

## Supplementary Materials

# Molecular modeling and *in vitro* evaluation of piplartine analogs against oral squamous cell carcinoma

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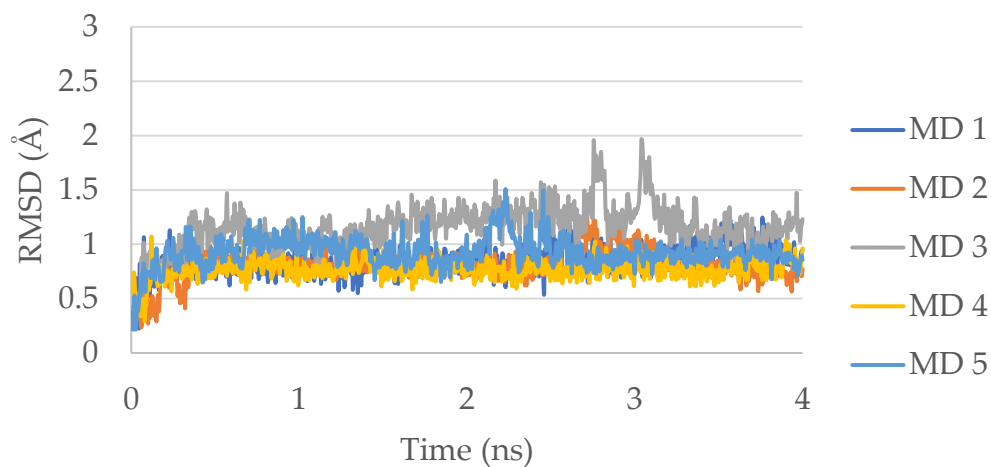
**Table S1.** Results of docking compound **9** to its potential targets.

| Target | Pose | PLP <sup>(a)</sup> | Z_PLP <sup>(b)</sup> | GS <sup>(c)</sup> | Z_GS <sup>(d)</sup> | CS <sup>(e)</sup> | Z_CS <sup>(f)</sup> | ASP <sup>(g)</sup> | Z_ASP <sup>(h)</sup> | Aggregated Z-score |
|--------|------|--------------------|----------------------|-------------------|---------------------|-------------------|---------------------|--------------------|----------------------|--------------------|
| STAT3  | 1    | 57.3               | 0.81                 | 30.87             | 1.26                | 21.98             | 1.43                | 28.65              | 2.02                 | 1.38               |
|        | 2    | 57.29              | 0.81                 | 26.19             | 0.76                | 23.89             | 2.01                | 27.81              | 1.76                 | 1.33               |
|        | 3    | 58.46              | 1.23                 | 34.51             | 1.65                | 20.2              | 0.88                | 24.59              | 0.76                 | 1.13               |
| NFKB   | 1    | 55.94              | 1.32                 | 17.32             | 0.84                | 17.94             | 1.48                | 27.24              | 0.92                 | 1.14               |
|        | 2    | 57.85              | 1.66                 | 14.27             | 0.66                | 15.57             | 0.61                | 30.48              | 1.48                 | 1.1                |
|        | 3    | 58.24              | 1.72                 | -2.85             | -0.34               | 18.22             | 1.58                | 29.51              | 1.31                 | 1.07               |
| CRM1   | 1    | 68.92              | 1.96                 | 22.79             | 0.36                | 29.78             | 2.31                | 35.11              | 1.97                 | 1.65               |
|        | 2    | 68.39              | 1.82                 | 25.61             | 0.54                | 27.96             | 1.45                | 34.06              | 1.6                  | 1.35               |
|        | 3    | 69.87              | 2.2                  | 11.89             | -0.31               | 27.24             | 1.1                 | 34.74              | 1.84                 | 1.21               |
| PI3K   | 1    | 68.72              | 2.12                 | 34.86             | 1.79                | 25.67             | 0.96                | 40.61              | 1.8                  | 1.67               |
|        | 2    | 67.41              | 1.79                 | 12.13             | -0.78               | 28.34             | 2.55                | 37.87              | 0.94                 | 1.13               |
|        | 3    | 67.45              | 1.8                  | 19.67             | 0.07                | 25.67             | 0.96                | 39.27              | 1.38                 | 1.05               |
| MTOR   | 4    | 65.72              | 1.37                 | 23.83             | 0.54                | 26.88             | 1.68                | 36.65              | 0.55                 | 1.03               |
|        | 1    | 69.98              | 1.32                 | 13.42             | 0.27                | 29.91             | 1.64                | 33.3               | 0.49                 | 0.93               |
|        | 1    | 41.12              | 2.17                 | -231.46           | 0.46                | 0.09              | 1.89                | 11.14              | 2.87                 | 1.85               |
| GSTP1  | 2    | 35.28              | 1.08                 | -223.56           | 1.13                | -0.94             | 1.52                | 4.74               | 1.11                 | 1.21               |
|        | 1    | 64.38              | 2.69                 | -14.28            | 1.15                | 18.09             | 1.69                | 28.46              | 1.93                 | 1.87               |
|        | 2    | 58.6               | 1.98                 | 5.49              | 1.73                | 9.06              | 0.46                | 26.16              | 1.61                 | 1.45               |
| AHR    | 3    | 46.37              | 0.48                 | -42.14            | 0.34                | 21.61             | 2.16                | 28.27              | 1.91                 | 1.22               |
|        | 4    | 53.98              | 1.41                 | -43.4             | 0.3                 | 17.96             | 1.67                | 23.13              | 1.19                 | 1.14               |
| MTNR1B | 1    | 61.17              | 2.38                 | 26.62             | 1.06                | 22.84             | 1.93                | 31.37              | 1.42                 | 1.7                |
|        | 2    | 54.57              | 0.84                 | 29.87             | 1.15                | 22.55             | 1.85                | 30.38              | 1.2                  | 1.26               |
|        | 1    | 52.18              | 1.48                 | 21.35             | 0.63                | 19.11             | 2.12                | 24.24              | 0.28                 | 1.13               |
| RELA   | 1    | 77.9               | 2.88                 | 6.34              | 0.68                | 22.18             | 2.46                | 23.78              | 0.72                 | 1.69               |
|        | 2    | 66.64              | 1.41                 | -2.93             | 0.21                | 18.74             | 1.48                | 30.88              | 2.01                 | 1.28               |
|        | 3    | 62.99              | 0.93                 | 9.88              | 0.85                | 20                | 1.84                | 22.76              | 0.53                 | 1.04               |
| RIPK2  | 1    | 58.05              | 1.56                 | 20.9              | 0.8                 | 24.15             | 1.06                | 27.18              | 1.11                 | 1.13               |
|        | 2    | 58.71              | 1.76                 | 12.6              | 0.34                | 25.53             | 1.52                | 25.97              | 0.75                 | 1.09               |
|        | 3    | 54.81              | 0.54                 | 24.24             | 0.99                | 23.09             | 0.71                | 29.8               | 1.88                 | 1.03               |
| DUSP3  | 1    | 51.3               | 0.55                 | 11.86             | 0.77                | 15.38             | 0.89                | 28.74              | 1.23                 | 0.86               |
|        | 1    | 68.86              | 2.43                 | 23.09             | 0.65                | 28.91             | 2.63                | 34.06              | 1.5                  | 1.8                |
|        | 2    | 68.05              | 2.24                 | 19.85             | 0.53                | 26.23             | 1.51                | 35.59              | 1.98                 | 1.56               |
| MCL1   | 3    | 64.29              | 1.37                 | 10.84             | 0.18                | 28.09             | 2.29                | 30.98              | 0.54                 | 1.09               |

