WORLDWIDE PDB PROTEIN DATA BANK

wwPDB X-ray Structure Validation Summary Report (i)

Nov 2, 2017 – 01:25 AM EDT

PDB ID	:	3T8M
Title	:	Rational Design of PI3K-alpha Inhibitors that Exhibit Selectivity Over the PI3K-beta Isoform
Authors	:	Murray, J.M.; Wiesmann, C.
Deposited on	:	unknown
Resolution	:	2.50 Å(reported)

The following versions of software and data (see references (1)) were used in the production of this report:

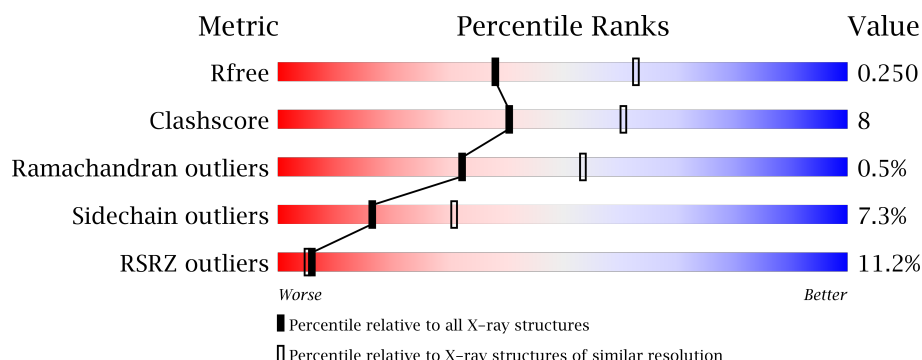|		
MolProbity	:	4.02b-467
Mogul	:	1.7.2 (RC1), CSD as538be (2017)
Xtriage (Phenix)	:	1.9-1692
EDS	:	rb-20030345
Percentile statistics	:	20161228.v01 (using entries in the PDB archive December 28th 2016)
Refmac	:	5.8.0135
CCP4	:	6.5.0
Ideal geometry (proteins)	:	Engh & Huber (2001)
Ideal geometry (DNA, RNA)	:	Parkinson et al. (1996)
Validation Pipeline (wwPDB-VP)	:	rb-20030345

1 Overall quality at a glance ⓘ

The following experimental techniques were used to determine the structure:
X-RAY DIFFRACTION

The reported resolution of this entry is 2.50 Å.

Percentile scores (ranging between 0-100) for global validation metrics of the entry are shown in the following graphic. The table shows the number of entries on which the scores are based.

Metric	Percentile Ranks	Value
Rfree		0.250
Clashscore		8
Ramachandran outliers		0.5%
Sidechain outliers		7.3%
RSRZ outliers		11.2%

Worse — Better

■ Percentile relative to all X-ray structures
▯ Percentile relative to X-ray structures of similar resolution

Metric	Whole archive (#Entries)	Similar resolution (#Entries, resolution range(Å))
R_{free}	100719	3846 (2.50-2.50)
Clashscore	112137	4554 (2.50-2.50)
Ramachandran outliers	110173	4463 (2.50-2.50)
Sidechain outliers	110143	4465 (2.50-2.50)
RSRZ outliers	101464	3876 (2.50-2.50)

The table below summarises the geometric issues observed across the polymeric chains and their fit to the electron density. The red, orange, yellow and green segments on the lower bar indicate the fraction of residues that contain outliers for >=3, 2, 1 and 0 types of geometric quality criteria. A grey segment represents the fraction of residues that are not modelled. The numeric value for each fraction is indicated below the corresponding segment, with a dot representing fractions <=5% The upper red bar (where present) indicates the fraction of residues that have poor fit to the electron density. The numeric value is given above the bar.

Mol	Chain	Length	Quality of chain
1	A	966	10% 65% 20% • 13%

2 Entry composition (i)

There are 3 unique types of molecules in this entry. The entry contains 6865 atoms, of which 0 are hydrogens and 0 are deuteriums.

In the tables below, the ZeroOcc column contains the number of atoms modelled with zero occupancy, the AltConf column contains the number of residues with at least one atom in alternate conformation and the Trace column contains the number of residues modelled with at most 2 atoms.

- Molecule 1 is a protein called Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma isoform.

