Supporting Information

Design, Synthesis, and Biological Evaluation of Potent Quinoline and Pyrroloquinoline Ammosamide Analogues as Inhibitors of Quinone Reductase 2

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Abbreviations used: CIMS, chemical ionization mass spectrometry; DIPEA, *N*.*N*-diisopropylethylamine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide, EIMS, electron impact mass spectrometry; ESIMS, electrospray ionization mass spectrometry; FAD, flavin adenine dinucleotide; HRMS, high resolution mass spectrometry; NCS, *N*-chlorosuccinimide; NMeH, *N*-methyldihydronicotinamide; PTSA, *p*-toluenesulfonic acid; QR2, quinone reductase 2; THF, tetrahydrofuran.

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ORTEP and Coordinates for the Crystal Structure of Compound 34

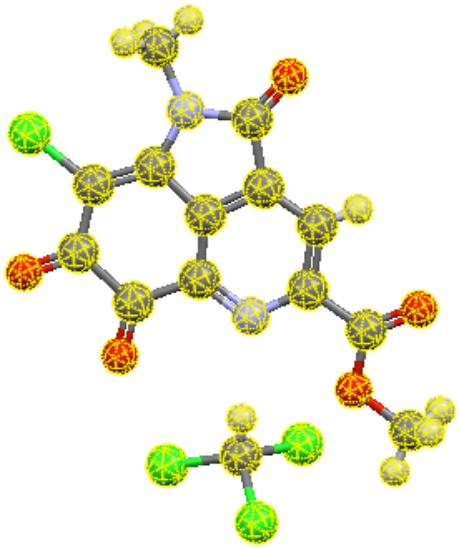

Figure S1. X-Ray Crystal structure (ORTEP) of compound **34** shown in ball and stick and colored according to atom type and X, Y and Z coordinates are shown in the below table.

Experimental Section for Crystallography of Compound 34

DATA COLLECTION

A orange plate of $C_{13}H_7ClN_2O_5,CHCl_3$ having approximate dimensions of 0.18 x 0.16 x 0.05 mm was mounted on a fiber in a random orientation. Preliminary examination and data collection were performed Cu K_α radiation (λ = 1.54184Å) on a Rigaku Rapid II equipped with confocal optics.

Cell constants for data collection were obtained from least-squares refinement, using the setting angles of 13857 reflections in the range $3 < \theta < 70°$. The orthorombic cell parameters and calculated volume are: a = 11.1237(4), b = 12.7728(5), c = 23.2174(7)Å, V = 3298.7(2)Å^3. For Z = 8 and F.W. = 426.04 the calculated density is 1.72 g/cm^3. The refined mosaicity from DENZO/SCALEPACK was (ref 1) was 0.48° indicating good crystal quality. The space group was determined by the program XPREP(ref 2). From the systematic presences of:

hk0 h=2n
h0l l=2n
0kl k=2n

and from subsequent least-squares refinement, the space group was determined to be P b c a(# 61).

The data were collected at a temperature of 150(1)K. Data were collected to a maximum 2θ of 140.5°.

DATA REDUCTION

A total of 13857 reflections were collected, of which 2950 were unique. Frames were integrated with DENZO-SMN (ref 1).

Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 69.6 /mm for Cu K_α radiation. An empirical absorption correction using SCALEPACK (ref 1) was applied. Transmission coefficients ranged from 0.681 to 0.706. Intensities of equivalent reflections were averaged. The agreement factor for the averaging was 3.4% based on intensity.

