Supporting Information

Halogen-enriched fragment libraries as leads for drug rescue of mutant p53

Rainer Wilcken[1,2], Xiangrui Liu[2], Markus O. Zimmermann[1], Trevor J. Rutherford[2], Alan R. Fersht[2], Andreas C. Joerger[2]* and Frank M. Boeckler[1]*

[1]Laboratory for Molecular Design and Pharmaceutical Biophysics, Department of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy, Eberhard-Karls-University Tubingen, Auf der Morgenstelle 8, 72076 Tubingen, Germany.

[2] MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 0QH, United Kingdom.

*To whom correspondence should be addressed. E-mail: acj2@mrc-lmb.cam.ac.uk (A.C.J.), frank.boeckler@uni-tuebingen.de (F.M.B.)

SUPPORTING METHODS

Quantum chemical calculations

We modeled the potential halogen bond interaction between a halogenated small molecule and Leu145 by employing iodobenzene and N-methylacetamide as ligand and protein models, respectively A geometry optimization was carried out at the MP2/TZVPP[1] level using the TURBOMOLE 6.2 suite of programs.[2,3] Relativistic effects for iodine were considered by an effective core potential (ECP).[4] The calculations were done in combination with the resolution of identity (RI) technique[5-8] and the frozen core approximation. The frozen core orbitals were attributed by the default setting in TURBOMOLE by which all orbitals possessing energies below 3.0 au are considered core orbitals. For all calculations the SCF convergence criterion was increased to 10^{-8} Hartree.

Input files for the generation of the iodo-interaction energy sphere were generated from optimized MP2/TZVPP geometries subject to certain constraints: the ligand C-I group was placed on the vector defined by the C=O group, with both the C=O•••I angle and the O•••I-C angle constrained to 180°; the bond distance was freely optimized. In order to generate a full sphere of input geometries for subsequent calculations, the optimized structure was transformed as follows: The oxygen atom was placed on the origin of the coordinate system and the entire complex was rotated until the iodine atom was positioned on the positive x-axis. a denotes the angle of rotation counter-clockwise around the z-axis, and denotes the angle of rotation counter-clockwise around the x-axis. a was gradually increased from 0° to 180° in steps of 5°. For each a-value, was varied from 0° to 355° in steps of 5°, leading to a total number of 2664 halogen positions distributed on a sphere. The structure of the ligand was not altered during this transformation process. Calculations were done as single point (SCF) calculations using the MP2/TZVPP method. For visualization purposes, several Python scripts were written and executed in PyMOL[9]. Interaction energies were partitioned into bins and spectrum colors (red to blue to purple) were assigned. At the positions of the iodine, small CONE objects with the appropriate coloring were generated.

References

(1) Weigend, F.; Ahlrichs, R. Phys. Chem. Chem. Phys. 2005, 7, 3297.

(2) Ahlrichs, R.; Bär, M.; Häser, M.; Horn, H.; Kölmel, C. Chem. Phys. Lett. 1989, 162, 165.

(3) TURBOMOLE v6.2 (June 2010), available from http://www.turbomole.com 2010.

(4) Peterson, K. A.; Figgen, D.; Goll, E.; Stoll, H.; Dolg, M. J. Chem. Phys. 2003, 119, 11113.

(5) Feyereisen, M.; Fitzgerald, G.; Komornicki, A. Chem. Phys. Lett. 1993, 208, 359.

(6) Weigend, F.; Häser, M.; Patzelt, H.; Ahlrichs, R. Chem. Phys. Lett. 1998, 294, 143.

(7) Hättig, C. Phys. Chem. Chem. Phys. 2005, 7, 59.

(8) Hellweg, A.; Hättig, C.; Höfener, S.; Klopper, W. Theor. Chem. Acc. 2007, 117, 587.

(9) DeLano, W. L., The PyMOL Molecular Graphics System. DeLano Scientific LLC, Palo Alto, CA, USA 2008.

