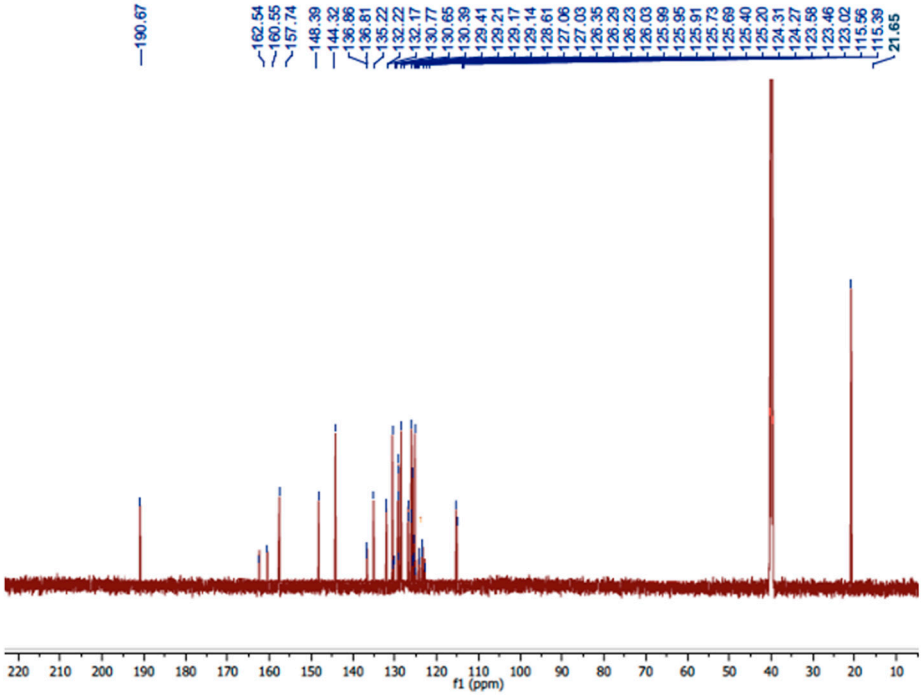
Spectrum S15: IR (KBr). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4,5-trimetoxyphenyl)prop-2-en-1-one **(E004)**



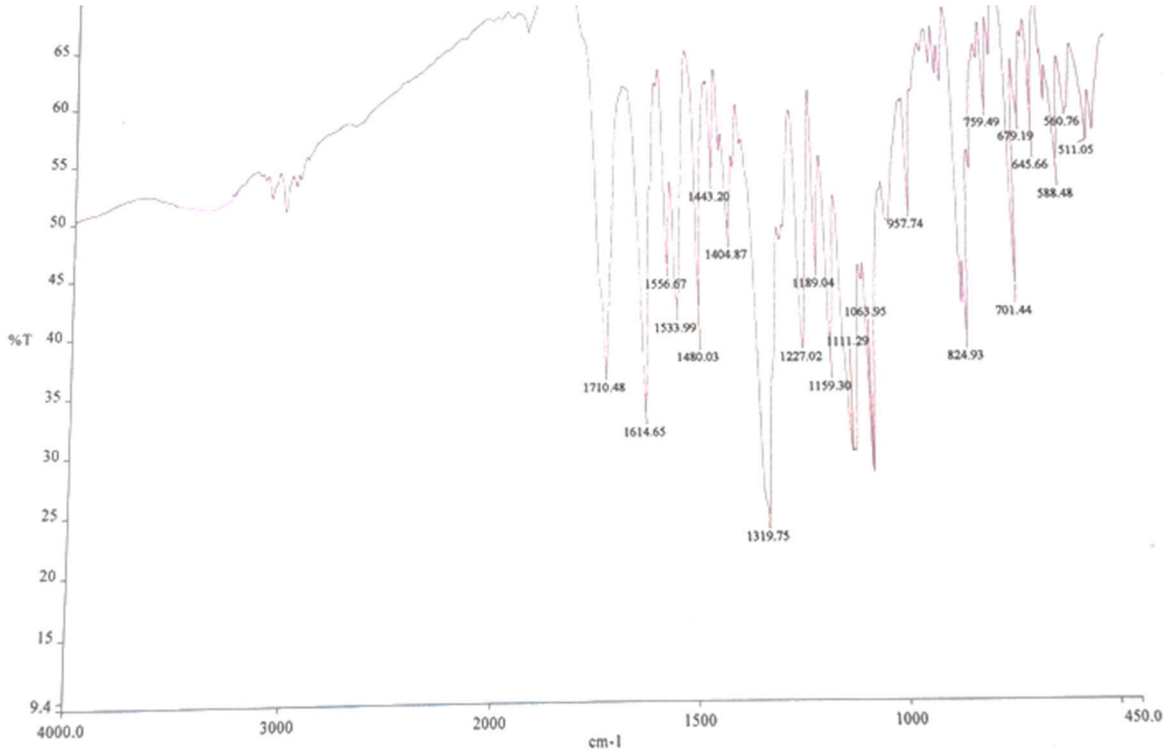
Spectrum S16: ^{1}H-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **(E005)**



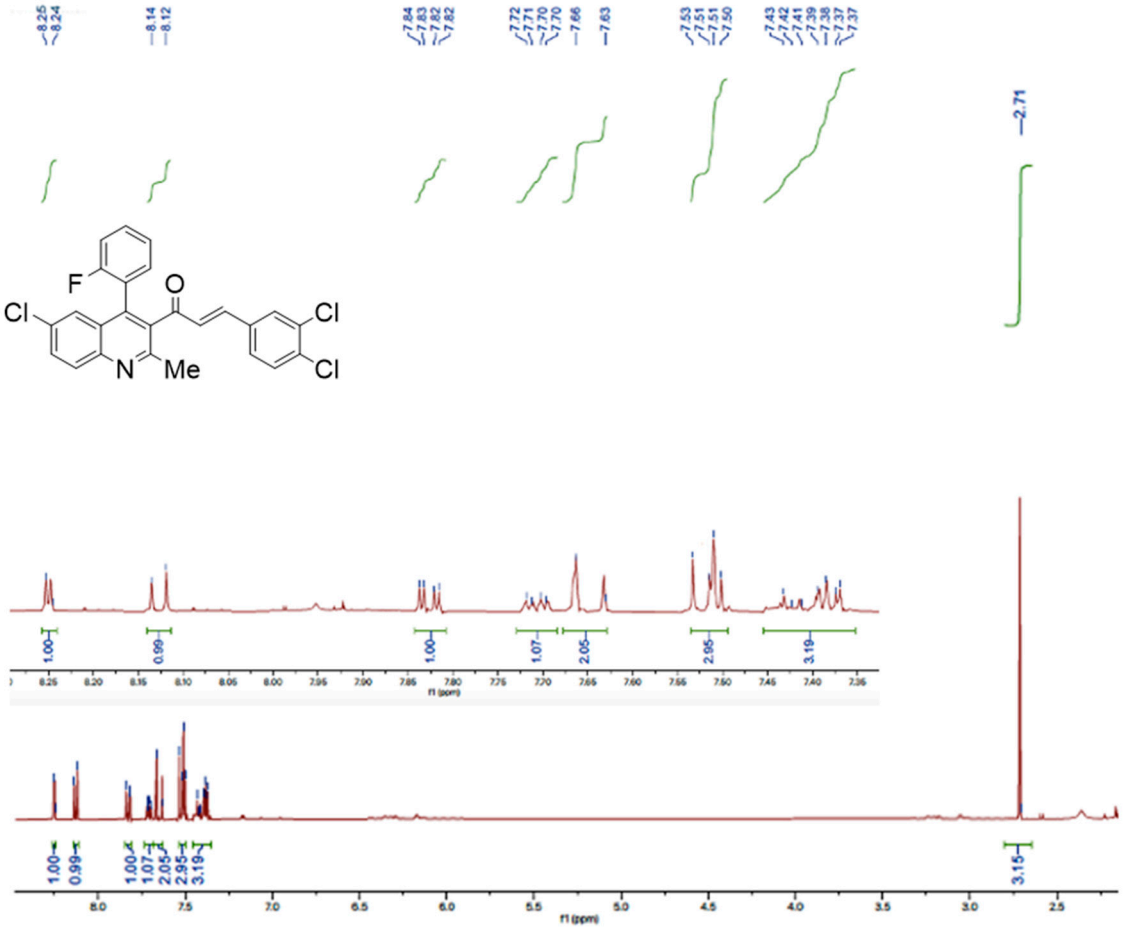
Spectrum S17: ^{13}C-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **(E005)**



