Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Development of a novel class of B-Raf^{V600E}-selective inhibitors through virtual screening and hierarchical hit optimization

Xiangqian Kong[a#], Jie Qin[b#], Zeng Li[a#], Adina Vultur[b], Linjiang Tong[a], Enguang Feng[a], Geena Rajan[b], Shien Liu[a], Junyan Lu[a], Zhongjie Liang[a], Mingyue Zheng[a], Weiliang Zhu[a], Hualiang Jiang[a], Meenhard Herlyn[b], Hong Liu[a]*, Ronen Marmorstein[b*] and Cheng Luo[a,c]*

[a]Drug Discovery and Design Center, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

[b]The Wistar Institute, Philadelphia, PA, 19104 USA

[c]Center for Systems Biology, Soochow University, Jiangsu 215006, China

Table of Contents

1. Validation of the Docking Protocol.

The reliability of various available docking methods (GLIDE 5.5,[1] GOLD 5.0, [2-4]AutoDock 4.2[5, 6]) against B-Raf was first evaluated regarding the two criteria. The first measurement is the root-mean-square deviation (RMSD) value between the best predicted docking pose and the corresponding experimental pose, while the other refers to the enrichment rate, which measures the number of known ligands in the top-ranked list relative to a random selection.

As presented in Figure S1, employing the average RMSD value as a measure, GLIDE outperformed the other two methods in recovering the bioactive conformations towards all 18 structural complexes. It gave the best average RMSD value (less than 0.9 Å) as well as the lowest standard deviation, reflecting the encouraging efficiency in exploring the conformational space in the ATP binding site of B-Raf. For the enrichment evaluations, 50 known inhibitors (Table S1) that specifically targeted the active conformation of B-Raf kinase were retrieved from ChEMBL,[7] mixing with the 950 compounds (Table S2) from the CDK2 decoy set in Directory of Useful Decoys (DUD).[8] The enrichment factors (EF) at 1%, 5% and 10% level of the ranked list were calculated for each of the docking methods (Table S3). Among the various docking protocols tested, GLIDE achieved the ideal EF at 1% sampling towards both of the representative structures of B-Raf, In addition, GLIDE exhibited comparable enrichment capability with GOLD at both 5% and 10% ranking levels. However, AutoDock showed inferior performances than GLIDE and GOLD at the three tested levels during our pilot study, and thus was not suitable in this case.

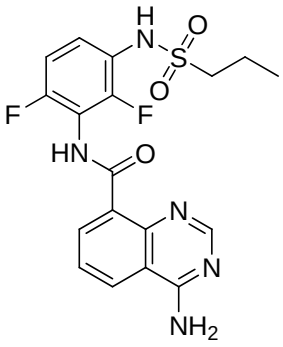
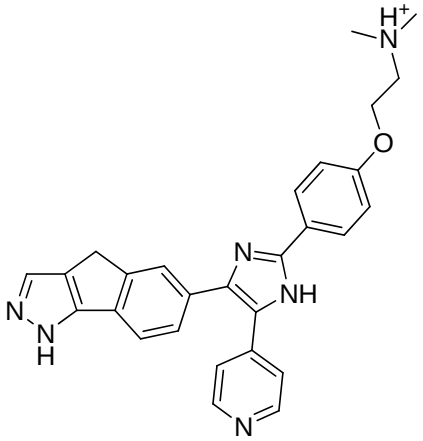
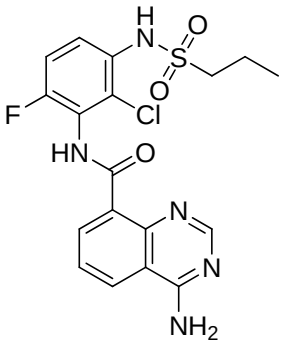
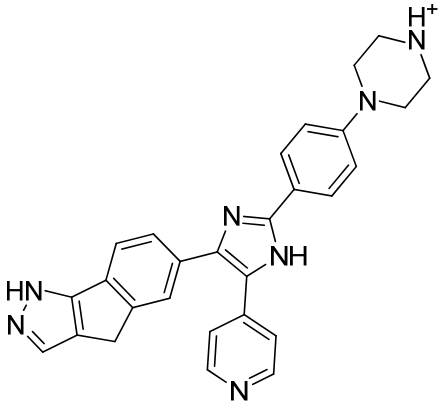
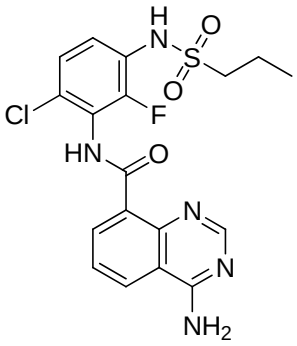
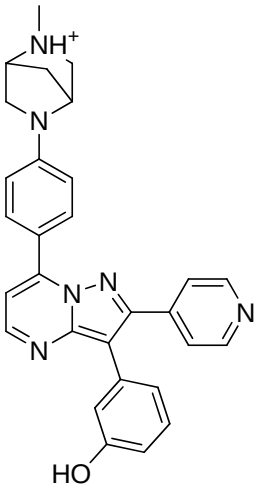
Taken together, GLIDE represented the most effective method regarding actives enrichment during our pilot study. GLIDE was therefore employed in the structure-based virtual screening study.

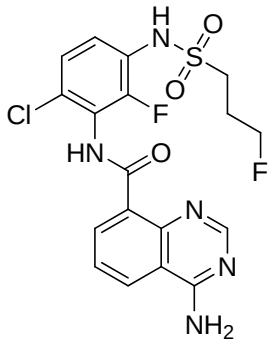
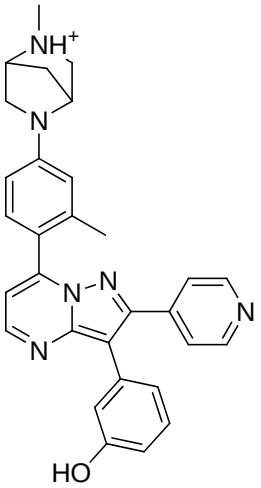
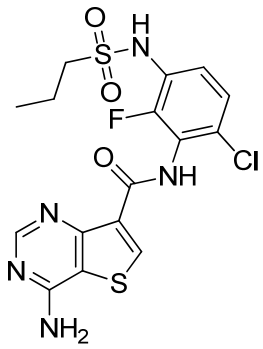
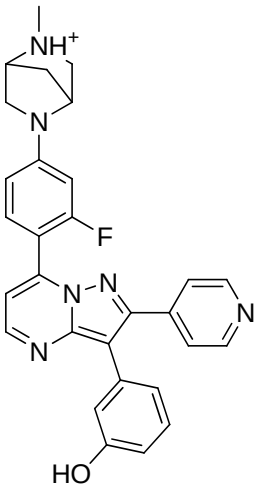
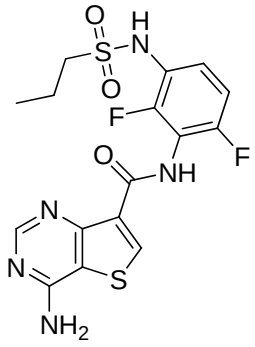
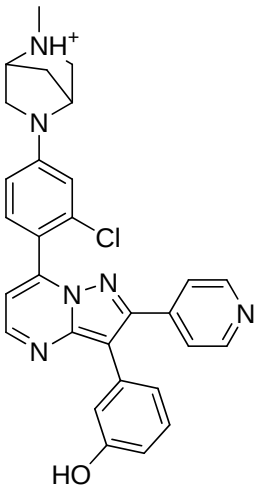
Figure S1: RMSD values calculated between docked and experimental poses. A color code bar is given based on the RMSD range listed below.

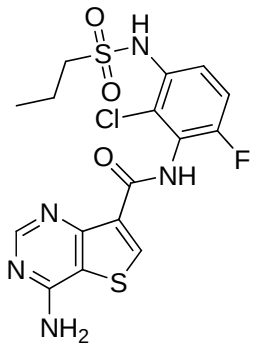
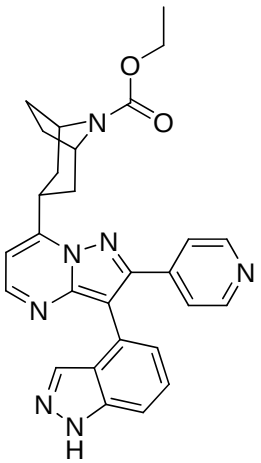
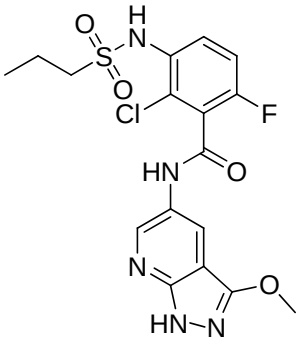
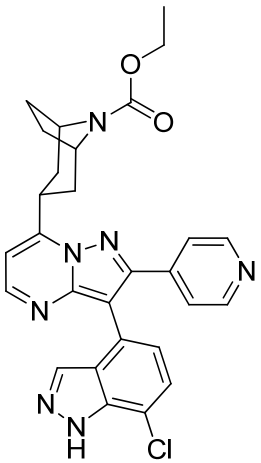
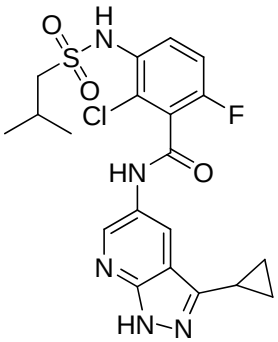
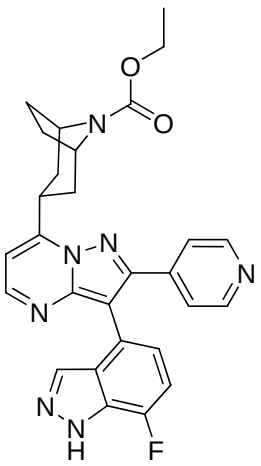
Protein(PDB ID)	GLIDE	GOLD	AutoDock
1UWJ	0.87	2.04	1.48
2FB8	2.33	2.18	2.29
3C4C	0.29	1.01	1.07
3C4D	0.84	1.47	1.25
3D4Q	1.14	1.58	1.05
3IDP	0.21	0.92	0.87
3II5	3.28	3.65	3.20
3OG7	0.39	1.23	1.29
3PPJ	0.22	1.45	4.14
3PPK	1.48	1.79	5.95
3PRF	1.46	1.24	1.32
3PRI	0.60	1.43	1.52
3PSB	0.23	7.83	4.50
3PSD	0.32	1.90	1.21
3Q96	0.32	3.06	7.50
3SKC	0.52	1.16	0.77
3TV4	0.67	1.08	0.95
3TV6	0.42	0.87	0.97
Mean(Å)	0.87	1.99	2.30
Std.dev.(Å)	0.80	1.58	1.91

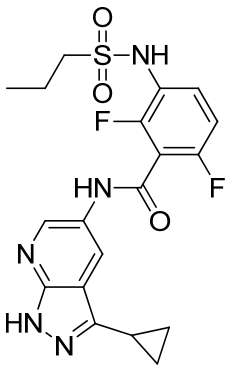
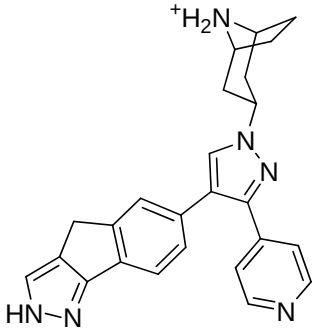
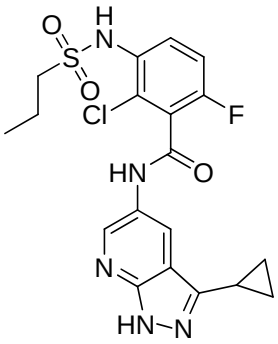
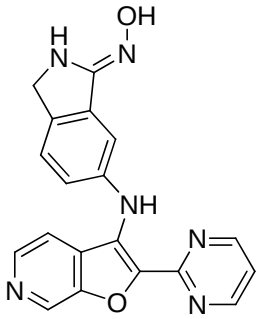
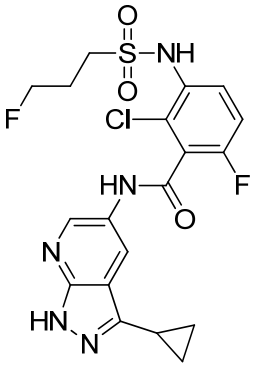
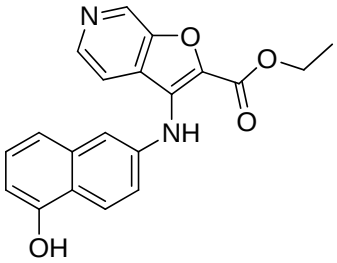
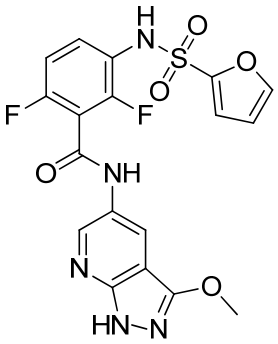
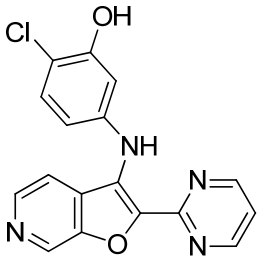
RMSD<1Å	1Å<RMSD<2Å	2Å<RMSD<5Å	RMSD>5Å

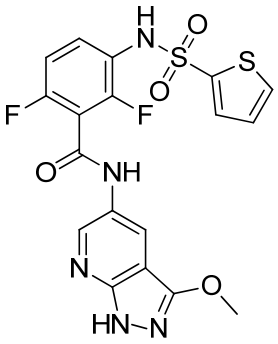
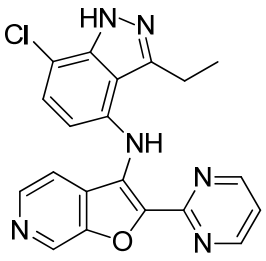
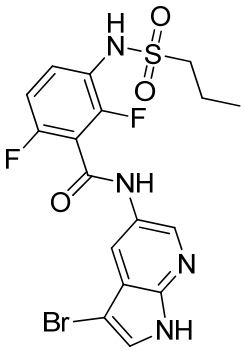
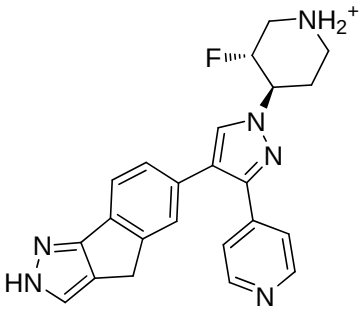
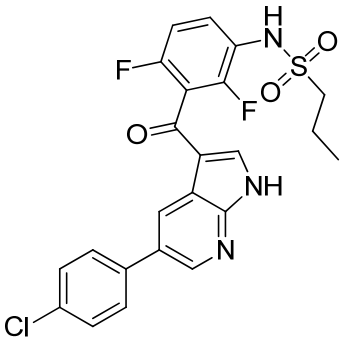
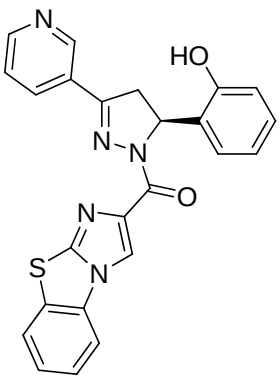
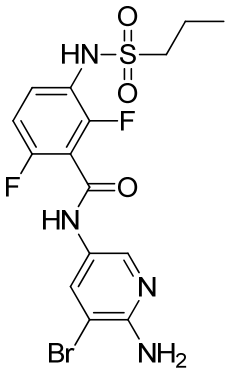
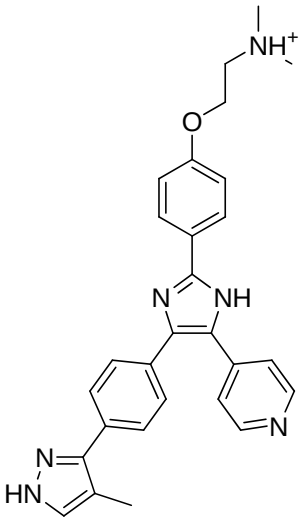
Table S1: Inhibitors of B-Raf^{V600E} used in the enrichment rate evaluation.

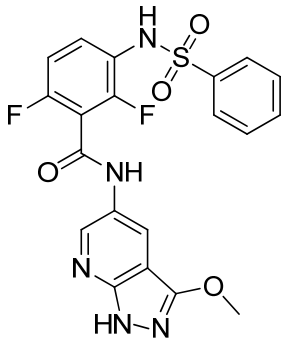
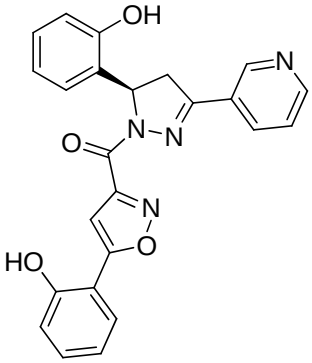
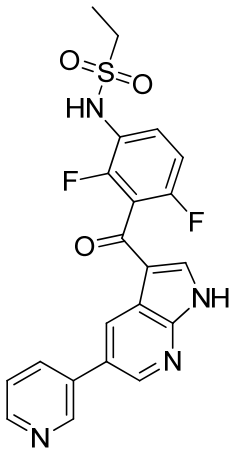
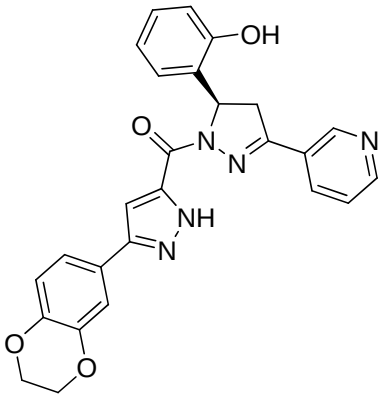
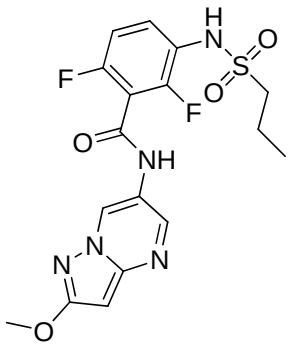
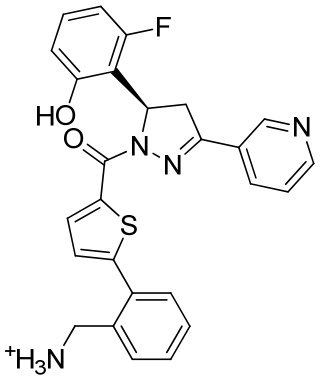
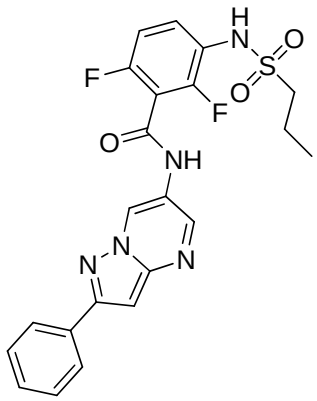
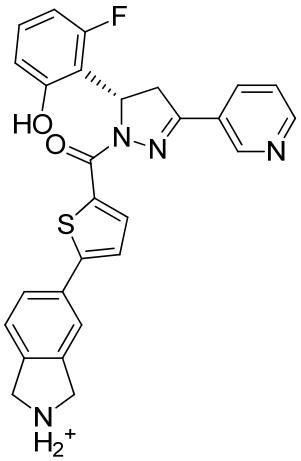
ID	Structure	ID	Structure
1		26	
2		27	
3		28	

