**Table 1**: Ligand structural information and After single point and geometry optimization energy minimization calculations

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Name of the inhibitor | Pubchem CID | Molecular formula ( Molecular weight g/mol) | STRUCTURE (2D) | After Single point Energy | After Geometry Optimization minimizing energy |
| Andrographolide  | 5318517 | C20H30O5(350.4) | Andrographolide.png | 83.60Kcal/mol | 43.22Kcal/mol |
| Arctigenin | 64981 | C21H24O6(372.4) | Arctigenin.png | 81.56Kcal/mol | 49.26Kcal/mol |
| Acanthoic acid | 9817887 | C20H30O2(302.5) | Acanthoic acid.png | 77.38Kcal/mol | 37.14Kcal/mol |
| Alpha pinene | 6654 | C10H16(136.23) | alpha-Pinene.png | 75.72Kcal/mol | 59.29Kcal/mol |
| Astaxanthin | 5281224 | C40H52O4(596.8) | Astaxanthin.png | 174.15Kcal/mol | 40.71Kcal/mol |
| Alpha solanine | 9549171 | C45H73NO15(868.1) | alpha-Solanine.png | 174.75Kcal/mol | 96.90Kcal/mol |
| Baicalin | 64982 | C21H18O11(446.4) | Baicalin.png | 116.23Kcal/mol | 22.71Kcal/mol |
| Baicalein | 5281605 | C15H10O5 (270.24) | Baicalein.png | 84.86Kcal/mol | 30.62Kcal/mol |
| Berberine | 2353 | C20H18NO4+(336.4) | Berberine.png | 77.51Kcal/mol | 28.71Kcal/mol |
| Betanin | 12300103 | C24H26N2O13(550.5) | Betanin, AldrichCPR.png | 143.39Kcal/mol | 31.49Kcal/mol |
| Brusatol | 73432 | C26H32O11(520.5) | Brusatol.png | 156.10Kcal/mol | 55.88Kcal/mol |
| Betulinic acid  | 64971 | C30H48O3(456.7) | Betulinic acid.png | 119.77Kcal/mol | 84.95Kcal/mol |
| Carnosol | 442009 | C20H26O4(330.4) | Carnosol.png | 92.79Kcal/mol | 61.67Kcal/mol |
| Celastrol | 122724 | C29H38O4(450.6) | Celastrol.png | 140.05Kcal/mol | 94.62Kcal/mol |
| Cairicoside I | 122230626 | C65H102O26(1299.5) | Cairicoside I.png | 321.53Kcal/mol | 86.50Kcal/mol |
| Codonolactone | 155948 | C15H20O3(248.32) | Atractylenolide III.png | 65.55Kcal/mol | 30.4Kcal/mol |
| Cordycepin | 6303 | C10H13N5O3(251.24) | Cordycepin.png | 56.38Kcal/mol | 28.73Kcal/mol |
| Costunolide | 5281437 | C15H20O2(232.32) | Costunolide.png | 63.24Kcal/mol | 17.16Kcal/mol |
| Cryptotanshinone | 160254 | C19H20O3(296.4) | Cryptotanshinone.png | 80.35Kcal/mol | 25.30Kcal/mol |
| Curcumin | 969516 | C21H20O6(368.4) | Curcumin.png | 112.18Kcal/mol | 10.98Kcal/mol |
| Eupatolide | 5281460 | C15H20O3(248.32) | Eupatolide.png | 64.93Kcal/mol | 18.60Kcal/mol |
| Gallic acid | 370 | C7H6O5(170.12) | Gallic acid.png | 46.89Kcal/mol | 5.58Kcal/mol |
| Gambogic acid | 9852185 | C38H44O8(628.7) | Gambogic acid.png | 170.80Kcal/mol | 44.92Kcal/mol |
