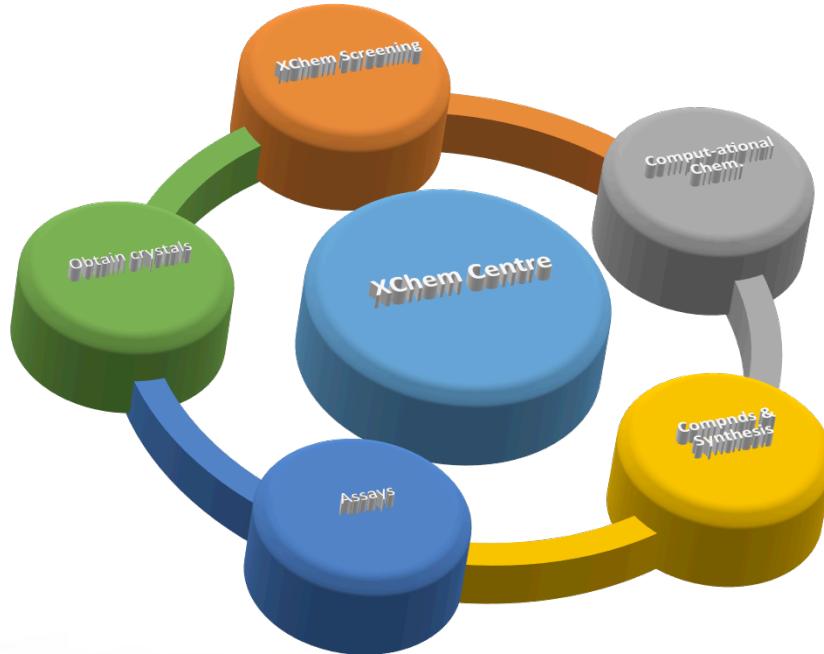


xChem follow-up meeting

Anthony Bradley
Project Leader, Ox XChem
Chemistry and SGC Oxford, Diamond



This meeting



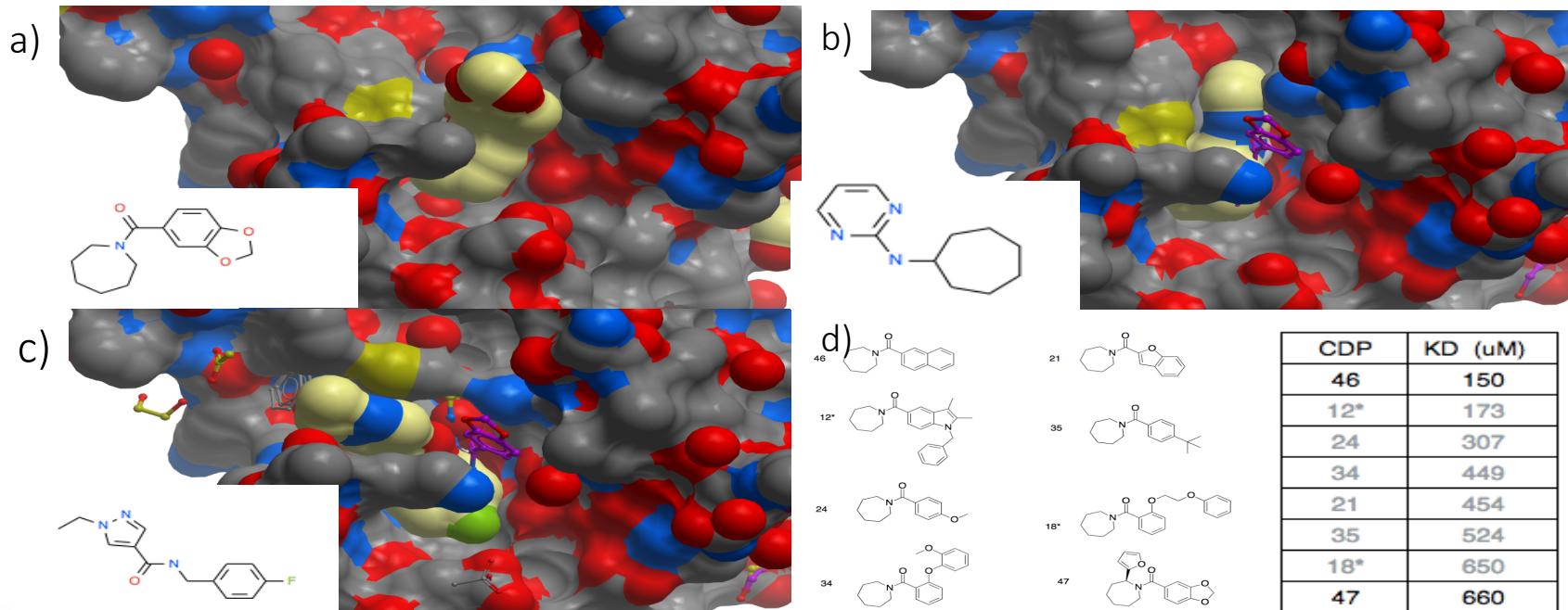
- Go through existing projects – update on progress (Anthony)
- Go through one target's hits
 - (Me this week – but target owner?)
- Prioritise
 - Computational work
 - Chemistry
 - Screening

Key questions

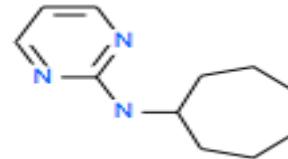
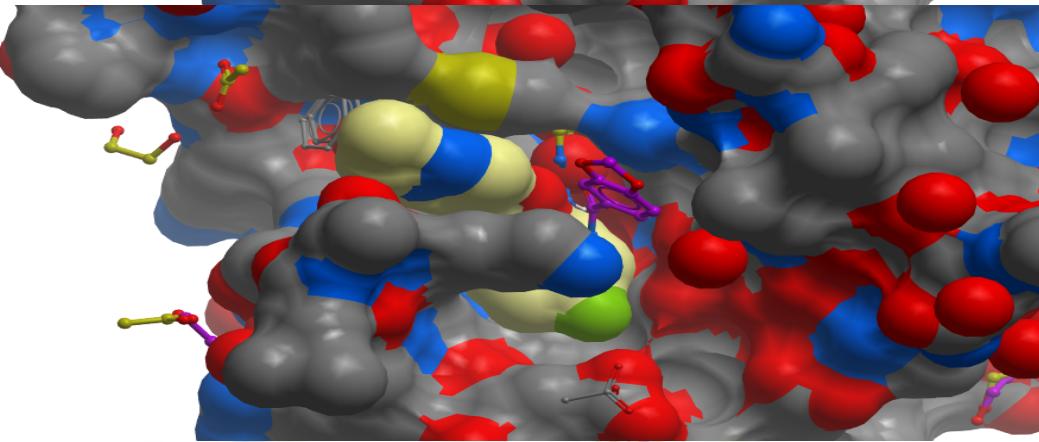
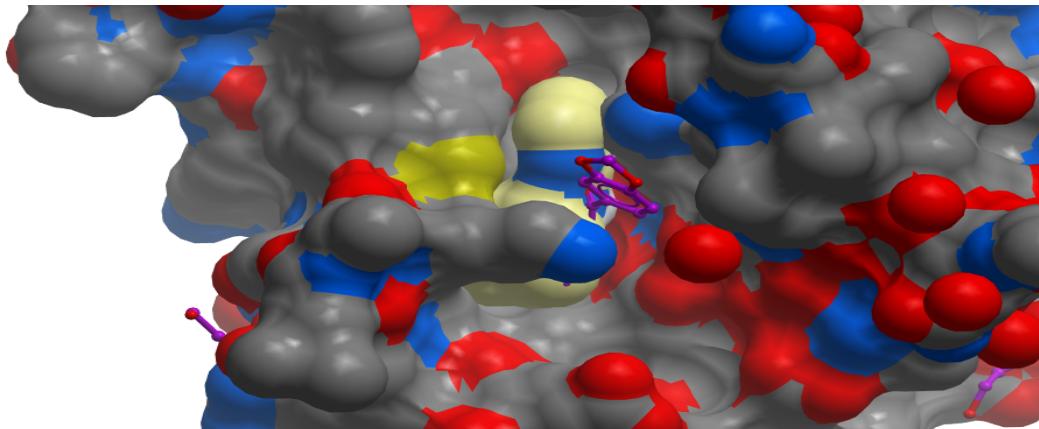
- Who invited?
 - Screening people?
 - Paul's chemists?
 - Target owner (e.g. Schofield if VIM2)
- How often?
 - Every two weeks?
- Format
 - 10 min update
 - 30 min target
 - 20 min priorities
- Method
 - Slides
 - 2D printouts of compounds
 - Tony write notes and I update spreadsheet
- Aim is to automate as much of this as possible

