Computational Simulations Identify Pyrrolidine-2,3-dione Derivatives as Novel Inhibitors of Cdk5/p25 Complex to Attenuate Alzheimer's Pathology

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Running title: Pyrrolidine-2,3-dione Derivatives Inhibit Cdk5/p25 Complex

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Supplementary Information

Figure S1

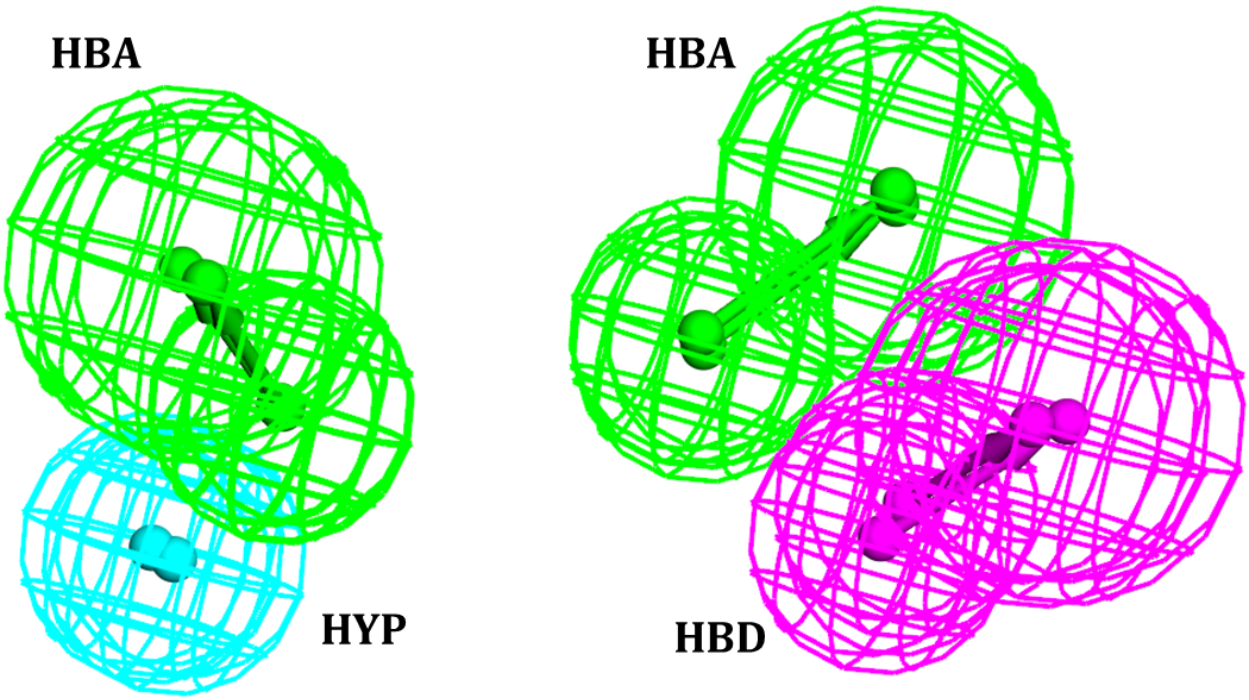


Figure S2

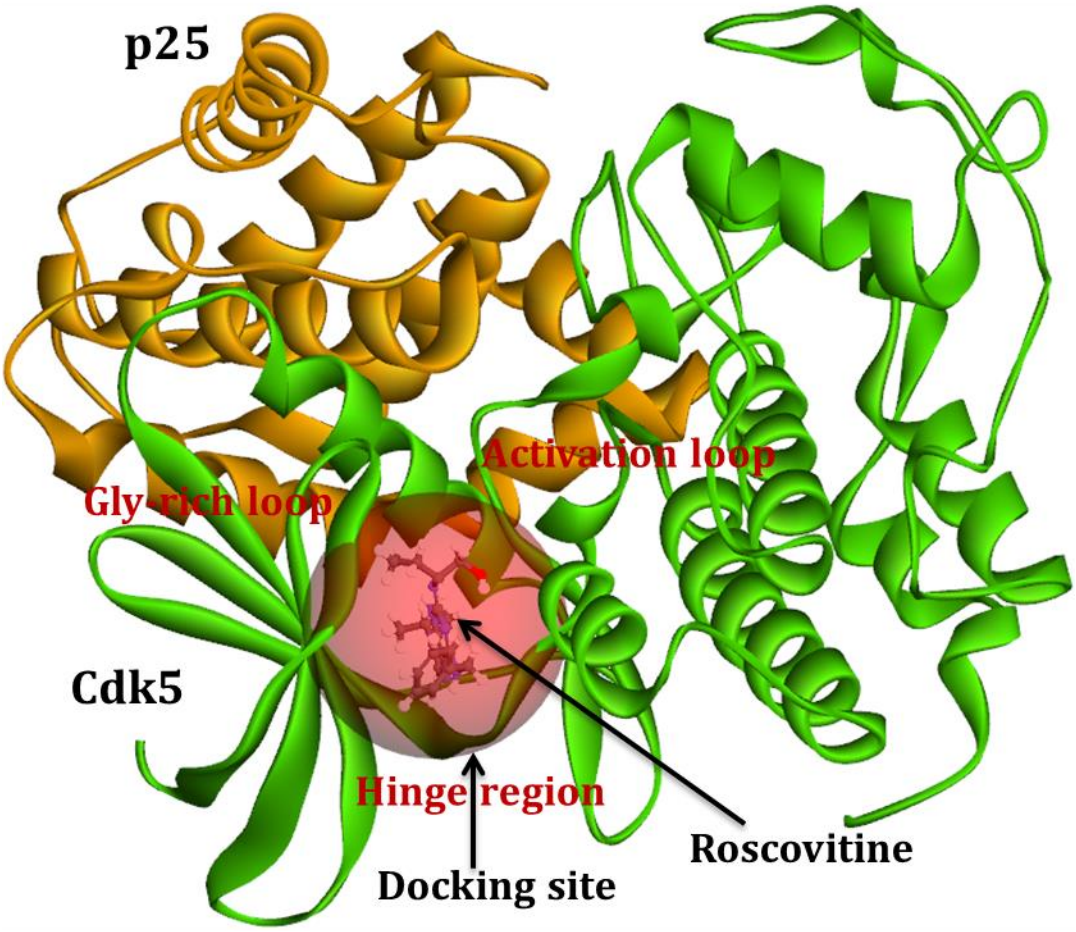
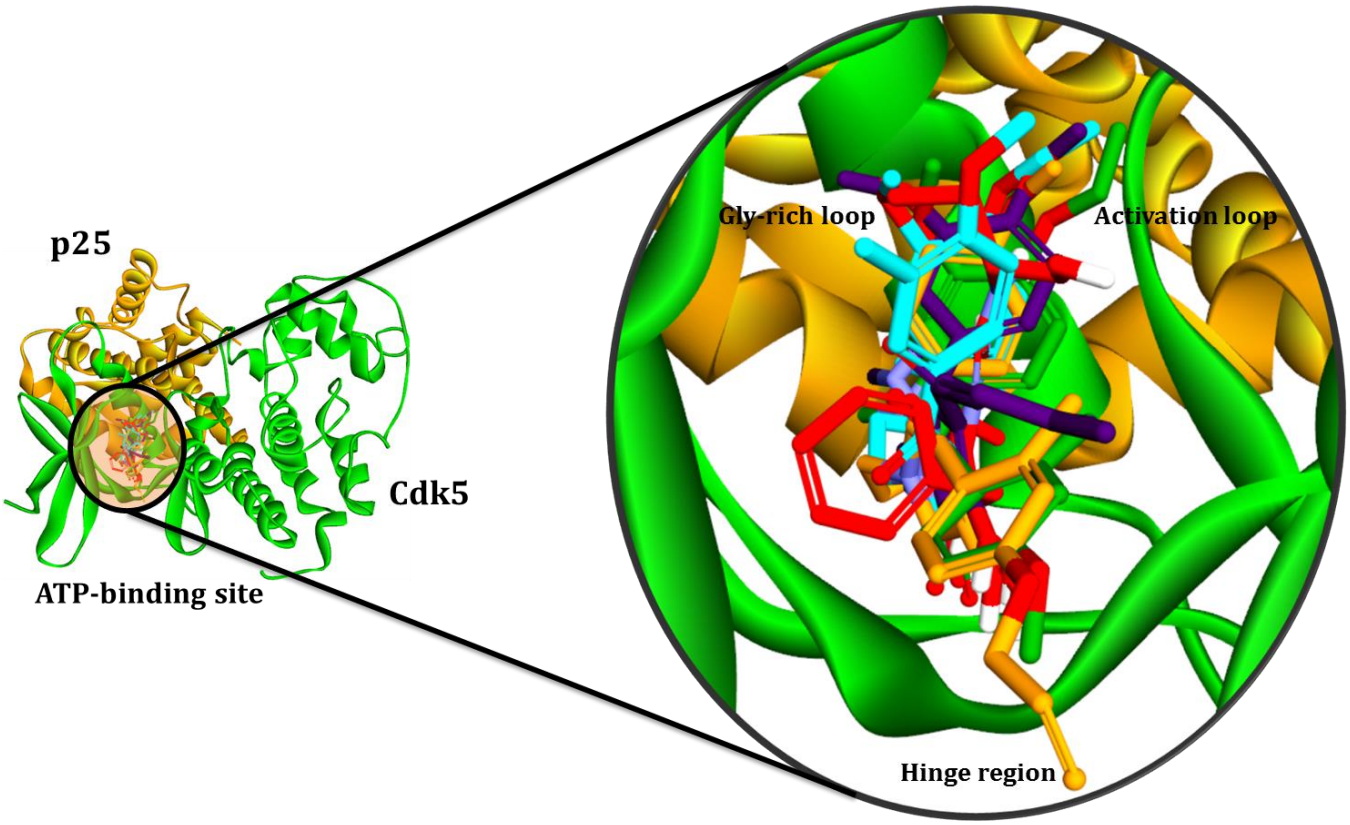