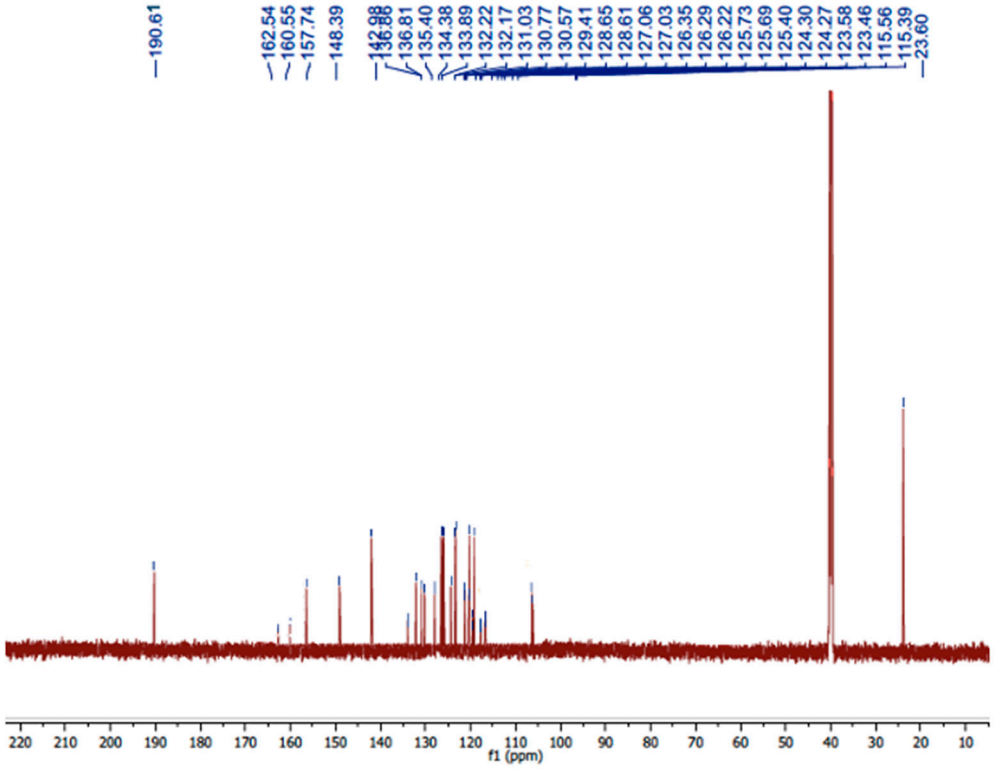
Spectrum S18: IR (KBr). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **(E005)**



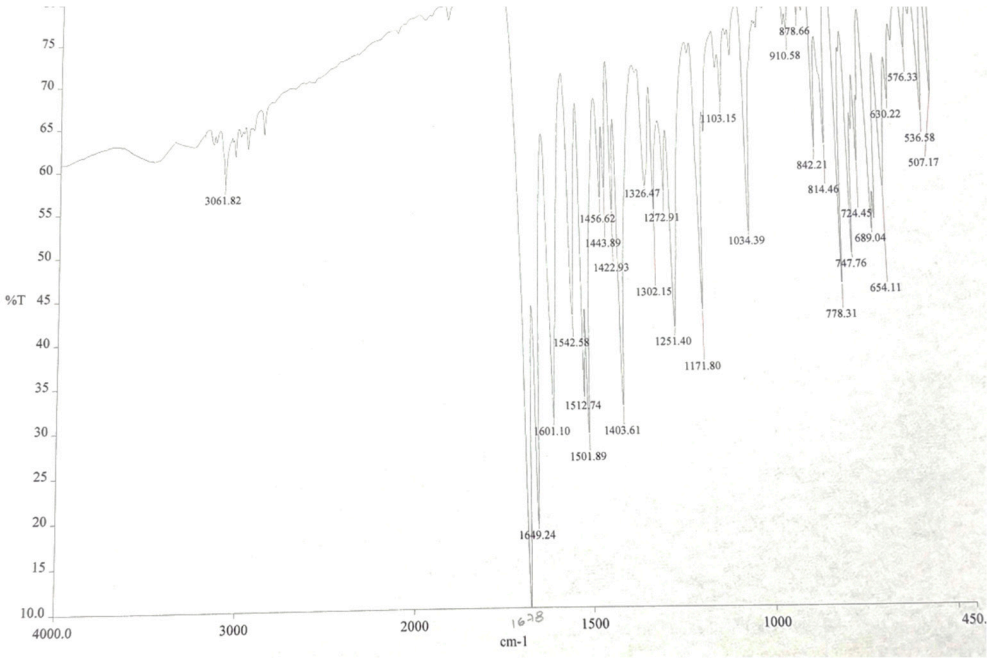
Spectrum S19: ^{1}H-NMR (DMSO-d_6). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4-dichlorophenyl)prop-2-en-1-one **(E006)**



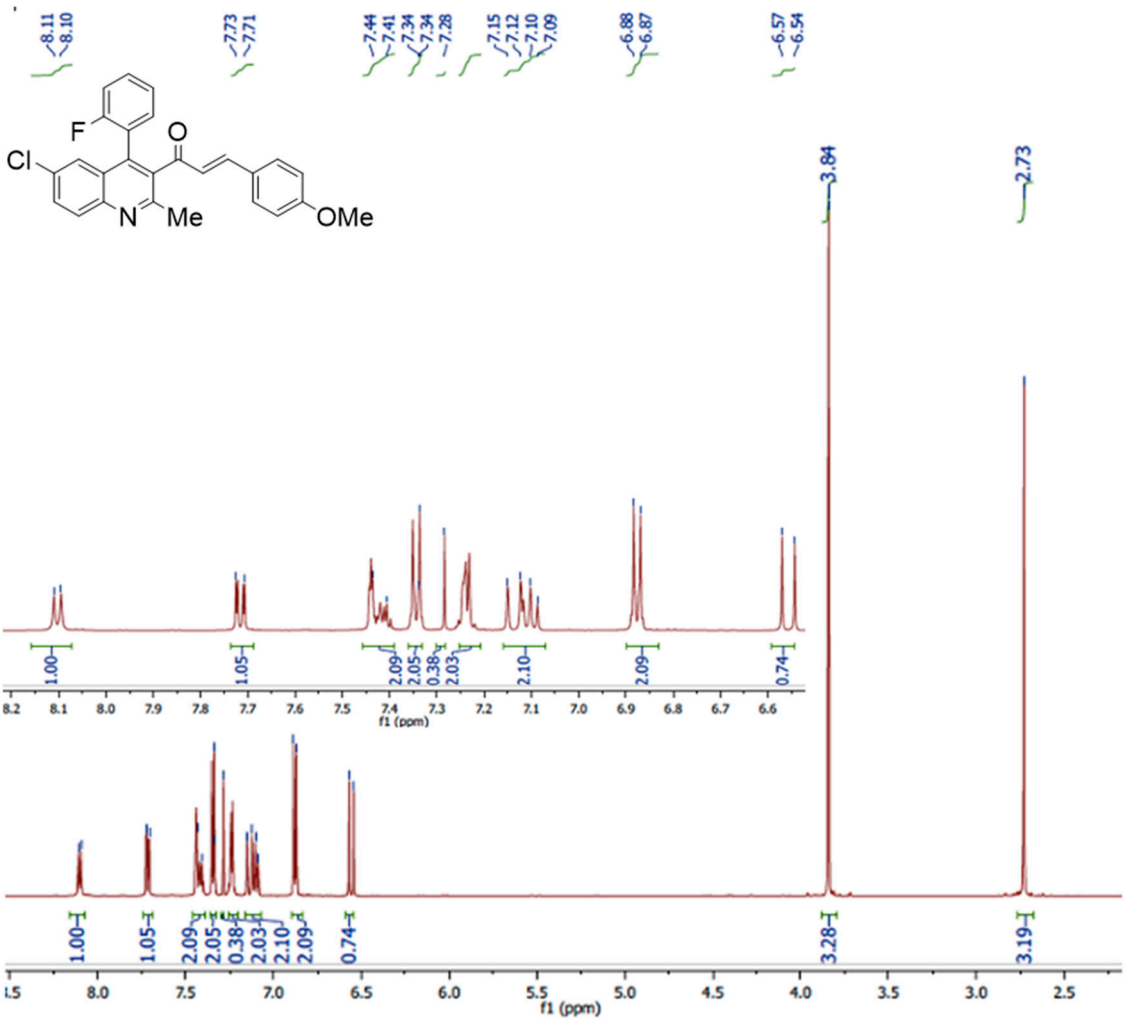
Spectrum S20: ^{13}C-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4-dichlorophenyl)prop-2-en-1-one **(E006)**



