

Supplementary Materials

Chemoinformatic Database Building and *in Silico* Hit-Identification of Multi-targeting Bioactive Compounds Extracted from Mushroom Species

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Table S1. Re-docking experiments details with the relative co-crystallized ligand of each PDB model.

Anticancer activity			
Target	PDB code	Co-crystallized ligand	G-score (kcal/mol)
c-Met	2WGJ	Crizotinib	-12.03
MEK1	4ARK	2-([(3R-3,4-Dihydroxy-butyl]oxy)-4-fluoro-6- [(2-fluoro-4-iodophenyl)-amino]benzamide	-8.64
SIRT1	4I5I	(6S)-2-Chloro-5,6,7,8,9,10-hexahydrocyclohepta[b]indole-6-carboxamide	-10.36
MEK2	1S9I	5-[3,4-Difluoro-2-(2-fluoro-4-iodophenylamino)-phenyl]-[1,3,4]oxadiazol-2-yl)-(2-morpholin-4-yl-ethyl)-amine	-8.61
SGK1	3HDM	4-(5-Phenyl-1H-pyrrolo[2,3-b]pyridin-3-yl)benzoic acid	-9.77
VEGFR2	3VHE	Pyrrolopyrimidine derivative	-13.9
EGFR	3POZ	Tak-285	-13.89
B-RAF V600E	3OG7	Vemurafenib	-12.24
PDK1	3NAX	1-(3,4-Difluorobenzyl)-2-oxo-N-[(1R)-2-[(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)oxy]-1-phenylethyl]-1,2-dihydropyridine-3-carboxamide	-18.82
Anti-inflammatory activity			
Target	PDB code	Co-crystallized ligand	G-score (kcal/mol)
COX-2	5IKR	Mefenamic Acid	-10.04
Adenosine A2A R	3RFM	Caffeine	-8.09
COX-1	1Q4G	α -Methyl-4-biphenylacetic acid	-10.73
Glucocorticoid	1M2Z	Dexamethasone	-12.35

Table S1. *Cont.*

Neurodegenerative activity			
Target	PDB code	Co-crystallized ligand	G-score (kcal/mol)
GSK3b	4ACC	5-[3,4-Difluoro-2-(2-fluoro-4-iodoanilino)phenyl]-N-(2-morpholin-4-ylethyl)-1,3,4-oxadiazol-2-amine	-9.15
AChE	4EY7	Donepezil	-12.79
MAO-B	2V5Z	Safinamide	-9.12
Metabolic disease activity			
Target	PDB code	Co-crystallized ligand	G-score (kcal/mol)
PPAR- α	3VI8	APHM13	-14.51
PPAR- γ	2PRG	Rosiglitazone	-12.46

