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**Figure S5**: Structures of docked hydroxychloroquine and hydroxychloroquine sulfate in the active sites of 5R7Y, 6M03 and 6LU7 proteins.

**Figure S6:** Different interactions between ligand-protein.

|  |  |
| --- | --- |
| **a)** |  |
| **b)** |  |
| **Figure S1:** Electron localization function (ELF) maps of hydroxychloroquine (a) on the plane of C23, C8, N3 atoms and of hydroxychloroquine sulfate (b) on the plane of N11, N13, N9. | |

|  |  |  |
| --- | --- | --- |
| **E(eV)** | **(a)** | **(b)** |
|  |  |
|  |  |
| **Figure S2:** Plots of the frontier molecular orbitals of hydroxychloroquine sulfate in gas phase (a) and in water (b) by using TD-DFT calculations. | | |

|  |  |
| --- | --- |
| **a) In gas phase** | |
|  |  |
| **b) In water** | |
|  |  |
| **Figure S3:** The density of states (DOS) plots of chloroquine derivatives in gas phase (a) and in water (b)  via Gauss-Sum program. | |

|  |
| --- |
| **(a)** |
| **(b)** |
| **Figure S4:** Molecular electrostatic potential (MEP) maps of hydroxychloroquine sulfate in gas phase (a) and in water (b). |

|  |  |  |
| --- | --- | --- |
|  |  |  |
| **5R7Y-Hydroxychloroquine** | **6M03- Hydroxychloroquine** | **6LU7- Hydroxychloroquine** |
|  |  |  |
| **5R7Y-Hydroxychloroquine sulfate** | **6M03- Hydroxychloroquine sulfate** | **6LU7- Hydroxychloroquine sulfate** |
| **Figure S5:** Structures of docked hydroxychloroquine and hydroxychloroquine sulfate in the active sites of 5R7Y, 6M03 and 6LU7 proteins. | | |

|  |  |
| --- | --- |
| **(A)** |  |
| **5R7Y-Hydroxychloroquine** | |
|  |  |
| **6M03- Hydroxychloroquine** | |
|  |  |
| **6LU7- Hydroxychloroquine** | |
| **(B)** |  |
| **5R7Y-Hydroxychloroquine** **sulfate** | |
|  |  |
| **6M03- Hydroxychloroquine** **sulfate** | |
|  |  |
| **6LU7- Hydroxychloroquine** **sulfate** | |
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**Table S4:** Amino acid residues-hydroxychloroquine interactions.

**Table S5:** Amino acid residues-hydroxychloroquine sulfate interactions.

**Table S1:** Calculated geometrical parameters for the hydroxychloroquine compound in the gas phase and in water compared with the experimental ones by using B3LYP/6-31G\* basis set.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Hydroxychloroquine** | | | | | | | |
| Parameters | Experimental | Theoretical | | Parameters | Experimental | Theoretical | |
|  |  | In the Gas | In Water |  |  | In the Gas | In Water |