Existing work

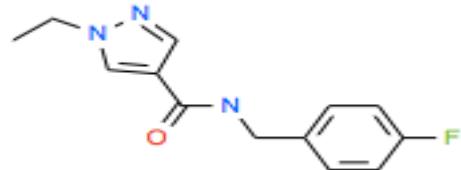
Crystal name?	Description / Hypothesis	Triaged	Chemistry?	Action?	Compounds by?	Screen by?	Potency? (pIC50)
OXA10OT-x0036	Moses - fluoro flat	Yes	Moses acetate. Schofiled off 5 Boronate	Make and test single follow-up	12th June - synthesis	Jurgen	>3.3
VIM2-x0002	Dixon (morphan) - cool chelator	Yes	Sulfonamides + R groups. Schofield and Dixon.	Make follow-ups on xtal structure	20th June	Jurgen	-3.5
DCP2B-x0146	Pocket one -	Yes	Explore rings and piperidines + enamine amides	Screen compounds - line up Laura	10th July	Laura	3.72
DPC2B-x0042	Boring Compound away	Yes	Maybe use later on in project	Bin??		Laura	>3.0
DCP2B-x0533	Pocket two -	Yes	SAR by cat / Enamine amide	Screen compounds - line up Laura	10th July	Laura	>3.0
DCP2B-x0033	Pocket three -	Yes	SAR by cat / Enamine amine	Screen compounds - line up Laura	10th July	Laura	>3.0
SHH	Amine	Yes	SAR by cat / tony synthesised	SPR weekend of 17th and week after tr	27th June	Lea	5.2
SHH- OX-65	Nicholas Parker	No	SAR by cupboard - and decide on plan	Give follow-up compounds to Lea - test	27th June	Lea	3.8



