Supplementary Material

Molecular Modelling Methods

Ligand and Receptor preparation
All ligands and receptors were prepared using SYBYL6.5 and used as MOL2 files. The ligands were designed with Gasteiger-Huckel charges and their structures were energy-minimised using the Tripos force-field (Clark et al., 1989). The receptors were prepared by manually removing all ligands and water molecules (except when relevant) from the structures. The hydrogen atoms were added automatically and the ionisation state of the pH sensitive residues in the active-site was checked manually.

GOLD docking
Each ligand was docked using the latest available version of GOLD (Jones et al., 1995) (version 2.1) in 25 independent runs, and for each of these a maximum number of 100000 operations were performed on a single population of 50 individuals. Operator weights for crossover, mutation and migration were used as default parameters (95, 95 and 10, respectively), as well as the hydrogen bonding (4.0 Å) and Van der Waals (2.5 Å) parameters. The $\alpha$ point in the centre of the active-site was introduced and the radius was set to 15 Å, with the automatic active-site detection on. Flexibility of the rings was allowed with the “flip ring corners” option.

Figure 2 – docking results of 8 (a) and 9 (b) at the active-site of *S. coelicolor* type II dehydroquinase compared with the position of 3 and glycerol (purple) (PDB code: 1GU1)
Synthetic Experimental

\((1S, 3R, 4R, 5S)-1\text{-Acetyl -5-allyl- 4-benzoylcyclohexane-1,3-carbolactone 12}\)

To a solution of lactone 11 (1.0 g, 3.31 mmol, 1.0 eqv) in anhydrous pyridine (30 ml) was added acetic anhydride (626 \(\mu\)l, 6.62 mmol, 2.0 eqv) dropwise. The solution was stirred for 12 h, under \(\text{N}_2\), at room-temperature. The solution was taken in Et\(_2\)O (150 ml) and washed with 1 M HCl (5 x 100 ml) and H\(_2\)O (100 ml). The organic layer was dried under Na\(_2\)SO\(_4\), filtered and the solvent evaporated. The product was further purified by column chromatography on silica gel, eluting with Et\(_2\)O:Hexane (2:1) to give the \textit{acetate 12} as a colourless oil (1.1 g, 96%).

\[ R_f\ 0.60 \text{ [Et}_2\text{O}:\text{Hex}; 2:1]; \]

\(\nu_{\text{max}}/\text{cm}^{-1}\) 1802 (CO), 1745 (CO), 1719 (CO), 1642 (C=C) and 1601 (Ar);

\(\delta_{\text{H}}\) (ppm) (400 MHz; CDCl\(_3\)) 8.00 (2 H, d, \(J\ 8.0\ \text{Hz}, 2\text{-ArH}\)), 7.60 (1 H, t, \(J\ 8.0\ \text{Hz}, 4\text{-ArH}\)), 7.47 (2 H, t, \(J\ 8.0\ \text{Hz}, 3\text{-ArH}\)), 5.69 (1 H, m, \(=\text{CH}\)), 5.18 (1 H, d, \(J\ 2.5\ \text{Hz}, =\text{CHH}\)), 5.12 (1 H, s, \(=\text{CHH}\)), 5.09 (1 H, dd, \(J\ 5.2\ \text{and } 1.4\ \text{Hz}, 4\text{-H}\)), 4.95 (1 H, dd, \(J\ 6.3\ \text{and } 3.7\ \text{Hz}, 3\text{-H}\)), 3.15 (1 H, ddd, \(J\ 11.3, 6.3\ \text{and } 2.5\ \text{Hz}, 2\text{eq-H}\)), 2.59 (1 H, d, \(J\ 11.3\ \text{Hz}, 6\text{ax-H}\)), 2.48-2.18 (4 H, m), 2.13 (3 H, s, OC\(_3\)H\(_3\)), 1.99 (1 H, dt, \(J\ 11.0\ \text{and } 2.2\ \text{Hz}, 1\text{'-CHH}\));

