

In Silico molecular docking of Chelidonic acid across multiple targets associated with carcinogenesis

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Supplementary Table 1: PDB structural information

Protein target	PDB ID	Resolution (Å)	Experimental method	Selected chain(s)	Biologically important co-factors included in this study	Native/co-crystallized ligand, cofactor or metal presented in the PDB
CAT	1DGF	1.50	X-ray diffraction	A–D	-	NADPH and heme; acetate also present
HO-1	3CZY	1.54	X-ray diffraction	A–B	-	Heme; AD8 inhibitor
GST	5J41	1.19	X-ray diffraction	A–B	-	Glutathione (GSH); 3LF ligand
GPX4	6HN3	1.01	X-ray diffraction	A	-	-
SOD	5VF9	1.82	X-ray diffraction	A–B	A-MN201; B-MN201	Mn ²⁺ ; phosphate and K ⁺
p53	2OCJ	2.05	X-ray diffraction	A–D	A-ZN501; B-ZN502 C-ZN503 ; D-ZN504	Zn ²⁺
Caspase-9	1JXQ	2.80	X-ray diffraction	A–D	-	Benzoxycarbonyl-Val-Ala-Asp-fluoromethyl ketone inhibitor
Caspase-3	5I9B	1.80	X-ray diffraction	A	-	Ac-Asp-Glu-Val-Asp-CMK inhibitor
c-Myc/Max	6G6K	1.35	X-ray diffraction	A–D	-	-
PCNA	1AXC	2.60	X-ray diffraction	A–F	-	p21/WAF1 peptide
PI3Kα	4JPS	2.20	X-ray diffraction	A–B	-	Inhibitor 1LT
mTOR	4JSV	3.50	X-ray diffraction	A–D	A-MG2602 ; A-MG2603 B-MG2602 ; B-MG2603	ADP; Mg-containing species
GR	3GRS	1.54	X-ray diffraction	A	-	FAD; phosphate ion
AKT1	3O96	2.70	X-ray diffraction	A	-	Allosteric inhibitor IQO
Keap1	4IQK	1.97	X-ray diffraction	A	-	Cpd 16/IQK inhibitor
COX-2	5KIR	2.70	X-ray diffraction	A–B	-	Rofecoxib (RCX)
IL-6	1ALU	1.90	X-ray diffraction	A	-	-
NF-κB p52	1A3Q	2.10	X-ray diffraction	A–B	-	κB DNA
TNF-α	2AZ5	2.10	X-ray diffraction	A–D	-	Small-molecule inhibitor 307
iNOS	3E7G	2.20	X-ray diffraction	A–D	-	AR-C95791 inhibitor; heme and tetrahydrobiopterin
MMP-9	1GKC	2.30	X-ray diffraction	A–B	A-ZN1450 ; A-ZN1451 B-ZN1451 ; B-ZN1452	Reverse hydroxamate inhibitor NFH; catalytic Zn ²⁺ and Ca ²⁺
MMP-2	7XJO	2.00	X-ray diffraction	A–B	A-ZN201 ; A-ZN202 B-ZN201 ; B-ZN202	Co-crystallized inhibitor peptide; Zn ²⁺ , Ca ²⁺ , B3P and Cl ⁻
VEGFR2	3VO3	1.52	X-ray diffraction	A	-	Inhibitor OKF; 1,2-ethanediol



Supplementary Table 2: PDB-specific grid-center coordinates used for molecular docking of chelidonic acid.

PDB ID	Center X	Center Y	Center Z
1DGF	20.321622	41.524748	42.604168
6HN3	1.072816	0.262203	0.424497
3O96	6.213637	-7.905167	17.324291
5I9B	-6.706459	-19.227497	-10.845607
1JXQ	19.491933	38.209451	27.231293
6G6K	-59.117363	-42.079924	-70.208978
5KIR	30.972705	24.147780	23.541909
3GRS	70.468083	51.355055	18.670686
5J41	9.449847	12.743079	85.624038
3CZY	11.812797	-10.496183	18.625599
1ALU	2.667288	-19.979977	9.043373
3E7G	46.203573	24.933044	54.592530
4IQK	-35.606775	0.358038	-17.076917
7XJO	42.316136	-42.700277	9.288394
1GKC	54.595593	21.235773	129.535194
4JSV	34.833511	-16.837606	-51.898479
1A3Q	16.694259	60.979849	0.706187
2OCJ	17.160537	21.298291	41.662153
1AXC	68.753603	22.600817	19.879681
4JPS	-9.620742	-24.702594	31.313709
5VF9	30.450973	28.765440	91.135624
2AZ5	-13.676367	71.597418	26.990358
3VO3	23.394901	-28.545357	-22.025835

