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Leader in Targeted Protein Modulation

The Evolving Chemical Space of Bifunctional Degraders Targeting the CNS

NX-5948 Case Study for Beyond-Rule-of-Five (bRo5) Drugs

Wylie Palmer

Executive Director, Medicinal Chemistry

Discovery on Target

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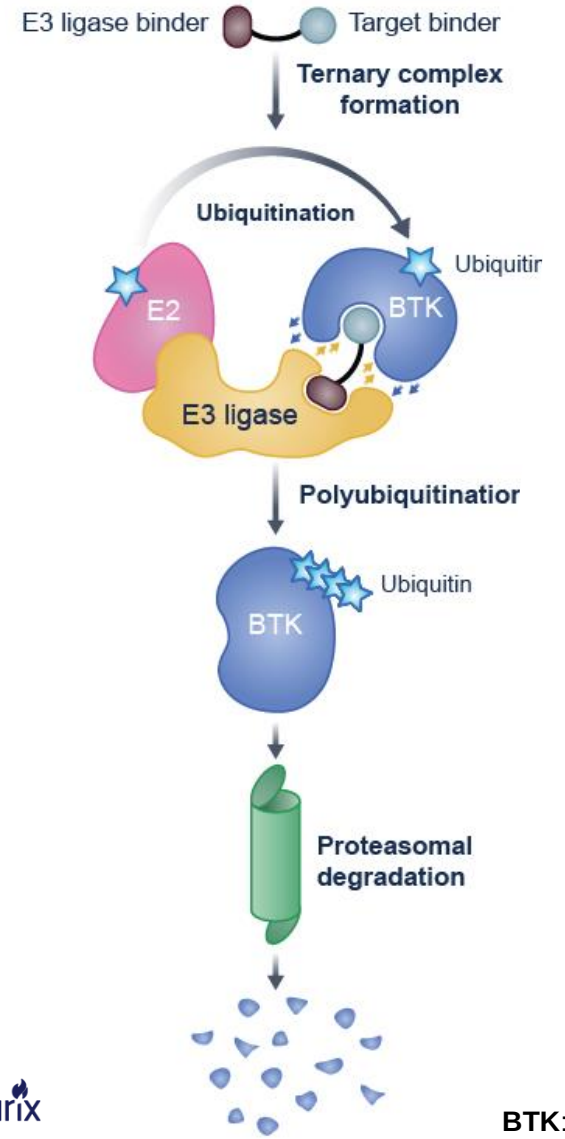
Why Do We Need BTK Degraders?



BTK degraders can overcome treatment-emergent resistance mutations

BTK degraders address BTK scaffolding function

BTK degraders show emerging activity in various B-cell malignancies

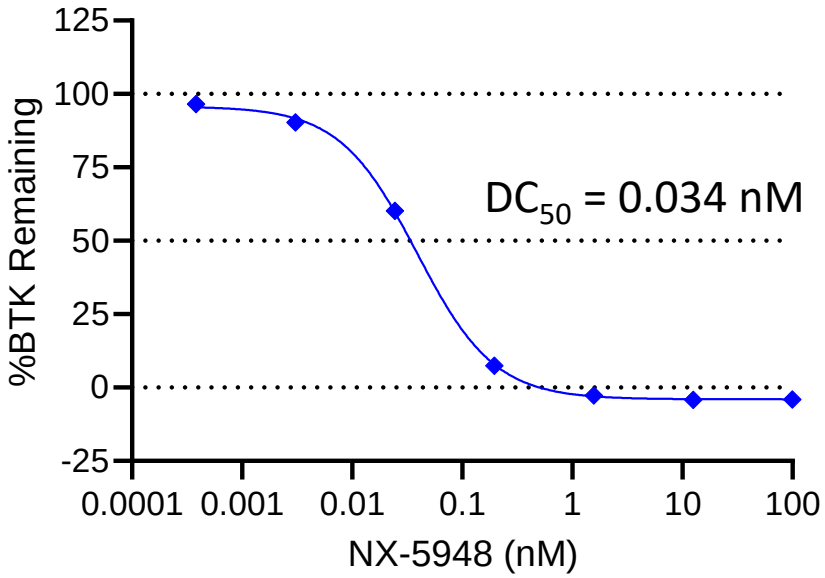
BTK degraders have the potential to replace BTK inhibitors in the clinic

BTK: Bruton's tyrosine kinase

BTK Degrader NX-5948 for the Treatment of B cell Malignancies

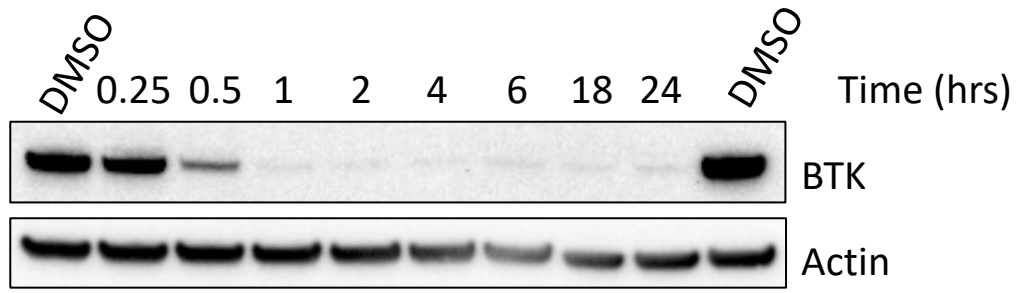
Optimized for Cellular Potency and Oral Bioavailability

Primary Human B cells



N=3 independent donors
4 hour treatment
SEM error bars are smaller than symbols

Ramos Cells (Human Burkitt Lymphoma)

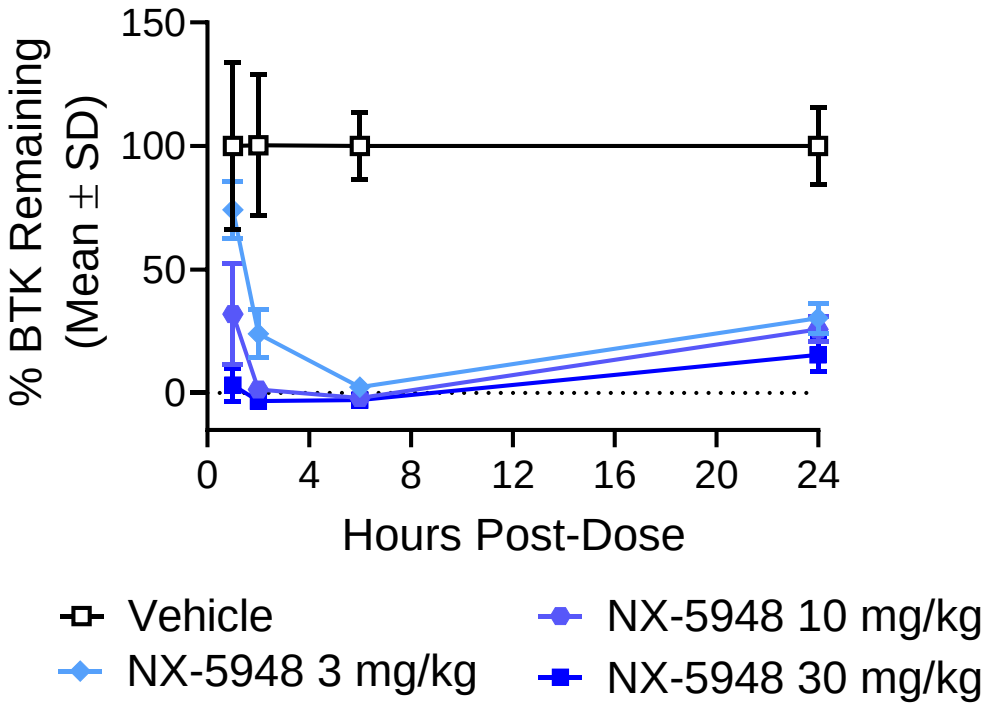


10 nM NX-5948

BTK Degrader NX-5948 for the Treatment of B cell Malignancies
Optimized for Cellular Potency and Oral Bioavailability

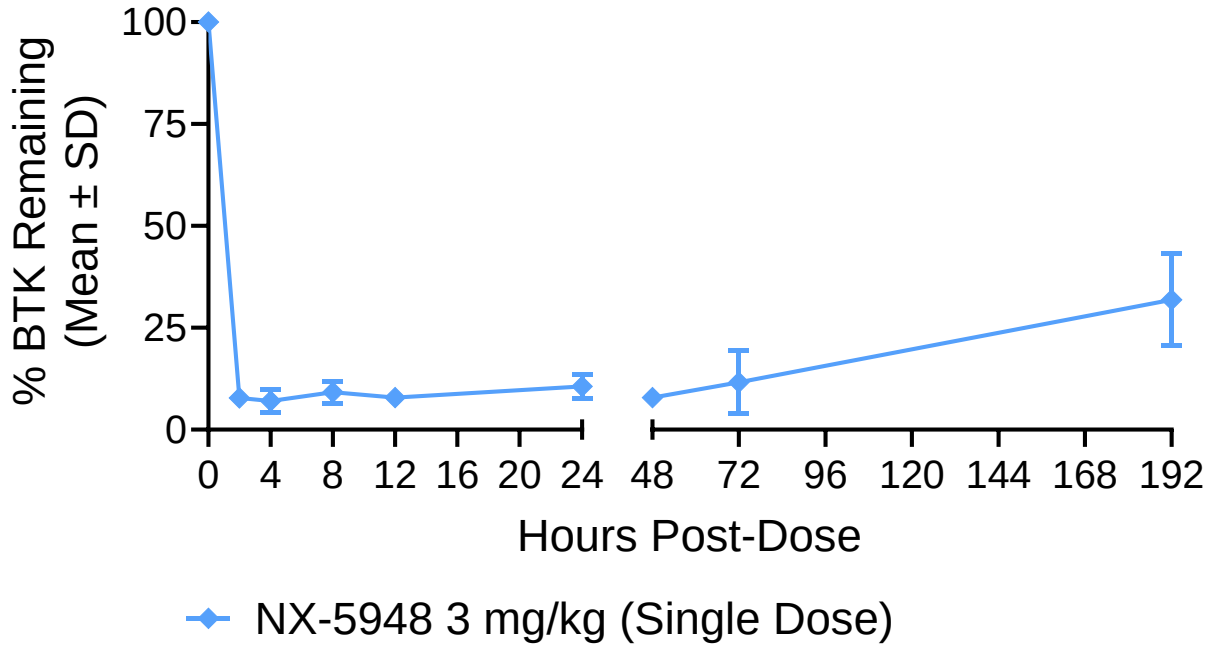
- A Single Oral Dose of NX-5948 Promotes Rapid and Complete BTK Degradation in Mouse and NHP B cells