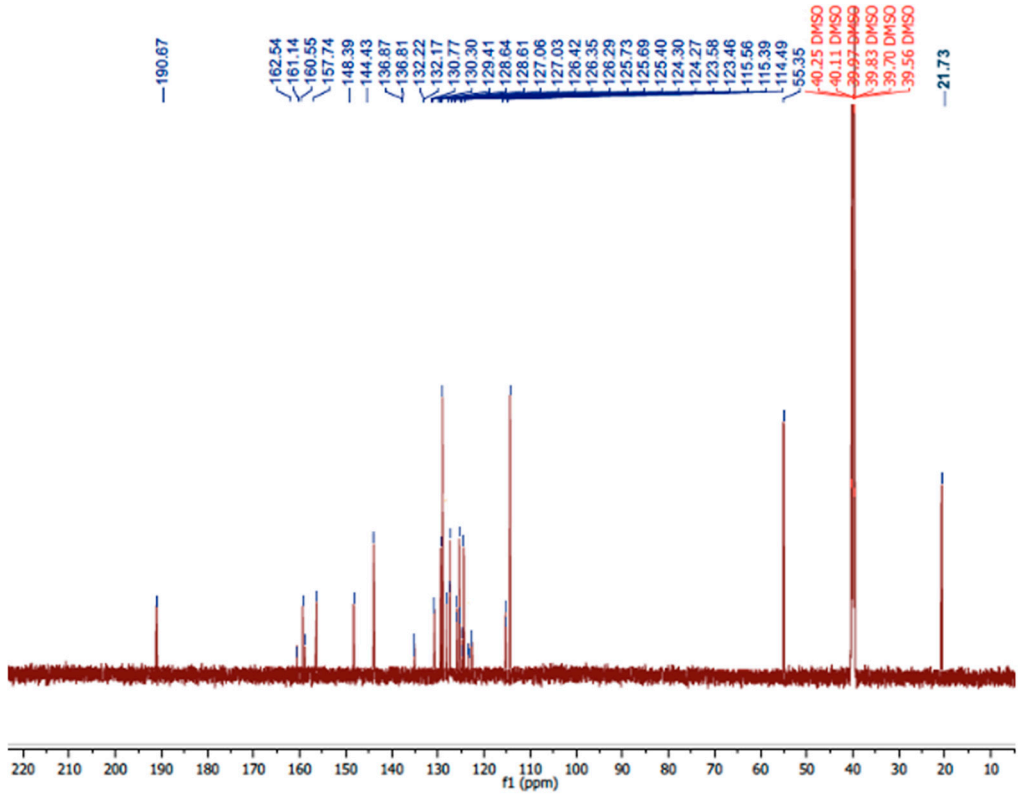
Spectrum S21: IR (KBr). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,4-dichlorophenyl)prop-2-en-1-one **(E006)**



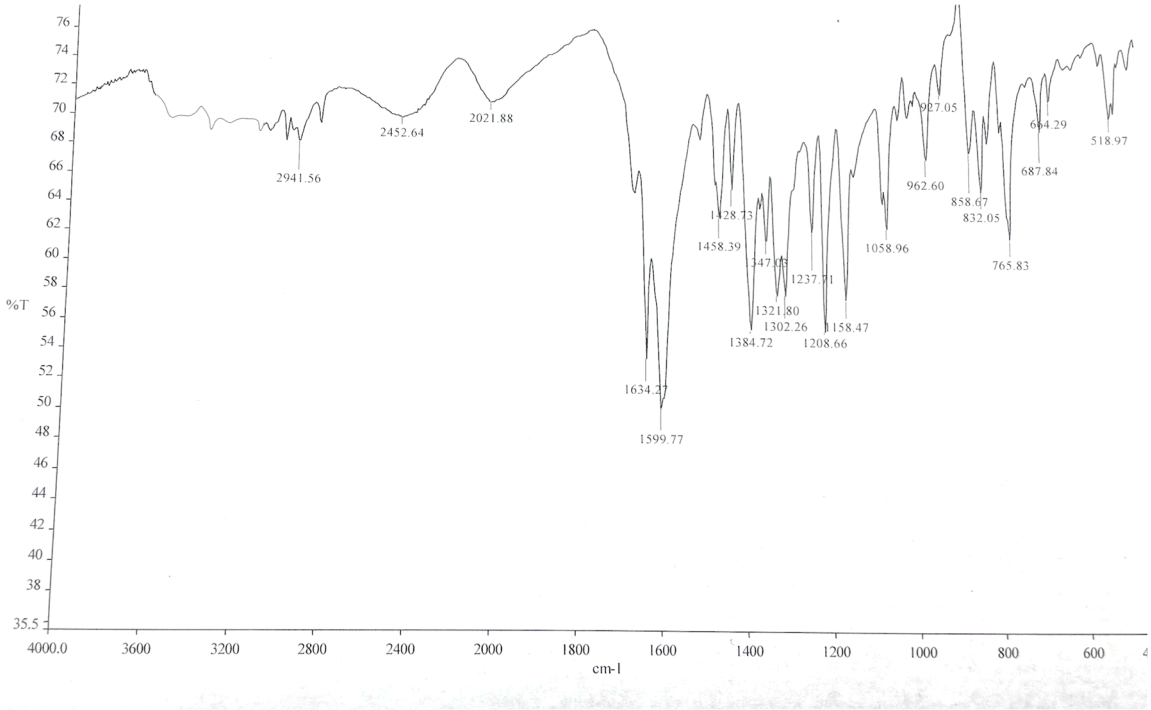
Spectrum S22: ^{1}H-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(4-metoxyphenyl)prop-2-en-1-one **(E007)**



