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Computer Virtual Screening for Small Molecule Compounds Targeting Human SOAT 1 for Inhibiting Hepatocellular Carcinoma

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Abstract

Background: Sterol O-acyltransferase 1 (SOAT1) is a membrane-binding protein plays roles in different cancer which makes it become a potential target for the treatment of multiple tumors.

Objective: Computer virtual screening was used to obtain small molecule compounds with strong binding force to SOAT1 based on the region N 421/H 460 region of Human SOAT1 protein. The effects of the top compounds on tumors were screened and validated at the cellular level.

Method: Schrodinger Maestro 11.4, and the 3D mapping software is used PyMol to target Human SOAT1 proteins for virtual screen. CCK8 method was used to verify the top 100 compounds screened in HepG2 cells.

Results: The structure, scoring values and compound supplementary information of the top 200 Discovery Diversity Set 50 and MCE Library top 200 compounds are shown in Appendix 1,2, respectively, and also the molecular docking scores. Make 2D and 3D mapping of the binding modes of five preferred compounds. The molecular docking diagram of the three optimal compounds was shown according to the scores. Twelve compounds showed the strongest inhibitory effect on HepG2 cells

(> 80%). 8 compounds showed significant inhibitory effect on HepG2 cells (inhibitory rate > 20%).

Conclusion: This study contributes to find small molecule compounds with strong binding force to SOAT1 providing small molecule compounds that may be useful for the treatment of multiple tumors.

Keywords: Sterol O-acyltransferase 1; Computer virtual screening; Molecular docking; Tumor targets; Hepatocellular carcinoma

Introduction

Sterol O-acyltransferase (SOAT) is a protein located in the endoplasmic reticulum and can convert cholesterol into cholesterol esters. It has been considered as an important factor in lipid homeostasis. Sterol O-acyltransferase 1 (SOAT1), also known as acyl-coenzyme A Cholesterol Acyl Transferase (ACAT 1), is a membrane-binding protein that uses long-chain fatty acyl coenzyme A to cholesterol to form cholesterol ester and coenzyme A **[1].** SOAT1 is not only closely related to atherosclerosis, Alzheimer's disease **[2].** Inhibition of ACAT1 have previously been shown to alleviate amyloid pathology **[3],** down-regulated the size of human hepatocellular carcinoma tumours **[4],** restrain the metastasis and growth of pancreatic cancer tumours **[5],** guard against prostate cancer **[6]** and heighten the antitumour response of immunotherapy and CD8+T cells **[7].** Then we verified 100 compounds in HepG2 cells which is reported as the results of drug activity screening experiments on 100 compounds. Yan Ning, et al. **[8].** The resolved three-dimensional structure of Human SOAT1 forms a tetramer structure through a limited contact interface (also known as the membrane plane), which consists of TM2, TM5, TM6 and IH 2 of the two SOAT1 protein molecules in the center (as shown in **Figure 1**). we use Schrodinger Maestro 11.4, and the 3D mapping software PyMol to target Human SOAT1 proteins for virtual screen in order to obtain small molecule compounds with strong binding force to SOAT1 based on the region where N 421/H 460 of Human SOAT1 protein.

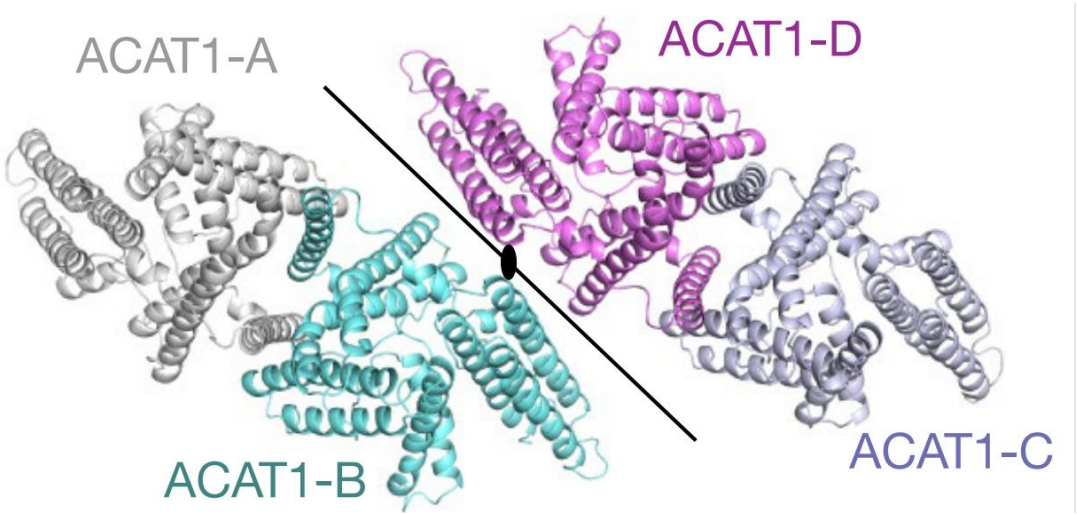


Figure 1: The crystal structure of Figure 1 Human SOAT1 [3].

Materials and Methods

Virtual screening

Through the preliminary literature research, this project will target Human SOAT1 proteins for virtual screening. The software used for virtual screening is Schrodinger Maestro 11.4, and the 3D mapping software is PyMol. The flow chart is as follows **Figure 2.** 1. Protein preparation: Download the crystal structure of Human SOAT1 (PDB ID: 6P2J) from the RCSB PDB database. Proteins were hydrowatered using the Protein Preparation Wizard module. Subsequently, energy optimization (OPLS2005 force field, RMSD of 0.30 A). The processed proteins were made with the Receptor Grid Generation module and generated centered on N 421 / H 460 with box size set to 20 A 20 A 20 A. 2. Compound preparation: to be Discovery Diversity Set 50(DDS-50, Including 50.2K compounds), MCE Bioactive Compound Library Plus (MCE Library, 2D format containing 12.6K compounds) for hydrogenation and energy optimization through Schrodinger software LigPrep Module, Outputs the 3D structure for virtual filtering.3. Molecular docking: Virtual Screening Workflow module is used for virtual screening, the prepared compounds are imported, and Glide module is used for molecular docking, that is, the receptors and ligand molecules dock with each other by geometric matching and energy matching. High-Throughput Screening (HTVS) mode in Glide module is first used to be used in Discovery Diversity Set 50. 3. Molecular docking: Virtual Screening Workflow module is used for virtual screening, the prepared compounds are imported, and Glide module is used for molecular docking, that is, the receptors and ligand molecules dock with each other by geometric matching and energy matching. High-Throughput Screening (HTVS) mode in Glide module is first used to be used in Discovery Diversity Set 50.

