Supporting Information

In silico screening applied in drug discovery: T001-10026247 as a novel fourth-generation EGFR inhibitor

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Table S1. ROC curve data

ID	TYPE[a]	5ZWJ Affinity (Kcal/mol)	6JRJ Affinity (Kcal/mol)	6LUD Affinity (Kcal/mol)
compound231	1	-9	-9.8	-10.1
compound313	1	-9.2	-10.9	-10
compound103	0	-8.9	-9.5	-10
compound312	1	-9.2	-10.5	-9.9
compound174	0	-11.6	-9.8	-9.9
compound229	1	-9.4	-9.3	-9.8
compound278	1	-9.9	-10.7	-9.7
compound286	1	-9.2	-8.8	-9.7
compound88	0	-11	-9.5	-9.6
compound230	1	-9.3	-9.5	-9.6
compound101	0	-9.8	-9.4	-9.6
compound284	1	-9.7	-9.6	-9.5
compound122	0	-8.8	-8.3	-9.4
compound97	0	-10.1	-8.2	-9.4
compound125	0	-9	-8.2	-9.4
compound29	0	-8.2	-9.2	-9.3
compound109	0	-7.6	-9.2	-9.3
compound289	1	-10.3	-8.9	-9.3
compound105	0	-9.2	-8.7	-9.3
compound290	1	-9.7	-8.2	-9.3
compound236	1	-8.9	-9.6	-9.2
compound37	0	-10.1	-9.3	-9.2
compound258	1	-8.7	-9.3	-9.2

compound255	1	-9.3	-9.2	-9.1
compound251	1	-9.4	-9.1	-9.1
compound99	0	-9.2	-9.1	-9.1
compound200	0	-9.8	-8.7	-9.1
compound204	0	-9	-7.8	-9.1
compound280	1	-10.1	-9.3	-9
compound232	1	-9.1	-9.2	-9
compound277	1	-9.7	-10.4	-8.9
compound233	1	-9.4	-9.3	-8.9
compound190	0	-11	-9.2	-8.9
compound306	1	-8.6	-9	-8.9
compound250	1	-10	-8.4	-8.9
compound135	0	-10.1	-8.3	-8.9
compound238	1	-9.5	-10.7	-8.8
compound119	0	-9.4	-9.6	-8.8
compound199	0	-9.2	-9.6	-8.8
compound296	1	-8.9	-9.3	-8.8
compound77	0	-8.8	-9.2	-8.8
compound31	0	-8.4	-8.7	-8.8
compound268	1	-9.3	-8.1	-8.8
compound89	0	-10.1	-7.4	-8.8
compound134	0	-9.3	-9.4	-8.7
compound107	0	-8.4	-9.4	-8.7
compound211	0	-8.6	-9	-8.7
compound303	1	-8.1	-8.7	-8.7

compound281	1	-9.5	-8.2	-8.7
compound96	0	-8.6	-8.2	-8.7
compound162	0	-9.8	-7.8	-8.7
compound52	0	-10.3	-7.7	-8.7
compound84	0	-8	-7.7	-8.7
compound40	0	-8.8	-7.6	-8.7
compound294	1	-8.2	-8.6	-8.6
compound108	0	-8.7	-8.5	-8.6
compound210	0	-8.5	-8.5	-8.6
compound269	1	-8.4	-8.3	-8.6
compound220	0	-9.6	-8.2	-8.6
compound173	0	-8.9	-8.2	-8.6
compound79	0	-8.9	-7.7	-8.6
compound292	1	-8.5	-7.7	-8.6
compound191	0	-9.8	-7.5	-8.6
compound104	0	-9.4	-9.2	-8.5
compound237	1	-8.5	-8.9	-8.5
compound198	0	-8.3	-8.7	-8.5
compound308	1	-8	-8.7	-8.5
compound118	0	-9.7	-8.5	-8.5
compound282	1	-9	-8.4	-8.5
compound267	1	-9.4	-8.1	-8.5
compound81	0	-9.3	-8.1	-8.5
compound247	1	-8.2	-8.1	-8.5
compound82	0	-8.2	-7.5	-8.5

compound129	0	-8.1	-6.9	-8.5
compound288	1	-8.6	-9.9	-8.4
compound249	1	-9.5	-9.4	-8.4
compound295	1	-10.1	-9.2	-8.4
compound283	1	-9.7	-8.6	-8.4
compound307	1	-7.8	-8.6	-8.4
compound168	0	-9	-8.4	-8.4
compound139	0	-8	-8.3	-8.4
compound117	0	-8.6	-8.2	-8.4
compound169	0	-7.5	-8.2	-8.4
compound223	1	-8.7	-8.1	-8.4
compound275	1	-8.4	-8.1	-8.4
compound279	1	-7.5	-8	-8.4
compound86	0	-8.9	-7.9	-8.4
compound43	0	-7.9	-7.8	-8.4
compound15	0	-9.2	-7.3	-8.4
compound297	1	-9.1	-8.9	-8.3
compound124	0	-8.5	-8.8	-8.3
compound274	1	-10.2	-8.7	-8.3
compound36	0	-8.4	-8.6	-8.3
compound314	1	-9	-8.5	-8.3
compound311	1	-8.7	-8.4	-8.3
compound260	1	-8.5	-8.4	-8.3
compound256	1	-8.2	-8.4	-8.3
compound123	0	-9	-8.3	-8.3

compound113	0	-8.2	-8.3	-8.3
compound310	1	-8.1	-8.2	-8.3
compound45	0	-8.4	-8.1	-8.3
compound309	1	-8.1	-8.1	-8.3
compound293	1	-7.8	-8.1	-8.3
compound276	1	-8.1	-8	-8.3
compound12	0	-8.7	-7.9	-8.3
compound6	0	-8.2	-7.9	-8.3
compound137	0	-8.6	-7.7	-8.3
compound133	0	-8.9	-7.5	-8.3
compound209	0	-8.9	-9.4	-8.2
compound144	0	-9.8	-9.3	-8.2
compound179	0	-9.3	-8.8	-8.2
compound257	1	-8.1	-8.8	-8.2
compound95	0	-7.4	-8.6	-8.2
compound94	0	-9.8	-8.4	-8.2
compound245	1	-8.9	-8.4	-8.2
compound302	1	-8.8	-8.4	-8.2
compound13	0	-7.2	-8.3	-8.2
compound228	1	-9.2	-8.1	-8.2
compound68	0	-8.1	-8.1	-8.2
compound141	0	-8.1	-8.1	-8.2
compound201	0	-8.4	-8	-8.2
compound145	0	-8.1	-8	-8.2
compound221	1	-8.4	-7.8	-8.2

compound273	1	-7.1	-7.7	-8.2
compound157	0	-9	-7.6	-8.2
compound152	0	-7.7	-7.6	-8.2
compound80	0	-7.8	-7.5	-8.2
compound301	1	-9	-8.7	-8.1
compound254	1	-8.5	-8.6	-8.1
compound215	0	-9.3	-8.4	-8.1
compound315	1	-8.9	-8.3	-8.1
compound243	1	-8.8	-8.3	-8.1
compound246	1	-8.8	-8.3	-8.1
compound207	0	-8.4	-8.3	-8.1
compound34	0	-8	-8.3	-8.1
compound143	0	-8.8	-8.2	-8.1
compound205	0	-8.1	-8.2	-8.1
compound225	1	-9.4	-8.1	-8.1
compound265	1	-8.6	-8.1	-8.1
compound186	0	-7.7	-8.1	-8.1
compound224	1	-9.5	-8	-8.1
compound181	0	-9.1	-7.8	-8.1
compound56	0	-8.5	-7.8	-8.1
compound183	0	-7.9	-7.8	-8.1
compound10	0	-9.2	-7.7	-8.1
compound46	0	-7.5	-7.7	-8.1
compound182	0	-10.3	-7.6	-8.1
compound44	0	-8.5	-7.6	-8.1