Supplementary Table 3: Basis of binding-site selection for the target proteins used for chelidonic acid docking

No.	Target protein	PDB ID	Binding-pocket basis
1	Catalase (CAT)	1DGF	Computationally predicted cavity
2	Glutathione reductase (GR)	3GRS	Computationally predicted cavity
3	Heme oxygenase-1 (HO-1)	3CZY	Co-crystallized ligand site / computationally predicted cavity
4	Glutathione S-transferase (GST)	5J41	Computationally predicted cavity
5	Glutathione peroxidase 4 (GPX4)	6HN3	Computationally predicted cavity
6	Superoxide dismutase (SOD)	5VF9	Computationally predicted cavity
7	p53	2OCJ	Computationally predicted cavity
8	Caspase-9	1JXQ	Computationally predicted cavity
9	Caspase-3	5I9B	Computationally predicted cavity
10	c-Myc/Max	6G6K	Computationally predicted cavity
11	PCNA	1AXC	Computationally predicted cavity
12	PI3K α	4JPS	Co-crystallized ligand site / computationally predicted cavity
13	mTOR	4JSV	Computationally predicted cavity
14	AKT1	3O96	Co-crystallized ligand site / computationally predicted cavity

15	Keap1	4IQK	Co-crystallized ligand site / computationally predicted cavity
16	COX-2	5KIR	Co-crystallized ligand site / computationally predicted cavity
17	IL-6	1ALU	Computationally predicted cavity
18	NF-κB p52	1A3Q	Computationally predicted cavity
19	TNF-α	2AZ5	Co-crystallized ligand site / computationally predicted cavity
20	iNOS	3E7G	Co-crystallized ligand site / computationally predicted cavity
21	MMP-9	1GKC	Co-crystallized ligand site / computationally predicted cavity
22	MMP-2	7XJO	Co-crystallized ligand site / computationally predicted cavity
23	VEGFR2	3VO3	Co-crystallized ligand site / computationally predicted cavity

Footnote: Binding cavities were identified using BIOVIA Discovery Studio and the geometric center of the selected cavity was used as the docking-box center. For targets with suitable co-crystallized ligands that were subjected to redocking validation, selected docking region corresponded to the co-crystallized ligand-binding region and successfully reproduced the crystallographic pose with RMSD <2.0 Å. For the remaining targets, the docking pocket was selected from computationally predicted cavities.

Supplementary Table 4: Target-specific justification for proteins not selected for RMSD validation

Target	PDB ID	Target-specific justification
CAT	1DGF	no suitable conventional co-crystallized small-molecule reference ligand was available in the selected structure.
GR	3GRS	no suitable conventional co-crystallized small-molecule reference ligand was available in the selected structure.
GST	5J41	although 3LF and GSH are present in the crystallographic complex, the structure contains multiple ligand-associated components, and no single reference ligand was selected for the present redocking validation protocol.
GPX4	6HN3	no suitable conventional co-crystallized small-molecule reference ligand was available in the selected structure.
SOD	5VF9	no suitable conventional co-crystallized small-molecule reference ligand was available in the selected structure.
p53	2OCJ	no suitable conventional co-crystallized small-molecule reference ligand was available in the selected structure.
Caspase-9	1JXQ	the crystallographic inhibitor is peptide-based and was not selected as a conventional small-molecule reference for the present CA docking validation.
Caspase-3	5I9B	the crystallographic inhibitor is peptide-based and was not selected as a conventional small-molecule reference for the present CA docking validation.
c-Myc/Max	6G6K	no suitable conventional co-crystallized small-molecule reference ligand was available in the selected structure.
PCNA	1AXC	crystallographic ligand is a p21/WAF1 peptide rather than a conventional small-molecule reference ligand.
mTOR	4JSV	no suitable conventional co-crystallized small-molecule reference ligand was available in the selected structure.
IL-6	1ALU	no suitable conventional co-crystallized small-molecule reference ligand was identified in the selected structure.
NF-κB p52	1A3Q	crystallographic component is κB DNA rather than a conventional small-molecule reference ligand.

