**Bifunctional Neuraminidase Inhibitory and Simultaneously Anti-*Mycoplasma pneumoniae* of Flavan-3-ols and Flavanones: Combined Molecular Docking, Virtual Screening, ADMET, and Synthesis Prediction**

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|  |  |  |
| --- | --- | --- |
| **PDB ID** | **Center (X,Y,Z)** | **Dimension (Å) (X,Y,Z)** |
| 3CL0 | X: -27.8, Y: -53.9, Z: 8.5 | X: 18.6, Y: 18.1, Z: 17.1 |
| 1PA4 | X: -3.2, Y: -1.3, Z: -7.4 | X: 22.3, Y: 19.7, Z: 21.7 |
| 6TLZ | X: -4.5, Y: -24.4, Z: 60.4 | X: 18.8, Y: 21.1, Z: 24.0 |

Table S2: Molecular docking simulations of N1-H274Y-oseltamivir protein (PDB ID: 3CL0) with Laninamivir and Oseltamivir (Ref: DOI 10.3897/pharmacia.71.e114967)

|  |  |  |  |
| --- | --- | --- | --- |
| **Molecule** | **Binding energy (kcal/mol)** | **K*i* value (nM)** | **H-bond** |
| Laninamivir | -8.1 (catalytic active site) | 1,145.7 | Asn294 Tyr347 Arg371 Arg292 Glu277 Glu227 Trp178  Arg152 |
| Oseltamivir | -6.7 (catalytic active site) | 12,187.7 | Glu119 Tyr406 Arg292 |

Table S3: Molecular docking simulations of N1-H274Y-oseltamivir protein (PDB ID: 3CL0) with 9 flavan-3-ols.

| **No.** | **ID code** | **Binding energy**  **(kcal/mol)** | **K*i* value (nM)** | **H-bond** | **Interaction with both the active site and the adjacent 430-cavity** |
| --- | --- | --- | --- | --- | --- |
| **1** | **FL-22** | **-9.9** | **54.8** | **ASP151 GLU227 ARG371 ARG430** | **+** |
| 2 | FL-6 | -9.1 | 211.6 | ASP151 ARG152 SER246 ASN294 TYR347 | − |
| 3 | FL-11 | -9 | 250.6 | ARG292 | − |
| 4 | FL-46 | -9 | 250.6 | ARG118  ASP151 ARG371 ILE427 GLY429 | − |
| 5 | FL-10 | -8.9 | 296.7 | ASP151 ARG152 ARG156 TRP178 GLU277 | − |
| 6 | FL-12 | -8.7 | 415.9 | GLU227 GLU277 ARG371 TYR406 | − |
| **7** | **FL-13** | **-8.5** | **583.0** | **ARG118 SER246 TYR406 ARG430** | **+** |
| 8 | FL-25 | -8.5 | 583.0 | ARG118 ARG152 TRP178 | − |
| **9** | **FL-26** | **-8.4** | **690.3** | **GLU119 ARG152 ARG156 GLU227** | **+** |
| Note: + Interacted with both the active site and the adjacent 430-cavity.  − Interacted with only one the active site or the adjacent 430-cavity. | | | | | |

Table S4: Molecular docking simulations of N1-H274Y-oseltamivir protein (PDB ID: 3CL0) with 122 flavanones.

