

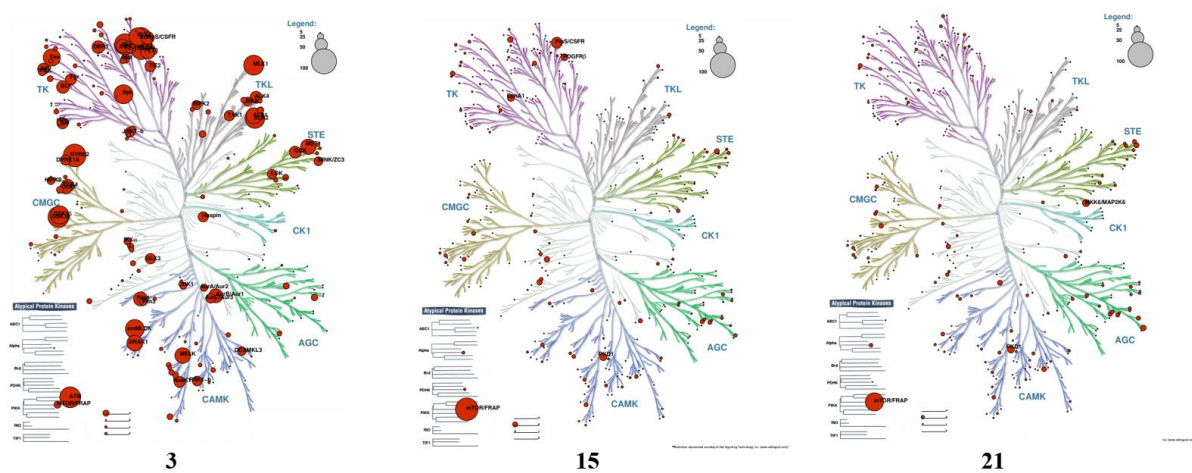
# Discovery and characterization of AZD6738, a potent inhibitor of ataxia telangiectasia mutated and rad3 related (ATR) kinase with application as an anti-cancer agent

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**Figure S1** – Kinome selectivity of compounds **3**, **15**, **21**; compounds tested at 1  $\mu$ M.



**Table T1. Kinase inhibition data for 2**

<b>Kinase assay</b>	<b>Compound 2</b>
PIK3C2G FRET-Adapta SP	61
CLK4 FRET-Lantha SP	57
PIK3CD/PIK3R1 FRET-Adapta SP	47
DNA-PK FRET-Z-Lyte SP	42
MAP4K4 (HGK) FRET-Z-Lyte SP	39
FRAP1 (mTOR) *Mn* Z-Lyte SP	39
IRAK3 FRET-Lantha SP	37
NTRK1 (TRKA) FRET-Z-Lyte SP	37
MAP2K2 (MEK2) Cascade Z-Lyte SP	35
PIK3C2B FRET-Adapta SP	32
PIK3CA/PIK3R3 FRET-Adapta SP	32
PIK3CA/PIK3R1 FRET-Adapta SP	32
FGFR1 *Mn* FRET-Z-Lyte SP	31
PIK3CB/PIK3R2 FRET-Adapta SP	31
MINK1 FRET-Z-Lyte SP	29
LCK FRET-Z-Lyte SP	29
CDK9/cyclin T1 FRET-Adapta SP	28
NEK2 FRET-Z-Lyte SP	27
MAPK8 (JNK1) Cascade Z-Lyte SP	27
NTRK3 (TRKC) FRET-Z-Lyte SP	26
PAK2 (PAK65) FRET-Z-Lyte SP	26
PIK3CG (p110 gamma) Adapta SP	26
CDK11 Cyclin C FRET-Lantha SP	25
ACVR2A FRET-Lantha SP	25
EGFR (ErbB1) *Mn* Z-Lyte SP	25
CLK2 FRET-Z-Lyte SP	25
FYN FRET-Z-Lyte SP	25
STK32B (YANK2) FRET-Lantha SP	24
MAP2K1 (MEK1) Cascade Z-Lyte SP	24
SRC Hu Phos FRET-Z-Lyte SP	24
PAK1 FRET-Z-Lyte SP	23
OXSRL FRET-Lantha SP	23
PDK1 Cascade FRET-Z-Lyte SP	23
PIK3CB FRET-Adapta SP	22
BMX FRET-Z-Lyte SP	22
CHEK1 (CHK1) FRET-Z-Lyte SP	21
PLK1 FRET-Z-Lyte SP	21
STK32C (YANK3) FRET-Lantha SP	21
RPS6KA1 (RSK1) FRET-Z-Lyte SP	20
YES1 FRET-Z-Lyte SP	20
PDK1 (Direct) FRET-Z-lyte SP	20
PIK3C3 (hVPS34) *Mn* Adapta SP	19
PTK2 (FAK) FRET-Z-Lyte SP	19
PRKCB2 (PKC Beta II) Z-Lyte SP	19
STK25 (YSK1) FRET-Z-Lyte SP	19
IRAK1 FRET-Adapta SP	19
NUAK2 FRET-Lantha SP	18
ALK FRET-Z-Lyte SP	18
IGF1R FRET-Z-Lyte SP	18
MYO3A (MYO3 alpha) Lantha SP	18
FLT3 Hu Phos FRET-Z-Lyte SP	18
GSG2 (Haspin) FRET-Adapta SP	18
TTK FRET-Lantha SP	17
MARK2 FRET-Z-Lyte SP	17
CDC7/DBF4 FRET-Lantha SP	17
CDK8/cyclin C FRET-Lantha SP	17
STK16 (PKL12) FRET-Lantha SP	16
PKN2 (PRK2) FRET-lantha SP	16
IRAK4 *Mn* FRET-Z-Lyte SP	16
NTRK2 (TRKB) *Mn* Z-Lyte SP	16
PRKG2 (PKG2) FRET-Z-Lyte SP	16
DYRK2 FRET-Lantha SP	16
RET Hu Phos FRET-Z-Lyte SP	16
TNK1 FRET-Z-Lyte SP	15
PKN1 (PRK1) FRET-Z-Lyte SP	15
CDKL5 FRET-Z-Lyte SP	15
CLK1 FRET-Z-Lyte SP	15
MYLK4 FRET-Lantha SP	15
EPHA7 FRET-Lantha SP	14

CDK6 Cyclin D1 FRET-Adapta SP	14
ABL1 Hu Phos FRET-Z-Lyte SP	14
CSNK2A2 (CK2alpha2) Z-Lyte SP	14
TGFBR1 (ALK5) FRET-Lantha SP	14
PAK3 FRET-Z-Lyte SP	14
PKMYT1 FRET-Lantha SP	14
CDK18/cyclin Y FRET-Z-Lyte SP	14
MAPK8 (JNK1) FRET-Lantha SP	14
PRKACG FRET-Lantha SP	14
FGFR2 *Mn* FRET-Z-Lyte SP	13
IKBKE (IKK epsilon) Z-Lyte SP	13
PDGFRB *Mn* FRET-Z-Lyte SP	13
MAPK12 (p38 gamma) Z-Lyte SP	13
LYN A Hu Phos FRET-Z-Lyte SP	13
DYRK1A FRET-Z-Lyte SP	13
MAPK3 (ERK1) FRET-Z-Lyte SP	13
CAMK1 (CaMK1) FRET-Adapta SP	13
MAPK10 (JNK3) Cascade Z-Lyte SP	12
PRKACB FRET-Lantha SP	12
AMPK A1/B2/G2 FRET-Z-Lyte SP	12
MAPK1 (ERK2) FRET-Z-Lyte SP	12
CDK14 (PFTK1)/cyclinY Lantha SP	12
CDK2/Cyclin O FRET-Lantha SP	12
WEE1 FRET-Lantha SP	12
SLK Hu Bind FRET-Lantha SP	12
PRKACA (PKA) FRET-Z-Lyte SP	12
PTK2B (FAK2) *Mn* Z-Lyte SP	12
DMPK FRET-Lantha SP	12
STK22B (TSSK2) FRET-Z-Lyte SP	12
AMPK A2/B2/G3 FRET-Z-Lyte SP	12
TAOK1 FRET-Lantha SP	12
PIK3C2A FRET-Adapta SP	12
CDK2/cyclin A1 FRET-Lantha SP	12
HIPK4 FRET-Z-Lyte SP	12
FER FRET-Z-Lyte SP	11
SNF1LK2 FRET-Z-Lyte SP	11
LRRK2 Hu Phos FRET-Adapta SP	11
MKNK2 (MNK2) FRET-Lantha SP	11
CHUK (IKK alpha) FRET-Adapta SP	11
MERTK (cMER) *Mn* Z-Lyte SP	11
PASK FRET-Z-Lyte SP	11
MATK (HYL) FRET-Z-Lyte SP	11
RPS6KB1 (p70S6K) Z-Lyte SP	11
ERN2 FRET-Lantha SP	11
MAPK7 (ERK5) FRET-Z-Lyte SP	11
VRK2 FRET-Lantha SP	11
CDK3/cyclin E1 FRET-Lantha SP	10
KDR (VEGFR2) FRET-Z-Lyte SP	10
AAK1 FRET-Lantha SP	10
BLK FRET-Z-Lyte SP	10
CDK4 Cyclin D1 *Mn* Adapta SP	10
PRKD1 (PKC mu) Z-Lyte SP	10
CDK2/cyclin A FRET-Z-Lyte SP	10
CDK17/cyclin Y FRET-Z-Lyte SP	10
INSRR (IRR) *Mn* Z-Lyte SP	10
RPS6KB2 FRET-Z-Lyte SP	10
bRAF Cascade FRET-Z-Lyte SP	10
FGFR3 *Mn* FRET-Z-Lyte SP	10
MUSK *Mn* FRET-Z-Lyte SP	9
LATS2 FRET-Lantha SP	9
TBK1 FRET-Z-Lyte SP	9
MST1R (RON) FRET-Z-Lyte SP	9
MAP4K1 (HPK1) FRET-Lantha SP	9
WNK2 FRET-Lantha SP	9
DCAMKL1 (DCLK1) FRET-Z-Lyte SP	9
EPHB4 FRET-Z-Lyte SP	9
MAPK10 (JNK3) FRET-Lantha SP	9
CDK1/cyclin B FRET-Z-Lyte SP	9
CAMK2G FRET-Lantha SP	9
CAMKK1 (Alpha) FRET-Lantha SP	9
MARK4 FRET-Z-Lyte SP	9
INSR *Mn* FRET-Z-Lyte SP	8

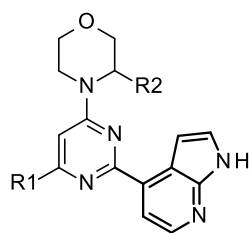
AMPK A2/B1/G1 FRET-Z-Lyte SP	8
NEK4 FRET-Z-Lyte SP	8
IKKKB (IKKbeta) FRET-Z-Lyte SP	8
AKT2 (PKB beta) FRET-Z-Lyte SP	8
MAP2K6 (MKK6) Cascade Z-Lyte SP	8
CDK16 (PCTK1)/cyclinY Lantha SP	8
ROCK2 FRET-Z-Lyte SP	8
DAPK3 (ZIPK) FRET-Z-Lyte SP	8
AMPK (A2/B2/G1) FRET-Lantha SP	8
NIM1K FRET-Z-Lyte SP	8
BMPR2 FRET-Lantha SP	8
CDK11 (Inactive) FRET-Lantha SP	8
CDK7/cyclin H/MNAT1 Adapta SP	8
PIM1 FRET-Z-Lyte SP	8
ERBB4 (HER4) *Mn* Z-Lyte SP	8
STK22D (TSSK1) FRET-Z-Lyte SP	8
MYLK3 Hu Bind FRET-Lantha SP	7
ADCK3 FRET-Lantha SP	7
CSNK2A1 (CK2alpha1) Z-Lyte SP	7
MET (cMet) FRET-Z-Lyte SP	7
EPHB1 FRET-Z-Lyte SP	7
CDK9/cyclin K FRET-Lantha SP	7
ABL2 (Arg) FRET-Z-Lyte SP	7
PAK4 FRET-Z-Lyte SP	7
PRKCH (PKC eta) Z-Lyte SP	7
JAK2 FRET-Z-Lyte SP	7
MAP3K10 (MLK2) FRET-Lantha SP	7
CDK5/p35 FRET-Z-Lyte SP	7
JAK1 FRET-Z-Lyte SP	6
FLT1 (VEGFR1) *Mn* Z-Lyte SP	6
ROS1 FRET-Z-Lyte SP	6
TESK1 FRET-Lantha SP	6
RPS6KA5 (MSK1) FRET-Z-Lyte SP	6
PRKCN (PKD3) FRET-Z-Lyte SP	6
KIT *Mn* FRET-Z-Lyte SP	6
STK3 (MST2) FRET-Z-Lyte SP	6
STK38 FRET-Lantha SP	6
NUAK1 (ARK5) FRET-Adapta SP	6
CDK5/p25 FRET-Z-Lyte SP	6
TYK2 FRET-Z-Lyte SP	6
MARK1 (MARK) FRET-Z-Lyte SP	6
DYRK1B FRET-Z-Lyte SP	6
braf FRET-Lantha SP	6
CLK3 FRET-Z-Lyte SP	6
EPHB2 FRET-Z-Lyte SP	6
ACVR1B (ALK4) *Mn* Z-Lyte SP	6
HIPK3 (YAK1) FRET-Z-Lyte SP	6
LIMK2 FRET-Lantha SP	6
LATS1 FRET-Lantha SP	5
PHKG2 FRET-Z-Lyte SP	5
HCK FRET-Z-Lyte SP	5
PLK4 FRET-Lantha SP	5
PI4K2A *Mn* FRET-Adapta SP	5
GSK3A FRET-Z-Lyte SP	5
ULK1 FRET-Lantha SP	5
PI4K2B *Mn* FRET-Adapta SP	5
RPS6KA3 (RSK2) FRET-Z-Lyte SP	5
MYO3B FRET-Lantha SP	5
MAPK9 (JNK2) FRET-Lantha SP	5
STK17A (DRAK1) FRET-Lantha SP	5
EEF2K FRET-Z-Lyte SP	5
PRKX FRET-Z-Lyte SP	5
AMPK A1/B2/G3 FRET-Z-Lyte SP	5
HIPK2 FRET-Z-Lyte SP	5
DDR1 FRET-Lantha SP	5
STK4 (MST1) FRET-Z-Lyte SP	5
MST4 FRET-Z-Lyte SP	5
AURKA (Aurora A) Z-Lyte SP	5
STK17B (DRAK2) FRET-Lantha SP	5
MAP2K2 (MEK2) FRET-Lantha SP	5
PRKG1 FRET-Z-Lyte SP	5
CAMKK2 (Beta) FRET-Lantha SP	5

TXK FRET-Z-Lyte SP	5
AMPK A1/B1/G1 FRET-Z-lyte SP	4
ROCK1 FRET-Z-Lyte SP	4
TAOK2 (TAO1) FRET-Z-Lyte SP	4
GRK1 FRET-Lantha SP	4
PRKCE (PKC epsilon) Z-Lyte SP	4
ZAP70 *Mn* FRET-Z-Lyte SP	4
MAPK11 (p38 beta) Z-Lyte SP	4
ADRBK2 (GRK3) FRET-Z-Lyte SP	4
AURKC (Aurora C) Z-Lyte SP	4
RPS6KA6 (RSK4) FRET-Z-Lyte SP	4
EPHA5 FRET-Z-Lyte SP	4
DYRK3 FRET-Z-Lyte SP	4
CSK FRET-Z-Lyte SP	4
GSK3B FRET-Z-Lyte SP	4
STK39 (STLK3) FRET-Lantha SP	4
AXL FRET-Z-Lyte SP	4
AKT3 (PKB gamma) Z-Lyte SP	4
SRMS (Srm) FRET-Z-Lyte SP	4
JAK3 FRET-Z-Lyte SP	4
MAP3K11 (MLK3) FRET-Lantha SP	4
EPHA4 FRET-Z-Lyte SP	4
NEK8 FRET-Lantha SP	4
MAPKAPK2 FRET-Z-Lyte SP	4
MAPK14 (p38a) Direct Z-Lyte SP	4
AMPK A2/B1/G3 FRET-Z-Lyte SP	3
MAP3K7/MAP3K7IP1 Lantha SP	3
SRPK1 FRET-Z-Lyte SP	3
MAPK14 (p38a) Cascade Z-Lyte SP	3
TNK2 (ACK) FRET-Lantha SP	3
ULK3 FRET-Lantha SP	3
BTK FRET-Z-Lyte SP	3
MAP4K5 (KHS1) FRET-Z-Lyte SP	3
RPS6KA2 (RSK3) FRET-Z-Lyte SP	3
KSR2 FRET-Z-Lyte SP	3
CAMK1G FRET-Z-Lyte SP	3
AMPK (A1/B1/G2) FRET-Lantha SP	3
SGK (SGK1) FRET-Z-Lyte SP	3
MAPK13 (p38 delta) Z-Lyte SP	3
NEK9 *Mn* FRET-Z-Lyte SP	3
LYN B FRET-Z-Lyte SP	3
CDK13 Cyclin K FRET-Lantha SP	3
NEK1 FRET-Z-Lyte SP	3
MAPK15 (ERK7) FRET-Lantha SP	3
PAK6 FRET-Z-Lyte SP	3
CHEK2 (CHK2) FRET-Z-Lyte SP	3
MLK4 FRET-Lantha SP	2
EPHB3 FRET-Z-Lyte SP	2
PIM2 FRET-Z-Lyte SP	2
MAP2K1 (MEK1) FRET-Lantha SP	2
WNK1 FRET-Lantha SP	2
AMPK (A2/B2/G2) FRET-Lantha SP	2
AMPK (A1/B1/G3) FRET-Lantha SP	2
MAP2K6 (MKK6) FRET-Lantha SP	2
EPHA1 FRET-Z-Lyte SP	2
MAP2K5 (MEK5) FRET-Lantha SP	2
EPHA3 FRET-Lantha SP	2
TGFBR2 FRET-Lantha SP	2
CSNK1E (CK1 epsilon) Z-Lyte SP	2
SGKL (SGK3) FRET-Z-Lyte SP	2
STK23 (MSSK1) FRET-Z-Lyte SP	2
STK33 FRET-Lantha SP	2
NLK FRET-Lantha SP	2
ERN1 FRET-Lantha SP	2
SYK FRET-Z-Lyte SP	2
STK24 (MST3) FRET-Z-Lyte SP	2
FGFR4 *Mn* FRET-Z-Lyte SP	2
MAPKAPK5 (PRAK) FRET-Z-Lyte SP	2
ANKK1 FRET-Lantha SP	2
MARK3 FRET-Z-Lyte SP	2
GRK5 *Mn* FRET-Z-Lyte SP	2
LTK (TYK1) FRET-Z-Lyte SP	2