| Gedunin | 12004512 | C28H34O7(482.6) | Gedunin.png | 309.07Kcal/mol | 225.87Kcal/mol |
| Genistein | 5280961 | C15H10O5(270.24) | Genistein.png | 85.22Kcal/mol | 37.07Kcal/mol |
| Gentiopicroside | 88708 | C16H20O9(356.32) | Gentiopicroside.png | 66.62Kcal/mol | 18.62Kcal/mol |
| Gigantol | 3085362 | C16H18O4(274.31) | Gigantol.png | 55.08Kcal/mol | 7.44Kcal/mol |
| Ginsenoside rb1 | 9898279 | C54H92O23(1109.3) | Ginsenoside rb1.png | 202.49Kcal/mol | 95.76Kcal/mol |
| Honokiol | 72303 | C18H18O2(266.3) | Honokiol.png | 63.78Kcal/mol | 28.46Kcal/mol |
| Helenalin | 23205 | C15H18O4(262.30) | Helenalin.png | 96.23Kcal/mol | 46.14Kcal/mol |
| Jatrophone | 5281373 | C20H24O3(312.4) | Jatrophone.png | 107.12Kcal/mol | 33.06Kcal/mol |
| Ligustrazine | 14296 | C8H12N2(136.19) | 2,3,5,6-Tetramethylpyrazine.png | 20.66Kcal/mol | 1.87Kcal/mol |
| Luteolin | 5280445 | C15H10O6(286.24) | Luteolin.png | 86.31Kcal/mol | 13.75Kcal/mol |
| Limonene | 22311 | C10H16(136.23) | Limonene.png | 25.5Kcal/mol | 12.84Kcal/mol |
| Lycopene | 446925 | C40H56(36.9) | Lycopene.png | 175.8Kcal/mol | 38.98Kcal/mol |
| Naringin | 442428 | [C](https://pubchem.ncbi.nlm.nih.gov/#query=C27H32O14)27H32O14(580.5) |  | 99.91Kcal/mol | 33.08Kcal/mol |
| Nimbolide | 12313376 | C27H30O7(466.5) | Nimbolide.png | 171.95Kcal/mol | 96.88Kcal/mol |
| Nitidine chloride | 25659 | C21H18ClNO4(383.8) | Nitidine chloride.png | 106.24Kcal/mol | 31.38Kcal/mol |
| Osthole | 10228 | C15H16O3(244.28) | Osthole.png | 61.29Kcal/mol | 8.65Kcal/mol |
| Oxymatrine | 114850 | C15H24N2O2(264.36) | Oxymatrine.png | 48.43Kcal/mol | 28.91Kcal/mol |
| Paeoniflorin | 442534 | C23H28O11(480.5) | Paeoniflorin.png | 150.59Kcal/mol | 87.94Kcal/mol |
| Paeonol | 11092 | C9H10O3(166.17) | Paeonol.png | 46.43Kcal/mol | 8.50Kcal/mol |
| Parthenolide | 7251185 | C15H20O3(248.32) | (-)-Parthenolide.png | 225.52Kcal/mol | 177.95Kcal/mol |
| Plectranthioc acid | 154731119 | C30H48O3(456.7) | Plectranthoic Acid.png | 125.92Kcal/mol | 95.95Kcal/mol |
| Phoyunnanin E | 101380569 | C30H26O5(466.5) | Phoyunnanin E.png | 102.00Kcal/mol | 26.41Kcal/mol |
| Piperlogumine | 101380569 | C30H26O5(466.5) | Piperlongumine.png | 92.93Kcal/mol | 18.36Kcal/mol |
| Plumbagin | 10205 | C11H8O3(188.18) | Plumbagin.png | 68.49Kcal/mol | 8.15Kcal/mol |
| Polyphyllin I | 11018329 | C44H70O16(855.0) | Polyphyllin I.png | 177.11Kcal/mol | 97.87Kcal/mol |
| Perillyl alcohol | 10819 | C10H16O(152.23) | Perillyl alcohol.png | 25.96Kcal/mol | 13.50Kcal/mol |
| Resveratrol | 445154 | C14H12O3(228.24) | Resveratrol.png | 60.41Kcal/mol | 10.75Kcal/mol |
