Potential Bruton tyrosine kinase inhibitors.

Computational comparison between natural compounds and generic drugs and specific BTK inhibitors

Draft study project

Alessandro Careglio [1]

[1] Department of Drug Science and Technology of the University of Turin (student and doctor. in herbalist's shop)

Correspondence: Alessandro Careglio Frazione Santa Maria 92/a La Morra 12064 (CN) Italy

alessandro.careglio@edu.unito.it

ABSTRACT

In this study project, a computational comparison between Brutus tyrosine kinase (BKT) inhibitor drugs and compounds present in plant species as secondary metabolites and common approved drugs is performed, using docking and Electrostatic complementarity scores with Flare Cresset.

The BKT protein model was downloaded from Protein Data Bank (PDB ID 5P9J)

And the compounds (synthetic and natural) were downloaded from PUBchem

A library of natural compounds and drugs of 2632 molecules was downloaded from selleckchem (2) summary of the results: emerged the drugs Ibrutinib Evobrutinib obtained the best scores considering the docking and complementary electrostatic field

From the screening of the compound library it emerged that many compounds obtained scores comparable to BKT inhibitor drugs and in particular the quinone compounds

From the Brunetton pharmacognosy text (6) from the chapter on quinone compounds and the related species that contain them

Rumex) and rhubarb were found to be the species with quinone compounds at comparable scores. From St. John's wort (*Hypericum perforatum)* and romice (genus to BTK inhibitors

Summary of the results: it emerged that the drugs Ibrutinib Evobrutinib obtained the best scores considering the docking and complementary electrostatic field

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Introduction

Bruton's tyrosine kinase (BTK) is a cytoplasmic, non-receptor protein tyrosine kinase belonging to the Tec kinase family and was first discovered in X-linked agammaglobulinemia. All cells of hematopoietic origin except plasma cells, natural killer cells and T lymphocytes express BTK6. While BTK was initially known for its critical role in the development of B cell adaptive immunity, more recent studies point to a crucial role of BTK in innate immunity (1)

inhibition of BTK activity reduces multiorgan injury/dysfunction (cardiac, renal, hepatic) caused by trauma (1)

Related to the COVID-19 pandemic, BTK inhibitors would reduce the cytokine storm and lung injury related to the severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2).(1)

BTK has emerged as a novel anti-apoptotic molecular target for the treatment of B-lineage leukemias and lymphomas. Early preclinical and clinical findings indicate that BTK inhibitors may be useful in the treatment of leukemias and lymphomas. BTK inhibitors may also be useful in the prevention and treatment of thromboembolic complications and inflammatory disorders.(5)

St. John's wort compounds are strongly not recommended if taken in conjunction with BTK inhibitors for the inhibition of the enzymatic cytochromes responsible for the metabolism of inhibitory drugs and from the scores obtained from this study project they could "displace" the drugs from their site of action or from plasma transport proteins

Quinone compounds are also contained in some species used for laxative effect (senna cascara), but any concomitant intake is highly unlikely as the inhibitor drugs have diarrhea or dysentery as a side effect

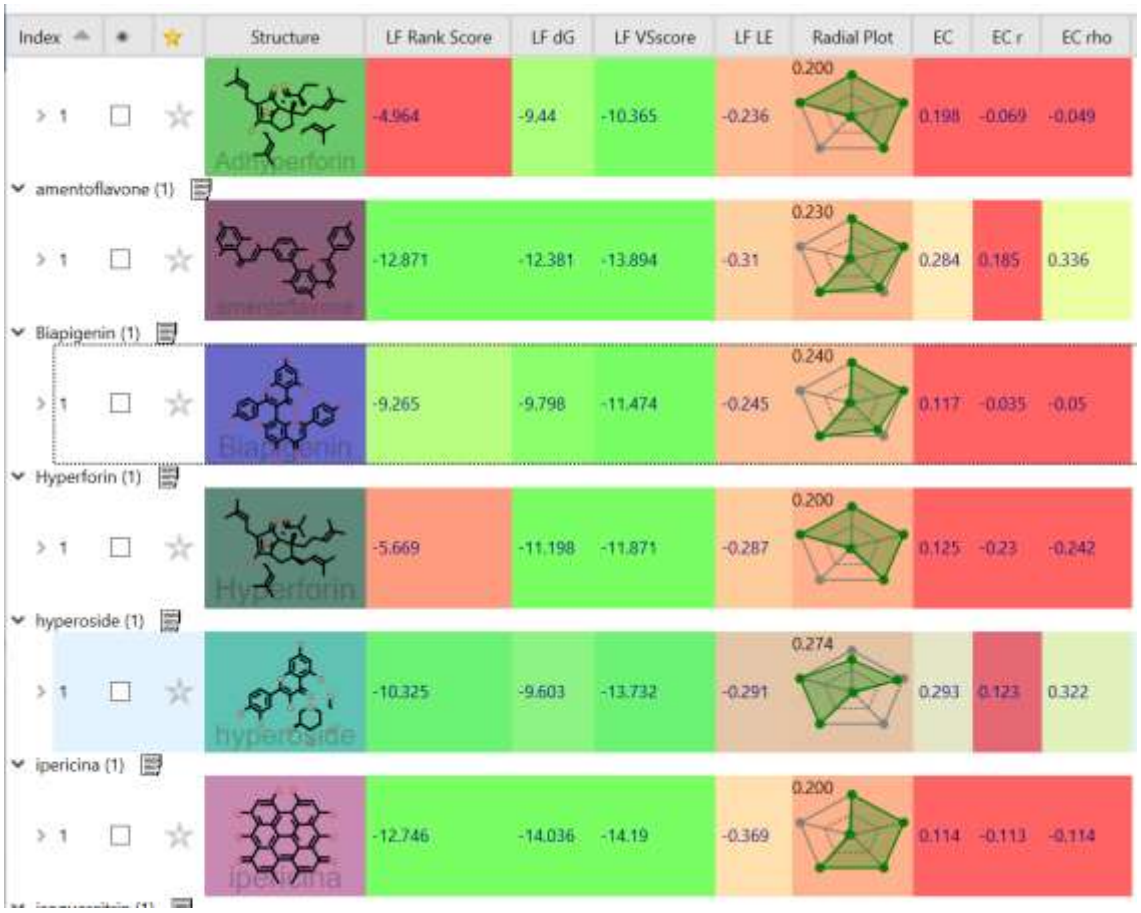
A different story is for aloe (*Aloe vera)* often used by cancer patients, aloe emodin could compete with BKt inhibitor drugs

Milk thistle compounds (silymarin, silibinin and silychristin) obtain interesting scores.

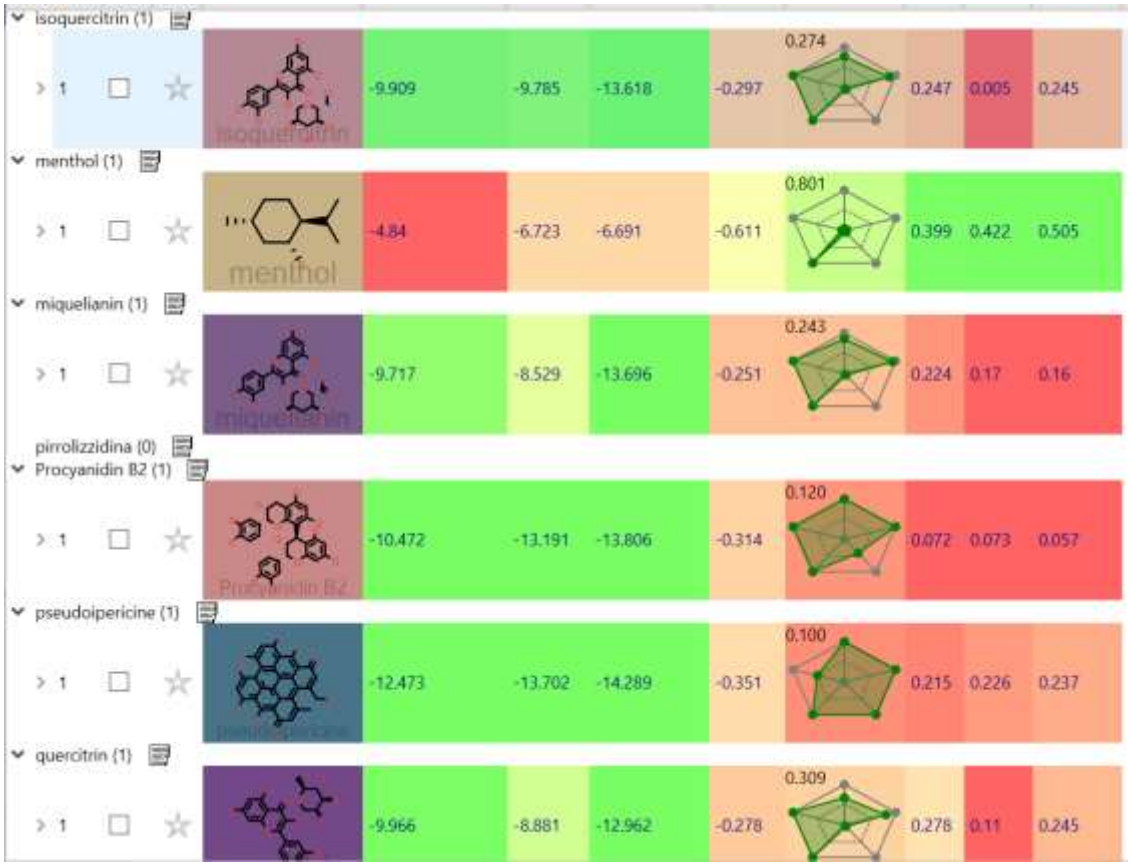
DOCKING BTK INHIBITOR DRUGS

A structure-based comparison is performed between Ibrutinib linked to Bruton's tyrosine kinase PDB ID 5P9J (8) with BTK inhibitor drugs

