**Structure, Volume *29***

## Supplemental Information

# Structure-guided design of a perampanel-derived pharmacophore targeting the SARS-CoV-2 main protease

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**Supplementary Information**

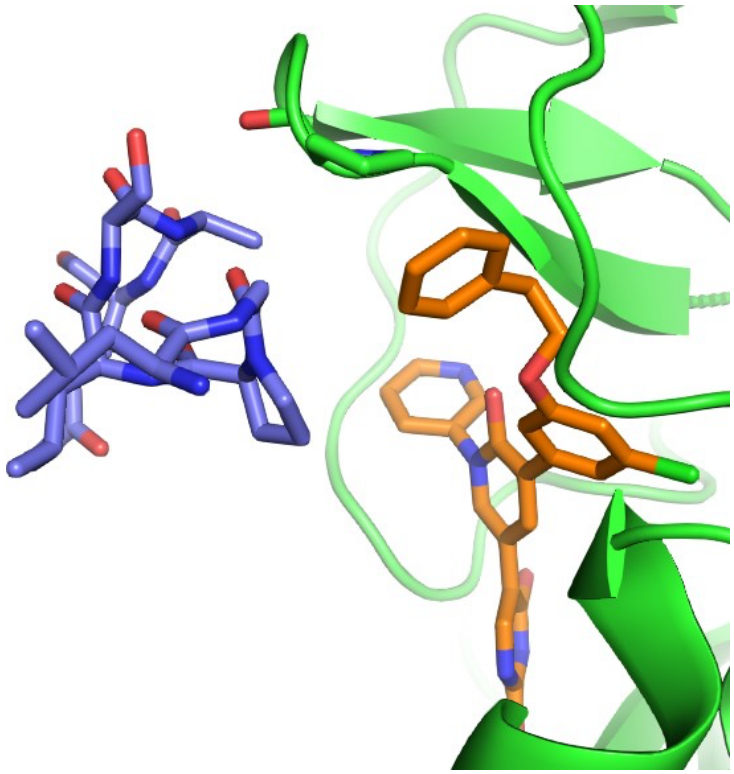

**Figure S1**. **Crystal structure of the complex of M$^{pro}$ with compound 15.** M$^{pro}$:**15** is shown with M$^{pro}$ in green, **15** in orange,and Leu$^{250}$-Gln$^{256}$ of a symmetry-related molecule that packs in close proximity to Pro$^{168}$ shown in blue. Related to Figure 4.

