Supporting Information

STK33 kinase inhibitor BRD-8899 has no effect on KRAS-dependent cancer cell viability

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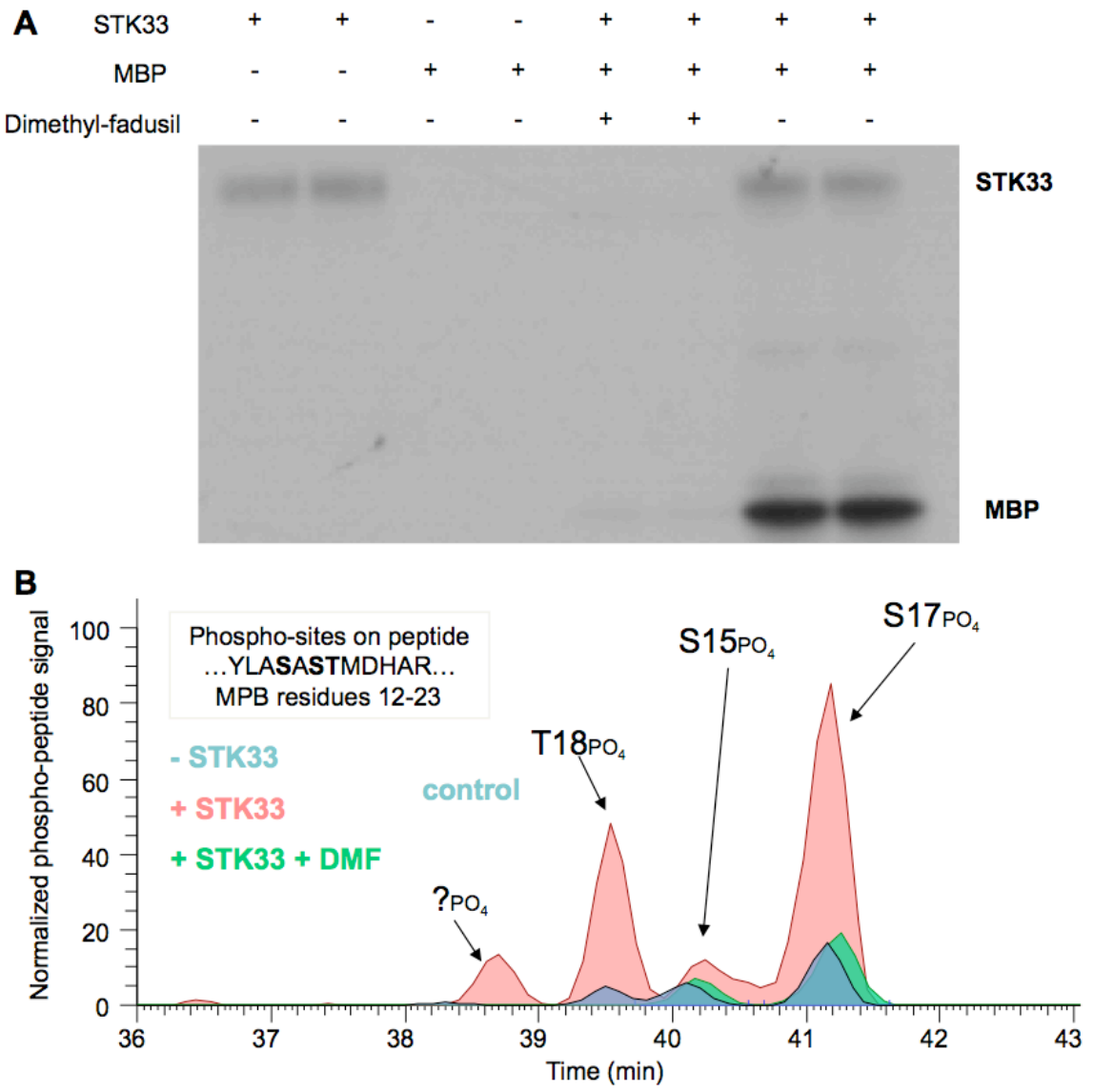


Figure S1. (A) Radiolabeled experiment confirming MBP phosphorylation and STK33 autophosphorylation. Kinase reactions were performed with 38.4 nM STK33, 24.5 μM MBP, and 100 μM ATP (28.6 μCi/mL [γ-^{32}P]-ATP). Reactions were initiated by the addition of ATP and incubated at 24 °C for 60 minutes. (B) Mass spectrometry data confirming phosphorylation of MBP by STK33. Kinase reactions were performed with 38.4 nM STK33, 24.5 μM MBP, and 100 μM ATP, in the absence and presence of 20 μM dimethylfasudil (DMF, **BRD7446**).

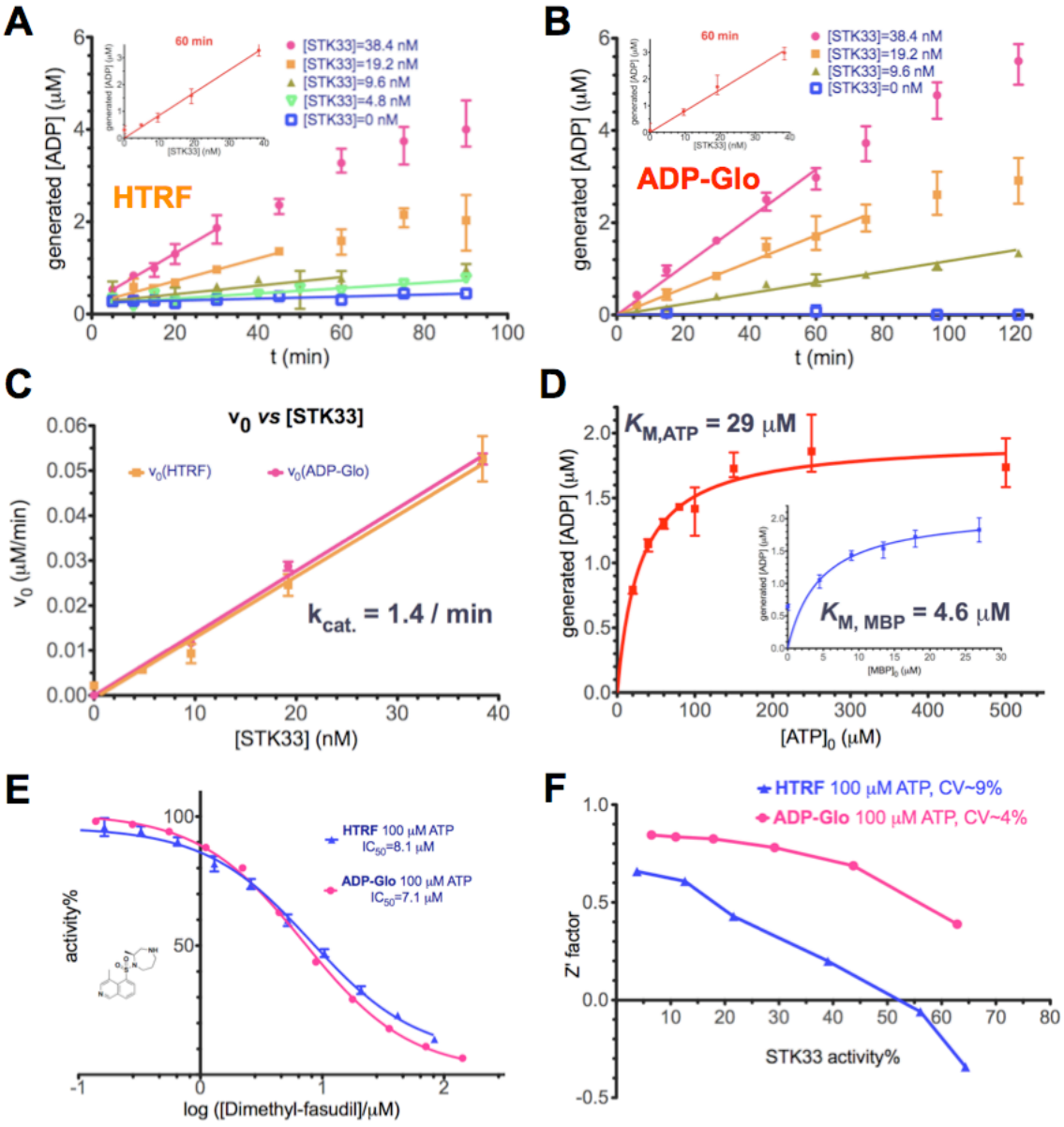


Figure S2. (A) The generation of ADP as a function of time and STK33 concentration (HTRF); (B) the generation of ADP as a function of time and STK33 concentration (ADP-Glo); (C) the initial velocity as a function of STK33 concentration; (D) determination of K_M; (E) dose-response curves of dimethyl fasudil; (F) Z' factors. Kinase reactions were performed with 38.4 nM STK33, 24.5 μM MBP, and 100 μM or 500 μM ATP. Reactions were initiated by the addition of ATP and incubated at 24 °C for 60~70 minutes. The error bars represent the range of 12 replicate values.

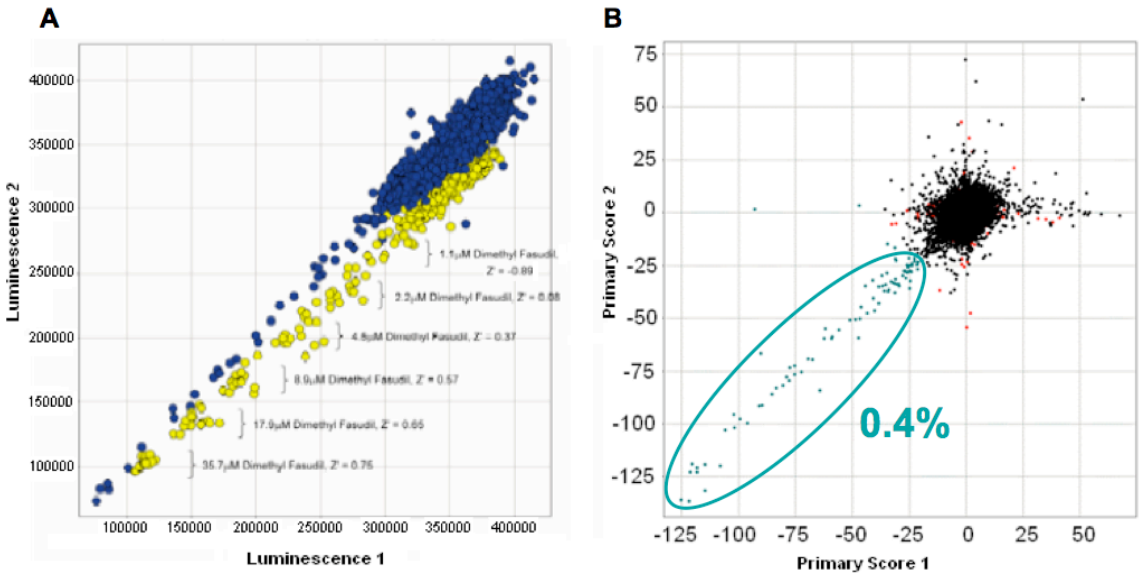


Figure S3. Results of plate replicates from the high throughput *in vitro* kinase screen. (A) Screen of 2,240 compounds under 100 µM ATP as a validation set, dimethyl fasudil is shown in yellow; (B) HTS screen of 27,500 compounds under 100 µM ATP, negative control DMSO is shown in red, and primary hits are shown in green. The hit rate is 0.4%. Negative control (DMSO) is scaled to 0, whereas positive control (89 µM dimethyl fasudil, 90% inhibition) is scaled to -100.

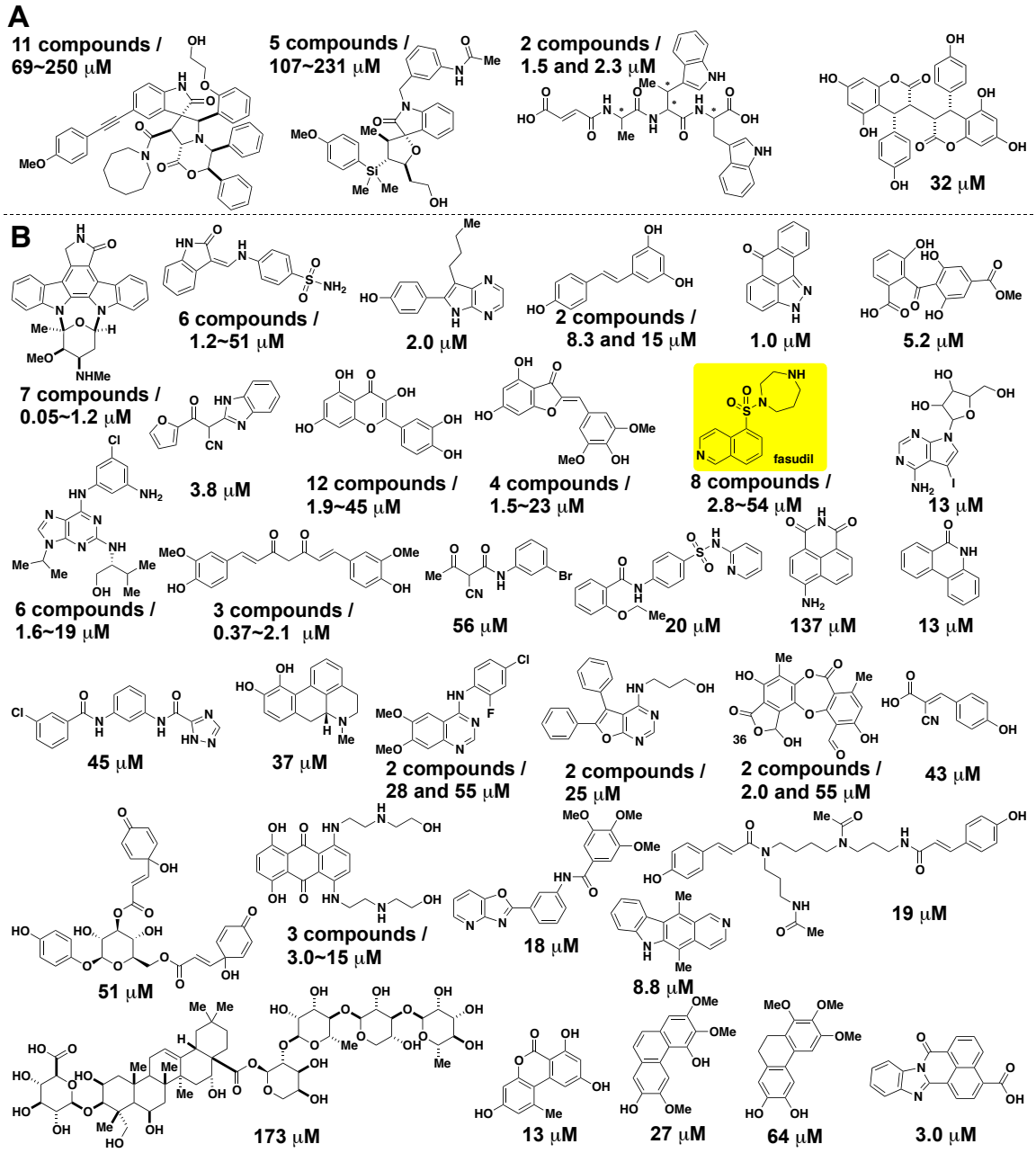


Figure S4. Clustering of primary hits and IC_{50} under 25 μM ATP. (A) ATP-noncompetitive inhibitors; (B) representative ATP-competitive inhibitors.

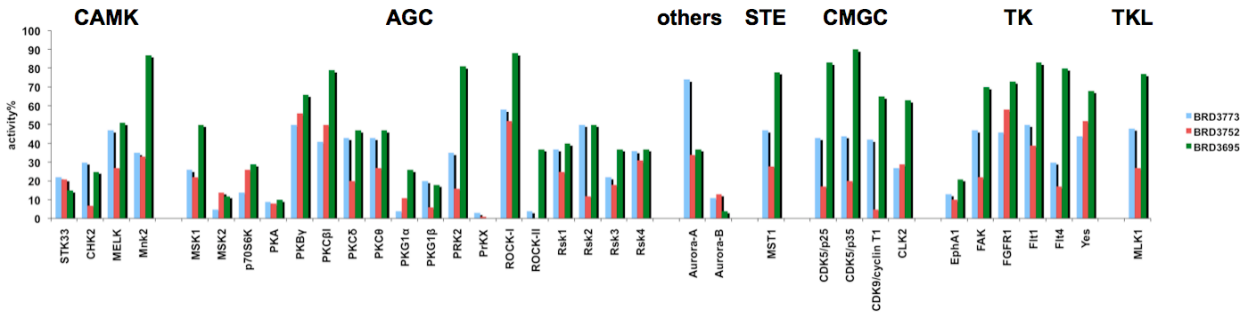


Figure S5. Biochemical kinase profiling of compounds **BRD3773**, **BRD3752** and **BRD3695** (2.5 μM) against 36 kinases under [ATP]=$K_{M,ATP}$. Y axial: the percent of kinase activity remained in the presence of the inhibitor.

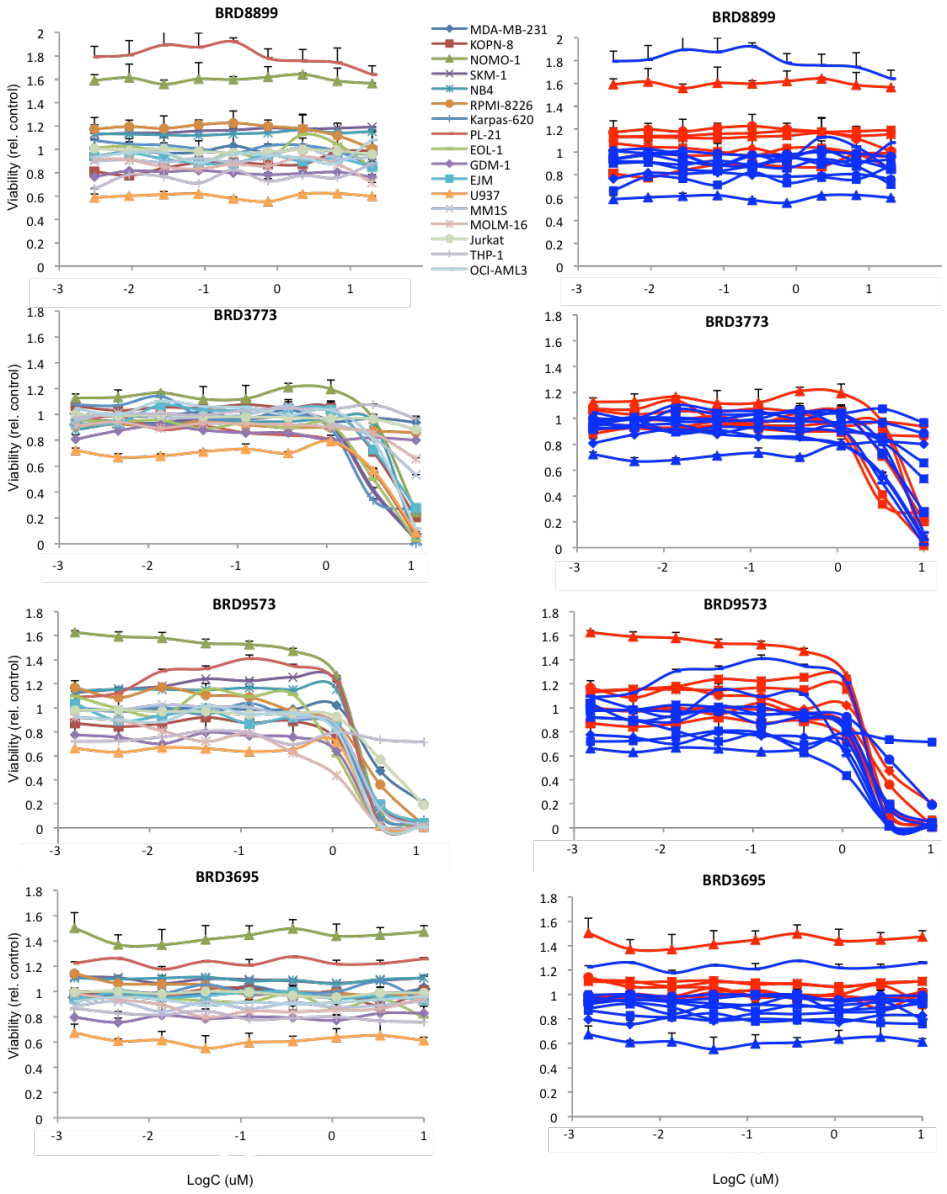


Figure S6. Cell viability assay for fasudil analogs BRD8899, BRD3773, BRD9573 and BRD3695. Dose-response curves of the indicated cell lines using CellTiter Glo as a measurement for viability. The luminescence values of each compound treatment divided by the median of all DMSO values for each individual cell line was taken as a measurement of relative viability. Error bars represent the standard deviation of three replicates. Curves to the left are color coded based on cell line and the right ones are the same plots, but showing KRAS mutant and KRAS wild-type cell lines depicted in red or blue, respectively.

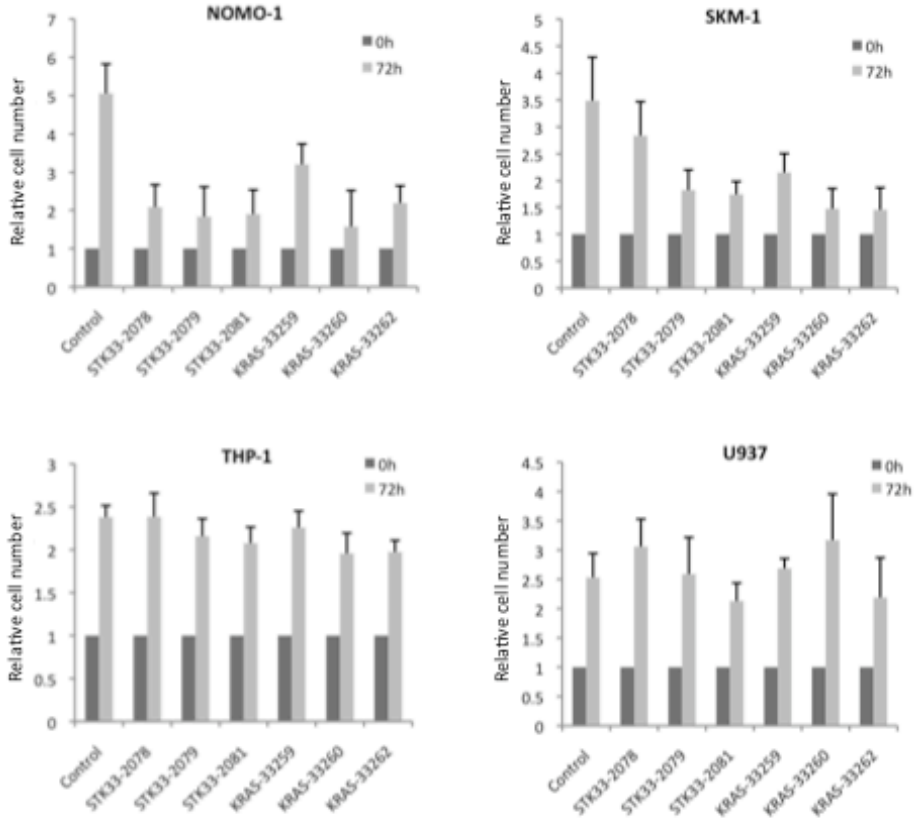
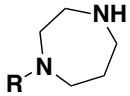


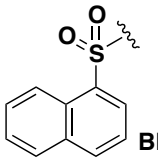
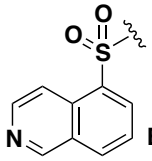
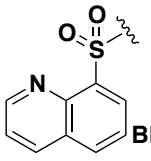
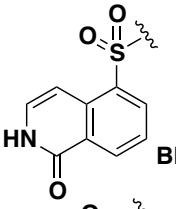
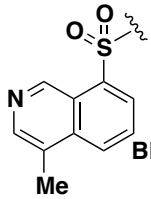
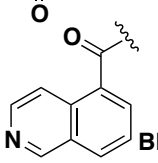
Figure S7. Effects of different *STK33* and *KRAS* shRNAs on cell viability. NOMO-1, SKM-1 (KRAS mutant), THP-1 and U937 (KRAS wild type) cells were transduced with shRNAs constructs targeting different regions of the *STK33* or *KRAS* transcripts, as well as with a nontargeting control shRNA. Cell number was measured using CellTiter Glo on days 4 (0 h) and 8 (72 h) post transduction. Experiments were performed in triplicate. All samples are normalized to time point 0h and are represented as mean ± SEM.

Table S1. Compound sources

Library Name	Compound Number	Hit Number
Commercial collection	1280	1
Natural products	1920	41
Bioactives	2560	61
Structural diversity (DOS)	960	0
Chemical biology library initiative (DOS)	9600	0
Kinase-biased	11520	8

Table S2.



R	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP	R	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP
 BRD5288	>186	>186	 fasudil BRD7868	14	29
 BRD1651	>186	>186	 BRD6825	5.3	11
 BRD4469	>186	>186	 BRD0811	>186	>186

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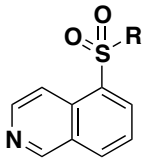


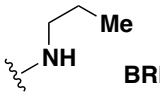
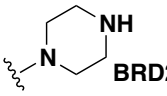
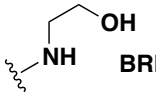
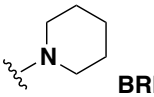
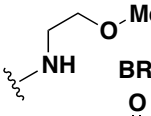
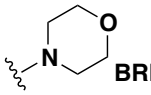
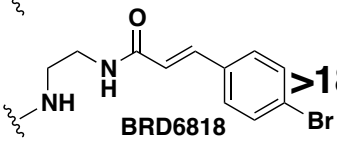
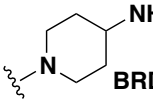
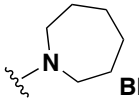
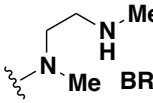
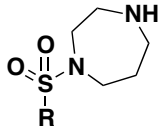
R	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP	R	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP
 BRD2998	>186	>186	 BRD2751	29	64
 BRD4220	110	>186	 BRD7527	>186	>186
 BRD7390	>186	>186	 BRD9836	>186	>186
 BRD6818	>186	>186	 BRD3518	26	60
 BRD0188	>186	>186	 BRD9802	36	175

Table S4.



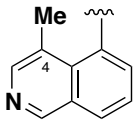
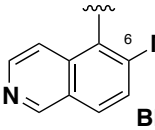
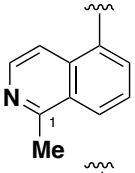
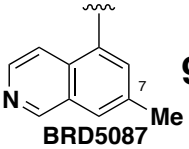
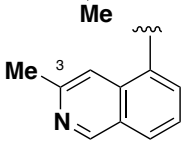
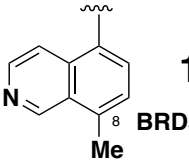
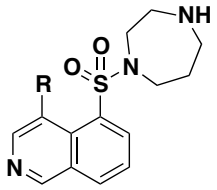
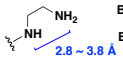
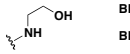
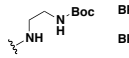
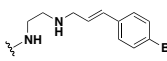
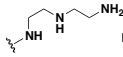
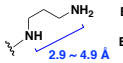
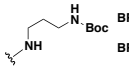
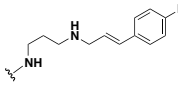
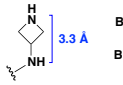
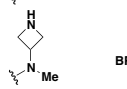
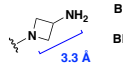
R	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP	R	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP
	0.19 BRD3773	0.56		12 BRD9726	26
	>186 BRD6042	>186		9.1 BRD5087	20
	30 BRD9852	51		176 BRD5257	205

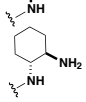
Table S5.



R	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP	R	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP
H fasudil BRD7868	14	29	Br BRD8880	24	49
Me BRD3773	0.19	0.56	NH_2 BRD2749	21	39
Me BRD5930	0.28	0.81	HO BRD7648	21	71
BRD5796	0.24	0.68	OH OH BRD5505	95	203
F F BRD8757	0.48	1.1	O BRD4734	6.9	18
BRD7032	0.94	2.9	Me O NH N BRD0859	26	74
Me BRD7132	1.6	3.2			
Me BRD9078	4.0	8.6	CO_2Me BRD7198	13	44

Table S6.

A	Compound	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP
	BRD7657 (R = H)	14	29
	BRD5549 (R = Me)	1.6	3.2
	BRD4220 (R = H)	110	>186
	BRD3610 (R = Me)	11	25
	BRD4153 (R = H)	>186	>186
	BRD9391 (R = Me)	52	>186
	BRD7647 (R = H)	2.2	6.6
	BRD9330 (R = Me)	2.1	4.6
	BRD4009 (R = H)	1.0	2.1
	BRD3407 (R = Me)	3.7	6.4
	BRD8531 (R = H)	46	98
	BRD6995 (R = Me)	1.8	4.7
	BRD9091 (R = H)	>186	>186
	BRD7177 (R = Me)	35	89
	BRD5149 (R = H)	8.6	16
	BRD8198 (R = Me)	2.8	6.6
	BRD4958 (R = H)	7.4	19
	BRD3966 (R = Me)	0.29	0.57
	(R = H)	--	--
	BRD9325 (R = Me)	0.65	1.2
	BRD5991 (R = H)	19	42
	BRD5337 (R = Me)	0.84	1.3

A	Compound	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP
	BRD7868 (R = H)	14	29
	BRD3773 (R = Me)	0.19	0.56
	BRD7364 (R = H)	71	>186
	BRD9027 (R = Me)	1.7	4.1
	BRD0322 (R = H)	23	30
	BRD5419 (R = Me)	1.2	2.1
	BRD0112 (R = H)	15	46
	BRD9740 (R = Me)	2.0	3.6
	(R = H)	--	--
	BRD1742 (R = Me)	2.7	5.3
	BRD3590 (R = H)	9.3	24
	BRD3752 (R = Me)	0.047	0.13
	BRD3490 (R = H)	16	41
	BRD0828 (R = Me)	3.7	13
	BRD3501 (R = H)	7.1	16
	BRD3695 (R = Me)	0.063	0.17
	BRD8943 (R = H)	10	39
	BRD9573 (R = Me)	4.8	10
	BRD7481 (R = H)	397	>714
	(R = Me)	--	--
	BRD7425 (R = H)	>714	>714
	(R = Me)	--	--

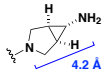
A	Compound	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP
	BRD2246 (R = H)	201	>714
	BRD7471 (R = Me)	4.2	11
	BRD2751 (R = H)	29	64
	BRD9575 (R = Me)	0.79	1.9
	BRD2297 (R = H)	16	31
	BRD4942 (R = Me)	1.4	4.2
	BRD0841 (R = H)	6.1	16
	BRD3376 (R = Me)	1.6	2.6
	BRD1199 (R = H)	62	>186
	BRD3436 (R = Me)	1.2	2.8
	BRD3033 (R = H)	13	31
	BRD2668 (R = Me)	2.6	5.6
	BRD0561 (R = H)	36	78
	BRD4209 (R = Me)	0.99	1.5
	BRD3518 (R = H)	26	60
	BRD2986 (R = Me)	1.2	2.8
	BRD5717 (R = H)	38	96
	BRD7682 (R = Me)	7.9	16
	BRD2594 (R = H)	16	47
	BRD5731 (R = Me)	2.3	5.1

Table S7.

