Design Team:-
Focussing the wisdom of the crowd

Ed Griffen
MedChemica

Role

- MedChem strategy (TPP, test cascade, compound strategy, *IP…*)
- Prioritizing compounds for make & test
- X-connections to synthesis, testing, comp chem, structure teams

Composition ~20 members:

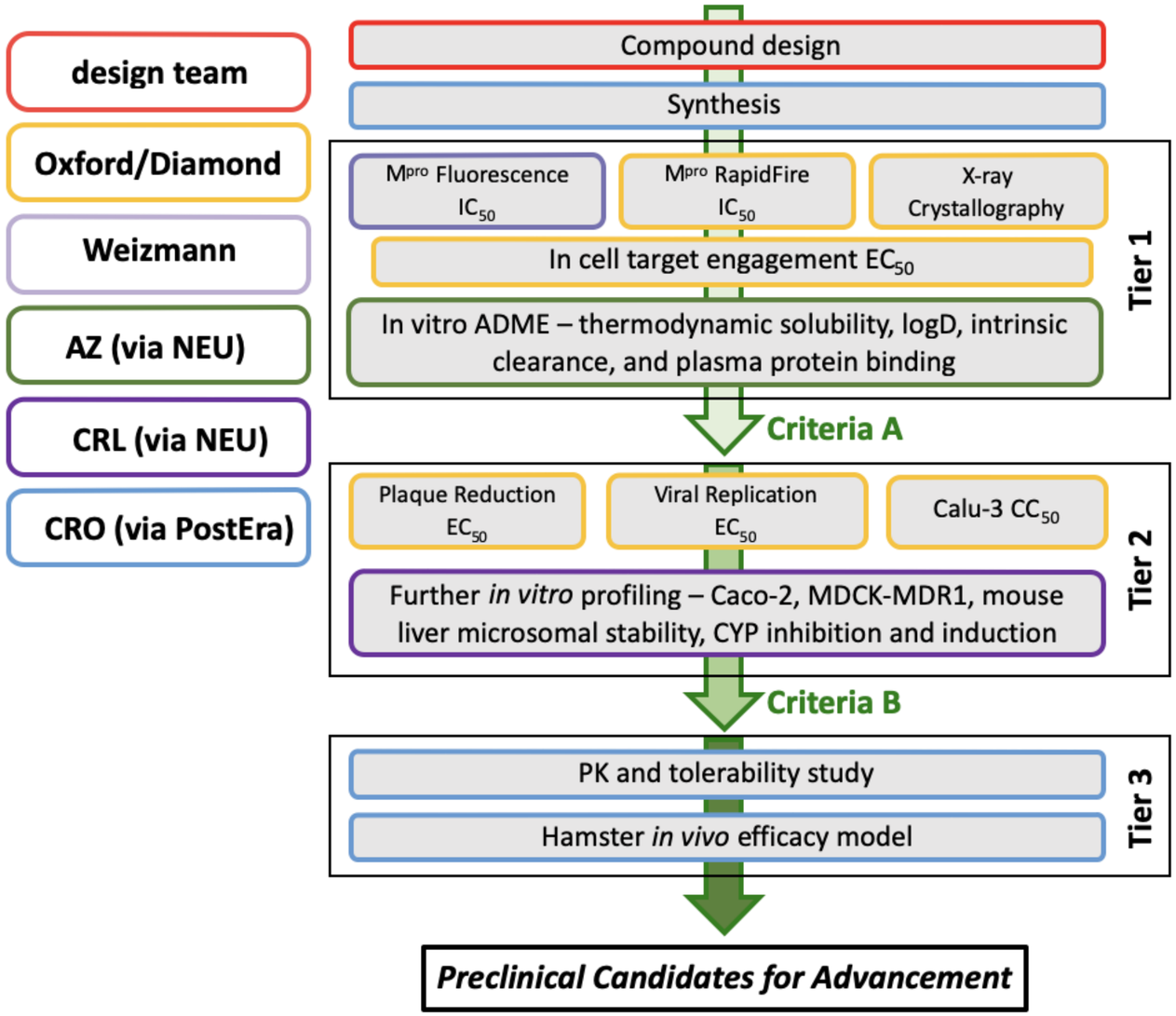
- UCB Comp & MedChem
- Thamespartners (Bruce & Ralph ex Pfizer)
- DNDi (Ben & Peter ex UCB & AZ)
- MedChemica (Ed ex AZ & Lauren A* Singapore)
- Postera (Alpha, Matt U of Cambridge)
- Bobby Glen(U of Cambridge, Imperial)
- Weizmann Institute, U of Oxford, Memorial S-K

Drugs have to meet a complex series of objectives to have a chance of working in the clinic

Target Product Profile (TPP) for oral SARS-CoV-2 main viral protease (Mpro) inhibitor

