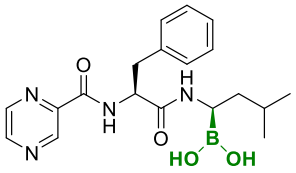
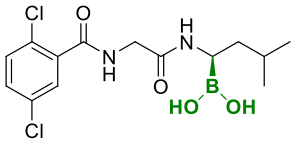
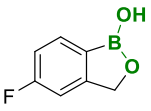


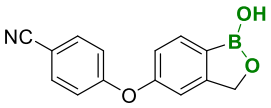
Bortezomib (FDA 2003)
Proteosome inhibitor
Multiple myeloma



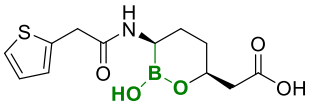
Ixazomib (FDA 2015)
Proteosome inhibitor
Multiple myeloma



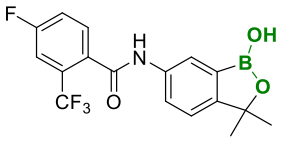
Tavaborole (FDA 2014)
leucyl-tRNA synthetase inhibitor
onychomycosis (fungal nail infection)



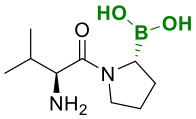
Crisaborole (FDA 2016)
PDE4-inhibotor
atopic dermatitis



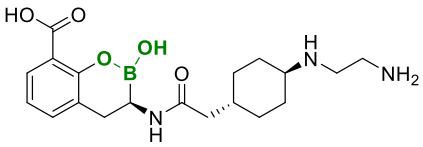
Vaborbactam (FDA 2017)
serine ß-lactamase inhibitor
antibacterial, complicated urinary tract infections



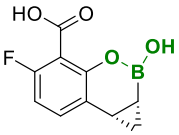
Acoziborole (EMA 2026)
CPSF3 endonuclease inhibitor
T.b. gambiense (*sleeping sickness)*



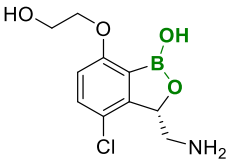
Talabostat (Phase II)
DPP inhibitor (including FAP, DPP8, and DPP9)
Advanced solid cancers



Taniborbactam (Phase III)
"pan-spectrum" ß-lactamase inhibitor
antibacterial, complicated urinary tract infections