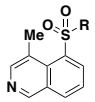
Kinase	activity%
PrKX(h)	3
PKG1α(h)	4
ROCK-II(h)	4
MSK2(h)	5
PKA(h)	9
Aurora-B(h)	11
EphA1(h)	13
p70S6K(h)	14
PKG1β(h)	20
Rsk3(h)	22
STK33(h)	22
MSK1(h)	26
CLK2(h)	27
CHK2(h)	30
Flt4(h)	30
Mnk2(h)	35
PRK2(h)	35
Rsk4(h)	36
Rsk1(h)	37
PKCβI(h)	41
CDK9/cyclin T1(h)	42
CDK5/p25(h)	43
PKCδ(h)	43
PKCθ(h)	43
CDK5/p35(h)	44
Yes(h)	44
FGFR1(h)	46
FAK(h)	47
MELK(h)	47
MST1(h)	47
MLK1(h)	48
Flt1(h)	50
PKBγ(h)	50
Rsk2(h)	50
AMPKα2(h)	51
BrSK2(h)	51
TAO1(h)	52
LOK(h)	54
Mer(h)	54
Fes(h)	56
PKCη(h)	56
Fgr(h)	57
KDR(h)	57
PTK5(h)	57
GRK7(h)	58
ROCK-I(h)	58
Src(1-530)(h)	58
PKCβII(h)	59
CDK7/cyclinH/MAT1(h)	60
SIK(h)	60
TrkA(h)	60
GCK(h)	61
LIMK1(h)	62
AMPKα1(h)	63
Hck(h)	64
Ret(h)	64
PKCμ(h)	66
FGFR3(h)	67
EphB1(h)	68
Haspin(h)	69
PKCε(h)	69

Kinase	activity%
ALK4(h)	70
SGK2(h)	70
Fyn(h)	71
CaMKIIβ(h)	72
FGFR2(h)	72
PhKγ2(h)	72
CaMKIIδ(h)	73
EphA2(h)	73
Plk3(h)	73
Aurora-A(h)	74
GRK5(h)	74
ARK5(h)	76
Lyn(h)	77
GRK6(h)	79
TAO3(h)	81
CLK3(h)	82
FGFR4(h)	82
BrSK1(h)	84
CDK2/cyclinE(h)	84
JNK3(h)	84
Lck(h)	84
PI3KC2α(h)	84
CaMKIV(h)	85
MST2(h)	85
Axl(h)	86
BRK(h)	86
cSRC(h)	87
PAK3(h)	87
Snk(h)	87
CDK1/cyclinB(h)	88
MARK1(h)	88
MST3(h)	88
PDK1(h)	88
ULK2(h)	88
VRK2(h)	88
Lck(h) activated	89
MKK6(h)	89
NLK(h)	90
Pyk2(h)	90
SAPK4(h)	90
IRAK1(h)	91
PASK(h)	91
DCAMKL2(h)	92
EphA5(h)	92
PKCα(h)	92
SGK3(h)	92
Bmx(h)	93
CDK3/cyclinE(h)	93
EphA7(h)	93
EphB2(h)	93
EphB4(h)	93
GSK3β(h)	93
LKB1(h)	93
PKCζ(h)	93
TAK1(h)	93
ULK3(h)	93
CDK2/cyclinA(h)	94
DRAK1(h)	94
Met(h)	94
PKD2(h)	94
Plk1(h)	94

Kinase	activity%
ASK1(h)	95
MAPKAP-K2(h)	95
NEK11(h)	95
TrkB(h)	95
IGF-1R(h)	96
IKKβ(h)	96
PKBα(h)	96
WNK3(h)	96
EphA8(h)	97
JAK3(h)	97
Rse(h)	97
SRPK1(h)	97
WNK2(h)	97
CDK6/cyclinD3(h)	98
IRR(h)	98
PIP5K1α(h)	98
Ron(h)	98
CaMKIIγ(h)	99
DYRK2(h)	99
Fer(h)	99
PI3 Kinase (p110β/p85α)(h)	99
PIP5K1γ(h)	99
PKBβ(h)	99
TAO2(h)	99
TBK1(h)	99
Tec(h) activated	99
TLK2(h)	99
Arg(h)	100
SAPK2b(h)	100
BTK(h)	101
DMPK(h)	101
EphA4(h)	101
Flt3(h)	101
Hck(h) activated	101
MAPKAP-K3(h)	101
MKK4(m)	101
MLCK(h)	101
Syk(h)	101
ZIPK(h)	101
MINK(h)	102
NEK2(h)	102
Pim-1(h)	102
PKCι(h)	102
RIPK2(h)	102
Txk(h)	102
CK1γ1(h)	103
c-RAF(h)	103
PAK5(h)	103
PI3 Kinase (p110δ/p85α)(h)	103
Tie2(h)	103
CK1δ(h)	104
eEF-2K(h)	104
EphB3(h)	104
IGF-1R(h), activated	104
IRAK4(h)	104
MRCKβ(h)	104
PAR-1Bα(h)	104
SAPK3(h)	104
EphA3(h)	105
MRCKα(h)	105
NEK3(h)	105

Kinase	activity%
PDGFRβ(h)	105
HIPK2(h)	106
HIPK3(h)	106
IKKα(h)	106
MAPK1(h)	106
PKCγ(h)	106
Src(T341M)(h)	106
Abl(h)	107
EGFR(h)	107
HIPK1(h)	107
MAPK2(h)	107
NEK7(h)	107
PAK2(h)	107
PIP4K2α(h)	107
PRAK(h)	107
ALK(h)	108
IR(h), activated	108
MSSK1(h)	108
PAK4(h)	108
PDGFRα(h)	108
PI3 Kinase (p120γ)(h)	108
CK1γ2(h)	109
DAPK2(h)	109
mTOR/FKBP12(h)	109
ACK1(h)	110
CSK(h)	110
MEK1(h)	110
NEK6(h)	110
PAK6(h)	110
CK1γ3(h)	111
CK2α2(h)	111
DAPK1(h)	111
ZAP-70(h)	111
CaMKI(h)	112
SAPK2a(h)	112
cKit(h)	113
ErbB4(h)	113
GSK3α(h)	113
Itk(h)	113
JNK1α1(h)	113
MuSK(h)	113
Pim-3(h)	113
Ros(h)	114
SRPK2(h)	114
mTOR(h)	115
SGK(h)	115
CHK1(h)	116
CK2(h)	116
IR(h)	116
CaMKIδ(h)	117
JNK2α2(h)	118
TSSK2(h)	119
Pim-2(h)	120
MKK7β(h)	122
DDR2(h)	123
JAK2(h)	136
Fms(h)	149
TSSK1(h)	195

Table S8.



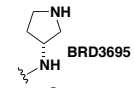
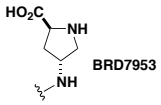
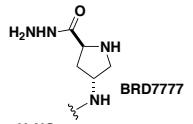
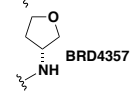
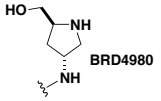
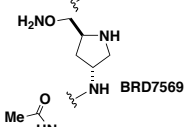
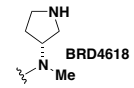
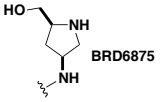
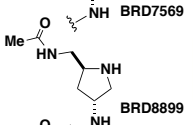
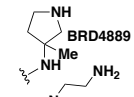
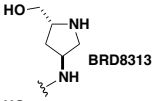
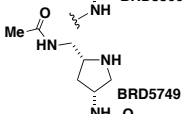
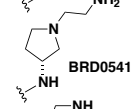
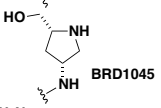
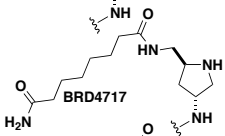
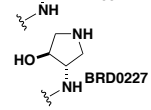
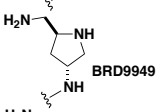
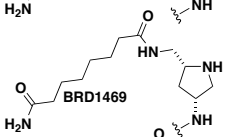
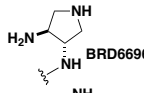
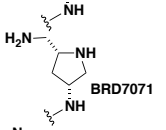
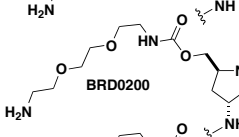
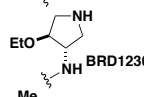
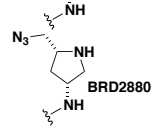
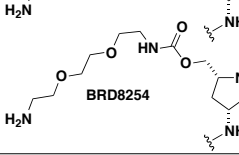
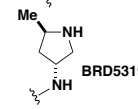
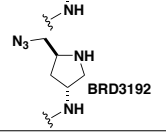
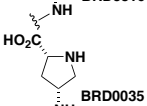
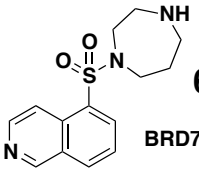
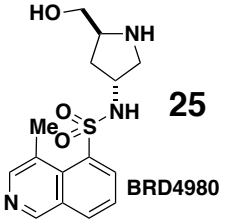
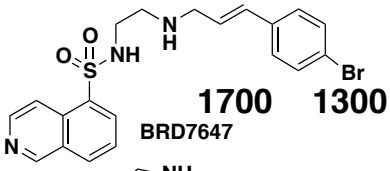
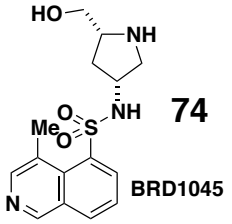
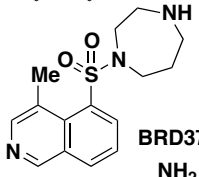
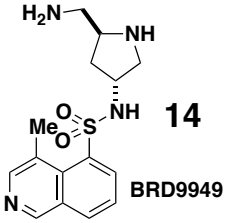
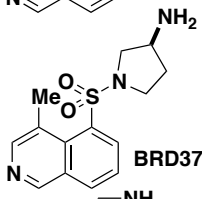
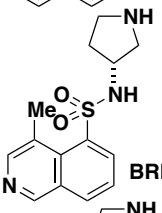
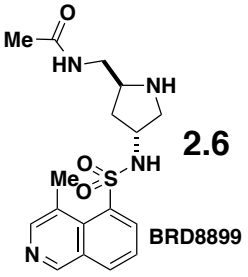
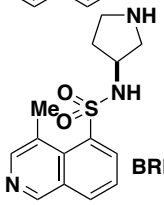
R	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP	R	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP	R	IC_{50} (μM) @ 25 μM ATP	IC_{50} (μM) @ 100 μM ATP
 BRD3695	0.063	0.17	 BRD7953	1.8	3.7	 BRD7777	2.0	4.6
 BRD4357	32	56	 BRD4980	0.037	0.090	 BRD7569	0.067	0.15
 BRD4618	1.2	3.2	 BRD6875	2.8	9.2	 BRD8899	0.011	0.025
 BRD4889	2.7	9.2	 BRD8313	0.81	3.2	 BRD5749	0.52	1.2
 BRD0541	5.9	10	 BRD1045	0.12	0.25	 BRD4717	0.073	0.14
 BRD0227	0.54	1.6	 BRD9949	0.020	0.032	 BRD1469	0.061	0.13
 BRD6696	0.42	1.7	 BRD7071	0.42	0.87	 BRD0200	0.084	0.21
 BRD1230	4.2	12	 BRD2880	0.24	0.53	 BRD8254	0.26	1.0
 BRD5319	0.065	0.14	 BRD3192	0.037	0.11			
 BRD0035	0.78	2.2						

Table S9. Comparison of the biochemical K_i with K_d in the Ambit binding assay

Compound	Biochemical K_i (nM)	Ambit K_d(nM)	Compound	Biochemical K_i (nM)	Ambit K_d(nM)
 BRD7868	6800	4600	 BRD4980	25	14
 BRD7647	1700	1300	 BRD1045	74	43
 BRD3773	89	130	 BRD9949	14	29
 BRD3752	35	120			
 BRD3695	20	32	 BRD8899	2.6	11
 BRD9573	3700	3200			

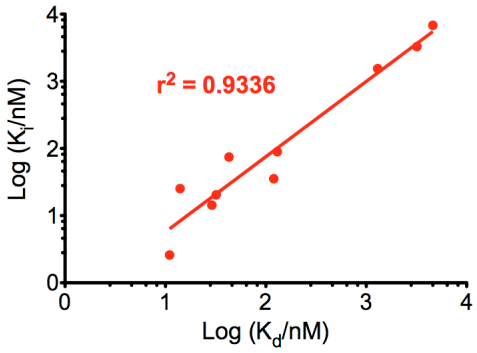


Table S10.

KINOMEscan Gene Symbol	Control%
RIOK1	2.6
MST4	4
STK33	11
RSK4(Kin.Dom.1-N-terminal)	11
AKT1	15
KIT(D816V)	15
ROCK1	16
FLT3(ITD)	19
EPHA1	20
FLT3(D835Y)	20
PRKCE	21
PRKCD	22
ROCK2	23
PRKX	25
ABL1(H396P)-nonphosphorylated	27
PIP5K1A	32
MST2	35
NEK5	36
GRK7	38
ULK1	38
ABL1(T315I)-phosphorylated	40
LZK	40
ABL1-phosphorylated	41
S6K1	41
MST3	42
PHKG2	43
RIOK3	43
ABL1(F317L)-phosphorylated	44
JAK3(JH1domain-catalytic)	46
PLK4	47
FLT3	48
MERTK	48
MET(M1250T)	48
DLK	50
PKAC-alpha	52
BIKE	55
CAMKK2	56
FLT3(N841I)	56
TBK1	56
AURKB	57
RSK2(Kin.Dom.1-N-terminal)	57
ABL1(F317L)-nonphosphorylated	58
EPHA3	58
AURKC	59
HIPK1	59
MAP4K3	59
IRAK3	60
SRC	61
ABL1(H396P)-phosphorylated	62
PHKG1	63
AKT3	65
CDK7	65
YSK1	66
ABL1(M351T)-phosphorylated	67
ABL1(Q252H)-phosphorylated	67
ABL1(Y253F)-phosphorylated	67
RSK3(Kin.Dom.2-C-terminal)	67
MELK	68
TRPM6	68
RET(M918T)	69
KIT(V559D,T670I)	70
PDGFRB	70
RSK4(Kin.Dom.2-C-terminal)	70
STK35	70
KIT	71
TRKB	71
ERN1	72
FGR	72
CDK2	73
WEE2	73
AAK1	74
ACVR1B	74
AXL	74
CDKL1	74

KINOMEscan Gene Symbol	Control%
DCAMKL2	74
PKN2	74
RSK1(Kin.Dom.2-C-terminal)	74
TESK1	74
BRSK1	75
EPHA2	75
ABL1(E255K)-phosphorylated	76
EPHB1	76
FAK	76
PRKCQ	76
RAF1	76
CSNK2A1	77
FRK	77
MEK3	77
EGFR(L861Q)	78
FGFR1	78
INSR	78
IRAK4	78
TYK2(JH1domain-catalytic)	78
CDK11	79
ZAK	79
ABL1-nonphosphorylated	80
KIT(D816H)	80
PRKD3	80
SRPK3	80
DCAMKL1	81
MARK4	81
PIP5K1C	81
FES	82
KIT(V559D)	82
MARK2	82
MST1R	82
PAK7	82
CLK1	83
CSF1R	83
PKNB(M.tuberculosis)	83
JNK1	84
LYN	84
PDPK1	84
PRKG1	84
EPHA6	85
GRK1	85
PIK3CG	85
PYK2	85
CDK3	86
EGFR(T790M)	86
ERK3	86
HIPK4	86
JAK2(JH1domain-catalytic)	86
PIP5K2B	86
SLK	86
TAOK1	86
TGFBR1	86
TLK1	86
TNNI3K	86
CSNK1A1	87
HPK1	87
LIMK2	87
MAP3K4	87
RSK1(Kin.Dom.1-N-terminal)	87
ANKK1	88
EGFR(G719C)	88
MAP4K5	88
PRKCH	88
DAPK1	89
KIT(L576P)	89
MAP3K3	89
MAP4K2	89
PIK3CA(E542K)	89
PRKG2	89
ACVR2A	90
CAMK1G	90
FGFR2	90
FGFR4	90

KINOMEscan Gene Symbol	Control%
JNK2	90
p38-gamma	90
PKAC-beta	90
SIK2	90
SNARK	90
TIE1	90
ULK2	90
ULK3	90
CAMK2G	91
DYRK1B	91
EPHA8	91
MYLK2	91
BMX	92
CDKL2	92
CDKL3	92
FLT3(D835H)	92
MAP4K4	92
MARK1	92
MKK7	92
MLK2	92
MRCKA	92
PIK3CA(I800L)	92
PRP4	92
STK36	92
TRKA	92
AKT2	93
EGFR(E746-A750del)	93
EGFR(L747-S752del, P753S)	93
PLK2	93
ABL1(F317I)-nonphosphorylated	94
ABL1(Q252H)-nonphosphorylated	94
ADCK4	94
EPHA5	94
EPHA7	94
GRK4	94
IRAK1	94
MARK3	94
p38-beta	94
RIOK2	94
LRRK2(G2019S)	95
PFTAIRE2	95
PIK3CB	95
SRMS	95
EGFR(L747-T751del,Sins)	96
EPHB2	96
ERBB4	96
GAK	96
PCTK1	96
RIPK4	96
TAK1	96
OSR1	97
RIPK1	97
BMPR2	98
EGFR(L858R)	98
LATS1	98
MYO3B	98
YANK3	98
CDK8	99
DMPK2	99
EPHB3	99
EPHB6	99
LATS2	99
ROS1	99
ABL1(F317I)-phosphorylated	100
ABL1(T315I)-nonphosphorylated	100
ABL2	100
ACVR1	100
ACVR2B	100
ACVRL1	100
ADCK3	100
ALK	100
AMPK-alpha1	100
AMPK-alpha2	100
ARK5	100

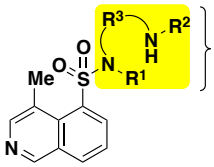
Table S10 (continued).

KINOMEscan Gene Symbol	Control%
ASK1	100
ASK2	100
AURKA	100
BLK	100
BMPR1A	100
BMPR1B	100
BRAF	100
BRAF(V600E)	100
BRK	100
BRSK2	100
BTK	100
CAMK1	100
CAMK1D	100
CAMK2A	100
CAMK2B	100
CAMK2D	100
CAMK4	100
CAMKK1	100
CASK	100
CDC2L1	100
CDC2L2	100
CDC2L5	100
CDK4-cyclinD1	100
CDK4-cyclinD3	100
CDK5	100
CDK9	100
CDKL5	100
CHEK1	100
CHEK2	100
CIT	100
CLK2	100
CLK3	100
CLK4	100
CSK	100
CSNK1A1L	100
CSNK1D	100
CSNK1E	100
CSNK1G1	100
CSNK1G2	100
CSNK1G3	100
CSNK2A2	100
CTK	100
DAPK2	100
DAPK3	100
DCAMKL3	100
DDR1	100
DDR2	100
DMPK	100
DRAK1	100
DRAK2	100
DYRK1A	100
DYRK2	100
EGFR	100
EGFR(G719S)	100
EGFR(L747-E749del, A750P)	100
EGFR(L858R,T790M)	100
EGFR(S752-I759del)	100
EIF2AK1	100
EPHA4	100
EPHB4	100
ERBB2	100
ERBB3	100
ERK1	100
ERK2	100
ERK4	100
ERK5	100
ERK8	100
FER	100
FGFR3	100
FGFR3(G697C)	100
FLT1	100
FLT3(K663Q)	100
FLT3(R834Q)	100
FLT4	100

KINOMEscan Gene Symbol	Control%
FYN	100
GCN2(Kin.Dom.2,S808G)	100
GSK3A	100
GSK3B	100
HCK	100
HIPK2	100
HIPK3	100
HUNK	100
ICK	100
IGF1R	100
IKK-alpha	100
IKK-beta	100
IKK-epsilon	100
INSRR	100
ITK	100
JAK1(JH1domain-catalytic)	100
JAK1(JH2domain-pseudokinase)	100
JNK3	100
KIT(A829P)	100
KIT(V559D,V654A)	100
LCK	100
LIMK1	100
LKB1	100
LOK	100
LRRK2	100
LTK	100
MAK	100
MAP3K1	100
MAP3K15	100
MAP3K2	100
MAPKAPK2	100
MAPKAPK5	100
MAST1	100
MEK1	100
MEK2	100
MEK4	100
MEK5	100
MEK6	100
MET	100
MET(Y1235D)	100
MINK	100
MKNK1	100
MKNK2	100
MLCK	100
MLK1	100
MLK3	100
MRCKB	100
MST1	100
MTOR	100
MUSK	100
MYLK	100
MYLK4	100
MYO3A	100
NDR1	100
NDR2	100
NEK1	100
NEK11	100
NEK2	100
NEK3	100
NEK4	100
NEK6	100
NEK7	100
NEK9	100
NIM1	100
NLK	100
p38-alpha	100
p38-delta	100
PAK1	100
PAK2	100
PAK3	100
PAK4	100
PAK6	100
PCTK2	100
PCTK3	100

KINOMEscan Gene Symbol	Control%
PDGFRA	100
PFCDPK1(P.falciparum)	100
PFPK5(P.falciparum)	100
PFTK1	100
PIK3C2B	100
PIK3C2G	100
PIK3CA	100
PIK3CA(C420R)	100
PIK3CA(E545A)	100
PIK3CA(E545K)	100
PIK3CA(H1047L)	100
PIK3CA(H1047Y)	100
PIK3CA(M1043I)	100
PIK3CA(Q546K)	100
PIK3CD	100
PIK4CB	100
PIM1	100
PIM2	100
PIM3	100
PIP5K2C	100
PKMYT1	100
PKN1	100
PLK1	100
PLK3	100
PRKCI	100
PRKD1	100
PRKD2	100
PRKR	100
QSK	100
RET	100
RET(V804L)	100
RET(V804M)	100
RIPK2	100
RIPK5	100
RPS6KA4(Kin.Dom.1-N-terminal)	100
RPS6KA4(Kin.Dom.2-C-terminal)	100
RPS6KA5(Kin.Dom.1-N-terminal)	100
RPS6KA5(Kin.Dom.2-C-terminal)	100
RSK3(Kin.Dom.1-N-terminal)	100
SBK1	100
SgK110	100
SGK3	100
SIK	100
SNRK	100
SRPK1	100
SRPK2	100
STK16	100
STK39	100
SYK	100
TAOK2	100
TAOK3	100
TEC	100
TGFBR2	100
TIE2	100
TLK2	100
TNIK	100
TNK1	100
TNK2	100
TRKC	100
TSSK1B	100
TTK	100
TXK	100
TYK2(JH2domain-pseudokinase)	100
TYRO3	100
VEGFR2	100
VRK2	100
WEE1	100
YANK1	100
YANK2	100
YES	100
YSK4	100
ZAP70	100

Table S11.



Amine

STK33 IC_{50} (μM) @ 25 μM ATP (K_m)

AurB IC_{50} (μM) @ 10 μM ATP (K_m)

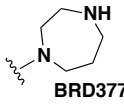
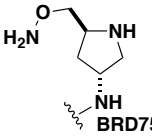
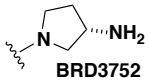
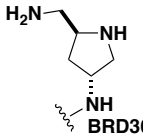
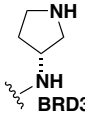
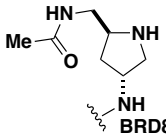
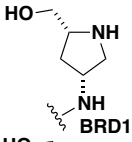
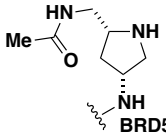
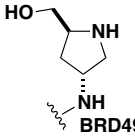
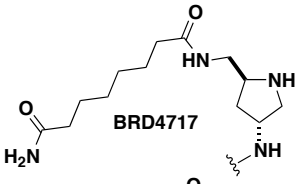
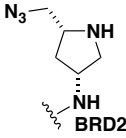
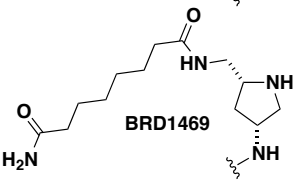
Amine	STK33	AurB	Amine	STK33	AurB
 BRD3773	0.19	0.31	 BRD7569	0.067	0.19
 BRD3752	0.047	0.22	 BRD3695	0.020	0.24
 BRD3695	0.063	0.17	 BRD8899	0.011	0.17
 BRD1045	0.12	0.55	 BRD5749	0.52	1.0
 BRD4980	0.037	0.40	 BRD4717	0.073	0.074
 BRD2880	0.24	0.68	 BRD1469	0.061	0.70
 BRD3192	0.037	0.11			

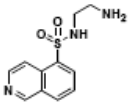
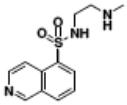
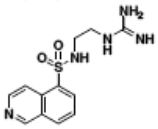
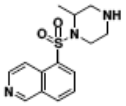
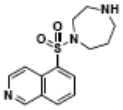
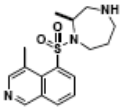
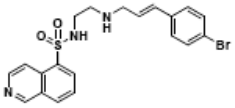
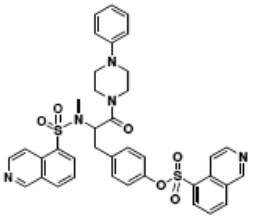
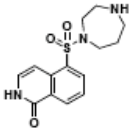
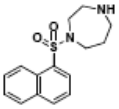
Table S12. Cell lines used for the cell-based screens.

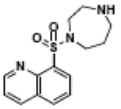
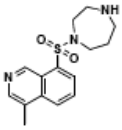
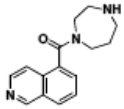
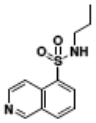
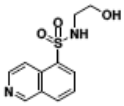
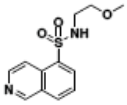
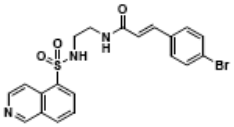
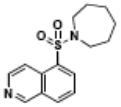
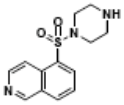
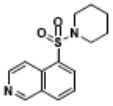
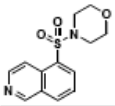
Name	Origin	KRAS status[i]
NOMO-1	AML	G13D
SKM-1	AML	K117N
NB4	AML	A18D
THP-1	AML	WT
U937	AML	WT
OCI-AML3	AML	WT
MOLM-16	AML	WT
PL-21	AML	WT
EOL-1	AML	WT
GDM-1	AML	WT
KOPN-8	ALL	G13D
JURKAT	ALL	WT
Karpas-620	Multiple myeloma	G13D
RPMI-8226	Multiple myeloma	G12A
EJM	Multiple myeloma	WT
MM.1S	Multiple myeloma	WT
DLD-1	Colon cancer	G13D
HCT-15	Colon cancer	G13D
COLO205	Colon cancer	WT
HeyA8	Ovarian cancer	G13D
OVCAR-3	Ovarian cancer	WT
CaOV3	Ovarian cancer	WT
OVCAR-8	Ovarian cancer	WT
KYSE-450	Esophageal cancer	WT
MDA-MB-231	Breast cancer	G13D

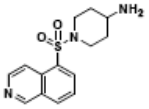
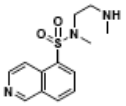
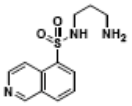
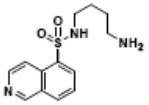
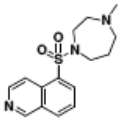
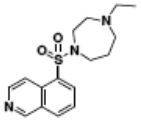
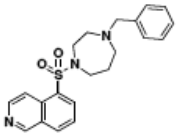
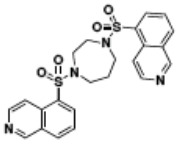
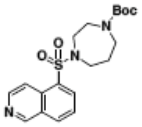
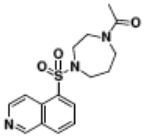
A549	NSCLC	G12S
H2009	NSCLC	G12A
H1792	NSCLC	G12C
H23	NSCLC	G12C
H1975	NSCLC	WT
H1568	NSCLC	WT
H1437	NSCLC	WT
H522	NSCLC	WT

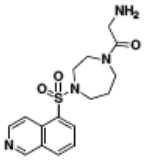
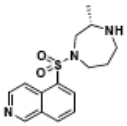
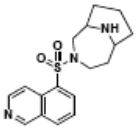
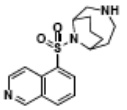
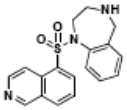
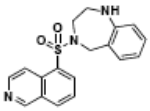
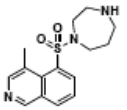
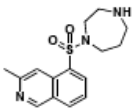
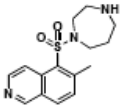
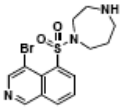
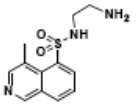
[i] According to the Catalogues of Somatic Mutations in Cancer (COSMIC).

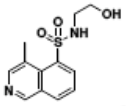
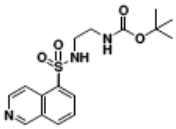
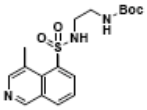
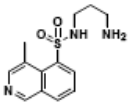
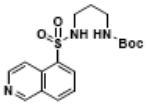
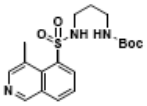
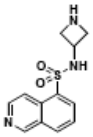
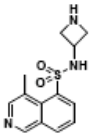
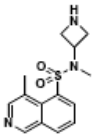
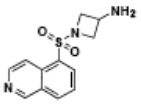
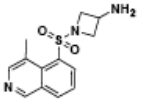
Table S13. Biochemical IC_{50} values for inhibition of STK33, synthesis yield and QC data

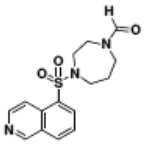
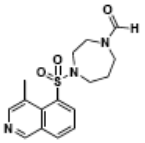
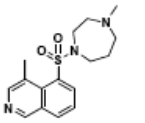
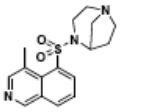
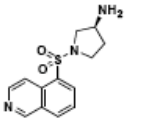
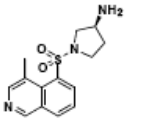
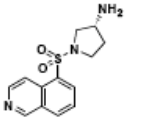
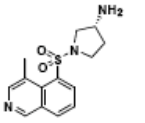
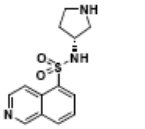
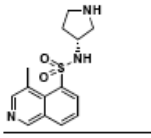
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD7657	29	14		252.08	252.16	0.41	
	BRD2343	43	20					
	BRD4375	67	34					
	BRD6846	84	39					
	BRD7868	31	14					
	BRD7446	4.3	2					
	BRD7647	6.6	2.2					
	BRD7136	>186	>186					
	BRD6825	11	5.3					
	BRD5288	>186	>186	99	291.12	291.08		

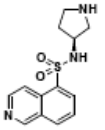
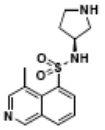
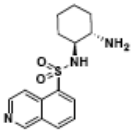
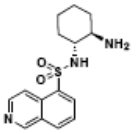
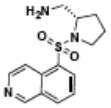
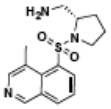
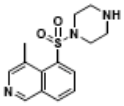
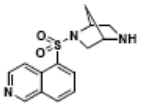
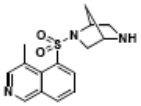
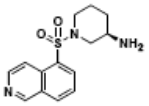
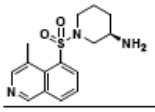
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD1651	>186	>186	99	292.16	292.23	0.72	
	BRD4469	>186	>186	21	306.13	306.23	0.88	3.72
	BRD0811	>186	>186	55	256.15	256.25	0.3	2.27
	BRD2998	>186	>186	59	251.09	251.11		2.49
	BRD4220	>186	100	57	253.07	253.16	0.79	1.5
	BRD7390	>186	>186	67	267.08	267.16	0.9	1.43
	BRD6818	>186	>186	45	462.03	462.06	1.29	3.55
	BRD0188	>186	>186	53	291.12	291.26	1.36	2.84
	BRD2751	64.00	29.00	99	279.09	278.15	0.94	
	BRD7527	>186	>186	31	277.1	277.18	1.24	3.72
	BRD9836	>186	>186	38	279.08	279.16	0.99	2.67

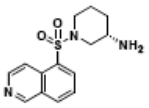
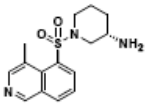
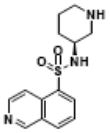
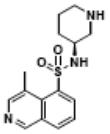
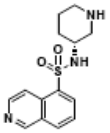
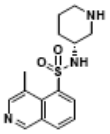
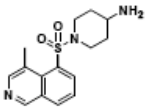
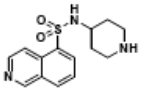
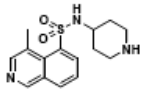
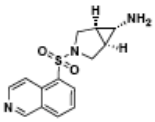
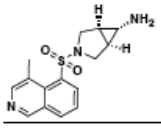
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD3518	60	26	54	292.11	292.18	0.83	4.24
	BRD9802	174	36	48	280.11	280.27	0.79	2.54
	BRD8531	98	46	74	266.1	266.12		1.03
	BRD1688	>714	259	25	280.11	280.15	0.79	1.8
	BRD0322	30	23	12	306.13	306.25	0.63	2.05
	BRD5039	48	42	10	320.15	320.2	0.73	2.02
	BRD5076	177	40	19	382.16	382.12	1.43	3.5
	BRD2660	165	98	10	483.12	483.2	1.21	
	BRD0272	>186	>186	47	392.17			
	BRD8033	>186	>186	42	334.12	334.3	0.91	1.67

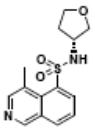
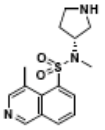
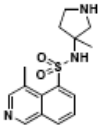
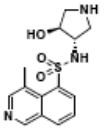
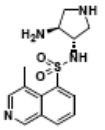
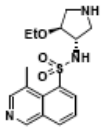
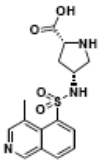
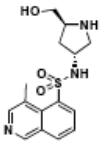
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD5624	>186	>186	50	349.14	349.17	0.84	3.33
	BRD4719	70	24	53	306.13	306.26	0.89	3.28
	BRD3954	127	64	25	332.15	332.15	0.83	4.27
	BRD2533	>714	107	42	332.15	332.2	0.95	3.3
	BRD1104	219	123	77	340.11	340.26	0.86	1.17
	BRD0114	>186	>186	4	340.11	340.21	1.23	3.68
	BRD3773	0.56	0.19	78	306.13	306.19	0.8	4.08
	BRD9852	51	30	55	306.13	306.21	0.87	2.51
	BRD9726	26	12	2	306.13	306.25	0.86	2.9
	BRD8880	49	24	51	372.02	372.13	1.5	1.5
	BRD5549	3.2	1.6	25	266.1	266.26	0.66	1.55

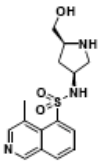
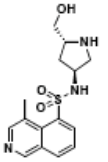
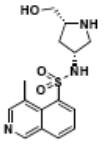
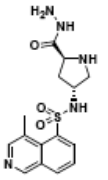
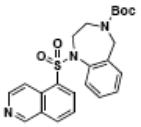
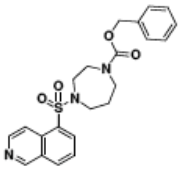
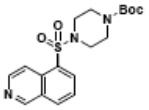
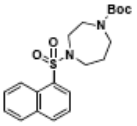
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD3610	**25**	**11**	40	267.08	267.21	0.86	1.6
	BRD4153	**>186**	**>186**	39	352.14			
	BRD9391	**>186**	**52**	95	366.15	366.4	1.13	
	BRD6995	**4.7**	**1.8**	21	280.11	280.2	0.7	1.75
	BRD9091	**>186**	**>186**	62	366.15			
	BRD7177	**89**	**35**	48	380.17	380.5	1.25	
	BRD4958	**19**	**7.4**	33	264.08	264.19	0.7	0.69
	BRD3966	**0.57**	**0.29**	45	278.1	278.2	0.81	1.88
	BRD9325	**1.2**	**0.65**	47	292.11	292.27	0.87	3.15
	BRD5991	**42**	**19**	55	264.08	264.2	0.84	3.38
	BRD5337	**1.3**	**0.84**	72	278.1	278.23	0.84	2.93