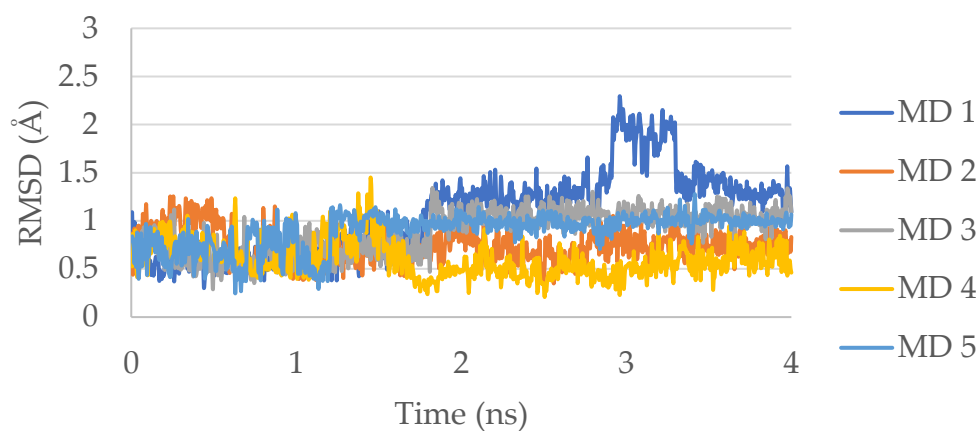
<sup>(a)</sup> PLP score. <sup>(b)</sup> PLP Z-score. <sup>(c)</sup> GoldScore score. <sup>(d)</sup> GoldScore Z-score. <sup>(e)</sup> ChemScore score. <sup>(f)</sup> ChemScore Z-score. <sup>(g)</sup> ASP score. <sup>(h)</sup> ASP Z-score.

**Table S2.** Predicted free energies of binding of compound **9** to its potential targets and their components.

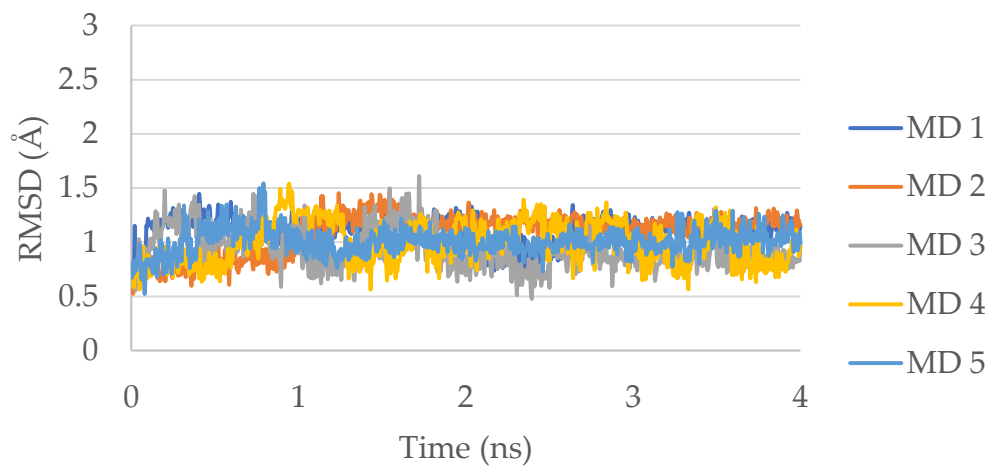
| Target | Pose | VD<br>WAALS | EEL    | EPB   | ENPOLAR | EDISPER | $\Delta G$<br>gas | $\Delta G$<br>solv. | $\Delta G$<br>Total | Estimated<br>Error |
|--------|------|-------------|--------|-------|---------|---------|-------------------|---------------------|---------------------|--------------------|
| STAT3  | 1    | -41.41      | -10.40 | 36.40 | -32.01  | 51.50   | -51.82            | 55.88               | 4.07                | 0.64               |
|        | 2    | -43.74      | -13.63 | 36.98 | -33.14  | 52.07   | -57.37            | 55.91               | -1.46               | 0.58               |
|        | 3    | -41.85      | -10.24 | 33.86 | -31.40  | 50.39   | -52.09            | 52.84               | 0.76                | 0.52               |
| NFKB   | 1    | -36.28      | -15.41 | 39.37 | -26.39  | 41.42   | -51.69            | 54.41               | 2.71                | 0.54               |
|        | 2    | -30.82      | -12.66 | 31.37 | -21.99  | 35.01   | -43.48            | 44.39               | 0.91                | 0.35               |
|        | 3    | -24.77      | -13.34 | 28.15 | -18.77  | 29.79   | -38.10            | 39.17               | 1.07                | 0.34               |
| CRM1   | 1    | -39.28      | -2.34  | 17.40 | -31.78  | 49.13   | -41.61            | 34.75               | -6.87               | 0.33               |
|        | 2    | -38.64      | -3.10  | 17.62 | -31.50  | 47.92   | -41.74            | 34.04               | -7.70               | 0.37               |
|        | 3    | -39.84      | -2.68  | 17.30 | -32.15  | 49.28   | -42.52            | 34.44               | -8.08               | 0.32               |
| PI3K   | 1    | -34.70      | -13.06 | 29.26 | -25.97  | 43.58   | -47.76            | 46.87               | -0.89               | 0.41               |
|        | 2    | -35.17      | -8.96  | 28.42 | -26.83  | 45.05   | -44.12            | 46.65               | 2.52                | 0.38               |
|        | 3    | -35.23      | -12.27 | 28.62 | -25.84  | 42.97   | -47.50            | 45.75               | -1.76               | 0.37               |
| MTOR   | 4    | -33.01      | -14.71 | 29.97 | -24.56  | 42.62   | -47.72            | 48.04               | 0.31                | 0.40               |
|        | 1    | -43.47      | -15.54 | 41.43 | -32.50  | 53.51   | -59.01            | 62.44               | 3.43                | 0.65               |
|        | 1    | -34.30      | -9.65  | 27.10 | -25.27  | 42.55   | -43.95            | 44.38               | 0.42                | 0.35               |
| GSTP1  | 2    | -40.04      | -5.41  | 27.95 | -28.56  | 46.78   | -45.45            | 46.17               | 0.72                | 0.38               |
|        | 1    | -51.41      | -11.76 | 35.44 | -36.66  | 58.70   | -63.17            | 57.47               | -5.70               | 0.43               |
|        | 2    | -50.80      | -12.43 | 38.39 | -35.18  | 57.71   | -63.23            | 60.92               | -2.30               | 0.46               |
| AHR    | 3    | -51.00      | -11.61 | 35.97 | -36.49  | 59.19   | -62.61            | 58.67               | -3.94               | 0.44               |
|        | 4    | -52.12      | -9.84  | 35.95 | -36.84  | 59.33   | -61.95            | 58.44               | -3.51               | 0.41               |
| MTNR1B | 1    | -51.34      | 25.58  | 0.00  | -36.59  | 59.45   | -25.76            | 22.86               | -2.90               | 0.45               |
|        | 2    | -49.90      | 28.41  | 0.00  | -35.90  | 59.67   | -21.49            | 23.77               | 2.27                | 0.41               |
|        | 1    | -21.73      | -15.60 | 29.34 | -17.23  | 28.29   | -37.33            | 40.40               | 3.07                | 0.35               |
| RELA   | 1    | -48.66      | -22.34 | 52.00 | -35.10  | 55.14   | -71.00            | 72.05               | 1.05                | 0.48               |
|        | 2    | -43.44      | -11.86 | 39.47 | -31.20  | 50.31   | -55.30            | 58.58               | 3.28                | 0.56               |
|        | 3    | -48.58      | -26.77 | 52.37 | -34.93  | 55.15   | -75.34            | 72.59               | -2.75               | 0.63               |
| MMP2   | 1    | -44.88      | -16.96 | 40.92 | -32.79  | 53.88   | -61.83            | 62.00               | 0.17                | 0.50               |
|        | 2    | -46.69      | -16.99 | 39.04 | -33.85  | 54.14   | -63.68            | 59.33               | -4.35               | 0.48               |
|        | 3    | -44.45      | -14.15 | 34.41 | -32.80  | 53.11   | -58.60            | 54.71               | -3.89               | 0.50               |
| RIPK2  | 1    | -27.59      | -4.70  | 25.99 | -21.23  | 35.25   | -32.29            | 40.01               | 7.72                | 0.56               |
|        | 1    | -37.71      | -5.36  | 22.86 | -28.81  | 46.35   | -43.07            | 40.40               | -2.67               | 0.33               |
|        | 2    | -38.17      | -3.32  | 20.60 | -27.67  | 43.57   | -41.49            | 36.50               | -4.99               | 0.42               |
| DUSP3  | 3    | -43.63      | -4.30  | 24.77 | -32.26  | 51.47   | -47.94            | 43.98               | -3.96               | 0.36               |