CDK9 (Inactive) FRET-Lantha SP	2
ADRBK1 (GRK2) FRET-Z-Lyte SP	2
MAP4K3 (GLK) FRET-Lantha SP	1
BRSK1 (SAD1) FRET-Z-Lyte SP	1
STK38L (NDR2) FRET-Lantha SP	1
PDGFRA *Mn* FRET-Z-Lyte SP	1
CDK4 Cyclin D3 *Mn* Adapta SP	1
CAMK2A FRET-Z-Lyte SP	1
SPHK2 FRET-Adapta SP	1
CAMK2B FRET-Z-Lyte SP	1
ERBB2 (HER2) *Mn* Z-Lyte SP	1
WNK3 FRET-Lantha SP	1
TEC FRET-Lantha SP	1
CSNK1D (CK1 delta) Z-Lyte SP	1
AKT1 (PKB alpha) Z-Lyte SP	1
PI4KB FRET-Adapta SP	1
PRKCA (PKC alpha) Z-Lyte SP	1
TLK2 FRET-Lantha SP	1
EPHA6 FRET-Lantha SP	1
MAP3K9 (MLK1) FRET-Z-Lyte SP	0
FRK (PTK5) FRET-Z-Lyte SP	0
ACVRL1 (ALK1) FRET-Lantha SP	0
FLT4 (VEGFR3) *Mn* Z-Lyte SP	0
CSNK1A1 FRET-Z-Lyte SP	0
RIPK3 FRET-Lantha SP	0
EPHA8 FRET-Z-Lyte SP	-0
PEAK1 FRET-Z-Lyte SP	-0
CDK5 (Inactive) FRET-Lantha SP	-0
MYLK (MLCK) FRET-Lantha SP	-0
CDK1/cyclin A2 FRET-Lantha SP	-0
AMPK (A1/B2/G1) FRET-Lantha SP	-0
MAP3K14 (NIK) FRET-Lantha SP	-0
CSNK1A1L FRET-Z-Lyte SP	-1
BRSK2 FRET-Lantha SP	-1
PRKCG (PKC gamma) Z-Lyte SP	-1
SRPK2 FRET-Z-Lyte SP	-1
PAK7 (KIAA1264) FRET-Z-Lyte SP	-1
RPS6KA4 (MSK2) FRET-Z-Lyte SP	-1
PTK6 (Brk) *Mn* FRET-Z-Lyte SP	-1
BMPR1A (ALK3) FRET-Lantha SP	-1
MAP3K19 (YSK4) FRET-Z-Lyte SP	-1
TLK1 FRET-Lantha SP	-1
PRKD2 (PKD2) Z-Lyte SP	-1
NEK6 FRET-Z-Lyte SP	-1
SIK1 FRET-Lantha SP	-1
ITK FRET-Z-Lyte SP	-1
TYRO3 (RSE) FRET-Z-Lyte SP	-2
ZAK FRET-Lantha SP	-2
MASTL FRET-Lantha SP	-2
FGR FRET-Z-Lyte SP	-2
AURKB (Aurora B) Z-Lyte SP	-2
CDC42 BPG FRET-Z-Lyte SP	-2
TESK2 Hu Bind FRET-Lantha SP	-3
RIPK2 FRET-Lantha SP	-3
PIP5K1C FRET-Adapta SP	-3
CSF1R (FMS) FRET-Z-Lyte SP	-3
DYRK4 FRET-Z-Lyte SP	-3
GRK6 FRET-Z-Lyte SP	-3
FYN A FRET-Lantha SP	-3
PI4KA FRET-Adapta SP	-3
PIM3 FRET-Z-Lyte SP	-3
ACVR1 (ALK2) FRET-Lantha SP	-3
PLK2 FRET-Z-Lyte SP	-4
CAMK1D FRET-Z-Lyte SP	-4
MAP3K3 (MEKK3) FRET-Lantha SP	-4
HUNK FRET-Lantha SP	-4
LIMK1 FRET-Lantha SP	-4
PRKCQ (PKC theta) Z-Lyte SP	-4
CDK2/Cyclin E1 FRET-Lantha SP	-5
PIP5K1A FRET-Adapta SP	-5
MAPKAPK3 FRET-Z-Lyte SP	-5
PLK3 FRET-Z-Lyte SP	-5

SPHK1 FRET-Adapta SP	-5
CAMK2D FRET-Z-Lyte SP	-5
CSNK1G3 (CK1gamma3) Z-Lyte SP	-5
PIP5K1B FRET-Adapta SP	-5
DCAMKL2 (DCK2) FRET-Z-Lyte SP	-5
MAP3K2 (MEKK2) FRET-Lantha SP	-5
SIK3 FRET-Lantha SP	-5
JAK2 JH1 JH2 FRET-Z-Lyte SP	-5
FES (FPS) FRET-Z-Lyte SP	-6
CAMK4 (CaMKIV) FRET-Z-Lyte SP	-6
TAOK3 (JIK) FRET-Lantha SP	-6
CSNK1G2 (CK1gamma2) Z-Lyte SP	-6
MAP3K5 (ASK1) FRET-Lantha SP	-7
EIF2AK2 (PKR) FRET-Lantha SP	-7
LRRK2 FL FRET-Adapta SP	-7
GRK7 FRET-Z-Lyte SP	-7
CDC42 BPA (MRCKA) Z-Lyte SP	-7
HIPK1 (Myak) FRET-Z-Lyte SP	-7
ABL1 FRET-Z-Lyte F317L SP	-8
CSNK1G1 (CK1gammal) Z-Lyte SP	-8
EPHA2 FRET-Z-Lyte SP	-9
GAK FRET-Lantha SP	-9
MAPK9 (JNK2) Cascade Z-Lyte SP	-9
ACVR2B FRET-Lantha SP	-9
PIP4K2A FRET-Adapta SP	-9
MAP2K3 (MEK3) FRET-Lantha SP	-10
DDR2 Hu Bind FRET-Lantha SP	-10
DAPK2 FRET-Lantha SP	-10
MAP4K2 (GCK) FRET-Z-Lyte SP	-10
NEK7 FRET-Z-Lyte SP	-10
PHKG1 FRET-Z-Lyte SP	-11
PRKCD (PKC delta) Z-Lyte SP	-11
TEK (Tie2) *Mn* FRET-Z-Lyte SP	-11
PRKCI (PKC iota) Z-Lyte SP	-12
DAPK1 FRET-Adapta SP	-12
MYLK2 FRET-Z-lyte SP	-12
MELK FRET-Z-Lyte SP	-12
CDC42 BPB (MRCKB) Z-Lyte SP	-12
SBK1 FRET-Z-Lyte SP	-12
AMPK A2/B1/G2 FRET-Z-Lyte SP	-12
CASK FRET-Lantha SP	-12
TNIK FRET-Lantha SP	-13
ICK FRET-Lantha SP	-13
PRKCZ (PKC zeta) Z-Lyte SP	-13
MAP3K8 (COT) Cascade Z-Lyte SP	-13
MAP2K4 (MEK4) FRET-Lantha SP	-14
ULK2 FRET-Lantha SP	-15
SGK2 FRET-Z-Lyte SP	-16
MKNK1 (MNK1) *Mn* Z-Lyte SP	-16
PRKCB1 (PKC beta I) Z-Lyte SP	-22
GRK4 FRET-Z-Lyte SP	-25

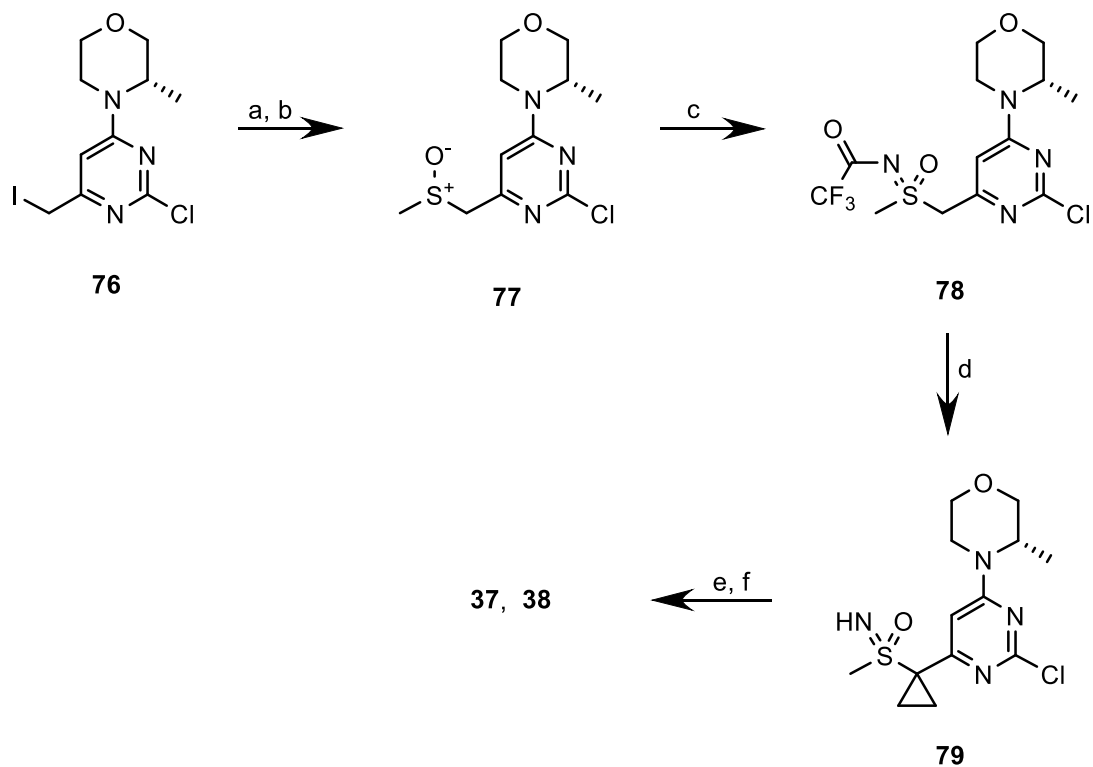
**Table T2. ATR activity data for 37, 38**



Compound	R1	R2	ATR cell IC <sub>50</sub> (μM) <sup>a</sup>
<b>2</b>		( <i>R</i> )-Me	0.074
<b>33</b>		( <i>R</i> )-Me	0.24
<b>37</b>	 Isomer 1	( <i>S</i> )-Me	3.6
<b>38</b>	 Isomer 2	( <i>S</i> )-Me	9.9

<sup>a</sup> See footnotes in Table 1 for assay uncertainty.

Scheme S1<sup>a</sup>



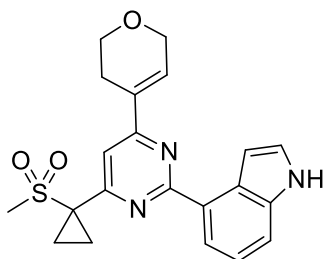
<sup>a</sup> Reagents: (a) NaSMe, ACN, rt; (b) NaIO<sub>4</sub>, EtOAc, MeOH, H<sub>2</sub>O, rt; (c) trifluoroacetamide, iodobenzene diacetate, Rh(OAc)<sub>2</sub> dimer, MgO, DCM, rt; (d) NaOH, 1,2-dibromoethane, tetra-octylammonium bromide, mTHF, 103 °C; (e) (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>, 2M Na<sub>2</sub>CO<sub>3</sub>, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine, DME:H<sub>2</sub>O (4:1), 90 °C; (f) chiral chromatography.

### Crystallisation method for compound 2:

Crystals for X-Ray diffraction were grown and isolated by slow evaporation to dryness in air from EtOAc.

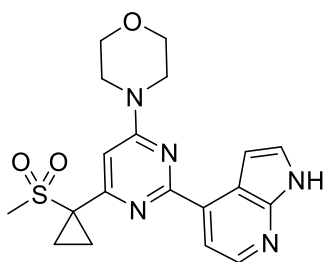
Compound **2** (approximately 10 g, 25 mmol) was suspended in MTBE (500 mL) and stirred at reflux for 2 hours. The suspension was allowed to cool slowly and stirred at room temperature overnight. The solid was collected by filtration and dried under vacuum to afford **2** (7.12 g) as a white crystalline solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.28 (3H, d), 1.44 (1H, dd), 1.47 - 1.58 (2H, m), 1.76 (1H, dt), 3.11 (3H, s), 3.26 (1H, dd), 3.52 (1H, td), 3.67 (1H, dd), 3.81 (1H, d), 3.85 (1H, d), 4.02 (1H, dd), 4.20 (1H, d), 4.59 (1H, s), 7.00 (1H, s), 7.23 (1H, dd), 7.57 - 7.62 (1H, m), 7.95 (1H, d), 8.34 (1H, d), 11.81 (1H, s); MS-ESI *m/z* 413 [MH<sup>+</sup>]. Mpt. (Buchi Melting Point B-545) 222°C. Chiral HPLC: (HP1100 System 7, 5µm Chiralcel OJ (250 mm x 4.6 mm) column eluting with heptane/(EtOH/MeOH 50/50)/TEA 50/50/0.1) R<sub>f</sub>, 9.836 99.8%.

Experimental details and data for compounds 7, 11 – 16, 32, 34 - 38, 40 – 45, 50 - 69, S/R-73, 77 – 79.



**4-(4-(3,6-Dihydro-2H-pyran-4-yl)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-indole (7).**

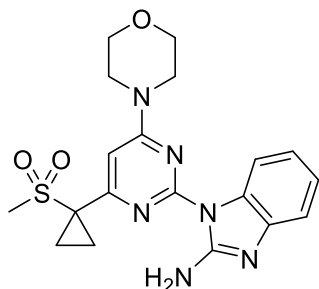
Bis(triphenylphosphine)palladium(II) chloride (22.30 mg, 0.03 mmol), **43** (100 mg, 0.32 mmol), 1H-indol-4-ylboronic acid (61.4 mg, 0.38 mmol) and sodium carbonate (2M aq.) (0.953 mL, 1.91 mmol) were suspended in DME:Water (4:1) (3 mL) and sealed into a microwave tube. The reaction was heated to 110 °C for 1 hour in the microwave reactor then cooled to room temperature. The reaction mixture was diluted with DCM (10 mL) and water (10 mL) then the layers separated. The organic layer was dried over MgSO<sub>4</sub>, filtered then concentrated *in vacuo*. The residue was purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in *iso*-hexane. Pure fractions were evaporated to dryness to afford **7** (80 mg, 64%) as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 1.72 - 1.75 (m, 2H), 1.81 - 1.84 (m, 2H), 2.67 - 2.73 (m, 2H), 3.29 (s, 3H), 3.91 (t, 2H), 4.37 - 4.40 (m, 2H), 7.26 (t, 2H), 7.43 (t, 1H), 7.52 (t, 1H), 7.61 (d, 1H), 7.68 (s, 1H), 8.19 (dd, 1H), 11.37 (s, 1H). MS-ESI *m/z* 396 [MH<sup>+</sup>]. HRMS-ESI *m/z* 396.1382 [MH<sup>+</sup>] requires C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S 396.1337.



**4-(6-(1-(Methylsulfonyl)cyclopropyl)-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrimidin-4-yl)morpholine (11).**

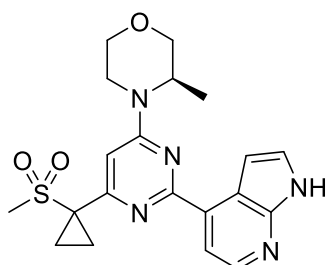
(11). Tetrakis(triphenylphosphine) palladium (0) (36.4 mg, 0.03 mmol) was added to **46** (100 mg, 0.31 mmol), 1H-pyrrolo[2,3-*b*]pyridin-4-ylboronic acid (51.0 mg, 0.31 mmol) and 2M sodium carbonate (0.63 mL, 1.26 mmol) in 1,4-dioxane (5 mL) under nitrogen. The resulting mixture was stirred at 90 °C for 18 hours. The reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and product containing fractions were evaporated to dryness. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ

silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures of water (containing 1% NH<sub>3</sub>) and MeOH/MeCN (3/1) as eluents. Fractions containing the desired compound were evaporated to dryness to afford **11** (89 mg, 71%) as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 1.61 - 1.64 (m, 2H), 1.72 - 1.75 (m, 2H), 3.30 (s, 3H), 3.73 - 3.82 (m, 8H), 7.00 (s, 1H), 7.23 (d, 1H), 7.61 (d, 1H), 7.94 (d, 1H), 8.35 (d, 1H), 11.84 (s, 1H). MS-ESI *m/z* 400 [MH<sup>+</sup>].