p25
Activation loop
Gly-rich loop
Cdk5
Hinge region
Roscovitine
Docking site

Figure S3



Superimposition of REF, Hit1, Hit2, Hit3, and Hit4

Figure S4

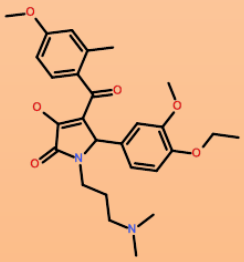
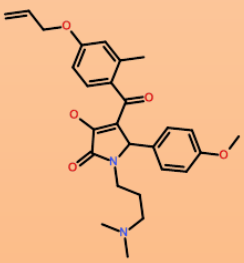
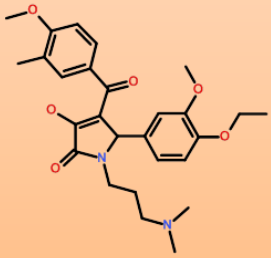
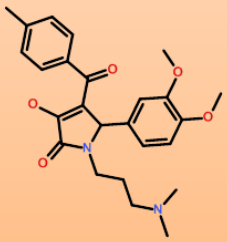
2D Structure	SMILE ID	2D Structure	SMILE ID
 Hit1	CCOc1ccc(cc1OC)C2N(CCCN(C)C)C(=O)C(=C2C(=O)c3ccc(OC)cc3C)O	 Hit2	COc1ccc(cc1)C2N(CCCN(C)C)C(=O)C(=C2C(=O)c3ccc(OCC=C)cc3C)O
 Hit3	CCOc1ccc(cc1OC)C2N(CCCN(C)C)C(=O)C(=C2C(=O)c3ccc(OC)c(C)c3)O	 Hit4	COc1ccc(cc1OC)C2N(CCCN(C)C)C(=O)C(=C2C(=O)c3ccc(C)cc3)O

Table S1. Docking results analysis.

Parameter	NCI	Asinex	Specs	Total
Compounds	205	291	307	308
ChemPLP Score (≥ 67.67)	56	143	127	326
ASP Score (≥ 26.32)	56	143	127	326
Cluster Analysis	29	69	62	160
H-bond Analysis (Cys83)	24	42	43	109
Commercially Available	12	38	41	91

Table S2. Molecular interactions between the Cdk5/p25 and ligands.

Compound	Hydrogen bonds (≤ 3.5 Å)				Other Interactions
	Amino Acid	Amino Acid Atom	Ligand Atom	Distance (Å)	
Ref	Cys83 Cys83 Asp86	HN O OD1	N16 H45 H27	2.2 1.7 1.6	Ile10, Phe80, Ala31, Val64, Leu133, Val18, Lys33,Cys83, Asp84, Phe82, Gly11
Hit1	Cys83 Cys83 Asn144	HN O HD22	O13 H41 O26	1.91 1.81 2.62	Ile10, Gly11, Glu12, Gly13, Val18, Ala31, Lys33, Phe80, Phe82, Asp84, Gln85, Asp86, Lys89, Gln130, Asn131, Leu133, Asn131
Hit2	Cys83 Cys83 Asn144	HN O HD22	O11 H38 O28	2.28 1.68 2.50	Ile0, Gly11, Glu12, Gly13, Val18, Ala31, Lys33, Phe80, Phe82, Asp84, Gln85, Asp86, Lys89, Leu133, Ala143
Hit3	Cys83 Cys83	HN O	O13 H41	1.67 1.83	Ile10, Glu12, Gly13, Thr14, Val18, Asn131, Asn144, Ala31, Lys33, Val64, Phe80, Phe82, Leu133, Lys33, Ala31, Ala143
Hit4	Cys83 Cys83 Asn144	HN O HD22	O10 H36 O26	1.80 1.84 2.08	Ile10, Glu12, Gly13, Val18, Ala31, Lys33, Val64, Phe80, Glu81, Phe82, Asp84, Gln85, Asp86, Leu133

Table S3. IUPAC name, PubChem ID and Supplier information of the final hit compounds.

Compounds	IUPAC* Name	PubChem ID	Vendor/Supplier (Product ID)
Hit1	(5S)-1-[3-(dimethylamino)propyl]-5-(4-ethoxy-3-methoxyphenyl)-4-[hydroxy-(4-methoxy-2-methylphenyl)methylidene]pyrrolidine-2,3-dione	1050287	ZINC (ZINC19929335)
Hit2	1-[3-(dimethylamino)propyl]-4-[hydroxyl-(2-methyl-4-prop-2-enoxyphenyl)methylidene]-5-(4-methoxyphenyl)pyrrolidine-2,3-dione	3146980	Enamine (BG06474602)
Hit3	(5S)-5-(3,4-dimethoxyphenyl)-1-[3-(dimethylamino)propyl]-4-[(4-thoxy-3-methylphenyl)-hydroxymethylidene]pyrrolidine-2,3-dione	1544486	ZINC (ZINC19928667)
Hit4	5-(3,4-dimethoxyphenyl)-1-[3-(dimethylamino)propyl]-4-[hydroxy-(4-methylphenyl)methylidene]pyrrolidine-2,3-dione	2908872	Enamine (BG06447444)