4		29	
5		30	
6		31	

7		32	
8		33	
9		34	

10		35	
11		36	
12		37	
13		38	

14		39	
15		40	
16		41	
17		42	

18		43	
19		44	
20		45	
21		46	

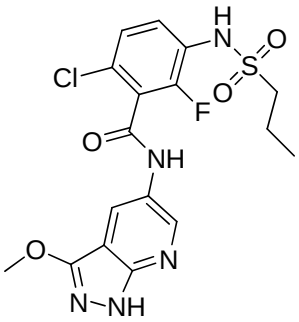
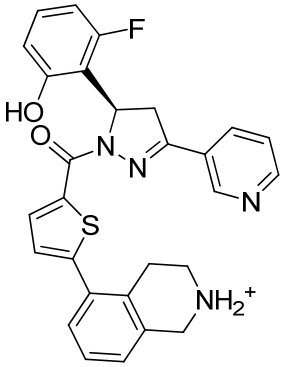
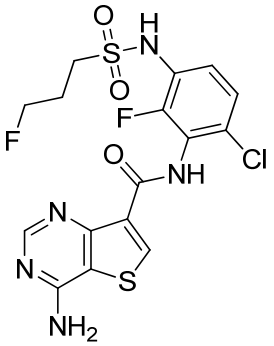
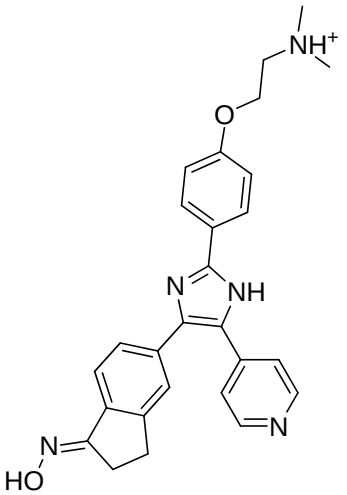
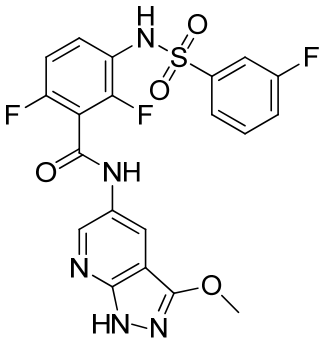
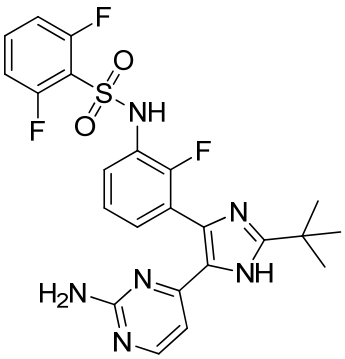
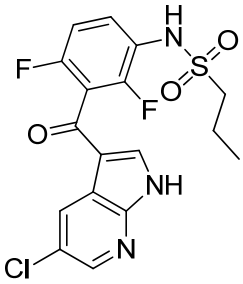
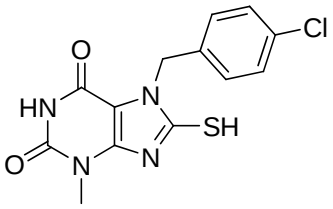
22		47	
23		48	
24		49	
25		50	

Table S2: Decoy compounds used in the enrichment rate evaluation.

ZINC ID	ZINC ID	ZINC ID	ZINC ID	ZINC ID
ZINC00497633	ZINC00727263	ZINC02628513	ZINC01486605	ZINC00539173
ZINC00848824	ZINC00538061	ZINC00077379	ZINC00030796	ZINC00046591
ZINC01491556	ZINC00235408	ZINC00774161	ZINC00707790	ZINC01066689
ZINC00784478	ZINC01069513	ZINC01690047	ZINC01274349	ZINC00472535
ZINC00784486	ZINC00531981	ZINC00858222	ZINC00041963	ZINC01921207
ZINC00090736	ZINC01137185	ZINC00191061	ZINC00905575	ZINC00958247
ZINC00784480	ZINC02230035	ZINC02342306	ZINC02241863	ZINC01220755
ZINC00562999	ZINC00200529	ZINC00352127	ZINC00546362	ZINC01397428
ZINC02398872	ZINC01796995	ZINC00174868	ZINC00103368	ZINC01795259
ZINC00053422	ZINC00616033	ZINC00340320	ZINC02447652	ZINC00208895
ZINC00645784	ZINC00902554	ZINC00892402	ZINC00545788	ZINC00205662
ZINC00634089	ZINC00464378	ZINC00111773	ZINC01490039	ZINC00472534
ZINC01768798	ZINC00550502	ZINC00559951	ZINC00804199	ZINC01642466
ZINC01366443	ZINC00020210	ZINC00516382	ZINC00444594	ZINC00820214
ZINC00784476	ZINC00020212	ZINC02218057	ZINC01021233	ZINC00073812
ZINC01125293	ZINC00216209	ZINC00179064	ZINC01485420	ZINC01034440
ZINC00425636	ZINC01489524	ZINC00240282	ZINC00067894	ZINC00422916
ZINC00582103	ZINC00467851	ZINC01250699	ZINC00144593	ZINC02503741
ZINC01679981	ZINC00634110	ZINC00111808	ZINC00241720	ZINC00200590
ZINC02485379	ZINC00616249	ZINC00867970	ZINC00419226	ZINC01408856
ZINC00848822	ZINC01123502	ZINC00980184	ZINC00462783	ZINC00389256
ZINC00732046	ZINC00266266	ZINC02626208	ZINC02640211	ZINC01121013
ZINC00457156	ZINC01069617	ZINC00466139	ZINC00419360	ZINC00414337
ZINC00588371	ZINC00837458	ZINC02281984	ZINC00493386	ZINC01287026
ZINC02394634	ZINC00581954	ZINC00424178	ZINC00318835	ZINC00414336
ZINC01019119	ZINC01464985	ZINC02331095	ZINC00429751	ZINC00026736
ZINC01750506	ZINC00433797	ZINC00138774	ZINC02208645	ZINC00108901
ZINC00416710	ZINC00612070	ZINC00264610	ZINC02091772	ZINC01188054
ZINC00037147	ZINC00035578	ZINC00086200	ZINC00240267	ZINC00600716
ZINC00524820	ZINC00581973	ZINC00136336	ZINC00288284	ZINC00026735
ZINC02123307	ZINC01226303	ZINC00609289	ZINC01438429	ZINC01414232
ZINC00184122	ZINC02230037	ZINC00201168	ZINC00240440	ZINC00414335
ZINC00270138	ZINC00561559	ZINC00892399	ZINC00508861	ZINC00819646
ZINC00822279	ZINC00063412	ZINC00228979	ZINC00928787	ZINC00552243
ZINC00204943	ZINC00730214	ZINC00371350	ZINC00337066	ZINC00314545
ZINC02222522	ZINC00030344	ZINC01427076	ZINC00061263	ZINC00477228
ZINC00582153	ZINC00423416	ZINC00290924	ZINC00420563	ZINC01933353
ZINC00024689	ZINC02241864	ZINC00638477	ZINC00835013	ZINC02364274
ZINC00093102	ZINC00801751	ZINC01468985	ZINC00344276	ZINC02501815
ZINC00290896	ZINC02414821	ZINC00071925	ZINC00368638	ZINC00385170
ZINC00367746	ZINC00581180	ZINC00368634	ZINC00042824	ZINC00716307

ZINC00634100	ZINC01516393	ZINC02444459	ZINC00809403	ZINC01406259
ZINC01111842	ZINC01933338	ZINC00523032	ZINC00013885	ZINC02490475
ZINC00907969	ZINC00496370	ZINC00063403	ZINC01059586	ZINC01086128
ZINC01238258	ZINC02273578	ZINC00619616	ZINC01122918	ZINC01817178
ZINC00902552	ZINC00024494	ZINC00948458	ZINC01226646	ZINC02474569
ZINC00011462	ZINC00296088	ZINC01123416	ZINC02362449	ZINC00200589
ZINC00338129	ZINC01504513	ZINC02636591	ZINC01257904	ZINC01438428
ZINC00285933	ZINC01009042	ZINC00311448	ZINC01774311	ZINC01564714
ZINC00146145	ZINC02433720	ZINC00806199	ZINC00084106	ZINC00480398
ZINC00822266	ZINC00216210	ZINC01282729	ZINC00080999	ZINC01148703
ZINC00129955	ZINC00463201	ZINC02285620	ZINC00368635	ZINC02218983
ZINC01055805	ZINC00249385	ZINC00241030	ZINC02464124	ZINC00269543
ZINC00594085	ZINC00460879	ZINC01508268	ZINC00173711	ZINC01583340
ZINC00188976	ZINC00892393	ZINC00544452	ZINC02286082	ZINC00312149
ZINC00558000	ZINC01234546	ZINC02366591	ZINC00602630	ZINC01438427
ZINC00803011	ZINC01493911	ZINC00835015	ZINC02635905	ZINC01287040
ZINC00524818	ZINC00999033	ZINC00179323	ZINC01226644	ZINC02119734
ZINC01921716	ZINC02055809	ZINC00171219	ZINC01752717	ZINC00882482
ZINC00478429	ZINC00892397	ZINC00253966	ZINC01762580	ZINC00899378
ZINC02475412	ZINC00360394	ZINC00546591	ZINC00046592	ZINC02064738
ZINC02602352	ZINC00182438	ZINC00288907	ZINC00716305	ZINC02228301
ZINC01648569	ZINC00620935	ZINC01562968	ZINC00531980	ZINC00013886
ZINC01472307	ZINC01006661	ZINC00628254	ZINC02282906	ZINC00537430
ZINC00585137	ZINC00452803	ZINC01226928	ZINC00704338	ZINC00205663
ZINC02404828	ZINC01062292	ZINC00058582	ZINC01177943	ZINC00632664
ZINC00645252	ZINC00229628	ZINC02441614	ZINC00755030	ZINC01121015
ZINC01054565	ZINC01683957	ZINC00488644	ZINC02319490	ZINC00314236
ZINC00029703	ZINC02444461	ZINC01178204	ZINC00002103	ZINC01419240
ZINC01673110	ZINC01923565	ZINC00371351	ZINC00536828	ZINC01770633
ZINC01893624	ZINC00638480	ZINC00469559	ZINC02358367	ZINC00184781
ZINC01131178	ZINC00463972	ZINC00449951	ZINC00469975	ZINC00420138
ZINC01768737	ZINC01922752	ZINC02461453	ZINC00472489	ZINC00884868
ZINC01426143	ZINC00230801	ZINC00182207	ZINC00251956	ZINC02222691
ZINC01759701	ZINC02218054	ZINC00612172	ZINC01130655	ZINC00044363
ZINC00035660	ZINC00514219	ZINC02293438	ZINC01475794	ZINC02107081
ZINC02242380	ZINC00463202	ZINC01150869	ZINC00006108	ZINC02622009
ZINC00474231	ZINC01159067	ZINC00199882	ZINC00366897	ZINC02090285
ZINC00859491	ZINC00949674	ZINC02455498	ZINC00629534	ZINC00011880
ZINC01504350	ZINC02432791	ZINC00753072	ZINC00359140	ZINC00536819
ZINC01196922	ZINC02438586	ZINC02288808	ZINC01849267	ZINC00808721
ZINC00978964	ZINC01248309	ZINC02443546	ZINC00536829	ZINC00479618
ZINC01013829	ZINC01427091	ZINC00405969	ZINC01414222	ZINC00616753
ZINC00244316	ZINC01902225	ZINC02342307	ZINC00484384	ZINC00414317
ZINC00474730	ZINC00296101	ZINC01841772	ZINC00136283	ZINC00112768

ZINC02242379	ZINC00314337	ZINC02208649	ZINC00958246	ZINC00466653
ZINC01128417	ZINC00516672	ZINC02639567	ZINC01059584	ZINC00610103
ZINC00423412	ZINC00956535	ZINC01177047	ZINC00953372	ZINC01001471
ZINC01136286	ZINC01257009	ZINC00621224	ZINC00778980	ZINC01468101
ZINC01226298	ZINC00099180	ZINC00773601	ZINC00800924	ZINC00405998
ZINC00177981	ZINC02283905	ZINC00327475	ZINC00029692	ZINC00819629
ZINC00524891	ZINC01055888	ZINC02461441	ZINC02241203	ZINC00305680
ZINC00002112	ZINC02636918	ZINC02285496	ZINC00405999	ZINC00115651
ZINC00423393	ZINC00461594	ZINC02390764	ZINC00892395	ZINC01829243
ZINC00524878	ZINC00804424	ZINC00262118	ZINC00536746	ZINC02622008
ZINC00621164	ZINC00889193	ZINC00303324	ZINC01409204	ZINC00112763
ZINC01323132	ZINC01086630	ZINC01410159	ZINC00552242	ZINC02359833
ZINC01097629	ZINC01020411	ZINC00195959	ZINC02499743	ZINC02351196
ZINC02432793	ZINC00201361	ZINC01233421	ZINC00131980	ZINC02391227
ZINC00581122	ZINC00423403	ZINC01127103	ZINC00524445	ZINC01518201
ZINC00835772	ZINC01053398	ZINC01966570	ZINC00809456	ZINC02406133
ZINC02195168	ZINC01875861	ZINC00471237	ZINC00972467	ZINC00806331
ZINC01191528	ZINC00680571	ZINC00471590	ZINC00656938	ZINC02201893
ZINC00954834	ZINC01475798	ZINC00850688	ZINC01565908	ZINC01287014
ZINC00754802	ZINC01078715	ZINC02134257	ZINC02355945	ZINC01287224
ZINC02629084	ZINC01487985	ZINC00466138	ZINC02370715	ZINC00260968
ZINC00181056	ZINC01559383	ZINC00035663	ZINC00088067	ZINC00989378
ZINC01232417	ZINC02280695	ZINC00112082	ZINC00232118	ZINC02064740
ZINC01057166	ZINC00017176	ZINC00264694	ZINC01085868	ZINC01556760
ZINC00582398	ZINC00359424	ZINC00368637	ZINC00532000	ZINC00845957
ZINC00444406	ZINC01191698	ZINC02412977	ZINC00618711	ZINC01314019
ZINC00582183	ZINC00475021	ZINC02425992	ZINC02230029	ZINC01933412
ZINC02229252	ZINC00444432	ZINC01133013	ZINC00200632	ZINC02089039
ZINC01026085	ZINC00859871	ZINC01458802	ZINC01649532	ZINC00798420
ZINC00454299	ZINC01440225	ZINC01646589	ZINC00108905	ZINC00989407
ZINC00438112	ZINC02206143	ZINC01445823	ZINC00505204	ZINC00051499
ZINC00596540	ZINC00605940	ZINC01501298	ZINC01178205	ZINC00798419
ZINC01067715	ZINC01633085	ZINC00116246	ZINC02406134	ZINC00314531
ZINC00837460	ZINC00357252	ZINC02394847	ZINC00415281	ZINC01475243
ZINC01803016	ZINC00370871	ZINC00302412	ZINC01000015	ZINC00809825
ZINC02503176	ZINC00582562	ZINC01398659	ZINC01218273	ZINC01486508
ZINC00291660	ZINC00073386	ZINC00682264	ZINC01086386	ZINC01091063
ZINC01943942	ZINC01170602	ZINC00396454	ZINC01148705	ZINC00542446
ZINC00160866	ZINC00427775	ZINC00444408	ZINC00386402	ZINC02497938
ZINC01542456	ZINC00790039	ZINC00463897	ZINC00496110	ZINC01021169
ZINC00263080	ZINC01191511	ZINC02551044	ZINC01402749	ZINC01275284
ZINC00594111	ZINC00091356	ZINC00140767	ZINC01414231	ZINC00685711
ZINC00289930	ZINC00261822	ZINC01149065	ZINC00243607	ZINC01639371
ZINC01054225	ZINC00570028	ZINC00250761	ZINC00030061	ZINC00444455

ZINC00486917	ZINC02331091	ZINC01743784	ZINC00621001	ZINC00828771
ZINC02213593	ZINC00537312	ZINC02032655	ZINC00797907	ZINC02359831
ZINC01742873	ZINC01422528	ZINC02282306	ZINC01741722	ZINC00632673
ZINC00499027	ZINC00175333	ZINC02394307	ZINC02103242	ZINC02624806
ZINC00949673	ZINC00950289	ZINC00619819	ZINC00183494	ZINC00385129
ZINC01063549	ZINC01464778	ZINC01062654	ZINC00809473	ZINC00612374
ZINC00099178	ZINC02565335	ZINC00063411	ZINC02295145	ZINC00087451
ZINC01428351	ZINC00510745	ZINC00381188	ZINC02571071	ZINC01331337
ZINC00899089	ZINC00778548	ZINC01659142	ZINC00466925	ZINC00232114
ZINC00423409	ZINC01118516	ZINC00798337	ZINC00527353	ZINC01314018
ZINC00508996	ZINC00029693	ZINC00619715	ZINC01059884	ZINC00384992
ZINC01151508	ZINC00753986	ZINC01159464	ZINC01820118	ZINC01933411
ZINC00573720	ZINC01430703	ZINC01438430	ZINC02616089	ZINC02251491
ZINC01125011	ZINC02366590	ZINC01933349	ZINC00419436	ZINC00385011
ZINC02205681	ZINC00242394	ZINC02437100	ZINC00545944	ZINC00420818
ZINC00998370	ZINC02627708	ZINC00210582	ZINC01458801	ZINC00809474
ZINC01395945	ZINC00192823	ZINC00516369	ZINC00031246	ZINC00202450
ZINC00288904	ZINC01468986	ZINC02279894	ZINC00056094	ZINC00384991
ZINC00613475	ZINC01921257	ZINC00192916	ZINC00090175	ZINC01921555
ZINC00612499	ZINC00023778	ZINC00304032	ZINC00408342	ZINC01287013
ZINC01076219	ZINC00299766	ZINC01088131	ZINC02643434	ZINC00385130
ZINC01009031	ZINC00303420	ZINC01496007	ZINC00020730	ZINC01287012
ZINC01324658	ZINC02229254	ZINC02193841	ZINC00200627	ZINC01442519
ZINC00508932	ZINC00067891	ZINC00131561	ZINC00602554	ZINC00627266
ZINC00581181	ZINC02239389	ZINC00773686	ZINC01269215	ZINC00971529
ZINC00626811	ZINC00082027	ZINC00859413	ZINC00034136	ZINC01331362
ZINC01079717	ZINC00136339	ZINC02568372	ZINC01864135	ZINC00538090
ZINC02569032	ZINC01050101	ZINC00545519	ZINC00299763	ZINC00033458
ZINC00307448	ZINC02230028	ZINC00030867	ZINC00257702	ZINC00539938
ZINC01410157	ZINC00296098	ZINC00468095	ZINC00719257	ZINC02224268
ZINC00171422	ZINC00485187	ZINC00778934	ZINC00958362	ZINC00620375
ZINC02443543	ZINC01002240	ZINC01049914	ZINC00522045	ZINC00202207
ZINC00676471	ZINC00379784	ZINC01921806	ZINC02490472	ZINC00942179
ZINC00092130	ZINC00046565	ZINC02294211	ZINC00809405	ZINC02364272
ZINC02624887	ZINC01933339	ZINC01398087	ZINC00075929	ZINC02351195
ZINC00596539	ZINC00091359	ZINC01923449	ZINC00138921	ZINC00232244
ZINC00582152	ZINC01021235	ZINC00311458	ZINC02201250	ZINC00828772
ZINC02139584	ZINC00463896	ZINC00730212	ZINC00414338	ZINC00160140
ZINC02239738	ZINC00031648	ZINC00131422	ZINC00795157	ZINC00386462
ZINC00894595	ZINC00628252	ZINC00122316	ZINC00312488	ZINC00718534
ZINC00297622	ZINC00338018	ZINC00269547	ZINC01409208	ZINC00800928
ZINC00419224	ZINC00076679	ZINC00859942	ZINC00015788	ZINC00994145
ZINC00493329	ZINC01050089	ZINC00545520	ZINC01290658	ZINC00537429
ZINC01472306	ZINC01287047	ZINC01088128	ZINC01420979	ZINC01820117