| **No.** | **ID code** | **Binding energy**  **(kcal/mol)** | **K*i* value (nM)** | **H-bond** | **Interaction with both the active site and the adjacent 430-cavity** |
| --- | --- | --- | --- | --- | --- |
| 1 | **FN-316** | **-11.7** | **2.6** | **VAL149 ILE427** | **+** |
| 2 | **FN-166** | **-11.4** | **4.4** | **VAL149 SER404 ILE427** | **+** |
| 3 | FN-642 | -10.5 | 19.9 | ARG118 ASP151 GLU277 TYR347 ASN369 ARG371 | + |
| 4 | FN-204 | -10.3 | 27.9 | ARG118 GLU276 GLU277  TYR347 | + |
| 5 | FN-709 | -10.3 | 27.9 | ARG152 ASN294 ARG371 | − |
| 6 | FN-152 | -10.1 | 39.1 | ARG118 VAL149 GLU276 GLU277 ASN369 | + |
| 7 | FN-154 | -10.1 | 39.1 | ARG118 VAL149  GLU276  ASN369  TYR406 | + |
| 8 | FN-330 | -9.9 | 54.8 | ARG118 GLU227 | + |
| 9 | FN-229 | -9.9 | 54.8 | TYR347 | − |
| 10 | FN-512 | -9.9 | 54.8 | ARG371 | − |
| 11 | FN-675 | -9.8 | 64.9 | ARG118 VAL149c  ARG224 GLY244 SER246 GLU277 ARG292 TYR347 | + |
| 12 | FN-150 | -9.8 | 64.9 | ARG118 ASP151  GLU276  GLU277  SER404  ILE427 | + |
| 13 | FN-411 | -9.8 | 64.9 | ARG152 SER246  GLU277 ASN294 TYR347 | − |
| 14 | FN-337 | -9.8 | 64.9 | VAL149 GLU276 GLU277 ASN369 | + |
| 15 | FN-201 | -9.7 | 76.8 | ARG152 GLU277 ARG292 TYR347  ARG371 | + |
| 16 | FN-241 | -9.7 | 76.8 | GLU119  ARG152  ASN294  TYR406 | − |
| 17 | FN-784 | -9.7 | 76.8 | ASP151  GLU277  ARG371  ILE427 | + |
| 18 | FN-118 | -9.7 | 76.8 | ARG118 ARG292 | + |
| 19 | FN-424 | -9.7 | 76.8 | TRP178  GLU276 | + |
| 20 | FN-107 | -9.7 | 76.8 | TYR347 | − |
| 21 | FN-158 | -9.6 | 91.0 | ARG371 | − |
| 22 | FN-193 | -9.5 | 107.7 | ARG152 ARG292 ASN294  TYR347  ARG371 | + |
| 23 | FN-272 | -9.5 | 107.7 | ARG118 GLU227  SER246 ARG371 TYR406 | − |
| 24 | FN-199 | -9.5 | 107.7 | ARG118 ASP151  SER246  ILE427 | + |
| 25 | FN-175 | -9.5 | 107.7 | ARG118 ARG292 ARG371 | + |
| 26 | FN-209 | -9.5 | 107.7 | SER246  ARG292 ASN294 | + |
| 27 | FN-303 | -9.5 | 107.7 | ARG118  ASP151  ARG292 | + |
| 28 | FN-457 | -9.5 | 107.7 | ARG118 VAL149  ARG371 | − |
| 29 | FN-750 | -9.5 | 107.7 | GLU227  ARG292 | + |
| 30 | FN-590 | -9.5 | 107.7 | ARG371 | − |
| 31 | FN-755 | -9.5 | 107.7 | ARG371 | − |
| 32 | FN-317 | -9.4 | 127.5 | ARG118  GLU227  SER246  ASN294 ARG371 TYR406 | − |
| 33 | FN-75 | -9.4 | 127.5 | ARG118 GLU227  TYR406 | + |
| 34 | FN-226 | -9.4 | 127.5 | ARG118 ASN369  ARG371 | − |
| 35 | FN-331 | -9.4 | 127.5 | ARG152  TRP178  SER246 | − |
| 36 | FN-258 | -9.4 | 127.5 | ARG118 ARG292 | − |
| 37 | FN-306 | -9.4 | 127.5 | ASP151  TRP178 | − |
| 38 | FN-225 | -9.3 | 151.0 | ARG118 ASP151  SER246  ILE427 | + |
| 39 | FN-383 | -9.3 | 151.0 | ASP151 SER246 GLU277 TYR347 | + |
| 40 | FN-632 | -9.3 | 151.0 | ASP151  ARG152 ASN294 | − |
| 41 | FN-820 | -9.3 | 151.0 | TRP178  GLU276 | + |
| 42 | FN-656 | -9.3 | 151.0 | - | − |
| 43 | FN-807 | -9.3 | 151.0 | - | − |
| 44 | FN-320 | -9.2 | 178.8 | ARG118 VAL149  ASP151  ARG292 ARG371 | − |
| 45 | FN-274 | -9.2 | 178.8 | ASP151  TRP178  GLU227  SER246 | − |
| 46 | FN-310 | -9.2 | 178.8 | ASP151  TRP178  SER246  ASN294 | − |
| 47 | FN-878 | -9.2 | 178.8 | ARG118 ASP151  TYR347  ARG371 | − |
| 48 | FN-180 | -9.2 | 178.8 | ARG118 SER404  ILE427 | + |
| 49 | FN-827 | -9.2 | 178.8 | ARG118 ARG152 ARG371 | + |
| 50 | FN-279 | -9.2 | 178.8 | ASP151  GLU227 | + |
| 51 | FN-370 | -9.2 | 178.8 | ARG118  ARG371 | − |
| 52 | FN-373 | -9.2 | 178.8 | ARG118  VAL149  GLU276  ASN369  TYR406 | − |
| 53 | FN-883 | -9.2 | 178.8 | ARG371 | − |
| 54 | FN-573 | -9.1 | 211.6 | ASP151 ARG152 GLU227 ARG292 ASN294  TYR347 | − |
| 55 | FN-221 | -9.1 | 211.6 | ARG118 VAL149 ASP151 TYR347 | − |
| 56 | FN-360 | -9.1 | 211.6 | ASP151 ARG371 SER404  TYR406 | + |
| 57 | FN-130 | -9.1 | 211.6 | TRP178 | + |
| 58 | FN-412 | -9.1 | 211.6 | ARG371 | − |
| 59 | FN-544 | -9.1 | 211.6 | GLU276 ASN294 | + |
