



Full wwPDB X-ray Structure Validation Report ⓘ

May 16, 2020 – 07:02 am BST

PDB ID : 4I1C
Title : Design and synthesis of thiophene dihydroisoquinolins as novel BACE-1 inhibitors
Authors : Loughheed, J.C.; Brecht, E.; Yao, N.H.
Deposited on : 2012-11-20
Resolution : 2.00 Å(reported)

This is a Full wwPDB X-ray Structure Validation Report for a publicly released PDB entry.

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

A user guide is available at

<https://www.wwpdb.org/validation/2017/XrayValidationReportHelp>

with specific help available everywhere you see the ⓘ symbol.

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

MolProbity : 4.02b-467
Mogul : 1.8.5 (274361), CSD as541be (2020)
Xtriage (Phenix) : 1.13
EDS : 2.11
buster-report : 1.1.7 (2018)
Percentile statistics : 20191225.v01 (using entries in the PDB archive December 25th 2019)
Refmac : 5.8.0158
CCP4 : 7.0.044 (Gargrove)
Ideal geometry (proteins) : Engh & Huber (2001)
Ideal geometry (DNA, RNA) : Parkinson et al. (1996)
Validation Pipeline (wwPDB-VP) : 2.11

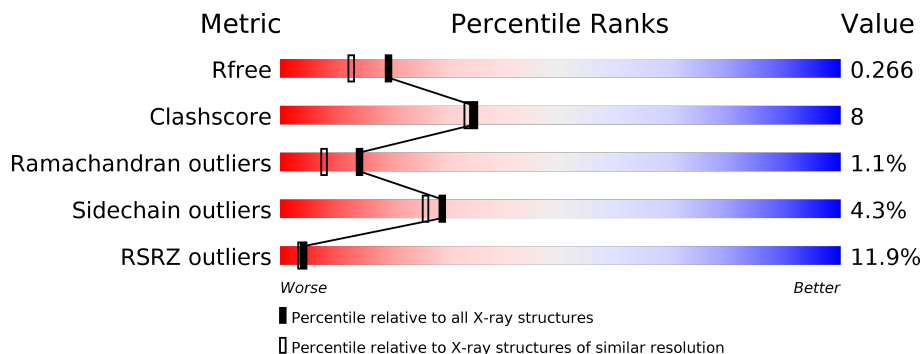
1 Overall quality at a glance

The following experimental techniques were used to determine the structure:

X-RAY DIFFRACTION

The reported resolution of this entry is 2.00 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}	130704	8085 (2.00-2.00)
Clashscore	141614	9178 (2.00-2.00)
Ramachandran outliers	138981	9054 (2.00-2.00)
Sidechain outliers	138945	9053 (2.00-2.00)
RSRZ outliers	127900	7900 (2.00-2.00)

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 respectively. 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 $\leq 5\%$. 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	406	

2 Entry composition

There are 4 unique types of molecules in this entry. The entry contains 3155 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 BETA-SECRETASE 1.

Mol	Chain	Residues	Atoms					ZeroOcc	AltConf	Trace
			Total	C	N	O	S			
1	A	378	2984	1906	500	564	14	0	0	0

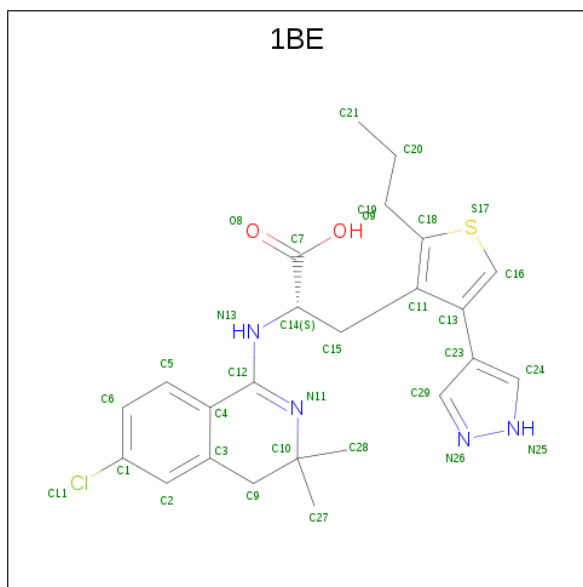
There are 9 discrepancies between the modelled and reference sequences:

Chain	Residue	Modelled	Actual	Comment	Reference
A	56	MET	-	EXPRESSION TAG	UNP P56817
A	454	ARG	-	EXPRESSION TAG	UNP P56817
A	455	SER	-	EXPRESSION TAG	UNP P56817
A	456	HIS	-	EXPRESSION TAG	UNP P56817
A	457	HIS	-	EXPRESSION TAG	UNP P56817
A	458	HIS	-	EXPRESSION TAG	UNP P56817
A	459	HIS	-	EXPRESSION TAG	UNP P56817
A	460	HIS	-	EXPRESSION TAG	UNP P56817
A	461	HIS	-	EXPRESSION TAG	UNP P56817

- Molecule 2 is ZINC ION (three-letter code: ZN) (formula: Zn).

Mol	Chain	Residues	Atoms		ZeroOcc	AltConf
2	A	3	Total	Zn	0	0
			3	3		

- Molecule 3 is N-(6-chloro-3,3-dimethyl-3,4-dihydroisoquinolin-1-yl)-3-[2-propyl-4-(1H-pyrazol-4-yl)thiophen-3-yl]-L-alanine (three-letter code: 1BE) (formula: C₂₄H₂₇ClN₄O₂S).



Mol	Chain	Residues	Atoms					ZeroOcc	AltConf	
			Total	C	Cl	N	O			S
3	A	1	32	24	1	4	2	1	0	0

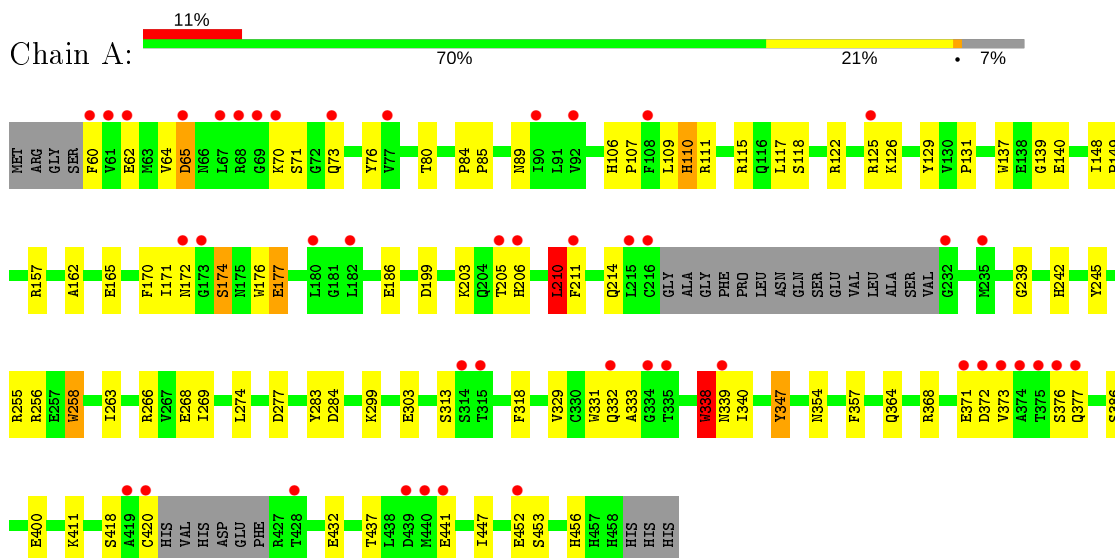
- Molecule 4 is water.

