Michal Heger, Rowan F. van Golen, Mans Broekgaarden, Martin C. Michel
The molecular basis for the pharmacokinetics and pharmacodynamics of curcumin and its metabolites in relation to cancer
*Pharmacological Reviews*

**Table S1**
*Excel file available upon request to Michal Heger*

*Summary of curcumin-target molecule interactions on the basis of molecular docking and/or site-directed mutagenesis studies. The interactions are categorized for the diketo and enol forms of curcumin. Data contain only those studies in which the interacting functional group of curcumin with the target molecule was not specified. Those studies in which the interacting functional group of curcumin was specified are summarized in Figure 2 (diketo form) and 3 (enolic form).*

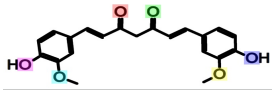
**Curcumin-protein/nucleic acid interactions: diketo**

| Nucleic acid / protein | Bonding site | Bonded amino acid or nucleic acid residues | Type of bond | Notes | Ref |
|---|---|---|---|---|---|
| DNA - d(GTATATAC) duplex sequence, *Actinopterygii* | minor groove | adenine, thymine | van der Waals, weak H-bonding, H2O bridges | | Koonammackal MV 2011 17 2805-16 |
| DNA - d(CGCGATATCGCG) duplex sequence, synthetic construct | minor groove | adenine, thymine | van der Waals, weak H-bonding, H2O bridges | | Koonammackal MV 2011 17 2805-16 |
| HIV-1 reverse transcriptase, human | cavity 1 (of 5), see paper | Gln161, Gln161, Pro140, Thr139, Ser134, Ser134, Val381 | H-bonding | | Seal A, Bioinformation 2011 5 430-3 |
| Glutathione-S-transferase (GST), *Brugia malayi* | GST active site | Gln62, Gln64, Pro51, Val202, Tyr106, Pro201, Tyr7 | H-bonding | | Azeez S, J Mol Model 2012 18 151-63 |
| Cyclooxygenase 2 (COX-2), mouse | COX-2 active site | Met113, Val116, Ile345, Val349, Leu359, Leu384, Trp387, Phe518, Ala527, Val523 | hydrophobic and aromatic | (1) diketo form also binds 2 allosteric sites in COX-2 | Maldonado-Rojas W, J Mol Graph Model 2011 30 157-66 |
| | | Ser530 | H-bonding | (2) enol form does not bind to COX-2 | |
| P-12-lipoxygenase (P-12-LOX), homology-modeled based on rabbit and soybean lipoxygenases and human autocrine motility factor | P-12-LOX active site | Glu355, Ile592, Phe351, Phe413 | not specified; AA association based on position relative to phenyl ring | | Jankun J, Mol Cancer Ther 2006 5 1371-82 |
| | | Trp143, Leu407, Leu360, Leu365 | not specified; AA association based on position relative to other phenyl ring | | |
| Aldose reductase 2 (ALR2), human | ALR2 active site | carbonyl-Trp20, methoxy-Leu300 | H-bonding | | Katsori AM, Eur J Med Chem 2011 46 2722-35 |
| Lipoxygenase (LOX), soybean | LOX active site | carbonyl-His513, hydroxyl-Arg726, Ser510, Asn713, Asp766, Ile770, Leu773, Ile857 | H-bonding | | Katsori AM, Eur J Med Chem 2011 46 2722-35 |
| Vitamin D receptor (VDR), human | VDR alternative pocket | Ser278, Cys288, Arg158, Tyr293, Pro156, His229, Leu233, Phe150, Ser237, Arg274 | H-bonding, hydrophobic, H2O bridges | | Menegaz D, Mol Endocrinol 2011 25 1289-1300 |
