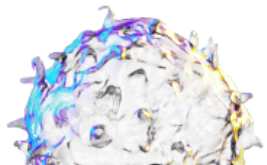
Discovery and Optimization of HIF-2α Inhibitors

Ken Lawson

Discovery on Target - Small Molecules for Cancer Targets – Part 2

September 28th, 2023



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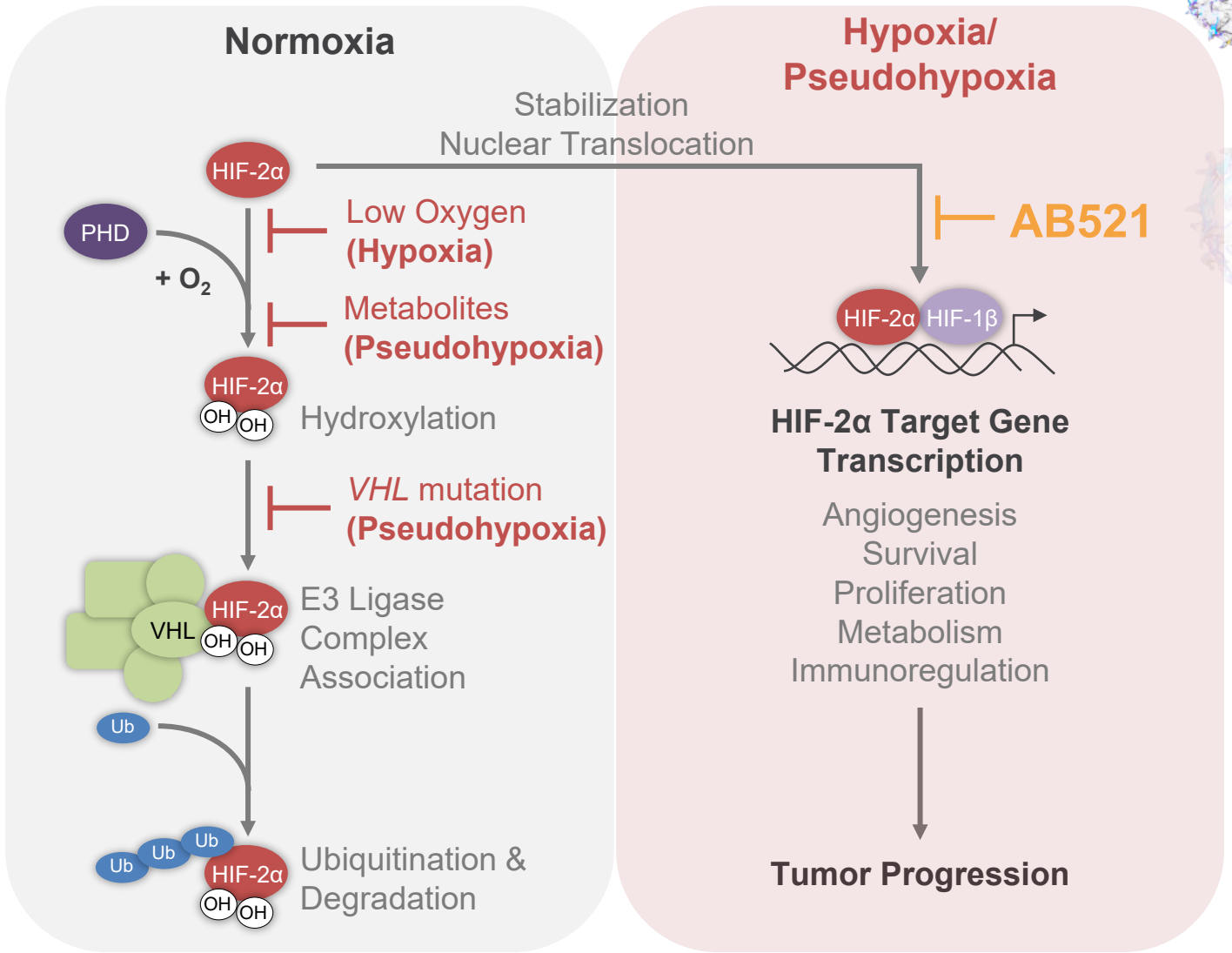
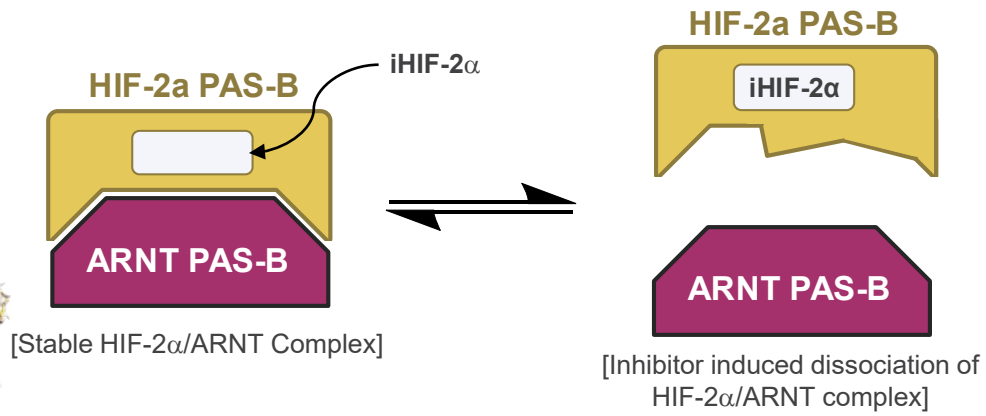
HIF-2α Drives Physiological Changes to Adapt to Low Oxygen That are Hijacked by the Tumor