compound87	0	-8.5	-7.6	-8.1
compound167	0	-8.3	-7.6	-8.1
compound78	0	-7.5	-7.4	-8.1
compound30	0	-8	-7	-8.1
compound259	1	-8.8	-10	-8
compound305	1	-9.9	-9.2	-8
compound55	0	-8.4	-8.5	-8
compound252	1	-9.1	-8.4	-8
compound206	0	-7.4	-8.4	-8
compound35	0	-8.7	-8.2	-8
compound244	1	-8.6	-8.2	-8
compound156	0	-8.5	-8.2	-8
compound154	0	-8.7	-8.1	-8
compound299	1	-8.6	-8	-8
compound266	1	-8.5	-8	-8
compound41	0	-8.1	-8	-8
compound63	0	-7.2	-8	-8
compound242	1	-8.7	-7.8	-8
compound270	1	-8.5	-7.8	-8
compound291	1	-8.2	-7.8	-8
compound241	1	-8.7	-7.7	-8
compound53	0	-7	-7.5	-8
compound317	1	-8.8	-8.7	-7.9
compound147	0	-9	-8.6	-7.9
compound203	0	-7.9	-8.4	-7.9

compound14	0	-9.5	-8.2	-7.9
compound2	0	-8.6	-8.2	-7.9
compound128	0	-8.6	-8.2	-7.9
compound264	1	-9.3	-8.1	-7.9
compound298	1	-8.5	-8.1	-7.9
compound116	0	-9.2	-7.9	-7.9
compound33	0	-9.6	-7.8	-7.9
compound166	0	-8.3	-7.8	-7.9
compound65	0	-8.2	-7.8	-7.9
compound7	0	-8.5	-7.7	-7.9
compound60	0	-9	-7.3	-7.9
compound184	0	-8	-7.3	-7.9
compound285	1	-8.1	-8.6	-7.8
compound319	1	-8.3	-8.4	-7.8
compound62	0	-8.1	-8.1	-7.8
compound300	1	-9.5	-8	-7.8
compound234	1	-8.3	-7.8	-7.8
compound239	1	-8.3	-7.8	-7.8
compound112	0	-8.1	-7.8	-7.8
compound59	0	-7.8	-7.8	-7.8
compound146	0	-7.8	-7.8	-7.8
compound240	1	-8.3	-7.7	-7.8
compound176	0	-8.2	-7.6	-7.8
compound227	1	-8.9	-7.4	-7.8
compound195	0	-8.5	-7.4	-7.8

compound93	0	-7.9	-7.4	-7.8
compound66	0	-8.7	-7.3	-7.8
compound151	0	-9.4	-7.1	-7.8
compound42	0	-8.4	-7.1	-7.8
compound261	1	-7.5	-8.8	-7.7
compound11	0	-8.1	-8.3	-7.7
compound85	0	-9.6	-8	-7.7
compound213	0	-7	-8	-7.7
compound26	0	-7.6	-7.9	-7.7
compound158	0	-8.7	-7.8	-7.7
compound235	1	-8.5	-7.8	-7.7
compound226	1	-8.8	-7.7	-7.7
compound318	1	-8.8	-7.7	-7.7
compound161	0	-8.6	-7.7	-7.7
compound170	0	-8.6	-7.7	-7.7
compound83	0	-7.8	-7.7	-7.7
compound114	0	-7.8	-7.7	-7.7
compound159	0	-7.9	-7.6	-7.7
compound120	0	-7.8	-7.6	-7.7
compound102	0	-8.6	-7.3	-7.7
compound5	0	-7.9	-7.1	-7.7
compound131	0	-9.4	-7	-7.7
compound172	0	-8.6	-8.4	-7.6
compound149	0	-7.4	-8	-7.6
compound140	0	-8.8	-7.9	-7.6

compound18	0	-8.3	-7.9	-7.6
compound316	1	-8.6	-7.8	-7.6
compound192	0	-7.5	-7.8	-7.6
compound164	0	-9.1	-7.7	-7.6
compound58	0	-7.5	-7.7	-7.6
compound1	0	-7.9	-7.6	-7.6
compound126	0	-7.4	-7.5	-7.6
compound136	0	-7.3	-7.5	-7.6
compound92	0	-8.5	-7.4	-7.6
compound39	0	-7	-6.4	-7.6
compound75	0	-8.6	-7.8	-7.5
compound148	0	-8.6	-7.8	-7.5
compound160	0	-8.3	-7.8	-7.5
compound32	0	-8.1	-7.6	-7.5
compound111	0	-7.1	-7.6	-7.5
compound142	0	-8.5	-7.5	-7.5
compound248	1	-8	-7.5	-7.5
compound19	0	-7.5	-7.5	-7.5
compound132	0	-7.4	-7.4	-7.5
compound212	0	-8.2	-7.3	-7.5
compound202	0	-8.1	-7.3	-7.5
compound216	0	-7.4	-7	-7.5
compound262	1	-7.1	-8.4	-7.4
compound90	0	-8.2	-8	-7.4
compound208	0	-8.8	-7.7	-7.4

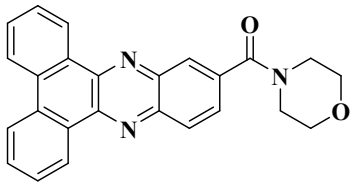
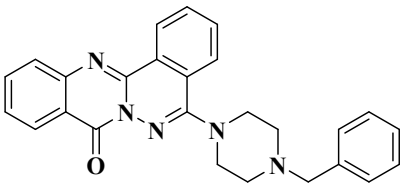
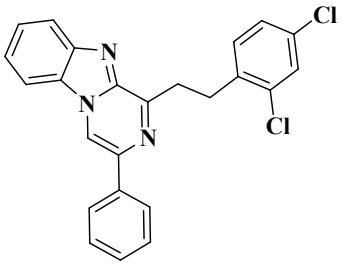
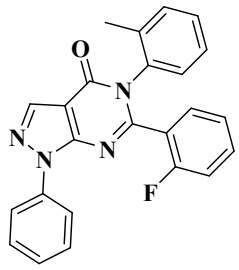
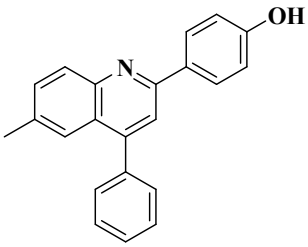
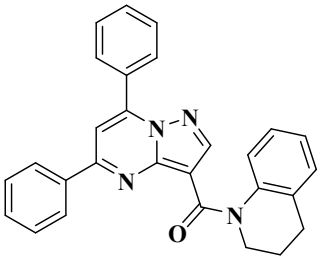
compound23	0	-8.8	-7.6	-7.4
compound214	0	-8.1	-7.5	-7.4
compound130	0	-9.1	-7.3	-7.4
compound9	0	-7.7	-7.2	-7.4
compound127	0	-7.8	-7.1	-7.4
compound16	0	-7.5	-6.5	-7.4
compound3	0	-8.1	-7.9	-7.3
compound110	0	-8	-7.7	-7.3
compound91	0	-7.6	-7.4	-7.3
compound222	1	-7.2	-7.2	-7.3
compound253	1	-8	-7.1	-7.3
compound153	0	-7.2	-7.1	-7.3
compound304	1	-8.1	-8	-7.2
compound49	0	-8	-7.9	-7.2
compound21	0	-7.7	-7.7	-7.2
compound47	0	-7.6	-7.5	-7.2
compound187	0	-7.2	-7.5	-7.2
compound24	0	-7.4	-7.4	-7.2
compound138	0	-7.2	-7.4	-7.2
compound272	1	-7	-7.3	-7.2
compound177	0	-6.5	-7.3	-7.2
compound185	0	-7.6	-7.2	-7.2
compound263	1	-8.2	-7	-7.2
compound218	0	-8	-6.9	-7.2
compound4	0	-7.1	-6.8	-7.2

