# SUPPORTING INFORMATION

# Quercetin and Luteolin are single-digit micromolar inhibitors of the SARS- CoV-2 RNA-dependent RNA polymerase

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#Equally contributed.

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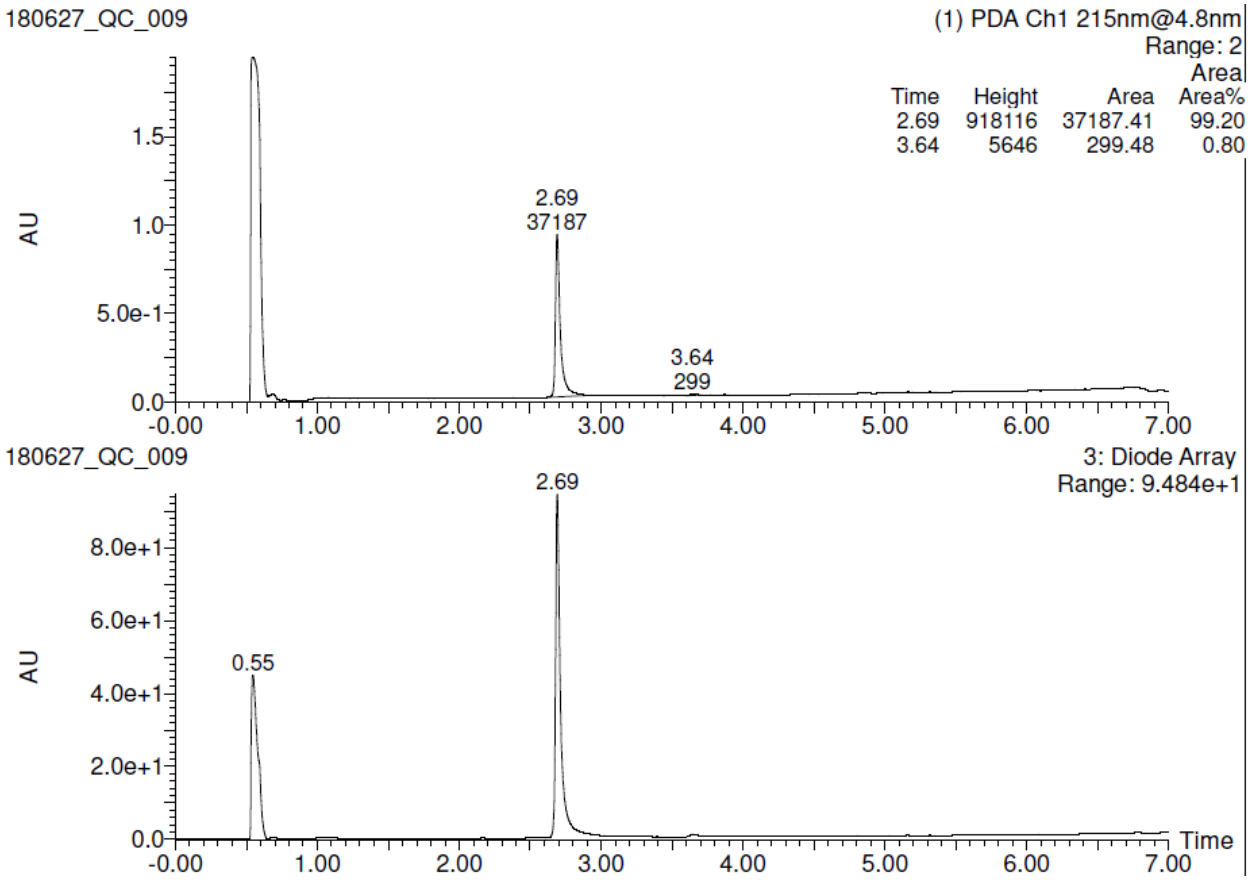
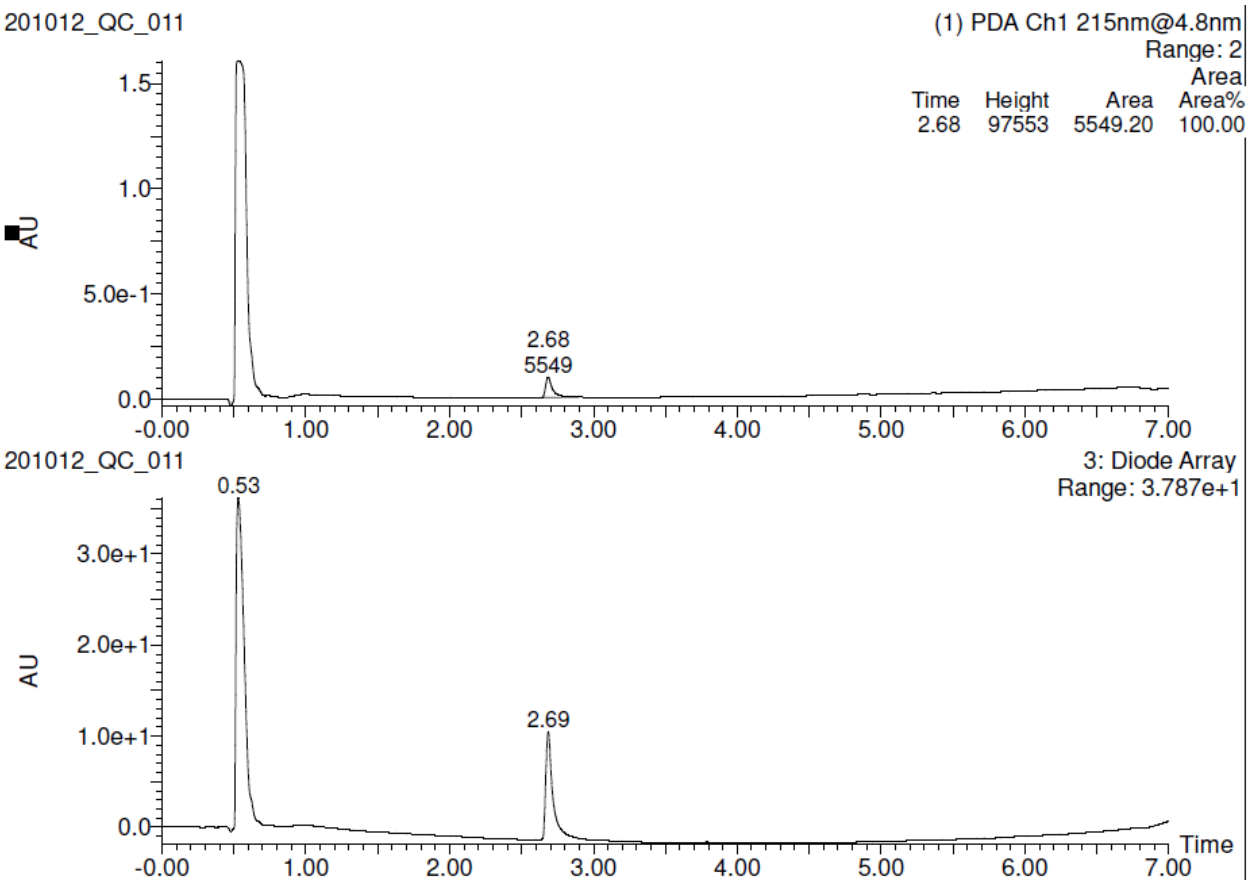
## 1. Chromatography analysis of luteolin and quercetin