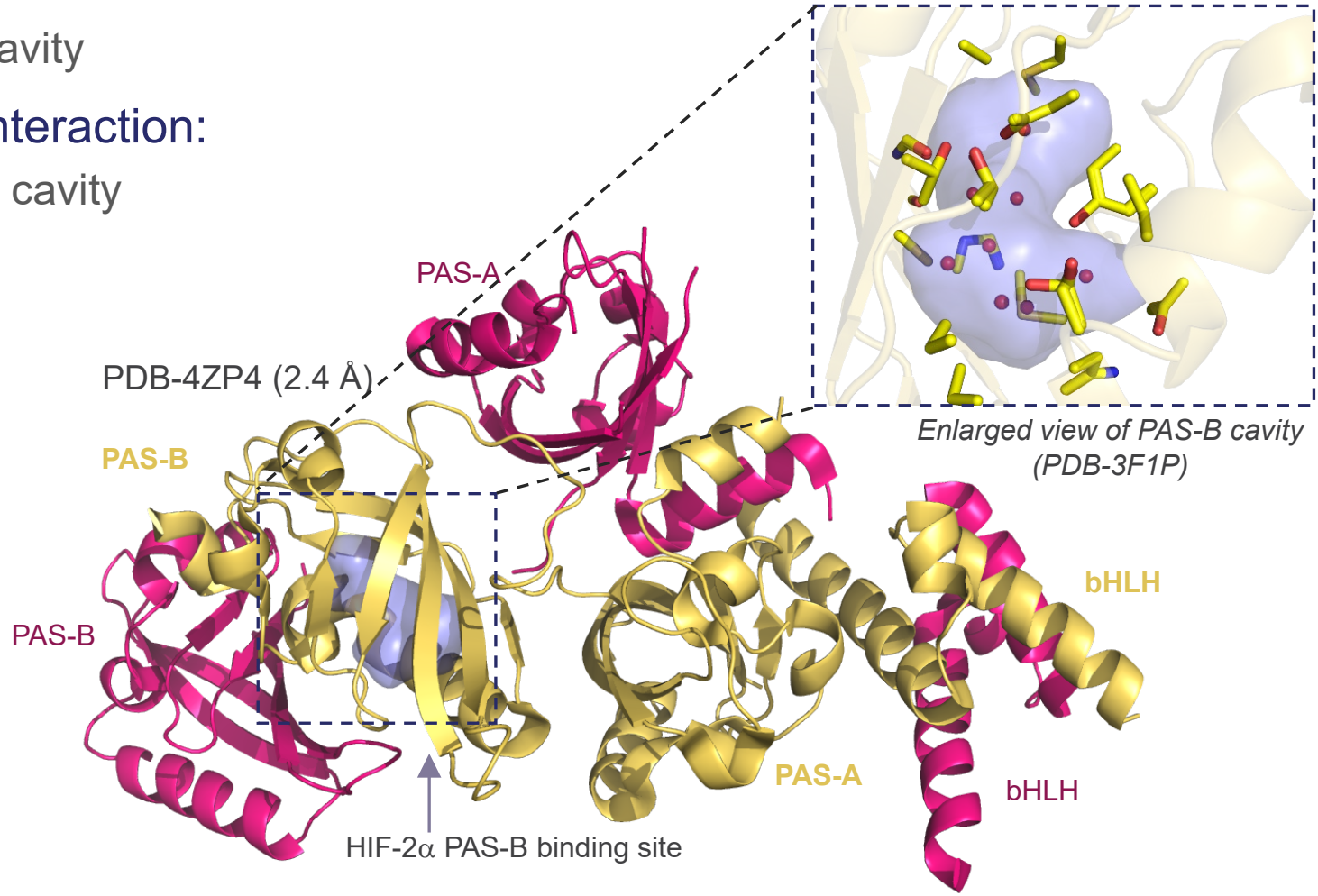
- HIF-2α protein levels are exquisitely controlled in the cell
- HIF-2α is a transcription factor comprised of two proteins
  - Stably-expressed β subunit (HIF-1β/ARNT)
  - Oxygen-sensitive α subunit (HIF-2α)
    - HIF-1α and HIF-3α isoforms exist
- Therapeutic Hypothesis
  - HIF-2α drives transcriptional changes that promote tumor progression in **hypoxia** or **pseudohypoxia**
  - Disrupting α-β dimer formation will prevent gene transcription and block tumor progression



Fundamentals of Targeting the HIF-2α/ARNT Complex

- X-ray crystal structure shows internal hydrophobic cavity (~290 Å^3) with 8 water molecules[1]
  - HIF-1α lacks analogous hydrophobic cavity
- Basis for regulation of protein-protein interaction:
  - Small molecule binds to HIF-2α PAS-B cavity
    - → conformational change
  - HIF dimerization disrupted
    - → gene transcription inactive





[1]*Proc. Natl. Acad. Sci. USA*, **2009**, 106: 450-455

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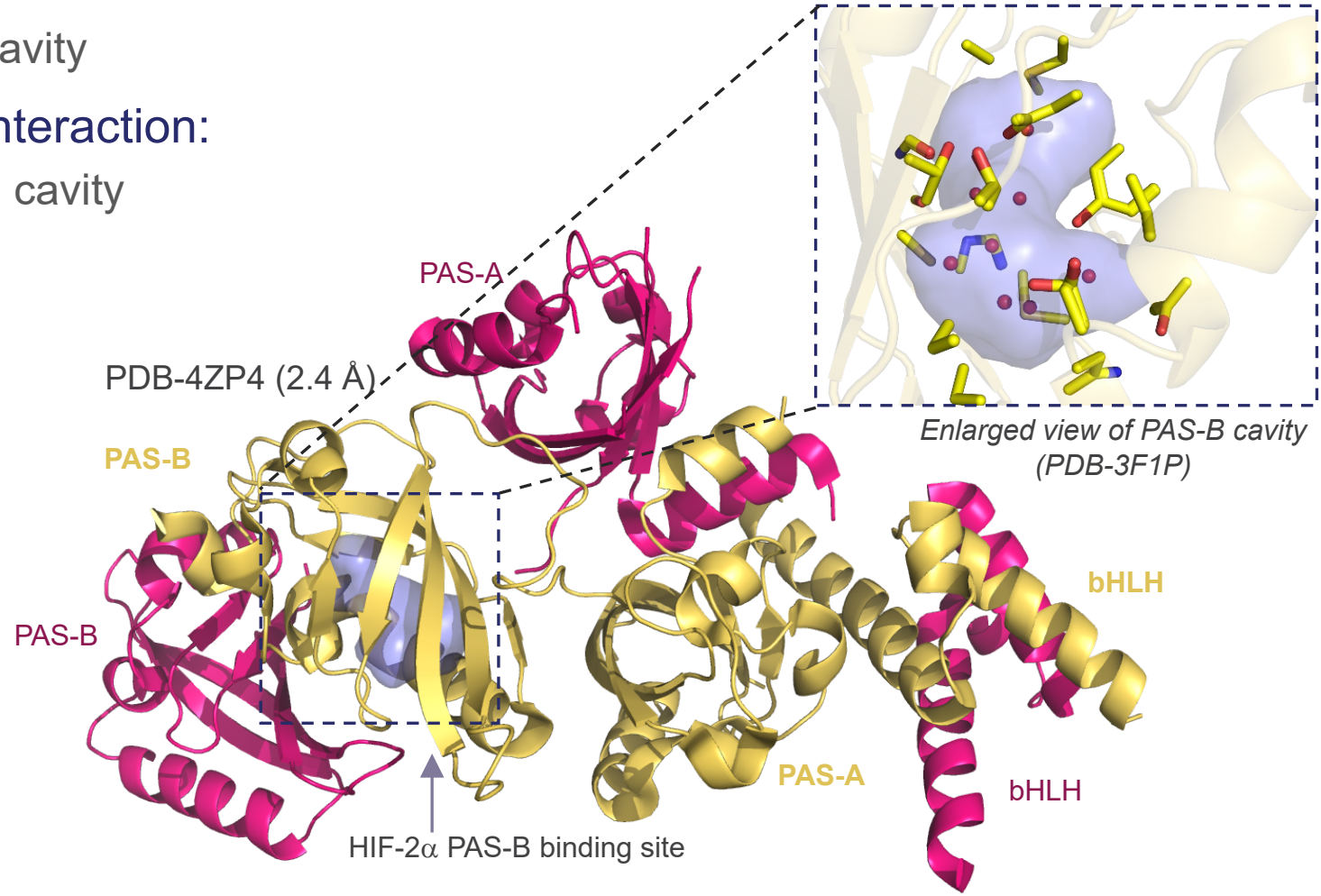
- Basis for regulation of protein-protein interaction:
  - Small molecule binds to HIF-2α PAS-B cavity
    → conformational change
  - HIF dimerization disrupted
    → gene transcription inactive
- Design challenges:
  - Small internal pocket limits ligand size
  - Binding affinity may not correlate with functional activity
  - High affinity ligands often possess undesirable physicochemical properties (high lipophilicity)
  - Intellectual property considerations