BTK Levels in Mouse Circulating B Cells



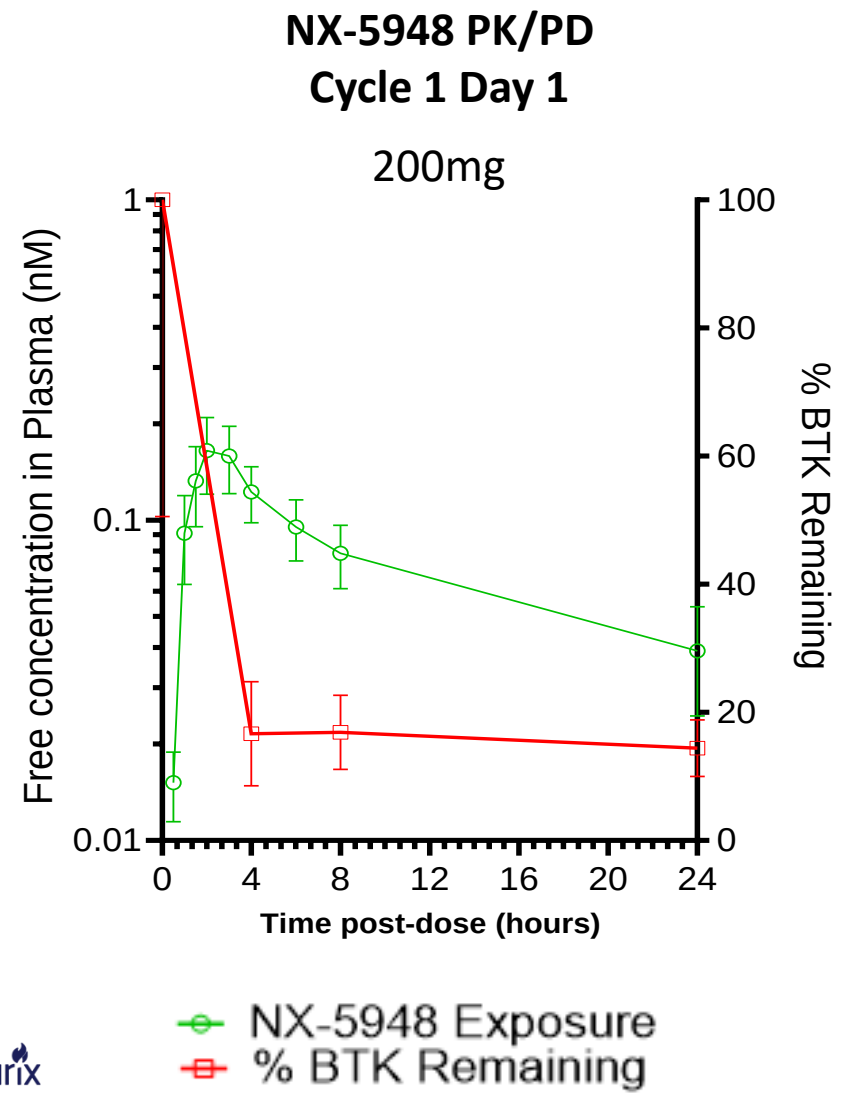
In mice, BTK levels increased 24 hours after single dose

BTK Levels in NHP Circulating B Cells



In cynomolgus monkeys, BTK levels remained suppressed at 48 hours and returned to 32% of baseline after 8 days

Clinically Active Doses of NX-5948 Show Lower Unbound Drug Exposure Than Covalent and Noncovalent BTK Inhibitors



NX-5948 requires lower exposure than BTK inhibitors for clinical responses

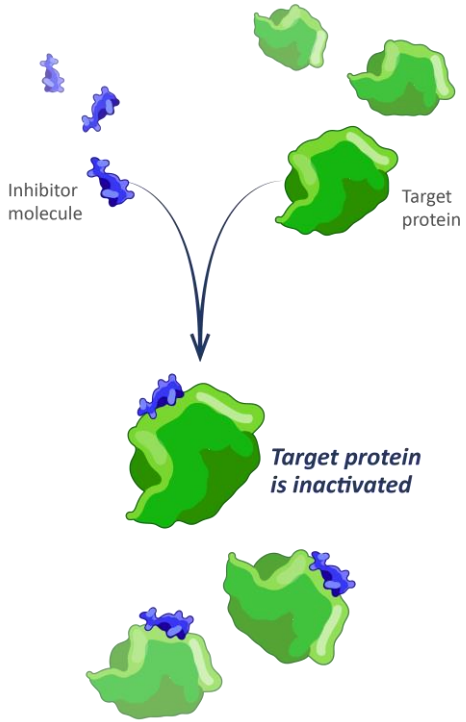
	Ibrutinib (560mg QD)[1]	Zanubrutinib (160mg BID)[1]	Pirtobrutinib (200mg QD)[1]	NX-5948 (200mg QD)
$Cmax_{free}$ (nM)	8.0	40	540	0.09
$Cmin_{free}$ (nM)	0.2	3.5	250	0.03

[1]clinically approved doses

Degraders Are PK Advantaged Due to Their Catalytic Mechanism of Action

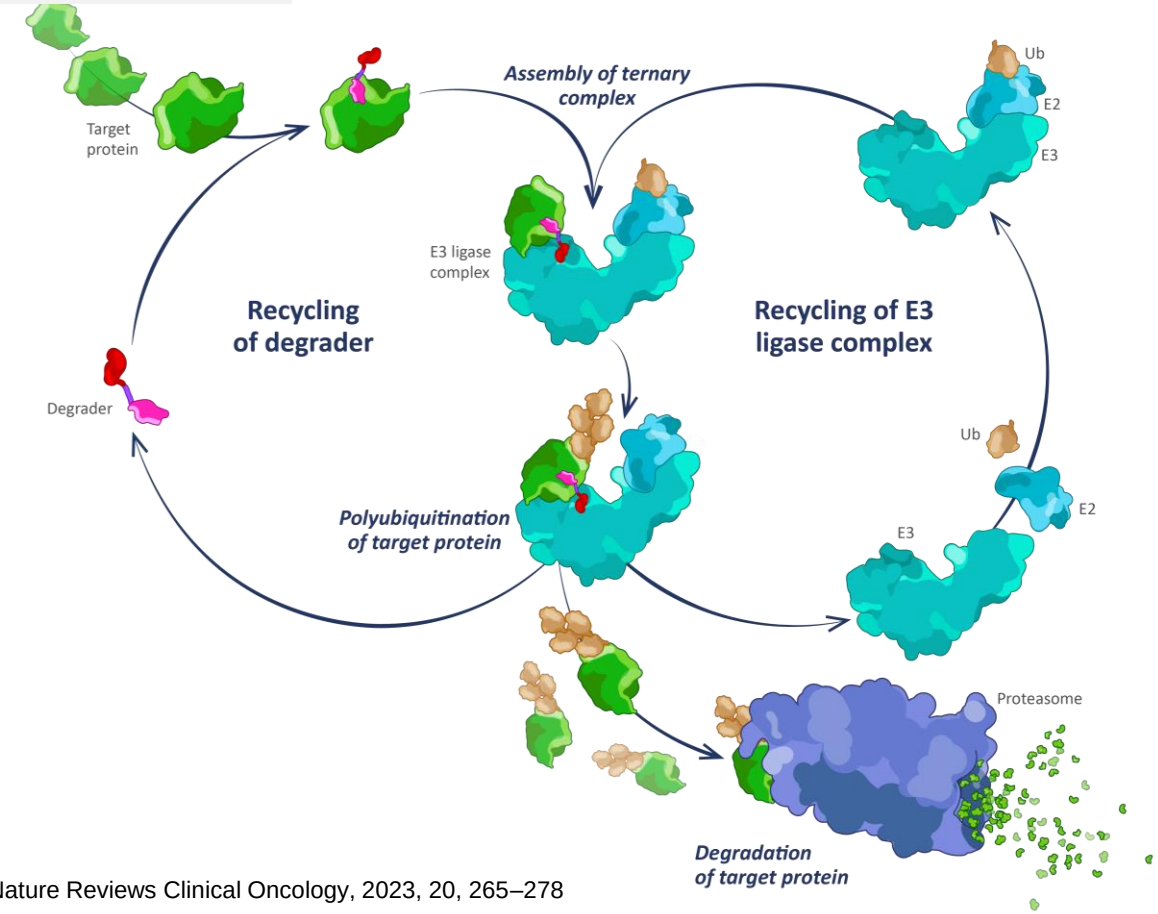
ONE inhibitor molecule inhibits ONE target protein