| Salvianolic acid A | 5281793 | C26H22O10 (494.4) | Salvianolic acid A.png | 141.70Kcal/mol | 13.73Kcal/mol |
| Sulforaphane | 5350 | C6H11NOS2(177.3) | Sulforaphane.png | 270.60Kcal/mol | 3.35Kcal/mol |
| Tanshinone IIA | 164676 | C19H18O3(294.3) | Tanshinone IIA.png | 86.22Kcal/mol | 31.05Kcal/mol |
| Triptolide | 107985 | C20H24O6(360.4) | Triptolide.png | 559.67Kcal/mol | 497.19Kcal/mol |
| Ursolic acid | 64945 | C30H48O3(456.7) | Ursolic acid.png | 113.94Kcal/mol | 82.21Kcal/mol |
| Withaferin A | 265237 | C28H38O6(470.6) | Withaferin A.png | 273.16Kcal/mol | 210.199Kcal/mol |

**Table 2**: MolDock score, rerank score, interaction, torsions and hbond energy of the docked compounds with N protein.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Name of the inhibitor** | **MolDock Score,****kcal/mol** | **Rerank Score,****kcal/mol** | **Interaction energy,****kcal/mol** | **Torsion angle,****kcal/mol** | **H-Bond,****kcal/mol** |
| Andrographolide  | -107.944 | -82.44 | -122.4 | 3 | -10.89 |
| Arctigenin | -110.939 | -80.25 | -113.42 | 7 | -9.58 |
| Acanthoic acid | -80.68 | -51.46 | -90.72 | 2 | -4.05 |
| Alpha pinene | -49.54 | -15.53 | -62.36 | 0 | 0 |
| Astaxanthin | -133.88 | -107.55 | -180.85 | 19 | -10.16 |
| Alpha solanine | -159.99 | -71.77 | -172.51 | 8 | -17.11 |
| Baicalin | -105.37 | -102.20 | -148.59 | 4 | -18.27 |
| Baicalein | -75.30 | -72.39 | -98.96 | 1 | -13.12 |
| Berberine | -117.98 | -57.97 | -123.15 | 2 | -2.6 |
| Betanin | -160.78 | -121.14 | -169.77 | 8 | -19.8 |
| Brusatol | -122.35 | -99.60 | -124.69 | 6 | -13.01 |
| Betulinic acid  | -105.32 | -63.60 | -109.40 | 2 | -5.28 |
| Carnosol | -64.60 | -36.71 | -82.93 | 1 | -10.86 |
| Celastrol | -100.725 | -28.27 | -121.27 | 1 | -9.25 |
| Cairicoside I | -285.68 | -36.03 | -245.10 | 24 | -16.8 |
| Codonolactone | -77.74 | -63.24 | -79.63 | 0 | -8.29 |
| Cordycepin | -90.37 | -76.89 | -97.15 | 2 | -10.49 |
| Costunolide | -92.71 | -57.96 | -76.99 | 0 | -2.4 |
| Cryptotanshinone | -102.47 | -47.45 | -108.00 | 0 | -4.66 |
| Curcumin | -133.59 | -96.70 | -122.56 | 10 | -11.79 |
| Eupatolide | -92.12 | -56.51 | -79.39 | 0 | -9.15 |
| Gallic acid | -79.03 | -69.79 | -86.67 | 1 | -13.41 |
| Gambogic acid | -164.94 | -102.58 | -147.09 | 11 | -8.5 |
| Gedunin | -119.97 | -94.78 | -121.98 | 3 | -5.06 |
| Genistein | -68.14 | -55.04 | -93.55 | 1 | -11.26 |
| Gentiopicroside | -109.99 | -94.47 | -129.60 | 4 | -11.85 |
| Gigantol | -112.45 | -87.08 | -111.03 | 5 | -6.4 |
| Ginsenoside rb1 | -172.65 | -114.14 | -183.54 | 11 | -18.50 |
