



wwPDB X-ray Structure Validation Summary Report

Feb 27, 2014 – 11:05 AM GMT

PDB ID : 4F08
Title : Discovery and Optimization of C-2 Methyl Imidazo-pyrrolopyridines as Potent and Orally Bioavailable JAK1 Inhibitors with Selectivity over JAK2
Authors : Murray, J.M.
Deposited on : 2012-05-03
Resolution : 2.82 Å (reported)

This is a wwPDB validation summary report for a publicly released PDB entry.

We welcome your comments at validation@mail.wwpdb.org

A user guide is available at <http://wwpdb.org/ValidationPDFNotes.html>

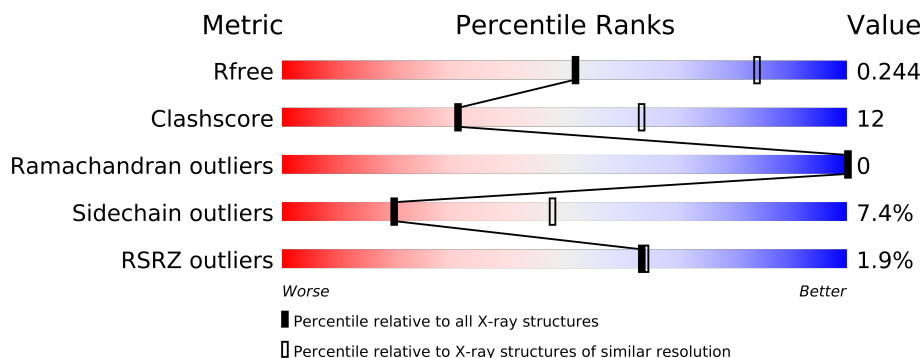
The following versions of software and data (see [references](#)) were used in the production of this report:

MolProbity	:	4.02b-467
Mogul	:	1.15 2013
Xtriage (Phenix)	:	dev-1323
EDS	:	stable22639
Percentile statistics	:	21963
Refmac	:	5.8.0049
CCP4	:	6.3.0 (Settle)
Ideal geometry (proteins)	:	Engh & Huber (2001)
Ideal geometry (DNA, RNA)	:	Parkinson et. al. (1996)
Validation Pipeline (wwPDB-VP)	:	stable22683

1 Overall quality at a glance



The reported resolution of this entry is 2.82 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	Whole archive (#Entries)	Similar resolution (#Entries, resolution range(Å))
R_{free}	66092	1963 (2.84-2.80)
Clashscore	79885	2478 (2.84-2.80)
Ramachandran outliers	78287	2429 (2.84-2.80)
Sidechain outliers	78261	2431 (2.84-2.80)
RSRZ outliers	66119	1966 (2.84-2.80)

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. The upper red bar (where present) indicates the fraction of residues that have poor fit to the electron density.

Mol	Chain	Length	Quality of chain
1	A	302	
1	B	302	

2 Entry composition i

There are 2 unique types of molecules in this entry. The entry contains 4804 atoms, of which 0 are hydrogen and 0 are deuterium.

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.

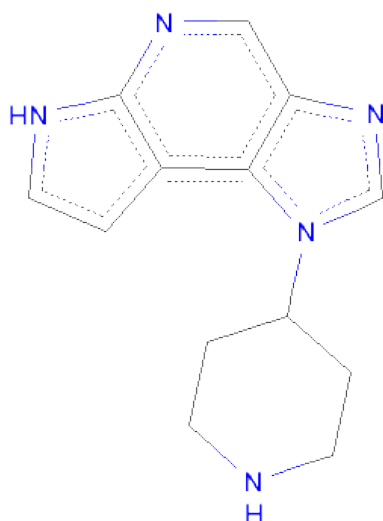
- Molecule 1 is a protein called Tyrosine-protein kinase JAK2.

Mol	Chain	Residues	Atoms						ZeroOcc	AltConf	Trace
1	A	290	Total	C	N	O	P	S	0	0	0
			2392	1517	412	447	2	14			
1	B	290	Total	C	N	O	P	S	0	0	0
			2376	1505	408	447	2	14			

There are 4 discrepancies between the modelled and reference sequences:

Chain	Residue	Modelled	Actual	Comment	Reference
A	831	GLY	-	EXPRESSION TAG	UNP O60674
A	832	SER	-	EXPRESSION TAG	UNP O60674
B	831	GLY	-	EXPRESSION TAG	UNP O60674
B	832	SER	-	EXPRESSION TAG	UNP O60674

- Molecule 2 is 1-(PIPERIDIN-4-YL)-1,6-DIHYDROIMIDAZO[4,5-D]PYRROLO[2,3-B]PYRIDINE (three-letter code: 1RS) (formula: C₁₃H₁₅N₅).



