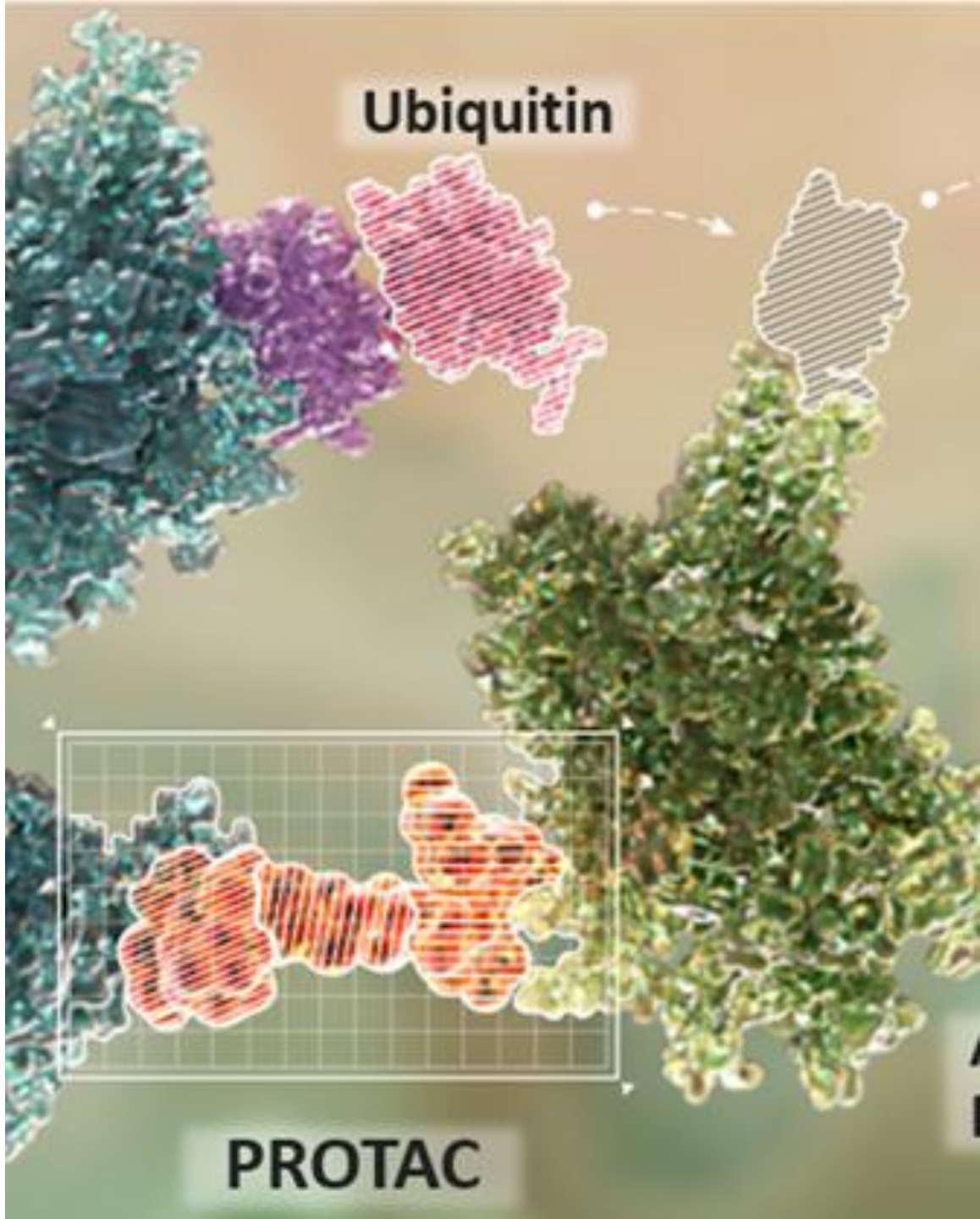
AstraZeneca

MedChem Design of PROTACs for the clinic

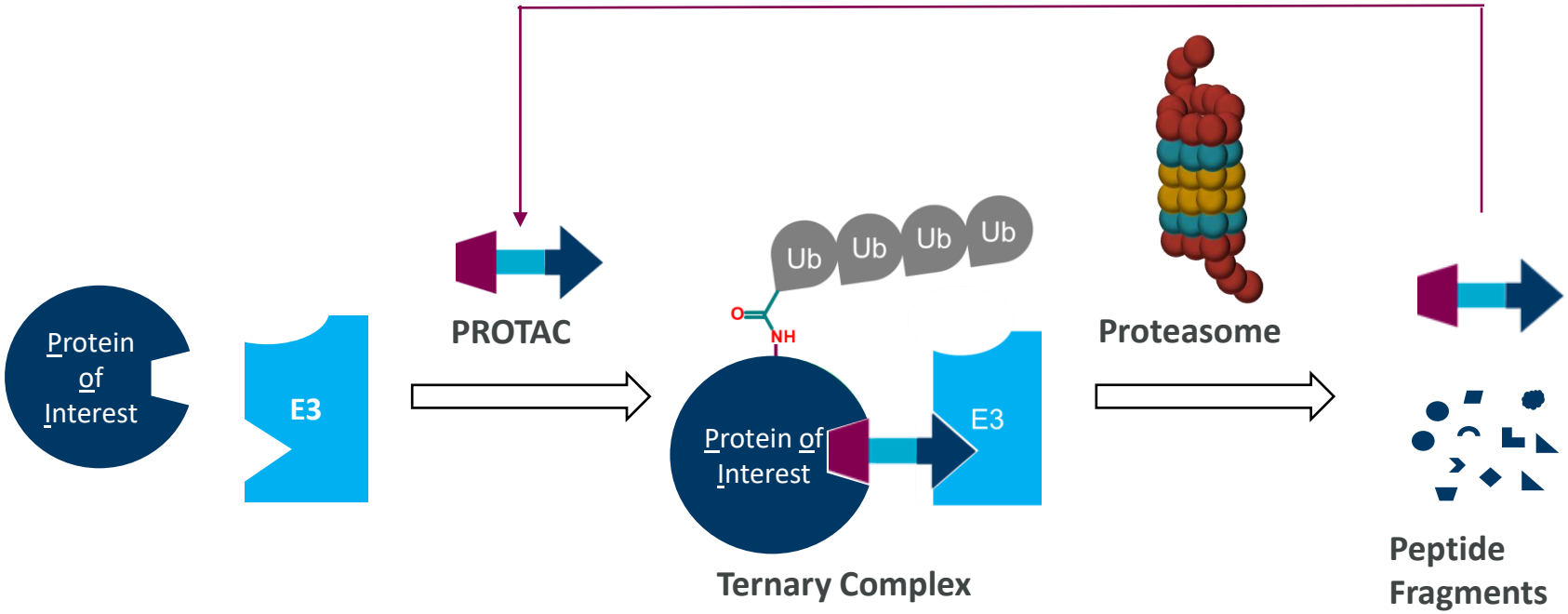
Markus Schade on behalf of the AZD9750 team

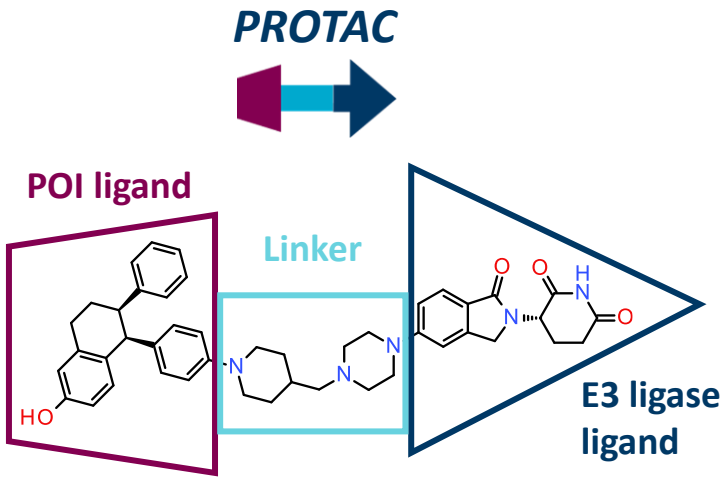
Sept 19, 2026

IASOC Conference, Ischia, Italy



Proteolysis-Targeting Chimeras (PROTACs): MoA, Benefits, Challenges





Potential Benefits:

- Access to Intractable Targets
  - Antagonise scaffolding fct.
  - Degrade targets indirectly
  - pan-mutant efficacy
- Better specificity via:
  - Ternary complex contacts
  - Tissue-selective E3 expression
- Catalytic MoA
- Prolonged PD *in vivo*

Challenges:

- bRo5 physical properties
- ADME (F%, metabolites)
- PK/PD (e.g. “hook effect”)
- E3 biology (cell type variation)
- Incomplete degradation