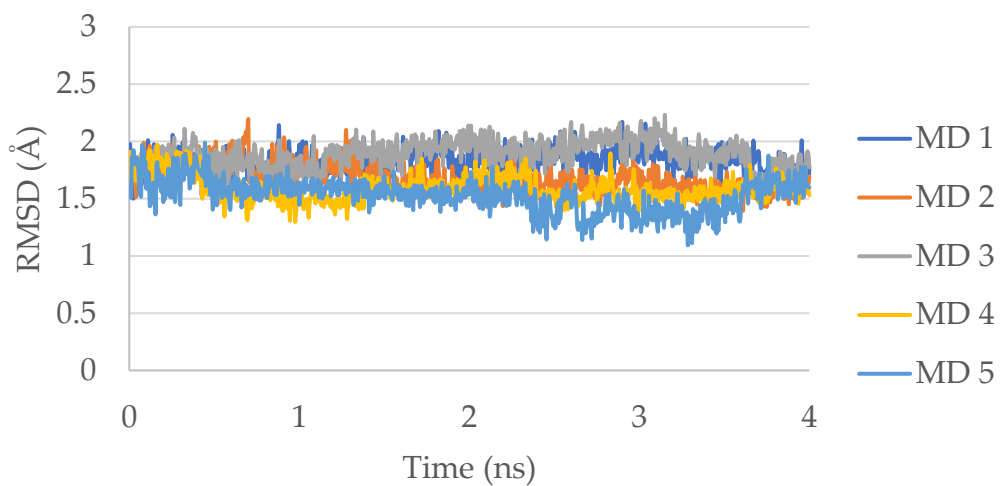
**Figure S1.** Ligand RMSD vs. time for the AHR-compound **9** complex (docking pose 1).



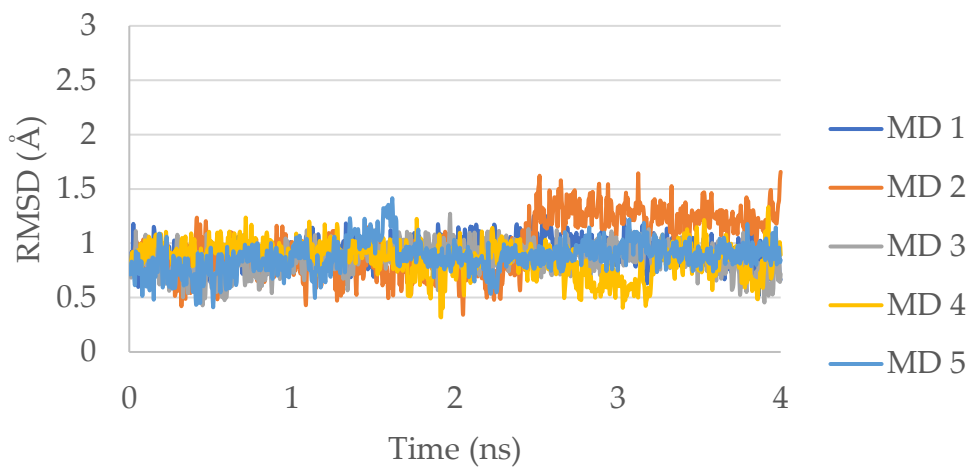
**Figure S2.** Ligand RMSD vs. time for the AHR-compound **9** complex (docking pose 2).



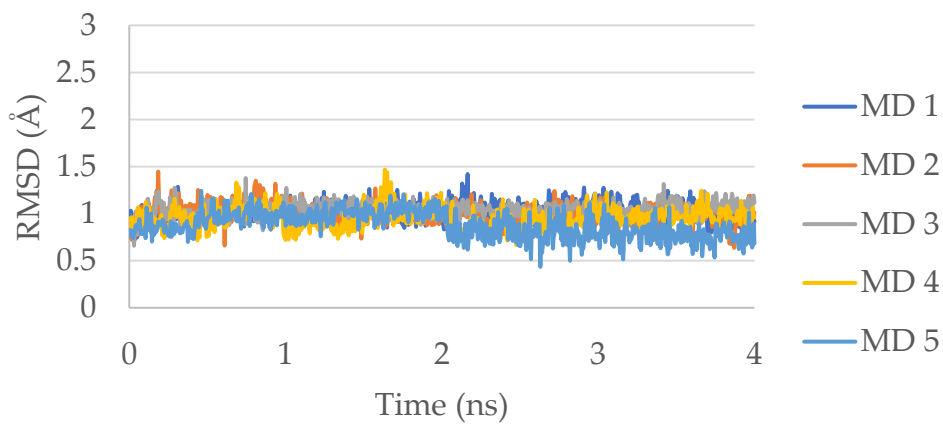
**Figure S3.** Ligand RMSD vs. time for the AHR-compound **9** complex (docking pose 3).



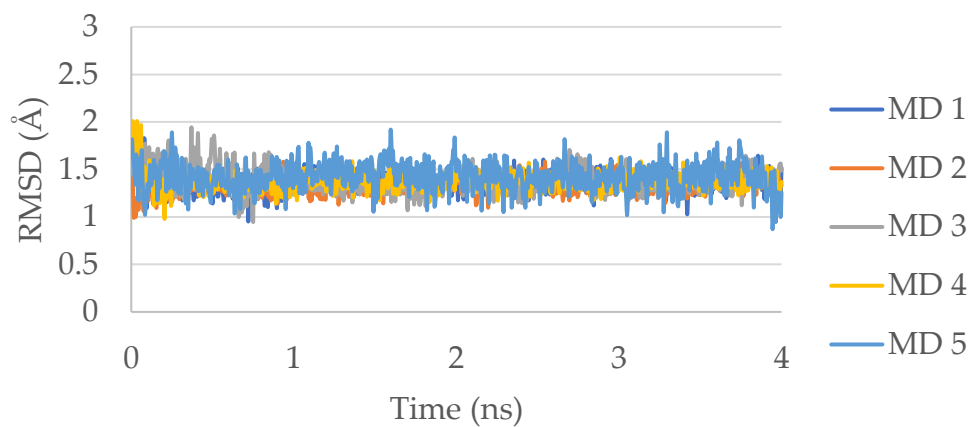
**Figure S4.** Ligand RMSD vs. time for the AHR-compound **9** complex (docking pose 4).



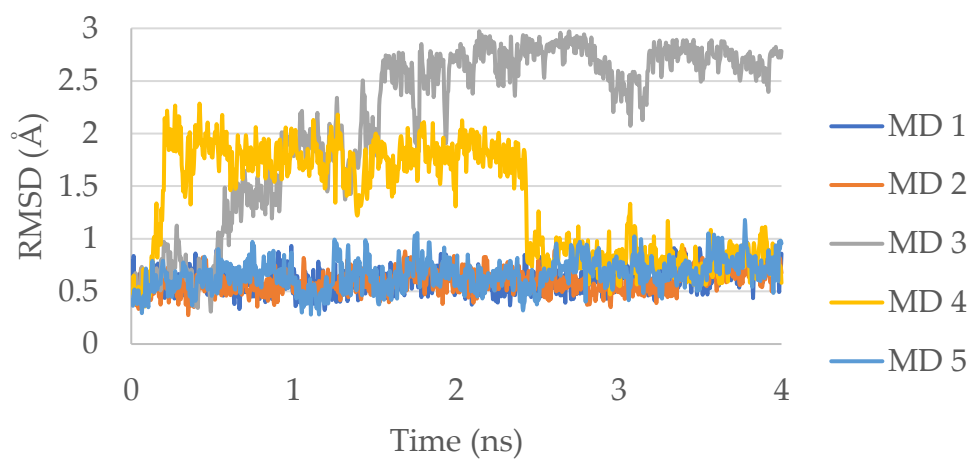
**Figure S5.** Ligand RMSD vs. time for the CRM1-compound **9** complex (docking pose 1).