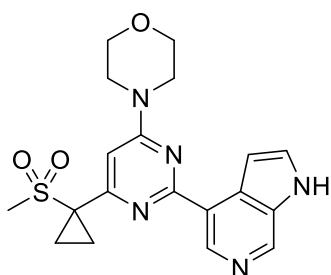
**1-(4-(1-(Methylsulfonyl)cyclopropyl)-6-morpholinopyrimidin-2-yl)-1H-benzo[d]imidazol-2-amine (12).**

Compound **46** (0.127 g, 0.4 mmol), 1H-benzo[d]imidazol-2-amine (0.053 g, 0.40 mmol) and sodium carbonate (0.170 g, 1.60 mmol) were suspended in DMA (4 mL) and sealed into a microwave tube. The reaction was heated to 160 °C for 4 hours in the microwave reactor then cooled to room temperature. The reaction mixture was purified by ion exchange chromatography, using an SCX column and the desired product was eluted using 7M NH<sub>3</sub>/MeOH in DCM. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures of water (containing 1% NH<sub>3</sub>) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **12** (0.031 g, 19 %) as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 1.59 - 1.62 (2H, m), 1.72 - 1.74 (2H, m), 3.18 (3H, s), 3.72 - 3.76 (8H, m), 6.87 (1H, s), 6.98 (1H, t), 7.09 (1H, t), 7.19 (1H, d), 7.63 (2H, s), 8.07 (1H, d). MS-ESI *m/z* 415 [MH<sup>+</sup>].



**(R)-3-Methyl-4-(6-(1-(methylsulfonyl)cyclopropyl)-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrimidin-4-yl)morpholine (13).** Bis(triphenylphosphine)palladium chloride (42.3 mg, 0.06 mmol), **47** (200 mg, 0.60

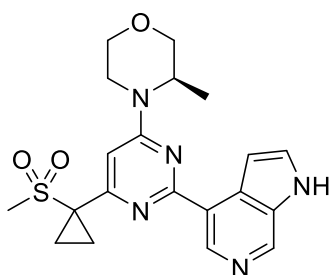
mmol), 1*H*-pyrrolo[2,3-*b*]pyridin-4-ylboronic acid (98 mg, 0.60 mmol) and 2M sodium carbonate (0.90 mL, 1.81 mmol) were suspended in DME:water (4:1) (5 mL) and sealed into a microwave tube. The reaction was heated to 110 °C for 1 hour in the microwave reactor and cooled to room temperature. The reaction mixture was diluted with DCM (10 mL) and washed with water (2 x 10 mL). The organic layer was separated and concentrated *in vacuo*. The resulting material was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures of water (containing 1% NH<sub>3</sub>) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to yield **13** (75 mg, 30%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): 1.39 (3H, d), 1.62 - 1.66 (2H, m), 1.72 - 1.77 (2H, m), 3.28 (3H, s), 3.31 - 3.35 (1H, m), 3.48 - 3.57 (1H, m), 3.65 - 3.71 (1H, m), 3.80 (1H, d), 3.98 - 4.05 (1H, m), 4.24 (1H, d), 4.61 (1H, bs), 6.96 (1H, s), 7.22 (1H, t), 7.59 (1H, t), 7.95 (1H, d), 8.36 (1H, d), and 11.28 (1H, s). MS-ESI *m/z* 414 [MH<sup>+</sup>].



#### 4-(6-(1-(methylsulfonyl)cyclopropyl)-2-(1*H*-pyrrolo[2,3-*c*]pyridin-4-yl)pyrimidin-4-yl)morpholine (**14**).

2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (22.99 mg, 0.05 mmol) and bis(dibenzylideneacetone)palladium(0) (27.7 mg, 0.05 mmol) were added to 4-bromo-1*H*-pyrrolo[2,3-*c*]pyridine (95 mg, 0.48 mmol), potassium acetate (355 mg, 3.62 mmol) and bis(pinacolato)diboron (306 mg, 1.21 mmol) in dioxane (8 mL) under nitrogen. The resulting solution was stirred at 100 °C overnight. LCMS showed very little conversion to product. Further portions of bis(dibenzylideneacetone)palladium(0) (14 mg, 0.025 mmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (22.99 mg, 0.05 mmol) were added and stirring was continued at 100 °C for 5 hours. The reaction mixture was allowed to cool to room temperature, then de-gassed again with a stream of nitrogen. Further portions of bis(dibenzylideneacetone)palladium(0) (14 mg, 0.025 mmol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (22.99 mg, 0.05 mmol) were added and stirring was continued at 95°C for 48 hours. LCMS showed no starting material remaining after this time. Compound **46** (153 mg, 0.48 mmol),

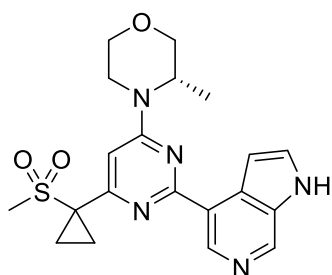
tetrakis(triphenylphosphine)palladium(0) (55.7 mg, 0.05 mmol) and 2M sodium carbonate (0.964 mL, 1.93 mmol) were added and heated at 100 °C for a further 2 hours. The reaction mixture was allowed to cool to room temperature and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH in DCM and pure fractions were evaporated to dryness. The crude product was further purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures of water (containing 1% NH<sub>3</sub>) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **14** (34.0 mg, 18 %) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.59 - 1.65 (2H, m), 1.70 - 1.76 (2H, m), 3.28 (3H, s), 3.73 - 3.80 (8H, m), 6.93 (1H, s), 7.27 (1H, bs), 7.72 (1H, t), 8.84 (1H, s), 9.06 (1H, s), 11.77 (1H, bs). MS-ESI *m/z* 400 [MH<sup>+</sup>]. HRMS-ESI *m/z* 400.1443 [MH<sup>+</sup>] requires C<sub>19</sub>H<sub>21</sub>N<sub>5</sub>O<sub>3</sub>S 400.1454.



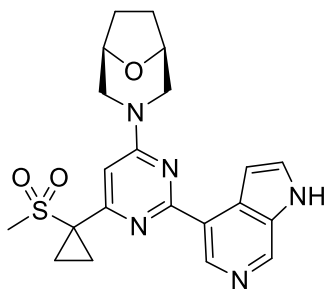
**4-{4-[1-(Methanesulfonyl)cyclopropyl]-6-[(3R)-3-methylmorpholin-4-yl]pyrimidin-2-yl}-1H-**

**pyrrolo[2,3-*c*]pyridine (15).** 1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium (II) (1.309 g, 1.81 mmol) was added to 4-bromo-1H-pyrrolo[2,3-*c*]pyridine (1.78 g, 9.04 mmol), potassium acetate (4.14 g, 42.19 mmol) and bis(pinacolato)diboron (7.65 g, 30.14 mmol) in dioxane (177 mL) under nitrogen. The resulting solution was stirred at 95 °C for 5 days. Compound **47** (2 g, 6.03 mmol), tetrakis(triphenylphosphine)palladium(0) (1.393 g, 1.21 mmol) and sodium carbonate (2M aq.) (24 mL, 48 mmol) were added and the mixture was heated at 95 °C overnight. The reaction mixture was quenched with water (100 mL) and extracted with DCM (3 x 100 mL). The organic layer was passed through a layer of silica eluting first with DCM and then a gradient of 5 to 50% MeOH in DCM. The solvent was evaporated and the residue dissolved in DCM (75 mL). The solution was extracted with 2N HCl (2 x 50 mL) and the aqueous was then basified with NaOH, and extracted with EtOAc (2 x 100 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and then evaporated. The residue was purified by flash chromatography on silica, eluting with

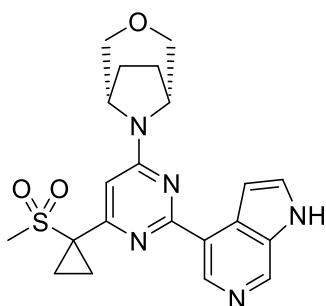
a gradient of 0 to 5% MeOH in DCM. Fractions were evaporated and the residue dissolved in DCM (17 mL) in a small conical flask and placed in a beaker of Et<sub>2</sub>O and acetonitrile (1:1). The system was sealed and left overnight. The resultant solid was collected by filtration and dried under vacuum to afford **15** (0.646 g, 26%); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.39 (3H, d), 1.63 (2H, dd), 1.85 - 1.95 (2H, m), 3.09 (3H, s), 3.39 (1H, td), 3.62 (1H, td), 3.77 (1H, dd), 3.79 - 3.90 (1H, m), 4.07 (1H, dd), 4.16 (1H, d), 4.56 (1H, s), 6.87 (1H, s), 7.42 (1H, d), 7.51 (1H, d), 8.89 (1H, s), 9.04 (1H, s), 9.30 (1H, s). MS-ESI *m/z* 414 [MH<sup>+</sup>].



**4-{4-[1-(Methanesulfonyl)cyclopropyl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl}-1H-pyrrolo[2,3-c]pyridine (16).** A mixture of sodium carbonate (2M aq.) (5.18 mL, 10.37 mmol), tetrakis(triphenylphosphine)palladium(0) (299 mg, 0.26 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-c]pyridine (380 mg, 1.56 mmol) and **48** (430 mg, 1.30 mmol) in dioxane (25 mL) were stirred at 95 °C for 3 hours. The reaction mixture was quenched with water (20 mL) extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and evaporated. The crude product was purified by ion exchange chromatography using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH. The crude product was purified by flash silica chromatography, elution gradient 0 to 10 % MeOH in DCM. Pure fractions were evaporated to dryness to afford a solid which was triturated with diethylether to yield **16** (100 mg, 19%) as a tan coloured solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.27 (3H, d), 1.58 - 1.64 (2H, m), 1.68 - 1.75 (2H, m), 3.22 - 3.30 (4H, m), 3.51 (1H, td), 3.66 (1H, dd), 3.79 (1H, d), 4.00 (1H, dd), 4.19 (1H, s), 4.60 (1H, s), 6.88 (1H, s), 7.26 (1H, s), 7.72 (1H, t), 8.83 (1H, s), 9.06 (1H, s), 11.80 (1H, br s). MS-ESI *m/z* 414 [MH<sup>+</sup>]. HRMS-ESI *m/z* 414.1600 [MH<sup>+</sup>] requires C<sub>20</sub>H<sub>23</sub>N<sub>5</sub>O<sub>3</sub>S 414.1624.

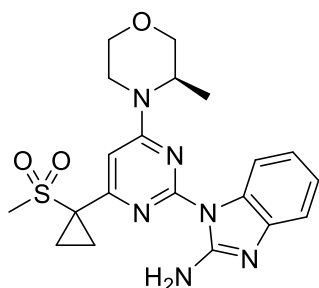


**3-(6-(1-(Methylsulfonyl)cyclopropyl)-2-(1*H*-pyrrolo[2,3-*c*]pyridin-4-yl)pyrimidin-4-yl)-8-oxa-3-azabicyclo[3.2.1]octane (17).** A mixture of sodium carbonate (2M aq.) (2.75 mL, 5.49 mmol), tetrakis(triphenylphosphine)palladium (0) (159 mg, 0.14 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*c*]pyridine (0.156M in dioxane) (5.28 mL, 0.82 mmol) and **44** (236 mg, 0.69 mmol) in dioxane (5 mL) were stirred at 95 °C for 18 hours. The reaction mixture was quenched with water (15 mL), extracted with EtOAc (2 x 10 mL) and the 2 layers filtered through a pad of celite to remove palladium solids and then the organic layer dried over MgSO<sub>4</sub>, filtered and evaporated. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and product fractions were evaporated to dryness to afford a brown gum. The crude product was purified by flash silica chromatography, elution gradient 0 to 10 % MeOH in DCM. Pure fractions were evaporated to dryness to afford **17** (63 mg, 22%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): 1.57 - 1.65 (2H, m), 1.66 - 1.77 (4H, m), 1.82 - 1.92 (2H, m), 3.18 (2H, dd), 3.29 (3H, s), 3.97 - 4.31 (2H, br m), 4.50 (2H, br s), 6.84 (1H, s), 7.25 (1H, t), 7.72 (1H, t), 8.83 (1H, s), 9.04 (1H, s), 11.80 (1H, s). MS-ESI *m/z* 426 [MH<sup>+</sup>]. HRMS-ESI *m/z* 426.1607 [MH<sup>+</sup>] requires C<sub>21</sub>H<sub>23</sub>N<sub>5</sub>O<sub>3</sub>S 426.1607.



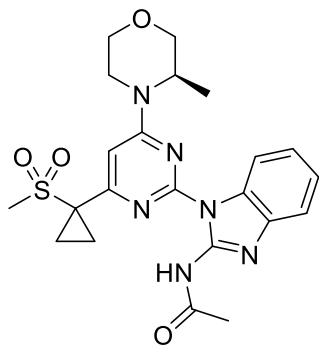
**8-(6-(1-(Methylsulfonyl)cyclopropyl)-2-(1*H*-pyrrolo[2,3-*c*]pyridin-4-yl)pyrimidin-4-yl)-3-oxa-8-azabicyclo[3.2.1]octane (18).** A mixture of sodium carbonate (2M solution) (3.86 mL, 7.72 mmol), tetrakis(triphenylphosphine)palladium (0) (223 mg, 0.19 mmol), **45** (332 mg, 0.97 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*c*]pyridine (6.19 mL, 0.97 mmol) in dioxane (6 mL)

were stirred at 95 °C for 18 hours. The reaction mixture was cooled, filtered through celite and washed with EtOAc. The liquors were diluted with water (20 mL), extracted with EtOAc (2 x 20 mL) and the organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product fraction was eluted from the column using 7M NH<sub>3</sub>/MeOH and evaporated to dryness to afford crude product. This was purified by flash silica chromatography, elution gradient 0 to 10 % MeOH in DCM to yield **18** (76 mg, 19%) as an off-white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.58 - 1.64 (2H, m), 1.69 - 1.74 (2H, m), 1.94 - 2.09 (4H, m), 3.29 (3H, s), 3.67 (4H, q), 4.49 - 4.97 (2H, br m), 6.86 (1H, s), 7.24 (1H, s), 7.70 (1H, t), 8.83 (1H, s), 9.05 (1H, s), 11.75 (1H, s). MS-ESI *m/z* 426 [MH<sup>+</sup>].

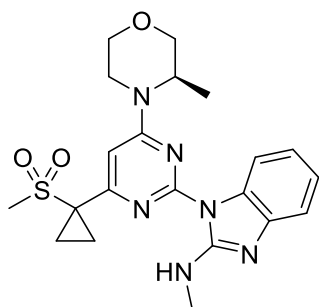


**(R)-1-(4-(3-Methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-**

**benzo[d]imidazol-2-amine (19).** Compound **51** (413 mg, 1.1 mmol), 1*H*-benzo[*d*]imidazol-2-amine (161 mg, 1.21 mmol) and cesium carbonate (717 mg, 2.20 mmol) were suspended in DMA (5 mL) and sealed into a microwave tube. The reaction was heated to 110 °C for 1 hour in the microwave reactor and cooled to room temperature. Water (20 mL) was added and the mixture extracted with EtOAc (2 x 20mL). The combined organics were dried over MgSO<sub>4</sub>, filtered then concentrated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 0 to 10 % MeOH in DCM . Pure fractions were evaporated to dryness to afford **19** (421 mg, 89 %) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.31 (d, 3H), 1.59 - 1.63 (m, 2H), 1.72 - 1.76 (m, 2H), 3.18 (s, 3H), 3.36 (dd, 1H), 3.53 (dt, 1H), 3.68 (dd, 1H), 3.81 (d, 1H), 4.02 (dd, 1H), 4.08 - 4.15 (m, 1H), 4.47 - 4.56 (brm, 1H), 6.83 (s, 1H), 6.98 (t, 1H), 7.09 (t, 1H), 7.20 (d, 1H), 7.61 (s, 2H), 8.09 (d, 1H). MS-ESI *m/z* 429 [MH<sup>+</sup>]. HRMS-ESI *m/z* 429.1709 [MH<sup>+</sup>] requires C<sub>20</sub>H<sub>24</sub>N<sub>6</sub>O<sub>3</sub>S 429.1712.

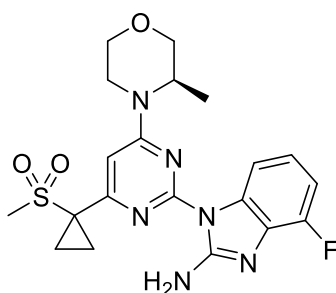


**(R)-N-(1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-benzo[d]imidazol-2-yl)acetamide (20).** DMAP (91 mg, 0.75 mmol) was added to **19** (320 mg, 0.75 mmol) in acetic anhydride (4 mL) and the resulting mixture was stirred at 90 °C for 3 hours. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in DCM (10 mL) and washed sequentially with saturated NaHCO<sub>3</sub> (10 mL), water (10 mL) and saturated brine (10 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 0 to 10 % MeOH in DCM. Pure fractions were evaporated to dryness to yield the diacetylated product which was dissolved in DCM (10 mL) and treated with 7M NH<sub>3</sub> in MeOH (2 mL) for 5 minutes. The mixture was concentrated *in vacuo* and purified by flash silica chromatography, elution gradient 0 to 10 % MeOH in DCM. Pure fractions were evaporated and triturated with ether to afford **20** (140 mg, 39.8 %) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 1.32 (d, 3H), 1.59 - 1.63 (m, 2H), 1.71 - 1.75 (m, 2H), 2.29 (s, 3H), 3.19 (dd, 3H), 3.34 - 3.38 (dt, 1H), 3.49 - 3.56 (m, 1H), 3.67 (dd, 1H), 3.80 (d, 1H), 4.02 (dd, 1H), 4.15 (d, 1H), 4.48 - 4.58 (m, 1H), 6.98 (s, 1H), 7.25 - 7.31 (m, 2H), 7.57 - 7.61 (m, 1H), 8.13 - 8.16 (m, 1H), 11.43 (s, 1H). MS-ESI *m/z* 471 [MH<sup>+</sup>]. HRMS-ESI *m/z* 471.1814 [MH<sup>+</sup>] requires C<sub>22</sub>H<sub>26</sub>N<sub>6</sub>O<sub>4</sub>S 471.1845.