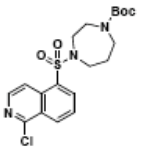
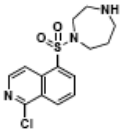
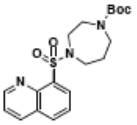
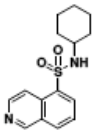
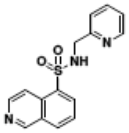
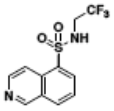
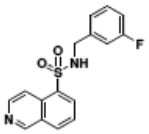
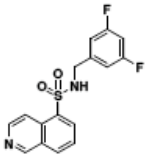
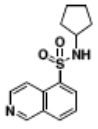
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD7364	>186	71.43	70	320.11	320.2	0.9	1.52
	BRD9027	4.1	1.7	85	334.12	334.47	1.05	2.57
	BRD5419	2.1	1.2	78	320.15	320.29	0.84	4.02
	BRD1742	5.3	2.7	59	318.13	318.25	0.88	3.48
	BRD3590	24	9.3	67	278.1	278.17	0.8	2.67
	BRD3752	0.13	0.047	75	292.11	292.21	0.8	3.63
	BRD3490	41	16	60	278.1	278.2	0.79	3.32
	BRD0828	13	3.7	75	292.11	292.21	0.84	3.67
	BRD3501	16	7.1	91	278.1	278.24	0.83	1.92
	BRD3695	0.17	0.063	60	292.11	292.24	0.73	2.47

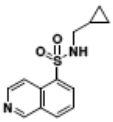
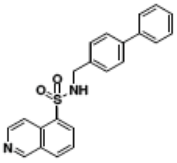
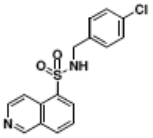
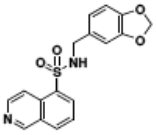
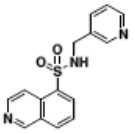
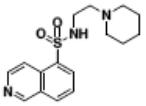
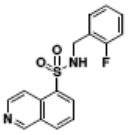
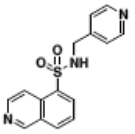
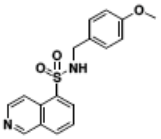
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD8943	39	10	42	278.1	278.24	0.78	2.44
	BRD9573	10	4.8	61	292.11	292.17	0.73	2.25
	BRD7481	>714	397.00	64	306.13	306.19	0.77	4.23
	BRD7425	>714	>714	64	306.13	306.19	0.78	4.24
	BRD2246	>714	201.00	53	292.11	292.23	0.82	2.07
	BRD7471	11	4.2	60	306.13	306.22	0.85	2.64
	BRD9575	1.9	0.79	87	292.11	292.21	0.83	4.24
	BRD2297	31	16	66	290.1	290.25	0.77	3.99
	BRD4942	4.2	1.4	69	304.11	304.22	0.82	4.2
	BRD0841	16	6.1	63	292.11	292.21	0.75	4.24
	BRD3376	2.6	1.6	92	306.13	306.21	0.84	4.27

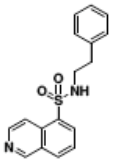
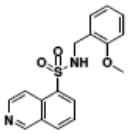
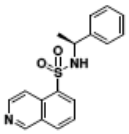
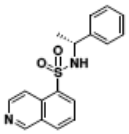
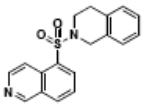
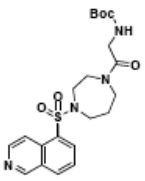
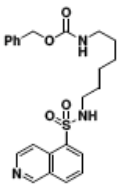
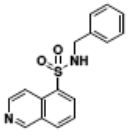
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD1199	>186	62	66	292.11	292.21	0.81	3.4
	BRD3436	2.8	1.2	77	306.13	306.22	0.88	2.67
	BRD3033	31	13	49	292.11	292.28	0.75	2.88
	BRD2668	5.6	2.6	31	306.13	306.28	0.8	3.95
	BRD0561	78	36	39	292.11	292.24	0.77	2.78
	BRD4209	1.5	0.99	38	306.13	306.21	0.8	3.95
	BRD2986	2.8	1.2	88	306.13	306.25	0.88	4.25
	BRD5717	96	38	26	292.11	292.18	0.72	3.98
	BRD7682	16	7.9	69	306.13	306.25	0.78	4.22
	BRD2594	47	16	67	290.1	290.21	0.84	2.09
	BRD5731	5.1	2.3	60	304.11	304.22	0.85	2.62

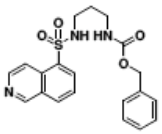
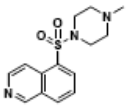
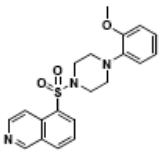
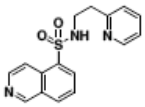
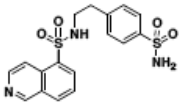
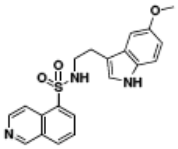
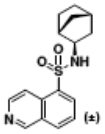
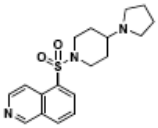
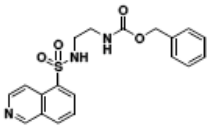
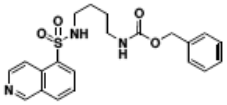
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD4357	**56**	**32**	92	293.1	292.97	0.97	1.92
	BRD4618	**3.2**	**1.2**	21	306.13	306.36	0.8	2.85
	BRD4889	**9.2**	**2.7**	5	306.13	306.3	0.74	3.87
	BRD0227	**1.6**	**0.54**	40	308.11	308.2	0.77	1.48
	BRD6696	**1.7**	**0.42**	54	307.13	307.26	0.9(acid)	0.75
	BRD1230	**12**	**4.2**	23	336.14	336.23	0.91(acid)	3.25
	BRD0035	**2.2**	**0.78**	2	336.1	336.21	0.64	0.66
	BRD4980	**0.09**	**0.037**	44	321.12	322.24	0.79	1.66

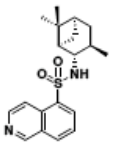
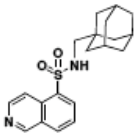
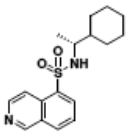
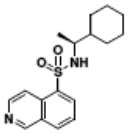
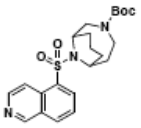
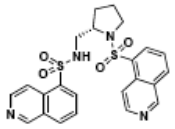
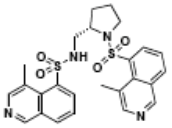
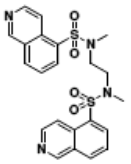
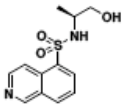
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD6875	**9.2**	**2.8**	77	322.12	322.21	0.63	1.98
	BRD8313	**3.2**	**0.81**	16	322.12	322.16	0.67	3.97
	BRD1045	**0.25**	**0.12**	45	321.12	322.21	0.7	1.83
	BRD7777	**4.6**	**2.0**	3	350.13	350.29	0.72	1.16
	BRD0119	**>186**	**>186**	40	440.17	439.95	1.52	3.87
	BRD5281	**>186**	**>186**	43	426.15	426.23	1.34	2.87
	BRD0649	**>186**	**>186**	65	378.15	378.26	1.31	3.97
	BRD9435	**>186**	**>186**	35	391.17	391.23	1.61	2.67

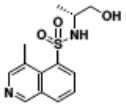
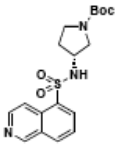
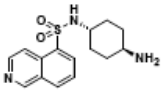
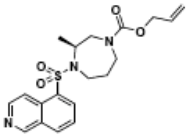
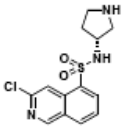
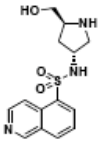
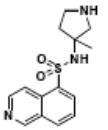
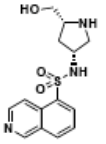
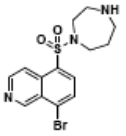
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD2109	>186	>186	85	426.13	426.25	1.57	2.25
	BRD0197	27.14	10.71		326.13	326.14	0.9	
	BRD9508	>186	>186	42	392.16	392.14	1.43	3.4
	BRD1968	>186	>186	51	291.12	291.21	1.3	3.98
	BRD2155	>186	>186	39	300.08	300.17	0.9	2.08
	BRD6736	>186	>186	12	291.04	291.14	1.11	0.92
	BRD8071	>186	>186	46	317.08	317.14	1.24	3.53
	BRD4041	>186	>186	49	335.07	335.13	1.28	3.62
	BRD3373	>186	>186	70	277.1	277.17	1.2	3.42

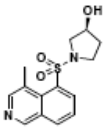
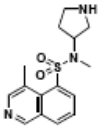
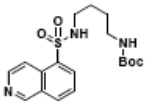
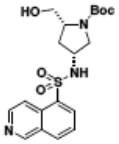
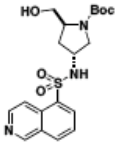
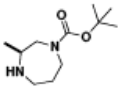
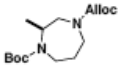
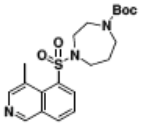
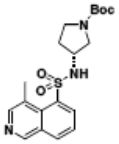
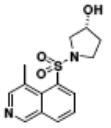
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD0572	>186	>186	53	263.09	263.13	1.12	2.67
	BRD8188	>186	>186	58	375.12	375.14	1.47	3.98
	BRD5670	>186	>186	50	333.05	333.1	1.33	4
	BRD1731	>186	>186	61	343.08	343.15	1.18	3.22
	BRD4553	>186	>186	39	300.08	300.18	0.83	1.87
	BRD9215	75.71	46.43	60	320.15	320.22	0.85	3.63
	BRD8584	>186	>186	61	317.08	317.14	1.21	3.37
	BRD9483	>186	>186	42	300.08	300.17	0.83	3.43
	BRD7266	>186	>186	6	329.1	329.18	1.2	3.4

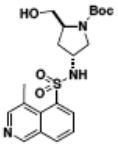
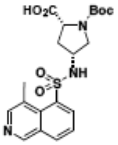
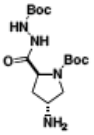
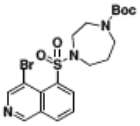
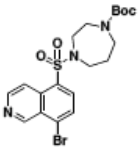
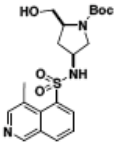
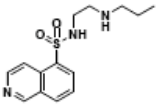
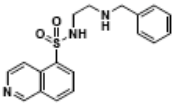
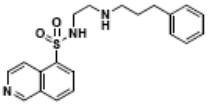
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD0698	>186	>186	90	313.1	313.19	1.26	3.98
	BRD7209	>186	>186	74	329.1	329.15	1.23	3.82
	BRD7538	>186	>186	64	313.1	313.19	1.27	3.88
	BRD7505	>186	>186	77	313.1	313.19	1.27	3.88
	BRD4836	>186	>186	30	325.1	325.19	1.4	3.37
	BRD9370	36	46	68	449.19	449.29	1.18	
	BRD0413	>186	>186	43	442.18	442.22	1.4	3.43
	BRD2850	>186	>186	61	299.09	299.13	1.17	3.13

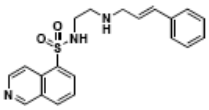
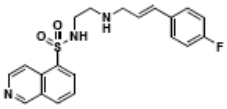
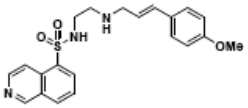
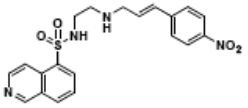
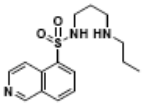
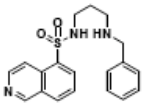
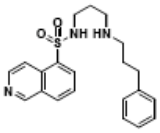
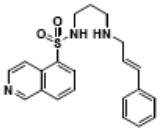
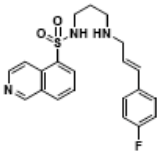
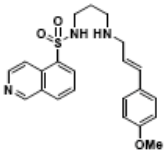
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD0886	>186	>186	54	400.14	400.16	1.21	
	BRD4857	351	104	83	292.11	292.19	0.87	0.39
	BRD4962	>714	>714	81	384.14	384.15	1.45	0.63
	BRD3419	>186	>186	37	314.1	314.17	0.87	0.39
	BRD3734	>186	>186	19	392.08	392.09	1.02	2.74
	BRD8652	>186	>186	32	382.12	382.15	1.21	3.28
	BRD1343	>186	>186	53	303.12	303.22	1.37	2.67
	BRD9796	33	16	17	346.16	346.2	0.96	3.93
	BRD9178	>186	>186	17	386.12	386.35	1.24	3.08
	BRD6382	>186	>186	28	414.15	413.97	1.32	3.99

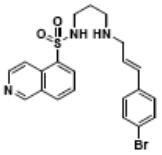
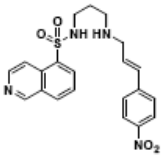
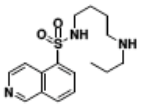
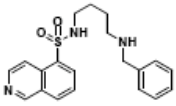
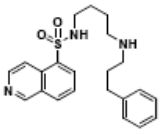
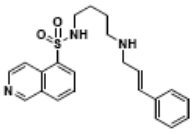
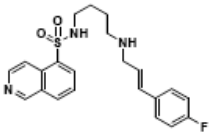
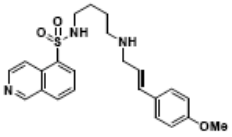
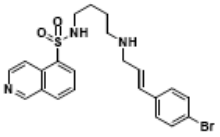
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD7394	>186	>186	64	345.17	345.22	1.58 (acid)	2.09
	BRD2520	>186	>186	49	357.17	357.24	1.60(acid)	2.58
	BRD7178	>186	>186	51	319.15	319.24	1.42(acid)	1.75
	BRD2867	>186	>186	58	319.15	319.31	1.43(acid)	1.77
	BRD4468	>186	>186	60	432.2	432.24	1.54	3.97
	BRD3078	>714	166	5	483.12	483.2	0.82	3.25
	BRD2024	12	6.1	5	511.15	511.23	1.29	4.07
	BRD5499	>186	>186	4	471.12	471.3	1.27	4.04
	BRD7388	>186	>186	62	267.08	267.13	0.86	1.4

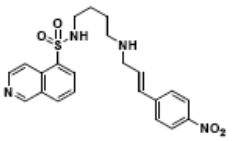
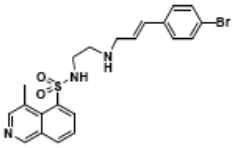
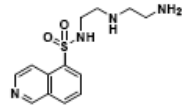
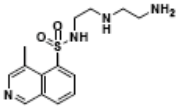
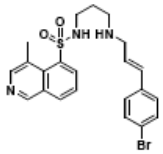
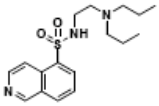
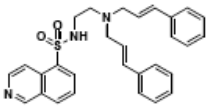
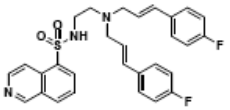
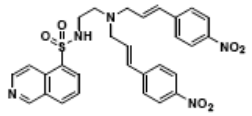
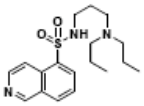
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD8939	**33**	**13**	61	281.1	281.25	0.92	2.1
	BRD9592	**>186**	**>186**	26	378.15	378.3	1.32	2.92
	BRD6645	**>357**	**102**	52	306.13	306.18	0.67(acid)	3.65
	BRD9304	**>186**	**>186**	88	390.15	390.57	1.29	
	BRD9082	**151**	**56**	58	312.06	312.16	0.91	1.43
	BRD1303	**7.9**	**2.6**	82	308.11	308.21	0.75	2.22
	BRD5165	**39**	**20**	7	292.11	292.28	0.8	2.6
	BRD7787	**16**	**6.2**	69	308.11	308.24	0.77	2.19
	BRD9509	**296**	**257**	38	372.02	372.19	0.91	3.92

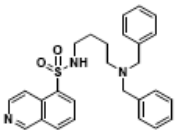
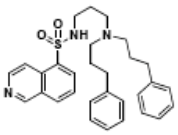
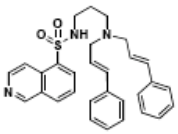
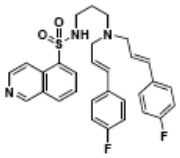
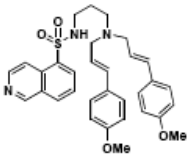
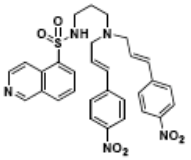
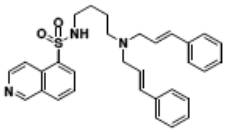
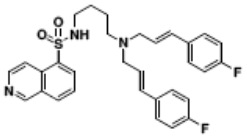
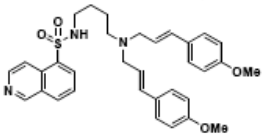
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD2334	**29**	**13**	73	293.1	293.22	0.97	2.3
	BRD4275	**7.2**	**3.8**	49	306.13	306.31	0.92	3.06
	BRD9773	**>186**	**>186**	75	380.17			
	**26**			41	408.16	408.27	1.2	3.92
	**27**			45	408.16	408.27	1.11	3.48
	**28**			27	215.18	215.2	2.72	3.95
	**29**			90	299.2	299.33	1.47	
	**9**			61	406.18	406.27	1.46	
	**10**			88	392.17	392.23	1.3	
	**25**			85	293.1	293.18	0.96	

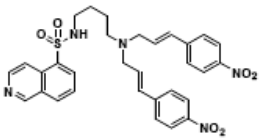
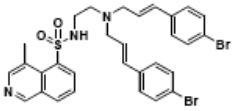
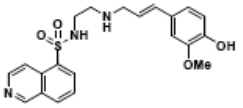
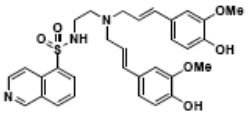
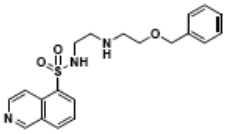
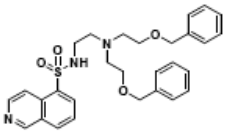
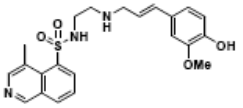
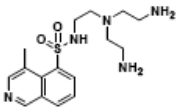
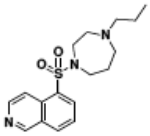
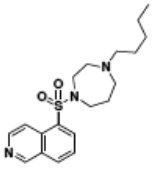
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	22			45	422.18	422.32	1.14	2.57
	30			16	436.16	436.36	1.13	3.18
	31			72	345.22	345.29	0.92	2.76
	3			84	222.99	223.08	1.07	
	4			48	472.08	472.18	1.45	
	6			57	472.08	472.24	1.64	
	32			80	422.18	422.24	1.22	3.33
	BRD5145	**56.43**	**27.14**	24	294.13	294.28	0.92	2
	BRD3055	**138**	**71**	32	342.13	342.14	1.07	2.44
	BRD5294	**78**	**31**	5	370.16	370.18	1.26	2.2

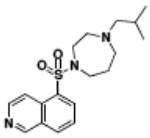
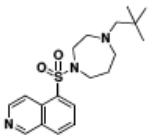
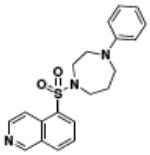
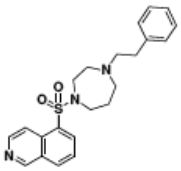
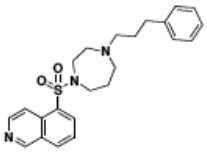
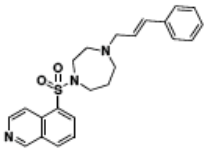
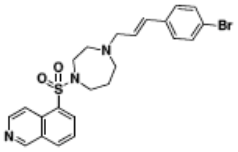
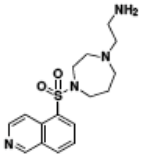
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD8469	35	16	28	368.15	368.15	1.12	3.18
	BRD3849	32	16	9	386.14	386.18	1.27	2.29
	BRD4701	55	25	18	398.16	398.25	1.15	2.2
	BRD3844	18	7.9	9	413.13	413.16	1.15	2.15
	BRD0073	166	64	2	308.15	308.22	0.8	3.31
	BRD2048	224	98	43	356.15	356.18	1.05	3.97
	BRD0124	246	111	15	384.18	384.22	1.27	2.59
	BRD5432	246	66	14	382.16	382.19	1.25	2.5
	BRD0277	41	21	12	400.15	400.21	1.25	2.57
	BRD7488	116	39	25	412.17	412.22	1.23	2.49

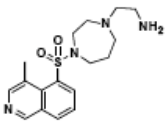
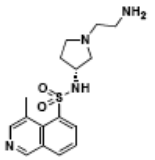
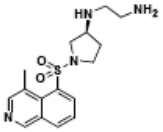
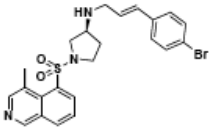
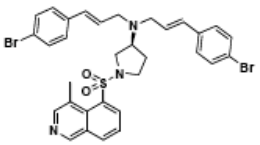
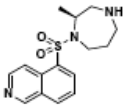
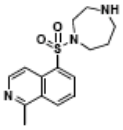
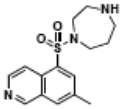
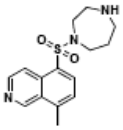
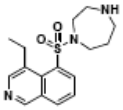
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD5149	18	8.6	16	460.07	460.13	1.42	3.51
	BRD9581	31	14	18	427.15	427.13	1.24	2.46
	BRD1524	>714	>714	17	322.16	322.22	0.94	3.6
	BRD6240	>714	181	22	370.16	370.18	1.12	3.28
	BRD0919	>186	>186	26	398.19	1.26	398.36	3.23
	BRD2874	359	104	23	396.18	396.26	1.14	4.07
	BRD1703	207	93	15	414.17	414.21	1.21	2.77
	BRD0939	189	88	13	426.19	426.25	1.33	2.93
	BRD6081	49	30	8	474.09	474.17	1.62	1.82

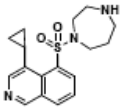
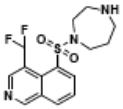
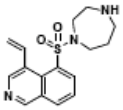
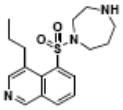
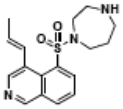
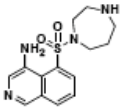
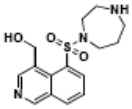
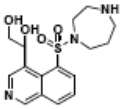
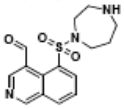
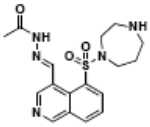
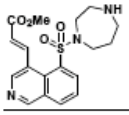
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD4397	64	26	5	441.16	441.16	1.33	1.75
	BRD9330	4.6	2.1	9	462.07	462.2	1.41	3.9
	BRD4009	2.1	1.0	34	295.13	295.15	0.47	3.97
	BRD3407	6.4	3.7	13	309.14	309.24	0.83	1.98
	BRD8198	6.6	2.8	6	474.09	474.2	1.35	4.09
	BRD6632	>186	46.43	25	336.18	336.22	0.98	4.02
	BRD3747	361	133	24	484.21	484.25	1.53	4.25
	BRD0756	172	136	8	520.19	520.3	1.88	3.95
	BRD2424	19	5.4	7	574.18	574.19	1.59	3.73
	BRD0330	>186	>186	11	350.19	350.23	0.96	4.18

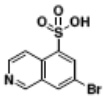
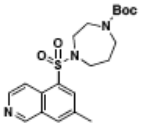
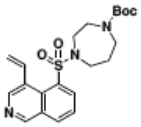
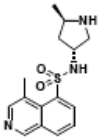
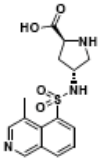
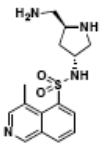
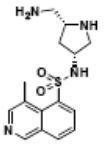
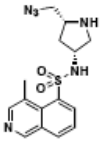
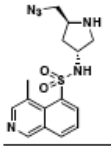
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD7012	>186	>186	6	460.21	460.31	1.47	4.27
	BRD8564	>186	>186	9	502.25	502.3	2.09	3.87
	BRD4835	213	114	13	498.22	498.28	1.82	4
	BRD3291	129	14	14	534.2	534.26	1.77	4
	BRD7419	77	46	18	558.24	558.3	1.76	3.88
	BRD8747	96	43	21	588.19	588.19	1.65	3.83
	BRD2686	216	161	24	512.24	512.32	2.48	4.34
	BRD5822	290	137	32	548.22	548.29	1.61	3.9
	BRD3146	238	126	16	572.26	572.27	1.92	4.05

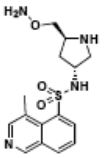
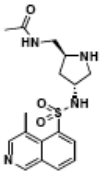
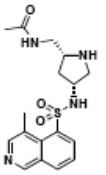
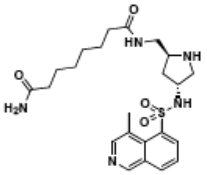
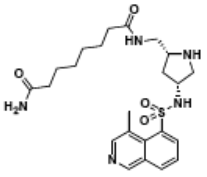
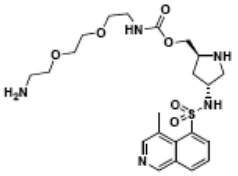
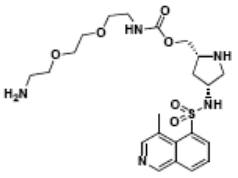
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD7402	63	53	19	602.21	602.22	1.76	3.28
	BRD3116	130	56	6	656.04	656.22	1.94	4.52
	BRD8902	16	5.9	11	414.15	414.22	1	1.8
	BRD3758	94	66	29	576.22	576.25	1.21	3.3
	BRD1600	35	16	19	386.16	386.22	1.15	2.74
	BRD5967	95	58	11	520.23	520.35	1.64	4.2
	BRD9159	7.9	3.1	12	428.17	428.28	1.01	2.39
	BRD3394	9.8	5.2	24	352.18	352.27	0.88	3.95
	BRD5363	24	56	40	334.16	334.19	0.91	4.02
	BRD1943	86	34	33	362.19	362.22	1.03	4.22

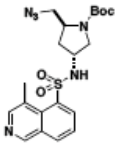
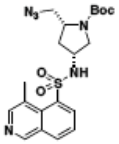
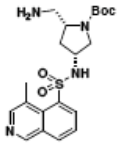
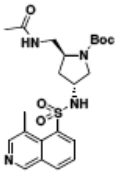
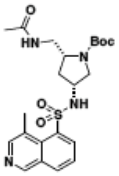
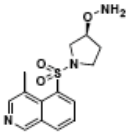
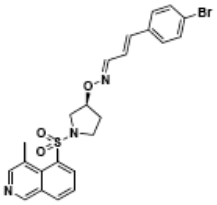
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD3295	>186	56	33	348.18	348.22	1	4.22
	BRD5665	>186	61	52	382.19	326.22	0.83	0.92
	BRD5656	212	88	27	368.15	368.15	1.46	3.78
	BRD6148	51	26	35	396.18	396.2	1.13	4.12
	BRD5445	34	27	34	410.2	410.2	1.16	4.22
	BRD8218	35	30	29	408.21	408.21	1.15	4.15
	BRD9569	39	29	50	488.09	488.13	1.52	4.15
	BRD0112	46	15	29	335.16	335.22	0.96	3.43

Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD9740	3.6	2.0	50	349.17	349.24	0.89	3.11
	BRD0541	10	5.9	25	336.16	335.27	0.8	3.3
	BRD1596	2.6	1.7	28	335.16	335.28	0.83	3.4
	BRD8155	3.2	1.7	67	488.09	488.05	1.19	2.66
	BRD3615	9.8	3.9	11	682.06	682.13	2	4.1
	BRD1869	59	50	89	306.13	306.29	0.88	2.29
	BRD6042	>186	>186	47	306.13	306.32	0.83	2.94
	BRD5087	20	9.1	80	306.13	306.25	0.96	3.68
	BRD5257	205	176	21	306.13	306.3	0.88	2.19
	BRD5930	0.81	0.28	20	320.15	320.3	0.82	2.93

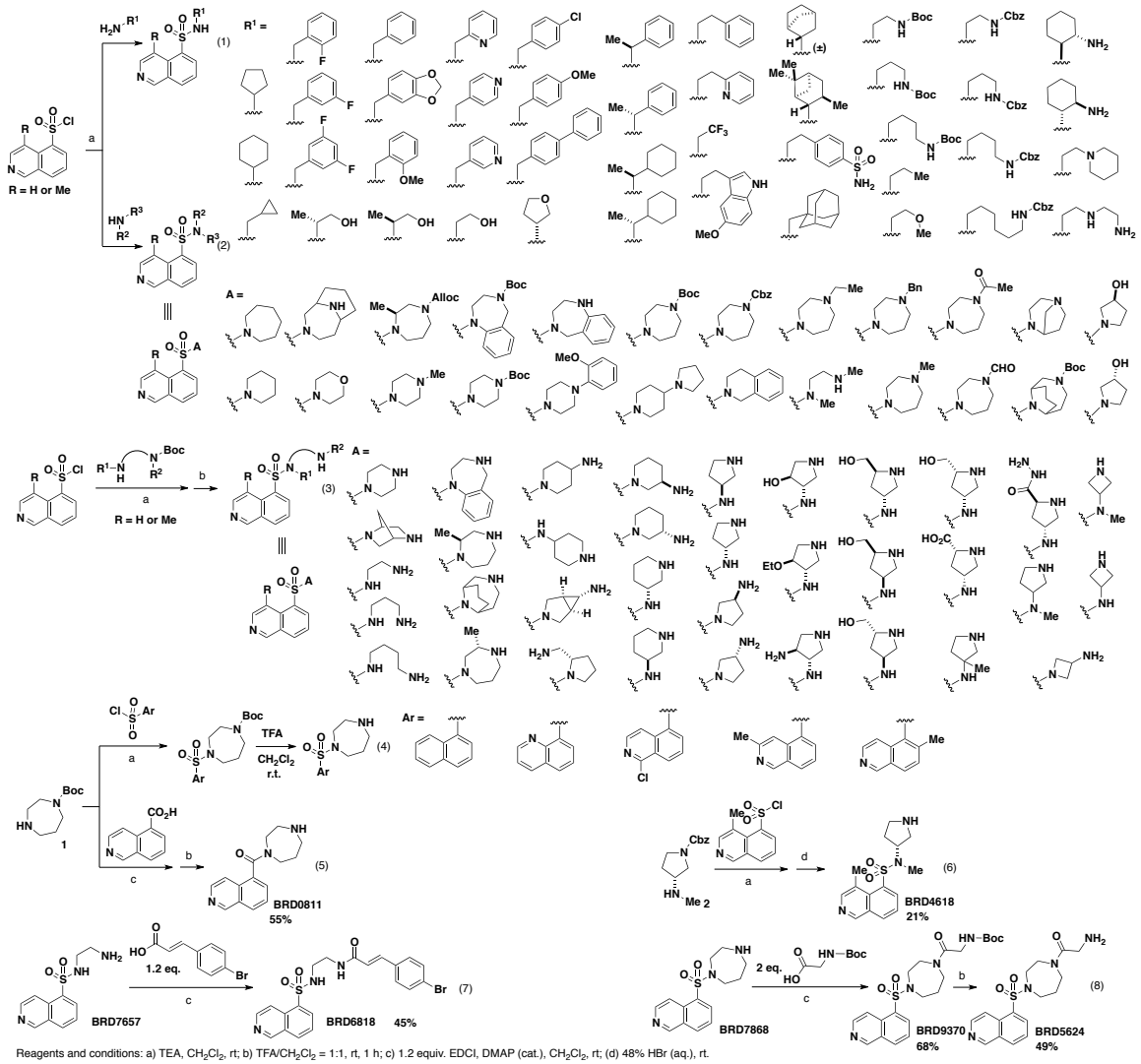
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD5796	**0.68**	**0.24**	57	332.15	332.27	0.96(acid)	3.08
	BRD8757	**1.1**	**0.48**	22	342.11	342.21	0.9	3.62
	BRD7032	**2.9**	**0.94**	71	318.13	318.31	0.8	3.4
	BRD7132	**3.2**	**1.6**	54	334.16	334.32	1.04	3.92
	BRD9078	**8.6**	**4.0**	84	332.15	332.29	0.99	3.21
	BRD2749	**39**	**21**	26	307.13	307.21	0.74	2.93
	BRD7648	**71**	**21**	17	322.12	322.26	0.59	2.73
	BRD5505	**203**	**95**	26	352.14	352.29	0.42	2.3
	BRD4734	**18**	**6.9**	20	320.11	320.16	0.77	1.82
	BRD0859	**74**	**26**	25	376.15	376.23	0.73	2.95
	BRD7198	**44**	**13**	75	376.14	376.23	0.98	2.74

Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	12			85				
	13			64	406.18	406.09	1.42	
	14			74	418.18	418.26	1.37	
	BRD5319	**0.14**	**0.065**	57	306.13	306.27	0.81	2.62
	BRD7953	**3.7**	**1.8**	7	336.1	336.19	0.59	0.99
	BRD9949	**0.032**	**0.02**	18	321.14	321.23	0.93	1.73
	BRD7071	**0.87**	**0.42**	76	321.14	321.31	0.86(acid)	1.67
	BRD2880	**0.53**	**0.24**	26	347.13	347.21	0.73(acid)	1.09
	BRD3192	**0.11**	**0.037**	55	347.13	347.3	0.79	1.9

Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	BRD7569	**0.15**	**0.067**	23	337.14	337.34	0.22	1.83
	BRD8899	**0.025**	**0.011**	11	363.15	363.25	0.88	2.4
	BRD5749	**1.2**	**0.52**	51	363.15	363.28	0.9	2.95
	BRD4717	**0.14**	**0.073**	34	476.24	476.26	0.82	3.04
	BRD1469	**0.13**	**0.061**	48	476.24	476.44	0.77	3.23
	BRD0200	**0.21**	**0.084**	24	496.23	496.29	0.68	3.88
	BRD8254	**1.0**	**0.26**	37	496.23	496.39	1	3.03

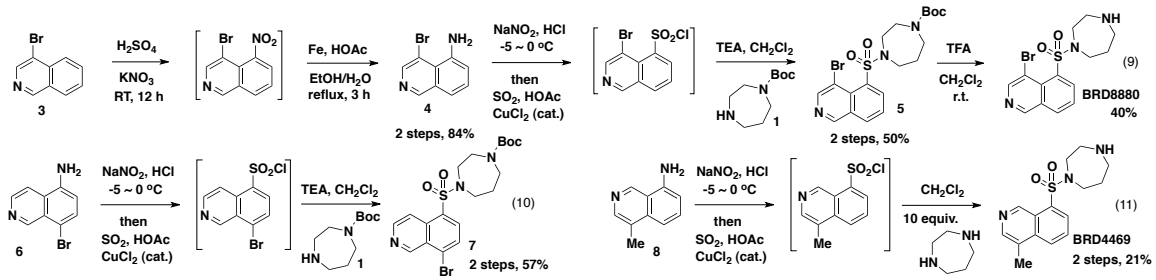
Structure	Compound	IC_{50} (μM) @ 100 μM ATP	IC_{50} (μM) @ 25 μM ATP	yield (%)	Mass ([M+H])	observed Mass	Rt (min) (LC MS)	Rt (min) (prepHPLC)
	23			82	447.18	447.39	1.41	
	18			69	447.18	447.39	1.42	
	19			46	421.19	421.46	1.15	2.37
	BRD2816	>186	>186	51	463.2	463.33	1.2	3.62
	33			43	463.2	463.58	1.25	
	BRD2916	31	15	68	308.11	308.2	0.96	2.88
	BRD6284	81		12	502.06	502.18	1.73	4.32

Scheme S1.