| **Bond lengths (Å)** | | | | | | | |
| Cl-C23 | 1.760 | 1.721 | 1.767 | C11-H34 | 1.097 | 1.095 | 1.096 |
| O2-C14 | 1.422 | 1.422 | 1.432 | C11-H35 | 1.095 | 1.096 | 1.095 |
| O2-H49 | 0.970 | 0.973 | 0.971 | C11-H36 | 1.095 | 1.095 | 1.095 |
| N3-C9 | 1.468 | 1.458 | 1.476 | C12-C15 | 1.529 | 1.519 | 1.526 |
| N3-C10 | 1.465 | 1.464 | 1.471 | C12-H37 | 1.108 | 1.097 | 1.106 |
| N3-C12 | 1.470 | 1.464 | 1.477 | C12-H38 | 1.095 | 1.093 | 1.094 |
| N4-C8 | 1.464 | 1.448 | 1.470 | C13-C16 | 1.445 | 1.418 | 1.449 |
| N4-C13 | 1.371 | 1.383 | 1.361 | C12- C17 | 1.394 | 1.403 | 1.399 |
| N4-H31 | 1.009 | 1.012 | 1.011 | C14-H39 | 1.102 | 1.091 | 1.098 |
| N5-C18 | 1.366 | 1.347 | 1.369 | C14-H40 | 1.094 | 1.095 | 1.094 |
| N5-C20 | 1.319 | 1.353 | 1.327 | C15-H41 | 1.096 | 1.094 | 1.095 |
| C6-C7 | 1.534 | 1.534 | 1.534 | C15-H42 | 1.095 | 1.096 | 1.095 |
| C6-C8 | 1.547 | 1.535 | 1.544 | C15-H43 | 1.096 | 1.096 | 1.096 |
| C6-H24 | 1.095 | 1.094 | 1.094 | C16-C18 | 1.432 | 1.411 | 1.431 |
| C6-H25 | 1.100 | 1.098 | 1.098 | C16- C19 | 1.418 | 1.405 | 1.417 |
| C7-C9 | 1.537 | 1.528 | 1.534 | C17-C20 | 1.407 | 1.380 | 1.400 |
| C7-H26 | 1.098 | 1.093 | 1.097 | C17-H44 | 1.083 | 1.084 | 1.082 |
| C7-H27 | 1.098 | 1.097 | 1.097 | C18-C21 | 1.420 | 1.392 | 1.420 |
| C8-C11 | 1.533 | 1.525 | 1.530 | C19-C22 | 1.378 | 1.392 | 1.379 |
| C8, H28 | 1.097 | 1.096 | 1.095 | C19-H45 | 1.087 | 1.086 | 1.085 |
| C9- H29 | 1.107 | 1.098 | 1.106 | C20-H46 | 1.090 | 1.085 | 1.089 |
| C9- H30 | 1.096 | 1.095 | 1.094 | C21-C23 | 1.374 | 1.397 | 1.373 |
| C10-C14 | 1.533 | 1.520 | 1.529 | C21-H47 | 1.084 | 1.089 | 1.084 |
| C10-H32 | 1.110 | 1.098 | 1.106 | C22-C23 | 1.411 | 1.389 | 1.409 |
| C10-H33 | 1.094 | 1.092 | 1.093 | C22-H48 | 1.084 | 1.087 | 1.084 |
| **RMSD Gas= 0.009 Å; RMSD Water= 0.002 Å** | | | | | | |  |
| **Bond angles (°)** | | | | | | | |
| C14-O2-H49 | 107.662 | 107.688 | 106.956 | N3-C12-H37 | 111.097 | 112.002 | 110.496 |
| C9-N3-C10 | 112.423 | 110.608 | 110.778 | N3-C12-H38 | 107.709 | 111.309 | 107.839 |
| C9-N3-C10 | 112.438 | 110.610 | 110.555 | C15-C12-H37 | 110.105 | 109.833 | 109.800 |
| C10-N3-C12 | 112.024 | 110.291 | 110.235 | C15-C12. H38 | 108.259 | 104.599 | 108.244 |
| C8-N4-C13 | 125.563 | 123.568 | 125.358 | H37-C12-H38 | 106.090 | 107.604 | 106.139 |
| C8-N4-H31 | 115.105 | 116.792 | 114.192 | N4-C13-C16 | 120.126 | 122.856 | 120.497 |
| C13-N4-H31 | 116.578 | 118.254 | 116.939 | N4-C13-C17 | 123.034 | 119.183 | 122.997 |