| Complex | Mpro: Mpro-6 | Mpro: Mpro-11 | Mpro: Mpro-29 | Mpro: Mpro-15 | Mpro: Mpro-16 | Mpro: Mpro-19 | Mpro: Mpro-50 | Mpro: Mpro-25 | Mpro: Mpro-23 |
|---|---|---|---|---|---|---|---|---|---|
| PDB ID | 7M8X | 7M8M | 7M8Z | 7M8Y | 7M8N | 7M8O | 7M90 | 7M91 | 7M8P |
| | | | | | | | | | |
| **Data collection** | | | | | | | | | |
| X-Ray Source | APS 24ID-E | APS 24ID-E | APS 24ID-E | APS 24ID-E | NSLS-II17-ID-1 | NSLS-II17-ID-1 | NSLS-II17-ID-1 | APS 24ID-E | APS 24ID-E |
| Wavelength, Å | 0.97918 | 0.97918 | 0.97918 | 0.97918 | 0.920106 | 0.920106 | 0.920106 | 0.97918 | 0.97918 |
| Space Group | C2 | P212121 | C2 | C2 | P212121 | P212121 | C2 | C2 | P212121 |
| Cell dimensions | | | | | | | | | |
| a, b, c (Å) | 96.831, 81.325, 54.553 | 67.790, 100.292, 103.036 | 97.711, 81.57, 54.567 | 115.371, 53.545, 44.719 | 67.306, 100.947, 104.137 | 67.841, 101.922, 103.797 | 96.807, 82.660, 54.667 | 97.9, 81.1, 54.7 | 68.18, 100.61, 104.35 |
| | | | | | | | | | |
| α, β, γ (˚) | 90, 116.827, 90 | 90, 90, 90 | 90, 116.678, 90 | 90, 103.198, 90 | 90, 90, 90 | 90, 90, 90 | 90, 117.53, 90 | 90, 116.6, 90 | 90, 90, 90 |
| Resolution (Å) | 48.652-1.751 (1.85-1.74) | 103.036-1.786 (1.88-1.78) | 48.758-1.8000 (1.90-1.79) | 56.162-1.761 (1.86-1.75) | 29.582-1.966 (2.07-1.96) | 29.503-2.449 (2.58-2.44) | 27.158-2.279 (2.40-2.27) | 48.781-1.961 (2.07-1.95) | 72.482-2.237 (2.36-2.23) |
| *R*merge | 0.074 (0.834) | 0.077 (0.813) | 0.092 (0.478) | 0.069 (0.440) | 0.136 (0.732) | 0.170 (0.710) | 0.063 (0.173) | 0.14 (0.465) | 0.064 (0.344) |
| $I / \sigma I$ | 9.88 (1.41) | 14.60 (2.52) | 7.87 (1.93) | 8.37 (1.98) | 6.24 (1.35) | 11.93 (3.19) | 11.77 (4.83) | 10.85 (4.34) | 10.52 (2.82) |
| Completeness (%) | 94.7 (98.0) | 99.6 (98.1) | 97.1 (90.8) | 96.7 (91.8) | 98.3 (97.7) | 99.5 (97.8) | 97.1 (98.1) | 96.9 (94.0) | 97.9 (92.3) |
| Redundancy | 3.440278486 | 6.802257804 | 3.374860441 | 2.660227318 | 3.074058904 | 13.37499545 | 3.046290425 | 3.317307692 | 3.11713985 |
| | | | | | | | | | |
| **Refinement** | | | | | | | | | |
| Resolution (Å) | 48.65-1.74 | 71.87-1.78 | 48.76-1.79 | 56.16-1.75 | 29.50-1.96 | 29.50-2.44 | 27.15-2.19 | 48.78-1.95 | 72.43-2.23 |
| No. reflections | 38,050 | 68,032 | 35,331 | 26,375 | 51,467 | 27,418 | 19,273 | 52,859 | 66,457 |
| *R*work / *R*free | 0.229/0.273 | 0.206/0.234 | 0.198/0.240 | 0.195/0.228 | 0.197/0.229 | 0.211/0.288 | 0.216/0.273 | 0.198/0.233 | 0.185/0.231 |
| No. atoms | | | | | | | | | |
| Protein | 2313 | 4669 | 2294 | 2357 | 4669 | 4756 | 2285 | 2342 | 4660 |
| Inhibitor | 53 | 51 | 58 | 58 | 116 | 55 | 61 | 51 | 55 |
| Water | 145 | 296 | 192 | 242 | 323 | 191 | 172 | 163 | 231 |
| *B*-factors | | | | | | | | | |
| Protein | 35.91 | 31.24 | 34.91 | 29.91 | 24.74 | 45.19 | 33.04 | 26.86 | 45.53 |
| Inhibitor | 34.69 | 33.07 | 36.24 | 34.08 | 24.81 | 44.14 | 31.3 | 28.45 | 49.67 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Water | 40.91 | 37.04 | 41.01 | 38.08 | 31.39 | 44.21 | 34.54 | 30.93 | 52.19 |
| R.m.s deviations | | | | | | | | | |
| Bond lengths (Å) | 0.007 | 0.006 | 0.007 | 0.007 | 0.007 | 0.007 | 0.009 | 0.007 | 0.007 |
| Bond angles(°) | 0.82 | 0.89 | 0.84 | 0.88 | 0.88 | 0.94 | 0.93 | 0.84 | 0.87 |
| Ramachandran | | | | | | | | | |
| Favored (%) | 97.99 | 97 | 98.63 | 98.67 | 97.17 | 92.48 | 95.41 | 97.32 | 97.01 |
| Allowed (%) | 2.01 | 2.83 | 1.37 | 1 | 2.33 | 7.17 | 4.24 | 2.68 | 2.82 |
| Outliers (%) | 0.00 | 0.17 | 0 | 0.33 | 0.5 | 0.35 | 0.35 | 0 | 0.17 |