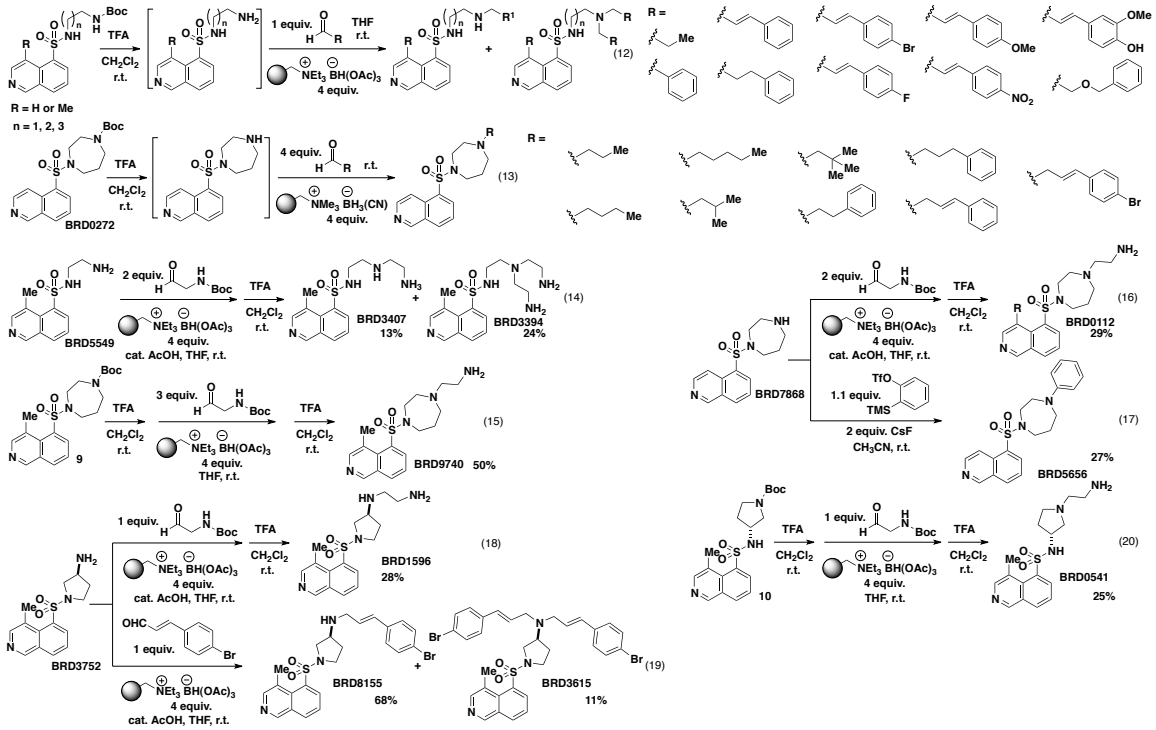


Reagents and conditions: a) TEA, CH_2Cl_2, rt; b) TFA/CH_2Cl_2 = 1:1, rt, 1 h; c) 1.2 equiv. EDCI, DMAP (cat.), CH_2Cl_2, rt; (d) 48% HBr (aq.), rt.

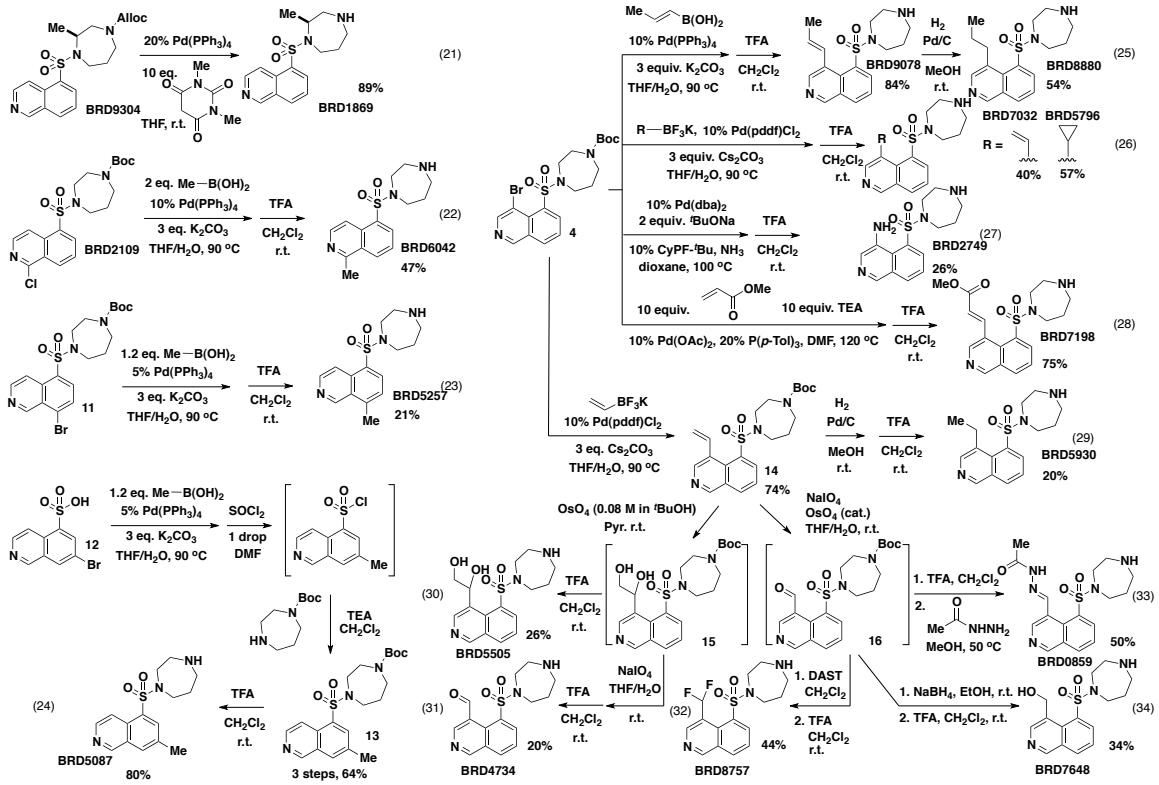
Scheme S2.



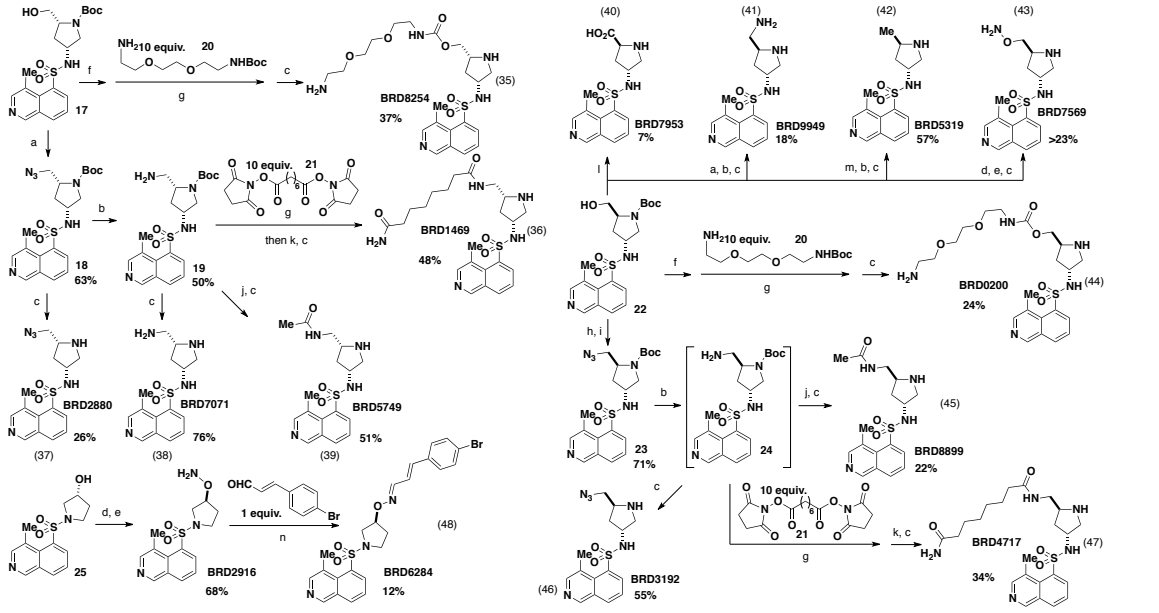
Scheme S3.



Scheme S4.



Scheme S5.



Reagents and conditions: a) 2 equiv. Bis(2,4-dichlorophenyl) phosphorochloridate, DMP, NaN_3, DMF, 60 °C; b) Pd/C, H_2, MeOH, rt, 3 h; c) TFA/CH_2Cl_2 = 1:1, rt, 1 h; d) N-Hydroxyphthalimide, 1.5 equiv. DIAD, 1.5 equiv. PPh_3, CH_2Cl_2, 0 °C ~ rt; e) N_2H_4, MeOH, rt; f) 10 equiv. CDI, CH_2Cl_2, rt, then CH_3CN/H_2O; g) DMF, rt; h) 1.5 equiv. MsCl, TEA, CH_2Cl_2, 0 °C ~ rt; i) 10 equiv. NaN_3, DMF, 90 °C, overnight; j) AcOH, 1.5 equiv. EDCI, CH_2Cl_2, rt; k) excess NH_3; l) 20% TEMPO, 2.5 eq. $PhI(OAc)_2$, CH_3CN/H_2O, rt; m) I_2, PPh_3, imidazole, THF, 0 °C ~ rt; n) cat. AcOH, DMSO, 60 °C.

Materials and Methods.

Human full length STK33 containing an amino terminal histidine tag purified from Sf21 cells was purchased from Millipore Corporation (catalog # 14-671-K). Myelin basic protein (bovine) was purchased from Millipore Corporation (catalog # 13-104). ATP, ADP, MOPS, $MgCl_2$, Brij-35, glycerol, 2-mercaptoethanol, and BSA were purchased from Sigma-Aldrich. The 384-well general plates were purchased from VWR (Corning 3570); 384-well low volume plates were purchased from Greiner Bio-One (384W SV, HiBase, PS, LUMITRAC 200, Medium Binding, 30uL/well, catalog # 784075). CyBi®-Well vario was purchased from CyBio AG. CyBi tips were purchased from CyBio AG (CyBi-Tip Trays 384 standard; catalog # OL 3800-25-513-N). HTRF Transcreener ADP assay was purchased from Cis-bio US (catalog # 62ADPPEC); ADP-Glo assays were purchased from Promega Corporation (catalog # V9103). The Envision 2012 multilabel reader was purchased from PerkinElmer, Inc. Multidrop Combi reagent dispenser and cassettes were purchased from Thermo Fisher Scientific, Inc.

Dry solvents were dispensed from a solvent purification system that passes solvents through packed columns (THF and CH_2Cl_2: dry neutral alumina; toluene: dry neutral alumina and Q5 reactant). Unless otherwise stated, all reagents were obtained from commercial sources and used without further purification. MP-triacetoxyborohydride (Macroporous triethylammonium methylpolystyrene triacetoxyborohydride) was purchased from Biotage (catalog# 800413, 1.8~2.4 mmol/g). ^{1}H NMR spectra were recorded on Varian Unity/Inova 500 (500MHz), or Bruker Ultrashield 300(300MHz) spectrometers. ^{1}H data are reported as follows: chemical shift in parts per million relative to $CHCl_3$ (7.27 ppm) or CH_3OH (4.30 and 3.67 ppm) multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened), coupling constant (Hz), and integration. ^{13}C magnetic resonance spectra were recorded on Varian Unity/Inova 500(125MHz) or Bruker Ultrashield 300(75MHz) spectrometers. ^{13}C chemical shifts are reported in parts per million relative to solvent. All ^{13}C spectra were determined with broadband decoupling.

Flash chromatography was performed either on EM Science silica gel 60 (230–400 mesh) or using a CombiFlash companion system (Teledyne ISCO, Inc.) with pre-packed FLASH silica gel columns (Biotage, Inc.). Compound purity and identity were determined by LC-MS (Alliance 2795, Waters, Milford, MA). Purity was measured by UV absorbance at 210 nm. Identity was determined on a SQ mass spectrometer by positive electrospray ionization. Mobile phase A consisted of either 0.01% ammonium hydroxide or 0.01% formic acid in water, while mobile phase B consisted of the same additives in acetonitrile. The gradient ran from 5% to 95% mobile phase B over 1.6 minutes at 3 mL/min. An XBridge C18, 3.5 um, 4.6x30 mm column was used with column temperature maintained at 40^{o}C. 5 µL of sample solution were injected. Compounds were purified by mass-directed purification on a Waters Autopurification system (Milford, MA) (reverse-phase prep-HPLC). Collection was triggered on the (M+H)+ and (M+Na)+ ions on a ZQ mass spectrometer using positive electrospray ionization. Mobile phase A consisted of either 0.2% ammonium hydroxide in water, while mobile phase B consisted of the same additive in acetonitrile. The gradient ran from 5% to 95% mobile phase B over 5.0 minutes at 44 mL/min. An XBridge OBD Prep

C18, 5 um, 19x50 mm column was used at room temperature. The solvent gradient is determined by the retention time (RT) measured in LC-MS.

Retention Time (RT) LC-MS (min)	Purification Inlet Method
0.46~0.60	prep5min_5iso
0.61~0.75	prep5min_10iso
0.76~0.84	prep5min_10_15
0.85~1.06	prep5min_15_30
1.07~1.32	prep5min_20_35
1.33~1.52	prep5min_30_45
1.53~1.73	prep5min_45_60
1.74~1.81	prep5min_55_75

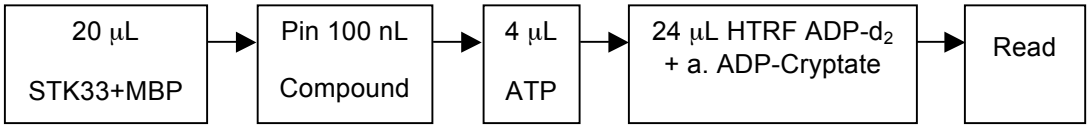
Kinase assay:

Kinase reactions were performed under10 mM MOPS-NaOH (pH 7.0), 10 mM $MgCl_2$, 0.3 mM EDTA, 0.001% Brij-35, 0.5% glycerol, 0.01% 2-mercaptoethanol, and 0.1 mg/mL BSA. Reactions were initiated by the addition of ATP and incubated at 30 ºC or room temperature for the indicated time. The enzyme concentration (STK33) and substrate concentration (MBP and ATP) were variable depending on the experiment. For inhibitors with IC_{50} < 200 nM, the STK33 concentration was reduced to 9.6 nM and the kinase reaction time was extended to 120 minutes. Negative control (DMSO) was scaled to 100% kinase activity, whereas positive control (0.16 μM staurosporine, 100% inhibition) was scaled to 0% kinase activity.

For the HTRF assay, ADP-d2 and a. ADP-Cryptate solution was mixed at a 1:1 ratio to make the detection mixture. The detection mixture was added with an equal volume of the kinase reaction. The plate was incubated at room temperature for 60 minutes, after which fluorescence was read on an Envision instrument.

For the ADP-Glo assay, the kinase reaction solution and ADP-Glo reagent were mixed at a 1:1 ratio (totally 20 μL), which were incubated at room temperature for 50 minutes. Kinase detection reagent (20 μL) was added. The mixture was further incubated for 25 ~ 40 minutes before the plate was read on Envision for luminescence intensity.

STK33 HTRF (Homogeneous Time Resolved Fluorescence) assay protocol for screening inhibitors



1. Add 20 mL total volume of STK33+MBP mixture (38.4 nM STK33, 24.5 μM MBP, 10 mM MOPS-NaOH, pH 7.0, 10 mM $MgCl_2$, 0.36 mM EDTA, 0.0012% Brij-35, 0.6% glycerol, 0.012% 2-mercaptoethanol, 0.12 mg/mL BSA) to 384-well general plates using Combi with Standard Cassette, high speed; fast spin down.
2. Pin transfer Compounds (100 nL)
3. After 15 minutes under room temperature, add 4 μL ATP (10 mM MOPS-NaOH, pH 7.0, 10 mM $MgCl_2$) with Combi, small cassette, high speed; note time of adding ATP to first plate, keep plates in order; spin down.
4. Incubate at room temperature for 70 minutes, starting from time of first plate from step 4.
5. Add 24 μL total volume of HTRF reagent mixture (1:1 mixture of ADP-d_2 and a. ADP-Cryptate) to the 384-well general plates using Combi with small Cassette, high speed; fast spin down.
6. Incubate at room temperature for 60 minutes; read fluorescence on Envision 1 (Protocol: Cisbio HTRF Protocol; Label:LANCE-Cisbio HTRF Protocol)

Standard Curve:

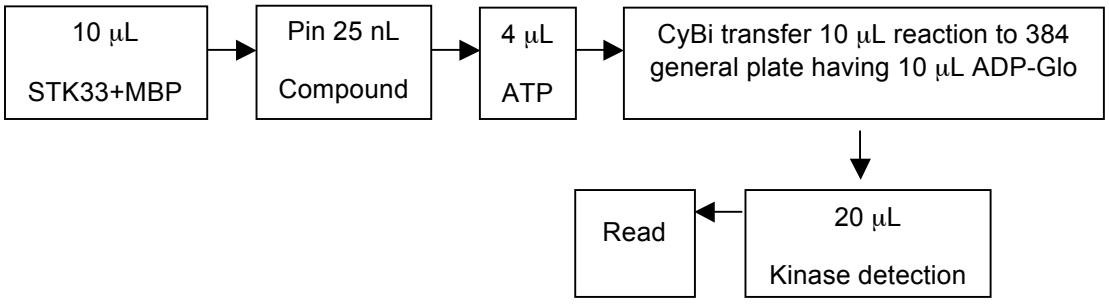
In order to calibrate the backgrounds under different ATP concentrations, standard curves are made based on the standard solutions with different ATP/ADP ratios. The ratio of emission intensity at 620 nm and 665 nm are calculated. Sigmoidal (variable slope) regression of ratio-[ADP] plot gives the equation:

Ratio = Bottom + (Top-Bottom)/ [1+(EC50/[ADP])^HillSlope]

Preparation of ATP to ADP conversion curves ([ATP]+[ADP]=100 mM)

% Conversion	100	33.33	11.11	3.70	1.23	0.41	0.14	0
[ADP] (mM)	100	33.33	11.11	3.70	1.23	0.41	0.14	0
[ATP] (mM)	0	66.67	88.99	96.30	98.77	99.59	99.86	100

STK33 ADP-Glo assay protocol for screening inhibitors



1. Add 10 mL total volume of STK33+MBP mixture (38.4 nM STK33, 24.5 μM MBP, 10 mM MOPS-NaOH, pH 7.0, 10 mM $MgCl_2$, 0.42 mM EDTA, 0.0014% Brij-35, 0.7% glycerol, 0.014% 2-mercaptoethanol, 0.14 mg/mL BSA) to 384-well low volume plates using Combi with Standard Cassette, high speed; fast spin down.
2. Pin transfer Compounds (25 nL)
3. After 15 minutes under room temperature, add 4 μL ATP (10 mM MOPS-NaOH, pH 7.0, 10 mM $MgCl_2$) with Combi, small cassette, high speed; note time of adding ATP to first plate, keep plates in order; spin down.
4. Incubate at room temperature for 70 minutes, starting from time of first plate from step 4.
5. Add 10 μL total volume of ADP-Glo reagent mixture to 384-well general plates using Combi with Standard Cassette, high speed.
6. Transfer 10 mL reaction mixture using CyBi (program file: STK33_v5) to 384-well general plates having the ADP-Glo reagent; note time of transfer.
7. Incubate at room temperature for 50 minutes.
8. Add 20 mL ADP-Glo kinase detection reagent using Combi with Standard Cassette, high speed; note time of transfer.
9. Incubate at room temperature for 35 minutes; read luminescence on Envision 1 (Protocol: Kinase-Glo 384 lum; Label: USLum-JoshK-US LUM 384 (cps))

Standard Curve:

In order to calibrate the backgrounds under different ATP concentrations, standard curves are made based on the standard solutions with different ATP/ADP ratios. Given the low conversion of ATP in the screening (<5%), the range of [ADP] is between 0 and 5 mM. Linear regression of Luminescence-[ADP] plot gives the equation:

Luminescence = HillSlope * [ADP] + Y-intercept

Preparation of ATP to ADP conversion curves ([ATP]+[ADP]=100 mM)

% Conversion	5	4	3	2	1.5	1	0.5	0
[ADP] (mM)	5	4	3	2	1.5	1	0.5	0
[ATP] (mM)	95	96	97	98	98.5	99	99.5	100

General procedure for synthesizing sulfonamides from sulfonyl chloride and amine:

The amine (1.5 ~ 5 equiv.) and TEA (5 equiv.) were dissolved in anhydrous dichloromethane in a 4 mL capped vial. The solution was cooled in an ice bath and sulfonyl chloride (1 equiv.) was added. The ice bath was then removed; the solution was allowed to warm to room temperature and stirred overnight. The volatiles were removed by purging air. For Boc-protected diamines, removal of the protection was affected by treating the residue with 1:1 TFA/CH_2Cl_2 for 1 h at room temperature. The volatiles were removed under reduced pressure. The residue was purified by prep-HPLC or flash chromatography over SiO_2.

General procedure for coupling carboxylic acid and amine:

To a solution of carboxylic acid (1~2 equiv.), amine (1 equiv.) and *N*,*N*-dimethylaminopyridine (DMAP, 0.1 equiv.) in dry CH_2Cl_2 was added *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCI, 1.2 equiv.) at 0 ^oC with stirring. The reaction mixture was stirred at room temperature overnight. The mixture was quenched with water and extracted with EtOAc. The organic layers were then washed with saturated brine, dried over sodium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by prep-HPLC.

General procedure for nitration and reduction to make aromatic amine:

In a 20 mL capped vial was 4-bromoisoquinoline **3** (3g, 14 mmol) in sulfuric acid (5 mL, 92 mmol) to give light yellow solution. Under ice-cooling, a solution of potassium nitrate (1.6 g, 16 mmol) in 3 mL sulfuric acid was added dropwise. After 20h of stirring under room temperature the reaction mixture was poured in iced water (80 mL) containing aqueous ammonia (20 mL) and extracted with EA (100 mL × 3). The extract was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. In a 500 mL round-bottom flask was the residue in adding EtOH/H_2O (80 mL) to give a yellow suspension. Acetic acid (6 g, 101 mmol) and iron (2.4 g, 43 mmol) were added. The solution was refluxed for 3 h. The acetic acid and alcohol were removed under vacuo. Saturated $NaHCO_3$ solution was added to basify the solution. Filtration was performed and the residue was extensively washed with EA. The filtrate was extracted with EA (100 mL × 4). The organic phase was combined and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was purified via flash chromatography on silica (80g column, eluted by 0~5% MeOH in CH_2Cl_2) to give 4-bromoisoquinolin-5-amine **4** (2.7 g, 12 mmol, 84% yield) as a yellow solid.

General procedure for synthesizing sulfonyl chloride from aromatic amine:

In a 20 mL capped vial, 4-bromoisoquinolin-5-amine **4** (106 mg, 0.475 mmol) was placed in concentrated hydrochloride acid (37% HCl, 2 mL) to give a yellow solution. Under ice-cooling, sodium nitrite (42.6 mg, 0.618 mmol) dissolved in water was added slowly. The stirring was continued for 15 minutes in an ice bath before the reaction mixture was pouring into the solution made by bubbling (15 min) sulfur dioxide into acetic acid (4 mL) in the presence of cupric chloride hydrate (50 mg, 0.293 mmol).

The mixture was stirred under room temperature for 1 h. Excess acetic acid was removed under reduced pressure. The solution was neutralized by adding a saturated $NaHCO_3$ solution, after which extraction with CH_2Cl_2 (20 mL × 3) was performed. The organic phase was combined and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the residue was dissolved in dry CH_2Cl_2 (3 mL). *Tert*-butyl 1,4-diazepane-1-carboxylate **1** (0.3 mL, 1.4 mmol) and TEA (0.1 mL, 0.72 mmol) were added. The mixture was stirred overnight under room temperature, concentrated, and purified by flash chromatography on silica (4g column, eluted by 0~100% EA in hexane) to give *tert*-butyl 4-(4-bromoisoquinolin-5-ylsulfonyl)-1,4-diazepane-1-carboxylate **5** (112 mg, 0.239 mmol, 50% yield) as a white solid.

General procedure for reductive amination:

MP-triacetoxyborohydride (4 equiv.) was added to the solution of amine (1 equiv.) and aldehyde (1~4 equiv.) in dry THF. The mixture was stirred overnight, after which filtration was performed, and the resin was washed with methanol. The combined solution was concentrated, and the product was purified by prep-HPLC.

General procedure for Suzuki coupling:

In a microwave tube, substrate (1 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), K_2CO_3(3 equiv), and boronic acid (1~3 equiv.) were added. The tube was sealed and THF/water was added through a syringe. After degassing, the resulting mixture was heated to 90 °C for 4-12 h before cooling to room temperature and filtering through Celite. Upon removal of the solvents, the residue was purified through flash chromatography or subjected to TFA/CH_2Cl_2 (1:1) solution for deprotection. The de-Boc product was purified by prep-HPLC. When Molander reagent was used instead of boronic acid, the $Pd(dppf)Cl_2$ was used as the palladium catalyst and Cs_2CO_3 was used as the base.

General procedure for hydrogenation:

In a round-bottom flask, substrate, palladium on activated charcol (10% Pd basis, 20~100% weight of substrate), and methanol were added. After degassing with hydrogen, the mixture was stirred under hydrogen at room temperature for 3 h before filtering through a syringe filter. Upon removal of the solvents, the residue was purified by prep-HPLC.

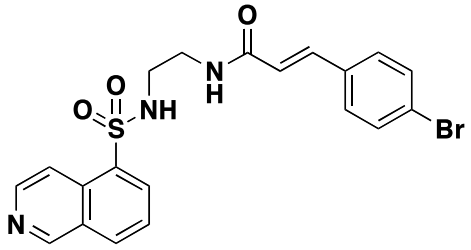
General procedure for Mitsunobu reaction:

To a stirred solution of alcohol substrate (1 equiv.), triphenylphosphine (1.5~2 equiv.), and N-hydroxyphthallimide (2 equiv.) in dry CH_2Cl_2, DIAD (2 equiv.) was added at 0 ºC. After 2~8 h at room temperature, the reaction mixture was concentrated. Hydrazine hydrate was added at room temperature to the crude product in methanol. The stirring was continued at the same temperature for 1 h. The solvent was removed under reduced pressure. The residue solid was purified by prep-HPLC or subjected to deprotection of Boc (1:1 TFA/CH_2Cl_2, 1 h, room temperature).

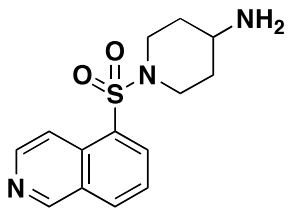
General procedure for converting hydroxyl group to azide:

Method 1: To a stirred solution of alcohol (1 equiv.) in dry DMF was added bis (2,4-dichlorophenyl) phosphorochloridate (1.5 ~ 3 equiv.) at room temperature. The reaction mixture was stirred at 60 ºC for 24 h and then quenched by the addition of water. The layers were separated and the aqueous layer was backextracted with EA. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate.

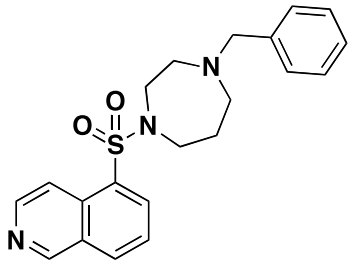
Method 2: To a stirred solution of alcohol (1 equiv.) in dry CH_2Cl_2 was added TEA (2 equiv.) and methanesulfonyl chloride (2 equiv.) at 0 ºC. The reaction mixture was stirred at 0 ºC for 2 h and then quenched by the addition of saturated $NaHCO_3$ (aq.). The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, and the residue was dissolved in dry DMF, after which NaN3 (10 equiv.) was added. The reaction mixture was stirred at 90 ºC for 8 h, after which DMF was removed under reduced pressure. The residue was partitioned between brine and EA. The aqueous phase was extracted by EA. The combined organic layer was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica (4g column, eluted by 0~100% EA in hexane) to give the azide.



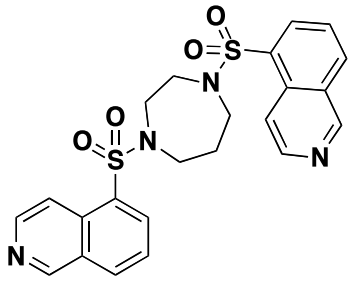
(*E*)-3-(4-bromophenyl)-*N*-(2-(isoquinoline-5-sulfonamido)ethyl)acrylamide (BRD6818). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 3.17 (2 H, td, J=3.7, 1.6 Hz), 3.49 (2 H, t, J=5.7 Hz), 6.22 (2 H, m), 7.31 (2 H, s), 7.43 (1 H, s), 7.49 (2 H, d, J=7.2 Hz), 7.71 (1 H, t, J=7.8 Hz), 8.19 (1 H, d, J=8.3 Hz), 8.45 (2 H, dd, J=7.3, 1.1 Hz), 8.69 (1 H, d, J=6.2 Hz), 9.32 (1 H, s) ppm.



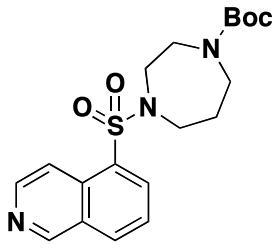
1-(isoquinolin-5-ylsulfonyl)piperidin-4-amine (BRD3518). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.32 - 1.45 (2 H, m), 1.52 (4 H, br. s.), 1.86 (2 H, d, J=13.2 Hz), 2.63 - 2.76 (3 H, m), 3.78 (2 H, d, J=12.7 Hz), 7.73 (1 H, t, J=7.6 Hz), 8.23 (1 H, d, J=7.8 Hz), 8.40 (1 H, d, J=6.3 Hz), 8.52 (1 H, d, J=6.3 Hz), 8.70 (1 H, d, J=5.9 Hz), 9.37 (1 H, s) ppm.



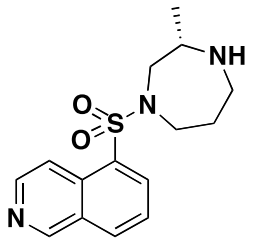
5-(4-benzyl-1,4-diazepan-1-ylsulfonyl)isoquinoline (BRD5076). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.18 (1 H, s), 1.69 - 1.88 (2 H, m), 2.53 - 2.73 (4 H, m), 3.34 - 3.48 (4 H, m), 3.56 (2 H, s), 7.07 - 7.30 (7 H, m), 7.61 (1 H, t, J=7.8 Hz), 8.12 (1 H, d, J=8.1 Hz), 8.28 (1 H, dd, J=7.3, 1.1 Hz), 8.39 (1 H, d, J=6.2 Hz), 8.61 (1 H, d, J=6.2 Hz), 9.28 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 28.2, 46.8, 48.1, 54.4, 55.9, 62.1, 117.7, 125.8, 127.2, 128.3, 128.8, 129.2, 131.7, 133.0, 133.3, 134.6, 145.0, 153.2 ppm.