| Honokiol | -82.89 | -50.03 | -88.17 | 5 | -7.4 |
| Helenalin | -101.44 | -44.15 | -94.11 | 0 | -6.9 |
| Jatrophone | -107.70 | -64.89 | -85.10 | 0 | -3.46 |
| Ligustrazine | -45.03 | -43.16 | -54.79 | 0 | -3.39 |
| Luteolin | -100.55 | -81.30 | -108.48 | 1 | -12.02 |
| Limonene | -54.03 | -47.23 | -59.15 | 1 | 0 |
| Lycopene | -150.00 | -98.54 | -149.19 | 29 | 0 |
| Naringin | -145.45 | -122.25 | -171.67 | 6 | -23.82 |
| Nimbolide | -127.16 | -90.66 | -116.72 | 4 | -12.05 |
| Nitidine chloride | -122.18 | -99.14 | -124.62 | 2 | -3.86 |
| Osthole | -91.72 | -70.25 | -95.01 | 4 | -3.9 |
| Oxymatrine | -67.72 | -64.05 | -86.77 | 0 | -3.48 |
| Paeoniflorin | -114.76 | -90.24 | -132.29 | 3 | -19.32 |
| Paeonol | -71.70 | -51.20 | -72.66 | 2 | -7.3 |
| Parthenolide | -101.17 | -70.32 | -85.69 | 0 | -5.0 |
| Plectranthioc acid | -78.65 | -7.22 | -95.51 | 1 | -6.36 |
| Phoyunnanin E | -130.07 | -66.91 | -144.87 | 3 | -10.75 |
| Piperlogumine | -105.33 | -81.94 | -11.20 | 6 | -6.46 |
| Plumbagin | -67.63 | -59.66 | -78.48 | 0 | -5.9 |
| Polyphyllin I | -166.78 | -53.30 | -202.25 | 8 | -18.28 |
| Perillyl alcohol | -57.33 | -49.25 | -64.05 | 2 | -5.0 |
| Resveratrol | -102.06 | -85.28 | -105.42 | 2 | -7.9 |
| Salvianolic acid A | -143.71 | -102.69 | -120.18 | 9 | -23.26 |
| Sulforaphane | -69.60 | -56.81 | -69.23 | 6 | -7.6 |
| Tanshinone IIA | -91.01 | -66.16 | -96.79 | 0 | -3.9 |
| Triptolide | -108.18 | -69.07 | -116.04 | 1 | -6.75 |
| Ursolic acid | -111.21 | -63.80 | -115.39 | 1 | -6.12 |
| Withaferin A | -108.41 | -84.51 | -125.63 | 3 | -10.33 |

**Table 3**: MolDock score, rerank score, interaction, torsions and hbond energy of the docked compounds with RdRp protein.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Name of the inhibitor** | **MolDock Score,****kcal/mol** | **Rerank Score,****kcal/mol** | **Interaction energy,****kcal/mol** | **Torsion angle,****kcal/mol** | **H-Bond,****kcal/mol** |
| Andrographolide  | -78.57 | -41.04 | -96.44 | 1 | -9.08 |
| Arctigenin | -103.39 | -58.12 | -108.45 | 7 | -6.7 |
| Acanthoic acid | -82.50 | -71.41 | -94.94 | 2 | -4.8 |
| Alpha pinene | -52.19 | -45.34 | -65.00 | 0 | 0 |
| Astaxanthin | -141.71 | -89.26 | -154.64 | 19 | -8.09 |
| Alpha solanine | -151.07 | -54.29 | -192.94 | 8 | -16.47 |
| Baicalin | -83.51 | -88.97 | -124.67 | 4 | -11.9 |
| Baicalein | -69.25 | -64.81 | -93.50 | 1 | -10.31 |
| Berberine | -92.68 | -63.35 | -97.33 | 2 | -4.5 |
| Betanin | -156.39 | -124.42 | -161.15 | 8 | -17.11 |
| Brusatol | -123.40 | -20.73 | -116.28 | 6 | -8.82 |