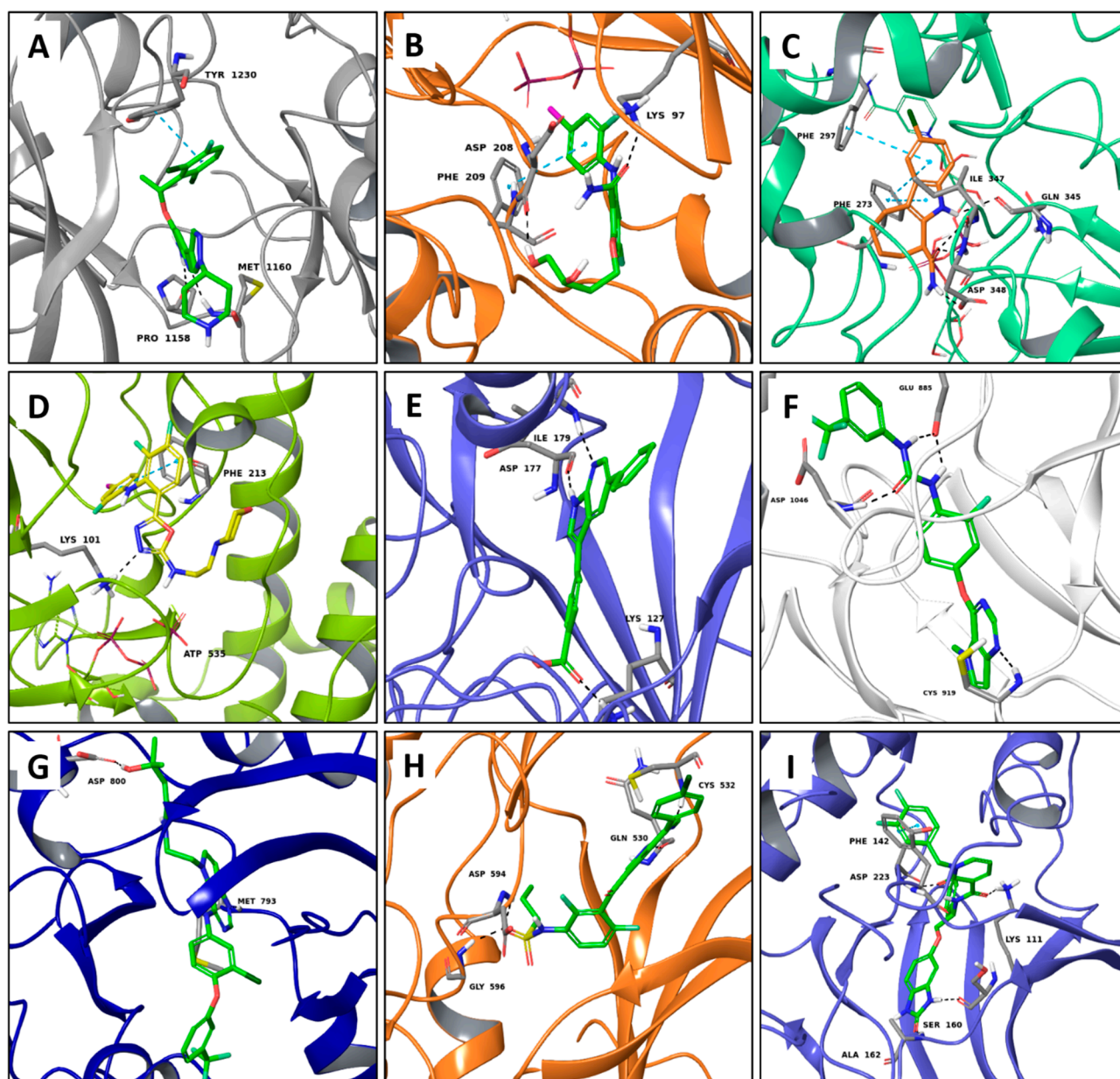


Figure S1. Re-docked best pose of the relative co-crystallized ligands in the anticancer PDB models: (A) c-Met (PDB code: 2WGJ); (B) MEK1 (PDB code: 4ARK); (C) SIRT1 (PDB code: 4I5I); (D) MEK2 (PDB code: 1S9I); (E) SGK1 (PDB code: 3HDM); (F) VEGFR2 (PDB code: 3VHE); (G) EGFR (PDB code: 3POZ); (H) B-RAF V600E (PDB code: 3OG7); (I) PDK1 (PDB code: 3NAX).

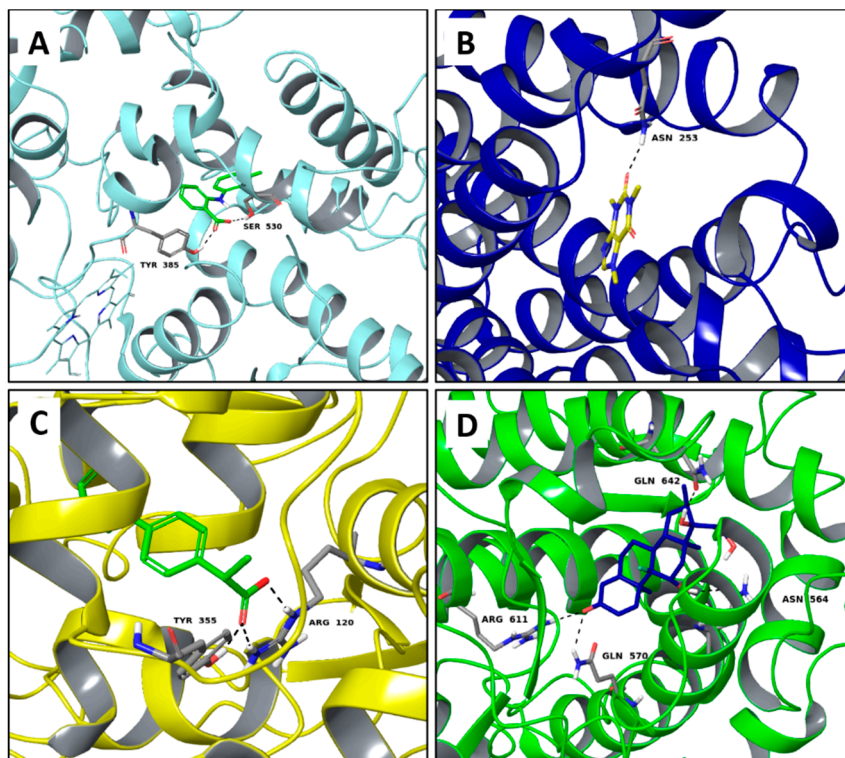


Figure S2. Re-docked best pose of the relative co-crystallized ligands in the anti-inflammatory PDB models: (A) COX-2 (PDB code: 5IKR); (B) Adenosine A2A R (PDB code: 3RFM); (C) COX-1 (PDB code: 1Q4G); (D) Glucocorticoid R (PDB code: 1M2Z).

