

Supplementary material

Multi-functional Neuroprotective Activity of Neohesperidin Dihydrochalcone:

**A novel scaffold for Alzheimer's disease Therapeutics identified via drug
repurposing screen**

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Result and Discussion

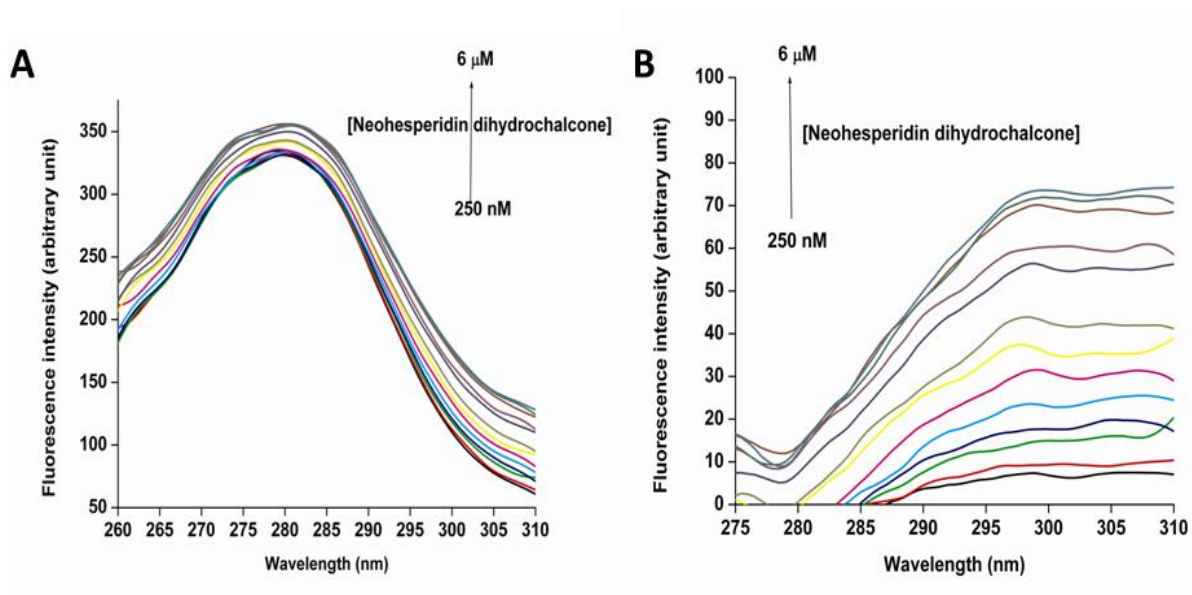


Fig. S1: **A:** Fluorescence excitation spectra of BACE1 ($\lambda_{\text{em}} = 340 \text{ nm}$) upon gradual addition of neohesperidin dihydrochalcone. **B:** Excitation difference spectra obtained by subtracting the excitation spectrum of BACE1 from each excitation spectrum of BACE1-neohesperidin dihydrochalcone complexes.