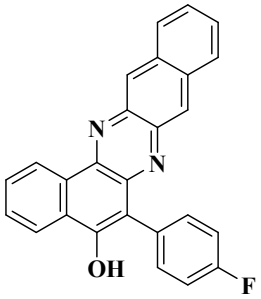
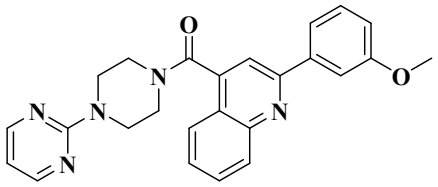
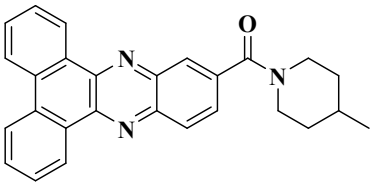
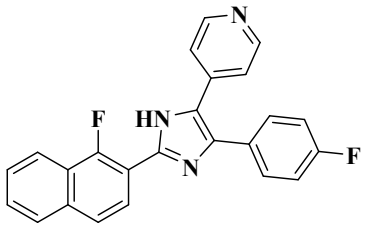
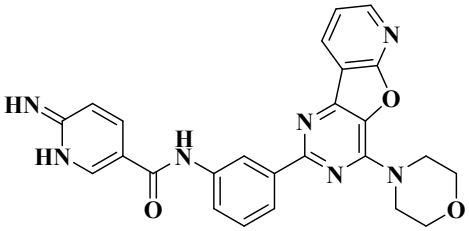
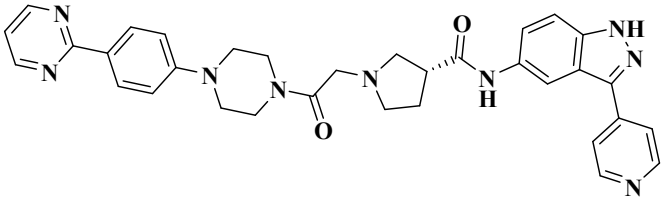
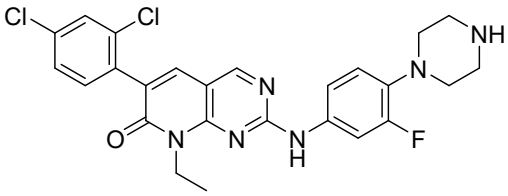
compound165	0	-8	-6.7	-7.2
compound38	0	-7.8	-8.2	-7.1
compound121	0	-7.7	-7.8	-7.1
compound287	1	-8.3	-7.5	-7.1
compound22	0	-7.3	-7.5	-7.1
compound70	0	-8.7	-7.3	-7.1
compound163	0	-7.8	-7.3	-7.1
compound150	0	-9.2	-7.2	-7.1
compound196	0	-8.1	-7.2	-7.1
compound217	0	-7.3	-7	-7.1
compound72	0	-8	-6.9	-7.1
compound178	0	-7.7	-6.8	-7.1
compound189	0	-7.8	-6.7	-7.1
compound219	0	-8.3	-7.5	-7
compound193	0	-7.3	-7.5	-7
compound67	0	-8.4	-7.4	-7
compound8	0	-8.6	-7.2	-7
compound25	0	-7.3	-7.2	-7
compound106	0	-7.8	-7.1	-7
compound100	0	-6.9	-6.3	-7
compound73	0	-7.2	-8	-6.9
compound194	0	-6.7	-7.4	-6.9
compound54	0	-7.2	-7.2	-6.9
compound76	0	-6.6	-6.8	-6.9
compound197	0	-6.5	-6.7	-6.9

compound180	0	-7.4	-6.6	-6.9
compound271	1	-6.7	-7.3	-6.8
compound20	0	-6.8	-6.9	-6.8
compound27	0	-6.6	-7.8	-6.7
compound57	0	-7.4	-7.4	-6.7
compound50	0	-7.8	-7.2	-6.7
compound188	0	-7.2	-6.8	-6.7
compound51	0	-7.1	-6.8	-6.7
compound115	0	-6.6	-6.6	-6.7
compound155	0	-6.9	-6.3	-6.7
compound175	0	-7.7	-6.9	-6.6
compound98	0	-7.6	-6.8	-6.6
compound64	0	-7.7	-7.1	-6.5
compound71	0	-6.9	-7	-6.5
compound171	0	-7.3	-6.4	-6.5
compound28	0	-7.1	-6.3	-6.5
compound74	0	-7.6	-6.5	-6.4
compound17	0	-7	-6.5	-6.4
compound61	0	-6.2	-6.7	-6.1
compound69	0	-6.2	-6.3	-6.1
compound48	0	-7.1	-6	-6.1
compound231	1	-9	-9.8	-10.1
compound313	1	-9.2	-10.9	-10

[a] 0 represents the inactive compound; 1 represents the active compound

Table S2. The information of 13 hit compounds

Compd.	Structure	Affinity (Kcal/mol)	Source
D008-10042524		-10.1	Spece
D008-10083445		-9.6	Spece
D008-10048904		-9.5	Spece
D008-10016012		-9.6	Spece
D008-10080218		-9.6	Spece
D008-10049026		-10.5	Spece

D008-10050038		-9.7	Spece
D008-10022050		-9.5	Spece
D008-10056747		-9.9	Spece
T001-10020615		-9.8	Bioactive Compound Library
T001-10013696		-9.6	Bioactive Compound Library
T001-10013986		-9.7	Bioactive Compound Library
T001-10026247		-9.5	Bioactive Compound Library

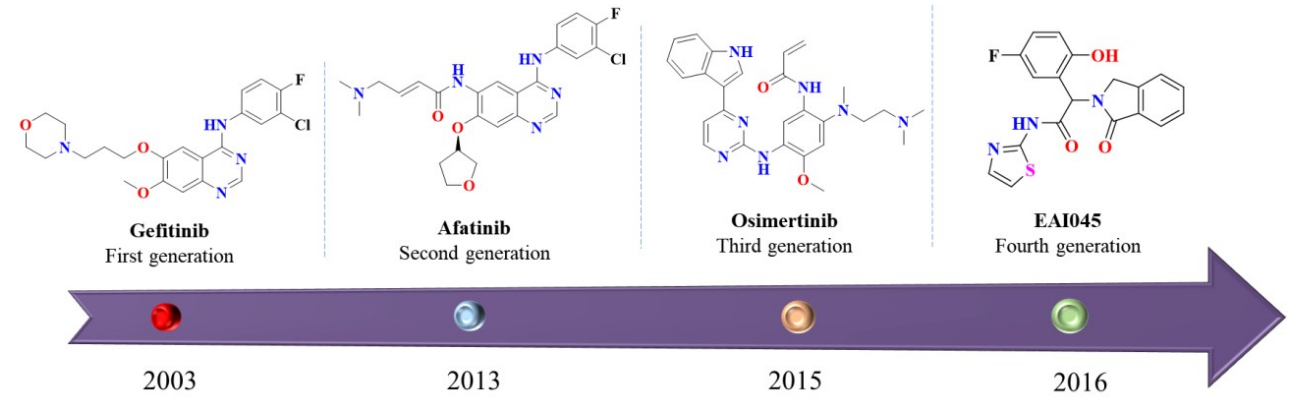


Figure S1 Typical EGFR inhibitors of the first to fourth generations.