New ligands opens up pocket



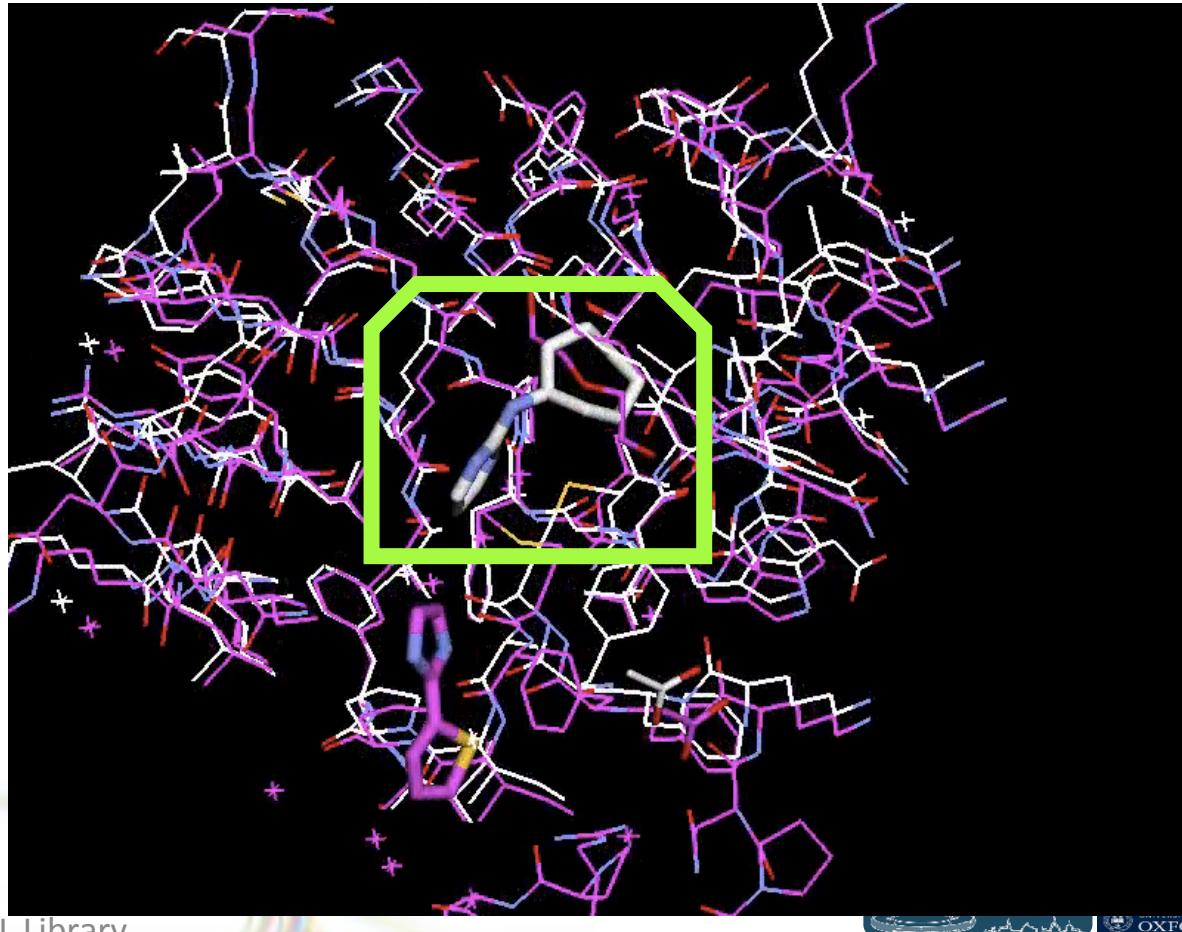
Shared greasy core



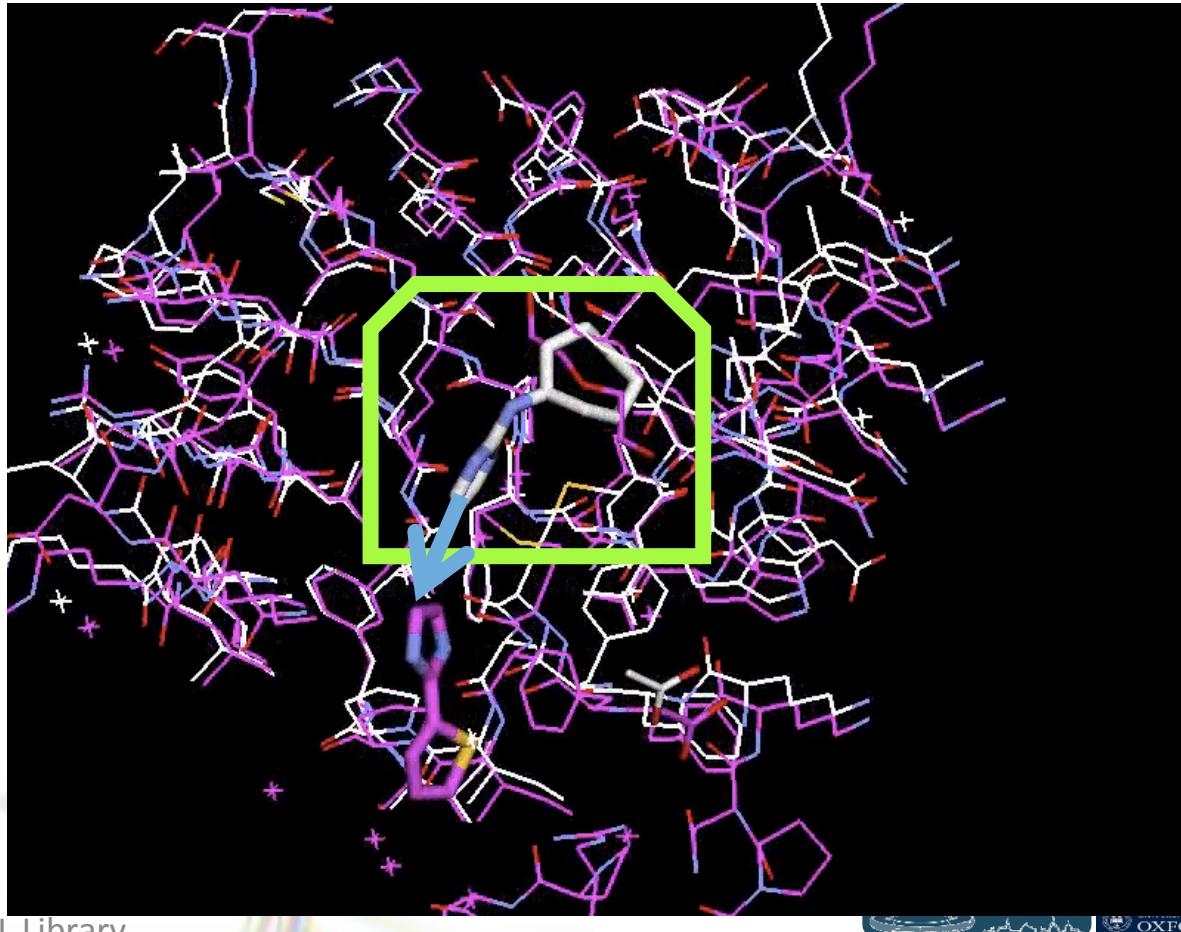
Moves methionine



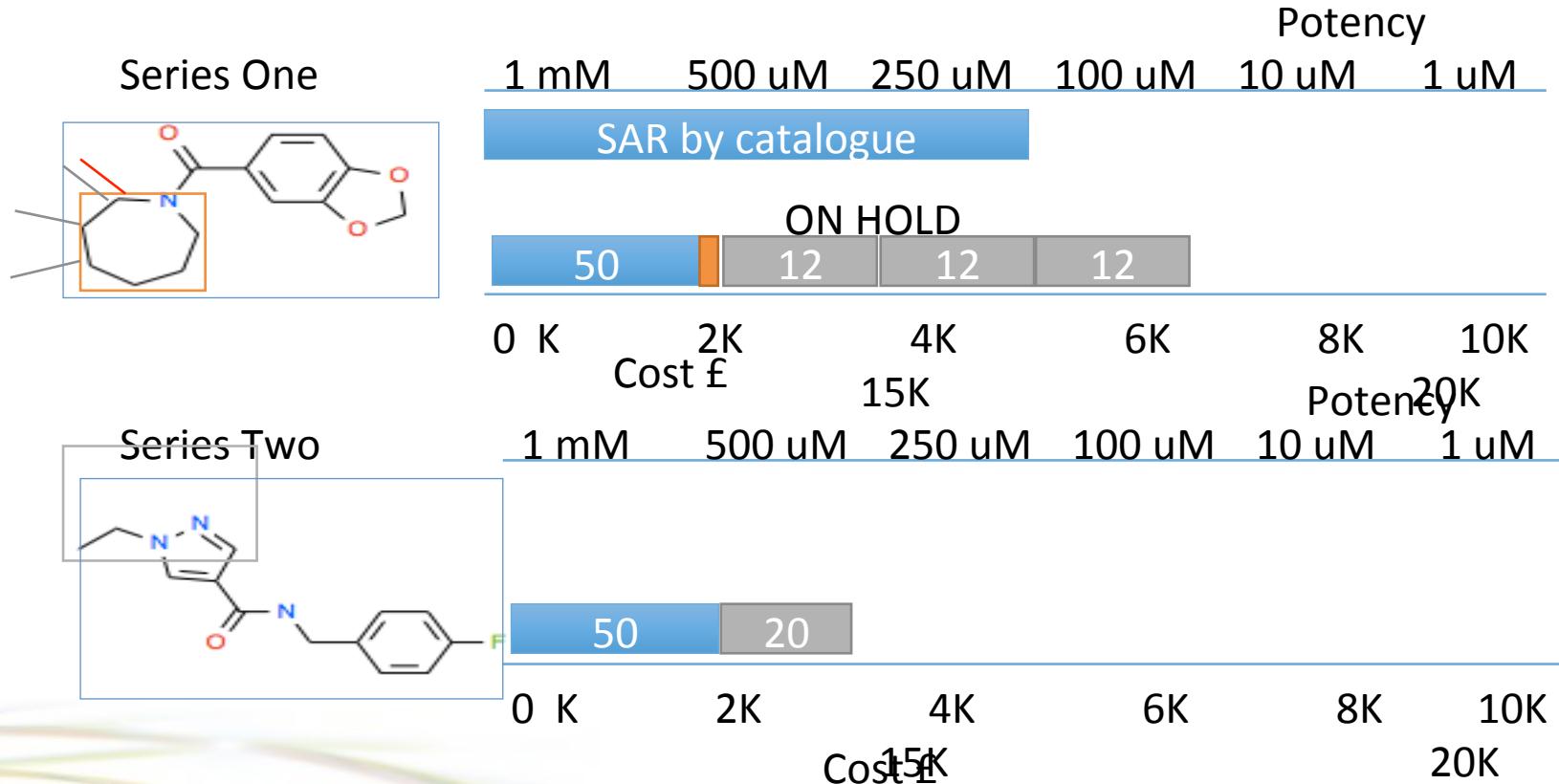
DCP2 – random hit



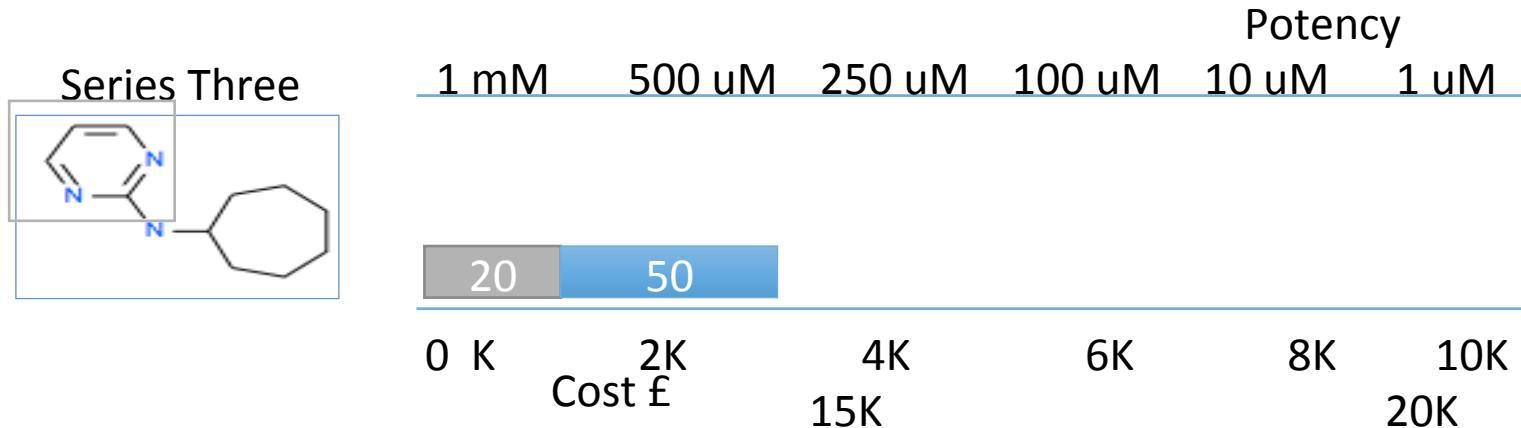
DCP2 – random hit



Current status



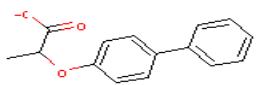
Current status



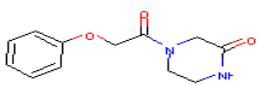
DCP2 – random hit???

NUDT7

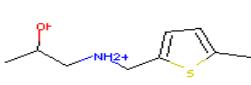
Xtal name	Compound Id	PLI	SMOG	Ease	Site	AB	PB	AA	Comment
NUDT7-x0129	DSPL - FMOPL000250a	-3.74	-6.85		4	1			
NUDT7-x0132	DSPL - FMOPL000730a	-3.45	-5.80		1	1			
NUDT7-x0140	DSPL - FMOPL00069 - N140771a	-3.53	-7.08		3	1			
NUDT7-x0149	DSPL - FMOPL00042 - N13802a	FAIL	-3.08		2	4			
NUDT7-x0151	DSPL - FMOPL00071 - N14094a	-1.26	-5.66		1	3			
NUDT7-x0159	DSPL - FMOPL00070 - N14090a	-3.35	-5.15		4	2			