STRUCTURE SOLUTION AND REFINEMENT

The structure was solved by direct methods using SIR2004 (ref 3). The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were located and their positions and anisotropic thermal parameters were refined. The structure was refined in full-matrix least-squares where the function minimized was $\Sigma w(|Fo|^2-|Fc|^2)^2$ and the weight w is defined as $1/[\sigma^2(Fo^2)+(0.0518P)^2+4.1407P]$ where $P=(Fo^2+2Fc^2)/3$. Scattering factors were taken from the "International Tables for Crystallography" (ref 4). 2950 reflections were used in the refinements. However, only the 2722reflections with $F_o^2>2\sigma(F_o^2)$ were used in, calculating R1. The final cycle of refinement included 258 variable parameters and converged (largest parameter shift was <0.01 times its su) with unweighted and weighted agreement factors of:

$$R1 = \Sigma |Fo - Fc| / \Sigma Fo = 0.041$$

$$R2 = SQRT (\Sigma w (Fo^2 - Fc^2)^2 / \Sigma w (Fo^2)^2) = 0.112$$

The goodness-of-fit parameter was 1.15. The highest peak in the final difference Fourier had a height of 0.35 e/A^3. The minimum negative peak had a height of -0.32 e/A^3.

Refinement was performed on a LINUX PC using SHELX-97 (ref 2). Crystallographic drawings were done using programs ORTEP (ref 5),and PLUTON (ref 6).

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(1) Z. Otwinowski and W. Minor, Methods Enzymol., 276, 307 (1997).
(2) G.M. Sheldrick Acta Cryst., A64, 112,(2008).
(3) M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini,G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori,and R. Spagna. , J. Appl. Cryst., 38, 381 (2005)
(4) "International Tables for Crystallography", Vol. C, Kluwer Academic Publishers, Utrecht, The Netherlands, (1992), Tables 4.2.6.8 and 6.1.1.4
(5) C. K. Johnson, ORTEPII, Report ORNL-5138, Oak Ridge National Laboratory, Tennessee, USA (1976)

(6) A. L. Spek, PLUTON. Molecular Graphics Program. Univ. of Ultrecht, The Netherlands (1991)

Positional Parameters and Their Standard Uncertainties for $C_{13}H_7ClN_2O_5,CHCl_3$ (34)

Atom	x	y	z	U(Å ^{2})
Cl4	0.05299(7)	0.15363(5)	0.61308(3)	0.0399(2)
Cl91	0.00168(7)	0.38674(7)	0.28700(3)	0.0463(2)
Cl92	-0.03446(8)	0.61061(7)	0.29078(3)	0.0510(2)
Cl93	-0.23829(7)	0.47118(6)	0.27912(3)	0.0437(2)
O1	-0.37605(19)	0.37852(19)	0.64885(9)	0.0454(6)
O5	0.16288(17)	0.24847(15)	0.51071(8)	0.0342(5)
O6	0.06192(16)	0.37465(14)	0.42993(8)	0.0312(5)
O91	-0.42092(18)	0.64327(15)	0.45501(8)	0.0362(5)
O92	-0.27131(17)	0.62281(14)	0.39092(8)	0.0316(5)
N2	-0.1993(2)	0.29284(18)	0.62421(9)	0.0324(6)
N8	-0.16165(19)	0.48092(15)	0.45651(9)	0.0246(5)
C1	-0.2923(3)	0.3670(2)	0.61639(11)	0.0335(7)
C3	-0.1142(2)	0.29866(19)	0.58121(11)	0.0276(6)
C4	-0.0086(2)	0.2501(2)	0.57026(11)	0.0293(7)
C5	0.0616(2)	0.28046(19)	0.51956(11)	0.0286(7)
C6	0.0076(2)	0.35837(19)	0.47388(11)	0.0255(6)
C7	-0.1073(2)	0.40964(19)	0.48994(10)	0.0242(6)
C9	-0.2651(2)	0.52209(19)	0.47621(11)	0.0263(6)
C10	-0.3197(2)	0.4958(2)	0.52882(11)	0.0279(6)
C11	-0.2629(2)	0.4222(2)	0.56181(10)	0.0275(6)
C12	-0.1571(2)	0.38006(19)	0.54213(10)	0.0256(6)
C21	-0.2053(4)	0.2171(3)	0.67114(15)	0.0469(10)
C91	-0.3278(2)	0.6024(2)	0.44003(11)	0.0281(6)
C93	-0.3294(3)	0.7019(3)	0.35544(14)	0.0396(8)
C911	-0.0948(3)	0.4880(2)	0.30990(12)	0.0357(8)
H10	-0.392(3)	0.526(2)	0.5394(13)	0.032(8)*
H21A	-0.136(4)	0.218(3)	0.6951(19)	0.071(13)*
H21B	-0.262(4)	0.243(3)	0.6972(19)	0.064(12)*
H21C	-0.220(4)	0.154(4)	0.6583(19)	0.073(14)*
H911	-0.108(3)	0.487(2)	0.3501(14)	0.034(8)*
H93A	-0.332(3)	0.767(3)	0.3764(14)	0.046(9)*
H93B	-0.415(4)	0.676(3)	0.3464(18)	0.075(13)*
H93C	-0.282(3)	0.708(2)	0.3215(15)	0.042(9)*