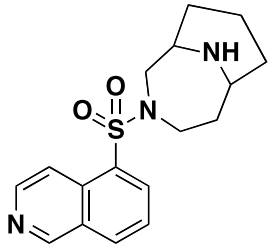
1,4-bis(isoquinolin-5-ylsulfonyl)-1,4-diazepane (BRD2660). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 2.13 (2 H, s), 3.55 - 3.64 (8 H, m), 7.73 (2 H, t, J=7.8 Hz), 8.20 - 8.43 (4 H, m), 8.72 (2 H, d, J=6.0 Hz), 9.39 (2 H, d, J=0.9 Hz) ppm.



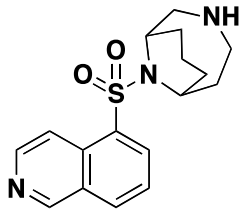
***tert*-butyl 4-(isoquinolin-5-ylsulfonyl)-1,4-diazepane-1-carboxylate (BRD0272).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.43 (9 H, s), 1.94 - 1.99 (2 H, m), 3.34 - 3.48 (4 H, m), 3.48 - 3.58 (4 H, m), 7.71 (1 H, t, J=7.8 Hz), 8.31 (1 H, d, J=8.1 Hz), 8.28 (1 H, dd, J=7.3, 1.1 Hz), 8.41 (1 H, d, J=6.2 Hz), 8.70 (1 H, d, J=6.2 Hz), 9.35 (1 H, s) ppm.



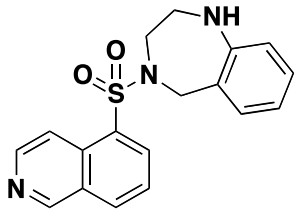
(*S*)-5-(3-methyl-1,4-diazepan-1-ylsulfonyl)isoquinoline (BRD4719). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.07 (3 H, d, J=6.3 Hz), 1.66 (2 H, d, J=2.4 Hz), 1.72 - 1.84 (1 H, m), 1.88 - 2.00 (1 H, m), 2.74 (1 H, dd, J=13.9, 10.0 Hz), 2.85 (1 H, ddd, J=14.0, 10.1, 4.1 Hz), 3.01 (1 H, ddd, J=9.6, 6.5, 2.9 Hz), 3.13 (1 H, dt, J=13.7, 4.6 Hz), 3.28 (1 H, ddd, J=14.0, 8.4, 5.4 Hz), 3.67 - 3.81 (2 H, m), 7.70 (1 H, t, J=7.8 Hz), 8.20 (1 H, d, J=7.8 Hz), 8.33 (1 H, d, J=7.3 Hz), 8.46 (1 H, d, J=6.3 Hz), 8.71 (1 H, d, J=5.9 Hz), 9.36 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 20.0, 31.2, 46.3, 47.9, 56.6, 57.8, 117.9, 126.1, 129.5, 131.9, 132.8, 133.5, 135.1, 145.3, 153.5 ppm.



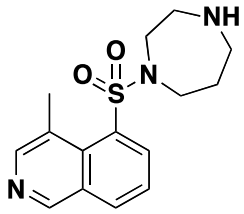
3-(isoquinolin-5-ylsulfonyl)-3,10-diazabicyclo[4.3.1]decane (BRD3954). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.05 - 1.22 (4 H, m), 1.31 - 1.58 (3 H, m), 1.58 - 1.79 (2 H, m), 1.79 - 1.98 (2 H, m), 1.98 - 2.21 (2 H, m), 3.01 - 3.17 (1 H, m), 3.17 - 3.34 (3 H, m), 3.41 - 3.59 (2 H, m), 7.62 (1 H, t, J=7.7 Hz), 8.12 (1 H, d, J=8.1 Hz), 8.23 (1 H, dd, J=7.3, 1.1 Hz), 8.43 (1 H, d, J=6.0 Hz), 8.62 (1 H, d, J=6.2 Hz), 9.27 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 15.4, 28.2, 31.0, 33.2, 47.0, 47.9, 49.9, 53.6, 117.6, 125.9, 129.2, 131.7, 132.5, 133.2, 134.7, 145.1, 153.2 ppm.



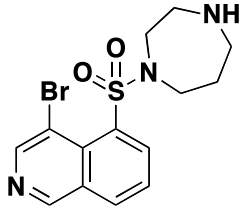
10-(isoquinolin-5-ylsulfonyl)-3,10-diazabicyclo[4.3.1]decane (BRD2533). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.14 - 1.78 (6 H, m), 2.23 (2 H, m), 2.88 - 3.21 (4 H, m), 4.12 - 4.23 (1 H, m), 4.30 - 4.41 (1 H, m), 7.72 (1 H, t, J=7.7 Hz), 8.18 - 8.27 (1 H, m), 8.39 (1 H, d, J=5.8 Hz), 8.46 - 8.55 (1 H, m), 8.72 (1 H, d, J=6.0 Hz), 9.38 (1 H, s) ppm.



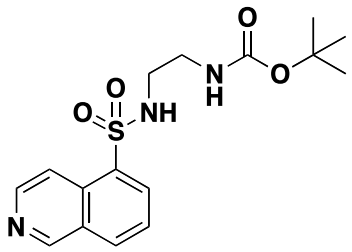
4-(isoquinolin-5-ylsulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepine (BRD0114). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 3.09 - 3.20 (2 H, m), 3.56 - 3.66 (2 H, m), 4.51 (2 H, s), 6.63 (1 H, d, J=7.5 Hz), 6.86 (1 H, d, J=7.5 Hz), 7.08 (1 H, d, J=1.5 Hz), 7.12 - 7.20 (1 H, m), 7.65 (1 H, t, J=7.7 Hz), 8.11 - 8.20 (1 H, m), 8.33 - 8.45 (2 H, m), 8.59 (1 H, d, J=6.0 Hz), 9.30 (1 H, d, J=0.8 Hz) ppm.



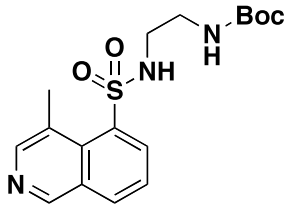
5-(1,4-diazepan-1-ylsulfonyl)-4-methylisoquinoline (BRD3773). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.76 (1 H, br. s.), 1.89 (2 H, dq, J=6.3, 6.1 Hz), 2.94 - 3.06 (7 H, m), 3.45 - 3.55 (2 H, m), 3.58 (2 H, t, J=6.2 Hz), 7.52 (1 H, t, J=7.7 Hz), 7.77 (1 H, d, J=7.3 Hz), 8.07 (1 H, d, J=8.1 Hz), 8.48 (1 H, s), 9.07 (1 H, s) ppm.



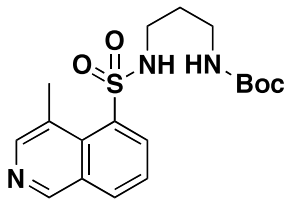
5-(1,4-diazepan-1-ylsulfonyl)-4-bromoisoquinoline (BRD8880). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.24 - 1.40 (10 H, m), 1.40 - 1.46 (3 H, m), 1.86 - 2.01 (2 H, m), 3.26 - 3.56 (9 H, m), 7.47 - 7.59 (1 H, m), 7.68 - 7.83 (1 H, m), 8.03 (1 H, d, J=8.1 Hz), 8.86 (1 H, s), 9.05 - 9.10 (1 H, m) ppm.



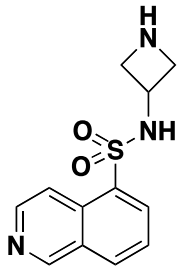
***tert*-butyl 2-(isoquinoline-5-sulfonamido)ethylcarbamate (BRD4153).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.33 - 1.43 (9 H, m), 2.97 - 3.11 (2 H, m), 3.13 - 3.26 (2 H, m), 4.70 - 4.84 (1 H, m), 5.66 - 5.80 (1 H, m), 7.67 - 7.76 (1 H, m), 8.22 (1 H, d, J=8.1 Hz), 8.36 - 8.47 (2 H, m), 8.71 (1 H, d, J=6.2 Hz), 9.37 (1 H, s) ppm.



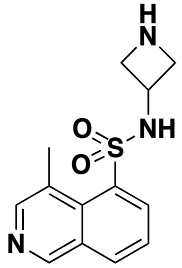
***tert*-butyl 2-(4-methylisoquinoline-5-sulfonamido)ethylcarbamate (BRD9391).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.29 - 1.43 (9 H, m), 1.71 - 1.93 (1 H, m), 3.00 (3 H, s), 3.17 - 3.39 (4 H, m), 4.97 - 5.10 (1 H, m), 5.98 - 6.21 (1 H, m), 7.50 (1 H, t, J=7.8 Hz), 8.05 (1 H, d, J=8.1 Hz), 8.30 (1 H, d, J=7.2 Hz), 8.46 (1 H, s), 9.06 (1 H, s) ppm.



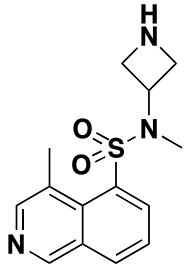
***tert*-butyl 3-(4-methylisoquinoline-5-sulfonamido)propylcarbamate (BRD7177).** ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.46 (9 H, s), 1.69 - 1.80 (2 H, m), 3.10 (3 H, s), 3.23 (2 H, q, J=5.9 Hz), 3.34 (2 H, d, J=5.4 Hz), 4.91 (1 H, t, J=5.9 Hz), 6.55 (1 H, br. s.), 7.56 (1 H, t, J=7.8 Hz), 8.12 (1 H, d, J=7.8 Hz), 8.32 (1 H, d, J=7.3 Hz), 8.54 (1 H, s), 9.13 (1 H, s) ppm.



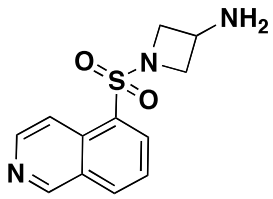
***N*-(azetidin-3-yl)isoquinoline-5-sulfonamide (BRD4958).** ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 2.36 (4 H, br. s.), 2.43 (7 H, br. s.), 2.49 (2 H, br. s.), 3.29 - 3.35 (2 H, m), 3.56 - 3.66 (2 H, m), 4.20 (1 H, t, J=7.1 Hz), 7.71 - 7.76 (1 H, m), 8.25 (1 H, d, J=8.3 Hz), 8.44 (2 H, dd, J=13.7, 6.8 Hz), 8.74 (1 H, d, J=6.3 Hz), 9.40 (1 H, s) ppm.



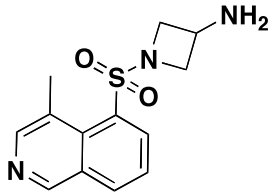
***N*-(azetidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD3966).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 2.05 (7 H, s), 3.09 (3 H, s), 3.72 (2 H, dd, J=8.7, 7.0 Hz), 3.86 - 4.01 (2 H, m), 4.33 (1 H, d, J=7.5 Hz), 7.62 (1 H, t, J=7.7 Hz), 8.17 (1 H, d, J=1.3 Hz), 8.41 (1 H, dd, J=7.3, 1.3 Hz), 8.57 (1 H, s), 9.17 (1 H, s) ppm.



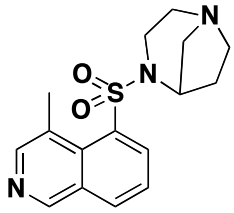
***N*-(azetidin-3-yl)-*N*,4-dimethylisoquinoline-5-sulfonamide (BRD9325).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.64 - 1.85 (2 H, m), 3.06 (3 H, s), 3.19 (3 H, s), 3.80 (2 H, t, J=8.6 Hz), 3.99 (2 H, t, J=8.4 Hz), 4.97 (1 H, t, J=7.8 Hz), 7.60 (1 H, t, J=7.7 Hz), 7.86 - 7.95 (1 H, m), 8.18 (1 H, d, J=8.1 Hz), 8.56 (1 H, s), 9.16 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 21.5, 31.1, 52.0, 52.2, 124.7, 127.6, 130.4, 130.7, 132.4, 134.7, 136.1, 148.7, 152.0 ppm.



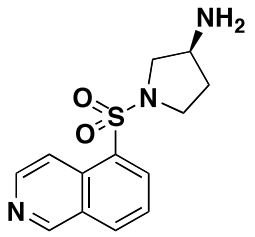
1-(isoquinolin-5-ylsulfonyl)azetidin-3-amine (BRD5991). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.09 (1 H, t, J=7.3 Hz), 1.26 - 1.66 (2 H, m), 3.57 - 3.70 (2 H, m), 3.70 - 3.83 (1 H, m), 3.96 - 4.10 (2 H, m), 7.74 (1 H, t, J=7.8 Hz), 8.26 (1 H, d, J=8.3 Hz), 8.38 - 8.51 (2 H, m), 8.72 (1 H, d, J=6.0 Hz), 9.37 (1 H, s) ppm.



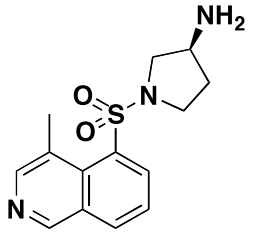
1-(4-methylisoquinolin-5-ylsulfonyl)azetidin-3-amine (BRD5337). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.62 (3 H, br. s.), 3.10 (3 H, s), 3.82 (2 H, t, J=7.1 Hz), 3.86 - 3.93 (1 H, m), 4.08 (2 H, t, J=7.3 Hz), 7.65 (1 H, t, J=7.8 Hz), 8.21 (1 H, d, J=8.3 Hz), 8.56 (1 H, s), 8.71 (1 H, d, J=7.3 Hz), 9.16 (1 H, s) ppm.



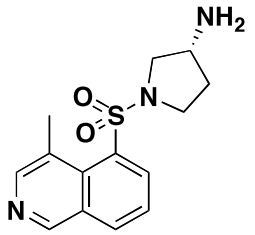
5-(1,4-diazabicyclo[3.2.1]octan-4-ylsulfonyl)-4-methylisoquinoline (BRD1742). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.13 - 1.31 (1 H, m), 1.95 - 2.12 (2 H, m), 2.17 - 2.36 (1 H, m), 2.54 - 2.66 (1 H, m), 2.74 - 2.83 (1 H, m), 2.94 - 3.19 (7 H, m), 3.19 - 3.41 (2 H, m), 4.26 - 4.38 (1 H, m), 7.66 (1 H, t, J=7.9 Hz), 8.21 (1 H, d, J=8.1 Hz), 8.46 - 8.60 (2 H, m), 9.17 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 21.4, 31.0, 39.5, 50.6, 52.6, 54.9, 59.9, 124.8, 127.5, 130.3, 132.5, 134.8, 134.9, 135.4, 148.8, 152.1 ppm.



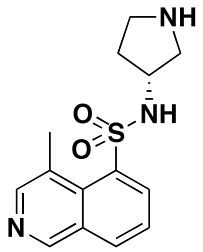
(*S*)-1-(isoquinolin-5-ylsulfonyl)pyrrolidin-3-amine (BRD3590). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.39 - 1.77 (2 H, m), 2.00 - 2.16 (1 H, m), 2.99 - 3.14 (1 H, m), 3.43 (1 H, ddd, J=9.6, 8.1, 5.7 Hz), 3.48 - 3.64 (3 H, m), 7.67 - 7.77 (1 H, m), 8.23 (1 H, d, J=8.3 Hz), 8.46 (1 H, dd, J=7.3, 1.3 Hz), 8.60 (1 H, d, J=6.2 Hz), 8.71 (1 H, d, J=6.2 Hz), 9.37 (1 H, d, J=0.9 Hz) ppm.



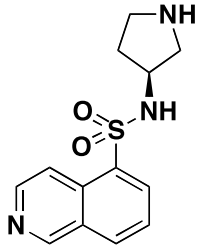
(*S*)-1-(4-methylisoquinolin-5-ylsulfonyl)pyrrolidin-3-amine (BRD3752). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.42 (2 H, br. s.), 1.84 - 1.96 (1 H, m), 2.19 - 2.34 (1 H, m), 3.05 - 3.13 (3 H, m), 3.23 - 3.35 (1 H, m), 3.62 - 3.79 (3 H, m), 3.84 - 3.94 (1 H, m), 7.62 (1 H, t, J=7.8 Hz), 8.16 (1 H, dd, J=8.2, 1.2 Hz), 8.49 (1 H, dd, J=7.5, 1.3 Hz), 8.56 (1 H, d, J=0.8 Hz), 9.15 (1 H, s) ppm; ^{13}C NMR (150 MHz, CHLOROFORM-d) δ = 21.6, 34.8, 46.8, 51.6, 56.5, 125.0, 127.7, 130.4, 131.2, 132.3, 134.3, 136.3, 148.5, 151.9 ppm.



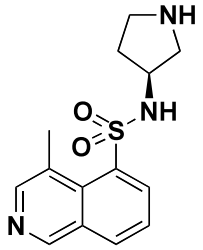
(*R*)-1-(4-methylisoquinolin-5-ylsulfonyl)pyrrolidin-3-amine (BRD0828). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.89 (1 H, ddd, J=12.6, 3.8, 3.7 Hz), 2.23 - 2.32 (1 H, m), 3.10 (3 H, s), 3.29 (1 H, dd, J=10.3, 3.4 Hz), 3.66 - 3.77 (3 H, m), 3.87 - 3.93 (1 H, m), 7.62 (1 H, t, J=7.8 Hz), 8.16 (1 H, d, J=8.3 Hz), 8.48 (1 H, d, J=7.3 Hz), 8.55 (1 H, s), 9.15 (1 H, s).



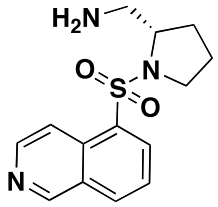
(*R*)-4-methyl-*N*-(pyrrolidin-3-yl)isoquinoline-5-sulfonamide (BRD3695). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.89 - 2.00 (1 H, m), 2.12 - 2.25 (1 H, m), 2.96 (1 H, dd, J=15.9, 9.5 Hz), 3.07 (3 H, s), 3.09 - 3.25 (2 H, m), 3.87 - 4.01 (1 H, m), 5.49 (1 H, br. s.), 7.60 (1 H, t, J=7.8 Hz), 8.06 - 8.19 (1 H, m), 8.44 - 8.52 (1 H, m), 8.54 (1 H, s), 9.06 - 9.18 (1 H, m) ppm; ^{13}C NMR (150 MHz, CHLOROFORM-d) δ = 22.0, 30.0, 33.4, 45.0, 53.7, 54.7, 125.1, 127.6, 130.4, 132.5, 132.5, 134.8, 137.1, 148.7, 152.2 ppm.



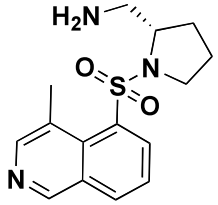
(*S*)-*N*-(pyrrolidin-3-yl)isoquinoline-5-sulfonamide (BRD8943). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.44 - 1.58 (1 H, m), 1.79 - 1.97 (1 H, m), 2.63 - 2.74 (1 H, m), 2.76 - 3.03 (3 H, m), 3.61 - 3.95 (2 H, m), 7.67 - 7.78 (1 H, m), 8.24 (1 H, d, J=8.3 Hz), 8.43 (1 H, d, J=6.2 Hz), 8.49 (1 H, dd, J=7.3, 1.1 Hz), 8.69 (1 H, d, J=6.0 Hz), 9.39 (1 H, s) ppm.



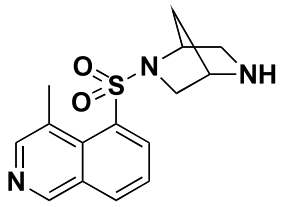
(*S*)-4-methyl-*N*-(pyrrolidin-3-yl)isoquinoline-5-sulfonamide (BRD9573).^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.85 - 1.96 (1 H, m), 2.19 (1 H, td, J=14.0, 7.6 Hz), 2.92 - 3.02 (1 H, m), 3.02 - 3.22 (6 H, m), 3.93 - 4.02 (1 H, m), 7.64 (1 H, t, J=7.8 Hz), 8.18 (1 H, d, J=7.8 Hz), 8.50 - 8.60 (2 H, m), 9.17 (1 H, s) ppm.



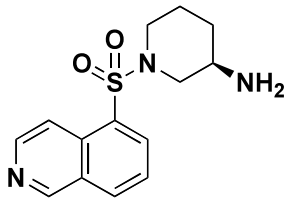
(*S*)-(1-(isoquinolin-5-ylsulfonyl)pyrrolidin-2-yl)methanamine (BRD2246). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.58 - 1.86 (4 H, m), 2.75 - 2.88 (2 H, m), 3.40 (2 H, t, J=6.6 Hz), 3.79 - 3.93 (1 H, m, J=7.3, 2.4, 1.3, 1.3 Hz), 7.74 (1 H, t, J=7.8 Hz), 8.24 (1 H, d, J=8.3 Hz), 8.46 (1 H, dd, J=7.4, 1.2 Hz), 8.63 - 8.75 (2 H, m), 9.37 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 24.4, 29.2, 46.1, 49.1, 62.3, 117.7, 126.0, 129.1, 132.2, 133.6, 133.7, 133.7, 145.2, 153.3 ppm.



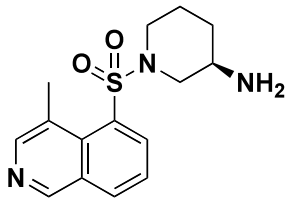
(*S*)-(1-(4-methylisoquinolin-5-ylsulfonyl)pyrrolidin-2-yl)methanamine (BRD7471). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.26 (2 H, d, J=2.9 Hz), 1.95 - 2.18 (4 H, m), 2.20 - 2.33 (1 H, m), 2.79 (1 H, dd, J=12.9, 7.6 Hz), 2.96 (1 H, dd, J=13.2, 4.4 Hz), 3.10 (3 H, s), 3.47 - 3.55 (1 H, m), 3.60 - 3.67 (1 H, m), 4.03 - 4.10 (1 H, m, J=7.4, 7.4, 3.9, 3.8 Hz), 7.62 (1 H, t, J=7.8 Hz), 8.17 (1 H, d, J=8.3 Hz), 8.22 (1 H, d, J=7.3 Hz), 8.56 (1 H, s), 9.15 (1 H, s) ppm; ^{13}C NMR (150 MHz, CHLOROFORM-d) δ = 21.7, 24.4, 29.3, 45.97, 49.6, 63.1, 124.7, 127.7, 130.3, 130.7, 132.3, 134.5, 136.3, 148.6, 151.9 ppm.



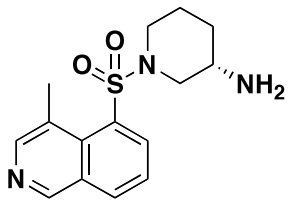
5-((1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptan-2-ylsulfonyl)-4-methylisoquinoline (BRD4942). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.89 (3 H, d, J=10.9 Hz), 2.00 - 2.10 (1 H, m), 2.98 - 3.14 (4 H, m), 3.29 - 3.45 (2 H, m), 3.51 (1 H, dd, J=9.1, 2.0 Hz), 3.89 (1 H, s), 4.45 (1 H, s), 7.64 (1 H, t, J=7.8 Hz), 8.13 - 8.23 (1 H, m), 8.46 - 8.60 (2 H, m), 9.16 (1 H, s) ppm.



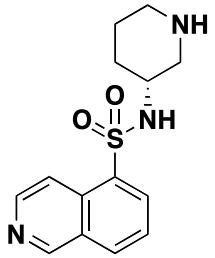
(*R*)-1-(isoquinolin-5-ylsulfonyl)piperidin-3-amine (BRD0841). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.01 - 1.18 (1 H, m), 1.18 - 1.44 (2 H, m), 1.60 (1 H, dd, J=10.2, 3.6 Hz), 1.71 - 1.88 (2 H, m), 2.42 (1 H, dd, J=11.6, 8.9 Hz), 2.61 - 2.74 (1 H, m), 2.84 - 2.97 (1 H, m), 3.49 - 3.72 (2 H, m), 7.72 (1 H, t, J=7.8 Hz), 8.22 (1 H, d, J=8.1 Hz), 8.38 (1 H, dd, J=7.3, 1.3 Hz), 8.51 (1 H, d, J=6.2 Hz), 8.68 (1 H, d, J=6.2 Hz), 9.35 (1 H, s) ppm.



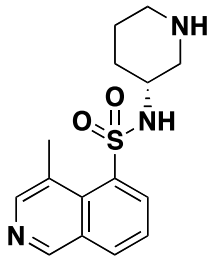
(*R*)-1-(4-methylisoquinolin-5-ylsulfonyl)piperidin-3-amine (BRD3376). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.27 - 1.48 (3 H, m), 1.65 - 1.83 (1 H, m), 1.83 - 1.96 (1 H, m), 1.98 - 2.11 (1 H, m), 2.84 (1 H, dd, J=12.2, 8.9 Hz), 2.99 - 3.17 (5 H, m), 3.68 - 3.86 (2 H, m), 7.62 (1 H, t, J=7.7 Hz), 8.09 (1 H, dd, J=7.5, 1.1 Hz), 8.17 (1 H, dd, J=8.1, 1.3 Hz), 8.56 (1 H, s), 9.15 (1 H, s) ppm; ^{13}C NMR (CHLOROFORM-d) δ = 21.4, 24.0, 33.4, 46.5, 47.7, 54.2, 124.8, 127.6, 130.3, 131.4, 132.4, 134.7, 136.5, 148.7, 152.0 ppm.



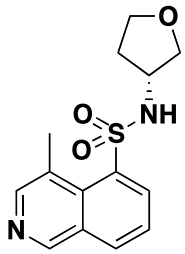
(*S*)-1-(4-methylisoquinolin-5-ylsulfonyl)piperidin-3-amine (BRD3436). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.05 - 1.19 (2 H, m), 1.21 - 1.31 (1 H, m), 1.39 - 1.66 (7 H, m), 1.71 - 1.91 (2 H, m), 2.37 - 2.48 (1 H, m), 2.62 - 2.74 (1 H, m), 2.86 - 2.97 (1 H, m), 3.49 - 3.73 (3 H, m), 7.66 - 7.78 (1 H, m), 8.23 (1 H, d, J=8.3 Hz), 8.36 - 8.43 (1 H, m), 8.51 (1 H, d, J=6.2 Hz), 8.69 (1 H, d, J=6.2 Hz), 9.36 (1 H, s) ppm.



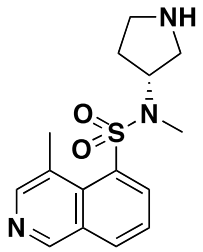
(*R*)-*N*-(piperidin-3-yl)isoquinoline-5-sulfonamide (BRD0561). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.31 - 1.67 (5 H, m), 1.98 - 2.07 (1 H, m), 2.45 (1 H, dd, J=11.6, 5.7 Hz), 2.59 - 2.79 (3 H, m), 3.31 - 3.42 (1 H, m), 7.72 (1 H, t, J=7.8 Hz), 8.23 (1 H, d, J=7.9 Hz), 8.47 (2 H, dd, J=15.2, 6.7 Hz), 8.74 (1 H, d, J=6.0 Hz), 9.39 (1 H, s) ppm.



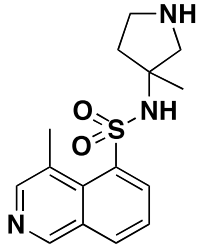
(*R*)-4-methyl-*N*-(piperidin-3-yl)isoquinoline-5-sulfonamide (BRD4209). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.51 (2 H, br. s.), 1.75 (4 H, br. s.), 2.69 - 2.87 (4 H, m), 2.92 - 3.02 (1 H, m), 3.05 - 3.16 (3 H, m), 3.50 (1 H, br. s.), 7.62 (1 H, t, J=7.8 Hz), 8.16 (1 H, dd, J=8.1, 1.3 Hz), 8.56 (1 H, d, J=0.8 Hz), 8.62 (1 H, dd, J=7.5, 1.3 Hz), 9.16 (1 H, s) ppm.



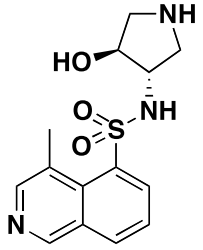
(*R*)-4-methyl-*N*-(tetrahydrofuran-3-yl)isoquinoline-5-sulfonamide (BRD4357). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.95 - 2.10 (1 H, m), 2.21 - 2.38 (1 H, m), 3.8 (3 H, s), 3.73 - 3.88 (3 H, m), 3.93 - 4.16 (2 H, m), 7.63 (1 H, t, J=7.8 Hz), 8.12 - 8.24 (1 H, m), 8.47 - 8.60 (2 H, m), 9.16 (1 H, s) ppm.



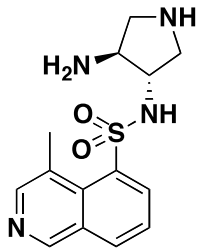
(*R*)-*N*,4-dimethyl-*N*-(pyrrolidin-3-yl)isoquinoline-5-sulfonamide (BRD4618). 1H NMR (300 MHz, CHLOROFORM-d) δ = 1.59 - 1.73 (7 H, m), 1.95 - 2.21 (2 H, m), 2.89 - 2.99 (2 H, m), 3.01 (3 H, s), 3.02 - 3.16 (5 H, m), 3.24 (1 H, dd, J=11.4, 8.2 Hz), 4.46 - 4.60 (1 H, m), 7.62 (1 H, t, J=7.9 Hz), 8.10 - 8.21 (2 H, m), 8.56 (1 H, s), 9.16 (1 H, s) ppm.



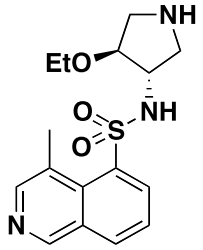
4-methyl-*N*-(3-methylpyrrolidin-3-yl)isoquinoline-5-sulfonamide (BRD4889). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.26 (1 H, t, J=7.1 Hz), 1.43 (3 H, s), 1.75 – 1.19 (1 H, m), 2.34 (2 H, s), 2.83 - 2.90 (1 H, m), 3.09 (3 H, s), 3.36 – 3.39 (1 H, m), 7.65 (1 H, d, J=8.3 Hz), 8.17 (1 H, dd, J=8.1, 1.5 Hz), 8.56 (1 H, s), 8.67 - 8.72 (1 H, m), 9.16 (1 H, s) ppm.



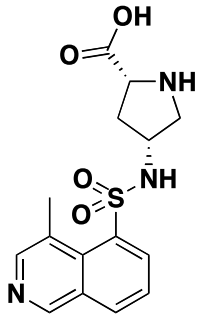
***N*-((3*S*,4*S*)-4-hydroxypyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD0227).** ^{1}H NMR (300 MHz, MeOD) δ = 2.74 - 2.85 (1 H, m), 2.88 - 2.98 (1 H, m), 3.05 (3 H, s), 3.11 - 3.19 (1 H, m), 3.31 - 3.39 (1 H, m), 3.60 (1 H, td, J=2.7, 0.9 Hz), 4.26 - 4.37 (1 H, m), 7.75 (1 H, t, J=7.7 Hz), 8.29 - 8.36 (1 H, m), 8.43 (1 H, s), 8.53 - 8.63 (1 H, m), 9.15 (1 H, s) ppm.



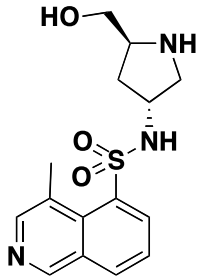
***N*-((3*S*,4*S*)-4-aminopyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD6696).** ^{1}H NMR (300 MHz, MeOD) δ = 1.76 - 1.91 (1 H, m), 2.55 - 2.67 (1 H, m), 2.84 - 2.95 (1 H, m), 3.00 - 3.08 (3 H, m), 3.14 - 3.24 (1 H, m), 3.24 - 3.32 (6 H, m), 7.77 (1 H, t, J=7.8 Hz), 8.33 (1 H, d, J=8.5 Hz), 8.45 (1 H, s), 8.55 (1 H, d, J=7.7 Hz), 9.16 (1 H, s) ppm.



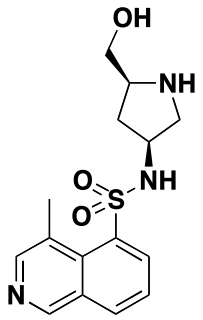
***N*-((3*S*,4*S*)-4-ethoxypyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD1230).** ^{1}H NMR (300 MHz, MeOD) δ = 1.07 (3 H, t, J=7.0 Hz), 2.81 - 2.91 (2 H, m), 2.98 - 3.16 (4 H, m), 3.42 (2 H, q, J=7.2 Hz), 3.64 - 3.73 (1 H, m), 4.01 (1 H, ddd, J=2.5, 1.2, 1.0 Hz), 7.74 (1 H, t, J=7.7 Hz), 8.33 (1 H, d, J=8.1 Hz), 8.44 (1 H, s), 8.58 (1 H, d, J=7.5 Hz), 9.16 (1 H, s) ppm.