| 60 | FN-774 | -9 | 250.6 | ARG118 TYR347  ARG371 SER404  ILE427 | − |
| 61 | FN-143 | -9 | 250.6 | ARG152 TRP178  ASN221  SER246 | − |
| 62 | FN-233 | -9 | 250.6 | ARG118 ASP151  GLU276  ASN294 | + |
| 63 | FN-238 | -9 | 250.6 | GLU227  ARG292  ASN294  TYR406 | − |
| 64 | FN-328 | -9 | 250.6 | ARG118 ASN325  ARG371 | − |
| 65 | FN-334 | -8.9 | 296.7 | ASP151  GLU277  ASN294  TYR347  SER404  TYR406  ILE427 | + |
| 66 | FN-106 | -8.9 | 296.7 | VAL149 THR225 GLU227 | + |
| 67 | FN-70 | -8.9 | 296.7 | ARG118 ARG371 | + |
| 68 | FN-518 | -8.9 | 296.7 | ARG118 ASP151 | − |
| 69 | FN-854 | -8.9 | 296.7 | ARG118 ARG371 | − |
| 70 | FN-514 | -8.9 | 296.7 | ARG118 | + |
| 71 | FN-599 | -8.9 | 296.7 | LYS432 | − |
| 72 | FN-611 | -8.9 | 296.7 | ARG371 | − |
| 73 | FN-821 | -8.9 | 296.7 | TYR406 | + |
| 74 | FN-744 | -8.8 | 351.3 | ARG118 VAL149  ASP151  SER246 | − |
| 75 | FN-847 | -8.8 | 351.3 | ARG118 GLU119  VAL149  TYR347 | + |
| 76 | FN-704 | -8.8 | 351.3 | ARG118 VAL149 | − |
| 77 | FN-515 | -8.8 | 351.3 | - | − |
| 78 | FN-842 | -8.8 | 351.3 | - | − |
| 79 | FN-207 | -8.7 | 415.9 | ARG118 GLU119  TRP178  GLU227  ASN294  TYR406 | − |
| 80 | FN-220 | -8.7 | 415.9 | ARG118 VAL149  ARG371 ILE427 | − |
| 81 | FN-643 | -8.7 | 415.9 | ARG118 VAL149  ASP151  ARG371 | − |
| 82 | FN-666 | -8.7 | 415.9 | TRP178  ARG224 GLU227 | − |
| 83 | FN-874 | -8.7 | 415.9 | ARG118  ARG371  TYR406 | + |
| 84 | FN-167 | -8.7 | 415.9 | GLU276 ASN294 | − |
| 85 | FN-371 | -8.7 | 415.9 | ARG118 ARG371 | − |
| 86 | FN-579 | -8.7 | 415.9 | ARG118 ASP151 | − |
| 87 | FN-791 | -8.7 | 415.9 | ARG292 TYR406 | − |
| 88 | FN-394 | -8.7 | 415.9 | ARG118 | + |
| 89 | FN-188 | -8.6 | 492.4 | ARG118 SER246  GLU277 ARG292 ARG371 | + |
| 90 | FN-288 | -8.6 | 492.4 | ARG118 GLU277  TYR347  ARG371 | + |
| 91 | FN-343 | -8.6 | 492.4 | ARG152 ASN294  ARG371  TYR406 | + |
| 92 | FN-428 | -8.6 | 492.4 | ASN221 ARG224 GLU227 SER246 | + |
| 93 | FN-853 | -8.6 | 492.4 | TYR347 ARG371 | − |
| 94 | FN-78 | -8.6 | 492.4 | VAL149 | − |
| 95 | FN-393 | -8.6 | 492.4 | ASN369 | − |
| 96 | FN-477 | -8.6 | 492.4 | SER246 | − |
| 97 | FN-668 | -8.5 | 583.0 | ARG118 GLU119 ASP151 ARG156 ARG292 ARG371 | + |
| 98 | FN-270 | -8.5 | 583.0 | VAL149  ASP151 GLU276 ARG292  TYR406 | + |
| 99 | FN-482 | -8.5 | 583.0 | ASP151  ASN221  GLY244  GLU277 | − |
| 100 | FN-843 | -8.5 | 583.0 | ASP151  TRP178  GLU276  ARG371 | − |
| 101 | FN-112 | -8.5 | 583.0 | ASP151  ARG152 GLU227 | − |
| 102 | FN-375 | -8.5 | 583.0 | ARG118  ARG371  TYR406 | − |
| 103 | FN-612 | -8.5 | 583.0 | ARG118 VAL149 | − |
| 104 | FN-710 | -8.5 | 583.0 | ARG118 VAL149 | − |
| 105 | FN-716 | -8.5 | 583.0 | ARG152 GLU276 | − |
| 106 | FN-701 | -8.5 | 583.0 | LYS432 | − |
| 107 | FN-868 | -8.5 | 583.0 | ARG118 ARG371 TYR406 | − |
| 108 | FN-325 | -8.4 | 690.3 | GLU227 SER246  ARG292 ASN294  TYR406 | − |
| 109 | FN-354 | -8.4 | 690.3 | ARG118 VAL149  ASP151  SER404  ILE427 | − |
| 110 | FN-483 | -8.4 | 690.3 | GLU119 TRP178  GLU277  ARG292 | − |
| 111 | FN-765 | -8.4 | 690.3 | ARG118 GLU276  ARG292  ARG371 | − |
| 112 | FN-493 | -8.4 | 690.3 | ARRG118 GLU119  TYR347 | − |
| 113 | FN-504 | -8.4 | 690.3 | ARG152 TRP178  GLY244 | − |
| 114 | FN-537 | -8.4 | 690.3 | ARG118 ASP151 GLU276 | + |
| 115 | FN-801 | -8.4 | 690.3 | TRP178 ARG224 SER246 | − |
| 116 | FN-863 | -8.4 | 690.3 | TYR347 ARG371 ARG430 | − |
| 117 | FN-237 | -8.4 | 690.3 | ARG152 TRP178 | − |
| 118 | FN-419 | -8.4 | 690.3 | ARG371 ILE427 | − |
| 119 | FN-531 | -8.4 | 690.3 | ARG371 ARG430 | − |
| 120 | FN-624 | -8.4 | 690.3 | ARG118 GLU227 | − |
| 121 | FN-871 | -8.4 | 690.3 | TYR347 LYS432 | − |
| 122 | FN-737 | -8.4 | 690.3 | ARG118 | − |
| Note: + Interacted with both the active site and the adjacent 430-cavity.  − Interacted with only one the active site or the adjacent 430-cavity. | | | | | |