\(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\), DEPT) 176.0 (C), 172.0 (C), 167.9 (C), 137.9 (CH), 136.4 (CH), 132.4 (CH), 132.0 (C), 131.3 (CH), 121.2 (CH\(_2\)), 79.6 (C), 78.0 (CH), 73.3 (CH), 41.3 (CH\(_3\)), 39.0 (CH), 36.5 (CH\(_2\)), 35.3 (CH\(_2\)), 23.9 (CH\(_3\));

LC/MS (ret. time/min.) 4.2 (ESI+) \(m/z\ 345\) (MH\(^+\));

HRMS calcd for C\(_{19}\)H\(_{20}\)O\(_6\): MNa\(^+\), 367.1158. Found: MNa\(^+\), 367.1168.
A solution of 12 (1.0 g, 2.90 mmol, 1.0 eqv.) and AIBN (95 mg, 0.58 mmol, 0.2 eqv.) in CCl₄ (10 ml) was bubbled slowly with HBr gas for 15 minutes at room temperature. The solution was stirred for a further 30 minutes. It was then taken up in Et₂O (100 ml) and washed with sat. NaHCO₃ (3 x 50 ml). The organic layer was dried with Na₂SO₄, filtered and the solvent evaporated to give the primary bromide 13 as a colourless oil (1.2 g, 97%).

R₉ 0.54 [Et₂O:Hexane; 2:1];

υₘₐₓ (NaCl)/cm⁻¹ 1801s (CO), 1746s (CO), 1719s (CO) and 1602s (Ar);

δH (400 MHz, CDCl₃): 7.97 (2 H, d, J 8.0 Hz, 2-ArH), 7.56 (1 H, t, J 8.0 Hz, 4-ArH), 7.43 (2 H, t, J 8.0 Hz, 3-ArH), 5.08 (1 H, d, J 2.5 Hz, 4-H), 4.88 (1 H, t, J 2.5 Hz, 3-H), 3.30 (2 H, td, J 6.6 and 1.5 Hz, 3’-CH₂), 3.12 (1 H, ddd, J 11.5, 6.0 and 2.3 Hz, 2-axi-H), 2.54 (1 H, d, J 11.5 Hz, 2-αx-H), 2.48 (1 H, m, 2’-CHH), 2.22 (1 H, m, 5-H), 2.10 (3 H, s, OCCH₃), 1.95-1.85 (3 H, m), 1.78 (1 H, m, 1’-CHH), 1.55 (1 H, m, 1’-CHH);

δC (100 MHz, DEPT, CDCl₃): 173.5 (C), 169.6 (C), 165.5 (C), 134.2 (CH), 130.1 (CH), 129.6 (C), 129.0 (CH), 77.1 (C), 75.7 (CH), 71.1 (CH), 36.7 (CH), 34.3 (CH₂), 34.1 (CH₂), 33.4 (CH₂), 33.0 (CH₂), 31.9 (CH₂), 21.6 (CH₃);

LC/MS (ret. time/min.) 4.3 (ESI+) m/z 424/426 (MH⁺);

(1S, 3R, 4R, 5S) - 4 - Acetyl - 5 - [(3 - phenyloxy)-propyl] - 1 - benzoylcyclohexane-1,3-carbolactone 14

A mixture of 13 (35 mg, 0.082 mmol, 1.0 eqv.), phenol (12 mg, 0.123 mmol, 1.5 eqv.), NaH (60% in mineral oil) (4 mg, 0.098 mmol, 1.2 eqv.) and KI (1.5 mg, 0.008 mmol, 0.1 eqv.) in MeCN (2 ml) was heated at reflux under N₂ for 1 h. The mixture was allowed to cool down to room temperature, taken up in Et₂O (20 ml) and washed with sat. NaHCO₃ (3 x 20 ml) and H₂O (20 ml). The organic layer was dried over Na₂SO₄, filtered and the solvent evaporated. The residue was purified by column chromatography on silica gel (Et₂O:Hex; 2:1) to give the product 14 as a colourless oil (25 mg, 69%).