| C18-N5-C20 | 116.103 | 118.216 | 115.707 | C16-C13-C17 | 116.814 | 117.961 | 116.475 |
| C7- C6-C8 | 115.584 | 112.558 | 115.428 | O2-C14-C10 | 111.626 | 108.744 | 111.550 |
| C7-C6-H24 | 108.083 | 110.806 | 109.303 | O2-C14-H39 | 111.322 | 105.561 | 110.474 |
| C7-C6-H25 | 109.415 | 108.807 | 109.450 | O2-C14-H40 | 106.260 | 108.018 | 106.051 |
| C8-C6-H24 | 109.118 | 110.229 | 108.273 | C10-C14-H39 | 110.910 | 114.171 | 111.212 |
| C8-C6- H25 | 107.774 | 108.405 | 107.602 | C10-C14-H40 | 109.354 | 111.369 | 109.723 |
| H24-C6-H25 | 106.503 | 105.767 | 106.398 | H39-C14-H40 | 107.145 | 108.659 | 107.620 |
| C6-C7-C9 | 112.713 | 111.079 | 113.661 | C12-C15-H41 | 112.229 | 112.488 | 112.490 |
| C6-C7-H26 | 109.647 | 112.882 | 109.956 | C12-C15-H42 | 110.306 | 111.764 | 110.897 |
| C6-C7-H27 | 110.788 | 109.112 | 109.954 | C12-C15-H43 | 110.256 | 109.583 | 109.766 |
| C9-C7-H26 | 109.531 | 112.943 | 109.934 | H41-C15-H42 | 107.905 | 108.974 | 107.985 |
| C9-C7-H27 | 107.614 | 105.628 | 106.925 | H41-C15-H43 | 107.431 | 106.470 | 107.420 |
| H26-C7-H27 | 106.330 | 104.667 | 106.095 | H42-C15-H43 | 108.588 | 107.296 | 108.121 |
| N4-C8-C6 | 113.451 | 110.262 | 112.812 | C13-C16-C18 | 117.788 | 119.173 | 117.997 |
| N4-C8-C11 | 108.386 | 108.603 | 108.384 | C13-C16-C19 | 123.822 | 120.489 | 123.404 |
| N4-C8-H28 | 106.593 | 110.682 | 106.917 | C18-C16-C19 | 118.388 | 120.338 | 118.596 |
| C6-C8-C11 | 113.258 | 110.948 | 113.285 | C13-C17-C20 | 119.730 | 118.684 | 119.882 |
| C6-C8-H28 | 107.483 | 109.288 | 107.510 | C13-C17-H44 | 121.342 | 122.776 | 121.217 |
| C11-C8-H28 | 107.282 | 107.012 | 107.612 | C20-C17-H44 | 118.925 | 118.532 | 118.899 |
| N3-C9-C7 | 113.471 | 110.343 | 114.827 | N5-C18-C16 | 123.899 | 121.852 | 123.966 |
| N3-C9-H29 | 111.192 | 111.531 | 110.261 | N5-C18-C21 | 116.936 | 120.090 | 117.043 |
| N3-C9-H30 | 107.973 | 111.549 | 107.834 | C16-C18-C21 | 119.164 | 118.058 | 118.989 |
| C7-C9-H29 | 109.522 | 109.210 | 109.145 | C16-C19-C22 | 121.708 | 120.395 | 121.757 |
| C7-C9-H30 | 108.185 | 106.685 | 108.161 | C16-C19-H45 | 120.722 | 122.788 | 120.687 |
| H29-C9-H30 | 106.182 | 107.350 | 106.234 | C22-C19-H45 | 117.556 | 116.815 | 117.554 |
| N3-C10-C14 | 112.642 | 110.672 | 112.716 | N5-C20-C17 | 125.648 | 124.114 | 125.967 |
| N3-C10-H32 | 111.503 | 111.680 | 111.329 | N5-C20- H46 | 115.992 | 115.027 | 115.928 |
| N3-C10-H33 | 109.439 | 112.960 | 109.256 | C17-C20-H46 | 118.356 | 120.859 | 118.102 |