Starred atoms were refined isotropically

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a^*_i a^*_j \mathbf{a}_i.\mathbf{a}_j$

Table of Bond Distances in Angstroms for $C_{13}H_7ClN_2O_5,CHCl_3$ (34)

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
Cl4	C4	1.726(3)	C3	C12	1.460(3)
Cl91	C911	1.763(3)	C4	C5	1.466(4)
Cl92	C911	1.761(3)	C5	C6	1.573(4)
Cl93	C911	1.761(3)	C6	C7	1.482(3)
O1	C1	1.207(3)	C7	C12	1.384(3)
O5	C5	1.215(3)	C9	C10	1.401(4)
O6	C6	1.205(3)	C9	C91	1.498(3)
O91	C91	1.211(3)	C10	C11	1.367(4)
O92	C91	1.328(3)	C10	H10	0.91(3)
O92	C93	1.457(3)	C11	C12	1.373(4)
N2	C3	1.378(3)	C21	H21A	0.94(4)
N2	C1	1.412(4)	C21	H21B	0.95(4)
N2	C21	1.460(4)	C21	H21C	0.88(4)
N8	C7	1.342(3)	C93	H93A	0.97(3)
N8	C9	1.347(3)	C93	H93B	1.01(4)
C1	C11	1.487(4)	C93	H93C	0.96(3)
C3	C4	1.351(4)	C911	H911	0.94(3)

Numbers in parentheses are standard uncertanties in the least significant digits.

Crystal Data and Date Collection Parameters for $C_{13}H_7ClN_2O_5$,$CHCl_3$ (34)

formula	$C_{14}H_8Cl_4N_2O_5$
formula weight	426.04
space group	P b c a (No. 61)
a, Å	11.1237(4)
b, Å	12.7728(5)
c, Å	23.2174(7)
V, $Å^3$	3298.7(2)
Z	8
d_{calc}, g cm^{-3}	1.716
crystal dimensions, mm	0.18x0.16x0.05
temperature, K	150.
radiation (wavelength, Å)	Cu K_α (1.54184)
monochromator	graphite
linear abs coef, mm^{-1}	6.959
absorption correction applied	empirical[a]
transmission factors: min, max	0.68, 0.71
diffractometer	Nonius KappaCCD
h, k, l range	0 to 13 0 to 15 0 to 27
2θ range, deg	6.92-140.47
mosaicity, deg	0.48
programs used	SHELXTL
F_{000}	1712.0
weighting $1/[\sigma^2(Fo^2)+(0.0518P)^2+4.1407P]$ where $P=(Fo^2+2Fc^2)/3$	
data collected	13857
unique data	2950
R_{int}	0.034
data used in refinement	2950
cutoff used in R-factor calculations	$F_o^2>2.0\sigma(F_o^2)$
data with $I>2.0\sigma(I)$	2722
number of variables	258
largest shift/esd in final cycle	0.00
$R(F_o)$	0.041
$R_w(F_o^2)$	0.112
goodness of fit	1.146

[a] Otwinowski Z. & Minor, W. Methods Enzymol. **1996**,276307.