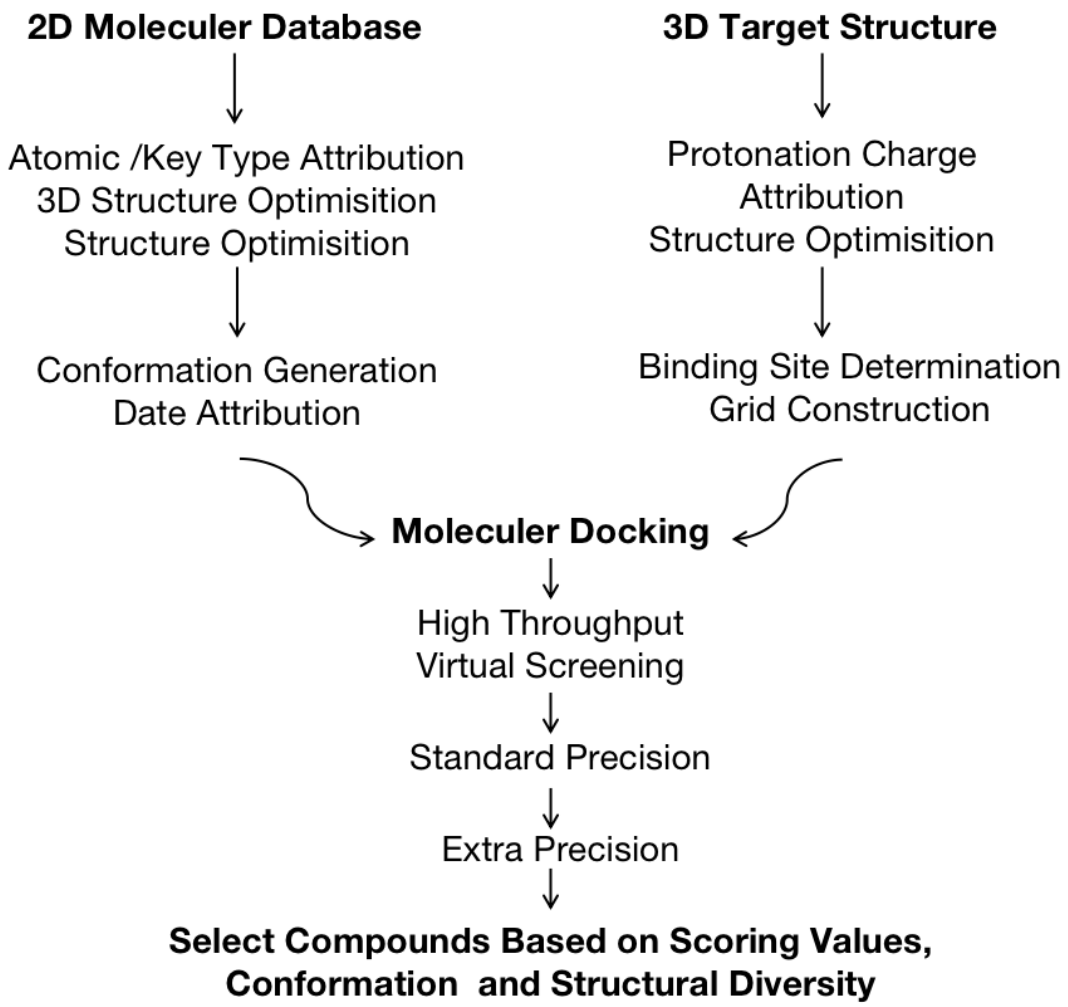


Figure 2: Virtual screening workflow based on molecular docking.

Table I: Cell activity of each group was measured by CCK 8.

Cell number/hole		Initial concentration(mL)	Volume required(mL)	Culture Medium(mL)	Bulk volume(mL)	final concentration(individual/mL)
Cell strain name	HepG2	3×10^6	4.02	55.98	60	2×10^5

Diluted cells were added to 96-well plates and placed in 37℃ 5% CO2The cells were incubated for 24 h and then medicated after being adherent. Diluted drugs were added to a 96-well plate with prepared cells was incubated at 37℃ 5% CO2 for 48 hours. The 100 compounds and their inhibition rates on HepG2 are shown in Table I. 10% CCK-8 reaction solution was prepared with complete medium (DMEM + 10%FBS) and added to a cell plate (96-well plate), 37℃ 5% CO2 After 2h of the incubator reaction, the absorbance at 450 nm was measured using a microplate reader, and an absorbance of 600 nm was used as the background reference. The data were analysed using Excel and GraphPad Prism.

Results

Top 200 compounds after docking with SOAT1 molecule by MCE Library

Table 1: Details of the top 200 compounds after docking with SOAT1 molecule by MCE Library.

Item	Catalog No.	Drug Name	docking score	CAS No.	Formula	Mw	Clinical Information
1	HY-N0636	Eriocitrin	-17.219	13463-28-0	C27H32O15	596.53	No Development Reported
2	HY-N0022	Isoacteoside	-16.398	61303-13-7	C29H36O15	624.5871	No Development Reported
3	HY-N0657	Pinoresinol Diglucoside	-16.201	63902-38-5	C32H42O16	682.67	No Development

							Reported
4	HY-N0033	Poliumoside	-15.976	94079-81-9	C35H46O19	770.7283	No Development Reported
5	HY-106139	Bimosiamose	-15.73	187269-40-5	C46H54O16	862.91	Phase 2
6	HY-N1412	1,3-Dicaffeoylquinic acid	-15.645	19870-46-3	C25H24O12	516.45	No Development Reported
7	HY-N0178	Diosmin	-15.085	520-27-4	C28H32O15	608.54	Launched
8	HY-14181	Cinaciguat	-14.965	329773-35-5	C36H39NO5	565.7	Phase 2
9	HY-N0058	4,5-Dicaffeoylquinic acid	-14.935	57378-72-0	C25H24O12	516.45	No Development Reported
10	HY-125286	AB-680	-14.882	2105904-82-1	C20H24ClFN4O9P2	580.82	Phase 1
11	HY-N0796	Procyanidin B2	-14.879	29106-49-8	C30H26O12	578.52	No Development Reported
12	HY-18644	CWHM-12	-14.556	1564286-55-0	C26H32BrN5O6	590.47	No Development Reported
13	HY-	Troxerutin	-14.461	7085-55-	C33H42O19	742.68	Launched

	N0139			4			
14	HY-N0359	Cynarin	-14.413	30964-13-7	C25H24O12	516.45	No Development Reported
15	HY-112534	GSTO-IN-2	-14.282	1202710-57-3	C33H52N2O9	620.77	No Development Reported
16	HY-W004360	BIBR 1087 SE	-14.195	212321-78-3	C32H37N7O5	599.68	No Development Reported
17	HY-N0154	Neohesperidin dihydrochalcone	-14.166	20702-77-6	C28H36O15	612.58	No Development Reported
18	HY-N0056	Isochlorogenic acid A	-14.156	2450-53-5	C25H24O12	516.45	No Development Reported
19	HY-111786	LHC-165	-14.034	1258595-14-0	C29H32F2N3O7P	603.55	Phase 1
20	HY-16780	Gemilukast	-14.025	1232861-58-3	C36H37F2NO5	601.68	No Development Reported
21	HY-112276	Beryllon II	-13.896	51550-25-5	C20H10N2Na4O15S4	650.59	No Development Reported
22	HY-	SIRT5 inhibitor 1	-13.893	2166487-	C31H39FN6O6S2	674.81	No

	112634			21-2			Development Reported
23	HY-P0081	Bax inhibitor peptide V5	-13.89	579492-81-2	C27H50N6O6S	586.79	No Development Reported
24	HY-111407	MK-8353	-13.858	1184173-73-6	C37H41N9O3S	691.84	Phase 1
25	HY-103628	PROTAC CDK9 Degrader-1	-13.823	2118356-96-8	C33H35N5O7	613.66	No Development Reported
26	HY-N6839	1,4-b-D-Xylopentaose	-13.755	49694-20-4	C25H42O21	678.59	No Development Reported
27	HY-10521	Darapladib	-13.747	356057-34-6	C36H38F4N4O2S	666.77	Phase 3
28	HY-12113	Oprozomib	-13.58	935888-69-0	C25H32N4O7S	532.61	Phase 2
29	HY-N0668	Rubusoside	-13.576	64849-39-4	C32H50O13	642.73	No Development Reported
30	HY-N7032	Uridine 5′-diphosphoglucose (disodium salt)	-13.569	28053-08-9	C15H22N2Na2O17P2	566.3	No Development Reported
31	HY-112416	AZD4320	-13.536	1357576-48-7	C45H48ClF3N4O7S3	945.53	No Development

							Reported
32	HY-N1444	Complanatuside	-13.528	116183-66-5	C28H32O16	624.54	No Development Reported
33	HY-N4213	Anemarrhenasaponin I	-13.488	163047-21-0	C39H66O14	758.93	No Development Reported
34	HY-P0288	[Leu5]-Enkephalin	-13.439	58822-25-6	C28H37N5O7	555.62	No Development Reported
35	HY-U00444	DDR1-IN-2	-13.425	1429617-90-2	C30H29F3N6O	546.59	No Development Reported
36	HY-B2087	Glycerol phenylbutyrate	-13.407	611168-24-2	C33H38O6	530.65	Launched
37	HY-13915	NSC348884	-13.401	81624-55-7	C38H40N10	636.79	No Development Reported
38	HY-F0001	NADH (disodium salt)	-13.381	606-68-8	C21H27N7Na2O14P2	665.44	No Development Reported
39	HY-109035	Inarigivir soproxil	-13.369	942123-43-5	C25H34N7O13PS	703.62	Phase 2
40	HY-15337	Hesperidin	-13.328	520-26-3	C28H34O15	610.56	Launched