High levels of drug needed to maintain complete target coverage



ONE degrader molecule promotes degradation of MULTIPLE target proteins

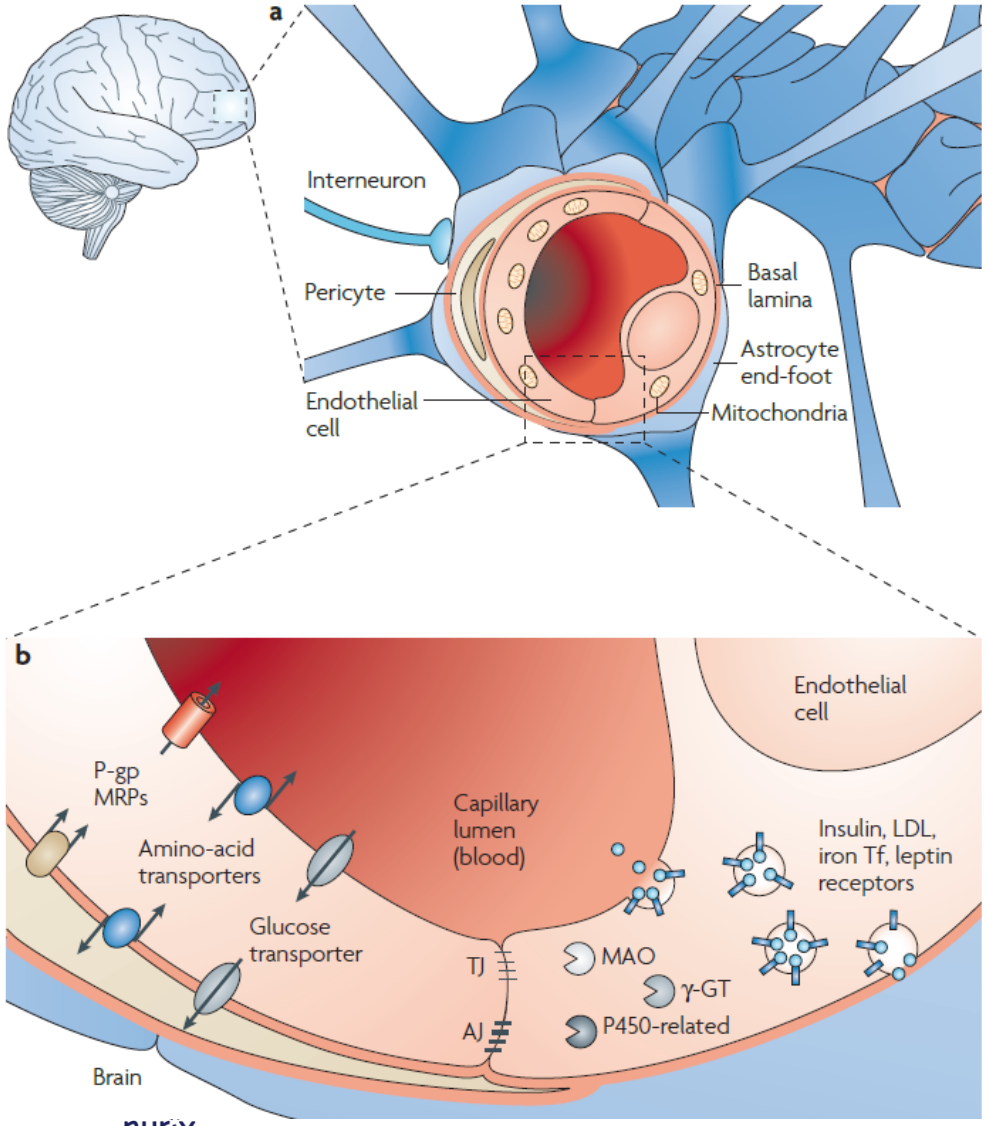
Lower levels of drug needed to achieve complete target removal



References

1. Chirnomas et al. Protein degraders enter the clinic — a new approach to cancer therapy. Nature Reviews Clinical Oncology, 2023, 20, 265–278

Designing Compounds With Optimal CNS Exposure:
For *small molecule* drugs, established metrics can aid in CNS-penetrant designs



(Cecchelli, et al., *Nat Rev Drug Dev*, 2007)

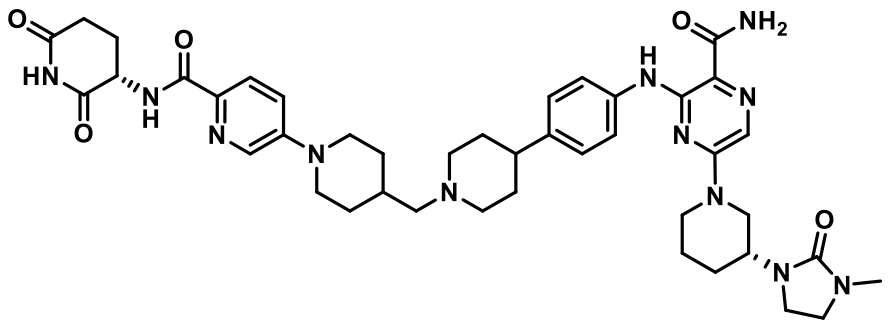
- The Blood Brain Barrier (BBB) is a selective barrier that protects the brain from harmful compounds and precisely regulates its microenvironment
- The CNS multiparameter optimization score (MPO score) defines chemical properties that are optimal for CNS therapeutic agents
- Metrics for CNS penetration are more restrictive than the Rule-of-Five for oral bioavailability
- Determining the parameters and characteristics that predict CNS exposure of degraders are of high interest

Property	BBB Penetration CNS MPO*	Oral Bioavailability Small Molecule Rule-of-5
MW	≤ 360	≤ 500
HBD	as low as possible (ideally 0)	≤ 5
ClogP	≤ 3	≤ 5
TPSA	40 to 90	≤ 140

*CNS MPO criteria for highest score of 1 (Wager, et al., *ACS Chem Neuro*, 2016)

Established Metrics for Predicting CNS Penetration Suggest NX-5948 Unlikely To Achieve CNS Exposure

NX-5948

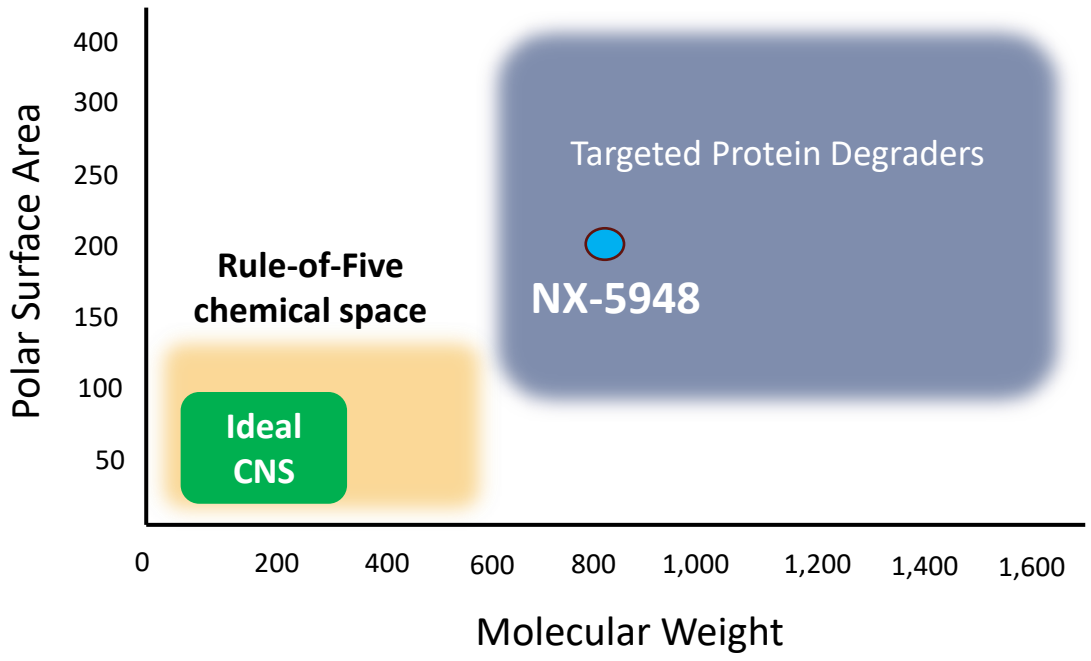


77% of marketed CNS drugs have an MPO score ≥ 4.0

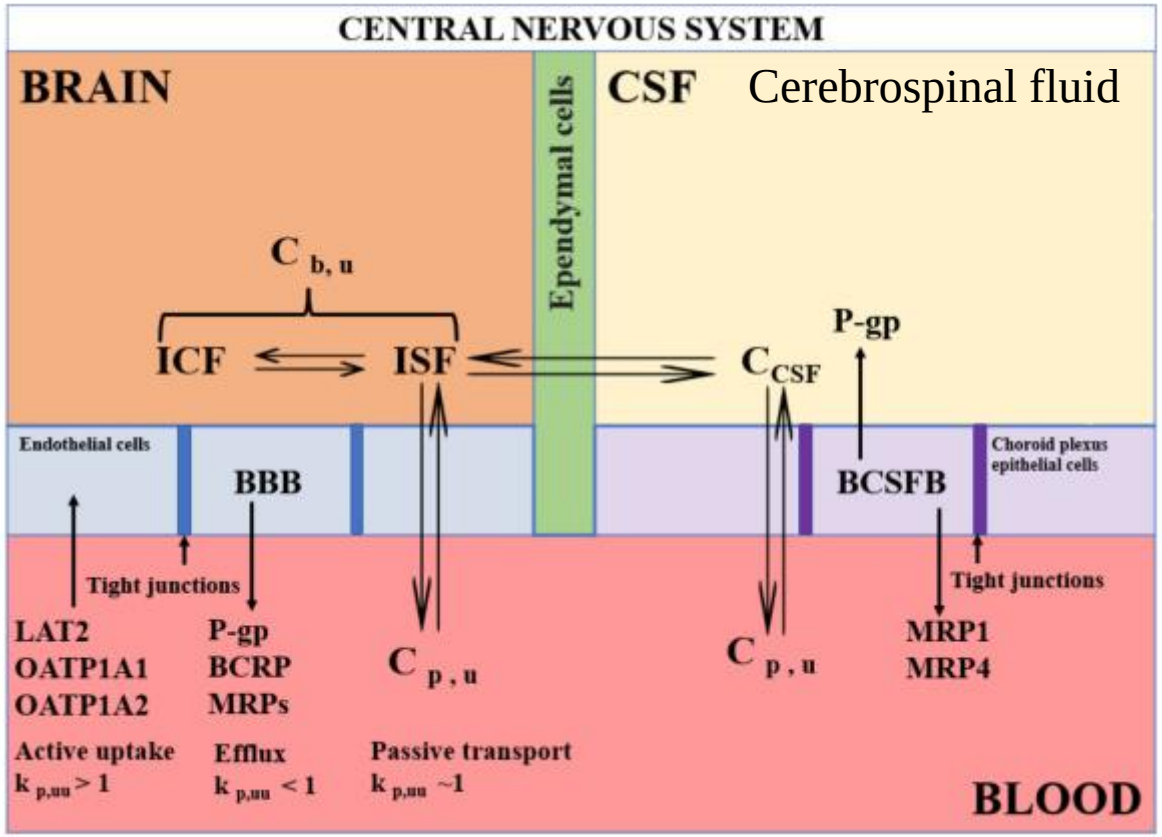
Property	More Desirable	Less Desirable	NX-5948 Property value	NX-5948 MPO score*
ClogP	≤ 3	> 5	3.6	0.7
ClogD	≤ 2	> 4	0.9	1.0
MW	≤ 360	> 500	807	0
TPSA	40 to 90	≤ 20, > 120	202	0
HBD	≤ 1	> 4	5	0
pKa	≤ 8	> 10	9.1 (measured)	0.45
			Total MPO score =	**2.2**

