Supporting Information

Benzo-isoquinoline-diones as Potent and Selective Inhibitors of BRPF2 and TAF1/TAF1L Bromodomains

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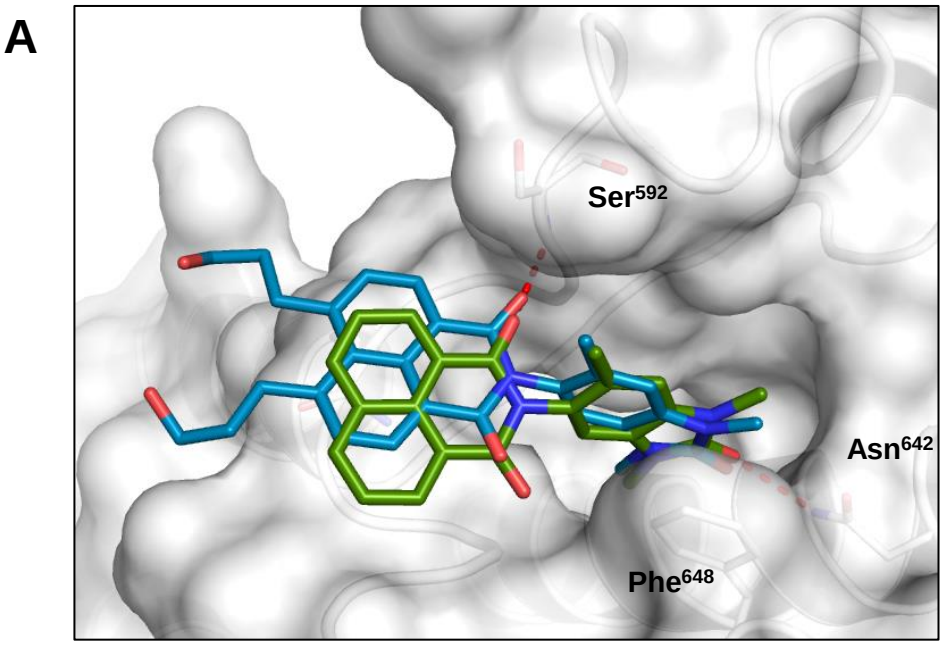
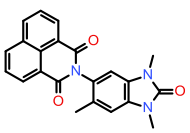
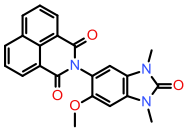
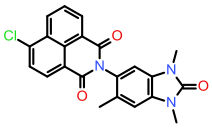
1. Figure S1

Binding mode of **5** in TAF1 BD2



2. Table S1

Cellular activity of **7**, **8** and **13** in NanoBRET™ assay

	Compound 7	Compound 8	Compound 13
			
BRPF2 BD IC_{50} [nM]	470	1500	675
BRPF1 BD IC_{50} [nM]	>10000	>10000	>10000
TAF1 BD2 cellular inhibition at 10 µM [%]	55	n.a.	35

n.a. = not available

3. Table S2

TSA results for **13** in a panel of 48 BDs

	Compound 13 10 µM
protein	ΔTm [K]
ASH1L	1.2
ATAD2	0.0
BAZ1A	-1.0
BAZ1B	-1.0
BAZ2A	0.0
BAZ2B	0.6
BRPF2	6.2
BRD2 BD1	0.3
BRD2 BD2	0.4
BRD3 BD1	-0.3
BRD3 BD2	0.1
BRD4 BD1	0.8
BRD4 BD2	1.3
BRD7	2.3
BRD9	-2.9
BRDT BD1	-1.0
BRDT BD2	-1.0
BRPF1A	-0.4
BRPF1B	1.3
BRPF3	1.1
BRWD3 BD2	-0.5
CECR2	3.5
CREBBP	1.3
EP300	3.5
FALZ	0.0
GCN5L2	-0.4
ATAD2B	0.2
SP140L	-1.4
MLL	-1.2
PB1 BD1	-1.1
PB1 BD2	-1.0
PB1 BD3	0.2
PB1 BD4	-0.3
PB1 BD5	-0.1
PB1 BD6	-0.7
PCAF	0.5
PHIP BD2	-2.4
SMARCA2	0.5
SMARCA4	0.0
SP140	-0.9
TAF1 BD2	2.2
TAF1 BD1	0.3
TAF1L BD1	-0.2
TAF1L BD2	1.6
TIF1-bromo	-1.2
TIF1-phd-bromo	0.1
TRIM28	0.3
WDR9 BD2	-1.4