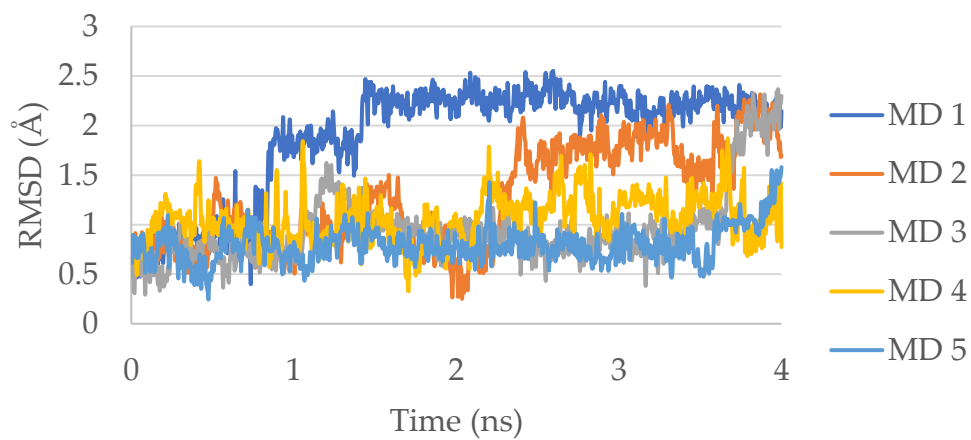
**Figure S6.** Ligand RMSD vs. time for the CRM1-compound **9** complex (docking pose 2).



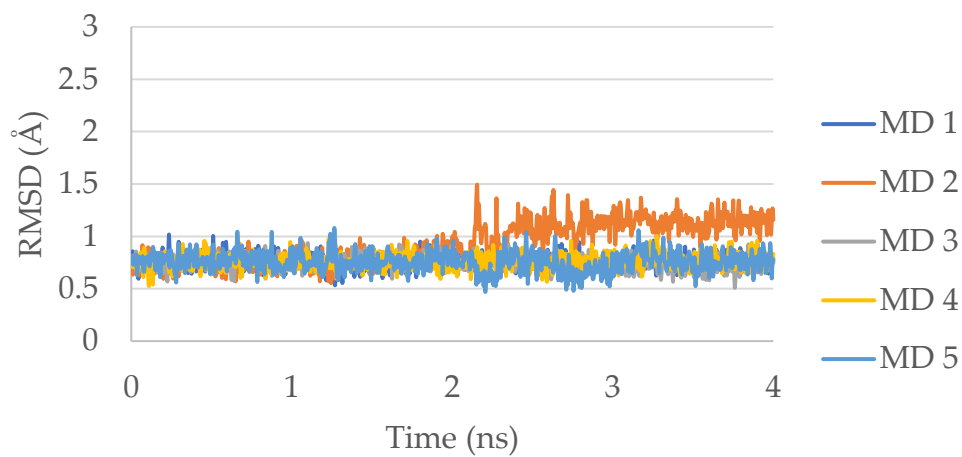
**Figure S7.** Ligand RMSD vs. time for the CRM1-compound **9** complex (docking pose 3).



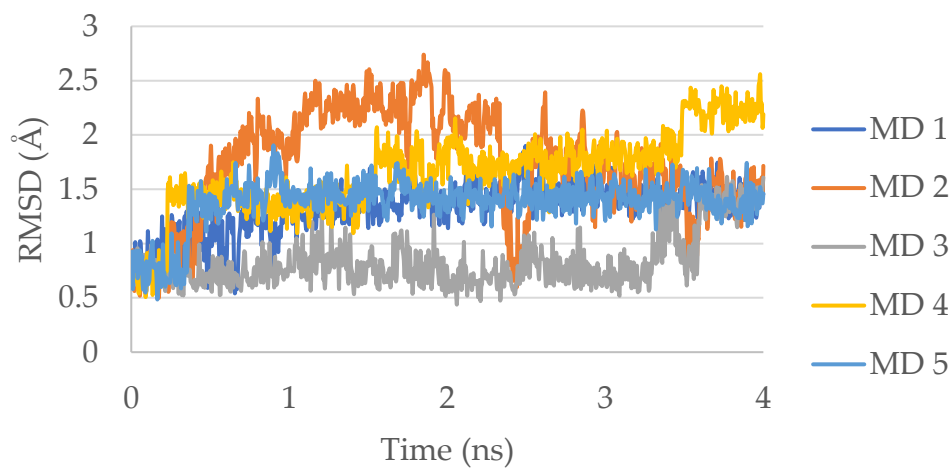
**Figure S8.** Ligand RMSD vs. time for the DUSP3-compound **9** complex (docking pose 1).



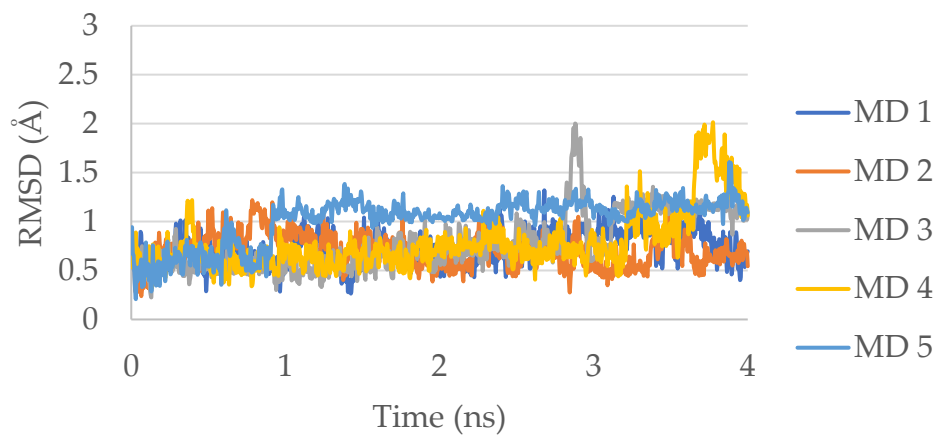
**Figure S9.** Ligand RMSD vs. time for the GSTP1-compound **9** complex (docking pose 1).



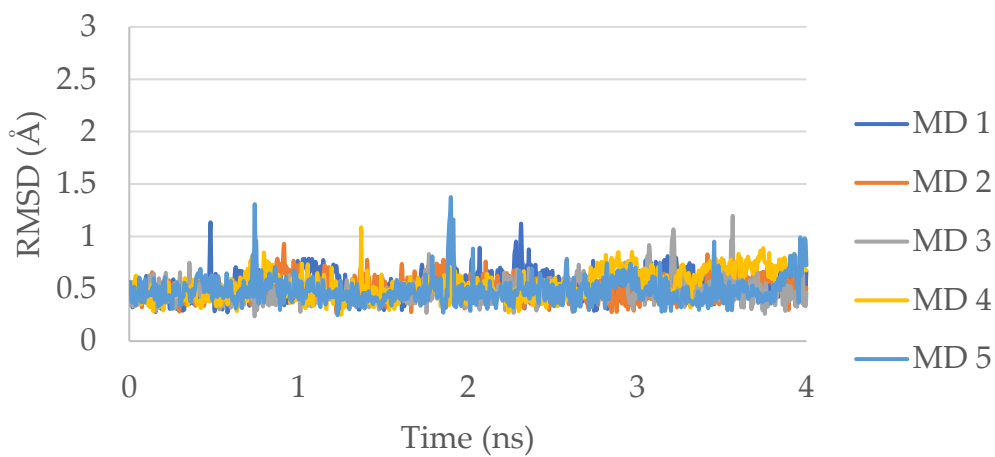
**Figure S10.** Ligand RMSD vs. time for the GSTP1-compound 9 complex (docking pose 2).