41	HY-D0003	Methyl Blue	-13.306	28983-56-4	C37H27N3Na2O9S3	755.84	No Development Reported
42	HY-127104	FMF-04-159-2	-13.258	2364489-81-4	C28H30Cl3N7O5S	683.01	No Development Reported
43	HY-F0003	NADPH (tetrasodium salt)	-13.25	2646-71-1	C21H26N7Na4O17P3	745.42	No Development Reported
44	HY-W013093	Uridine triphosphate (trisodium salt)	-13.236	19817-92-6	C9H12N2Na3O15P3	484.14	Phase 3
45	HY-N0318	Salvianolic acid A	-13.233	96574-01-5	C26H22O10	494.45	Phase 1
46	HY-16274	Lapaquistat acetate	-13.226	189060-13-7	C33H41ClN2O9	645.14	No Development Reported
47	HY-15747	Deltarasin	-13.222	1440898-61-2	C40H37N5O	603.75	No Development Reported
48	HY-10127	AZD1152	-13.178	722543-31-9	C26H31FN7O6P	587.54	Phase 3
49	HY-14925	Lapaquistat	-13.165	189059-71-0	C31H39ClN2O8	603.1	Phase 3
50	HY-112683	V-9302	-13.15	1855871-76-9	C34H38N2O4	538.68	No Development

							Reported
51	HY-N0457	Cichoric Acid	-13.141	6537-80-0	C22H18O12	474.37	No Development Reported
52	HY-102011	BMS-1166	-13.124	1818314-88-3	C36H33ClN2O7	641.11	No Development Reported
53	HY-129701	MCL-1/BCL-2-IN-3	-13.122	2163793-55-1	C27H25BrN2O5S	569.47	No Development Reported
54	HY-15300	Skepinone-L	-13.103	1221485-83-1	C24H21F2NO4	425.42	No Development Reported
55	HY-N0755	Rhoifolin	-13.068	17306-46-6	C27H30O14	578.52	No Development Reported
56	HY-103038	ML327	-13.06	1883510-31-3	C19H18N4O4	366.37	No Development Reported
57	HY-P1228	HAEGTFT	-13.057	926018-95-3	C33H47N9O12	761.78	No Development Reported
58	HY-100885	Acelarin	-13.041	840506-29-8	C25H27F2N4O8P	580.47	Phase 3
59	HY-	(S,R,S)-AHPC-C6-	-13.016	1835705-	C38H59ClN4O7S	751.42	No

	103605	PEG3-C4-Cl		55-9			Development Reported
60	HY-15148	Tipranavir	-12.958	174484-41-4	C31H33F3N2O5S	602.66	Launched
61	HY-10452	Ixazomib citrate	-12.92	1239908-20-3	C20H23BCl2N2O9	517.12	Launched
62	HY-100518	T-26c	-12.885	869296-13-9	C24H21N3O6S	479.51	No Development Reported
63	HY-P0098	[D-Ala2]leucine-enkephalin	-12.879	64963-01-5	C29H39N5O7	569.65	No Development Reported
64	HY-43961	E3 ligase Ligand 8	-12.831	1225383-33-4	C31H34N2O6	530.61	No Development Reported
65	HY-14736	Azilsartan (medoxomil)	-12.824	863031-21-4	C30H24N4O8	568.53	Launched
66	HY-50846	SCH772984	-12.813	942183-80-4	C33H33N9O2	587.67	No Development Reported
67	HY-103460	IRL 2500	-12.808	169545-27-1	C36H35N3O4	573.68	No Development Reported
68	HY-100493	BP-1-102	-12.79	1334493-07-0	C29H27F5N2O6S	626.59	No Development

							Reported
69	HY-N0184	Glycyrrhizic acid	-12.767	1405-86-3	C42H62O16	822.93	Launched
70	HY-14440	MP7	-12.752	1001409-50-2	C28H22F2N4O4	516.5	No Development Reported
71	HY-12647	GPR40 Activator 2	-12.69	1312787-30-6	C28H29NO6S2	539.66	No Development Reported
72	HY-19904	Adomeglivant	-12.681	1488363-78-5	C32H36F3NO4	555.63	Phase 2
73	HY-104037	Cintirorgon	-12.651	2055536-64-4	C27H23F6NO6S	603.53	Phase 2
74	HY-15836	BAY 87-2243	-12.648	1227158-85-1	C26H26F3N7O2	525.53	Phase 1
75	HY-128064	Adenosine amine congener	-12.647	96760-69-9	C28H32N8O6	576.6	No Development Reported
76	HY-100747	PSB-12379	-12.637	1802226-78-3	C18H23N5O9P2	515.35	No Development Reported
77	HY-77521	Dabigatran (ethyl ester hydrochloride)	-12.63	211914-50-0	C27H30ClN7O3	499.56	No Development Reported
78	HY-	EPZ004777	-12.623	1338466-	C28H41N7O4	539.67	No

	15227			77-5			Development Reported
79	HY-N2068	Didymin	-12.62	14259-47-3	C28H34O14	594.56	No Development Reported
80	HY-10396	Emricasan	-12.586	254750-02-2	C26H27F4N3O7	569.5	No Development Reported
81	HY-N0852	Benzoylpaeoniflorin	-12.572	38642-49-8	C30H32O12	584.57	No Development Reported
82	HY-100506	GLPG0187	-12.555	1320346-97-1	C29H37N7O5S	595.71	Phase 1
83	HY-129395	CC-92480	-12.543	2259648-80-9	C32H30FN5O4	567.61	Phase 2
84	HY-50938	D149 Dye	-12.478	786643-20-7	C42H35N3O4S3	741.94	No Development Reported
85	HY-15555	EPZ005687	-12.421	1396772-26-1	C32H37N5O3	539.67	No Development Reported
86	HY-B1028	Pantethine	-12.412	16816-67-4	C22H42N4O8S2	554.72	Phase 3
87	HY-10163	Dabigatran	-12.41	211914-51-1	C25H25N7O3	471.51	Phase 4

88	HY-10801	CAY10650	-12.352	1233706-88-1	C28H25NO6	471.5	No Development Reported
89	HY-15226	AZ505	-12.332	1035227-43-0	C29H38Cl2N4O4	577.54	No Development Reported
90	HY-103318	PD173212	-12.308	217171-01-2	C38H53N3O3	599.85	No Development Reported
91	HY-101295	Pan-RAS-IN-1	-12.272	1835283-94-7	C36H41Cl2F3N6O2	717.65	No Development Reported
92	HY-F0002	NADP (sodium salt)	-12.254	1184-16-3	C21H27N7NaO17P3	744.41	No Development Reported
93	HY-13803	Tazemetostat	-12.238	1403254-99-8	C34H44N4O4	572.74	Launched
94	HY-111594	Homo-PROTAC cereblon degrader 1	-12.213	2244520-98-5	C32H32N6O10	660.63	No Development Reported
95	HY-12678	Entrectinib	-12.209	1108743-60-7	C31H34F2N6O2	560.64	Launched
96	HY-128382	Brilliant Black BN	-12.193	2519-30-4	C28H17N5Na4O14S4	779.75	No Development Reported

97	HY-15835	CUDC-427	-12.178	1446182-94-0	C29H36N6O4S	564.7	Phase 1
98	HY-12492	VER-246608	-12.178	1684386-71-7	C28H23ClF2N4O4	552.96	No Development Reported
99	HY-10514	BX795	-12.168	702675-74-9	C23H26IN7O2S	591.47	No Development Reported
100	HY-101040	Q203	-12.123	1334719-95-7	C29H28ClF3N4O2	557.01	Phase 2
101	HY-15498	Rimegepant	-12.117	1289023-67-1	C28H28F2N6O3	534.56	Launched
102	HY-12425	DGAT1-IN-1	-12.101	1449779-49-0	C30H28F3N3O4	551.56	No Development Reported
103	HY-N0482	Acemetacin	-12.09	53164-05-9	$C_{21}H_{18}ClNO_6$	415.82	No Development Reported
104	HY-19320	Orexin 2 Receptor Agonist	-12.077	1796565-52-0	C32H34N4O5S	586.7	No Development Reported
105	HY-D0819	CY5-SE	-12.058	146368-14-1	C37H43N3O10S2	754.89	No Development Reported
106	HY-	ARRY-380 (analog)	-12.044	937265-	C29H27N7O4S	569.63	No

