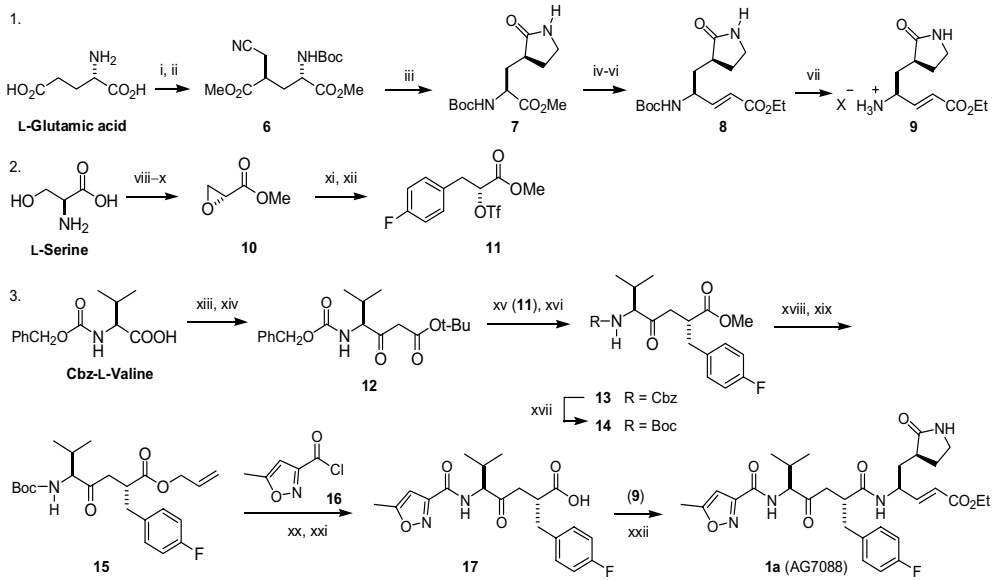
Supplementary data

Table SI: Inter- and intra-interactions of SARS $3CL^{pro}$ dimers

Atom pairs in the interacting amino acid residues with minimal contact distances (< 3.5 Å) are listed.

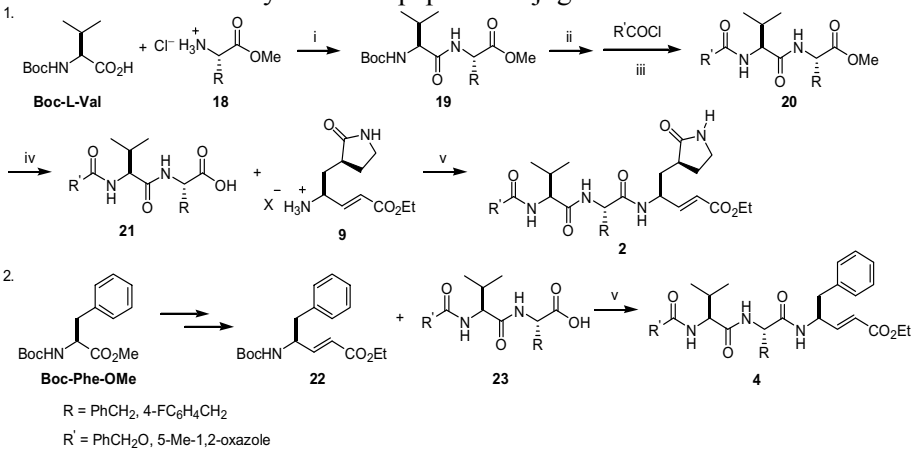
Residue 1	Atom 1	Residue 2	Atom 2	Distance (Å)
Interactions of N-terminus from protomer A				
A Ser1	Og	B Glu166	OE2	2.56
A Ser1	N	B Glu166	OE1	2.48
A Ser1	N	B His172	N	2.83
A Gly2	O	B Ser139	Og	2.90
A Lys5	N	AGlu290	OE1	2.53
A Ala7	N	B Val125	O	3.01
A Ala7	O	B Val125	N	2.74
Interactions of N-terminus from protomer B				
B Ser1	N	AGlu166	OE1	2.95
B Ser1	N	A His172	N	3.16
B Ala7	N	A Val125	O	3.04
B Ala7	O	A Val125	N	2.80
Interactions of C-terminus from protomer A				
A Ser301	N	A Val297	N	2.62
A Val303	O	B Ser123	Og	3.53
A Gln306	OE1	A Lys12	NZ	3.19

Scheme S1. Synthesis of AG7088 (Compound 1)



Reagents and conditions: (i) Me_3SiCl, MeOH, 0 °C, 18 h; then Boc_2O, Et_3N, 0–25 °C, 4 h; 96%. (ii) $LiN(SiMe_3)_2$, THF, −78 °C, 3 h; then $BrCH_2CN$, 3.5 h; 82%. (iii) H_2, cat. PtO_2, MeOH, $CHCl_3$, 25 °C, 12 h; then NaOAc, reflux, 12 h; 81%. (iv) $NaBH_4$, LiCl, THF, EtOH, 25 °C, 18 h; 89%. (v) pyridine-SO_3, Me_2SO, CH_2Cl_2, (*i*-Pr)$_2$NEt, −10 °C, 3 h. (vi) $[EtO_2CCHPO(OEt)_2]^- Na^+$, THF, −78 °C, 1 h; 75% yield for two steps. (vii) HCl, 1,4-dioxane, rt, 2 h. (viii) HBr, $NaNO_2$, KBr, H_2O, −10 °C, 12 h. (ix) KOH, EtOH, 0 °C, 12 h. (x) Me_2SO_4, CH_2Cl_2, cat. $(PhCH_2)Et_3N^+ Cl^-$, rt, 24 h; 70% for three steps. (xi) 4-FC_6H_4MgBr, CuBr-Me_2S, THF, −35 °C, 1 h; 86%. (xii) $(CF_3SO_2)_2O$, 2,6-lutidine, CH_2Cl_2, 0 °C, 40 min. (xiii) 1,1'-carbonyldiimidazole, THF, rt, 1 h. (xiv) CH_3CO_2t-Bu, $LiN(i\text{-}Pr)_2$, THF, −78 °C, 1 h; 65%. (xv) NaH, THF, 0 °C, 30 min; then triflate **11**, THF, 0 °C to rt, 24 h. (xvi) CF_3CO_2H, CH_2Cl_2, rt, 24 h; 71% for two steps. (xvii) H_2, Pd/C, Boc_2O, MeOH, rt, 10 h; 83%. (xviii) LiOH (1.1 equiv), H_2O, 1 h, 0 °C; 90%. (xix) allyl iodide, Cs_2CO_3, DMF, 45 °C, 5 h; 85%. (xx) *N*-methylmorpholine (NMM), CH_2Cl_2, 0–25 °C, 2 h; 88%. (xxi) $Pd(PPh_3)_4$, morphloine, THF, 25 °C, 3 h; 84%. (xxii) HOBt, EDCI, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0–25 °C, 20 h; 70%.

Scheme S2. Combinatorial synthesis of peptide conjugated esters **2a**−**d** and **4a**−**d**.



Reagents and conditions: (i) DCC, HOBt, Et_3N, DMF, CH_2Cl_2, 0–25 °C, 12–24 h; 81–89%. (ii) CF_3CO_2H, CH_2Cl_2, 25 °C, 3 h. (iii) NMM, CH_2Cl_2, 0–25 °C, 4 h. (iv) LiOH, MeOH, 0 °C, 2 h. (v) HOBt, EDCI, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0–25 °C, 20 h.