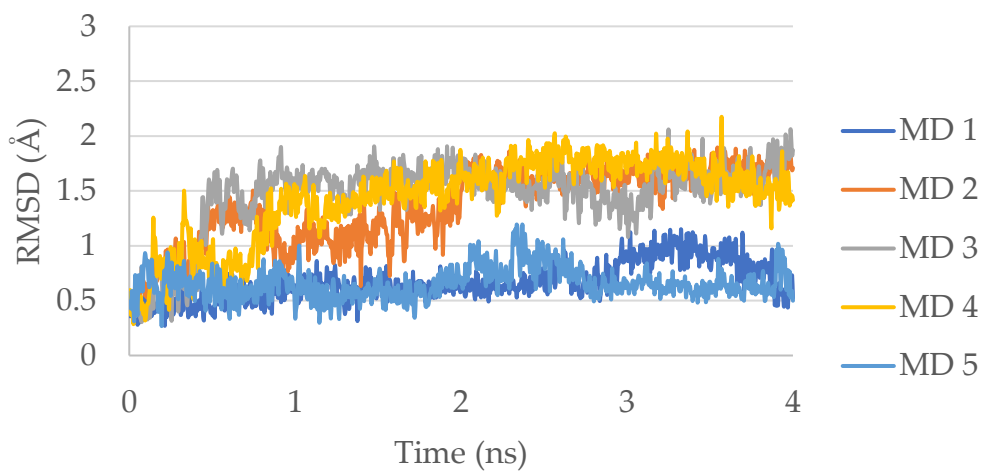
**Figure S11.** Ligand RMSD vs. time for the MCL1-compound 9 complex (docking pose 1).



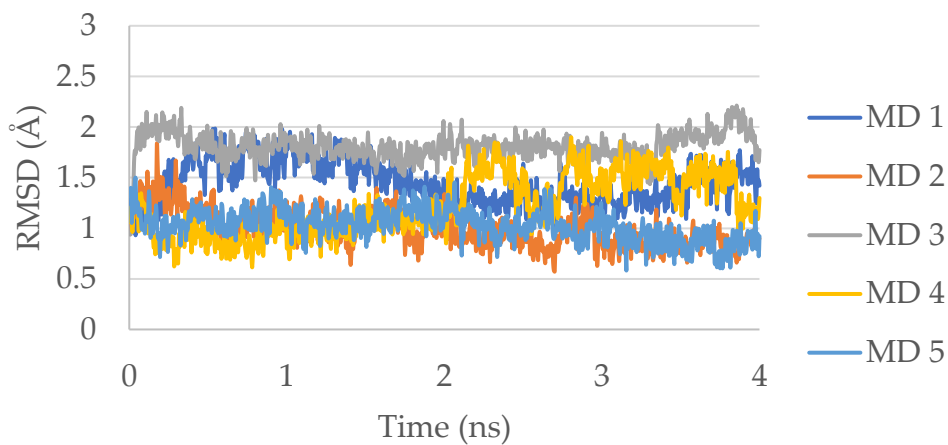
**Figure S12.** Ligand RMSD vs. time for the MCL1-compound 9 complex (docking pose 2).