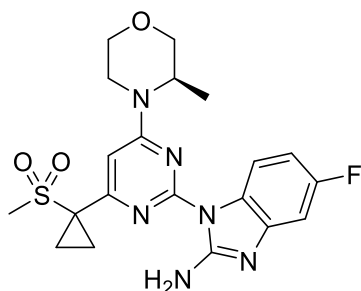
**N-Methyl-1-{4-[(3R)-3-methylmorpholin-4-yl]-6-[1-(methylsulfonyl)cyclopropyl]pyrimidin-2-yl}-1H-benzimidazol-2-amine (21).** Compound **51** (4.595 g, 12.24 mmol) was added to *N*-methyl-1H-

benzo[d]imidazol-2-amine (1.981 g, 13.46 mmol) and cesium carbonate (3.99 g, 12.24 mmol) in DMA (50 mL). The resulting suspension was stirred at 90 °C for 18 hours. The reaction mixture was filtered and the solvent removed under reduced pressure. The reaction mixture was diluted with EtOAc (150 mL) and washed sequentially with water (2 x 100 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated. The residue was purified by flash chromatography on silica, eluting with a gradient of 0 to 5% MeOH in DCM. Pure fractions were evaporated to afford an oil which was triturated with MTBE (20 mL) to give a white solid. The solid was purified by crystallisation from EtOAc/*iso*-hexane to afford **21** (2.824 g, 52%). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.29 (3H, d), 1.59 - 1.68 (2H, m), 1.71 - 1.80 (2H, m), 3.04 (3H, d), 3.17 (3H, s), 3.31 (1H, s), 3.51 (1H, td), 3.66 (1H, dd), 3.80 (1H, d), 4.01 (1H, dd), 4.12 (1H, d), 4.53 (1H, s), 6.72 (1H, s), 6.95 - 7.02 (1H, m), 7.09 (1H, t), 7.26 (1H, d), 8.10 (1H, d), 8.57 - 8.65 (1H, m). MS-ESI *m/z* 443 [MH<sup>+</sup>]. HRMS-ESI *m/z* 443.1865 [MH<sup>+</sup>] requires C<sub>21</sub>H<sub>26</sub>N<sub>6</sub>O<sub>3</sub>S 443.1875.

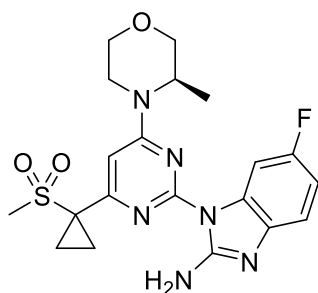


**(R)-4-Fluoro-1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-benzo[d]imidazol-2-amine (22)**. Cyanic bromide (115 mg, 1.09 mmol) was added to **61** (383 mg, 0.91 mmol) in MeOH (10 mL) and the resulting mixture was stirred at room temperature for 40 hours. The mixture was quenched with 1N NaOH (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (10 mL) then purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and product fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford **22** (351mg, 87%). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 1.30 (3H, d), 1.60 - 1.63 (2H, m), 1.72 - 1.75 (2H, m), 3.17 (3H, s), 3.35 (1H, dd), 3.53 (1H, dt), 3.66 (1H, dd), 3.80 (1H, d), 4.01 (1H, dd), 4.08 - 4.15 (1H, m), 4.47 - 4.54 (1H, m), 6.85

(1H, s), 6.92 - 6.97 (2H, m), 7.77 (2H, s), 7.91 - 7.94 (1H, m). MS-ESI  $m/z$  447 [MH<sup>+</sup>]. HRMS-ESI  $m/z$  447.1615 [MH<sup>+</sup>] requires C<sub>20</sub>H<sub>23</sub>FN<sub>6</sub>O<sub>3</sub>S 447.1618.

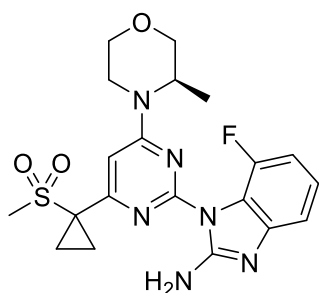


**(R)-5-Fluoro-1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-benzo[d]imidazol-2-amine (23).** Cyanogen bromide (56.7 mg, 0.54 mmol) was added to **62** (188 mg, 0.45 mmol) in MeOH (5 mL). The resulting mixture was stirred at room temperature for 18 hours then the mixture was washed with 1N NaOH and extracted with EtOAc (2 x 10 mL). The organic layer was separated then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 0 to 10 % MeOH in DCM. Pure fractions were evaporated to dryness to afford **23** (97 mg, 49%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.29 (3H, d), 1.58 - 1.64 (2H, m), 1.71 - 1.75 (2H, m), 3.17 (3H, s), 3.29 - 3.32 (1H, m), 3.53 (1H, td), 3.67 (1H, dd), 3.80 (1H, d), 4.01 (1H, dd), 4.08 - 4.13 (1H, m), 4.46 - 4.54 (1H, m), 6.78 (1H, td), 6.83 (1H, s), 6.98 (1H, dd), 7.83 (2H, s), 8.05 (1H, dd). MS-ESI  $m/z$  447 [MH<sup>+</sup>]. HRMS-ESI  $m/z$  447.1615 [MH<sup>+</sup>] requires C<sub>20</sub>H<sub>23</sub>FN<sub>6</sub>O<sub>3</sub>S 447.1618.

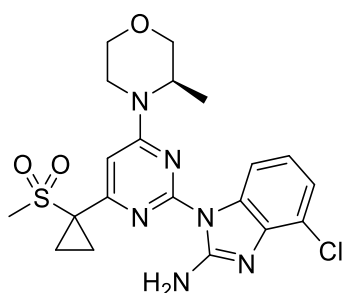


**(R)-6-Fluoro-1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-benzo[d]imidazol-2-amine (24).** Cyanic bromide (138 mg, 1.30 mmol) was added to **63** (456 mg, 1.08 mmol) in MeOH (10 mL) and the resulting mixture was stirred at room temperature for 4 hours. The reaction was quenched with 1M aq NaOH solution (2 mL) followed by the addition of more water and the product was then extracted into ethyl acetate (2 x 50mL). The organic layers were combined and washed with water (2 x 20 mL), brine (20 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to afford crude product.

The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford **24** (310 mg, 64%) as a pale pink solid after trituration with diethyl ether. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.32 (3H, d), 1.59 - 1.63 (2H, m), 1.73 - 1.76 (2H, m), 3.17 (3H, s), 3.35 (1H, td), 3.53 (1H, td), 3.67 (1H, dd), 3.81 (1H, d), 4.02 (1H, dd), 4.07 - 4.11 (1H, m), 4.48 - 4.53 (1H, m), 6.85 (1H, s), 6.93 (1H, dt), 7.16 (1H, dd), 7.60 - 7.62 (2H, m), 7.89 (1H, dd). MS-ESI *m/z* 447 [MH<sup>+</sup>]. HRMS-ESI *m/z* 447.1615 [MH<sup>+</sup>] requires C<sub>20</sub>H<sub>23</sub>FN<sub>6</sub>O<sub>3</sub>S 447.1618.

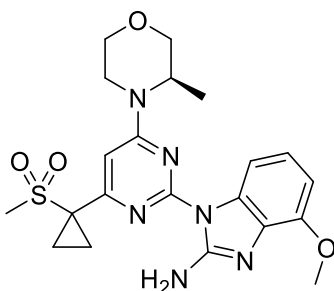


**(R)-7-Fluoro-1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-benzo[d]imidazol-2-amine (25)**. Cyanic bromide (0.066 g, 0.63 mmol) was added **64** (0.176 g, 0.42 mmol) in MeOH (10 mL) and the resulting mixture was stirred at room temperature for 50 hours. The reaction was quenched with NaOH (1M aq.) (2 mL) followed by the addition of more water and the product was then extracted into EtOAc (2 x 50mL). The organic layers were combined and washed with water (2 x 20 mL), brine (20 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% formic acid) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **25** (0.163 g, 87%) as a beige solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.25 (3H, d), 1.59 - 1.68 (2H, m), 1.68 - 1.77 (2H, m), 3.18 (3H, s), 3.23 (1H, td), 3.45 (1H, td), 3.59 (1H, dd), 3.74 (1H, d), 3.95 (1H, dd), 4.13 (1H, bs), 4.50 (1H, bs), 6.75 - 6.82 (1H, m), 6.83 (1H, s), 7.02 - 7.10 (2H, m), 7.24 (1H, s), 8.16 (1H, s). MS-ESI *m/z* 447 [MH<sup>+</sup>]. HRMS-ESI *m/z* 447.1615 [MH<sup>+</sup>] requires C<sub>20</sub>H<sub>23</sub>FN<sub>6</sub>O<sub>3</sub>S 447.1618.



**(R)-4-Chloro-1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-**

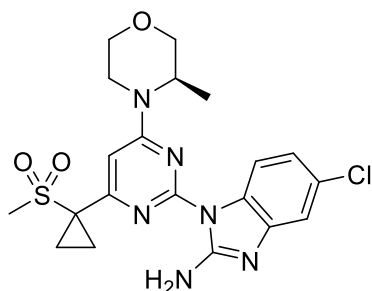
**benzo[d]imidazol-2-amine (26).** Cyanic bromide (0.278 g, 2.62 mmol) was added to **65** (0.270 g, 0.62 mmol) in MeOH (10 mL) and the resulting mixture was stirred at room temperature for 35 hours. The reaction mixture was diluted with EtOAc then washed with dilute NaOH (aq.). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and evaporated. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% formic acid) and MeCN as eluents. The fractions containing desired product were combined and evaporated to dryness to yield **26** (68 mg, 24%) as a light pink solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.29 (3H, d), 1.57 - 1.64 (2H, m), 1.69 - 1.76 (2H, m), 3.16 (3H, s), 3.30 (1H, td), 3.52 (1H, td), 3.66 (1H, dd), 3.79 (1H, d), 4.01 (1H, dd), 4.06 - 4.15 (1H, m), 4.49 (1H, br s), 6.84 (1H, s), 6.97 (1H, t), 7.15 (1H, d), 7.90 (2H, s), 8.04 (1H, d). MS-ESI *m/z* 463, 465 [MH<sup>+</sup>]. HRMS-ESI *m/z* 463.1319 [MH<sup>+</sup>] requires C<sub>20</sub>H<sub>23</sub>ClN<sub>6</sub>O<sub>3</sub>S 463.1306.



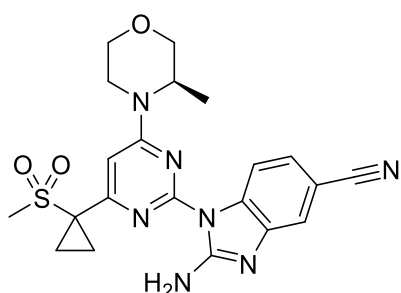
**(R)-4-Methoxy-1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-**

**benzo[d]imidazol-2-amine (27).** Cyanic bromide (84 mg, 0.79 mmol) was added to **66** (285 mg, 0.66 mmol) in MeOH (8 mL) and the resulting mixture was stirred at room temperature for 40 hours. The mixture was quenched with 1N NaOH (aq.) (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water (10 mL) and then purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and product fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford **27** (236 mg, 78 %) as a pale yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.30 (3H, d), 1.59 - 1.62 (2H, m), 1.72 - 1.75 (2H, m), 3.17 (3H, s), 3.34 (1H, dd), 3.52 (1H, td), 3.67 (1H, dd), 3.80 (1H, d), 3.89 (3H, s), 4.01 (1H, dd), 4.08 - 4.14

(1H, m), 4.48 - 4.54 (1H, m), 6.72 (1H, d), 6.83 (1H, s), 6.91 (1H, t), 7.48 (2H, s), 7.73 (1H, d). MS-ESI  $m/z$  459  $[MH^+]$ . HRMS-ESI  $m/z$  459.1814  $[MH^+]$  requires  $C_{21}H_{26}N_6O_4S$  459.1823.

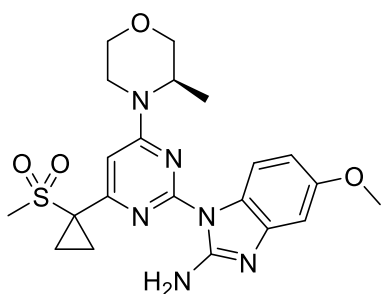


**(R)-5-Chloro-1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-benzo[d]imidazol-2-amine (28).** Cyanic bromide (143 mg, 1.35 mmol) was added to **67** (493 mg, 1.13 mmol) in MeOH (10 mL) and the resulting mixture was stirred at room temperature for 18 hours. Reaction quenched with NaOH (1M aq.) (2 mL) followed by the addition of more water and extracted into EtOAc (2 x 50 mL). The organic layers were combined and washed with water (2 x 20 mL) and brine (20 mL). The combined organic layers were dried over  $MgSO_4$ , filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **28** (291 mg, 56%) as an off white solid after trituration with ether.  $^1H$  NMR (400 MHz, DMSO- $d_6$ ): 1.30 (3H, d), 1.58 - 1.63 (2H, m), 1.72 - 1.75 (2H, m), 3.16 (3H, s), 3.32 - 3.37 (1H, m), 3.52 (1H, td), 3.67 (1H, dd), 3.79 (1H, d), 4.01 (1H, dd), 4.08 - 4.11 (1H, m), 4.45 - 4.54 (1H, m), 6.83 (1H, s), 6.99 (1H, dd), 7.20 (1H, d), 7.81 (2H, s), 8.06 (1H, d). MS-ESI  $m/z$  463, 465  $[MH^+]$ . HRMS-ESI  $m/z$  463.1319  $[MH^+]$  requires  $C_{20}H_{23}ClN_6O_3S$  463.1350.

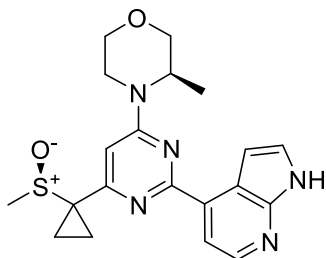


**(R)-2-Amino-1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-benzo[d]imidazole-5-carbonitrile (29).** Cyanic bromide (113 mg, 1.06 mmol) was added to **68** (380 mg, 0.89 mmol) in MeOH (10 mL) and the resulting mixture was stirred at room temperature for 40 hours. The mixture was quenched with NaOH (1N aq.) (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic

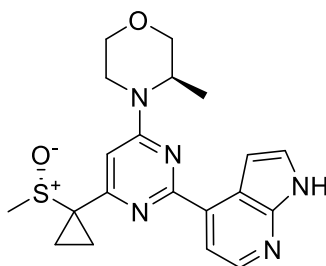
layers were washed with water (10 mL) then purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and product fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford **29** (162 mg, 40%) as an off white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.30 (3H, d), 1.61 - 1.64 (2H, m), 1.72 - 1.76 (2H, m), 3.17 (3H, s), 3.35 (1H, dd), 3.53 (1H, td), 3.67 (1H, dd), 3.80 (1H, d), 4.01 (1H, dd), 4.07 - 4.14 (1H, m), 4.46 - 4.54 (1H, m), 6.87 (1H, s), 7.40 (1H, dd), 7.60 (1H, d), 7.92 (2H, s), 8.20 (1H, d). MS-ESI *m/z* 454 [MH<sup>+</sup>]. HRMS-ESI *m/z* 454.1661 [MH<sup>+</sup>] requires C<sub>21</sub>H<sub>23</sub>N<sub>7</sub>O<sub>3</sub>S 454.1639.



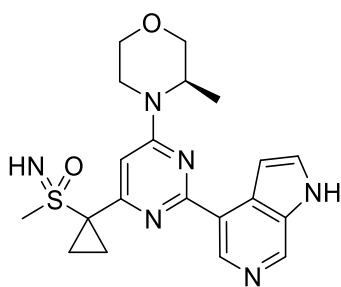
**(R)-5-Methoxy-1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)-1H-benzo[d]imidazol-2-amine (30)**. Cyanic bromide (0.143 g, 1.35 mmol) was added to **69** (0.390 g, 0.90 mmol) in MeOH (20 mL) and the resulting mixture was stirred at room temperature for 35 hours. The mixture was quenched with NaOH (1N aq.) (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water (10 mL) then purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and product fractions were evaporated to dryness to afford crude product. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH<sub>3</sub>) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford **30** (330 mg, 80%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.29 (3H, d), 1.54 - 1.62 (2H, m), 1.72 (2H, dd), 3.15 (3H, s), 3.30 - 3.36 (1H, m), 3.52 (1H, td), 3.66 (1H, dd), 3.75 (3H, s), 3.78 (1H, t), 4.00 (1H, dd), 4.08 (1H, d), 4.49 (1H, s), 6.56 (1H, dd), 6.76 (1H, d), 6.78 (1H, d), 7.66 (2H, s), 7.97 (1H, d). MS-ESI *m/z* 459 [MH<sup>+</sup>].