NUDT7-x0220	DSPL - FMOPL00067 - N14061a	-3.03	-5.54		4	1			
NUDT7-x0299	Schofield Boronate	NA	NA		1	4			Stacked
NUDT7-x0286	Spencer/Khan	-2.62	-7.44		4	1			Nice interactions
NUDT7-x0254	DSPL - FMOPL00027 - N13657a	-2.41	-5.27		4	2			
NUDT7-x0303	Adam Nelson Isomer	1.17	-4.62		4	1			
NUDT7-x0304	Adam Nelson Isomer	-1.20	-5.44		4	1			
NUDT7-x0333	Pauls Misc - J492_132	-1.67	-5.22		5	3			Stacked
NUDT7-x0374	DSPL - FMOPL000087a	NA	NA		1	3			Stacked
NUDT7-x0384	DSPL - FMOPL000555a	-3.32	-5.75		3	3			
NUDT7-x0389	DSPL - FMOPL000091a	-1.49	-6.23		4	3			
NUDT7-x0399	DSPL - FMOPL000560a	NA	NA		4	3			Stacked
NUDT7-x0436	DSPL - FMOPL000476a	-2.34	-4.81		5	3			
NUDT7-x0438	DSPL - FMOPL000587a	NA	NA		4	3			Stacked
NUDT7-x0452	DSPL - FMOPL000260a	-2.35	-5.72		2	3			
NUDT7-x0503	DSPL - FMOPL000110a	NA	NA		1	3			Stacked