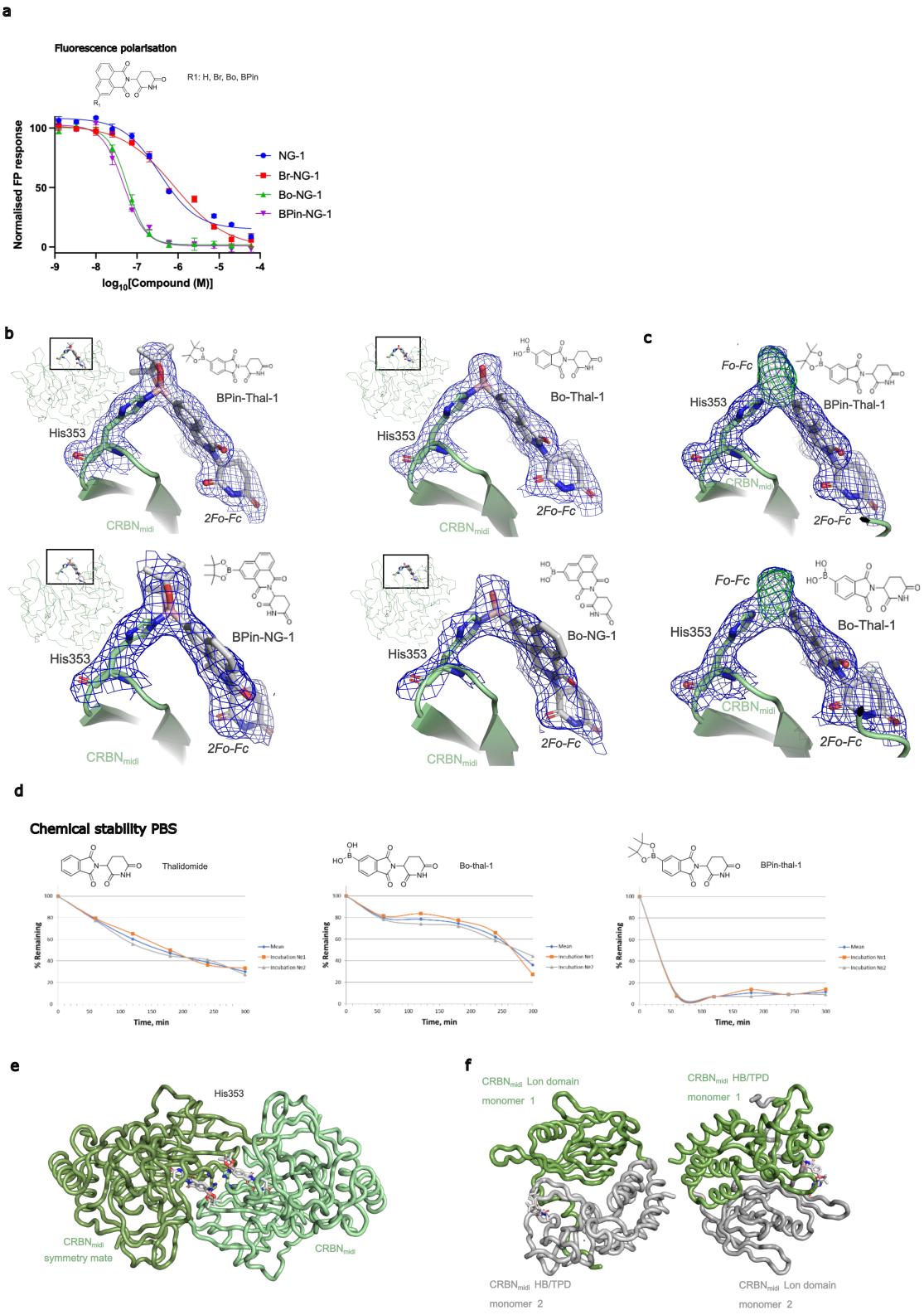


Xeruborbactam (Phase I)
"pan-spectrum" ß-lactamase inhibitor
antibacterial, complicated urinary tract infections



Ganfeborole (Phase II)
leucyl-tRNA synthetase inhibitor
Antibacterial, Tuberculosis