Property	Target range	Rationale
protease assay	IC_{50} < 50 nM	Extrapolation from other anti-viral programs
viral replication assay	EC_{50} < 5 µM	Suppression of virus at achievable blood levels
plaque reduction assay	EC_{50} < 5 µM	Suppression of virus at achievable blood levels
route of administration	oral	bid/tid - compromise PK for potency if pharmacodynamic effect achieved
solubility	> 5 mg/mL	Aim for biopharmaceutical class 1 assuming <= 750 mg dose
half-life	> 8 h (human) est from rat and dog	Assume PK/PD requires continuous cover over plaque inhibition for 24 h max bid dosing
safety	Only reversible and monitorable toxicities No significant DDI - clean in 5 CYP450 isoforms hERG and NaV1.5 IC_{50} > 50 µM No significant change in QTc Ames negative No mutagenicity or teratogenicity risk	No significant toxicological delays to development DDI aims to deal with co-morbidities / therapies,<SEP>cardiac safety for COVID-19 risk profile<SEP>cardiac safety for COVID-19 risk profile<SEP>Low carcinogenicity risk reduces delays in manufacturing<SEP>Patient group will include significant proportion of women of childbearing age

Getting a drug into the clinic requires collecting key data demonstrating effectiveness and safety



Does it block Mpro? How does it bind?

Does it work in cells?

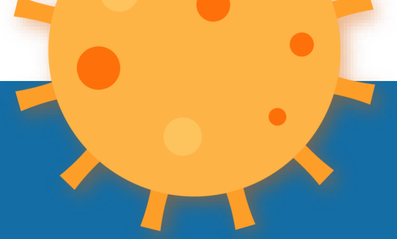
Does it have a chance of working in humans?

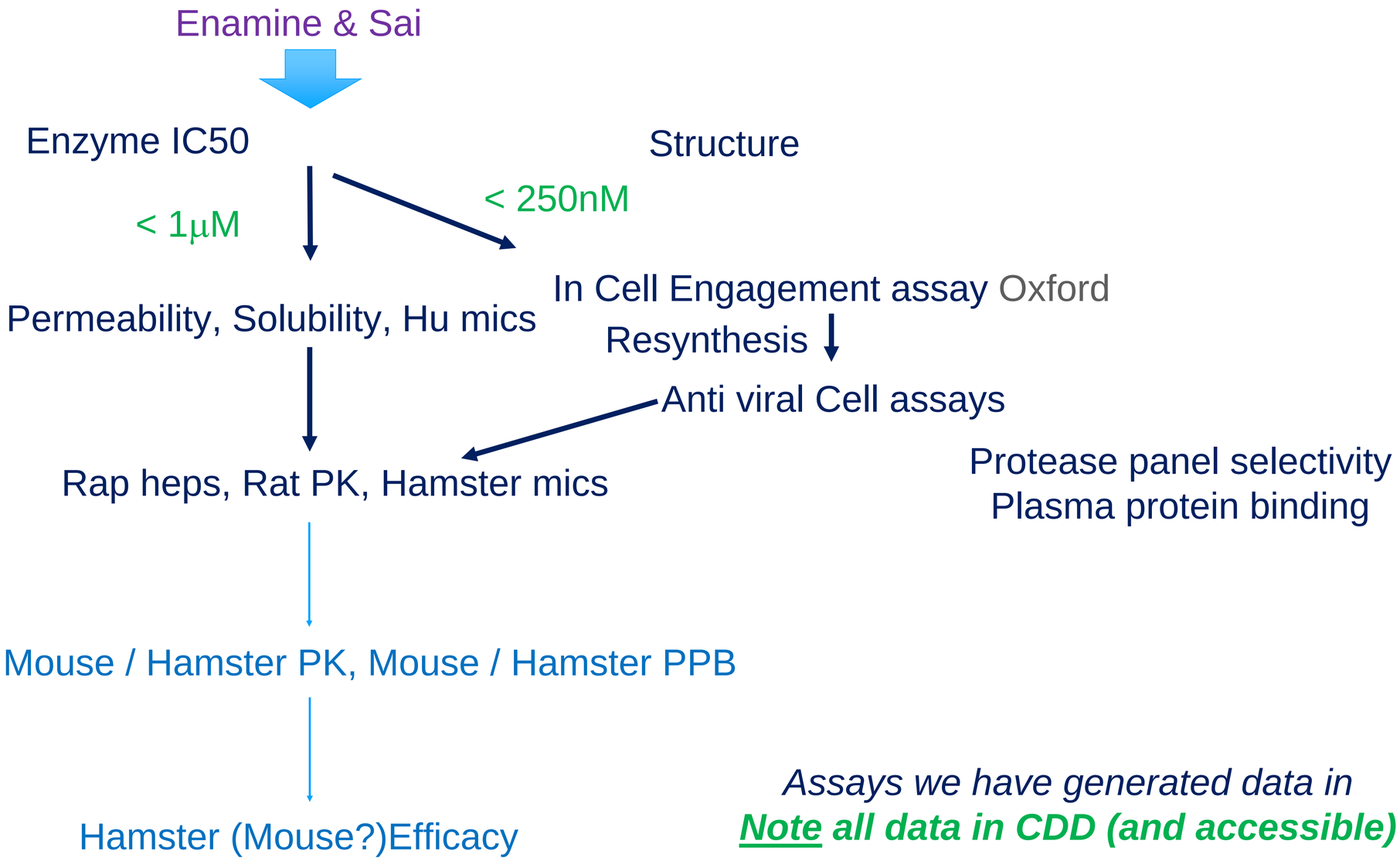
Does it kill the virus in cells?