[1]*Proc. Natl. Acad. Sci. USA*, **2009**, 106: 450-455

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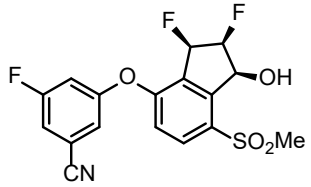
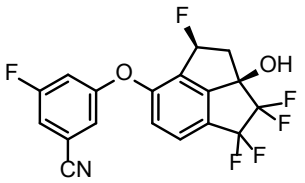
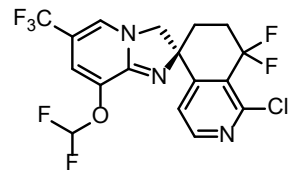
Status and Characterization of Clinical HIF-2α Inhibitors

- HIF-2α inhibition (Belzutifan) has demonstrated significant clinical activity in patients with advanced ccRCC[1]

Assay	Belzutifan (Peloton/Merck)	AB521 (Arcus)	NKT2152[a] (NiKang)	Compound A[b] (Novartis)
		Structure not disclosed		
ccRCC Clinical Trial Status	**Phase 3[c]**	**Phase 1/1b**	**Phase 1/2**	**Phase 1/1b**
HIF-2α Reporter Gene Assay[d] IC_{50} (nM)	17 ± 10 (n = 8)	8.2 ± 2.5 (n = 24)	5.3 ± 1.4 (n = 3)	19 ± 8.7 (n = 9)
Reporter Control[d] IC_{50} (nM)	> 10,000	> 10,000	> 10,000	> 10,000
HIF-2α 786-O Luc. 100% Serum IC_{50} (nM)	62 ± 6.6 (n = 4)	47 ± 14 (n = 24)	120 ± 13 (n = 2)	270 ± 73 (n = 9)

[a]Prepared according to WO2022086822. [b]Prepared according to WO2021220170, compound A. [c]Belzutifan is approved for treatment of VHL disease. [d]786-O renal adenocarcinoma cells (mutant for VHL and HIF-1α) stably expressing HIF or control CMV luciferase (Luc) reporter constructs

- Arcus's clinical HIF-2α inhibitor, AB521, is presently in clinical development and has demonstrated a favorable PK/PD and safety profile in healthy human volunteers

[1]McDermott, et. al. (2022) ESMO; DCO: Feb 1, 2022; Albiges (2023) ASCO; DCO: SEP 29, 2022

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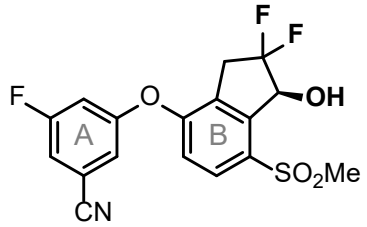
Design and Discovery of Arcus Back-up HIF-2α Inhibitors

- Pharmacophore mapping and structure-aided design approach toward novel starting points



PT2385

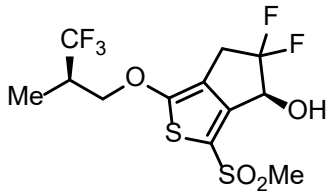
HIF-2α Biochemical (SPA) IC_{50} = 35.7 nM

HIF-2α Cell-Based (Luc) IC_{50} = 27.4 nM

HIF-2α 100% Serum (Luc) IC_{50} = 186 nM

(Peloton's 1st-generation HIF-2a inhibitor)

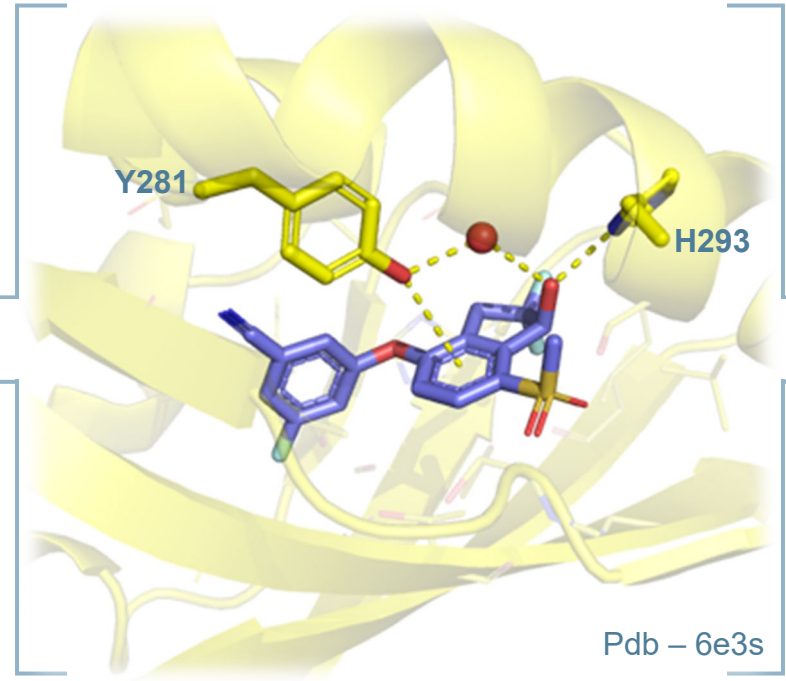
Cycloalkyl[c]thiophenes HIF-2α inhibitors by Merck KGaA[3]

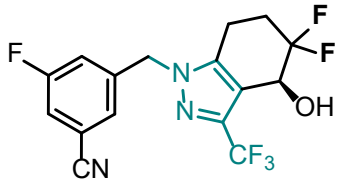


ITC: K_D = 42 nM

VEGF-A ELISA IC_{50} = 305 nM

PT2385 bound to HIF-2α PAS-B domain[1]





Compound 1

HIF-2α Biochemical IC_{50} > 20,000 nM

HIF-2α Cell-Based IC_{50} > 10,000 nM

HIF-2α 100% Serum (Luc) IC_{50} > 40,000 nM

Tetrahydroindazole Core Design

Key HIF-2α PAS-B/inhibitor interactions:

*Y281 n → π** - Interaction is stronger when aromatic ring (B) is electron deficient[2]