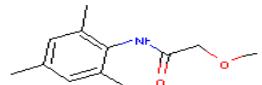
NUDT7A-x0129



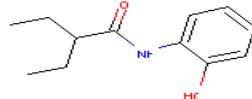
NUDT7A-x0132



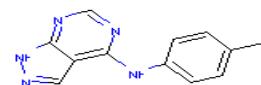
NUDT7A-x0140



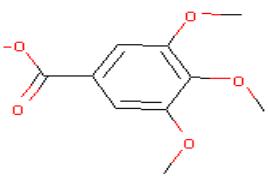
NUDT7A-x0151



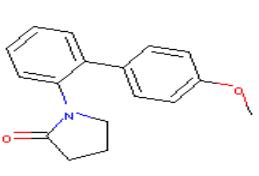
NUDT7A-x0159



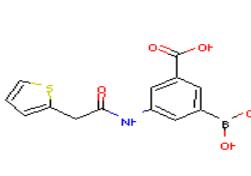
NUDT7A-x0220



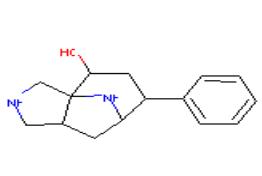
NUDT7A-x0254



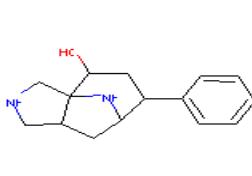
NUDT7A-x0286



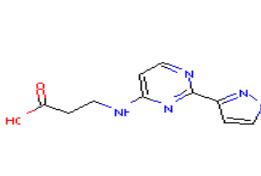
NUDT7A-x0299



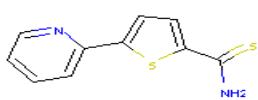
NUDT7A-x0303



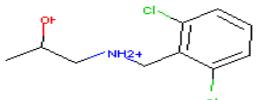
NUDT7A-x0304



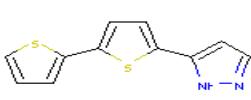
NUDT7A-x0333



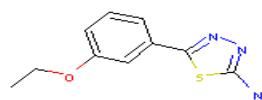
NUDT7A-x0374



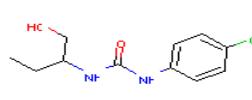
NUDT7A-x0384



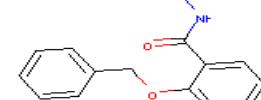
NUDT7A-x0389



NUDT7A-x0399



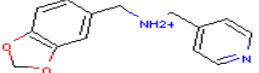
NUDT7A-x0436



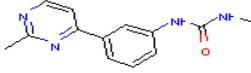
NUDT7A-x0438



NUDT7A-x0452



NUDT7A-x0497

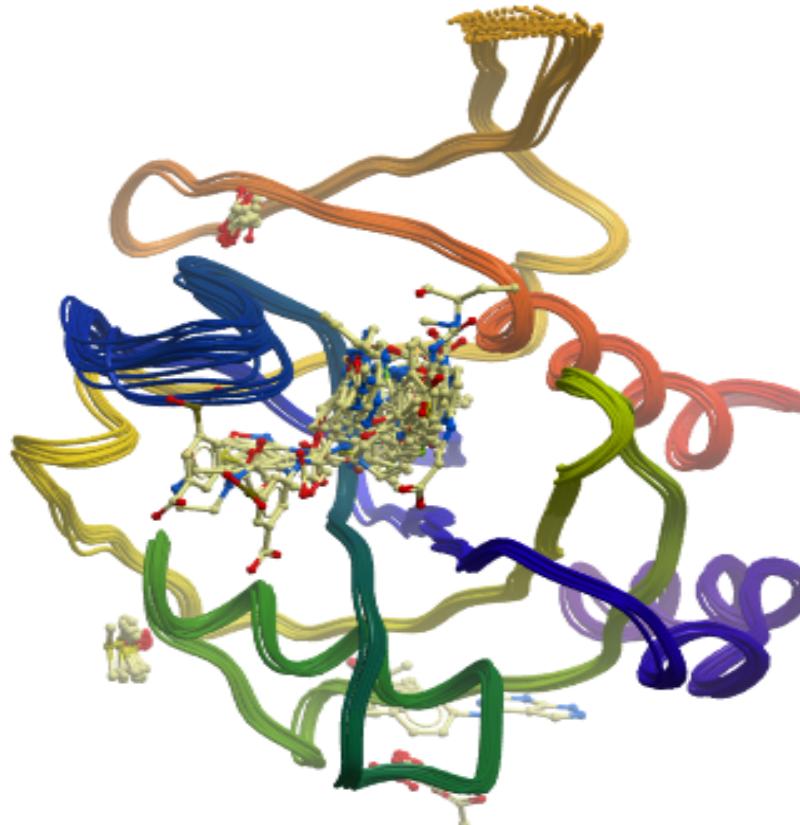


NUDT7A-x0503

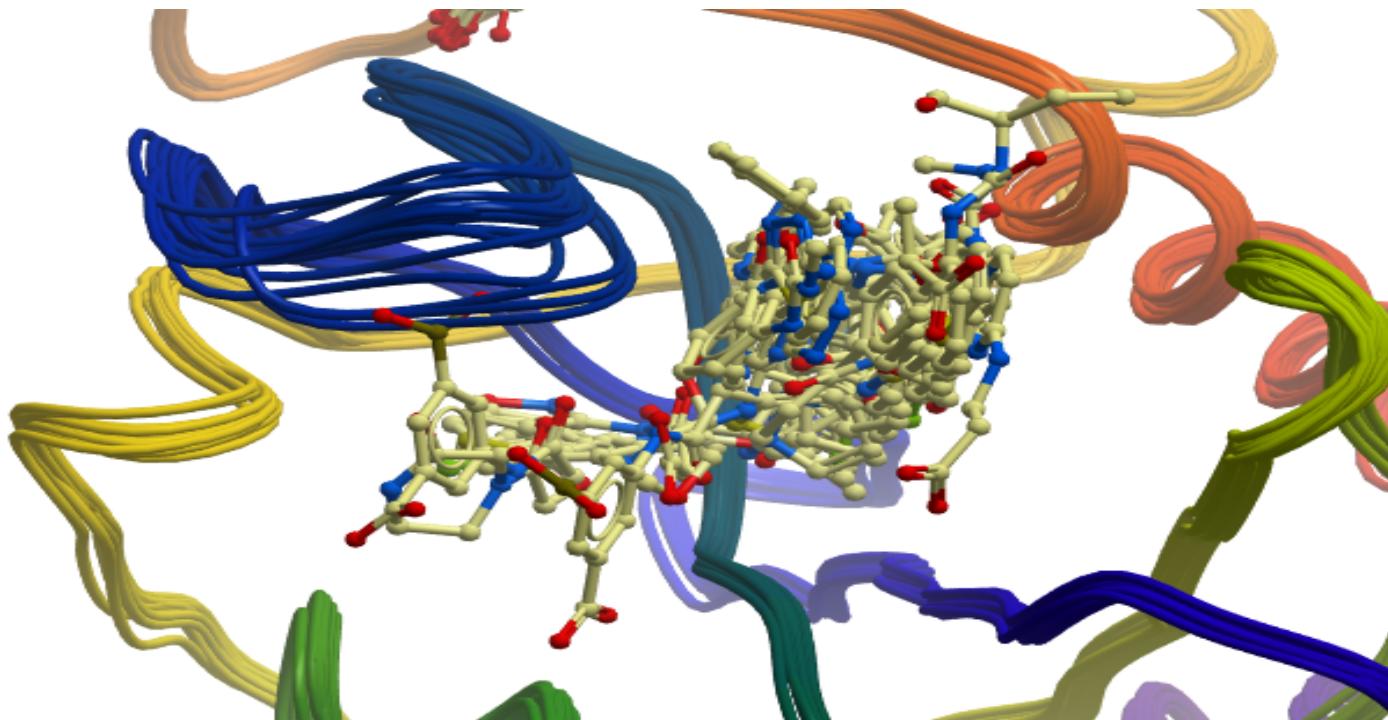
Screening / NUDIX update

- Laura – Rapid Fire on all in next few weeks – NUDT7 core priority
- SPR also possible – Tony give compounds