ZINC01151507	ZINC00111293	ZINC02637648	ZINC01921497	ZINC01270673
ZINC00242784	ZINC01133011	ZINC00543176	ZINC00471591	ZINC00377620
ZINC00892400	ZINC00063405	ZINC01414899	ZINC01647428	ZINC00036871
ZINC01430048	ZINC00288913	ZINC02394556	ZINC00523794	ZINC01751661
ZINC00371036	ZINC00501669	ZINC02620245	ZINC02263907	ZINC01921444
ZINC02334610	ZINC00268949	ZINC01150082	ZINC01175432	ZINC00464766
ZINC00147887	ZINC00270140	ZINC01677089	ZINC00620845	ZINC00060962
ZINC00545600	ZINC01216699	ZINC01490962	ZINC00144849	ZINC01757600
ZINC00493385	ZINC00218284	ZINC00156146	ZINC00911865	ZINC00833420
ZINC02344649	ZINC02281793	ZINC00804384	ZINC00480399	ZINC00706105
ZINC00016242	ZINC00522668	ZINC00859873	ZINC00537288	ZINC02350476
ZINC00803803	ZINC00463141	ZINC01086387	ZINC00970022	ZINC00536909
ZINC00350899	ZINC00471238	ZINC01468998	ZINC01408883	ZINC02206022
ZINC00423413	ZINC01164451	ZINC01516501	ZINC01757601	ZINC01261422
ZINC00182687	ZINC00030345	ZINC00037928	ZINC00306331	ZINC01270674
ZINC00291524	ZINC01063649	ZINC00230102	ZINC01132406	ZINC00480397
ZINC00026882	ZINC01501285	ZINC00302347	ZINC00406639	ZINC01901294

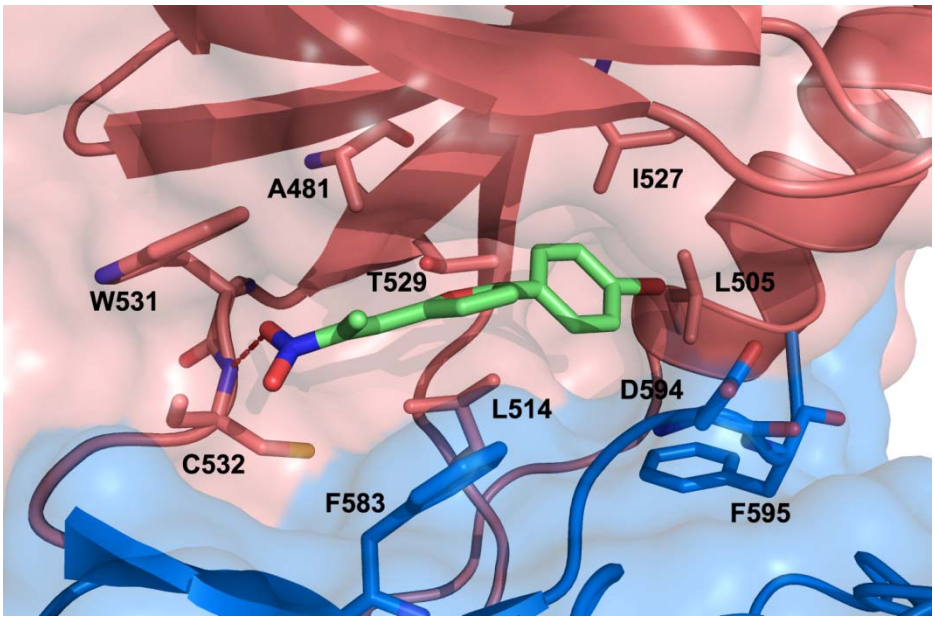
Table S3: Enrichment Factor (EF) calculations of 50 B-Raf inhibitors mixed with 950 decoys.[a]

Docking Program	Database Sampled					
	1%EF (2000[a])		5%EF (2000[a])		10%EF (1000[a])	
	3OG7	2FB8	3OG7	2FB8	3OG7	2FB8
GLIDE	2000	2000	1080	1120	640	700
GOLD	2000	1800	1200	960	780	540
AutoDock	2000	1400	960	680	680	500

a. Database sampled at 1%, 5%, and 10% of hits. b. Theoretical ideal enrichment factors.

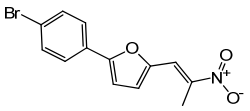
2. Predicted Binding Mode of Hit 1 with B-Raf^{V600E}

Figure S2. Predicted binding mode of hit 1 in the ATP binding site of B-Raf^{V600E}. The N-lobe of the B-Raf kinase is depicted in pink while the C-lobe is in blue. The stick representation corresponds to hit 1, and key residues in the N-lobe and C-lobes are highlighted in green, pink, and blue, respectively. A hydrogen bond interaction with the hinge region of B-Raf kinase is shown as a red dashed line.



3. The Anti-proliferation Activity of Hit 1

Table S4: *In vitro* inhibition rate (%) of tumor growth for hit 1

Compound	Structure	A375	HCT-116
1		94.4%[a]	68.1%[a]

[a] Results obtained from the average of two independent experiments.

4. References

1. Glide, version 5.5, Schrödinger, LLC, New York, NY, 2009.

2. G. Jones, P. Willett and R. C. Glen, *J Mol Biol*, 1995, 245, 43-53.

3. G. Jones, P. Willett, R. C. Glen, A. R. Leach and R. Taylor, *J Mol Biol*, 1997, 267, 727-748.

4. M. L. Verdonk, J. C. Cole, M. J. Hartshorn, C. W. Murray and R. D. Taylor, *Proteins*, 2003, 52, 609-623.

5. G. M. Morris, D. S. Goodsell, R. S. Halliday, R. Huey, W. E. Hart, R. K. Belew and A. J. Olson, *J Comput Chem*, 1998, 19, 1639-1662.

6. R. Huey, G. M. Morris, A. J. Olson and D. S. Goodsell, *J Comput Chem*, 2007, 28, 1145-1152.

7. A. Gaulton, L. J. Bellis, A. P. Bento, J. Chambers, M. Davies, A. Hersey, Y. Light, S. McGlinchey, D. Michalovich, B. Al-Lazikani and J. P. Overington, *Nucleic Acids Res*, 2012, 40, D1100-1107.

8. N. Huang, B. K. Shoichet and J. J. Irwin, *J Med Chem*, 2006, 49, 6789-6801.

5. The Purity Analysis of the Synthesized Compounds

5.1 The HPLC analyses of all the synthesized compounds.

The HPLC analyses were determined by the instrumentation with the system given in the following table.

HPLC Analyses Results			
Equipment	Agilent 1100 Series HPLC with binary pump, photodiode array detector (DAD).		
Column	Agilent Eclipse XDB-C18 (4.6 × 150 mm, 5 μm) reversed phase column.		
Condition	The mobile phase was a mixture of H_2O/MeCN = 40:60 (v/v) with 0.1% CF_3COOH (v/v) as an additive. The flow rate was 0.6 mL/min. Purity was calculated by the peak area on the UV detection wavelength 214 nm.		
Results	**Compd**	**Retention time (min)**	**Purity (%)**
	16a	**8.272**	**> 99**
	16b	**7.360**	**> 99**
	16c	**7.371**	**97.33**
	16d	**7.245**	**97.68**
	16e	**8.743**	**> 99**
	16f	**7.496**	**> 99**
	16g	**7.180**	**> 99**
	17a	**7.830**	**98.21**
	17b	**7.759**	**> 99**
	17c	**7.129**	**96.98**
	17d	**8.707**	**> 99**

	17e	**7.963**	**> 99**
	17f	**7.052**	**98.19**
	19a	**6.694**	**> 99**
	19b	**8.974**	**> 99**
	19c	**7.938**	**> 99**
	19d	**8.520**	**98.42**
	19e	**8.068**	**97.60**
	19g	**12.262**	**> 99**
	19h	**7.372**	**> 99**
	19i	**12.530**	**> 99**
	19j	**13.343**	**> 99**
	19k	**7.683**	**> 99**
	22a	**8.717**	**> 99**
	22b	**7.458**	**> 99**
	22c	**6.921**	**> 99**
	22e	**8.955**	**> 99**
	22f	**10.928**	**98.72**
	22g	**11.369**	**> 99**
	22h	**6.460**	**> 99**
	22i	**11.294**	**> 99**
	22j	**12.464**	**> 99**
	22k	**8.926**	**> 99**

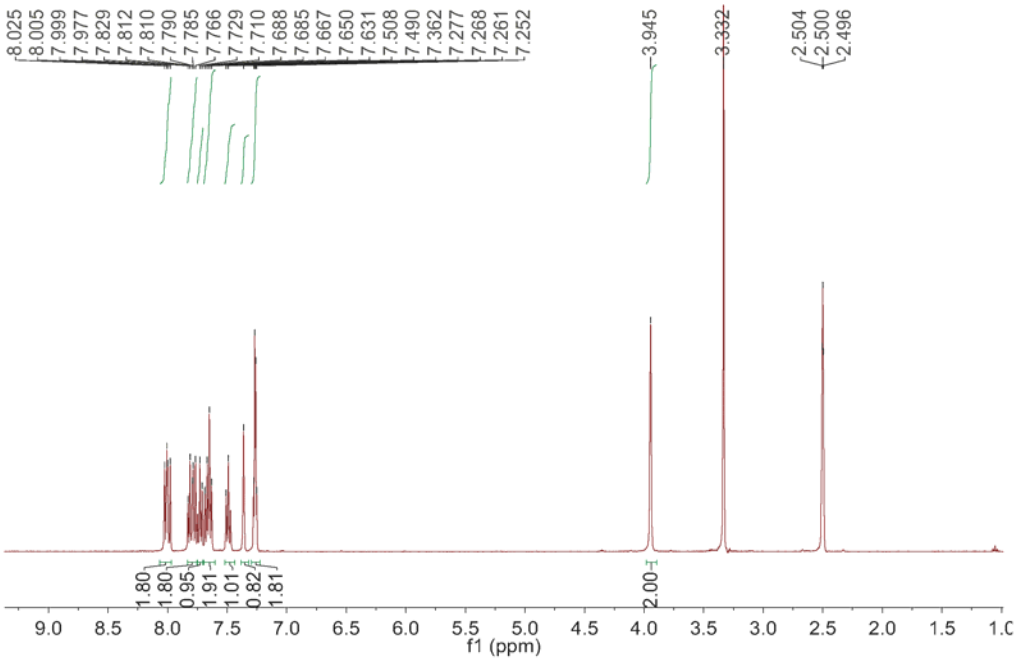
	22l	**10.237**	**98.49**
	22m	**6.211**	**97.77**
	22n	**8.177**	**98.50**
	22o	**8.229**	**97.19**
	22p	**7.964**	**98.11**
	22q	**7.524**	**> 99**

5.2 ^{1}H-NMR Spectral Scans

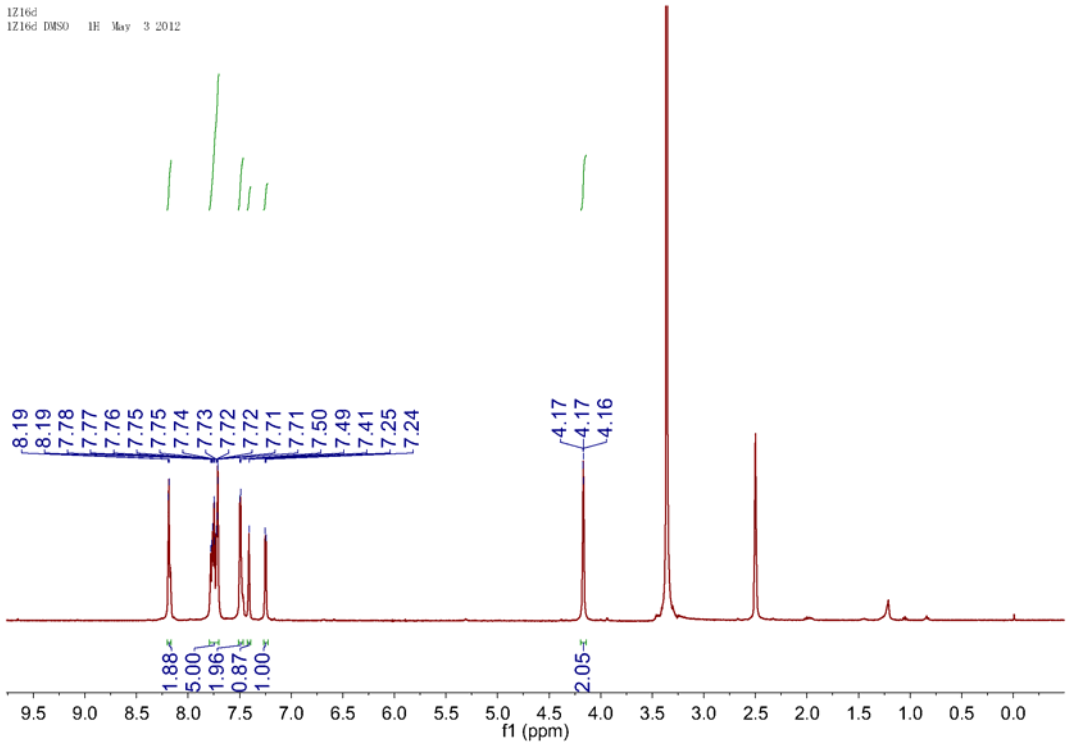
^{1}H-NMR spectra scan was an evidence of purity (95% at least) of each compound.

^{1}H-NMR spectra were performed on a Brucker AMX-400 (IS as TMS). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane.

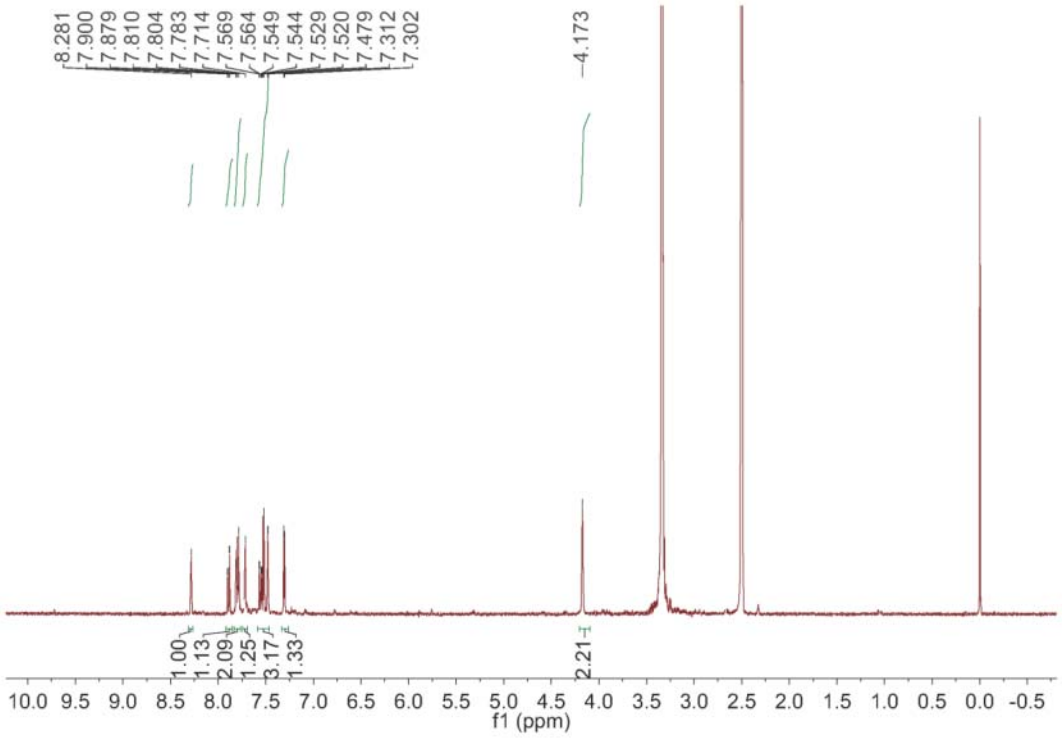
2-[5-(2-nitro-phenyl)-furan-2-ylmethylene]-indan-1-one (16a):



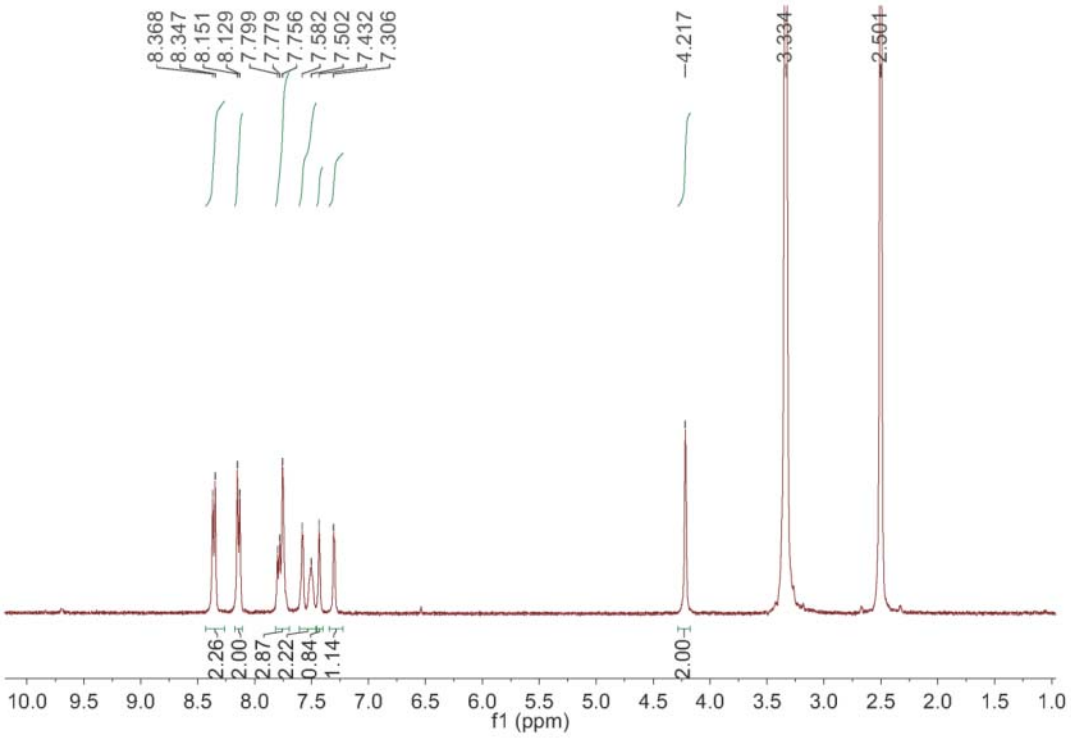
2-[5-(3-trifluomethyl-phenyl)-furan-2-ylmethylene]-indan-1-one (16b):



