

Neuroprotective role of hydroxychloroquine and trimebutine in alzheimer's disease: Network pharmacology and molecular simulations

Renukaradhya Maharudraiah¹, Krishna Kant², Madhusudhan Reddy Alimeneti³, Roma Kumari Gupta⁴, Sunil Kumar Kurmi⁴, Santosh Prasad Chaudhary Kurmi⁴, Aleesha Mujeeb Shaheen⁵ & Mahalakshmi Suresha Biradar^{5*}

¹Department of Pharmacology, KLE College of Pharmacy, Bengaluru-560010, KLE Academy of Higher Education and Research, Belagavi-590 010, Karnataka, India

²Department of Biosciences and Biotechnology, Indian Institute of Technology Kharagpur-721 302, West Bengal, India

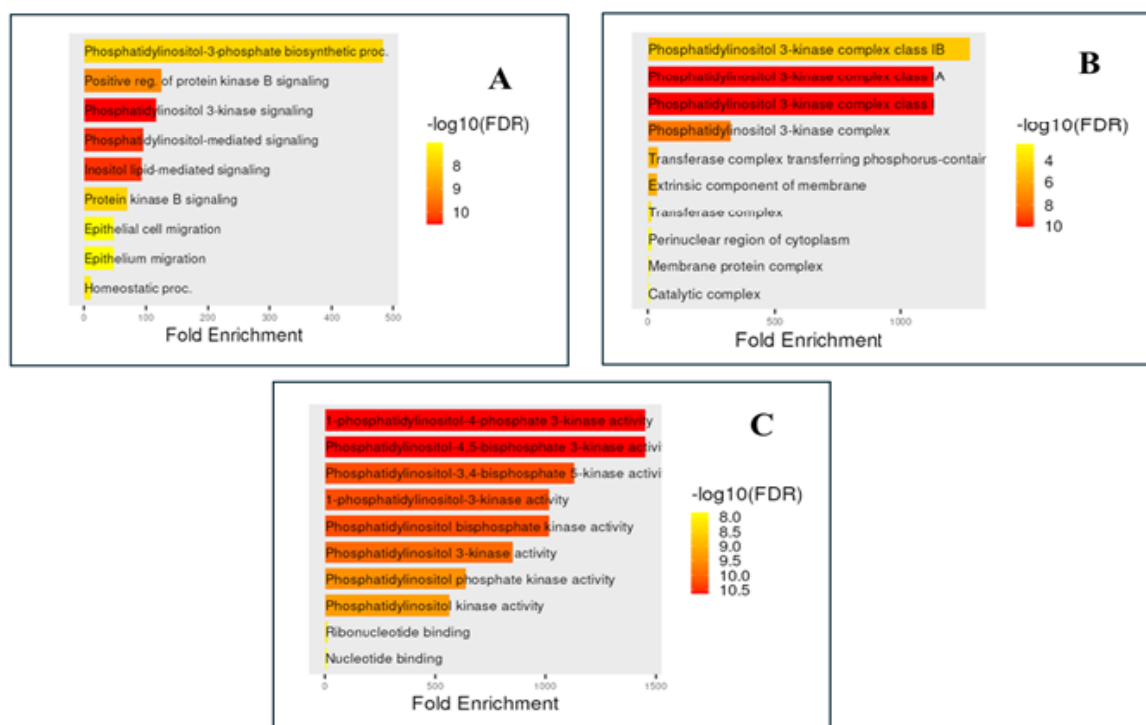
³Department of Pharmacognosy, Princeton College of Pharmacy, Ghatkesar, Hyderabad-501 301, Telangana, India

⁴Department of Pharmacy, Universal College of Medical Sciences, Bhairahawa-32900, Nepal