| Betulinic acid  | -97.43 | -21.71 | -109.25 | 2 | -4.05 |
| Carnosol | -65.30 | -54.71 | -83.73 | 1 | -8.58 |
| Celastrol | -80.87 | -66.33 | -100.83 | 1 | -10.03 |
| CairicosideI | -201.55 | -38.06 | -187.12 | 24 | -7.29 |
| Codonolactone | -74.66 | -60.57 | -76.58 | 0 | -6.24 |
| Cordycepin | -86.39 | -70.50 | -90.72 | 2 | -9.16 |
| Costunolide | -97.27 | -72.13 | -81.55 | 0 | -2.5 |
| Cryptotanshinone | -84.58 | -69.34 | -84.71 | 0 | -2.0 |
| Curcumin | -139.05 | -84.62 | -119.16 | 10 | -1.36 |
| Eupatolide | -87.92 | -64.60 | -75.19 | 0 | -4.9 |
| Gallic acid | -57.60 | -32.54 | -64.72 | 1 | -13.04 |
| Gambogic acid | -164.15 | -96.60 | -141.70 | 11 | -10.46 |
| Gedunin | -112.33 | -83.70 | -113.51 | 3 | -3.6 |
| Genistein | -70.18 | -70.39 | -98.21 | 1 | -9.02 |
| Gentiopicroside | -89.50 | -56.30 | -106.50 | 4 | -20.08 |
| Gigantol | -94.75 | -72.94 | -104.39 | 5 | -7.08 |
| Ginsenoside rb1 | -147.04 | -112.25 | -175.82 | 11 | -19.13 |
| Honokiol | -82.84 | -72.23 | -90.51 | 5 | -7.00 |
| Helenalin | -98.80 | -76.76 | -91.48 | 0 | -8.0 |
| Jatrophone | -104.69 | -72.77 | -82.09 | 0 | -4.74 |
| Ligustrazine | -49.03 | -44.10 | -58.79 | 0 | -2.5 |
| Luteolin | -99.88 | -72.35 | -96.76 | 1 | -10.15 |
| Limonene | -53.51 | -45.84 | -58.64 | 1 | 0 |
| Lycopene | -159.57 | -77.27 | -131.20 | 29 | 0 |
| Naringin | -134.00 | -94.96 | -152.97 | 6 | -18.25 |
| Nimbolide | -138.56 | -102.70 | -136.41 | 4 | -15.61 |
| Nitidine chloride | -106.14 | -76.65 | -101.11 | 2 | -5.19 |
| Osthole | -80.39 | -55.40 | -84.35 | 4 | -5.30 |
| Oxymatrine | -66.42 | -62.34 | -85.47 | 0 | -2.0 |
| Paeoniflorin | -104.34 | -79.60 | -120.53 | 3 | -13.28 |
| Paeonol | -61.62 | -52.00 | -62.32 | 2 | -8.1 |
| Parthenolide | -93.43 | -67.25 | -77.96 | 0 | -5.0 |
| Plectranthioc acid | -95.26 | -77.56 | -108.66 | 1 | -4.7 |
| Phoyunnanin E | -125.92 | -56.65 | -134.39 | 3 | -11.57 |
| Piperlogumine | -107.52 | -82.01 | -109.57 | 6 | -9.30 |
| Plumbagin | -55.15 | -51.81 | -65.99 | 0 | -5.5 |
| Polyphyllin I | -140.21 | -103.76 | -161.01 | 8 | -18.45 |
| Perillyl alcohol | -53.41 | -43.87 | -64.93 | 2 | -3.0 |
| Resveratrol | -93.44 | -64.43 | -96.54 | 2 | -6.3 |
| Salvianolic acid A | -150.83 | -100.05 | -126.55 | 9 | -11.02 |
| Sulforaphane | -65.40 | -49.94 | -65.87 | 6 | -8.17 |
| Tanshinone IIA | -85.99 | -54.53 | -91.76 | 0 | -3.5 |
| Triptolide | -97.82 | -76.40 | -105.53 | 1 | -5.27 |
| Ursolic acid | -110.67 | -60.04 | -116.76 | 1 | -6.0 |
| Withaferin A | -105.21 | -83.42 | -118.83 | 3 | -7.40 |