| C14-C10-H32 | 109.576 | 110.157 | 109.285 | C18-C21-C23 | 120.189 | 121.619 | 120.041 |
| C14-C10-H33 | 107.286 | 104.952 | 107.501 | C18-C21-H47 | 117.814 | 118.959 | 118.291 |
| H32-C10-H33 | 106.098 | 106.126 | 106.490 | C23-C21-H47 | 121.997 | 119.422 | 121.667 |
| C8-C11-H34 | 111.648 | 112.951 | 111.637 | C19-C22-C23 | 119.097 | 119.579 | 118.714 |
| C8-C11-H35 | 110.685 | 109.931 | 110.823 | C19-C22-H48 | 120.974 | 119.414 | 120.773 |
| C8-C11-H36 | 110.440 | 111.222 | 110.075 | C23-C22-H48 | 119.928 | 121.007 | 120.511 |
| H34-C11-H35 | 107.997 | 106.322 | 108.009 | Cl-C23-C21 | 120.006 | 119.974 | 119.521 |
| H34-C11-H36 | 107.464 | 108.638 | 107.955 | Cl-C23C22 | 118.551 | 120.015 | 118.581 |
| H35-C11-H36 | 108.481 | 107.521 | 108.221 | C21-C23-C22 | 121.441 | 120.012 | 121.896 |
| N3-C12-C15 | 113.257 | 111.181 | 113.977 |  |  |  |  |
| **RMSD Gas= 1.700 °; RMSD Water=0.367 °** | | | | | | | |

**Table S2:** Optimized parameters for the hydroxychloroquine sulfate in the gas phase and water compared with the experimental ones by using B3LYP/6-31G\* basis set.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Hydroxychloroquine sulfate** | | | | | | | | | | | | | |
| Parameters | Experimental | | Theoretical | | | | Parameters | Experimental | | | Theoretical | | |
|  |  | | In the Gas | | In Water | |  |  | | | In the Gas | | In Water |
| **Bond lengths (Å)** | | | | | | | | | | | | | |
| S-O2 | 1.457(3) | 1.459 | | 1.503 | | C22-C40 | | | 1.410(4) | 1.404 | | 1.084 | |
| S-O3 | 1.438(3) | 1.630 | | 1.522 | | C23-H24 | | | 0.970 | 1.084 | | 1.405 | |
| S-O4 | 1.497(4) | 1.491 | | 1.510 | | C23-C25 | | | 1.361(5) | 1.399 | | 1.381 | |
| S-O5 | 1.430(8) | 1.528 | | 1.534 | | C23-C34 | | | 1.375 | 1.387 | | 1.379 | |
| O4-H14 | 1.9922 | 1.002 | | 1.862 | | C25-C40 | | | 1.368(5) | 1.385 | | 1.091 | |
| Cl-C25 | 1.742(3) | 1.757 | | 1.757 | | C26-H27 | | | 0.930 | 1.094 | | 1.092 | |
| O7-H8 | 0.82(3) | 0.969 | | 0.971 | | C26-H28 | | | 0.970 | 1.090 | | 1.537 | |
| O7-C42 | 1.325(4) | 1.425 | | 1.429 | | C26-C47 | | | 1.516(5) | 1.543 | | 1.091 | |
| N9-H10 | 0.89(4) | 1.078 | | 1.058 | | C29-H30 | | | 0.970 | 1.091 | | 1.091 | |
| N9-C26 | 1.499(4) | 1.510 | | 1.517 | | C29-H31 | | | 0.980 | 1.094 | | 1.517 | |
| N9-C29 | 1.495(4) | 1.507 | | 1.511 | | C29-C42 | | | 1.504(5) | 1.517 | | 1.093 | |
| N9-C50 | 1.504(4) | 1.509 | | 1.516 | | C32-H33 | | | 1.001 | 1.103 | | 1.533 | |