Table S5: 2D and 3D interactions of N1-H274Y-oseltamivir protein (PDB ID: 3CL0) with 9 flavan-3-ols.

| **No.** | **ID code** | **2D interaction** | **3D interaction** |
| --- | --- | --- | --- |
| 1 | **FL-22** |  |  |
| 2 | FL-6 |  |  |
| 3 | FL-11 |  |  |
| 4 | FL-46 |  |  |
| 5 | FL-10 |  |  |
| 6 | FL-12 |  |  |
| 7 | **FL-13** |  |  |
| 8 | FL-25 |  |  |
| 9 | **FL-26** |  |  |

Table S6: 2D and 3D interactions of N1-H274Y-oseltamivir protein (PDB ID: 3CL0) with 122 flavanones.

| **No.** | **ID code** | **2D interaction** | **3D interaction** |
| --- | --- | --- | --- |
| 1 | **FN-316** |  |  |
| 2 | **FN-166** |  |  |
| 3 | FN-642 |  |  |
| 4 | FN-204 |  |  |
| 5 | FN-709 |  |  |
| 6 | FN-152 |  |  |
| 7 | FN-154 |  |  |
| 8 | FN-330 |  |  |
| 9 | FN-229 |  |  |
| 10 | FN-512 |  |  |
| 11 | FN-675 |  |  |
| 12 | FN-150 |  |  |
| 13 | FN-411 |  |  |
| 14 | FN-337 |  |  |
| 15 | FN-201 |  |  |
| 16 | FN-241 |  |  |
| 17 | FN-784 |  |  |
| 18 | FN-118 |  |  |
| 19 | FN-424 |  |  |
| 20 | FN-107 |  |  |
| 21 | FN-158 |  |  |
| 22 | FN-193 |  |  |
| 23 | FN-272 |  |  |
| 24 | FN-199 |  |  |
| 25 | FN-175 |  |  |
| 26 | FN-209 |  |  |
| 27 | FN-303 |  |  |
| 28 | FN-457 |  |  |
| 29 | FN-750 |  |  |
| 30 | FN-590 |  |  |
| 31 | FN-755 |  |  |
| 32 | FN-317 |  |  |
| 33 | FN-75 |  |  |
| 34 | FN-226 |  |  |
| 35 | FN-331 |  |  |
| 36 | FN-258 |  |  |
| 37 | FN-306 |  |  |
| 38 | FN-225 |  |  |
| 39 | FN-383 |  |  |
| 40 | FN-632 |  |  |
| 41 | FN-820 |  |  |
| 42 | FN-656 |  |  |
| 43 | FN-807 |  |  |
| 44 | FN-320 |  |  |
| 45 | FN-274 |  |  |
| 46 | FN-310 |  |  |
| 47 | FN-878 |  |  |
| 48 | FN-180 |  |  |
| 49 | FN-827 |  |  |
| 50 | FN-279 |  |  |
| 51 | FN-370 |  |  |
| 52 | FN-373 |  |  |
| 53 | FN-883 |  |  |
| 54 | FN-573 |  |  |
| 55 | FN-221 |  |  |
| 56 | FN-360 |  |  |
| 57 | FN-130 |  |  |
| 58 | FN-412 |  |  |
| 59 | FN-544 |  |  |
| 60 | FN-774 |  |  |
| 61 | FN-143 |  |  |
| 62 | FN-233 |  |  |
| 63 | FN-238 |  |  |
| 64 | FN-328 |  |  |
| 65 | FN-334 |  |  |
| 66 | FN-106 |  |  |
| 67 | FN-70 |  |  |
| 68 | FN-518 |  |  |
| 69 | FN-854 |  |  |
| 70 | FN-514 |  |  |
| 71 | FN-599 |  |  |
| 72 | FN-611 |  |  |
| 73 | FN-821 |  |  |
| 74 | FN-744 |  |  |
| 75 | FN-847 |  |  |
| 76 | FN-704 |  |  |
| 77 | FN-515 |  |  |
| 78 | FN-842 |  |  |
| 79 | FN-207 |  |  |
| 80 | FN-220 |  |  |
| 81 | FN-643 |  |  |
| 82 | FN-666 |  |  |
| 83 | FN-874 |  |  |
| 84 | FN-167 |  |  |
| 85 | FN-371 |  |  |
| 86 | FN-579 |  |  |
| 87 | FN-791 |  |  |
| 88 | FN-394 |  |  |
| 89 | FN-188 |  |  |
| 90 | FN-288 |  |  |
| 91 | FN-343 |  |  |
| 92 | FN-428 |  |  |
| 93 | FN-853 |  |  |
| 94 | FN-78 |  |  |
| 95 | FN-393 |  |  |
| 96 | FN-477 |  |  |
| 97 | FN-668 |  |  |
| 98 | FN-270 |  |  |
| 99 | FN-482 |  |  |
| 100 | FN-843 |  |  |
| 101 | FN-112 |  |  |
| 102 | FN-375 |  |  |
| 103 | FN-612 |  |  |
| 104 | FN-710 |  |  |
| 105 | FN-716 |  |  |
| 106 | FN-701 |  |  |
| 107 | FN-868 |  |  |
| 108 | FN-325 |  |  |
| 109 | FN-354 |  |  |
| 110 | FN-483 |  |  |
| 111 | FN-765 |  |  |
| 112 | FN-493 |  |  |
| 113 | FN-504 |  |  |
| 114 | FN-537 |  |  |
| 115 | FN-801 |  |  |
| 116 | FN-863 |  |  |
| 117 | FN-237 |  |  |
| 118 | FN-419 |  |  |
| 119 | FN-531 |  |  |
| 120 | FN-624 |  |  |
| 121 | FN-871 |  |  |
| 122 | FN-737 |  |  |