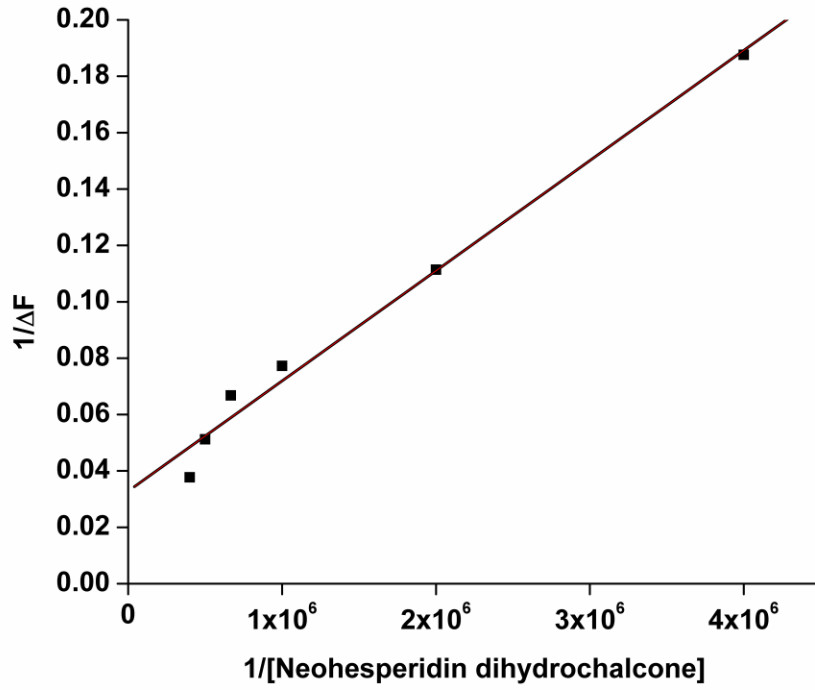


Fig. S2: Double reciprocal plot using fluorescence intensity data for neohesperidin dihydrochalcone binding to BACE1.

Table S1: List of compound and their predicted activities obtained from the *in silico* virtual screening of an in house developed dataset using the developed multi-target screening protocol

Compound name	BACE1		Anti-A β activity	Antioxidant activity (TEAC)	
	Docking score	IC ₅₀ predicted (nM)	IC ₅₀ predicted (nM)	5 parameter-model	4 parameter-model
Hesperidin	-38.7363	1409.288798	88.28765872	0.688493747	0.665732869
Datiscin	-38.3346	12.46809205	92.66164375	0.657657837	0.659781297
Neohesperidin dihydrochalcone	-36.67	248.141841	77.94	0.556800992	0.883486667
Diosmin	-36.9216	288.8683761	272.3955447	0.723602402	0.531251293
D-(+)-Raffinose pentahydrate	-36.7014	1548.460032	0.37230597	0.077196925	0.143021062
Didymin	-36.6885	239.607275	4132.377612	0.541127992	0.586273143
Peltatoside	-34.3517	1158.510569	69.19902892	0.718290297	0.850942079
Oleuropein	-34.1546	32.8700224	2285.598803	0.167455725	0.203282503
Isorhoifolin	-32.7672	0.309243087	426.0886836	0.412952405	185.5666809
Isorhamnetin-3-O-rutinoside	-32.3747	261.0958687	41.56234088	0.637969623	0.668036205
Narirutin	-32.2794	113.3965913	193.8652636	0.617731859	0.831955314
Eriocitrin	-31.483	794.6941206	62.21570117	0.738244126	0.698393197
Flavanomarein	-31.1496	141.1887197	225.4239212	1.284990746	1.138675562
Rhoifolin	-29.9971	32.31469044	977.0122297	0.631102645	0.743019138
Maltotriose	-29.9517	573.9842822	0.073012967	0.069951978	0.211836114
Neoeriocitrin	-29.8783	9.16854E-06	359.4181463	0.692309036	219.0786217
Amygdalin	-29.6618	126.9404402	841.7827077	0.171159102	0.759451423

Sciadopitysin	-29.511	30.59849035	1336.903314	9.234215383	9.64050979
Saponarin	-29.3091	6.504291551	362.4933135	0.664354682	0.80686337
Neodiosmin	-29.1865	986.0524125	41.94691249	0.685488226	0.909703781
Robinin	-29.1145	222.3821886	8.152672562	0.37471407	0.629796148
Linarin	-28.7275	36.71977404	414.6675015	0.579161921	0.62936125
Aristolochic acid	-28.5487	6.144690317	335196.905	1.958393685	2.687818879
Naringin	-28.11	267.4853494	203.1421291	0.607715062	0.823000312
Luteolin-3',7-di-O-glucoside	-27.0711	718.7866461	33.32728996	0.662216504	0.875386813
Quercetin-3,4'-di-O-glucoside	-27.0132	117.4356619	27.20194762	0.70291045	0.821296553
Gentianose	-26.5373	3019.95172	0.222894832	0.07730365	0.157108615
Fraxin	-25.9137	5.251701096	9556.524994	0.274852695	0.33581493
Isorhamnetin-3-O-glucoside	-25.8574	1474.347983	2087.372704	1.087176359	0.969616506
Kaempferol-7-O-neohesperidoside	-25.8215	753.5290502	65.93256931	0.603253708	0.602004864
Neohesperidin	-25.0251	45.25848374	44.76102262	0.663590256	0.768599327
Psoromic acid	-24.7807	135.3630091	72694.23992	0.764891791	4.244240644
Sissotrin	-24.7341	594.8397741	9543.331283	0.803526122	0.874580923
Fortunellin	-24.5764	17.94733627	347.2961749	0.593745047	0.608975751
Protohypericin	-24.4967	2702.713432	9.149555587	1301.667316	486.9675252
Luteolin-4'-O-glucoside	-24.3332	475.9923797	846.2525688	1.158510569	1.517399721
Rutinose	-24.2496	3965.51868	3.025519804	0.108617549	0.13620718
Aloin A	-23.8745	246.831169	543.2503315	1.534616983	0.712524825
Lanatoside B	-23.7288	23.2434184	0.268720006	0.017615704	0.01680351