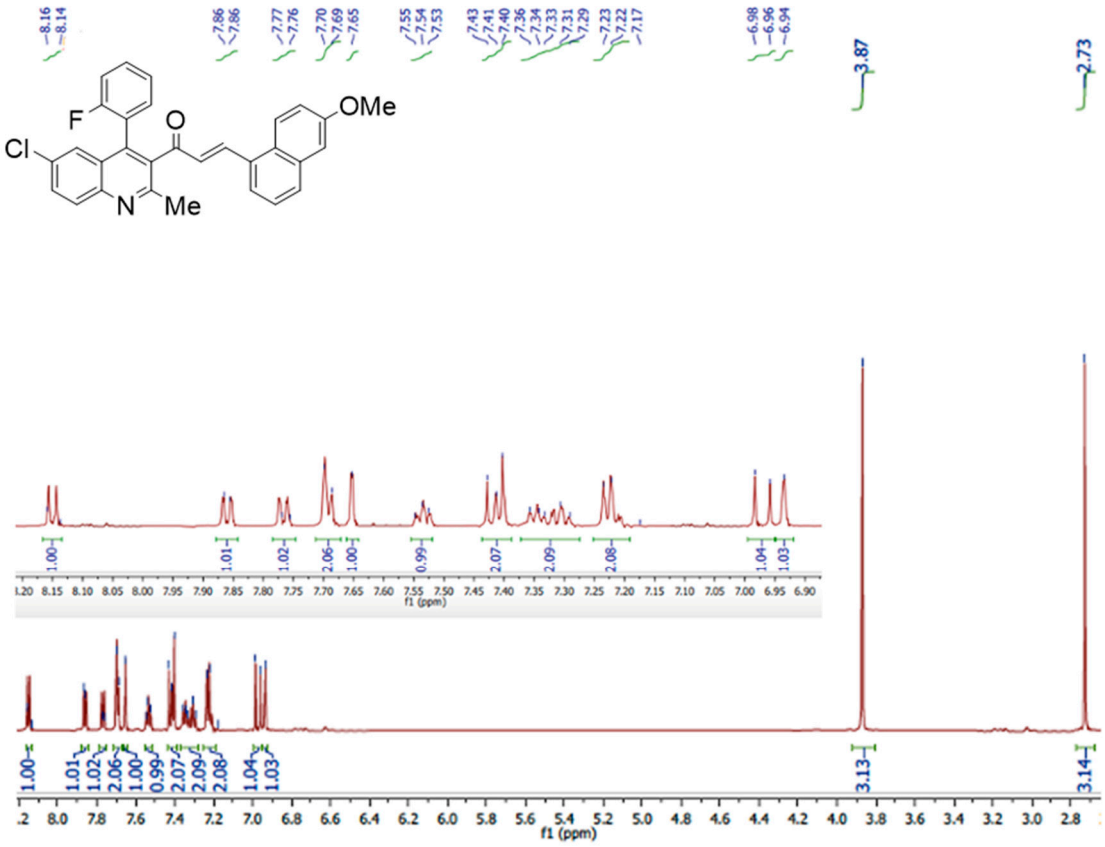
Spectrum S23: ^{13}C-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(4-metoxyphenyl)prop-2-en-1-one **(E007)**



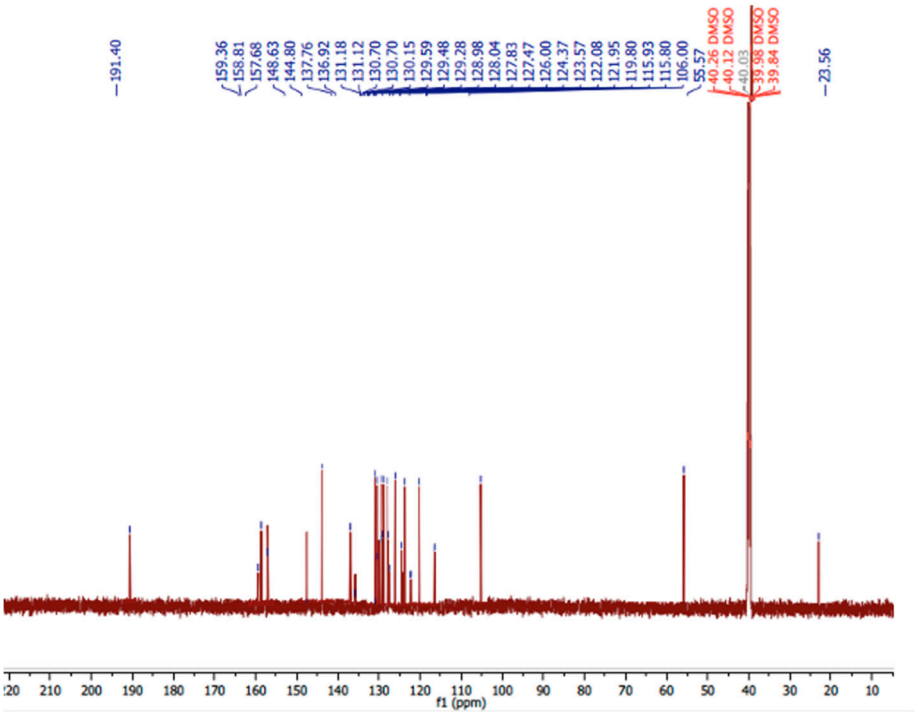
Spectrum S24: ^{13}C-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(4-metoxyphenyl)prop-2-en-1-one **(E007)**



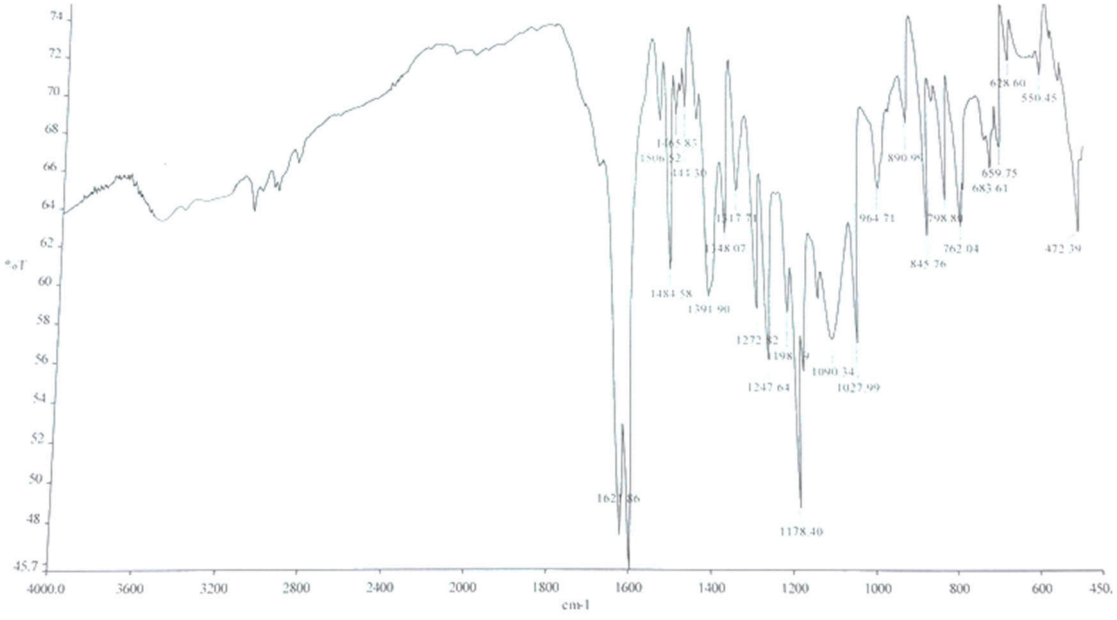
Spectrum S25: ^{1}H-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(6-metoxynapthalen-2-yl)prop-2-en-1-one **(E008)**