	10531			83-3			Development Reported
107	HY-17628	Cefiderocol	-12.02	1225208-94-5	C30H34ClN7O10S2	753.22	Launched
108	HY-100681	GSK2837808A	-12.014	1445879-21-9	C31H25F2N5O7S	649.62	No Development Reported
109	HY-112588	dBET6	-12.006	1950634-92-0	C42H45ClN8O7S	841.37	No Development Reported
110	HY-12305	Q-VD-OPh	-11.99	1135695-98-5	C26H25F2N3O6	513.49	No Development Reported
111	HY-15372	GW 6471	-11.988	880635-03-0	C35H36F3N3O4	619.67	No Development Reported
112	HY-122562	MT-802	-11.986	2231744-29-7	C41H41N9O8	787.82	No Development Reported
113	HY-111453	AZD7594	-11.98	1196509-60-0	C32H32F2N4O6	606.62	Phase 2
114	HY-101803	CP671305	-11.929	445295-04-5	C23H19FN2O7	454.4	No Development Reported
115	HY-	LV-320	-11.928		C29H26ClNO2S2	520.11	No

	112711						Development Reported
116	HY-104077	Remdesivir	-11.917	1809249-37-3	C27H35N6O8P	602.58	Phase 3
117	HY-130246	NF-56-EJ40	-11.914	2380230-73-7	C27H29N3O3	443.54	No Development Reported
118	HY-14792B	Inolitazone (dihydrochloride)	-11.91	223132-38-5	C27H28Cl2N4O4S	502.58	Phase 2
119	HY-114228	PROTAC BET degrader-2	-11.905	2093388-33-9	C41H42N10O6	770.84	No Development Reported
120	HY-P0073	Tyr-Gly-Gly-Phe-Met-OH	-11.903	58569-55-4	C27H35N5O7S	573.66	No Development Reported
121	HY-19883	Lusutrombopag	-11.86	1110766-97-6	C29H32Cl2N2O5S	591.55	Launched
122	HY-15745	PSI-7409	-11.847	1015073-42-3	C10H16FN2O14P3	500.16	No Development Reported
123	HY-14914	Azilsartan	-11.828	147403-03-0	C25H20N4O5	456.45	Launched
124	HY-13463	Avatrombopag	-11.804	570406-98-3	C29H34Cl2N6O3S2	649.65	Launched
125	HY-	Bafetinib	-11.792	859212-	C30H31F3N8O	576.62	Phase 2

	50868			16-1			
126	HY-19741	A-1331852	-11.782	1430844-80-6	C38H38N6O3S	658.81	No Development Reported
127	HY-17376	Ezetimibe	-11.774	163222-33-1	C24H21F2NO3	409.43	Launched
128	HY-10941	VER-155008	-11.765	1134156-31-2	C25H23Cl2N7O4	556.4	No Development Reported
129	HY-120635	BMS-1001 (hydrochloride)	-11.764	2113650-04-5	C35H35ClN2O7	594.65	No Development Reported
130	HY-10922	Camicinal	-11.743	923565-21-3	C25H33FN4O	424.55	Phase 2
131	HY-18972	PLX8394	-11.742	1393466-87-9	C25H21F3N6O3S	542.53	Phase 2
132	HY-N2522	Carboxyatractyloside (dipotassium)	-11.737	33286-30-5	C31H44K2O18S2	770.82	No Development Reported
133	HY-15830	25,26-Dihydroxyvitamin D3	-11.731	29261-12-9	C27H44O3	416.64	No Development Reported
134	HY-13955	Telmisartan	-11.716	144701-48-4	C33H30N4O2	514.62	Launched
135	HY-	MYCi361	-11.715	2289690-	C26H16ClF9N2O2	594.86	No

	129600			31-7			Development Reported
136	HY-10450	Dapagliflozin	-11.691	461432-26-8	C21H25ClO6	408.87	Launched
137	HY-13245	PF-4136309	-11.664	1341224-83-6	C29H31F3N6O3	568.59	No Development Reported
138	HY-18007	ALW-II-41-27	-11.648	1186206-79-0	C32H32F3N5O2S	607.69	No Development Reported
139	HY-123844	dBET57	-11.632	1883863-52-2	C34H31ClN8O5S	699.18	No Development Reported
140	HY-D0965	Procion Blue HB	-11.619	12236-82-7	C29H20ClN7O11S3	774.16	No Development Reported
141	HY-100619	BMS-986020	-11.616	1257213-50-5	C29H26N2O5	482.53	Phase 2
142	HY-101785	eIF4A3-IN-2	-11.614	2095677-20-4	C25H19Br2ClN4O2	602.71	No Development Reported
143	HY-111386	E-7386	-11.61	1799824-08-0	C39H48FN9O4	725.85	Phase 1
144	HY-32709	Telcagepant	-11.588	781649-09-0	C26H27F5N6O3	566.52	Phase 3

145	HY-13057	O6BTG-octylglucoside	-11.576	382607-78-5	C24H34BrN5O7S	616.53	No Development Reported
146	HY-129681	MCL-1/BCL-2-IN-1	-11.571		C31H27BrN2O3S	587.53	No Development Reported
147	HY-122826	ZXH-3-26	-11.57	2243076-67-5	C38H37ClN8O7S	785.27	No Development Reported
148	HY-13315	Montelukast (sodium)	-11.549	151767-02-1	C35H35ClNNaO3S	586.18	Launched
149	HY-10095	Olcegepant	-11.545	204697-65-4	C38H47Br2N9O5	869.65	Phase 2
150	HY-13979	DDR1-IN-1	-11.537	1449685-96-4	C30H31F3N4O3	552.59	No Development Reported
151	HY-100947	VH-298	-11.533	2097381-85-4	C27H33N5O4S	523.65	No Development Reported
152	HY-15623	Hoechst 33258 analog	-11.528	258843-62-8	C29H30N6O3	510.59	No Development Reported
153	HY-16961	Sitravatinib	-11.523	1123837-84-2	C33H29F2N5O4S	629.68	Phase 3
154	HY-	Dabigatran (ethyl	-11.522	429658-	C27H29N7O3	499.56	No

	17378	ester)		95-7			Development Reported
155	HY-B0955	Oxethazaine	-11.512	126-27-2	C28H41N3O3	467.64	Launched
156	HY-D0721	6-CFDA	-11.484	########	C25H16O9	460.39	No Development Reported
157	HY-70035	Otamixaban	-11.483	193153-04-7	C25H26N4O4	446.5	Phase 3
158	HY-19708	KIRA6	-11.479	1589527-65-0	C28H25F3N6O	518.53	No Development Reported
159	HY-17492	Zafirlukast	-11.474	107753-78-6	C31H33N3O6S	575.68	Launched
160	HY-B1396	Nefazodone (hydrochloride)	-11.473	82752-99-6	C25H33Cl2N5O2	470.01	Launched
161	HY-116677	Tris (benzyltriazolylmethyl) amine	-11.451	510758-28-8	C30H30N10	530.63	No Development Reported
162	HY-114263	NXT629	-11.451	1454925-59-7	C35H39N5O3S	609.78	No Development Reported
163	HY-16994	OICR-0547	-11.45	1801873-49-3	C28H29F3N4O4	542.55	No Development Reported

164	HY-125815	Reactive Blue 4	-11.449	13324-20-4	C23H14Cl2N6O8S2	637.43	No Development Reported
165	HY-N0243	Theaflavin	-11.445	########	C29H24O12	564.49	No Development Reported
166	HY-12090	Anacetrapib	-11.437	875446-37-0	C30H25F10NO3	637.51	Phase 3
167	HY-P0275	Proctolin	-11.429	57966-42-4	C30H48N8O8	648.75	No Development Reported
168	HY-101838	dBET1	-11.402	1799711-21-9	C38H37ClN8O7S	785.27	No Development Reported
169	HY-19988	THZ1-R	-11.399	1621523-07-6	C31H30ClN7O2	568.07	No Development Reported
170	HY-13262	Lumacaftor	-11.394	936727-05-8	C24H18F2N2O5	452.41	Launched
171	HY-N2331	Proscillaridin A	-11.392	466-06-8	C30H42O8	530.65	No Development Reported
172	HY-128604	XY101	-11.369	2349368-16-5	C25H20F7NO4S	563.48	No Development Reported