Supplementary Table 5: Co-crystallized ligand redocking validation and chelidonic acid docking results for selected target proteins.

Target	PDB	Native ligand	RMSD (Å)	Redocked ligand docking score (kcal/mol)	CA docking score (kcal/mol)	Residues contacting redocked ligand	Residues contacting chelidonic acid	Interactions with redocked ligand	Interactions with chelidonic acid
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HO-1	3CZ Y	AD890 1	1.134	-7.1	-6.1	Asp140, Arg136,Thr135	Lys148, Glu162, Gln145, Phe169, Pro99, Thr168, Ala94	H-bond, C-H, π -cation	H-bond; C-H; π -sigma; π -alkyl
AKT1	3O9 6	IQO44 4	0.436	-14.7	-6.3	Asn54, Ile84, Trp80, Ser205, Leu210, Leu264, Lys268, Val270, Arg273, Tyr326	Trp80, Ser205, Thr211, Ala212, Leu213	H-bond, π - π Stacked, C-H, alkyl, π -alkyl, π -cation	H-bond; C-H; π - π stacked; π -alkyl
COX-2	5KIR	RCX60 1	1.609	-8.2	-6.6	Arg61, Lys546, Ile124, His122, Pro542, Ala543	Arg333, Gln241, Trp139	H-bond, C-H, π -cation, π -sigma, π - π T-shaped, π -alkyl	H bond
Keap1	4IQ K	IQK70 1	0.521	-9.4	-6.3	Tyr525, Ser508, Ser555, Arg415, Ala556, Tyr334, Ser602, Tyr572, Phe577	Val606, Gly367, Gly558, Ala366, Val465	H-bond, C-H, π -cation, π -sigma, π - π stacked, π -alkyl	H-bond; C-H; π -sigma
MMP-9	1GK C	NFH1 448	1.640	-6.4	-6.9	Leu188, Ala189, Glu402, Gly186, Tyr423, Val398, His401	His401, His405, Glu402, Leu188, Ala189	H-bond, C-H, π -sigma, alkyl, alkyl	H-bond; π -anion; π -alkyl
MMP-2	7XJ O	B3P20 6	1.898	-4.8	-6.2	Asp26, Arg67, Asn64, His70, His98, Asp101	Arg67, Phe65, Asn64	H-bond	H-bond; C-H; π -alkyl
PI3K α	4JPS	1LT11 02	0.877	-9.1	-6.5	Asn465, Asn467, Ser474, Thr679, Val461, Pro447, Pro449	His670, Phe666, Arg818, Met811, Cys838	H-bond, C-H, alkyl, π -alkyl	H-bond; π -cation; π - π T-shaped
VEGF R2	3VO 3	OKF20 01	1.666	-10.3	-6.1	Ala866, Val848, Val899, Cys1045, Leu889, Arg1027, Asp1046, Lys868, Phe1047, Ile888, Glu885, Val916	Asp998, His1004, Asn1040, Ser1037, Lys1039, Phe921	C-H, π -cation, π -anion, π -sigma, alkyl, π -alkyl	H-bond; π - π T-shaped
iNOS	3E7 G	AT290 6	1.416	-5.5	-5.6	Arg301, Ile277, Arg278, Pro281, Lys298	Ala262, Trp496, Arg266, Asn283, Phe286, Ala282, Glu285	H-bond, C-H, π -cation, alkyl	H-bond; π - π T-shaped; π -alkyl
TNF- α	2AZ 5	3071	0.703	-9.3	-5.8	Tyr59, Gly121	Ser60, Leu120, Tyr151, Gly121	Halogen (Flurine), π -alkyl	Van der Waals; H-bond; amide π -stacked

Supplementary Table 6: Residue-level assessment of the binding-site relevance of chelidonic acid across the selected protein targets