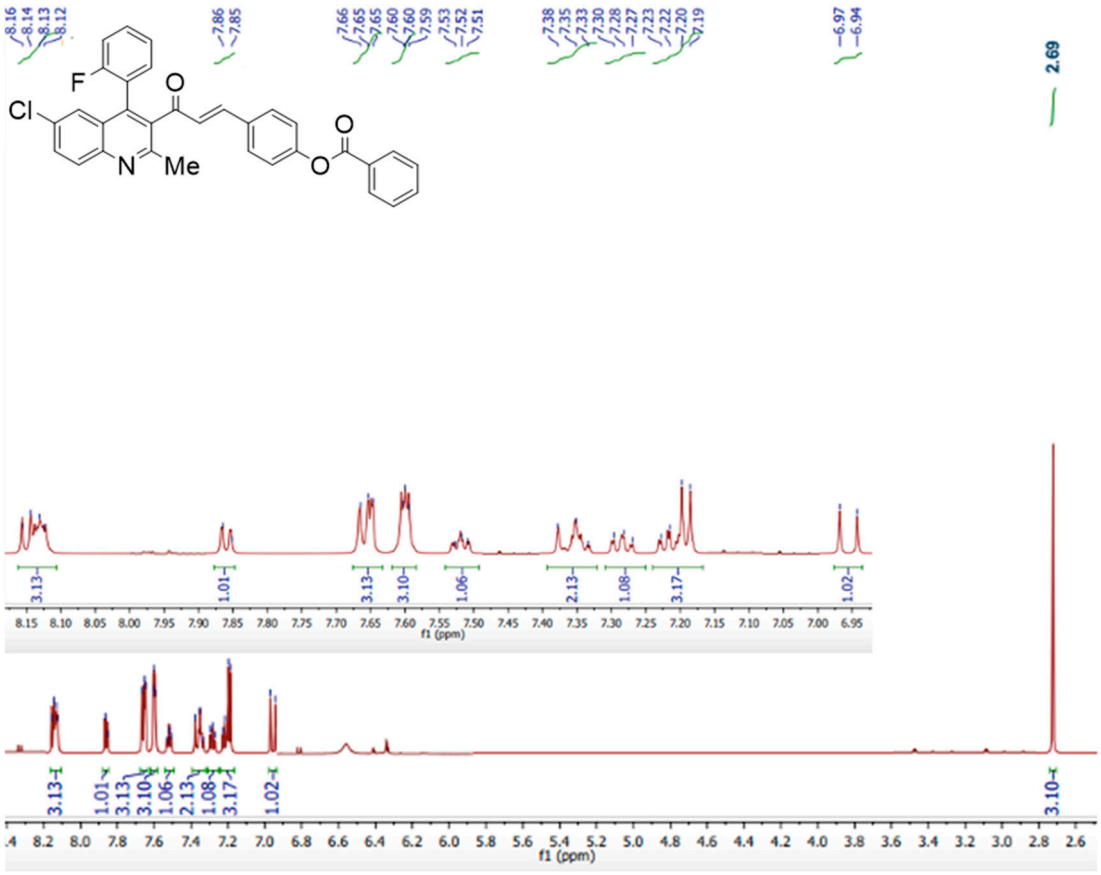
Spectrum S26: ^{13}C-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(6-metoxynapthalen-2-yl)prop-2-en-1-one **(E008)**



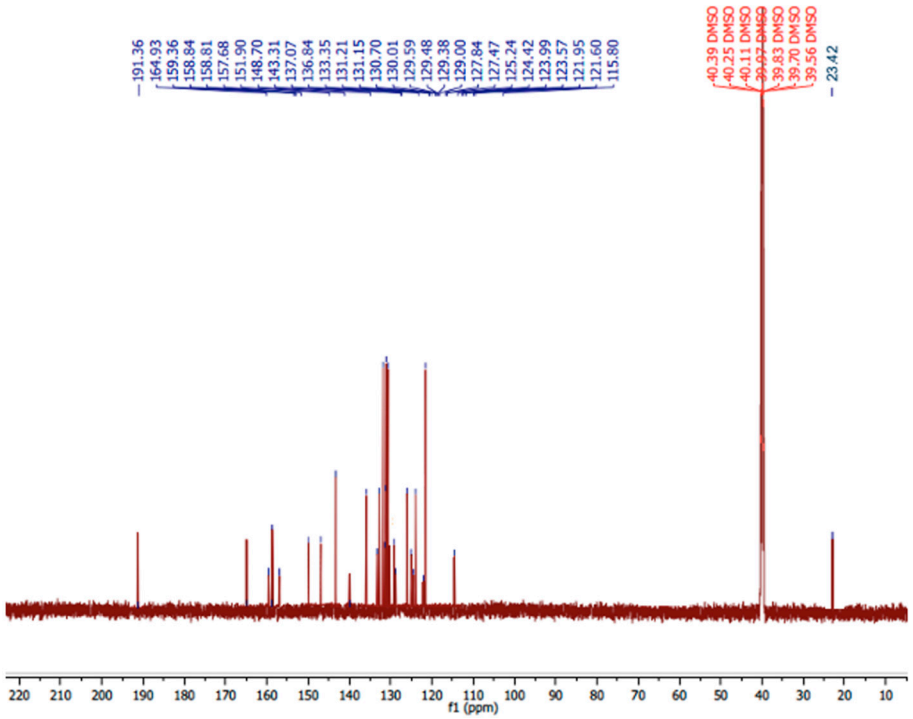
Spectrum S27: IR (KBr). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(6-metoxynapthalen-2-yl)prop-2-en-1-one **(E008)**



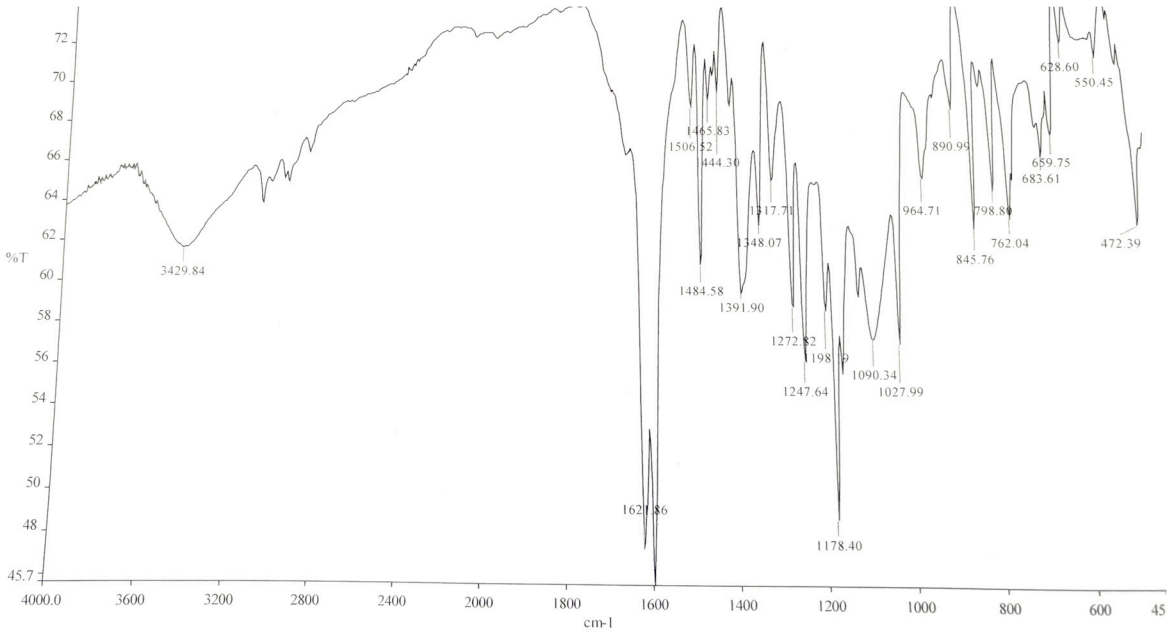
Spectrum S28: ^{1}H-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-oxoprop-1en-1-yl)phenyl benzoate **(E009)**