Clinical PROTAC landscape in early 2026

≥ 52 Clinical stage PROTACs

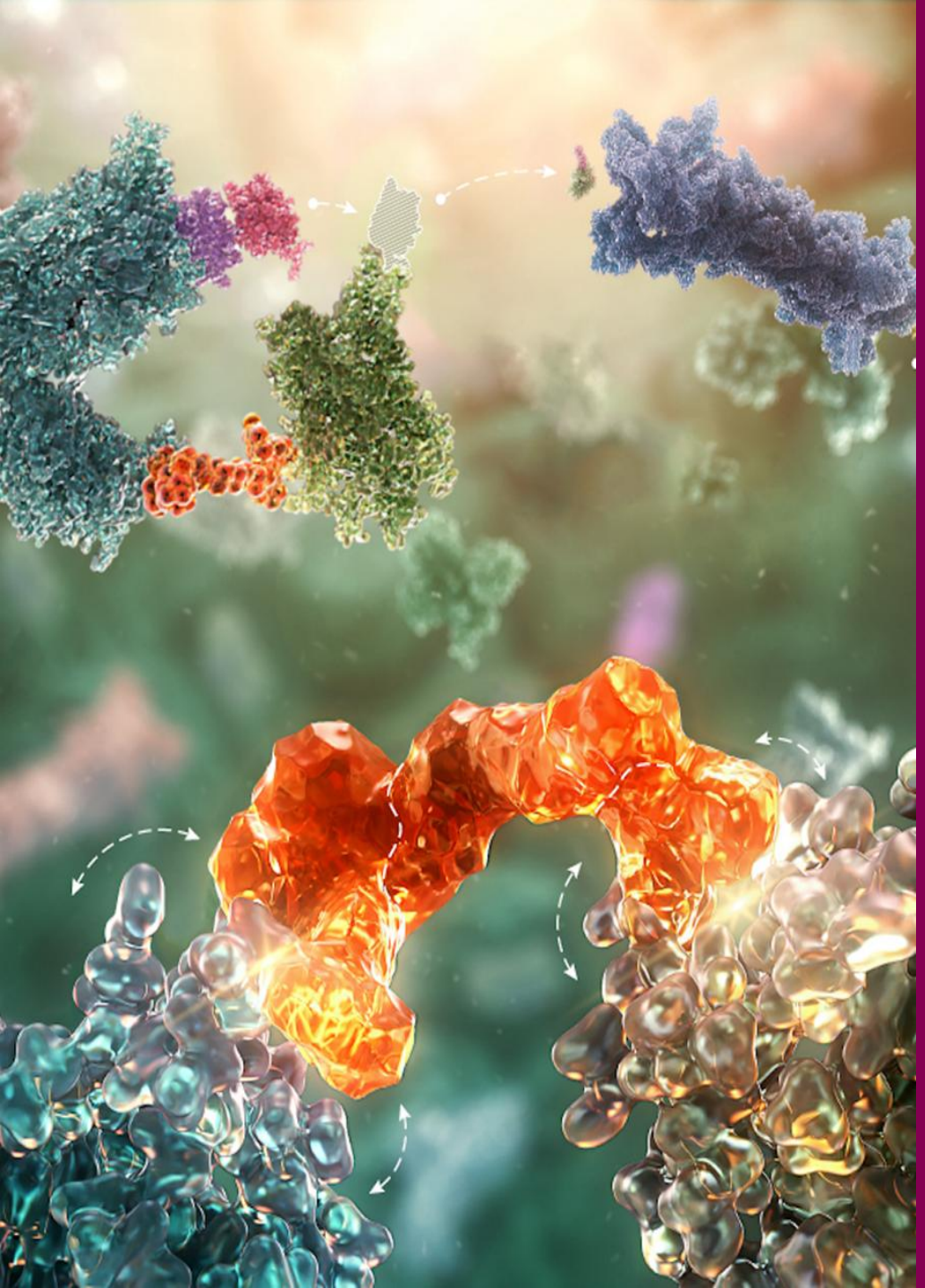
thereof **≥ 38** aim at established SM targets

41 of 52 dosed orally

Primary Target	Primary Indication	Status		No. PROTACs	Drug names
AR	Prostate cancer	Phase I - III	NHR	10	BMS-986365, HRS-5041, ARV-766, QLH12016, GT-20029, AH-001, HP518, SHR-3591, GDC-2992
ER	Breast cancer	Phase I - III	NHR	5	Vepdegestran (FDA approval 06/2026), SIM-0270, HRS-1358, HP-568, AC-699
BTK	B-cell malignancies	Phase I - III	Kinases	8	BGB-16673, ABBV-101, AC-676, HSK-29116, NX-2127, NX-5948, TQB-3019, UBX-303061
EGFR	Lung cancer	Phase I	Kinases	3	BG-60366, HSK-40118, CFT-8919
IRAK4	Autoimmune Diseases	Phase II	Kinases	2	BGB-45035, LT-002-158
LRRK2	Parkinson's disease	Phase II	Kinases	2	DNL151 (BIIB122), ARV-102
BRAF (V600E)	Solid Tumors	suspended	Kinases	1	CFT1946
NTRK	Solid Tumors	Phase II	Kinases	1	CG001419
PIP4K2C kinase	Solid Tumors	Phase I	Kinases	1	LRK-4189
CDK2	Advanced Solid Tumors	Phase I	Kinases	1	NKT-3964
CDK4/CDK6	Advanced Solid Tumors	Phase I	Kinases	1	BTX-9341
Bcl6	Lymphoma	Phase I - II		4	BMS-986458, ARV-393, HSK-47977, TLN-121
KRAS G12D	Solid Tumors	Phase I		2	ASP-3082, ASP-4396
SMARCA2	Advanced Solid Tumors	Phase I		2	PRT7732, PRT3789
BRD4	Advanced Solid Tumors	Phase I - II		2	RNK-05047, MT-4561
BcL-xL	Liquid + Solid Tumors	Phase I		1	DT-2216
EZH2	Non-Hodgkin Lymphomas	Phase I		1	AXT-1003
KAT2A, KAT2B	Acute Myeloid Leukemia	Phase I		1	AUTX-703
MDM2	Liquid + Solid Tumors	Phase I		1	KT-253
STAT3	Liquid + Solid Tumors	Phase I		1	KT-333
STAT6	Atopic dermatitis	Phase I		1	KT-621
BTB-7A, WIZ	Sickle Cell Disease	Phase I - II		1	BMS-986470