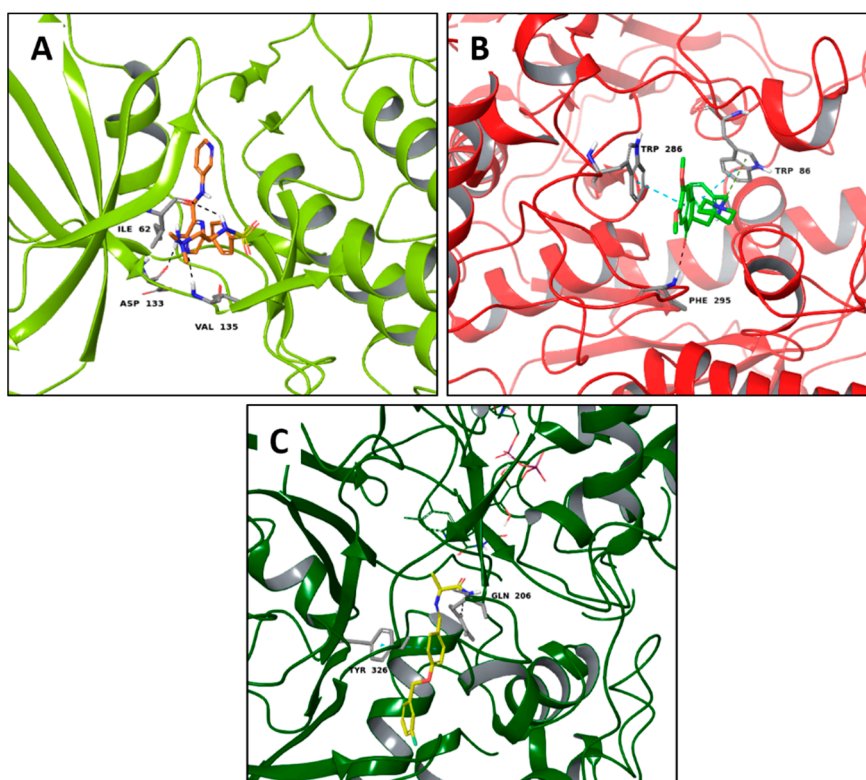


Figure S3. Re-docked best pose of the relative co-crystallized ligands in the main targets involved in the neurodegenerative diseases: (A) GSK3 β (PDB code: 4ACC); (B) AChE (PDB code: 4EY7); (C) MAO-B (PDB code: 2V5Z).

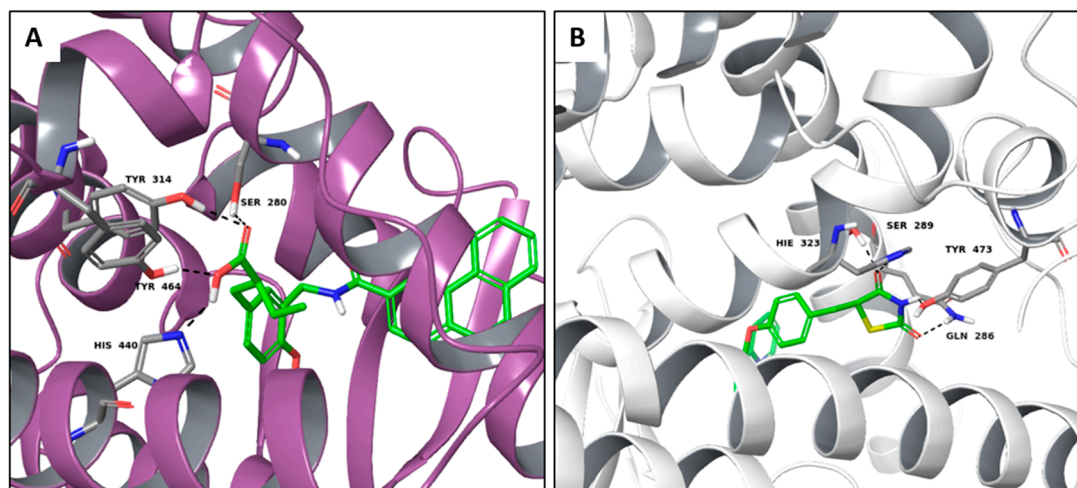


Figure S4. Re-docked best pose of the relative co-crystallized ligands in the main targets involved in the metabolic diseases: (A) PPAR- α (PDB code: 3VI8); (B) PPAR- γ (PDB code: 2PRG).

Table S2. Non-selective MTAs.

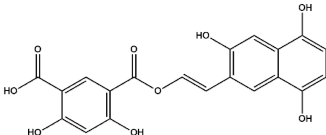
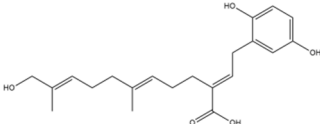
Name	2D Structure	Targets	G-score (kcal/mol)
Fuscoprine		Aurora B kinase	-8.76
		c-Met	-9.48
		VEGFR2	-10.37
		EGFR	-10.43
		ERK1	-8.56
		B-RAF wt	-10.05
		B-RAF V600E	-9.1
		BMX	-8.74
		Akt	-8.99
		CDK2	-9.2
		SGK1	-9.36
		CA IX	-8.2
		SIRT1	-8.58
		PKA C- α	-9.7
		PPAR- α	-8.98
		AChE	-9.97
		BuChE	-8.83
		MAO-B	-8.84
AdenosneA2A R	-8.1		
Glucocorticoid R	-9.72		
Ganomycin A		c-Met	-8.65
		VEGFR2	-8.65
		B-RAF wt	-8.17
		B-RAF V600E	-8.41
		MEK1	-9.24
		PDK1	-9.36
		IGF-1R	-8.12
		PPAR- γ	-9.09
		COX-1	-8.27
		AChE	-8.54