Docking St. John's wort compounds



Index	Structure	LF Rank Score	LF dG	LF VSscore	LF LE	Radial Plot	EC	EC r	EC rho
1		-4.964	-9.44	-10.365	-0.236	0.200	0.198	-0.069	-0.049
amentoflavone (1)									
1		-12.871	-12.381	-13.894	-0.31	0.230	0.284	0.185	0.336
Biapigenin (1)									
1		-9.265	-9.798	-11.474	-0.245	0.240	0.117	-0.035	-0.05
Hyperforin (1)									
1		-5.669	-11.198	-11.871	-0.287	0.200	0.125	-0.23	-0.242
hyperoside (1)									
1		-10.325	-9.603	-13.732	-0.291	0.274	0.293	0.123	0.322
ipericina (1)									
1		-12.746	-14.036	-14.19	-0.369	0.200	0.114	-0.113	-0.114

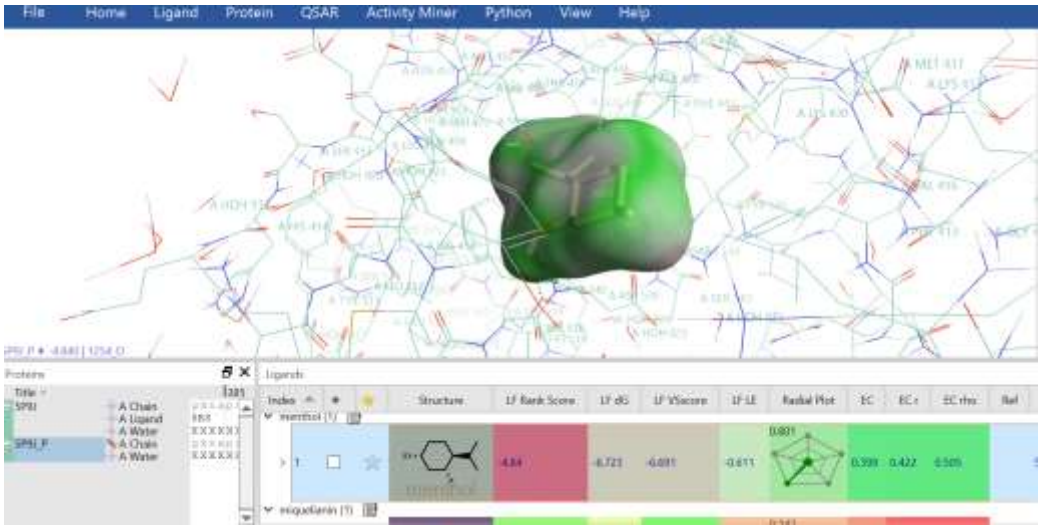


isoquercitrin (1)									
1		-9.909	-9.785	-13.618	-0.297	0.274	0.247	0.005	0.245
menthol (1)									
1		-4.84	-6.723	-6.691	-0.611	0.801	0.399	0.422	0.505
miquelianin (1)									
1		-9.717	-8.529	-13.696	-0.251	0.243	0.224	0.17	0.16
pirrolizzidina (0)									
Procyanidin B2 (1)									
1		-10.472	-13.191	-13.806	-0.314	0.120	0.072	0.073	0.057
pseudoipericine (1)									
1		-12.473	-13.702	-14.289	-0.351	0.100	0.215	0.226	0.237
quercitrin (1)									
1		-9.966	-8.881	-12.962	-0.278	0.309	0.278	0.11	0.245

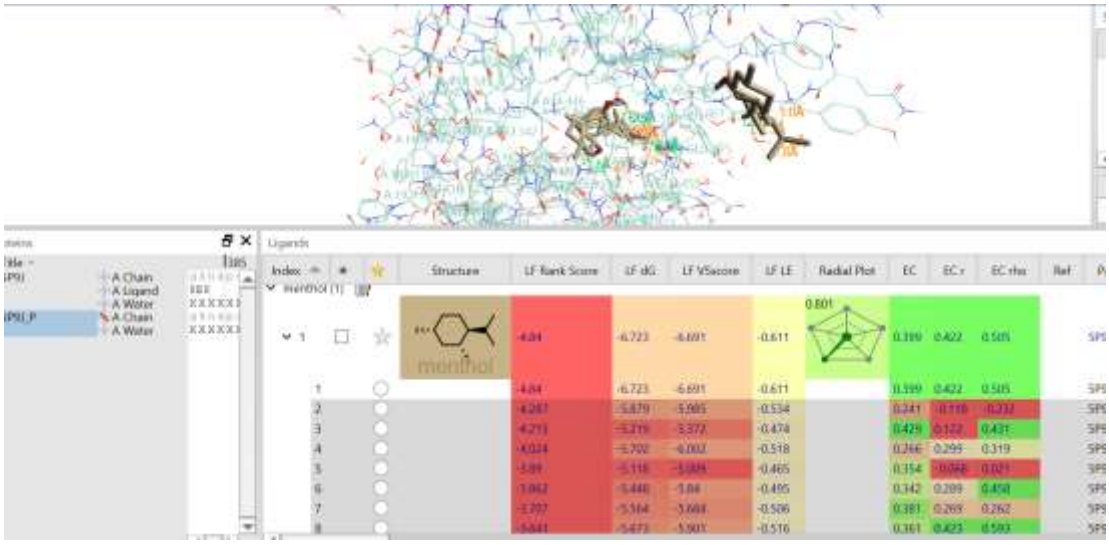
Comment on the results of docking of St. John's wort compounds

The binding affinity (ΔG) of amentoflavone, hyperoside, hypericin, pseudohypericin and procyanidin B2 is superior to BTK inhibitors in these compounds.

A different story for menthol:



The EC values indicate that menthol adapts particularly well to a part of the binding pocket and considering its decongestant action it is possible that it influences the BTK towards the activation of metabolic pathways and reduces inflammation

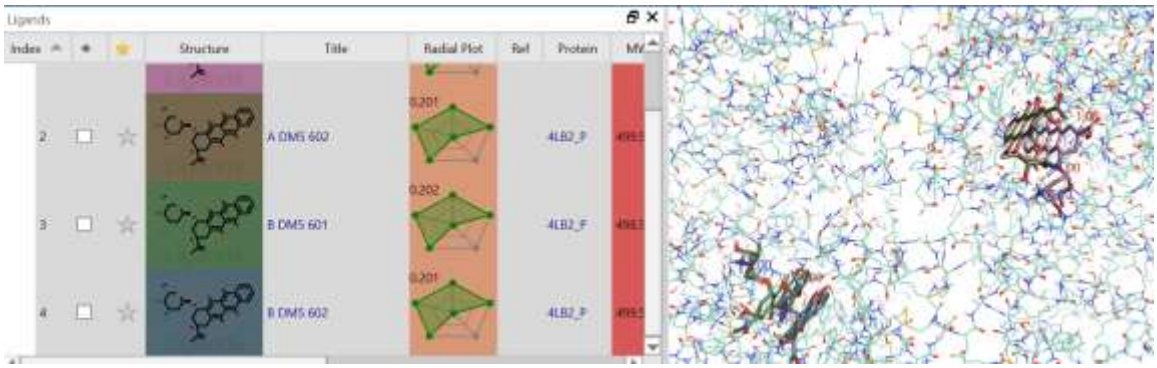


The 8 conformations of menthol are grouped into two areas, one inside the pocket and one outside

Albumin binding competition between BTK inhibitors and St. John's wort compounds

Human albumin template downloaded from PDB complexed with hydrarubicin (a quinone with a high affinity for BKT) is used