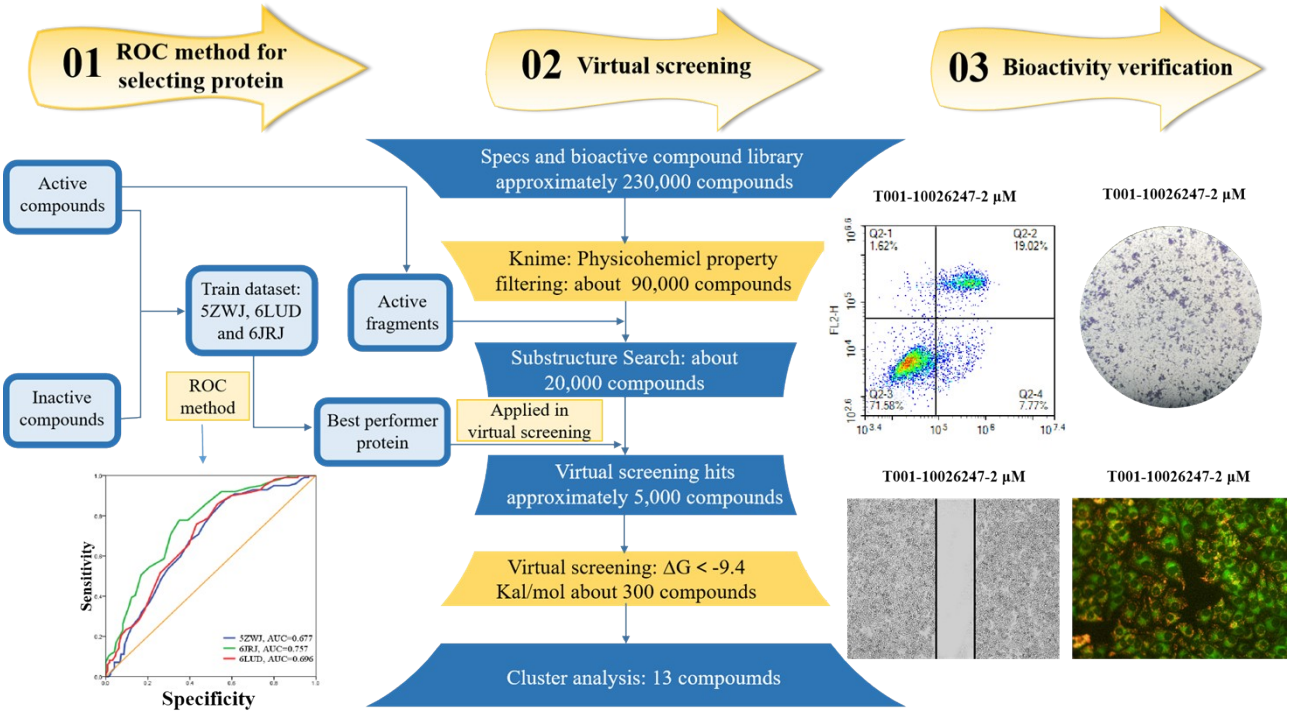


Figure S2. The workflow of drug discovery strategy applied to discover active compounds against EGFR target

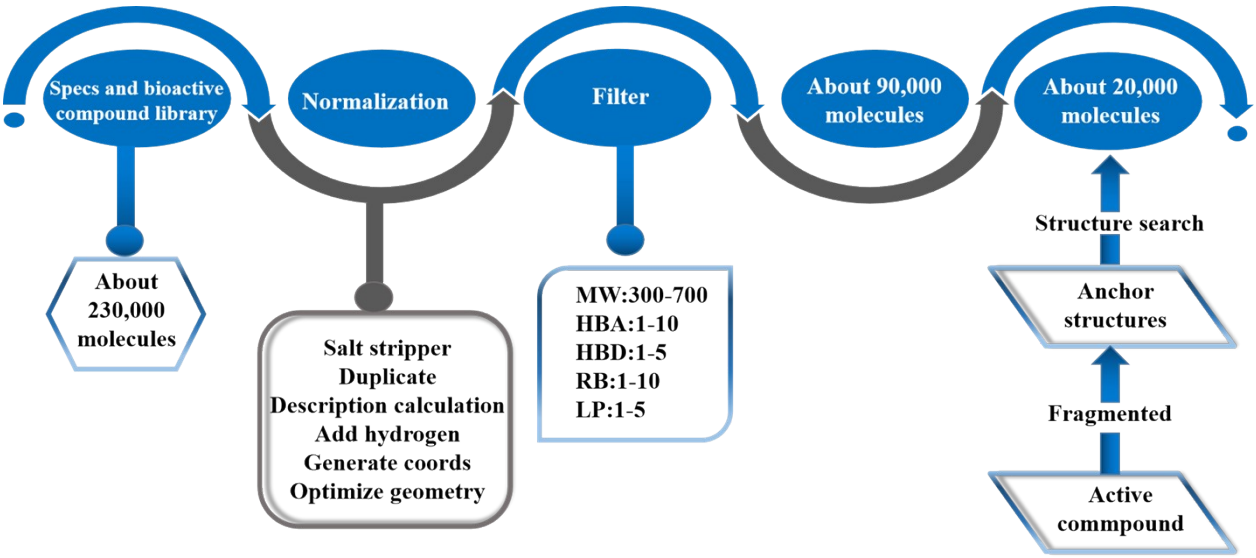


Figure S3. Workflow of physicochemical property filtering and substructure search using Knime software.

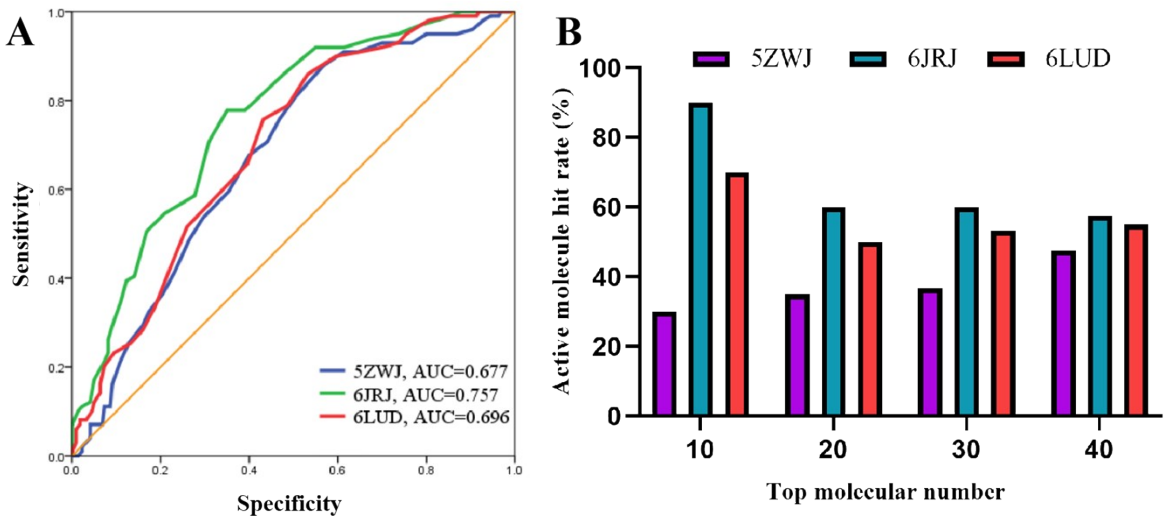


Figure S4. (A) Evaluation of the recognition ability of three proteins with Vina by ROC curves; (B) Active compound hits for the three proteins

