Table SI. Genes correlated with RTKN2 in cholangiocarcinoma.

RTKN2-correlated genes	Spearman's correlation coefficient	q-Value
ARID5B	0.82521	$3.64\text{x}10^{-05}$
CLEC2D	0.787955	0.000327
UQCRFS1	-0.76947	0.000746
MME	0.757423	0.001092
GPR19	0.754902	0.001092
MAMSTR	0.75098	0.001145
DGKA	0.744538	0.001385
ARHGEF19	0.742577	0.001385
LINC00636	0.735006	0.001866
TSHR	0.729848	0.002182
MYB	0.728291	0.002182
NHERF1	-0.71821	0.003356
TIMM10	-0.70672	0.005439
WWC1	-0.70364	0.005848
KLHDC7A	-0.70168	0.005986
ATP5MC3	-0.69608	0.007026
KLRG1	0.695518	0.007026
FAM110A	0.691597	0.007801
TNFRSF13C	0.690756	0.007801
COX7B	-0.68739	0.008609
DNAJB13	0.677638	0.012531
YES1P1	0.67274	0.014713
RBP1	0.670588	0.015037
NDUFS3	-0.67003	0.015037
C17ORF100	0.668067	0.015037
HOXA1	0.667787	0.015037
LYPD3	0.666947	0.015037
SLC37A4	-0.66639	0.015037
FOXO3B	0.664706	0.015548
TMPO	0.663866	0.015551
BPIFB1	0.661247	0.016501
GPAT2	0.660504	0.016501
ZNF821	0.659664	0.016501
LRRIQ3	0.658543	0.016501
MSANTD2	0.658543	0.016501
NYNRIN	0.655742	0.017487
FAM216B	0.655668	0.017487
C10ORF88B	0.654062	0.018133
IGSF10	0.652567	0.018728
POC1B-GALNT4	0.647104	0.021647
DAAM2-AS1	0.646544	0.021647
HIVEP2-DT	0.646218	0.021647

UBE3D	0.645098	0.021647
LINC02014	0.644982	0.021647
NUDT4	0.643137	0.021647
TEX26-AS1	0.643094	0.021647
ECSIT	-0.64258	0.021647
NDUFA4	-0.64258	0.021647
LINC02021	0.641176	0.021647
HOTAIRM1	0.640616	0.021647
RARG	0.640616	0.021647
HOXD8	0.640336	0.021647
PLCB4	0.640056	0.021647
TMPRSS13	0.640056	0.021647
TCEA3	-0.63922	0.021647
CEMIP	0.639216	0.021647
DGAT2-DT	0.634186	0.025388
CDCA4	0.633613	0.025388
LINC03047	0.633445	0.025388
GEMIN2	0.632493	0.025841
NDUFA1	-0.63193	0.025938
CYSTM1	-0.63109	0.026304
NDUFB5	-0.62885	0.027615
ANKRD65	0.628852	0.027615
BCL11B	0.62577	0.030024
ATP5F1A	-0.62493	0.030024
LINC02482	0.62493	0.030024
COX8A	-0.62437	0.030024
TEX21P	0.62437	0.030024
RNFT2	0.622969	0.030842
SALL4	0.621849	0.030842
TBC1D32	0.621569	0.030842
UQCRQ	-0.62129	0.030842
CHL1	0.621289	0.030842
C10ORF67	0.621218	0.030842
FENDRR	0.619048	0.032815
HOXA4	0.617953	0.033232
RRN3P1	0.617927	0.033232
MSRA	-0.61737	0.033449
BCL2L14	0.616807	0.033577
CGAS	0.616527	0.033577
HASPIN	0.615686	0.034047
CNTNAP1	0.615406	0.034047
GPR137	-0.61457	0.034619
GAU1	0.613875	0.03484
LINC00837	0.613686	0.03484
RUFY3	0.612885	0.035385

ZGRF1	0.612325	0.035652
TIGD2	0.610644	0.0371
LINC02732	0.610474	0.0371
TMX2	-0.61008	0.037175
HOXA2	0.608726	0.037899
HOXA9	0.608416	0.037899
TXK	0.608123	0.037899
SAP30-DT	0.607843	0.037899
DNAJB6P3	0.607801	0.037899
LINC00954	0.607563	0.037899
ZNF589	0.607283	0.037899
NABP1	0.605882	0.039297
CRLF3	0.604482	0.040661
TVP23C	0.604202	0.040661
VIRMA-DT	0.603922	0.040661
LINC03060	0.603641	0.040661
FMO2	0.603081	0.041016
NINJ1	-0.60196	0.042139
MYOSLID	0.601009	0.042378
COL4A6	0.60084	0.042378
WNT16	0.599902	0.042378
CHODL	0.59986	0.042378
HIF3A	0.59972	0.042378
SKI	0.59944	0.042378
GPC2	0.59916	0.042378
RCC2	0.59888	0.042378
LINC01505	0.598327	0.042378
TMEM151A	-0.59804	0.042378
ESRRA	-0.59804	0.042378
ZNF24TR	0.597759	0.042378
GOT1	-0.59776	0.042378
LINC00989	0.597561	0.042378
HOXB4	0.597199	0.042378
RN7SL672P	0.597115	0.042378
ZNF286B	0.596919	0.042378
CDCA7	0.596639	0.042378
SEMA4A	0.596639	0.042378
SIGLEC6	0.596349	0.042382
STARD9	0.596078	0.042382
CCDC190	0.595784	0.042382
WRAP73	0.595518	0.042382
COX5B	-0.59524	0.042382
SFR1	0.594678	0.042382
KLHL17	0.594398	0.042382
SMIM45	0.594004	0.042382