Mol	Chain	Residues	Atoms		ZeroOcc	AltConf
4	A	136	Total	O	0	0
			136	136		

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: BETA-SECRETASE 1



4 Data and refinement statistics

Property	Value	Source
Space group	C 2 2 21	Depositor
Cell constants a, b, c, α , β , γ	75.16Å 103.07Å 97.98Å 90.00° 90.00° 90.00°	Depositor
Resolution (Å)	24.65 – 2.00 23.63 – 2.00	Depositor EDS
% Data completeness (in resolution range)	95.8 (24.65-2.00) 96.0 (23.63-2.00)	Depositor EDS
R_{merge}	(Not available)	Depositor
R_{sym}	(Not available)	Depositor
$\langle I/\sigma(I) \rangle$ ¹	1.75 (at 1.99Å)	Xtrriage
Refinement program	REFMAC	Depositor
R, R_{free}	0.207 , 0.262 0.209 , 0.266	Depositor DCC
R_{free} test set	1261 reflections (5.05%)	wwPDB-VP
Wilson B-factor (Å ²)	32.5	Xtrriage
Anisotropy	0.095	Xtrriage
Bulk solvent k_{sol} (e/Å ³), B_{sol} (Å ²)	0.38 , 53.2	EDS
L-test for twinning ²	$\langle L \rangle = 0.48$, $\langle L^2 \rangle = 0.31$	Xtrriage
Estimated twinning fraction	No twinning to report.	Xtrriage
F_o, F_c correlation	0.95	EDS
Total number of atoms	3155	wwPDB-VP
Average B, all atoms (Å ²)	37.0	wwPDB-VP

Xtrriage's analysis on translational NCS is as follows: *The largest off-origin peak in the Patterson function is 6.35% of the height of the origin peak. No significant pseudotranslation is detected.*

¹Intensities estimated from amplitudes.

²Theoretical values of $\langle |L| \rangle$, $\langle L^2 \rangle$ 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: ZN, 1BE

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	0.94	5/3059 (0.2%)	0.96	4/4156 (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	1

All (5) bond length outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(Å)	Ideal(Å)
1	A	331	TRP	CD2-CE2	6.59	1.49	1.41
1	A	137	TRP	CD2-CE2	5.86	1.48	1.41
1	A	258	TRP	CD2-CE2	5.42	1.47	1.41
1	A	338	TRP	CD2-CE2	5.13	1.47	1.41
1	A	347	TYR	CE1-CZ	5.13	1.45	1.38

All (4) bond angle outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(°)	Ideal(°)
1	A	277	ASP	CB-CG-OD1	5.92	123.62	118.30
1	A	199	ASP	CB-CG-OD2	5.70	123.43	118.30
1	A	210	LEU	CA-CB-CG	5.50	127.94	115.30
1	A	177	GLU	CB-CA-C	-5.35	99.69	110.40

There are no chirality outliers.

All (1) planarity outliers are listed below:

Mol	Chain	Res	Type	Group
1	A	338	TRP	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	2984	0	2892	48	2
2	A	3	0	0	0	0
3	A	32	0	26	1	0
4	A	136	0	0	6	2
All	All	3155	0	2918	49	2

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.

All (49) 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:64:VAL:HG12	1:A:65:ASP:OD1	1.58	1.04
1:A:266:ARG:NH2	1:A:268:GLU:OE2	2.15	0.79
1:A:60:PHE:CZ	1:A:239:GLY:HA3	2.21	0.76
1:A:186:GLU:OE2	1:A:256:ARG:NH1	2.18	0.75
1:A:76:TYR:CD1	1:A:89:ASN:HB3	2.25	0.71
1:A:313:SER:HB2	1:A:340:ILE:HD12	1.74	0.69
1:A:60:PHE:CE2	1:A:239:GLY:HA3	2.33	0.64
1:A:255:ARG:HD2	1:A:263:ILE:HD11	1.84	0.59
1:A:205:THR:O	1:A:206:HIS:HB3	2.03	0.59
1:A:214:GLN:NE2	1:A:420:CYS:HB3	2.18	0.58
1:A:140:GLU:HB3	4:A:721:HOH:O	2.03	0.57
1:A:318:PHE:CD2	1:A:329:VAL:HG11	2.41	0.56
1:A:118:SER:HB2	4:A:690:HOH:O	2.06	0.54
1:A:60:PHE:O	1:A:64:VAL:HG23	2.08	0.53
1:A:80:THR:CG2	1:A:85:PRO:HB3	2.39	0.53
1:A:109:LEU:HD21	1:A:170:PHE:CD2	2.44	0.52
3:A:504:1BE:H25	3:A:504:1BE:H15	1.91	0.52
1:A:71:SER:HB3	1:A:400:GLU:OE1	2.10	0.51
1:A:333:ALA:HB2	1:A:377:GLN:O	2.11	0.50