**Figure S13.** Ligand RMSD vs. time for the MCL1-compound **9** complex (docking pose 3).

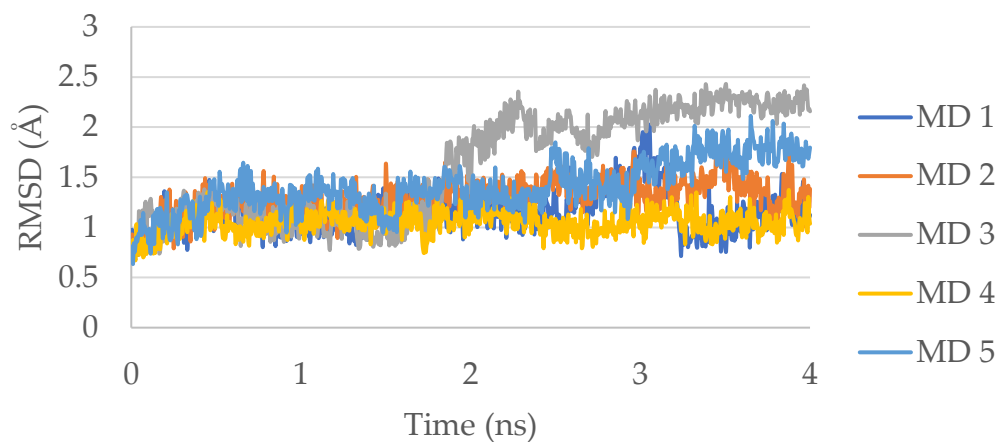


**Figure S14.** Ligand RMSD vs. time for the MMP2-compound **9** complex (docking pose 1).

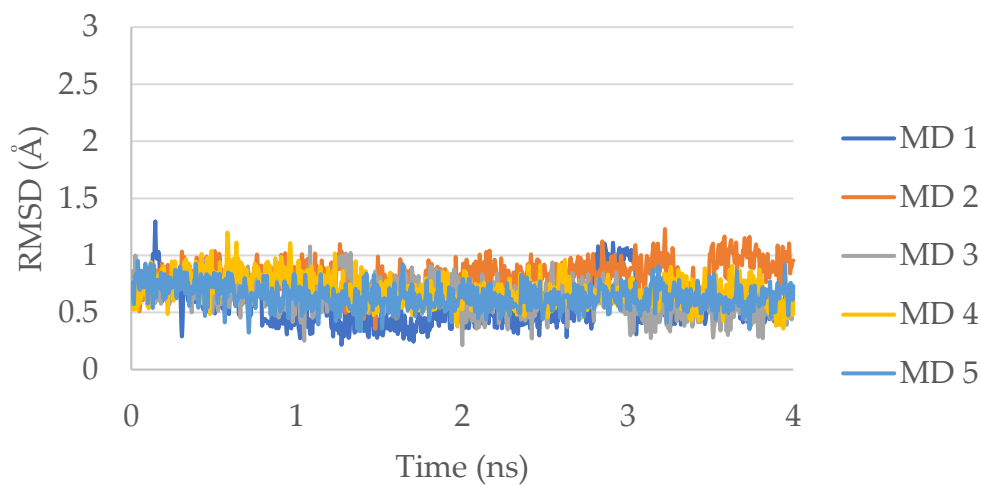


**Figure S15.** Ligand RMSD vs. time for the MMP2-compound **9** complex (docking pose 2).

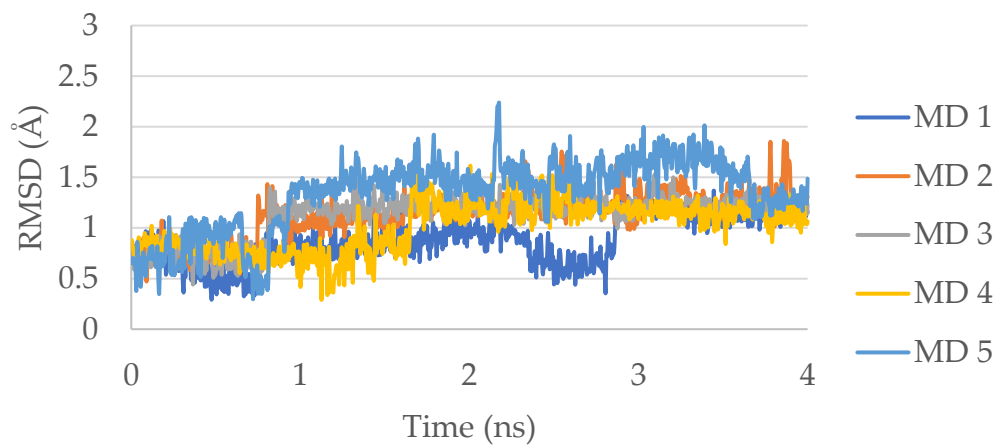




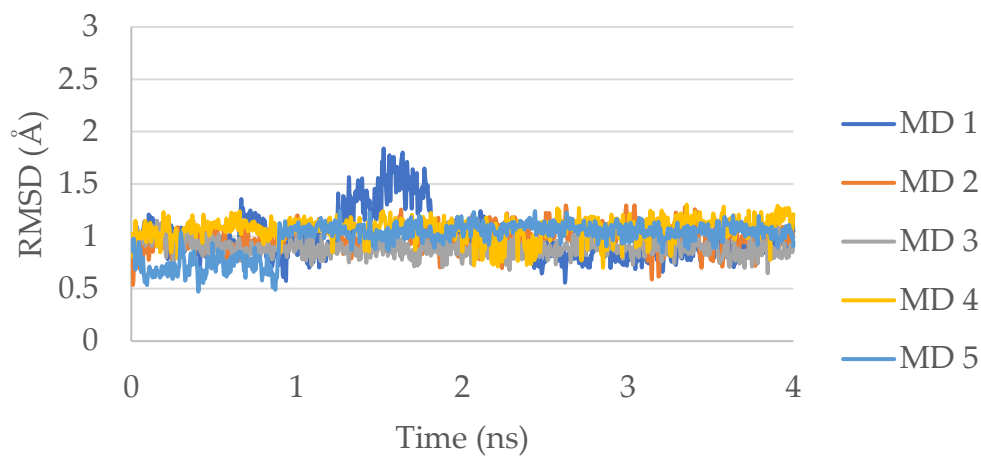
**Figure S16.** Ligand RMSD vs. time for the MMP2-compound **9** complex (docking pose 3).



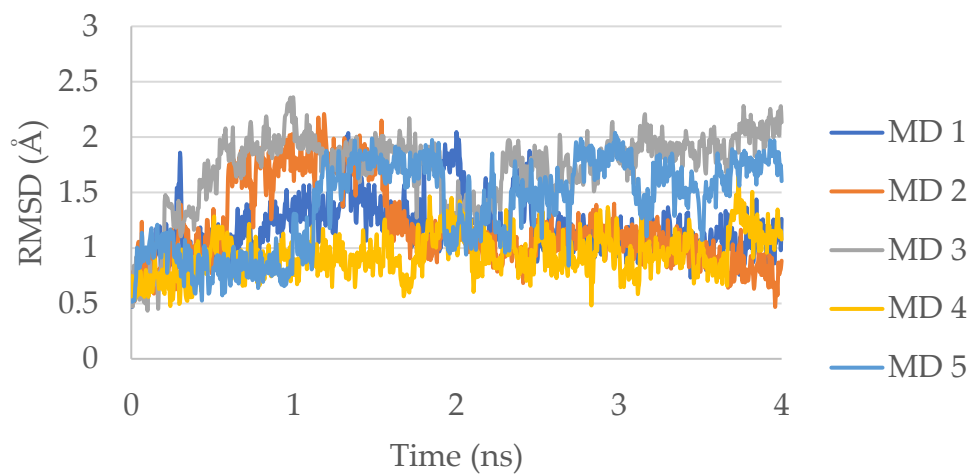
**Figure S17.** Ligand RMSD vs. time for the MTNR1B-compound **9** complex (docking pose 1).



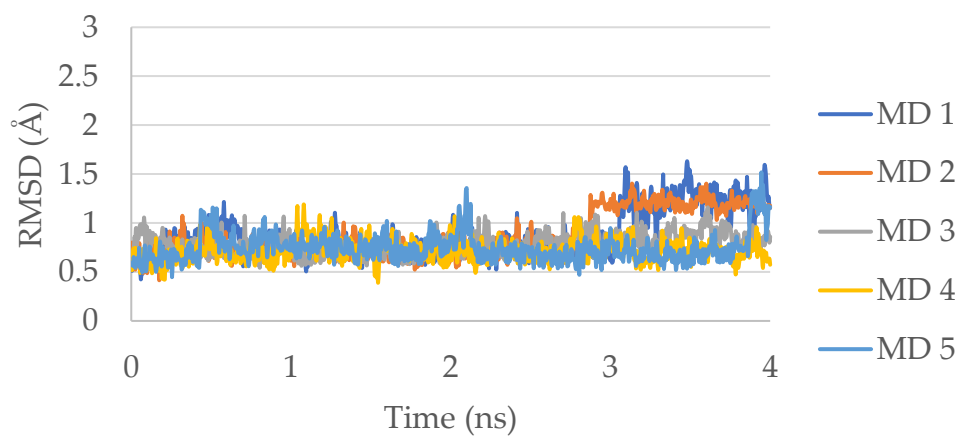
**Figure S18.** Ligand RMSD vs. time for the MTNR1B-compound **9** complex (docking pose 2).



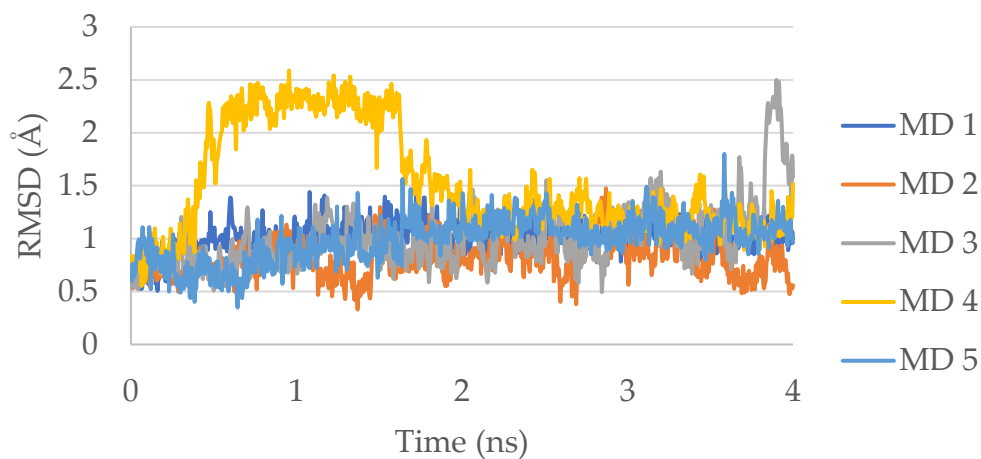
**Figure S19.** Ligand RMSD vs. time for the mTOR-compound **9** complex (docking pose 1).



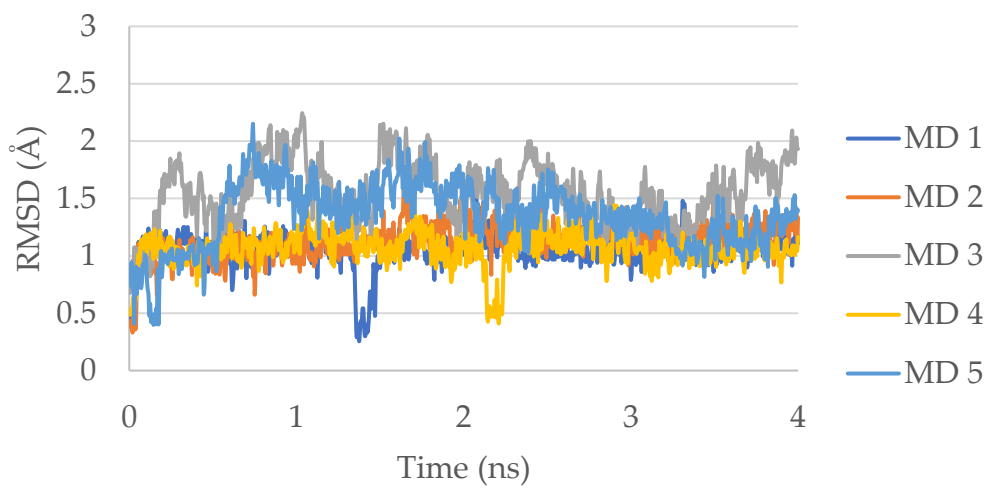
**Figure S20.** Ligand RMSD vs. time for the NFκB-compound **9** complex (docking pose 1).