H293-[PT2385]-[H_2O]-Y281 Hydrogen bonding network is critical for binding

A-Ring – Hydrophobic/non-specific interactions

[1]*J. Med. Chem.* **2018**, 61, 21, 9691–9721; [2]*Phys. Chem. Chem. Phys.*, **2015**, 9596; [3]*J. Med. Chem.* **2023**, 66, 13, 8666–8686

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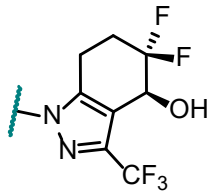
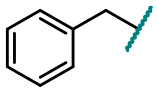
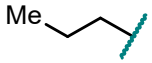
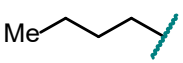
Moderate-to-Good Potency Observed with Aliphatic A-Ring Replacements

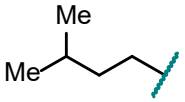
- Incorporation of lipophilic side-chains led to significant potency gains
  - Generally good correlation between biochemical binding (SPA) and cell-based functional assays (786-O Luciferase)

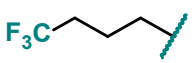


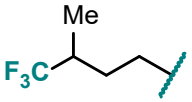












Compound ID	2	3	4	5	6	7
HIF-2α Biochemical IC_{50} (nM)	> 20,000	4,850	946	164	**89.2**	**44.1**
HIF-2α Cell-Based (nM)	> 10,000	4,610	727	154	**59.2**	**116**
HIF-2α Cell-Based 100% Serum IC_{50} (nM)	> 40,000	> 40,000	> 40,000	4,780	**736**	**965**

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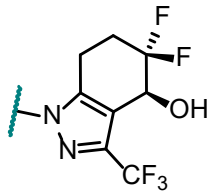

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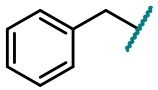		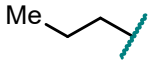	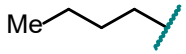	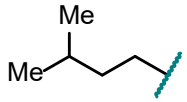	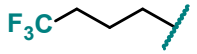	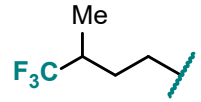
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Hepatocyte CL_{int} (μL/min/10^6 cells) hu / rat	-	-	**95 / 190**	-	**260 / 110**	**270 / 160**
CYP Inh. IC_{50} (μM) 2C8 / 2C9 / 2C19 / 2D6 / 3A4	-	-	-	-	-	>40 / >40 / 8.1 / 18 / 30
CYP TDI (% Act. loss, 30 min) 2C8 / 2C9 / 2D6 / 3A4	-	-	-	-	-	0 / 0 / 2 / 6

- Lipophilic inhibitors offered sub-optimal properties (oils) and poor hepatocyte stability

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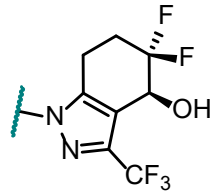
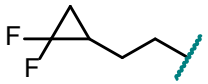
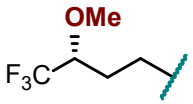
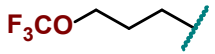
Balancing Polarity of Side-Chains Reduces Hepatocyte Intrinsic Clearance

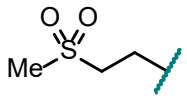
- Sulfone-containing side-chains ‘0113 and 0309 demonstrate reduced clearance to human and rat hepatocytes
  - Reduced HIF-2α potency was observed with incorporation of polar groups

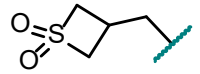


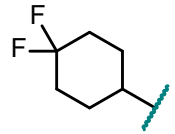












Compound ID	8	9	10	11	12	13
HIF-2α Biochemical IC_{50} (nM)	65.2	n.d.	n.d.	205	153	692
HIF-2α Cell-Based (nM)	49.3	12.9	29.5	383	342	767
HIF-2α Cell-Based 100% Serum IC_{50} (nM)	328	**59.0**	230	2,200	570	> 40,000
Hepatocyte CL_{int} (μL/min/10^6 cells) hu / rat	235 / 174	63 / 184	216 / 198	**< 2.7** / 32.2	15.3 / < 2.7	**< 2.7** / 4.8
cLogP	4.3	3.0	4.4	1.6	2.5	3.9

- Cyclic motifs exhibit reduced potency, but improved hepatocyte stability despite high lipophilicity

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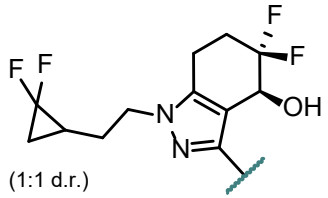
A Highly Electron Deficient Pyrazole is Required to Retain HIF-2α Potency

- Strong electron withdrawing groups (e.g. $–CF_3$) are highly preferred at pyrazole C3 position
  - Sulfone and nitrile groups lead to reduced SAR, contrasting published SAR for binding in this region



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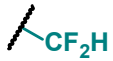

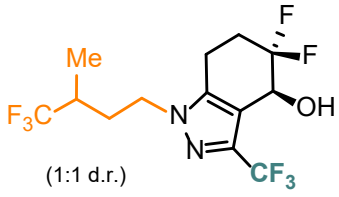

(1:1 d.r.)

Compound ID	14	15	16	8	7	17	18
HIF-2α Biochemical IC_{50} (nM)	n.d.	n.d.	n.d.	**65.2**	**44.1**	2,150	797
HIF-2α Cell-Based (nM)	> 10,000	> 10,000	1,380	**49.3**	**116**	4,100	973
HIF-2α Cell-Based 100% Serum IC_{50} (nM)	> 40,000	> 40,000	10,600	**328**	**965**	> 30,000	6,600

- Reducing lipophilicity by replacement of trifluoromethyl group was untenable

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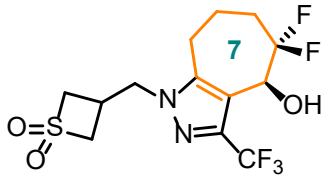
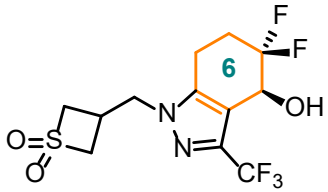
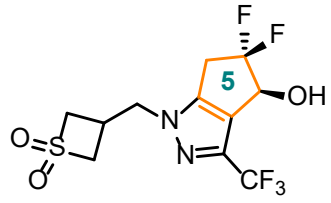
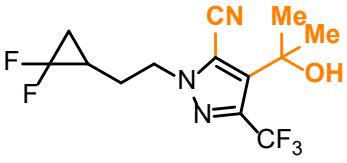
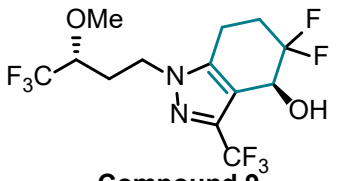
[6,5] and [5,5]-Cycloalkyl-Pyrazole Inhibitors Exhibit Similar Potency

- Investigation of cycloalkyl-carbinol revealed [6,5] and [5,5] rings systems exhibited similar potency
  - Larger [7,5] rings or acyclic inhibitor designs were inactive

Compound ID	19	12	20	21
				
HIF-2α Cell-Based (nM)	> 10,000	342	208	> 10,000
HIF-2α Cell-Based 100% Serum IC_{50} (nM)	> 40,000	570	411	> 40,000
Hepatocyte CL_{int} (μL/min/10^6 cells) hu / rat	n.d.	15.3 / < 2.7	5.0 / 47	n.d.