Could it cause bad side effects?

Can a pill be made?

Flexible Critical Path Cascade



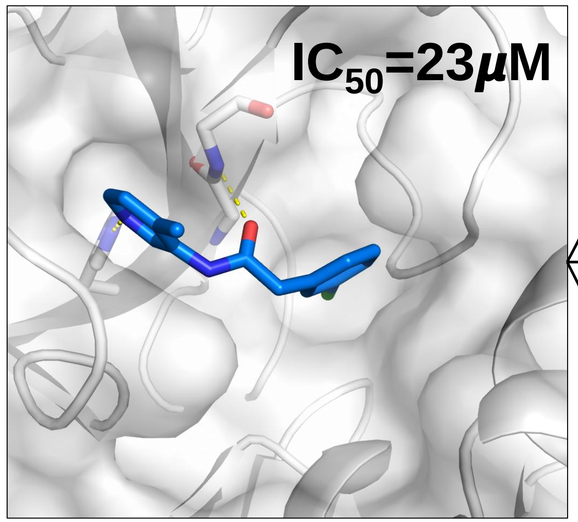


Assays we have generated data in

***Note* all data in CDD (and accessible)**

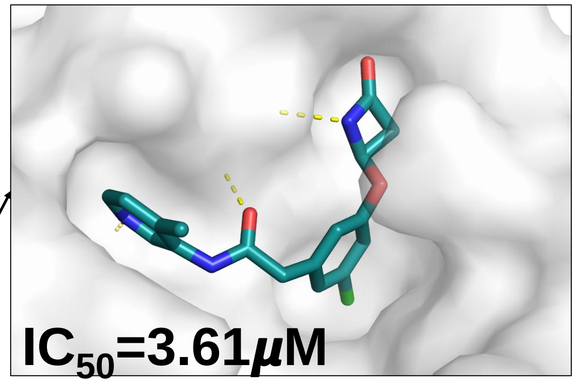
Aminopyridines

~300 compounds with an amino pyridine substructure tested

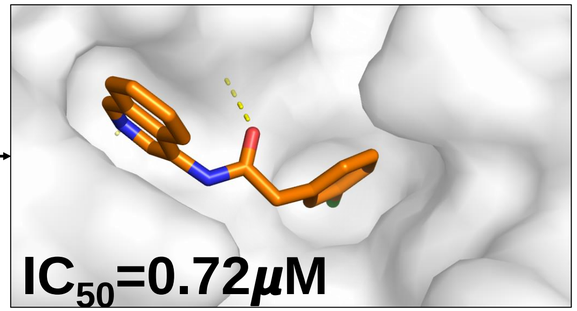


~ 40 with IC_{50} <10 μM

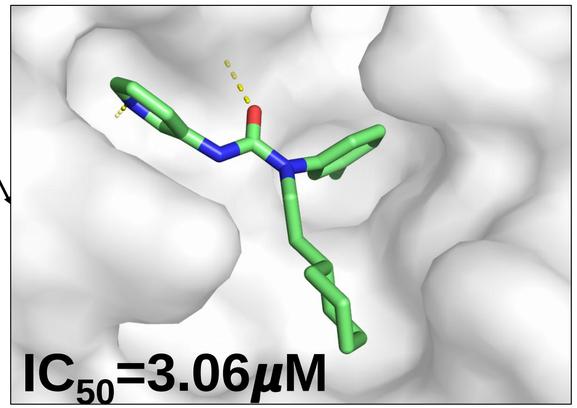
6.4x



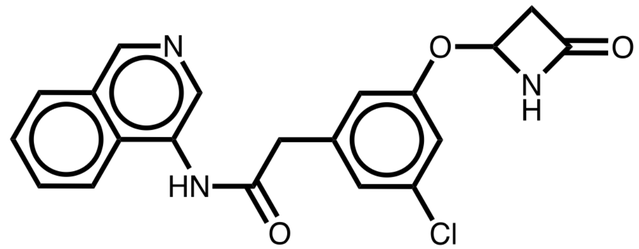