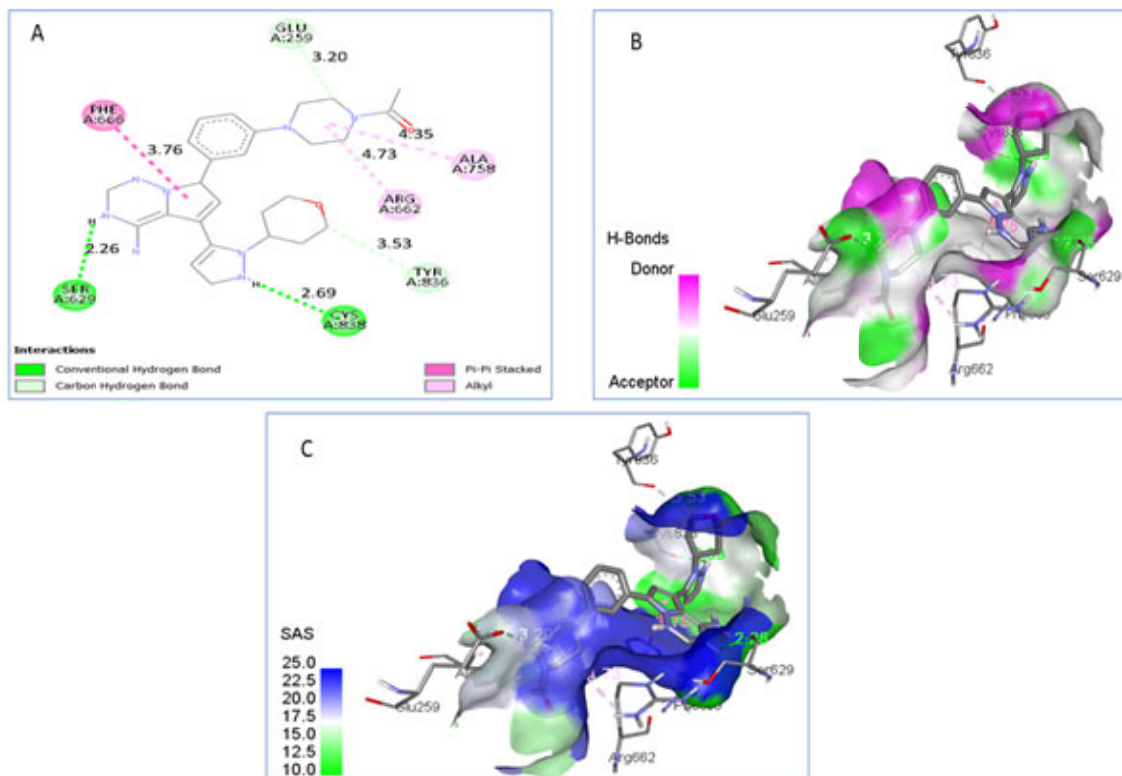
⁵Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy, Bengaluru-560 027, Karnataka, India