| N11-H12 | 0.821 | 1.009 | | 1.015 | | C32-C36 | | | 1.530(4) | 1.538 | | 1.083 | |
| N11-C20 | 1.333(4) | 1.365 | | 1.346 | | C34-H35 | | | 0.950 | 1.083 | | 1.095 | |
| N11-C22 | 1.368(3) | 1.389 | | 1.377 | | C36-H37 | | | 0.980 | 1.095 | | 1.095 | |
| N13-H14 | 0.81(4) | 1.840 | | 1.033 | | C36-H38 | | | 0.980 | 1.097 | | 1.095 | |
| N13-C16 | 1.3307 | 1.302 | | 1.334 | | C36-H39 | | | 0.980 | 1.095 | | 1.084 | |
| N13-C32 | 1.475(4) | 1.465 | | 1.475 | | C40-H41 | | | 0.960 | 1.086 | | 1.097 | |
| C15-C16 | 1.406(4) | 1.485 | | 1.459 | | C42-H43 | | | 0.991 | 1.100 | | 1.099 | |
| C15-C22 | 1.406(4) | 1.415 | | 1.418 | | C42-H44 | | | 0.991 | 1.101 | | 1.080 | |
| C15-C34 | 1.454(4) | 1.408 | | 1.4141 | | C45-H46 | | | 0.950 | 1.081 | | 1.095 | |
| C16-C45 | 1.410(4) | 1.457 | | 1.4219 | | C47-H48 | | | 0.991 | 1.094 | | 1.095 | |
| C17-H18 | 0.970 | 1.099 | | 1.096 | | C47-H49 | | | 0.989 | 1.097 | | 1.090 | |
| C17-H19 | 0.980 | 1.096 | | 1.095 | | C50-H51 | | | 0.989 | 1.091 | | 1.092 | |
| C17-C32 | 1.526(4) | 1.542 | | 1.536 | | C50-H52 | | | 0.990 | 1.093 | | 1.521 | |
| C17-C47 | 1.527(4) | 1.537 | | 1.536 | | C50-C53 | | | 1.403(4) | 1.526 | | 1.095 | |
| C20-H21 | 0.970 | 1.085 | | 1.083 | | C53-H54 | | | 0.979 | 1.095 | | 1.093 | |
| C20-C45 | 1.361(5) | 1.357 | | 1.370 | | C53-H55 | | | 0.980 | 1.095 | | 1.093 | |
| C53-H56 | 0.970 | 1.093 | | 1.407 | |  | | |  |  | |  | |
| **RMSD Gas= 0.111 Å; RMSD Water= 0.155 Å** | | | | | | | | | | | | | |
|  | **Bond lengths (°)** | | | | | | | | | | |  | |
| O2-S-O3 | 111.0(2) | 105.252 | | 109.979 | | H31-C29-C42 | | | 108.9 | 110.447 | | 105.310 | |
| O2-S-O4 | 104.2(2) | 116.274 | | 110.904 | | N13-C32-C17 | | | 108.9 | 108.723 | | 108.134 | |
| O2-S-O5 | 111.1(4) | 114.268 | | 109.524 | | N13-C32-H33 | | | 108.8 | 110.701 | | 107.730 | |
| O3-S-O4 | 106.3(2) | 107.085 | | 109.710 | | N13-C32-C36 | | | 110.8(4) | 110.620 | | 110.400 | |
| O3-S-O5 | 102.0(4) | 103.986 | | 107.798 | | C17-C32-H33 | | | 108.8 | 107.657 | | 109.167 | |
| O4-S-O5 | 122.0(4) | 108.918 | | 108.860 | | C17-C32-C36 | | | 111.43 | 110.185 | | 109.195 | |
| S-O3-H14 | 118(2) | 110.240 | | 113.728 | | H33-C32-C36 | | | 108.83 | 108.909 | | 107.577 | |
| H8-O7-C42 | 117(2) | 108.249 | | 107.157 | | C15-C34-C23 | | | 121.04 | 121.743 | | 121.474 | |
| H10-N9-C26 | 124.6(2) | 105.974 | | 108.658 | | C15-C34-H35 | | | 119.4 | 119.734 | | 116.517 | |
| H10-N9-C29 | 121(2) | 103.756 | | 104.530 | | C23-C34-H35 | | | 119.4 | 118.520 | | 118.305 | |