Rₚ 0.55 [Et₂O:Hexane; 2:1];
νmax (NaCl)/cm⁻¹ 1800s (CO), 1745s (CO), 1719s (CO), 1600s (Ar) and 1586s (Ar);
δH (400 MHz, CDCl₃): 8.02 (2 H, d, J 7.9 Hz, 2-ArH), 7.59 (1 H, t, J 7.9 Hz, 4-ArH), 7.47 (2 H, t, J 7.9 Hz, 3-ArH), 7.25 (2 H, dd, J 7.4 and 1.0 Hz, 3''-ArH), 6.91 (1 H, t, J 7.4 Hz, 4''-ArH), 6.85 (2 H, dd, J 7.4 and 1.0 Hz, 2''-ArH), 5.21 (1 H, t, J 2.7 Hz, 4-H), 4.94 (1 H, dd, J 6.2 and 3.8 Hz, 3-H), 3.94 (2 H, t, J 6.0 Hz, 3'-CH₂), 3.15 (1 H, m, 2eq-H), 2.61 (1 H, d, J 11.4 Hz, 2ax-H), 2.53 (1 H, m, 2'-CH₂H), 2.31 (1 H, m, 5-H), 2.14 (3 H, s, OCCH₃), 1.95-1.50 (5 H, m);
δC (100 MHz, DEPT, CDCl₃): 172.1 (C), 168.1 (C), 164.0 (C), 157.7 (C), 132.5 (CH), 128.5 (CH), 128.2 (CH), 127.5 (C), 127.4 (CH), 119.5 (CH), 113.3 (CH), 75.6 (C), 74.2 (CH), 69.8 (CH), 65.9 (CH₂), 35.6 (CH), 32.7 (CH₂), 32.6 (CH₂), 29.9 (CH₂), 26.4 (CH₂), 20.0 (CH₃);
LC/MS (ret. time/min.) 4.5 (ESI+) m/z 439 (MH⁺)
A solution of carbolactone 14 (35 mg, 0.08 mmol, 1.0 eqv.) in H<sub>2</sub>O/MeCN (1:1) (2 ml) was treated with NaOH (100 mg/ml solution) (128 µl, 0.32 mmol, 4.0 eqv.) and stirred for 3 h at room temperature. Amberlite IR-120 (H) (50 mg) was added, and the mixture stirred for a further 30 min. The solution was filtered and lyophilised to give the acid 7 as a colourless glass (34 mg, quantitative).

\[ \text{υ}_{\text{max}} \text{(NaCl)/cm}^{-1} \quad 3060\text{b} (\text{OH}), 1662\text{s} (\text{CO}), 1600\text{s} (\text{Ar}); \]

\[ \delta_{\text{H}} \text{(400 MHz, CDCl}_3\text{): 7.28 (2 H, t, J 7.5 Hz, 3''-ArH), 6.95 (3 H, m, 4''-ArH), 3.97 (2 H, t, J 6.3 Hz, 3'-CH}_2\text{), 5.21 (1 H, m, 3-H), 3.08 (1 H, t, J 9.2 Hz, 4-H), 1.90-1.10 (9 H, m);} \]

\[ \delta_{\text{C}} \text{(100 MHz, DEPT, D}_{2}\text{O): 176.1 (C), 158.5 (C), 130.3 (CH), 121.9 (CH), 115.4 (CH), 78.5 (CH), 76.0 (C), 71.8 (CH), 69.4 (CH}_2\text{), 41.1 (CH}_2\text{), 38.5 (CH}_2\text{), 37.8 (CH), 27.6 (CH}_2\text{), 25.7 (CH}_2\text{);} \]

MS (ESI-) m/z 309 [(M-H)\text{-}] HRMS calcd for C<sub>16</sub>H<sub>21</sub>O<sub>6</sub>: [(M-H)\text{-}], 309.1344. Found: [(M-H)\text{-}], 309.1339.