Received 15 August 2025; revised 06 May 2026

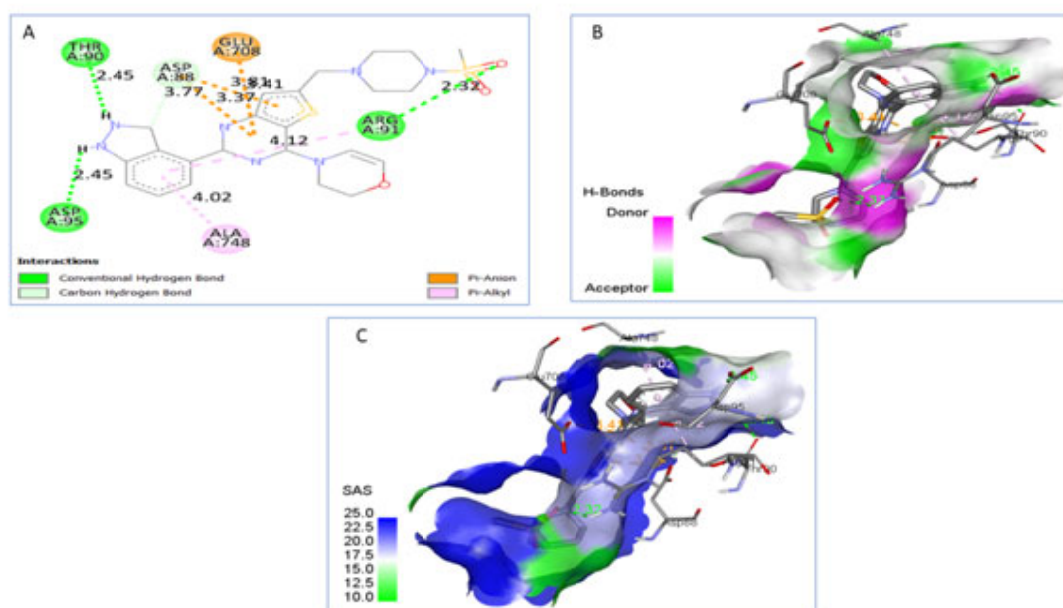
Supplementary data



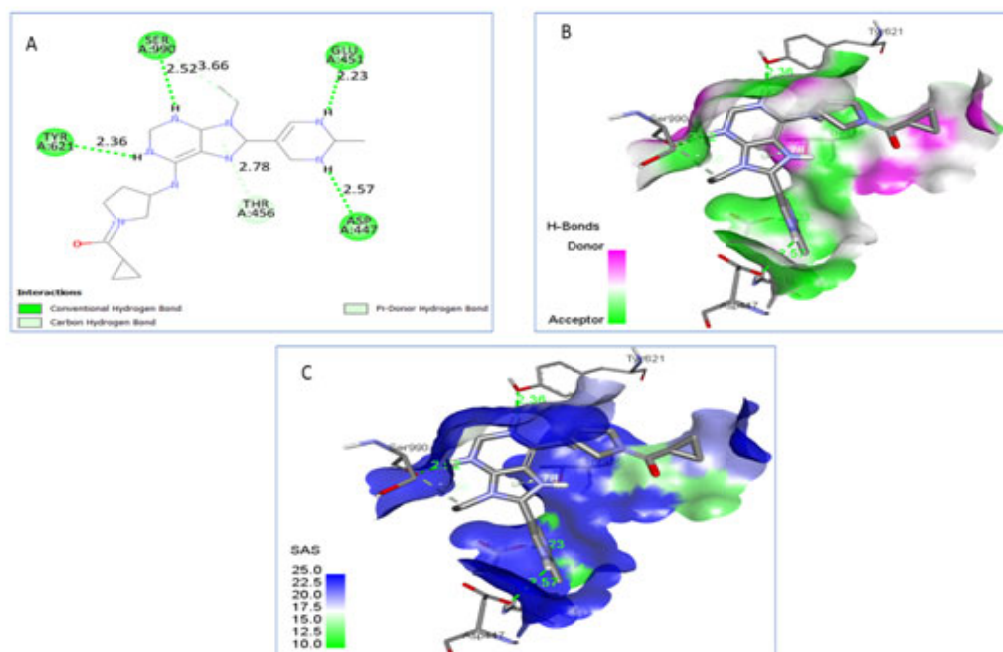
Suppl. Fig. S1 — Gene ontology association mechanism interaction in different pathways of target genes. Where (a) represents biological process, (b) represents Cellular components, and (c) represents Molecular functions



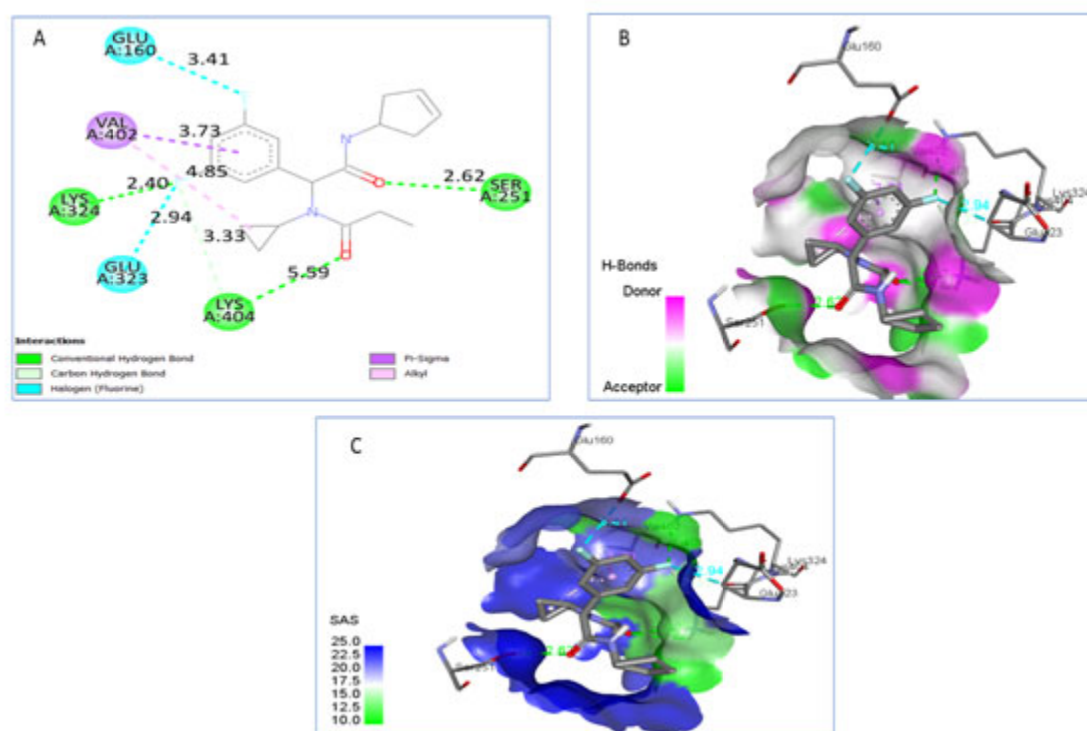
Suppl. Fig. S2 — Docking visualization where A represents 2D structure, B represents H-bonds, C represents SASA of Cocrystal ligand of 5ubr complex