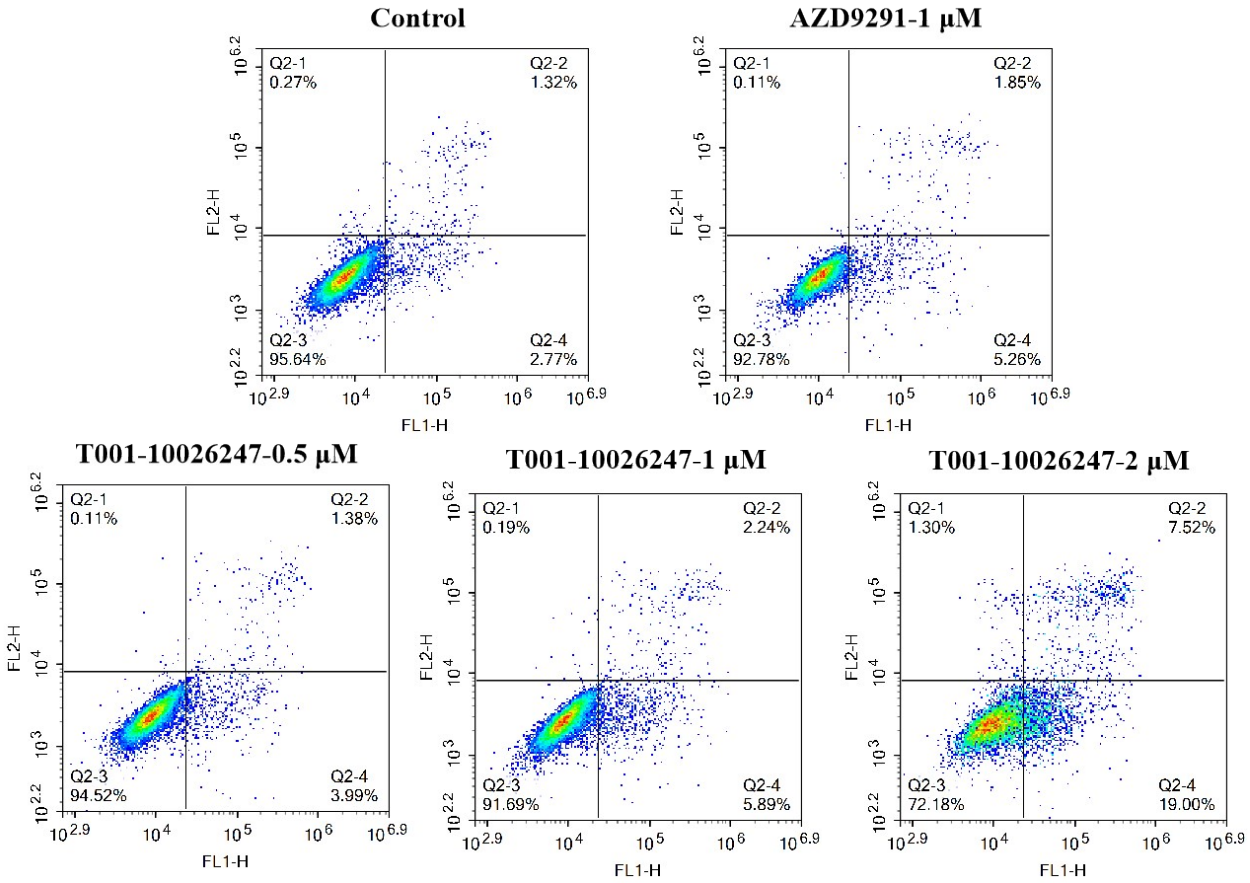


Figure S5. Cell-apoptosis analysis of compound **T001-10026247**. (Q2-1: mechanical damage; Q2-2: late apoptotic; Q2-3: living cells; Q2-4: early apoptotic).

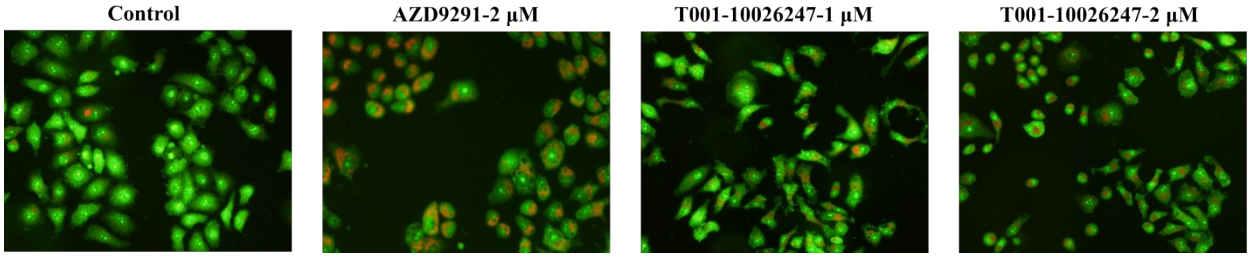


Figure S6. Cell morphology observed by fluorescence microscopy of compound **T001-10026247**

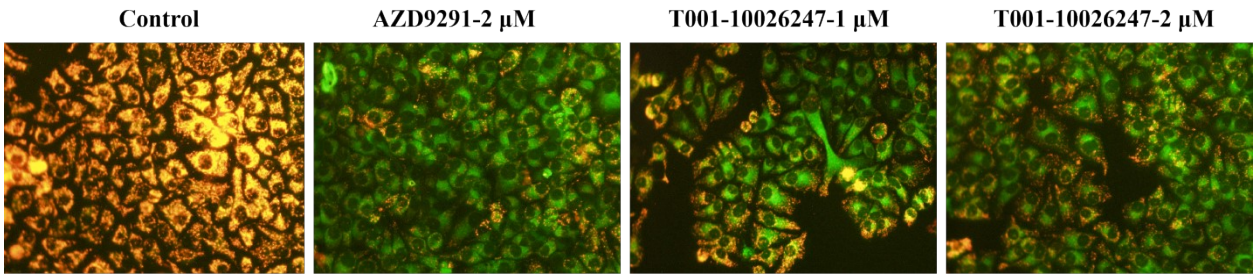


Figure S7. Fluorescent probe JC-1 detects the induction of apoptosis in H1975 cells by compound **T001-10026247**.