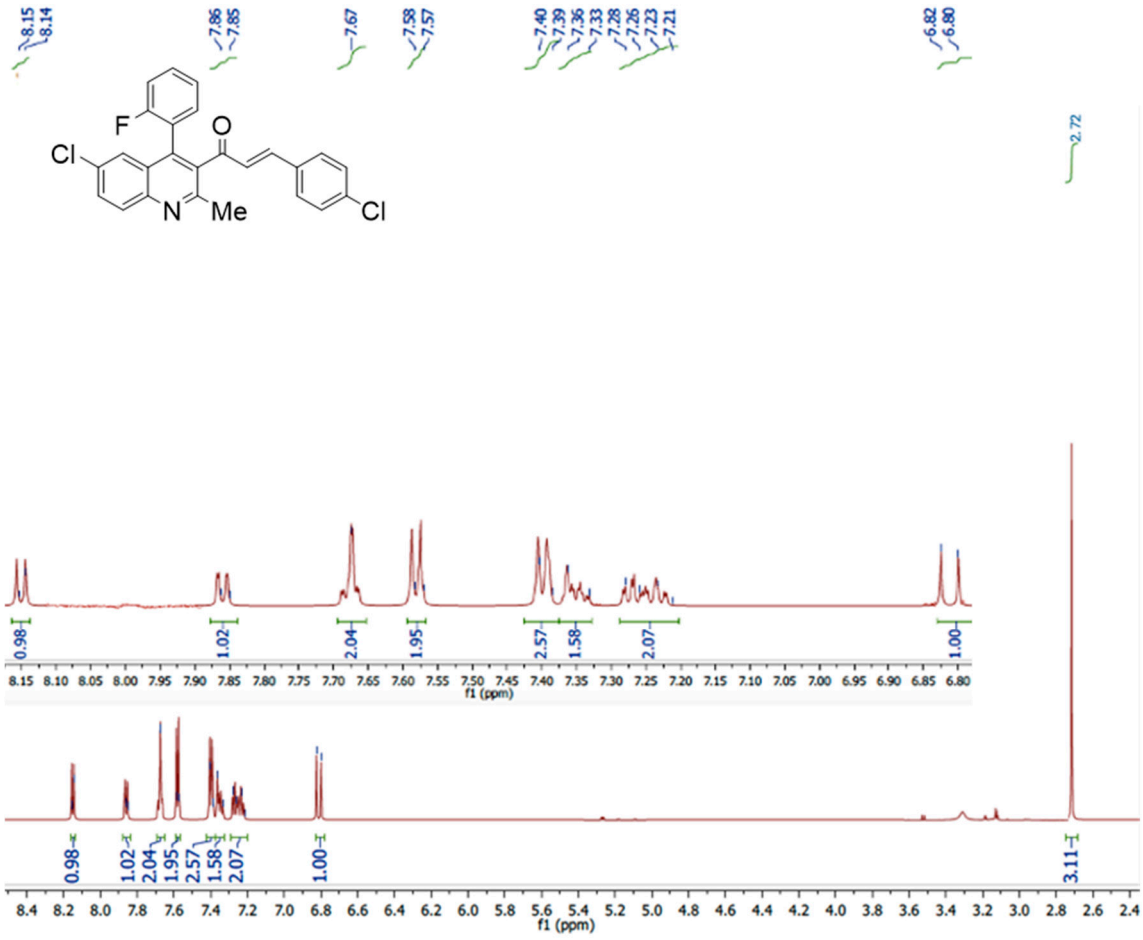
Spectrum S29: ^{13}C-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-oxoprop-1en-1-yl)phenyl benzoate **(E009)**



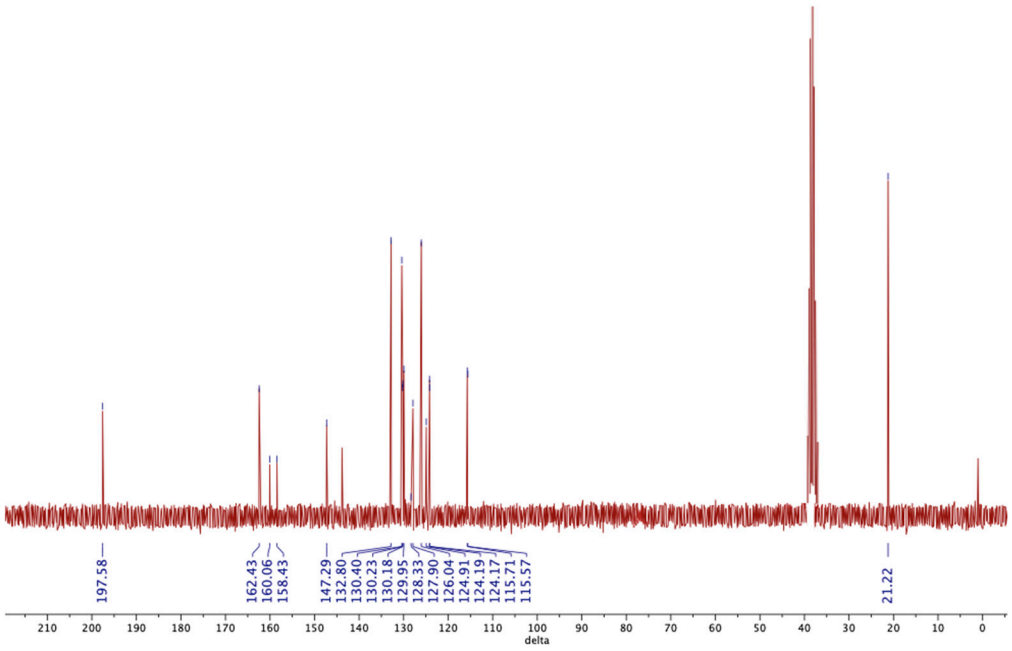
Spectrum S30: IR (KBr). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-oxoprop-1en-1-yl)phenyl benzoate **(E009)**



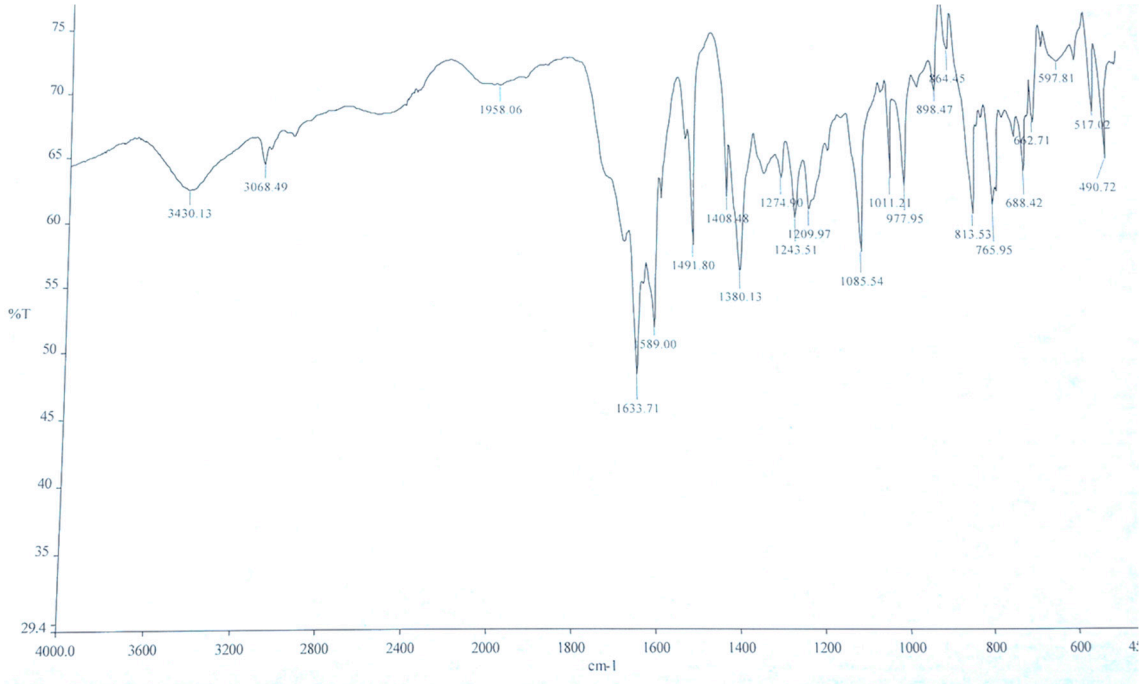
Spectrum S31: ^{1}H-NMR (DMSO-d_6). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3- (4-cholrophenyl)prop-2-en-1-one **(E010).**