AZD9750

PROTACS may be competitive for many Smol targets



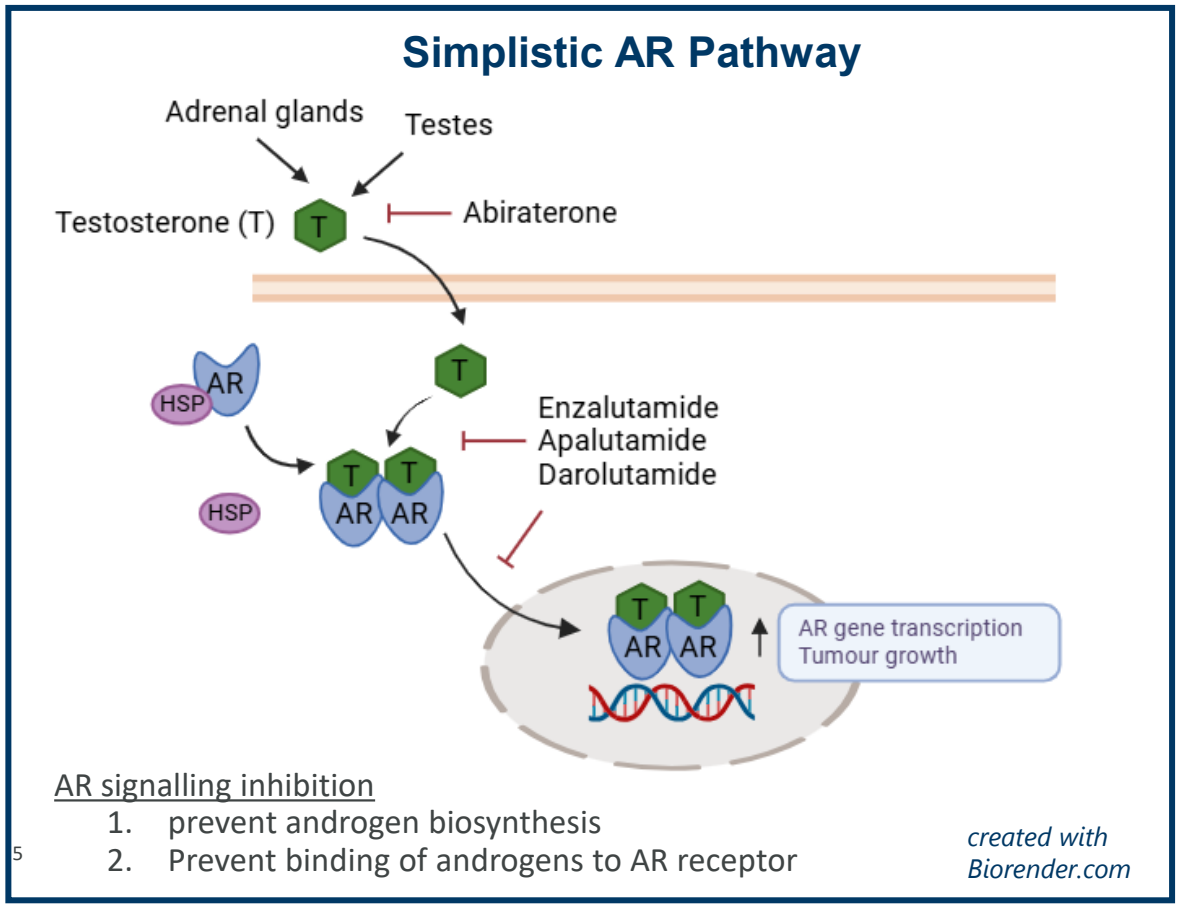
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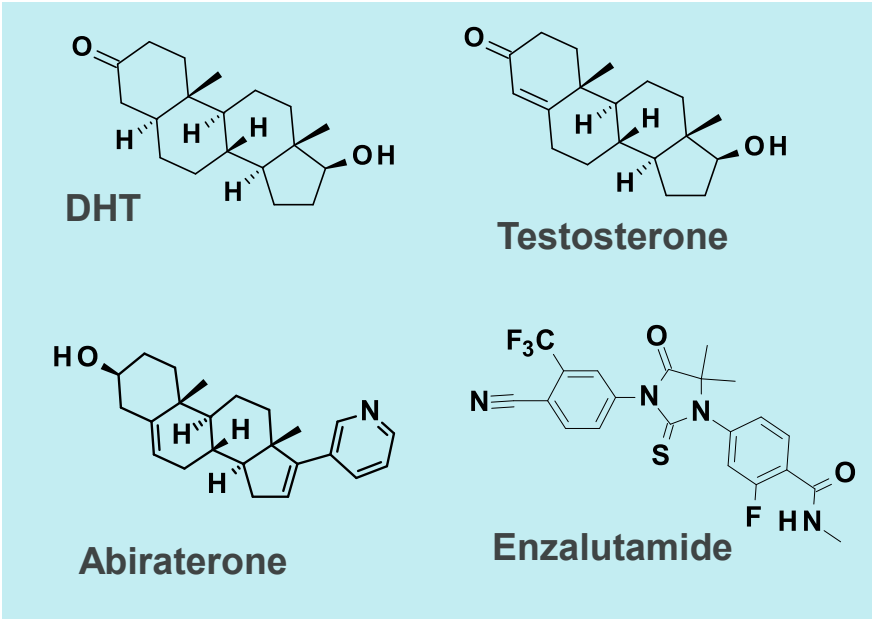
Discovery of AZD9750:

A clinical-stage, oral Androgen Receptor Degrader for the Treatment of Prostate Cancer (NCT07336446)

Castration Resistant Prostate Cancer (CRPC)

- **Prostate cancer:** leading cause of cancer-related death in men
- Androgen Receptor (AR) major driver of prostate cancer
- Testosterone & dihydrotestosterone (DHT) endogenous AR agonists
- New hormonal agents e.g. abiraterone & enzalutamide CRPC SoC





Resistance due to AR overexpression, signal amplification, splice variants & AR mutations

AR LBD mutations present in 10-20% patients (L702H, T878A, H875Y, F877L etc)

→ Switch enzalutamide to **agonist**

- Allow **alternative** steroids as agonists
  - Removing androgens no longer effective

Exploiting legacy equity & FEP to deliver novel POI ligand

Hit Identification

Pharmacophore 17,309

Historic AR 2,566

cell-based luciferase

1,054

concentration response

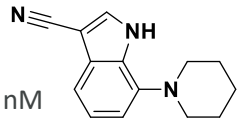
207

rat AR binding

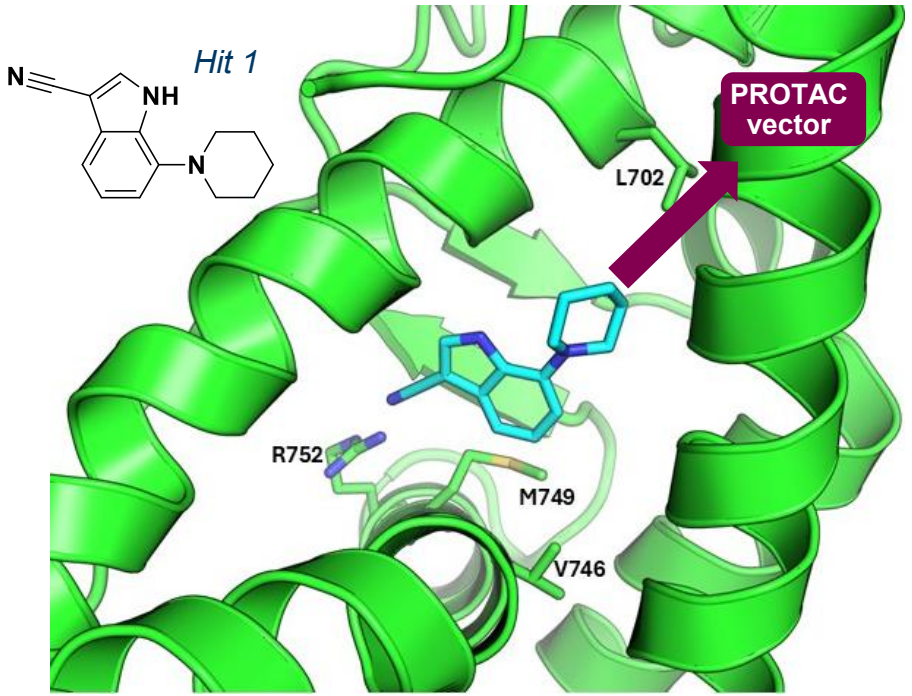
human AR binding

Hit 1

IC_{50} = 300 nM



human AR binding IC50 300 nM



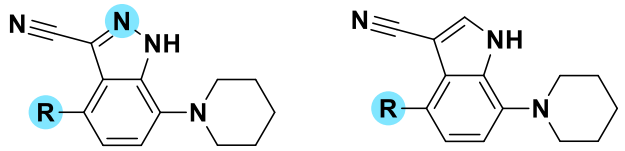
*Modelled pose for **hit 1** using AR protein template from RCSB structure 5T8E, with ligand docked into the pocket of the cognate steroid ligand DHT*

Virtual systematic enumeration

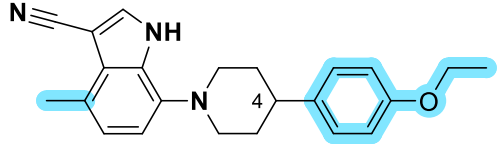
- **1K cpds** triaged by active learning FEP target >10-fold potency↑
- **12 cpds** synthesised
- Indazole, 4-subsitution potent
- PROTAC **vector** identified

hu AR IC_{50} <10 nM

R = Cl, Me, F



***PROTAC vector**: hu AR IC_{50} <10 nM*

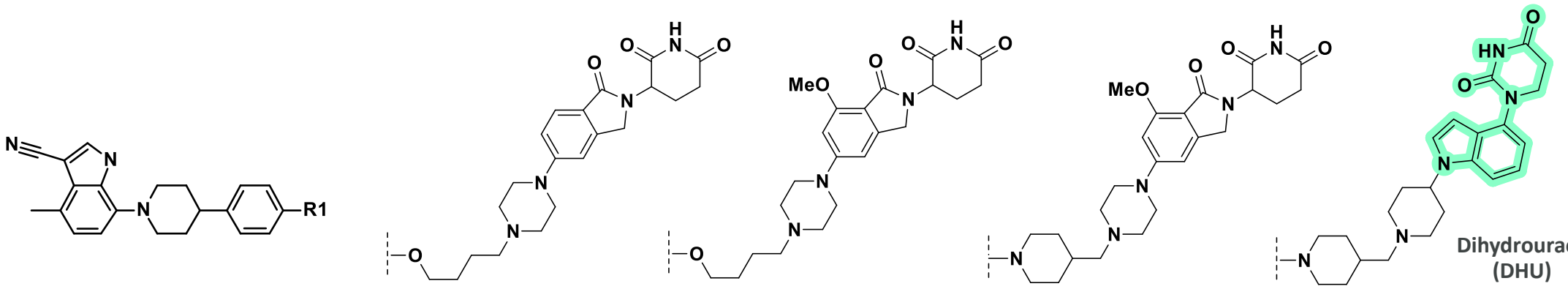


***Free Energy Perturbation (FEP)** is a computational method used to estimate how the energy of a system changes when you make small modifications to predict cpd affinity*

