Supporting Information

Title:

Optimization of a Potent Class of Arylamide Colony-stimulating Factor-1 Receptor Inhibitors Leading to Anti-inflammatory Clinical Candidate 4-Cyano-*N*-[2-(1-cyclohexen-1-yl)-4-[1-[(dimethylamino)acetyl]-4-piperidinyl]phenyl]-1*H*-imidazole-2-carboxamide (JNJ-28312141).

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Contents:

Table S1 Data Collection and Refinement Statistics

	Compound **8**	Compound **49**
Data Collection		
Detector/Source	Mar M165/ IMCA	Mar M165/ IMCA
Wavelength (Å)	1.0	1.0
Resolution (Å)	2.1 (2.17-2.1)	2.4 (2.49-2.0)
Space Group	R3	R3
Unit Cell Parameters (Å)	82.9 82.9 144.4	81.1 81.1 142.6
No. of reflections	74439	44757
No. of unique reflections	21192	13458
Redundancy	3.5 (3.8)	3.3 (3.5)
Completeness (%)	97.2 (100.0)	98.8 (100)
R_{merge} (%)	7.5 (29.0)	5.9 (23.7)
I/σ(I)	15.3 (4.1)	18.2 (4.8)
Refinement		
Resolution (Å)	2.1	2.4
No. of reflections / R_{free} set	20404 / 1924	12852 / 639
R-factor (%) / R_{free} (%)	20.8 / 26.0	20.9 / 26.4
R.M.S Deviation from ideal geometry		
Bonds (Å)	0.003	0.003
Angles (°)	0.888	0.815
Average B-factors (Å^2)		
Protein	46.6	60.2
Ligand	35.0	46.1
Ramachandran Plot		
Preferred Regions (%)	94.6	95.2
Allowed Regions (%)	3.4	4.1
Disallowed Regions (%)	2	0.7

$R_{merge} = \sum_i \left| I_i - \langle I_i \rangle \right| / \sum_i I_i$, where $\langle I_i \rangle$ is the average of I_i over all symmetry equivalents.

$R_{work} = 100 \sum \left\| F_o \right| - \left| F_c \right\| / \sum \left| F_o \right|$, where $\left| F_o \right|$ and $\left| F_c \right|$ are the observed and calculated structure factor amplitudes, respectively.

The R_{free} factor is the R factor calculated for a selected subset of reflections excluded from refinement.

R.M.S.: root mean square deviation.

Crystallization and Structure Determination

Crystallization and structure determination was carried out essentially as described previously.[1] In case that the co-crystallization did not yield any crystals, crystals of the arylamide (Compound 1 in [1]) were soaked overnight of for several days in a solution containing 1-5mM of the compound of interest in DMSO and a stabilization solution of 25 % PEG3350, 100 mM sodium acetate, pH 5.5, 200 mM Li_2SO_4, 5 mM dithiothreitol.

References

[1] Schubert, C.; Schalk-Hihi, C.; Struble, G.T.; Ma, H.C.; Petrounia, I. P.; Brandt, B.; Deckman, I. C.; Patch, R. J.; Player, M. R.; Spurlino, J. C.; Springer, B. A. Crystal structure of the tyrosine kinase domain of colony-stimulating factor-1 receptor (cFMS) in complex with two inhibitors. *J. Biol. Chem*. **2007**, *282*, 4094-4101. PDB:2I0Y.