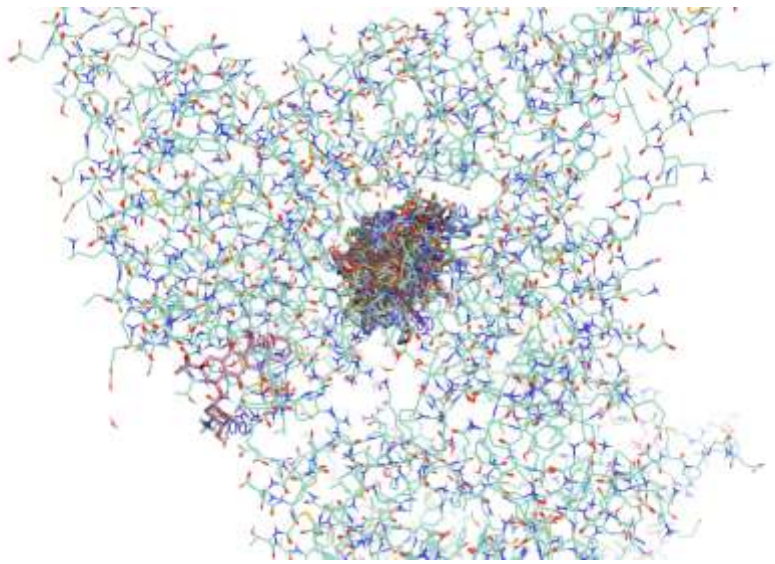
(PDB ID 4LB2)



The binding of hydrarubicin in the crystallized is concentrated in two positions

The active site size is set to 60 Angstroms

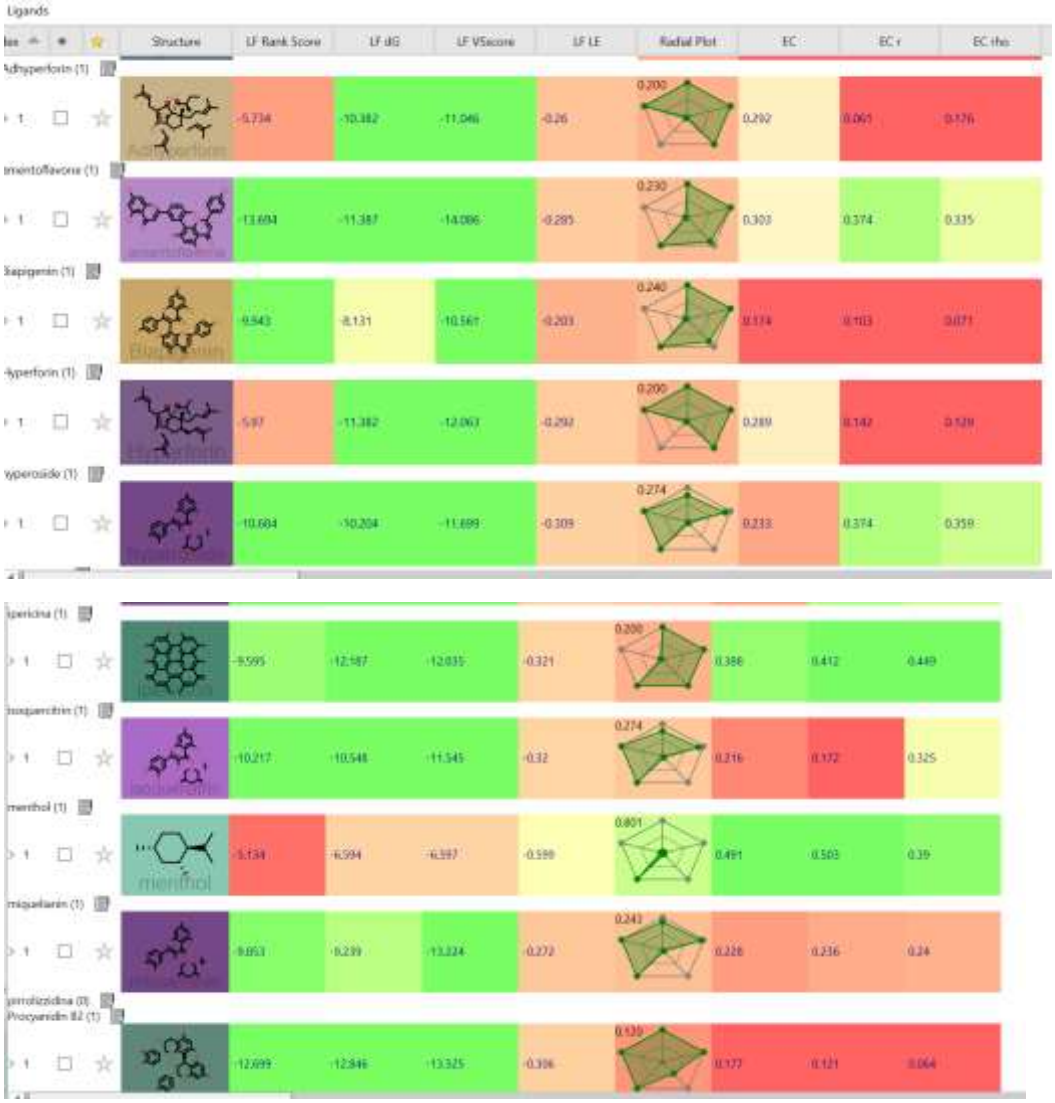
A large grid is chosen (about 2000 "heavy" atoms) which occupies about 1/3 of the protein

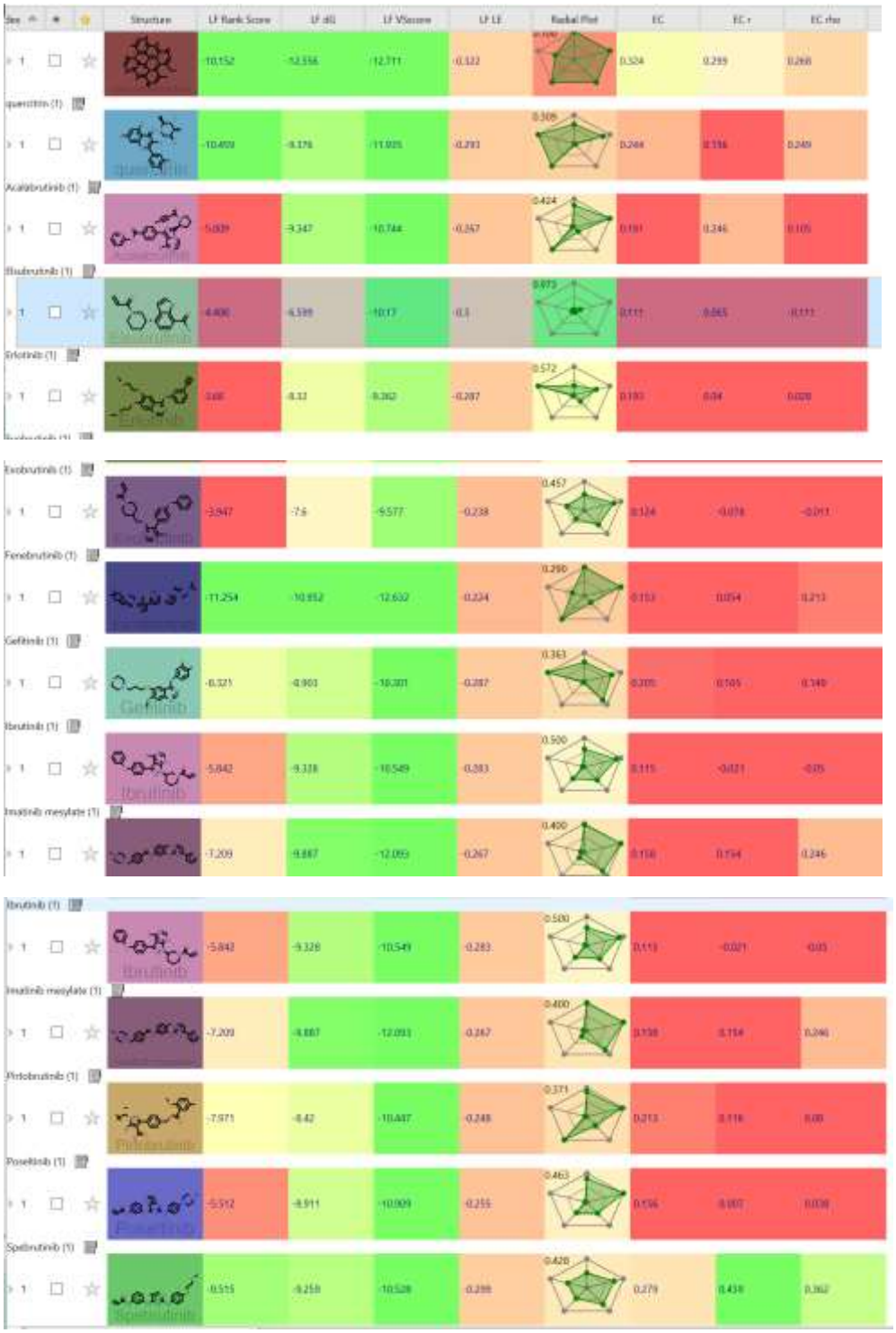


The 14 BTK compounds and the 13 tested compounds from St. John's wort were found to have a high affinity for a single site (except for one cocrystallized hydrarubicin molecule).