Initial PROTACs: low-complexity linkers & E3 variation

Linker rigidification + DHU offers optimal rodent PK profile

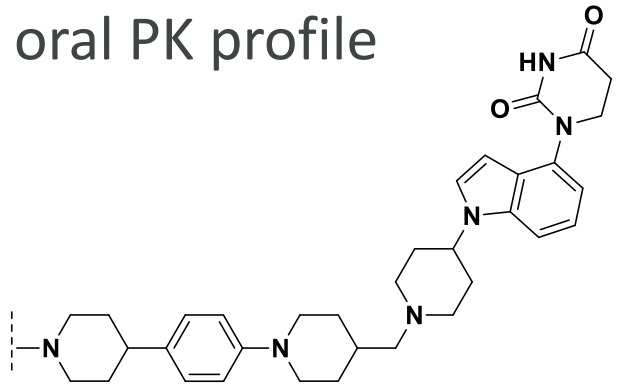
DHU properties
chemical stability ↑
no racemisation ✓
no Ikaros, Aiolos degradation ✓

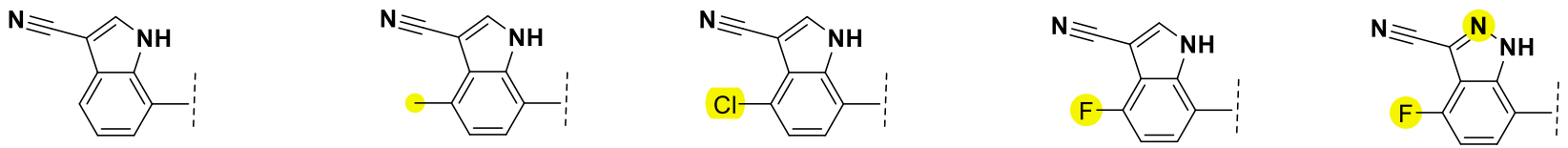


Cpd	A	B	C	D
AR DC_{50} (nM) / (D_{max})	5 (96)	14 (99)	9 (97)	11 (99)
AR L702H DC_{50} (nM) / (D_{max})	23 (83)	27 (75)	24 (85)	47 (96)
Rat Heps CLint (µL/min/10^6 cells)	18	17	3	<1
Rat CL (ml/min/kg)	45	43	28	6
Rat F (%)	7	2	14	60

POI ligand optimisation

- **4-Cl or F** offer promising WT/L702H mutant activity + acceptable oral PK profile
- Indazole & indole tolerated
- **Cpd E** selected for in vivo assessment

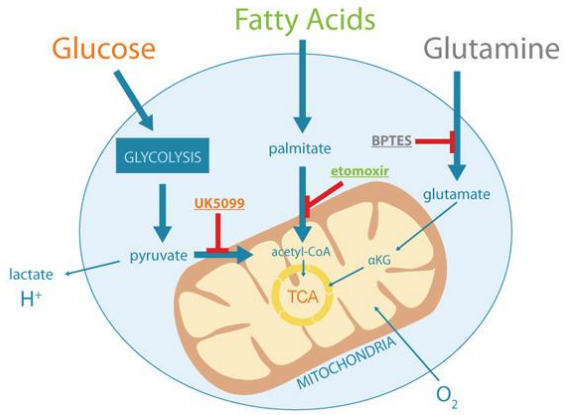




Cpd		D	E		
AR DC_{50} (nM) / (D_{max})	65 (82)	11 (99)	8 (102)	10 (100)	6 (102)
AR L702H DC_{50} (nM) / (D_{max})	58 (87)	47 (96)	12 (108)	13 (103)	38 (96)
Rat Heps CLint (µL/min/10^6 cells)	<1	<1	<1	<1	<1
Rat CL (ml/min/kg)	-	6	3	6	-
Rat F (%)	-	60	45	63	-

Assessment of mitochondrial toxicity in HEPG2 cells

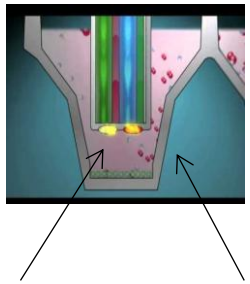
Glucose / Galactose mitotoxicity assay

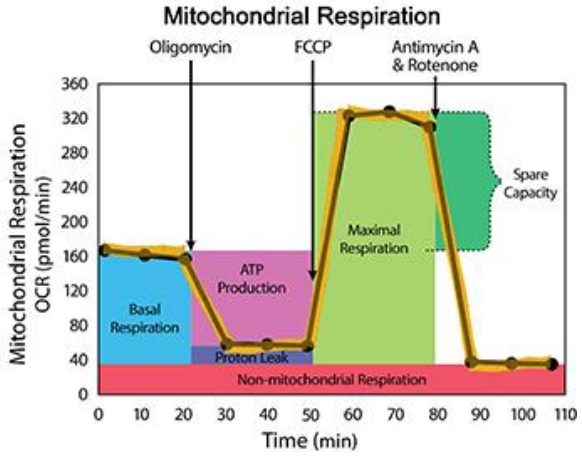


- Mitochondrial dysfunction is often lethal (KO, genetic disorders, Inh)
- Cells fed with **glucose** generate ATP from mitochondria and glycolysis (~50/50)
- Cells fed with **galactose** can only generate ATP from mitochondria
- The ratio of toxicity in cells fed with Glucose vs Galactose indicates specific mitochondrial toxicity over other general cytotoxicity
- Mitotoxins have been known to cause DILI

Seahorse Extracellular Flux (XF) assay



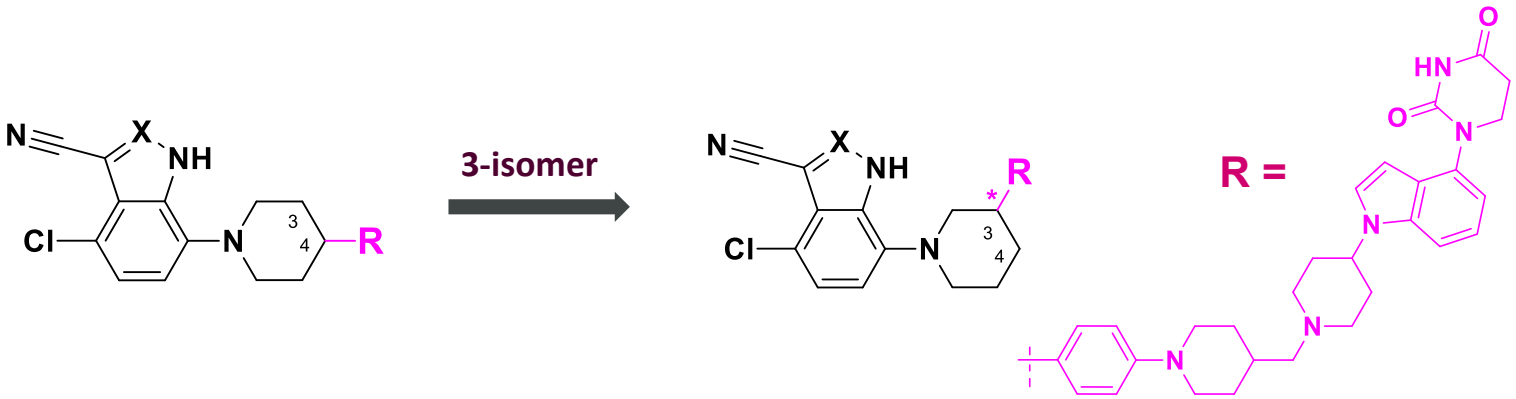


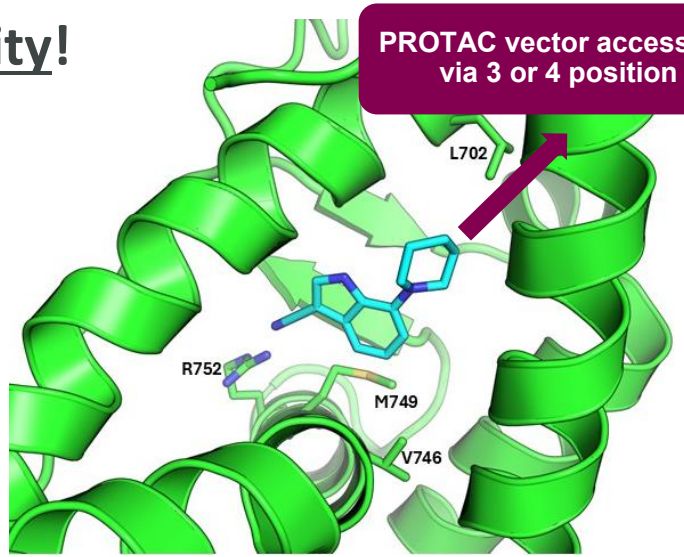


- Measure the respiration of cells, via O2 in supernatant, over time at different drug concentrations
- Ideally should not change (mitochondria unaffected)