32x

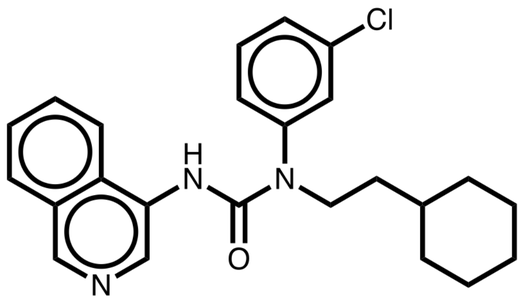


7.5x



IC_{50}=0.26μM

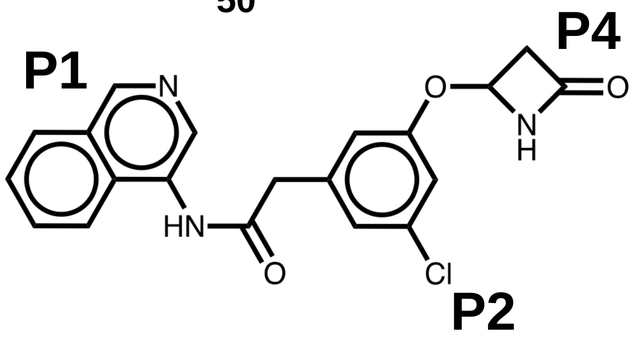


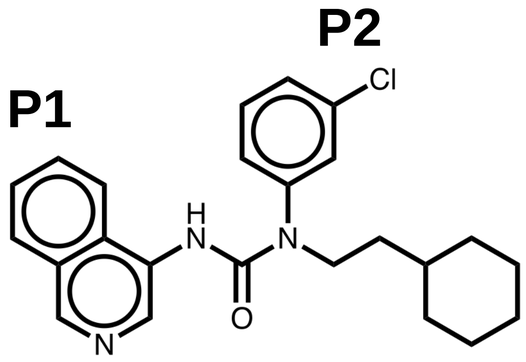


IC_{50}=0.27μM

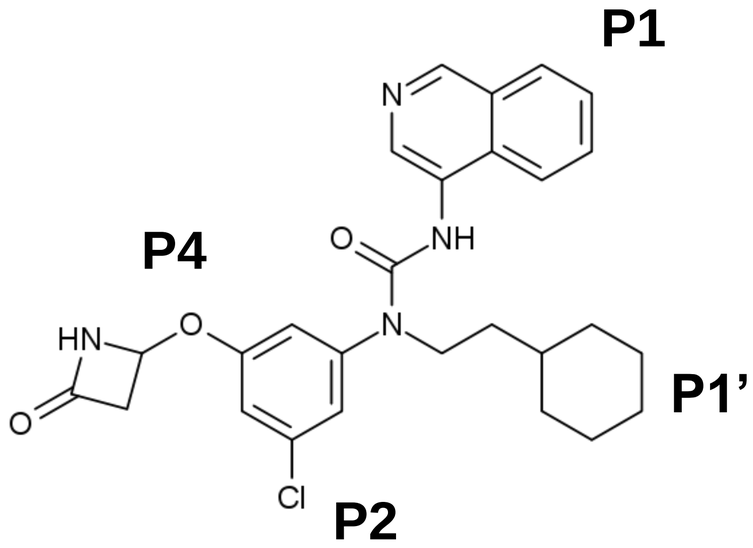
Aminopyridines – understanding SAR

IC_{50}= 260nM



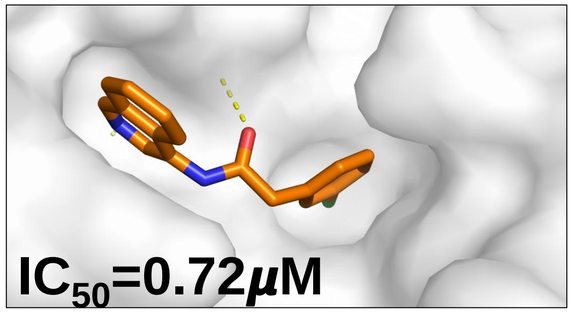


IC_{50}= 270nM

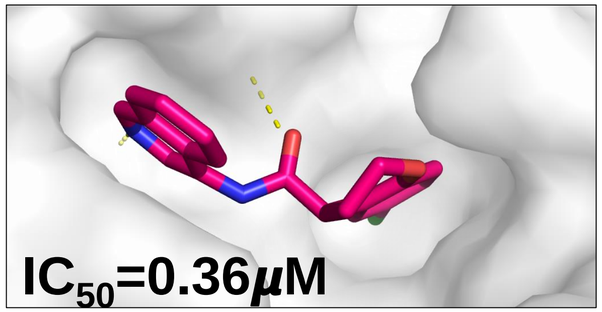


IC_{50}= 57nM

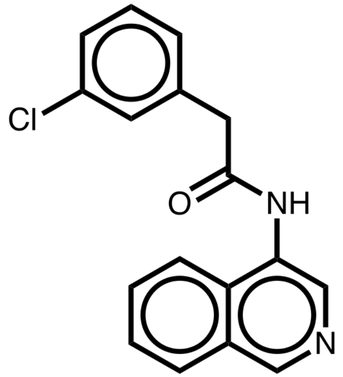
Aminopyridines - benzopyrans