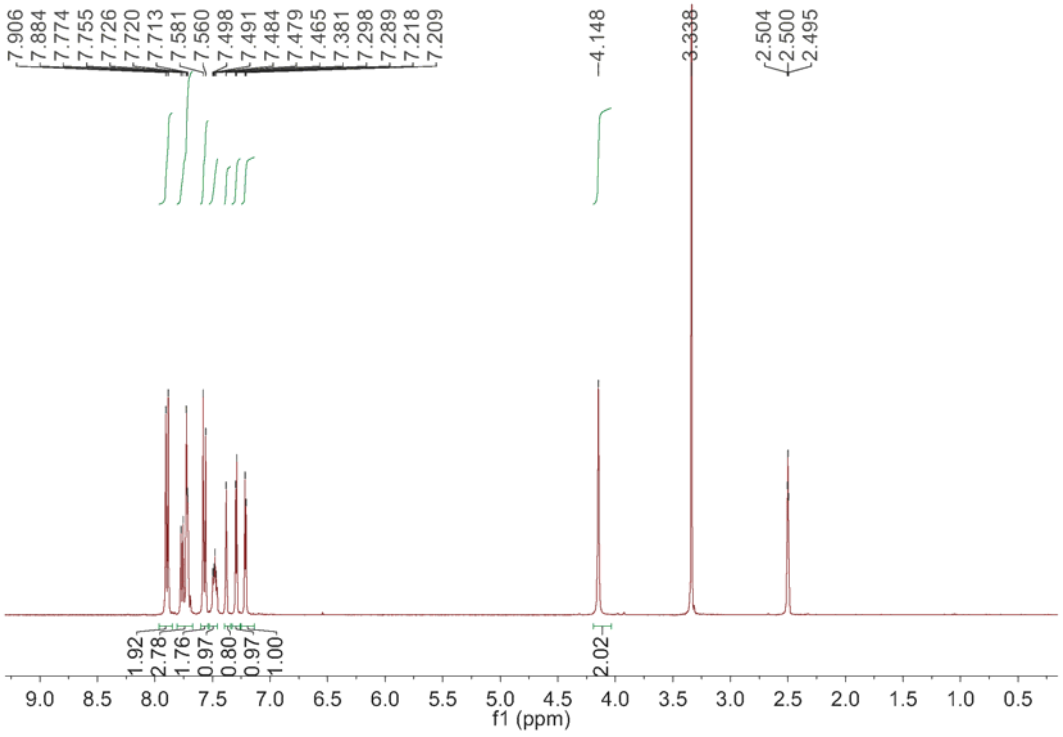
2-[5-(3-trifluomethyl)-furan-2-ylmethylene]-5-chloro-indan-1-one (16c):



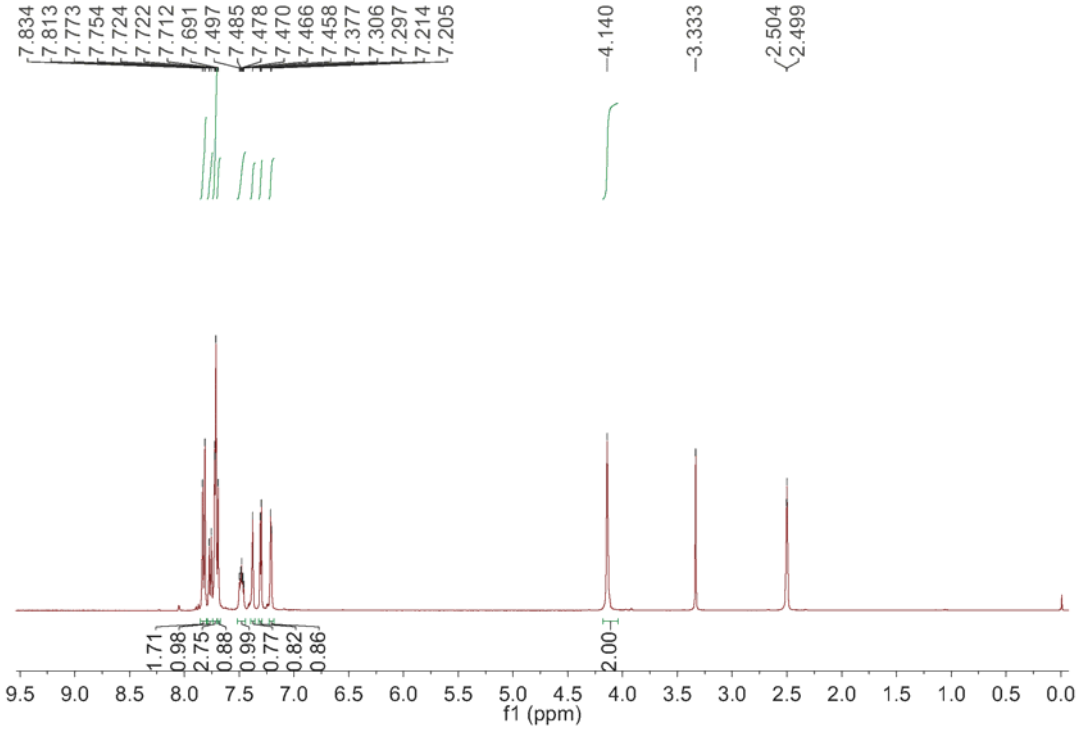
2-[5-(4-nitro-phenyl)-furan-2-ylmethylene]-indan-1-one (16d):



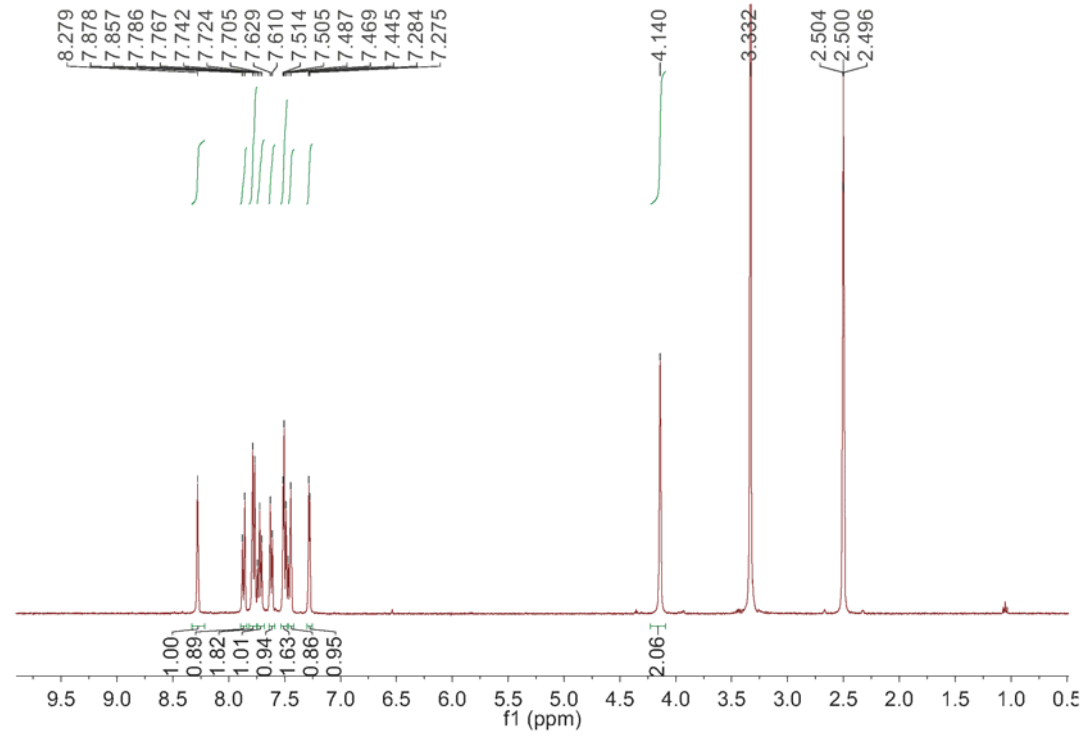
2-[5-(4-chloro-phenyl)-furan-2-ylmethylene]-indan-1-one (16e):



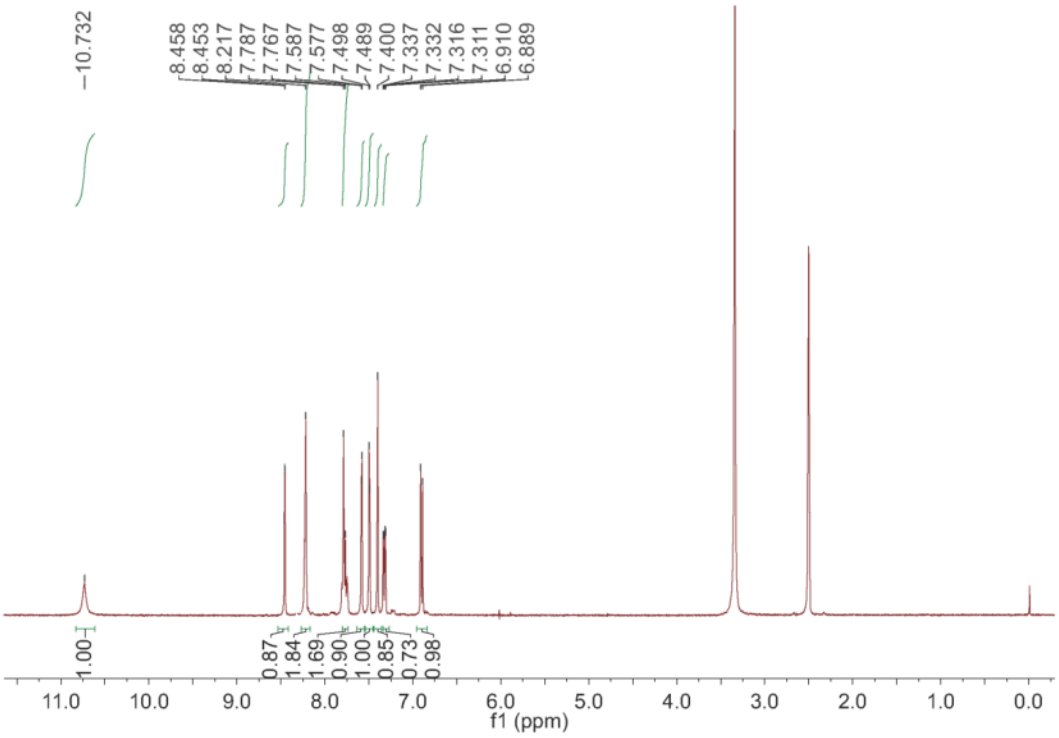
2-[5-(4-bromo-phenyl)-furan-2-ylmethylene]-indan-1-one (16f):



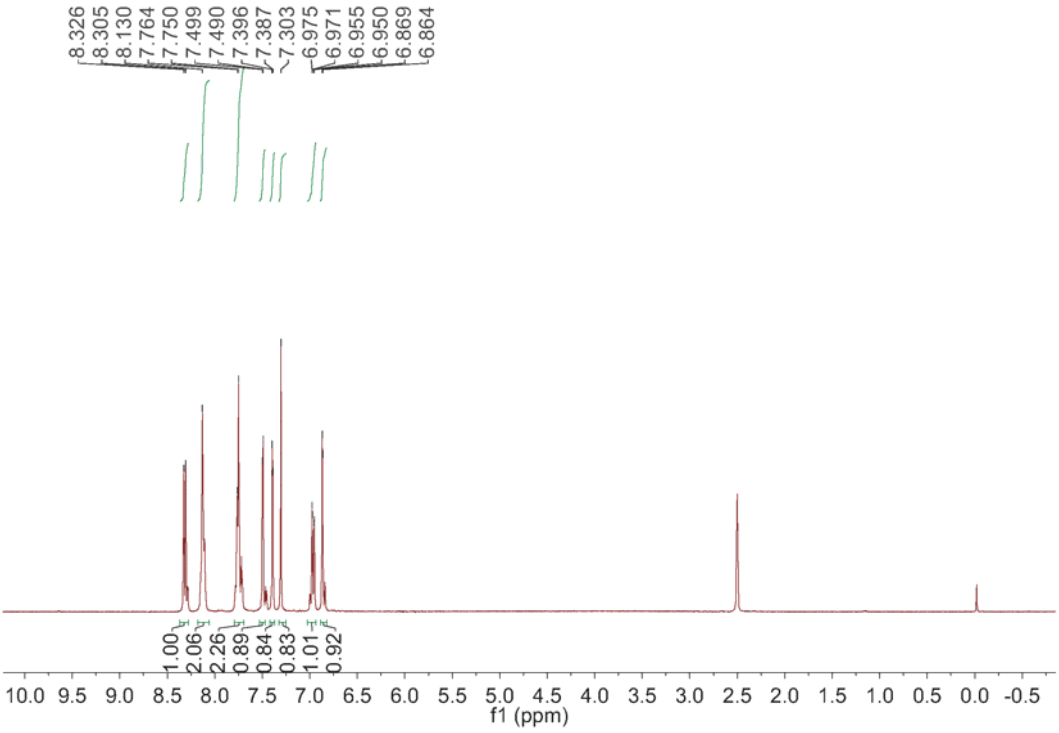
2-[5-(2-chloro-5-trifluomethyl)-furan-2-ylmethylene]-indan-1-one (16g):



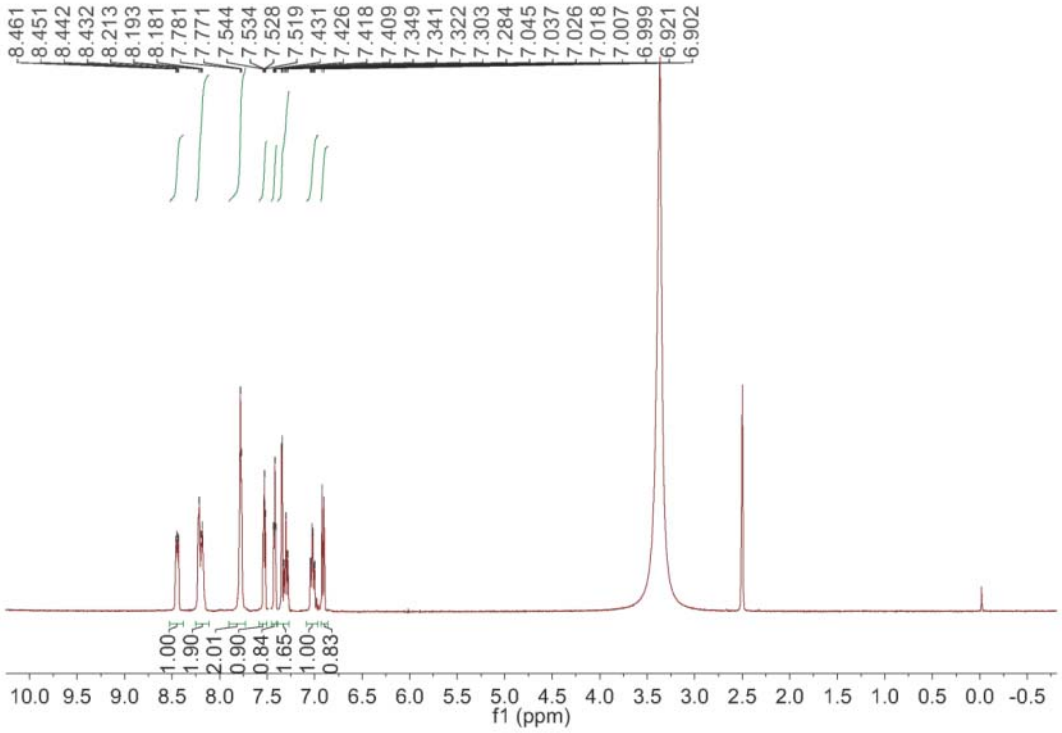
3-[5-(3-trifluomethyl-phenyl)-furan-2-ylmethylene]-1,3-dihydro-indol-2-one (17a):



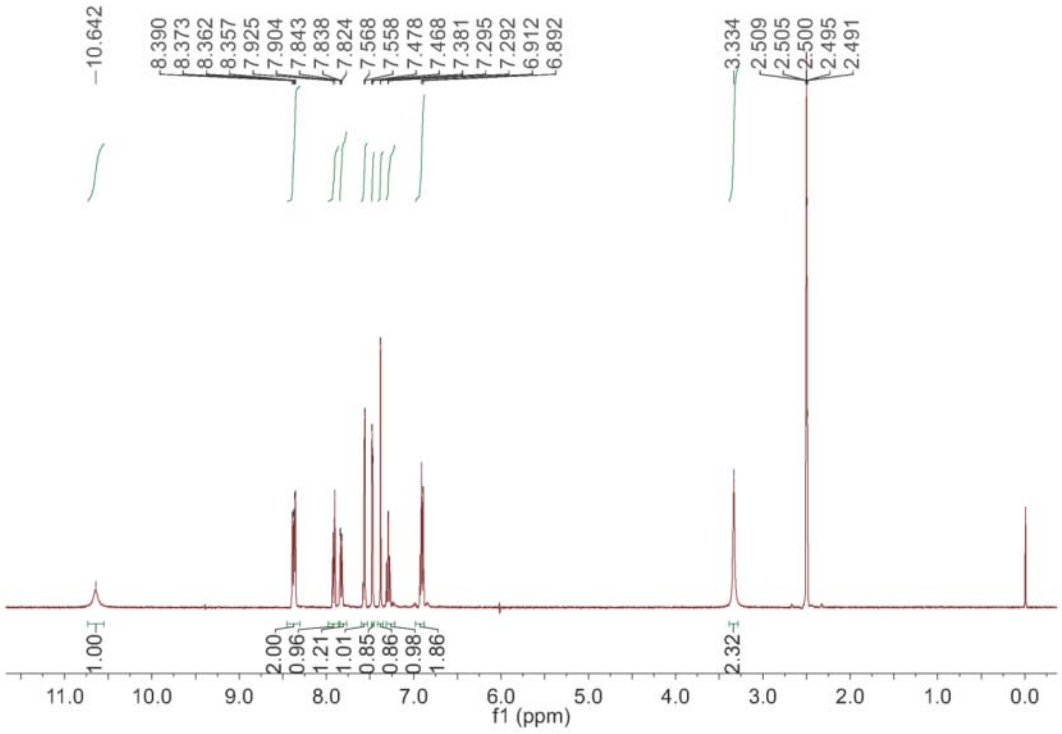
3-[5-(3-trifluomethyl-phenyl)-furan-2-ylmethylene]-6-chloro-1,3-dihydro-indol-2-one (17b):