Mol	Chain	Residues	Atoms					ZeroOcc	AltConf	Trace
1	A	841	Total 6812	C 4371	N 1164	O 1242	S 35	0	0	0

There are 7 discrepancies between the modelled and reference sequences:

Chain	Residue	Modelled	Actual	Comment	Reference
A	143	MET	-	EXPRESSION TAG	UNP P48736
A	1103	HIS	-	EXPRESSION TAG	UNP P48736
A	1104	HIS	-	EXPRESSION TAG	UNP P48736
A	1105	HIS	-	EXPRESSION TAG	UNP P48736
A	1106	HIS	-	EXPRESSION TAG	UNP P48736
A	1107	HIS	-	EXPRESSION TAG	UNP P48736
A	1108	HIS	-	EXPRESSION TAG	UNP P48736

- Molecule 2 is N 2 -{2-chloro-4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}-N 2 ,N 8 -dimethyl-4,5-dihydrothieno[3,2-d][1]benzoxepine-2,8-dicarboxamide (three-letter code: 3T8) (formula: $C_{28}H_{29}ClN_4O_4S$).

3T8
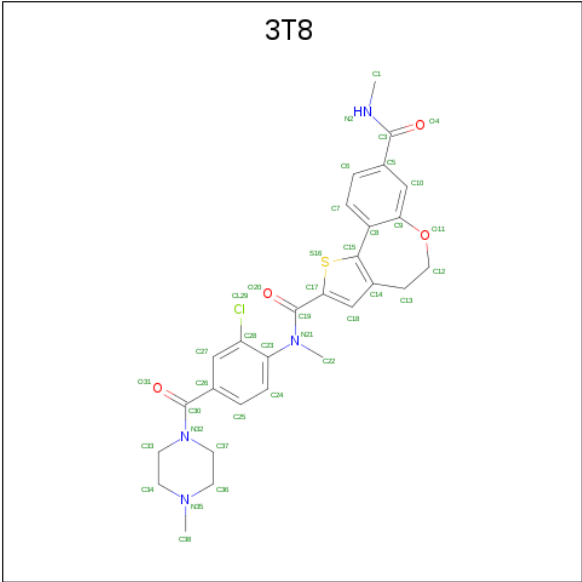
Mol	Chain	Residues	Atoms						ZeroOcc	AltConf
			Total	C	Cl	N	O	S		
2	A	1	38	28	1	4	4	1	0	0

- Molecule 3 is water.

Mol	Chain	Residues	Atoms		ZeroOcc	AltConf
			Total	O		
3	A	15	15	15	0	0

3 Residue-property plots (i)

These plots are drawn for all protein, RNA and DNA chains in the entry. The first graphic for a chain summarises the proportions of the various outlier classes displayed in the second graphic. The second graphic shows the sequence view annotated by issues in geometry and electron density. Residues are color-coded according to the number of geometric quality criteria for which they contain at least one outlier: green = 0, yellow = 1, orange = 2 and red = 3 or more. A red dot above a residue indicates a poor fit to the electron density (RSRZ > 2). Stretches of 2 or more consecutive residues without any outlier are shown as a green connector. Residues present in the sample, but not in the model, are shown in grey.

