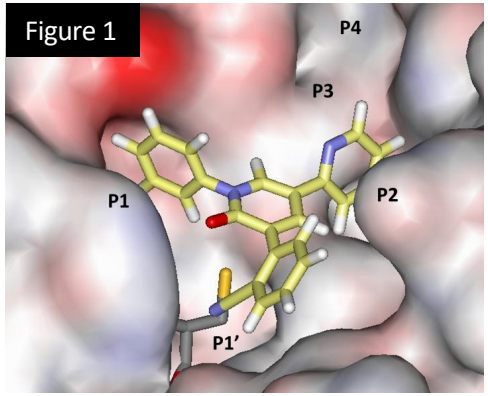
OCR8038: 20 nM SARS-CoV-2 Protease Inhibitors

Yale

Structure-based design of M^{pro} Antagonists



- Potent (IC_{50} sub-20nM) series of small molecule, non-peptidic, non-covalent, inhibitors of the SARS- CoV-2 main protease (M^{pro}) (Table 1).
- Weak binding non-antiviral approved drug (Table 1/Cmpd 1) optimized for M^{pro} inhibition (Table 1/Cmpds 18 - 25).
- High-resolution co-crystal structures of complexes (Figure 1).
- Demonstrated anti-viral properties in vitro (Table 2).
- Synergy with remdesivir (Figure2)
- Drug-like properties & commercially viable synthetic routes

Table 1. Measured activities for inhibition of SARS-CoV-2 M^{pro}.

Cmpd	IC_{50} (μM)	Cmpd	IC_{50} (μM)	Cmpd	IC_{50} (μM)
1	100-250[a]	**11**	0.120 ± 0.016	**21**	0.018 ± 0.002
2	9.99 ± 2.50	**12**	0.25 ± 0.09	**22**	0.036 ± 0.004
3	6.38 ± 1.21	**13**	0.19 ± 0.03	**23**	0.020 ± 0.005
4	4.02 ± 1.36	**14**	0.128 ± 0.015	**24**	0.037 ± 0.004
5	0.14 ± 0.02	**15**	0.110 ± 0.013	**25**	0.025 ± 0.003
6	0.47 ± 0.02	**16**	0.100 ± 0.007	**26**	0.170 ± 0.022
7	0.28 ± 0.05	**17**	0.110 ± 0.035	**27**	0.120 ± 0.006
8	0.51 ± 0.02	**18**	0.024 ± 0.007		
9	1-10 [a]	**19**	0.037 ± 0.007		
10	1.20 ± 0.03	**20**	0.036 ± 0.003		

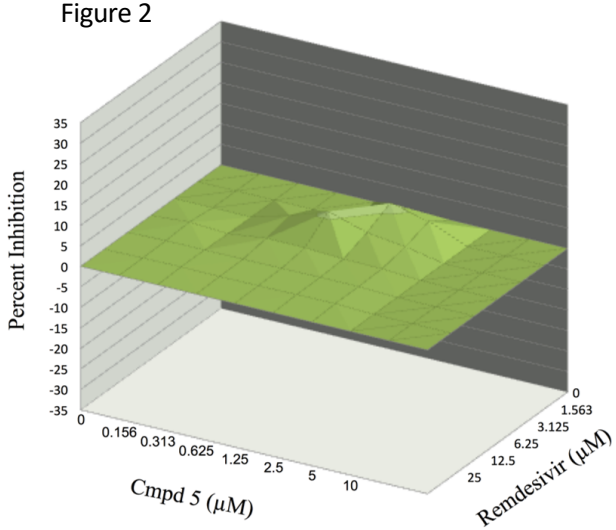
[a] Fluorescence of compound interfered with assay.

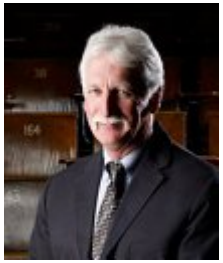
Table 2. Anti-SARS-CoV-2 activity and cellular toxicity (μM).

Compound	EC_{50} MTT	EC_{50} Plaque	CC_{50} Vero E6	CC_{50} NHBE
remdesivir	1.1 ± 0.2	0.77[a]	72 ± 28	41 ± 2
5	2.5 ± 0.7	1.5	22 ± 7.2	20 ± 2
14	NA[b]	3.2[c]	12.3 ± 7.0	17.5 ± 5.5
21	NA[b]	11.3[c]	1.7 ± 0.9	2 ± 0.1
23	NA[b]	0.84	1.15 ± 0.5	3.5 ± 1.0
26	2.0 ± 0.7	0.98	>100	>100
27	1.1 ± 0.5	ND[d]	22± 8	25± 5

[a] Ref. 24. [b] NA = not active. [c] Drop in viral titer/incomplete inhibition. [d] ND = not determined

Figure 2





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