Table of Bond Angles in Degrees for $C_{13}H_7ClN_2O_5,CHCl_3$ (34)

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C91	O92	C93	114.3(2)	C9	C10	H10	120.9(19)
C3	N2	C1	111.9(2)	C10	C11	C12	118.5(2)
C3	N2	C21	127.5(3)	C10	C11	C1	134.7(2)
C1	N2	C21	120.4(2)	C12	C11	C1	106.7(2)
C7	N8	C9	117.0(2)	C11	C12	C7	121.9(2)
O1	C1	N2	124.5(2)	C11	C12	C3	110.6(2)
O1	C1	C11	130.0(3)	C7	C12	C3	127.4(2)
N2	C1	C11	105.4(2)	N2	C21	H21A	112(2)
C4	C3	N2	135.1(2)	N2	C21	H21B	105(3)
C4	C3	C12	119.5(2)	H21A	C21	H21B	102(3)
N2	C3	C12	105.3(2)	N2	C21	H21C	111(3)
C3	C4	C5	119.6(2)	H21A	C21	H21C	113(4)
C3	C4	Cl4	124.4(2)	H21B	C21	H21C	113(4)
C5	C4	Cl4	116.0(2)	O91	C91	O92	124.5(2)
O5	C5	C4	122.8(2)	O91	C91	C9	122.1(2)
O5	C5	C6	117.0(2)	O92	C91	C9	113.4(2)
C4	C5	C6	120.2(2)	O92	C93	H93A	108.3(18)
O6	C6	C7	124.7(2)	O92	C93	H93B	108(2)
O6	C6	C5	119.1(2)	H93A	C93	H93B	112(3)
C7	C6	C5	116.1(2)	O92	C93	H93C	104.9(19)
N8	C7	C12	120.7(2)	H93A	C93	H93C	111(3)
N8	C7	C6	122.9(2)	H93B	C93	H93C	113(3)
C12	C7	C6	116.4(2)	Cl92	C911	Cl93	110.55(17)
N8	C9	C10	124.8(2)	Cl92	C911	Cl91	110.08(15)
N8	C9	C91	118.2(2)	Cl93	C911	Cl91	109.85(15)
C10	C9	C91	116.9(2)	Cl92	C911	H911	108.6(16)
C11	C10	C9	117.1(2)	Cl93	C911	H911	104.9(17)
C11	C10	H10	122.0(19)	Cl91	C911	H911	112.8(17)

Numbers in parentheses are standard uncertanties in the least significant digits.

Crystallographic Data for $C_{13}H_7ClN_2O_5,CHCl_3$ (34)

$C_{14}H_8Cl_4N_2O_5$	formula weight = 426.04
a = 11.1237(4)Å	space group Pbca (No. 61)
b = 12.7728(5)Å	T = 150. K
c = 23.2174(7)Å	λ = 1.54184Å
V = 3298.7(2)Å ^{3}	ρ_{calc} = 1.716g cm^{-3}
	μ = 6.959mm^{-1}
	transmission coeff = 0.681-0.706
	$R(F_o)^a$ = 0.041
	$R_w(F_o^2)^b$ = 0.112

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[a] $R = \Sigma\ ||F_o| - |F_c||/\Sigma\ |F_o|$ for $F_o^2 > 2\sigma(F_o^2)$