CACNB1	0.593838	0.042382
CRAT	-0.59384	0.042382
ARMC2	0.593557	0.042382
NT5DC2	0.593277	0.042382
TEX14	0.593277	0.042382
CPNE8-AS1	-0.59328	0.042382
ATP2A3	0.592437	0.04321
PTCH2	0.591597	0.043512
EEF1A1P23	0.591455	0.043512
NUDCD1	0.591317	0.043512
GPI	-0.59132	0.043512
ADAT2	0.591036	0.043592
CMA1	0.590602	0.043887
C21ORF91	0.589916	0.044534
HSPE1P27	0.589356	0.044709
TMC3-AS1	0.589356	0.044709
FAM24B	0.588796	0.045082
GRIFIN	0.58852	0.045082
SUCLG1	-0.58824	0.045082
ATG16L2	0.588235	0.045082
EIF3K	-0.58768	0.045575
OR10A2	0.587032	0.046192
ATP23	0.586555	0.046281
LINC00910	0.586555	0.046281
SLC22A18	-0.58571	0.046828
ZNF707	0.585434	0.046828
PELP1-DT	0.585414	0.046828
GRIK2	0.585213	0.046828
SLC16A1-AS1	0.585154	0.046828
LINC02917	0.58435	0.047466
ADAMTS6	0.584314	0.047466
ALG1L2	0.584034	0.047585
BTN2A3P	0.583754	0.047705
SYTL2	0.583193	0.048001
CFAP73	0.582674	0.048001
CSRP2	0.582633	0.048001
GPR142	0.581942	0.048001
TMEM120A	-0.58179	0.048001
FTLP12	0.581579	0.048001
HAPLN3	0.581513	0.048001
AGR2	0.581513	0.048001
FBXW10	0.581487	0.048001
RHEBL1	0.580952	0.048001
RNU6-482P	0.580875	0.048001
ANKRD65-AS1	0.580659	0.048001

MTCO1P40	-0.58011	0.048001
CHCHD10	-0.57983	0.048001
MIR222HG	0.579832	0.048001
CHMP2A	-0.57983	0.048001
JPH3	0.579452	0.048001
C12ORF56	0.579388	0.048001
HGD	-0.57927	0.048001
CXCL5	0.579272	0.048001
COX6B1	-0.57871	0.048001
POLR2KP1	0.578449	0.048001
COQ9	-0.57787	0.048001
CASP2	0.577871	0.048001
SLC38A5	0.577591	0.048001
HMGB2	0.577311	0.048001
LINC00365	-0.57731	0.048001
APCS	-0.57731	0.048001
LINC02669	0.577031	0.048001
ASB3	0.577031	0.048001
MLXIP	0.577031	0.048001
PABPC1P4	0.577031	0.048001
RPIA	0.577031	0.048001
STK32A-AS1	0.577014	0.048001
KIZ-AS1	0.576831	0.048001
DNER	-0.57675	0.048001
TARID	0.576594	0.048001
ZNF785	0.57619	0.048001
FANCE	0.57619	0.048001
CDC7	0.57619	0.048001
FOXB1	0.575951	0.048001
CCDC88C	0.57591	0.048001
DFFB	0.57591	0.048001
TAS2R20	0.57563	0.048173
SCPEP1	0.57451	0.049574

Table SII. Outputs of the CAVITY module (CavityPlus 2022 web server)using the MD-minimized RTKN2 structure.

Site	PredictedmaximumpKa	PredictedaveragepKa	Drug score	Druggability
1	8.87	6.83	-2	Medium
2	9.59	6.88	4037	Strong
3	11.37	7	-228	Weak
4	11.41	6.99	563	Medium
5	11.61	6.89	3544	Strong
6	11.69	6.85	119	Medium
7	11.84	6.68	57	Medium
8	11.08	6.42	-357	Weak
9	10.9	6.36	1062	Strong
10	10.75	6.3	-620	Weak
11	10.74	6.3	245	Medium
12	10.04	6.06	-83	Medium
13	9.37	5.83	-122	Medium
14	9.28	5.8	277	Medium
15	9.25	5.79	-322	Weak
16	9.21	5.78	-7	Medium
17	8.33	5.47	-829	Weak
18	8.32	5.47	-382	Weak
19	8.26	5.45	-1233	Weak
20	7.98	5.36	-825	Weak
21	7.57	5.21	-818	Weak
22	7.21	5.09	-923	Weak
23	7.19	5.08	-599	Weak
24	7.09	5.05	-1280	Weak
25	6.98	5.01	-830	Weak
26	6.64	4.89	-1188	Weak
27	6.13	4.72	-1117	Weak
28	5.9	4.64	-1173	Weak
29	5.82	4.62	-1532	Weak
30	5.61	4.54	-1250	Weak
31	5.44	4.49	-1482	Weak

The selection for docking-based virtual screening was mainly based on the level of druggability.MD, molecular dynamics; RTKN2, Rhotekin 2.