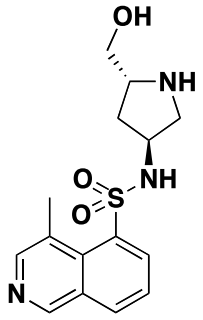
(2*R*,4*R*)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidine-2-carboxylic acid (BRD0035). ^{1}H NMR (500 MHz, METHANOL-d4) δ = 1.24 - 1.34 (4 H, m), 1.70 (2 H, dd, J=6.3, 3.4 Hz), 1.89 - 1.96 (2 H, m), 2.07 (2 H, d, J=14.2 Hz), 3.08 (3 H, s), 3.17 - 3.21 (1 H, m), 3.35 - 3.39 (2 H, m), 3.47 (1 H, d, J=2.0 Hz), 3.80 (1 H, s), 4.01 (1 H, s), 7.82 (1 H, t, J=7.8 Hz), 8.38 (1 H, d, J=8.3 Hz), 8.49 (1 H, s), 8.55 (1 H, d, J=7.3 Hz), 9.21 (1 H, s) ppm.



***N*-((3*R*,5*S*)-5-(hydroxymethyl)pyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD4980).** ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.94 (2 H, t, J=6.1 Hz), 2.05 (1 H, s), 3.04 (1 H, dd, J=11.2, 3.9 Hz), 3.10 (3 H, s), 3.16 - 3.24 (1 H, m), 3.36 (1 H, d, J=4.9 Hz), 3.52 - 3.59 (2 H, m), 3.97 (1 H, s), 7.66 (1 H, t, J=7.6 Hz), 8.21 (1 H, d, J=7.8 Hz), 8.53 (1 H, d, J=8.3 Hz), 8.58 (1 H, s), 9.19 (1 H, s) ppm.

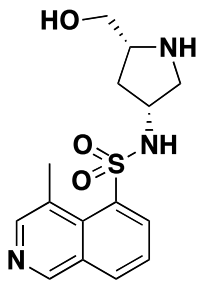


***N*-((3*S*,5*S*)-5-(hydroxymethyl)pyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD6875).** ^{1}H NMR (300 MHz, MeOD) δ = 1.61 (1 H, s), 2.29 (1 H, s), 2.88 - 2.96 (1 H, m), 3.05 (3 H, s), 3.06 - 3.14 (1 H, m), 3.15 - 3.24 (3 H, m), 3.57 (2 H, d, J=4.7 Hz), 3.83 (1 H, s), 7.76 (1 H, t, J=7.8 Hz), 8.33 (1 H, d, J=8.1 Hz), 8.44 (1 H, s), 8.51 (1 H, d, J=7.5 Hz), 9.16 (1 H, s) ppm.

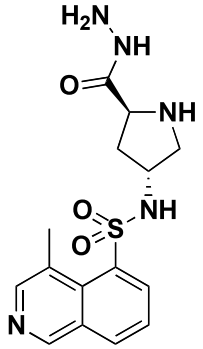


***N*-((3*S*,5*R*)-5-(hydroxymethyl)pyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD8313).** ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.13 - 1.19 (2 H, m), 1.24 - 1.36 (2 H, m), 1.90 - 1.97 (2 H, m), 3.00 - 3.06 (1 H, m), 3.08 - 3.13 (2 H, m), 3.21 (1 H, dd, J=10.3, 4.9 Hz), 3.32 - 3.41 (1 H, m), 3.53 - 3.60 (2 H, m), 3.98 (1 H, dd, J=6.6, 4.6

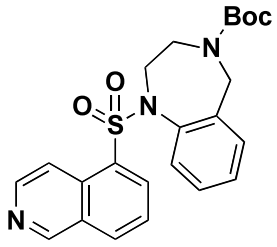
Hz), 7.62 - 7.69 (1 H, m), 8.21 (1 H, d, J=7.3 Hz), 8.53 (1 H, d, J=8.3 Hz), 8.56 - 8.60 (1 H, m), 9.15 - 9.21 (1 H, m) ppm.



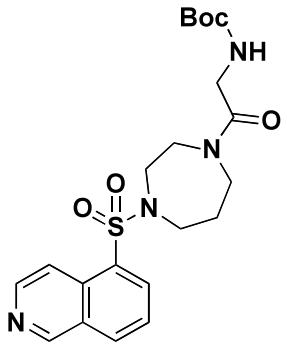
***N*-((3*R*,5*R*)-5-(hydroxymethyl)pyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD1045).** ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.81 (2 H, br. s.), 2.32 (1 H, ddd, J=13.8, 9.6, 7.3 Hz), 3.06 (1 H, dd, J=11.2, 4.9 Hz), 3.09 (3 H, s), 3.17 (1 H, d, J=10.7 Hz), 3.43 - 3.49 (1 H, m), 3.61 (1 H, dd, J=10.7, 3.9 Hz), 3.77 (1 H, dd, J=11.0, 2.7 Hz), 3.90 - 3.97 (1 H, m), 7.63 (1 H, t, J=7.8 Hz), 8.16 (1 H, d, J=8.3 Hz), 8.53 - 8.57 (2 H, m), 9.15 (1 H, s) ppm.



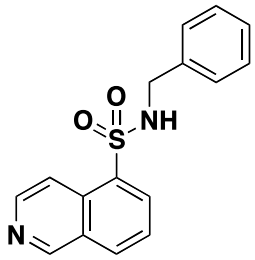
***N*-((3*R*,5*S*)-5-(hydrazinecarbonyl)pyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD7777).** ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.14 (2 H, t, J=7.3 Hz), 1.20 (2 H, t, J=6.8 Hz), 2.10 (2 H, s), 2.24 - 2.33 (2 H, m), 3.06 - 3.13 (4 H, m), 3.32 (2 H, d, J=6.8 Hz), 3.40 (1 H, d, J=6.8 Hz), 3.78 - 3.83 (1 H, m), 3.93 (1 H, d, J=5.4 Hz), 4.00 (1 H, d, J=6.3 Hz), 7.67 (1 H, t, J=7.6 Hz), 8.22 (1 H, d, J=7.3 Hz), 8.46 - 8.50 (1 H, m), 8.58 (1 H, s), 9.19 (1 H, s) ppm.



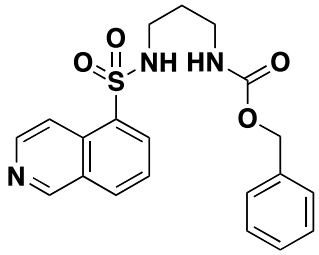
***tert*-butyl 1-(isoquinolin-5-ylsulfonyl)-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepine-4(5*H*)-carboxylate (BRD0119).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.31 - 1.37 (9 H, m), 3.48 - 3.77 (3 H, m), 3.85 - 4.13 (3 H, m), 6.92 - 7.02 (1 H, m), 7.08 - 7.25 (3 H, m), 7.61 - 7.74 (1 H, m), 8.08 - 8.17 (1 H, m), 8.20 - 8.28 (1 H, m), 8.31 - 8.41 (1 H, m), 8.56 (1 H, ddd, J=4.8, 2.1, 1.0 Hz), 9.32 - 9.42 (1 H, br.s.) ppm.



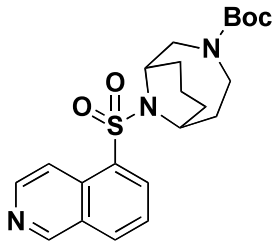
***tert*-butyl 2-(4-(isoquinolin-5-ylsulfonyl)-1,4-diazepan-1-yl)-2-oxoethylcarbamate (BRD9370).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.23 (1 H, t, J=7.2 Hz), 1.31 - 1.44 (9 H, s), 1.92 - 2.00 (2 H, m), 2.02 (1 H, s), 3.31 - 3.60 (6 H, m), 3.61 - 3.77 (2 H, m), 3.88 (2 H, dd, J=9.3, 4.4 Hz), 5.45 (1 H, d, J=15.3 Hz), 7.60 - 7.72 (1 H, m), 8.19 (1 H, d, J=8.1 Hz), 8.26 - 8.37 (2 H, m), 8.61 - 8.71 (1 H, m), 9.33 (1 H, s) ppm.



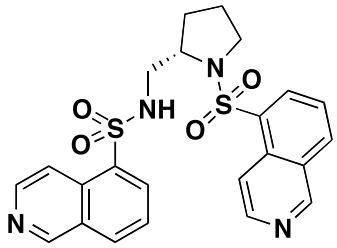
***N*-benzylisoquinoline-5-sulfonamide (BRD2850).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 4.05 - 4.20 (2 H, m), 5.40 - 5.62 (1 H, m), 6.94 - 7.08 (2 H, m), 7.08 - 7.20 (3 H, m), 7.67 (1 H, t, J=7.8 Hz), 8.18 (1 H, d, J=8.3 Hz), 8.35 - 8.48 (2 H, m), 8.57 - 8.71 (1 H, m), 9.25 - 9.38 (1 H, br.s.) ppm.



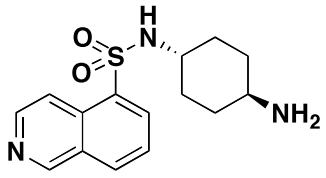
benzyl 3-(isoquinoline-5-sulfonamido)propylcarbamate (BRD0886). ^{1}H NMR (300 MHz, MeOD) δ = 2.86 (2 H, t, J=7.0 Hz), 3.01 (2 H, t, J=6.7 Hz), 4.94 - 4.98 (2 H, m), 7.21 - 7.32 (5 H, m), 7.72 - 7.81 (1 H, m), 8.31 - 8.46 (2 H, m), 8.53 (1 H, d, J=6.6 Hz), 8.57 - 8.63 (1 H, m), 9.35 (1 H, s) ppm.



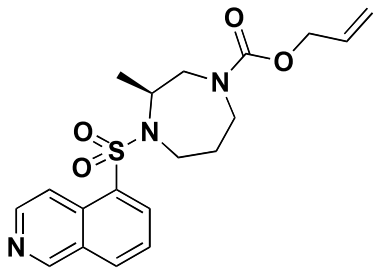
***tert*-butyl 10-(isoquinolin-5-ylsulfonyl)-3,10-diazabicyclo[4.3.1]decane-3-carboxylate (BRD4468).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.22 - 1.38 (2 H, m), 1.38 - 1.52 (9 H, m), 1.64 - 1.84 (3 H, m), 2.13 – 2.28 (1 H, m), 3.09 - 3.28 (2 H, m), 3.87 - 4.12 (2 H, m), 4.17 - 4.41 (2 H, m), 7.71 (1 H, t, J=7.7 Hz), 8.22 (1 H, d, J=8.3 Hz), 8.35 (3 H, d, J=6.4 Hz), 8.48 (1 H, d, J=7.3 Hz), 8.72 (1 H, dd, J=6.2, 2.3 Hz), 9.38 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 14.8, 15.1, 28.3, 28.5, 28.5, 31.1, 31.3, 32.3, 33.3, 46.1, 46.3, 49.2, 49.3, 52.5, 52.6, 53.0, 54.6, 79.8, 117.4, 125.9, 129.2, 131.2, 133.3, 133.6, 135.2, 145.2, 153.5, 154.4, 155.1 ppm.



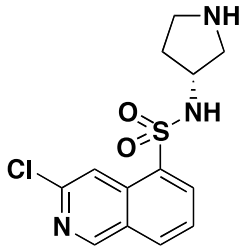
(*S*)-*N*-((1-(isoquinolin-5-ylsulfonyl)pyrrolidin-2-yl)methyl)isoquinoline-5-sulfonamide (BRD3078). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.45 - 1.75 (4 H, m), 2.98 - 3.09 (2 H, m), 3.14 - 3.33 (2 H, m), 3.64 - 3.78 (1 H, m), 5.52 (1 H, s), 7.04 - 7.15 (2 H, m), 7.65 (2 H, ddd, J=10.5, 7.9, 7.6 Hz), 8.11 - 8.21 (2 H, m), 8.26 (1 H, dd, J=7.3, 1.1 Hz), 8.32 - 8.40 (2 H, m), 8.50 (1 H, d, J=6.2 Hz), 8.56 - 8.61 (1 H, m), 8.68 (1 H, d, J=6.2 Hz), 9.28 (1 H, s), 9.33 (1 H, s) ppm.



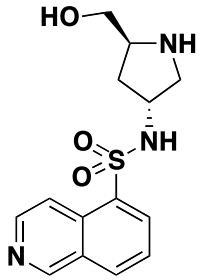
***N*-((1*r*,4*r*)-4-aminocyclohexyl)isoquinoline-5-sulfonamide (BRD6645).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 0.96 - 1.26 (5 H, m), 1.66 - 1.81 (4 H, m), 2.50 - 2.62 (1 H, m), 3.12 (1 H, dddd, J=8.0, 5.4, 2.2, 1.5 Hz), 4.57 - 4.71 (1 H, m), 7.74 (1 H, t, J=7.8 Hz), 8.24 (1 H, d, J=8.1 Hz), 8.39 (1 H, d, J=6.2 Hz), 8.50 (1 H, d, J=7.3 Hz), 8.73 (1 H, d, J=6.2 Hz), 9.40 (1 H, s) ppm.



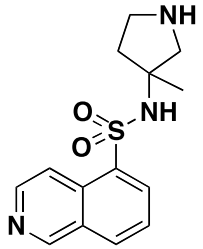
(*S*)-allyl 4-(isoquinolin-5-ylsulfonyl)-3-methyl-1,4-diazepane-1-carboxylate (BRD9304). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 0.71 - 0.87 (3 H, m), 1.07 - 1.23 (1 H, m), 1.45 - 1.75 (2 H, m), 2.91 - 3.16 (3 H, m), 3.55 - 3.81 (2 H, m), 3.81 - 3.96 (1 H, m), 4.17 - 4.38 (2 H, m), 4.38 - 4.60 (1 H, m), 5.03 - 5.29 (2 H, m), 5.68 - 5.96 (1 H, m), 7.62 (1 H, t, J=7.8 Hz), 8.13 (1 H, d, J=8.5 Hz), 8.20 - 8.28 (1 H, m), 8.37 (1 H, dd, J=13.6, 7.3 Hz), 8.61 (1 H, t, J=5.3 Hz), 9.27 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 16.5, 16.6, 28.7, 29.2, 41.1, 47.7, 48.0, 51.6, 51.9, 53.3, 53.5, 53.6, 66.1, 66.2, 117.3, 117.5, 117.6, 125.9, 129.0, 129.1, 131.4, 131.5, 132.9, 133.0, 133.6, 133.6, 133.7, 134.0, 135.16, 145.2, 153.2, 153.3, 155.1, 155.3 ppm.



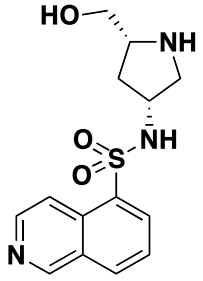
(*R*)-3-chloro-*N*-(pyrrolidin-3-yl)isoquinoline-5-sulfonamide (BRD9082). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.45 - 1.63 (1 H, m), 1.84 - 2.04 (1 H, m), 2.74 (1 H, dd, J=11.2, 3.3 Hz), 2.79 - 3.08 (3 H, m), 3.78 - 3.88 (1 H, m), 3.88 - 4.12 (2 H, m), 7.72 (1 H, dd, J=8.1, 7.3 Hz), 8.24 (1 H, d, J=8.1 Hz), 8.43 - 8.55 (2 H, m), 9.20 (1 H, s) ppm.



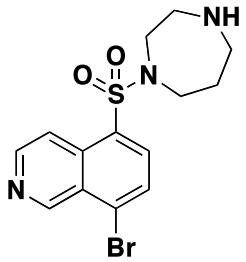
***N*-((3*R*,5*S*)-5-(hydroxymethyl)pyrrolidin-3-yl)isoquinoline-5-sulfonamide (BRD1303).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.38 - 1.51 (1 H, m), 1.58 - 1.70 (1 H, m), 1.95 - 2.14 (1 H, m), 2.72 - 2.87 (2 H, m), 2.90 - 3.04 (1 H, m), 3.22 - 3.36 (1 H, m), 3.36 - 3.63 (3 H, m), 3.74 - 3.87 (1 H, m), 7.68 - 7.81 (1 H, m), 8.18 - 8.31 (1 H, m), 8.39 - 8.46 (1 H, m), 8.46 - 8.54 (1 H, m), 8.70 - 8.77 (1 H, m), 9.38 - 9.42 (1 H, m) ppm.



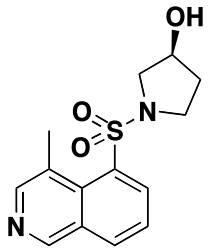
***N*-(3-methylpyrrolidin-3-yl)isoquinoline-5-sulfonamide (BRD5165).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.19 (3 H, s), 1.52 - 1.65 (1 H, m), 1.86 - 2.04 (2 H, m), 2.49 - 2.62 (1 H, m), 2.75 - 2.88 (2 H, m), 2.90 - 3.05 (1 H, m), 7.64 (1 H, t, J=7.6 Hz), 8.09 - 8.19 (1 H, m), 8.29 (1 H, d, J=6.2 Hz), 8.43 (1 H, dd, J=7.5, 1.3 Hz), 8.64 (1 H, d, J=5.8 Hz), 9.30 (1 H, s) ppm.



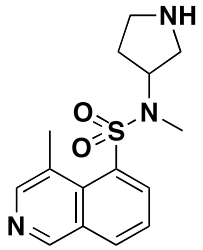
***N*-((3*R*,5*R*)-5-(hydroxymethyl)pyrrolidin-3-yl)isoquinoline-5-sulfonamide (BRD7787).** ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.34 (1 H, d, J=14.2 Hz), 1.49 (1 H, t, J=7.1 Hz), 2.03 (2 H, ddd, J=13.9, 9.5, 7.3 Hz), 2.74 - 2.89 (2 H, m), 3.30 (1 H, dd, J=9.0, 4.1 Hz), 3.41 (1 H, dd, J=10.7, 3.4 Hz), 3.54 - 3.66 (2 H, m), 3.76 - 3.86 (1 H, m), 7.73 (1 H, t, J=7.8 Hz), 8.23 (1 H, d, J=8.3 Hz), 8.41 (1 H, d, J=6.3 Hz), 8.49 (1 H, d, J=7.3 Hz), 8.71 (1 H, d, J=6.3 Hz), 9.34 - 9.42 (1 H, m) ppm.



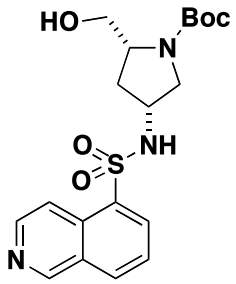
5-(1,4-diazepan-1-ylsulfonyl)-8-bromoisoquinoline (BRD9509). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 2.03 - 2.22 (2 H, m), 2.81 - 3.15 (9 H, m), 3.22 - 3.34 (4 H, m), 3.50 - 3.58 (2 H, m), 3.89 - 3.99 (2 H, m), 7.67 (1 H, dd, J=8.3, 4.7 Hz), 7.95 (1 H, d, J=8.3 Hz), 8.31 - 8.39 (1 H, m), 8.67 (1 H, dd, J=8.5, 1.1 Hz), 9.08 (1 H, dd, J=2.7, 1.0 Hz) ppm.



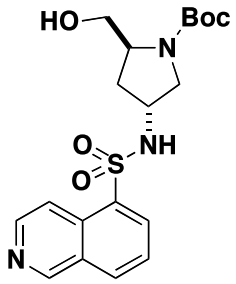
(*S*)-1-(4-methylisoquinolin-5-ylsulfonyl)pyrrolidin-3-ol (BRD2334). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 2.07 - 2.33 (2 H, m), 2.40 (1 H, m), 3.10 (3 H, s), 3.59 (1 H, d, J=11.3 Hz), 3.64 - 3.87 (3 H, m), 4.66 - 4.77 (1 H, m), 7.61 (1 H, t, J=7.5 Hz), 8.15 (1 H, d, J=8.5 Hz), 8.39 (1 H, d, J=7.3 Hz), 8.55 (1 H, s), 9.14 (1 H, s) ppm.



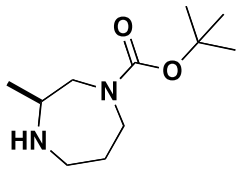
***N*,4-dimethyl-*N*-(pyrrolidin-3-yl)isoquinoline-5-sulfonamide (BRD4275).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.96 - 2.20 (2 H, m), 2.89 - 3.04 (5 H, m), 3.04 - 3.15 (4 H, m), 3.18 - 3.31 (1 H, m), 4.43 - 4.60 (1 H, m), 7.62 (1 H, t, J=7.7 Hz), 8.07 - 8.23 (2 H, m), 8.56 (1 H, s), 9.16 (1 H, s) ppm.



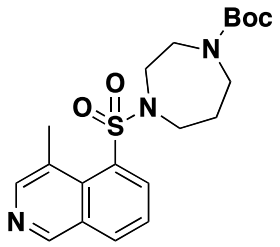
(2*R*,4*R*)-*tert*-butyl 2-(hydroxymethyl)-4-(isoquinoline-5-sulfonamido)pyrrolidine-1-carboxylate (26). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.34 (4 H, br. s.), 1.38 (6 H, br. s.), 1.43 - 1.50 (1 H, m), 1.51 (1 H, d, J=6.3 Hz), 1.58 (6 H, s), 1.66 - 1.75 (1 H, m), 2.13 - 2.27 (1 H, m), 2.30 - 2.43 (1 H, m), 2.95 (1 H, br. s.), 3.02 - 3.13 (1 H, m), 3.13 - 3.27 (1 H, m), 3.33 - 3.45 (2 H, m), 3.45 - 3.54 (1 H, m), 3.86 (2 H, d, J=4.9 Hz), 3.96 - 4.20 (2 H, m), 6.91 (1 H, dd, J=6.8, 3.4 Hz), 7.73 (1 H, t, J=7.8 Hz), 8.11 - 8.20 (1 H, m), 8.24 (1 H, d, J=8.3 Hz), 8.39 (1 H, d, J=5.9 Hz), 8.49 (1 H, d, J=7.3 Hz), 8.60 (1 H, dd, J=6.6, 2.7 Hz), 8.71 (1 H, d, J=2.4 Hz), 9.38 (1 H, br. s.) ppm.



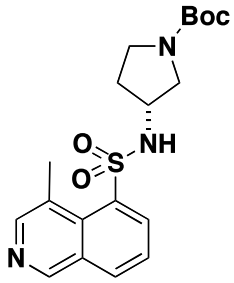
(2*S*,4*R*)-*tert*-butyl 2-(hydroxymethyl)-4-(isoquinoline-5-sulfonamido)pyrrolidine-1-carboxylate (27). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.28 - 1.42 (9 H, s), 1.55 - 1.79 (2 H, m), 1.79 - 1.96 (1 H, m), 3.13 - 3.25 (1 H, m), 3.29 - 3.43 (1 H, m), 3.43 - 3.54 (1 H, m), 3.54 - 3.67 (1 H, m), 3.82 - 4.03 (2 H, m), 5.26 - 5.42 (1 H, m), 7.76 (1 H, t, J=7.8 Hz), 8.27 (1 H, d, J=8.1 Hz), 8.40 (1 H, d, J=6.0 Hz), 8.50 (1 H, dd, J=7.4, 1.2 Hz), 8.72 (1 H, d, J=6.0 Hz), 9.41 (1 H, s) ppm.



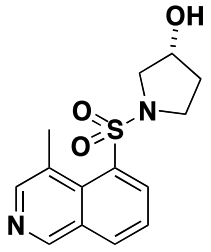
(*S*)-*tert*-butyl 3-methyl-1,4-diazepane-1-carboxylate (28). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 0.97 - 1.12 (3 H, m), 1.32 - 1.51 (9 H, m), 1.58 - 1.79 (2 H, m), 1.79 - 2.03 (1 H, m), 2.53 - 2.78 (2 H, m), 2.82 - 2.97 (1 H, m), 3.02 - 3.29 (2 H, m), 3.61 - 3.83 (1 H, m) ppm.



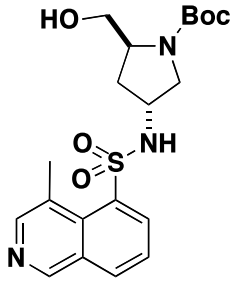
***tert*-butyl 4-(4-methylisoquinolin-5-ylsulfonyl)-1,4-diazepane-1-carboxylate (9).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.40 - 1.57 (10 H, m), 2.06 (2 H, d, J=5.8 Hz), 2.99 - 3.13 (3 H, m), 3.45 - 3.73 (8 H, m), 5.31 (2 H, s), 7.59 (1 H, t, J=7.6 Hz), 7.74 (1 H, s), 8.07 - 8.22 (1 H, m), 8.56 (1 H, s), 9.15 (1 H, s) ppm.



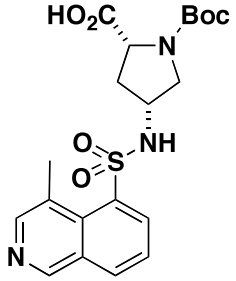
(*R*)-*tert*-butyl 3-(4-methylisoquinoline-5-sulfonamido)pyrrolidine-1-carboxylate (10). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.35 (9 H, br. s.), 1.97 (2 H, br. s.), 2.11 (1 H, br. s.), 2.97 (3 H, s), 3.28 (4 H, br. s.), 3.92 (1 H, br. s.), 6.19 (1 H, br. s.), 7.49 (1 H, s), 8.04 (1 H, br. s.), 8.44 (1 H, br. s.), 9.05 (1 H, s) ppm.



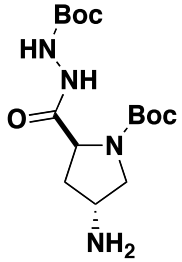
(*R*)-1-(4-methylisoquinolin-5-ylsulfonyl)pyrrolidin-3-ol (25). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 2.07 (2 H, br. s.), 3.01 (3 H, s), 3.52 (1 H, s), 3.64 (3 H, d, J=3.6 Hz), 4.63 (1 H, br. s.), 7.43 - 7.60 (1 H, m), 8.04 (1 H, s), 8.30 (1 H, s), 8.45 (1 H, s), 9.04 (1 H, s) ppm.



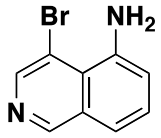
(2*S*,4*R*)-*tert*-butyl 2-(hydroxymethyl)-4-(4-methylisoquinoline-5-sulfonamido)pyrolidine-1-carboxylate (22). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.46 (9 H, br. s.), 1.68 (2 H, br. s.), 2.01 (1 H, d, J=3.4 Hz), 2.08 - 2.21 (1 H, m), 3.07 (3 H, s), 3.52 (1 H, br. s.), 3.55 - 3.67 (2 H, m), 3.70 (1 H, br. s.), 4.07 (1 H, br. s.), 4.15 (2 H, br. s.), 5.29 (1 H, br. s.), 7.64 (1 H, t, J=7.8 Hz), 8.20 (1 H, d, J=7.8 Hz), 8.49 (1 H, d, J=7.3 Hz), 8.57 (1 H, s), 9.18 (1 H, s) ppm.



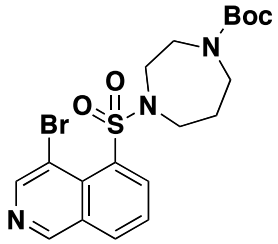
(2*R*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidine-2-carboxylic acid (30). ^{1}H NMR (300 MHz, MeOD) δ = 1.11 - 1.18 (1 H, m), 1.21 - 1.27 (1 H, m), 1.34 - 1.41 (9 H, m), 1.98 - 2.10 (1 H, m), 2.64 (1 H, dd, J=6.7, 5.9 Hz), 3.02 (3 H, s), 3.32 - 3.41 (1 H, m), 3.53 - 3.62 (1 H, m), 3.74 (1 H, dd, J=10.7, 6.2 Hz), 3.86 - 3.97 (1 H, m), 4.10 - 4.21 (1 H, m), 7.74 (1 H, t, J=7.9 Hz), 8.13 (1 H, s), 8.31 (1 H, d, J=8.1 Hz), 8.42 (1 H, s), 8.53 (1 H, d, J=7.5 Hz), 9.14 (1 H, s) ppm.



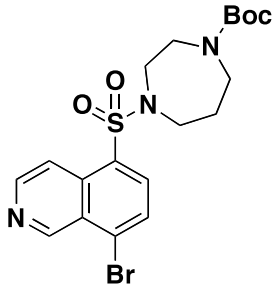
(2*S*,4*R*)-*tert*-butyl 4-amino-2-(2-(*tert*-butoxycarbonyl)hydrazinecarbonyl)pyrroledine-1-carboxylate (31). ^{1}H NMR (500 MHz, METHANOL-d4) δ = 1.26 - 1.37 (1 H, m), 1.42 - 1.53 (19 H, m), 1.93 - 1.97 (1 H, m), 2.00 - 2.15 (1 H, m), 2.17 - 2.30 (1 H, m), 2.85 - 2.90 (1 H, m), 2.99 - 3.04 (1 H, m), 3.13 - 3.23 (1 H, m), 3.61 - 3.75 (2 H, m), 4.28 - 4.39 (1 H, m) ppm.



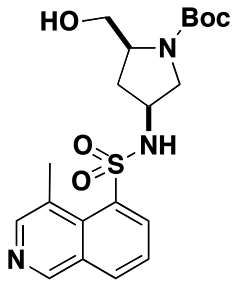
4-bromoisoquinolin-5-amine (3). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 5.25 (2 H, br. s.), 6.94 (1 H, d, J=7.3 Hz), 7.35 - 7.39 (1 H, m), 7.42 (1 H, t, J=7.8 Hz), 8.53 (1 H, s), 9.00 (1 H, s) ppm.



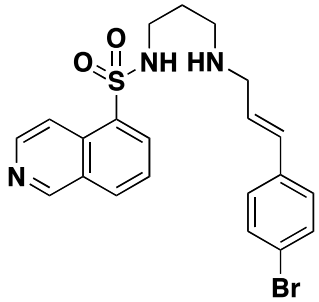
***tert*-butyl 4-(4-bromoisoquinolin-5-ylsulfonyl)-1,4-diazepane-1-carboxylate (4).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.32 - 1.47 (10 H, m), 1.57 (1 H, s), 2.00 (2 H, br. s.), 3.43 (4 H, s), 3.56 (5 H, br. s.), 7.60 (1 H, s), 7.79 (1 H, s), 8.09 (1 H, s), 8.93 (1 H, s), 9.14 (1 H, s) ppm.



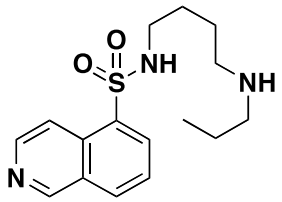
***tert*-butyl 4-(8-bromoisoquinolin-5-ylsulfonyl)-1,4-diazepane-1-carboxylate (6).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.37 - 1.46 (9 H, m), 1.98 (2 H, t, J=5.8 Hz), 3.43 (2 H, t, J=5.9 Hz), 3.50 - 3.65 (6 H, m), 7.63 (1 H, dd, J=8.4, 4.1 Hz), 7.91 (1 H, d, J=7.9 Hz), 8.34 (1 H, d, J=7.9 Hz), 8.62 (1 H, d, J=8.9 Hz), 9.06 (1 H, br. s.) ppm; ^{13}C NMR (150 MHz, CHLOROFORM-d) δ = 14.5, 21.3, 28.7, 28.8, 45.9, 46.5, 48.5, 50.3, 50.4, 51.3, 51.8, 53.7, 60.6, 79.9, 80.0, 123.0, 123.3, 128.2, 128.6, 129.5, 129.6, 133.1, 136.3, 136.4, 137.5, 137.7, 144.7, 151.8, 151.9, 155.2, 155.5 ppm.



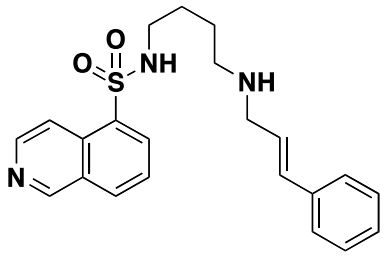
(2*S*,4*S*)-*tert*-butyl 2-(hydroxymethyl)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidine-1-carboxylate (32). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.20 - 1.28 (1 H, m), 1.37 - 1.45 (9 H, m), 1.89 - 2.15 (1 H, m), 2.49 (1 H, dddd, J=5.2, 3.8, 2.3, 1.1 Hz), 2.98 - 3.11 (3 H, m), 3.48 - 3.68 (3 H, m), 3.88 - 4.06 (2 H, m), 4.14 - 4.30 (1 H, m), 7.59 (1 H, t, J=7.6 Hz), 8.07 - 8.17 (1 H, m), 8.44 - 8.57 (2 H, m), 9.11 (1 H, br. s.) ppm.



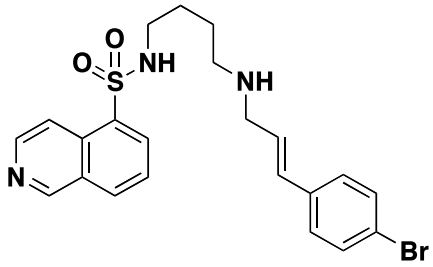
(*E*)-*N*-(3-(3-(4-bromophenyl)allylamino)propyl)isoquinoline-5-sulfonamide (BRD5149). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 2.50 - 2.63 (2 H, m), 2.93 - 3.03 (2 H, m), 3.16 - 3.26 (2 H, m), 6.14 (1 H, dt, J=15.9, 6.1 Hz), 6.32 - 6.47 (1 H, m), 7.11 - 7.20 (2 H, m), 7.32 - 7.42 (2 H, m), 7.62 (1 H, t, J=7.7 Hz), 8.12 (1 H, d, J=8.1 Hz), 8.32 - 8.41 (2 H, m), 8.56 (1 H, d, J=6.2 Hz), 9.29 (1 H, s) ppm.