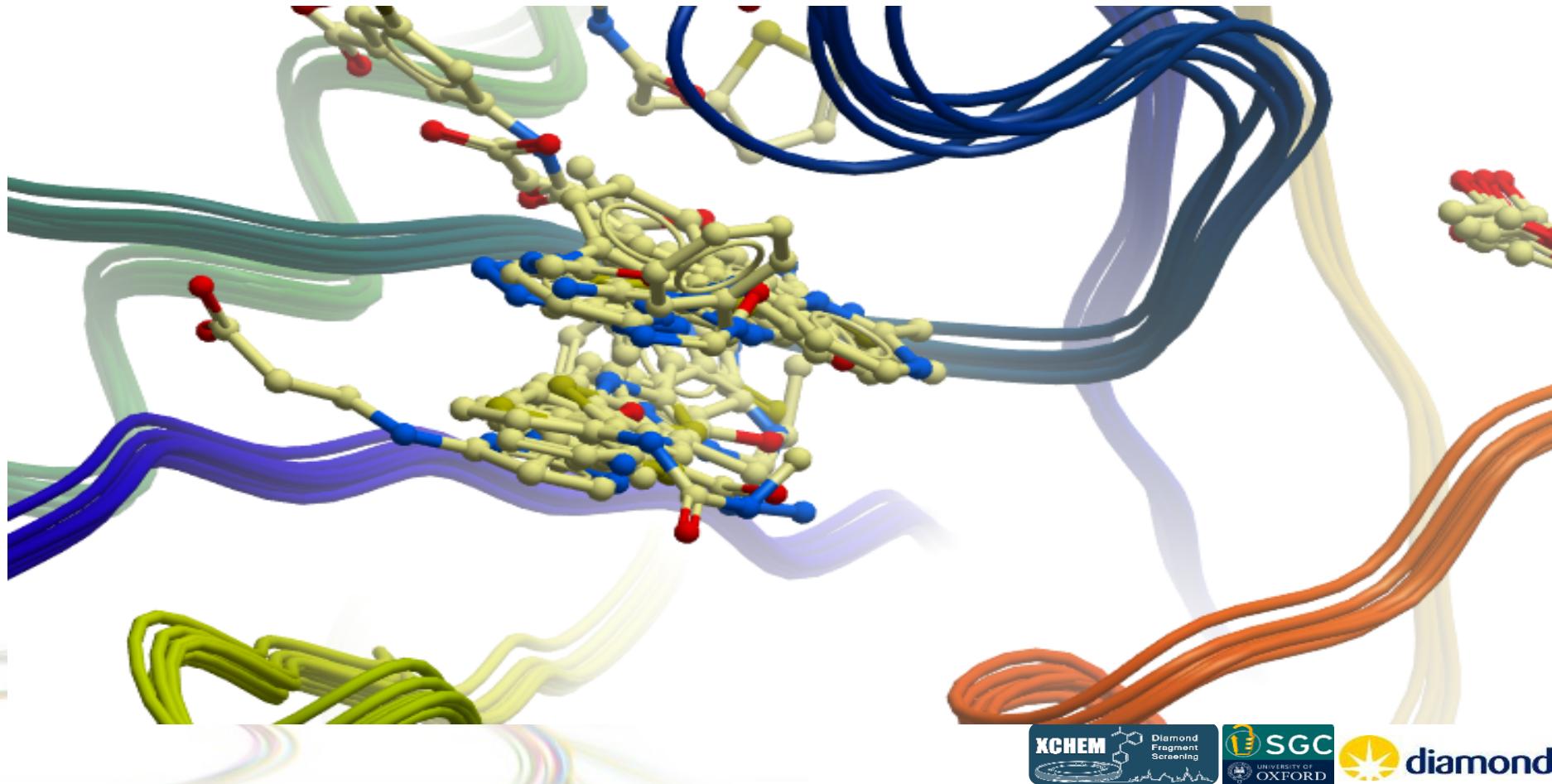
NUDT7 Overview



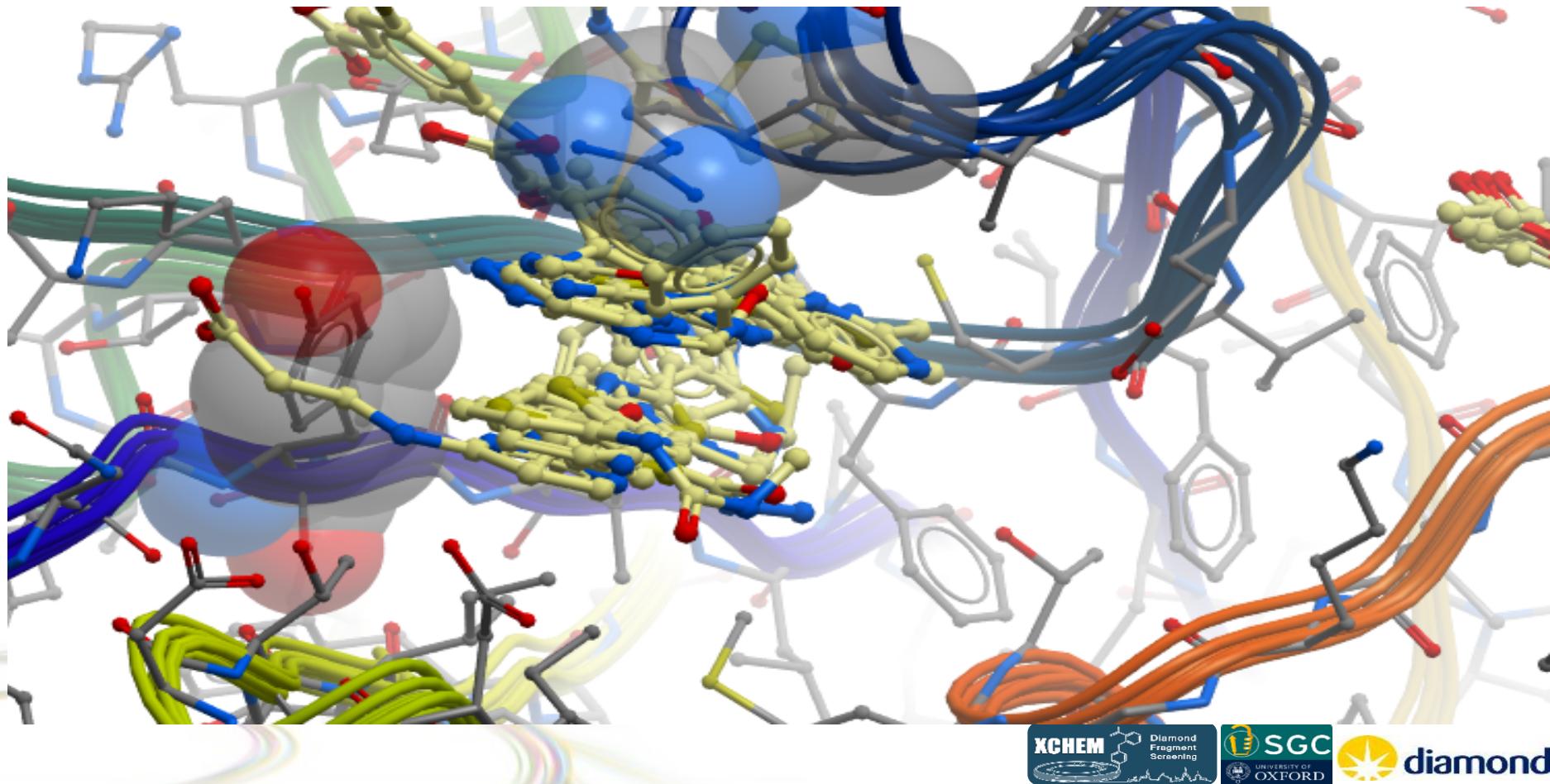
NUDT7 Loop



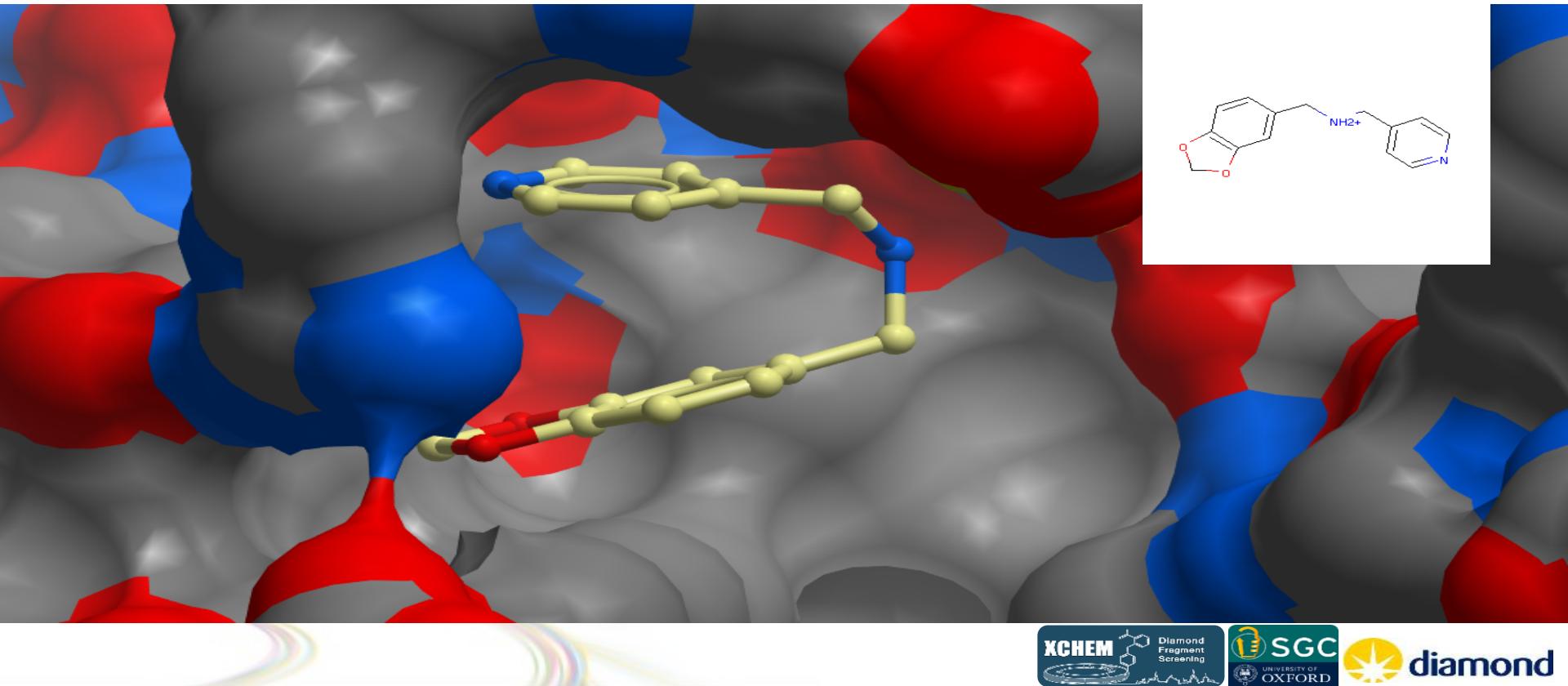
Stacking