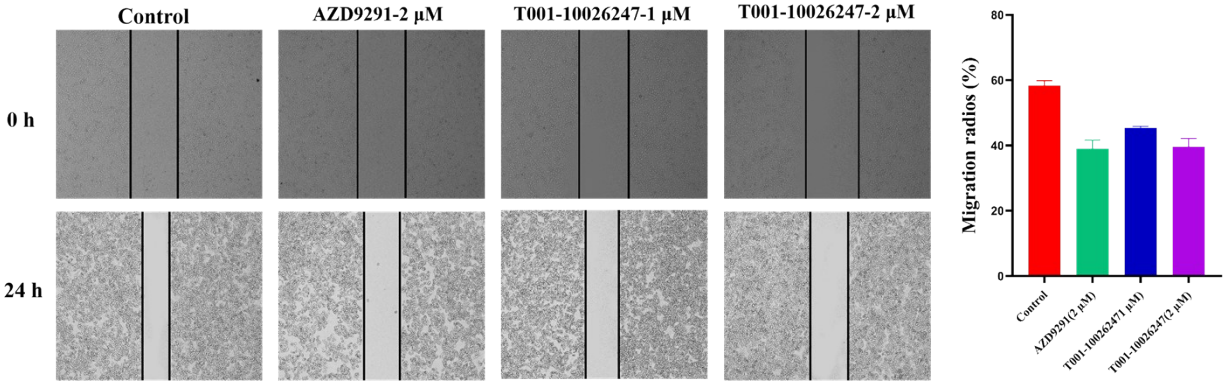


Figure S8. *In vitro* wound healing assays were performed on H1975 cells with different concentrations of **T001-10026247**. Quantitative analyses of the percentage of wound closure at 24 h compared with 0 h were shown on the right.

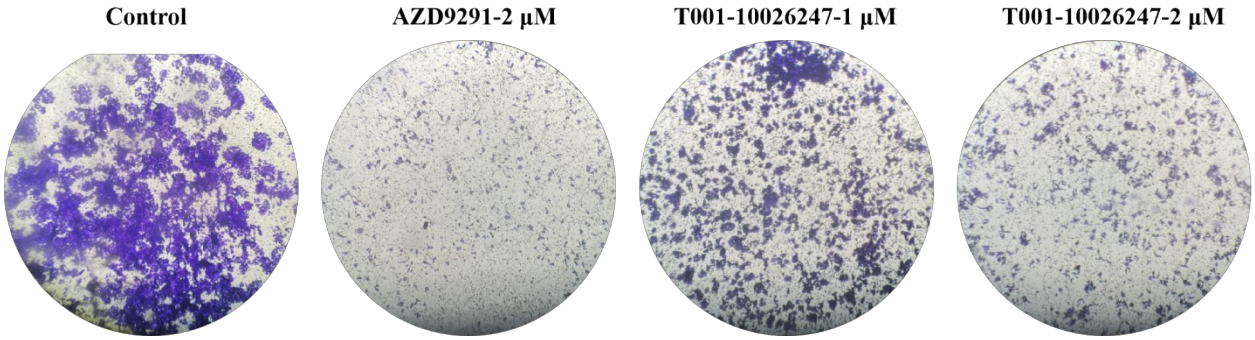


Figure S9. Transwell assay of cell invasion.

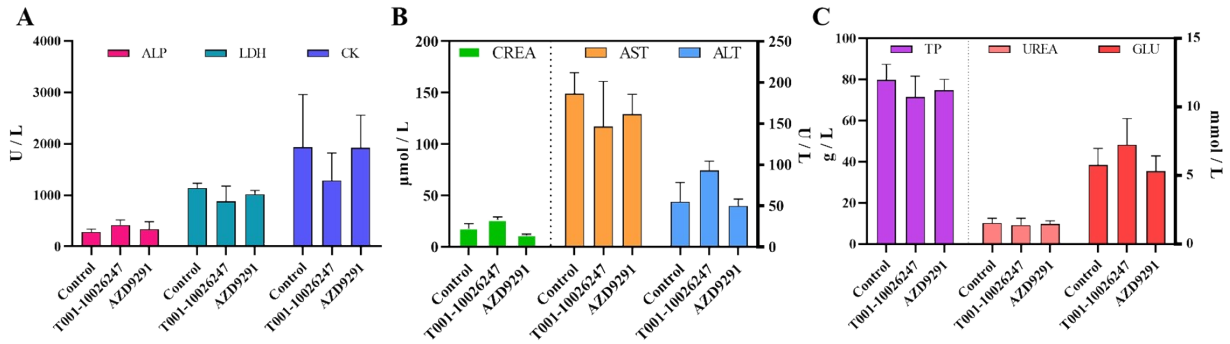


Figure S10. The results of blood biochemical analysis of mice in the blank group (0.9% saline), positive administration group (**AZD9291**, 70 mg/kg) and **T001-10026247** (70 mg/kg) administration group. (A) ALP, LDH, CK；(B) CREA, AST, ALT; (C) TP, UREA, GLU.

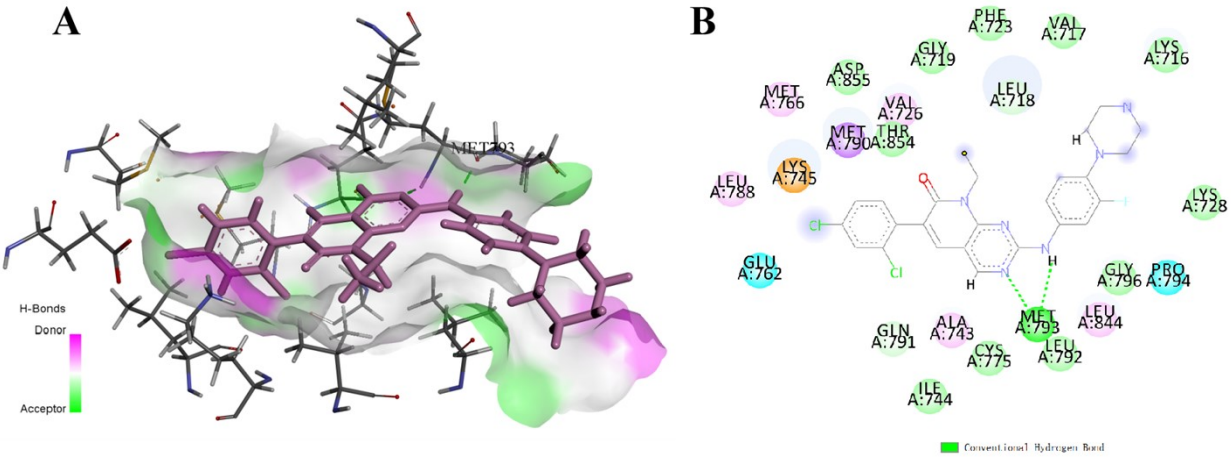


Figure S11. (A) The binding mode of compound **T001-10026247** with protein 6JRJ is as follows (3D). (B) The binding mode of compound **T001-10026247** with protein 6JRJ is as follows (2D).

Table S3. Cell proliferation activity evaluation of hit compounds in H1975, A549 and H460 cells.

Compd.	IC_{50}(μM±SD)[a]		
	H1975	**A549**	**H460**
D008-10042524	78.33±7.53	>100	>100
D008-10083445	>100	>100	>100
D008-10048904	**17.32±1.87**	**30.47±3.67**	**25.58±2.52**
D008-10016012	>100	85.53±9.65	98.53±10.41
D008-10080218	**37.90±4.09**	**34.68±4.24**	**41.52±4.86**
D008-10049026	>100	51.58±5.74	>100
D008-10050038	>100	65.86±7.31	53.80±52.98
D008-10135686	**16.78±2.35**	**15.12±2.03**	**35.37±4.23**
D008-10056747	>100	>100	>100
T001-10020615	77.93±6.98	68.44±6.90	82.41±9.21
T001-10013696	**43.42±4.21**	**41.97±4.56**	**35.84±5.72**
T001-10013986	>100	>100	>100
T001-10026247	**0.26±0.01**	**0.74±0.08**	**2.65±0.22**
AZD9291[b]	4.951±0.51	4.47±0.45	5.38±0.49

[a] The values are an average of three separate determinations.