\( (1S, 3R, 4R, 5S) - 5 - [(3 - \text{Phenylxyloxy})\text{-propyl}] - 1,3,4 - \text{cyclohexane - 1 - carboxylic acid 7} \)

\( (1S, 3R, 4R, 5S) - 4 - \text{Acetyl} - 5 - [(3 - (2 - \text{nitrophenylxyloxy})\text{-propyl})] - 1 - \text{benzoylcyclohexane-1,3-carbolactone 15} \)
A mixture of 13 (160 mg, 0.38 mmol, 1.0 eqv.), o-nitrophenol (79 mg, 0.57 mmol, 1.5 eqv.), NaH (60% in mineral oil) (23 mg, 0.57 mmol, 1.5 eqv.) and KI (13 mg, 0.08 mmol, 0.2 eqv.) in MeCN (2 ml) was heated at reflux under N₂ for 18 h. The mixture was allowed to cool down to room temperature, taken up in Et₂O (20 ml) and washed with 1 M HCl (3 x 20 ml) and H₂O (20 ml). The organic layer was dried over Na₂SO₄, filtered and the solvent evaporated. The residue was purified by column chromatography on silica gel (Et₂O:Hex; 2:1) to give the product 15 as a yellow oil (20 mg, 11%).

Rᶠ 0.28 [Et₂O:Hexane; 2:1];

υₓ(mx (NaCl)/cm⁻¹ 1800s (CO), 1745s (CO), 1719s (CO), 1608s (Ar) and 1583s (Ar);

δₓH (400 MHz, CDCl₃): 8.01 (2 H, dd, J 8.2 and 1.2 Hz, 2-ArH), 7.79 (1 H, dd, J 8.1 and 1.7 Hz, 3''-ArH), 7.60 (1 H, t, J 8.2 Hz, 4-ArH), 7.48 (3 H, m), 7.04 (2 H, m), 5.19 (1 H, t, J 3.4 Hz, 4-H), 4.95 (1 H, dd, J 6.2 and 3.4 Hz, 3-H), 4.09 (2 H, t, J 5.7 Hz, 3'-CH₂), 3.18 (1 H, ddd, J 11.1, 6.2 and 2.4 Hz, 2eq-H), 2.60 (1 H, d, J 11.1 Hz, 2ax-H), 2.57 (1 H, dd, J 12.4 and 9.0 Hz, 2'CH/H), 2.43 (1 H, m, 5-H), 2.14 (3 H, s, OCCH₃), 2.00-1.80 (3 H, m), 1.71 (1 H, m, 1'-CH/H);

δₓC (100 MHz, DEPT, CDCl₃): 174.7 (C), 170.7 (C), 166.6 (C), 153.7 (C), 141.0 (C), 135.5 (CH), 135.0 (CH), 131.1 (CH), 130.7 (C), 130.0 (CH), 127.0 (CH), 121.7 (CH), 115.9 (CH), 78.4 (C), 76.8 (CH), 72.2 (CH), 70.6 (CH₂), 37.9 (CH), 35.4 (CH₂), 35.1 (CH₂), 32.5 (CH₂), 28.5 (CH₂), 22.6 (CH₃);

LC/MS (ret. time/min.) 4.4 (ESI+) m/z 484 (MH⁺).
min. The solution was filtered and lyophilised to give the acid 8 was a yellow glass (39 mg, quantitative).

$\delta_{H}$ (400 MHz; D$_2$O): 7.78 (1 H, d, $J$ 7.7 Hz, 3''-ArH), 7.51 (1 H, t, $J$ 7.7 Hz, 5''-ArH), 7.13 (1 H, d, $J$ 7.7 Hz, 6''-ArH), 6.96 (1 H, t, $J$ 7.7 Hz, 4''-ArH), 4.06 (2 H, m, 3'-CH$_2$), 3.53 (1 H, m), 3-H), 3.03 (1 H, t, $J$ 9.6 Hz, 4-H), 2.31 (1 H, dt, $J$ 13.7, 4.3 Hz, 2$_{eq}$-H), 2.31 (1 H, m), 2.00-1.48 (6 H, m), 1.20 (1 H, m);