Suppl. Fig. S3 — Docking visualization where A represents 2D structure, B represents H-bonds, C represents SASA of Cocrystal ligand of 2y3a complex



Suppl. Fig. S4 — Docking visualization where A represents 2D structure, B represents H-bonds, C represents SASA of Cocrystal ligand of 7lm2 complex



Suppl. Fig. S5 — Docking visualization where A represents 2D structure, B represents H-bonds, C represents SASA of Cocrystal ligand of 8jn9 complex

Suppl. Table S1 — Gene Ontology (GO) Biological Process Enrichment Analysis of Common Targets					
Enrichment FDR	Pathway Genes	Fold Enrichment	Pathway biological	Genes	
3.66E-07	21	229.3835	GO:0036092 phosphatidylinositol-3-phosphate biosynthetic proc.	PIK3CB	PIK3CG PIK3CA PIK3CD
1.73E-07	122	59.22606	GO:0051897 positive reg. of protein kinase B signaling	IGF1R SRC	PIK3CG PIK3CA PIK3CD PIK3CB
2.45E-08	153	55.09701	GO:0014065 phosphatidylinositol 3-kinase signaling	PIK3CB KIT SRC	PIK3CG PIK3CA IGF1R PIK3CD
5.85E-08	187	45.07937	GO:0048015 phosphatidylinositol-mediated signaling	PIK3CB KIT SRC	PIK3CG PIK3CA IGF1R PIK3CD
5.85E-08	191	44.1353	GO:0048017 inositol lipid-mediated signaling	PIK3CB KIT SRC	PIK3CG PIK3CA IGF1R PIK3CD
6.06E-07	318	26.50894	GO:0010631 epithelial cell migration	PIK3CB SRC PIK3CA	PIK3CG TACR1 KIT PIK3CD
6.06E-07	321	26.26119	GO:0090132 epithelium migration	PIK3CB SRC PIK3CA	PIK3CG TACR1 KIT PIK3CD
6.21E-07	327	25.77933	GO:0090130 tissue migration	PIK3CB SRC PIK3CA	PIK3CG TACR1 KIT PIK3CD
6.06E-07	527	18.28103	GO:0008015 blood circulation	NOS2 PDE2A	NOS1 TACR1 PIK3CA DRD5 PIK3CG SRC
1.73E-07	615	17.62336	GO:0003013 circulatory system proc.	NOS2 DRD5 SRC PDE2A	NOS1 ABCB1 TACR1 PIK3CA PIK3CG
2.45E-08	1194	12.10315	GO:0009628 response to abiotic stimulus	EGLN1 TACR1 PDE2A	NOS1 NOS2 PIK3CB IGF1R KIT SRC ABCB1 BIRC2 PIK3CA
7.47E-07	1172	10.27528	GO:1901698 response to nitrogen compound	DRD5 TACR1 PRKCQ	EGLN1 PDE2A PIK3CG IGF1R SRC BIRC2 PIK3CA
3.39E-07	1752	8.248378	GO:1901700 response to oxygen-containing compound	NOS2 PIK3CG PRKCQ	NOS1 IGF1R DRD5 EGLN1 PDE2A BIRC2 TACR1 PIK3CA SRC
5.53E-07	1916	7.542358	GO:0042592 homeostatic proc.	IGF1R SRC NOS2	TACR1 EGLN1 PIK3CB PIK3CG PIK3CA KIT DRD5 PIK3CD
7.47E-07	2609	6.000545	GO:0071310 cellular response to organic substance	IGF1R KIT DRD5 SRC PRKCQ NOS1	PIK3CG BIRC2 PIK3CA PIK3CB PIK3CD
3.66E-07	3602	5.014977	GO:0010646 reg. of cell communication	PDE10A PIK3CB PIK3CA	IGF1R KIT PDE2A SRC PIK3CG BIRC2 TACR1 EGLN1 DRD5 PIK3CD NOS2 PRKCQ
3.66E-07	3615	4.996943	GO:0023051 reg. of signaling	PDE10A PIK3CB PIK3CA	IGF1R KIT PDE2A SRC PIK3CG BIRC2 TACR1 EGLN1 DRD5 PIK3CD NOS2 PRKCQ
3.66E-07	4424	4.355382	GO:0006950 response to stress	NOS2 PRKCQ KIT DRD5	EGLN1 IGF1R SRC NOS1 PIK3CB PIK3CG BIRC2 TACR1 PIK3CA ABCB1 PDE2A
7.47E-07	4821	3.996725	GO:0042221 response to chemical	NOS2 SRC BIRC2 TACR1	NOS1 EGLN1 IGF1R KIT DRD5 ABCB1 PDE2A PIK3CB PIK3CG PIK3CD PRKCQ