Designing out Mitotoxicity

- ***3S & 3R*-isomer potent** having suitable exit vector
- ***3S*-isomer potent + acceptable rodent PK profile YET <u>no mitotoxicity</u>!**
- **Cpd G** selected for in vivo SV assessment





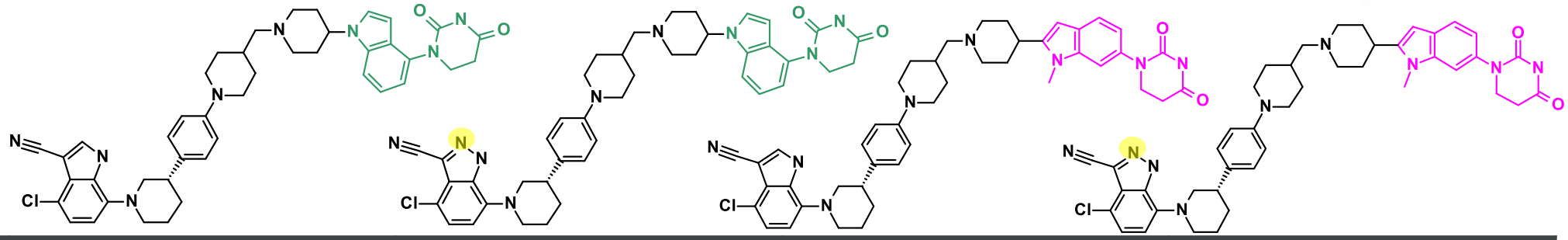
Cpd	link	X = C / N	AR DC_{50} (nM) / (D_{max})	AR L702H DC_{50} (nM) / (D_{max})	Galactose IC_{50} (μM)	Glu / Gal	Rat CL (ml/min/kg)	Rat F (%)
E	4	indole	8 (102)	12 (108)	0.4	>390	3	45
F	*3S*	indole	9 (102)	18 (105)	>100	-	4	38
	3R	indole	9 (92)	7 (106)	1.9	>52	-	-
G	*3S*	indazole	7 (105)	9 (104)	20	-	6	46
	3R	indazole	6 (92)	4 (104)	4.7	>21	-	-

Further DHU optimisation led to AZD9750

- **C-linked DHU** equipotent & maintains attractive properties of **N-linked DHU**
- **Cpd H & I** potent CRBN binders → hu CRBN binding 50-150nM
- **Cpd H & I** selected for in vivo SV assessment



N-linked 4-DHU overlay with **C-linked 6-DHU** in CRBN

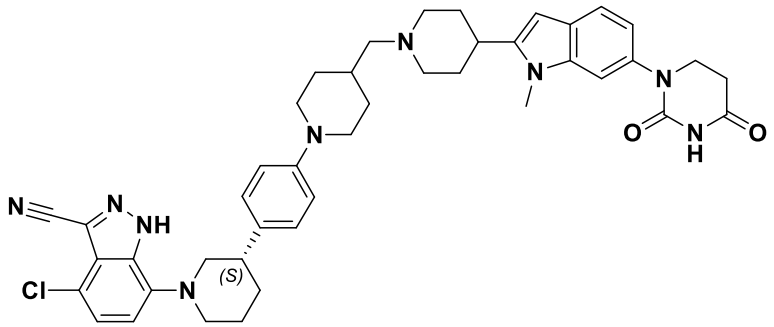


Cpd	F	G	H	I
AR DC_{50} (nM) / (D_{max})	9 (102)	7 (105)	7 (107)	10 (108)
AR L702H DC_{50} (nM) / (D_{max})	18 (105)	9 (104)	6 (109)	12 (110)
Galactose IC_{50} (μM) (Glu / Gal)	>100 (-)	20 (-)	30 (1.7)	85 (1.8)
Rat CL (ml/min/kg)	4	6	4	5
Rat F (%)	38	46	36	53

AZD9750: rigid, polarity-balanced, stable linker

Pharmacokinetic properties in mouse, rat & dog

- Low total clearance & high volume of distribution across species
- Good oral bioavailability

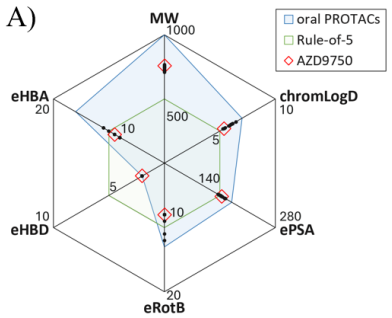


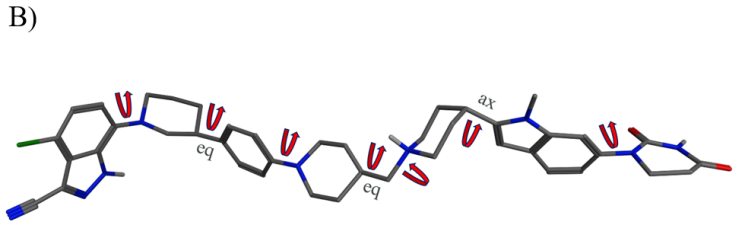
Species	Mouse	Rat	Dog
CL (mL/min/kg)	7.8	5.3	0.81
Vss (L/kg)	4.3	14	16
T1/2 (h)	7.6	31	297
Oral F (%)	47	53	40

Calculated properties & *in vitro* DMPK data

- Beyond Rule-of-5: MW 758, ChromLogD 5.4, HBA 11
- Rule-of-oral-PROTACs: eHBD ≤2 & ePSA ≤ 170 (blue area)
- NMR solution conformation extended & no HBD / HBA shielding

MW	eHBA	eHBD	eRotB	Chrom LogD	ePSA (Å^2)
758	11	2	8	5.4	145



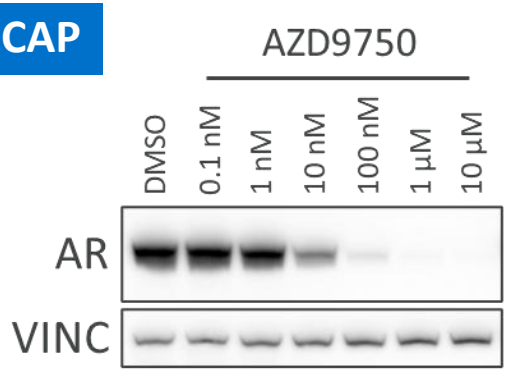


Schade et al. J. Med. Chem. 2024, 13106

AZD9750 selectively degrades WT & L702H mutant AR

AZD9750 degrades wild type, LBD mutant & amplified AR

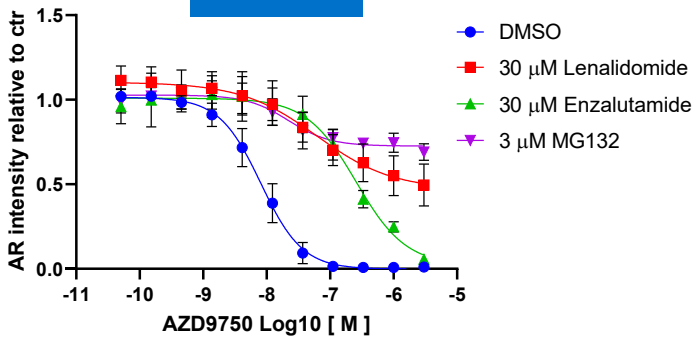
LNCAP



Cell line	AR mutation(s)	DC_{50} (nM)	D_{max} (%)
VCAP	AMP WT	1.9	98
LAPC4	WT	4.5	95
LNCaP	T878A	9.0	97
C4-2	T878A	4.1	92
LNCaP L702H*	L702H/T878A	29	87
MDA-PCa-2b	L702H/T878A	24	96
LNCaP H875Y*	H875Y/T878A	5.4	98
22Rv1	H875Y	1.7	99