Glycitin	-23.6008	839.0734899	2435.0058	0.834449387	0.806677605
Syringetin-3-O-glucoside	-23.4617	371.0222886	1374.041975	0.900326431	0.811708325
Ononin	-23.3663	739.0945503	6486.344335	0.809282222	0.954552897
4-deoxyphloridzin	-23.3084	253.1628639	780.3689842	1.183041556	0.764539626
Piperine	-23.0781	4544.645372	11122438.17	0.181886305	0.153497038
Icariin	-22.6963	516.2974737	218.6250894	0.563637656	0.381944271
4',6,7-trihydroxy isoflavone	-22.3716	28608.82361	1158.510569	1.461503972	2.173201519
Glycocholic acid	-22.0943	734.0066592	0.004879777	0.067951649	316227766
Lariciresinol	-22.0722	175.5092458	4134.28108	0.883893622	0.922783882
Kaempferol-3-O-glucoside	-21.8926	172.0679561	1029.674601	1.091440336	1.413513628
Ursodeoxycholic acid	-21.5457	4830.58802	3.15427824	0.064002951	0.007259388
Poncirin	-21.1663	64.44659847	594.2921586	0.568591025	0.700809532
Tectorigenin	-21.0812	2652.772459	46762.74537	1.14182619	1.397655056
D-melibiose	-20.9825	5432.503315	0.263997613	0.113579512	0.187283708
Puerarin	-20.8924	833.6811846	5114.462516	1.249683397	0.74954895
Ajmalicine	-20.8658	3793.14985	26662.44668	0.206395393	0.062632536
Beta-Boswellic acid	-20.8212	184.5015419	6.077150616	0.053789809	0.004759924
Sennidine A	-20.761	11324.00363	3.37442671	12.15346179	18.97142704
Baicalein	-20.7146	875.7900363	5153.47294	1.320383231	1.867669386
Helicin	-20.6092	623.1606189	3966.431879	0.357519719	0.525412015
D-(-)-salicin	-20.4627	1108.919448	37748.52617	0.405041945	0.637382301
Carnosol	-20.354	146.5885335	2379.030446	0.223975235	0.061305579
Chitobiose	-20.3434	169.6680232	451.3360253	0.077037113	0.061503524