Table S7: Predicted "drug-likeness" parameters for potential anti-NA candidates using the SwissADME online tool.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **No.** | **Parameters** | **FL22** | **FN166** | **FN316** | **ChEMBL 1779463** |
| 1 | Formula | C29H24O12 | C30H20O10 | C30H22O10 | C30H22O8 |
| 2 | Molecular weight | 564.49 | 540.47 | 542.49 | 510.49 |
| 3 | Number rotatable bonds | 2 | 3 | 3 | 3 |
| 4 | Number H-bond acceptors | 12 | 10 | 10 | 8 |
| 5 | Number H-bond donors | 9 | 6 | 6 | 4 |
| 6 | Topological Polar Surface Area, TPSA (Å2) | 217.60 | 177.89 | 173.98 | 133.52 |
| 7 | Log Po/w(iLOGP) | 1.82 | 2.53 | 3.00 | 2.86 |
| 8 | Water Solubility | Moderately | Poorly | Poorly | Poorly |
| 9 | Lipinski's rule violations | 3 | 2 | 2 | 1 |

Table S8: Binding energies and K*i* values of five similarities were selected from the "SwissSimilarity" online tool, which performed molecular docking screening for 3CL0 protein.

|  |  |  |
| --- | --- | --- |
| **ID code** | **Bingding energy (kcal/mol)** | **K*i* value (nM)** |
| **ChEMBL1779463** | **-11.4** | **4.4** |
| ChEMBL3763296 | -9.2 | 178.8 |
| ChEMBL3765207 | -9 | 250.6 |
| ChEMBL4075132 | -9 | 250.6 |
| ChEMBL4086291 | -8.5 | 583.0 |

Table S9: The binding energies of the 30S ribosome-binding factor (PDB ID: 1PA4) with control (ZINC-04259381), 10 ligands from the decoy list from http://dudez.docking.org., and 5 active ligands from the "SwissSimilarity" online tool. These molecular docking results were carried out for the active site.