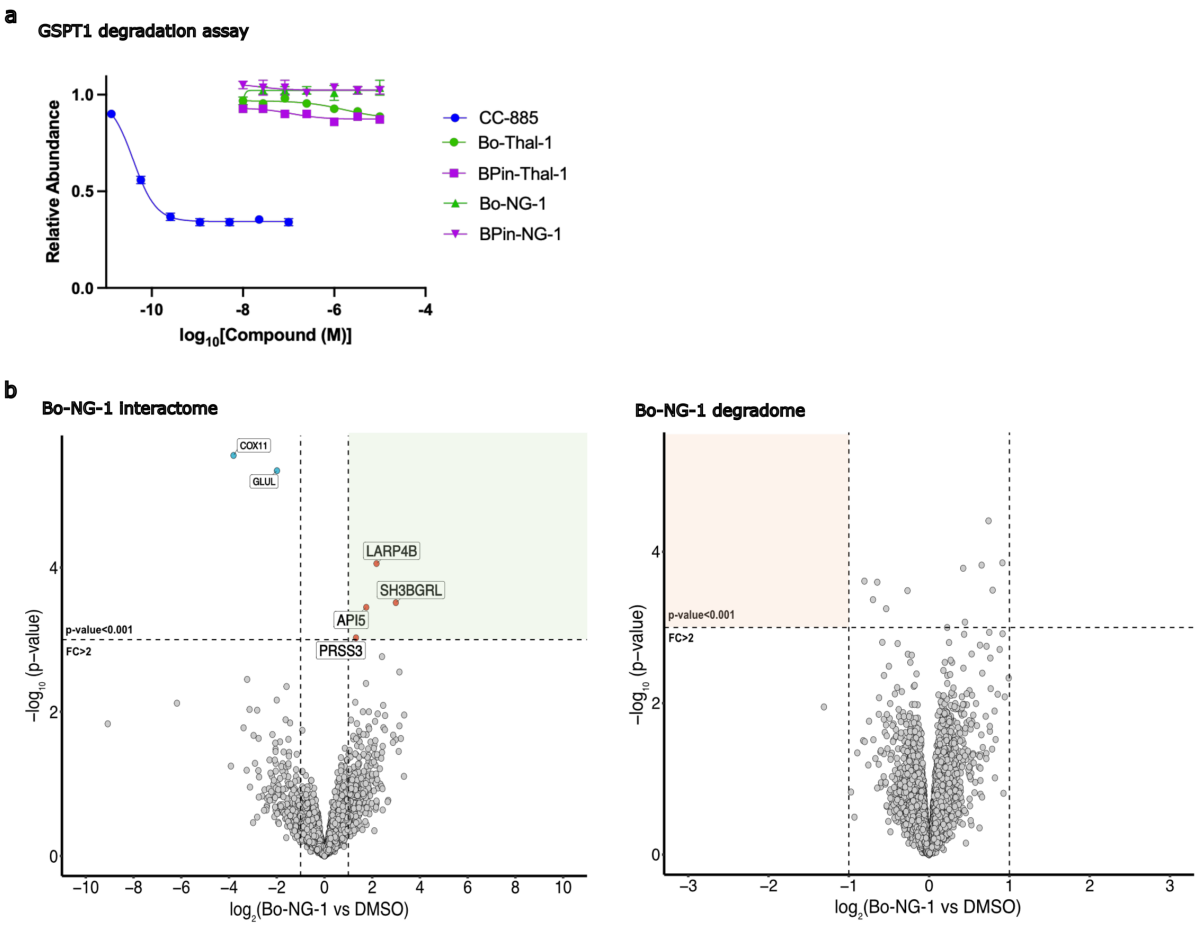
Supplementary Figure 1: Boron containing compounds currently approved or in clinical trials



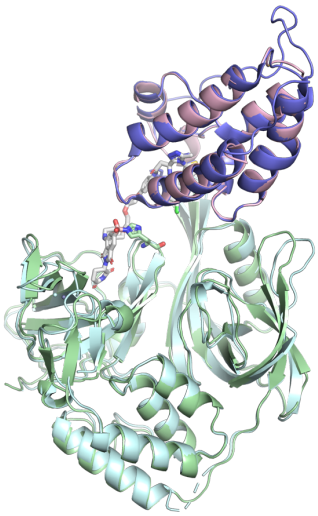
Supplementary Figure 2: Crystal structure and ligand binding validation. A) Competitive fluorescence polarization assay comparing IC50s of naphthylamide glutarimide Bo-IMiDs (Bo-NG-1 and BPin-NG-1; R1 = Bo/BPin, R2 = H) against equivalent unmodified (NG-1; R1 and R2 = H) or bromine modified (Br-NG-1; R1 = Br, R2 = H) control compounds **B)** Crystal structures of CRBNmidi (green) in complex with BPin-Thal-1, Bo-Thal-1, BPin-NG-1 and Bo-NG-1 (grey), respectively. Blue mesh represents 2Fo-Fc electron density map of ligands covalently bound to His353, contoured at 1σ. **C)** Omit maps of the CRBN-midi after deletion of boronate group contoured at 1σ (BPin-Thal-1 top and Bo-Thal-1 bottom)**. D)** Chemical stability analysis of Thalidomide, Bo-Thal-1 and BPin-Thal-1 in PBS buffered at 7.4. **E)** Crystallographic symmetry mate showing direct head-to-head interaction commonly captured in binary CRBM-midi structures. **F)** Crystallographic symmetry mate showing common domain swap in CRBN-midi binary ligand structures.