Result of docking between BTK inhibitors and St. John's wort compounds on human serum albumin:

Hypericin, if taken after the iBKT drug, having a greater affinity (ΔG) than a better electrostatic complementarity, is likely to displace the drug from the protein causing a plasma peak and a risk of intoxication.




Structure
LF Rank Score
LF dG
LF VScore
LF LE
Radial Plot
EC
EC r
EC rho
quercetin (1)
Acalabrutinib (1)
Ibrutinib (1)
Erlotinib (1)
Evobrutinib (1)
Fenebrutinib (1)
Gefitinib (1)
Ibrutinib (1)
Imatinib mesylate (1)
Ibrutinib (1)
Imatinib mesylate (1)
Pirtobrutinib (1)
Poseltinib (1)
Spebrutinib (1)

Docking romice compounds

- Chrysophanol
- citreorosein
- emodin
- nepodin
- physcion
- Pulmatin
- resveratrol
- rumexneposides
- torachrysone

Docking rhubarb and ivy compounds

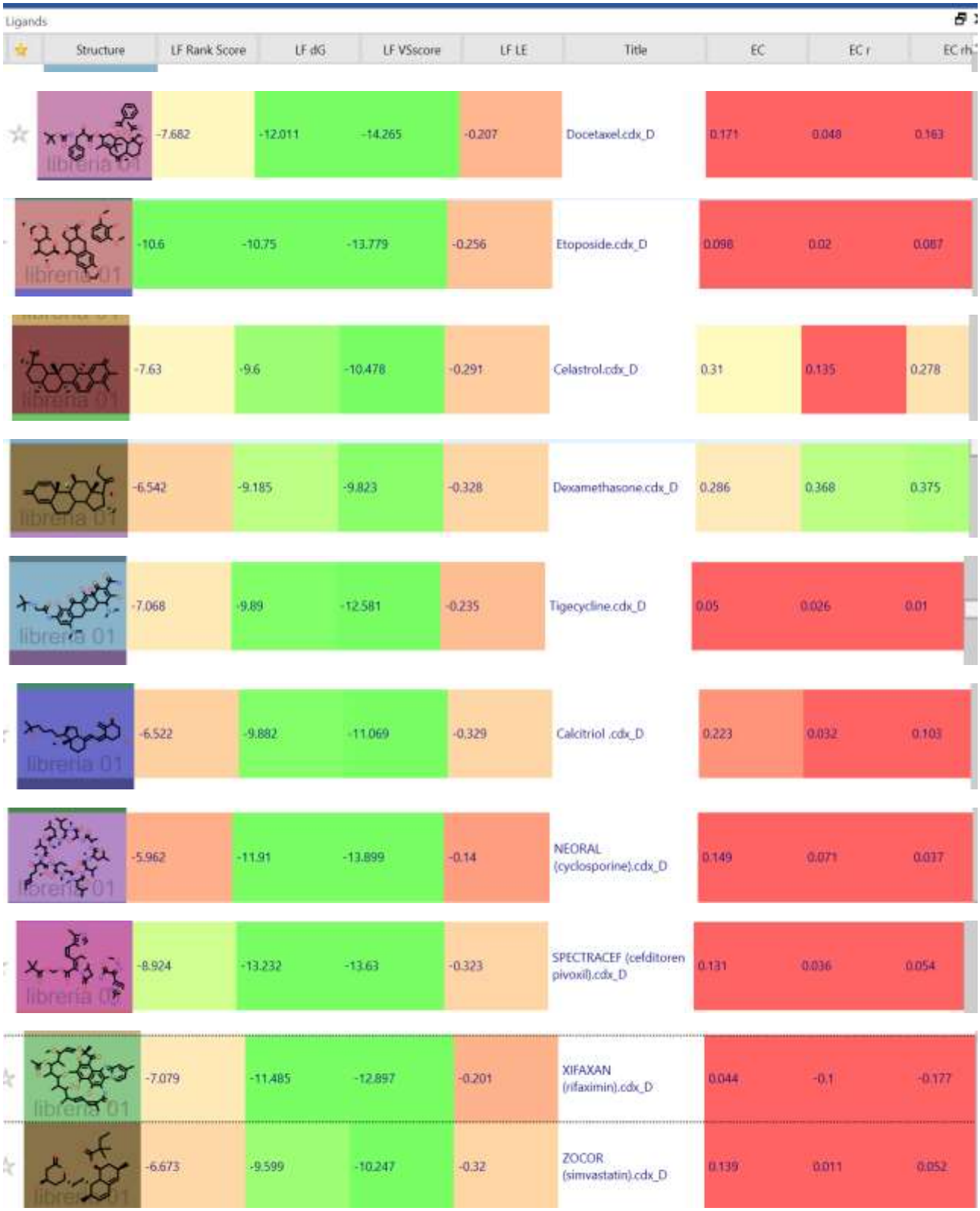
- 2d ederacodide C
- 2D Structure alpha ederin
- beta carotene
- beta sitosterol
- caffeic acid
- campesterol
- chlorogenic acid
- cholesterol
- cis vaccenic acid
- emetin
- falcarinol
- falcarinone
- hederagenin
- hidroxycinnamic acid
- kaempferol
- oleanolic acid
- oleic acid
- palmitoleic acid
- panaxydol
- petroselinic acid
- quercetin
- rosmarinic acid
- scopolin
- stigmasterol
- Structure2D_helixoside
- vitamin c
- vitamin E

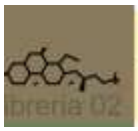
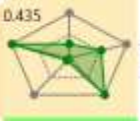
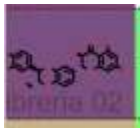
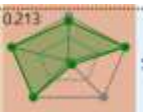
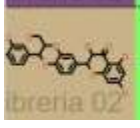
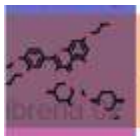
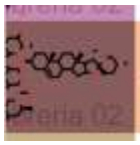
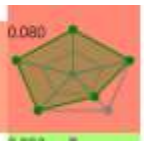
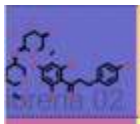
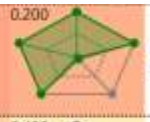
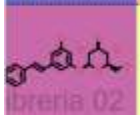
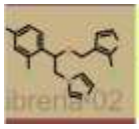
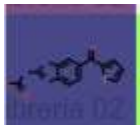
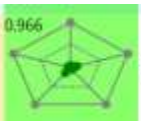
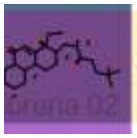
- emodin
- Emodin-8-glucoside
- glucorhein
- lindleyine
- Rhapontin
- rhein
- rutin Quercetin 3-rutinoside
- Zeaxanthin

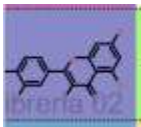
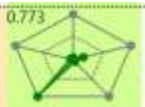
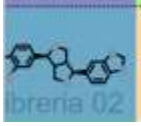
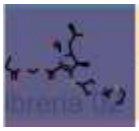
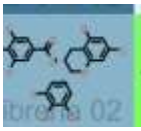
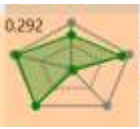
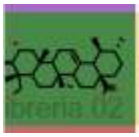
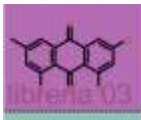
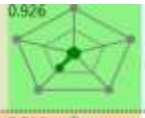
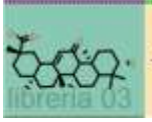
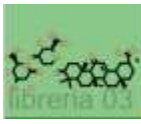
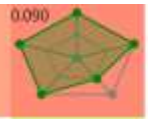
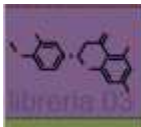
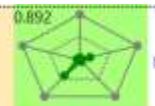
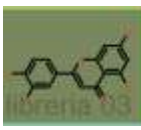
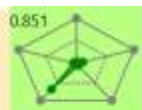