Trehalose	-20.2298	3184.197522	0.558984802	0.141123715	0.13743584
Chenodeoxycholic acid	-20.1691	4584.584692	1.097488555	0.064714262	0.007407983
Digitoxigenin	-19.8806	109.6983259	29.63466349	0.052856694	0.006886523
Matairesinol	-19.8008	62.54606617	9490.738339	0.785416463	0.52589616
Verbenaline	-19.4418	2881.376435	4716.284553	0.067421747	0.041001524
Stachyose	-19.2823	315.3552025	0.043611397	0.045782552	0.191249364
Alpha-Sophorose	-19.1636	381.9442708	0.644614396	0.132525667	0.173141031
Demissidine	-18.7496	773.7488205	3.347341331	0.058979352	0.008707631
Isomaltose	-18.4698	573.3238387	27.88688463	0.134865231	0.227300295
Prunetin	-18.43	798.7300061	12894.3662	1.061695557	1.099765268
Proscillaridin A	-18.3991	26.21199039	104.2317429	0.045582695	0.011225353
D-(+)-saccharose	-18.3894	4258.925077	1.521948651	0.132892356	0.161733506
5,6-benzoflavone	-18.3512	812.6433766	4391.36969	2.917427014	2.09652478
L-(-)-mannose	-18.3297	20225.53415	1039.441375	0.365342335	0.202162221
Corynanthine	-18.2705	1716.326863	13255.61861	0.211494949	0.073198132
Beta-Gentiobiose	-18.2689	57.70321353	10.48576209	0.128765643	0.19155787
Deoxycorticosterone acetate	-18.066	66.81900434	175.0652708	0.053629037	0.005516962
Aucubin	-17.9236	396.4605691	732.8245331	0.106757895	0.169824365
Inulin	-17.8985	61.67369945	0.453941617	0.043521114	0.09191788
Cinchonidine	-17.7837	59.93768983	14315.28504	0.230303215	0.11529222
Cucurbitacin I	-17.6236	343.9537114	404.3896205	0.079634269	0.032374271
Apomorphine	-17.4423	12022.64435	8532.965702	1.21338885	0.359749335
7,8-benzoflavone	-17.2833	545.7578611	7.989139417	2.70520387	3522086356
Lactulose	-17.2521	453.6281532	27.27093323	0.121478662	0.189321528

Ethyl-rhoeagenine	-17.0891	1921.321311	4620617.302	0.532966608	2.558585887
Cucurbitacin E	-17.0392	123.2537098	1022.556939	0.06007586	0.031666495
Beta-ecdysone	-16.9404	362.9108896	3.224036872	0.094406088	0.012708667
Digoxin	-16.7083	50.48937562	1.040159644	0.029586937	0.01008556
Myristicin aldehyde	-16.6419	1328.311706	1073989412	0.222792209	1.375308097
Gitoxin	-16.5613	0.189190794	1.532145465	0.033158891	0.010430377
Homatropine	-16.2942	1283.80777	51963.69201	0.172822387	0.048050731
Protopine	-16.1931	3543.235349	6947043.207	0.647142616	0.996974844
DI-laudanosine	-15.7198	2009.092813	658415.4299	0.618728328	0.667728633
Myricanol	-15.693	2235.115653	2025.349607	1.108664139	0.611223439
5-methoxyflavanone	-15.6884	3518.033738	88920.11179	0.660085207	0.59319844
Vialinin A	-15.653	3235.936569	323.4446709	30.95993213	49.00044228
Andrographolide	-15.5857	503.6165574	513.4521775	0.0575705	0.010678248
Karanjin	-15.5574	2259.956084	23211.32861	0.6475898	0.905315592
Celastrol	-15.5104	2045.97348	202.348505	0.225060873	0.052966344
Bromolaudonosin	-15.5047	3397.817118	7103951.7	0.565457541	1.256897898
Ajmaline	-15.4643	4895.533198	887.7690494	0.272082118	0.119426306
Flavan-3-ol	-15.4297	2453.578741	981.0336406	0.819218969	0.997232216
Lithocholic acid	-15.396	2194.320195	2.257875546	0.06060382	0.006002055
Ipriflavone	-15.3924	371.5352291	220902.1791	0.661911612	0.416965382
Cytisine	-15.2061	11622.51191	2244915.508	0.081021448	0.023453086
Rotenone	-15.0891	2475.711306	7542233.958	0.61687902	0.578895269
Oleocanthal	-14.9403	359.6665093	414572.0318	0.247001733	0.281643673
Neoruscogenin	-14.9027	10594.97655	84.97672708	0.055834162	0.035131768
L-hyoscyamine	-14.7354	1061.695557	81564.27871	0.222535858	0.056780603