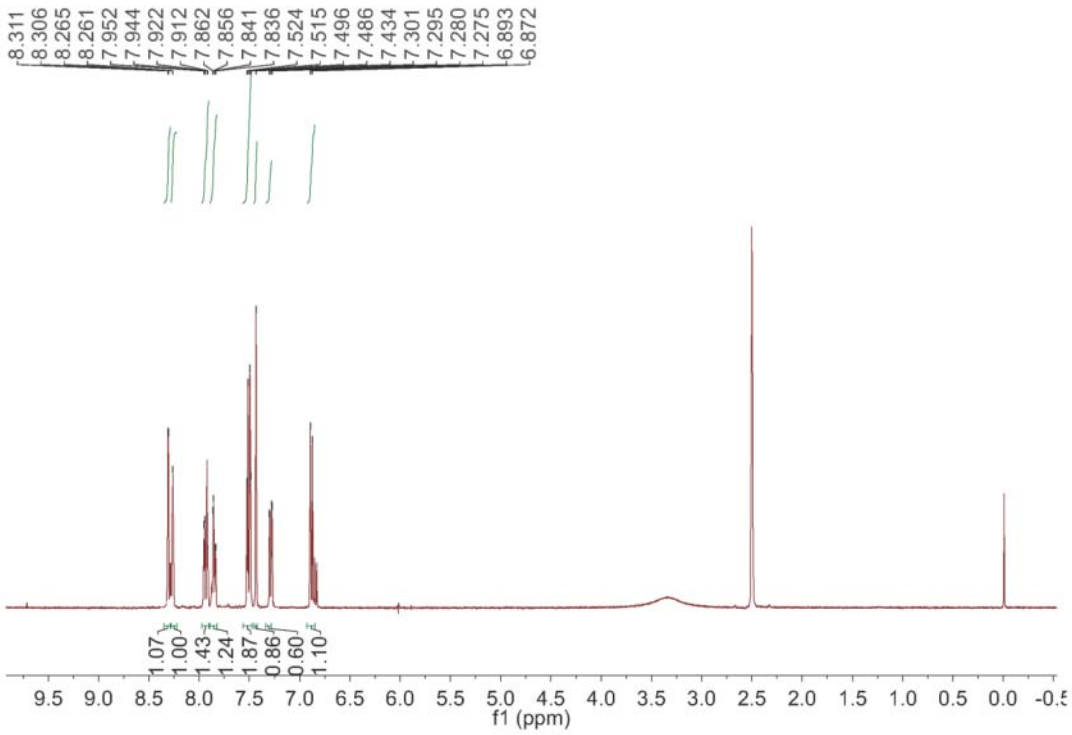
3-[5-(3-trifluomethyl-phenyl)-furan-2-ylmethylene]-5-chloro-1,3-dihydro-indol-2-one (17c):



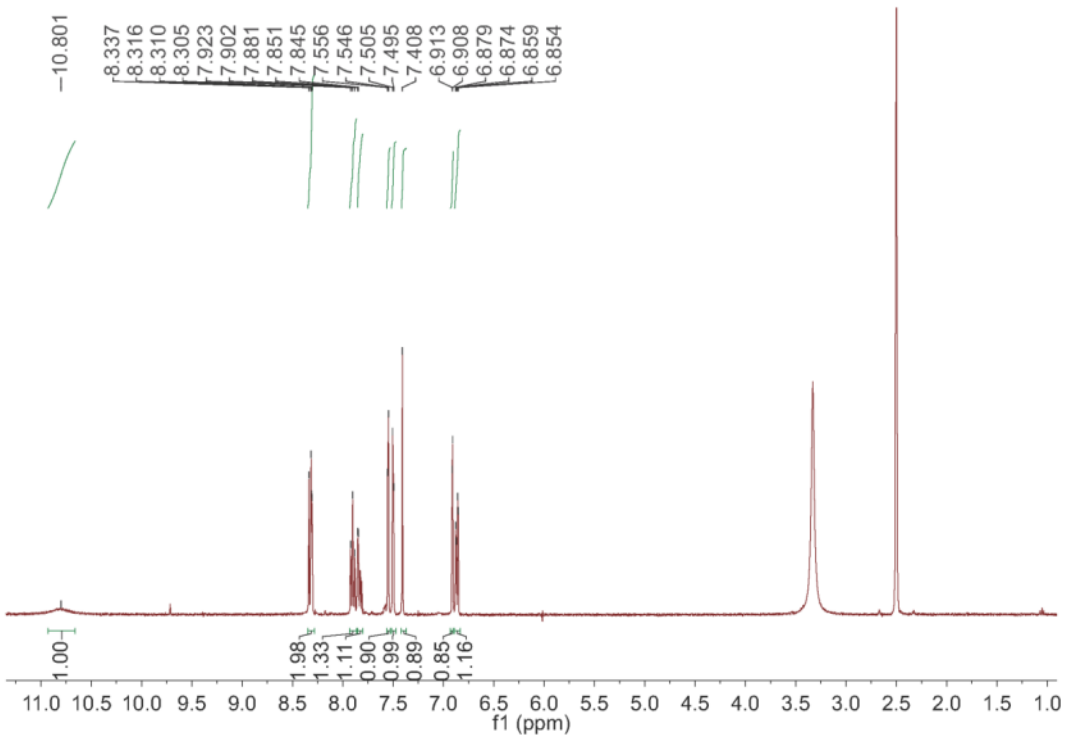
3-[5-(2-chloro-5-trifluomethyl)-furan-2-ylmethylene]-1,3-dihydro-indol-2-one (17d):



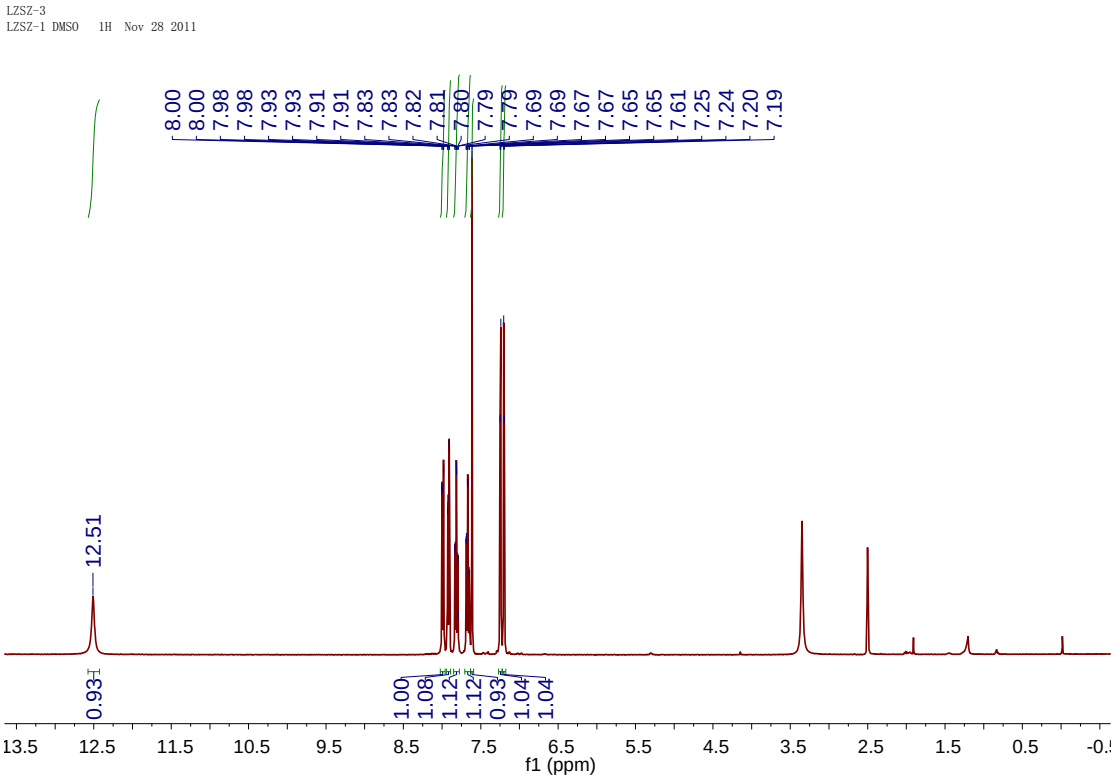
3-[5-(2-chloro-5-trifluomethyl)-furan-2-ylmethylene]-5-chloro-1,3-dihydro-indol-2-one (17e):



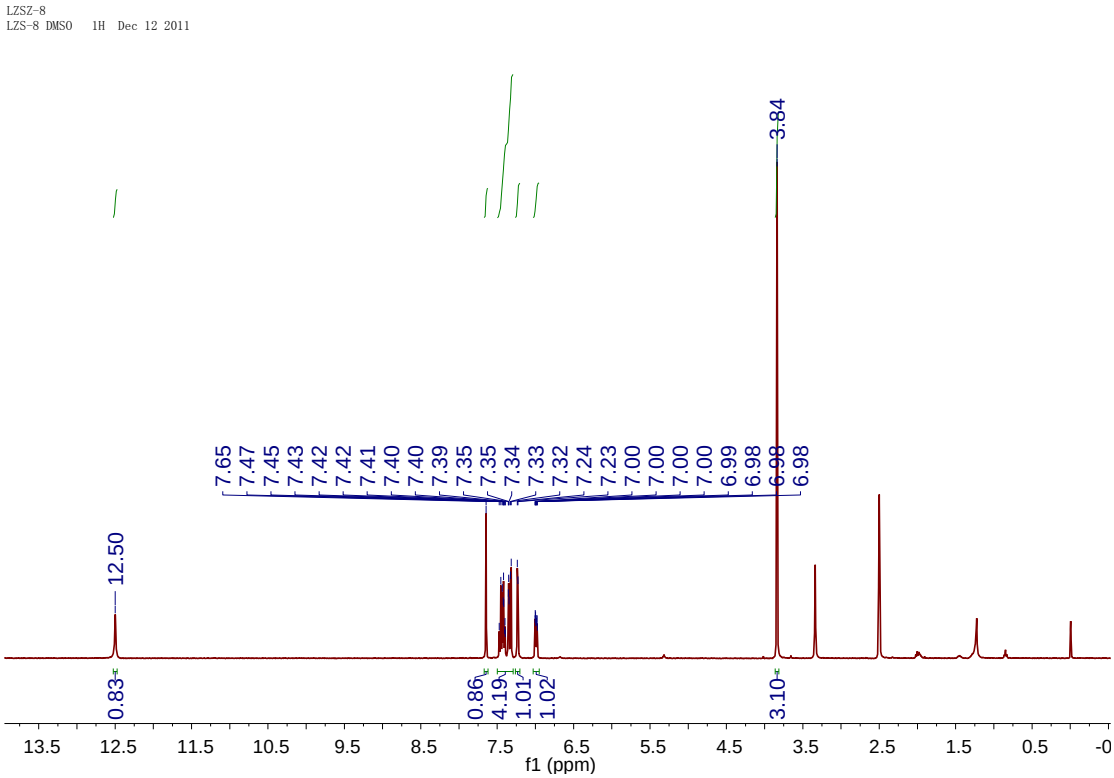
3-[5-(2-chloro-5-trifluomethyl)-furan-2-ylmethylene]-6-chloro-1,3-dihydro-indol-2-one (17f):



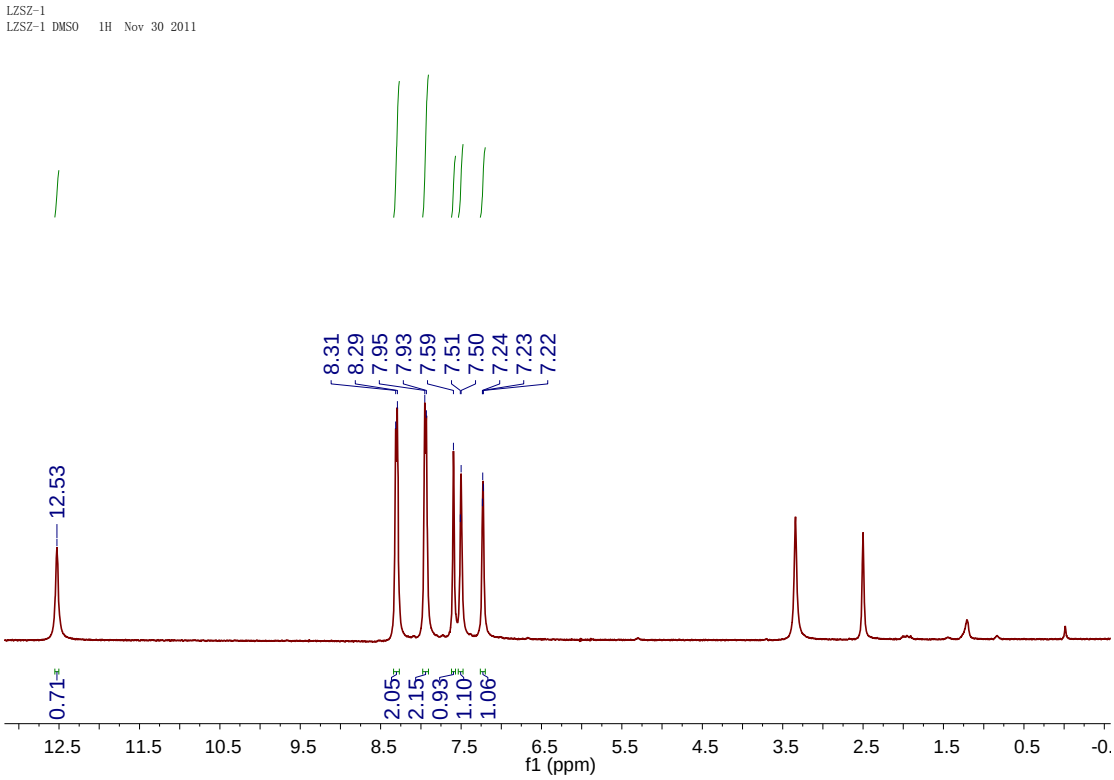
5-[5-(2-nitro-phenyl)-furan-2ylmethylene]-thiazolidine-2,4-dione (19a):



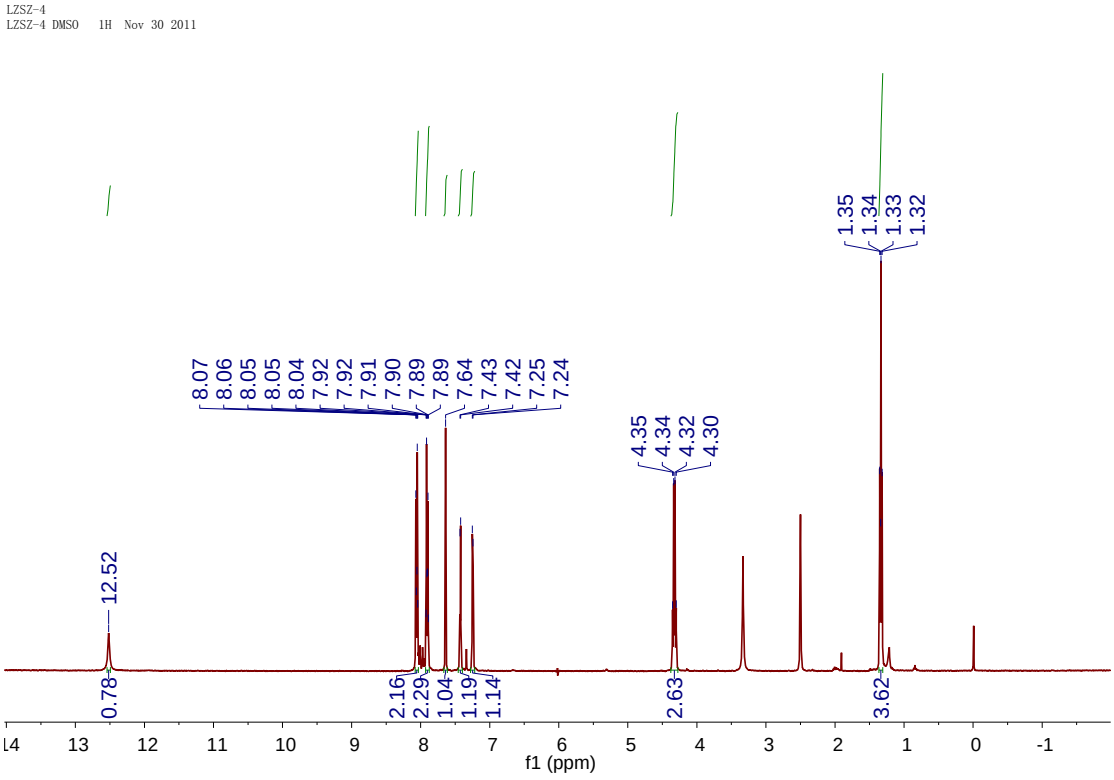
5-[5-(3-methoxy-phenyl)-furan-2ylmethylene]-thiazolidine-2,4-dione (19b):



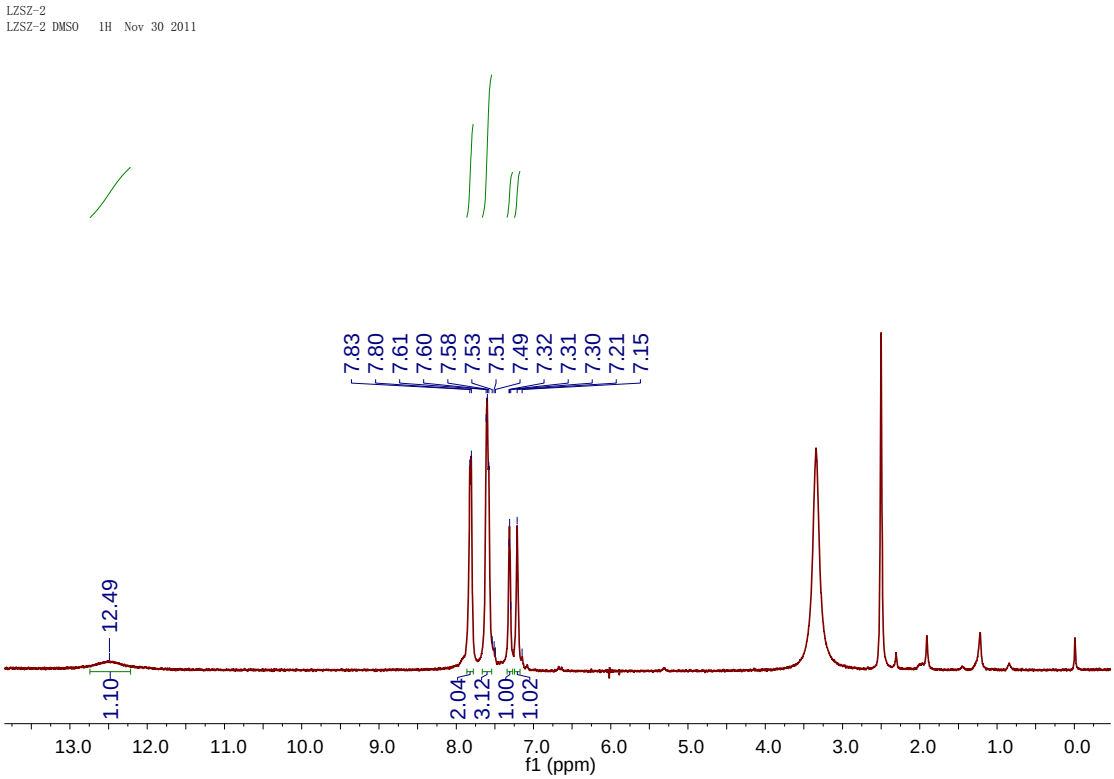
5-[5-(4-nitro-phenyl)-furan-2ylmethylene]-thiazolidine-2,4-dione (19c):