Suppl. Table S2 — Gene Ontology (GO) Cellular Component Enrichment Analysis of Common Targets

Enrichment FDR	Fold Enrichment	Cellular Component Pathway	Genes
0.000153	602.1316	GO:0005944 phosphatidylinositol 3-kinase complex class IB	PIK3CG PIK3CA
3.33E-09	535.2281	GO:0005943 phosphatidylinositol 3-kinase complex class IA	PIK3CG PIK3CA PIK3CB PIK3CD
3.33E-09	535.2281	GO:0097651 phosphatidylinositol 3-kinase complex class I	PIK3CG PIK3CA PIK3CB PIK3CD
0.023957	301.0658	GO:0005899 insulin receptor complex	IGF1R
0.023957	301.0658	GO:0035867 alphav-beta3 integrin-IGF-1-IGF1R complex	IGF1R
5.48E-07	155.3888	GO:0005942 phosphatidylinositol 3-kinase complex	PIK3CB PIK3CG PIK3CA PIK3CD
0.023957	26.46732	GO:0005901 caveola	SRC IGF1R
0.006704	19.96016	GO:0009898 cytoplasmic side of plasma membrane	SRC BIRC2 KIT
0.000164	18.13649	GO:0061695 transferase complex transferring phosphorus-containing groups	PIK3CB PIK3CG PIK3CA IGF1R PIK3CD
0.000164	18.02789	GO:0019898 extrinsic component of membrane	PIK3CB PIK3CG PIK3CA PIK3CD SRC
0.003466	13.7238	GO:0045121 membrane raft	SRC BIRC2 IGF1R NOS1
0.003466	13.68481	GO:0098857 membrane microdomain	SRC BIRC2 IGF1R NOS1
0.023957	10.6572	GO:0014069 postsynaptic density	NOS1 EGLN1 SRC
0.023957	10.47185	GO:0032279 asymmetric synapse	NOS1 EGLN1 SRC
0.005795	7.819891	GO:0048471 perinuclear region of cytoplasm	PDE2A SRC NOS2 NOS1 PIK3CA
0.009714	6.559168	GO:1990234 transferase complex	PIK3CB PIK3CG PIK3CA IGF1R PIK3CD
0.023957	6.363346	GO:0098552 side of membrane	SRC BIRC2 KIT ABCB1
0.010262	4.976294	GO:0098796 membrane protein complex	PIK3CB PIK3CG PIK3CA IGF1R PIK3CD BIRC2
0.019039	3.676338	GO:0030054 cell junction	NOS1 PDE2A SRC PIK3CA EGLN1 KIT DRD5

Suppl. Table S3 — Gene Ontology (GO) Molecular Function Enrichment Analysis of Common Targets