Cellobiose	-14.7282	10141.44874	6.270468637	0.145948622	0.187845156
Ginkgolide A	-14.6433	170.4119319	335.505775	0.02131572	0.054726793
Diosgenin	-14.5171	399.5765566	18.92343619	0.055169621	0.023993853
Harmaline	-14.4865	4870.796665	576235.4864	0.219533095	0.474569693
Pilocarpine	-14.4662	54.03809121	473260.2186	0.051003502	0.031088517
Cucurbitacin D	-14.3841	17.72148045	112.8236122	0.082451773	0.028536454
Ginkgolide B	-14.2578	82.20533434	340.251462	0.020691882	0.068580398
Cymarol	-14.1704	1.953439656	40.30881213	0.043954162	0.021777098
Alpha-ecdysone	-14.1475	71.17049723	7.001643594	0.08731724	0.011651987
Abietic acid	-14.0298	1242.224241	470.6520991	0.051156403	0.012246162
Hypophyllantin	-13.9385	2274.573631	618585.8765	0.608135001	1.406047524
Sparteine	-13.807	67390.70504	8.258477692	0.055118831	1.53391E-05
Cytochalasin	-13.6931	332.2002845	17108.02988	0.16931678	0.050933087
Cymarol	-13.288	5.869485039	9.552125065	0.045196	0.010036909
Marrubiin	-13.1813	15.85988376	177.9098527	0.062230029	0.015527445
Guggulsterone E	-13.0869	77464.01448	3697.430335	0.068754321	0.015801561
Isoflavan	-13.0251	6918.309709	1237.656138	0.646844664	0.939723311
Seneciophyllin	-12.8609	6423.918168	1008091.609	0.05098002	0.04995742
Parthenolide	-12.7032	220.4448716	107225.974	0.035156044	0.014972696
Eburnamonine	-12.6344	5833.107765	22898.12912	0.220495637	0.087236855
18-alpha-Glycyrrhetic acid methyl ester	-12.6329	19.72422736	30.8318795	0.051594095	0.008990834
Elemolic acid	-12.5566	2096.52478	41.20975191	0.051736852	0.008588157
Guggulsterone Z	-12.4091	88267.33207	1425.607594	0.06948643	0.01619571
Beta-Amyrin acetate	-11.9193	138.5798223	54.38761317	0.038841858	0.004111497

Alpha-Boswellic acid	-11.8618	971.4042517	7.46276902	0.05365374	0.00480618
Conessin	-11.8403	39454.81397	26.74853494	0.052323887	1.29211E-05
Phyllantine	-11.7172	450.4016782	388508.0304	0.564286941	0.644762841
Sarsapogenine	-11.4613	514.5173214	2.284546489	0.052601727	0.021032941
Ginkgolide C	-11.455	58.04970272	279.5117054	0.021517906	0.079250133
Alpha-Acetylboswellic acid	-11.1469	145.0774789	36.04126286	0.040888389	0.006277692
Guaiol	-11.1071	1290.921994	8.731724006	0.064239182	0.011835865
Betulin diacetate	-10.9823	2715.18859	739.9459543	0.03353513	0.00686594
Cedrol	-10.7859	1208.370182	0.336511569	0.070339617	0.009490738
Lupeol acetate	-10.1884	2224.333998	91.0122812	0.039856577	0.00496478
Tomatidine	-10.1825	1384.203682	3.037386092	0.059648565	0.019966411
Sclareol	-9.9749	6103.795856	11.88775922	0.065871871	0.011468325
Caulophyllogenin	-9.3954	1037.528416	2.712688961	0.065569217	0.008943345
Friedelin	-9.3814	16904.40932	3.964605691	0.052227592	0.005661089
Nootkatone	-9.3146	73451.38682	493.6282431	0.061773186	0.010730007
Alpha-Pineneoxide	-9.0677	16630.2968	13.80384265	0.048741625	0.02748527
Dihydrocarveol	-8.7013	2351.79791	20516.34531	0.072193816	0.013819744
Norcamphor	-8.3612	3291546.539	90.55240723	0.084664237	0.022898129
Lanatoside C	-8.338	93.90743969	0.341743293	0.017901936	0.019801587
Lupeol	-7.9729	609.2562597	3.464974158	0.053174082	0.008717661
Isobornyl acetate	-7.7658	1857.376729	699.5197811	0.044575888	0.010894317
Betulinic acid	-7.4054	9538.937428	12.34241088	0.050815944	0.007282827
Beta-acetyl boswellic acid	-7.3869	897.8421709	16.74942876	0.040234629	0.008348338
Sabinyol acetate	-7.2868	1936.421964	20878.53395	0.042884465	0.019164611