Targ et	PDB ID	Native/ co- crystallize d ligand	Native/co- crystallized ligand	CA-interacting residues	Commo n residues	Experimentally established key catalytic/functi onal residues	CA overlap with catalytic/ functional residues	Interpretation
HO- 1	3CZ Y	AD8	Asp140, Arg136, Thr135	Lys148, Glu162, Gln145, Phe169, Pro99, Thr168, Ala94	None	His25, Tyr58, Thr135, Arg136, Gly139, Asp140, Gly143 (Schuller et al. 1999)	None	No direct residue-level overlap with the native/co-crystallized ligand -interacting or experimentally established key catalytic/functional residues
AKT 1	3O9 6	IQO	Asn54, Ile84, Trp80, Ser205, Leu210, Leu264, Lys268, Val270, Arg273, Tyr326	Trp80, Ser205, Leu210, Thr211, Ala212, Leu213	Trp80, Ser205, Leu210	Lys179, Asp274, Thr308, Ser473 (Kumar et al. 2025)	None	Partial overlap with the native/co-crystallized ligand -interacting - associated residue set, but no overlap with experimentally established key catalytic/functional residues.
COX -2	5KIR	RCX	Arg61, Lys546, Ile124, His122, Pro542, Ala543	Arg333, Gln241, Trp139	None	Arg120, Tyr348, Tyr355, Tyr385, Ser530 (Rouzer et al. 2020)	None	No direct residue-level overlap with the native/co-crystallized ligand interacting or experimentally established key catalytic/functional residues.
Kea p1	4IQ K	IQK	Tyr525, Ser508, Ser555, Arg415, Ala556, Tyr334, Ser602, Tyr572, Phe577	Val606, Gly367, Gly558, Ala366, Val465	None	Tyr334, Arg380, Asn382, Arg415, Arg483, Ser508, Tyr525, Tyr572, Phe577 (Lo et al. 2006)	None	No direct residue-level overlap with the native/co-crystallized ligand interacting or experimentally established key Nrf2- binding/functional residues.
MM P-9	1GK C	NFH	Leu188, Ala189, Glu402, Gly186, Tyr423, Val398, His401	His401, His405, His411, Glu402, Leu188, Ala189	His401, Glu402, Leu188, Ala189	His401, Glu402, His405, His411 (Rowse et al.2002)	His401, Glu402, His405, His411	CA overlapped the native/co-crystallized ligand -associated region and all key catalytic

								residues.
MM P-2	7XJ O	B3P	Asp26, Arg67, Asn64, His70, His98, Asp101	Arg67, Phe65, Asn64	Arg67, Asn64	His121, His125, His131, Glu130 (Alrumaihi et al. 2023; Takeuchi et al. 2022)	None	Partial overlap with the native/co-crystallized ligand -associated region, but no overlap with experimentally established key catalytic/functional residues.
PI3 Kα	4JPS	1LT	Asn465, Asn467, Ser474, Thr679, Val461, Pro447, Pro449	His670, Phe666, Arg818, Met811, Cys838	None	Lys776, His917, Asp933, His936 (Maheshwari et al. 2017)	None	No direct residue-level overlap with the reported native/co- crystallized ligand - interacting or experimentally established key catalytic/functional residues
VEG FR2	3VO 3	OKF	Ala866, Val848, Val899, Cys1045, Leu889, Arg1027, Asp1046, Lys868, Phe1047, Ile888, Glu885, Val916	Asp998, His1004, Asn1040, Ser1037, Lys1039, Phe921	None	Lys868, Glu885, Cys919, Asp1046, Phe1047 (Rampogu et al. 2019)	None	No direct residue-level overlap with the reported native/co- crystallized ligand - interacting or experimentally established key catalytic/functional residues.
iNO S	3E7 G	AT2906	Arg301, Ile277, Arg278, Pro281, Lys298	Ala262, Trp496, Arg266, Asn283, Phe286, Ala282, Glu285	None	Glu377, Arg381, Asp382, Tyr347, Tyr373, Trp463 (Le et al. 2024; Erdogan et al. 2024)	None	No direct residue-level overlap with the native/co-crystallized ligand -interacting or experimentally established key catalytic/functional residues
TNF -α	2AZ 5	307	Tyr59, Gly121	Ser60, Leu120, Tyr151, Gly121	Gly121	His15, Leu57, Ile58, Tyr59, Ser60, Tyr119, Leu120, Gly121, Gly122, Gln149, Val150, Tyr151,	Ser60, Leu120, Gly121, Tyr151	Partial overlap with the native ligand-associated residue set and overlap with experimentally established some key catalytic/functional