[b] Used as the positive control.

Table S4. The activity of hit compounds against $EGFR^{T790M/C797S/L858R}$ and $EGFR^{T790M/L858R}$.

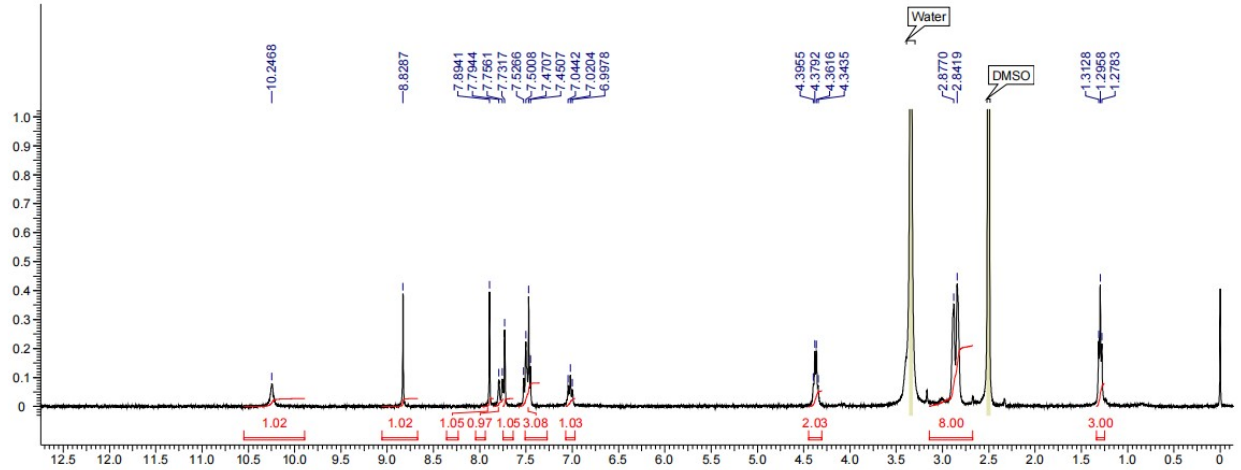
Compd.	IC_{50}(μM)	
	$EGFR^{T790M/C797S/L858R}$	**$EGFR^{T790M/L858R}$**
D008-10042524	＞10.0	ND
D008-10083445	＞10.0	ND
D008-10048904	**4.82**	ND
D008-10016012	＞10.0	ND
D008-10080218	**3.18**	ND
D008-10049026	＞10.0	ND
D008-10050038	＞10.0	ND
D008-10135686	**2.37**	ND
D008-10056747	＞10.0	ND
T001-10020615	＞10.0	ND
T001-10013696	**3.33**	ND
T001-10013986	＞10.0	ND
T001-10026247	**2.29**	**1.63**

[a] ND: Not done.

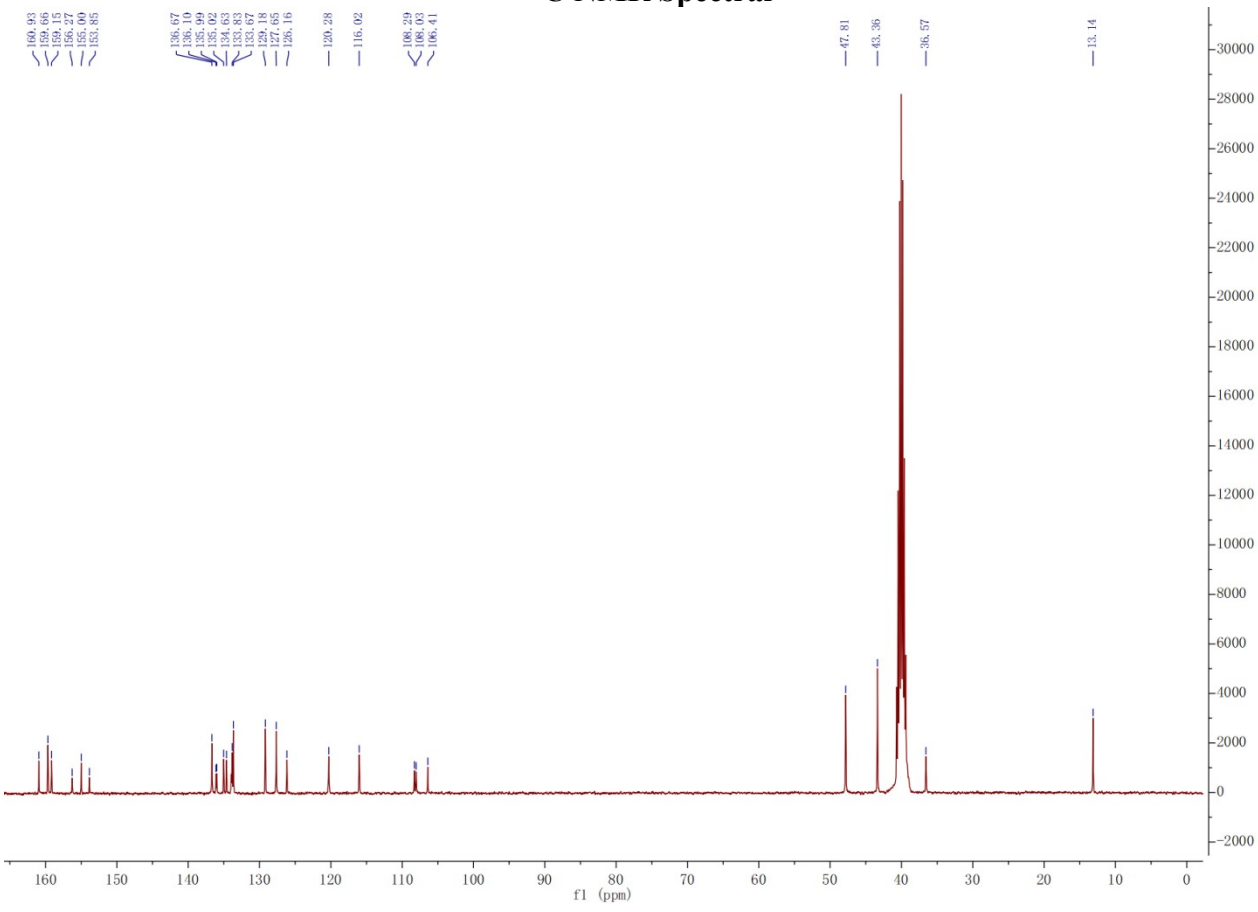
1H, 13C, HRMS & HPLC-purity spectrum of the compound T001-10026247

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.30 (t, J=6.90 Hz, 3 H), 2.88 (s, 4 H), 2.84 (s, 4 H), 4.37 (q, J=7.03 Hz, 2 H), 7.02 (t, J=9.29 Hz, 1 H), 7.36 - 7.59 (m, 3H), 7.73 (d, J=1.51 Hz, 1 H), 7.78 (d, J=15.31 Hz, 1 H), 7.89 (s, 1 H), 8.83(s,1H), 10.25(br.s.,1H), ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.93, 159.66, 159.15, 156.27, 155.00, 153.85, 136.67,136.10, 135.99, 135.02, 134.63, 133.83, 133.67, 129.18, 127.65, 126.16, 120.28, 116.02, 108.29, 108.03, 106.41, 47.81, 43.36, 36.57, 13.14. LC-MS (HPLC: MeOH/H_2O (KH_2PO_4 = 20 mM) = 1:1); tR: 8.252 min, purity: 98.8%. ESI-MS (m/z): $[M + H]^-$, calcd for $C_{25}H_{23}Cl_6FN_6O$: 513.1373, found, 513.1374.