Table S2. *Cont.*

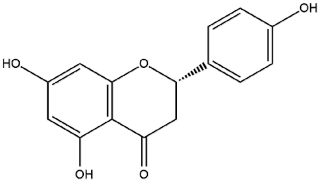
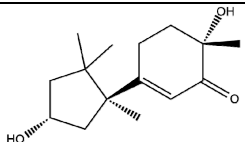
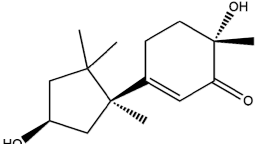
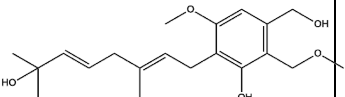
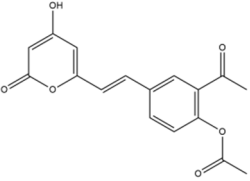
Narigenin		c-Met VEGFR2 EGFR EGFR V948R ERK2 B-RAF wt PI3K α PI3K γ BMX CDK2 IGFR PPAR- γ AChE MAO-A COMT COX-1 COX-2 AdenosineA2A R Glucocorticoid R	-8.2 -9.44 -8.23 -8.2 -8.55 -9.15 -8.25 -8.14 -8.52 -9.02 -8.72 -8.42 -9.03 -8.18 -8.67 -8.22 -8.86 -8.97 -8.74
Enokipodin G		c-Met GSK3 β PPAR- α Glucocorticoid R	-8.64 -8.08 -8.03 -9.74
Enokipodin H		c-Met GSK3 β SIRT1 PPAR- α Glucocorticoid R	-8.79 -8.21 -8.4 -8.11 -8.59
Hericenol C		MEK1 SIRT1 PPAR- α PPAR- γ AChE Glucocorticoid R	-8.37 -8.34 -8.34 -8.33 -8.49 -8.13
Acetylhispidin		c-Met VEGFR2 EGFR B-RAF wt PPAR- α PPAR- γ AChE MAO-B Glucocorticoid R	-8.9 -9.59 -8.57 -8.28 -8.87 -8.6 -8.22 -8.2 -8.32

Table S2. *Cont.*

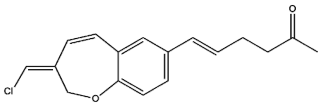
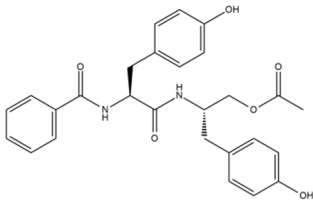
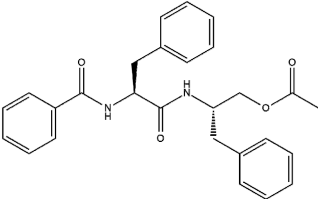
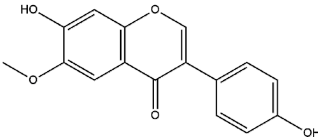
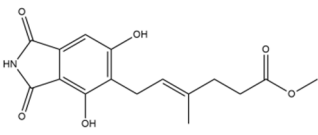
Pterulone B		VEGFR2 MEK1 PI3Kγ SIRT1 PPAR-α PPAR-γ MAO-A MAO-B COX-1 Glucocorticoid R	-8.45 -8.77 -8.1 -8.31 -8.36 -8.08 -8.28 -8.7 -8.4 -9.19
Cordyceamide B		c-Met EGFR PI3K γ PDK1 PPAR- α PPAR- γ AChE BuChE IL-17A AdenosineA2A R	-9.21 -8.41 -9.81 -11.09 -9.13 -10.12 -10.05 -9.93 -10.27 -8.69
Aurantiamide Acetate		Aurora B kinase c-Met EGFR PDK1 PPAR- α PPAR- γ AChE BuChE IL-17A AdenosineA2A R	-8.13 -8.09 -8.24 -10.6 -10.24 -8.45 -9.55 -8.83 -9.95 -9.2
Glycitein		VEGFR B-RAF wt B-RAF V600E PDK1 SIRT1 PPAR- γ AChE COMT COX-1 AdenosineA2A R Glucocorticoid R VEGFR2 EGFR	-9.79 -8.11 -8.18 -8.23 -8.4 -8.14 -8.39 -8.05 -8.47 -8.39 -9.03 -9.3 -8.56
Erinacerin T		B-RAF wt B-RAF V600E CDK2 SIRT1 PKA C- α PPAR- α PPAR- γ AChE Glucocorticoid R	-8.7 -9.59 -8.15 -9.17 -9.57 -9.06 -10.34 -8.57 -8.91