173	HY-109078	Vecabrutinib	-11.363	1510829-06-7	C22H24ClF4N7O2	529.92	Phase 2
174	HY-13041	LX-1031	-11.352	945976-76-1	C28H25F3N4O4	538.52	Phase 2
175	HY-16782	Pexmetinib	-11.349	945614-12-0	C31H33FN6O3	556.63	Phase 2
176	HY-N1401	20(R)-Ginsenoside Rh2	HY-N1401	112246-15-8	$C_{36}H_{62}O_8$	622.87	No Development Reported
177	HY-15102	MK-0429	-11.335	227963-15-7	C23H29N5O4	439.51	No Development Reported
178	HY-N1401	20(R)-Ginsenoside Rh2	-11.334	112246-15-8	C36H62O8	622.87	No Development Reported
179	HY-12280	THZ2	-11.332	1604810-84-5	C31H28ClN7O2	566.05	No Development Reported
180	HY-12325	GSK2194069	-11.331	1332331-08-4	C25H24N4O3	428.48	No Development Reported
181	HY-50691	GW-1100	-11.329	306974-70-9	C27H25FN4O4S	520.58	No Development Reported
182	HY-	THZ1	-11.311	1604810-	C31H28ClN7O2	566.05	No

	80013			83-4			Development Reported
183	HY-100185	SAR-100842	-11.304	1195941-38-8	C27H27NO5	445.51	Phase 2
184	HY-126216	TAM-IN-2	-11.301	2135642-56-5	C31H27F2N7O3	583.59	No Development Reported
185	HY-15306	Eltrombopag	-11.296	496775-61-2	C25H22N4O4	442.47	Launched
186	HY-100337	WWL70	-11.295	947669-91-2	C27H23N3O3	437.49	No Development Reported
187	HY-101772	Ziritaxestat	-11.291	1628260-79-6	C30H33FN8O2S	588.7	Phase 3
188	HY-D0722	5(6)-CFDA	-11.289	124387-19-5	C25H16O9	460.39	No Development Reported
189	HY-13990	NVP-TNKS656	-11.26	1419949-20-4	C27H34N4O5	494.58	No Development Reported
190	HY-11999	CGI-1746	-11.259	910232-84-7	C34H37N5O4	579.69	No Development Reported
191	HY-112679	GLP-1 receptor agonist 2	-11.25	2230197-64-3	C30H31ClFN5O4	580.05	No Development

							Reported
192	HY-16040	AM095 (free acid)	-11.241	1228690-36-5	C27H24N2O5	456.49	No Development Reported
193	HY-108886	JWG-071	-11.239	2250323-50-1	C34H44N8O3	612.77	No Development Reported
194	HY-19608	GSK1016790A	-11.208	942206-85-1	C28H32Cl2N4O6S2	655.61	No Development Reported
195	HY-112587	MC3482	-11.2		C33H38N4O8	618.68	No Development Reported
196	HY-12744	Genz-123346 (free base)	-11.197	491833-30-8	C24H38N2O4	418.57	No Development Reported
197	HY-10425	A-443654	-11.196	552325-16-3	C24H23N5O	397.47	No Development Reported
198	HY-16975	SH-4-54	-11.189	1456632-40-8	C29H27F5N2O5S	610.59	No Development Reported
199	HY-13406	TAK-779	-11.187	229005-80-5	C33H39ClN2O2	495.67	No Development Reported

200	HY-105685	SRX246	-11.186	512784-93-9	C42H49N5O5	703.87	Phase 2

HepG2 cells treated with top 100 compounds at 10uM which were screened for drug activity by molecular docking (see Annex I for detailed data)

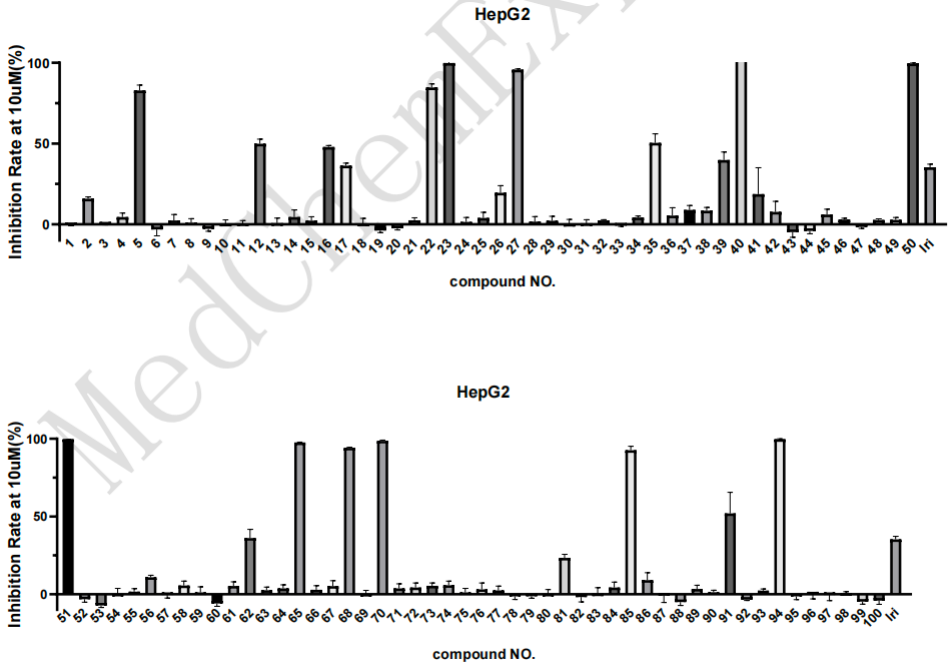


Figure 4: HepG2 cells treated with top 100 compounds at 10uM.

The initial screening results showed that 20 out of the 100 compounds had significant growth of HepG2 cells at 10 M concentration

As a potentially effective anticancer drug, its action at the cellular level is also very important, at least not greater than 10um. Therefore, we detected the effects of the top 100 compounds on the proliferation level of HepG2 cells at a dose of 10um. The top 100 compounds are listed in the extend table. The initial screening results showed that 20 out of the 100 compounds had significant growth of HepG2 cells at 10 uM concentration, and the following 12 compounds had the strongest inhibition on HepG 2 cells (more

than 80%).

Table 2: 12compounds had the strongest inhibition on HepG 2 cells (more than 80%).

Number	Cat.No.	Name	inhibition rate(mean value)(%)
5	HY-50877	GSK 461364	82.86
22	HY -100506	G LPG 0187	84.77
23	HY16961	Si travatinib	99.88
27	HY10454	Del anzomib	95.72
40	HY12678	Entr ectinib	100.35
50	HY13905	Flu matinib(mesylate)	99.63
51	HY10521	Darapladib	99.64
65	HY10452	Ixazom ib citrate	97.58
68	HY16782	Pexme tinib	94.14
70	HY -12113	Oprozomib	98.65
85	HY-32721	Nera tinib	92.61
94	HY14667	Lomit apide	99.66

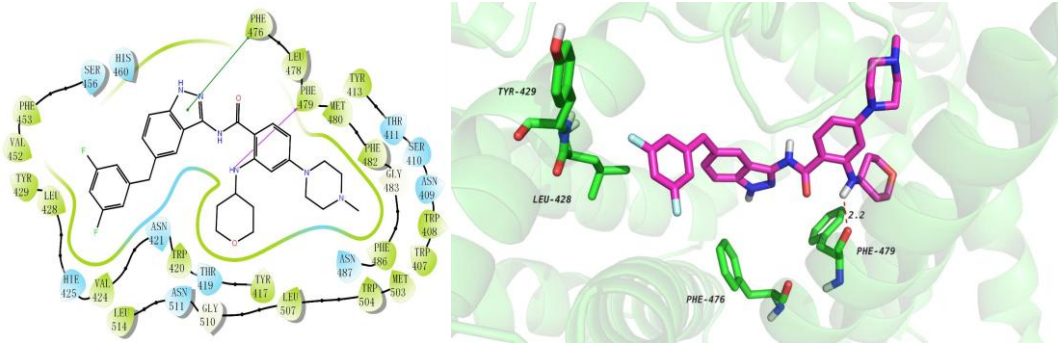
The following 8 compounds have a significant inhibitory effect on HepG 2 cells (the inhibition rate is greater than 20%).

Table 3: 8 compounds have a significant inhibitory effect on HepG 2 cells (the inhibition rate is greater than 20%).