*Each property assigned a score from 0.0 to 1.0 and summed. 77% of marketed CNS drugs had an MPO score ≥ 4.0 (Wager, et al., *ACS Chem Neuro*, 2016)

Beyond Rule-of-Five chemical space



CNS Penetration Involves Both the BBB as Well as the Blood Cerebrospinal Fluid Barrier (BCSFB)

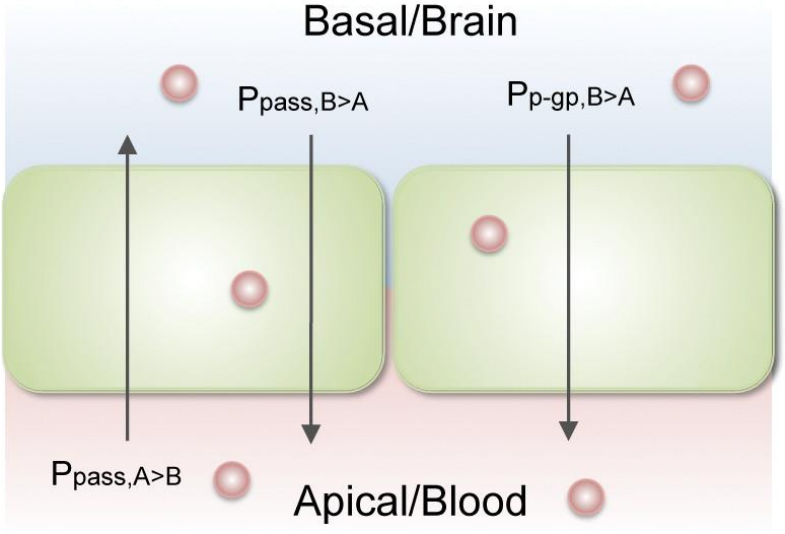


Adapted from Agarwal, P., et. al., *J. Controlled Release.* 372, 661−673.

- Drugs can cross the BBB by diffusion or active transport
- The BBB and BCSFB barriers have different transporters expressed and as such direct access can be more (or less) restrictive for one barrier over the other
- The free drug-concentration in brain drives efficacy and at steady-state is equal on both sides of a membrane
- Unbound brain-to-plasma ratio:

  $Kp,uu = [brain]_u/[plasma]_u$

MDCK-MDR1 Permeability Assay Indicates NX-5948 Has Moderate Passive Permeability but Has Potential To Be a Substrate for Major Efflux Transporters



ACS Chem. Neurosci. 2013, 4, 2, 361–367

Permeability Results in MDCK-MDR1 Cell Line

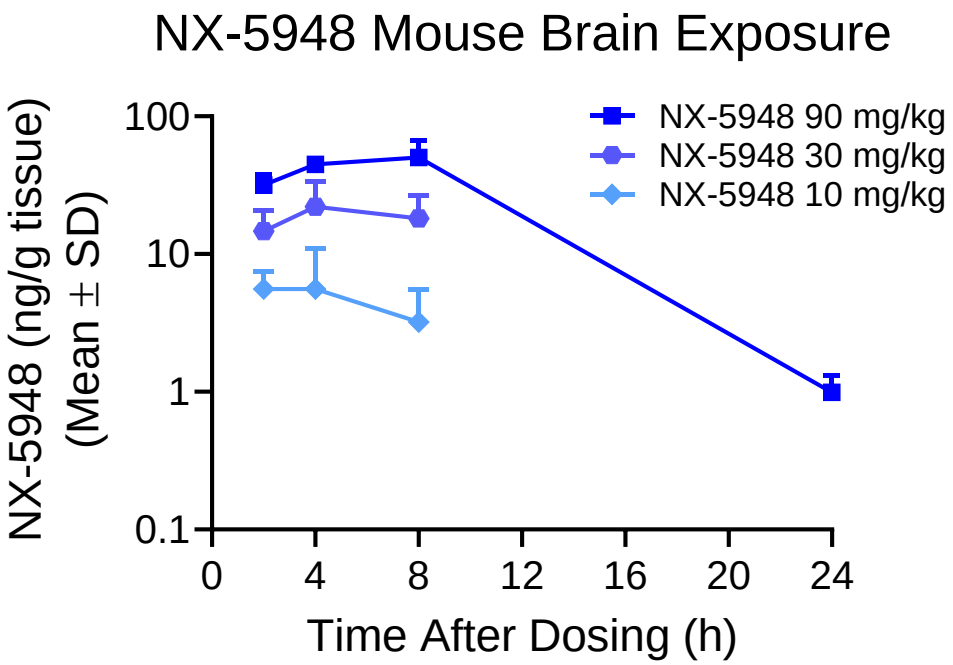
Compound (3 μM)[1]	**P_{app}, A-B** (10^{-6} cm/s)	**P_{app}, B-A** (10^{-6} cm/s)	**Efflux Ratio** (B-A/A-B)	**A-B Permeability Ranking[2]**
NX-5948	0.47	19	40	Low
NX-5948 + 100 μM Verapamil	3.8	5.5	1.4	Medium
Controls:				
Metoprolol	31	31	1	High
Imatinib	1.8	47	27	Medium

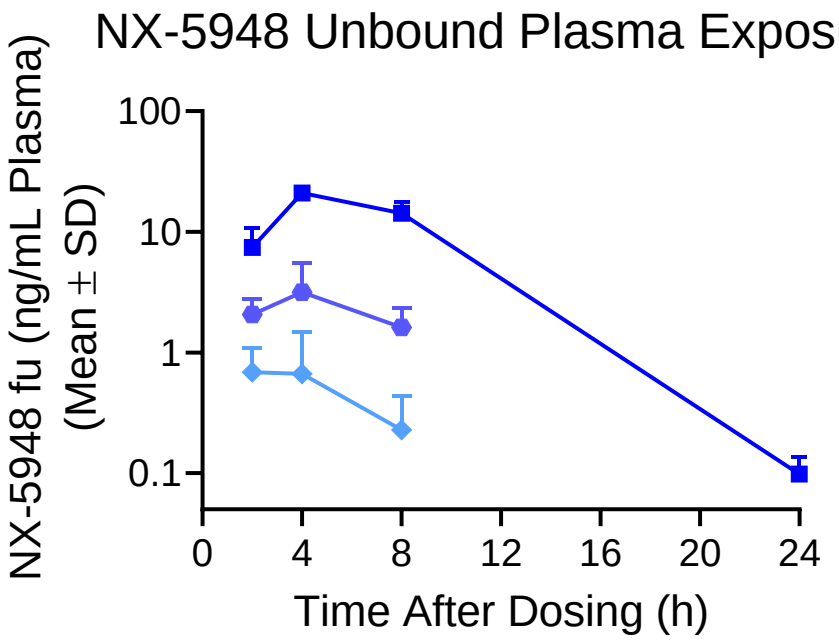
[1]NX-5948 aqueous solubility in PBS at pH 7.4 = 9.7 μM; conditions with NX-5948 include 3% BSA.
[2]Permeability ranking P_{app}(10^{-6} cm/s): Low < 1, high > 10

- Based on an analysis of drugs with CNS and non-CNS indications, compounds with passive permeability >1.5 10^{-6} cm/s and efflux ratio <2.5 were most likely to be CNS penetrant[3]
- NX-5948 has an efflux ratio of 40 in MDCK-MDR1 cells indicating the compound is a potential substrate for major active transporters like P-gp
- Reliable permeability measurements are typically a challenge for degraders compared to small molecules. NX-5948, however, was well behaved with solubility exceeding the test concentration and acceptable recoveries for each condition

[3]Doan, et. al., *J. Pharmacol. Exp. Ther.* 303, 1029–1037.