Enrichment FDR	Fold Enrichment	Molecular function Pathway	Genes
1.30E-09	688.1504	GO:0035005 1-phosphatidylinositol-4-phosphate 3-kinase activity	PIK3CB PIK3CG PIK3CA PIK3CD
1.30E-09	688.1504	GO:0046934 phosphatidylinositol-4,5-bisphosphate 3-kinase activity	PIK3CB PIK3CG PIK3CA PIK3CD
1.87E-09	535.2281	GO:0052812 phosphatidylinositol-3,4-bisphosphate 5-kinase activity	PIK3CB PIK3CG PIK3CA PIK3CD
2.22E-09	481.7053	GO:0016303 1-phosphatidylinositol-3-kinase activity	PIK3CB PIK3CG PIK3CA PIK3CD
2.22E-09	481.7053	GO:0052813 phosphatidylinositol bisphosphate kinase activity	PIK3CB PIK3CG PIK3CA PIK3CD

3.66E-09	401.4211	GO:0035004 phosphatidylinositol 3-kinase activity	PIK3CB PIK3CG PIK3CA PIK3CD
7.48E-07	361.2789	GO:0043560 insulin receptor substrate binding	IGF1R PIK3CB PIK3CA
1.12E-08	301.0658	GO:0016307 phosphatidylinositol phosphate kinase activity	PIK3CB PIK3CG PIK3CA PIK3CD
1.74E-08	267.614	GO:0052742 phosphatidylinositol kinase activity	PIK3CB PIK3CG PIK3CA PIK3CD
8.40E-07	12.87982	GO:0016773 phosphotransferase activity alcohol group as acceptor	PRKCQ SRC PIK3CB PIK3CG PIK3CA IGF1R KIT PIK3CD
2.78E-07	7.661593	GO:0032559 adenylyl ribonucleotide binding	ABCB1 PDE10A PIK3CB PRKCQ PIK3CG PIK3CA IGF1R KIT PIK3CD SRC PDE2A
2.80E-07	7.608785	GO:0030554 adenylyl nucleotide binding	ABCB1 PDE10A PIK3CB PRKCQ PIK3CG PIK3CA IGF1R KIT PIK3CD SRC PDE2A
1.12E-08	7.374197	GO:0032553 ribonucleotide binding	NOS2 NOS1 ABCB1 PDE10A PDE2A PIK3CB PRKCQ PIK3CG PIK3CA IGF1R KIT PIK3CD SRC
2.89E-09	7.080926	GO:0000166 nucleotide binding	NOS2 NOS1 ABCB1 PDE10A NQO2 PDE2A PIK3CB PRKCQ PIK3CG PIK3CA IGF1R KIT PIK3CD SRC
2.89E-09	7.077953	GO:1901265 nucleoside phosphate binding	NOS2 NOS1 ABCB1 PDE10A NQO2 PDE2A PIK3CB PRKCQ PIK3CG PIK3CA IGF1R KIT PIK3CD SRC
1.40E-09	6.868421	GO:0043168 anion binding	NOS2 NOS1 ABCB1 PDE10A NQO2 PDE2A PIK3CB PRKCQ PIK3CG PIK3CA EGLN1 IGF1R KIT PIK3CD SRC
1.87E-09	6.585471	GO:0036094 small molecule binding	NOS2 NOS1 ABCB1 PDE10A NQO2 PDE2A PIK3CB PRKCQ PIK3CG PIK3CA EGLN1 IGF1R KIT PIK3CD SRC
1.70E-06	6.290073	GO:0032555 purine ribonucleotide binding	ABCB1 PDE10A PDE2A PIK3CB PRKCQ PIK3CG PIK3CA IGF1R KIT PIK3CD SRC
7.07E-08	6.249669	GO:0097367 carbohydrate derivative binding	NOS2 NOS1 ABCB1 PDE10A PDE2A PIK3CB PRKCQ PIK3CG PIK3CA IGF1R KIT PIK3CD SRC
1.73E-06	6.248535	GO:0017076 purine nucleotide binding	ABCB1 PDE10A PDE2A PIK3CB PRKCQ PIK3CG PIK3CA IGF1R KIT PIK3CD SRC

Suppl. Table S4 — Enrichment FDR, Fold Enrichment, and Pathway of target genes in KEGG pathway.