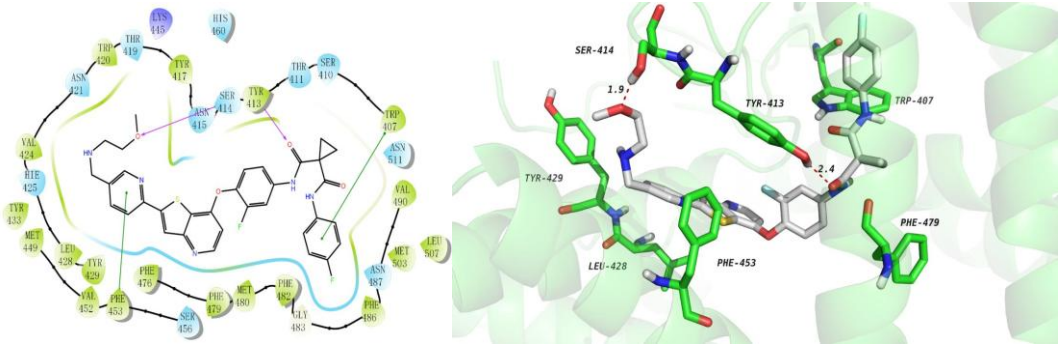
Number	Cat.No.	Name	inhibition rate (mean value) (%)
12	HY - 111407	MK -8353	49.87
16	HY - 111386	E -7386	47.84
17	HY - 100885	Acelarin	36.32
35	HY - 50868	Baf etinib	50.44
39	HY - 101772	Zir itaxestat	39.85
62	HY - 75839	Dronedarone (Hydrochloride)	36.16
81	HY - 13299	MK -8033	23.42

Computer molecular docking was performed on the top five compounds

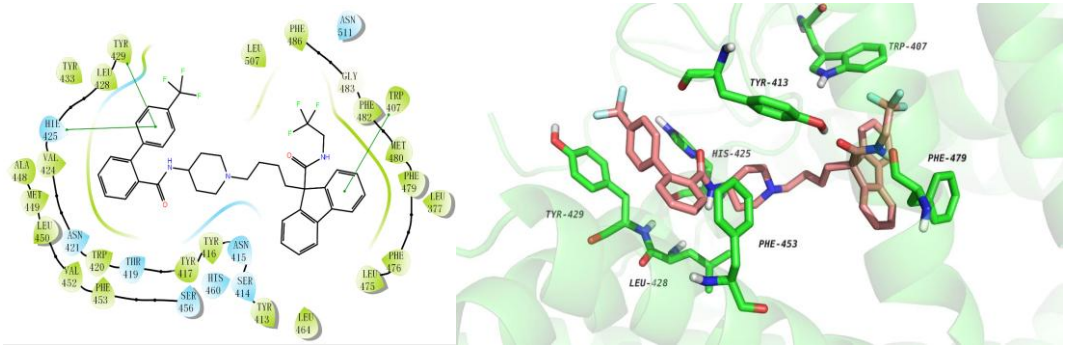
Among the 20 compounds screened by the above method, we selected the listed compounds to conduct molecular docking with SOAT1 again. The top 5 compounds with docking score were screened by this method, as shown below.



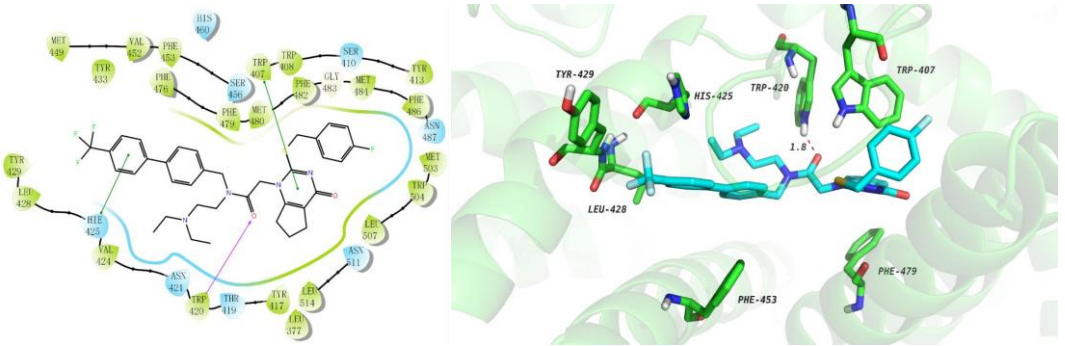
A. HY-12678 Docking score: -12.209.



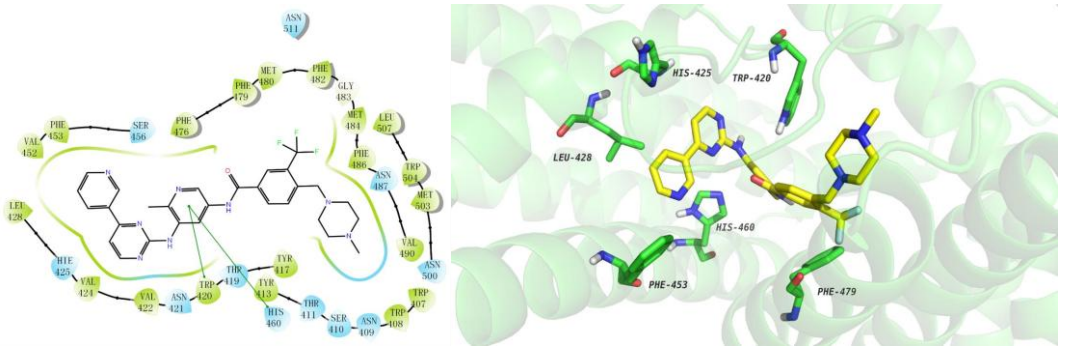
B. HY-16961 Docking score: -11.523



C. HY-14667 Docking score: -10.665



D. HY-10521Docking score: -13.7479



E. HY-13905 Docking score: -11.166

Figure 5: Top five compounds by computer molecular docking.

Supplementary Table 1: The following figure is a bar chart of the inhibition rate at 100 drug concentrations at 10 M (see Table 1 for detailed data).

	Cat.No.	Name	CAS No.	M.Wt	inhibition rate(mean value) (%)	S TD
1	HY -	Keta nserin	74050-98-	395.43	-0.53	0.35

	10562		9			
2	HY - 109078	V ecabrutinib	1510829-06-7	529.92	15.94	1.03
3	HY - 17492	Zafir lukast	107753-78-6	575.68	-0. 10	0.25
4	HY - 16973	F luralaner	864731-61-3	556.29	4.5	2.46
5	HY - 50877	GSK 461364	9.29E+08	543.6	82.86	3.33
6	HY - 103683	PF -06409577	1467057-23-3	341.79	-3.2	3.89
7	HY - 15306	El trombopag	496775-61-2	442.47	2.42	3.67
8	HY - 14181	Cinacig uat	329773-35-5	565.7	1.06	2.5
9	HY - 13955	Telmisa rtan	144701-48-4	514.62	-2.79	1.45
10	HY - 13803	Tazemeto stat	1403254-99-8	572.74	0.41	2.39
11	HY - 15337	Hes peridin	520-26-3	610.56	0.59	1.7
12	HY - 111407	MK -8353	1184173-73-6	691.84	49.87	2.89
13	HY - 19904	Ado meglivant	1488363-78-5	555.63	0.8	3.05

14	HY - 15516	Sotagliflozi n	1018899-041	424.94	4.54	4.4
15	HY - 15835	C UDC -427	1446182-94-0	564.7	2.37	2.32
16	HY - 111386	E -7386	1799824-08-0	725.85	47.84	0.99
17	HY - 100885	Acel arin	840506-29-8	580.47	36.32	1.56
18	HY - 10450	Dapagl iflozin	461432-26-8	408.87	0.45	3.27
19	HY - 101040	Q 203	1334719-95-7	557.01	-3.81	1.3
20	HY - 13262	Lum acaftor	936727-05-8	452.41	-2.41	1.04
21	HY - 70035	Otamixaban	193153-04-7	446.5	2.51	1.54
22	HY - 100506	GLPG 0187	1320346-971	595.71	84.77	2. 14
23	HY - 16961	Sitravatinib	1123837-84-2	629.68	99.88	0.2
24	HY -N 0482	Phillyrin	487-41-2	534.55	1.49	2.81
25	HY -B 1904	Fluphenazine decanoate	5002-471	591.77	3.98	3.53
26	HY -	Flum atinib	895519-	562.59	19.53	4.45