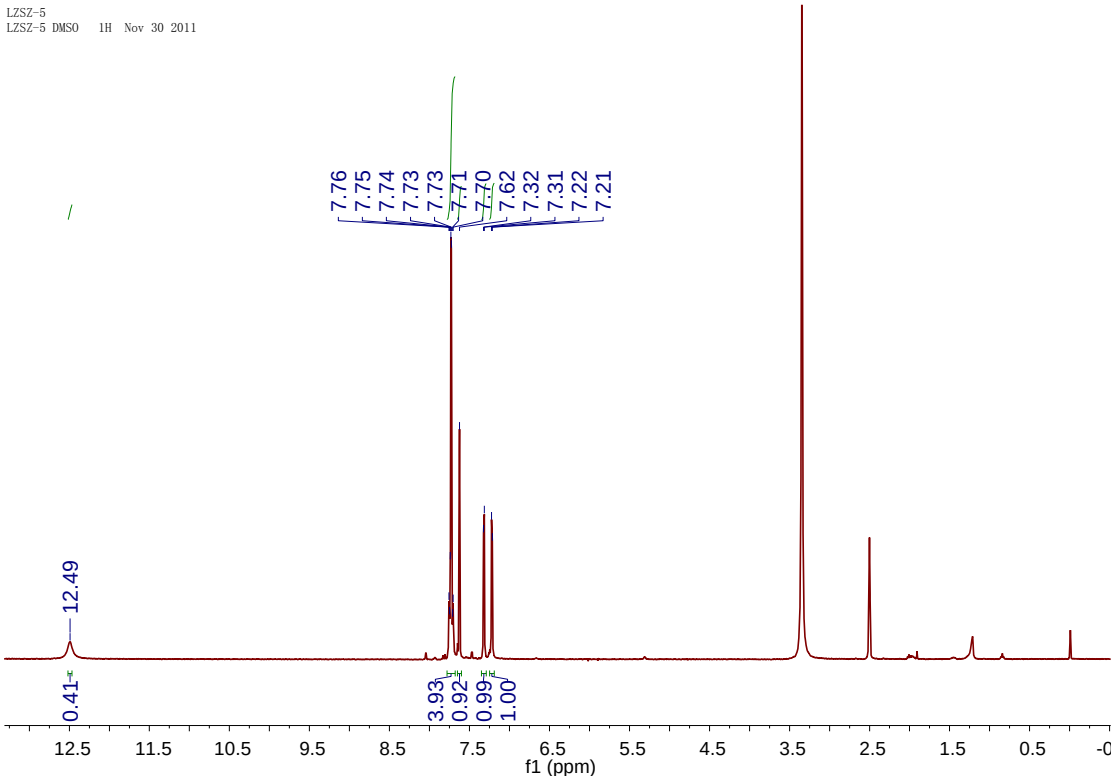
4-{5-[(2,4-dioxo-thiazolidin-5-ylidene)methyl]-furan-2-yl}benzoic acid ethyl ester (19d):



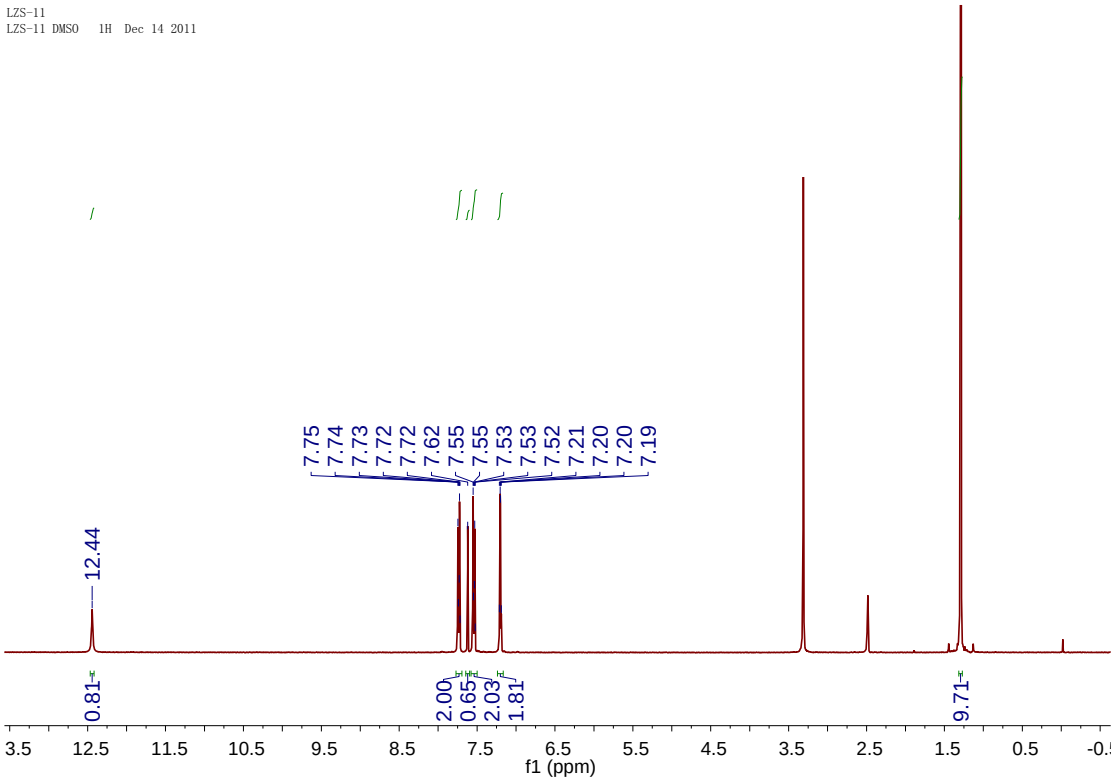
5-[5-(4-chloro-phenyl)-furan-2ylmethylene]-thiazolidine-2,4-dione (19e):



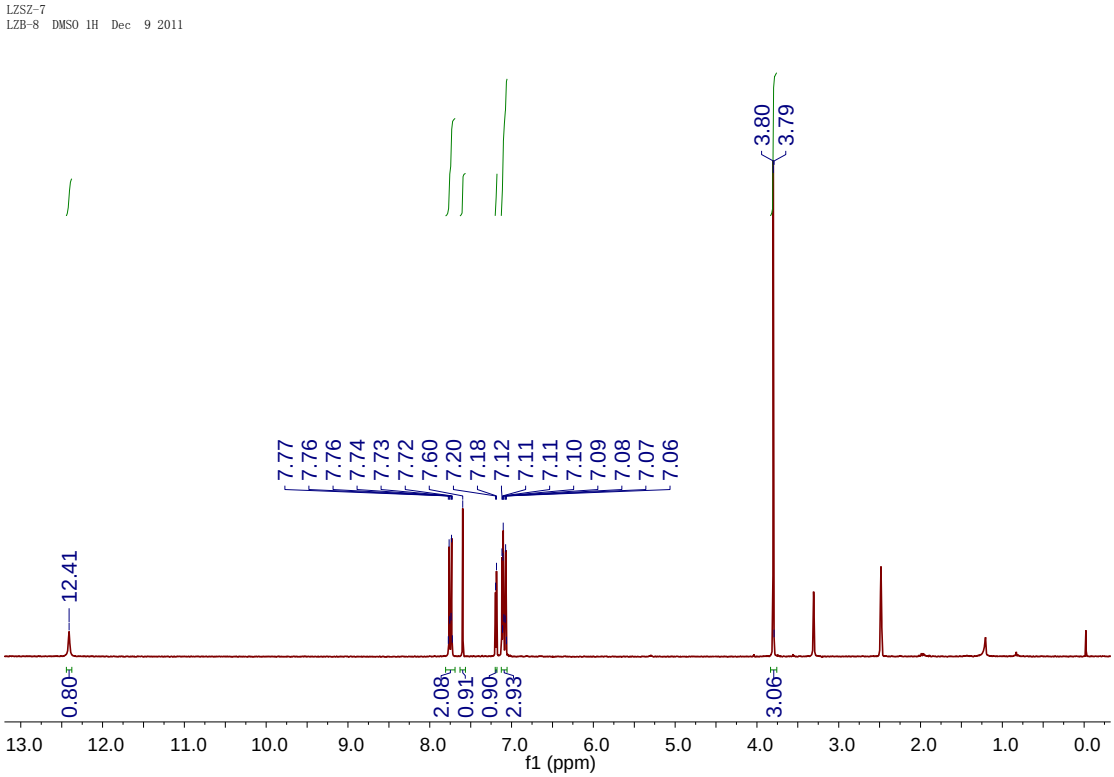
5-[5-(4-bromo-phenyl)-furan-2ylmethylene]-thiazolidine-2,4-dione (19):



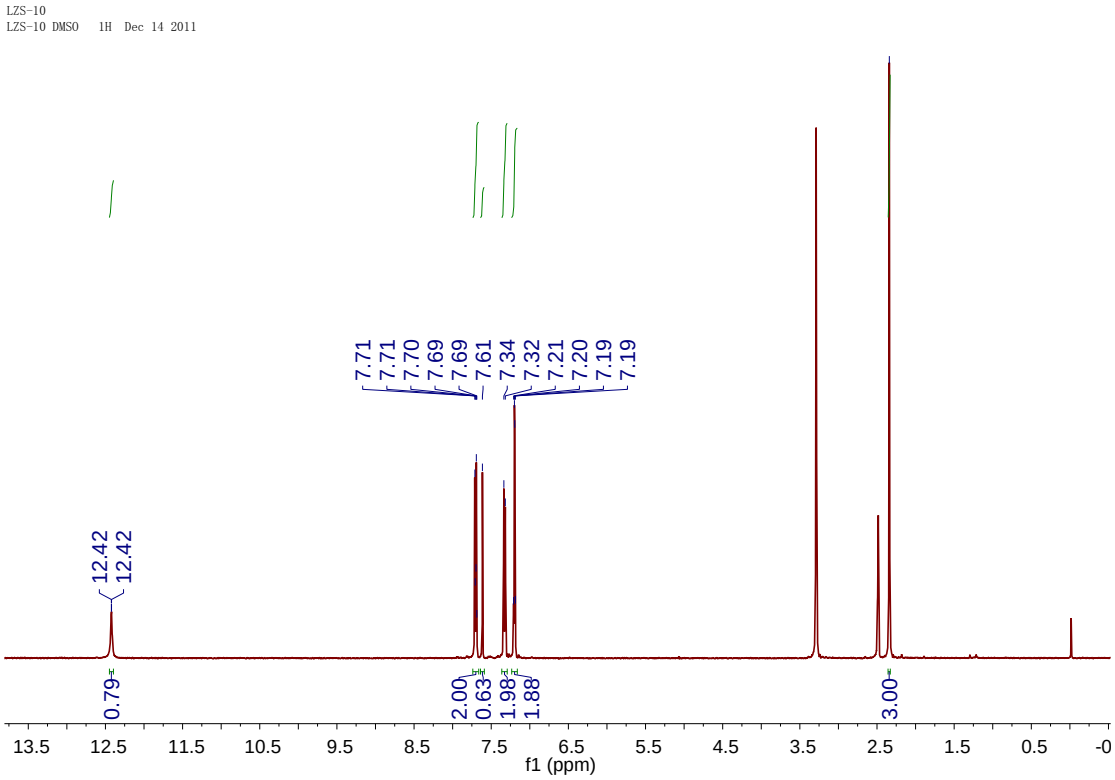
5-[5-(4-methyl-phenyl)-furan-2ylmethylene]-thiazolidine-2,4-dione (19g):



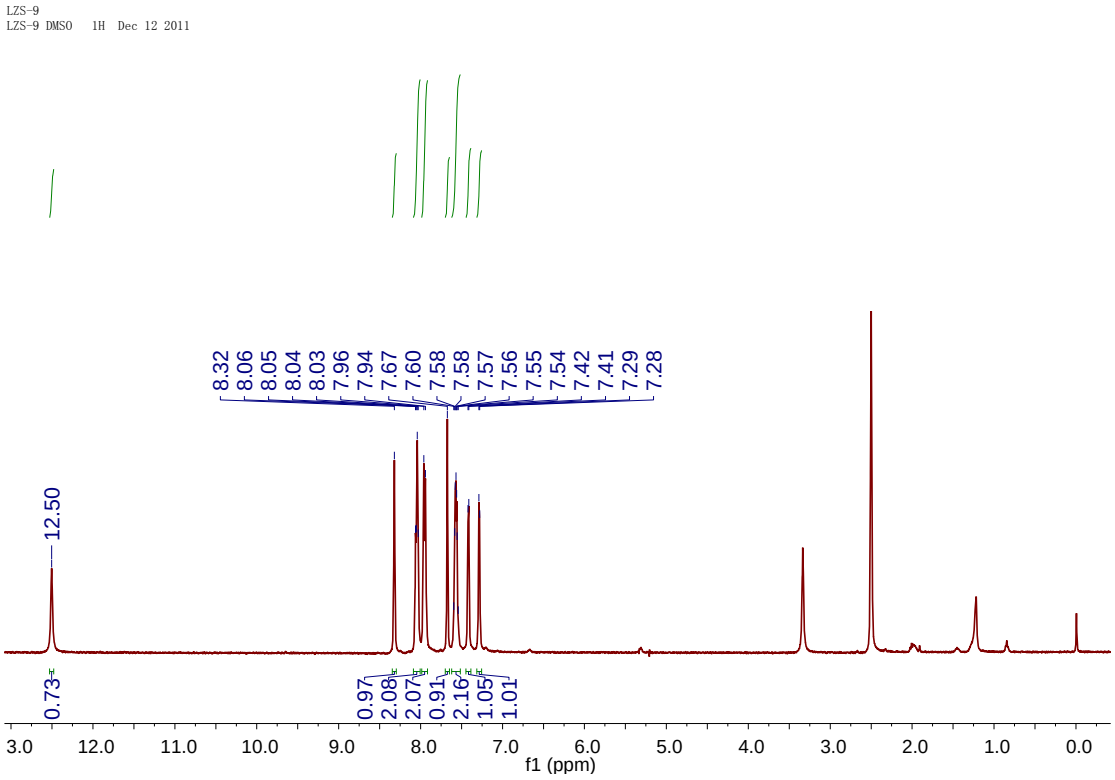
5-[5-(4-methoxy-phenyl)-furan-2ylmethylene]-thiazolidine-2,4-dione (19h):



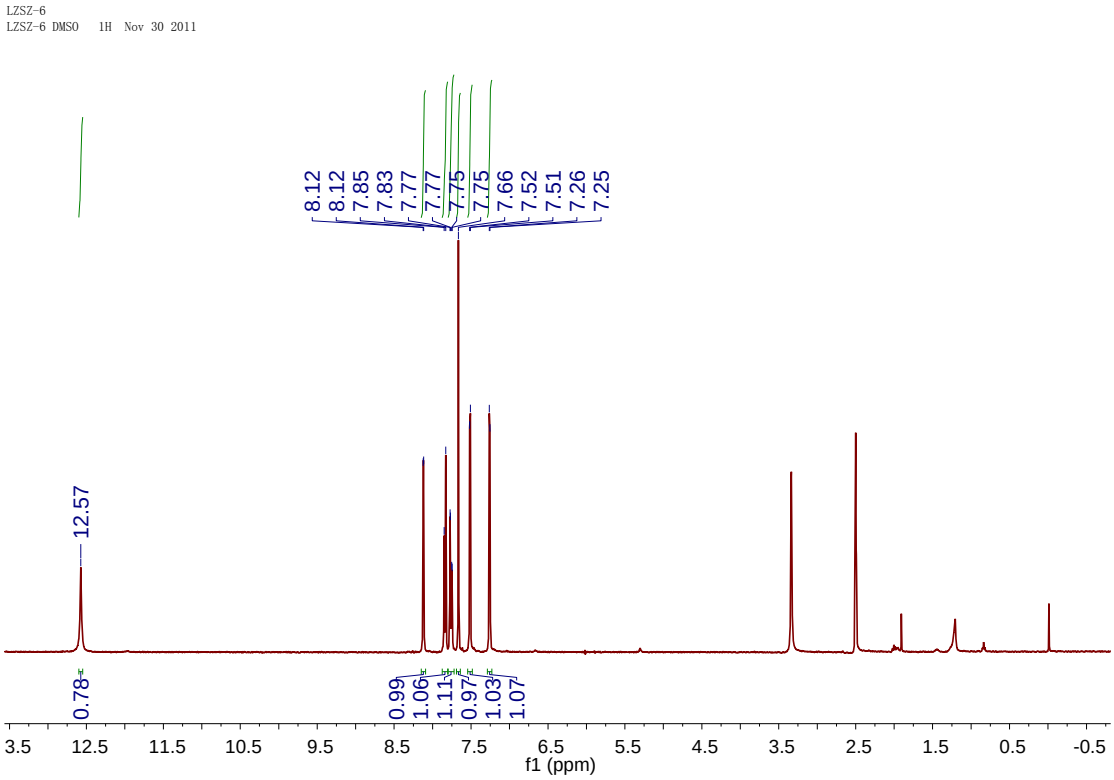
5-[5-(4-tert-butyl-phenyl)-furan-2ylmethylene]-thiazolidine-2,4-dione (19i):



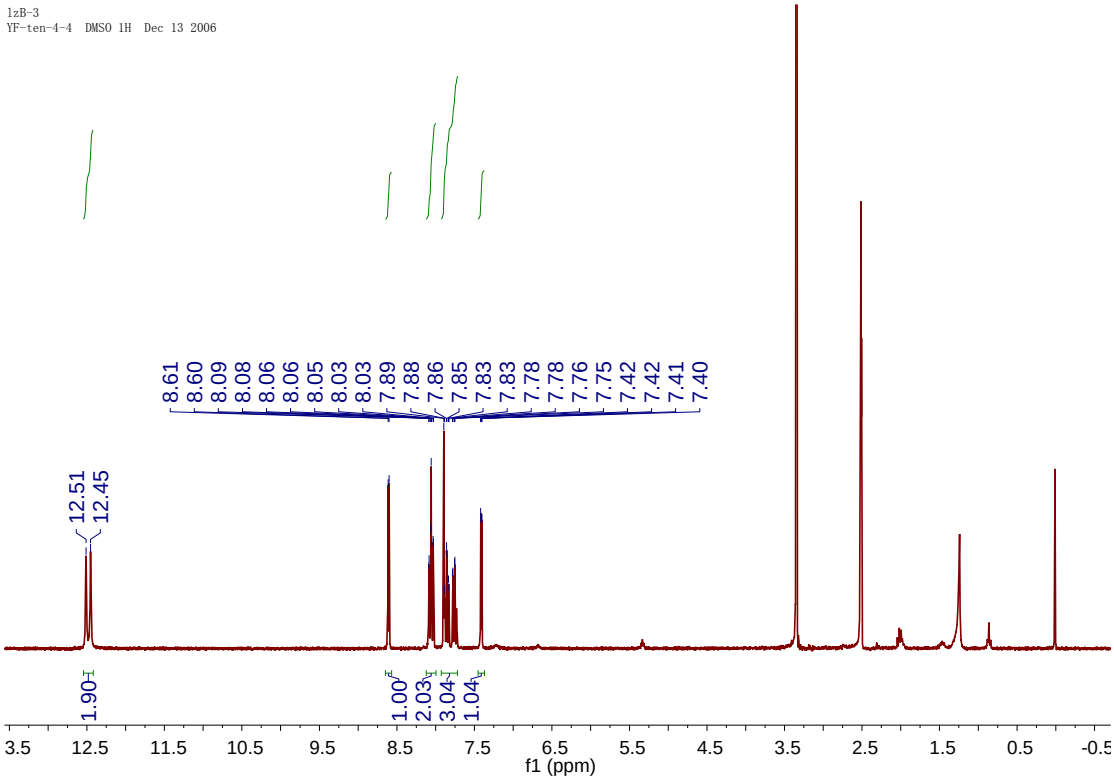
5-[5-(2-naphthyl)-furan-2ylmethylene]-thiazolidine-2,4-dione (19j):