Table S2. *Cont.*

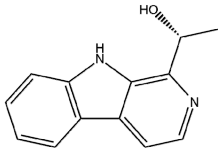
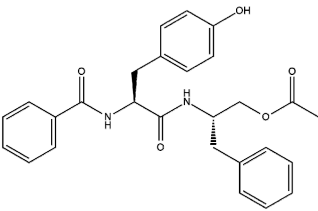
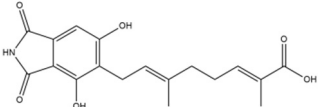
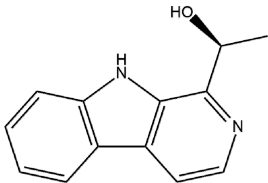
Cordysin C		MEK1 GSK3 β CDK2 SIRT1 Insulin R IGF-1R PPAR- α MAO-A COMT COX-1 Glucocorticoid R	-8.95 -8.09 -8.51 -8.77 -8.28 -8.92 -8.29 -8.61 -8.59 -8.35 -9.24
Cordyceamide A		c-Met EGFR MEK1 PDK1 IGF-1R PPAR- α PPAR- γ AChE BuChE IL-17A AdenosineA2A R	-9.22 -8.64 -9.42 -10.26 -8.89 -9.86 -8.79 -10.23 -9.51 -10.54 -8.05
Erinacerin S		c-Met VEGFR2 B-RAF V600E PDK1 CDK2 SIRT1 PKA C- α PPAR- α PPAR- γ AChE AdenosineA2A	-8.28 -8.46 -8.29 -8.98 -8.27 -9.49 -9.81 -9.85 -10.65 -8.77 -8.54
Cordysin D		ERK2 P38 MAP kinase PDK1 GSK3 β CDK2 SIRT1 Insulin R PPAR- α MAO-A COMT COX-1 Glucocorticoid R	-8.24 -8.1 -8.24 -8.64 -8.0 -8.51 -8.5 -8.18 -8.25 -8.62 -8.66 -8.76

Table S2. *Cont.*

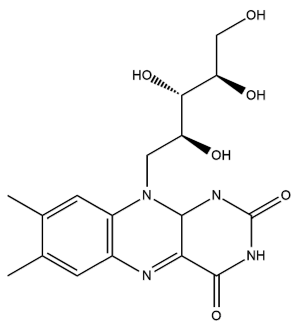
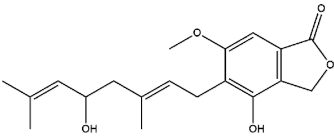
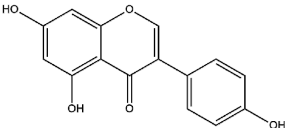
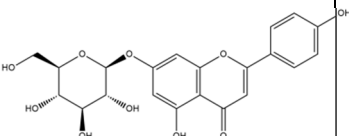
Riboflavin		EGFR V948R B-RAF wt MEK1 PI3K γ GSK3 β CDK2 Insulin R PPAR- γ AChE BuChE COMT AdenosineA2A R Glucocorticoid R	-8.62 -9.55 -8.63 -9.32 -8.67 -8.06 -8.56 -8.14 -8.75 -8.32 -9.1 -8.0 -8.74
Erinacerin B		c-Met VEGFR2 EGFR B-RAF V600E MEK1 SIRT1 Insulin R PKA C- α PPAR- α PPAR- γ AChE MAO-A AdenosineA2A R Glucocorticoid R	-8.44 -8.26 -8.35 -8.94 -8.03 -8.86 -8.94 9.17 -8.86 -9.55 -8.59 -8.17 -8.02 -9.74
Genistein		c-Met VEGFR2 EGFR ERK2 B-RAF wt MEK1 SIRT1 IGF-R1 PPAR- γ AChE COMT COX-1 COX-2 AdenosineA2A R	-8.19 -10.36 -8.26 -8.82 -8.21 -8.04 -8.01 -8.21 -8.01 -8.26 -8.45 -9.05 -8.54 -8.76
Apigenin-7-glucoside		VEGFR2 EGFR ERK1 B-RAF wt MEK1 PI3K γ PDK1 BMX CDK2 Insulin R PPAR- α PPAR- γ AChE COMT AdenosineA2A R	-8.69 -9.73 -8.13 -8.99 -9.24 -8.51 -8.02 -9.48 -9.22 -8.43 -8.18 -9.22 -9.87 -8.25 -9.76

Table S2. Cont.