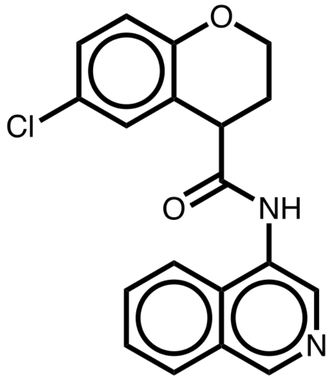


IC_{50}=0.72μM

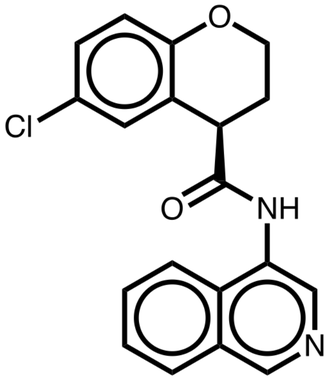


IC_{50}=0.36μM

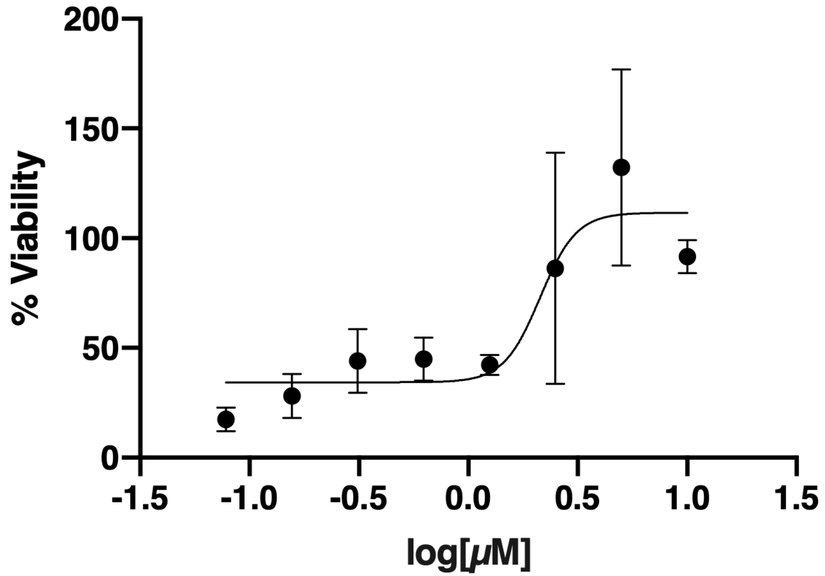




IC_{50}=0.14μM

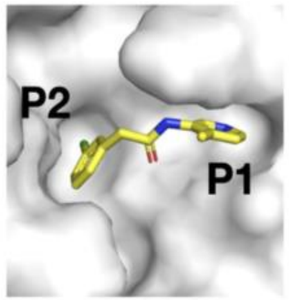


Viral activity assay
(Live SARS-CoV-2)
EC_{50} = 2 μM

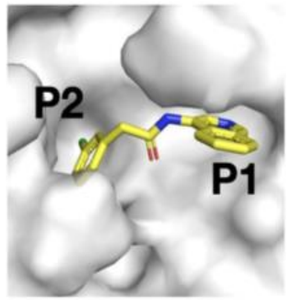


With the Israel Institute of Biological Research

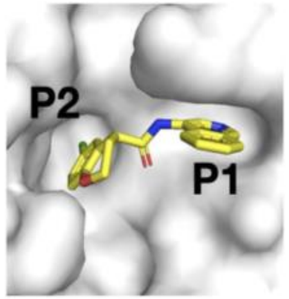
Aminopyridines – progression since August