|  |  |  |  |
| --- | --- | --- | --- |
| **ID code** | **SMILES Structure** | **Bingding energy (kcal/mol)** | **K*i* value (nM)** |
| ZINC-04259381 | O=C(Nc1cccc(C(F)(F)F)c1)O[C@@H]1CO[C@H]2[C@@H]1OC[C@@H]2n1nnnc1SC1CCCC1 | -9.2 | 178.76 |
| **10 ligands from the decoy list** | | | | |
| P24612505 | [H]/N=C/1\C(=C/c2ccc(o2)c3ccc(cc3)[N+](=O)[O-])\C(=O)N=C4N1N=C(S4)[C@H](CC)c5ccccc5 | -7.8 | 1,901.49 |
| P14692054 | Cc1ccc(cc1NC(=O)[C@@H](C)OC(=O)c2ccc(cc2)n3c(cc(n3)C)C)S(=O)(=O)N(C)C | -7.8 | 1,901.49 |
| P62076135 | c1ccc(cc1)CNC(=O)c2cc3ccc(cc3oc2=O)OC(=O)CCN4C(=O)c5ccccc5C4=O | -7.7 | 2,251.33 |
| P23910165 | C[C@@H]1C[C@H](CN(C1)S(=O)(=O)c2ccc(cc2)C(=O)O[C@@H](C)C(=O)N3CC(=O)Nc4c3cccc4)C | -7.3 | 4,424.04 |
| P51626718 | CCOC(=O)[C@H]1CCCN(C1)C(=O)CN2CC3=C(C2=O)[C@H](NC(=O)N3CC=C)c4cccc(c4)Cl | -6.9 | 8,693.58 |
| P42372189 | Cc1c(sc(c1C(=O)OC)NC(=O)COC(=O)CN2C(=O)c3cc(c(cc3C2=O)Cl)Cl)C | -6.8 | 10,293.04 |
| P53436225 | CCOC(=O)C1=C(N(C(=O)N[C@H]1c2ccccc2OC)C)CN3CCN([C@@H](C3)C)C(=O)C4CC4 | -6.5 | 17,083.57 |
| P53436156 | CCOC(=O)C1=C(N(C(=O)N[C@@H]1c2cccc(c2)Cl)C)CN3CCN(CC3)C(=O)c4ccco4 | -6.2 | 28,353.94 |
| P25783792 | C=CCOc1ccc(cc1)/C(=C/2\[C@H](N(C(=O)C2=O)Cc3cccnc3)c4ccc(cc4)[N+](=O)[O-])/O | -5.9 | 47,059.61 |
| P33700532 | CCOC(=O)N1CCN(CC1)[C@H](c2ccccc2OC)c3c(cc(n(c3=O)Cc4ccco4)C)O | -5.8 | 55,717.71 |
| **05 active ligands** | | | | |
| CHEMBL3120949 | C[C@@H]1CC[C@H]2[C@@H](C)[C@@H](C[C@H](OC(=O)NC3=CC=CC(=C3)C(F)(F)F)[C@H]3O[C@@H]4O[C@@]5(C)CC[C@H]6[C@H](C)CC[C@@H]([C@H]3C)[C@@]46OO5)O[C@@H]3O[C@@]4(C)CC[C@@H]1[C@@]23OO4 | -9.7 | 76.83 |
| CHEMBL3120950 | C[C@@H]1CC[C@H]2[C@@H](C)[C@@H](C[C@H](OC(=O)NC3=CC=C(C=C3)C(F)(F)F)[C@H]3O[C@@H]4O[C@@]5(C)CC[C@H]6[C@H](C)CC[C@@H]([C@H]3C)[C@@]46OO5)O[C@@H]3O[C@@]4(C)CC[C@@H]1[C@@]23OO4 | -9.2 | 178.76 |
| CHEMBL493507 | [O-][N+](=O)O[C@@H]1CO[C@@H]2[C@H](CO[C@H]12)OC(=O)NC1=CC=CC(=C1)C(F)(F)F | -9.1 | 211.65 |
| CHEMBL1945572 | [O-][N+](=O)C1=CN2C[C@@H](COC2=N1)OC(=O)NC1=CC(=CC=C1)C1=CC=C(C=C1)C(F)(F)F | -9 | 250.58 |
| CHEMBL4591995 | CC(C)COC(=O)NC[C@@H]1CC[C@H]2[C@H](COC3=C(C=C(NC(=O)C4=CC=C(C=C4)C(F)(F)F)C=C3)C(=O)N2C)O1 | -8.5 | 583.02 |

Table S10: The binding energies of the immunodominant protein P40/P90 complex (PDB ID: 6TLZ) with control (3′-sialyllactose), two inactive ligands, and seven active ligands from the "SwissSimilarity" online tool. These molecular docking results were carried out for the sialic acid binding site.