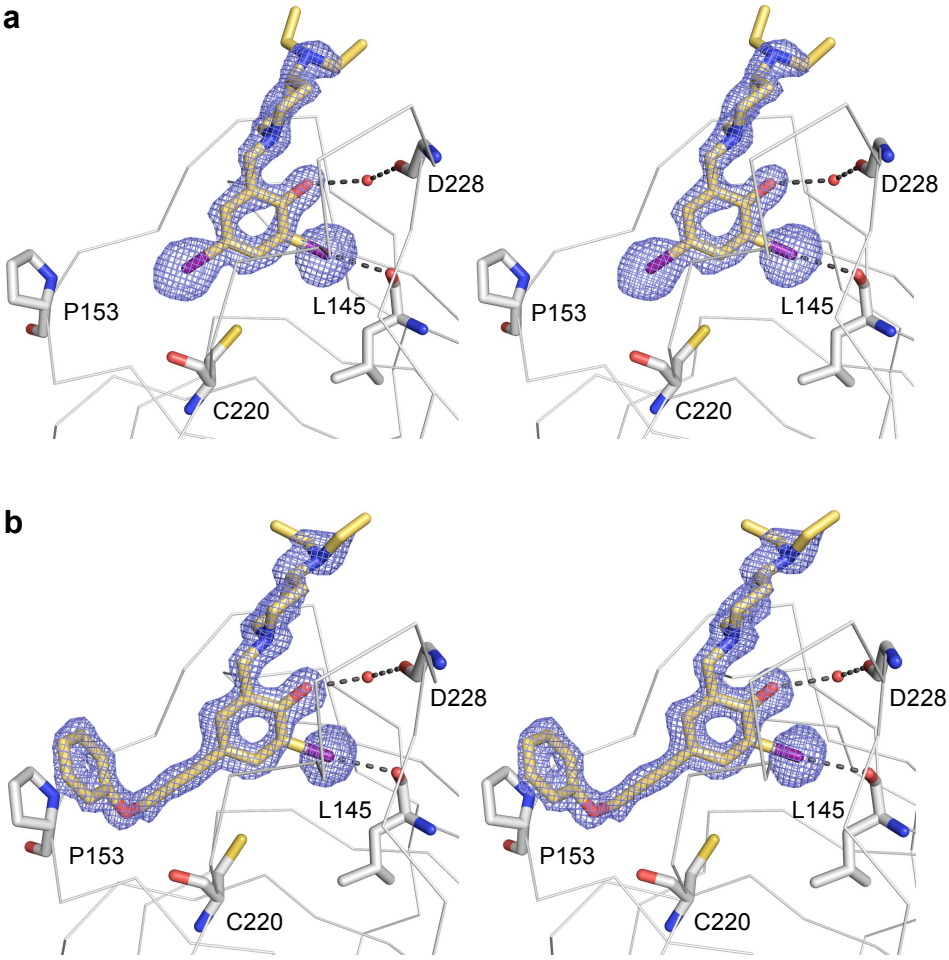

Figure S1. Electron density maps for ligands bound to the Y220C mutant. Simulated-annealing omit (F_o-F_c) electron-density maps for ligands **4** (a) and **12**/PhiKan5176 (b) in complex with the Y220C mutant are shown at a contour level of 3.0 sigma