**Table S1**. **Diffraction data and refinement statistics.** Related to Figures 4, 5, and STAR Methods.

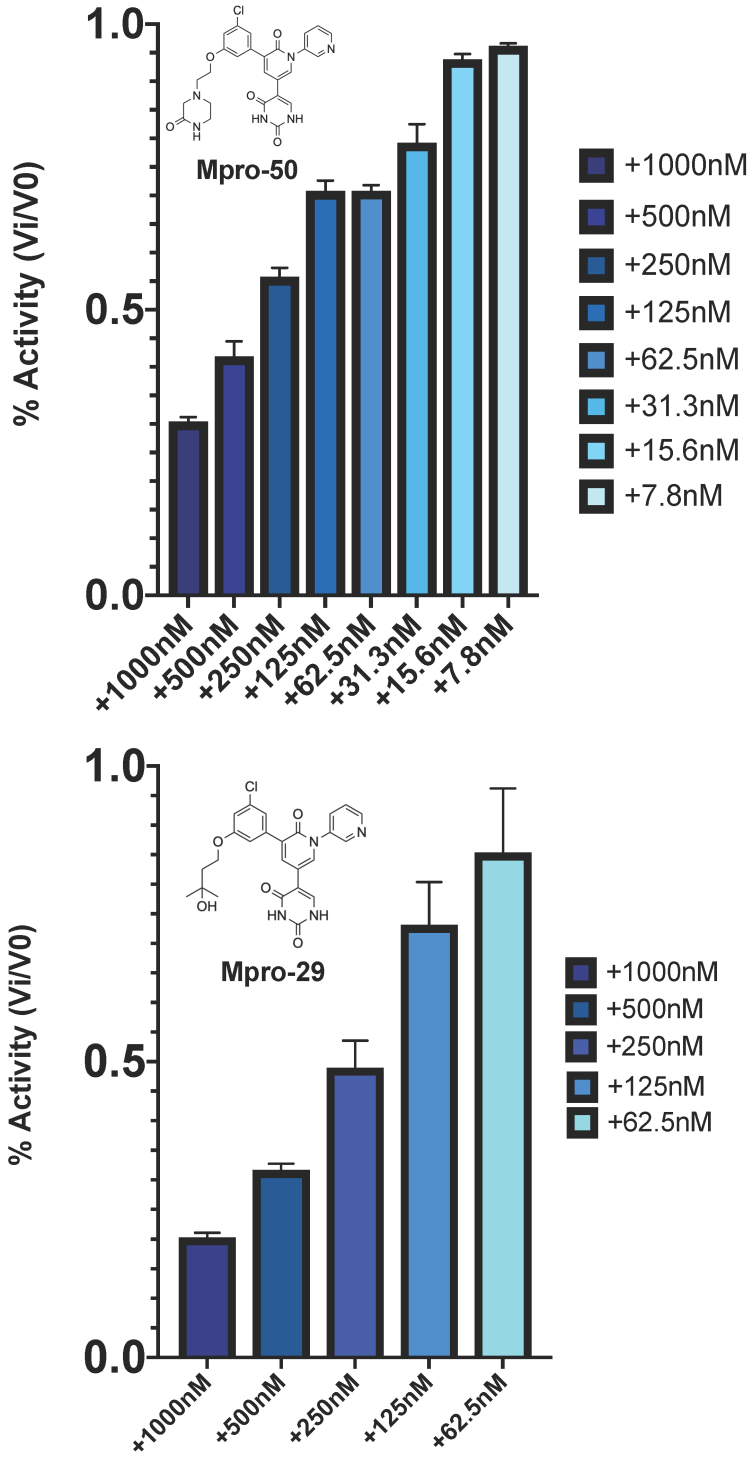


**Figure S2. %Activity (Vi/V0) of M$^{pro}$ with compounds 50 (top) and 29 (bottom).