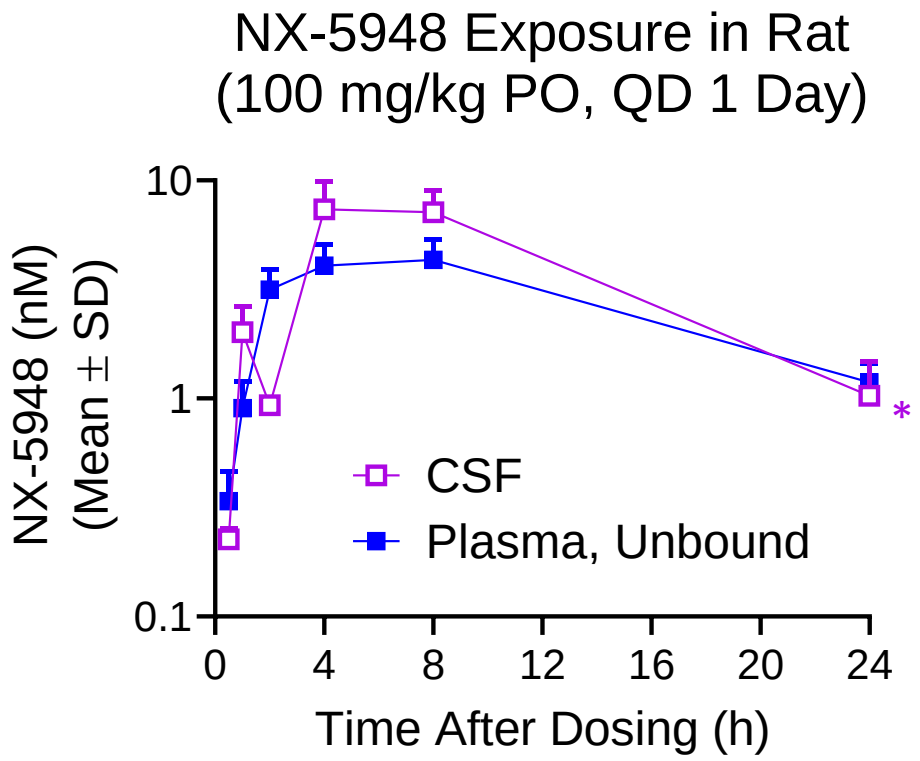
Preclinically, a Single Oral Dose of NX-5948 in Mice Results in Dose-Dependent Brain Exposure



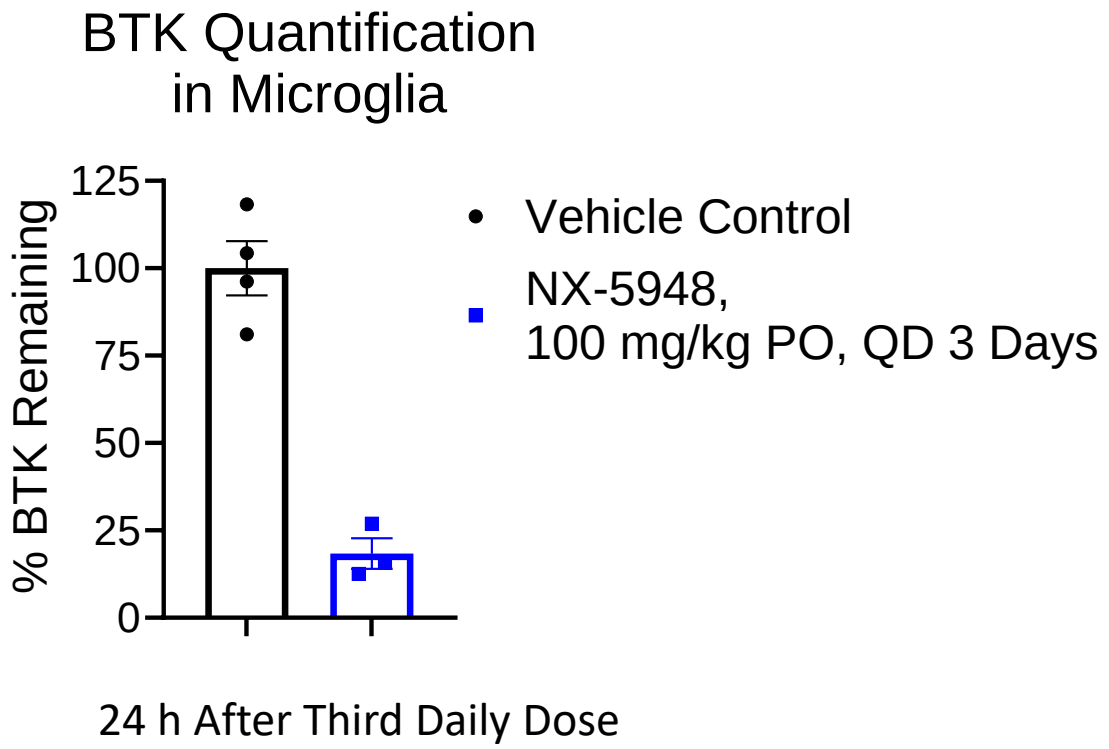


Mouse plasma protein binding = 99.6%

A More Detailed Rat Study Shows Oral Dosing of NX-5948 Gives Similar CSF and Unbound Plasma Exposures Resulting in BTK Degradation in Microglia



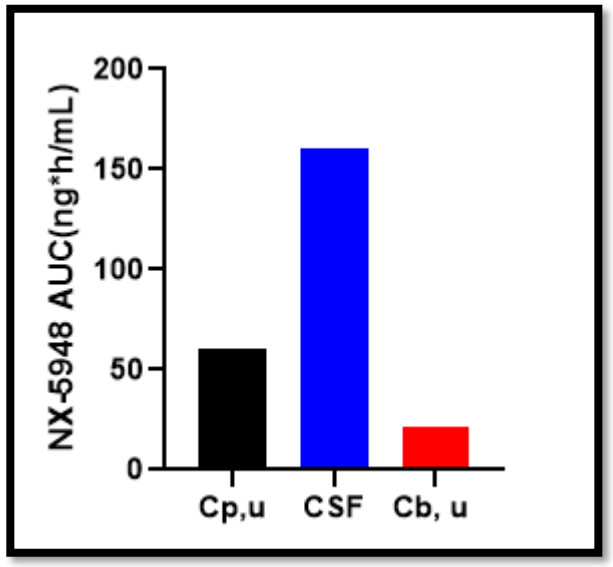
Rat plasma protein binding = 98.4%



*One of three CSF samples collected at 24 h was excluded as an outlier based on criteria defined by Motulsky et al., Detecting outliers when fitting data with nonlinear regression – a new method based on robust nonlinear regression and the false discovery rate. BMC Bioinformatics 7, 123 (2006).

Daily Oral Dosing of NX-5948 in Rat Study Demonstrates That NX-5948 Achieves Free Drug Levels in the Brain Consistent With Expectations for CNS-Penetrant Drugs

NX-5948 Unbound Exposures in Rat on Day 7 (Plasma, CSF, Brain)



NX-5948 Exposure in Rat (Day 7, 100 mg/kg, QD dosing)

PK Parameters	Plasma	Brain	CSF
C_{min} (ng/mL)	153	98	2.21
$AUC_{0\text{-}24\ Total}$ (ng*h/mL)	11,153	3,228	160
$AUC_{0\text{-}24\ Unbound}$ (ng*h/mL)	60	21	160
$K_{p,uu}$ ($C_{b,u}$ or CSF/$C_{p,u}$)	-	**0.35**	**2.7**

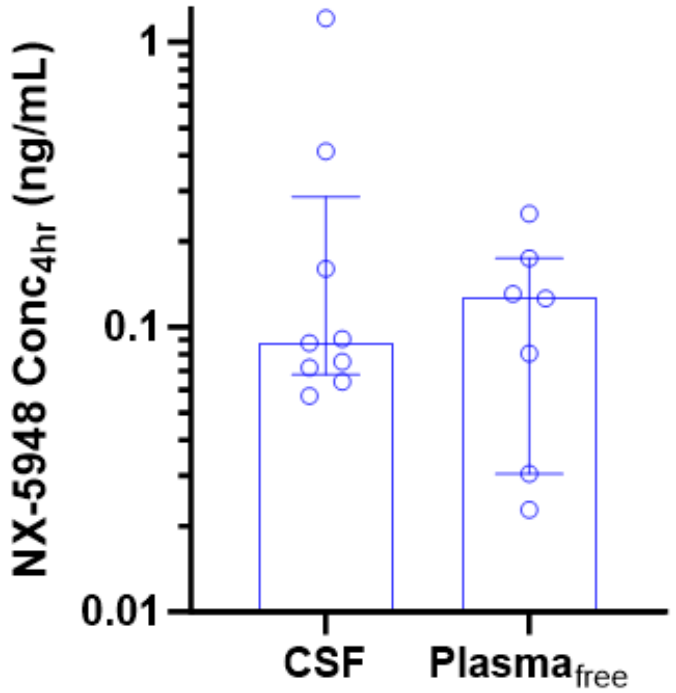
Oral bioavailability in this study, *F* = 17%

- CSF levels are 2.7-fold higher than unbound plasma levels on day 7
- Compounds with brain Kp,uu > 0.30 are considered brain penetrant*

*Kalvass, JC et al., *Drug Metab Dispos.* 2007, 25 (4) 660-666.

Detectable Levels of NX-5948 in CSF of Patients With CNS Involvement

- 9 patients with available PK data had detectable levels of NX-5948 in CSF
- CSF exposure correlates with free plasma exposure
- CSF exposure is above the C_{min} free value = 0.024 ng/mL (0.03 nM) in plasma observed for BTK clinical PD
- Clinical activity observed in both primary central nervous system lymphoma (PCNSL) and chronic lymphocytic leukemia (CLL) with CNS involvement, despite multiple prior lines of treatment including BTKi[1,2]



LLOQ: 0.01ng/mL (CSF); 0.1ng/mL (total plasma)
Note: 9 patients with CSF PK measured and 7 (of 9) have plasma PK values measured