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Atom-1	Atom-2	Interatomic distance (Å)	Clash overlap (Å)
1:A:174:SER:HB2	1:A:176:TRP:CD1	2.47	0.50
1:A:371:GLU:OE1	1:A:376:SER:HA	2.11	0.50
1:A:299:LYS:HE3	1:A:303:GLU:OE1	2.12	0.49
1:A:129:TYR:CE1	1:A:131:PRO:HG3	2.49	0.48
1:A:171:ILE:HG13	1:A:174:SER:HB3	1.96	0.48
1:A:111:ARG:O	1:A:177:GLU:HG3	2.14	0.47
1:A:174:SER:HB2	1:A:176:TRP:NE1	2.30	0.46
1:A:283:TYR:HA	1:A:284:ASP:HA	1.71	0.45
1:A:452:GLU:OE1	1:A:456:HIS:HE1	2.00	0.45
1:A:386:SER:HB2	4:A:613:HOH:O	2.17	0.44
1:A:115:ARG:HH12	1:A:140:GLU:CD	2.20	0.44
1:A:214:GLN:HE22	1:A:420:CYS:HB3	1.82	0.44
1:A:84:PRO:HD2	1:A:117:LEU:O	2.17	0.44
1:A:347:TYR:HA	1:A:357:PHE:O	2.17	0.44
1:A:70:LYS:HB3	1:A:73:GLN:OE1	2.18	0.43
1:A:139:GLY:HA3	1:A:162:ALA:O	2.19	0.43
1:A:338:TRP:CH2	1:A:364:GLN:HG3	2.54	0.43
1:A:203:LYS:HE2	1:A:203:LYS:HB3	1.87	0.43
1:A:242:HIS:CE1	1:A:245:TYR:HH	2.37	0.42
1:A:354:ASN:HB2	1:A:437:THR:O	2.18	0.42
1:A:186:GLU:CD	1:A:256:ARG:HH11	2.22	0.41
1:A:332:GLN:O	1:A:333:ALA:C	2.59	0.41
1:A:106:HIS:CG	1:A:107:PRO:HD2	2.56	0.41
1:A:411:LYS:NZ	4:A:730:HOH:O	2.53	0.41
1:A:284:ASP:HB2	1:A:447:ILE:HG12	2.03	0.41
1:A:125:ARG:HD3	4:A:634:HOH:O	2.19	0.41
1:A:269:ILE:HD12	1:A:274:LEU:HG	2.02	0.41
1:A:210:LEU:HD23	1:A:211:PHE:N	2.37	0.40
1:A:368:ARG:HA	1:A:368:ARG:HD3	1.87	0.40
1:A:432:GLU:OE2	4:A:601:HOH:O	2.22	0.40

All (2) 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	Interatomic distance (Å)	Clash overlap (Å)
1:A:110:HIS:ND1	4:A:734:HOH:O[3_555]	1.81	0.39
1:A:122:ARG:NH2	4:A:694:HOH:O[7_555]	2.05	0.15

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	372/406 (92%)	361 (97%)	7 (2%)	4 (1%)	14 8

All (4) Ramachandran outliers are listed below:

Mol	Chain	Res	Type
1	A	339	ASN
1	A	373	VAL
1	A	172	ASN
1	A	372	ASP

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	325/348 (93%)	311 (96%)	14 (4%)	29 26

All (14) residues with a non-rotameric sidechain are listed below:

Mol	Chain	Res	Type
1	A	62	GLU
1	A	65	ASP
1	A	110	HIS
1	A	126	LYS
1	A	148	ILE
1	A	149	PRO
1	A	157	ARG

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Mol	Chain	Res	Type
1	A	165	GLU
1	A	174	SER
1	A	210	LEU
1	A	258	TRP
1	A	418	SER
1	A	441	GLU
1	A	453	SER

Some sidechains can be flipped to improve hydrogen bonding and reduce clashes. All (5) such sidechains are listed below:

Mol	Chain	Res	Type
1	A	110	HIS
1	A	159	ASN
1	A	214	GLN
1	A	355	GLN
1	A	456	HIS

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](#)

Of 4 ligands modelled in this entry, 3 are monoatomic - leaving 1 for Mogul analysis.