File
Home
Ligand
Protein
QSAR
Activity Miner
Python
View
Help
Ligands
ndex
Structure
LF Rank Score
LF dG
LF VSscore
LF LE
Radial Plot
EC
EC r
1
-7.799
-10.535
-13.809
-0.351
0.175
0.146
Rhapontin
rhein (1)
1
-8.842
-7.932
-9.435
-0.378
0.813
0.36
0.207
rhein
rutin
Quercetin 3-rutinoside (1)
1
-8.505
-6.862
-14.069
-0.16
0.200
0.236
0.333
Zeaxanthin (1)
1
-3.277
-9.625
-11.419
-0.229
0.187
0.198
0.019
rosmarinic acid (1)
1
-7.69
-9.207
-11.004
-0.354
0.508
0.002
-0.081
scopolin (1)
1
-6.276
-6.941
-10.071
-0.278
0.528
0.162
0.112
scopolin
stigmasterol (1)
1
-6.629
-10.308
-10.776
-0.344
0.184
0.201
0.011
stigmasterol
vitamin E (1)
1
-6.236
-9.626
-10.269
-0.311
0.209
0.311
0.114
vitamin E

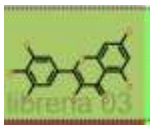
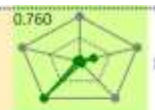
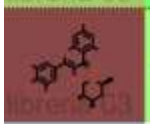
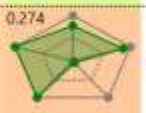
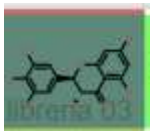
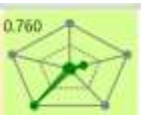
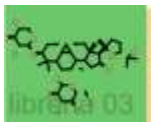
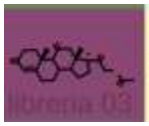
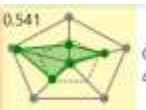
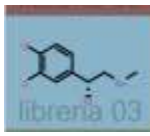
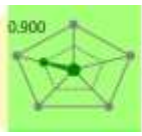
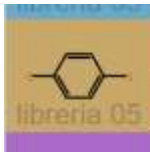
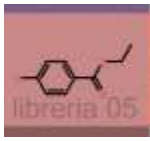
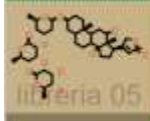
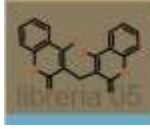
Docking compound library (2632) (ref 2)

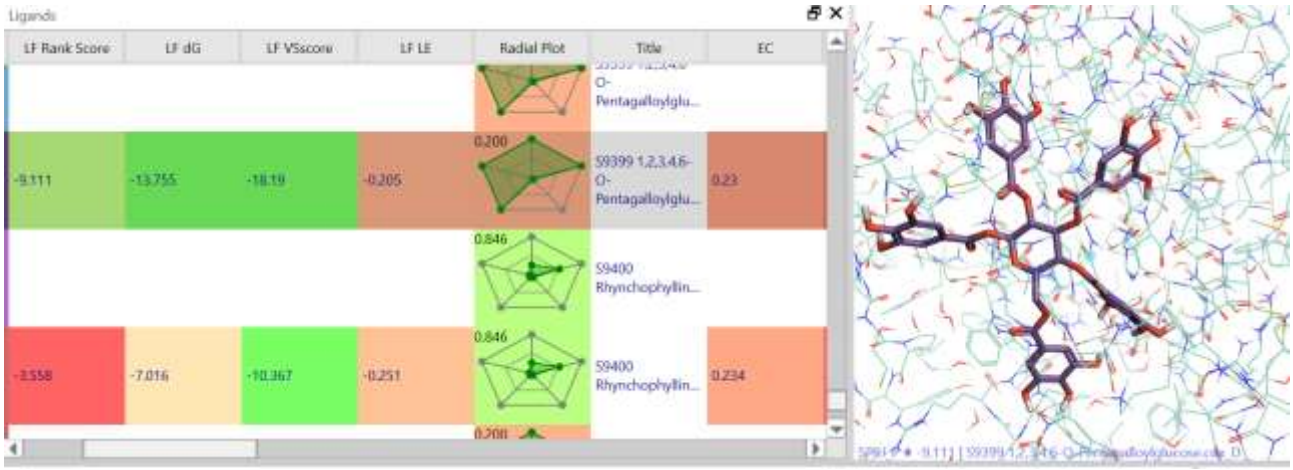
Below are the compounds in the library with scores similar to or higher than the reference drugs



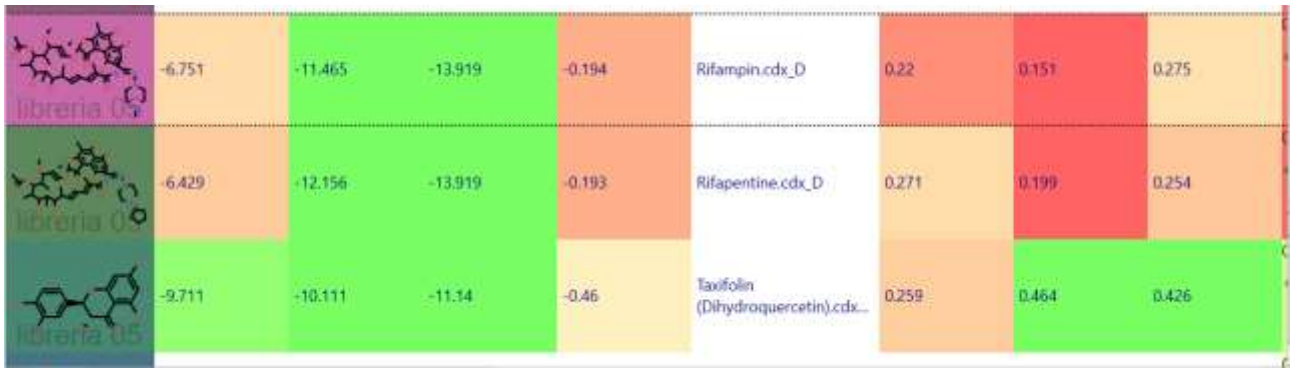
	-7.401	-11.062	-12.006	-0.395	 0.435	CHENIX (chenodiol).cdx...	0.239	0.218	0.282
	-10.794	-12.494	-14.017	-0.357	 0.213	Silibinin.cdx_D	0.224	0.1	0.231
	-12.401	-12.768	-13.817	-0.365	 0.213	Silymarin.cdx_D	0.112	0.056	0.055
	-6.25	-9.28	-14.599	-0.178	 0.200	Troxerutin.cdx_D	0.246	0.198	0.32
	-7.821	-9.974	-12.496	-0.332	 0.375	Aloin.cdx_D	0.286	0.028	0.468
	-6.205	-9.19	-15.38	-0.151	 0.080	Dioscin.cdx_D	0.173	0.055	0.018
	-9.71	-8.815	-10.117	-0.401	 0.892	Diosmetin.cdx_D	0.301	0.341	0.417
	-6.33	-6.536	-14.058	-0.159	 0.200	Naringin Dihydrochalcon...	0.193	0.058	0.298
	-8.484	-8.825	-12.5	-0.315	 0.439	Polydatin.cdx_D	0.124	0.038	0.147
	-8.435	-9.362	-9.875	-0.407	 0.356	TZ-3 (tioconazole)cd...	0.342	0.362	0.443
	-9.652	-8.758	-9.7	-0.417	 0.966	Nocodazole.cd...	0.196	0.076	0.082
	-7.361	-11.969	-12.631	-0.352	 0.129	Hydroxyecdyso...	0.162	0.02	0.142

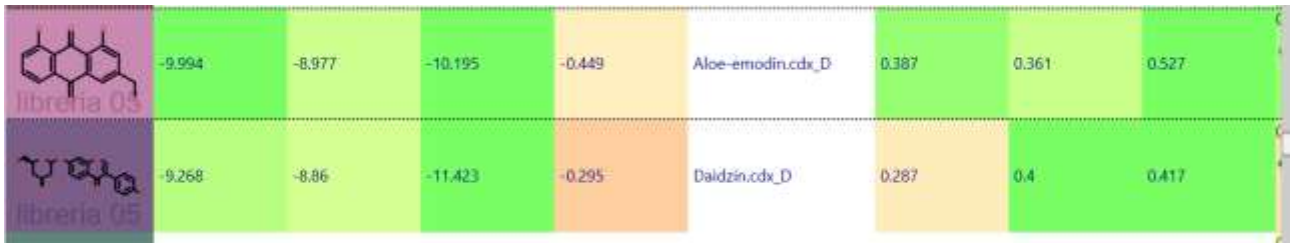
	-9.529	-8.967	-10.263	-0.408		Quercetin.cdx_D	0.323	0.47	0.516
	-6.656	-9.074	-10.214	-0.349		Sesamin.cdx_D	0.108	0.239	0.184
	-9.28	-8.694	-9.624	-0.435		Naringenin.cdx...	0.311	0.453	0.476
	-6.906	-11.192	-11.761	-0.339		Tebipenem pivoxil.cdx_D	0.175	0.211	0.093
	-4.963	-10.943	-13.896	-0.177		ivermectin.cdx_D	0.265	0.055	0.226
	-11.011	-11.499	-13.4	-0.348		(-)-Epigallocatechin gallate.cdx_D	0.159	0.115	0.247
	-6.772	-9.975	-10.565	-0.285		Asiatic acid.cdx_D	0.252	0.215	0.225
	-10.544	-9.175	-10.2	-0.459		Emodin.cdx_D	0.377	0.476	0.506
	-6.913	-10.574	-11.067	-0.311		Enoxolone.cdx_D	0.363	0.393	0.495
	-6.056	-9.343	-15.59	-0.161		Glycyrrhizic acid.cdx_D	0.056	-0.004	-0.108
	-9.738	-9.242	-10.225	-0.42		Hesperetin.cdx_D	0.208	0.333	0.31
	-9.046	-9.241	-15.44	-0.215		Hesperidin.cdx_D	0.259	0.11	0.307
	-10.059	-9.531	-10.466	-0.454		Luteolin.cdx_D	0.29	0.488	0.425

