Discovery and characterization of a novel potent type II native and mutant BCR-ABL inhibitor (CHMFL-074) for Chronic Myeloid Leukemia (CML)

Supplementary Materials

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CLUSTAL O(1.2.1) multiple sequence alignment


1T46:A|KIT    GNNYVYIDPTQLPYDHKWEFPRNRLSFGKTLGAGAFGKVVEATAYGLIKSDAAMTVAVKM
PDGFRA        -----------------------LVLGRVLGSGAFGKVVEGTAYGLSRSQPVMKVAVKM
PDGFRB        -----------------------LVLGRTLGSGAFGQVVEATAHGLSHSQATMKVAVKM
                                     * .:*.. **:****.*** **.** .:*. .* .*****

1T46:A|KIT    LKPSAHLTEREALMSELKVLSYLGNHMNIVNLLGACTIGGPTLVITEYCCYGDLLNFLRR
PDGFRA        LKPTARSSEKQALMSELKIMTHLGPHLNIVNLLGACTKSGPIYIITEYCFYGDLVNYLHK
PDGFRB        LKSTARSSEKQALMSELKIMSHLGPHLNVVNLLGACTKGGPIYIITEYCRYGDLVDYLHR
              ** .*: .*:.:*******:.::** *.*.******** .**  .***** ****.::*::

1T46:A|KIT    KRDSFICSKTSPAIMEDDELALDLEDLLSFSYQVAKGMAFLASKNCIHRDLAARNILLTH
PDGFRA        NRDSFE--------------GLTLLDLLSFTYQVARGMEFLASKNCVHRDLAARNVLLAQ
PDGFRB        NKHTFP--------------VLSYMDLVGFSYQVANGMEFLASKNCVHRDLAARNVLICE
              ::..:*              *   **:.*.**** ** *******.*********.*. .

1T46:A|KIT    GRITKICDFGLARDIKNDSNYVVKGNARLPVKWMAPESIFNCVYTFESDVWSYGIFLWEL
PDGFRA        GKIVKICDFGLARDIMHDSNYVSKGSTFLPVKWMAPESIFDNLYTTLSDVWSYGILLWEI
PDGFRB        GKLVKICDFGLARDIMRDSNYISKGSTFLPLKWMAPESIFNSLYTTLSDVWSFGILLWEI
              *.:.:********** .****. **:. **.*:********:  .** *****.**.***:

1T46:A|KIT    FSLGSSPYPGMPVDSKFYKMIKEGFRMLSPEHAPAEMYDIMKTCWDADPLKRPTFKQIVQ
PDGFRA        FSLGGTPYPGMMVDSTFYNKIKSGYRMAKPDHATSEVYEIMVKCWNSEPEKRPSFYHLSE
PDGFRB        FTLGGTPYPELPMNEQFYNAIKRGYRMAQPAHASDEIYEIMQKCWEEKFEIRPPFSQLVL
              *:**..****  : .:**: .*: *.**  * **  *:.*.** . *  ** * ::

1T46:A|KIT    LIEKQISESTNHI
PDGFRA        IVENLL-------
PDGFRB        LLERLL-------
              ::*. :
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Supplementary Figure S1: Sequence alignment of PDGFR α/β with cKit.

Supplementary Table S1: Kinomewide selectivity profiling of CHMFL-074 with DiscoveRx's KinomeScan™ technology. See Supplementary_Table_S1

Supplementary Table S2: Potential targets revealed by KinomeScan™ Profiling bear the % control number less than 1 at 1 μM concentration of CHMFL-074

Kinases	% Control
ABL1(E255K)-phosphorylated	0.3
ABL1(H396P)-nonphosphorylated	0.15
ABL1(H396P)-phosphorylated	0.3
ABL1(M351T)-phosphorylated	1
ABL1(Q252H)-nonphosphorylated	0.75
ABL1(Q252H)-phosphorylated	0.4
ABL1(Y253F)-phosphorylated	0.3
ABL1-nonphosphorylated	0.25
ABL1-phosphorylated	0.2
ABL2	0.8
BLK	0
CSF1R	0.2
DDR1	0.6
DDR2	0
KIT(L576P)	1
KIT(V559D)	0.45
LCK	0.2
LOK	0.1
PDGFRB	0.2
RET	0.05
RET(M918T)	0.15

Supplementary Table S3: Crystal structure data collection and refinement statistics

Structure and PDB ID	ABL1/CHMFL-074 complex 5HU9
Data collection*	
Space group	$C222_1$
Cell dimensions	
a, b, c (Å)	37.8, 108.4, 146.3
α, β, γ (°)	90.0, 90.0, 90.0
Resolution (Å)	50–1.53 (1.56–1.53)
$R_{p.i.m.}$ (%)**	2.8 (35.8)
I/σ	27.1 (2.0)
Completeness (%)	97.7 (89.6)
Redundancy	12.0 (10.1)
Refinement	
Resolution (Å)	43.56–1.53
No. reflections	44775
R_{work}/R_{free}	0.185/0.196
No. atoms	
Protein	2251
Ligand/ion	135
Water	365
B-factors	
Protein	28.4
Ligand/ion	31.5
Water	42.8
R.m.s. deviations	
Bond lengths (Å)	0.023
Bond angles (°)	1.689
Ramachandran Plot	
Favoured region	97.50%
Allowed region	2.50%
Outliers	0.00%