	13904		901			
27	HY - 10454	Delan zomib	847499-27-8	413.28	95.72	0.47
28	HY - 101056	Bre nsocatib	1802148-05-5	420.46	1.73	3.09
29	HY - 10562A	Ketanserin (tartrate)	83846-83-7	545.51	2.2	2.75
30	HY - 13041	LX1031	945976-761	538.52	0.34	2.73
31	HY - 100459	GSK 3179106	1627856-64-7	467.41	0.68	2. 17
32	HY - 109565	ASTX 660	1799328-861	539.68	2.44	0.47
33	HY - 111453	V elsecorat	1196509-60-0	606.62	-0.8	0.46
34	HY -N 0178	Dios min	520-27-4	608.54	4.22	0.94
35	HY - 50868	Baf etinib	8.59E+08	576.62	50.44	5.57
36	HY - 19883	Lus utrombopag	1110766-97-6	591.55	5.41	4.88
37	HY - 109035	In arigivir soproxil	942123-43-5	703.62	8.93	2.76
38	HY - 100619	BMS -986020	1257213-50-5	482.53	8.48	2

39	HY - 101772	Ziri taxestat	1628260-79-6	588.7	39.85	4.88
40	HY - 12678	En trectinib	1108743-60-7	560.64	100.35	0.32
41	HY - 13315	Montelukast(sodium)	151767-021	608. 17	18.7	16.36
42	HY - 105685	SR X 246	512784-93-9	703.87	7.7	6.54
43	HY - 106139	Bimosi amose	187269-40-5	862.91	-4.78	3.26
44	HY -B 2087	Glycerol p henylbutyrate	611168-24-2	530.65	-4.06	1.76
45	HY - 15836	BAY 87-2243	1227158-851	525.53	6.08	3.26
46	HY - 106910	Saredutant	142001-63-6	552.53	3	0.76
47	HY - 15498	Rimeg epant	1289023-671	534.56	-1.65	0.89
48	HY - 100419	BFH 772	890128-811	439.39	2.67	0.76
49	HY - 12090	Ana cetrapib	875446-37-0	637.51	2.76	1.53
50	HY - 13905	Fl umatinib (mesylate)	895519-91-2	658.69	99.63	0.2
51	HY -	Dar apladib	356057-	666.77	99.64	0.07

	10521		34-6			
52	HY - 10095	Olcegepa nt	204697-65-4	869.65	-3. 16	1.9
53	HY - 32709	Telcagep ant	781649-09-0	566.52	-7. 19	1.28
54	HY - 10127	Baras ertib	722543-31-9	587.54	0.27	3.53
55	HY - 50898	Lapat inib	231277-92-2	581.06	1.7	1.93
56	HY -B 0955	Oxethaza ine	126-27-2	467.64	10.95	1.31
57	HY - 103088	E 7046	1369489-71-3	483.39	-0.41	1.99
58	HY - 15185	N irogacestat	1290543-63-3	489.64	5.65	2.86
59	HY - 12355	Si ponimod	1230487-00-9	516.6	1. 19	3.6
60	HY - 15148	Tiprana vir	174484-41-4	602.66	-5.91	1.81
61	HY -N 0184	Glycyrrhi zic acid	1405-86-3	822.93	5.39	2.63
62	HY - 75839	Dr onedarone (Hydr ochloride)	141625-93-6	593.22	36. 16	5.6
63	HY -B 1028	Pa ntethine	16816-67-4	554.72	2.6	2.03

64	HY -N 0318	Salvian olic acid A	96574-01-5	494.45	3.76	2.33
65	HY - 10452	Ixazo mib citrate	1239908-20-3	517. 12	97.58	0.23
66	HY - 15440A	Foste msavir	864953-29-7	583.49	2.91	2.64
67	HY -N 0139	Troxeru tin	7085-55-4	742.68	5.24	3.49
68	HY - 16782	Pexme tinib	94561412-0	556.63	94. 14	0.42
69	HY - 14736	Azi lsartan medoxomil	863031-21-4	568.53	0.24	2.3
70	HY - 12113	Oprozo mib	935888-69-0	532.61	98.65	0.49
71	HY - 10922	Camicina l	923565-21-3	424.55	3.82	2.94
72	HY - 104037	Cinti rorgon	2055536-64-4	603.53	4.3	2.97
73	HY - 14792B	Ino litazone (dihy drochloride)	223132-38-5	575.51	5.41	1.91
74	HY -B 1396	Nefa zodone (hydro chloride)	82752-99-6	506.47	5.85	2.63
75	HY - 125286	AB -680	2105904-821	580.82	1.27	2.48
76	HY -	Foste msavir Tris	864953-	704.62	3. 15	4. 16

	15440B		39-9			
77	HY -B 0584	Trav oprost	157283-68-6	500.55	2.53	2.76
78	HY - 14914	Azi lsartan	147403-03-0	456.45	-1.35	2
79	HY - 117571	Zato lmilast	1606974-33-7	405.8	-1.22	1.3
80	HY - 17376	Ezetim ibe	163222-331	409.43	0.3	2.77
81	HY - 13299	MK -8033	1001917-37-8	471.53	23.42	2.28
82	HY -B 1090	Cinn arizine	298-57-7	368.51	-1.77	3. 10
83	HY - 15196	TA K -285	871026-44-7	547.96	0.49	3.76
84	HY - 10320	Doram apimod	285983-48-4	527.66	4.36	3.44
85	HY - 32721	Ne ratinib	698387-09-6	557.04	92.61	2.59
86	HY - 13501	M ubritinib	366017-09-6	468.47	9. 13	4.73
87	HY - 15463	Imati nib	152459-95-5	493.6	-0.88	4.39
88	HY - 13055A	Telot ristat ethyl	1033805-22-9	574.98	-4.99	2.24

89	HY - 107456	E 6130	1427058-33-0	556.06	3.41	2.39
90	HY - 50683	JNJ -38877605	943540-75-8	377.35	1.28	1.28
91	HY -B 0674	Eb astine	90729-43-4	469.66	52.03	13.57
92	HY - 112723	ACT-709478	1838651-58-3	425.41	-3.42	0.57
93	HY - 16974	Afo xolaner	1093861-60-9	625.87	2.31	1. 11
94	HY - 14667	Lom itapide	18243112-5	693.72	99.66	0.25
95	HY - 10240	M ericitabine	940908-79-2	399.41	-1.29	2. 15
96	HY - 15651	Alve lestat	84814111-7	545.53	-0.04	2.96
97	HY - 19344	Lifit egrast	1025967-78-5	615.48	-0.38	3.74
98	HY - 19436	Solabegron	252920-94-8	410.89	0.65	1.08
99	HY -B 0645	Prednisolone (disodium phosphate)	125-02-0	484.39	-4.74	1.63
100	HY -W 013093	Uridine triphosphate (trisodium salt)	19817-92-6	550.09	-4. 12	2.31
PC	HY -	Iri notecan	100286-	586.69	35.37	1.93

	16562A		90-6			

Discussion

SOAT1 is involved in the storage of cholesterol esters, free absorption of cholesterol and lipoprotein synthesis. SOAT contains two enzymes, SOAT1 and SOAT2, but the differences between these two enzymes remain controversial. It has been shown that in adult liver, SOAT1 is the main enzyme with higher expression levels than SOAT 2 and plays a more important role in cholesterol homeostasis. Sterol O-acyltransferase 1 (SOAT1), also known as acyl-coenzyme A Cholesterol Acyl Transferase (ACAT 1), is a membrane-binding protein that uses long-chain fatty acyl coenzyme A to cholesterol to form cholesterol ester and coenzyme A **[1].** The role of SOAT1 in cancer becomes another area of interest, which makes SOAT1 gradually become a potential target for the treatment of multiple human diseases. With the development of cryo-electron microscopy, the structure of Soat1 was elucidated. Structural studies of Human SOAT1 suggest that oleoCoA is surrounded by two conserved residues of Human SOAT1, Asn 421 and His 460. His 460 is highly conserved among the enzymes of the MBOAT family and has been shown to be essential for catalytic activity **[9].** The mutation of the asparagine at position 421 of the ACAT1 enzyme to alanine that causes inactivation of the ACAT1 enzyme suggests that Asn 421 is important for the catalytic activity of Human SOAT1 and that Asn421 is in turn the second enzymatic active site of Human SOAT1 **[10].** Therefore, this project is based on computer virtual screening based on the region where N 421 / H 460 of Human SOAT1 protein is located Selected, expect to obtain small molecule compounds with strong binding force to the target protein. The structure, scoring values and compound supplementary information of the top 200 Discovery Diversity Set 50 and MCE Library top 200 compounds are found in our study, respectively. We also statistic the molecular docking scores. The higher the absolute value of (docking_score), the stronger the binding force of the compound and the protein. Attxes 1.1 and 2.1 are sdf files, attachments 1.2 and 2.2 containing structure, goods number, docking score, and attachments 1.3 and 2.3 are Excel tables containing details of compounds. The Excel table includes Chemical Names (chemical name), MW (molecular weight), clogP (lipid water distribution coefficient indicates the lipid solubility and water solubility of the compound. The larger the value indicates the better the fat solubility, the smaller or even negative value indicates the better the water solubility), Rotating Bonds (number of rotatable keys), TPSA (topological polar surface area, PSA estimated value. Compounds with PSA greater than 140 Angstroms square tend to be poor when permeabilizing cell membranes, while compounds with PSA less than 60 Angstroms square usually perform well when permeating cell membranes), HB Acceptor (Hydrogen Bond Acceptor, hydrogen bond receptor), HB Donor (hydrogen bond donor), FSP 3 hybridization, etc. Attachment 2.3 The MCE Library form contains the Cas.No, Formula (structure), Clinical Information (clinical information) and other data. As described in Yan Ning et al. **[8]** research of structure of Human SOAT1, in each dimer, two monomers show approximately C2 symmetry around the axis perpendicular to the membrane plane, while dimerization is mainly mediated by the formation of extensive van der Waals interactions between TM 1 of one monomer and the luminal segment of TM 6 and the cytoplasmic segment of TM 9. Each TM1 fragment consists of the remaining T M domains of relative monomers. Two monomers of TM1, TM5, TM6 and TM9 coat a deep hydrophobic sac that opens to the lumen side, consisting of numerous hydrophobic residues on TM 6 and a monomer on TM9 versus TM1 from another monomer (labeled TM1) The hydrophobic residues are formed by the contact of