| H10-N9-C50 | 119(2) | 106.085 | | 105.701 | | C32-C36-H37 | | | 109.4 | 111.336 | | 109.514 | |
| C26-N9-C29 | 120.7(3) | 112.513 | | 112.251 | | C32-C36-H38 | | | 109.5 | 110.889 | | 109.346 | |
| C26-N9-C50 | 111(3) | 111.976 | | 110.214 | | C32-C36-H39 | | | 109.5 | 109.845 | | 110.281 | |
| C29-N9-C50 | 113.6(2) | 115.492 | | 114.943 | | H37-C36-H38 | | | 109.5 | 108.297 | | 108.250 | |
| H12-N11-C20 | 122.7(3) | 119.849 | | 119.481 | | H37-C36-H39 | | | 109.4 | 107.945 | | 111.016 | |
| H12-N11-C22 | 117.9(2) | 118.746 | | 118.685 | | H38-C36-H39 | | | 109.4 | 108.431 | | 110.320 | |
| C20-N11-C22 | 120.5(2) | 121.371 | | 121.826 | | C22-C40-C25 | | | 118.35 | 118.899 | | 117.363 | |
| H14-O3-C16 | 123.2(2) | 125.649 | | 119.418 | | C22-C40-H41 | | | 120.4 | 120.493 | | 121.401 | |
| H14-N13-C32 | 116.8(2) | 109.438 | | 113.637 | | C25-C40-H41 | | | 120.5 | 120.607 | | 120.540 | |
| C16-N13-C32 | 124.220 | 120.621 | | 125.627 | | O7-C42-C29 | | | 113.5(2) | 109.628 | | 108.453 | |
| O3-H14-N13 | 158.274 | 170.474 | | 119.046 | | O7-C42-H43 | | | 108.8 | 111.329 | | 111.226 | |
| C16-C15-C22 | 118.5(3) | 120.331 | | 123.312 | | O7-C42-H44 | | | 108.8 | 111.264 | | 108.254 | |
| C16-C15-C34 | 122.3(3) | 122.186 | | 117.621 | | C29-C42-H43 | | | 108.8 | 110.914 | | 110.557 | |
| C22-C15-C34 | 119.0(3) | 117.473 | | 120.493 | | C29-C42-H44 | | | 108.8 | 106.467 | | 106.304 | |
| N13-C16-C15 | 120.9(3) | 119.613 | | 122.373 | | H43-C42-H44 | | | 107.7 | 107.113 | | 110.998 | |
| N13-C16-C45 | 122.292 | 125.735 | | 117.130 | | C16-C45-C20 | | | 119.2(2) | 121.579 | | 119.729 | |
| C15-C16-C45 | 117.313 | 114.652 | | 118.1982 | | C16-C45-H46 | | | 120.8 | 120.359 | | 121.804 | |
| H18-C17-H19 | 107.5 | 107.128 | | 107.352 | | C20-C45-H46 | | | 120.8 | 117.986 | | 118.463 | |
| H18-C17-C32 | 109.062 | 108.721 | | 108.775 | | C17-C47-C26 | | | 109.5 | 112.437 | | 107.219 | |
| H18-C17-C47 | 108.6 | 110.546 | | 109.395 | | C17-C47-H48 | | | 109.5 | 106.821 | | 109.803 | |
| H19-C17-C32 | 109.8 | 108.761 | | 110.374 | | C17-C47-H49 | | | 109.5 | 110.628 | | 110.387 | |
| H19-C17-C47 | 109.7 | 108.373 | | 114.139 | | C26-C47-H48 | | | 109.4 | 109.395 | | 110.530 | |
| C32-C17-C47 | 112.826 | 113.124 | | 115.883 | | C26-C47-H49 | | | 109.7 | 110.448 | | 112.710 | |
| N11-C20-H21 | 118.5 | 115.417 | | 121.878 | | H48-C47-H49 | | | 108.181 | 106.889 | | 110.336 | |
| N11-C20-C45 | 122.875 | 122.255 | | 122.231 | | N9-C50-H51 | | | 109.047 | 107.522 | | 109.269 | |