4. Table S3

Molecular properties and physicochemical profile of **5**

	Compound 5
MW [g/mol^{-1}]	429
TPSA [Å^2]	81
logD (pH = 7.5)	2.0
Solubility from solid pH = 6.5 [mg/L]	10
Solubility PEG400/EtOH/H_2O = 60/10/30 [mg/L]	2262
Solubility Solutol/EtOH/H_2O = 40/10/70 [mg/L]	1630
BEI / LLE BRPF2	16.72 / 4.72
BEI / LLE TAF1	18.86 / 5.65
Plasma stability after 4 h: human / rat [%]	100 / 100
Chemical stability after 24 h: pH = 1 / 7 / 10 [%]	100 / 100 / 100

5. Table S4

BD selectivity profile of **5**

	Compound 5	
target	**% at 100 nM**	**% at 1000 nM**
ATAD2A	93	87
ATAD2B	73	59
BAZ2A	53	41
BAZ2B	68	14
BRPF2	0	0
BRD2 BD1	75	15
BRD2 BD2	72	74
BRD3 BD1	96	71
BRD3 BD2	91	89
BRD4 BD1	82	71
BRD4 BD2	70	14
BRD7	68	18
BRD9	87	75
BRDT(1)	93	91
BRDT(2)	79	8.8
BRPF1	97	25
CECR2	74	15
CREBBP	30	0
EP300	41	0.5
FALZ	72	37
GCN5L BD2	100	69
PBRM1 BD2	74	70
PBRM1 BD5	81	70
PCAF	88	71
SMARCA2	73	56
SMARCA4	100	100
TAF1 BD2	0.8	0.2
TAF1L BD2	0.7	0
TRIM24 (PHD,BD)	81	78
TRIM33 (PHD,BD)	92	96
WDR9 BD2	61	50

6. Table S5

Anti-proliferative activity of **5**

Cell line	Origin	GI_{50} [nM]
MOLM-13	Acute monocytic leukemia	1060
MV4-11	Myelomonocytic leukemia	2630
769-P	Renal cell adenocarcinoma	3210
Jurkat	Acute T cell leukemia	3900
NCI-H526	Small cell lung cancer	6860
CHL-1	Melanoma	7400
5637	Urinary bladder	7980
MDA-MB-231	Breast adenocarcinoma	>10000
MDA-MB-453	Breast carcinoma	>10000
NCI-H1299	Non-small cell lung cancer	>10000
SW-403	Colorectal adenocarcinoma	>10000
SW-480	Colorectal adenocarcinoma	>10000

7. Table S6

Crystallographic data for **7** in BRPF2 BD and **5** in TAF1 BD2: data collection and refinement statistics

	BRPF2 BD-Compound 7 (PDB code 5N49)	**TAF1 BD2-Compound 5** (PDB code 5MG2)
Data Collection		
Space group (no.)	$P2_12_12_1$	$P3_121$
Unit cell parameters,	56.6, 56.9, 102.3	64.7, 64,7, 101.1
a, b, c [Å],		
Resolution limit [Å]	38.00-1.90 (2.03-1.94)	101.08-1.75 (1.85-1.75)
No. of reflections	96508	24216
No. of uniques	26623	3618
Multiplicity	3.6 (3.7)	7.4 (7.8)
I/sigI	13.0 (2.4)	17.3 (2.80)
R_meas [%]	5.7 (50.4)	6.1 (69.3)
Completeness [%]	99.6 (99.6)	96.3 (100)
Refinement		
Resolution limit [Å]	38.00-1.94 (2.03-1.94)	56.07-1.75 (1.85-1.75)
R (work) / R(free) [%]	18.1 /21.9	18.6 /22.0
Mean B value [Å^2]	28.8/22.8/35.3	41.8 / 34.5 / 47.4
(protein/other/water)		
RMSD bond length [Å]	0.017	0.010
RMSD bond angles [deg]	1.990	1.277
Ramachandran:		
Favored [%]	98.7	100
Allowed [%]	1.3	0
Disallowed [%]	0	0

** Values in parentheses correspond to the highest resolution shell*.