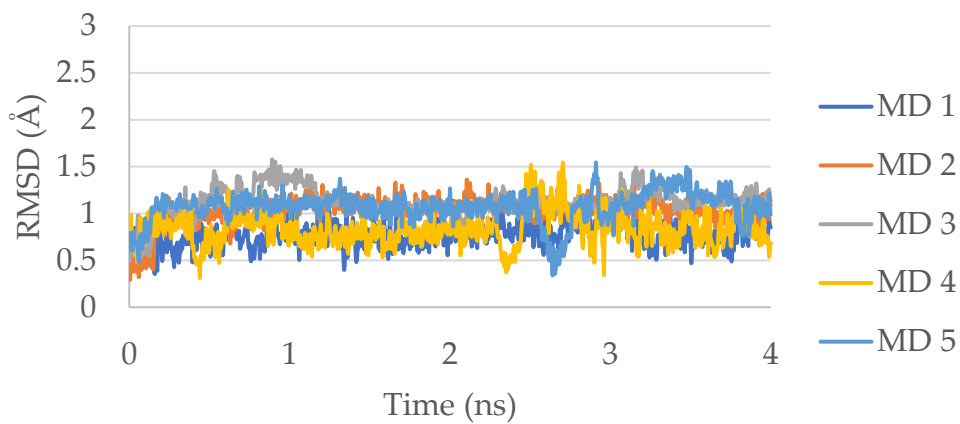
**Figure S21.** Ligand RMSD vs. time for the NFκB-compound **9** complex (docking pose 2).



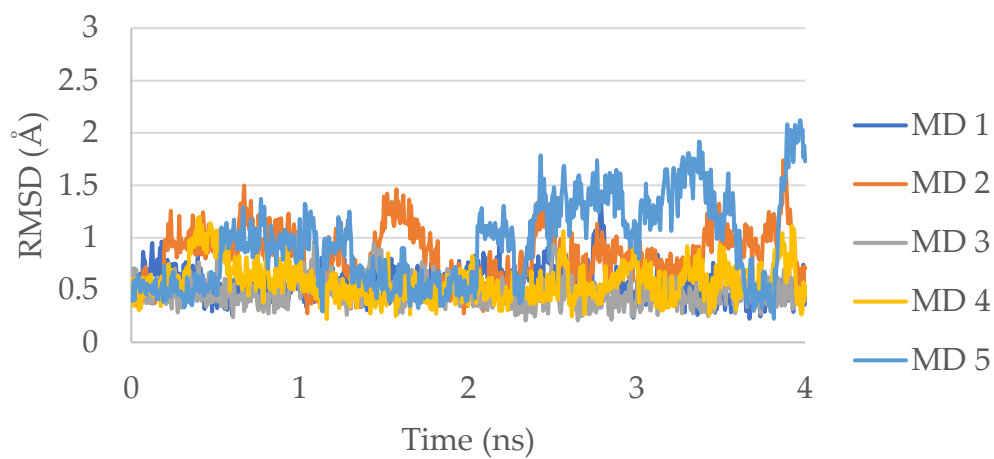
**Figure S22.** Ligand RMSD vs. time for the NFKB-compound **9** complex (docking pose 3).



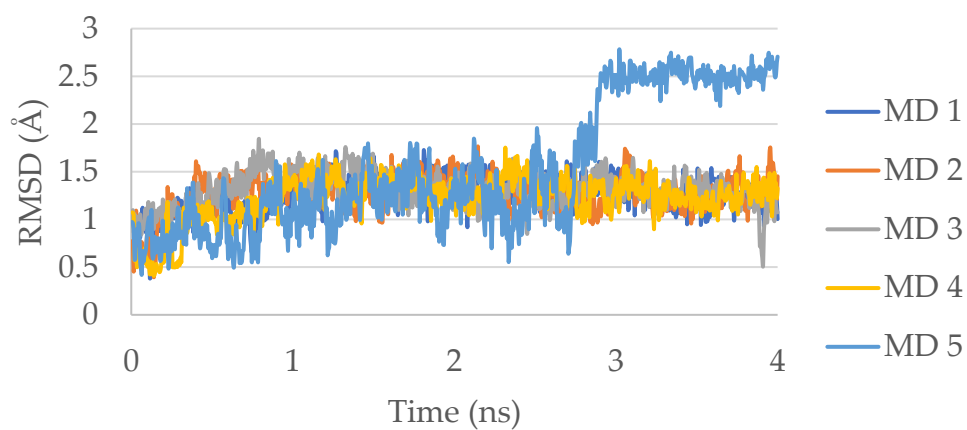
**Figure S23.** Ligand RMSD vs. time for the PI3KA-compound **9** complex (docking pose 1).



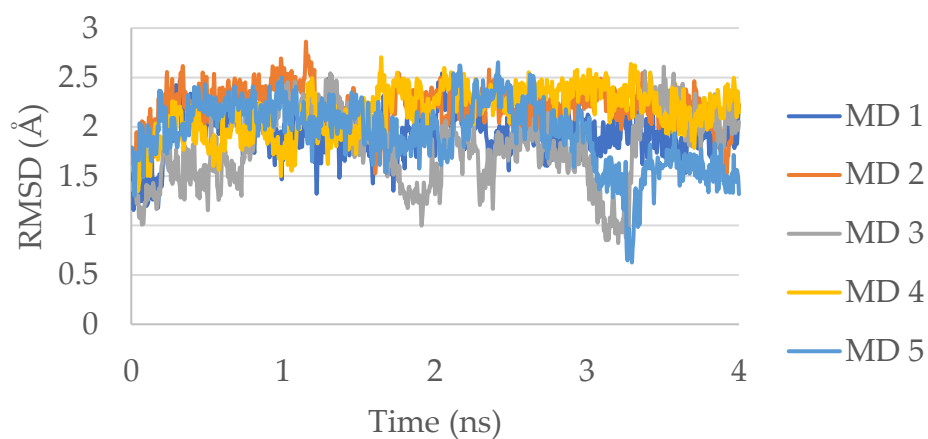
**Figure S24.** Ligand RMSD vs. time for the PI3KA-compound **9** complex (docking pose 2).



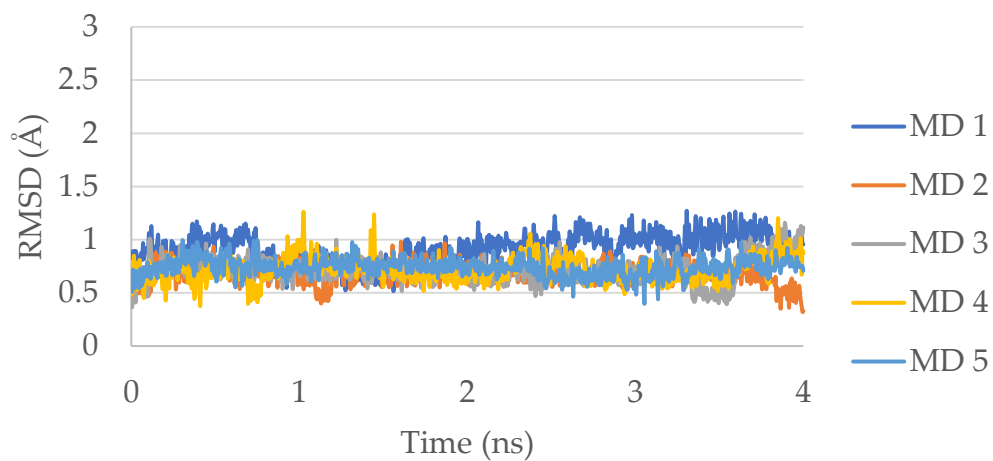
**Figure S25.** Ligand RMSD vs. time for the PI3KA-compound **9** complex (docking pose 3).