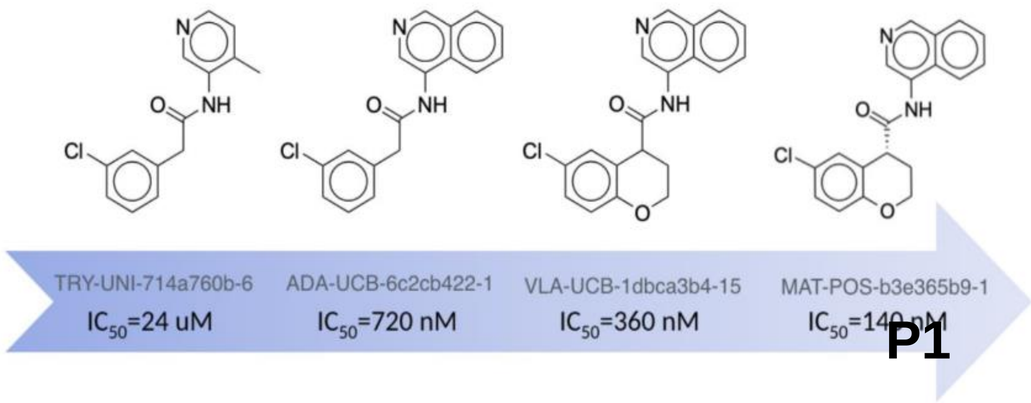
DiamondMX/XChem x2646



DiamondMX/XChem x10959

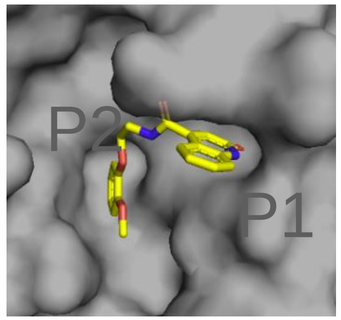


DiamondMX/XChem x11498

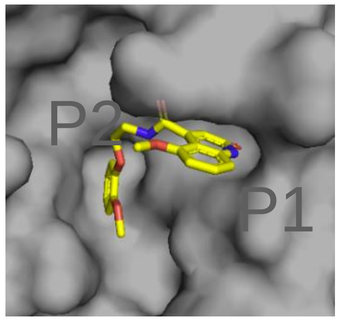


Assay	Type	August	December	TPP goal
Tier 1		**JOR-UNI-2fc98d0b-12**	**MAT-POS-b3e365b9-1**	
Mpro inhibition (Fluorescence)	IC50	3.1 µM	141 nM	<50 nM
Mpro inhibition (RapidFire)	IC50	3.3 µM	257 nM	<50 nM
thermodynamic solubility	solubility		34 µM	>10 µM
plasma protein binding	fraction unbound		12±2% unbound	>1% unbound
Tier 2				
VeroE6 antiviral activity (CPE)	IC50		1.57 µM	<5 µM
VeroE6 antiviral activity (qPCR)	IC50	7.31 µM	2.63 µM	<5 µM
VeroE6 cytotoxicity	CC50	25.5 µM	>500 µM	>100 µM
A549 cytotoxicity	CC50	14.1 µM	>100 µM	>100 µM
Calu-3 cytotoxicity	CC50	18.2 µM	>100 µM	>100 µM
protease selectivity at 100 µM	40 human protease panel		<12%	<40%
MDCK-MDR1	Papp		41±1 x10^-6 cm/s	>10 x10^-6 cm/s
human liver	CLint		98.3 µg/min/mg protein	<10 µg/min/mg protein
microsomal stability	t 1/2		14.1 min	>120 min
Tier 3				
rat oral bioavailability	t 1/2		1 h	>8 h