• Molecule 1: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma isoform
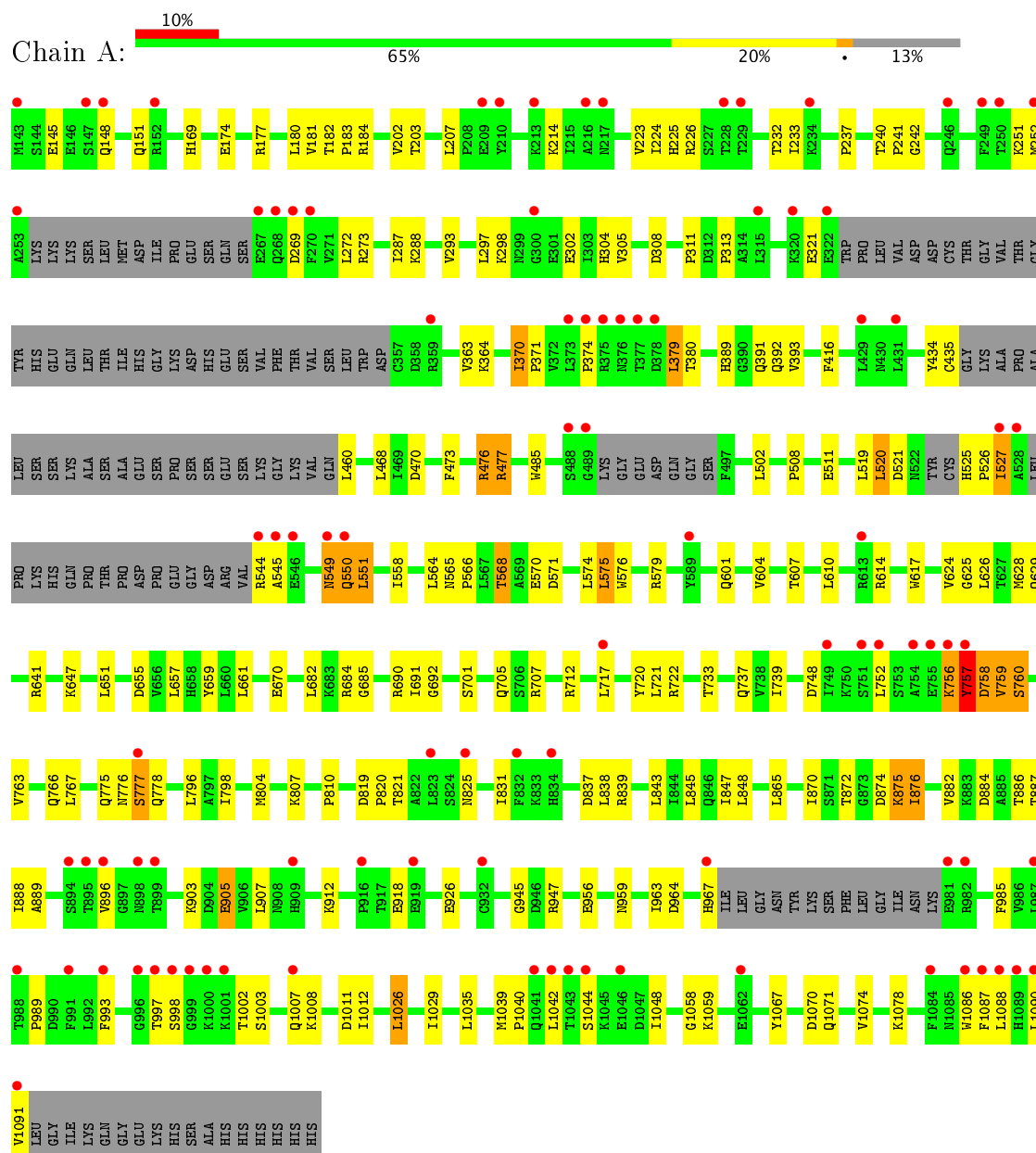
4 Data and refinement statistics (i)

Property	Value	Source
Space group	C 1 2 1	Depositor
Cell constants a, b, c, α, β, γ	143.22Å 67.65Å 106.63Å 90.00° 95.55° 90.00°	Depositor
Resolution (Å)	19.86 – 2.50 19.86 – 2.50	Depositor EDS
% Data completeness (in resolution range)	99.8 (19.86-2.50) 99.8 (19.86-2.50)	Depositor EDS
R_{merge}	0.47	Depositor
R_{sym}	(Not available)	Depositor
$<I/\sigma(I)>$ [1]	2.69 (at 2.50Å)	Xtriage
Refinement program	PHENIX dev_833	Depositor
R, R_{free}	0.204 , 0.254 0.198 , 0.250	Depositor DCC
R_{free} test set	1742 reflections (4.94%)	DCC
Wilson B-factor (Å^2)	70.5	Xtriage
Anisotropy	0.066	Xtriage
Bulk solvent k_{sol}(e/Å^3), B_{sol}(Å^2)	0.29 , 63.1	EDS
L-test for twinning[2]	$<|L|> = 0.50$, $<L^2> = 0.33$	Xtriage
Estimated twinning fraction	No twinning to report.	Xtriage
F_o,F_c correlation	0.96	EDS
Total number of atoms	6865	wwPDB-VP
Average B, all atoms (Å^2)	106.0	wwPDB-VP

Xtriage's analysis on translational NCS is as follows: *The largest off-origin peak in the Patterson function is 4.68% of the height of the origin peak. No significant pseudotranslation is detected.*

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[1]Intensities estimated from amplitudes.
[2]Theoretical values of $<|L|>$, $<L^2>$ for acentric reflections are 0.5, 0.333 respectively for untwinned datasets, and 0.375, 0.2 for perfectly twinned datasets.

5 Model quality (i)

5.1 Standard geometry (i)

Bond lengths and bond angles in the following residue types are not validated in this section: 3T8

The Z score for a bond length (or angle) is the number of standard deviations the observed value is removed from the expected value. A bond length (or angle) with $|Z| > 5$ is considered an outlier worth inspection. RMSZ is the root-mean-square of all Z scores of the bond lengths (or angles).