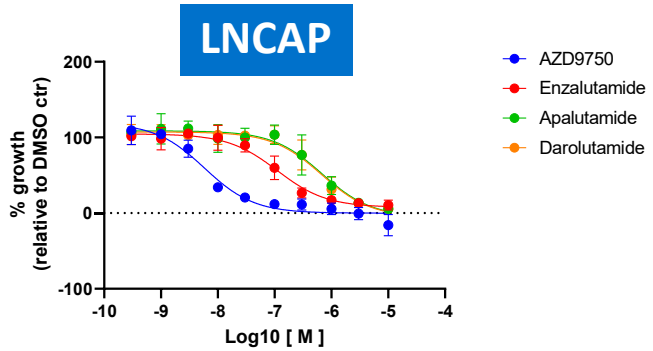
AZD9750 degrades AR through PROTAC-induced mechanism

LNCAP



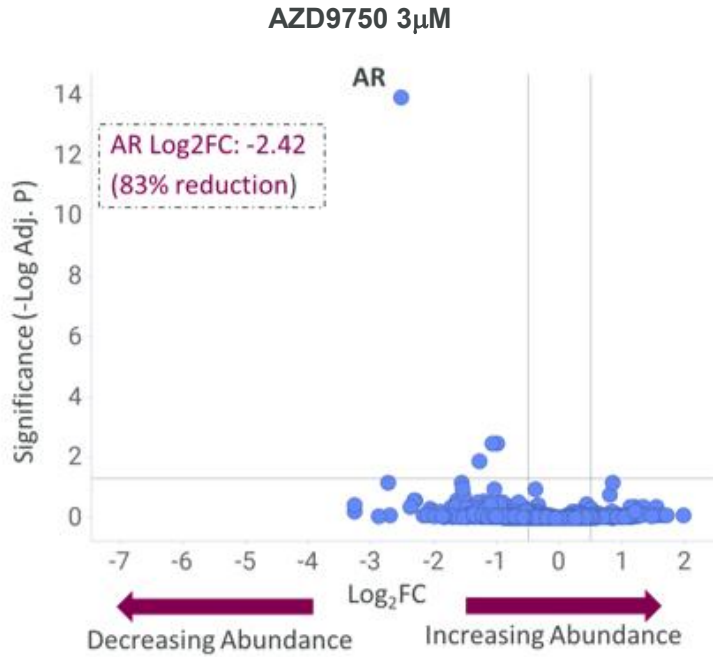
AZD9750 inhibits proliferation more potently than enzalutamide

LNCAP

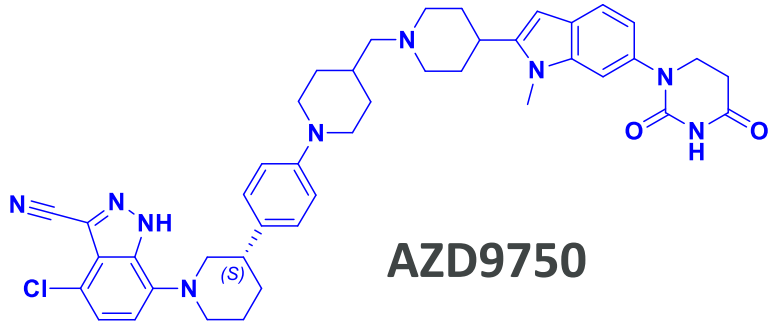


AZD9750 exhibits clean global proteomics profile

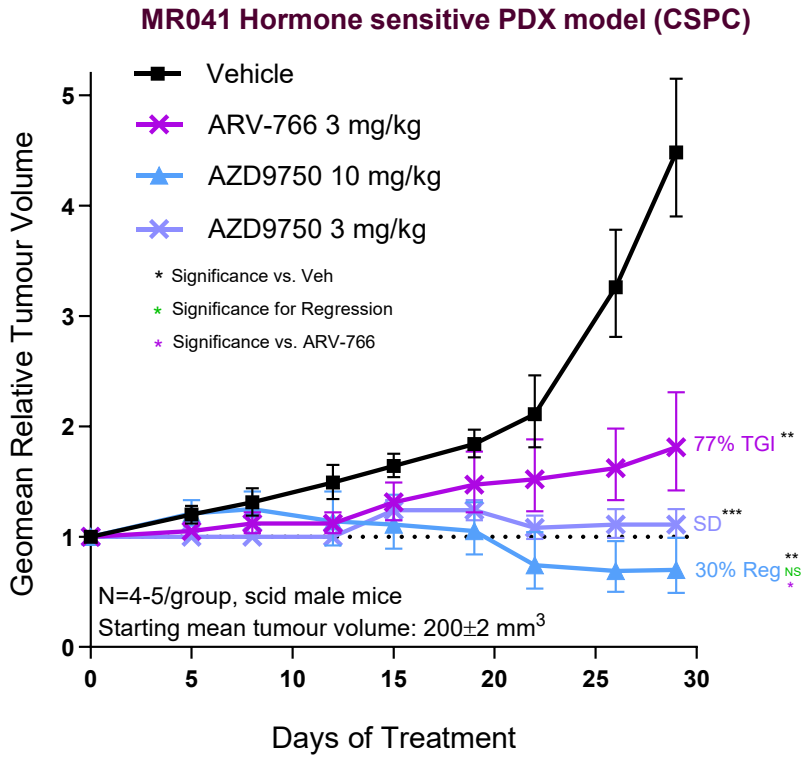
LNCAP



Conclusions AZD9750



- **Directed AR equity screen** & **AI-ML computational** methods delivered novel cyanoindole POI ligand & PROTACs
- **Linker rigidification + novel DHU E3 binder** yielded optimal rodent PK
- **Mitotoxicity** flag removed via **linker isomeric** switching
- Seminal vesicle (SV) ***in vivo*** **triage** identified clinical candidate **AZD9750**



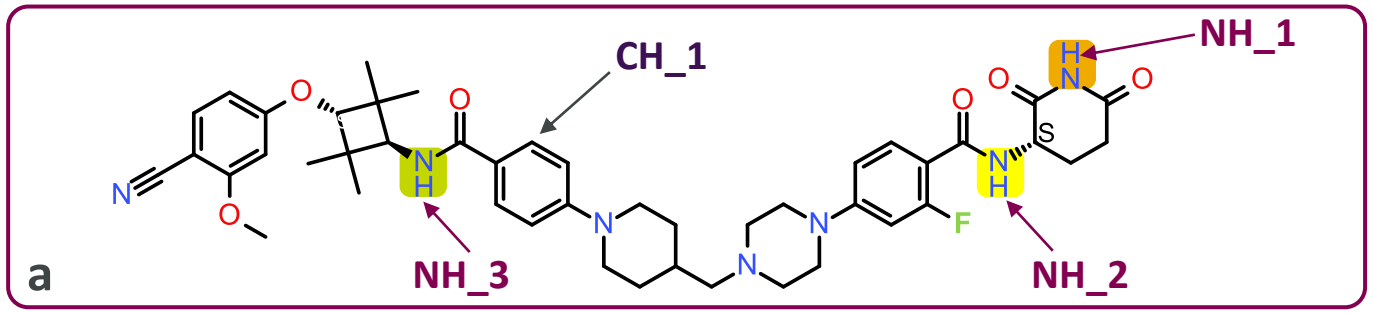
Published on 29 Jan 2026: doi/10.1021/acs.jmedchem.5c03138

3.

Designing balanced polarity, permeability and rigidity into clinical-stage PROTACs