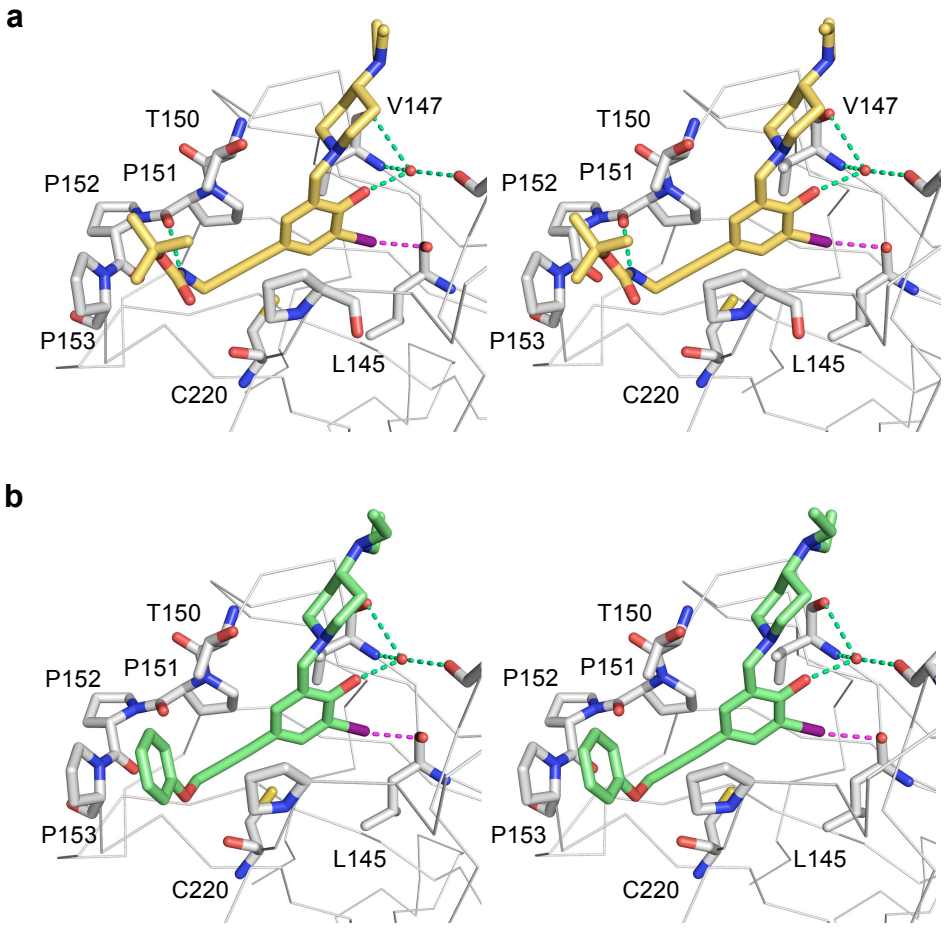

Figure S2. Crystal structures of Y220C-ligand complexes. Shown are stereo views of the binding modes of PhiKan5174 (a) and PhiKan5176 (b). The halogen bond between the iodine and the carbonyl oxygen of Leu145 is indicated by a magenta broken line.

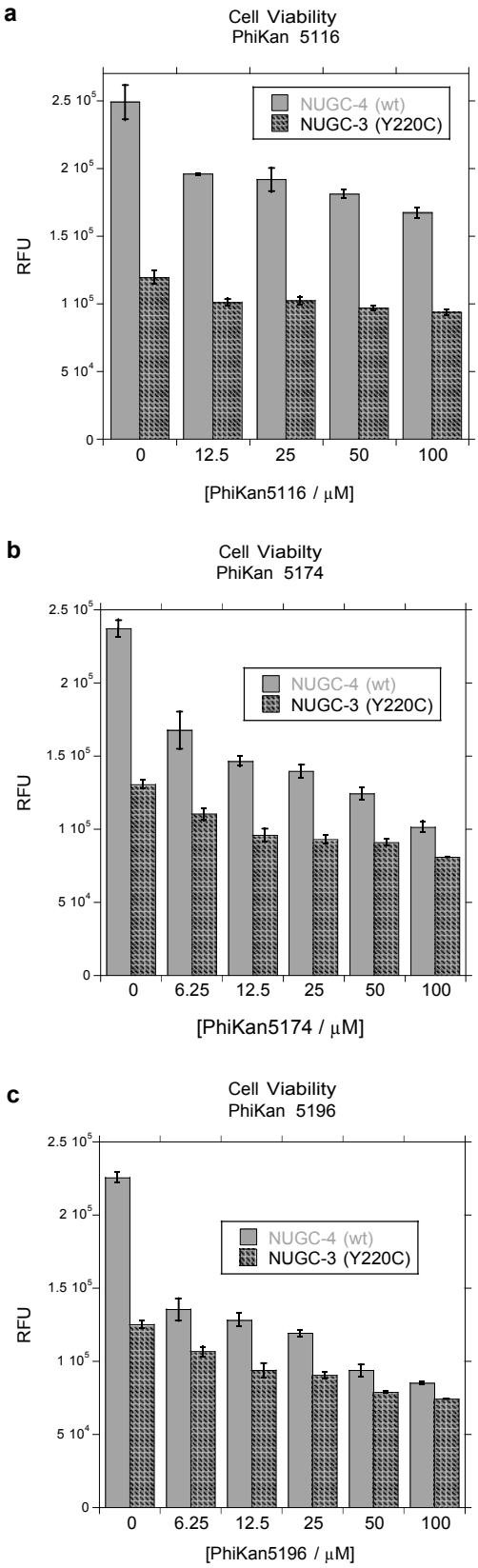

Figure S3. Cell viability of NUGC-3 (Y220C) and NUGC-4 (wild-type p53) cells after treatment with different concentrations of (a) PhiKan5116, (b) PhiKan5174, and (c) PhiKan5196.