Mol	Chain	Bond lengths		Bond angles	
		RMSZ	#$|Z| > 5$	RMSZ	#$|Z| > 5$
1	A	0.62	0/6958	0.84	11/9412 (0.1%)

Chiral center outliers are detected by calculating the chiral volume of a chiral center and verifying if the center is modelled as a planar moiety or with the opposite hand. A planarity outlier is detected by checking planarity of atoms in a peptide group, atoms in a mainchain group or atoms of a sidechain that are expected to be planar.

Mol	Chain	#Chirality outliers	#Planarity outliers
1	A	0	5

There are no bond length outliers.

The worst 5 of 11 bond angle outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(^{o})	Ideal(^{o})
1	A	712	ARG	NE-CZ-NH1	-7.79	116.41	120.30
1	A	684	ARG	NE-CZ-NH2	-6.88	116.86	120.30
1	A	777	SER	N-CA-C	-6.87	92.46	111.00
1	A	684	ARG	NE-CZ-NH1	6.51	123.55	120.30
1	A	870	ILE	CG1-CB-CG2	-6.27	97.61	111.40

There are no chirality outliers.

All (5) planarity outliers are listed below:

Mol	Chain	Res	Type	Group
1	A	756	LYS	Peptide
1	A	757	TYR	Peptide
1	A	759	VAL	Peptide
1	A	776	ASN	Peptide
1	A	777	SER	Peptide

5.2 Too-close contacts (i)

In the following table, the Non-H and H(model) columns list the number of non-hydrogen atoms and hydrogen atoms in the chain respectively. The H(added) column lists the number of hydrogen atoms added and optimized by MolProbity. The Clashes column lists the number of clashes within the asymmetric unit, whereas Symm-Clashes lists symmetry related clashes.

Mol	Chain	Non-H	H(model)	H(added)	Clashes	Symm-Clashes
1	A	6812	0	6843	112	0
2	A	38	0	29	3	0
3	A	15	0	0	1	0
All	All	6865	0	6872	112	0

The all-atom clashscore is defined as the number of clashes found per 1000 atoms (including hydrogen atoms). The all-atom clashscore for this structure is 8.

The worst 5 of 112 close contacts within the same asymmetric unit are listed below, sorted by their clash magnitude.

Atom-1	Atom-2	Interatomic distance (Å)	Clash overlap (Å)
1:A:705:GLN:NE2	1:A:837:ASP:OD1	1.90	1.03
1:A:804:MET:HE2	1:A:831:ILE:HG12	1.67	0.76
1:A:759:VAL:HA	1:A:760:SER:HB2	1.70	0.74
1:A:947:ARG:NH2	1:A:963:ILE:O	2.23	0.71
1:A:549:ASN:OD1	1:A:550:GLN:NE2	2.24	0.70

There are no symmetry-related clashes.

5.3 Torsion angles (i)

5.3.1 Protein backbone (i)

In the following table, the Percentiles column shows the percent Ramachandran outliers of the chain as a percentile score with respect to all X-ray entries followed by that with respect to entries of similar resolution.

The Analysed column shows the number of residues for which the backbone conformation was analysed, and the total number of residues.

Mol	Chain	Analysed	Favoured	Allowed	Outliers	Percentiles
1	A	825/966 (85%)	780 (94%)	41 (5%)	4 (0%)	32 53

All (4) Ramachandran outliers are listed below:

Mol	Chain	Res	Type
1	A	758	ASP
1	A	896	VAL
1	A	545	ALA
1	A	527	ILE

5.3.2 Protein sidechains (i)

In the following table, the Percentiles column shows the percent sidechain outliers of the chain as a percentile score with respect to all X-ray entries followed by that with respect to entries of similar resolution.

The Analysed column shows the number of residues for which the sidechain conformation was analysed, and the total number of residues.

Mol	Chain	Analysed	Rotameric	Outliers	Percentiles	
1	A	754/864 (87%)	699 (93%)	55 (7%)	16	31

5 of 55 residues with a non-rotameric sidechain are listed below:

Mol	Chain	Res	Type
1	A	647	LYS
1	A	760	SER
1	A	1026	LEU
1	A	682	LEU
1	A	717	LEU

Some sidechains can be flipped to improve hydrogen bonding and reduce clashes. 5 of 7 such sidechains are listed below:

Mol	Chain	Res	Type
1	A	550	GLN
1	A	1007	GLN
1	A	766	GLN
1	A	304	HIS
1	A	775	GLN

5.3.3 RNA (i)

There are no RNA molecules in this entry.