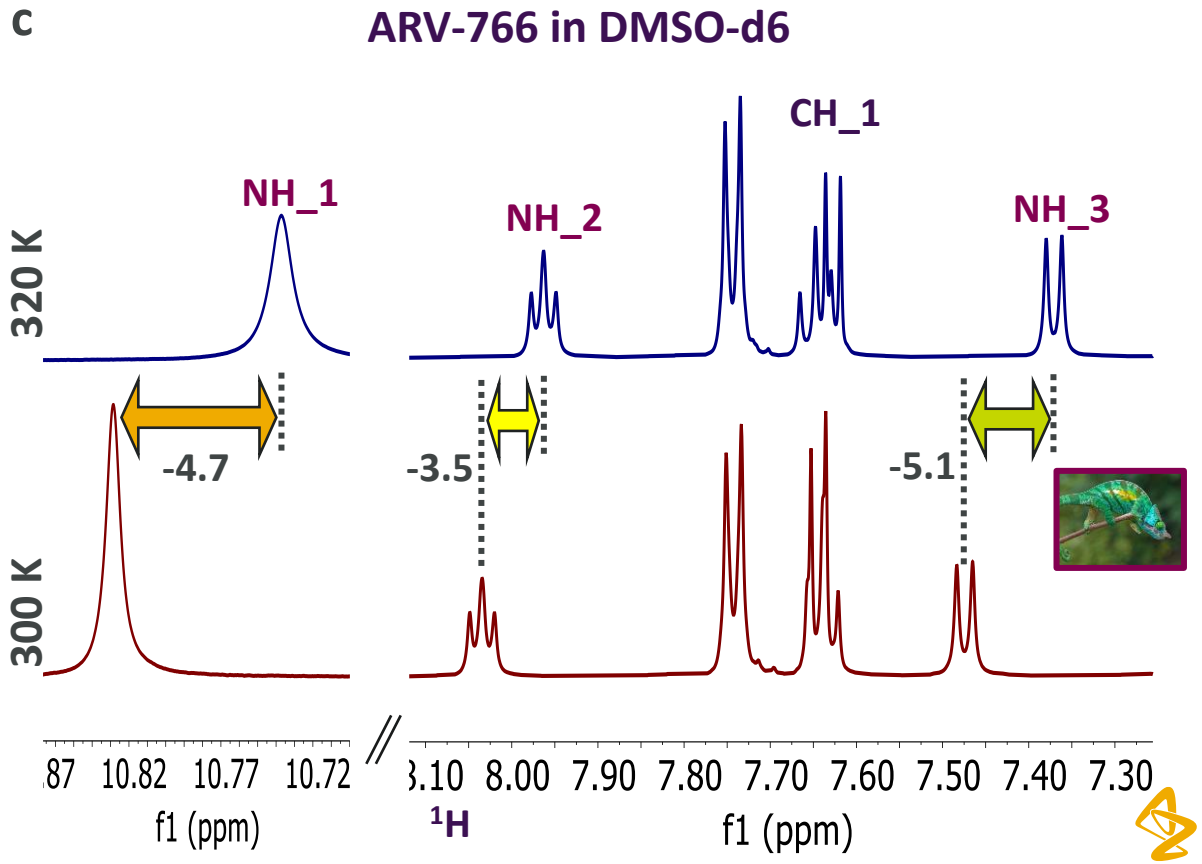
-NH -OH How many solvent-exposed HBD (eHBD) in oral PROTAC ARV-766 ?

Clinical Phase 1/2, oral
Mw 808



NMR solvation assay results:
- = solvent-exposed HBD (eHBD)
- = shielded HBD in DMSO+$CDCl_3$
- = shielded HBD in $CDCl_3$ only

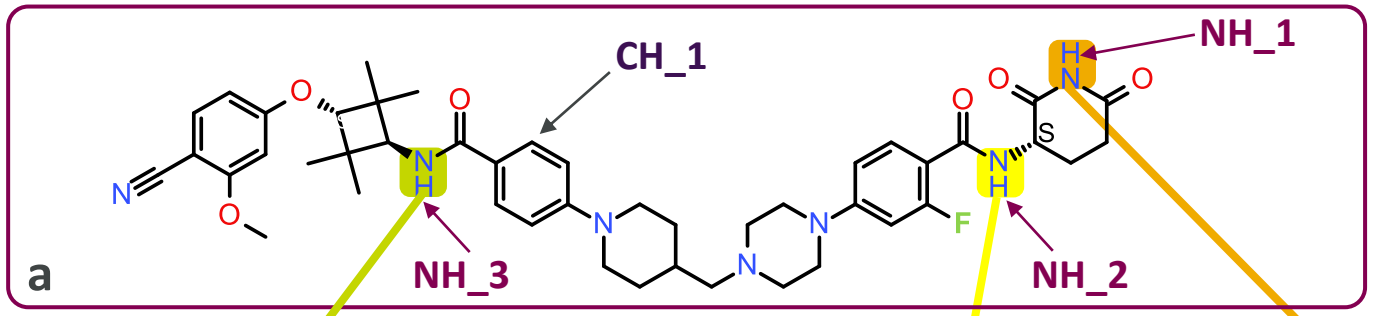




-NH -OH NMR experiment identifies 1 solvated, 1 chameleonic, 1 fully shielded HBD

PROTAC ARV-766

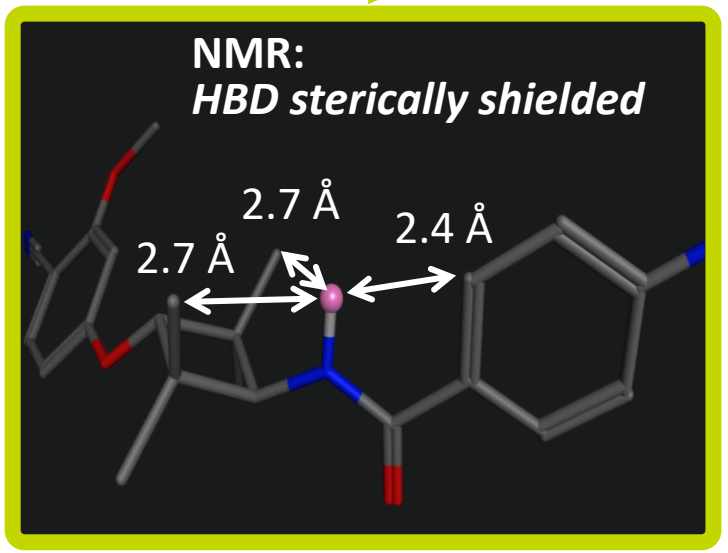
Clinical Phase 1/2, oral
Mw 808

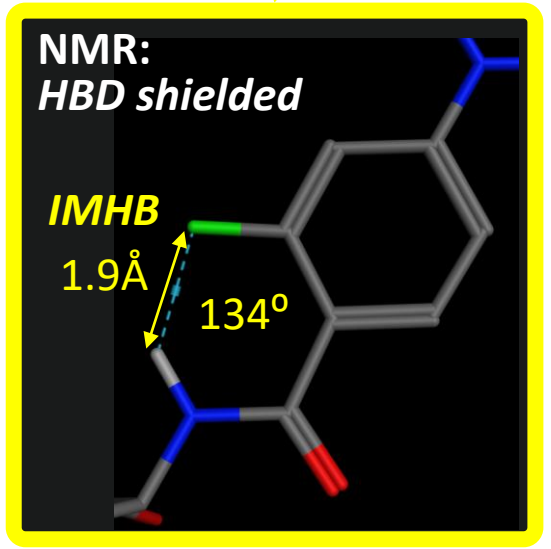


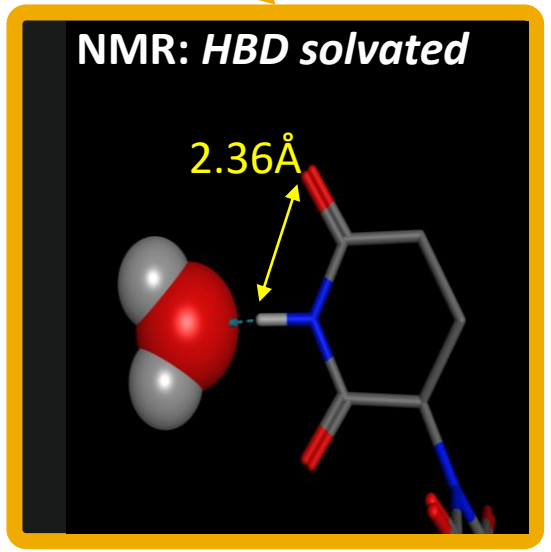
NMR solvation assay results:

- = solvent-exposed HBD (eHBD)
- = shielded HBD in DMSO+$CDCl_3$
- = shielded HBD in $CDCl_3$ only



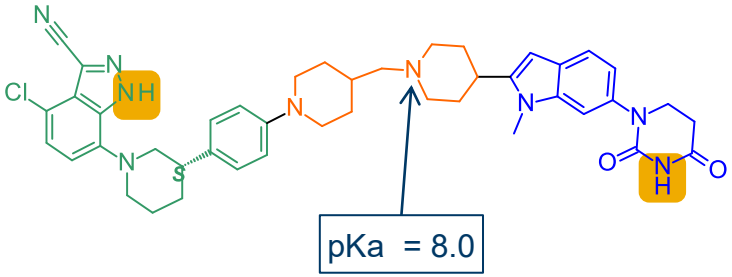






LogD capping designs in clinical-stage, oral AR degraders

Shielded H-bond donor complexity present in 3 out of 4 clinical AR PROTACs

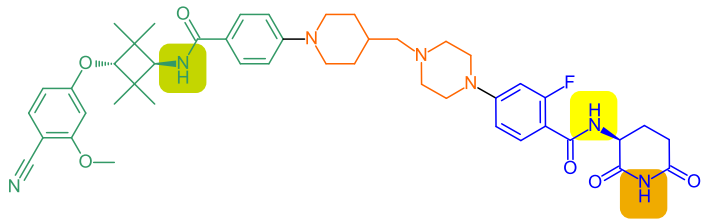


AZD9750 [1]
AstraZeneca
AR : CRBN

DC_{50}(AR-wt) [nM]	5
ChromLogD	5.4
ePSA [Å^2]	145
Basic centres	1
eHBD / HBD	**2** / 2