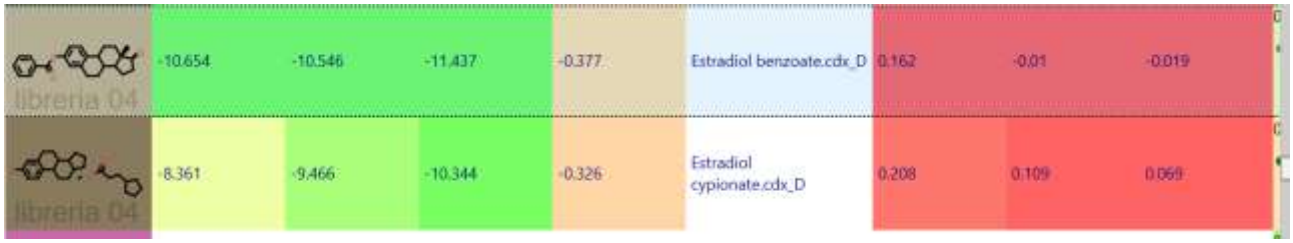
	-10.501	-10.412	-11.434	-0.453	 0.760	Myricetin.cdx_D	0.3	0.369	0.453
	-9.53	-9.924	-13.296	-0.301	 0.274	Myricitrin.cdx_D	0.226	0.189	0.194
	-10.389	-10.664	-12.111	-0.464	 0.760	Dihydromyricet...	0.272	0.364	0.376
	-6.465	-12.251	-17.476	-0.223	 0.090	Astragaloside A.cdx_D	0.24	0.166	0.346
	-7.95	10.133	-10.599	-0.349	 0.541	Cortisone acetate.cdx_D	0.087	0.065	0.03
	-5.792	-6.853	-7.793	-0.527	 0.900	L-Adrenaline.cdx_D	0.288	0.446	0.472
	-4.85	-4.613	-5.062	-0.577	S4580 Hydroquinone.cdx_D		0.295	0.484	0.363
	-9.38	-7.45	-8.669	-0.414	Danthron.cdx_D		0.379	0.447	0.505
	-5.462	-5.387	-5.807	-0.449	Ethylparaben.cdx_D		0.396	0.521	0.473
	-11.009	-11.275	-11.98	-0.403	Flavopiridol hydrochloride.cdx_D		0.231	0.188	0.245
	-6.648	-12.755	-14.26	-0.156	Anidulafungin.cdx_D		0.187	0.012	0.134
	-6.874	-9.649	-14.423	-0.175	Digoxin .cdx_D		0.232	0.071	0.245
	-10.974	-8.887	-10.367	-0.355	Dicoumarol.cdx_D		0.184	0.169	0.045