| Lipoxygenase 3 (LOX-3), soybean | LOX-3 active site | Tyr207, Arg562, Asn558, Glu527 (inner core of binding cavity) | not specified; AA association based on position relative to phenyl ring | | Skrzypcak-Jankun E, Int J Mol Med 2003 12 17-24 |
| | | Asp766, Thr575, H2O molecules (outer part of binding cavity) | not specified; AA association based on position relative to other phenyl ring | | |
| FtsZ, *Escherichia coli* | FtsZ active site | Gly20, Gly21, Gly109, Thr132, Asn165 | H-bonding | | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | | Gly69, Ala70, Gly71, Ala72, Met104, Gly106, Thr108, Phe135, Glu138, Phe182, Ala185, Asn186 | hydrophobic | | |
| FtsZ, *Bacillus subtilis* | FtsZ active site | Gly21, Gly22, Gly72, Thr133, Asn166 | H-bonding | | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | | Gly20, Leu69, Gly70, Ala73, Gly104, Thr109, Pro135, Glu139, Arg143, Ala186, Asp187 | hydrophobic | | |
| Histone deacetylase 8 (HDAC8), human | HDAC8 entrance cavity | Arg37, Pro35, Ile34, Phe152 | not specified; AA association based on proximity of curcumin-AA contacts | | Bora-Tatar G, Bioorg Med Chem 2009 17 5219-28 |
| | | Asp29, Tyr111, Tyr100 | H-bonding | | |
| Phospholipase A2 (PLA2), porcine | PLA2 active site | Asp49 | H-bonding | | Dileep KV, Interdiscip Sci Comput Life Sci 2011 3 189-97 |
| Glyoxalase 1 (GLO1), human | GLO1 active site | Met65 | H2O bridge | | Liu M, Biophys Chem 2010 147 28-34 |
| | | Met157, Leu160, Leu162, Met179, Phe62, Glu69, Leu92 | hydrophobic (based on curcumin-AA proximity) | | |
| Aldo-keto reductase AKR1B10, human | AKR1B10 active site | His111 | H-bonding | | Matsunaga T, Biochem Biophys Res Commun 2009 389 128-32 |
| | | Val301 | hydrophobic | | |
| Glutathione-S-transferase (GST), *Meloidogyne incognita*, homology modeled based on GST from Caenorhabditis elegans | cavity 1 (of 3), see paper | Ile168, Glu169, Met170, Tyr197, Lys200, Lys202, Cys203 | H-bonding | | Babu RO, Bioinformation 2012 8 319-25 |
| Tetanolysin-O, *Clostridium tetani*, homology-modeled based on perfringolysin-O of *Clostridium perfringens* | entire toxin | Asn89 | H-bonding | | Skariyachan S, Interdiscip Sci Comput Life Sci 2012 4 273-81 |
| Glycogen synthase kinase 3β (GSK-3β) | active site | Val35, Gln185, Lys85 | H-bonding | | Elumalai M, Acta Pol Pharm 2012 69 237-45 |
| Deltatoxin, *Clostridium perfringens*, homology-modeled based on α-hemolysin of *Staphylococcus aureus* | entire toxin | Leu246, Thr142 | H-bonding | | Skariyachan S, Bioinformation 2011 6 375-9 |
| | | Lys140, Thr148, Asn186, Thr187, Ser252 | not specified | | |
| Cyclooxygenase 2 (COX-2), mouse | COX-2 active site | Ala562 | H-bonding | Keto/enol isomer not specified, deduced from structure | Padhye S, Pharm Res 2009 26 2438-45 |
| B-cell lymphoma 2 (Bcl-2), human | Bcl-2 active site | Gly141, Asn143, Gly145, Arg146, His184, Trp188 | polar, including H-bonding | | Luthra PM, Biochem Biophys Res Commun 2009 384 420-5 |
| Immunoglobulin G (IgG), human | CDR of Fab domain | His35, Arg96, Tyr99 | H-bonding | | Liu Y, Immunobiology 2008 213 651-61 |
| | | Tyr91, Ala92, Tyr94, Tyr98 | hydrophobic | | |