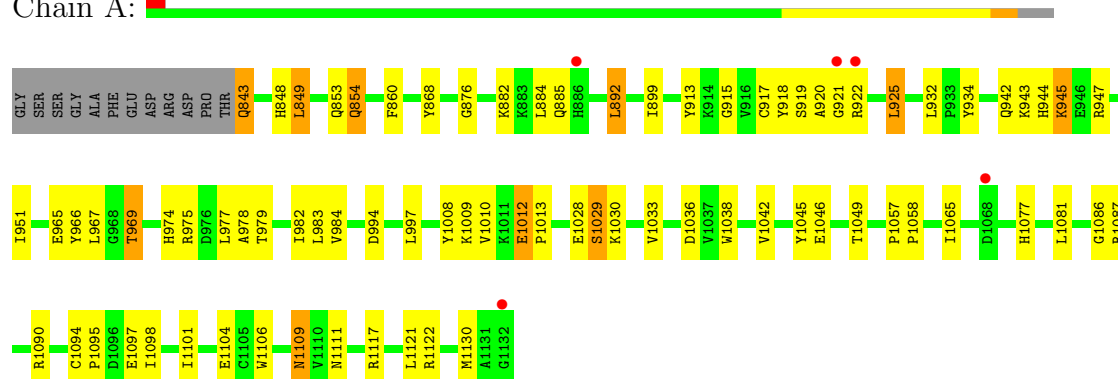
Mol	Chain	Residues	Atoms			ZeroOcc	AltConf
2	A	1	Total	C	N	0	0
			18	13	5		
2	B	1	Total	C	N	0	0
			18	13	5		

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 errors 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.

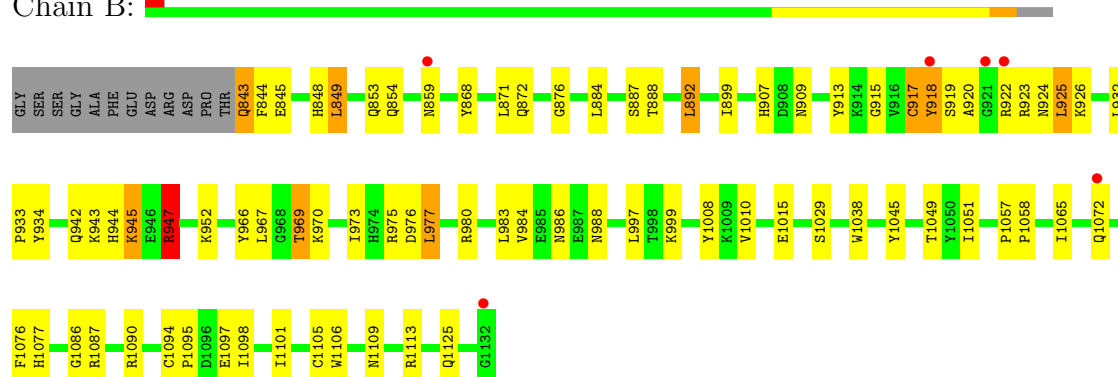
- Molecule 1: Tyrosine-protein kinase JAK2

Chain A:



- Molecule 1: Tyrosine-protein kinase JAK2

Chain B:



4 Data and refinement statistics

Property	Value	Source
Space group	P 41	Depositor
Cell constants a, b, c, α , β , γ	110.92Å 110.92Å 70.73Å 90.00° 90.00° 90.00°	Depositor
Resolution (Å)	49.61 – 2.82 49.61 – 2.82	Depositor EDS
% Data completeness (in resolution range)	99.6 (49.61-2.82) 99.7 (49.61-2.82)	Depositor EDS
R_{merge}	0.10	Depositor
R_{sym}	(Not available)	Depositor
$\langle I/\sigma(I) \rangle$ ¹	3.17 (at 2.81Å)	Xtriage
Refinement program	BUSTER 2.11.2	Depositor
R, R_{free}	0.213 , 0.241 0.210 , 0.244	Depositor DCC
R_{free} test set	1034 reflections (5.22%)	DCC
Wilson B-factor (Å ²)	54.7	Xtriage
Anisotropy	0.038	Xtriage
Bulk solvent k_{sol} (e/Å ³), B_{sol} (Å ²)	0.34 , 33.3	EDS
Estimated twinning fraction	0.031 for h,-k,-l	Xtriage
L-test for twinning	$\langle L \rangle = 0.50$, $\langle L^2 \rangle = 0.34$	Xtriage
Outliers	0 of 20852 reflections	Xtriage
F_o, F_c correlation	0.93	EDS
Total number of atoms	4804	wwPDB-VP
Average B, all atoms (Å ²)	58.0	wwPDB-VP

Xtriage's analysis on translational NCS is as follows: *The largest off-origin peak in the Patterson function is 3.68% of the height of the origin peak. No significant pseudotranslation is detected.*

¹Intensities estimated from amplitudes.