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
3	1BE	A	504	-	26,35,35	2.82	3 (11%)	26,51,51	8.14	5 (19%)

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
3	1BE	A	504	-	-	2/10/33/33	0/4/4/4

All (3) bond length outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(Å)	Ideal(Å)
3	A	504	1BE	C13-C11	11.74	1.50	1.40
3	A	504	1BE	C19-C18	5.39	1.53	1.50
3	A	504	1BE	C4-C12	3.99	1.51	1.46

All (5) bond angle outliers are listed below:

Mol	Chain	Res	Type	Atoms	Z	Observed(°)	Ideal(°)
3	A	504	1BE	C16-C13-C11	30.20	120.01	111.69
3	A	504	1BE	C13-C16-S17	-26.94	105.01	112.53
3	A	504	1BE	C16-C13-C23	-6.56	115.56	125.52
3	A	504	1BE	C2-C1-CL1	-2.80	115.66	119.15
3	A	504	1BE	C29-C23-C24	2.76	113.65	105.21

There are no chirality outliers.

All (2) torsion outliers are listed below:

Mol	Chain	Res	Type	Atoms
3	A	504	1BE	C16-C13-C23-C29
3	A	504	1BE	C11-C18-C19-C20

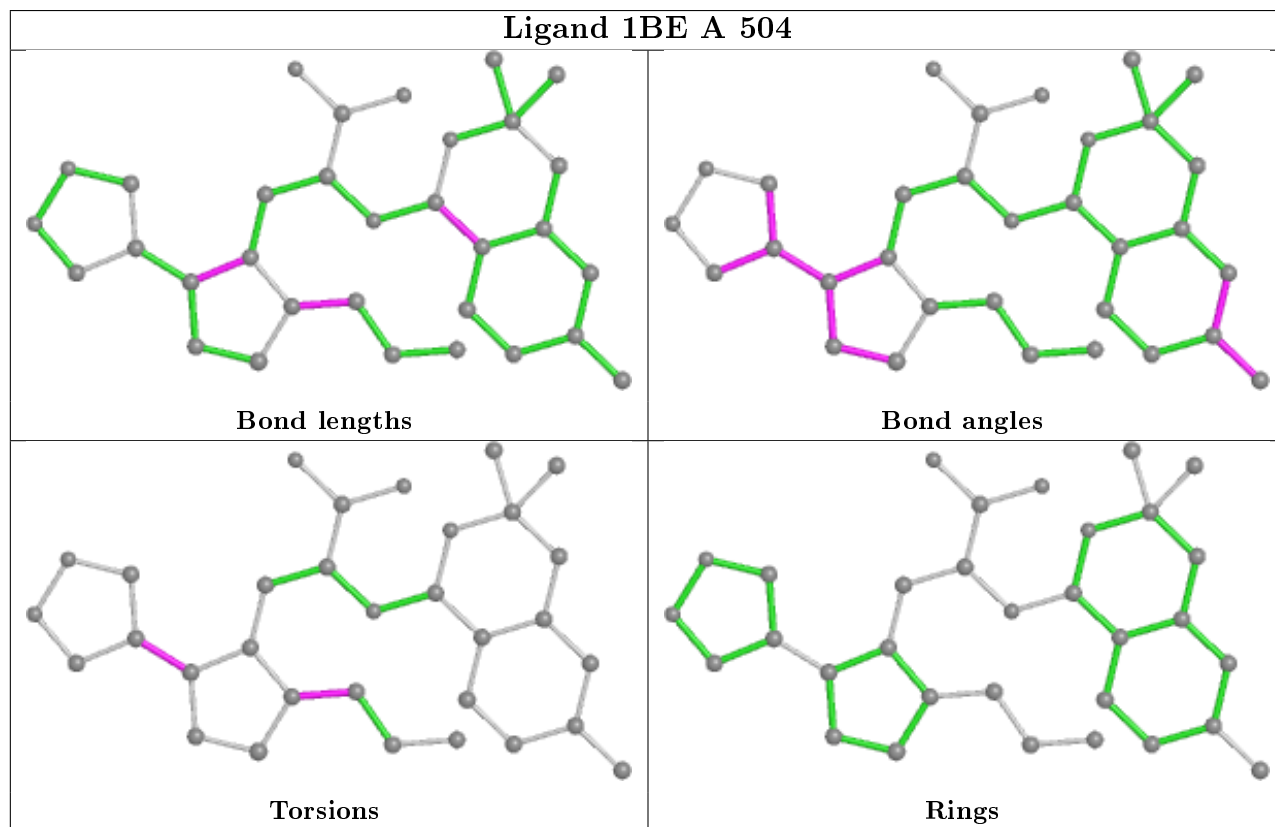
There are no ring outliers.