**(R)-3-Methyl-4-(6-(1-((R)-methylsulfinyl)cyclopropyl)-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrimidin-4-yl)morpholine (31).** X-Phos 2nd generation Buchwald precatalyst (0.182 g, 0.23 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (1.00 g, 4.10 mmol), **R-73** (1.46 g, 4.62 mmol) and cesium carbonate (3.01 g, 9.25 mmol) in degassed 1,4-dioxane (40 mL) and water (10 mL) under nitrogen. The resulting solution was stirred at 90 °C for 60 minutes. The reaction mixture was evaporated to remove the organic solvent then diluted with EtOAc (100 mL) and washed with water (100 mL). The organic layer was dried with MgSO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 25 to 100% 3:1 EtOAc/EtOH in heptane. Pure fractions were evaporated to dryness to afford **31** as an off white solid. The product was purified by crystallisation from *n*-butanol/heptane to afford **31** (0.988 g, 53%) as a white crystalline solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.38 (d, J = 6.8 Hz, 3H), 1.49 - 1.6 (m, 3H), 1.67 - 1.79 (m, 1H), 2.67 (s, 3H), 3.38 (td, J = 3.9, 12.8 Hz, 1H), 3.57 - 3.68 (m, 1H), 3.77 (dd, J = 3.0, 11.5 Hz, 1H), 3.86 (d, J = 11.5 Hz, 1H), 4.08 (dd, J = 3.8, 11.5 Hz, 1H), 4.16 (d, J = 12.8 Hz, 1H), 4.53 (s, 1H), 6.50 (s, 1H), 7.36 (dd, J = 1.7, 3.4 Hz, 1H), 7.51 (dd, J = 2.2, 3.3 Hz, 1H), 8.08 (d, J = 5.1 Hz, 1H), 8.46 (d, J = 5.1 Hz, 1H), 11.07 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) 10.27, 12.81, 13.64, 37.30, 39.38, 43.35, 47.22, 66.76, 71.00, 98.99, 102.70, 115.50, 118.76, 126.43, 137.80, 142.38, 150.49, 162.03, 163.37, 163.87. HRMS-ESI *m/z* 398.1656 [MH<sup>+</sup>] C<sub>20</sub>H<sub>23</sub>N<sub>5</sub>O<sub>2</sub>S requires 398.1651. Chiral HPLC: (HP1100 system 4, 5 μm Chiralpak AS-H (250 mm × 4.6 mm) column, eluting with heptane/EtOH/MeOH 2:1:1) *R<sub>f</sub>* = 2.51, >99%.



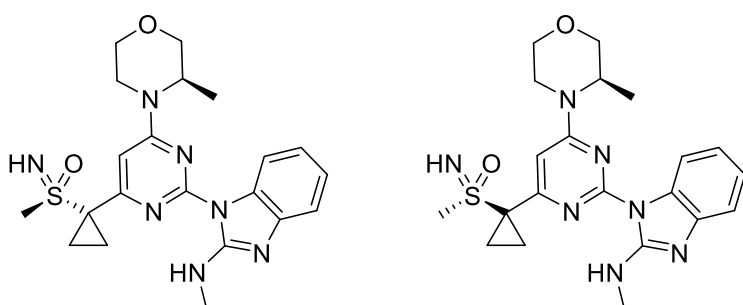
**(R)-3-Methyl-4-(6-(1-((S)-methylsulfinyl)cyclopropyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)pyrimidin-4-yl)morpholine (32).** X-Phos 2nd generation Buchwald precatalyst (0.055 g, 0.07 mmol) was added to 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (0.340 g, 1.39 mmol), **S-73** (0.44 g, 1.39 mmol) and cesium carbonate (0.908 g, 2.79 mmol) in degassed 1,4-dioxane (40 mL) and water (10 mL) under nitrogen. The resulting solution was stirred at 90 °C for 60 minutes. The reaction mixture was evaporated to remove the organic solvent then diluted with EtOAc (100 mL) and washed with water (100 mL). The organic layer was dried with MgSO<sub>4</sub>, filtered and evaporated. The residue was purified by flash chromatography on silica, eluting with a gradient of 25 to 100% 3:1 EtOAc/EtOH in heptane. Pure fractions were evaporated to dryness to afford **32** (0.371 g, 67%) as an off white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 1.39 (d, *J* = 6.8 Hz, 3H), 1.49 – 1.62 (m, 3H), 1.73 (ddd, *J* = 2.6, 4.2, 11.2 Hz, 1H), 2.66 (s, 3H), 3.38 (td, *J* = 3.9, 12.8 Hz, 1H), 3.63 (td, *J* = 3.1, 11.9 Hz, 1H), 3.78 (dd, *J* = 3.0, 11.5 Hz, 1H), 3.87 (d, *J* = 11.4 Hz, 1H), 4.04 – 4.11 (m, 1H), 4.12 – 4.21 (d, 1H), 4.53 (s, 1H), 6.51 (s, 1H), 7.36 (dd, *J* = 1.1, 3.3 Hz, 1H), 7.51 (dd, *J* = 1.7, 3.3 Hz, 1H), 8.08 (d, *J* = 5.1 Hz, 1H), 8.45 (d, *J* = 5.2 Hz, 1H), 11.03 (s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) 10.23, 12.85, 13.63, 37.27, 39.39, 43.32, 47.23, 66.74, 71.01, 98.97, 102.69, 115.50, 118.75, 126.42, 137.80, 142.36, 150.45, 162.05, 163.37, 163.86. HRMS-ESI *m/z*: 398.1656 [MH<sup>+</sup>] C<sub>20</sub>H<sub>24</sub>N<sub>5</sub>O<sub>2</sub>S requires 398.1651. Chiral HPLC: (HP1100 system 4, 5 μm Chiralpak AS-H (250 mm × 4.6 mm) column, eluting with heptane/EtOH/MeOH 2:1:1) *R<sub>f</sub>* = 3.424, >99%.



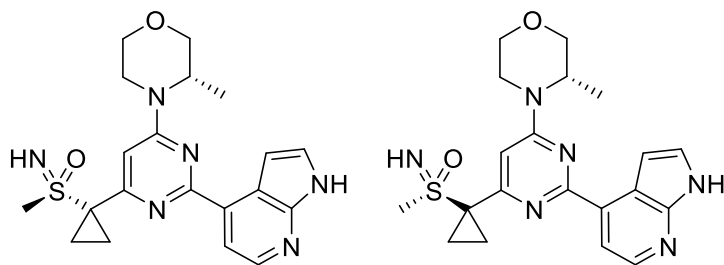
**4-{4-[(3*R*)-3-Methylmorpholin-4-yl]-6-[1-(*S*-methylsulfonyl)cyclopropyl]pyrimidin-2-yl}-1*H*-pyrrolo[2,3-*c*]pyridine (34).** 1,1'-Bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.906 g, 1.25 mmol) was added to *tert*-butyl 4-bromo-1*H*-pyrrolo[2,3-*c*]pyridine-1-carboxylate (1.24 g, 4.17 mmol), potassium acetate (2.87 g, 29.21 mmol) and bis(pinacolato)diboron (4.73 g, 18.63 mmol) in 1,4-dioxane (100 mL) under nitrogen. The resulting solution was stirred at reflux for 3 days to afford an approximate 2:1 mixture

of boc to de-boc product. To this mixture was added dichlorobis(triphenylphosphine)palladium(II) (0.017 g, 0.02 mmol), compound **75SR** (0.318 g, 0.96 mmol), 2M aqueous sodium carbonate solution (0.577 mL, 1.15 mmol) under nitrogen. The reaction mixture was stirred at 90 °C for 6 hours. The reaction mixture was concentrated, diluted with EtOAc (400 mL), and then washed sequentially with water (300 mL) and saturated brine (75 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and then evaporated directly onto silica (30 g). The resulting powder was purified by flash chromatography on silica, eluting with a gradient of 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford *tert*-butyl 4-(4-((*R*)-3-methylmorpholino)-6-(1-(*S*-methylsulfonimidoyl)cyclopropyl)pyrimidin-2-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-1-carboxylate (0.227 g, 46%); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 1.28 (3H, d), 1.40 - 1.61 (3H, m), 1.68 (9H, s), 1.76 (1H, dd), 3.09 (3H, d), 3.24 (1H, m), 3.52 (1H, t), 3.67 (1H, dd), 3.79 (2H, d), 4.00 (1H, dd), 4.19 (1H, s), 4.56 (1H, s), 7.00 (1H, d), 7.57 (1H, d), 8.00 (1H, d), 9.25 (1H, s), 9.37 (1H, s); MS-ESI *m/z* 513 [MH<sup>+</sup>].

*Tert*-butyl 4-(4-((*R*)-3-methylmorpholino)-6-(1-(*S*-methylsulfonimidoyl)cyclopropyl)pyrimidin-2-yl)-1*H*-pyrrolo[2,3-*c*]pyridine-1-carboxylate (0.223 g, 0.44 mmol) was added to TFA (5 mL) and DCM (5 mL). The resulting solution was stirred at room temperature for 1 hour. The reaction mixture was evaporated and the residue was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH<sub>3</sub>) and MeCN as eluents. Fractions containing the desired compound were evaporated and the residue was triturated with diethylether to give a solid which was collected by filtration and dried under vacuum to afford **34** (0.086 g, 48%); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 1.29 (3H, d), 1.40 - 1.60 (3H, m), 1.76 (1H, d), 3.11 (3H, s), 3.12 - 3.21 (1H, m), 3.53 (1H, t), 3.68 (1H, d), 3.80 (2H, d), 4.01 (1H, d), 4.20 (1H, s), 4.58 (1H, s), 6.95 (1H, d), 7.28 (1H, s), 7.71 (1H, s), 8.83 (1H, s), 9.08 (1H, s), 11.75 (1H, s); MS-ESI *m/z* 413 [MH<sup>+</sup>].



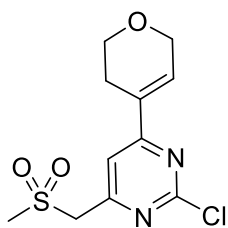
***N*-Methyl-1-{4-[(3*R*)-3-methylmorpholin-4-yl]-6-[1-((*R*)-*S*-methylsulfonimidoyl)cyclopropyl]pyrimidin-2-yl}-1*H*-benzimidazol-2-amine (35) and *N*-Methyl-1-{4-[(3*R*)-3-methylmorpholin-4-yl]-6-[1-((*S*)-*S*-methylsulfonimidoyl)cyclopropyl]pyrimidin-2-yl}-1*H*-benzimidazol-2-amine (36).** Cesium carbonate (942 mg, 2.89 mmol) was added to **75SR** (319 mg, 0.96 mmol) and *N*-methyl-1*H*-benzo[*d*]imidazol-2-amine (284 mg, 1.93 mmol) in DMA (10 mL). The resulting suspension was stirred at 80 °C for 45 hours. A further portion of *N*-methyl-1*H*-benzo[*d*]imidazol-2-amine (284 mg, 1.93 mmol), cesium carbonate (942 mg, 2.89 mmol) and sodium methanesulfinate (98 mg, 0.96 mmol) were added and the suspension was stirred at 80 °C for 70 hours. The reaction mixture was filtered and then evaporated. The residue was dissolved in EtOAc (250 mL) and washed sequentially with water (250 mL) and saturated brine (75 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated onto silica gel (5 g). The resulting powder was purified by flash chromatography on silica, eluting with a gradient of 0 to 5% MeOH in DCM. Pure fractions were evaporated and the residue was purified by preparative chiral chromatography on a Merck 50mm, 20µm Chiralpak AS column, eluting isocratically with 70% *iso*-hexane in IPA (modified with Et<sub>3</sub>N) as eluent. The fractions containing the desired compound were evaporated to afford **36** (166 mg, 39%) as the first eluting compound. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): 1.29 (3H, d), 1.47 (2H, dq), 1.55 - 1.66 (1H, m), 1.69 - 1.89 (1H, m), 3.01 (3H, s), 3.04 (3H, d), 3.30 - 3.39 (1H, m), 3.52 (1H, td), 3.66 (1H, dd), 3.80 (1H, d), 3.95 (1H, s), 4.01 (1H, dd), 4.09 (1H, d), 4.51 (1H, s), 6.77 (1H, s), 6.97 (1H, t), 7.08 (1H, t), 7.25 (1H, d), 8.08 (1H, d), 8.67 (1H, d). MS-ESI *m/z* 442 [MH<sup>+</sup>]. Chiral HPLC: (HP1100 System 4, 20µm Chiralpak AS (250mm x 4.6mm) column eluting with *iso*-hexane/IPA/TEA 70/30/0.1) R<sub>f</sub>, 12.219 >99% and compound **35**: (123 mg, 29%) as the second eluting compound. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): 1.33 (3H, t), 1.45 - 1.61 (2H, m), 1.61 - 1.68 (1H, m), 1.80 - 1.89 (1H, m), 3.07 (3H, s), 3.09 (3H, d), 3.39 (1H, dd), 3.58 (1H, td), 3.72 (1H, dd), 3.86 (1H, d), 4.01 (1H, s), 4.06 (1H, dd), 4.15 (1H, d), 4.55 (1H, s), 6.82 (1H, s), 7.03 (1H, t), 7.14 (1H, t), 7.31 (1H, d), 8.14 (1H, d), 8.73 (1H, d). MS-ESI *m/z* 442 [MH<sup>+</sup>]. Chiral HPLC: (HP1100 System 4, 20µm Chiralpak AS (250mm x 4.6mm) column eluting with *iso*-hexane/IPA/TEA 70/30/0.1) R<sub>f</sub>, 25.093 >99%.



**Compounds (37) and (38):** 4-{4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-((*R*)-*S*-methylsulfonimidoyl)cyclopropyl]pyrimidin-2-yl}-1*H*-pyrrolo[2,3-*b*]pyridine, and 4-{4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-((*S*)-*S*-methylsulfonimidoyl)cyclopropyl]pyrimidin-2-yl}-1*H*-pyrrolo[2,3-*b*]pyridine. Bis(triphenylphosphine)palladium(II)chloride (0.053 g, 0.08 mmol) was added to **79** (0.50 g, 1.51 mmol), 1*H*-pyrrolo[2,3-*b*]pyridin-4-ylboronic acid (0.367 g, 2.27 mmol) and sodium carbonate (2M aq.) (2.23 mL, 4.46 mmol) in degassed DME:H<sub>2</sub>O (4:1) (10 mL) under nitrogen. The resulting suspension was stirred at 90 °C for 2 hours. The reaction mixture was allowed to cool to room temperature then filtered. Reverse phase silica gel (2 g) was added to the filtrate and the solvent removed in vacuo. The resulting powder was purified by flash reverse phase chromatography, eluting with a gradient of 20 to 40% acetonitrile in water with 1% ammonium hydroxide as modifier. Pure fractions were evaporated to dryness to afford 4-{4-[(3*S*)-3-methylmorpholin-4-yl]-6-[1-(*S*-methylsulfonimidoyl)cyclopropyl]pyrimidin-2-yl}-1*H*-pyrrolo[2,3-*b*]pyridine (0.433 g, 70%) as a yellow crystalline solid. <sup>1</sup>H NMR (400 MHz, DMSO, 22°C) 1.28 (3H, d), 1.38 – 1.61 (3H, m), 1.71 – 1.82 (1H, m), 3.11 (3H, s), 3.28 (1H, td), 3.52 (1H, t), 3.67 (1H, dd), 3.75 – 3.87 (2H, m), 4.01 (1H, dd), 4.21 (1H, s), 4.58 (1H, s), 7.00 (1H, d), 7.23 (1H, d), 7.59 (1H, d), 7.95 (1H, d), 8.34 (1H, d), 11.81 (1H, s). MS-ESI *m/z* 413 [MH<sup>+</sup>].