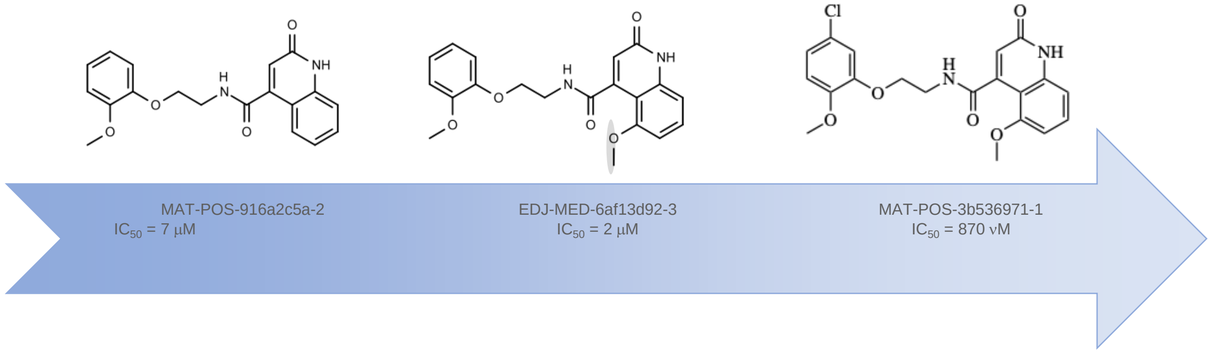
Quinolones – progression since August

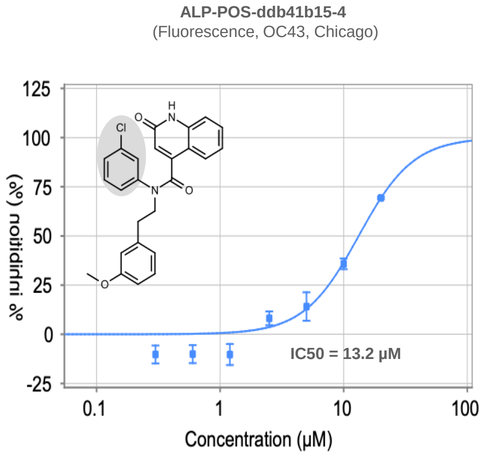


Diamond MX/XChem x2910



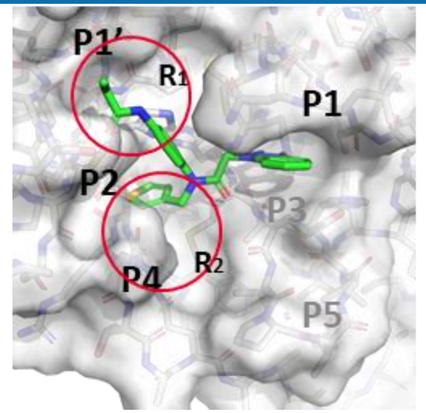
Diamond MX/XChem 11294

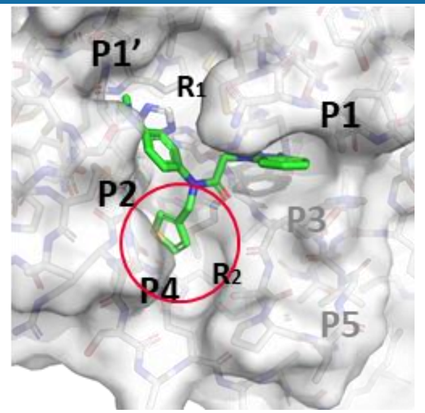


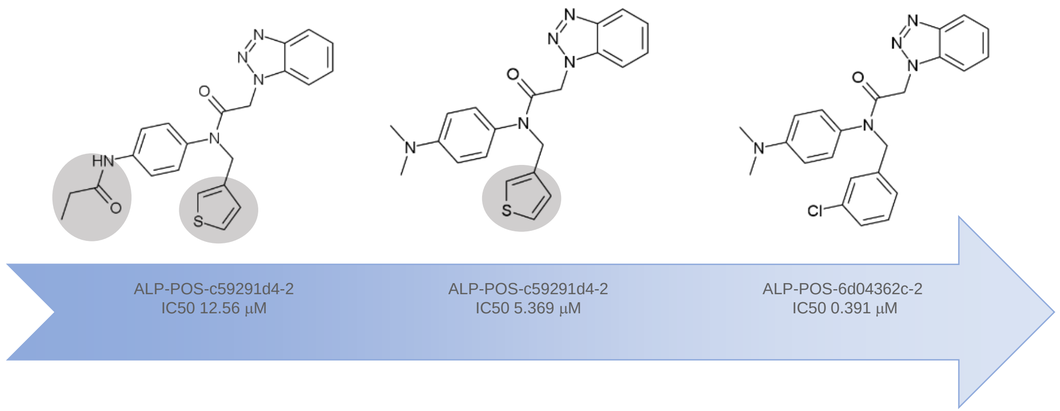


Assay	Type	August	December	December	TPP goal
Tier 1		**MAT-POS-916a2c5a-2**	**EDJ-MED-6af13d92-3**	**MAT-POS-3b536971-1**	
Mpro inhibition (Fluorescence)	IC50	7.5 µM	2.03 µM	870 nM	<50 nM
Mpro inhibition (RapidFire)	IC50	3.5 µM	2.08 µM		<50 nM
thermodynamic solubility	solubility		84 µM		>10 µM
plasma protein binding	fraction unbound		29.5±0.7% unbound		>1% unbound
Tier 2					
VeroE6 antiviral activity (fluorescence, OC43)	IC50		>20 µM		<5 µM
VeroE6 antiviral activity (CPE)	IC50		not active		<5 µM
VeroE6 cytotoxicity	CC50		>20 µM		>100 µM
A549 cytotoxicity	CC50		>10 µM		>100 µM
Calu-3 cytotoxicity	CC50		>100 µM		>100 µM
protease selectivity at 100 µM	40 human protease panel		<10%		<40%
MDCK-MDR1	Papp		2.0±0.1 x 10^-6 cm/s		>10 x 10^-6 cm/s
human liver	CLint		19.3 µg/min/mg protein		<10 µg/min/mg protein
microsomal stability	t 1/2		71.9 min		>120 min
Tier 3					
rat oral bioavailability	t 1/2		43 min		>8 h

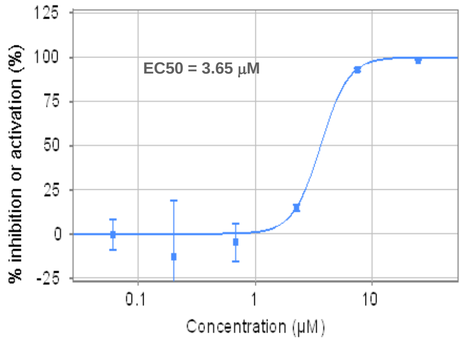
Benzotriazoles – progression since August





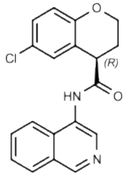
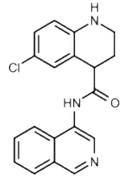
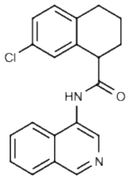
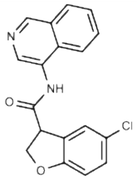


ALP-POS-c59291d4-2
(qPCR, SARS-CoV-2, Radboud)