1 monomer is involved in 1 short contact:

Mol	Chain	Res	Type	Clashes	Symm-Clashes
3	A	504	1BE	1	0

The following is a two-dimensional graphical depiction of Mogul quality analysis of bond lengths,

bond angles, torsion angles, and ring geometry for all instances of the Ligand of Interest. In addition, ligands with molecular weight > 250 and outliers as shown on the validation Tables will also be included. For torsion angles, if less than 5% of the Mogul distribution of torsion angles is within 10 degrees of the torsion angle in question, then that torsion angle is considered an outlier. Any bond that is central to one or more torsion angles identified as an outlier by Mogul will be highlighted in the graph. For rings, the root-mean-square deviation (RMSD) between the ring in question and similar rings identified by Mogul is calculated over all ring torsion angles. If the average RMSD is greater than 60 degrees and the minimal RMSD between the ring in question and any Mogul-identified rings is also greater than 60 degrees, then that ring is considered an outlier. The outliers are highlighted in purple. The color gray indicates Mogul did not find sufficient equivalents in the CSD to analyse the geometry.



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

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	378/406 (93%)	0.58	45 (11%) 4 4	20, 34, 64, 100	3 (0%)

All (45) RSRZ outliers are listed below:

Mol	Chain	Res	Type	RSRZ
1	A	374	ALA	7.0
1	A	375	THR	6.9
1	A	373	VAL	6.5
1	A	439	ASP	6.5
1	A	206	HIS	6.1
1	A	377	GLN	4.7
1	A	335	THR	4.3
1	A	61	VAL	4.2
1	A	180	LEU	4.1
1	A	334	GLY	3.9
1	A	376	SER	3.7
1	A	62	GLU	3.6
1	A	173	GLY	3.5
1	A	69	GLY	3.5
1	A	73	GLN	3.5
1	A	68	ARG	3.4
1	A	172	ASN	3.4
1	A	182	LEU	3.3
1	A	420	CYS	3.2
1	A	205	THR	3.0
1	A	428	THR	2.9
1	A	60	PHE	2.9
1	A	332	GLN	2.8
1	A	235	MET	2.8
1	A	67	LEU	2.7
1	A	77	VAL	2.5
1	A	92	VAL	2.5

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Mol	Chain	Res	Type	RSRZ
1	A	339	ASN	2.5
1	A	315	THR	2.4
1	A	371	GLU	2.3
1	A	452	GLU	2.3
1	A	216	CYS	2.3
1	A	125	ARG	2.3
1	A	90	ILE	2.2
1	A	65	ASP	2.2
1	A	314	SER	2.2
1	A	419	ALA	2.2
1	A	232	GLY	2.2
1	A	108	PHE	2.1
1	A	70	LYS	2.1
1	A	372	ASP	2.1
1	A	215	LEU	2.1
1	A	441	GLU	2.1
1	A	211	PHE	2.0
1	A	440	MET	2.0

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](#)