5 Model quality

5.1 Standard geometry

Bond lengths and bond angles in the following residue types are not validated in this section: 1RS, PTR

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	0.54	0/2409	0.64	2/3240 (0.1%)
1	B	0.56	0/2392	0.63	0/3220
All	All	0.55	0/4801	0.64	2/6460 (0.0%)

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	B	0	1

There are no bond length outliers.

All (2) bond angle outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(°)	Ideal(°)
1	A	1090	ARG	NE-CZ-NH2	-5.48	117.56	120.30
1	A	922	ARG	CB-CA-C	-5.16	100.09	110.40

There are no chirality outliers.

All (1) planarity outliers are listed below:

Mol	Chain	Res	Type	Group
1	B	947	ARG	Sidechain

5.2 Close contacts

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 hydrogens

added by MolProbity. The Clashes column lists the number of clashes within the asymmetric unit, and the number in parentheses is this value normalized per 1000 atoms of the molecule in the chain. The Symm-Clashes column gives symmetry related clashes, in the same way as for the Clashes column.

Mol	Chain	Non-H	H(model)	H(added)	Clashes	Symm-Clashes
1	A	2392	0	2356	57	3
1	B	2376	0	2327	54	3
2	A	18	0	15	1	0
2	B	18	0	15	2	0
All	All	4804	0	4713	111	3

Clashscore is defined as the number of clashes calculated for the entry per 1000 atoms (including hydrogens) of the entry. The overall clashscore for this entry is 12.

The worst 5 of 111 close contacts within the same asymmetric unit are listed below.

Atom-1	Atom-2	Distance(Å)	Clash(Å)
1:B:920:ALA:H	1:B:923:ARG:HA	1.26	0.99
1:B:907:HIS:CD2	1:B:909:ASN:H	1.81	0.98
1:A:951:ILE:HD13	1:A:1130:MET:SD	2.05	0.96
1:A:1104:GLU:OE2	1:A:1122:ARG:NH1	2.01	0.93
1:B:907:HIS:HD2	1:B:909:ASN:H	1.10	0.93

All (3) symmetry-related close contacts are listed below. The label for Atom-2 includes the symmetry operator and encoded unit-cell translations to be applied.

Atom-1	Atom-2	Distance(Å)	Clash(Å)
1:A:853:GLN:OE1	1:B:947:ARG:NH2[1_554]	1.90	0.30
1:A:853:GLN:OE1	1:B:947:ARG:CZ[1_554]	2.05	0.15
1:A:853:GLN:OE1	1:B:947:ARG:NH1[1_554]	2.16	0.04

5.3 Torsion angles

5.3.1 Protein backbone ⓘ

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	286/302 (95%)	275 (96%)	11 (4%)	0	100	100
1	B	286/302 (95%)	278 (97%)	8 (3%)	0	100	100

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Mol	Chain	Analysed	Favoured	Allowed	Outliers	Percentiles	
All	All	572/604 (95%)	553 (97%)	19 (3%)	0	100	100

There are no Ramachandran outliers to report.

5.3.2 Protein sidechains ⓘ

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	260/271 (96%)	241 (93%)	19 (7%)	20	49
1	B	257/271 (95%)	238 (93%)	19 (7%)	20	48
All	All	517/542 (95%)	479 (93%)	38 (7%)	20	48

5 of 38 residues with a non-rotameric sidechain are listed below:

Mol	Chain	Res	Type
1	A	1097	GLU
1	B	849	LEU
1	B	1029	SER
1	B	843	GLN
1	B	853	GLN

Some sidechains can be flipped to improve hydrogen bonding and reduce clashes. 5 of 23 such sidechains are listed below:

Mol	Chain	Res	Type
1	A	1112	GLN
1	B	848	HIS
1	B	1077	HIS
1	B	843	GLN
1	B	854	GLN

5.3.3 RNA ⓘ

There are no RNA chains in this entry.