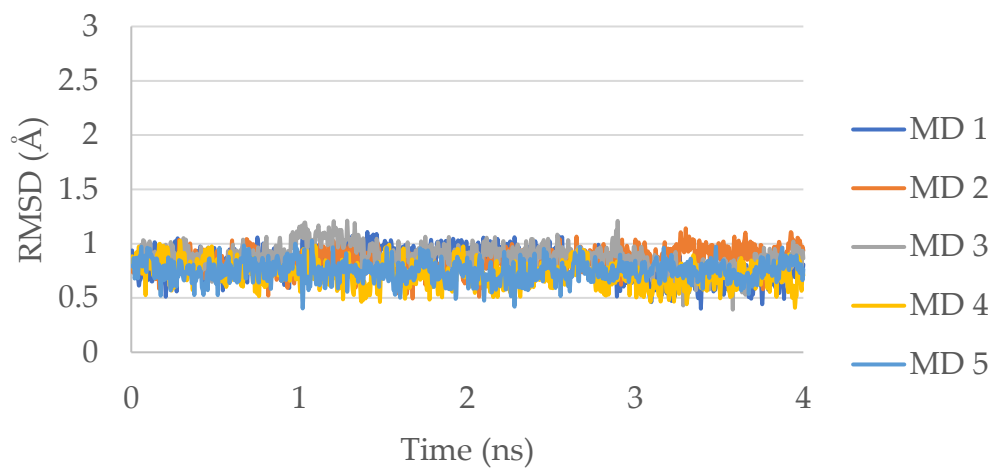
**Figure S26.** Ligand RMSD vs. time for the PI3KA-compound **9** complex (docking pose 4).



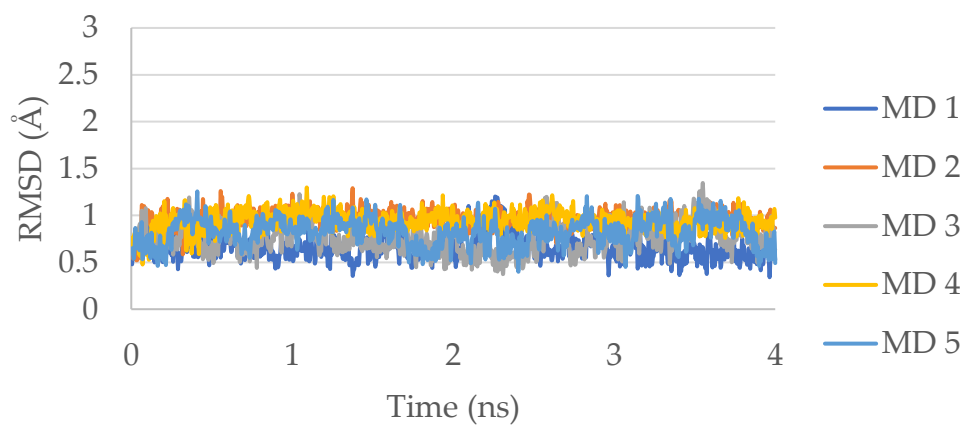
**Figure S27.** Ligand RMSD vs. time for the RELA-compound **9** complex (docking pose 1).



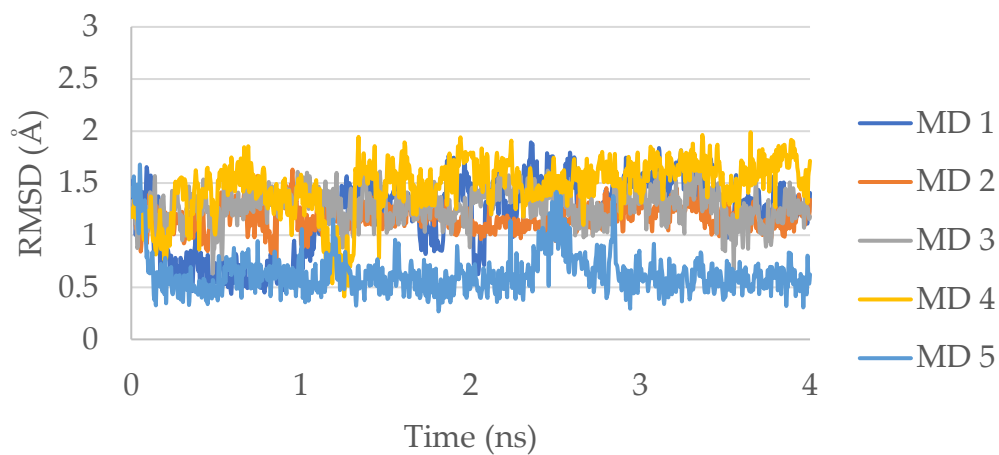
**Figure S28.** Ligand RMSD vs. time for the RIPK2 -compound **9** complex (docking pose 1).



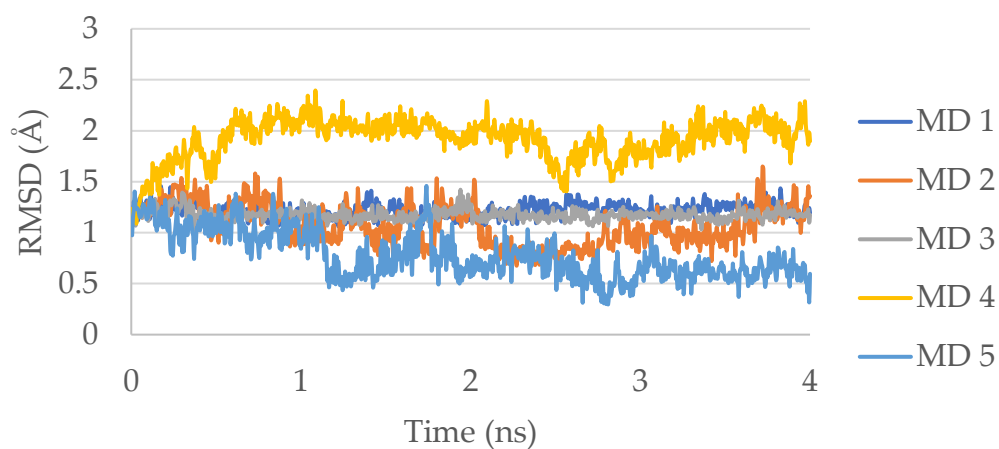
**Figure S29.** Ligand RMSD vs. time for the RIPK2 -compound **9** complex (docking pose 2).



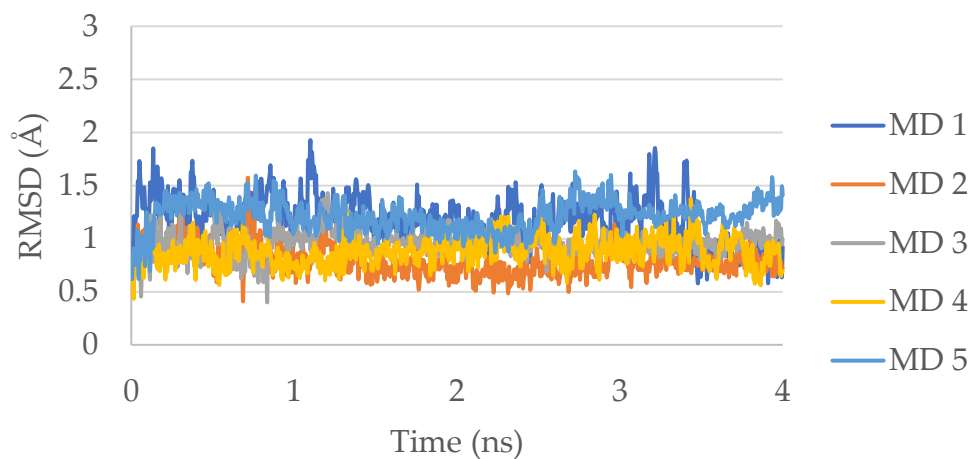
**Figure S30.** Ligand RMSD vs. time for the RIPK2 -compound **9** complex (docking pose 3).



**Figure S31.** Ligand RMSD vs. time for the STAT3 -compound **9** complex (docking pose 1).



**Figure S32.** Ligand RMSD vs. time for the STAT3 -compound **9** complex (docking pose 2).



**Figure S33.** Ligand RMSD vs. time for the STAT3 -compound **9** complex (docking pose 3).