|  |  |  |  |
| --- | --- | --- | --- |
| **ID code/Name** | **SMILES Structure** | **Bingding energy (kcal/mol)** | **K*i* value (µM)** |
| 3′-Sialyllactose | CC(N[C@@H]1[C@@H](O)C[C@@](C(O)=O)(O[C@H]2[C@@H](O)[C@@H](CO)O[C@@H](O[C@H]3[C@H](O)[C@H](O)C(O)O[C@@H]3CO)[C@@H]2O)O[C@H]1[C@H](O)[C@H](O)CO)=O | -6.1 | 33.57 |
| **02 decoy ligands** | | | | |
| Laninamivir | O=C(C1=C[C@H](NC(N)=N)[C@@H](NC(C)=O)[C@H]([C@H](OC)[C@H](O)CO)O1)O | -5.3 | 129.63 |
| Oseltamivir | CCOC(C1=C[C@H]([C@@H]([C@H](C1)N)NC(C)=O)OC(CC)CC)=O | -4.9 | 254.74 |
| **07 active ligands** | | | |
| CHEMBL1874250 | CC(=O)N[C@@H]1C(O)O[C@@H](CO)[C@@H](O[C@@H]2O[C@@H](CO)[C@H](O)[C@H](O[C@@]3(C[C@@H](O)[C@@H](NC(C)=O)[C@@H](O3)[C@H](O)[C@H](O)CO)C(O)=O)[C@@H]2O)[C@@H]1O | -6.5 | 17.08 |
| CHEMBL1852527 | CC(=O)N[C@@H]1[C@@H](O)C[C@@](O[C@H]2[C@@H](O)[C@@H](CO)O[C@@H](O[C@H]3[C@@H](O)[C@@H](CO)O[C@H](OCC4=CC=CC=C4)[C@@H]3NC(C)=O)[C@@H]2O)(O[C@H]1[C@H](O)[C@H](O)CO)C(O)=O | -6.3 | 23.95 |
| CHEMBL1222111 | CC(=O)N[C@@H]1[C@@H](O)[C@H](O)[C@@H](CO)O[C@H]1OC[C@H]1O[C@@H](O)[C@H](NC(C)=O)[C@@H](O[C@@H]2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2NC(C)=O)[C@@H]1O[C@@H]1O[C@H](CO)[C@@H](O)[C@H](O)[C@H]1NC(C)=O | -6.2 | 28.35 |
| CHEMBL4281777 | CCCO[C@@H]1O[C@H](CO)[C@@H](O[C@@H]2O[C@H](CO)[C@H](O)[C@H](O[C@@]3(C[C@H](O)[C@@H](NC(C)=O)[C@@H](O3)[C@H](O)[C@H](O)CO)C(O)=O)[C@H]2O)[C@H](O[C@@H]2O[C@@H](C)[C@@H](O)[C@@H](O)[C@@H]2O)[C@@H]1O | -6.1 | 33.57 |
| CHEMBL1213635 | CC(=O)N[C@@H]1[C@@H](O)C[C@@](O[C@@H]2[C@@H](O)[C@H](O[C@@H]3[C@@H](CO)OC(O)[C@H](O)[C@H]3O)O[C@H](CO)[C@@H]2O[C@H]2O[C@H](CO)[C@H](O)[C@H](O[C@@H]3O[C@H](CO)[C@H](O)[C@H](O)[C@H]3O)[C@H]2NC(C)=O)(O[C@H]1[C@H](O)[C@H](O)CO)C(O)=O | -6.1 | 33.57 |
| CHEMBL1222109 | CC(=O)N[C@@H]1[C@@H](O)[C@H](O)[C@@H](CO)O[C@H]1OC[C@H]1O[C@@H](O)[C@H](NC(C)=O)[C@@H](O[C@@H]2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2NC(C)=O)[C@@H]1O | -6.1 | 33.57 |
| CHEMBL442728 | COC1=CC=C(O[C@@H]2O[C@H](CO[C@@]3(C[C@H](O)[C@@H](NC(=O)CO)[C@@H](O3)[C@H](O)[C@H](O)CNCC3CCCCC3)C(O)=O)[C@H](O)[C@H](O)[C@H]2O)C=C1 | -6.1 | 33.57 |

Table S11: Percentage of HBs occupancy between N1-H274Y-oseltamivir protein (PDB ID: 3CL0) and the immunodominant protein P40/P90 complex (PDB ID: 6TLZ) with ChEMBL1779463.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **No.** | **H-bond donors** | | **H-bond acceptors** | **% H-bond occupancy** |
| **PDB ID: 3CL0** | | | | |
| 1 | LIG1-Side | GLU227-Side | | 40.25% |
| 2 | LIG1-Side | GLU119-Side | | 24.44% |
| 3 | ARG371-Main | LIG1-Side | | 24.11% |
| 4 | LIG1-Side | VAL149-Main | | 9.87% |
| 5 | ARG292-Side | LIG1-Side | | 7.24% |
| 6 | ARG156-Side | LIG1-Side | | 0.08% |
| 7 | TYR347-Side | LIG1-Side | | 0.03% |
| 8 | ARG118-Side | LIG1-Side | | 0.01% |
| 9 | LIG1-Side | TYR347-Side | | 0.01% |
| **PDB ID: 6TLZ** | | | | |
| 1 | ARG226-Side | LIG1-Side | | 23.75% |
| 2 | LIG1-Side | THR632-Main | | 23.40% |
| 3 | LIG1-Side | ASN233-Main | | 11.50% |
| 4 | LIG1-Side | ASN223-Side | | 5.56% |
| 5 | THR632-Main | LIG1-Side | | 5.17% |
| 6 | LIG1-Side | LEU630-Main | | 1.22% |
| 7 | LEU630-Main | LIG1-Side | | 0.83% |
| 8 | ASN223-Side | LIG1-Side | | 0.02% |
| 9 | THR632-Side | LIG1-Side | | 0.01% |

Figure S1: The structure of five similarities was selected from the "SwissSimilarity" online tool.

|  |
| --- |
| ChEMBL1779463 |
| ChEMBL3763296 |
| ChEMBL3765207 |
| ChEMBL4075132 |
| ChEMBL4086291 |

Figure S2: 3D molecular docking binding into the active site and 2D interaction diagrams of 30S RbfA (PDB ID: 1PA4) with ZINC04259381.