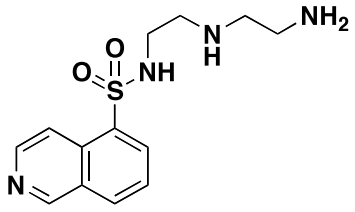
***N*-(4-(propylamino)butyl)isoquinoline-5-sulfonamide (BRD1524).** ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 0.99 (3 H, t, J=7.5 Hz), 1.55 - 1.62 (2 H, m), 1.62 - 1.75 (4 H, m), 2.69 - 2.76 (4 H, m), 2.90 - 2.97 (2 H, m), 7.70 (1 H, t, J=7.9 Hz), 8.20 (1 H, d, J=8.4 Hz), 8.43 (1 H, d, J=7.3 Hz), 8.53 (1 H, d, J=6.2 Hz), 8.68 (1 H, d, J=6.2 Hz), 9.36 (1 H, s) ppm.



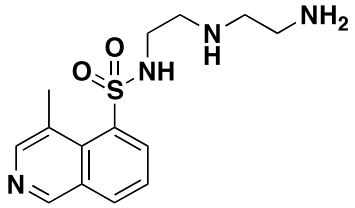
(*E*)-*N*-(4-(cinnamylamino)butyl)isoquinoline-5-sulfonamide (BRD2874). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.39 - 1.65 (4 H, m), 2.56 - 2.70 (2 H, m), 2.91 (2 H, t, J=5.6 Hz), 3.47 (2 H, d, J=6.4 Hz), 6.34 - 6.49 (1 H, m), 6.53 - 6.66 (1 H, m), 7.20 - 7.37 (3 H, m), 7.37 - 7.47 (2 H, m), 7.60 - 7.71 (1 H, m), 8.17 (1 H, d, J=8.1 Hz), 8.44 (1 H, dd, J=7.3, 1.1 Hz), 8.53 (2 H, q, J=6.2 Hz), 9.34 (1 H, s) ppm.



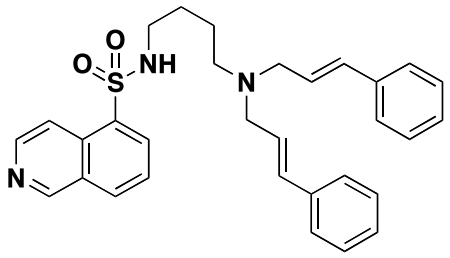
(*E*)-*N*-(4-(3-(4-bromophenyl)allylamino)butyl)isoquinoline-5-sulfonamide (BRD6081). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.33 - 1.56 (4 H, m), 2.49 - 2.62 (2 H, m), 2.82 (2 H, t, J=5.7 Hz), 3.30 - 3.40 (2 H, m), 6.26 - 6.40 (1 H, m), 6.40 - 6.51 (1 H, m), 7.14 - 7.24 (2 H, m), 7.29 - 7.39 (2 H, m), 7.53 - 7.64 (1 H, m), 8.09 (1 H, d, J=8.3 Hz), 8.30 - 8.44 (2 H, m), 8.45 - 8.51 (2 H, m), 9.26 (1 H, s) ppm.



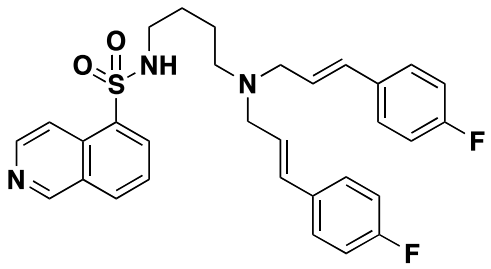
***N*-(2-(2-aminoethylamino)ethyl)isoquinoline-5-sulfonamide (BRD4009).** ^{1}H NMR (300 MHz, MeOD) δ = 2.56 - 2.70 (4 H, m), 2.71 - 2.83 (4 H, m), 2.84 - 2.99 (4 H, m), 7.80 (1 H, t, J=7.9 Hz), 8.38 (1 H, d, J=8.3 Hz), 8.41 - 8.48 (1 H, m), 8.49 - 8.56 (1 H, m), 8.58 - 8.64 (1 H, m), 9.37 (1 H, s) ppm.



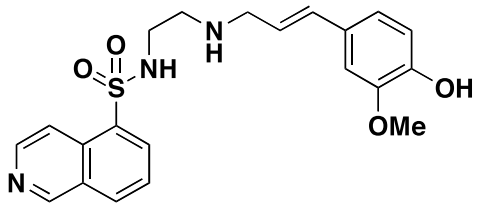
***N*-(2-(2-aminoethylamino)ethyl)-4-methylisoquinoline-5-sulfonamide (BRD3407).** ^{1}H NMR (300 MHz, MeOD) δ = 1.85 (1 H, s), 2.58 - 2.69 (2 H, m), 2.70 - 2.80 (3 H, m), 2.95 - 3.00 (3 H, m), 3.10 - 3.19 (4 H, m), 7.70 (1 H, d, J=7.9 Hz), 8.21 - 8.30 (1 H, m), 8.33 - 8.41 (2 H, m), 9.09 (1 H, s) ppm.



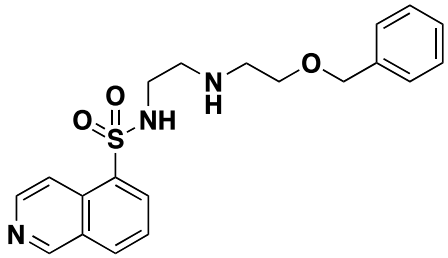
***N*-(4-(dicinnamylamino)butyl)isoquinoline-5-sulfonamide (BRD2686).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.33 - 1.56 (4 H, m), 2.25 - 2.43 (2 H, m), 2.72 - 2.87 (2 H, m), 3.10 - 3.24 (4 H, m), 6.11 - 6.29 (2 H, m), 6.32 - 6.46 (2 H, m), 7.03 - 7.29 (10 H, m), 7.43 - 7.51 (1 H, m), 8.00 (1 H, d, J=8.1 Hz), 8.28 (1 H, dd, J=7.3, 1.1 Hz), 8.34 - 8.44 (2 H, m), 9.18 (1 H, s) ppm.



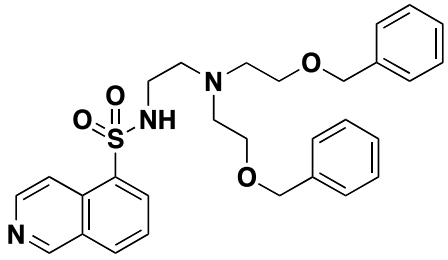
***N*-(4-(bis((*E*)-3-(4-fluorophenyl)allyl)amino)butyl)isoquinoline-5-sulfonamide (BRD5822).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 2.42 - 2.60 (2 H, m), 2.96 (2 H, t, J=5.2 Hz), 3.32 (4 H, d, J=6.8 Hz), 6.30 (2 H, dt, J=15.8, 6.8 Hz), 6.43 - 6.58 (2 H, m), 6.94 - 7.08 (4 H, m), 7.30 - 7.40 (4 H, m), 7.65 (1 H, t, J=7.8 Hz), 8.18 (1 H, d, J=8.3 Hz), 8.43 (1 H, dd, J=7.3, 1.1 Hz), 8.56 (2 H, q, J=6.2 Hz), 9.35 (1 H, s) ppm.



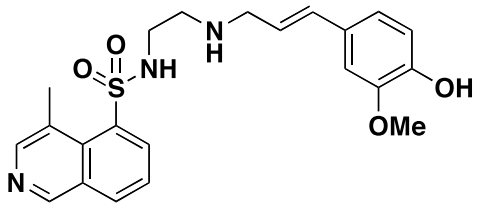
(*E*)-*N*-(2-(3-(4-hydroxy-3-methoxyphenyl)allylamino)ethyl)isoquinoline-5-sulfonamide (BRD8902). ^{1}H NMR (300 MHz, MeOD) δ = 1.86 - 1.95 (1 H, m), 2.01 (1 H, s), 2.53 - 2.65 (2 H, m), 2.95 - 3.04 (3 H, m), 3.13 - 3.22 (3 H, m), 3.79 - 3.87 (3 H, m), 5.80 - 5.98 (1 H, m), 6.31 (1 H, d, J=15.4 Hz), 6.67 - 6.81 (2 H, m), 6.92 (1 H, s), 7.76 (1 H, t, J=7.9 Hz), 8.32 (1 H, d, J=8.5 Hz), 8.44 (1 H, d, J=7.3 Hz), 8.49 - 8.56 (1 H, m), 8.57 - 8.64 (1 H, m), 9.32 (1 H, s) ppm.



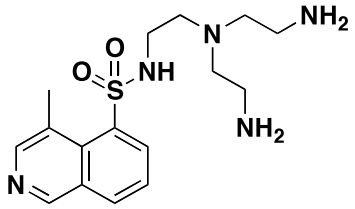
***N*-(2-(2-(benzyloxy)ethylamino)ethyl)isoquinoline-5-sulfonamide (BRD1600).** ^{1}H NMR (300 MHz, MeOD) δ = 2.52 - 2.65 (4 H, m), 2.96 (2 H, t, J=6.1 Hz), 3.44 (2 H, t, J=5.3 Hz), 4.45 (2 H, s), 7.20 - 7.35 (5 H, m), 7.79 (1 H, t, J=7.8 Hz), 8.37 (1 H, d, J=8.1 Hz), 8.42 - 8.48 (1 H, m), 8.50 - 8.55 (1 H, m), 8.56 - 8.62 (1 H, m), 9.36 (1 H, s) ppm.



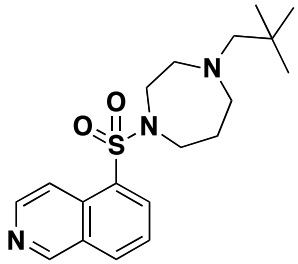
***N*-(2-(bis(2-(benzyloxy)ethyl)amino)ethyl)isoquinoline-5-sulfonamide (BRD5967).** ^{1}H NMR (300 MHz, MeOD) δ = 2.44 - 2.59 (4 H, m), 2.92 (2 H, t, J=6.3 Hz), 3.27 - 3.34 (4 H, m), 4.32 - 4.41 (4 H, m), 7.10 - 7.34 (10 H, m), 7.69 - 7.79 (1 H, m), 8.28 - 8.36 (1 H, m), 8.37 - 8.44 (1 H, m), 8.44 - 8.57 (2 H, m), 9.27 - 9.35 (1 H, m) ppm.



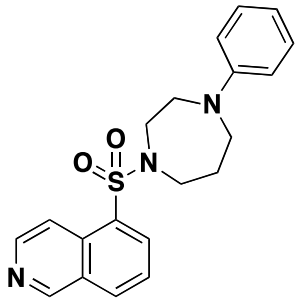
(*E*)-*N*-(2-(3-(4-hydroxy-3-methoxyphenyl)allylamino)ethyl)-4-methylisoquinoline-5-sulfonamide (BRD9159). ^{1}H NMR (300 MHz, MeOD) δ = 2.89 - 3.00 (2 H, m), 3.00 - 3.09 (3 H, m), 3.31 - 3.38 (1 H, m), 3.44 - 3.51 (1 H, m), 3.83 (3 H, s), 6.08 (1 H, d, J=15.4 Hz), 6.45 - 6.60 (1 H, m), 6.71 (1 H, d, J=8.1 Hz), 6.79 - 6.88 (1 H, m), 6.98 (1 H, s), 7.68 - 7.79 (1 H, m), 8.28 - 8.34 (1 H, m), 8.39 (1 H, dd, J=7.6, 1.4 Hz), 8.44 (1 H, s), 8.52 (1 H, s), 9.15 (1 H, s) ppm.



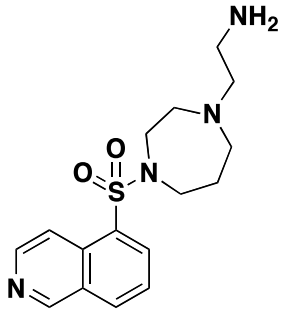
***N*-(2-(bis(2-aminoethyl)amino)ethyl)-4-methylisoquinoline-5-sulfonamide (BRD3394).** ^{1}H NMR (300 MHz, MeOD) δ = 2.51 - 2.59 (3 H, m), 2.61 - 2.68 (2 H, m), 2.73 - 2.81 (3 H, m), 2.95 - 3.01 (3 H, m), 3.11 - 3.18 (3 H, m), 7.70 (1 H, d, J=7.7 Hz), 8.26 (1 H, dd, J=8.2, 0.8 Hz), 8.34 (1 H, s), 8.35 - 8.40 (1 H, m), 9.09 (1 H, s) ppm.



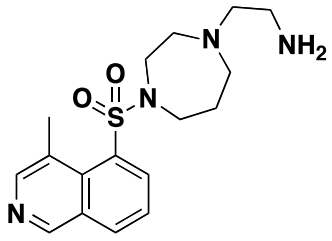
5-(4-neopentyl-1,4-diazepan-1-ylsulfonyl)isoquinoline (BRD5665). ^{1}H NMR (300 MHz, MeOD) δ = 0.81 - 0.93 (9 H, m), 1.87 - 2.02 (2 H, m), 2.35 - 2.46 (2 H, m), 2.89 - 3.09 (4 H, m), 3.42 - 3.61 (4 H, m), 7.71 (1 H, t, J=7.9 Hz), 8.22 (1 H, d, J=8.5 Hz), 8.31 - 8.39 (1 H, m), 8.47 (1 H, d, J=6.2 Hz), 8.61 - 8.76 (1 H, br.s.), 9.37 (1 H, br.s.) ppm.



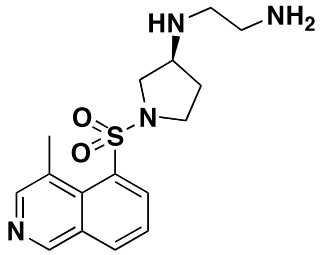
5-(4-phenyl-1,4-diazepan-1-ylsulfonyl)isoquinoline (BRD5656). Compound **BRD5656** was synthesized following the known procedure.[1] ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.91 - 2.07 (2 H, m), 3.22 (2 H, t, J=6.0 Hz), 3.43 - 3.52 (2 H, m), 3.52 - 3.67 (4 H, m), 6.53 (2 H, d, J=7.9 Hz), 6.59 (1 H, t, J=7.3 Hz), 7.05 - 7.12 (2 H, m), 7.56 (1 H, t, J=7.8 Hz), 8.08 (1 H, d, J=8.3 Hz), 8.21 (1 H, dd, J=7.4, 1.2 Hz), 8.31 (1 H, d, J=6.2 Hz), 8.55 (1 H, d, J=6.2 Hz), 9.24 (1 H, s) ppm.



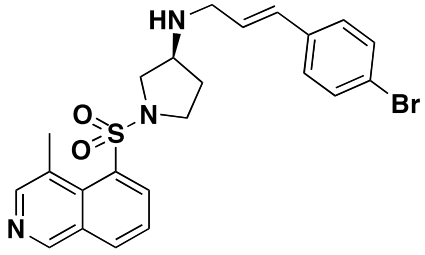
2-(4-(isoquinolin-5-ylsulfonyl)-1,4-diazepan-1-yl)ethanamine (BRD0112). ^{1}H NMR (500 MHz, METHANOL-d4) δ = 1.89 (2 H, t, J=5.9 Hz), 2.70 (2 H, t, J=5.9 Hz), 2.79 (4 H, td, J=11.1, 5.6 Hz), 2.87 (2 H, t, J=5.9 Hz), 3.49 - 3.57 (4 H, m), 7.85 (1 H, t, J=7.8 Hz), 8.43 (2 H, d, J=7.3 Hz), 8.54 (1 H, d, J=6.3 Hz), 8.65 (1 H, d, J=5.9 Hz), 9.41 (1 H, s) ppm.



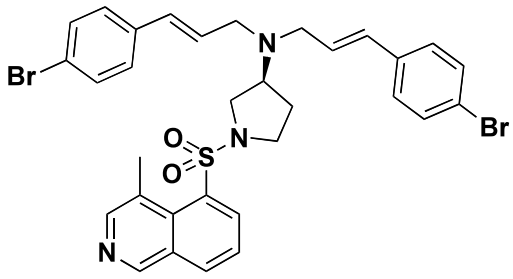
2-(4-(4-methylisoquinolin-5-ylsulfonyl)-1,4-diazepan-1-yl)ethanamine (BRD9740). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.73 (5 H, br. s.), 1.96 - 2.08 (2 H, m), 2.70 (2 H, t, J=5.9 Hz), 2.82 (2 H, t, J=5.9 Hz), 2.87 - 2.95 (4 H, m), 3.10 (3 H, s), 3.59 - 3.71 (4 H, m), 7.61 (1 H, t, J=7.8 Hz), 7.87 (1 H, d, J=7.3 Hz), 8.16 (1 H, d, J=7.8 Hz), 8.57 (1 H, s), 9.16 (1 H, s) ppm.



(*S*)-*N*^{1}-(1-(4-methylisoquinolin-5-ylsulfonyl)pyrrolidin-3-yl)ethane-1,2-diamine (BRD1596). ^{1}H NMR (300 MHz, MeOD) δ = 1.97 - 2.10 (1 H, m), 2.26 - 2.40 (1 H, m), 2.73 - 2.86 (2 H, m), 2.86 - 2.94 (2 H, m), 3.06 (3 H, s), 3.39 (1 H, dd, J=9.2, 4.7 Hz), 3.55 - 3.66 (2 H, m), 3.66 - 3.79 (2 H, m), 7.78 (1 H, t, J=7.8 Hz), 8.37 (1 H, dd, J=8.4, 1.2 Hz), 8.43 (1 H, dd, J=7.5, 1.3 Hz), 8.47 (1 H, s), 9.19 (1 H, s) ppm.

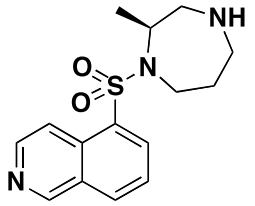


(*S*,*E*)-*N*-(3-(4-bromophenyl)allyl)-1-(4-methylisoquinolin-5-ylsulfonyl)pyrrolidin-3-amine (BRD8155). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.94 - 2.07 (1 H, m), 2.23 - 2.40 (1 H, m), 3.10 (3 H, s), 3.41 - 3.52 (3 H, m), 3.61 - 3.78 (4 H, m), 6.24 - 6.40 (1 H, m), 6.49 - 6.61 (1 H, m), 7.21 - 7.30 (3 H, m), 7.42 - 7.52 (2 H, m), 7.57 (1 H, t, J=7.8 Hz), 8.15 (1 H, dd, J=8.2, 1.2 Hz), 8.49 (1 H, dd, J=7.5, 1.3 Hz), 8.56 (1 H, s), 9.15 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 21.6, 32.6, 46.9, 49.8, 53.6, 57.4, 125.0, 127.8, 128.4, 130.6, 131.1, 131.8, 134.4, 148.5, 151.9 ppm.

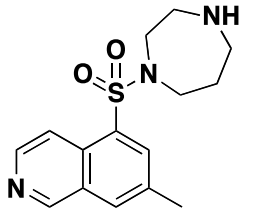


(*S*)-*N*,*N*-bis((*E*)-3-(4-bromophenyl)allyl)-1-(4-methylisoquinolin-5-ylsulfonyl)pyrrolidin-3-amine (BRD3615). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.60 (3 H, td, J=3.5, 2.0 Hz), 3.09 (3 H, s), 3.35 - 3.47 (5 H, m), 3.48 - 3.66 (3 H, m), 3.72 (2 H, s), 3.77 - 3.88 (1 H, m), 6.20 - 6.34 (2 H, m), 6.45 - 6.57 (2 H, m), 7.20 - 7.31 (6 H, m), 7.44

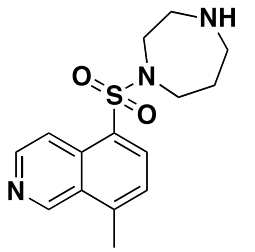
- 7.51 (4 H, m), 7.57 (1 H, t, J=7.8 Hz), 8.11 - 8.22 (2 H, m), 8.57 (1 H, s), 9.16 (1 H, s) ppm.



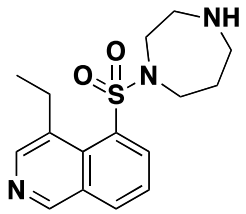
(*S*)-5-(2-methyl-1,4-diazepan-1-ylsulfonyl)isoquinoline (BRD1869). Sulfonamide **BRD9304** (20 mg, 0.051 mmol, 1 equiv.) and *N,N'*-dimethylbarbituric acid (80 mg, 0.51 mmol, 10 equiv.) were dissolved in dry THF (2.6 mL). After the addition of tetrakis(triphenylphosphine)palladium(0) (6 mg, 0.0051 mmol, 0.1 equiv.), the solution was degassed with nitrogen and stirred for 2 h under room temperature. The solution was filtered through a short column of Celite and the column was washed by EA. The solvent was removed under reduced pressure and the residue was purified by prep-HPLC. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 0.75 - 0.85 (3 H, m), 1.46 - 1.61 (2 H, m), 1.61 - 1.84 (2 H, m), 2.51 (1 H, dd, J=14.5, 8.7 Hz), 2.62 - 2.75 (1 H, m), 3.02 - 3.31 (3 H, m), 3.88 - 4.01 (1 H, m), 4.03 - 4.16 (1 H, m), 7.71 (1 H, t, J=7.8 Hz), 8.21 (1 H, d, J=8.3 Hz), 8.40 (1 H, d, J=6.2 Hz), 8.56 - 8.61 (1 H, m), 8.72 (1 H, d, J=6.2 Hz), 9.36 (1 H, s) ppm.



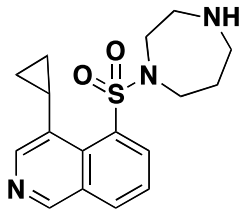
5-(1,4-diazepan-1-ylsulfonyl)-7-methylisoquinoline (BRD5087). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.65 (3 H, s), 1.85 (2 H, t, J=5.9 Hz), 2.64 (3 H, s), 2.90 - 3.04 (4 H, m), 3.40 - 3.56 (4 H, m), 7.97 (1 H, s), 8.24 (1 H, d, J=1.7 Hz), 8.39 (1 H, d, J=6.2 Hz), 8.64 (1 H, d, J=6.2 Hz), 9.28 (1 H, s) ppm.



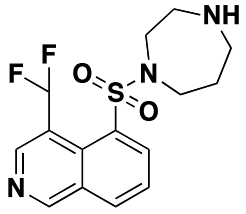
5-(1,4-diazepan-1-ylsulfonyl)-8-methylisoquinoline (BRD5257). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 2.07 - 2.17 (2 H, m), 2.78 (3 H, s), 3.20 - 3.41 (4 H, m), 3.49 - 3.58 (2 H, m), 3.96 (2 H, ddd, J=5.0, 3.6, 1.1 Hz), 7.44 - 7.50 (1 H, m), 7.58 (1 H, dd, J=8.5, 4.1 Hz), 8.35 - 8.48 (3 H, m), 9.05 (1 H, dd, J=4.1, 1.5 Hz) ppm.



5-(1,4-diazepan-1-ylsulfonyl)-4-ethylisoquinoline (BRD5930). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.38 (3 H, t, J=7.4 Hz), 1.93 - 2.05 (2 H, m), 3.05 - 3.16 (4 H, m), 3.55 - 3.71 (6 H, m), 7.62 (1 H, d, J=7.9 Hz), 7.82 - 7.90 (1 H, m), 8.12 - 8.20 (1 H, m), 8.64 (1 H, s), 9.15 (1 H, s) ppm.

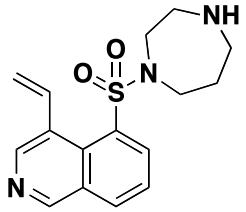


5-(1,4-diazepan-1-ylsulfonyl)-4-cyclopropylisoquinoline (BRD5796). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 0.80 - 0.92 (2 H, m), 1.18 - 1.28 (2 H, m), 1.90 - 2.02 (2 H, m), 3.02 - 3.15 (4 H, m), 3.16 - 3.30 (1 H, m), 3.51 - 3.68 (4 H, m), 7.56 - 7.66 (1 H, m), 7.87 (1 H, d, J=7.2 Hz), 8.10 - 8.20 (1 H, m), 8.54 (1 H, s), 9.13 (1 H, s) ppm.

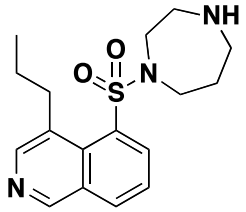


5-(1,4-diazepan-1-ylsulfonyl)-4-(difluoromethyl)isoquinoline (BRD8757). To a solution of **14** (8.5 mg, 0.02 mmol) in 2 mL THF/water (1:1) was added a solution of OsO_4 in *t*-BuOH (0.08 M, 5 µL, 0.4 µmol, 0.02 equiv.) and sodium periodate (8.7 mg, 0.04 mmol, 2 equiv.). The reaction mixture was stirred overnight under room temperature. 2 mL 1 M $NaHSO_3$ (aq.) was added. After a further 90 minutes the mixture was diluted with 2 mL water and extracted first with $CHCl_3$ (3 x 4 mL) and then with EA (3 x 4 mL). Drying over sodium sulfate and the evaporation of the solvent from the organic phase gave an oily residue (**16**). Under nitrogen, the mixture of the crude product

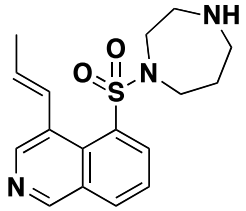
16 and DAST (0.05 mL, 0.4 mmol, 20 equiv.) in dry CH_2Cl_2 was refluxed for 16 h. The reaction was quenched with water and extracted with EA. The organic layers were then washed with saturated brine, dried over sodium sulfate, filtered, and evaporated under reduced pressure. The residue was treated with TFA/CH_2Cl_2 (1:1) at room temperature. The volatiles were removed under reduced pressure and the residue was purified by prep-HPLC to afford **BRD8757** (1.5 mg, 22% yield over 3 steps). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.19 - 1.30 (5 H, m), 1.67 - 1.87 (19 H, m), 2.01 - 2.12 (3 H, m), 3.14 - 3.23 (4 H, m), 3.62 - 3.71 (4 H, m), 7.70 - 7.78 (1 H, m), 8.04 - 8.09 (1 H, m), 8.25 - 8.31 (1 H, m), 8.36 (1 H, t, J=53 Hz), 9.26 (1 H, s), 9.44 (1 H, s) ppm.



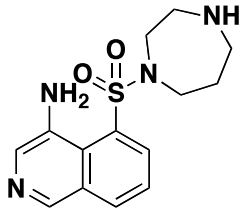
5-(1,4-diazepan-1-ylsulfonyl)-4-vinylisoquinoline (BRD7032). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.90 - 2.22 (3 H, m), 3.03 - 3.16 (3 H, m), 3.48 - 3.67 (4 H, m), 5.53 (1 H, dd, J=10.7, 1.5 Hz), 5.68 (1 H, dd, J=17.0, 1.5 Hz), 7.66 (1 H, t, J=7.8 Hz), 7.91 - 8.07 (2 H, m), 8.19 (1 H, dd, J=8.0, 1.0 Hz), 8.74 (1 H, d, J=0.8 Hz), 9.24 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 31.2, 47.6, 48.9, 51.1, 52.6, 117.2, 125.3, 129.8, 129.9,130.0, 130.3, 134.0, 136.2, 136.9, 146.4, 153.0 ppm.



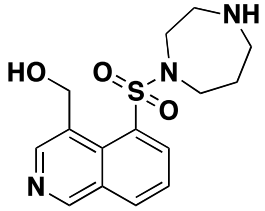
5-(1,4-diazepan-1-ylsulfonyl)-4-propylisoquinoline (BRD7132). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.06 (3 H, t, J=7.3 Hz), 1.65 - 1.77 (3 H, m), 1.90 - 2.03 (2 H, m), 3.06 - 3.14 (3 H, m), 3.49 - 3.70 (6 H, m), 7.59 (1 H, t, J=7.7 Hz), 7.85 (1 H, dd, J=7.3, 1.4 Hz), 8.10 - 8.19 (1 H, m), 8.61 (1 H, s), 9.14 (1 H, s) ppm.



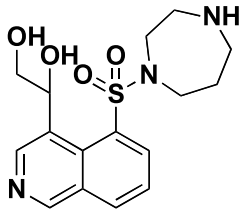
(*E*)-5-(1,4-diazepan-1-ylsulfonyl)-4-(prop-1-enyl)isoquinoline (BRD9078). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.63 - 1.82 (2 H, m), 1.90 - 2.01 (2 H, m), 2.06 (3 H, d, J=6.3 Hz), 3.10 (4 H, d, J=5.9 Hz), 3.51 - 3.69 (4 H, m), 6.09 (1 H, dd, J=15.4, 6.6 Hz), 7.58 - 7.73 (2 H, m), 7.92 (1 H, d, J=7.3 Hz), 8.16 (1 H, d, J=7.8 Hz), 8.67 (1 H, s), 9.19 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 19.1, 31.9, 48.1, 49.3, 51.4, 53.3, 125.4, 125.4, 129.8, 129.8, 130.1, 130.3, 130.8, 130.9, 134.1, 136.8, 146.5, 152.5 ppm.



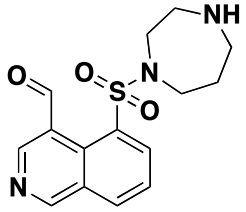
5-(1,4-diazepan-1-ylsulfonyl)isoquinolin-4-amine (BRD2749). Compound **BRD2749** was synthesized following the known procedure.[2] ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.85 - 1.92 (2 H, m), 3.02 - 3.08 (4 H, m), 3.54 - 3.58 (2 H, m), 3.60 (2 H, t, J=6.1 Hz), 7.56 (1 H, t, J=7.8 Hz), 8.03 (1 H, d, J=7.3 Hz), 8.08 (1 H, d, J=9.3 Hz), 8.16 (1 H, s), 8.69 (1 H, s) ppm.



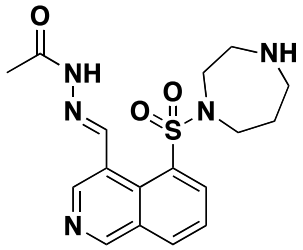
(5-(1,4-diazepan-1-ylsulfonyl)isoquinolin-4-yl)methanol (BRD7648). To a solution of **14** (8.5 mg, 0.02 mmol) in 2 mL THF/water (1:1) was added a solution of OsO_4 in *t*-BuOH (0.08 M, 5 µL, 0.4 µmol, 0.02 equiv.) and sodium periodate (8.7 mg, 0.04 mmol, 2 equiv.). The reaction mixture was stirred overnight under room temperature. 2 mL 1 M $NaHSO_3$ (aq.) were added. After a further 90 minutes the mixture was diluted with 2 mL water and extracted first with $CHCl_3$ (3 x 4 mL) and then with EA (3 x 4 mL). Drying over sodium sulfate and evaporation of the solvent from the organic phase gave an oily residue (**16**). To the crude **16** dissolved in 1.5 mL ethanol, $NaBH_4$ (6 mg, 0.15 mmol) was added at room temperature. The mixture was stirred for 1 h at the same temperature, quenched with water and extracted with EA. The organic layers were then washed with saturated brine, dried over sodium sulfate, filtered, and evaporated under reduced pressure. The residue was treated with TFA/CH_2Cl_2 (1:1) at room temperature. The volatiles were removed under reduced pressure, and the residue was purified by prep-HPLC to afford **BRD7648** (2.2 mg, 34% yield over 3 steps). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.98 (2 H, dt, J=12.2, 6.1 Hz), 3.09 - 3.17 (4 H, m), 3.60 - 3.65 (2 H, m), 3.69 (2 H, t, J=6.3 Hz), 5.41 - 5.47 (2 H, m), 7.67 (1 H, t, J=7.8 Hz), 7.95 (1 H, d, J=7.8 Hz), 8.23 (1 H, d, J=8.3 Hz), 8.81 (1 H, s), 9.28 (1 H, s) ppm.



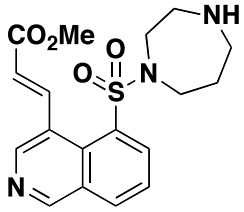
1-(5-(1,4-diazepan-1-ylsulfonyl)isoquinolin-4-yl)ethane-1,2-diol (BRD5505). To a solution of **14** (6.1 mg, 0.014 mmol) in 1 mL dry pyridine was added a solution of OsO_4 in t-BuOH (0.08 M, 0.4 mL, 0.016 mmol). The reaction mixture was stirred overnight under room temperature. 2 mL 1 M $NaHSO_3$ (aq.) were added. After a further 90 minutes the mixture was diluted with 2 mL water and extracted first with $CHCl_3$ (3 x 4 mL) and then with EA (3 x 4 mL). Drying over sodium sulfate and the evaporation of the solvent from the organic phase gave an oily residue that was subjected to TFA/CH_2Cl_2 (1:1) directly. The final product was purified by prep-HPLC to afford **BRD5505** (1.3 mg, 26% yield). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 2.88 - 2.93 (2 H, m), 2.98 (1 H, s), 3.00 - 3.06 (2 H, m), 3.22 (1 H, s), 3.41 (2 H, d, J=5.9 Hz), 3.45 - 3.54 (3 H, m), 3.71 - 3.82 (3 H, m), 3.84 - 3.90 (2 H, m), 6.42 (1 H, dd, J=8.1, 4.1 Hz), 7.69 (1 H, t, J=7.6 Hz), 8.24 (1 H, d, J=8.3 Hz), 8.40 (1 H, d, J=7.3 Hz), 9.07 (1 H, s), 9.28 (1 H, s) ppm.