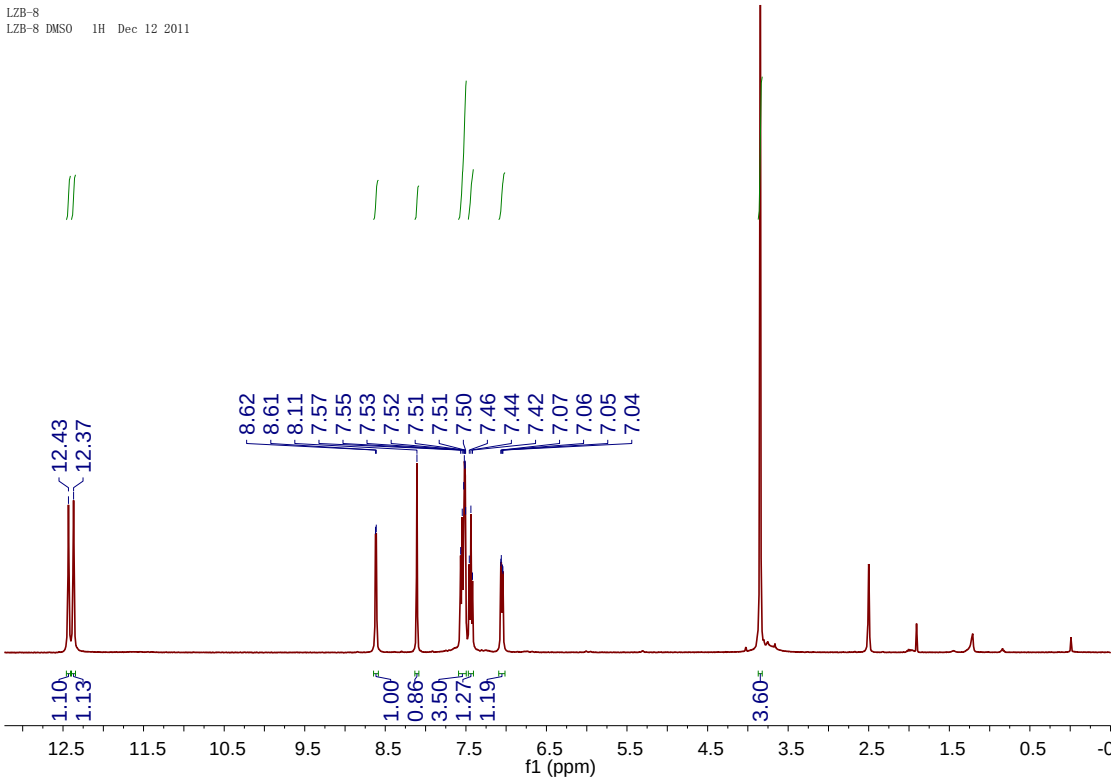
5-[5-(2-chloro-5-trifluomethyl)-furan-2ylmethylene]-thiazolidine-2,4-dione (19k):



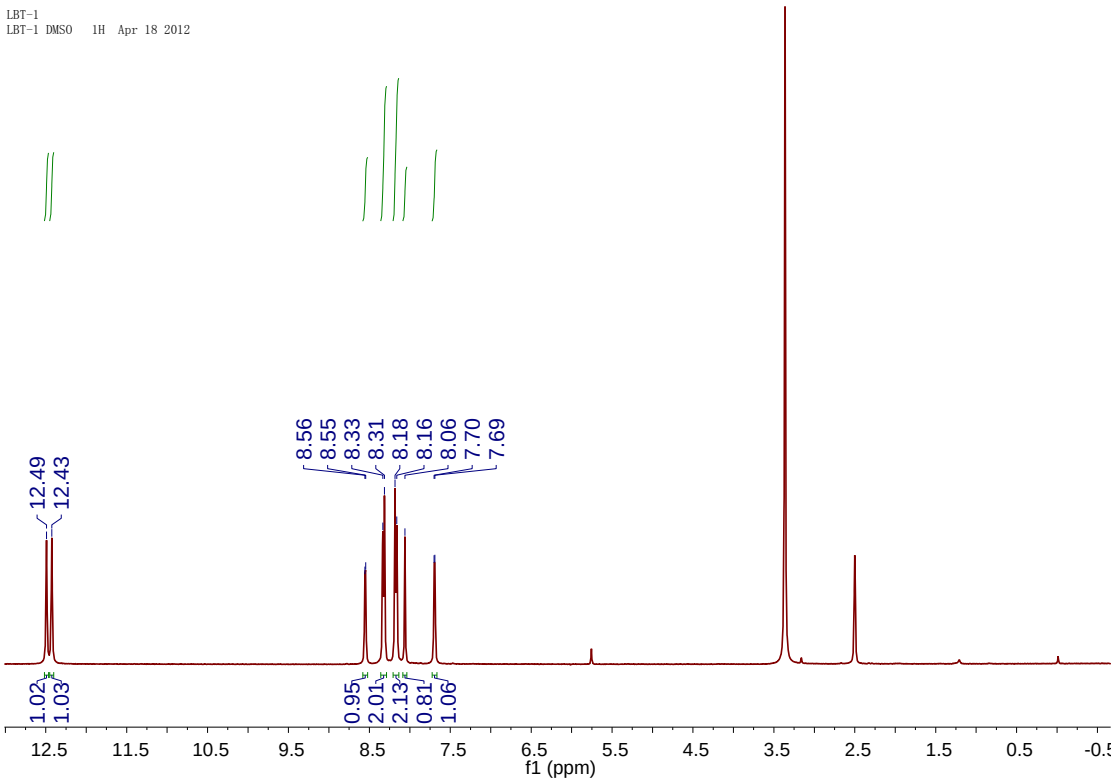
5-[5-(2-nitro-phenyl)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22a):



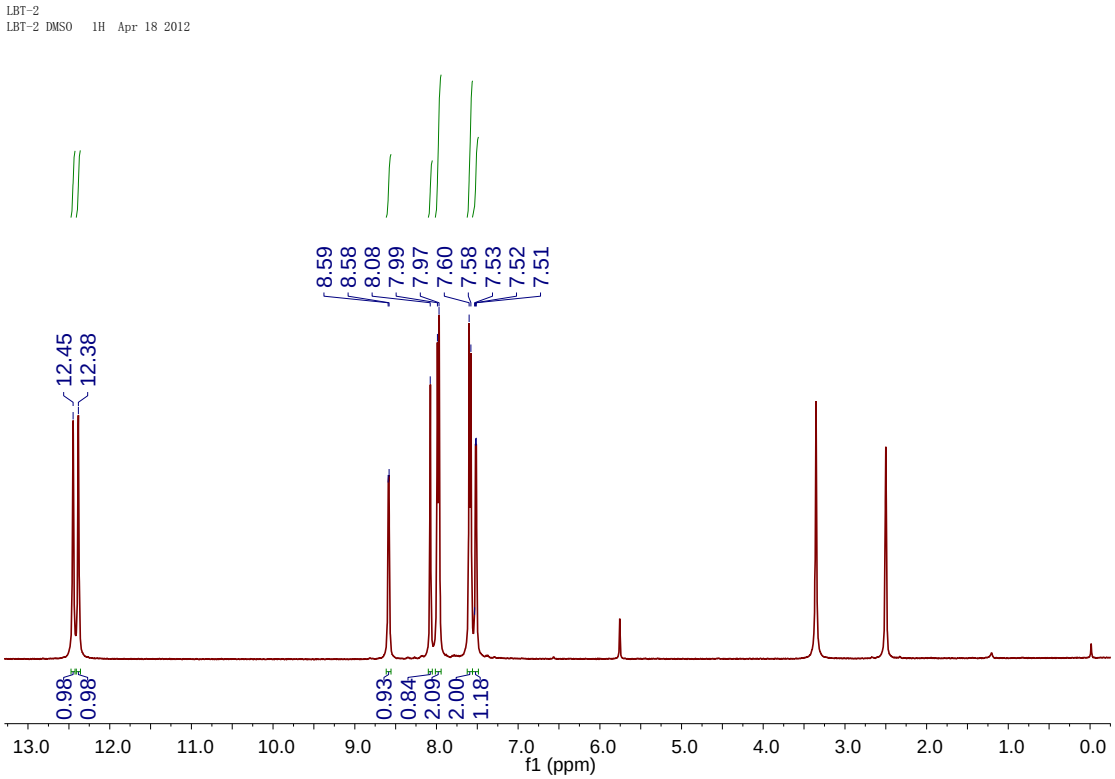
5-[5-(3-methoxy-phenyl)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22b):



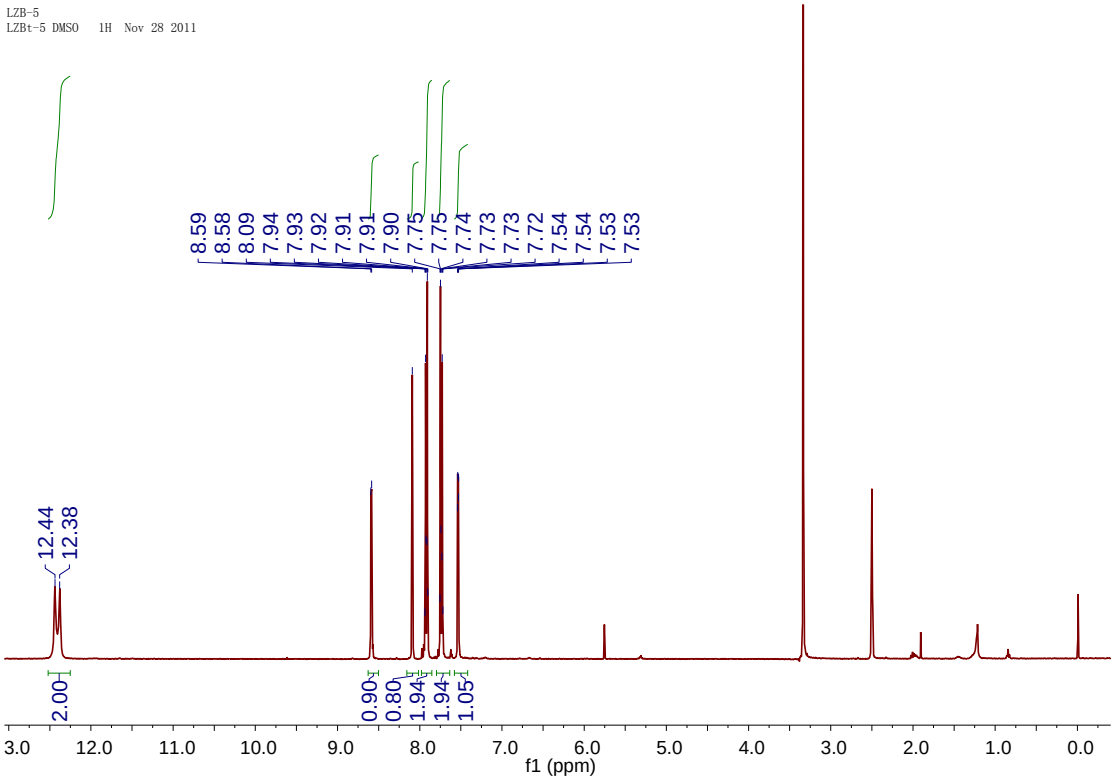
5-[5-(4-nitro-phenyl)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22c):



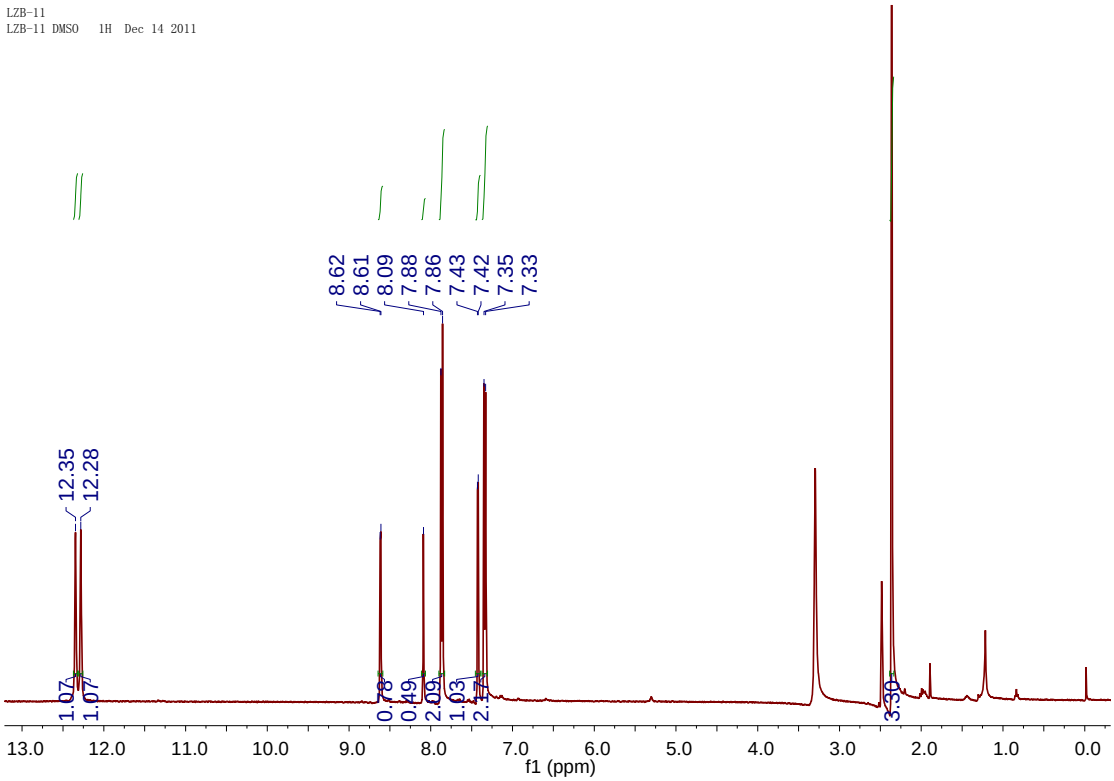
5-[5-(4-chloro-phenyl)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22e):



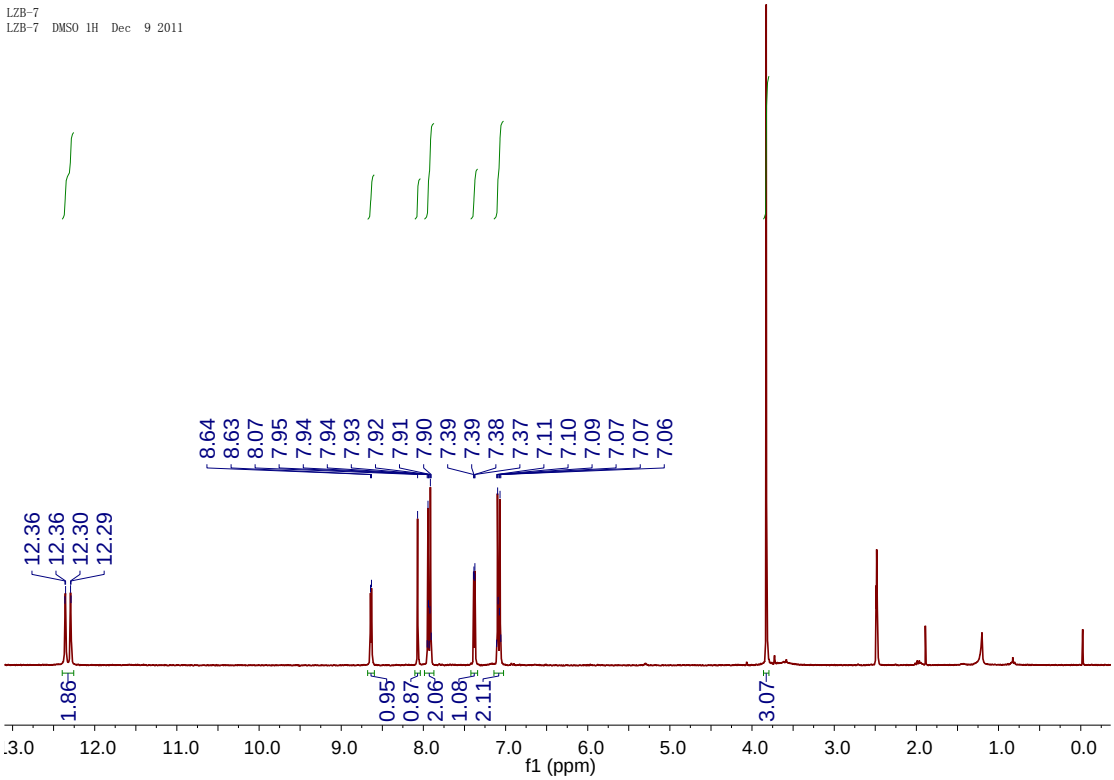
5-[5-(4-bromo-phenyl)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22f):



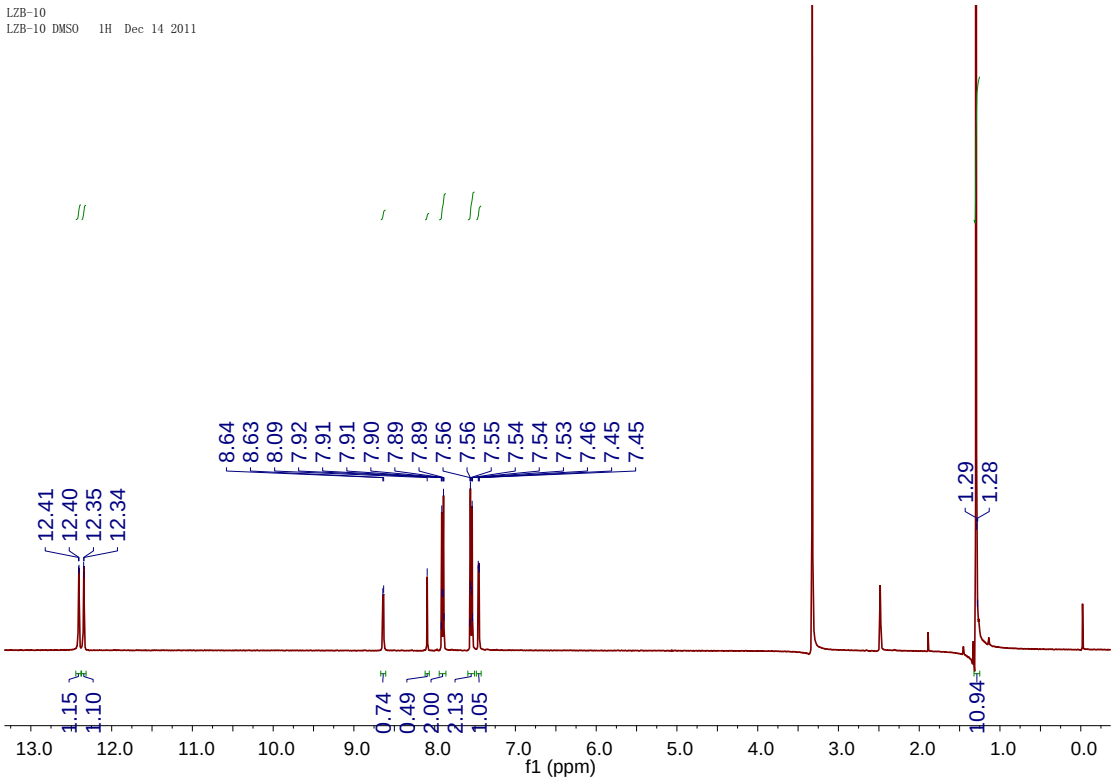
5-[5-(4-methyl-phenyl)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22g):