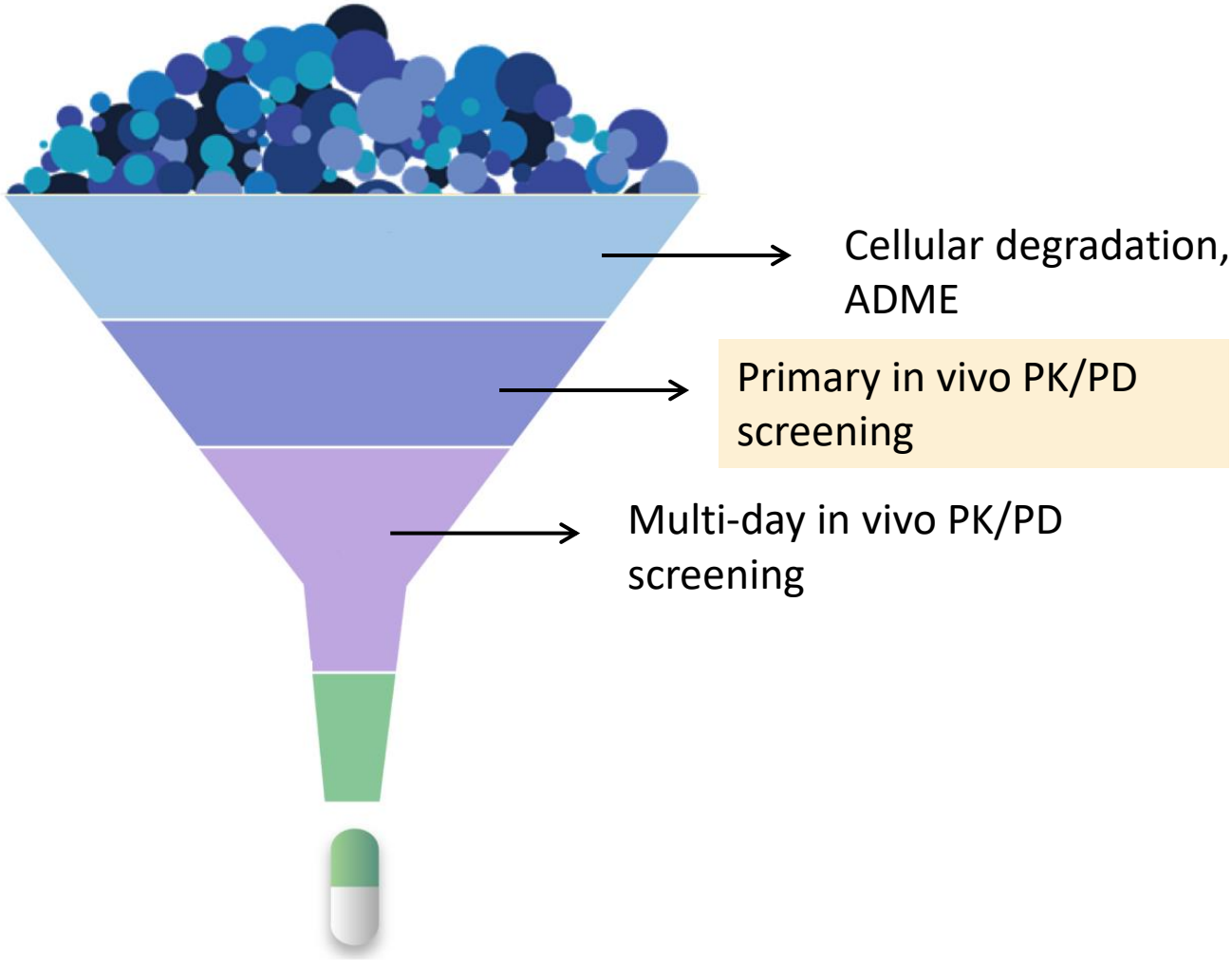
[1]Hansen GM. Oral presentation at AACR Annual Meeting 2024, San Diego, CA. April 9, 2024
[2]Linto K. Oral presentation at EHA Hybrid Congress, Madrid, Spain. June 16, 2024

Can We Identify Additional CNS-Penetrant Degraders?

>12,000 Nurix degraders synthesized between 2022-2023 plotted by MW vs PSA

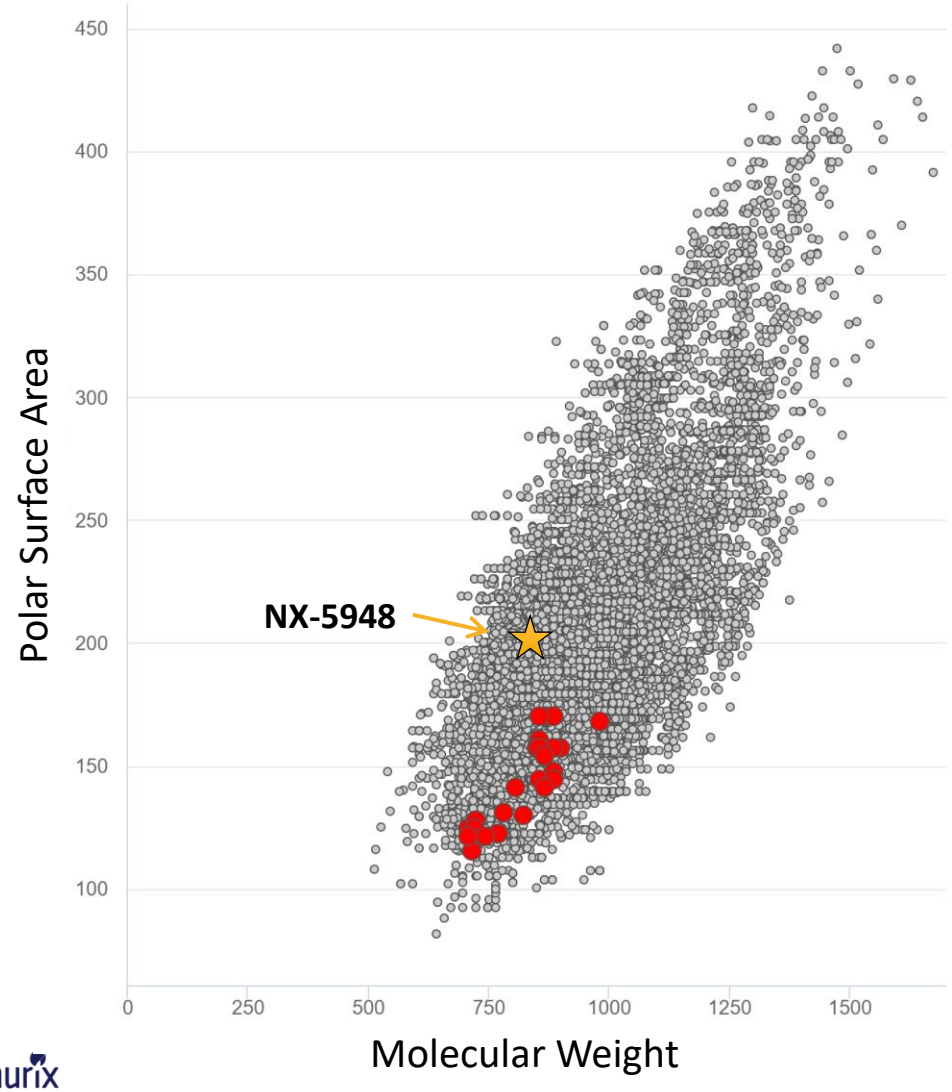
- Compounds represent 34 programs, colored by target
- Broad property space anchored by profile of target binder
- Represents a larger property range vs. public database

Empirical Testing Funnel for Identifying Degraders With CNS Exposure



- When there is no rule-book for designing compounds to achieve specific properties you are forced to take an empirical approach
- We performed in vivo screening early in our testing funnel across several programs to monitor for compounds displaying brain or CSF exposure
- All programs that have entered in vivo screening have identified degraders showing CNS exposure

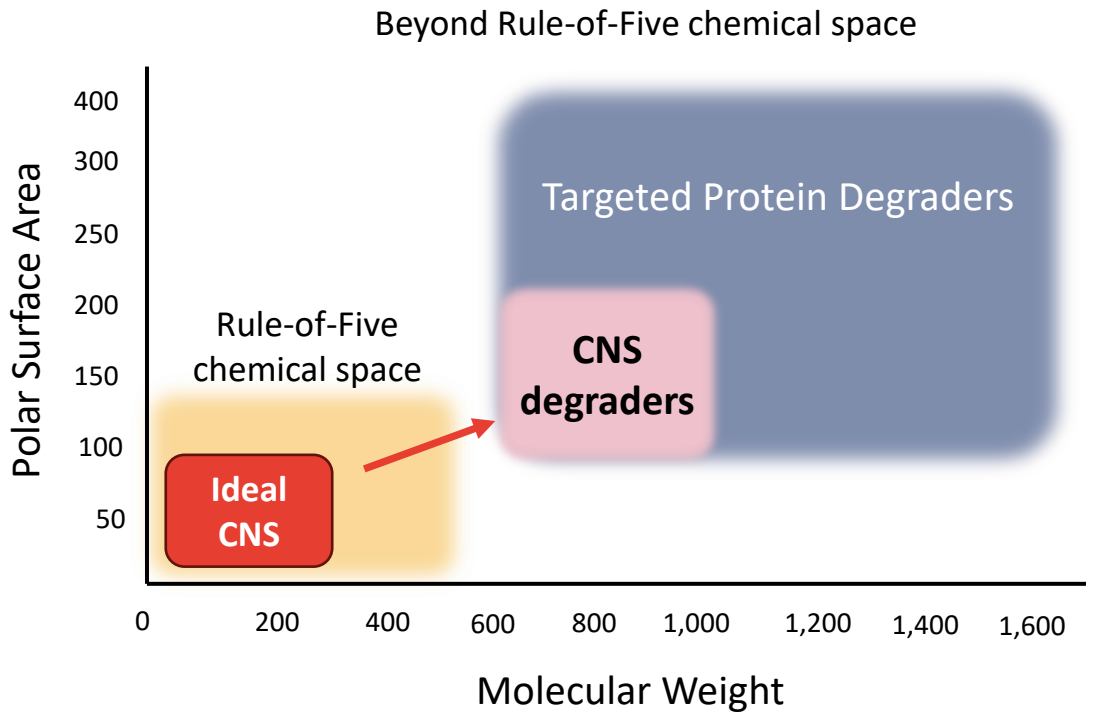
Degraders With CNS Exposure Are Much More Prevalent Than Expected



- CNS exposure
- No CNS exposure, or not selected for PK/PD screening

- >50% of Degraders emerging from dedicated in vivo testing funnel show CNS exposure