**Table 4**: Amino acid residues around active site and docked against N protein

|  |  |  |
| --- | --- | --- |
| **Name of the Inhibitor** | **Amino acid residues around active site**  | **Ligand binding amino acids** |
| Alpha solanine | Asp129A, Lys62B, Glu68B, Lys128A, Asp64B, Arg89A, Glu119A, Pro118A, Asn154D, Ile131B, Ile132B, Trp132B, Trp133B, Ala126B, Gly125B, Asn127B, His146D, Ile147D, Trp53D, Asn78D, Asn151A, Asn49A, Asn155D, Thr50A | Arg89A, Asn127B, Asn155D, Gly125B, Asn78D, Asn49A, Ile131B  |
| Baicalin | Trp109B, Lys66B, Lue65B, Asp64B, Ile132B, Arg90B, Gly130B, Ile131B, Trp133B, Asn49A, Asp129B,Lys128B, Asn154B, Asn151D, Asn127B, Asn155B, Arg150D, Trp53B, Thr149D | Asn151D, Thr149D, Asn127B, Asn155D, Asn154D, Gly130B, Asp129B, Asp64B |
| Betanin | Trp133B, Lys128B, Asn127B, Trp53D, Asn78D, Asn49A, Thr50A, Ala51A, Arg89A, Ala91A, Arg90A, Thr92A, Lys66B, Glu63B, Pro169B, Lys170B | Asn127B, Arg89A, Arg90A, Thr92A, Glu63B, Lys66B |
| Cairicoside I | Trp53D, Ile147D, Ile158D, Asn78D, Asn155D, Asn154D, Asn127B, Asn151A, Thr50A, Pro118A, Tyr112A, Ser52A, Ala51A, Gly125B, Ile131B, Trp133B, Ile132B, Arp69B, The67B, Pro68B, Val159C, Tyr110A, Asp64B, Trp109B, Lue65B, The67B | Asn49A, Asn127B, Asn154D, Asn78D, Thr50A, Pro68B, Lys66B |
| Ginsenoside rb1 | Arg108A, Arg93A, Thr92A, Ana91A, Tyr110A, Ser52A, Tyr112A, Ala51A, Arg89A, Thr50A, Tro118A, Asn49A, Lys66B, Asn155D, Asn154D, Asn151D, Asn127B, Gly125B, Trp133B, Ile132B, Ile131B, Lys128B, Ala126B, Thr149D, Asn151D, Arg150D, Trp53D | Asn155D, Asn151D, Thr149D, Asn127B, Asn49A, Lys128B, Ile131B, Thr50A, Tyr112A |
| Naringin | Arg90A, Arg89A, Thr92A, Tyr110A, Tyr112A, Ser52A, Pro118A, Glu63B, Ala51A, Thr50A, Asn49A, Lys66B, Trp153B, Ile132B, Phe67B | Trp133B, Thr50A, Thr92A, Glu63B, Lys66B, Arg89A, Ser52A, Tyr122A |
| Paeoniflorin | Trp53D, Asn155D, Thr50A, Asn49A, Asn127B, Asp129B, Lys128B, Ala126B, Gly125B, Gly130B, Tle131B, Trp133B, Lys66B | Asn127B,Thr50A, Ile131B, Ala126B, Lys128B, ASN 49A |
| Polyphyllin I | Thr50D, Thr149D, Gly148D, Tle147D, Trp53D, Asn51D, Asn155D, Asn154D, Asp129D, lys128D, Asn127B, gly130B, Thr50A, Ala51A, Lys66B, Pro152A, Asn49A, Ile132B, Trp133B, Phe67B, Pro68B, Arg69B, Gln161C | Arg69B, Trp133B, Phe67B |
| Salvianolic acid A | Tyr112A, Arg89A, Pro118A, Thr50A, Asn154D, Asn155D, Trp53D, Asn127B, Asn49A, Lys66B, Asp64B, Lys128B, Asp129B, Ile131B, Gly130B, Arg90B | Asn49A, Thr50A, Arg89A, Gly130B, Asp129B, Ile131B, Lys128B, Asn127B, Tyr112A  |

**Table 5**: Amino acid residues around active site and docked against RdRp protein

|  |  |  |
| --- | --- | --- |