Further Investigation of [5,5]-Core Scaffold Revealed SAR Divergence

- Broadly, HIF-2α potency for acyclic pyrazole-N1 side chains track well
- In contrast, substituted cyclohexane substituents are only well-tolerated in [5,5]-core
  - Cyclohexane containing analog ‘1190 exhibited Low CL_{int} in human hepatocytes

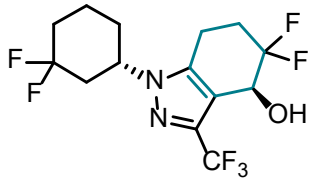


Compound 9

HIF-2α Luc IC_{50} = 12.9 nM_1

HIF-2α 100% Serum IC_{50} = 59 nM_1

Hep. CL_{int} (h / r; µL/min/10^6cells) = 63 / 184

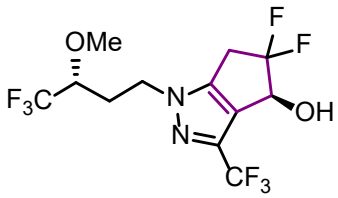


Compound 22

HIF-2α Luc IC_{50} = 6.5 $µM^1$

HIF-2α 100% Serum IC_{50} > 40.0 $µM^1$

Hep. CL_{int} (h / r; µL/min/10^6cells) = n.d.

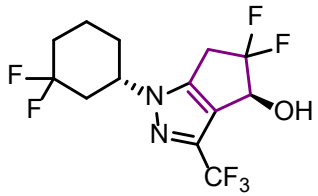


Compound 23

HIF-2α Luc IC_{50} = 19.9 nM_1

HIF-2α 100% Serum IC_{50} = 172 nM_1

Hep. CL_{int} (h / r; µL/min/10^6cells) = 98 / 227

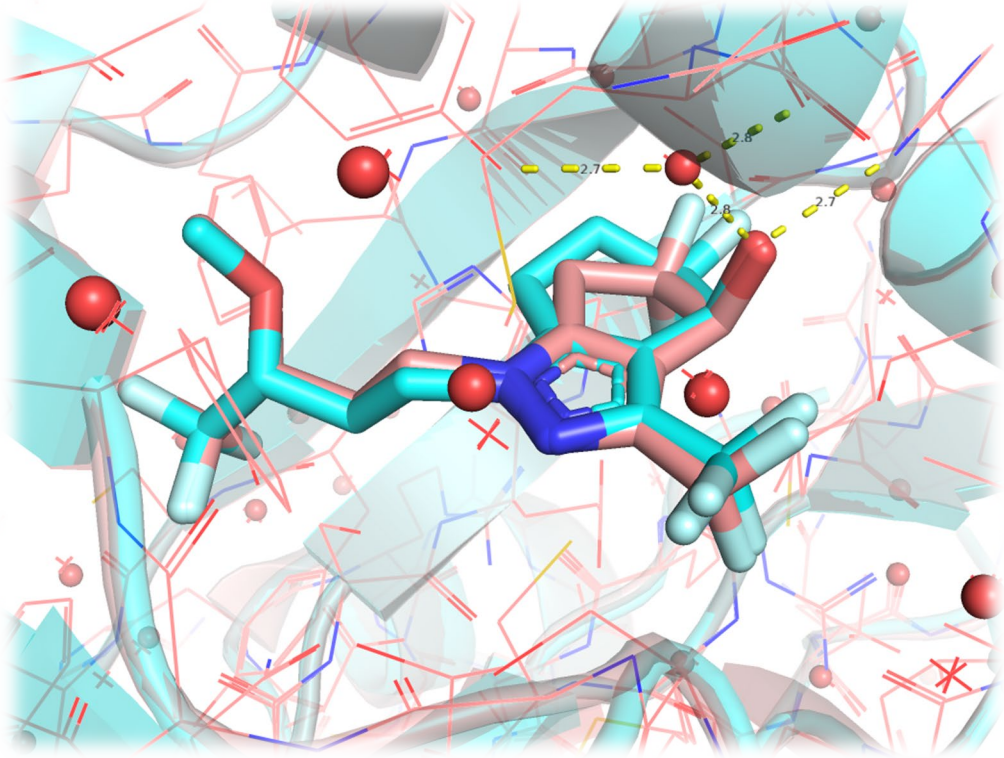


Compound 24

HIF-2α Luc IC_{50} = 35.3 nM_1

HIF-2α 100% Serum IC_{50} = 422 nM_1

Hep. CL_{int} (h / r; µL/min/10^6cells) = 6.3 / 23



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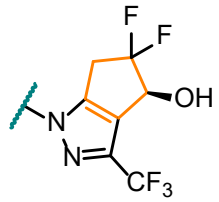
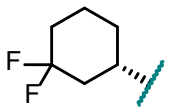
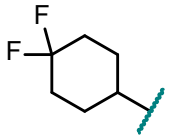
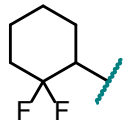
Further Optimization of B-Ring Cyclohexane Increased Potency and Improved Metabolic Stability in vitro

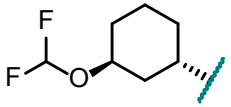
- Pharmacokinetic properties were highly variable, but broadly improved with increased polarity of cyclohexyl group
  - *Syn*-fluorine substitution proved optimal pathway to increase polarity without diminishing target potency

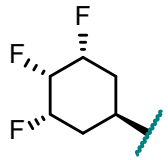


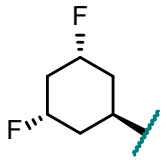


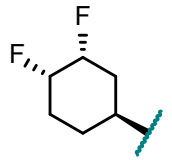












Compound ID	24	25	26	27	28	29	30
HIF-2α Cell-Based (nM)	41.3	86.6	3,530	92.4	60.4	206	39.2
HIF-2α Cell-Based 100% Serum IC_{50} (nM)	372	628	> 40,000	1,790	**336**	1,070	**154**
Hepatocyte CL_{int} (μL/min/10^6 cells) hu / rat	6.3 / 23	26 / 70	n.d.	38 / 42	**6.3** / 3.9	13 / 24	**5.0** / 13
cLogP	4.4	3.8	4.4	5.5	3.1	3.7	3.3

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- Pharmacokinetic properties were highly variable, but broadly improved with increased polarity of cyclohexyl group
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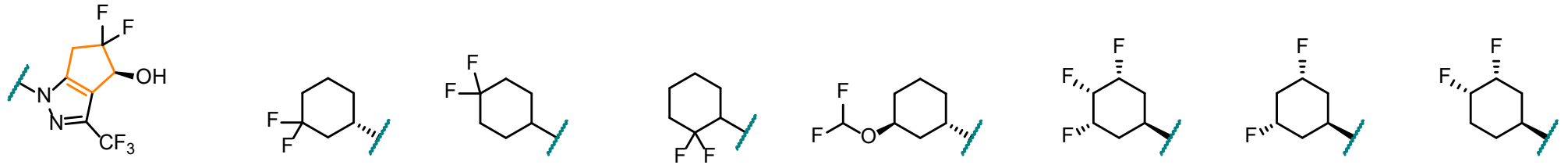