Empirical Screening for CNS-Penetrant Degraders Is a Viable Discovery Strategy



- Molecular weight range limitation of small molecule design space for CNS is not relevant for degraders
- MW and 2D descriptors, such as polar surface area (PSA), are insufficient to predict CNS penetration
- The chemical space for CNS penetrant degraders is emerging, still needs to be defined

Hydrogen Bond Donor (HBD) Count Is the Most Restrictive Parameter for bRo5 Degrader Design

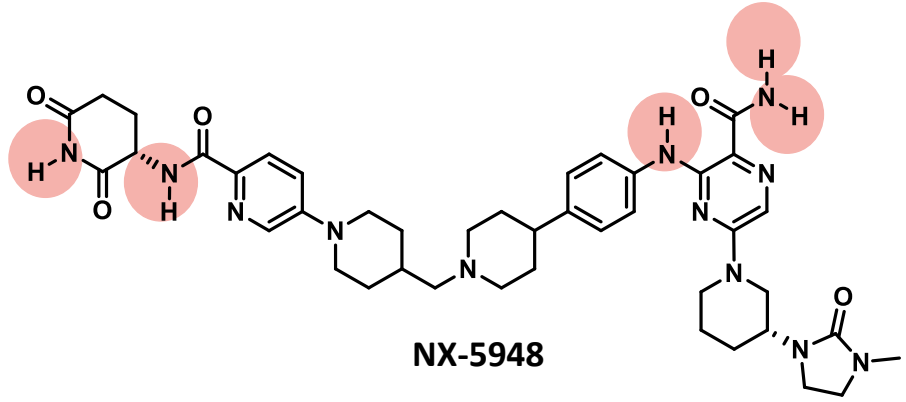
Property	BBB Penetration CNS MPO*	Oral Bioavailability Small molecule Rule-of-5	Oral Bioavailability PROTAC*
MW	≤ 360	500	950
HBD	as low as possible (ideally 0)	5	≤ 4 (≤ 2 unsatisfied)
ClogP	≤ 3	5	7
TPSA	40 to 90	140	200

*Keith R. Hornberger and Erika M.V. Araujo, *J. Med. Chem.* **2023**, 66, 8281-8287

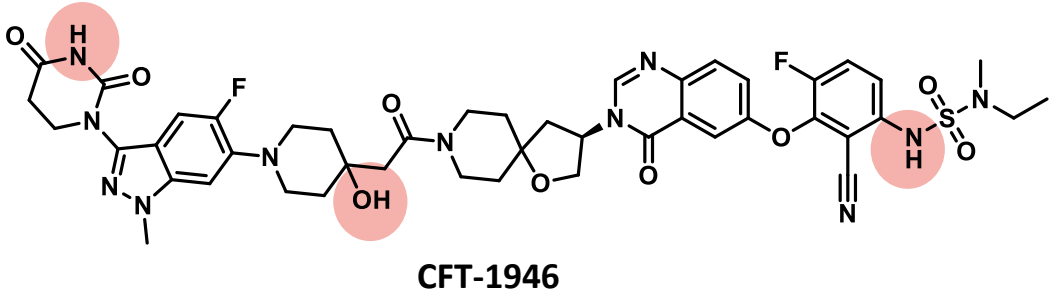
- Increasing evidence that to effectively achieve oral bioavailability for bRo5 compounds it is ideal to have ≤ 4 HBDs
- Most of the surveyed compounds with 3 to 4 HBDs contained 1 or 2 internally satisfied HBDs, so the cut-off value is more specifically ≤ 2 unsatisfied HBDs*

Clinical Orally Bioavailable Bi-functional Degraders Have up to Five HBDs

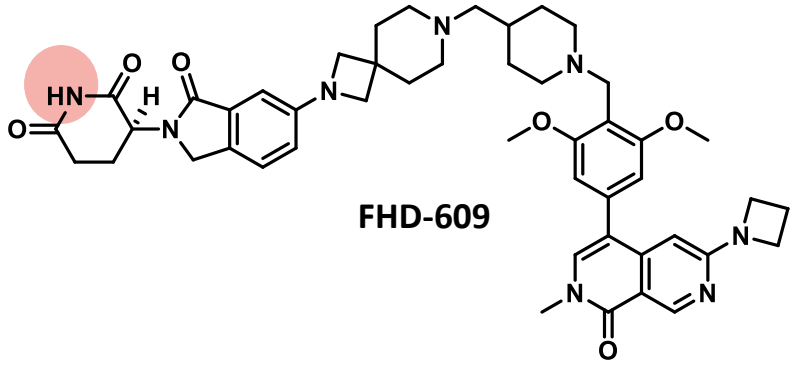
Company ID	Company	Protein Target(s)	HBDs
NX-5948	Nurix	BTK	**5**
NX-2127	Nurix	BTK	**4**
KT-413	Kymera	IRAK4, Ikaros, Aiolos	**4**
BMS-986365	BMS	Androgen receptor	**3**
CFT-1946	C4 Therapeutics	BRAF V600E	**3**
ARV-110	Arvinas	Androgen receptor	**2**
ARV-471	Arvinas	Estrogen receptor	**2**
ARV-766	Arvinas	Androgen receptor	**2**
FHD-609	Foghorn	BRD9	**1**



NX-5948



CFT-1946

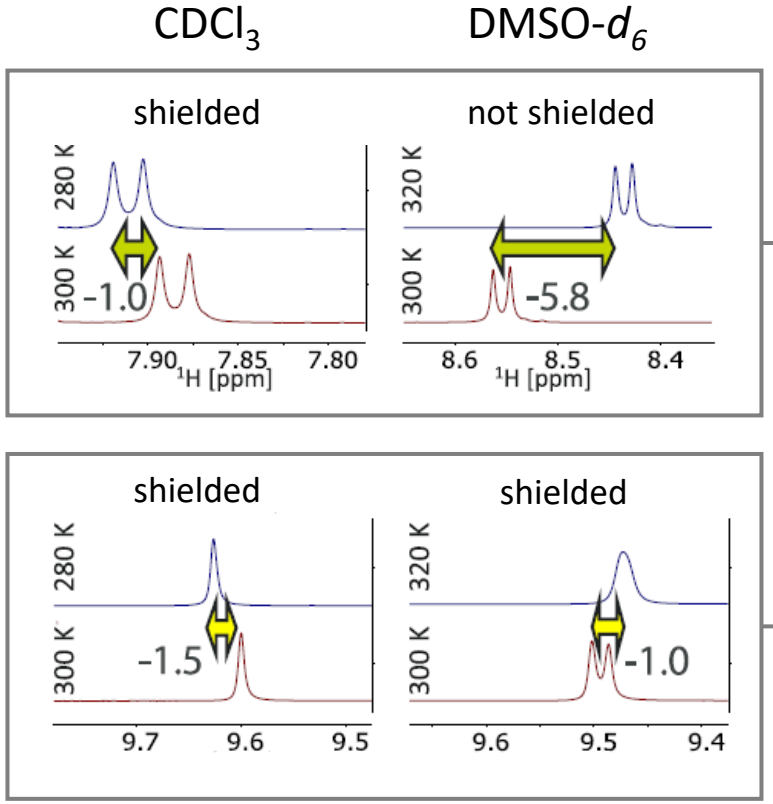


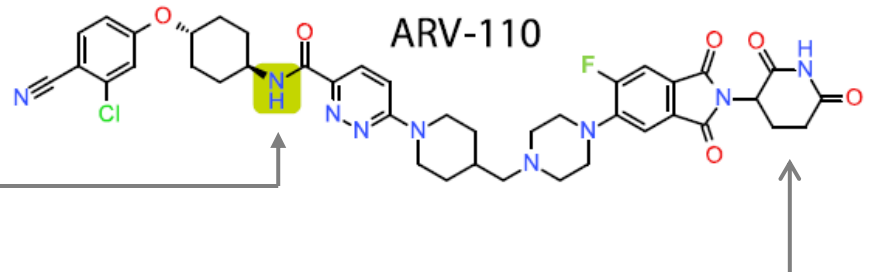
FHD-609

- NX-5948 appears to be an outlier amongst clinical compounds, with 5 HBDs

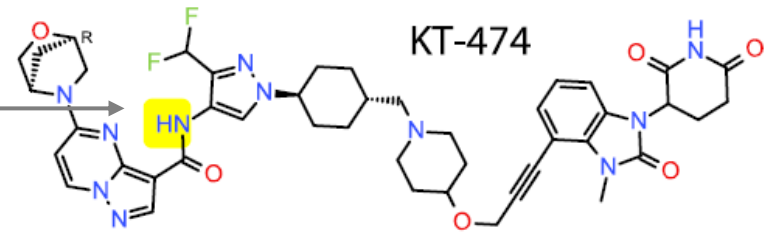
^{1}H NMR Experiments To Determine Exposed HBDs for Bi-functional Degraders

- Temperature-dependent ^{1}H-NMR shifts of HBDs correlate with amount of solvent shielding
- Shielding of HBD is indicated if shift ratio:
  parts-per-billion (ppb) / temperature in Kelvin ≥ −3.0 ($CDCl_3$) or ≥ −3.5 (DMSO)
- Chloroform has a low dielectric constant mimicking a lipid bi-layer





Shielded in both solvents



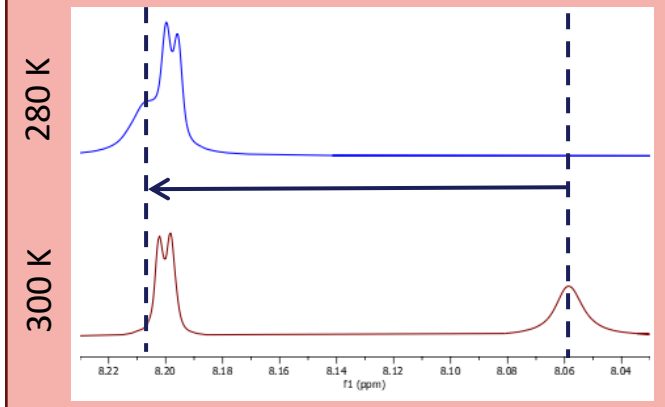
- Markus Schade and co-authors (AstraZeneca) studied 4 clinical PROTACs and other pre-clinical compounds using NMR to distinguish shielded from un-shielded HBDs
- Their results defined an upper limit of eHBD ≤ 2 for oral F% in non-polar environments