$\delta_{C}$ (100 MHz, DEPT, D$_2$O): 177.4 (C), 152.3 (C), 138.4 (C), 135.0 (CH), 125.4 (CH), 120.3 (CH), 115.0 (CH), 76.8 (CH), 74.6 (C), 70.1 (CH), 69.8 (CH$_2$), 36.3 (CH$_2$), 36.2 (CH$_2$), 34.6 (CH), 26.3 (CH$_2$), 24.5 (CH$_2$);

LC/MS (ret. time/min.) 3.4 (ESI+) m/z 356 (MH$^+$);

HRMS calcd for C$_{16}$H$_{21}$NO$_8$: MNa$^+$, 378.1165. Found: MNa$^+$, 378.1160.

(1$S$, 3$R$, 4$R$, 5$S$) - 4 - Acetyl - 5 - [3 - (2-methoxycarbonylphenyloxy) - propyl] - 1 - benzoylecyclohexane-1,3-carbolactone 16

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{AcO} \\
\text{O} & \quad \text{OBz} \\
\end{align*}
\]

A mixture of 13 (170 mg, 0.40 mmol, 1.0 eqv.), methyl salicylate (78 $\mu$l, 0.60 mmol, 1.5 eqv.), NaH (60% in mineral oil) (24 mg, 0.60 mmol, 1.5 eqv.) and KI (13 mg, 0.08 mmol, 0.2 eqv.) in MeCN (2 ml) was heated to reflux under N$_2$ for 24 h. The mixture was allowed to cool down to room temperature, taken up in Et$_2$O (20 ml) and washed with 1 M HCl (3 x 20 ml) and H$_2$O (20
The organic layer was dried over Na$_2$SO$_4$, filtered and the solvent evaporated. The residue was purified by column chromatography on silica gel (Et$_2$O:Hex; 2:1) to give the product 16 as a colourless oil (45mg, 23%).

$R_f$ 0.36 [Et$_2$O:Hexane; 2:1];
$\nu_{\text{max}}$(NaCl)/cm$^{-1}$ 1801s (CO), 1745s (CO), 1718s (CO), 1601s (Ar) and 1583s (Ar);
$\delta$$_H$ (400 MHz, CDCl$_3$): 8.01 (2 H, dd, $J$ 8.2 and 1.2 Hz, 2-ArH), 7.75 (1 H, dd, $J$ 7.7 and 1.8 Hz, 3''-ArH), 7.60 (1 H, t, $J$ 8.2 Hz, 4-ArH), 7.45 (3 H, m, 3-ArH and 5''-ArH), 6.93 (2 H, m, 4''-ArH and 6''-ArH), 5.19 (1 H, t, $J$ 2.8 Hz, 4-H), 4.94 (1 H, dd, $J$ 6.2 and 2.8 Hz, 3-H), 4.02 (2 H, t, $J$ 5.8 Hz, 3''-CH$_2$), 3.83 (3 H, s, OCH$_3$), 3.16 (1 H, ddd, $J$ 11.2, 6.2 and 2.3 Hz, 2eq-H), 2.61 (1 H, d, $J$ 11.2 Hz, 2ax-H), 2.55 (1 H, dd, $J$ 13.6 and 9.0 Hz, 2'''-CHH), 2.40 (1 H, m), 2.13 (3 H, s, OCCH$_3$), 2.00-1.80 (3 H, m), 1.70 (1 H, m);
$\delta$$_C$ (100 MHz, DEPT, CDCl$_3$): 172.0 (C), 168.0 (C), 165.6 (C), 163.9 (C), 157.1 (C), 132.4 (CH), 132.1 (CH), 130.4 (CH), 128.5 (CH), 128.1 (C), 127.4 (CH), 119.3 (C), 119.0 (CH), 112.0 (CH), 77.2 (C), 75.8 (CH), 71.3 (CH), 44.0 (CH$_2$), 37.2 (CH), 34.3 (CH$_2$), 34.2 (CH$_2$), 32.4 (CH$_2$), 28.0 (CH$_2$), 21.6 (CH$_3$);
LC/MS (ret. time/min.) 4.4 (ESI+) m/z 498 (MH$^+$).