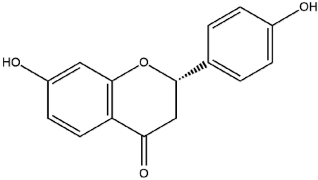
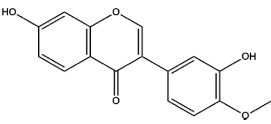
Liquiritigenin		c-Met	-8.43
		VEGFR2	-10.26
		EGFR	-8.13
		EGFR V948R	-8
		ERK1	-8.4
		B-RAF wt	-9.29
		B-RAF V600E	-8.06
		MEK1	-8.65
		PI3K- α	-8.1
		PI3K- γ	-8.0
		BMX	-8.42
		CDK2	-9.06
		SGK1	-8.3
		SIRT1	-8.10
		AChE	-8.93
		MAO-A	-8.86
		COMT	-8.26
		COX-1	-8.39
		COX-2	-9.32
		AdenosineA2A R	-8.74
		Glucocorticoid R	-9.58
Calycosin		VEGFR2	-9.64
		EGFR	-8.43
		ERK2	-8.25
		B-RAF wt	-8.19
		BMX	-8.29
		CDK2	-8.81
		SIRT1	-8.61
		Insulin R	-8.01
		IGF-1R	-8.12
		PPAR- α	-8.70
		PPAR- γ	-8.20
		AChE	-8.83
		COX-1	-8.64
		COX-2	-8.00
		AdenosineA2A R	-8.06
		Glucocorticoid R	-9.87

Table S3. Classification of edible and not edible mushrooms with species and family.

Edible mushrooms		Toxic mushrooms	
Species	Family	Species	Family
<i>Agaricus arvensis</i>	Agaricaceae	<i>Agaricus xanthodermum</i>	Agaricaceae
<i>Agaricus bisporus</i>	"	<i>Chlorophyllum rachodes</i>	"
<i>Agaricus bitorquis</i>	"	<i>Lepiota brunneoincarnata</i>	"
<i>Agaricus campestris</i>	"	<i>Lepiota helveola</i>	"
<i>Agaricus subrufescens</i>	"	<i>Lepiota subincarnata</i>	"
<i>Macrolepiota procera</i>	"	<i>Amanita aminoaliphatica</i>	Amanitaceae
<i>Albatrellus pescaprae</i>	Albatrellaceae	<i>Amanita junquillea</i>	"
<i>Amanita caesarea</i>	Amanitaceae	<i>Amanita muscaria</i>	"
<i>Amanita rubescens</i>	"	<i>Amanita ovoidea</i>	"

Table S3. Cont.