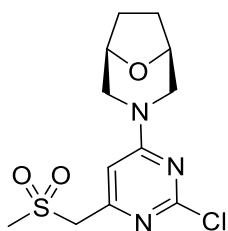
4-{4-[(3*S*)-3-Methylmorpholin-4-yl]-6-[1-(*S*-methylsulfonimidoyl)cyclopropyl]pyrimidin-2-yl}-1*H*-pyrrolo[2,3-*b*]pyridine (0.427 g, 1.04 mmol) was purified by preparative HPLC (Chiralcel AD 50mm x 250mm), using Heptane/EtOH/MeOH/TEA 70/15/15/0.1 as eluent. The fractions containing product were evaporated. Each sample was stirred in MTBE (2 mL) for 5 days and the resulting solids isolated by filtration. First eluting compound (140 mg, 33%); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) 1.29 (3H, d), 1.43 – 1.58 (3H, m), 1.73 – 1.8 (1H, m), 3.11 (3H, d), 3.25 (1H, d), 3.53 (1H, td), 3.67 (1H, dd), 3.81 (2H, d), 4.02 (1H, dd), 4.22 (1H, d), 4.57 (1H, s), 7.00 (1H, s), 7.23 (1H, dd), 7.57 – 7.61 (1H, m), 7.95 (1H, d), 8.34 (1H, d), 11.75 (1H, s); <sup>13</sup>C NMR (176 MHz, DMSO, 27°C) 11.28, 12.27, 13.35, 38.93, 41.17, 46.52, 47.88, 66.03, 70.20, 101.57,

102.83, 114.62, 117.75, 127.27, 136.73, 142.25, 150.17, 161.93, 162.68, 163.26; MS-ESI  $m/z$  413 [ $MH^+$ ]. Chiral HPLC: (HP1100 system 4, 20  $\mu m$  Chiralpak AS-H (250 mm  $\times$  4.6 mm) column, eluting with heptane/(EtOH/MeOH) 70/30 TEA 0.1%)  $R_f$  = 8.498 min, 100%. Second eluting compound (175 mg, 41%);  $^1H$  NMR (400 MHz, DMSO, 30°C) 1.29 (3H, d), 1.41 – 1.62 (3H, m), 1.72 – 1.8 (1H, m), 3.11 (3H, d), 3.25 (1H, d), 3.53 (1H, td), 3.68 (1H, dd), 3.77 – 3.86 (2H, m), 4.02 (1H, dd), 4.20 (1H, d), 4.60 (1H, s), 7.01 (1H, s), 7.23 (1H, d), 7.56 – 7.61 (1H, m), 7.95 (1H, d), 8.34 (1H, d), 11.76 (1H, s).  $^{13}C$  NMR (176 MHz, DMSO, 30°C) 11.32, 12.26, 13.43, 38.96, 41.19, 46.52, 47.85, 66.02, 70.24, 101.57, 102.86, 114.62, 117.75, 127.27, 136.74, 142.25, 150.17, 161.94, 162.67, 163.26. MS-ESI  $m/z$  413 [ $MH^+$ ]. Chiral HPLC: (HP1100 system 4, 20  $\mu m$  Chiralpak AS-H (250 mm  $\times$  4.6 mm) column, eluting with heptane/(EtOH/MeOH) 70/30 TEA 0.1%)  $R_f$  = 14.052 min, 100%.

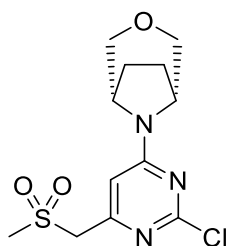


**2-Chloro-4-(3,6-dihydro-2H-pyran-4-yl)-6-(methylsulfonylmethyl)pyrimidine (40).**

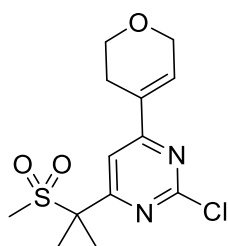
Tetrakis(triphenylphosphine)palladium(0) (0.28 g, 0.24 mmol) was added to **39** (1.5 g, 6.22 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 g, 5.71 mmol) and cesium carbonate (7.37 g, 22.62 mmol) in degassed 1,4-dioxane (60 mL) and water (10 mL) under nitrogen. The resulting suspension was stirred at room temperature for 12 hours. The reaction mixture was diluted with EtOAc (50 mL) and washed sequentially with water (250 mL) and saturated brine (250 mL). The organic layer was dried with  $Na_2SO_4$ , filtered and evaporated to afford crude product. The crude product was purified by flash neutral alumina chromatography, eluting with 40% EtOAc in petroleum ether. Pure fractions were evaporated to dryness to afford **40** (1.200 g, 66%) as a white solid.  $^1H$  NMR (400 MHz,  $CDCl_3$ ): 2.59 (m, 2H), 3.01 (s, 3H), 3.93 (m, 2H), 4.37 (s, 2H), 4.41 (d, 2H), 7.16 (t, 1H), 7.40 (s, 1H). MS-ESI  $m/z$  289, 291 [ $MH^+$ ].



**3-(2-Chloro-6-(methylsulfonylmethyl)pyrimidin-4-yl)-8-oxa-3-azabicyclo[3.2.1]octane (41).** Compound **39** (218 mg, 0.90 mmol), 8-oxa-3-azabicyclo[3.2.1]octane hydrochloride (135 mg, 0.90 mmol) and triethylamine (0.251 mL, 1.81 mmol) were dissolved in DCM (5 mL) at room temperature. The reaction mixture was stirred for 2 hours then quenched with water (10 mL) and the product extracted with DCM (2 x 10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 0 to 100 % MeOH in DCM. Pure fractions were evaporated to dryness to afford **41** (227 mg, 79%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 1.63 (q, *J* = 6.6 Hz, 2H), 1.79 - 1.89 (m, 2H), 3.11 (s, 3H), 3.00 - 3.16 (s, 2H), 3.56 (s, 1H), 4.15 (s, 1H), 4.38 - 4.53 (m, 1H), 4.44 (s, 3H), 6.88 (s, 1H). MS-ESI *m/z* 318, 320 [MH<sup>+</sup>].

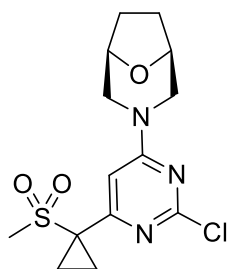


**8-(2-Chloro-6-(methylsulfonylmethyl)pyrimidin-4-yl)-3-oxa-8-azabicyclo[3.2.1]octane (42).** Compound **39** (500 mg, 2.07 mmol), 3-oxa-8-azabicyclo[3.2.1]octane hydrochloride (310 mg, 2.07 mmol) and triethylamine (0.632 mL, 4.56 mmol) were dissolved in DCM (5 mL) at room temperature. The reaction mixture was stirred for 18 hour then quenched with water (10 mL) and the product extracted with DCM (2 x 10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford **42** (645 mg, 98 %) as a white solid. MS-ESI *m/z* 318, 320 [MH<sup>+</sup>].



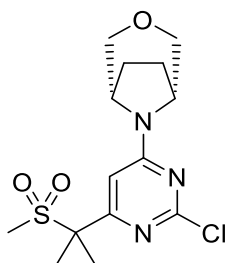
**2-Chloro-4-(3,6-dihydro-2H-pyran-4-yl)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidine (43).** 1,2-Dibromoethane (0.107 mL, 1.25 mmol) was added to **40** (300 mg, 1.04 mmol) in DMF (7 mL) at 0° C. Sodium hydride (60% dispersion in oil) (83 mg, 2.08 mmol) was added portionwise and the resulting mixture stirred at 0 °C for 2 hours and then room temperature for a further 2 hours. A second portion of 1,2-dibromoethane

(0.107 mL, 1.25 mmol) and sodium hydride (60% dispersion in oil) (83 mg, 2.08 mmol) was added and the reaction mixture left to stir at room temperature for 16 hours. Water (20 mL) was added and the mixture extracted with EtOAc (2 x 10 mL). The combined organics were dried over MgSO<sub>4</sub>, filtered then concentrated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 20 to 50% *iso*-hexane in EtOAc. Pure fractions were evaporated to dryness to afford **43** (105 mg, 32%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.64 - 1.68 (m, 2H), 1.75 - 1.78 (m, 2H), 2.40 - 2.60 (m, 2H, obscured by DMSO peak), 3.20 (s, 3H), 3.83 (t, 2H), 4.34 (q, 2H), 7.23 - 7.24 (m, 1H), 7.84 (s, 1H). MS-ESI *m/z* 314, 316 [MH<sup>+</sup>].



**3-(2-Chloro-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-4-yl)-8-oxa-3-azabicyclo[3.2.1]octane (44).**

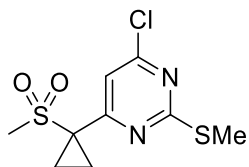
Sodium hydroxide (50% aq.) (0.952 mL, 17.86 mmol) was added to **41** (227 mg, 0.71 mmol), 1,2-dibromoethane (0.062 mL, 0.71 mmol) and tetra-octylammonium bromide (39.1 mg, 0.07 mmol) in toluene (8 mL). The resulting mixture was stirred at 60 °C for 3 hours and then diluted with EtOAc (25 mL), washed with water (20 mL) and brine (20 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to afford **44** (236 mg, 96 %) as a pale yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO) 1.52 (d, *J* = 4.6 Hz, 2H), 1.63 (d, *J* = 11.1 Hz, 4H), 1.74 - 1.93 (m, 2H), 3.15 (dd, *J* = 5.4, 12.7 Hz, 2H), 3.19 (s, 3H), 3.80 (d, *J* = 35.6 Hz, 1H), 4.11 (d, *J* = 5.4 Hz, 1H), 4.38 - 4.49 (m, 2H), 6.89 (s, 1H). MS-ESI *m/z* 344, 346 [MH<sup>+</sup>].



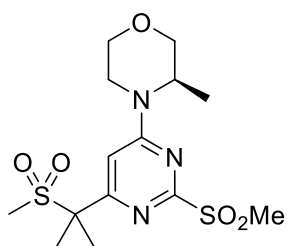
**8-(2-Chloro-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-4-yl)-3-oxa-8-azabicyclo[3.2.1]octane (45).**

Sodium hydroxide (50% aq.) (2.71 mL, 50.74 mmol) was added to **42** (645 mg, 2.03 mmol), 1,2-dibromoethane (0.175 mL, 2.03 mmol) and tetra-octylammonium bromide (111 mg, 0.20 mmol) in toluene (10 mL). The resulting slurry was stirred at 60 °C for 3 hours, then diluted with EtOAc (25 mL), washed with

water (20mL) and brine (20mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to yield a solid which was triturated with hexane to afford **45** (582 mg, 83 %) as a brown solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 1.47 - 1.53 (m, 2H), 1.62 (d, *J* = 2.0 Hz, 2H), 1.95 (d, *J* = 29.0 Hz, 4H), 3.20 (s, 3H), 3.52 - 3.63 (m, 4H), 4.54 (s, 2H), 6.88 (s, 1H). MS-ESI *m/z* 344, 346 [MH<sup>+</sup>].

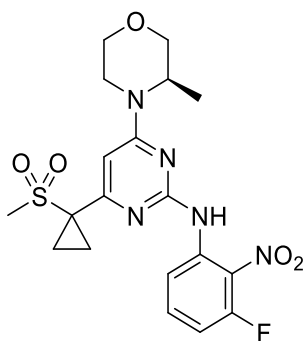


**4-Chloro-2-methylsulfanyl-6-(1-methylsulfonylcyclopropyl)pyrimidine (50).** Sodium hydroxide (50% aq.) (31.7 mL, 593.49 mmol) was added to **49** (6 g, 23.74 mmol), 1,2-dibromoethane (6.14 mL, 71.22 mmol) and tetrabutylammonium bromide (0.765 g, 2.37 mmol) in toluene (150 mL). The resulting mixture was stirred at 60 °C for 8 hours. Water (50 mL) was added and the mixture was extracted with toluene (40 mL x 2). The toluene layers were dried over MgSO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford a yellow solid which was triturated with ether to yield **50** (1.550 g, 23%) as white crystalline solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.68 (dd, 2H), 1.76 (dd, 2H), 2.56 (s, 3H), 3.22 (s, 3H), 7.59 (s, 1H). MS-ESI *m/z* 279 [MH<sup>+</sup>].

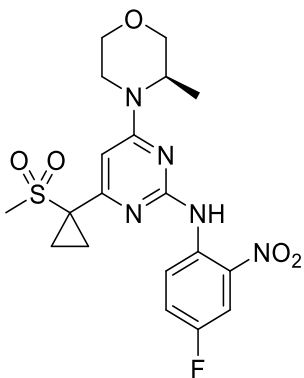


**(R)-3-Methyl-4-(2-(methylsulfonyl)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-4-yl)morpholine (51).** (*R*)-3-methylmorpholine (61.8 mg, 0.61 mmol) was added to **50** (142 mg, 0.51 mmol) and *N,N*-diisopropylethylamine (0.22 mL, 1.27 mmol) in dioxane (3 mL) and stirred at 80 °C for 18 hours. The mixture was cooled, and water (10 mL) added and extracted with DCM (2 x 5mL). The combined organics were purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and pure fractions were evaporated to dryness to afford (*R*)-3-methyl-4-(6-(1-(methylsulfonyl)cyclopropyl)-2-(methylthio)pyrimidin-4-yl)morpholine (83 mg, 47%) as a yellow oil. MS-

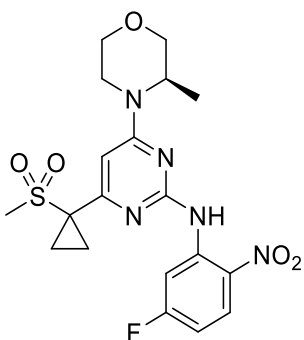
ESI  $m/z$  344  $[MH^+]$ . Sodium tungstate dihydrate (0.030 g, 0.09 mmol) and tetrabutylammonium hydrogen sulfate (0.093 g, 0.27 mmol) were added to (*R*)-3-methyl-4-(6-(1-(methylsulfonyl)cyclopropyl)-2-(methylthio)pyrimidin-4-yl)morpholine (1.570 g, 4.57 mmol) in ethyl acetate (40 mL) at 0°C. Hydrogen peroxide (35% aq solution) (1.20 mL, 13.71 mmol) was added dropwise and the reaction allowed to warm to room temperature and stirred for 6 hours. The reaction mixture was diluted with EtOAc (100 mL) and washed twice with sodium metabisulfite solution (10% aq., 50 mL) and then with saturated brine. The organic layer was dried over  $MgSO_4$ , filtered and evaporated to afford **51** (1.695 g, 99%) as a white solid.  $^1H$  NMR (400 MHz,  $CDCl_3$ ): 1.36 (3H, d), 1.55 (2H, q), 1.87 (2H, q), 3.02 (3H, s), 3.25 (3H, s), 3.30 - 3.41 (1H, m), 3.56 (1H, td), 3.70 (1H, dd), 3.81 (1H, d), 4.04 (1H, dd), 4.11 (1H, s), 4.36 (1H, s), 7.05 (1H, s). MS-ESI  $m/z$  376  $[MH^+]$ . HRMS-ESI  $m/z$  376.1001  $[MH^+]$  requires  $C_{14}H_{21}N_3O_5S_2$  376.1040.



**(*R*)-*N*-(3-Fluoro-2-nitrophenyl)-4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-amine (**52**).** Palladium (II) acetate (21.65 mg, 0.10 mmol), xantphos (84 mg, 0.14 mmol), 3-fluoro-2-nitroaniline (188 mg, 1.21 mmol), cesium carbonate (786 mg, 2.41 mmol) and **47** (400 mg, 1.21 mmol) were suspended in 1,4-dioxane (5 mL) and sealed into a microwave tube. The reaction was heated to 80 °C for 1 hour in the microwave reactor and cooled to room temperature. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M  $NH_3/MeOH$  and pure fractions were evaporated to dryness to afford **52** (576 mg, 106%) as a brown solid. MS-ESI  $m/z$  452  $[MH^+]$ .

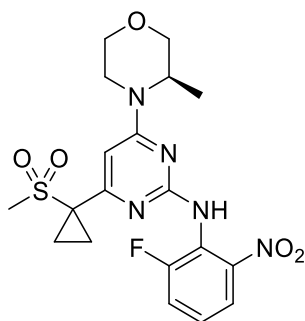


**(R)-N-(4-Fluoro-2-nitrophenyl)-4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-amine (53).** Palladium(II) acetate (10.83 mg, 0.05 mmol), xantphos (41.9 mg, 0.07 mmol), 4-fluoro-2-nitroaniline (94 mg, 0.60 mmol), cesium carbonate (393 mg, 1.21 mmol) and **47** (200 mg, 0.60 mmol) were suspended in 1,4-dioxane (5 mL) and sealed into a microwave tube. The reaction was heated to 80 °C for 1 hour in the microwave reactor and cooled to room temperature. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and pure fractions were evaporated to dryness to afford **53** as a yellow solid. MS-ESI *m/z* 425 [MH<sup>+</sup>].

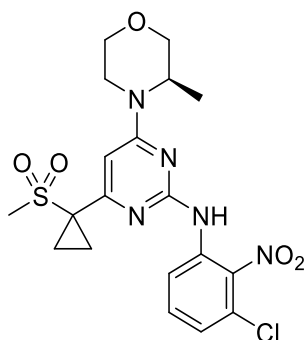


**(R)-N-(5-Fluoro-2-nitrophenyl)-4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-amine (54).** Palladium(II) acetate (21.65 mg, 0.10 mmol), xantphos (84 mg, 0.14 mmol), 5-fluoro-2-nitroaniline (188 mg, 1.21 mmol), cesium carbonate (786 mg, 2.41 mmol) and **47** (400 mg, 1.21 mmol) were suspended in 1,4-dioxane (10 mL) and sealed into a microwave tube. The reaction was heated to 80 °C for 1 hour in the microwave reactor and cooled to room temperature. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and pure fractions were evaporated to dryness to afford **54** (572 mg, 100%) as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.22 (3H, d), 1.49 - 1.53 (2H, m), 1.63 - 1.66 (2H, m), 3.18 (3H, s), 3.18 - 3.23

(1H, m), 3.45 (1H, td), 3.60 (1H, dd), 3.75 (1H, d), 3.95 (1H, dd), 3.97 - 4.03 (1H, m), 4.35 - 4.44 (1H, m), 6.60 (1H, s), 7.02 (1H, ddd), 8.24 (1H, dd), 8.39 (1H, dd), 10.04 (1H, s). MS-ESI  $m/z$  452 [ $MH^+$ ].