						Ile155 (Bhat et al. 2023)		residues
CAT	1DG F	-	-	Arg72, Arg112, Ser114, Ala133, Val146, Phe334, His362	-	His75, Asn148, Tyr358, Arg72, Arg112, Arg365, Tyr370 (Putnam et al. 2000)	Arg72, Arg112	CA overlaps two reported experimentally established some key catalytic/functional residues
GR	3GR S	-	-	Gly29, Gly32, Thr57, Gly157, Asp331, Leu338, Thr339, Ala342	-	Cys58, Cys63, Lys66, Tyr197, Glu201, His467, Glu472 (Berkholz et al. 2008; Karplus and Schulz.1987)	None	No direct overlap with experimentally established key catalytic/functional residues.
GST	5J41	-	-	Arg74, Gly80, Tyr79, Ala86	-	Tyr7, Arg13, Lys44, Tyr108, Ile104 (Prejanò et al.2018)	None	No direct overlap with experimentally established key catalytic/functional residues.
GPX 4	6HN 3	-	-	Lys90, Ala94, Lys99, Phe100, Met102	-	Sec46, Gln81, Trp136, Asn137 (Moosmayer et al., 2021)	None	No direct overlap with experimentally established key catalytic/functional residues.
SOD	5VF 9	-	-	Thr55, Val54, Ile72, Gln47, Ser75	-	His30, Tyr34, Gln143, Glu162, Tyr166 (Azadmanesh et al. 2017)	None	No direct overlap with experimentally established key catalytic/functional residues.
p53	2OC J	-	-	Tyr107, Asn239, Leu137, His179	-	Lys120, Ser241, Arg248, Arg273, Ala276, Cys277, Arg280 (Lion et al. 2015)	None	No direct overlap with experimentally established key DNA-binding/functional residues.
Cas pas e-9	1JX Q	-	-	Ala376, Val379, Trp360, Arg372, Ile356	-	Cys285, His237, Trp340, Arg341, Arg179 (Renatus et al. 2001)	None	No direct overlap with experimentally established key catalytic/substrate-recognition residues.
Cas pas	5I9B	-	-	Arg64, Gln161, Ser120, Arg207,	-	His121, Cys163, Gly122	Cys163	CA directly overlaps the catalytic cysteine.

e-3				Cys163		(Chéreau. 2003)		
c-Myc/Ma x	6G6 K	-	-	Arg214, Leu210, Lys944, Thr947, Ser224	-	Lys355, Arg356, His359, Glu363, Arg367 (Sammak et al. 2019)	None	No direct overlap with experimentally established key DNA-binding/functional residues.
PCNA	1AX C	-	-	Lys13, Lys80, Arg146, Arg149, Ala82	-	Met40, Val45, Leu47, Leu126, Ile128, Pro129, Gln131, Tyr133, Pro234, Tyr250, Ala252, Pro253 (Gulbis et al.1996)	None	No direct overlap with selected p21-binding/functional residues.
mTOR	4JSV	-	-	Ile2237, Leu2185, Ile2356, Gly2238, Val2240, Tyr2225	-	Asp2338, Asn2343, Asp2357 (Yang et al., 2013)	None	No direct overlap with experimentally established key DNA-binding/functional residues.
IL-6	1AL U	-	-	Thr43, Glu106, Arg104, Thr163, Gln156	-	Arg31, Phe75, Gln76, Arg114, Lys129, Arg169, Gln176, Arg180, Arg183, Gln184 (Bobby et al.2014)	None	No direct overlap with experimentally established key receptor-binding/functional residues.
NF-κB p52	1A3 Q	-	-	Lys221, Lys252, Tyr285, Ser226	-	Arg52, Arg54, Tyr55, Cys57, Glu58, His62, Lys143, Lys221 (Cramer et al. 1997)	Lys221	CA directly overlaps with the experimentally established key DNA-binding/functional residue.

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