** Related to Table 1.

## NMR spectral data for synthesis of compounds 29 and 50

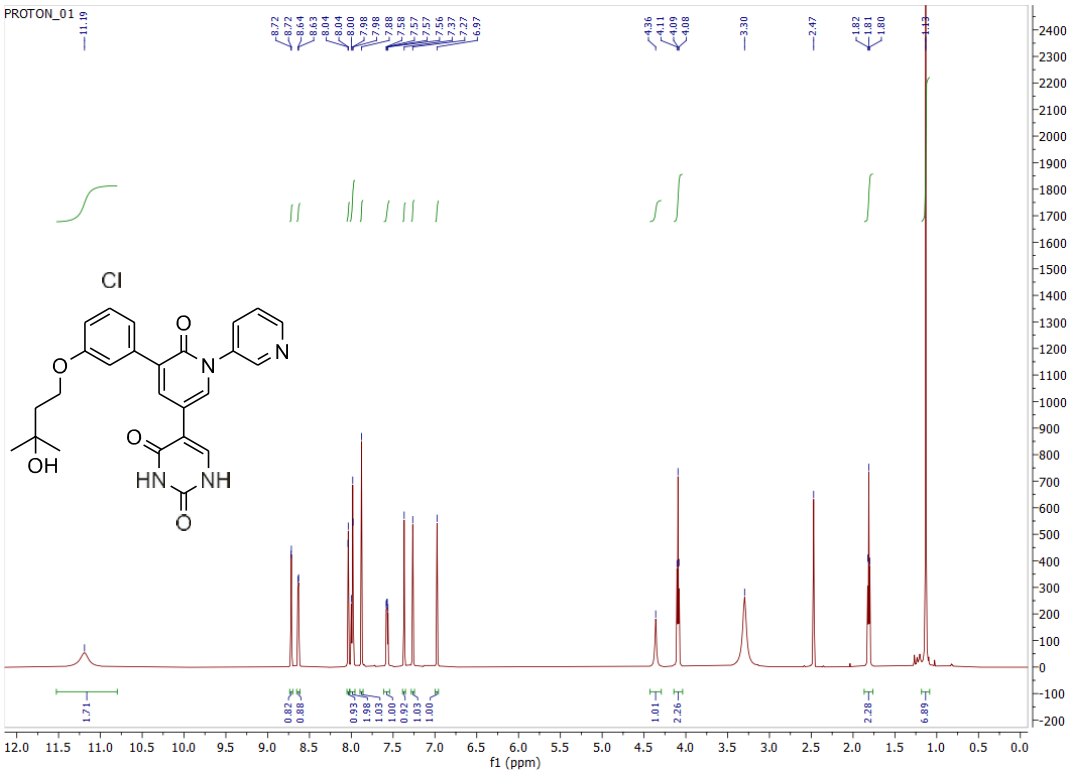


**Figure S3. 29**, **$^{1}$H NMR (600 