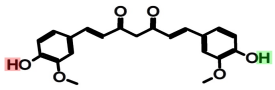
**Curcumin-protein/nucleic acid interactions: enol**

| Nucleic acid / protein | Bonding site | Bonded amino acid or nucleic acid residues | Type of bond | | Ref |
|---|---|---|---|---|---|
| DNA - d(GTATATAC) duplex sequence, *Actinopterygii* | minor groove | adenine, thymine | van der Waals, weak H-bonding, H2O bridges | | Koonammackal MV 2011 17 2805-16 |
| DNA - d(CGCGATATCGCG) duplex sequence, synthetic construct | minor groove | adenine, thymine | van der Waals, weak H-bonding, H2O bridges | | Koonammackal MV 2011 17 2805-16 |
| DNA - d(CTTCCTCATGTATATACATGAGGA) duplex sequence, brown rat | minor groove | adenine, thymine | van der Waals, possible H-bonding | Na+ ions essential for curcumin-poly(dA-dT) binding | Zsila F, Org Biomol Chem 2004 2 2902-10 |
| Cyclooxygenase 1 (COX-1), mouse | COX-1 active site | Tyr385, Leu384, Phe518, Met522, Ser530 | not specified; AA association based on position relative to phenyl ring | | Selvam C, Bioorg Med Chem Lett 2005 15 1793-7 |
| | | Ile523, Ala526, Gly526, Glu524, Ser353, Leu359, Val349, Leu352 | not specified; AA association based on position relative to methine segment | | |
| | | Tyr355, His90, Leu357, Arg120, Glu524 | not specified; AA association based on position relative to other phenyl ring | | |
| Thioredoxin reductase (TrxR), rat | TrxR active site, F-chain | His108 | H-bonding | | Singh DV, Bioinformation 2009 4 187-92 |
| | | Arg351, Lys29, Leu112 | hydrophobic | | |
| | TrxR active site, E-chain | AAs in the Ser495-Gly499 stretch, Ser483, Trp467 | hydrophobic, H-bonding | | |
| α1-acid glycoprotein (AGP), human | AGP site 2, central pocket | Asn75, Glu69, Thr67, Thr76, Thr77, Tyr78 | H-bonding | | Zsila F, Bioorg Med Chem 2004 12 3239-45 |
| | | Phe49 | hydrophobic | | |
| | AGP site 3, binding site | Glu84, Asn15, Phe114 | secondary interactions | | |
| Glycogen synthase kinase-3 β (GSK-3β), human | GSK-3β active site | Val135, Ile62 | H-bonding (Ile62 via 2 H2O bridges) | | Bustanji Y, J Enzyme Inhib Med Chem 2009 24 771-8 |
| | | Arg141 (side-chain guanidino) | charge transfer | | |
| | | enolic cα-carbon | hydrophobic | | |
| Glyoxalase 1 (GLO1), human | GLO1 active site | Met179, Glu172 | H-bonding (Glu172 also via H2O bridge) | | Liu M, Biophys Chem 2010 147 28-34 |
| Glyoxalase 1 (GLO1), human | GLO1 active site | Lys156 | H-bonding | | Yuan M, J Bioorg Med Chem 2011 19 1189-96 |
| Albumin, human | subdomain IIA | Lys199, Arg218, Ser287, Arg257, Lys286 | H-bonding | | Zsila F, Tetrahedron Asymmetry 2003 14 2433-44 |
| | | Leu238, Leu260, Ala291, Ala215, Trp214 | hydrophobic | | |
| HIV-1 integrase, human | chain A, active site | His67, Thr66, Lys155 | H-bonding | | Vajragupta O, Bioorg Med Chem Lett 2005 15 3364-8 |
| | | Asn120, Ser119, Thr93 | possible H-bonding | | |
| | | Asp116, Asp64, Glu92, Lys159 | not specified | | |
| HIV-1 protease, human | chains A and B, active site | Asp29, Asp30 | H-bonding | | Vajragupta O, Bioorg Med Chem Lett 2005 15 3364-8 |

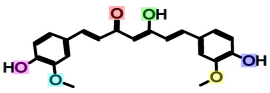
**Data for Figures 2 and 3 (main manuscript)**