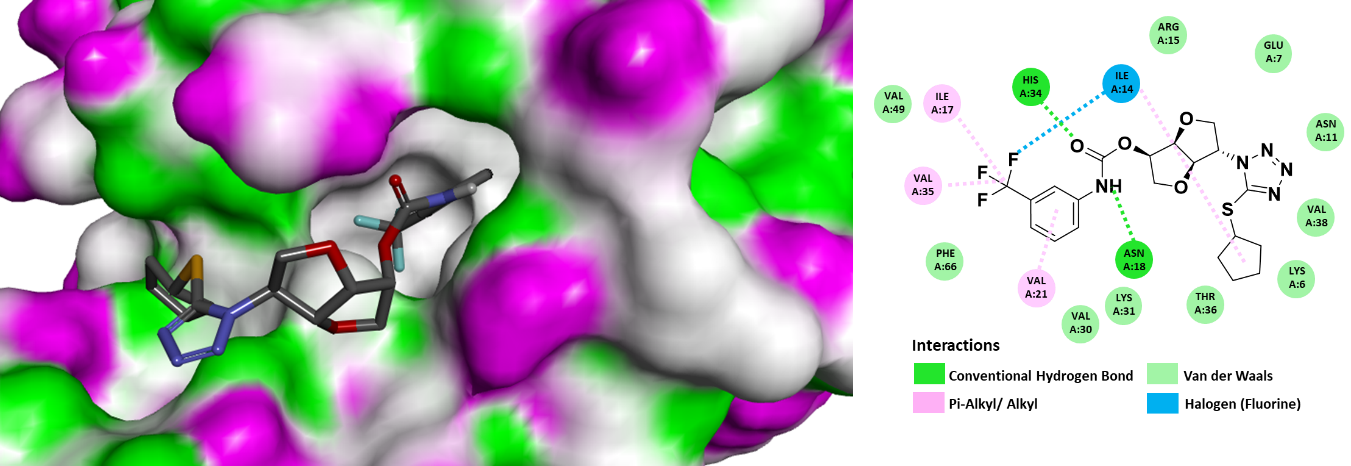


Figure S3: 3D molecular docking binding into sialic acid cell receptor and 2D interaction diagrams of the immunodominant protein P40/P90 complex (PDB ID: 6TLZ) with 3′-sialyllactose.

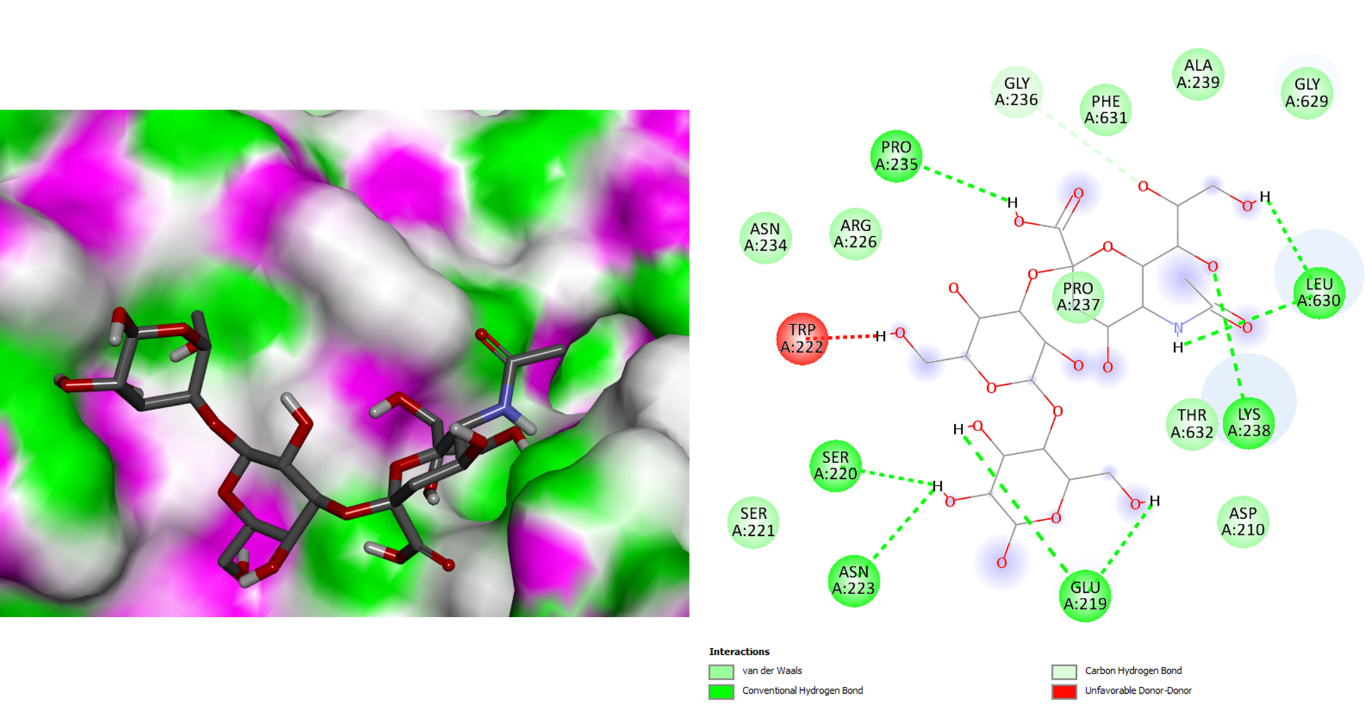


Figure S4: Number of HBs and RMSD between ChEMBL1779463 with PDB ID: 3CL0 (A, C) and 6TLZ (B, D) during dynamic simulation time 500 ns.