MHz, DMSO-$d_6$)**. Related to STAR Methods.

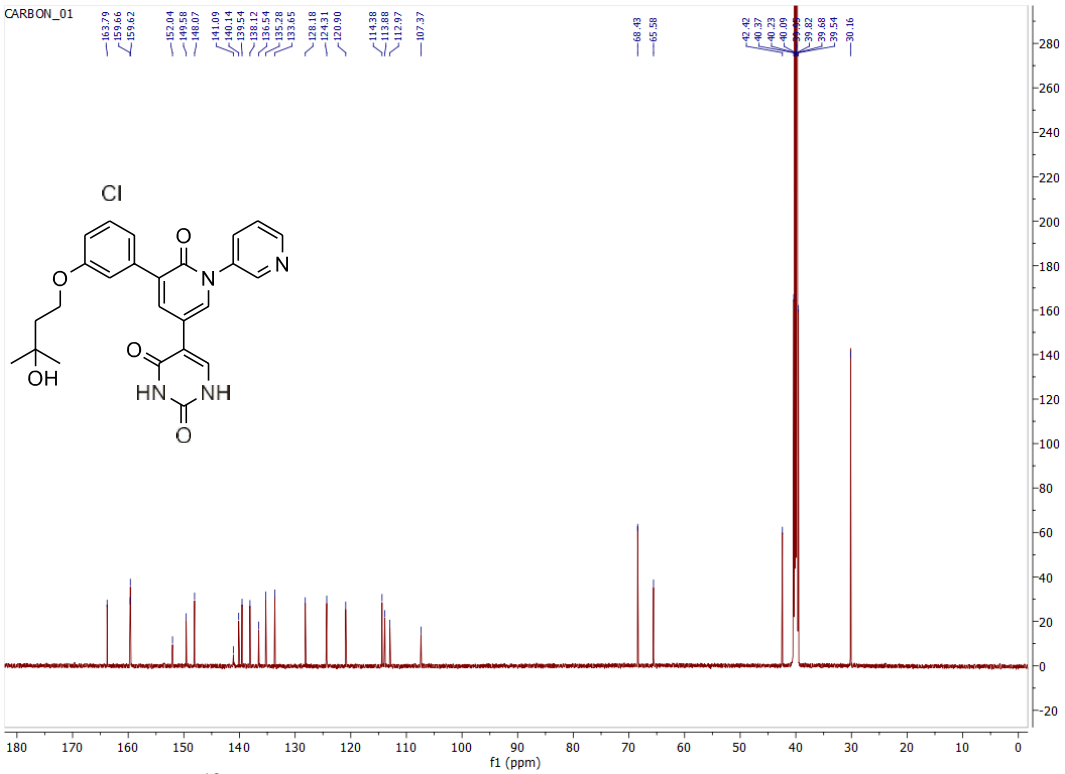


**Figure S4. 29, $^{13}$C NMR (151 MHz, DMSO-$d_6$).** Related to STAR Methods.

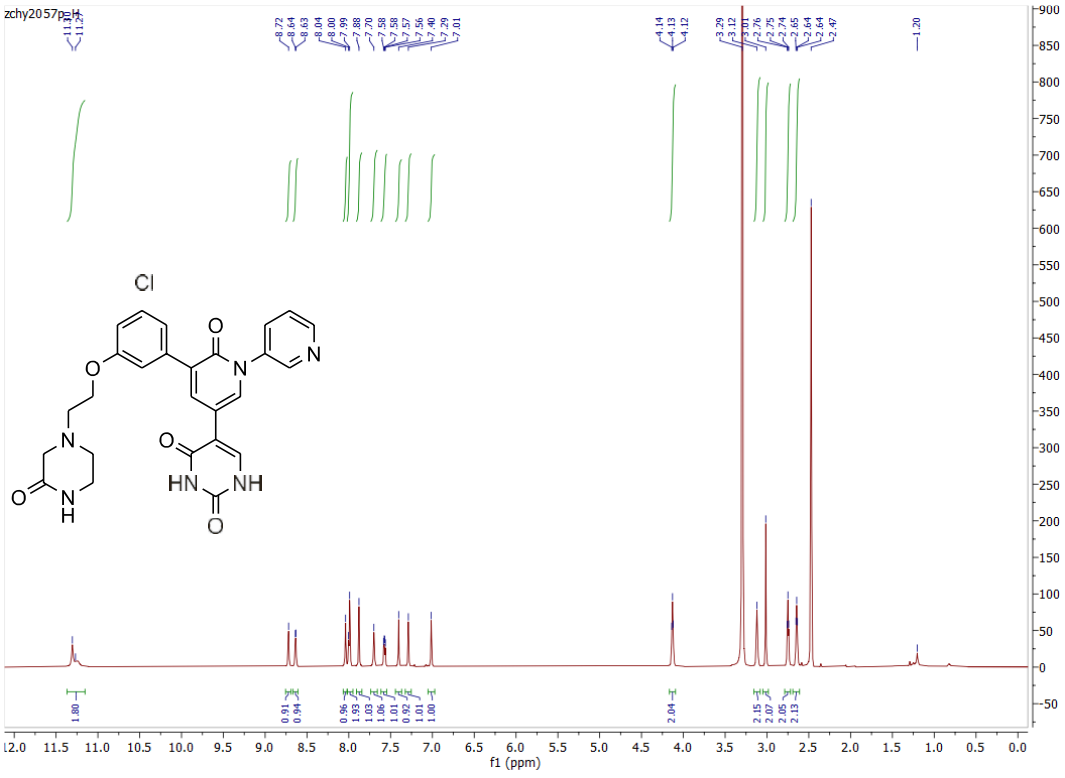