Supplementary Table 1: Crystallographic statistics

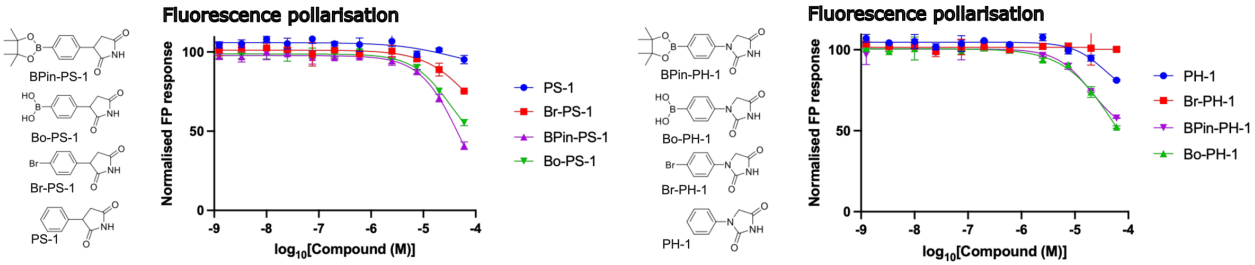
Dataset	Bo-Thal-1	BPin-Thal-1	Bo-NG-1	BPin-NG-1	Bo-ARV-825	BPin-PDU-3	BPin-PDU-1	PBin-PG-1
Beamline	Diamond beamline I04	Diamond beamline I04	Diamond beamline I04	Diamond beamline I04	Diamond beamline I04	Diamond beamline I03	Diamond beamline I03	Diamond beamline I03
Wavelength (Å)	0.95374	0.95374	0.95374	0.95374	0.95374	0.97627	0.97627	0.97625
Unit cell parameters (Å) (a, b, c)	52.78, 94.99, 149.17	52.39, 95.70, 151.28	52.68, 95.45, 148.22	52.45, 95.52, 151.75	53.93, 100.04, 111.35	53.40, 94.78, 146.07	52.769, 94.662, 147.31	52.8, 95.04, 145.92
(α, β, γ)	90°, 90°, 90°	90°, 90°, 90°	90°, 90°, 90°	90°, 90°, 90°	90°, 90°, 90°	90°, 90°, 90°	90°, 90°, 90°	90°, 90°, 90°
Space group	*C 2 2 21*	*C 2 2 21*	*P 21 21 21*	*C 2 2 21*	*P 21 21 21*	*P 21 21 21*	*C 2 2 21*	*P 21 21 21*
Resolution range (Å)	49.72 - 1.8	50.43 - 1.7	49.41 - 2.2	47.76 – 2.2	74.41 - 2.8*	94.78 - 2.8	73.65 - 2.5*	72.96 - 2.4
Unique reflections	25793	30493	48443	23370	16702	14676	9094	31421
CC(1/2): Overall (Outershell)	0.998 (0.615)	0.999 (0.634)	0.999 (0.617)	0.999 (0.508)	0.979 (0.744)	0.994 (0.538)	0.999 (0.529)	0.005 (0.521)
I/sig(I): Overall (Outershell)	12.1 (1.0)	10.9 (0.9)	12.4 (1.5)	11.4 (1.0)	6.4 (1.6)	5.5 (0.9)	10.4 (1.1)	10.8 (0.8)
Completeness Spherical (%): Overall (Outershell)	99.9 (99.7)	100 (100)	99.8 (100)	100 (100)	50.9 (8.3)*	100 (100)	71.6 (17.4)*	99.9 (99.7)
Multiplicity: Overall (Outershell)	13.5 (14.0)	12.9 (12.1)	13.4 (13.3)	13.4 (13.3)	12.8 (13.2)	13.1 (13.9)	12.9 (13.8)	13.6 (12.8)
R_{cryst} (%)	23.79	19.32	22.82	23.15	21.07	25.49	22.90	24.11
R_{free} (%)	27.13	23.17	26.35	25.99	26.60	29.23	28.01	29.15
Wilson *B* factor (Å^2)	32.19	27.47	42.57	48.05	40.19	58.61	55.95	63.53
Average total *B* factor (Å^2)	55.1	41.7	58.1	66.8	38.1	74.3	62.6	81.2
R.m.s.d. bond length (Å^2)	0.013	0.017	0.005	0.002	0.003	0.003	0.004	0.006
R.m.s.d. bond angle (°)	1.430	1.475	0.834	0.536	0.509	0.690	0.642	0.850
Clashscore	9.81	5.26	5.05	4.82	7.94	9.38	7.80	9.06
Ramachadran favored (%)	97.48	98.12	97.79	95.91	97.65	96.81	97.13	97.77
Ramachandran disallowed (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.32	0.0
Rotamer outliers (%)	1.47	1.44	2.3	1.85	1.74	2.37	0.40	2.82
PDB code	31LZ	31MA	31MC	31MB	31MG	31ME	31MD	31MF