The chromatographic analyses were run on an ACQUITY UPLC BEH C18 (50x2.1mmID, particle size 1.7µm) with a VanGuard BEH C18 pre-column (5x2.1mmID, particle size 1.7µm) (LogD>1). The mobile phase was 10mM $NH_4OAc$ in $H_2O$ at pH 5 adjusted with AcOH (A) and 10mM $NH_4OAc$ in $CH_3CN$-$H_2O$ (95:5) at pH 5 (B). The mobile-phase B proportion increased from 10 % to 90 % in 7 min.

**Luteolin**



**Quercetin**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Range: 2
Area
Time Height Area Area%
2.68 97553 5549.20 100.00
AU
1.5
1.0
5.0e-1
0.0
2.68
5549
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00
201012_QC_011
3: Diode Array
Range: 3.787e+1
0.53
3.0e+1
2.0e+1
1.0e+1
0.0
2.69
AU
Time
-0.00 1.00 2.00 3.00 4.00 5.00 6.00 7.00

## 2. Computational studies - Detail

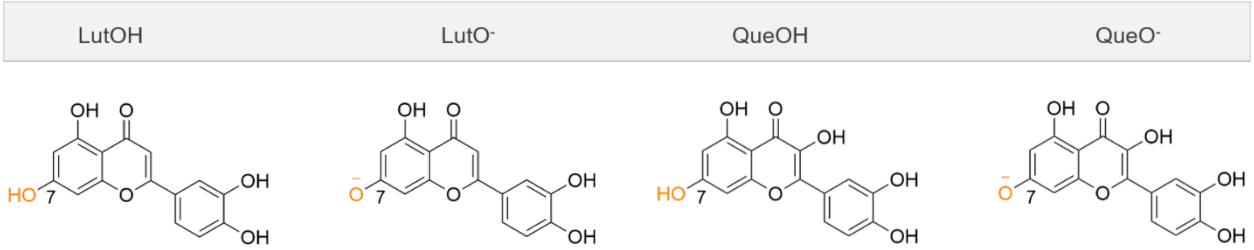


**Figure S1.** Chemical structures of luteolin and quercetin in different protonation states.

**Table S1.** Docking scores of both ligands in each protonation state, obtained from XP Glide for both binding pockets (i.e. $B_{RNA}$ and $B_{NTP}$).

| $B_{RNA}$ binding pocket | | $B_{NTP}$ binding pocket | |
|---|---|---|---|
| **Name** | **GScore** | **Name** | **GScore** |
| *$QueO^-$ | -7,689 | *$QueO^-$ | -7,62 |
| $QueO^-$ | -7,656 | QueOH | -5,443 |
| $QueO^-$ | -7,541 | *LutOH | -5,228 |
| $QueO^-$ | -7,25 | LutOH | -5,172 |
| $QueO^-$ | -7,191 | LutOH | -4,746 |
| $QueO^-$ | -7,168 | QueOH | -4,534 |
| $QueO^-$ | -6,554 | $QueO^-$ | -4,309 |
| *$LutO^-$ | -6,175 | $QueO^-$ | -4,199 |
| $LutO^-$ | -6,122 | QueOH | -4,178 |
| $LutO^-$ | -6,081 | QueOH | -4,098 |
| QueOH | -5,977 | QueOH | -4,076 |
| QueOH | -5,939 | $QueO^-$ | -4,054 |
| QueOH | -5,935 | $QueO^-$ | -3,807 |
| QueOH | -5,927 | $LutO^-$ | -3,464 |
| QueOH | -5,923 | $QueO^-$ | -3,354 |
| $LutO^-$ | -5,869 | QueOH | -3,351 |
| QueOH | -5,801 | $QueO^-$ | -3,209 |
| QueOH | -5,722 | LutOH | -3,181 |
| QueOH | -5,48 | LutOH | -3,077 |
| QueOH | -5,446 | LutOH | -3,074 |
| QueOH | -5,439 | $LutO^-$ | -3,039 |
| $LutO^-$ | -5,21 | LutOH | -2,902 |
| $LutO^-$ | -5,187 | LutOH | -2,889 |
| $LutO^-$ | -5,161 | LutOH | -2,864 |
| $LutO^-$ | -5,111 | | |
| $LutO^-$ | -5,028 | | |
| $LutO^-$ | -4,99 | | |
| $LutO^-$ | -4,899 | | |
| $LutO^-$ | -4,88 | | |
| $LutO^-$ | -4,603 | | |
| $LutO^-$ | -4,34 | | |
| $LutO^-$ | -4,148 | | |
| $QueO^-$ | -3,95 | | |
| $QueO^-$ | -3,828 | | |
| LutOH | -3,501 | | |
| LutOH | -3,009 | | |
| LutOH | -2,945 | | |
| LutOH | -2,89 | | |
| $LutO^-$ | -2,469 | | |