<i>Volvariella volvacea</i>	Amanitaceae	<i>Amanita pantherina</i>	Amanitaceae
<i>Auricularia auricula-judae</i>	Auriculariaceae	<i>Amanita phalloides</i>	"
<i>Boletus aereus</i>	Boletaceae	<i>Amanita proxima</i>	"
<i>Boletus appendiculatus</i>	"	<i>Amanita smithiana</i>	"
<i>Boletus edulis</i>	"	<i>Amanita verna</i>	"
<i>Boletus erythropus</i>	"	<i>Amanita virosa</i>	"
<i>Boletus luridus</i>	"	<i>Panaeolus cyanescens</i>	Bolbitiaceae
<i>Boletus pinicola</i>	"	<i>Panaeolus semiovatus</i>	"
<i>Boletus regius</i>	"	<i>Boletus pulchrotinctus</i>	Boletaceae
<i>Boletus reticulatus</i>	"	<i>Boletus rhodoxanthus</i>	"
<i>Boletus subappendiculatus</i>	"	<i>Boletus rubrosanguineus</i>	"
<i>Leccinum aurantiacum</i>	"	<i>Boletus satanas</i>	"
<i>Leccinum scabrum</i>	"	<i>Ramaria pallida</i>	Clavariaceae
<i>Xerocomus badius</i>	"	<i>Coprinus atramentarius</i>	Coprinaceae
<i>Cantharellus cibarius</i>	Cantharellaceae	<i>Cordyceps sinensis</i>	Cordycipitaceae
<i>Cantharellus lutescens</i>	"	<i>Cortinarius orellanoides</i>	Cortinariaceae
<i>Craterellus cornucopioides</i>	"	<i>Cortinarius orellanus</i>	"
<i>Coprinus comatus</i>	Coprinaceae	<i>Galerina autumnalis</i>	"
<i>Fistulina hepatica</i>	Fistulinaceae	<i>Galerina marginata</i>	"
<i>Ramaria botrytis</i>	Clavariaceae	<i>Gymnopilus spectabilis</i>	Crepidotaceae
<i>Hericium erinaceus</i>	Hericiaceae	<i>Cudonia circinans</i>	Cudoniaceae
<i>Hydnum repandum</i>	Hydnaceae	<i>Gyromitra esculenta</i>	Discinaceae
<i>Hydnum rufescens</i>	"	<i>Gyromitra fastigiata</i>	"
<i>Hygrophorus hypothejus</i>	Hygrophoraceae	<i>Gyromitra gigas</i>	"
<i>Hygrophorus marzuolus</i>	"	<i>Gyromitra infula</i>	"
<i>Hygrophorus pudorinus</i>	"	<i>Entoloma nidorosum</i>	Entolomataceae
<i>Hygrophorus russula</i>	"	<i>Entoloma sinuatum</i>	"
<i>Marasmius oreades</i>	Marasmiaceae	<i>Ganoderma lucidum</i>	Ganodermataceae
<i>Flammulina velutipes</i>	"	<i>Helvella crispa</i>	Helvellaceae
<i>Grifola frondosa</i>	Meripilaceae	<i>Inonotus obliquus</i>	Hymenochaetaceae
<i>Morchella costata</i>	Morchellaceae	<i>Inocybe bongardii</i>	Inocybaceae
<i>Morchella elata</i>	"	<i>Inocybe erubescens</i>	"
<i>Morchella esculenta</i>	"	<i>Inocybe geophylla</i>	"
<i>Lentinula edodes</i>	Omphalotaceae	<i>Inocybe rimosa</i>	Cortinariaceae
<i>Armillaria mellea</i>	Physalacriaceae	<i>Mycena inclinata</i>	Marasmiaceae
<i>Pisolithus arhizus</i>	Pisolithaceae	<i>Mycena pelianthina</i>	"
<i>Pleurotus ostreatus</i>	Pleurotaceae	<i>Mycena pura</i>	"
<i>Laetiporus sulphureus</i>	Polyporaceae	<i>Mycena rosea</i>	"
<i>Polyporus umbellatus</i>	"	<i>Omphalotus illudens</i>	Omphalotaceae
<i>Lactarius deliciosus</i>	Russulaceae	<i>Omphalotus olearius</i>	"
<i>Lactarius salmonicolor</i>	"	<i>Paxillus involutus</i>	Paxillaceae
<i>Lactarius sanguifluus</i>	"	<i>Paxillus rubicundulus</i>	"
<i>Lactarius semisanguifluus</i>	"	<i>Lenzites betulina</i>	Polyporaceae
<i>Russula aurea</i>	"	<i>Trametes versicolor</i>	"
<i>Russula chloroides</i>	"	<i>Psathyrella candolleana</i>	Psathyrellaceae
<i>Russula cyanoxantha</i>	"	<i>Psathyrella conopilus</i>	"
<i>Russula delica</i>	"	<i>Ramaria formosa</i>	Ramariaceae
<i>Russula vesca</i>	"	<i>Ramaria fumigata</i>	"
<i>Russula virescens</i>	"	<i>Russula emetica</i>	Russulaceae
<i>Stropharia rugosoannulata</i>	Strophariaceae	<i>Scleroderma geaster</i>	Sclerodermataceae
<i>Suillus bellini</i>	Suillaceae	<i>Hypholoma sublateritium</i>	Strophariaceae
<i>Suillus bellinii</i>	"	<i>Psilocybe coprophila</i>	"
<i>Suillus granulatus</i>	"	<i>Psilocybe cyanescens</i>	"
<i>Suillus luteus</i>	"	<i>Psilocybe merdaria</i>	"
<i>Tremella fuciformis</i>	Tremellaceae	<i>Psilocybe muscorum</i>	"

Table S3. Cont.

<i>Clitocybe geotropa</i>	Tricholomataceae	<i>Psilocybe semilanceata</i>	Strophariaceae
<i>Leucopaxillus giganteus</i>	"	<i>Psilocybe serbica</i>	"
<i>Lepista inversa</i>	"	<i>Stropharia aeruginosa</i>	"
<i>Lepista nuda</i>	"	<i>Stropharia semiglobata</i>	"
<i>Lepista sordida</i>	"	<i>Clitocybe acromelalga</i>	Tricholomataceae
<i>Lyophyllum fumosum</i>	"	<i>Clitocybe amoenolens</i>	"
<i>Tricholoma columbetta</i>	"	<i>Clitocybe candicans</i>	"
<i>Tricholoma imbricatum</i>	"	<i>Clitocybe cerussata</i>	"
<i>Tricholoma portentosum</i>	"	<i>Clitocybe dealbata</i>	"
<i>Tricholoma stans</i>	"	<i>Clitocybe nebularis</i>	"
<i>Tricholoma terreum</i>	"	<i>Clitocybe phyllophila</i>	"
		<i>Clitocybe rivulosa</i>	"
		<i>Tricholoma auratum</i>	"
		<i>Tricholoma equestre</i>	"
		<i>Tricholoma josserandii</i>	"
		<i>Tricholoma pardinum</i>	"
		<i>Tricholoma saponaceum</i>	"
		<i>Tricholoma sciodes</i>	"
		<i>Tricholoma virgatum</i>	"

Table S4. Abbreviations of the 43 targets, selected for structure-based virtual screening studies, with the relative PDB accession code and resolution of X-ray model in Å, RMSD value after re-docking simulation between the experimental pose of the inhibitor into the X-ray and the best pose generated by our docking protocol and G-score.