| H21-C20-C45 | 118.5(3) | 122.324 | | 119.480 | | N9-C50-H52 | | | 109.031 | 105.386 | | 109.915 | |
| N11-C22-C15 | 120.149 | 119.487 | | 119.104 | | N9-C50-C53 | | | 113.6(3) | 112.905 | | 108.169 | |
| N11-C22-C40 | 118.8 | 119.163 | | 121.412 | | H51-C50-H52 | | | 107.8 | 109.100 | | 106.205 | |
| C15-C22-C40 | 121.3(3) | 121.346 | | 120.366 | | H51-C50-C53 | | | 109.1 | 111.750 | | 106.802 | |
| H24-C23-C25 | 120.3(2) | 120.489 | | 120.446 | | H52-C50-C53 | | | 109.0 | 109.920 | | 105.412 | |
| H24-C23-C34 | 120.1(2) | 120.359 | | 119.186 | | C50-C53-H54 | | | 109.5 | 108.667 | | 114.161 | |
| C25-C23-C34 | 119.1(3) | 119.152 | | 118.912 | | C50-C53-H55 | | | 109.5 | 111.092 | | 108.452 | |
| Cl-C25-C23 | 118.47 | 119.635 | | 119.197 | | C50-C53-H56 | | | 109.4 | 111.965 | | 111.486 | |
| Cl-C25-C40 | 119.01(3) | 119.011 | | 121.886 | | H54-C53-H55 | | | 109.5 | 108.252 | | 110.197 | |
| C23-C25-C40 | 122.9(3) | 121.349 | | 106.428 | | H54-C53-H56 | | | 109.5 | 107.414 | | 107.923 | |
| N9-C26-H27 | 108.7 | 107.423 | | 107.002 | | H55-C53-H56 | | | 109.4 | 109.311 | | 111.601 | |
| N9-C26-H28 | 108.7 | 105.347 | | 113.158 | | N9-C29-H31 | | | 108.9 | 104.656 | | 112.358 | |
| N9-C26-C47 | 113.3(3) | 111.985 | | 107.787 | | N9-C29-C42 | | | 114.0(2) | 116.279 | | 108.132 | |
| H27-C26-H28 | 107.7 | 109.224 | | 111.672 | | H30-C29-H31 | | | 107.8 | 107.963 | | 107.665 | |
| H27-C26-C47 | 108.8 | 112.563 | | 110.502 | | H30-C29-C42 | | | 108.9 | 110.012 | | 108.993 | |
| H28-C26-C47 | 108.5 | 110.002 | | 107.294 | | N9-C29-H30 | | | 108.9 | 107.071 | | 108.364 | |
| **RMSD Gas= 2.523 °; RMSD Water= 3.125 °** | | | | | | | | | | | | | |

**Table S3:** Calculated total energies (E), RMS Cartesian force, dipole moments (µ) and Maximum Cartesian force of chloroquine derivatives by using B3LYP/6-31G\* level of theory.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **B3LYP/6-31G\* method** | | | | |
| Molecules | E (Hartree) | RMS Cartesian force | µ (D) | Maximum Cartesian force |
| **In gas phase** | | | | |
| Hydroxychloroquine | -1401.2376 | 0.0090 | 7.33 | 0.0325 |
| Hydroxychloroquine sulfate | -2101.4778 | 0.0721 | 12.65 | 0.2606 |
| **In water** | | | | |
| Hydroxychloroquine | -1401.2620 | 0.0020 | 11.04 | 0.0079 |
| Hydroxychloroquine sulfate | -2101.5608 | 0.0015 | 29.85 | 0.0112 |