5.4 Non-standard residues in protein, DNA, RNA chains (i)

There are no non-standard protein/DNA/RNA residues in this entry.

5.5 Carbohydrates (i)

There are no carbohydrates in this entry.

5.6 Ligand geometry (i)

1 ligand is modelled in this entry.

In the following table, the Counts columns list the number of bonds (or angles) for which Mogul statistics could be retrieved, the number of bonds (or angles) that are observed in the model and the number of bonds (or angles) that are defined in the Chemical Component Dictionary. The Link column lists molecule types, if any, to which the group is linked. The Z score for a bond length (or angle) is the number of standard deviations the observed value is removed from the expected value. A bond length (or angle) with $|Z| > 2$ is considered an outlier worth inspection. RMSZ is the root-mean-square of all Z scores of the bond lengths (or angles).

Mol	Type	Chain	Res	Link	Bond lengths			Bond angles		
					Counts	RMSZ	#$|Z| > 2$	Counts	RMSZ	#$|Z| > 2$
2	3T8	A	1	-	36,42,42	0.99	1 (2%)	51,61,61	1.66	11 (21%)

In the following table, the Chirals column lists the number of chiral outliers, the number of chiral centers analysed, the number of these observed in the model and the number defined in the Chemical Component Dictionary. Similar counts are reported in the Torsion and Rings columns. '-' means no outliers of that kind were identified.

Mol	Type	Chain	Res	Link	Chirals	Torsions	Rings
2	3T8	A	1	-	-	0/22/46/46	0/4/5/5

All (1) bond length outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(Å)	Ideal(Å)
2	A	1	3T8	C3-N2	3.26	1.37	1.33

The worst 5 of 11 bond angle outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(^{o})	Ideal(^{o})
2	A	1	3T8	O20-C19-N21	-3.42	116.38	121.54
2	A	1	3T8	O31-C30-N32	-2.72	117.64	122.36
2	A	1	3T8	C14-C15-S16	-2.22	107.50	111.79

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Mol	Chain	Res	Type	Atoms	Z	Observed(^{o})	Ideal(^{o})
2	A	1	3T8	C33-C34-N35	-2.12	108.36	110.79
2	A	1	3T8	C26-C30-N32	2.50	122.00	118.77

There are no chirality outliers.

There are no torsion outliers.

There are no ring outliers.

1 monomer is involved in 3 short contacts:

Mol	Chain	Res	Type	Clashes	Symm-Clashes
2	A	1	3T8	3	0

5.7 Other polymers (i)

There are no such residues in this entry.

5.8 Polymer linkage issues (i)

There are no chain breaks in this entry.

6 Fit of model and data (i)

6.1 Protein, DNA and RNA chains (i)

In the following table, the column labelled '#RSRZ> 2' contains the number (and percentage) of RSRZ outliers, followed by percent RSRZ outliers for the chain as percentile scores relative to all X-ray entries and entries of similar resolution. The OWAB column contains the minimum, median, 95th percentile and maximum values of the occupancy-weighted average B-factor per residue. The column labelled 'Q< 0.9' lists the number of (and percentage) of residues with an average occupancy less than 0.9.

Mol	Chain	Analysed	<RSRZ>	#RSRZ>2			OWAB(Å²)	Q<0.9
1	A	841/966 (87%)	0.46	94 (11%)	6	5	47, 97, 180, 235	0

The worst 5 of 94 RSRZ outliers are listed below:

Mol	Chain	Res	Type	RSRZ
1	A	528	ALA	18.8
1	A	1044	SER	12.7
1	A	375	ARG	10.9
1	A	1086	TRP	8.7
1	A	544	ARG	8.5

6.2 Non-standard residues in protein, DNA, RNA chains (i)

There are no non-standard protein/DNA/RNA residues in this entry.

6.3 Carbohydrates (i)

There are no carbohydrates in this entry.

6.4 Ligands (i)

In the following table, the Atoms column lists the number of modelled atoms in the group and the number defined in the chemical component dictionary. LLDF column lists the quality of electron density of the group with respect to its neighbouring residues in protein, DNA or RNA chains. The B-factors column lists the minimum, median, 95th percentile and maximum values of B factors of atoms in the group. The column labelled 'Q< 0.9' lists the number of atoms with occupancy less than 0.9.

Mol	Type	Chain	Res	Atoms	RSCC	RSR	LLDF	B-factors(Å²)	Q<0.9
2	3T8	A	1	38/38	0.94	0.15	-0.10	63,85,109,116	0

6.5 Other polymers (i)

There are no such residues in this entry.