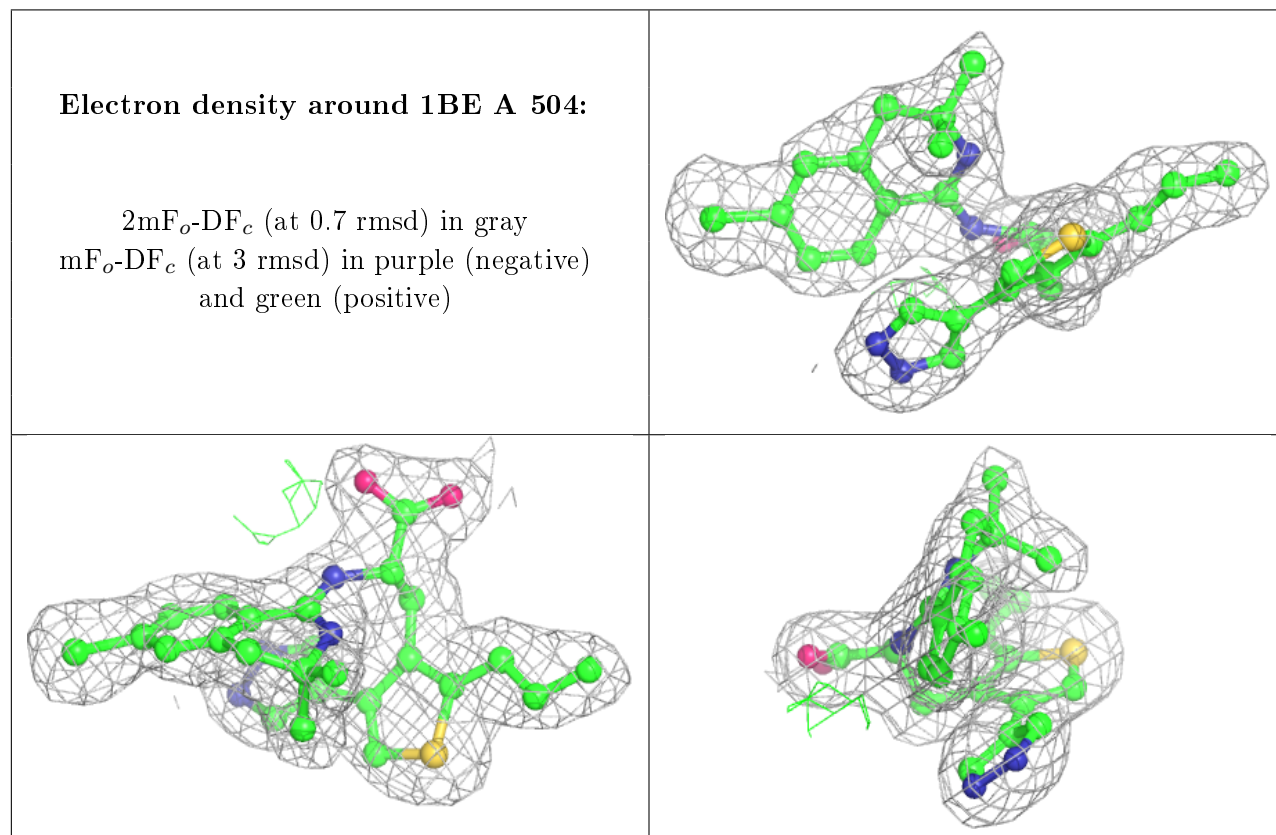
There are no carbohydrates in this entry.

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. 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	B-factors(Å ²)	Q<0.9
2	ZN	A	502	1/1	0.91	0.07	85,85,85,85	0
3	1BE	A	504	32/32	0.94	0.11	23,28,33,34	0
2	ZN	A	501	1/1	0.97	0.03	51,51,51,51	0
2	ZN	A	503	1/1	0.98	0.13	73,73,73,73	0

The following is a graphical depiction of the model fit to experimental electron density of all instances of the Ligand of Interest. In addition, ligands with molecular weight > 250 and outliers as shown on the geometry validation Tables will also be included. Each fit is shown from different orientation to approximate a three-dimensional view.



6.5 Other polymers [i](#)

There are no such residues in this entry.