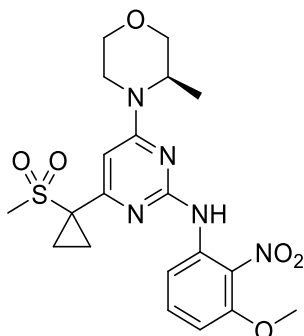


**(R)-N-(2-Fluoro-6-nitrophenyl)-4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-amine (55).** Palladium(II) acetate (0.030 g, 0.13 mmol), xantphos (0.115 g, 0.20 mmol), 2-fluoro-6-nitroaniline (0.285 g, 1.83 mmol), cesium carbonate (1.082 g, 3.32 mmol) and **47** (0.551 g, 1.66 mmol) were suspended in 1,4-dioxane (7 mL) in a microwave tube. The reaction was heated to 80 °C for 5 hours in the microwave reactor and cooled to room temperature. The reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M  $NH_3/MeOH$ . The crude product was purified by flash silica chromatography, elution gradient 0 to 10 % EtOAc in DCM. Fractions containing product were evaporated to dryness to afford **55** (0.390 g, 52%) as a yellow foam.  $^1H$  NMR (400 MHz, DMSO- $d_6$ ): 1.12 (3H, d), 1.38 - 1.42 (2H, m), 1.48 - 1.59 (2H, m), 3.08 (3H, s), 3.36 (1H, td), 3.52 (1H, dd), 3.66 (1H, d), 3.86 (1H, td), 4.23 (1H, br s), 4.40 (1H, br s), 6.36 (1H, s), 6.92 (1H, s), 7.36 - 7.44 (1H, m), 7.66 (1H, t), 7.79 (1H, d), 9.16 (1H, s). MS-ESI  $m/z$  452 [ $MH^+$ ].



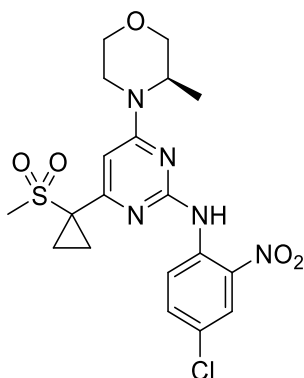
**(R)-N-(3-Chloro-2-nitrophenyl)-4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-amine (56).** Palladium(II) acetate (0.022 g, 0.10 mmol), xantphos (0.084 g, 0.14 mmol), 3-chloro-2-nitroaniline (0.208 g, 1.21 mmol), cesium carbonate (0.786 g, 2.41 mmol) and **47** (0.400 g, 1.21 mmol) were suspended in dioxane (5 mL), placed under nitrogen and sealed into a microwave tube. The reaction was

heated to 80 °C for 1 hour in the microwave reactor and cooled to room temperature. The crude product was purified by ion exchange chromatography using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and evaporated. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in DCM. Fractions containing product were evaporated to dryness to afford **56** (0.302 g, 53%) as a dark red foam. MS-ESI *m/z* 468, 470 [MH<sup>+</sup>].



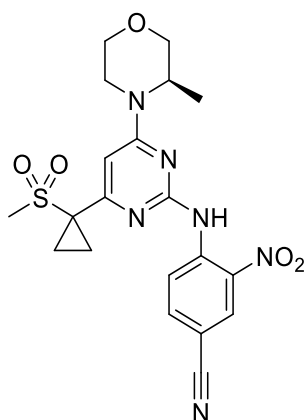
**(R)-N-(3-Methoxy-2-nitrophenyl)-4-(3-methylmorpholino)-6-(1-**

**(methylsulfonyl)cyclopropyl)pyrimidin-2-amine (57).** Palladium(II) acetate (19.42 mg, 0.09 mmol), xantphos (75 mg, 0.13 mmol), 3-methoxy-2-nitroaniline (200 mg, 1.19 mmol), cesium carbonate (705 mg, 2.16 mmol) and **47** (359 mg, 1.08 mmol) were suspended in 1,4-dioxane (5 mL) and sealed into a microwave tube. The reaction was heated to 80 °C for 1 hour in the microwave reactor and cooled to room temperature. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and pure fractions were evaporated to dryness to afford **57** (380 mg, 76%) as a brown gum. MS-ESI *m/z* 464 [MH<sup>+</sup>].

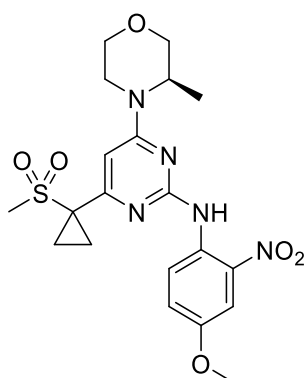


**(R)-N-(4-Chloro-2-nitrophenyl)-4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-amine (58).** Palladium(II) acetate (21 mg, 0.09 mmol), xantphos (80 mg, 0.14 mmol), 4-chloro-2-nitroaniline (200 mg, 1.16 mmol), cesium carbonate (754 mg, 2.31 mmol) and **47** (384 mg, 1.16 mmol) were

suspended in dioxane (10 mL) and sealed into a microwave tube. The reaction was heated to 80 °C for 1 hour in the microwave reactor and cooled to room temperature. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH in MeOH and pure fractions were evaporated to dryness to afford **58** (542 mg, 100%). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.18 (3H, d), 1.46 - 1.49 (2H, m), 1.57 - 1.62 (2H, m), 3.09 - 3.16 (1H, m), 3.16 (3H, s), 3.42 (1H, td), 3.57 (1H, dd), 3.72 (1H, d), 3.93 (1H, dd), 3.97 - 4.00 (1H, m), 4.28 - 4.40 (1H, m), 6.51 (1H, s), 7.77 (1H, dd), 8.09 (1H, d), 8.15 (1H, d), 9.77 (1H, s). MS-ESI *m/z* 468, 470 [MH<sup>+</sup>].

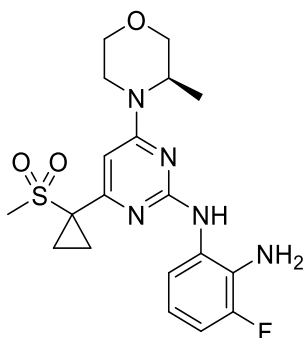


**(R)-4-(4-(3-Methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-ylamino)-3-nitrobenzonitrile (59)**. Palladium(II) acetate (21.65 mg, 0.10 mmol), xantphos (84 mg, 0.14 mmol), 4-amino-3-nitrobenzonitrile (197 mg, 1.21 mmol), cesium carbonate (786 mg, 2.41 mmol) and **47** (400 mg, 1.21 mmol) were suspended in dioxane (5 mL) and sealed into a microwave tube. The reaction was heated to 80 °C for 1 hour in the microwave reactor and cooled to room temperature. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and pure fractions were evaporated to dryness to afford **59** (501 mg, 91%) as a brown solid. MS-ESI *m/z* 459 [MH<sup>+</sup>].



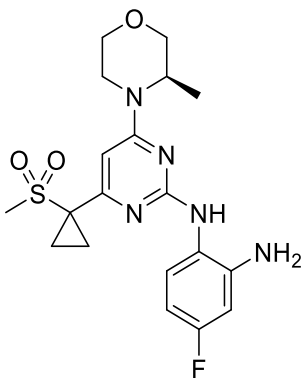
**(R)-N-(4-Methoxy-2-nitrophenyl)-4-(3-methylmorpholino)-6-(1-**

**(methylsulfonyl)cyclopropyl)pyrimidin-2-amine (60).** Palladium(II) acetate (0.022 g, 0.10 mmol), xantphos (0.084 g, 0.14 mmol), 4-methoxy-2-nitroaniline (0.203 g, 1.21 mmol), cesium carbonate (0.786 g, 2.41 mmol) and **47** (0.400 g, 1.21 mmol) were suspended in dioxane (5 mL) and sealed into a microwave tube. The reaction was heated to 80 °C for 1 hour in the microwave reactor and cooled to room temperature. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and evaporated to dryness. DCM was added and the solids discarded. The DCM solution was purified by flash silica chromatography, elution gradient 0 to 10% EtOAc in DCM. Pure fractions were evaporated to dryness to afford **60** (0.560 g, 100%) as an orange solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.18 (3H, d), 1.40 - 1.49 (2H, m), 1.53 - 1.62 (2H, m), 3.11 (1H, td), 3.14 (3H, s), 3.42 (1H, td), 3.57 (1H, dd), 3.71 (1H, d), 3.83 (3H, s), 3.91 (1H, dd), 3.97 (1H, d), 4.32 (1H, br s), 6.43 (1H, s), 7.28 - 7.38 (1H, m), 7.52 (1H, d), 7.98 (1H, d), 9.40 (1H, s). MS-ESI *m/z* 464 [MH<sup>+</sup>].

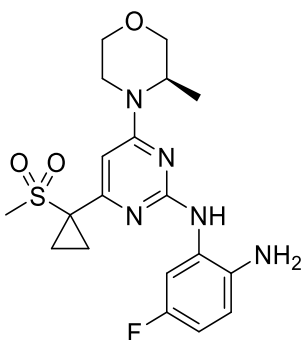


**(R)-3-Fluoro-N1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)benzene-**

**1,2-diamine (61).** Indium (400 mg, 3.48 mmol) was added to **52** (576 mg, 1.28 mmol) in EtOH (20 mL) and sat. NH<sub>4</sub>Cl (aq.) (4 mL) and stirred at reflux for 3 hours. The mixture was cooled then filtered through celite, washing with EtOH. The liquors were concentrated to remove EtOH and then water (10 mL) and DCM (20 mL) added and the layers separated. The organics were dried over MgSO<sub>4</sub>, filtered then concentrated *in vacuo* to yield crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10 % MeOH in DCM. Pure fractions were evaporated to dryness to afford **61** (383 mg, 71%) as a brown solid. MS-ESI *m/z* 422 [MH<sup>+</sup>].

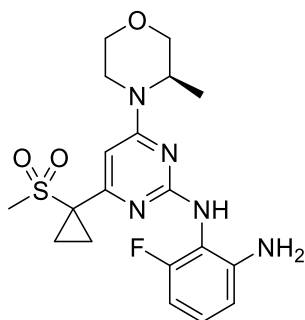


**(R)-4-Fluoro-N1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)benzene-1,2-diamine (62).** Zinc (196 mg, 3.00 mmol) was added to **53** (271 mg, 0.6 mmol) in acetic acid (4 mL) and the resulting suspension was stirred at room temperature for 18 hours. The reaction was incomplete and further zinc (100 mg) was added and the suspension was stirred at room temperature for a further 3 hours. The reaction mixture was diluted with DCM and the liquors decanted onto an SCX2 cartridge. The desired product was eluted from the column using 7M NH<sub>3</sub>/MeOH and concentrated *in vacuo*. The crude product was purified by flash silica chromatography, elution gradient 30 to 50 % EtOAc in isohexane. Pure fractions were evaporated to dryness to afford **62** (188 mg, 74%) as a red brown solid. MS-ESI *m/z* 422 [MH<sup>+</sup>].

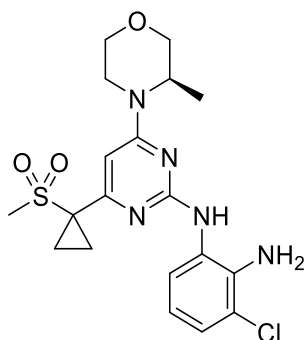


**(R)-5-Fluoro-N1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)benzene-1,2-diamine (63).** Indium (435 mg, 3.79 mmol) was added to **54** (570 mg, 1.26 mmol) and saturated ammonium chloride solution (5 mL) in EtOH (25 mL) and reaction mixture was stirred at reflux for 3 hours. The mixture was cooled, then filtered through celite and washed with EtOH. The liquors were concentrated to remove EtOH and then water (20 mL) and DCM (70 mL) were added and the layers separated. The organics were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **63** (460 mg, 86%) as a purple gum. <sup>1</sup>H NMR (400 MHz, DMSO-

d6): 1.19 (3H, d), 1.45 - 1.49 (2H, m), 1.54 - 1.59 (2H, m), 3.10 - 3.20 (1H, m), 3.20 (3H, s), 3.39 - 3.45 (1H, m), 3.57 (1H, dd), 3.71 (1H, d), 3.92 (1H, dd), 3.99 (1H, d), 4.31 - 4.42 (1H, m), 4.79 (2H, s), 6.34 (1H, s), 6.61 - 6.72 (2H, m), 7.42 (1H, dd), 8.18 (1H, s). MS-ESI  $m/z$  422 [ $MH^+$ ].

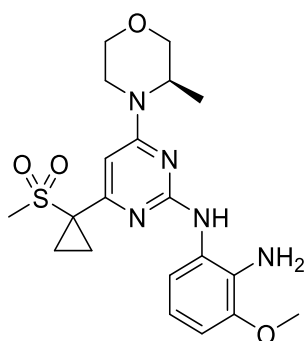


**(R)-6-Fluoro-N1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)benzene-1,2-diamine (64).** Indium (0.316 g, 2.76 mmol) was added to **55** (0.390 g, 0.86 mmol) and saturated ammonium chloride solution (3 mL) in EtOH (15 mL) and reaction mixture was stirred at reflux for 3.5 hours. The mixture was cooled, then filtered through celite and washed with EtOH. The liquors were concentrated to remove EtOH and then water (20 mL) and DCM (70 mL) were added and the layers separated. The organics were washed with brine, dried over  $MgSO_4$ , filtered and concentrated *in vacuo* to yield crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in DCM. Fractions containing product were evaporated to dryness to afford **64** (0.176 g, 48%) as a light yellow gum.  $^1H$  NMR (400 MHz, DMSO- $d_6$ ): 1.23 (3H, d), 1.35 (2H, q), 1.68 (2H, q), 2.96 (3H, s), 3.17 (1H, td), 3.47 (1H, td), 3.61 (1H, dd), 3.71 (1H, d), 3.92 (2H, m), 4.17 - 4.26 (2H, m), 6.27 (1H, s), 6.38 (1H, s), 6.45 - 6.55 (2H, m), 6.97 (1H, td), 7.27 (1H, s). MS-ESI  $m/z$  422 [ $MH^+$ ].



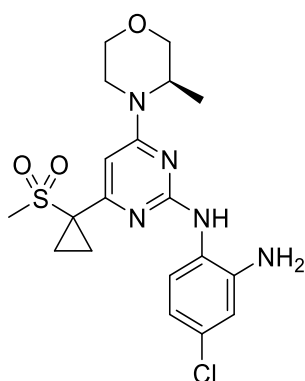
**(R)-3-Chloro-N1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)benzene-1,2-diamine (65).** Indium (0.454 g, 3.95 mmol) was added to **56** (0.580 g, 1.24 mmol) and sat  $NH_4Cl$  (aq.) (3 mL) in EtOH (15 mL). The reaction mixture was stirred at reflux for 3.5 hours. The reaction mixture was

filtered through celite and the filtrate concentrated *in vacuo*. The crude product was separated between DCM and water. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to yield a purple solid. The crude product was purified by flash silica chromatography, elution gradient 0 to 70% EtOAc in DCM. Pure fractions were evaporated to dryness to afford **65** (0.270 g, 50%) as a red film. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.25 (1H, d), 1.27 - 1.29 (3H, d), 1.36 - 1.43 (2H, m), 1.70 - 1.78 (2H, m), 3.01 (3H, s), 3.14 - 3.27 (1H, td), 3.47 - 3.54 (1H, td), 3.63 - 3.67 (1H, dd), 3.73 - 3.76 (1H, d), 3.90 - 3.93 (1H, m), 3.94 - 3.98 (1H, dd), 4.22 (2H, bs), 6.32 (1H, s), 6.43 (1H, s), 6.68 - 6.72 (1H, t), 7.12 - 7.14 (1H, dd), 7.29 - 7.31 (1H, dd). MS-ESI *m/z* 438, 440 [MH<sup>+</sup>].

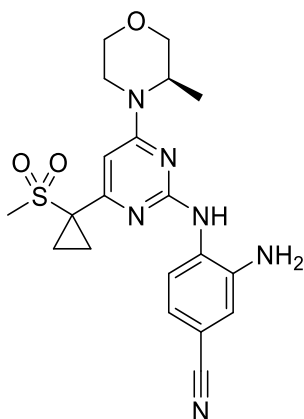


**(R)-3-Methoxy-N1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-**

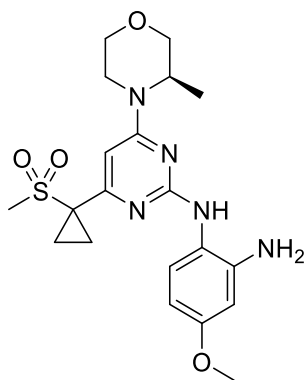
**yl)benzene-1,2-diamine (66).** Indium (282 mg, 2.46 mmol) was added to **57** (380 mg, 0.82 mmol) in ethanol (10 mL) and sat NH<sub>4</sub>Cl (aq.) (2 mL) and the resulting mixture was stirred at reflux for 4 hours. The mixture was cooled, filtered through a pad of celite, washing with EtOH. The filtrate was concentrated *in vacuo* and then water (10 mL) and DCM (20 mL) were added and the layers separated. The organic layer was dried over MgSO<sub>4</sub>, filtered then concentrated *in vacuo* to yield crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford **66** (285 mg, 80%) as a pale brown solid. MS-ESI *m/z* 434 [MH<sup>+</sup>].