*Markus Schade et al., *J. Med. Chem.* **2024**, 67, 13106−13116

Temperature and Solvent-dependent ^{1}H-NMR Shift Experiments Indicate NX-5948 Has Solvent Exposed and Shielded HBDs

NH-1 is not shielded (solvent exposed)

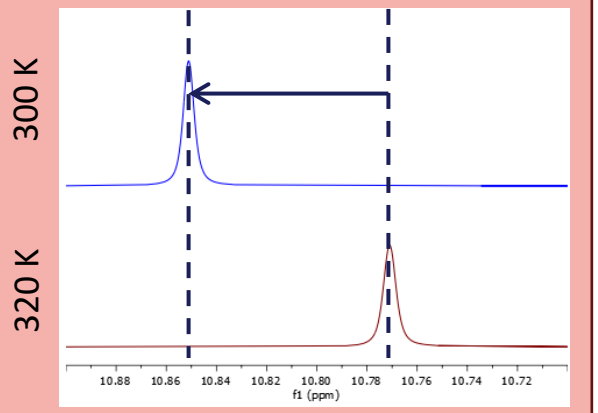
$CDCl_3$



$\delta(CDCl_3)$ = - 0.15 ppm

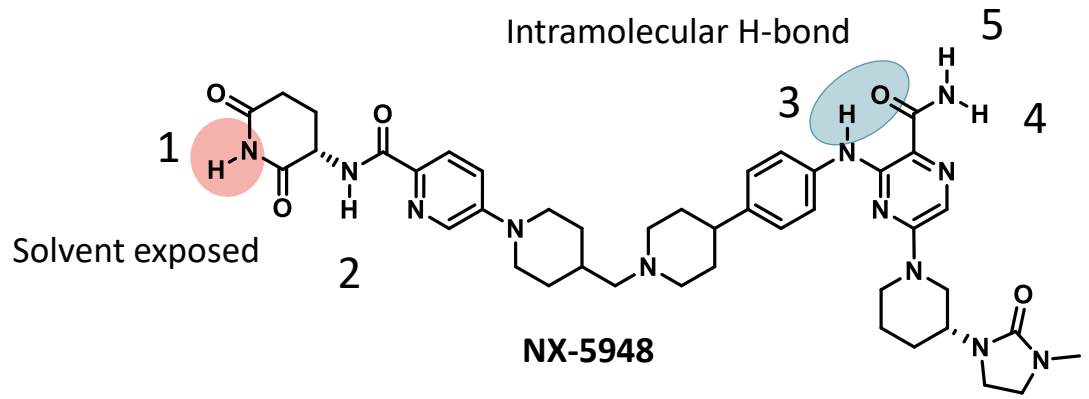
ppb/K_{CDCl3} = **- 7.4**

DMSO-d_6



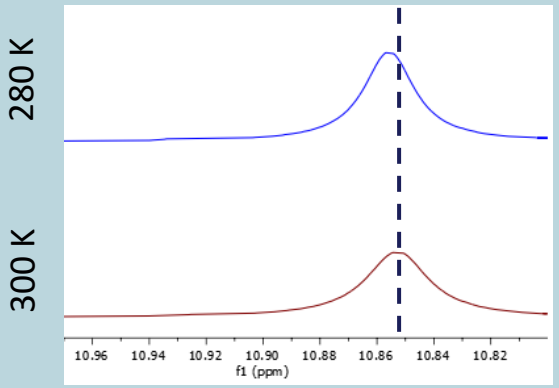
$\delta(DMSO)$ = - 0.82 ppm

ppb/K_{DMSO} = **- 4.1**



NH-3 is shielded from solvent

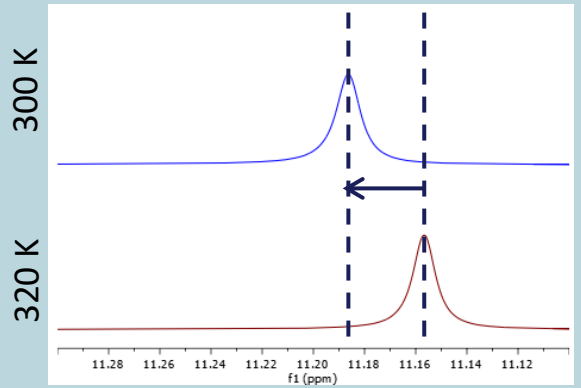
$CDCl_3$



$\delta(CDCl_3)$ = - 0.0027 ppm

ppb/K_{CDCl3} = **- 0.14**

DMSO-d_6

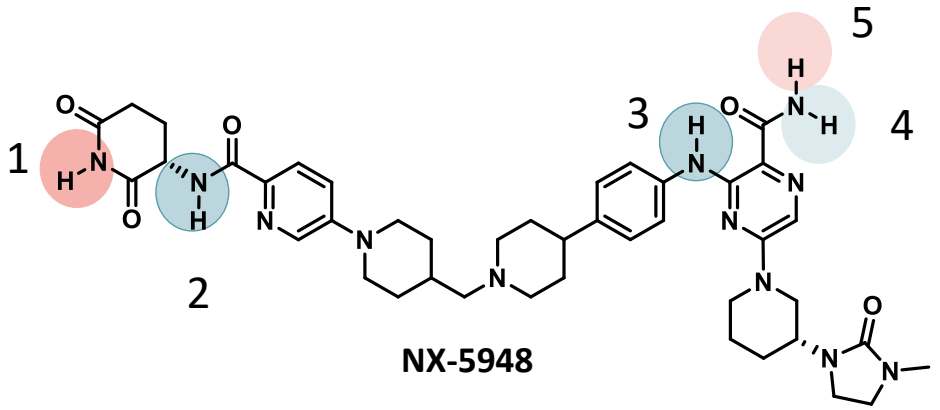


$\delta(DMSO)$ = - 0.030 ppm

ppb/K_{DMSO} = **- 1.5**

- Large NMR shifts for NH-1 in both solvents indicate it is solvent exposed
- Small NMR shifts for NH-3 in both solvents indicate it is not solvent exposed and engaged in an intramolecular H-bond

Overall ^{1}H-NMR Shift Experiments Demonstrate NX-5948 Contains Only Two Exposed Hydrogen Bond Donors



NX-5948

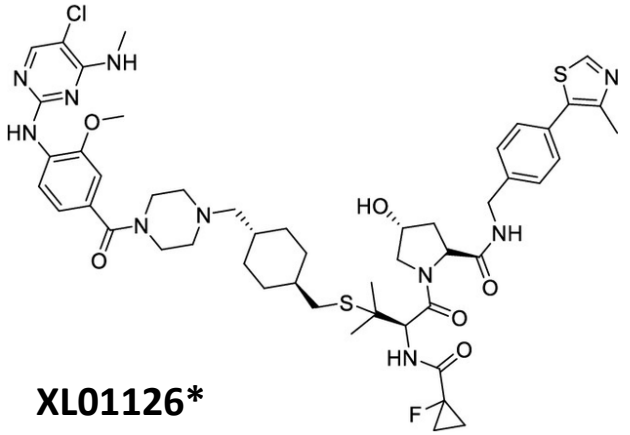
NH #	Non-polar	polar	Overall
1	Non-shielded	Non-shielded	Exposed
2	shielded	~shielded	Not exposed
3	shielded	shielded	Not exposed
4	shielded	~Non-shielded	Less exposed
5	~Non-shielded	Non-shielded	Exposed

- NH atoms #1 and #5 are non-shielded in both solvents and indicates both HBDs are exposed
- Two exposed HBDs for NX-5948 is in-line with degrader oral bioavailability metric and acceptable for CNS penetration

Degraders Targeting CNS Indications in Clinical and Preclinical Development

Molecule	Protein Target	E3 Ligase	Route of Admin.	Disease / Indication	Phase
NX-5948	BTK	CRBN	PO	Primary CNS lymphoma	Phase 1
CFT-8919	EGFR-L858R	CRBN	PO	CNS metastasized tumors	Phase 1
ARV-102	LRRK2	CRBN	PO	Progressive supranuclear palsy and Parkinson's	Phase 1
XL01126	LRRK2	VHL	PO	Parkinson's disease	Preclinical
ORI-113	mHTT	Unknown/undisclosed		Huntington's disease	Preclinical
PRX302	Tau	SPiDEM™ technology		Alzheimer's disease	Preclinical
PRX303	α-Synuclein	SPiDEM™ technology		Parkinson's disease	Preclinical
APN tau degrader	Tau	Unknown/undisclosed		Tauopathies	Preclinical
APN α-Syn degrader	α-Synuclein	Unknown/undisclosed		Synucleinopathies	Preclinical
Amphista degrader	Multiple CNS targets	Non-CRBN, Non-VHL	IV and PO	Multiple CNS indications	Preclinical

Adapted from Agarwal, P., et. al., *J. Controlled Release.* 372, 661−673.



XL01126*
MW = 1020
CLogD = 4.44
TPSA = 194.3
HBD = 5 (eHBD = ?)
Mouse *F* = 15%

*Liu, X., et. Al., *J. Am. Chem. Soc.* 2022, 144, 37, 16930–16952.

- A growing number of degraders are being developed to treat CNS diseases
- XL01126, first reported VHL-based degrader that is orally bioavailable with CNS exposure*

In Summary

- A new class of CNS drugs with beyond-Rule-of-Five chemical properties is rapidly emerging
- We are still learning the “rules” to predict CNS penetration of degraders
- ADME (absorption, distribution, metabolism, and excretion) properties of degraders may limit overall exposures; however, because of their catalytic MOA, very low concentrations are needed to drive pharmacology
- NX-5948 is a CNS-penetrant, orally bioavailable, BTK degrader in Phase 1 trials for the treatment of B cell diseases with potential to treat patients with CNS involvement

Thank you

nurix