Enrichment FDR	Fold Enrichment	Pathway	Genes
1.69E-06	81.64496	Path: hsa04370 VEGF signaling pathway	PIK3CA, PIK3CB, PIK3CD, SRC
1.93E-06	77.6944	Path: hsa04213 Longevity regulating pathway-multiple species	IGF1R, PIK3CA, PIK3CB, PIK3CD
1.91E-07	76.21919	Path: hsa01521 EGFR tyrosine kinase inhibitor resistance	IGF1R, PIK3CA, PIK3CB, PIK3CD, SRC
2.38E-06	71.89631	Path: hsa05221 Acute myeloid leukemia	KIT, PIK3CA, PIK3CB, PIK3CD
2.38E-06	70.83901	Path: hsa05211 Renal cell carcinoma	PIK3CA, PIK3CB, PIK3CD, EGLN1
2.38E-06	68.81504	Path: hsa04917 Prolactin signaling pathway	PIK3CA, PIK3CB, PIK3CD, SRC

2.38E-06	68.81504	Path: hsa05230 Central carbon metabolism in cancer	KIT, PIK3CA, PIK3CB, PIK3CD
4.14E-08	66.28972	Path: hsa04066 HIF-1 signaling pathway	IGF1R, NOS2, PIK3CA, PIK3CB, PIK3CD, EGLN1
2.53E-07	65.44908	Path: hsa05222 Small cell lung cancer	BIRC2, NOS2, PIK3CA, PIK3CB, PIK3CD
2.53E-07	63.38227	Path: hsa01522 Endocrine resistance	IGF1R, PIK3CA, PIK3CB, PIK3CD, SRC
2.53E-07	61.442	Path: hsa04750 Inflammatory mediator reg. of TRP channels	PIK3CA, PIK3CB, PIK3CD, PRKCQ, SRC
5.76E-08	56.01224	Path: hsa04926 Relaxing signalling pathway	NOS1, NOS2, PIK3CA, PIK3CB, PIK3CD, SRC
7.45E-07	48.559	Path: hsa04611 Platelet activation	PIK3CA, PIK3CB, PIK3CD, PIK3CG, SRC
1.29E-06	42.70437	Path: hsa04140 Autophagy-animal	IGF1R, PIK3CA, PIK3CB, PIK3CD, PRKCQ
1.39E-06	40.96133	Path: hsa05224 Breast cancer	IGF1R, KIT, PIK3CA, PIK3CB, PIK3CD
1.39E-06	40.68457	Path: hsa04072 Phospholipase D signalling pathway	KIT, PIK3CA, PIK3CB, PIK3CD, PIK3CG
2.53E-07	36.12789	Path: hsa04510 Focal adhesion	BIRC2, IGF1R, PIK3CA, PIK3CB, PIK3CD SRC
2.53E-07	34.40752	Path: hsa04015 Rap1 signalling pathway	IGF1R, KIT, PIK3CA, PIK3CB, PIK3CD SRC
2.38E-06	20.41124	Path: hsa04151 PI3K-Akt signalling pathway	IGF1R, KIT, PIK3CA, PIK3CB, PIK3CD, PIK3CG
1.91E-07	18.17756	Path: hsa05200 Pathways in cancer	BIRC2, IGF1R, KIT, NOS2, PIK3CA, PIK3CB, PIK3CD, EGLN1

Suppl. Table S5 — Common Molecular Targets of Hydroxychloroquine, Trimebutine, and Alzheimer's Disease (AD)

NQO2	PRKCQ	PDE2A	PDE10A	ABCB1	TACR1	DRD5
NOS1	IGF1R	NOS2	DPP9	BIRC2	SRC	EGLN1
KIT	PIK3CD	PIK3CB	PIK3CG	PIK3CA		

Suppl. Table S6 — Validation of the proteins

Region	PDBID: 5UBR		PDBID: 2Y3A		PDBID: 7LM2		PDBID: 8JN9	
	No of Residues	Percentage	No of Residues	Percentage	No of Residues	Percentage	No of Residues	Percentage
Most favoured regions [A, B, L]	718	90.2%	899	81.8%	920	92.6%	350	88.4%
Additional allowed regions [a, b, l, p]	72	9.0%	182	16.6%	74	7.4%	44	11.1%
Generously allowed regions [~a, ~b, ~l, ~p]	5	0.6%	15	1.4%	0	0%	1	0.3%
Disallowed regions [XX]	1	0.1%	3	0.3%	0	0%	1	0.3%

Total (non-Gly, non-Pro)	796	100%	1099	100%	994	100%	396	100%
End-residues (excl. Gly and Pro)	12		13		21		2	
Glycine residues	38		56		47		31	
Proline residues	41		44		42		22	
Total number of residues	887		1212		1104		451	