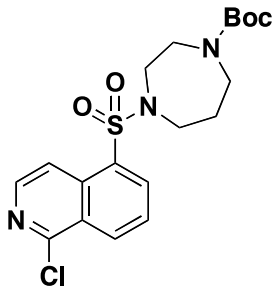
5-(1,4-diazepan-1-ylsulfonyl)isoquinoline-4-carbaldehyde (BRD4734). To a solution of the crude diol **15** in 2 mL THF/water (1:1) was added $NaIO_4$ (3.5 mg, 0.0162 mmol) at 0 ºC. The solution was warmed to room temperature and stirred overnight, then diluted with ethyl acetate before it was quenched with an aqueous 20% $Na_2S_2O_3$ solution. The organic layer was separated, washed with an aqueous 20% $Na_2S_2O_3$ solution, water and brine, dried over sodium sulfate, filtered and concentrated. The residue was treated by 1:1 TFA/CH_2Cl_2 for 1 h at room temperature. The volatiles were removed under reduced pressure, and the residue was purified by prep-HPLC to afford **BRD4734** 0.9 mg in 20% yield over three steps. ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.88 - 1.94 (2 H, m), 3.02 - 3.10 (4 H, m), 3.45 - 3.50 (2 H, m), 3.53 (2 H, t, J=6.1 Hz), 7.83 (1 H, d, J=7.8 Hz), 8.32 (2 H, dd, J=11.5, 7.6 Hz), 9.05 (1 H, s), 9.49 (1 H, s), 11.01 (1 H, s) ppm.



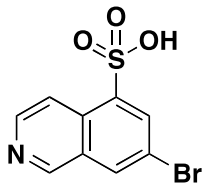
(*E*)-*N*'-((5-(1,4-diazepan-1-ylsulfonyl)isoquinolin-4-yl)methylene)acetohydrazide (BRD0859). To the solution of **BRD4734** (1 equiv.) and acetohydrazide (1 equiv.) in dry methanol, was added a catalytic amount of acetic acid (0.1 equiv.). The mixture was stirred overnight under 50 ºC, after which the solution was concentrated and the product **BRD0859** was purified by prep-HPLC. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.91 - 1.98 (2 H, m), 2.05 (1 H, s), 2.43 (3 H, s), 2.91 (1 H, s), 2.98 (1 H, s), 3.04 - 3.15 (4 H, m), 3.54 - 3.66 (4 H, m), 7.73 (1 H, d, J=8.7 Hz), 7.99 (1 H, dd, J=7.3, 1.1 Hz), 8.25 (1 H, dd, J=8.6, 1.0 Hz), 9.05 (1 H, s), 9.10 (1 H, s), 9.35 (1 H, s) ppm.



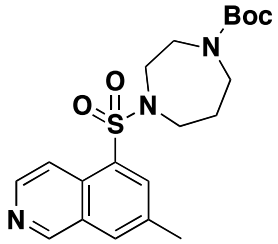
(*E*)-methyl 3-(5-(1,4-diazepan-1-ylsulfonyl)isoquinolin-4-yl)acrylate (BRD7198). In a 5 mL microwave tube was added **4** (9.9 mg, 0.021 mmol, 1 equiv.), tri-o-tolylphosphine (1.3 mg, .0.004 mmol, 0.2 equiv.), diacetoxypalladium (0.5 mg, 0.002 mmol, 0.1 equiv.) in dry DMF. The solution was degassed with nitrogen, and TEA (0.03 mL, 0.21 mmol, 10 equiv.) and methyl acrylate (0.02 mL, 0.21 mmol, 10 equiv.) were added through a syringe. The mixture was stirred overnight under 120 ºC, after which the solution was filtered through a short column of Celite and the column was washed by EA. The solvent was removed under reduced pressure, and the residue was treated with TFA/CH_2Cl_2 (1:1). The final product was purified by prep-HPLC to give **BRD7198** (5.9 mg, 0.016 mmol, 75% yield) as a white solid. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.88 - 1.99 (2 H, m), 3.03 - 3.12 (4 H, m), 3.50 - 3.66 (4 H, m), 3.88 (3 H, s), 6.37 (1 H, d, J=15.4 Hz), 7.67 - 7.78 (1 H, m), 8.08 (1 H, dd, J=7.3, 0.8 Hz), 8.18 - 8.29 (1 H, m), 8.76 (1 H, s), 9.01 (1 H, d, J=15.1 Hz), 9.32 (1 H, s) ppm.



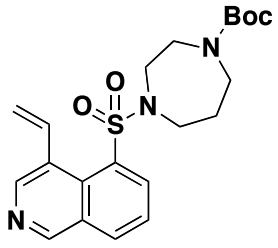
***tert*-butyl 4-(1-chloroisoquinolin-5-ylsulfonyl)-1,4-diazepane-1-carboxylate (BRD2109).** ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.45 (9 H, s), 1.94 - 2.05 (2 H, m), 3.34 - 3.47 (4 H, m), 3.50 - 3.65 (4 H, m), 7.13 - 7.23 (1 H, m), 7.24 - 7.31 (1 H, m), 7.74 - 7.82 (1 H, m), 8.31 - 8.41 (1 H, m), 8.41 - 8.49 (1 H, m), 8.66 (1 H, d, J=8.3 Hz) ppm.



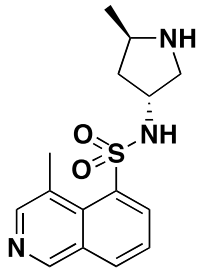
7-bromoisoquinoline-5-sulfonic acid (12).[3] ^{1}H NMR (300 MHz, DMSO-d6) δ = 8.41 (1 H, d, J=2.3 Hz), 8.68 - 8.79 (2 H, m), 8.99 (1 H, d, J=6.6 Hz), 9.73 (1 H, s) ppm.



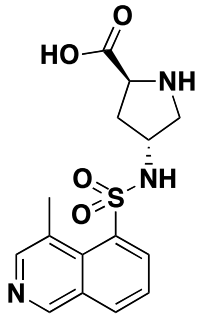
***tert*-butyl 4-(7-methylisoquinolin-5-ylsulfonyl)-1,4-diazepane-1-carboxylate (13).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.23 - 1.41 (9 H, m), 1.83 - 1.94 (2 H, m), 2.55 (3 H, s), 3.22 - 3.37 (4 H, m), 3.37 - 3.52 (4 H, m), 7.89 (1 H, s), 8.12 (1 H, d, J=11.3 Hz), 8.26 (1 H, d, J=6.2 Hz), 8.55 (1 H, d, J=5.7 Hz), 9.19 (1 H, s) ppm.



***tert*-butyl 4-(4-vinylisoquinolin-5-ylsulfonyl)-1,4-diazepane-1-carboxylate (14).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.51 (9 H, s), 2.01 – 2.10 (2 H, m), 3.36 - 3.71 (8 H, m), 5.52 (1 H, dd, J=10.8, 1.2 Hz), 5.68 (1 H, dd, J=16.9, 1.4 Hz), 7.64 (1 H, t, J=7.7 Hz), 7.80 - 8.04 (2 H, m), 8.19 (1 H, d, J=8.1 Hz), 8.63 - 8.86 (1 H, m), 9.12 - 9.39 (1 H, m) ppm; ^{13}C NMR (150 MHz, CHLOROFORM-d) δ = 28.5, 28.6, 28.7, 28.9, 45.9, 46.4, 49.3, 50.5, 50.5, 51.9, 52.2, 80.2, 80.3, 117.6, 125.6, 125.6, 129.9, 130.2, 130.5, 134.4, 134.4, 136.3, 137.1, 146.7, 153.3, 155.5 ppm.

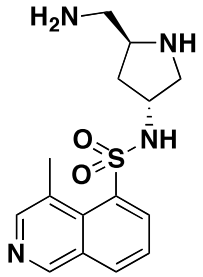


4-methyl-*N*-((3*R*,5*R*)-5-methylpyrrolidin-3-yl)isoquinoline-5-sulfonamide (BRD5319). To a solution of **22** (10 mg, 0.024 mmol, 1 equiv.) in dry THF (0.5 mL) was added triphenylphosphine (12.5 mg, 0.047 mmol, 2 equiv), imidazole (6.5 mg, 0.095 mmol, 4 equiv), and iodine (12 mg, 0.047 mmol, 2 equiv) at room temperature. The mixture was refluxed for 2 h. The solvent was evaporated and the residue was dissolved in EA (10 mL), washed with $Na_2S_2O_3$ (aq.), dried over sodium sulfate, and concentrated. The residue was further subjected to hydrogenation and deprotection as described in the general procedure to afford **BRD5319** (4.1 mg, 57% yield over 3 steps), which is purified by prep-HPLC. ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.19 (3 H, d, J=6.3 Hz), 1.26 (2 H, t, J=7.1 Hz), 1.69 (1 H, ddd, J=13.4, 8.3, 8.1 Hz), 2.94 (1 H, dd, J=11.2, 4.9 Hz), 3.09 (3 H, s), 3.37 - 3.48 (2 H, m), 3.74 (1 H, q, J=6.8 Hz), 3.94 - 4.04 (1 H, m), 7.64 (1 H, t, J=7.8 Hz), 8.18 (1 H, d, J=7.8 Hz), 8.51 (1 H, d, J=7.3 Hz), 8.57 (1 H, s), 9.17 (1 H, s) ppm.

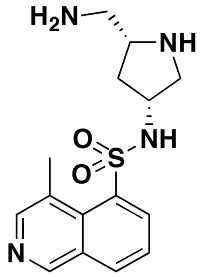


(2*S*,4*R*)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidine-2-carboxylic acid (BRD7953). To a 4 mL capped vial were added alcohol **22** (14.8 mg, 0.035 mmol, 1 equiv.), TEMPO (1.1 mg, 0.007 mmol, 0.2 equiv.), and bis-acetoxy-iodobenzene (BAIB) (30 mg, 0.093 mmol, 2.7 equiv.) in 0.5 mL acetonitrile/water (1:1). The reaction mixture

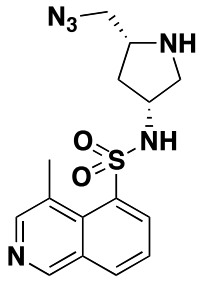
was stirred for 2 h and quenched with a saturated aqueous Na_2SO_3 solution (3 mL). Acetonitrile was evaporated under reduced pressure, acidified with a 1 M HCl solution (pH~3). The acidic aqueous phase was extracted three times with EA. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated *in vacuo* to yield an oily residue that was subjected to TFA/CH_2Cl_2 (1:1) directly. Final product **BRD7953** (0.8 mg, 7% yield over two steps) was purified by prep-HPLC. ^{1}H NMR (300 MHz, MeOD) δ = 1.27 (1 H, s), 1.91 (1 H, d, J=1.1 Hz), 2.41 (2 H, dd, J=7.5, 6.6 Hz), 3.01 - 3.06 (3 H, m), 3.95 (1 H, d, J=6.2 Hz), 4.10 (1 H, s), 7.74 - 7.82 (1 H, m), 8.32 - 8.38 (1 H, m), 8.38 - 8.43 (1 H, m), 8.45 (1 H, s), 9.17 (1 H, s) ppm.



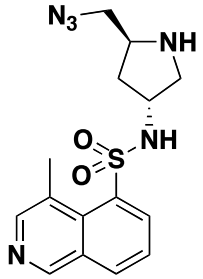
***N*-((3*R*,5*S*)-5-(aminomethyl)pyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD9949).** ^{1}H NMR (500 MHz, METHANOL-d4) δ = 1.76 - 1.89 (1 H, m), 2.11 (1 H, s), 2.62 - 2.76 (2 H, m), 2.98 (1 H, dd, J=11.5, 5.1 Hz), 3.09 (3 H, s), 3.19 (1 H, dd, J=11.5, 6.1 Hz), 3.35 - 3.44 (1 H, m), 3.81 - 3.92 (1 H, m), 7.80 (1 H, t, J=7.8 Hz), 8.37 (1 H, d, J=8.3 Hz), 8.45 - 8.55 (2 H, m), 9.21 (1 H, s) ppm.



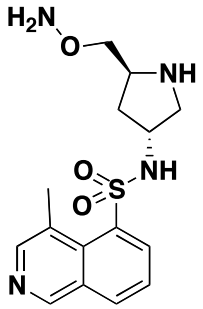
***N*-((3*R*,5*R*)-5-(aminomethyl)pyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD7071).** ^{1}H NMR (300 MHz, MeOD) δ = 2.69 - 2.74 (1 H, m), 2.85 (1 H, d, J=7.3 Hz), 3.01 - 3.07 (3 H, m), 3.10 - 3.19 (2 H, m), 3.78 (2 H, s), 7.71 - 7.80 (1 H, m), 8.33 (1 H, d, J=8.3 Hz), 8.44 (1 H, s), 8.46 - 8.53 (1 H, m), 9.16 (1 H, s) ppm; ^{13}C NMR (150 MHz, MeOD) δ = 20.9, 34.9, 36.2, 52.0, 52.3, 54.9, 55.0, 58.8, 63.8, 125.7, 125.8, 128.5, 130.6, 132.5, 132.6, 134.6, 134.6, 137.5, 137.6, 146.7, 151.7 ppm.



***N*-((3*R*,5*R*)-5-(azidomethyl)pyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD2880).** ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 2.31 - 2.39 (1 H, m), 3.02 - 3.10 (2 H, m), 3.12 (3 H, s), 3.37 - 3.45 (2 H, m), 3.49 - 3.56 (1 H, m), 3.96 (1 H, d, J=3.4 Hz), 5.38 (1 H, d, J=8.3 Hz), 7.65 (1 H, t, J=7.8 Hz), 8.20 (1 H, d, J=8.3 Hz), 8.56 - 8.63 (2 H, m), 9.18 (1 H, s) ppm.

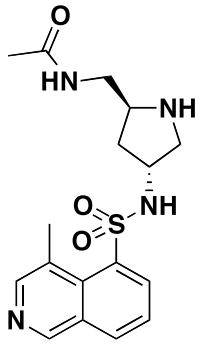


***N*-((3*R*,5*S*)-5-(azidomethyl)pyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD3192).** ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.96 - 2.08 (2 H, m), 3.00 (1 H, dd, J=11.2, 4.6 Hz), 3.09 (3 H, s), 3.26 (2 H, dt, J=11.7, 5.9 Hz), 3.31 - 3.40 (1 H, m), 3.50 - 3.60 (1 H, m), 3.94 - 4.03 (1 H, m), 7.64 (1 H, t, J=7.8 Hz), 8.20 (1 H, dd, J=8.2, 1.2 Hz), 8.51 (1 H, dd, J=7.5, 1.3 Hz), 8.57 (1 H, s), 9.18 (1 H, s) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 21.7, 36.5, 53.0, 54.9, 55.6, 56.0, 124.9, 127.1, 130.2, 132.2, 132.8, 134.9, 148.7, 152.1 ppm.

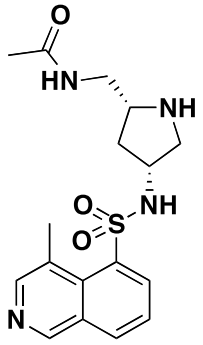


***N*-((3*R*,5*S*)-5-(aminooxymethyl)pyrrolidin-3-yl)-4-methylisoquinoline-5-sulfonamide (BRD7569).** ^{1}H NMR (500 MHz, METHANOL-d4) δ = 1.87 - 1.96 (1 H, m), 2.00 - 2.08 (1 H, m), 2.92 (1 H, dd, J=11.2, 5.9 Hz), 3.08 (3 H, s), 3.25 (1 H, dd, J=11.5, 6.1 Hz),

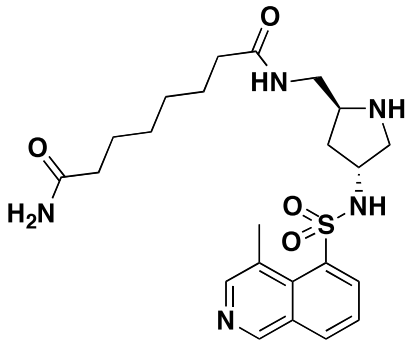
3.52 - 3.62 (2 H, m), 3.63 - 3.69 (1 H, m), 3.83 - 3.90 (1 H, m), 7.79 (1 H, t, J=7.8 Hz), 8.36 (1 H, d, J=8.3 Hz), 8.48 (1 H, s), 8.51 (1 H, d, J=7.3 Hz), 9.19 (1 H, s) ppm.



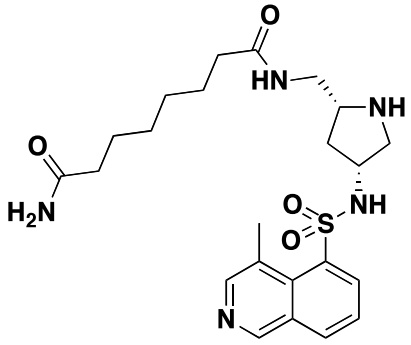
***N*-(((2*S*,4*R*)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidin-2-yl)methyl)acetamide (BRD8899).** ^{1}H NMR (500 MHz, METHANOL-d4) δ = 1.78 - 1.87 (1 H, m), 1.93 (3 H, s), 1.98 - 2.06 (1 H, m), 2.87 (1 H, dd, J=11.2, 5.9 Hz), 3.05 - 3.08 (3 H, m), 3.17 - 3.28 (3 H, m), 3.38 - 3.46 (1 H, m), 3.81 - 3.88 (1 H, m), 7.78 (1 H, t, J=7.8 Hz), 8.35 (1 H, d, J=8.3 Hz), 8.46 (1 H, s), 8.49 (1 H, d, J=6.3 Hz), 9.18 (1 H, s) ppm; ^{13}C NMR (150 MHz, METHANOL-d4) δ = 22.2, 22.7, 37.5, 44.6, 54.2, 55.9, 58.4, 127.0, 129.9, 132.0, 133.8, 133.8, 135.9, 138.8, 148.0, 153.0, 173.8 ppm.



***N*-(((2*R*,4*R*)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidin-2-yl)methyl)acetamide (BRD5749).** ^{1}H NMR (500 MHz, METHANOL-d4) δ = 1.52 (1 H, dd, J=8.1, 5.1 Hz), 1.91 - 1.98 (3 H, m), 2.26 - 2.38 (1 H, m), 2.86 - 2.92 (1 H, m), 3.02 - 3.06 (3 H, m), 3.11 (1 H, dd, J=11.2, 6.8 Hz), 3.19 (1 H, dd, J=14.9, 8.1 Hz), 3.23 - 3.28 (2 H, m), 3.80 (1 H, t, J=7.3 Hz), 7.75 (1 H, t, J=7.8 Hz), 8.32 (1 H, d, J=7.8 Hz), 8.44 (1 H, s), 8.47 (1 H, d, J=7.3 Hz), 9.15 (1 H, s) ppm.

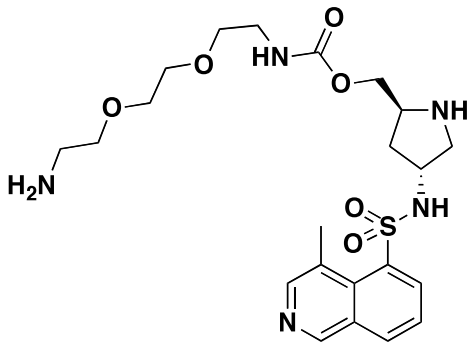


***N*^{1}-(((2*S*,4*R*)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidin-2-yl)methyl)octanediamide (BRD4717).** To bis(2,5-dioxopyrrolidin-1-yl) octanedioate **21** (10 equiv.) dissolved in 1 mL DMF was added amine **24**, which was obtained by hydrogenation of azide **24** (11 mg, 0.024 mmol, 1 equiv.). The reaction mixture was stirred at room temperature overnight, after which ammonia (2 mL, 1 mmol, 0.5 M in THF) was added. The reaction mixture was stirred at room temperature for 2 h and volatiles were removed under reduced pressure to yield an oily residue. The residue was subjected to TFA/CH_2Cl_2 (1:1) directly, and the final product **BRD4717** (4 mg, 34% yield over four steps) was purified by prep-HPLC. ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.39 (3 H, td, J=12.0, 6.3 Hz), 1.49 - 1.56 (5 H, m), 1.56 - 1.73 (36 H, m), 2.18 (2 H, dddd, J=8.3, 5.6, 5.4, 2.7 Hz), 2.22 - 2.30 (3 H, m), 2.81 - 2.87 (1 H, m), 2.90 - 2.92 (3 H, m), 2.97 - 3.00 (3 H, m), 3.04 (1 H, dd, J=12.0, 4.6 Hz), 3.08 - 3.11 (3 H, m), 3.15 (1 H, d, J=12.2 Hz), 3.56 - 3.62 (2 H, m), 3.94 (1 H, ddd, J=4.5, 2.4, 2.3 Hz), 5.50 - 5.55 (1 H, m), 6.02 - 6.08 (1 H, m), 6.19 (1 H, dd, J=6.3, 4.4 Hz), 7.65 (1 H, t, J=7.8 Hz), 8.04 (1 H, s), 8.19 (1 H, d, J=8.3 Hz), 8.49 (1 H, d, J=6.3 Hz), 8.56 (1 H, s), 9.17 (1 H, s) ppm.

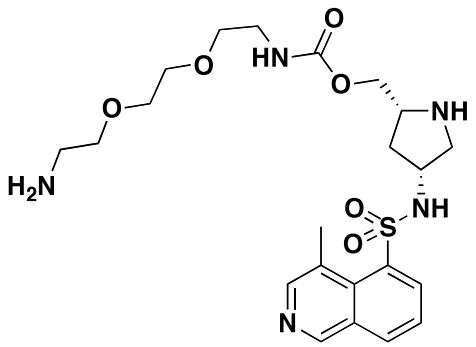


***N*^{1}-(((2*R*,4*R*)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidin-2-yl)methyl)octanediamide (BRD1469).** To bis(2,5-dioxopyrrolidin-1-yl) octanedioate **21** (10 equiv.) dissolved in 1 mL DMF, was added amine **19**, which was obtained by hydrogenation of azide **18** (6.7 mg, 0.015 mmol, 1 equiv.). The reaction mixture was stirred at room temperature overnight, after which ammonia (2 mL, 1 mmol, 0.5 M in THF) was added. The reaction mixture was stirred at room temperature for 2 h and volatiles were removed under reduced pressure to yield an oily residue. The residue was subjected to TFA/CH_2Cl_2 (1:1) directly, and the final product **BRD1469** (3.4 mg, 48% yield over four steps) was purified by prep-HPLC. ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.34 -

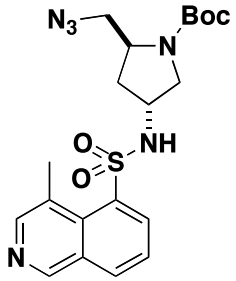
1.47 (4 H, m), 1.54 (2 H, d, J=9.3 Hz), 1.64 (14 H, br. s.), 1.67 - 1.87 (7 H, m), 2.19 - 2.34 (5 H, m), 3.02 - 3.13 (4 H, m), 3.23 (1 H, dd, J=11.2, 6.3 Hz), 3.30 - 3.43 (2 H, m), 3.47 - 3.56 (1 H, m), 3.84 - 3.93 (1 H, m), 5.53 (1 H, br. s.), 6.05 (1 H, br. s.), 6.32 (1 H, d, J=4.9 Hz), 7.65 (1 H, t, J=7.8 Hz), 8.17 (1 H, d, J=7.8 Hz), 8.48 (1 H, d, J=7.3 Hz), 8.56 (1 H, s), 9.16 (1 H, s) ppm.



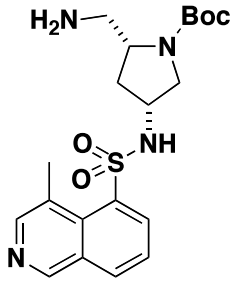
((2*S*,4*R*)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidin-2-yl)methyl 2-(2-(2-aminoethoxy)ethoxy)ethylcarbamate (BRD0200). Compound **BRD0200** was synthesized following known procedure.[4] ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.83 (2 H, dd, J=14.4, 7.1 Hz), 1.91 - 2.15 (13 H, m), 2.91 (2 H, t, J=5.1 Hz), 2.99 - 3.08 (2 H, m), 3.10 (3 H, s), 3.23 (1 H, dd, J=11.2, 5.4 Hz), 3.39 (2 H, q, J=5.0 Hz), 3.51 - 3.61 (4 H, m), 3.61 - 3.69 (6 H, m), 3.92 - 4.00 (2 H, m), 4.06 (1 H, dd, J=11.2, 4.4 Hz), 5.56 (1 H, br. s.), 7.65 (1 H, t, J=7.6 Hz), 8.19 (1 H, d, J=6.8 Hz), 8.51 (1 H, d, J=6.3 Hz), 8.57 (1 H, s), 9.17 (1 H, s) ppm.



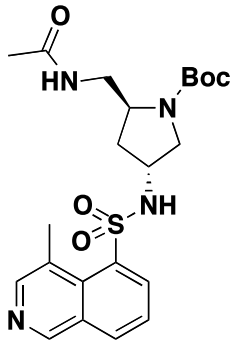
((2*R*,4*R*)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidin-2-yl)methyl 2-(2-(2-aminoethoxy)ethoxy)ethylcarbamate (BRD8254). Compound **BRD8254** was synthesized following known procedure.**Error! Bookmark not defined.** ^{1}H NMR (300 MHz, MeOD) δ = 2.33 (1 H, s), 2.78 - 2.92 (3 H, m), 2.99 - 3.08 (3 H, m), 3.09 - 3.19 (1 H, m), 3.48 - 3.59 (4 H, m), 3.59 - 3.65 (4 H, m), 3.80 (1 H, d, J=7.5 Hz), 3.96 - 4.11 (2 H, m), 7.72 - 7.82 (1 H, m), 8.31 - 8.38 (1 H, m), 8.42 - 8.54 (2 H, m), 9.17 (1 H, s) ppm.



(2*S*,4*R*)-*tert*-butyl 2-(azidomethyl)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidine-1-carboxylate (23). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 1.45 (9 H, s), 2.01 - 2.07 (1 H, m), 2.07 - 2.29 (2 H, m), 2.97 - 3.08 (3 H, m), 3.23 - 3.35 (1 H, m), 3.35 - 3.60 (1 H, m), 3.60 - 3.70 (1 H, m), 3.96 - 4.20 (3 H, m), 5.87 - 6.08 (1 H, m), 7.60 (1 H, t, J=7.5 Hz), 8.16 (1 H, d, J=8.3 Hz), 8.44 (1 H, d, J=6.6 Hz), 8.48 - 8.64 (1 H, m), 9.00 - 9.32 (1 H, m) ppm; ^{13}C NMR (75 MHz, CHLOROFORM-d) δ = 13.7, 14.2, 21.1, 21.7, 28.4, 30.7, 55.2, 60.4, 64.4, 124.9, 132.2, 132.4, 134.9, 136.6, 148.5, 152.0 ppm.

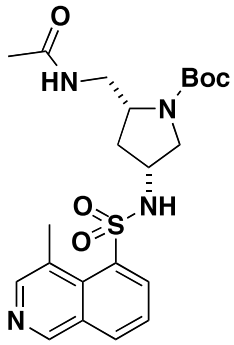


(2*R*,4*R*)-*tert*-butyl 2-(aminomethyl)-4-(4-methylisoquinoline-5-sulfonamido)pyrrolidine-1-carboxylate (19). ^{1}H NMR (300 MHz, MeOD) δ = 1.43 (9 H, s), 1.85 -1.97 (1 H, m), 2.42 – 2.53 (1 H, m), 3.06 (3 H, s), 3.71 - 3.87 (3 H, m), 7.72 - 7.80 (1 H, m), 8.33 (1 H, d, J=8.1 Hz), 8.44 (1 H, s), 8.51 (1 H, d, J=7.7 Hz), 9.16 (1 H, s) ppm.

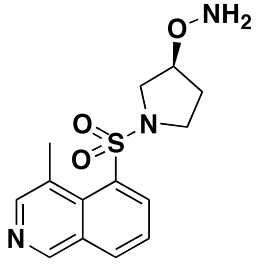


(2*S*,4*R*)-*tert*-butyl 2-(acetamidomethyl)-4-(4-methylisoquinoline-5-sulfonamido) pyrrolidine-1-carboxylate (BRD2816). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.19 - 1.32 (1 H, m), 1.46 (9 H, br. s.), 1.94 (3 H, s), 2.01 - 2.09 (1 H, m), 2.16 - 2.27 (1 H, m), 3.07 (3 H, s), 3.15 - 3.26 (1 H, m), 3.33 - 3.45 (1 H, m), 3.45 - 3.55 (1 H, m), 3.55 - 3.71

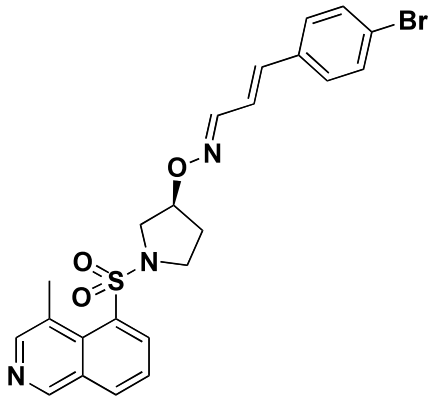
(1 H, m), 3.94 - 4.17 (2 H, m), 6.00 - 6.16 (1 H, m), 7.13 (1 H, d, J=3.9 Hz), 7.66 (1 H, t, J=7.6 Hz), 8.20 (1 H, d, J=7.8 Hz), 8.47 (1 H, d, J=7.3 Hz), 8.50 - 8.66 (1 H, m), 9.06 - 9.29 (1 H, m) ppm.



(2*R*,4*R*)-*tert*-butyl 2-(acetamidomethyl)-4-(4-methylisoquinoline-5-sulfonamido) pyrrolidine-1-carboxylate (33). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ = 1.37 - 1.54 (9 H, m), 2.01 - 2.12 (4 H, m), 2.25 - 2.38 (1 H, m), 3.03 - 3.15 (3 H, m), 3.50 - 3.73 (4 H, m), 3.93 (1 H, br. s.), 4.03 (1 H, d, J=6.3 Hz), 6.73 (1 H, br. s.), 7.62 (1 H, t, J=7.6 Hz), 7.96 (1 H, br. s.), 8.15 (1 H, d, J=8.3 Hz), 8.38 (1 H, d, J=6.3 Hz), 8.56 (1 H, s), 9.15 (1 H, s) ppm; ^{13}C NMR (150 MHz, CHLOROFORM-d) δ = 22.0, 23.5, 28.7, 28.8, 34.1, 44.0, 53.3, 54.3, 56.5, 80.8, 125.1, 127.9, 130.4, 131.5, 132.6, 134.6, 137.1, 148.6, 148.7, 152.1, 172.3 ppm.



(*S*)-*O*-(1-(4-methylisoquinolin-5-ylsulfonyl)pyrrolidin-3-yl)hydroxylamine (BRD2916). ^{1}H NMR (300 MHz, CHLOROFORM-d) δ = 2.05 - 2.25 (2 H, m), 2.25 - 2.37 (1 H, m), 2.94 - 3.13 (4 H, m), 3.48 - 3.68 (3 H, m), 3.68 - 3.86 (2 H, m), 4.40 - 4.52 (1 H, m), 5.43 - 5.60 (2 H, m), 7.56 - 7.69 (1 H, m), 8.12 - 8.30 (2 H, m), 8.56 (1 H, s), 9.16 (1 H, s) ppm.



(1*E*,2*E*)-3-(4-bromophenyl)acrylaldehyde *O*-(*S*)-1-(4-methylisoquinolin-5-ylsulfonyl) pyrrolidin-3-yl oxime (BRD6284). To the solution of oxyamine **BRD2916** (1 equiv.) and trans-4-Bromocinnamaldehyde (1 equiv.) in dry methanol, was added a catalytic amount of acetic acid (0.1 equiv.). The mixture was stirred overnight under 50 ºC, after which the solution was concentrated and the product was purified by prep-HPLC. ^{1}H NMR (500 MHz, METHANOL-d4) δ = 2.42 (2 H, br. s.), 3.07 (3 H, s), 3.65 (2 H, d, J=7.8 Hz), 3.77 (2 H, d, J=3.9 Hz), 3.83 (2 H, s), 6.95 (1 H, d, J=9.8 Hz), 7.01 - 7.07 (1 H, m), 7.48 (2 H, m), 7.55 (2 H, m), 7.76 (1 H, s), 8.17 (1 H, d, J=9.8 Hz), 8.32 - 8.38 (2 H, m), 8.48 (1 H, s), 9.19 (1 H, s) ppm.

References:

1. Liu Z, Larock RC (2006) Facile N-arylation of amines and sulfonamides and o-arylation of phenols and arenecarboxylic acids. *J Org Chem* 71:3198-3209.

2. Vo GD, Hartwig JF (2009) Palladium-catalyzed coupling of ammonia with aryl chlorides, bromides, iodides, and sulfonates: a general method for the preparation of primary arylamines. *J Am Chem Soc* 131:11049-11061.

3. Joseph S, Li R, Myers MR, Aburub A, Dai JP, Schmid CR (2007) *PCT Int Appl* WO 2007149730 A2 20071227.

4. Wang X, Imber BS, Schreiber SL (2008) Small-molecule reagents for cellular pull-down experiments. *Bioconjugate Chem* 19:585-587.