*in red selected poses for subsequent MD simulations

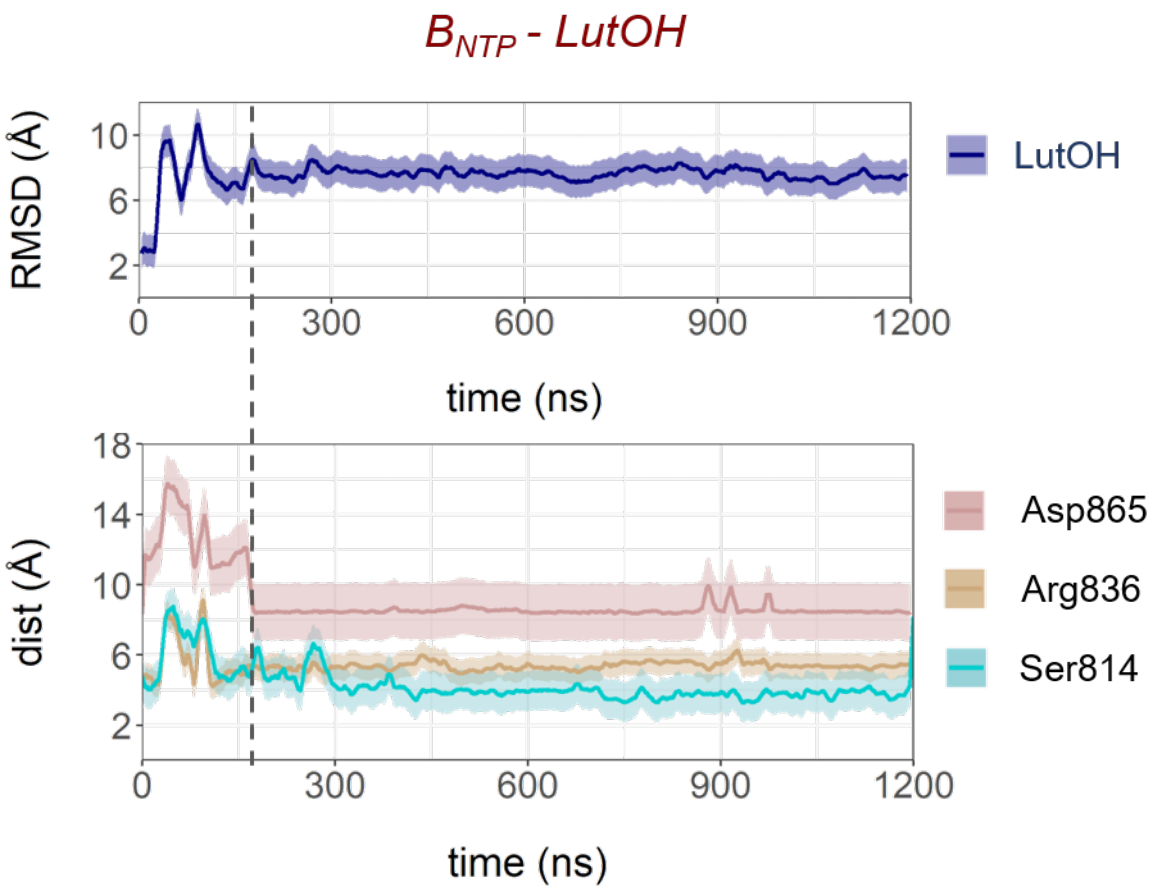


**Figure S2.** MD simulation of the $B_{NTP}$-LutOH system. (Top) Time evolution of the root mean square deviation (RMSD) for the heavy atoms of LutOH. (Bottom) Time evolution of the distances between the center of mass (C.O.M.) of the heavy atoms of the LutOH ligand and i) the C.O.M. of the heavy atoms of the guanidinium group of Arg836 (in light brown), ii) the C.O.M. of the heavy atoms of the carboxyl group of Asp865 (in pink), and iii) the C.O.M. of the heavy atoms of the side chain of Ser814 (in cyan). The dashed line marks the reorganization of LutOH.