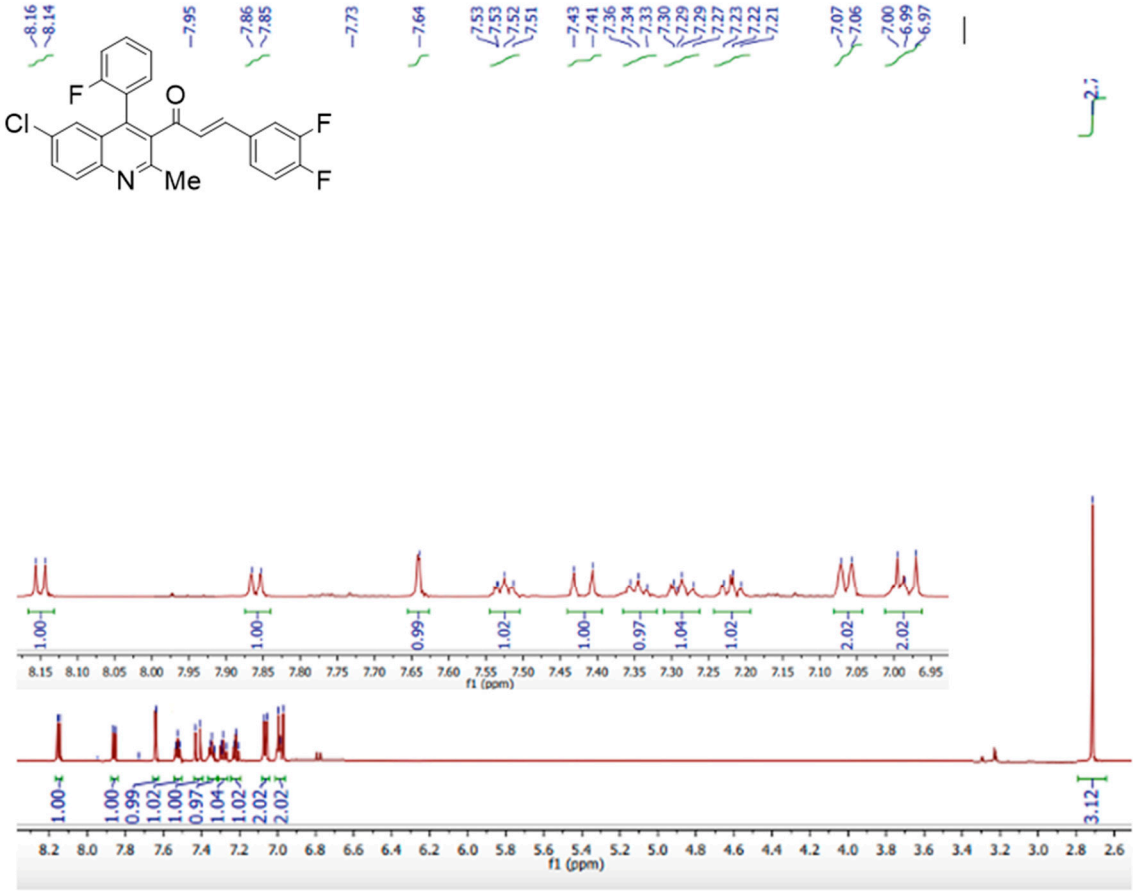
Spectrum S32: ^{13}C-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3- (4-cholrophenyl)prop-2-en-1-one **(E010).**



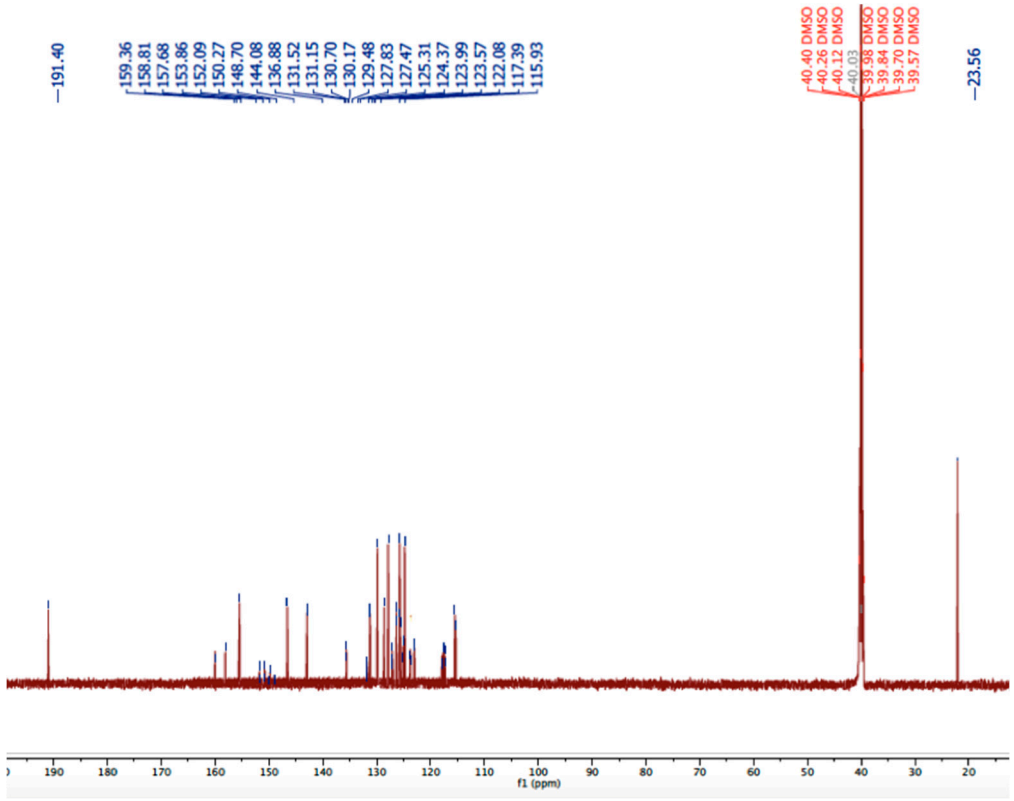
Spectrum S33: ^{13}C-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3- (4-cholrophenyl)prop-2-en-1-one **(E010).**



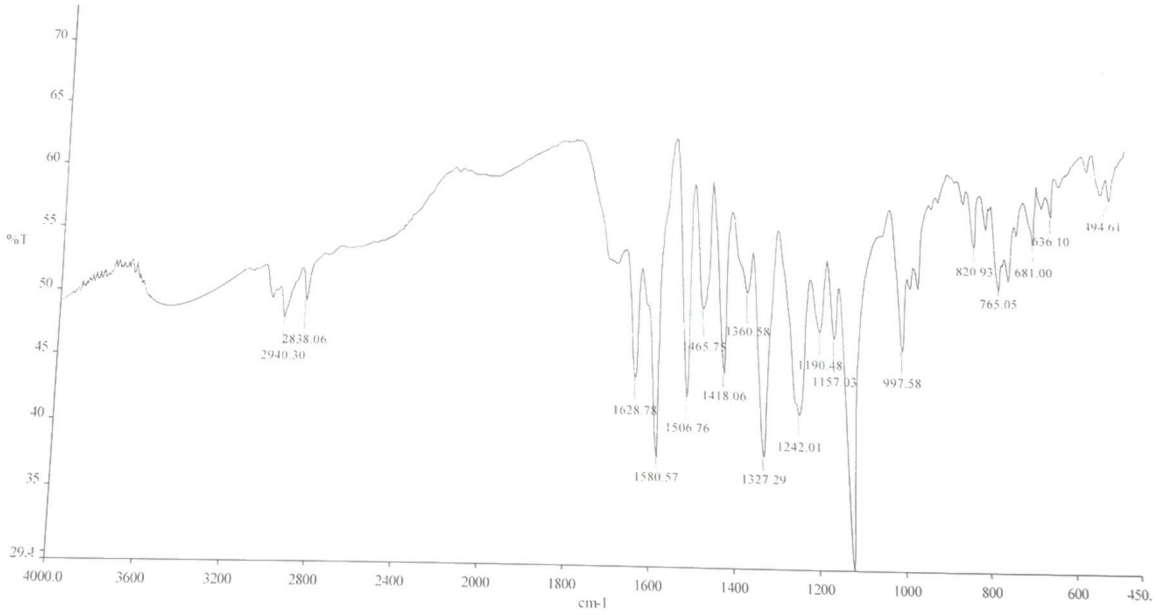
Spectrum S34: ^{1}H-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,5-difluorophenyl)prop-2-en-1-one **(E011)**