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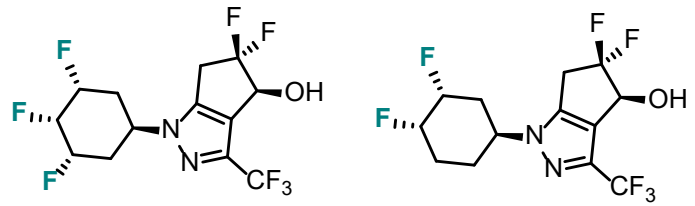
cLogP	4.4	3.8	4.4	5.5	3.1	3.7	3.3

Lead Inhibitors Exhibit Encouraging Potency and Pharmacokinetic Profile



Compound ID	28	30
HIF-2α Cell-Based (nM)	60.4	39.2
HIF-2α Cell-Based 100% Serum IC_{50} (nM)	336	154
Hepatocyte CL_{int} ($\mu L/min/10^6$ cells) hu / rat	6.3 / 3.9	5.0 / 13
CYP Inh. IC_{50} (μM) 2C8 / 2C9 / 2C19 / 2D6 / 3A4	>40 / >40 / >40 / >40 / >40	>40 / >40 / >40 / >40 / >40
CYP TDI (% Act. loss, 30 min) 2C8 / 2C9 / 2D6 / 3A4	0 / 0 / 0 / 3.7	0 / 0 / 0 / 0
MDCK-II-MDR1 P_{app} (A-B, cm/s•10-6)	30 (ER = 0.9)	33 (ER = 0.6)
Plasma Protein Binding (%Unbound, UC)	n.d.	23% / 21%
Rat PK Parameters: CL (L/h/kg) / %F	2.5 / 129%	5.2 / 67%

Progress towards target profile for 2nd-Gen Inhibitors

- **Favorable attributes of lead inhibitors**
  - ✓ *Target potency in HIF-2α serum assay*
  - ✓ *Low CL_{int} in human hepatocytes*
  - ✓ *Clean CYP inhibition profile*
  - ✓ *High permeability/predicted oral bioavailability*
- **Areas for continued optimization**
  - ○ *Poor correlation of systemic clearance in rodents with in vitro predictors*

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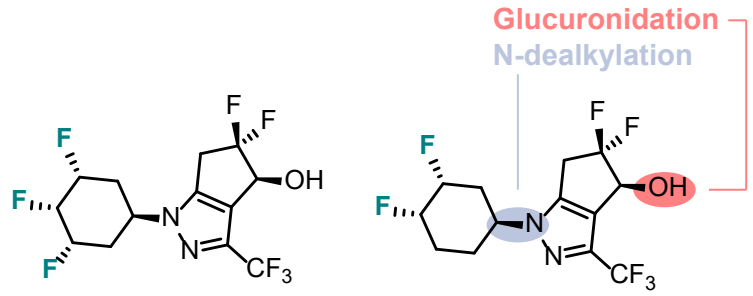
Metabolite ID Reveals O-Glucuronidation as Primary Metabolic Pathway



Compound ID	28	30
HIF-2α Cell-Based (nM)	60.4	39.2
HIF-2α Cell-Based 100% Serum IC_{50} (nM)	336	154
Hepatocyte CL_{int} ($\mu L/min/10^6$ cells) hu / rat	6.3 / 3.9	5.0 / 13
CYP Inh. IC_{50} (μM) 2C8 / 2C9 / 2C19 / 2D6 / 3A4	>40 / >40 / >40 / >40 / >40	>40 / >40 / >40 / >40 / >40
CYP TDI (% Act. loss, 30 min) 2C8 / 2C9 / 2D6 / 3A4	0 / 0 / 0 / 3.7	0 / 0 / 0 / 0
MDCK-II-MDR1 P_{app} (A-B, cm/s•10-6)	30 (ER = 0.9)	33 (ER = 0.6)
Plasma Protein Binding (%Unbound, UC)	n.d.	23% / 21%
Rat PK Parameters: CL (L/h/kg) / %F	2.5 / 129%	5.2 / 67%

Progress towards target profile for 2nd-Gen Inhibitors

- **Favorable attributes of lead inhibitors**
  - ✓ *Target potency in HIF-2α serum assay*
  - ✓ *Low CL_{int} in human hepatocytes*
  - ✓ *Clean CYP inhibition profile*
  - ✓ *High permeability/predicted oral bioavailability*
- **Areas for continued optimization**
  - ○ *Poor correlation of systemic clearance in rodents with in vitro predictors*
  - ○ *Metabolite ID identified unfavorable metabolic pathway*

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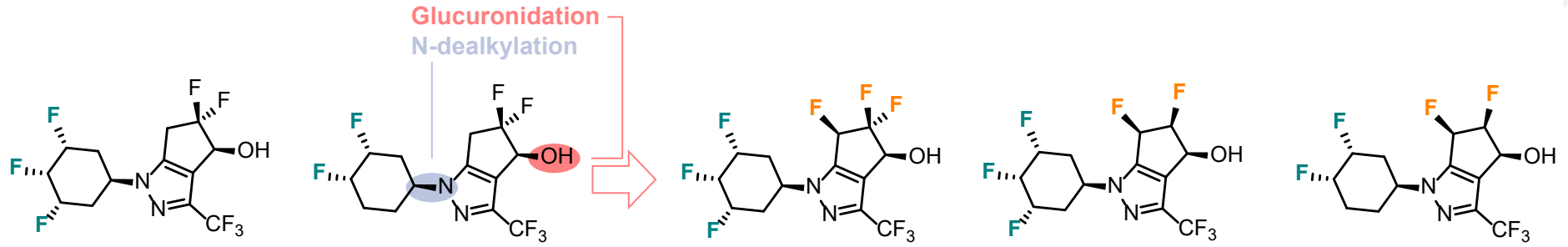
Tuning Cyclopentapyrazole Fluorine Pattern Reduces Clearance and Minimizes O-Glucuronidation