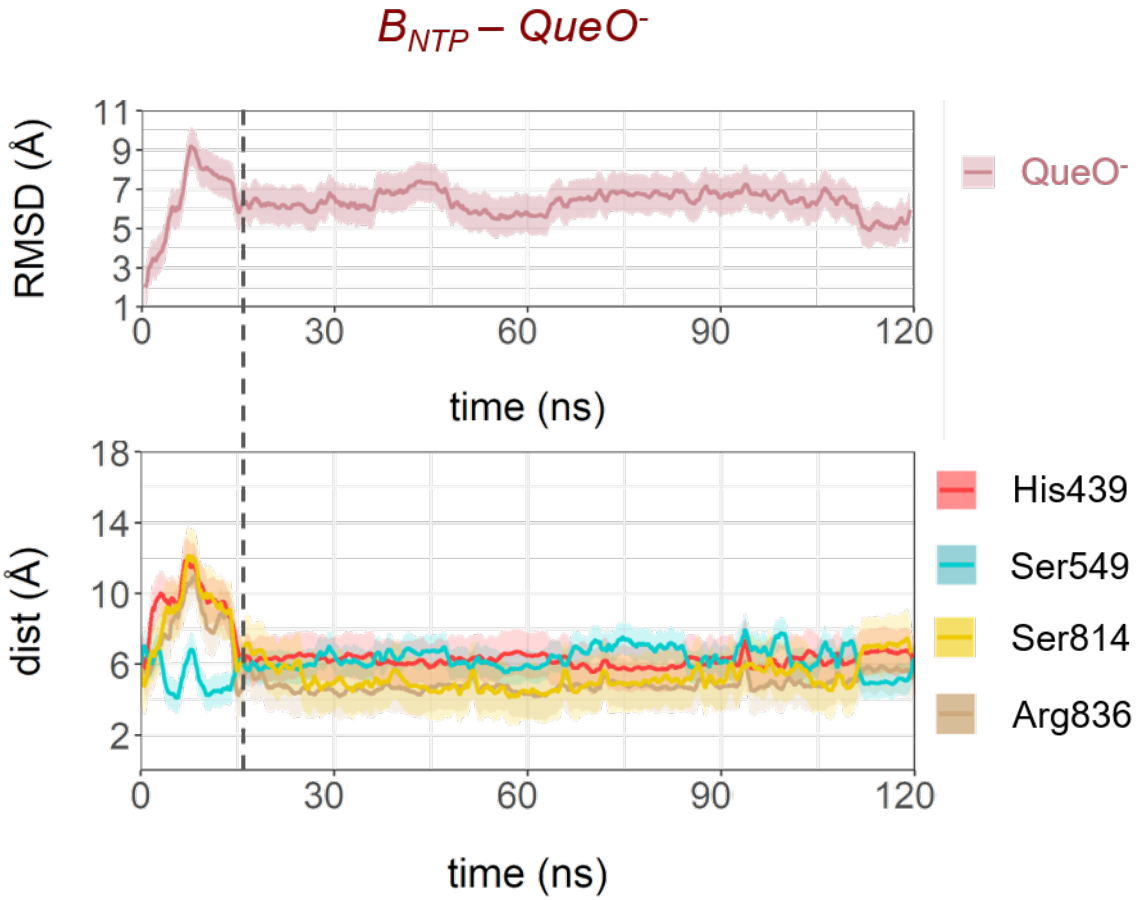


**Figure S3.** MD simulation of the $B_{NTP}$-$QueO^-$ system. (Top) Time evolution of the root mean square deviation (RMSD) for the heavy atoms of $QueO^-$. (Bottom) Time evolution of the distances between the center of mass (C.O.M.) of the heavy atoms of the $QueO^-$ ligand and i) the C.O.M. of the heavy atoms of the guanidinium group of Arg836 (in light brown), ii) the C.O.M. of the heavy atoms of the side chain of Ser549 (in pink), iii) the C.O.M. of the heavy atoms of the side chain of Ser814 (in cyan). The dashed line marks the reorganization of LutOH, and iv) the C.O.M. of the heavy atoms of imidazole group of His439. The dashed line marks the reorganization of LutOH.