Target	PDB models	Resolution(Å)	RMSD (Å)	G-score (Kcal/mol)
Akt Kinase	4GV1	1.49	1.06	-11.63
Aurora A kinase	2X81	2.91	0.47	-9.38
Aurora B kinase	2VRX	1.86	0.74	-10.18
BMX	3SXR	2.4	0.89	-11.29
B-Raf kinase	2FB8	2.9	0.68	-10.95
B-Raf Kinase V600E	3OG7	2.45	1.62	-12.24
c-Met kinase	2WGJ	1.2	0.85	-12.03
CDK2	4KD1	1.7	1.39	-11.61
EGFR Kinase	3POZ	1.5	0.89	-13.89
EGFR Kinase V948R	4I22	1.71	1.01	-8.71
ERK1	2ZOQ	2.39	0.37	-9.26
ERK2	4ZZN	1.45	0.58	-12.41
GSK3β	4ACC	2.21	1.20	-9.15
P38 MAP Kinase	3GCP	2.25	0.99	-12.06
MEK1	4ARK	2.6	0.71	-8.64
MEK2	1S9I	3.2	0.38	-8.61
PDK1	3NAX	1.75	0.34	-18.82
PI3Kα	5UBR	2.4	0.92	-10.48
PI3Kγ	3DBS	2.8	0.78	-9.34
SGK1	3HDM	2.6	0.68	-9.77
VEGFR2	3VHE	1.55	0.34	-13.90
SIRT1	4I5I	2.5	0.19	-10.36
5LOX	3V99	2.25	1.51	-4.54

Table S4. Cont.

COX-1	1Q4G	2.0	0.27	-10.73
COX-2	5IKR	2.34	0.36	-10.04
IL-17A	5HI5	1.8	0.33	-13.67
Adenosine A2A R	3RFM	3.6	0.69	-8.09
Glucocorticoid R	1M2Z	2.5	0.32	-12.35
DPP-4	4LKO	2.43	0.92	-6.11
IGF-1R	3I81	2.08	0.32	-10.07
Insulin R	5HHW	1.79	0.31	-12.48
PKA C- α	3POO	1.6	0.23	-12.35
HMG-CoA reductase	1HWL	2.1	0.81	-7.06
PPAR- α	3VI8	1.75	0.23	-14.51
PPAR- γ	2PRG	2.3	0.67	-12.46
AChE	4EY7	2.35	0.20	-12.79
BACE-1	5HU1	1.5	0.22	-6.6
BuChE	1P0M	2.38	Not ligand	
COMT	5LSA	1.5	0.23	-8.53
MAO-A	2Z5X	2.2	0.83	-7.675
MAO-B	2V5Z	1.6	0.58	-9.12
CA IX	5FL4	1.82	1.18	-5.67
CA XII	4WW8	1.42	1.51	-4.95

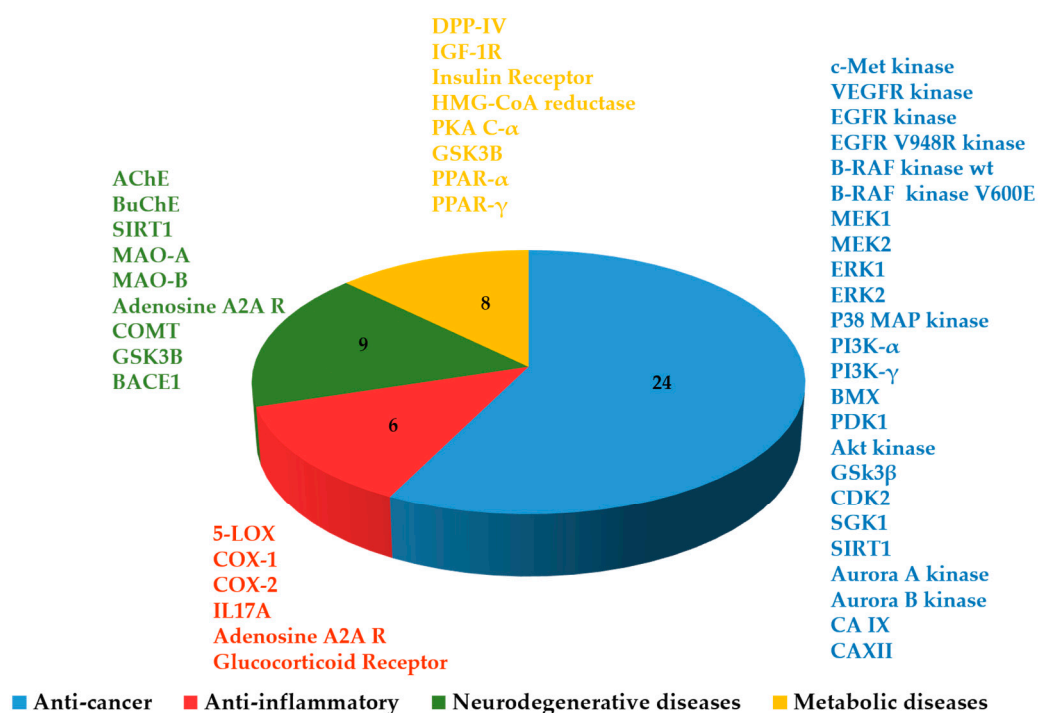


Figure S5. Clustering of biological targets.