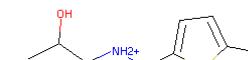
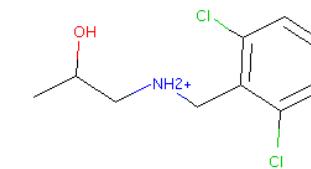
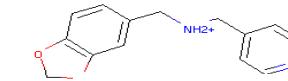
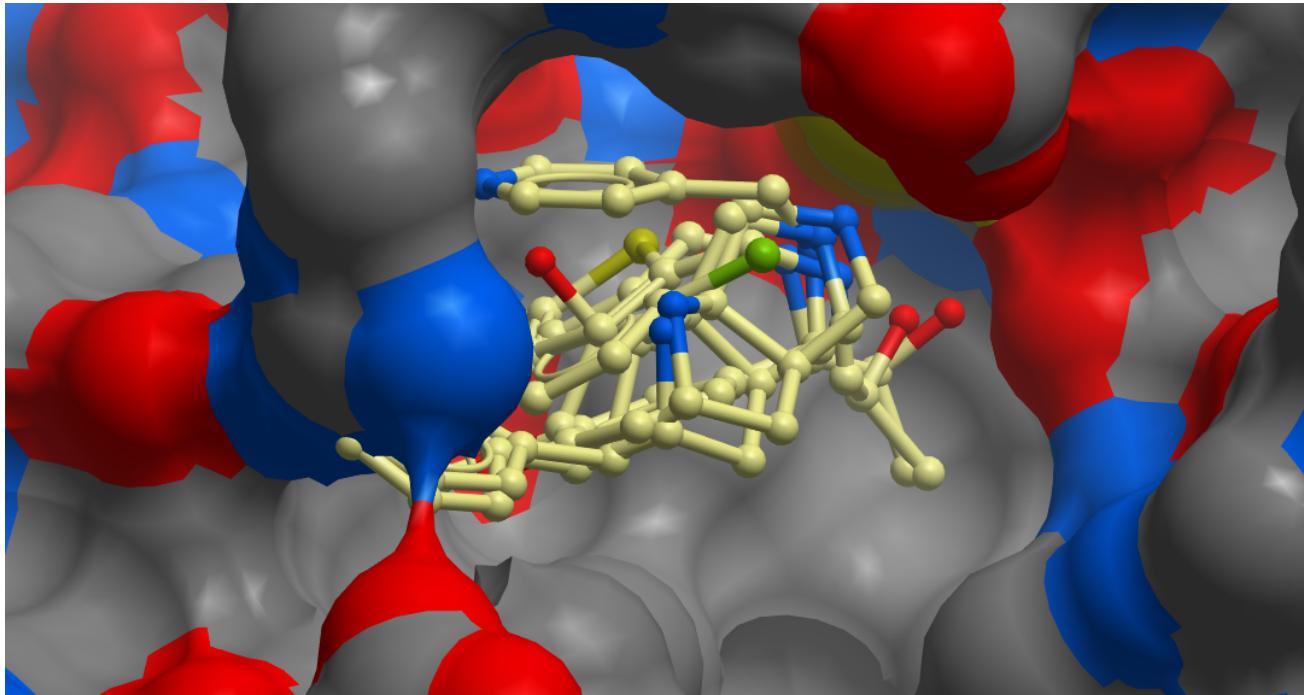
Stacking