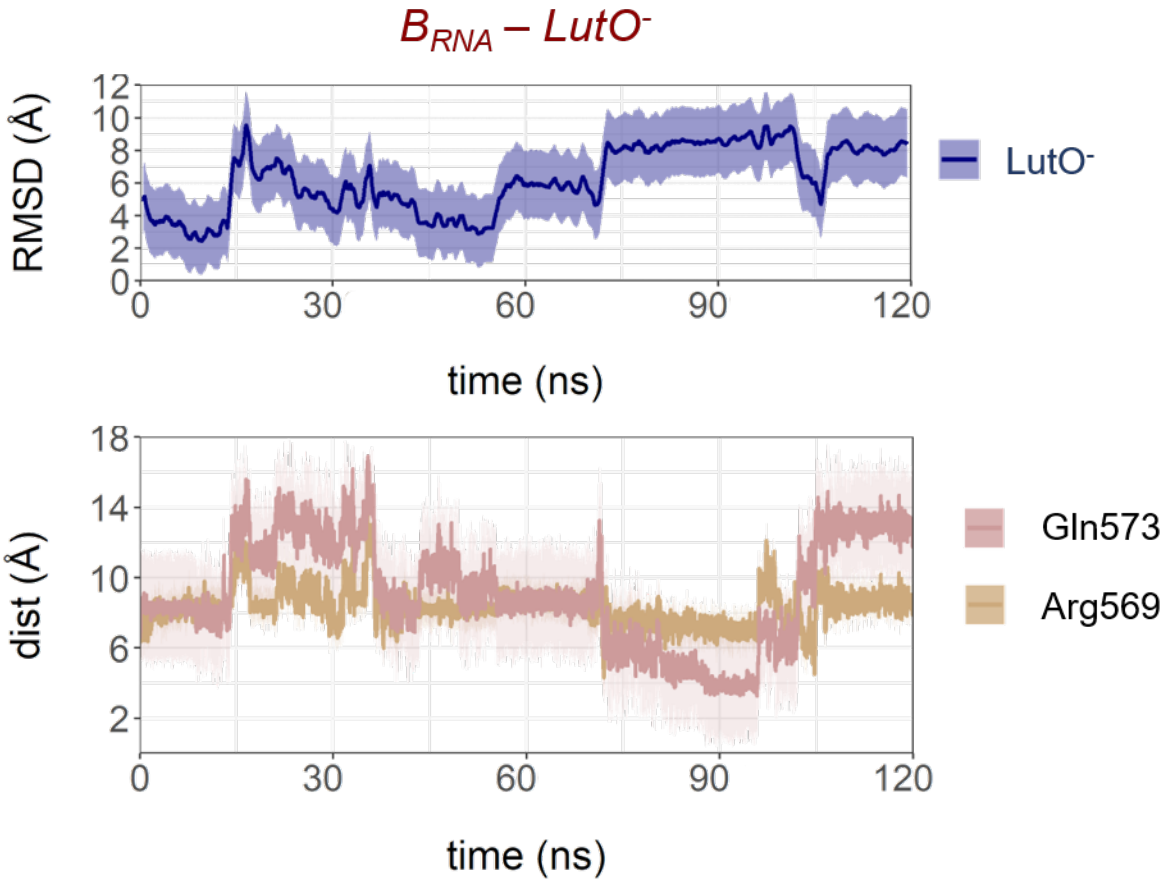


**Figure S4.** MD simulation of the $B_{RNA}$-$LutO^-$ system. (Top) Time evolution of the root mean square deviation (RMSD) for the heavy atoms of $LutO^-$. (Bottom) Time evolution of the distances between the center of mass (C.O.M.) of the heavy atoms of the $LutO^-$ ligand and i) the C.O.M. of the heavy atoms of the guanidinium group of Arg569 (in light brown), ii) the C.O.M. of the heavy atoms of the side chain of Gln573 (in pink).