Compound ID	28	30	31	32	33
HIF-2α Cell-Based (nM)	60.4	39.2	14.0	104	52.0
HIF-2α Cell-Based 100% Serum IC_{50} (nM)	336	154	62.4	269	190
Hepatocyte CL_{int} ($\mu L/min/10^6$ cells) hu / rat	6.3 / 3.9	5.0 / 13	8.7 / 21	<2.7 / <2.7	< 2.7 / 3.3
CYP Inh. IC_{50} (μM) 2C8 / 2C9 / 2C19 / 2D6 / 3A4	>40 / >40 / >40 / >40 / >40	>40 / >40 / >40 / >40 / >40	>40 / >40 / >40 / >40 / >40	>40 / >40 / 25 / >40 / >40	>40 / >40 / >40 / >40 / >40
CYP TDI (% Act. loss, 30 min) 2C8 / 2C9 / 2D6 / 3A4	0 / 0 / 0 / 3.7	0 / 0 / 0 / 0	0 / 0 / 0 / 0.1	2.5 / 0 / 0.5 / 0	0 / 0 / 0 / 0
MDCK-II-MDR1 P_{app} (A-B, cm/s•10-6)	30 (ER = 0.9)	33 (ER = 0.6)	-	29 (ER = 1.0)	31 (ER = 0.8)
Plasma Protein Binding (%Unbound, UC)	n.d.	23% / 21%	-	48% / 47%	47% / 60%
Rat PK Parameters: CL (L/h/kg) / %F	2.5 / 129%	5.2 / 67%	-	2.8 / 149%	1.3 / 35%

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Compound 33 is Projected to have a Pharmacokinetic Profile Suitable for QD Dosing

- **Compound 33** is stable to human hepatocytes and intestinal microsomes, and it exhibits low efflux potential (Caco-2)

Species	*Hepatocytes*			*In vivo*		
	CL_{int} (µL/min/10^6 cells)	$T_{1/2}$ (h)	$f_{u,p}$	CL (L/h/kg)	Vss (L/kg)	$T_{1/2}$ (h)
Mouse	33.5	10.8	0.443	2.13	1.59	1.56
Rat	3.20	10.3	0.597	1.25	3.1	2.71
Dog	540	>40	0.576	0.740	0.98	1.55
Human	1.00	>40	0.465	0.064[a] *projected*	1.12 *projected*	12 *projected*

Table: Summary of experimental PK parameters in mouse, rat, and dog. Rats were dosed 0.5 mg/kg IV in DMAC:EtOH:polyethylene glycol (31.6:36.8:31.6). Mice were dosed 1 mg/kg IV in DMAC:Ethanol:Propylene Glycol:Saline (10:10:30:50). Dogs were dosed 1.0 mg/kg IV in DMA/PG/water (1:1:1).

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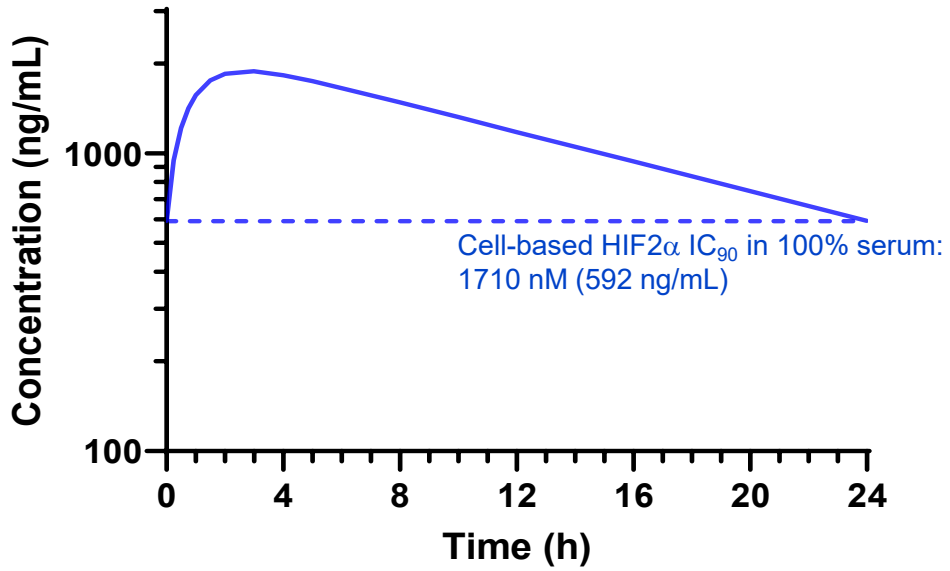
Compound 33 is Projected to have a Pharmacokinetic Profile Suitable for QD Dosing

Predicted steady state human PK profile of Compound 33



Predicted Human PK Parameters	
CL (L/h/kg)	0.064
V_{ss} (L/h)	1.12
$T_{1/2}$ (h)	12
Potency and Exposure Target of 33	
HIF-2α 100% human serum IC_{50} (nM)	190
HIF-2α 100% human serum IC_{90} (nM)	1710

- **Compound 33 is predicted to possess excellent oral bioavailability and limited potential for DDI in humans**

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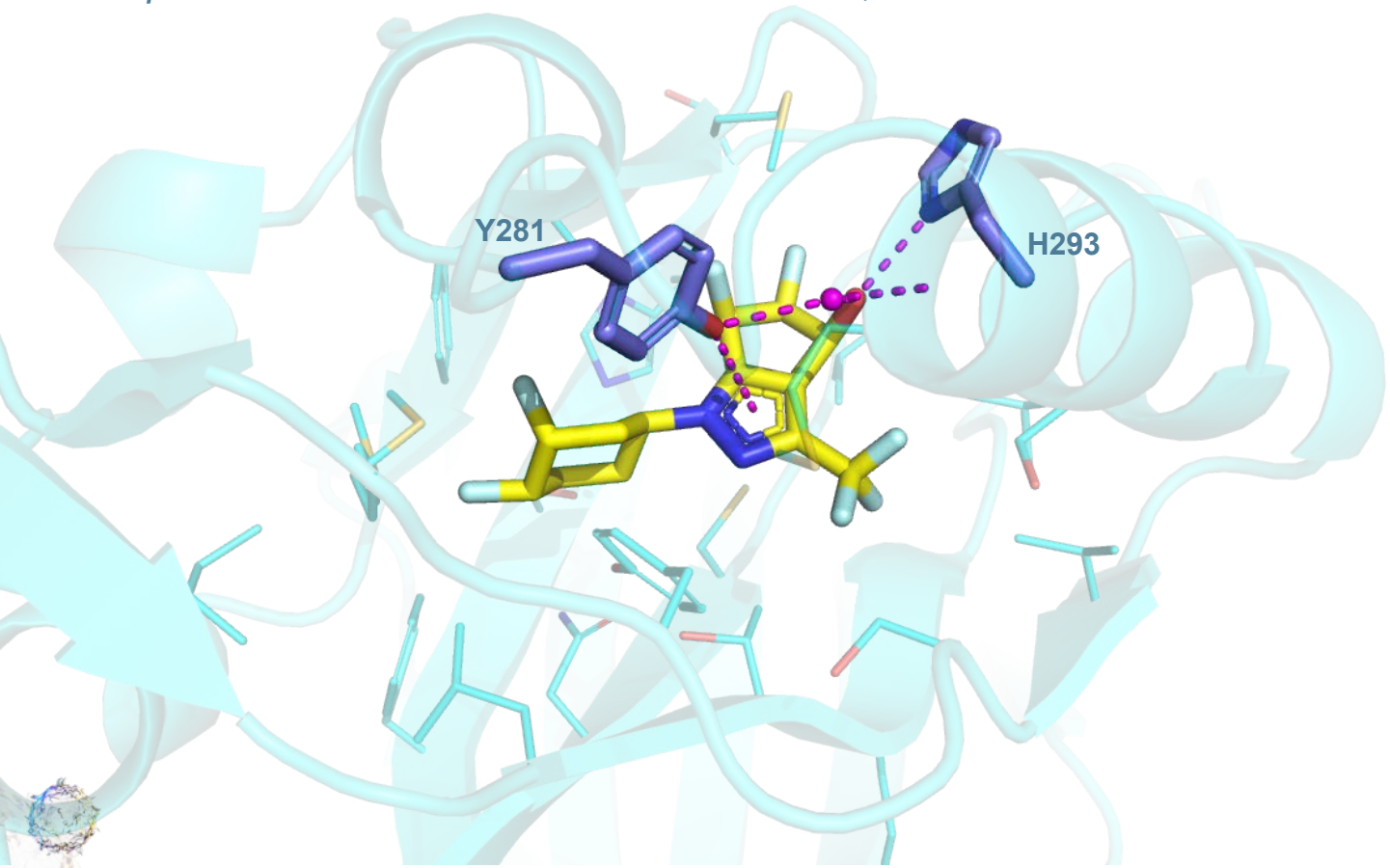
Compound 33 is Projected to have a Pharmacokinetic Profile Suitable for QD Dosing

