

Supporting Information

Discovery of Kinase Spectrum Selective Macrocyle (16E)-14-Methyl-20-oxa-5,7,14,26-tetraaza- tetracyclo[19.3.1.1(2,6).1(8,12)]heptacos- 1(25),2(26),3,5,8(27),9,11,16,21,23-decaene (SB1317/TG02), a Potent Inhibitor of Cyclin Dependant Kinases (CDKs), Janus Kinase 2 (JAK2) and Fms-LikeTyrosine Kinase-3 (FLT3) for the Treatment of Cancer

Anthony D. William,* Angeline C.-H. Lee, Kee Chuan Goh, Stéphanie Blanchard, Anders Poulsen, Ee Ling Teo, Harish Nagaraj, Chai Ping Lee, Haishan Wang, Meredith Williams, Eric T. Sun, Changyong Hu, Ramesh Jayaraman, Mohammed Khalid Pasha, Kantharaj Ethirajulu, Jeanette M. Wood and Brian W. Dymock

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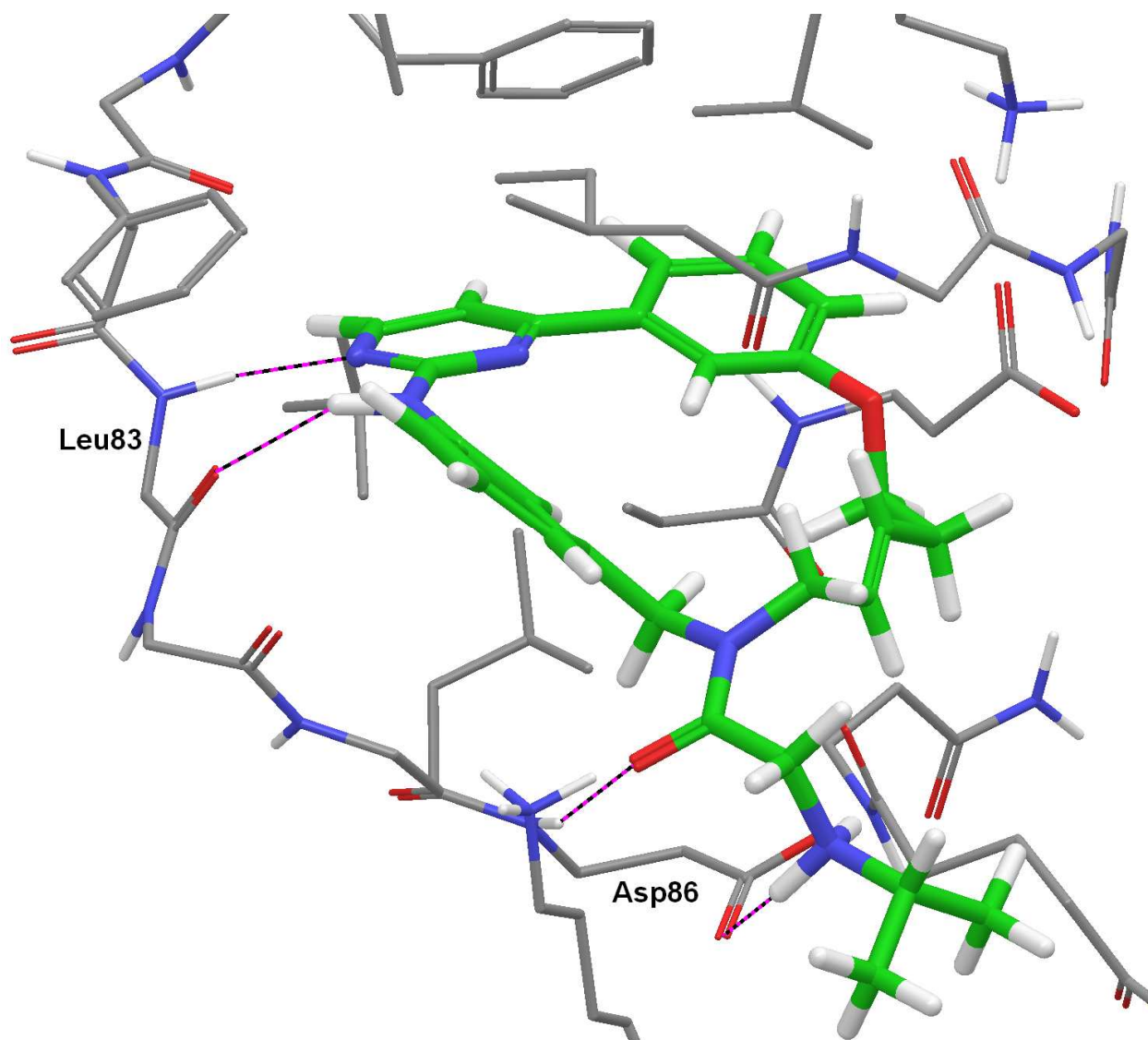
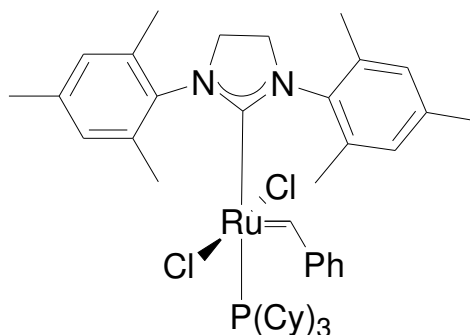