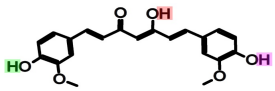
| | H-bond accepting oxygens - diketo | Ref |
|---|---|---|
| left =O | Gln1226, side-chain amino proton, DNA methyltransferase 1 (human) | Yoo J, J Comput Aided Mol Des 2011 25 555-67 |
| | Trp111, aldose reductase 2 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Lys263, aldose reductase 1 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | His513, lipoxygenase (soybean) | Katsori AM, Eur J Med Chem 2011 46 2722-35 |
| | Gly20, FtsZ (*Escherichia coli*) | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | Gly21, FtsZ (*Escherichia coli*) | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | Gly22, FtsZ (*Bacillus subtilis*) | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | Thr1, 20S proteasome β5 CT-like subunit, origin unspecified | Milacic V, Cancer Res 2008 68 7283-92 |
| | Gln11, tubulin chain A (bovine) | Li J, Toxicol Appl Pharmacol 2012 265 190-9 |
| right =O | Lys1462, side-chain amino proton, DNA methyltransferase 1 (human) | Yoo J, J Comput Aided Mol Des 2011 25 555-67 |
| | His110, aldose reductase 2 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Ser215, aldose reductase 1 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Gln267, PfATP6 (*Plasmodium falciparum*) | Ji HF, Bioorg Med Chem Lett 2009 19 2453-5 |
| | Gly109, FtsZ (*Escherichia coli*) | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | Gly21, FtsZ (*Bacillus subtilis*) | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | Lys254, tubulin chain B (bovine) | Li J, Toxicol Appl Pharmacol 2012 265 190-9 |
| left OH | Arg1311, 2 guanidino protons, DNA methyltransferase 1 (human) | Yoo J, J Comput Aided Mol Des 2011 25 555-67 |
| | Tyr50, aldose reductase 1 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Lys80, aldose reductase 1 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Ala985, PfATP6 (*Plasmodium falciparum*) | Ji HF, Bioorg Med Chem Lett 2009 19 2453-5 |
| | Tyr100, amidic carbonyl, histone deacetylase 8 (human) | Bora-Tatar G, Bioorg Med Chem 2009 17 5219-28 |
| | Asp1, monomeric amyloid beta peptide (Aβ)9-40 (human) | Ngo ST, J Phys Chem B 2012 116 10165-75 |
| | Ser26, hexameric amyloid beta peptide (Aβ)9-40 (human) | Ngo ST, J Phys Chem B 2012 116 10165-75 |
| right OH | His1458, imidazole amino proton, DNA methyltransferase 1 (human) | Yoo J, J Comput Aided Mol Des 2011 25 555-67 |
| | Thr266, aldose reductase 1 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Arg269, aldose reductase 1 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Ile1041, PfATP6 (*Plasmodium falciparum*) | Ji HF, Bioorg Med Chem Lett 2009 19 2453-5 |
| | Leu1040, PfATP6 (*Plasmodium falciparum*) | Ji HF, Bioorg Med Chem Lett 2009 19 2453-5 |
| | Asp29, side-chain carbonyl, histone deacetylase 8 (human) | Bora-Tatar G, Bioorg Med Chem 2009 17 5219-28 |
| | Met65, via H2O bridge, glyoxalase I (human) | Liu M, Biophys Chem 2010 147 28-34 |
| left OCH3 | Leu300, aldose reductase 2 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Leu301, aldose reductase 2 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Thr132, FtsZ (*Escherichia coli*) | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | Asn165, FtsZ (*Escherichia coli*) | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | Thr133, FtsZ (*Bacillus subtilis*) | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | Asn166, FtsZ (*Bacillus subtilis*) | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | Gln257, amidic proton, protein kinase C δ (homology modeled) | Majhi A, Bioorg Med Chem 2010 18 1591-8 |
| | Thr242, amidic proton, protein kinase C δ C1b subdomain | Mamidi N, Chem Phys Lipids 2012 165 320-30 |
| right OCH3 | Trp20, aldose reductase 2 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Thr19, aldose reductase 2 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Lys263, aldose reductase 1 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Gly72, FtsZ (*Bacillus subtilis*) | Kaur S, Eur J Med Chem 2010 45 4209-14 |
| | Tyr111, side-chain hydroxyl proton, histone deacetylase 8 (human) | Bora-Tatar G, Bioorg Med Chem 2009 17 5219-28 |
| | Lys28, side-chain amino proton, hexameric amyloid beta peptide (Aβ)9-40 (human) | Ngo ST, J Phys Chem B 2012 116 10165-75 |