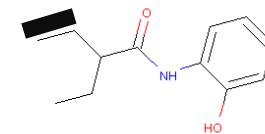
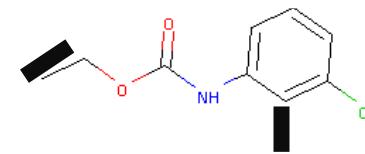
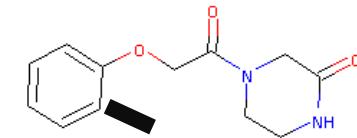
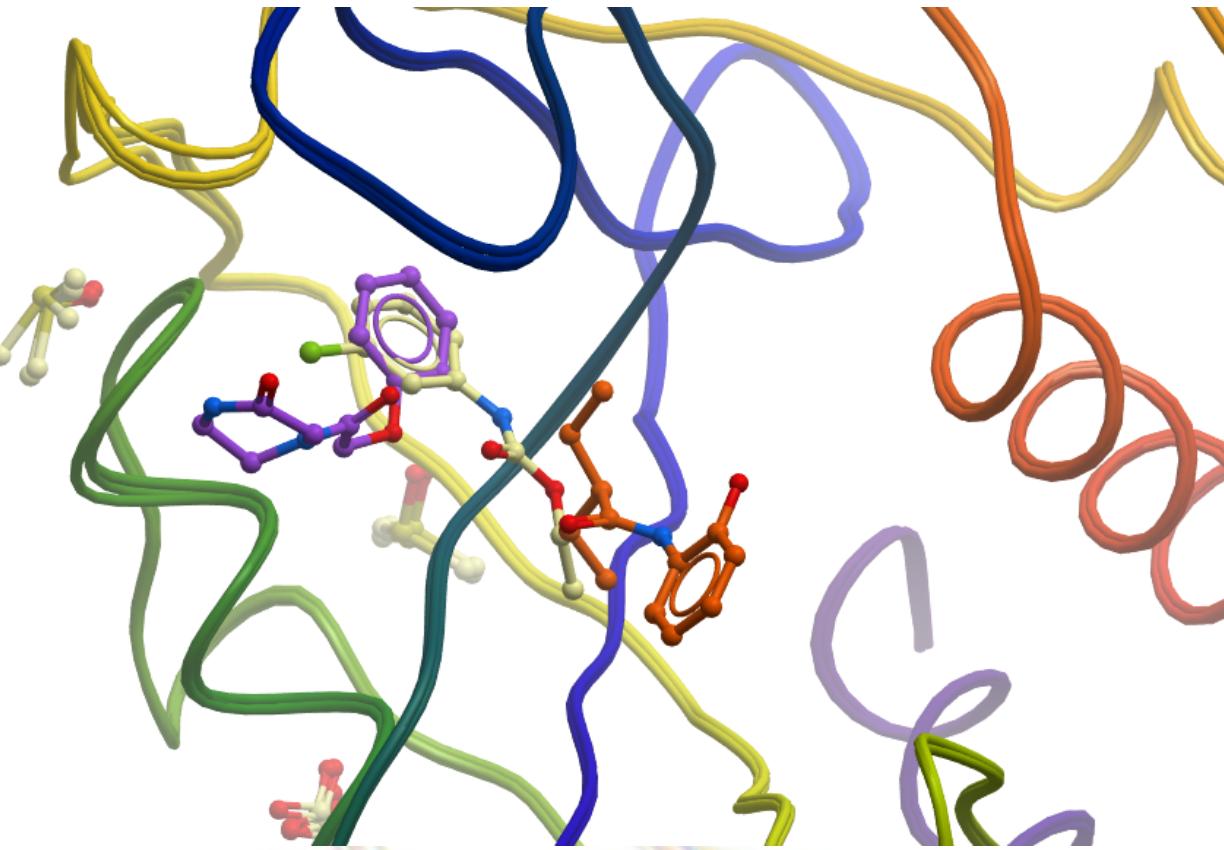
Self Stack – x0497

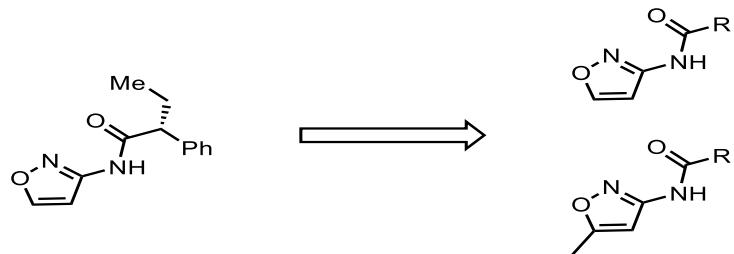


N-H-S – 0140,303,304,384,49⁷

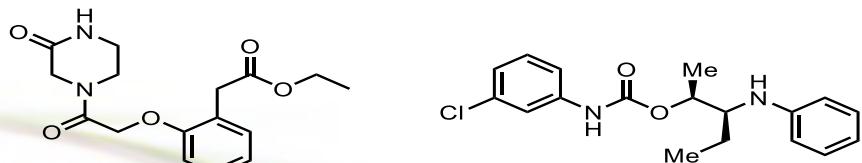
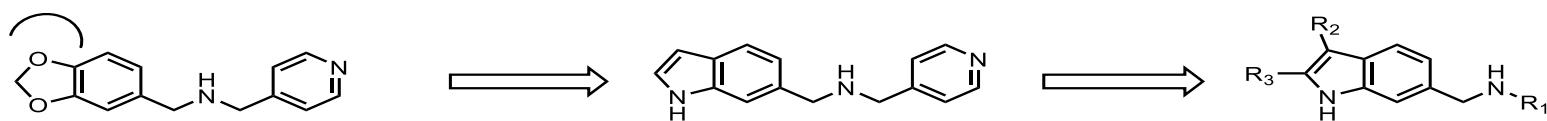


NUDT7 merging projects - 452,159,132





hydrophobic



Fragment linking

NUDT7

Xtal name	Compound Id	PLI	SMOG	Ease	Site	AB	PB	AA	Comment
NUDT7-x0129	DSPL - FMOPL000250a	-3.74	-6.85		4	1			
NUDT7-x0132	DSPL - FMOPL000730a	-3.45	-5.80		1	1			
NUDT7-x0140	DSPL - FMOPL00069 - N140771a	-3.53	-7.08		3	1			
NUDT7-x0149	DSPL - FMOPL00042 - N13802a	FAIL	-3.08		2	4			
NUDT7-x0151	DSPL - FMOPL00071 - N14094a	-1.26	-5.66		1	3			
NUDT7-x0159	DSPL - FMOPL00070 - N14090a	-3.35	-5.15		4	2			
NUDT7-x0220	DSPL - FMOPL00067 - N14061a	-3.03	-5.54		4	1			
NUDT7-x0299	Schofield Boronate	NA	NA		1	4			Stacked
NUDT7-x0286	Spencer/Khan	-2.62	-7.44		4	1			Nice interactions
NUDT7-x0254	DSPL - FMOPL00027 - N13657a	-2.41	-5.27		4	2			
NUDT7-x0303	Adam Nelson Isomer	1.17	-4.62		4	1			
NUDT7-x0304	Adam Nelson Isomer	-1.20	-5.44		4	1			
NUDT7-x0333	Pauls Misc - J492_132	-1.67	-5.22		5	3			Stacked
NUDT7-x0374	DSPL - FMOPL000087a	NA	NA		1	3			Stacked
NUDT7-x0384	DSPL - FMOPL000555a	-3.32	-5.75		3	3			
NUDT7-x0389	DSPL - FMOPL000091a	-1.49	-6.23		4	3			
NUDT7-x0399	DSPL - FMOPL000560a	NA	NA		4	3			Stacked
NUDT7-x0436	DSPL - FMOPL000476a	-2.34	-4.81		5	3			
NUDT7-x0438	DSPL - FMOPL000587a	NA	NA		4	3			Stacked
NUDT7-x0452	DSPL - FMOPL000260a	-2.35	-5.72		2	3			
NUDT7-x0503	DSPL - FMOPL000110a	NA	NA		1	3			Stacked