**Figure S5. 50, $^{1}$H NMR (600 MHz, DMSO-$d_6$).** Related to STAR Methods.

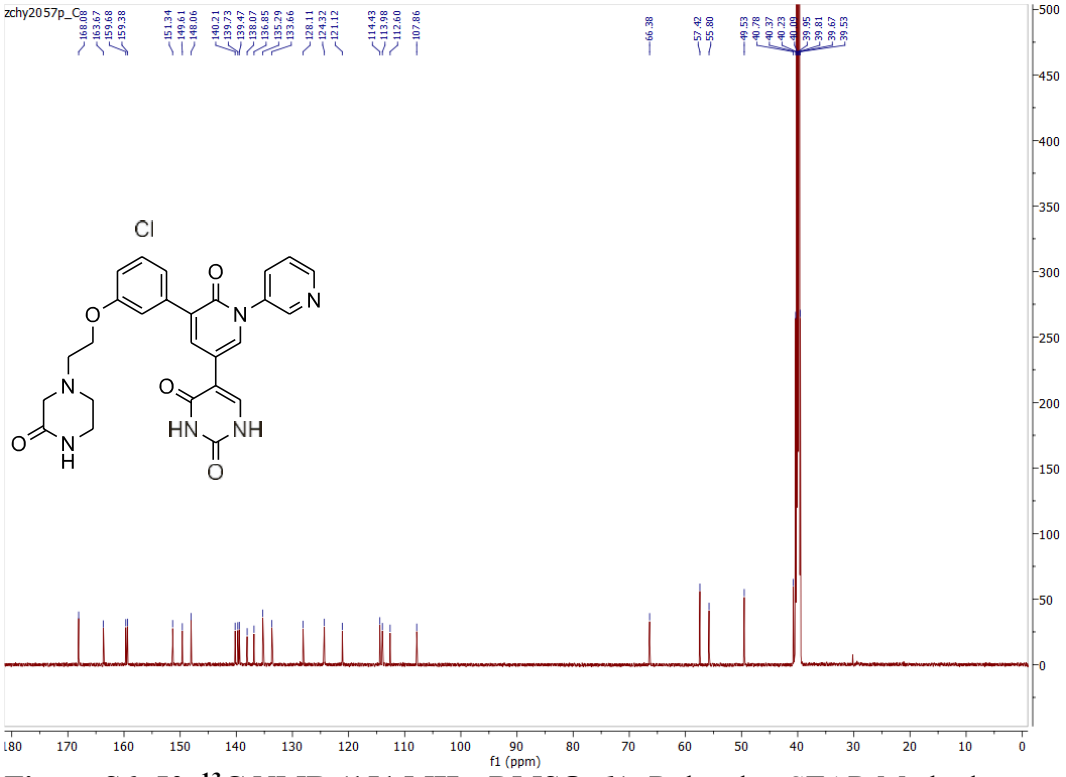


**Figure S6. 50, $^{13}$C NMR (151 MHz, DMSO-$d_6$)**. Related to STAR Methods.