(1$S$, 3$R$, 4$R$, 5$S$) - 5 - [3 - (2-carboxyphenyloxy) - propyl] - 1,3,4 - cyclohexane - 1 - carboxylic acid 9

A solution of carbolactone 16 (25 mg, 0.05 mmol, 1.0 eqv.) in H$_2$O/MeCN (1:1) (2 ml) is treated with NaOH (100 mg/ml solution) (100 µl, 0.25 mmol, 5.0 eqv.) and stirred for 5 h at room temperature. The solution was neutralised with Amberlite IR-120 (H$^+$), filtered and lyophilised to give the diacid 9 as a colourless glass in quantitative yield (24 mg).

HPLC retention time (organic acids column): 34 minutes;
Biochemical Experimental

Assay for type I and type II dehydroquinases

Both type I and type II dehydroquinase enzymes were assayed by monitoring product formation. The initial rate of increase in absorbance at 234 nm, due to the enone-carboxylate chromophore of 3-dehydroshikimate (ε = 1.2 x 10⁴ M⁻¹cm⁻¹), was measured. The assays were performed at 25 °C in potassium phosphate (0.05 M, pH 7.0) buffer (type I dehydroquinase) or Tris-HCl (0.05 M, pH 7.0) buffer (type II dehydroquinase). A standard assay of dehydroquinase includes:

100 µl of buffer (0.5 M, pH 7)
10 µl of enzyme solution (in buffer 0.05 M, pH 7)
x µl of substrate (3-dehydroquinate, ammonium salt) solution (in water)
y µl of inhibitor solution (in water)
(890 – x – y) µl of water

The assay mixture was prepared in situ on the cuvette, and the assay was initiated by addition of the enzyme solution to the mixture. The enzyme solutions were diluted from the concentrated stocks to 6.0 µg/ml (S. typhi type I dehydroquinase) and 5.1 µg/ml (S. coelicolor type II dehydroquinase).

Enzyme kinetics
The kinetic parameters for type I and type II dehydroquinases were obtained by measuring the initial rates of reaction over a range of substrate concentrations (0.1 $K_M$ -10 $K_M$). The data was fitted to Michaelis-Menten plots using the software *Lines&Kinetics* by least-squares fit, and the values for $K_M$ and $v_{max}$ were calculated using the Direct Linear method with the same software.

**Enzyme inhibition**

The inhibition kinetic data was obtained by measuring the initial rates of reaction over a range of inhibitor concentrations (typically 4 different concentrations) at 4 different substrate concentrations (between $K_M$ and 3 $K_M$). The inhibition constants $K_I$ and standard deviation values were obtained by least-squares fitting using the software *GraFit* (Erithacus).
Crystallisation and X-ray Data Collection

Recombinant *Streptomyces coelicolor* DHQase purified from *Escherichia coli* as described previously (White *et al.*, 1990) and dialyzed into 20 mM Tris/HCl, pH 7.5, 0.5 mM DTT. The protein was concentrated using Centricon-10 centrifugal concentrators (Amicon) to 6 mg/ml. The inhibitor (1*S*, 3*R*, 4*R*, 5*S*) - 5 - [(3 - Phenyl oxy)-propyl] - 1,3,4 - cyclohexane - 1 - carboxylic acid (7) was suspended in dialysis buffer and added to the protein at a final concentration of 4 mM and incubated at 20°C for 30 minutes. Crystals were grown using the sitting-drop vapour-diffusion method using commercial and in house PEG Ions screens. The best crystals were grown by equilibrating a mixture of 1µl protein solution and 1µl precipitant solution (15%PEG8K, 0.2M NaKPhosphate, 0.1M MOPS pH 6.5) against 0.8ml of the precipitant solution.