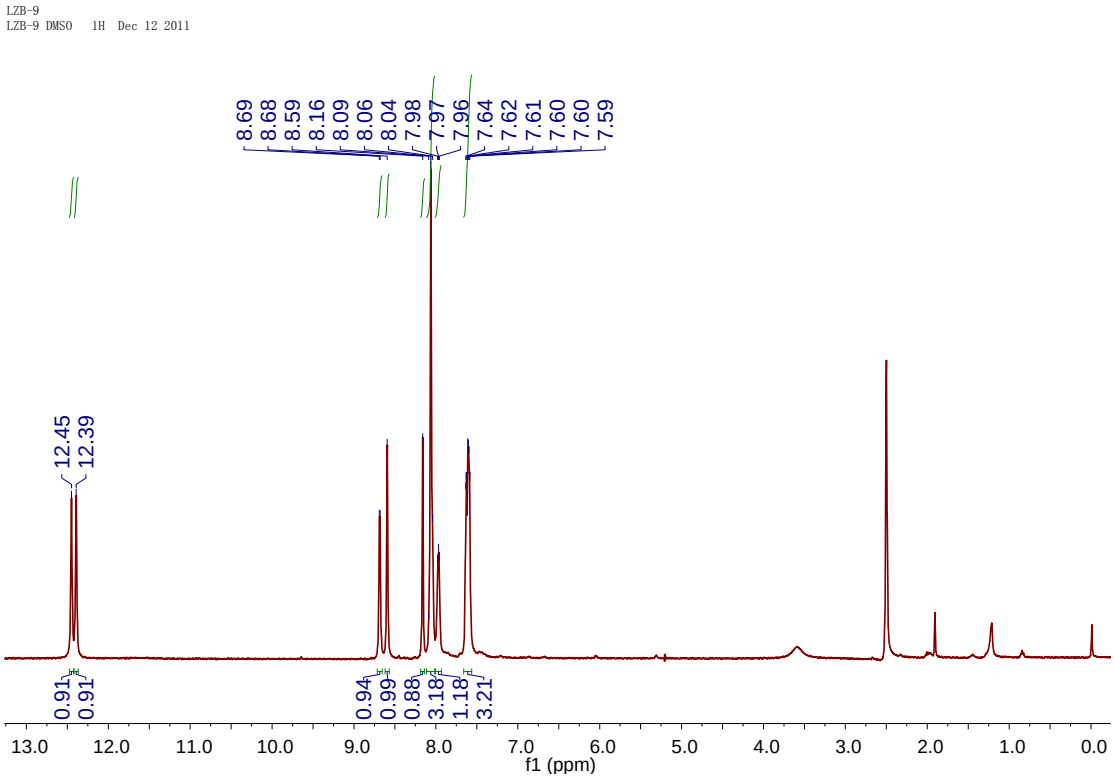
5-[5-(4-methoxy-phenyl)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dion e (22h):



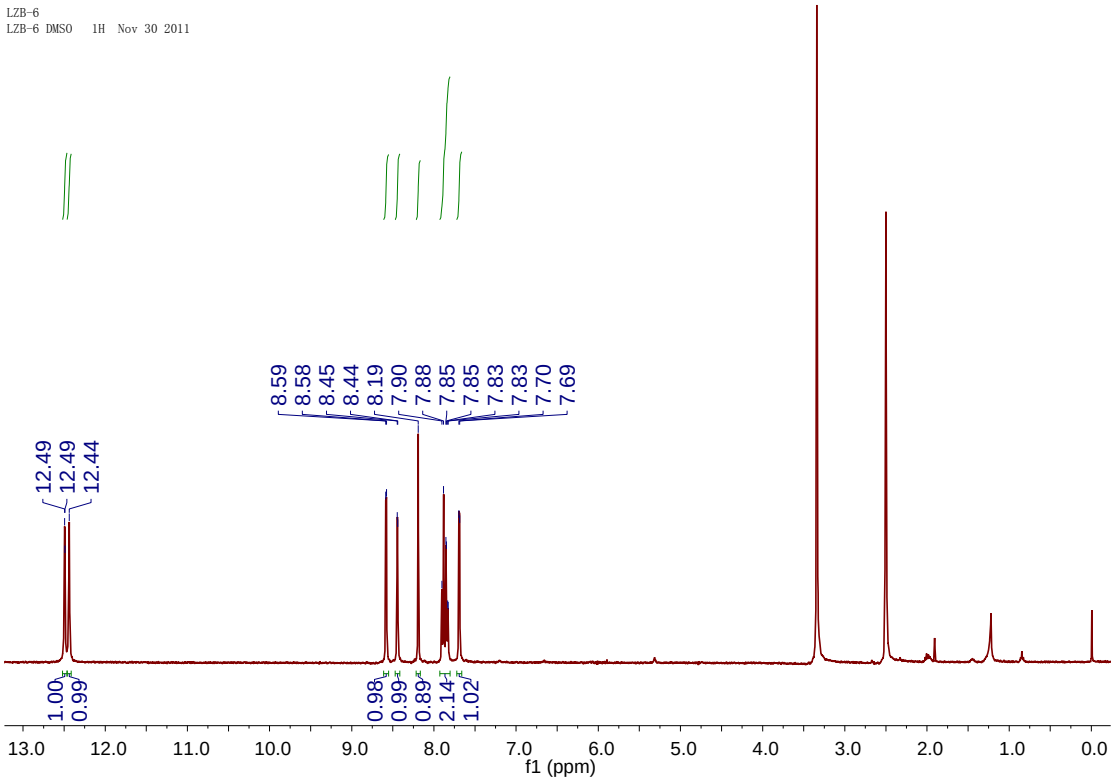
5-[5-(4-tert-butyl-phenyl)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dion e (22i):



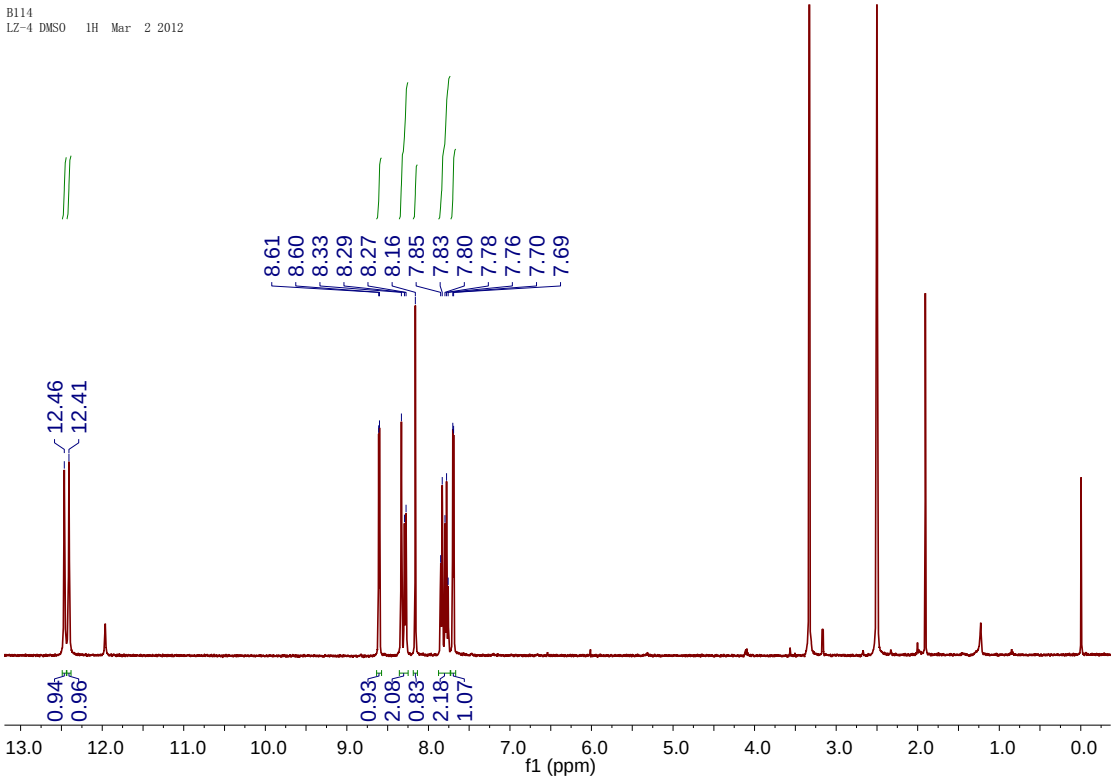
5-[5-(2-naphthyl)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22j):



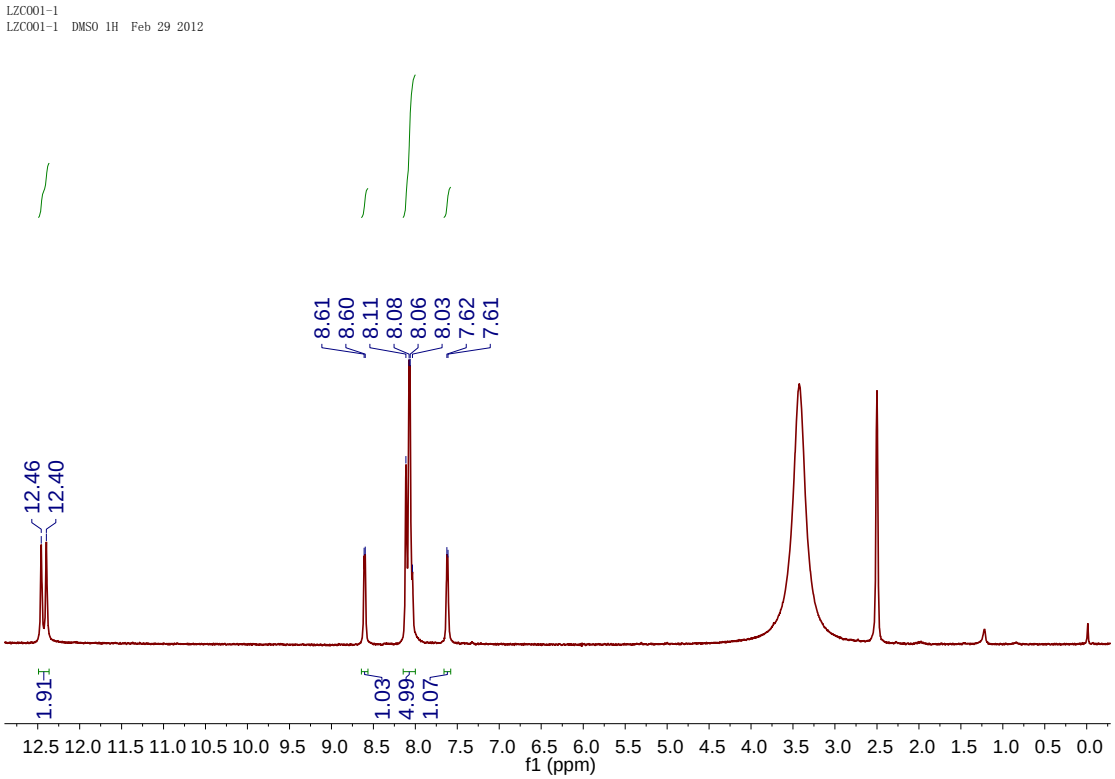
5-[5-(2-chloro-5-trifluomethyl)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22k):



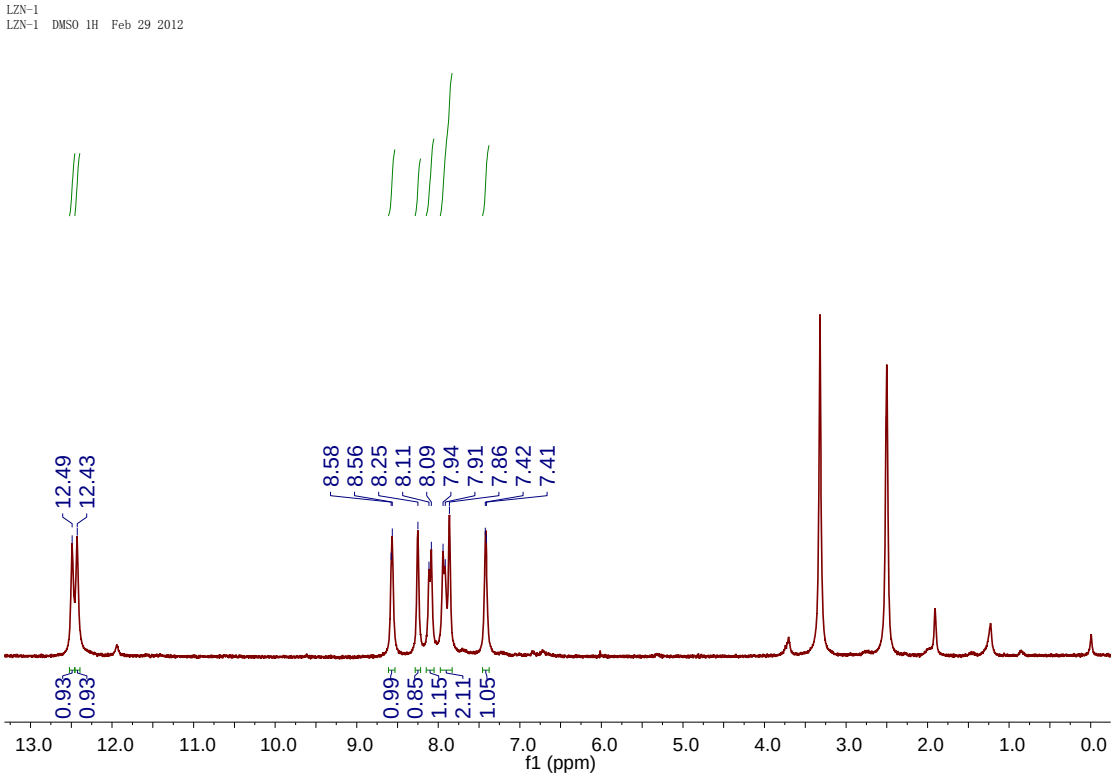
5-[5-(3-trifluomethyl-phenyl)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22l):



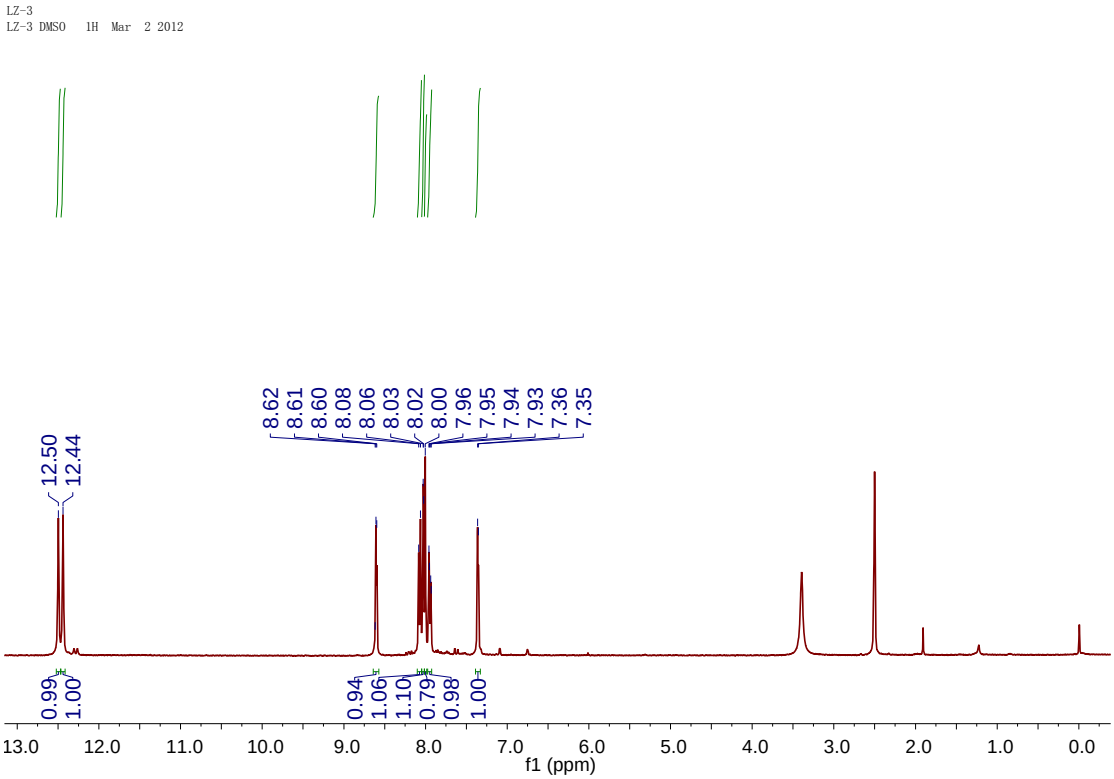
4-[5-(4,6-dioxo-2-thioxo-tetrahydro-pyrimidin-5-ylidenemethyl)furan-2-yl]benzoic acid (22m):



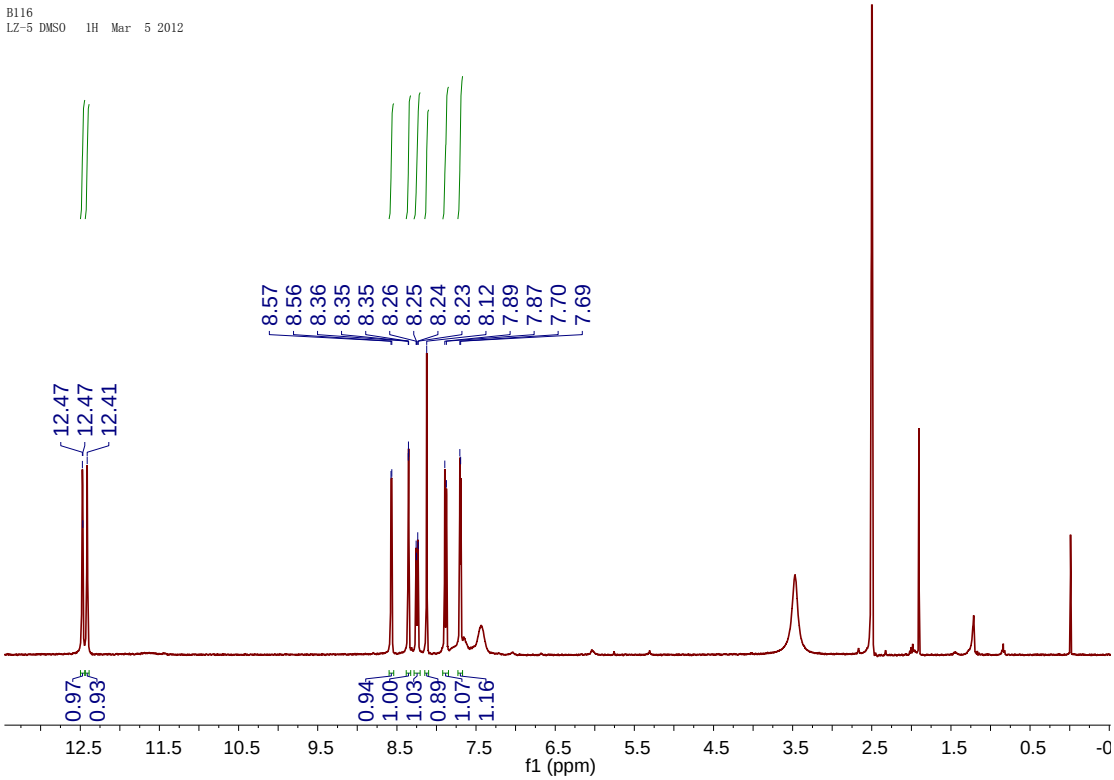
5-[5-(2-nitro-4-chloro)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22n):



5-[5-(2-trifluomethyl-4-chloro)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22o):



5-[5-(3-trifluomethyl-4-chloro)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dione (22p):



5-[5-(3,4-methylenedioxy)-furan-2ylmethylene]-2-thioxo-dihydro-pyrimidine-4,6-dio

ne (22q):