the. Within the cell, the hydrophobic residues on each monomer IH1 interact to stabilize the dimer. Virtual screening is Schrodinger Maestro 11.4, and the 3D mapping software is PyMol in our study. After computer molecular docking, 100 optimal compounds were screened out as shown in **Table 1.** HepG2 cells treated with top 100 compounds at 10uM which were screened for drug activity by molecular docking in **Figure 4.** 12compounds had the strongest inhibition on HepG 2 cells (more than 80%) as shown in **Table 2.** We have a choice of 5 preferred compounds act on Human SOAT1 protein as shown in result **Figure 5** with -13.7479, -12.209, -11.523, -11.166 and -10.665, respectively. We also found 8 compounds have a significant inhibitory effect on HepG 2 cells (the inhibition rate is greater than 20%) in Table3. In the 3D figure, the C skeleton of Human SOAT1 protein is shown in green, the N atom is shown in blue, and the O atom is shown in red, H atoms are shown as white and HY-12678 as rose stick in **Figure 5A.** Hydrogen bond lengths are shown in red dotted lines, bond lengths. The longer the hydrogen bond, the weaker the hydrogen bond. Hy-12678 can form one hydrogen bond with Human SOAT1 protein, one π-π action and multiple hydrophobic interactions. NH linked to the tetrahydropyran ring can form one hydrogen bond with PHE479 as a hydrogen bond donor. The distance is 2.2a; Pyrazole ring can form a π-π interaction with PHE476. In addition, HY-12678 can form multiple hydrophobic interactions with residues such as LEU428, VAL452, PHE479 and LEU478. The C skeleton of Human SOAT1 protein is shown in green, the N atom is shown in blue, and the O atom is shown in Red, H atoms shown as white, and HY-16961 as gray stick in **Figure 5B.** Hydrogen bond lengths are shown in red dotted lines, bond lengths. The longer the hydrogen bond, the weaker the hydrogen bond. Hy-16961 can form two hydrogen bonds, two π-π interactions and multiple hydrophobic interactions with Human SOAT1 protein. One amide bond carbonyl group acts as hydrogen bond receptor and forms one hydrogen bond with TYR4132.4 A; The oxygen atom at the end of Linker acts as hydrogen bond acceptor to form A hydrogen bond with SER414 at A distance of 1.9 A. The 4-fluorophenyl group can form a π-π interaction with TRP407. Pyridine ring can form a π-π interaction with PHE453. In addition, HY-16961 acts hydrophobic with residues such as LEU428, TYR429, PHE476 and PHE482. The C skeleton of Human SOAT1 protein is shown in green, N atom is shown in blue, O atom is shown in bright red, H atom is shown in white, and HY-14667 is shown in bean paste color stick in **Figure 5C.** Hydrogen bond lengths are shown as red dashed lines. The longer the bond length, the weaker the hydrogen bond. Hy-14667 had three π-π interactions with Human SOAT1 protein and many hydrophobic interactions. The 4-trifluoromethyl phenyl group had two π-π interactions with HIS425 and TYR429. The benzene ring of fluorene group on the other side can form a π-π interaction with TRP407. In addition, HY-14667 can form hydrophobic interaction with TYR429, LEU428, PHE453, PHE479, TRP407, TYR413 and other amino acid residues. The C skeleton of Human SOAT1 protein is shown in green, N atom is shown in blue, O atom is shown in bright red, H atom is shown in white, and HY-10521 is shown in light blue stick in **Figure 5D.** Hydrogen bond lengths are shown as red dashed lines. The longer the bond length, the weaker the hydrogen bond. Hy-10521 can form one hydrogen bond with Human SOAT1 protein, two π-π interactions and multiple hydrophobic interactions. The amide bond carbonyl group acts as hydrogen bond receptor and forms one hydrogen bond with TRP420 at A distance of 1.8 A. The 4-trifluoromethyl phenyl group can form a π-π interaction with HIS425. The pyrimidine group can form a π-π interaction with TRP420. In addition, HY-10521 can be associated with TYR429, LEU428, PHE453, PHE479, TRP407, TYR413Isoamino acid residues form hydrophobicity. The C skeleton of Human SOAT1 protein is shown in green, N atom is shown in blue, O atom is shown in bright red, H atom is shown in white, and HY-13905 is shown in light yellow stick in **Figure 5E.** Hydrogen bond lengths are shown as red dashed lines. The longer the bond

length, the weaker the hydrogen bond. Hy-13905 could form two π-π interactions and multiple hydrophobic interactions with Human SOAT1 protein. The pyridine group in the middle could form two π-π interactions with TRP420 and HIS460. The compounds can form hydrophobic interactions with residues such as LEU428, VAL452, PHE453, PHE479, PHE482, TRP407 and TYR413. In the next step, the five compounds screened above can be further verified to determine their inhibitory effect on HCC cells and provide reference for clinical application. The limitation of this study is that the effects of the three small molecular compounds screened on the proliferation, migration, invasion and other abilities of tumor cells were not proved experimentally, which is also one of our next work. This study contributes to find small molecule compounds with strong binding force to SOAT1 providing small molecule compounds that may be useful for the treatment of multiple tumors.

References

1. Hofmann Kay. A superfamily of membrane -bound O -acyltransferases with implications for wnt signaling. Trends Biochem Sci. 2000;25(3):111-112.
2. Zhang Yufang. Analysis of the e-QTL localization and genetic regulation network of Soat1 gene. Jiangsu Med. 2014;40(2):135-7.
3. Shibuya Y, Chang CC, Chang TY. ACAT1/SOAT1 as a therapeutic target for Alzheimer's disease. Future Med Chem. 2015;7(18):2451-67.
4. Jiang Y. Proteomics identifies new therapeutic targets of early-stage hepatocellular carcinoma. Nature. 2019;567(7747):257-61.
5. Li J. Abrogating cholesterol esterification suppresses growth and metastasis of pancreatic cancer. Oncogene. 2016;35(50):6378-88.
6. Yue S. Cholesteryl ester accumulation induced by PTEN loss and PI3K/AKT activation underlies human prostate cancer aggressiveness. Cell Metab. 2014;19(3):393-406.
7. Yang W. Potentiating the antitumour response of CD8+ T cells by modulating cholesterol metabolism. Nature. 2016;531(7596):651-5.
8. Qian Hongwu. Structural basis for catalysis and substrate specificity of human ACAT 1. Nature. 2020;581(7808):333-8.
9. Guo Zhan -Yun. The active site His-460 of human acyl-coenzyme A: cholesterol acyltransferase 1 resides in a hith erto undisclosed transmembrane domain. J Biol Chem. 2005;280(45):37814-26.
10. Yu Chunjiang. Role of the N -terminal hydrophilic domain of acyl - coenzyme A: cholesterol acyltransferase 1 on the enzyme 's quaternary structure and catalytic efficiency. Biochemistry. 2002;41(11):3762-9.

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