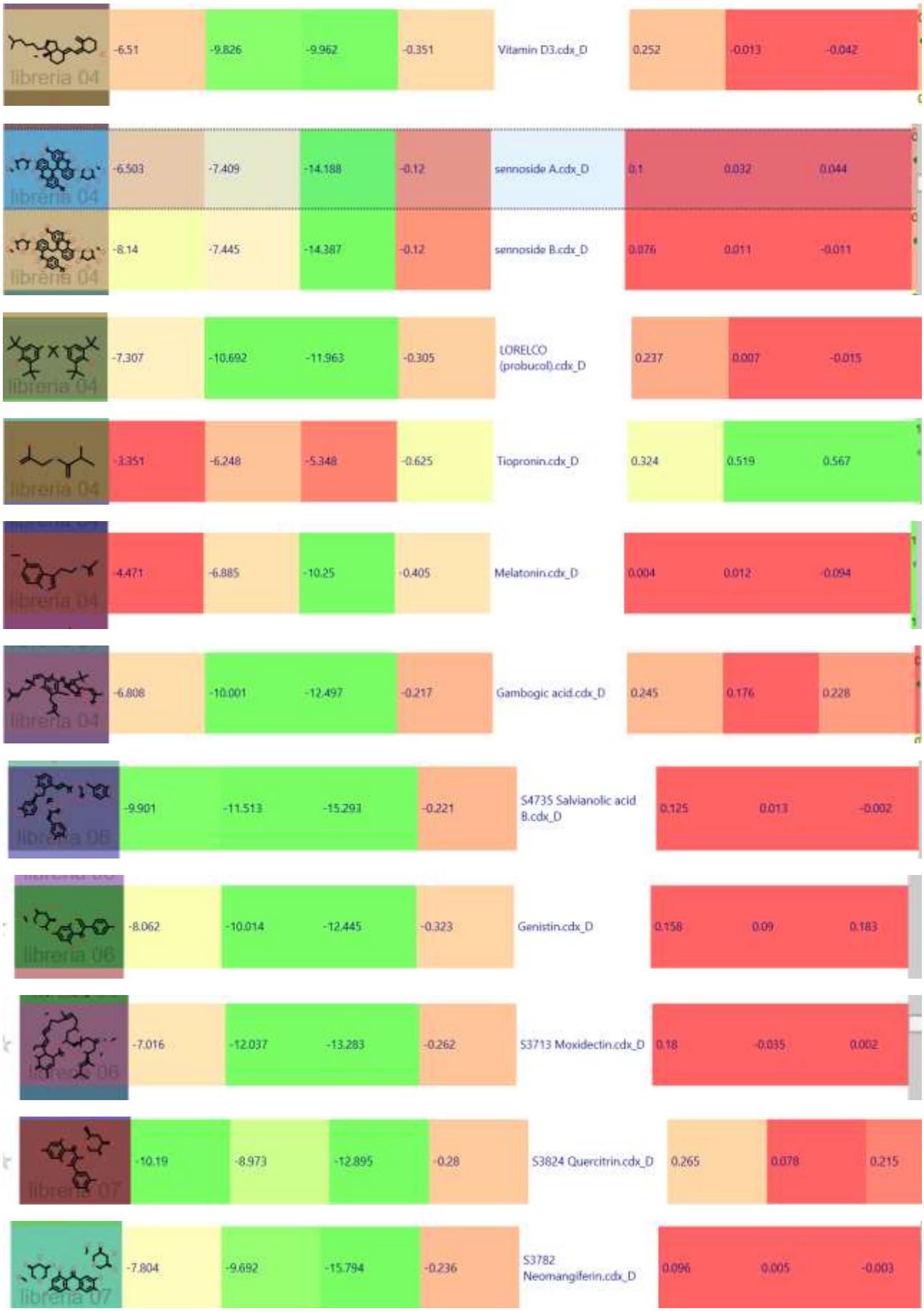


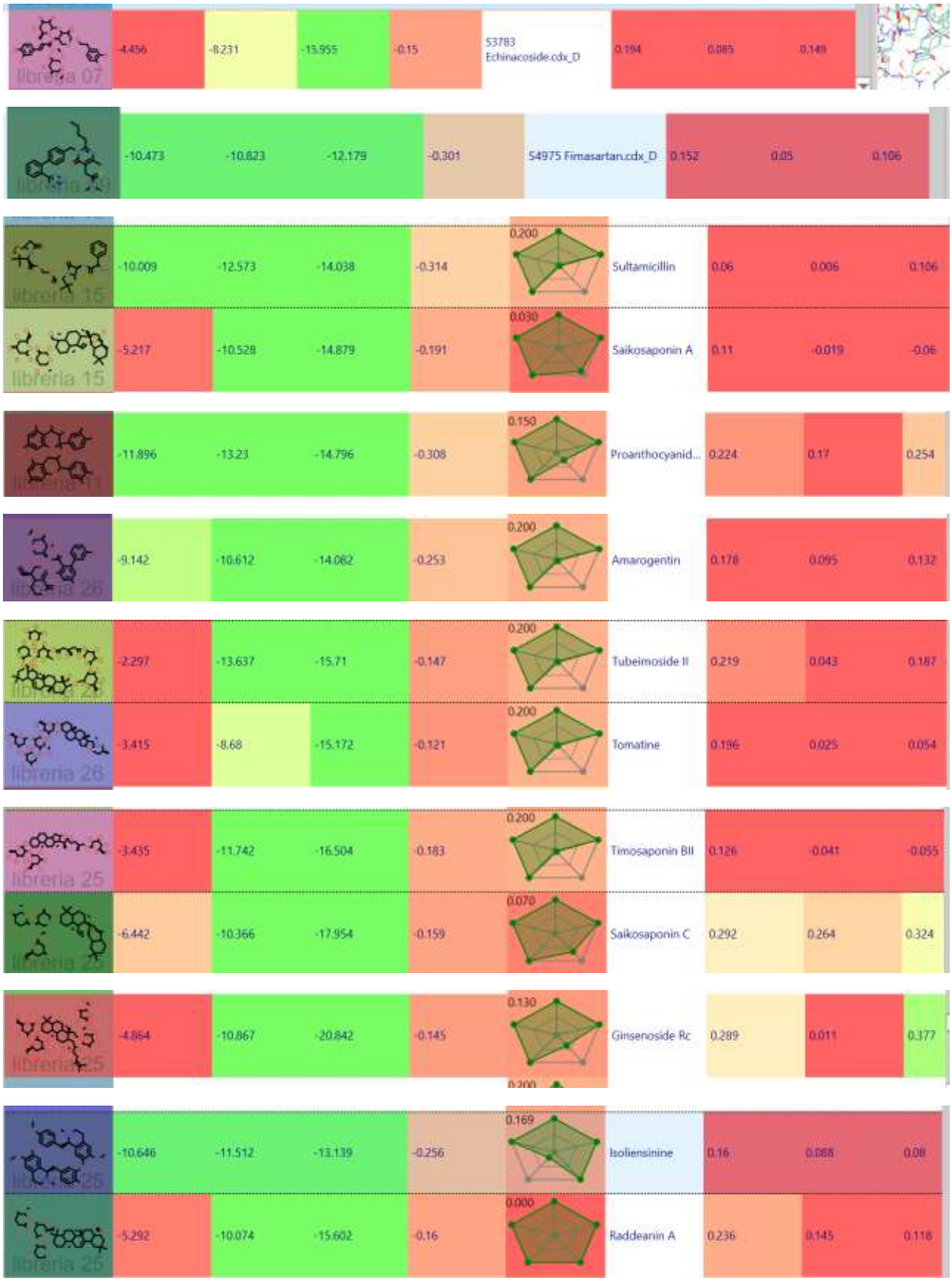
pentagalloylglucose

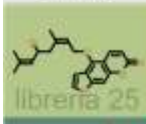
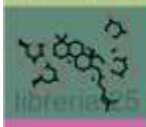
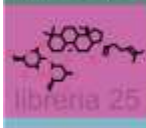
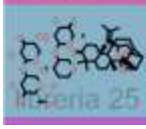
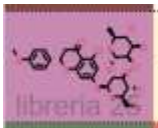
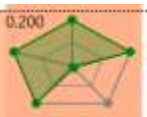
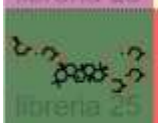
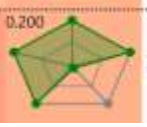
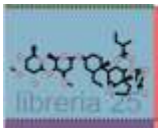
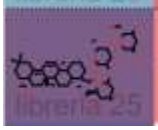
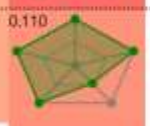
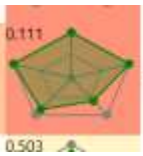
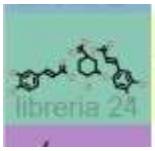
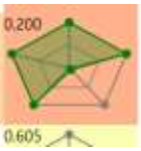
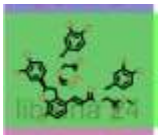
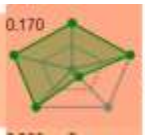


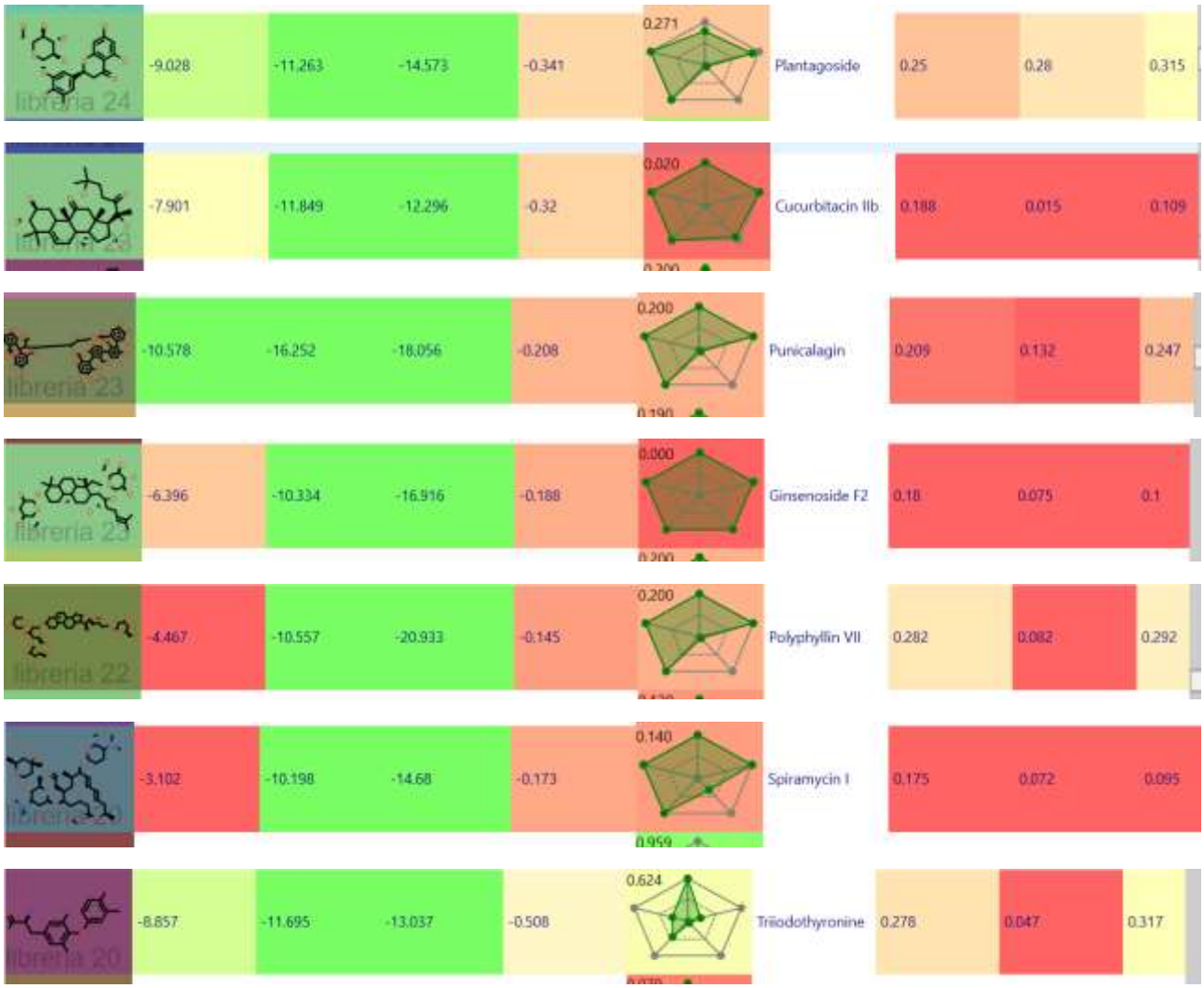





-6.51
-9.826
-9.962
-0.351
Vitamin D3.cdx_D
0.252
-0.013
-0.042
-6.503
-7.409
-14.188
-0.12
sennoside A.cdx_D
0.1
0.032
0.044
-8.14
-7.445
-14.387
-0.12
sennoside B.cdx_D
0.076
0.011
-0.011
-7.307
-10.692
-11.963
-0.305
LORELCO (probucol).cdx_D
0.237
0.007
-0.015
-3.351
-6.248
-5.348
-0.625
Tiopronin.cdx_D
0.324
0.519
0.567
-4.471
-6.885
-10.25
-0.405
Melatonin.cdx_D
0.004
0.012
-0.094
-6.808
-10.001
-12.497
-0.217
Gambogic acid.cdx_D
0.245
0.176
0.228
-9.901
-11.513
-15.293
-0.221
S4735 Salvianolic acid B.cdx_D
0.125
0.013
-0.002
-8.062
-10.014
-12.445
-0.323
Genistin.cdx_D
0.158
0.09
0.183
-7.016
-12.037
-13.283
-0.262
S3713 Moxidectin.cdx_D
0.18
-0.035
0.002
-10.19
-8.973
-12.895
-0.28
S3824 Quercitrin.cdx_D
0.265
0.078
0.215
-7.804
-9.692
-15.794
-0.236
S3782 Neomangiferin.cdx_D
0.096
0.005
-0.003