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

4 non-standard protein/DNA/RNA residues are 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	$\# Z > 2$
1	PTR	A	1007	1	16,16,17	4.60	3 (18%)	20,22,24	1.07	1 (5%)
1	PTR	A	1008	1	16,16,17	4.71	3 (18%)	20,22,24	1.94	4 (20%)
1	PTR	B	1007	1	16,16,17	4.57	2 (12%)	20,22,24	1.33	2 (10%)
1	PTR	B	1008	1	16,16,17	4.75	3 (18%)	20,22,24	1.22	1 (5%)

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
1	PTR	A	1007	1	-	0/9/11/13	0/1/1/1
1	PTR	A	1008	1	-	0/9/11/13	0/1/1/1
1	PTR	B	1007	1	-	0/9/11/13	0/1/1/1
1	PTR	B	1008	1	-	0/9/11/13	0/1/1/1

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

Mol	Chain	Res	Type	Atoms	Z	Observed(Å)	Ideal(Å)
1	B	1008	PTR	O-C	17.94	1.23	1.11
1	A	1008	PTR	O-C	17.58	1.23	1.11
1	B	1007	PTR	O-C	17.48	1.23	1.11
1	A	1007	PTR	O-C	17.34	1.23	1.11
1	B	1008	PTR	OH-CZ	-5.26	1.27	1.40

The worst 5 of 8 bond angle outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(°)	Ideal(°)
1	A	1008	PTR	C-CA-N	-7.15	106.69	113.83
1	B	1007	PTR	C-CA-N	-5.08	108.75	113.83

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Mol	Chain	Res	Type	Atoms	Z	Observed(°)	Ideal(°)
1	B	1008	PTR	C-CA-N	-4.99	108.84	113.83
1	A	1007	PTR	C-CA-N	-4.29	109.55	113.83
1	A	1008	PTR	OH-CZ-CE2	2.61	127.27	119.23

There are no chirality outliers.

There are no torsion outliers.

There are no ring outliers.

5.5 Carbohydrates ⓘ

There are no carbohydrates in this entry.

5.6 Ligand geometry ⓘ

2 ligands are 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	1RS	A	1201	-	21,21,21	1.44	5 (23%)	29,30,30	2.18	11 (37%)
2	1RS	B	1201	-	21,21,21	1.35	3 (14%)	29,30,30	2.11	10 (34%)

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	1RS	A	1201	-	-	0/0/12/12	0/1/4/4
2	1RS	B	1201	-	-	0/0/12/12	0/1/4/4

The worst 5 of 8 bond length outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(Å)	Ideal(Å)
2	B	1201	1RS	C2-N3	-3.04	1.28	1.34
2	A	1201	1RS	C2-N3	-3.01	1.28	1.34
2	A	1201	1RS	C5-C4	-2.68	1.38	1.41
2	B	1201	1RS	C7-N6	-2.49	1.31	1.34
2	A	1201	1RS	C7-N6	-2.42	1.31	1.34

The worst 5 of 21 bond angle outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(°)	Ideal(°)
2	B	1201	1RS	C8-C9-C4	-5.54	116.89	119.94
2	A	1201	1RS	C8-C9-C4	-5.15	117.10	119.94
2	A	1201	1RS	C5-N6-C7	4.28	122.70	116.62
2	A	1201	1RS	C11-N10-C9	4.02	130.94	125.26
2	B	1201	1RS	C11-N10-C9	3.84	130.68	125.26

There are no chirality outliers.

There are no torsion outliers.

There are no ring outliers.

5.7 Other polymers ⓘ

There are no such residues in this entry.

5.8 Polymer linkage issues

There are no chain breaks in this entry.

6 Fit of model and data ⓘ

6.1 Protein, DNA and RNA chains ⓘ

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(Å ²)	Q<0.9
1	A	290/302 (96%)	-0.11	5 (1%) 67 67	30, 51, 109, 167	0
1	B	290/302 (96%)	-0.12	6 (2%) 60 61	32, 51, 107, 167	0
All	All	580/604 (96%)	-0.11	11 (1%) 64 64	30, 51, 108, 167	0

The worst 5 of 11 RSRZ outliers are listed below:

Mol	Chain	Res	Type	RSRZ
1	A	921	GLY	7.5
1	B	859	ASN	4.9
1	B	922	ARG	4.3
1	A	1132	GLY	4.2
1	B	921	GLY	4.2

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

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	RSR	LLDF	B-factors(Å ²)	Q<0.9
1	PTR	B	1007	16/17	0.18	0.38	54,59,99,104	0
1	PTR	A	1008	16/17	0.16	-0.28	34,61,77,79	0
1	PTR	B	1008	16/17	0.17	-0.48	51,82,101,103	0
1	PTR	A	1007	16/17	0.15	-0.71	41,57,103,109	0

6.3 Carbohydrates

There are no carbohydrates in this entry.

6.4 Ligands

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	RSR	LLDF	B-factors(Å ²)	Q<0.9
2	1RS	A	1201	18/18	0.15	-0.24	20,20,20,20	0
2	1RS	B	1201	18/18	0.12	-1.15	20,20,20,20	0

6.5 Other polymers

There are no such residues in this entry.