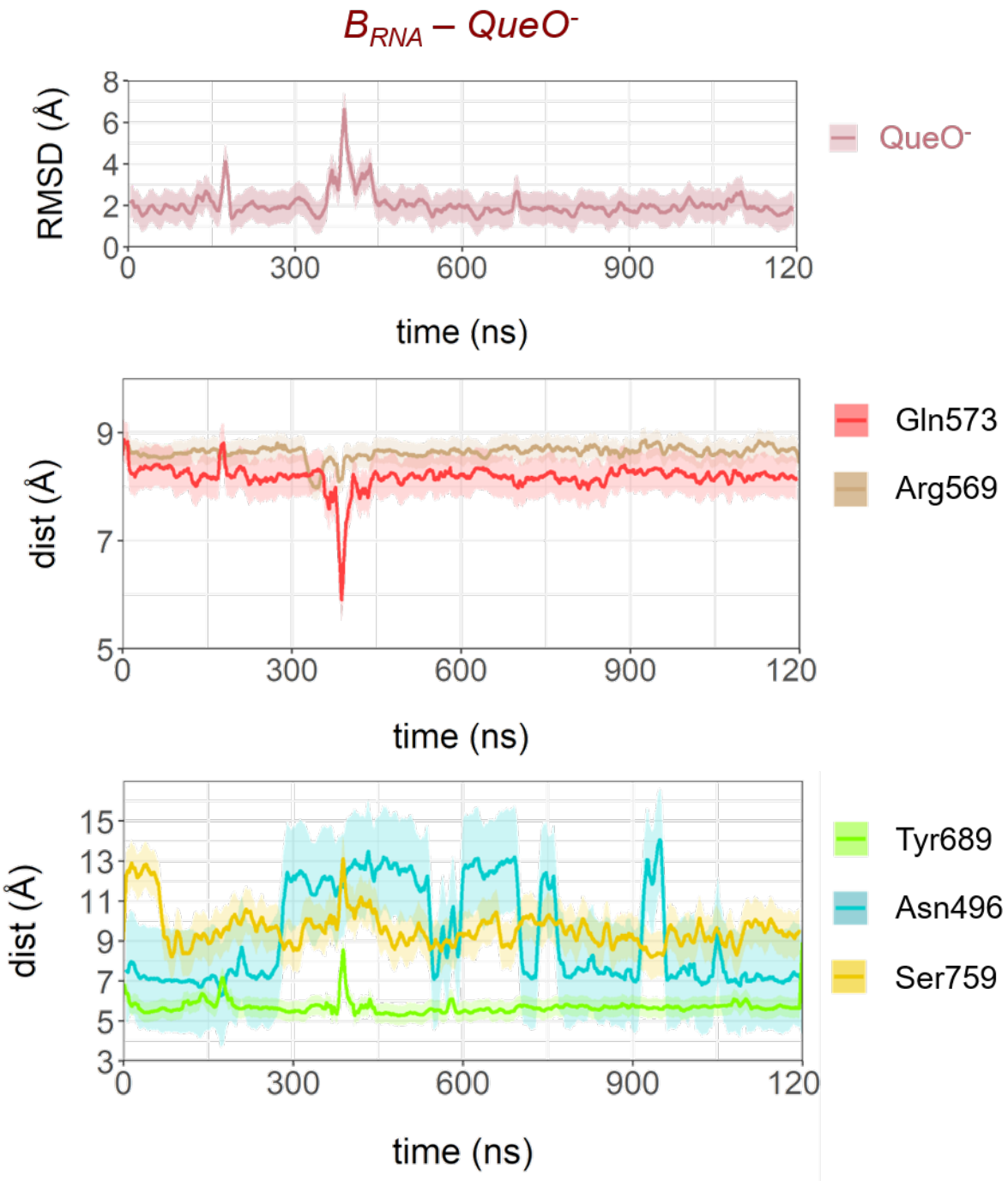


**Figure S5.** MD simulation of the $B_{RNA}$-$QueO^-$ system. (Top) Time evolution of the root mean square deviation (RMSD) for the heavy atoms of $QueO^-$. (Middle) Time evolution of the distances between the center of mass (C.O.M.) of the heavy atoms of the $QueO^-$ ligand and i) the C.O.M. of the heavy atoms of the guanidinium group of Arg569 (in light brown), ii) the C.O.M. of the heavy atoms of the side chain of Gln573 (in pink). (Bottom) Time evolution of the distances between the center of mass (C.O.M.) of the heavy atoms of the $QueO^-$ ligand and i) the C.O.M. of the heavy atoms of the side chain of Tyr689 (in green), ii) the C.O.M. of the heavy atoms of the side chain of Asn496 (in blue), and iii) the C.O.M. of the heavy atoms of the side chain of Ser759 (in yellow).