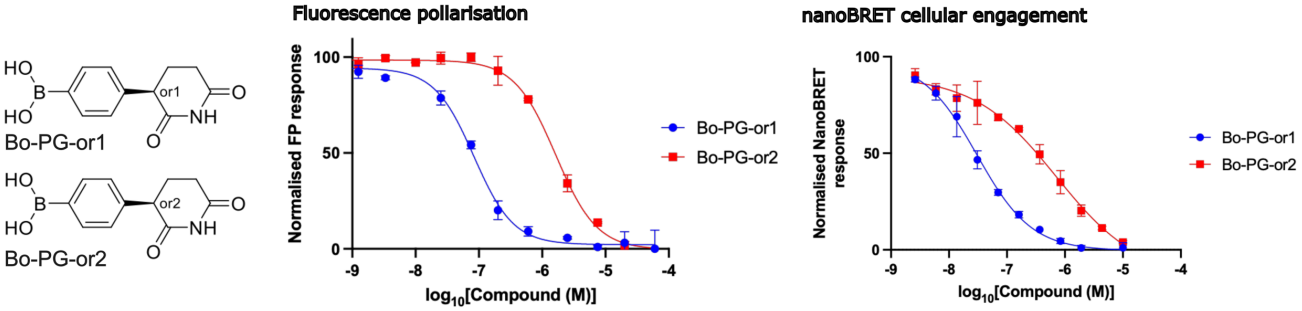
Supplementary Figure 3: Molecular Glue profiling. **A)** GSPT1 degradation curves for modified thalidomide and naphthylamide glutarimide series. Data are presented as ± SD (n = 2). **B)** Scatterplot displaying relative FC in protein enrichment after FLAG-tagged CRBN_ΔHBD pulldown with incubation of 5 µM Bo-Thal-1 vs. DMSO control in MOLT4 lysates (left). Scatterplot displaying relative FC in protein abundance following treatment of MOLT-4 cells for 5h with 1 µM Bo-Thal-1 vs. DMSO (right). Proteomic hits are identified via fold-change above 2 and log10 p value below 0.001 (n = 3).



Supplementary Figure 4: Structure overlay of CRBN-midi Bo-Thal-1 crystal structure (cyan) and BRD4 JQ1 bound structure (PDB3MXF)(blue) with the Bo-ARV-825 ternary complex structure (green/pink).



Supplementary Figure 5: Competitive fluorescence polarization assay comparing IC50s of 5 member ring PS and PH Bo-IMiDs vs Br and unmodified controls. Data are presented as ± SD (n = 2).



Supplementary Figure 6: Competitive fluorescence polarization assay and NanoBRET cellular engagement assay comparing IC50s of isolated Bo-PG-1 enantiomers (Bo-PG-or1 and Bo-PG-or2). Data are presented as ± SD (n = 2).

	Bo-Thalidomide-1	Bo-EM-12-1
Molecular Weight	302,0	288.1
TPSA	124.01	106.94
cLog P	-0.019	-0.242
kinetic solubility, pH 7.4, µM	379±2	335±1
Plasma stability ($T_{1/2}$, min)	347	530
HLM stability ($T_{1/2}$, min)	163.7	287.6
Caco-2 permiability, P_{app} (AB), 10^{-6} cm/s (efflux ratio)	<1 (5.9)	<1 (5.3)

Supplementary Figure 7: Table comparing ADME properties of Bo-IMiDs: Bo-Thal-1 and Bo-EM12-1.