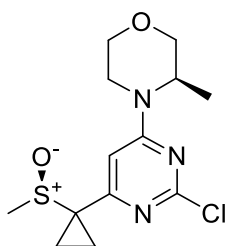
**(R)-4-Chloro-N1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)benzene-1,2-diamine (67).** Indium (417 mg, 3.63 mmol) was added to **58** (566 mg, 1.21 mmol) in EtOH (25 mL) and sat NH<sub>4</sub>Cl (aq.) (5 mL) and stirred at reflux for 3 hours. The mixture was cooled then filtered through celite, washing with EtOH. The liquors were concentrated *in vacuo* and then water (20 mL) and DCM (75 mL) added and the layers separated. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, then filtered and concentrated *in vacuo* to yield crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 4% MeOH in DCM. Pure fractions were evaporated to dryness to afford **67** (497 mg, 94%) as a pale brown gum. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.17 (3H, d), 1.43 - 1.46 (2H, m), 1.53 - 1.57 (2H, m), 3.09 (1H, td), 3.18 (3H, s), 3.40 (1H, td), 3.55 (1H, dd), 3.70 (1H, d), 3.91 (1H, dd), 3.98 (1H, d), 4.29 - 4.37 (1H, m), 5.16 (2H, s), 6.28 (1H, s), 6.54 (1H, dd), 6.75 (1H, d), 7.33 (1H, d), 8.16 (1H, s). MS-ESI *m/z* 438, 440 [MH<sup>+</sup>].



**(R)-3-Amino-4-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-ylamino)benzonitrile (68).** Indium (400 mg, 3.48 mmol) was added to **59** (501 mg, 1.09 mmol) in EtOH (10 mL) and sat NH<sub>4</sub>Cl (aq.) (2 mL) and stirred at reflux for 3 hours. The mixture was cooled then filtered through celite, washing with EtOH. The liquors were concentrated *in vacuo* and then water (10 mL) and DCM (20 mL) added and the layers separated. The organic layer was dried over MgSO<sub>4</sub>, filtered then concentrated *in vacuo* to yield **68** (380 mg, 81%) as a brown solid. MS-ESI *m/z* 429 [MH<sup>+</sup>].

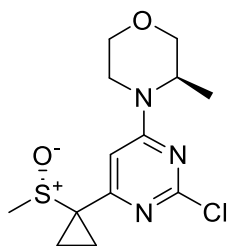


**(R)-4-Methoxy-N1-(4-(3-methylmorpholino)-6-(1-(methylsulfonyl)cyclopropyl)pyrimidin-2-yl)benzene-1,2-diamine (69).** Indium (0.443 g, 3.85 mmol) was added to **60** (0.560 g, 1.21 mmol) in EtOH (15 mL) and sat NH<sub>4</sub>Cl (aq.) (3 mL) and stirred at reflux for 3.5 hours. The mixture was cooled then filtered through celite, washing with EtOH. The liquors were concentrated *in vacuo* and then water and DCM were added and the layers separated. The organic layer was dried over MgSO<sub>4</sub>, filtered then concentrated *in vacuo* to yield a purple solid. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in DCM. Pure fractions were evaporated to dryness to afford **69** (0.390 g, 75%) as a light purple foam. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): 1.16 - 1.17 (3H, d), 1.19 (1H, t), 1.38 - 1.44 (2H, m), 1.48 - 1.57 (2H, m), 3.07 (1H, td), 3.14 (3H, s), 3.37 (1H, td), 3.54 (1H, dd), 3.66 (3H, s), 3.78 (1H, d), 3.89 (1H, dd), 3.97 (1H, d), 4.31 (1H, br s), 4.79 (1H, br s), 6.14 (1H, dd), 6.20 (1H, s), 6.31 (1H, d), 7.08 (1H, dd), 7.94 (1H, s). MS-ESI *m/z* 434 [MH<sup>+</sup>].

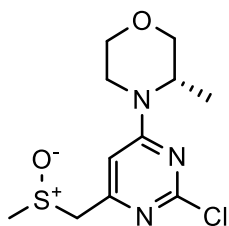


**(R)-4-(2-Chloro-6-(1-((R)-methylsulfinyl)cyclopropyl)pyrimidin-4-yl)-3-methylmorpholine (R-73).** 1,2-dibromoethane (7.32 mL, 84.89 mmol) was added to **R-72** (2.46 g, 8.49 mmol), tetra-octylammonium bromide (0.464 g, 0.85 mmol) and sodium hydroxide (50% aq.) (50 mL, 946.94 mmol) in mTHF (100 mL). The resulting mixture was stirred at 60 °C for 150 minutes. The reaction mixture was diluted with mTHF (250 mL) and washed with water (250 mL). The organic layer was dried with MgSO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was dissolved in DCM (10 mL) then purified by flash silica

chromatography, elution gradient 25 to 100% 3:1 EtOAc/EtOH in heptane. Pure fractions were evaporated to dryness to afford **R-73** (1.460 g, 54.5 %) as a beige oil which crystallised on standing. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.28 - 1.35 (m, 4H), 1.39 (ddd, J = 4.9, 6.9, 8.9 Hz, 1H), 1.52 (ddd, J = 5.1, 7.1, 9.2 Hz, 1H), 1.62 (ddd, J = 4.9, 7.1, 10.0 Hz, 1H), 2.57 (s, 3H), 3.29 (td, J = 3.8, 13.0 Hz, 1H), 3.53 (td, J = 3.1, 12.0 Hz, 1H), 3.65 - 3.72 (m, 1H), 3.77 (d, J = 11.6 Hz, 1H), 4.00 (dd, J = 3.9, 11.6 Hz, 1H), 4.11 (s, 1H), 4.31 (s, 1H), 6.58 (s, 1H). MS-ESI *m/z* 316, 318 [MH<sup>+</sup>].

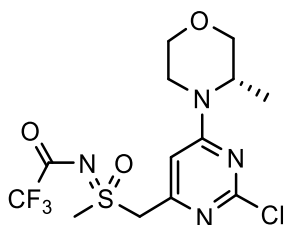


**(R)-4-(2-chloro-6-(1-((S)-methylsulfinyl)cyclopropyl)pyrimidin-4-yl)-3-methylmorpholine (S-73).** 1,2-Dibromoethane (4.27 mL, 34.96 mmol) was added to **S-72** (1.013 g, 3.50 mmol), tetra-octylammonium bromide (0.191 g, 0.35 mmol) and sodium hydroxide (50% aq.) (10 mL, 189.39 mmol) in mTHF (30 mL). The resulting mixture was stirred at 60°C for 150 minutes. The reaction mixture was diluted with mTHF (100 mL) and washed with water (100 mL). The organic layer was dried with MgSO<sub>4</sub>, filtered and evaporated. The residue was dissolved in DCM (5 mL) and then purified by flash chromatography on silica, eluting with a gradient of 25 to 100% 3:1 EtOAc/EtOH in heptane. Pure fractions were evaporated to dryness to afford **S-73** (0.452 g, 41%) as a beige solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 1.29 – 1.37 (m, 4H), 1.40 (ddd, J = 4.9, 6.9, 9.0 Hz, 1H), 1.53 (ddd, J = 5.1, 7.1, 9.2 Hz, 1H), 1.62 (ddd, J = 4.9, 7.1, 10.1 Hz, 1H), 2.57 (s, 3H), 3.29 (td, J = 3.9, 12.9 Hz, 1H), 3.55 (td, J = 3.1, 12.0 Hz, 1H), 3.65 – 3.71 (m, 1H), 3.79 (d, J = 11.6 Hz, 1H), 4.00 (dd, J = 3.9, 11.6 Hz, 2H), 4.35 (s, 1H), 6.59 (s, 1H). *m/z*: ES+ MH<sup>+</sup> 316, 318. Chiral HPLC: (HP1100, 3µm Chiralcel AS (50 mm x 4.6 mm) column eluting with *iso*-hexane/EtOH 50/50) R<sub>f</sub>, 0.996 >98.2%.



**(3S)-4-(2-Chloro-6-[(methylsulfinyl)methyl]-4-pyrimidinyl)-3-methylmorpholine (77).**

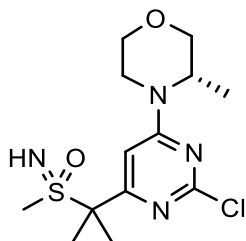
Sodium methanethiolate in water (2.82 g, 8.45 mmol) was added to **76** (2.391 g, 6.76 mmol) in acetonitrile (23 mL). The resulting solution was stirred at room temperature for 40 minutes. The reaction mixture was evaporated to dryness and redissolved in EtOAc (50 mL) and washed with water (50 mL). The organic layer was separated then sodium meta-periodate (1.497 g, 7.00 mmol) was added in one portion followed by the addition of water (25 mL) and methanol (25 mL). The resulting solution was stirred at room temperature for 3 days at which point it tested negative for peroxides. The reaction mixture was filtered then evaporated to remove the methanol. The organic layer was separated then dried over MgSO<sub>4</sub>, filtered and evaporated to afford crude product. The aqueous layer was washed with EtOAc (5 x 50 mL). The organic layers were combined, then dried over MgSO<sub>4</sub>, filtered and evaporated onto silica gel (20 g). The resulting powder was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford **77** (1.200 g, 59 %). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 30°C) 1.33 (3H, d), 2.62 (3H, d), 3.30 (1H, td), 3.53 (1H, td), 3.68 (1H, dd), 3.72 – 3.8 (2H, m), 3.94 (1H, dd), 4.00 (1H, dd), 4.02 (1H, s), 4.32 (1H, s), 6.42 (1H, d). MS-ESI m/z 290, 292 [MH<sup>+</sup>].



**N-[(2-Chloro-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-4-yl)methyl](methyl)oxido-λ6-**

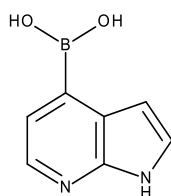
**sulfanylidene]-2,2,2-trifluoroacetamide (78).** Iodobenzene diacetate (6.54 g, 20.29 mmol) was added to **77** (5.88 g, 20.29 mmol), 2,2,2-trifluoroacetamide (4.59 g, 40.58 mmol), magnesium oxide (3.27 g, 81.16 mmol) and rhodium(II) acetate dimer (0.224 g, 0.51 mmol) in DCM (169 mL) under air. The resulting suspension was stirred at room temperature for 3 days. Further 2,2,2-trifluoroacetamide (1.15 g, 10.15 mmol), magnesium oxide (0.818 g, 20.29 mmol), rhodium(II) acetate dimer (0.056 g, 0.13 mmol) and iodobenzene diacetate (1.64 g, 5.07 mmol) were added and the suspension was stirred at room temperature for a further 24 hours. The reaction mixture was filtered and silica gel (3 g) was added to the filtrate and then the mixture was evaporated. The resulting powder was purified by flash chromatography on silica, eluting with a gradient of 20 to 50%

EtOAc in isohexane. Fractions containing product were evaporated and the residue was triturated with *iso*-hexane/MTBE to give a solid which was collected by filtration and dried under vacuum to afford **78** (6.64 g, 82%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 1.33 (3H, d), 3.28 (1H, dd), 3.43 (3H, d), 3.46 - 3.59 (1H, m), 3.62 - 3.71 (1H, m), 3.79 (1H, d), 3.90 - 4.50 (2H, br s), 4.21 (1H, s), 4.66 (1H, dd), 4.86 (1H, dd), 6.50 (1H, d). MS-ESI m/z 401, 403 [MH<sup>+</sup>].



**(3S)-4-(2-Chloro-6-(1-(S-methylsulfonimidoyl)cyclopropyl)pyrimidin-4-yl)-3-methylmorpholine (79).**

Sodium hydroxide (50% aq.) (1 mL, 18.75 mmol) was mixed with a solution of **78**, 1,2-dibromoethane (2.051 mL, 23.80 mmol) and tetra-octylammonium bromide (0.130 g, 0.24 mmol) in mTHF (14 mL) in a HTPTFE coil (25 mL) at 103 °C with a pumping rate of 0.4 mL/min. The mixture was transferred to a separating funnel, diluted with mTHF (40 mL) and washed with water (20 mL). The organic layer was dried MgSO<sub>4</sub> and concentrated in vacuo to afford **79** (0.506 g, 64.3 %). <sup>1</sup>H NMR (400, CDCl<sub>3</sub>) 3.78 (1H, s), 4.32 (1H, brs), 3.98 (2H, dd), 3.78 (1H, d), 3.66 (1H, d), 3.52 (1H, t), 3.28 (1H, t), 3.09 (3H, s), 2.35 (1H, brs), 1.71 (2H, m), 1.42 (2H, m), 1.33 (3H, d). MS-ESI m/z 331, 333 [MH<sup>+</sup>].



**1H-Pyrrolo[2,3-b]pyridin-4-ylboronic acid**

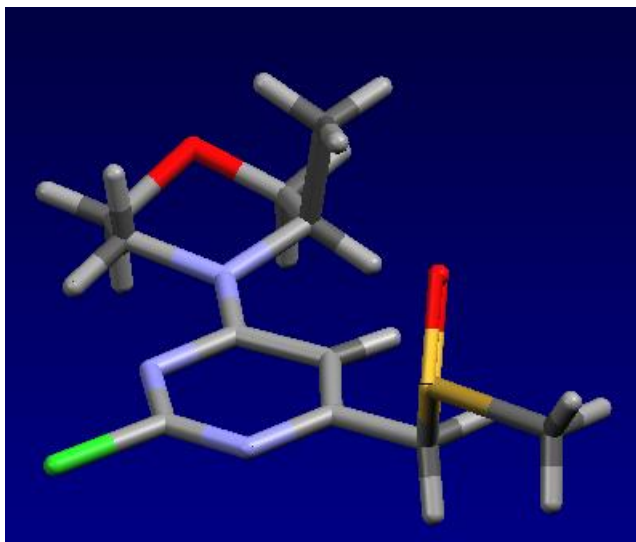
Sodium hydride (60% oil dispersion) (103 g, 2569.38 mmol) was added portionwise to 4-bromo-1H-pyrrolo[2,3-b]pyridine (405 g, 2055.50 mmol) in THF (10000 mL) at 5 °C under nitrogen. The resulting mixture was stirred at 20 °C for 45 minutes. The reaction was cooled to -74 °C and triisopropyl borate (1423 mL, 6166.51 mmol) was added over 10 minutes. A solution of *n*-butyllithium (1.6M in hexanes) (2950 mL, 4727.66 mmol) was added dropwise over 45 minutes. The reaction mixture was allowed to warm to room temperature then quenched with water (6000 mL). The reaction mixture filtered, then the filtrate was washed

with EtOAc (4000 mL). The aqueous layer was acidified to pH 6 with 2M HCl (1000 mL) and the resulting precipitate was isolated by filtration to afford **1H-Pyrrolo[2,3-b]pyridin-4-ylboronic acid** (139 g, 42%) as a white solid. The aqueous layer was extracted with EtOAc (4 x 5000 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford further **1H-Pyrrolo[2,3-b]pyridin-4-ylboronic acid** (175g, 53%) as a white solid. MS-ESI *m/z* 161 [MH<sup>-</sup>].

### Crystal formation method and X-ray structure of R-72

The compound was crystallised from dichloromethane and diethyl ether by vapour diffusion. A small-molecule crystal structure (Figure S2) confirmed the expected chirality of the sulfoxide group.

**Figure S2** – Geometry of sulfoxide **R-72** confirms R chirality of sulfoxide stereocenter.



## Assay descriptions

**Aqueous solubility.** Solubility is measured from dried DMSO. In brief, 50  $\mu$ l, 10 mM compound in DMSO solution is evaporated to dryness in a 1.5 mL glass vial before adding 500  $\mu$ l, 0.1 M pH 7.4 phosphate buffer. Stir Stix is inserted to the vials and shaking at 750 rpm is performed at a constant temperature of 25°C for 20-24 hours. After two centrifugation steps with a tip wash between to ensure that no residues of the dried compound are interfering. Up to 10 buffer samples are pooled and diluted on dilution plates in five sequential steps (20-125000 times) with 1:1 acetonitrile/water (0.1% formic acid), including 1nM Verapamil as internal standard. Standard samples are from 10 mM DMSO stock solutions and are pooled and diluted on dilution plates in five sequential steps (100-625000 times) with 1:1 acetonitrile/water (0.1% formic acid), including 1nM Verapamil as internal standard and diluted 1-10000 times. Buffer samples from dilution 1000-125000 times and standard samples from dilution 5000-625000 times are analysed by UPLC-MS/MS. The standards are assumed to be 100% dissolved and used to calculate the concentration of the buffer samples. Three QC samples Astemizole (low), Phenytoin (mid) & Chlorpromazine (high) are included in each run to ensure the quality of the assay.

**LogD<sub>7.4</sub>.** Lipophilicity is measured using the “traditional” shake flask method. Compounds are dissolved in DMSO and up to 10 different compounds are pooled to a concentration of 1mM and then 10 $\mu$ l of the compound mixture is transferred to the assay plate containing 500  $\mu$ l saturated octanol and 500  $\mu$ l saturated phosphate buffer in a dedicated automation system giving a compound start concentration of about 10  $\mu$ M. The assay plate is initially vigorously shaken for 1 minute and equilibrated for 3 hours on a shaker and finally centrifuged for 30 min to separate the phases before sampling first the octanol samples and after removal of the octanol the buffer samples. Octanol samples are diluted on dilution plates in five sequential steps (100-1000000 times) with 1:1 acetonitrile/water (0.1% formic acid), including internal standard (IS). Buffer samples are diluted 1-10000 times. Octanol samples from dilution 100-1000000 times and buffers samples from dilution 10-10000 times are analysed by UPLC-MS/MS and LogD values are calculated as the logarithm of the ratio of the compound concentrations in octanol and buffer. As quality controls, Caffeine (LogD<sub>7.4</sub> = 0) added in each run. Cyclobenzaprine (LogD<sub>7.4</sub> = 2.8) and Nicardipine (LogD<sub>7.4</sub>  $\approx$  4.7) is added to each pool.

It is a challenge using automation removing the octanol and sampling the buffer sample. As it is critical avoiding octanol contamination in the buffer sample. Nicardepine is a good indicator of octanol contamination in the buffer sample. Less lipophilic compounds are not that affected by octanol contamination.

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