| | H-bond donors - diketo | Ref |
|---|---|---|
| left OH | Glu1265, side-chain carbonyl, DNA methyltransferase 1 (human) | Yoo J, J Comput Aided Mol Des 2011 25 555-67 |
| | Gln184, aldose reductase 1 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Leu251, amidic carbonyl, protein kinase C δ (homology modeled) | Majhi A, Bioorg Med Chem 2010 18 1591-8 |
| | Ser96, 20S proteasome β5 CT-like subunit, origin unspecified | Milacic V, Cancer Res 2008 68 7283-92 |
| | Leu251, amidic carbonyl, protein kinase C δ C1b subdomain | Mamidi N, Chem Phys Lipids 2012 165 320-30 |
| | Lys28, hexameric amyloid beta peptide (Aβ)9-40 (human) | Ngo ST, J Phys Chem B 2012 116 10165-75 |
| | Phe108, amidic carbonyl, nonameric amyloid beta peptide (Aβ)9-40 (human) | Ngo ST, J Phys Chem B 2012 116 10165-75 |
| right OH | Leu1454, amidic carbonyl, DNA methyltransferase 1 (human) | Yoo J, J Comput Aided Mol Des 2011 25 555-67 |
| | Ile260, aldose reductase 2 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Ser264, aldose reductase 1 (human) | Muthenna P, FEBS Lett 2009 583 3637-42 |
| | Gly254, protein kinase C theta C1B subdomain (human) | Das J, Bioorg Med Chem 2011 19 6196-202 |



| | H-bond accepting oxygens - enol | Ref |
|---|---|---|
| right =O | Gln267, PfATP6 (*Plasmodium falciparum*) | Ji HF, Bioorg Med Chem Lett 2009 19 2453-5 |
| | Arg120, cyclooxygenase 2 (human) | Selvam C, Bioorg Med Chem Lett 2005 15 1793-7 |
| | Val135, amidic proton, glycogen synthase kinase-3 β (human) | Bustanji Y, J Enzyme Inhib Med Chem 2009 24 771-8 |
| left OH (top) | Glu172, via H2O bridge, glyoxalase I (human) | Liu M, Biophys Chem 2010 147 28-34 |
| | Ile62, amidic carbonyl via 2 H2O bridges, glycogen synthase kinase-3 β (human) | Bustanji Y, J Enzyme Inhib Med Chem 2009 24 771-8 |
| left OH (bottom) | Arg141, guanidino proton, glycogen synthase kinase-3 β (human) | Bustanji Y, J Enzyme Inhib Med Chem 2009 24 771-8 |
| right OH | Ile1041, PfATP6 (*Plasmodium falciparum*) | Ji HF, Bioorg Med Chem Lett 2009 19 2453-5 |
| | Leu1040, PfATP6 (*Plasmodium falciparum*) | Ji HF, Bioorg Med Chem Lett 2009 19 2453-5 |
| | Lys85, side-chain amino proton, glycogen synthase kinase-3 β (human) | Bustanji Y, J Enzyme Inhib Med Chem 2009 24 771-8 |
| left OCH3 | | |
| right OCH3 | | |



| | H-bond donors - enol | Ref |
|---|---|---|
| top OH (left) | Glu172, glyoxalase I (human) | Liu M, Biophys Chem 2010 147 28-34 |
| | Val135, amidic carbonyl, glycogen synthase kinase-3 β (human) | Bustanji Y, J Enzyme Inhib Med Chem 2009 24 771-8 |
| left OH (bottom) | | |
| right OH (bottom) | Met179, amidic carbonyl, glyoxalase I (human) | Liu M, Biophys Chem 2010 147 28-34 |