[b] $R_w = [\Sigma\ w\ (|F_o^2| - |F_c^2|)^2 / \Sigma\ w\ |F_o^2|^2]^{1/2}$

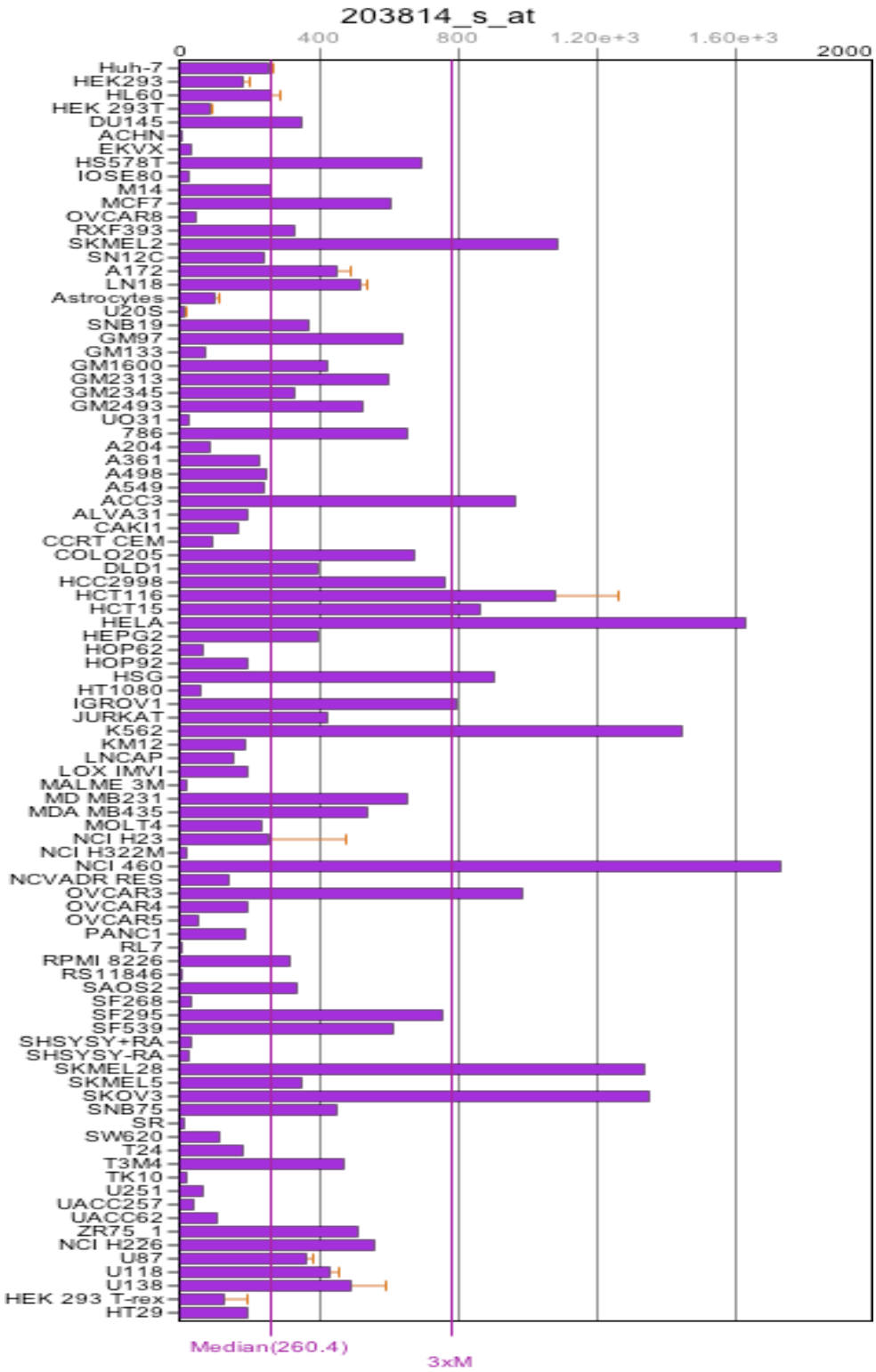
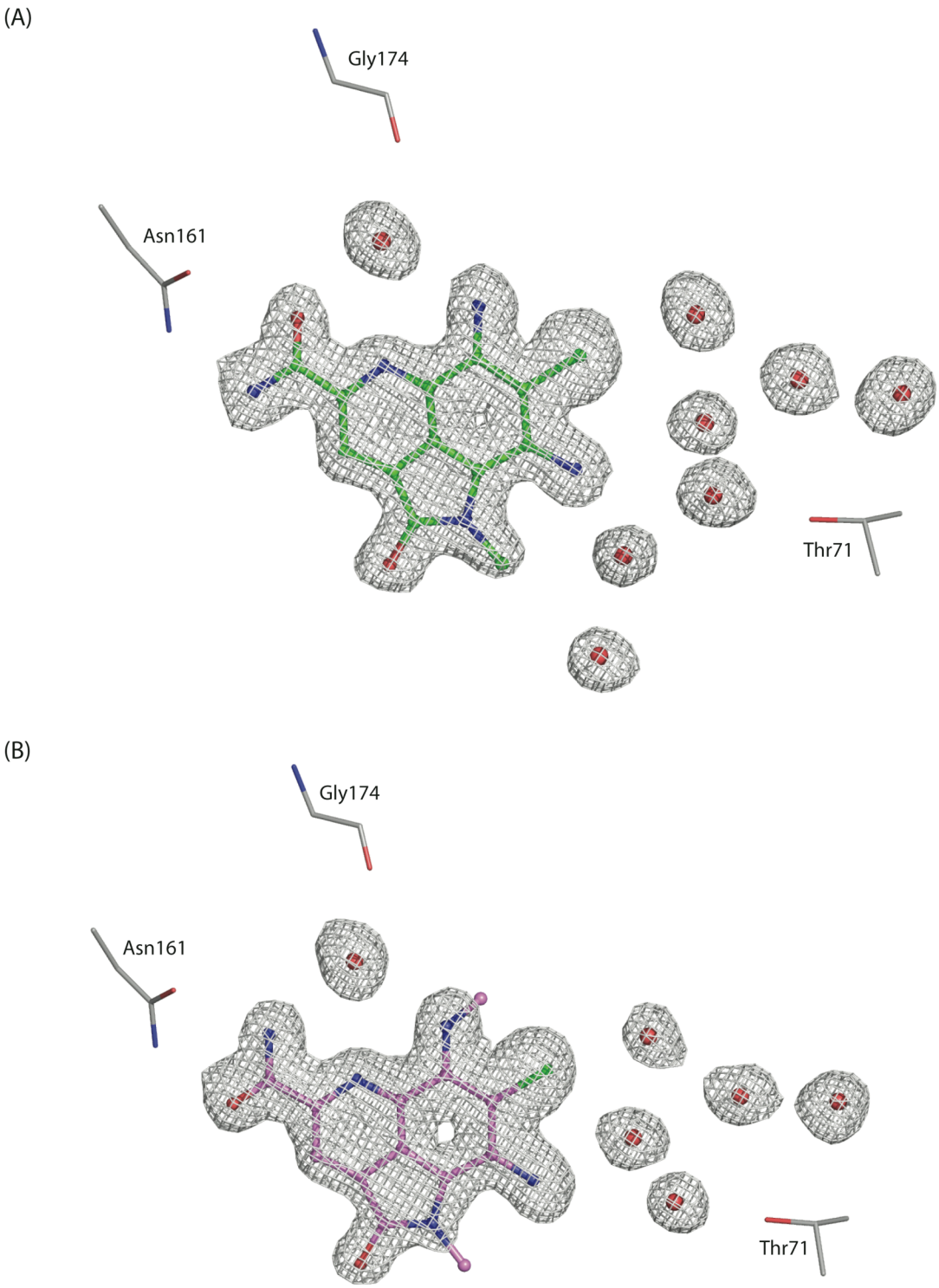


Figure S2. Gene expression profile for quinone reductase 2 (NQO2 or QR2) in the NCI-60 cell lines. Data are from the BioGPS database at website http://biogps.org/#goto=genereport&id=4835. The majority of cell lines exhibit expression of the QR2 gene.



Supplemental Figure S3. Fo-Fc Electron density omit maps contoured at 3σ. Electron density is shown in grey. Water molecules (red spheres) and ammosamide B (A) and compound **38** (B) were omitted from the map calculations.