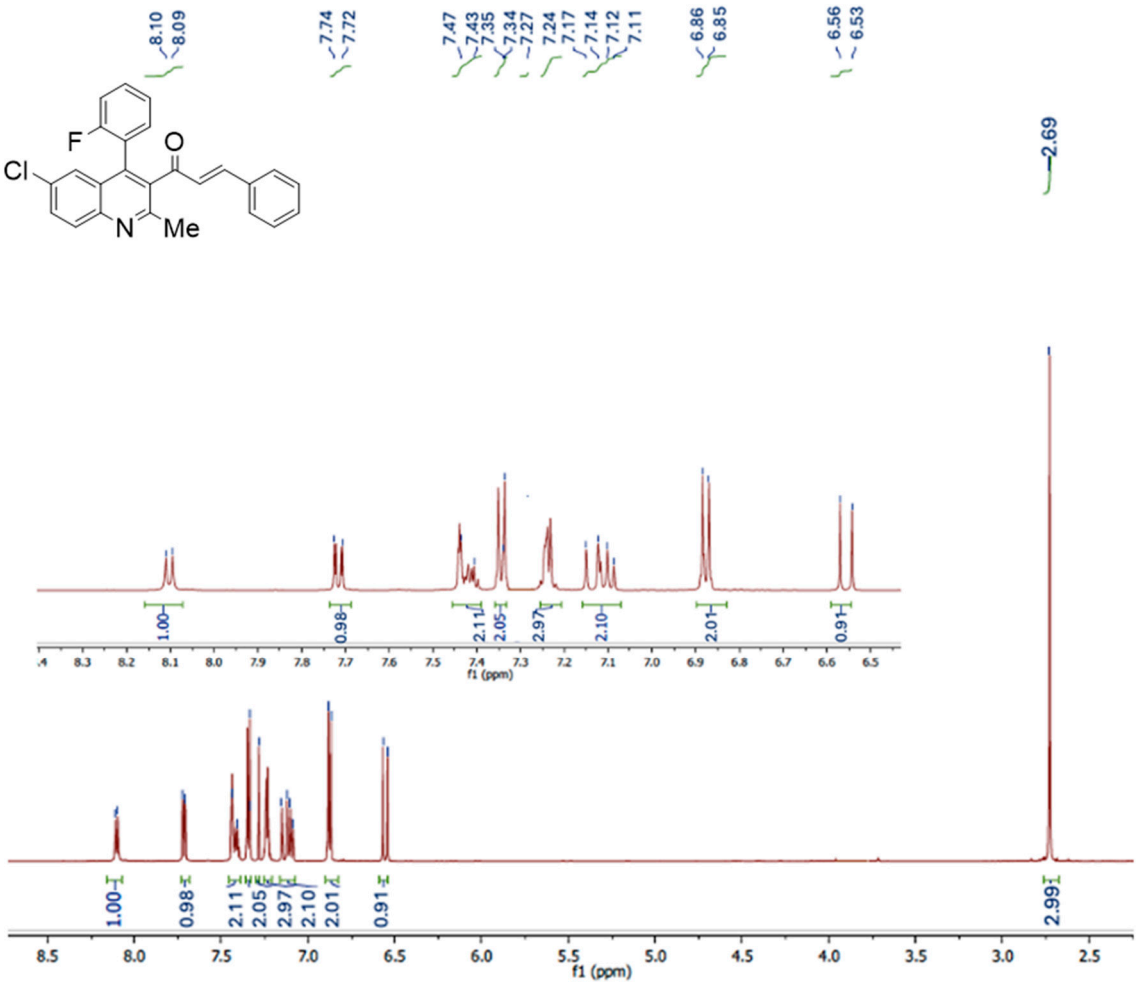
Spectrum S35: ^{13}C-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,5-difluorophenyl)prop-2-en-1-one **(E011)**



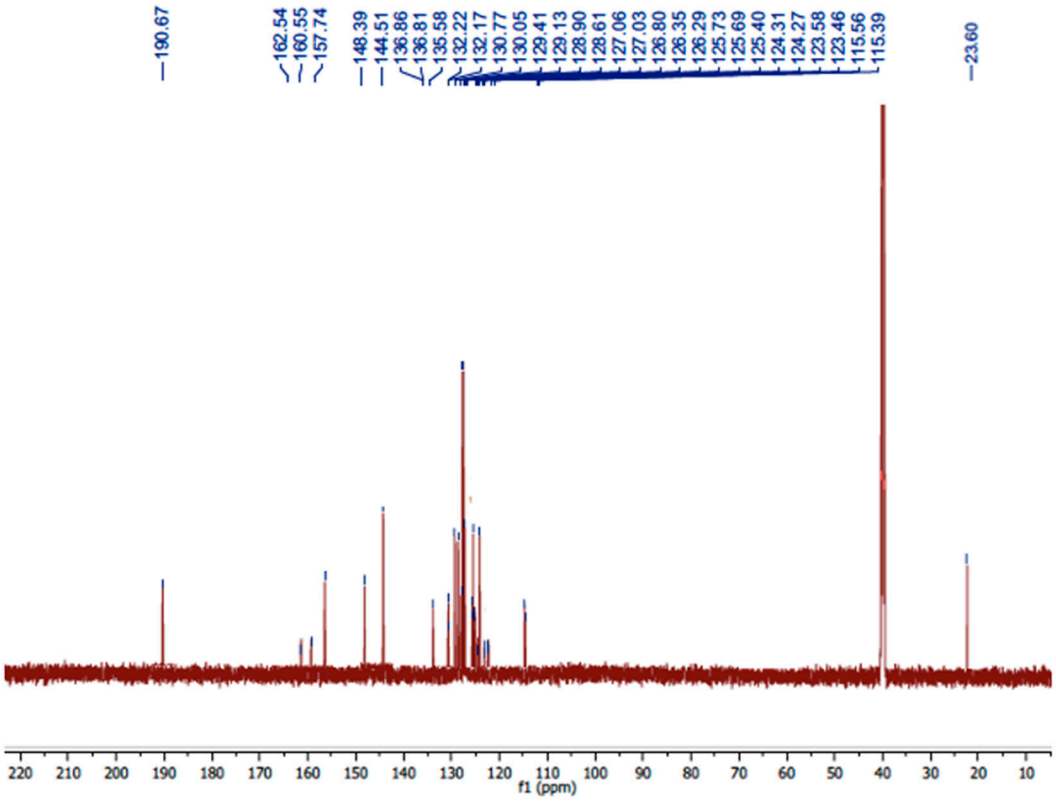
Spectrum S36: IR (KBr). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-(3,5-difluorophenyl)prop-2-en-1-one **(E011)**



Spectrum S37: ^{1}H-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-phenylprop-2-en-1-one **(E012)**



Spectrum S38: ^{13}C-NMR (DMSO-d$_6$). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-phenylprop-2-en-1-one **(E012)**



Spectrum S39: IR (KBr). (*E*)-1-(6-chloro-4-(2-fluorophenyl)-2-methylquinolin-3-yl)-3-phenylprop-2-en-1-one **(E012)**