*Compound **33** bound to HIF-2α/ARNT dimer, 1.9Å resolution*



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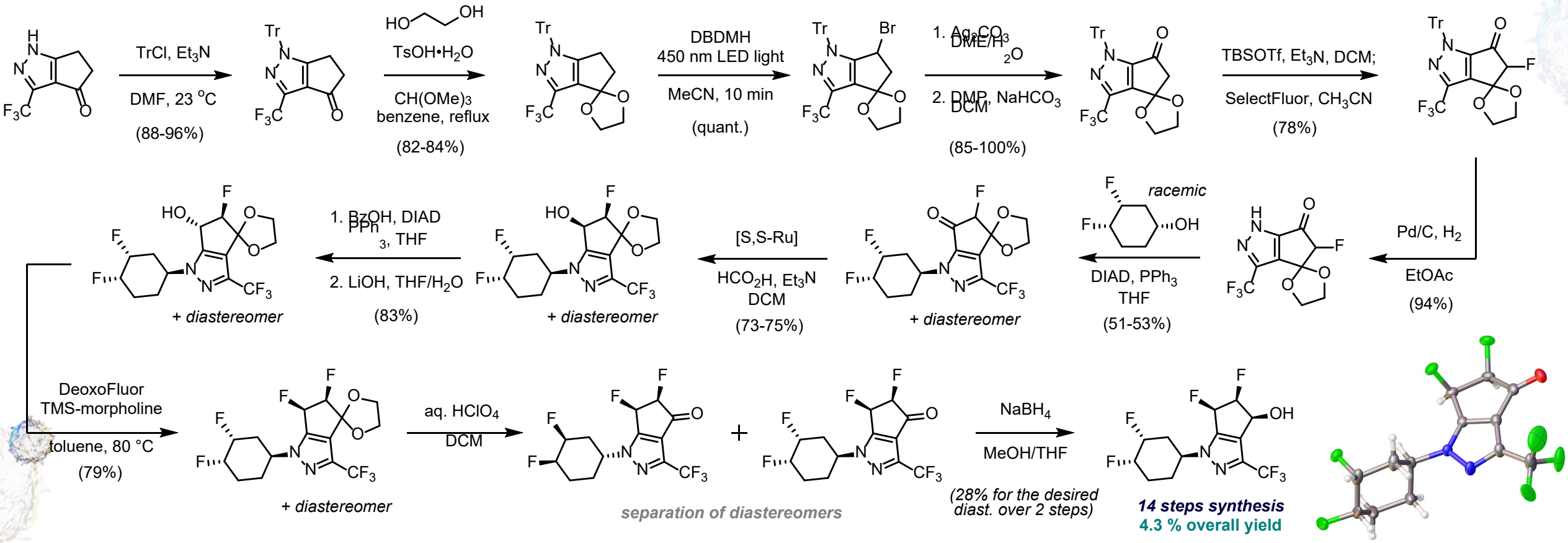
Compound 33 is Synthesized in high Stereochemical Purity following 14-steps which Install six Stereocenters

- With minimal optimization the current synthetic route enabled the preparation of gram quantities of **33** to support preclinical characterization



Arcus Inhibitors Potently Inhibit HIF-2α Function under Physiologically Relevant Conditions

Characterization of 33 , AB521, and select competitor molecules in clinical development

	Assay	Compound 33	AB521	Belzutifan	Compound A[a] (Novartis)
Potency	HIF-2α Cell-Based IC_{50} (nM)	52.0 ± 1.2 (n = 2)	8.21 ± 2.48 (n = 24)	16.9 ± 10.1 (n = 8)	18.9 ± 8.7 (n = 9)
	Cell-Based Reporter Control (nM)	> 10,000	> 10,000	> 10,000	> 10,000
	HIF-2α Cell-Based 100% Serum IC_{50} (nM)	190 ± 54 (n = 2)	46.49 ± 14.2 (n = 24)	61.78 ± 6.58 (n = 4)	265 ± 73 (n = 9)
DMPK	Rat PK Parameters: CL (L/h/kg) / %F	1.25 / 35%	0.909 / 51%	1.14 / -	0.08 / 80%
	Hepatocyte CL_{int} (μL/min/10^6 cells) human / rat	<2.7 / 3.3	<2.7 / <2.7	<2.7 / 22.0	<2.7 / 3.2
	CYP TDI (% Activity loss, 30 min) 2C8 / 2C9 / 2D6 / 3A4	0.0 / 0.0 / 0.0 / 0.0	7.9 / 2.9 / 1.3 / 9.4	0.0 / 0.0 / 4.1 / 2.7	0.0 / 0.0 / 0.0 / 0.0
	CYP Inh. IC_{50} (μM) 2C8 / 2C9 / 2C19 / 2D6 / 3A4	>40 / >40 / >40 / >40 / >40	>40 / 37.0 / 30.4 / >40 / >40	>40 / >40 / 23.7 / >40 / >40	19.6 / 38.6 / 4.03 / 2.17 / >40

[a]Prepared according to WO2021220170, compound A.

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Compound 33 is a Potent and Selective Inhibitor of HIF-2α

- Hypoxia inducible factors (HIFs) are responsible for driving transcriptional changes upon exposure to low oxygen (Hypoxia)
- Iterative interrogation of structure activity relationship trends and structure-based design culminated in the discovery of potent and selective backup HIF-2α inhibitors
  - Structurally distinct from AB521 and competitor molecules
- Compound **33** potently binds the HIF-2α PAS-B domain and inhibits HIF-2α function in vitro
- Compound **33** is predicted to possess excellent oral bioavailability and low DDI potential in humans


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