X-ray diffraction data were collected at SRS Daresbury on beamline 14.1 using the CCD Quantum-4 detector (ADSC). Crystals were flash frozen at 100K in a stream of gaseous nitrogen using an Oxford Cryosystems cryostream, with artificial mother liquor with 20% glycerol used as a cryoprotectant. The crystals diffracted to 1.7Å and appeared to be I centered tetragonal with unit cell dimension a=198.42Å and c=396.6Å, however the data only merged successfully in P1

\[ a=196.61 \quad b=196.48 \quad c=240.63 \quad \alpha=65.91 \quad \beta=65.91 \quad \gamma=90.01. \]

A summary of the data collection statistics is shown in table 1. The data were integrated with DENZO and scaled using

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**Figure 3** – Inhibition curves for *S. coelicolor* type II dehydroquinase with: 7, 8 and 9.
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SCALEPACK (Otwinowski and Minor, 1997). Merged intensity data were converted to structure factor amplitudes using Truncate from the CCP4 suite of programs (CCP4, 1994) and 5% of reflections flagged for use in calculation of the free-R factor.

**Structure solution & Refinement**

The structure was solved by molecular replacement using the program AMoRe (Navaza, 1994). The *S. coelicolor* DHQase dodecamer (PDB accession code 1GU1) was used as the search model against X-ray data between 12Å and 5.2Å (90735 reflections). Sixteen dodecamers were correctly located in the structure with a resulting correlation coefficient of 73.1% and R-factor of 38.2% after rigid body refinement in AMoRe. Refinement was performed with REFMAC5 (Murshudov et al., 1997). Weighted difference Fourier maps calculated and averaged 16fold using CCP4 programs (CCP4, 1994), these clearly indicated the presence of a ligand within the active site. The ligand 7 was built and minimised using INSIGHT II (Accelrys) and fitted into the averaged structure (dodecamer A) using QUANTA (Accelrys). The unit cell contents was regenerated using the non crystallographic symmetry (NCS) before refinement.

Rounds of model refinement were performed using NCS restraints as implemented in REFMAC (Murshudov et al., 1997). Model building and manual correction of models was performed using QUANTA (Accelrys), solvent molecules were added automatically using ARP (Perrakis et al., 1997). Final model building using the entire unit cell contents was performed using COOT (Emsley et al., 2004). This resulted in a model with a final $R_{work}$ of 19.7% and $R_{free}$ of 24.7 %. The geometry of the model was either inside or better than expected values determined using PROCHECK (Laskowski et al., 1993). The final model statistics are shown in Table 1.

**Data Collection Details**

| Data Set | 7 |
| Space Group | P1 |
| Unit Cell Dimensions (Å) | $a=196.616$  $b=196.487$  $c=240.626$  $\alpha=65.91$  $\beta=65.91$  $\gamma=90.01$ |
| Resolution Range (Å) | 30.0 – 1.7 |
| Observations | 23,150,474 |
| Unique Reflections | 3,041,559 |
| Completeness (%)$^a$ | 93.7 (89.6) |
| Wilson B (Å²) | 17.4 |
| $R_{merge}$ (%) | 17.1 |

**Refinement Statistics**
Resolution Range (Å) 27.0 – 1.7  
R-factor (R_{work}/R_{free}) 19.7/24.7  
Number of Atoms\(^a\) 216,516 / 6,308 / 28,398  
Rms Bond Length Deviation (Å) 0.021  
Rms Bond Angle Deviation (º) 1.85  
Mean B-factor (Å\(^2\))\(^e\) 15 / 25 / 33  
Rms Backbone Deviation (Å) 0.12  
Coordinate Error (Å)\(^f\) 0.164

\(^a\) values for highest resolution shell shown in brackets  
\(^b\) R\(_{merge}\) = \(\frac{\sum |I - <I>|}{\sum <I>}\)  
\(^c\) R factor = \(\frac{\sum |F_o - F_c|}{\sum F_o}\)  
\(^d\) number of atoms of protein, heteroatoms and water molecules respectively  
\(^e\) mean B factor for protein, inhibitor and water atoms respectively  
\(^f\) calculated using the method of Cruickshank (Cruickshank, 1999)

References


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