Figure S1: **26r** docked into CDK2. The linker nitrogen has been modified to an amide which is unable to form a salt bridge to Asp86. However the basic amine of the solubility tag may form a salt bridge to Asp86 and the carbonyl of the amide may hydrogen bond to the backbone NH of Asp86. The isopropyl group clashes with the protein.

Figure S2: Structures of metathesis catalysts employed

Grubbs 2nd generation catalyst ($C_{46}H_{65}Cl_2N_2PRu$): [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium:



Zhan-1B catalyst ($RuCl_2[C_{21}H_{26}N_2][C_{12}H_{17}NO_3S]$): 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene[2-(i-propoxy)-5-(N,N-dimethylaminosulfonyl)phenyl]methylen ruthenium (II) dichloride:

<http://www.zannanpharma.com/en/product.asp>

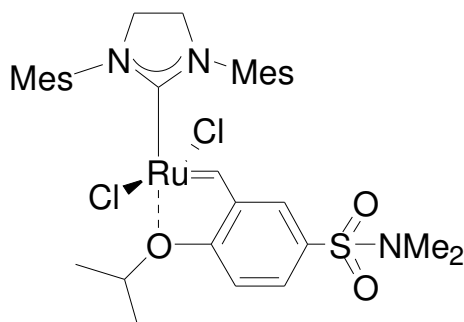


Table S1. Pharmacokinetic parameters after single intravenous or oral administration of 27j to nude mice

	<i>IV</i>	<i>PO</i>
Dose (mg/kg)	10	50
C_{max} (ng/ml)		2
T_{max} (h)		28
K_{el} (h⁻¹)	0.03	0.1
T_{1/2} (h)	23	6.75
CL (L/h/kg)	16.6	
CL/F (L/h/kg)		324
V_d (L/kg)	549	
V_d_{ss} (L/kg)	437	
V_z/F (L/kg)		3154
MRT (h)	26.4	10.2
AUC_{0-last} (ng.h/ml)	371	135
AUC_{0-inf} (ng.h/ml)	603	154
Extrapolate area (%)	38.5	12.6
R²	0.99	0.69
F (%)		5.11

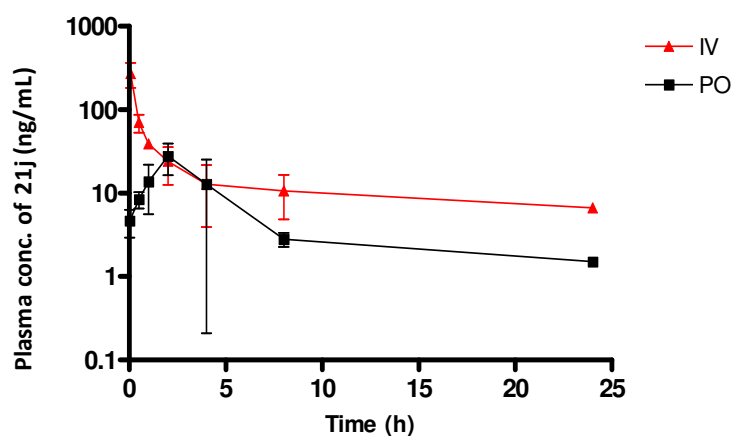


Figure S3: Plasma/time profile of 27j in mice