**Table S4:** Amino acid residues-hydroxychloroquine interactions.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ligand** | **Target protein** | **Binding residue** | **Type** | **Atoms** | **Bond length** | **Interactions** |
| Hydroxychloroquine | 5R7Y | A:MET49  A:CYS44  A:HIS41  A:HIS164  A:GLU166  A:ASN142  A:HIS142  A:HIS163  A:PHE140 | Methionine  Cysteine  Histidine  Histidine  GlutamicAcid  Asparagine  Histidine  Histidine  Phenylalanine | Cl  Cl  Cl  H46  H27  H32, H38  C14  C14,  C14,H33 | 4.06  5.05  4.75  2.65  2.72  3.02  2.15  3.06  3.25 | Alkyl  Pi- Alkyl  Pi-Pi T-shaped  Carbon-H bond  Carbon-H bond  Carbon-H bond  Carbon-H bond  Carbon-H bond  Carbon-H bond |
| 6M03 | A:ASN142  A:THR25  A:THR25  A:CYS145  A:LEU27 | Asparagine  Threonine  Threonine  Cysteine  Leucine | O2  N4  Pyridine  Pyridine  Pyridine | 2.75  3.27  3.68  4.93  5.05 | Conventional H-bond  Conventional H-bond  Pi-Sigma  Pi-Alkyl  Pi-Alkyl |
| 6LU7 | A:MET165  A:MET49  A:HIS163  A:GLU166  A:LEU141  A:ASN142  A:CYS145  A:HIS164  A:HIS41 | Methionine  Methionine  Histidine GlutamicAcid  Leucine  Asparagine  Cysteine  Histidine  Histidine | Benzene  Benzene  H39  H46  H33, H38  H37  H49  H49  Cl | 5.26  5.20  2.53  2.56  2.98  1.92  1.93  2.26  2.98 | Pi-Sulfur  Pi-Alkyl  Carbon H-bond Carbon H-bond  Carbon H-bond  Carbon H-bond  Conventional H-bond  Conventional H-bond  Conventional H-bond |

**Table S5:** Amino acid residues-hydroxychloroquine sulfate interactions.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ligand** | **Target protein** | **Binding residue** | **Type** | **Atoms** | **Bond length** | **Interactions** |
| Hydroxychloroquine sulfate | 5R7Y | A:HIS41  A:CYS145  A:CYS145  A:LEU141  A:THR25  A:SER46 | Histidine  Cysteine  Cysteine  Leucine  Threonine  Serine | S1  Benzene  Pyridine  H21  O4  H19 | 4.10  5.28  3.26  2.83  3.32  1.89 | Pi-Sulfur  Pi-Alkyl  Pi Donor H-bond  Carbon H-bond  Conventional H-bond  Conventional H-bond |
| 6M03 | A:LEU286  A:MET276  A:LEU287  A:TYR239  A:LEU287  A:THR199 | Leucine  Methionine  Leucine  Threonine  Leucine  Threonine | Cl  Cl  Benzene  Pyridine  H15  H23 | 4.74  4.91  5.09  3.71  2.95  1.93 | Alkyl  Alkyl  Pi-Alkyl  Pi Donor H-bond  Carbon H-bond  Carbon H-bond |
| 6LU7 | A:MET165  A:MET165  A:MET165  A:HIS41  A:HIS41  A:HIS164  A:CYS145 | Methionine  Methionine  Methionine  Histidine  Histidine  Histidine  Cysteine | Cl  Benzene  Cl  C18  O1  O1  O1 | 3.71  5.48  3.21  4.88  3.16  3.31  2.62 | Alkyl  Pi-Sulfur  Halogen  Pi-Alkyl  Conventional H-bond  Conventional H-bond  Conventional H-bond |