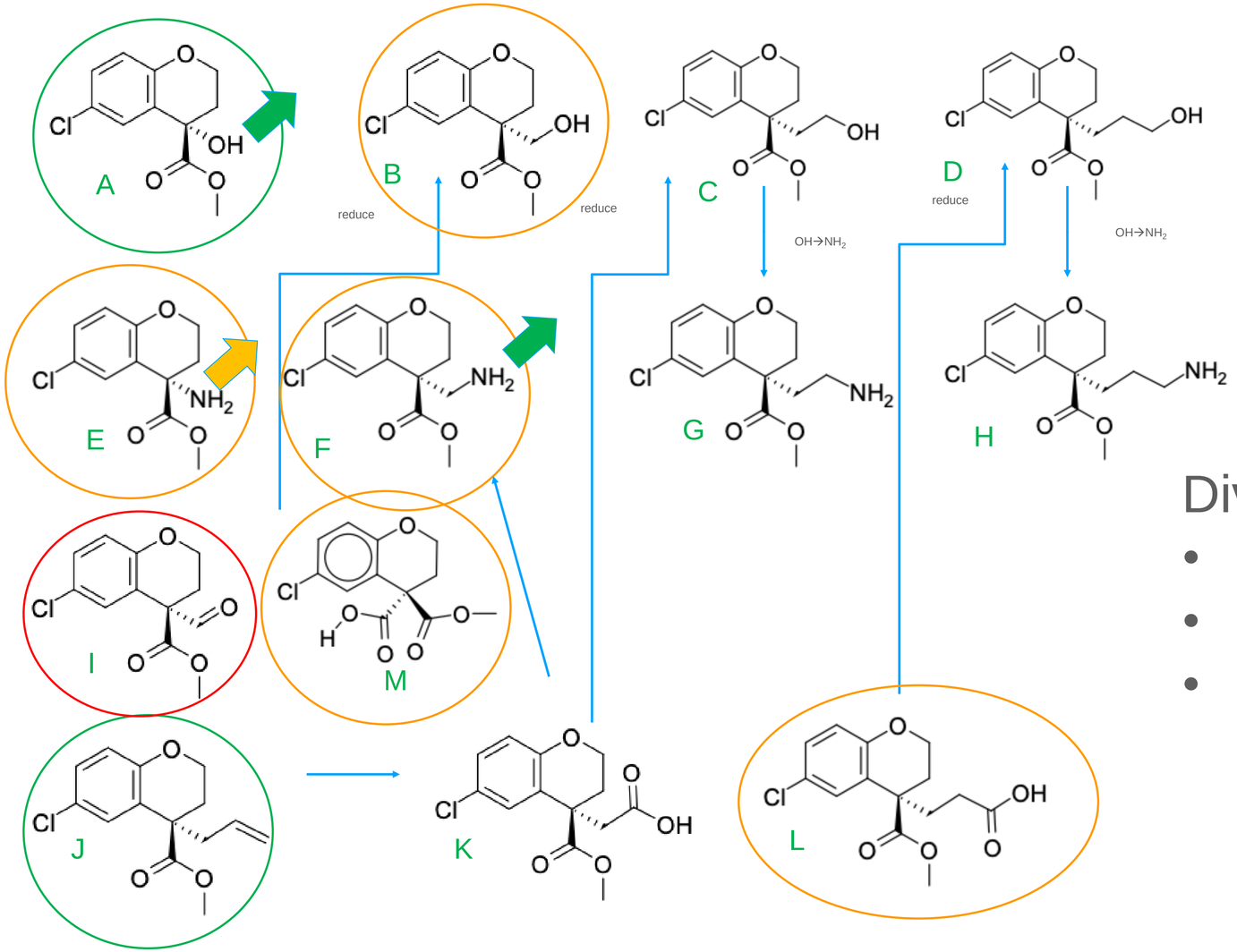


Assay	Type	August	December	TPP goal
Tier 1		**ALP-POS-c59291d4-2**	**ALP-POS-6d04362c-2**	
Mpro inhibition (Fluorescence)	IC50	1.63 µM	497 nM	<50 nM
Mpro inhibition (RapidFire)	IC50	12.6 µM	391 nM	<50 nM
Tier 2				
VeroE6 antiviral activity (Fluorescence, OC43)	IC50	>20 µM		<5 µM
VeroE6 antiviral activity (CPE)	IC50	not active		<5 µM
VeroE6 antiviral activity (CPE)	IC50	3.65 µM		<5 µM
VeroE6 cytotoxicity	CC50	>100 µM		>100 µM
A549 cytotoxicity	CC50	>20 µM		>100 µM
Calu-3 cytotoxicity	CC50	>100 µM		>100 µM
protease selectivity at 100 µM		<35%		<40%
MDCK-MDR1	Papp			>10 x10^-6 cm/s
human liver	CLint	641 µg/min/mg protein		<10 µg/min/mg protein
microsomal stability	t 1/2	2.16 min		>120 min

Aminopyridines – clearance & solubility

Molecule Name	Structure	CDD Number	SMILES	Synonyms	Projects	Batch Name	External ID		HLM t 1/2	HLM Clint(uL/min/mg)	PBS solubility, 24h, pH 7.4, µM
CVD-0013192		CDD-23865	Clc1ccc2OCC[C@@H](C(=O)N		Compound	001	MAT-POS-b3e365b9-1		48.12	34.71	22
CVD-0013212		CDD-23865	Clc1ccc2NCCC(C(=O)Nc3cncc		Compound	001	ALP-POS-477dc5b7-2		95	18	94
CVD-0013211		CDD-23865	Clc1ccc2CCCC(C(=O)Nc3cncc		Compound	001	ALP-POS-477dc5b7-1		15	111	74
CVD-0012962			Clc1ccc2OCC(C(=O)Nc3cncc4		Compound	001	MAT-POS-f7918075-2		125	13	89

Aminopyridines - reach to P1’



Diversification led by:

- FEP,
- pharmacophore clusters
- ML