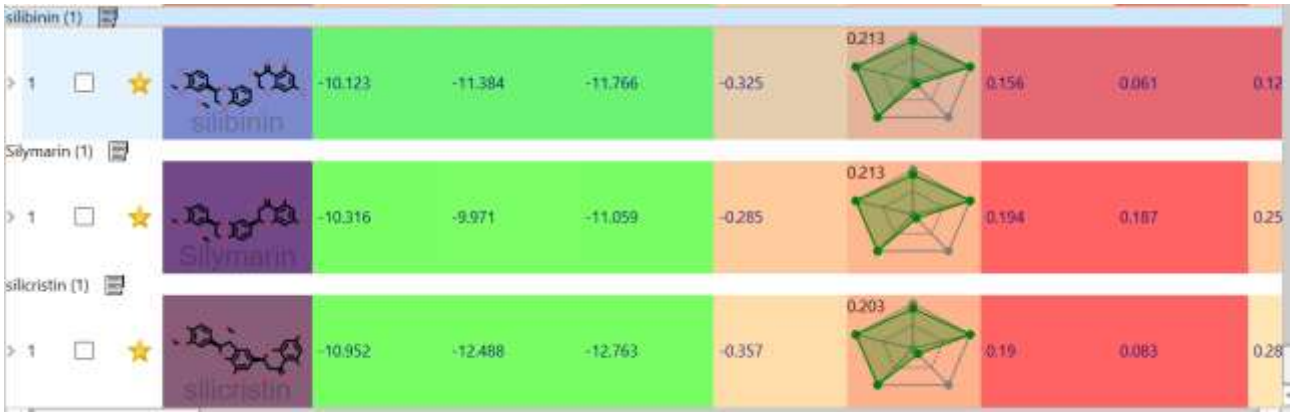

-4.456
-8.231
-15.955
-0.15
53783
Echinacoside.cdx_D
0.194
0.085
0.149
-10.473
-10.823
-12.179
-0.301
S4975 Fimasartan.cdx_D
0.152
0.05
0.106
-10.009
-12.573
-14.038
-0.314
0.200
Sultamicillin
0.06
0.006
0.106
-5.217
-10.528
-14.879
-0.191
0.030
Saikosaponin A
0.11
-0.019
-0.06
-11.896
-13.23
-14.796
-0.308
0.150
Proanthocyanid...
0.224
0.17
0.254
-9.142
-10.612
-14.082
-0.253
0.200
Amarogentin
0.178
0.095
0.132
-2.297
-13.637
-15.71
-0.147
0.200
Tubeimoside II
0.219
0.043
0.187
-3.415
-8.68
-15.172
-0.121
0.200
Tomatine
0.196
0.025
0.054
-3.435
-11.742
-16.504
-0.183
0.200
Timosaponin BII
0.126
-0.041
-0.055
-6.442
-10.366
-17.954
-0.159
0.070
Saikosaponin C
0.292
0.264
0.324
-4.864
-10.867
-20.842
-0.145
0.130
Ginsenoside Rc
0.289
0.011
0.377
-10.646
-11.512
-13.139
-0.256
0.169
Isoliensinine
0.16
0.088
0.08
-5.292
-10.074
-15.602
-0.16
0.000
Raddeanin A
0.236
0.145
0.118

Structure	LF Rank Score	LF dG	LF VSscore	LF LE	Radial Plot	Name	EC	EC r	EC
	-8.386	-9.493	-10.461	-0.365	 0.614	Notopterol	0.308	0.232	0.319
	-4.185	-11.571	-19.555	-0.154	 0.130	Ginsenoside Rb3	0.176	0.062	0.116
	-6.494	-10.443	-15.153	-0.193	 0.000	Ginsenoside Rk1	0.211	0.028	0.022
	-2.368	-7.972	-15.084	-0.109	 0.140	Jujuboside B	0.176	0.079	0.107
	-7.419	-9.904	-14.063	-0.236	 0.200	Poncirin	0.187	0.07	0.15
	-3.475	-13.181	-23.164	-0.153	 0.200	Macranthoidin A	0.142	0.038	0.042
	-4.708	-10.093	-13.833	-0.18	 0.020	Tenacissoside H	0.219	0.079	0.243
	-5.331	-11.611	-17.699	-0.176	 0.110	Buddlejasaponin IVb	0.219	0.01	0.183
	-5.192	-13.582	-14.76	-0.295	 0.001	Solanesol (Nonaisoprenol)	0.246	0.075	0.113
	-9.697	-11.552	-12.788	-0.269	 0.111 0.503	Irinotecan	0.275	0.084	0.282
	-9.113	-11.297	-12.924	-0.297	 0.030	Gossypol	0.257	0.09	0.278
	-7.743	-12.255	-13.374	-0.331	 0.200 0.605	Cynarin	0.177	0.009	0.115
	-10.161	-12.562	-15.203	-0.237	 0.170	9''-Methyl salvianolate B	0.196	0.147	0.215


libreria 24
-9.028
-11.263
-14.573
-0.341
0.271
Plantagoside
0.25
0.28
0.315
-7.901
-11.849
-12.296
-0.32
0.020
Cucurbitacin IIb
0.188
0.015
0.109
libreria 23
-10.578
-16.252
-18.056
-0.208
0.200
Punicalagin
0.209
0.132
0.247
libreria 23
-6.396
-10.334
-16.916
-0.188
0.000
Ginsenoside F2
0.18
0.075
0.1
libreria 22
-4.467
-10.557
-20.933
-0.145
0.200
Polyphyllin VII
0.282
0.082
0.292
-3.102
-10.198
-14.68
-0.173
0.140
Spiramycin I
0.175
0.072
0.095
libreria 20
-8.857
-11.695
-13.037
-0.508
0.624
Triiodothyronine
0.278
0.047
0.317

Pubchem https://pubchem.ncbi.nlm.nih.gov/compound/Milk-thistle

Milk thistle is a substance derived from any of several Old World thorny shrubs and subshrubs, including the plant Silybum marianum. The active chemical component of milk thistle is silymarin, which is a combination of flavonoids such as silibinin, dehydrosilybinin, silychristin, and silidianin. These compounds are antioxidants and can alter the structure of the liver cell membrane, thus blocking the absorption of toxins; they can also stimulate the production of new liver cells. Furthermore, milk thistle can increase cellular levels of adenosine triphosphate (ATP), showing dose-dependent cytoprotection of cardiac myocytes against doxorubicin. The silibinin component of milk thistle has been shown to inhibit mitogenic and cell survival-mediated signaling. by the growth factor receptor, thus inhibiting tumor growth.



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Nikita M Patel, Filipe RMB Oliveira, Hanna Pillmann Ramos, Eleonora Aimaretti, Gustavo Ferreira Alves, Sina M Coldewey, Massimo Collino

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(misspelling "Bruton")

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Fatih M Uckun

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7. Ability of Bruton's Tyrosine Kinase Inhibitors to Sequester Y551 andPrevent Phosphorylation Determines Potency for Inhibition of Fc Receptor but not B-Cell Receptor Signaling

Andrew T. Bender, Anna Gardberg, Albertina Pereira, Theresa Johnson, Yin Wu, Roland Grenningloh, Jared Head, Federica Morandi, Philipp Haselmayer, and Lesley Liu-Bujalski

Molecular Pharmacology March 2017, 91 (3) 208-219; DOI: https://doi.org/10.1124/mol.116.107037

8. 5P9J

BTK1 COCRYSTALLIZED WITH IBRUTINIB

PDB DOI: 10.2210/pdb5P9J/pdb

https://www.rcsb.org/structure/5P9J

Contacts:

alessandrocareglio@gmail.com

alessandrocareglio@edu.unito.it

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Thanks to Cresset for the academic license of Flare

TABLES:

TABLE 1: BTK inhibitors

- Acalabrutinib
- Elsubrutinib
- Erlotinib
- Evobrutinib
- Fenebrutinib
- Gefitinib
- Ibrutinib
- Imatinib mesylate
- Pirtobrutinib
- Poseltinib
- Spebrutinib
- Structure2D Btk inhibitor
- Tirabrutinib
- Zanubrutinib