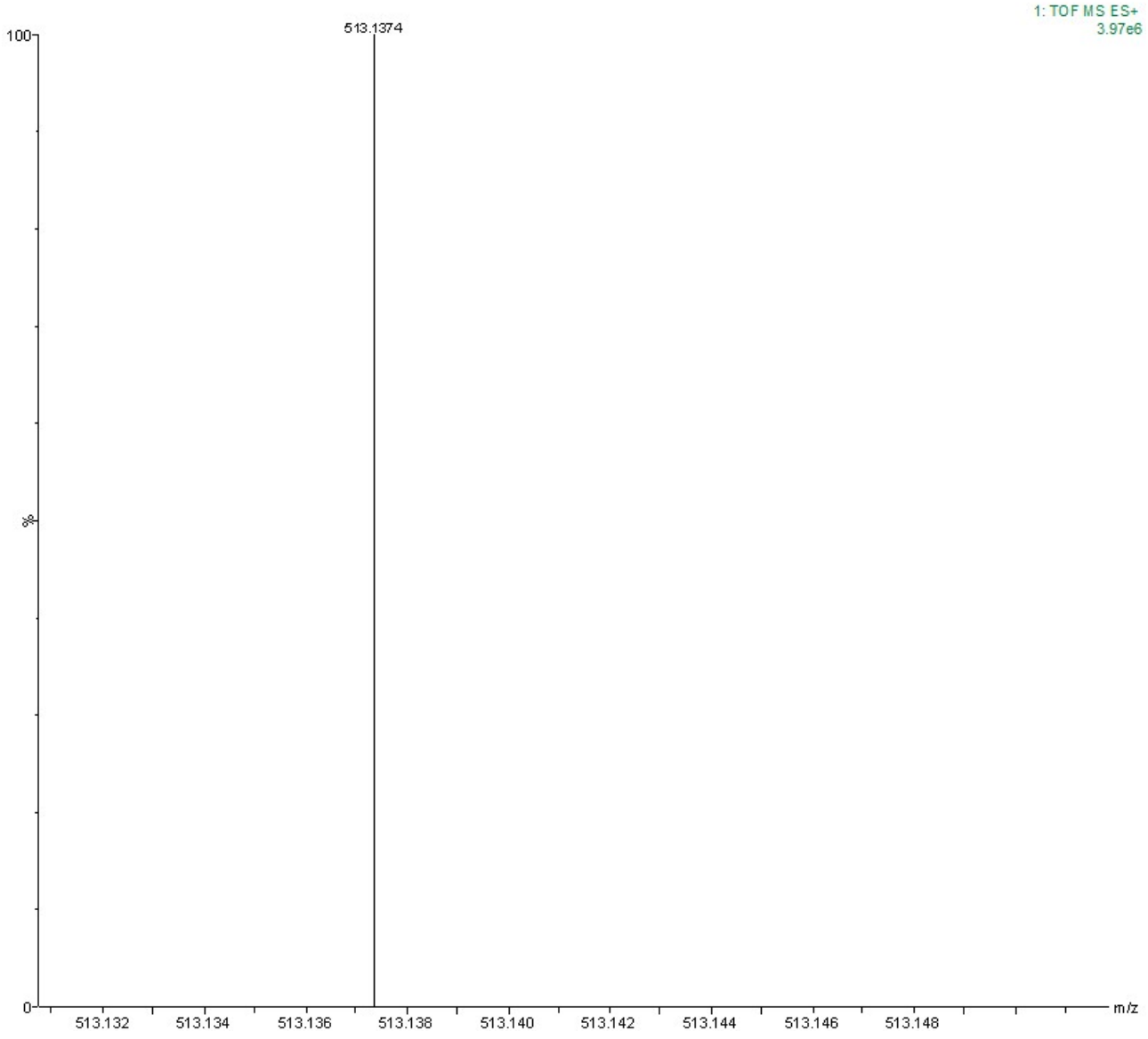
^{1}H NMR Spectral



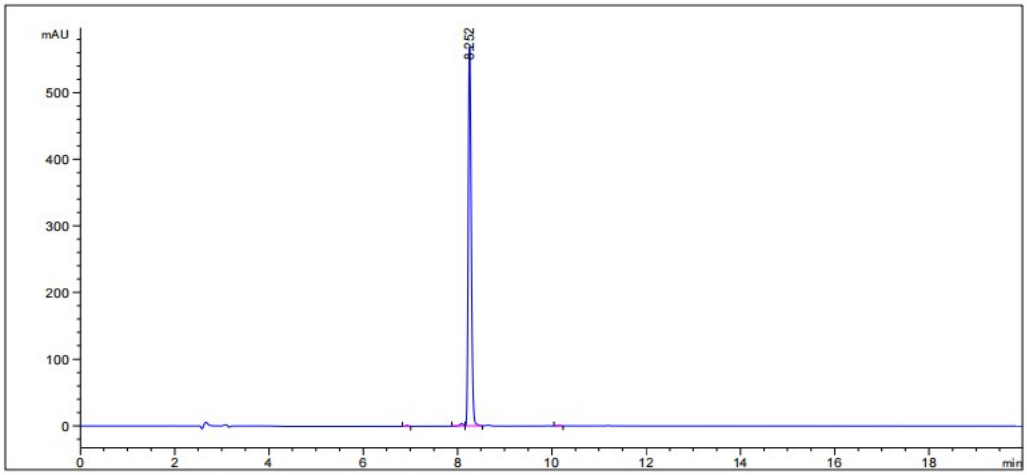
^{13}C NMR Spectral



High resolution mass spectrum



HPLC-pur

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                      Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

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Peak RetTime Type  Width     Area      Height     Area
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   1   6.924 MM    0.0630    4.85375    1.28319   0.1915
   2   8.081 BV    0.0768   21.07841    4.14324   0.8318
   3   8.252 VV    0.0687 2504.21411  569.86847  98.8193
   4  10.158 MM    0.0893    3.98793 7.44103e-1   0.1574

Totals :                  2534.13421  576.03900
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Proteins and software involved in the manuscript

Proteins:

6JRJ[1] (DOI: 10.2210/pdb6jrj/pdb) https://www.wwpdb.org/pdb?id=pdb_00006jrj;

5ZWJ[2] (DOI: 10.2210/pdb5zwj/pdb) https://www.wwpdb.org/pdb?id=pdb_00005zwj;

6LUD[3] (DOI: 10.2210/pdb6lud/pdb) https://www.wwpdb.org/pdb?id=pdb_00006lud.

Software:

Vina[4] (https://vina.scripps.edu/);

DUD-E[5,6] online application (http://dude.docking.org/generate);

Knime[7,8] (https://www.knime.com/)；

OpenBabel[9] (http://openbabel.org/wiki/Main_Page)；

Discovery Studio[10] (http://www.discoverystudio.net/).

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