Lupenone	-7.0419	12820.35349	24.13237137	0.05041967	0.007256046
Beta-Amyrin	-6.872	480.8393484	3.045790305	0.052432432	0.008822669
Neohesperidose heptaacetate	-6.5921	0.304649171	222997503	0.008064919	0.143946132
Cholesterol	-6.1286	724.1024218	9.418895965	0.057782989	0.00865765
Cholesteryl acetate	-5.7565	187.7586699	275.4228703	0.039636929	0.004345102
Eucalyptol	-5.4435	5592.42283	7.954263981	0.057956213	0.01437474
Cycloartenol	-5.1056	665.2731562	8.478128603	0.05332121	0.009711806
Terpinyl acetate	-5.0934	1645.129159	12433.68899	0.045561708	0.013567505
Fucosterol	-4.6058	675.7716994	17.45420209	0.05322308	0.009808441
Ergosterol	-4.421	752.6620171	119.4263062	0.05310067	0.012336728
Betulinic acid methyl ester	-4.364	758.9269934	30.30400298	0.048250298	0.007158137
Beta-sitosterol	-4.2923	756.1361471	5.995149258	0.054550659	0.008163944
Stigmasterol	-3.7098	711.8688673	19.95721794	0.056272991	0.009910601
Betulin	-3.5559	864.1716206	2.534544963	0.055131524	0.010308607
Cycloartenol acetate	-1.3934	198.2896289	130.5870166	0.039165169	0.004520641
18-beta-Glycyrrhetic acid methylester	N.D.	15.41700453	38.87764949	0.05514422	0.009942601
11-keto-beta-Boswellic acid	N.D.	150.3834348	5.468900223	0.062115502	0.007512768
D-(+)-Raffinose undecaacetate	N.D.	151.2167849	48528.85002	0.014371431	0.072727725
Ursolic acid methylester	N.D.	453.6281532	33.64340936	0.04995742	0.007640117
3-O-Acetyl-11-keto-beta-Boswellic acid	N.D.	610.6607405	28.106062	0.040926066	0.012122718
Oleanolic acid	N.D.	679.672972	28.79386738	0.049283325	0.00793049

methyl ester					
Alpha-Amyrin	N.D.	710.2316143	3.318180448	0.054865583	0.008336812
Boswellic acid alpha	N.D.	971.4042517	7.46276902	0.05365374	0.00480618
Erythrodiol	N.D.	1166.003892	1.562068231	0.05900652	0.010406388
18-beta-Glycyrrhetic acid	N.D.	1242.796438	7.032342269	0.060283714	0.009908319
Uvaol	N.D.	1358.000719	2.398280631	0.062215701	0.01081185
Echinocystic acid	N.D.	1793.081377	3.907509117	0.059142544	0.008384941
18-alpha-Glycyrrhetic acid	N.D.	1896.705921	45.16479049	0.057623549	0.014750271
Calestrol	N.D.	2045.97348	202.348505	0.225060873	0.052966344
Asiatic acid	N.D.	4060.691534	1.432847598	0.067842212	0.010029978
Ursolic acid	N.D.	4080.374267	11.74627056	0.051558467	0.007751754
Hypericin	N.D.	5349.337509	3.738522511	381.0658234	152.6159766
D-melezitose	N.D.	5432.503315	0.263997613	0.113579512	0.187283708
Hederagenin	N.D.	6429.837541	4.048554594	0.060939656	0.008912509
Oleanolic acid	N.D.	8877.690494	3.3954708	0.053826978	0.008033411
Cholesteryl chloride	N.D.	343162.6398	45.77201167	0.041638972	1.75509E-05
Alpha-Humulene	N.D.	10384844.55	155.2029601	0.048061796	1.28351E-05
(-)-Trans caryophyllene	N.D.	10468874.66	192.9301047	0.047446043	1.37499E-05
Beta-Cedrene	N.D.	11122438.17	13.32293779	0.048551204	1.03062E-05
Camphene	N.D.	12820353.49	20.8257188	0.049934419	1.27761E-05
Alpha-Cedrene	N.D.	13430741.8	4.8674332	0.048696753	9.38642E-06
Ledene	N.D.	13598781.63	39.70086781	0.049842521	1.15239E-05

N.D.- Not docked