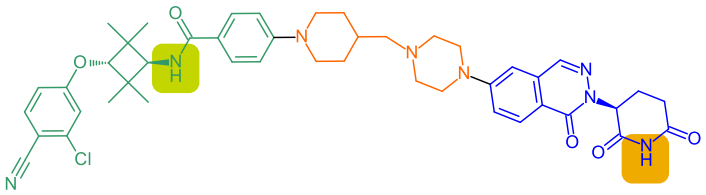
ARV-766
Arvinas/Novartis
AR : CRBN

DC_{50}(AR-wt) [nM]	6
ChromLogD	5.3
ePSA [Å^2]	118
Basic centres	1
eHBD / HBD	**1** / 3



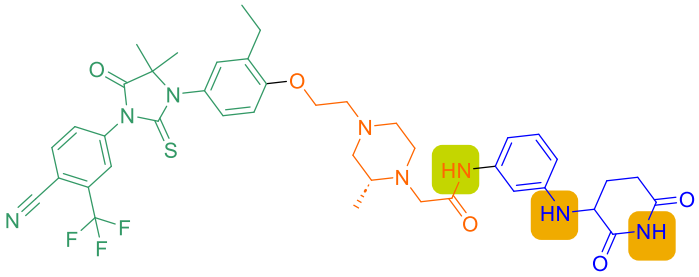
GDC-2992
Genentech
AR : CRBN

DC_{50}(AR-wt) [nM]	3
ChromLogD	6.3
ePSA [Å^2]	127
Basic centres	1
eHBD / HBD	**1** / 2



BMS-986365 [2,3]
BMS
AR : CRBN

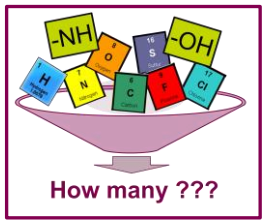
DC_{50}(AR-wt) [nM]	5
ChromLogD	5.3
ePSA [Å^2]	107
Basic centres	1
eHBD / HBD	**2** / 3



NMR solvation assay results:

- = solvent-exposed HBD (eHBD)
- = shielded HBD in DMSO+$CDCl_3$
- = shielded HBD in $CDCl_3$ only

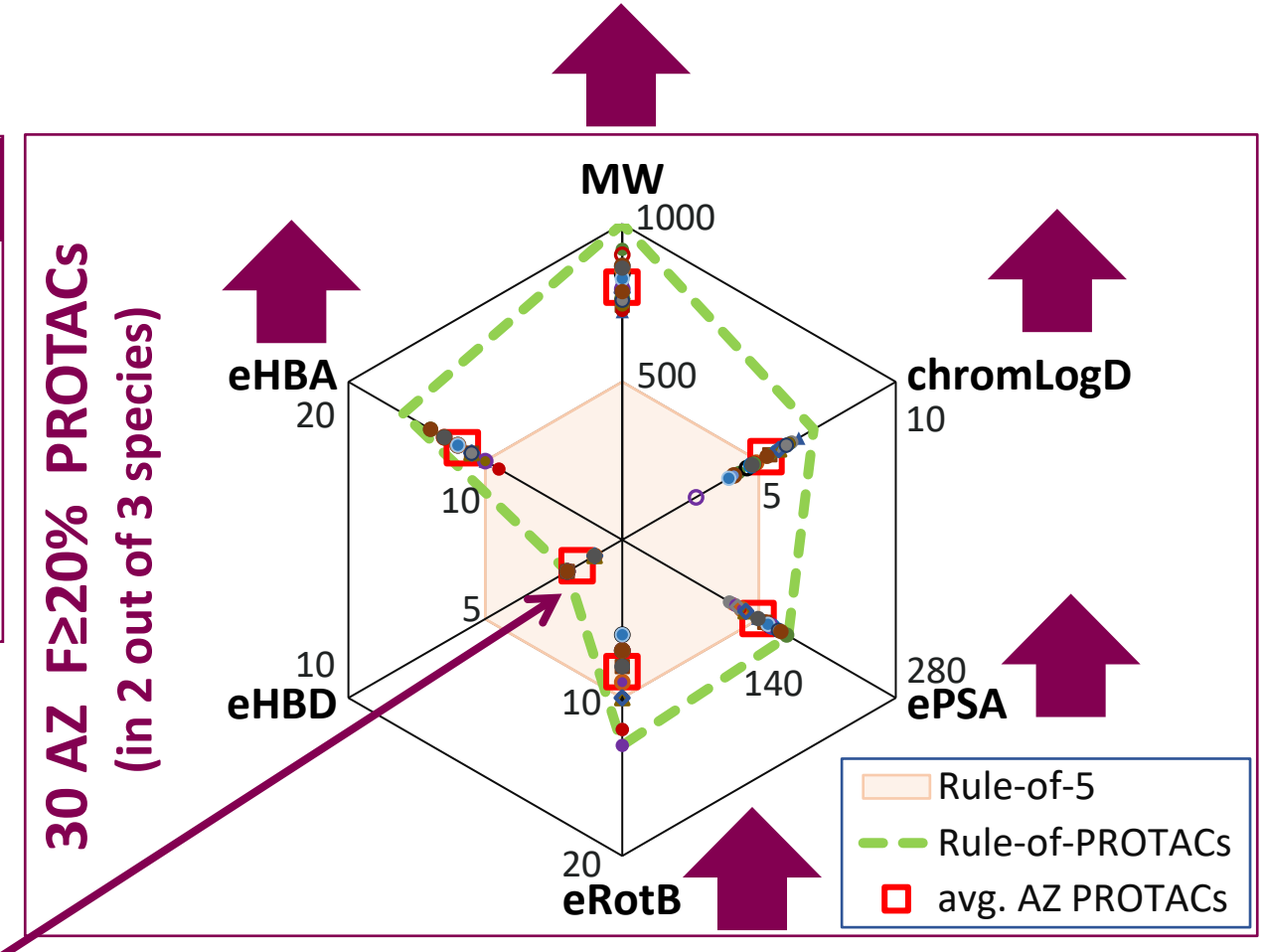
[1] doi/10.1021/acs.jmedchem.5c03138; [2] doi/10.1021/acs.jmedchem.6c01590; [3] “terminated”; PR Jul 30, 2026



Rule-of-oral-PROTACs

Rule-of-oral-PROTACs	
MW	≤ 1000
eHBD	≤ 2
eHBA	≤ 19
ePSA	≤ 170
chromLogD	≤ 7
eRotB	≤ 13

eHBD, eHBA, eRotB determined by NMR

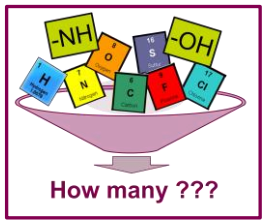


Reach beyond Ro5 as target requires

Restrict below Ro5

e = solvent exposed property

Schade M. et al. *J.Med.Chem.* (2024) 67, 15, 13106;
Scott J.J. et al. *RSC Med.Chem.* (2025) 16, 449-456.



Rule-of-oral-PROTACs vs. oral-PROTACs literature

Rule-of-oral-PROTACs [1]	
MW	≤ 1000
eHBD	≤ 2
eHBA	≤ 19
ePSA	≤ 170
chromLogD	≤ 7
eRotB	≤ 13

Arvinas Publication oral PROTACs [2]	
MW	≤ 950
$HBD_{unsatisfied}$	≤ 2
HBA	≤ 15
tPSA	≤ 200
$LogD_{calc.}$	≤ 6
RotB	≤ 14

Industry Perspective oral PROTACs [3]	
MW	≤ 900
HBD	≤ 5
HBA	≤ 14
tPSA	≤ 200
LogD	3 - 5
RotB	n.d.

1. Schade M. et al. *J.Med.Chem.* (2024) 67, 15, 13106.
e = solvent exposed property

2. K.R. Hornberger & E.M.V. Araujo . *J. Med. Chem.* (2023) 66, 12, 8281.

3. Volak L.P. et al. Drug Metab Dispos (2023) 51, 792.

Similar Guidelines

Violations [3]	
CFT-1946	MW = 958
CFT-1946	HBA = 20
CFT-1946	tPSA = 238
CFT-1946	$LogD_p$ = 2.0
GDC-2992	chromLogD = 6.3

Summary and Key Learnings

1

Cellular Tool PROTACs often tolerate flexible, low complexity linkers, enabling:

- high-throughput synthesis
- *facile exploration of optimal E3 motifs & linker length*

2

Clinical-stage PROTACs contain rigid, ring-rich linkers with balanced polarity, ensuring:

- metabolic stability *in vivo*
- sufficient solubility, permeability and desirable biodistribution

3

Shielded H-bond donors, frequently designed into oral clinical PROTACs,

- rigidify the local conformation
- increase solubility while maintaining permeability if only detected in apolar chloroform

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