| **Name of the Inhibitor** | **Amino acid residues around active site**  | **Ligand binding amino acids** |
| Alpha solanine | Val557A, Ser682A, Lys545A, Thr556A, Arg555A, Asp62A, Asp760A, Asp452A, Arg624A, Cys622A, Arg553A, Tyr455A, Lys551A, Lys621A, Pro620A, Lys798A, Tyr619A, Ala554A | Lys621A, Cys622A, Tyr619A, Asp760A, Asp623A |
| Betanin | Lys545A, Lys500A, Val557A, Gly683A, Thr556A, Ser685A, Ala554A, Asp452A, Arg553A, Tyr455A, Lys621A, Arg624A, Asp623A, Asn691A, Ser759A, Thr687A, Ala688A, Ser759A, Lys545A  | Ala688A, Thr556A, Arg624A, Arg555A, Asp452A, Lys621A, Asp623A, Lys545A |
| Gentiopicroside | Tyr619A, Cys622A, Pro620A, Lys621A, Tyr458A, Asp623A, Arg624A, Tyr455A, Tyr458A, Arg553A, Asp452A, Ala554A, Arg555A, Tyr556A | Tyr619A, Cys622A, Asp623A, Lys621A, Arg555A, Ala554A |
| Ginsenoside rb1 | Ala688A, Thr687A, Ser759A, Asn691A, Asp760A, Ser682A, Asp623A, Tyr619A, Cys622A, Arg555A, Thr556A, Asp618A, Pro620A, Lys621A, Asp452A, Ala554A, Tyr455A, Lys798A, Arg553A | Lys798A, Asp618A, Arg555A, Asp452A, Ala554A, Lys621A, Arg553A, Asp760A, Ser759A |
| Naringin | Ala550A, Ser549A, Lys551A, Ala554A, Arg555A, Arg553A, Asp452A, Thr556A, Tyr455A, Arg624A, Lys621A, Ser682A, Asp623A, Cys622A, Thr687A, Asn691A | ASN 691A, Arg624 A, Thr556A, Lys621A, Cys622A, Asp623A |
| Polyphyllin I | Thr556A, Ala554A, Asp452A, Ser682A, Thr687A, Arg553A, Tyr455A, Arg624A, Asp623A, Ser759A, Leu758A, Asp760A, Cys622A, Lys798A, Pro620A, Asp648A, Tyr619A, Lys798A, Lys551A | Asp623A, Thr556A, Arg555A, Ala554A, Asp452A, Ser759A, Lys798A  |
| Cairicoside I | Lys500A, Ala685A, Asp684A, Gly683A, Ala558A, Val557A, Ser682A, Thr687A, Ala688A, Ser759A, Leu758A, Asp761A, Cys813A, Ser814A, Asp760A, Tyr619A, Lys545A, Asp623A, Cys622A, Thr556A, Arg624A, Asp452A, Tyr455A, Arg553A, Lys621A, Pro620A,  | Asp684A, Asp761A, Asp760A, Lys545A, Lys621A, Arg624A, Ser628A |

**Table 6**. Pharmacokinetic properties of top-scoring ligands.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Property | Model Name | Alpha solanine | Betanin | Cairicoside I | Ginsenoside rb1 | Naringin | Polyphyllin I | Unit |
| Absorption | Water solubility | -3.021 | -2.86 | -2.89 | -2.834 | -2.91 | -3.34 | log mol/L |
| Caco2 permeability | -0.623 | -0.95 | 0.114 | -1.385 | -0.65 | -0.779 | log Papp in 10–6 cm/s |
| Intestinal absorption(Human) | 16.89 | 0 | 37.32 | 0 | 25.79 | 51.19 | %Absorbed |
| Skin Permeability | -2.73 | -2.73 | -2.73 | -2.735 | -2.73 | -2.73 | log Kp |
| Distribution | VDss(Human) | -0.279 | -1.70 | 0.541 | -0.62 | 0.61 | -0.304 | log l/kg |
| Fraction unbound(Human) | 0.537 | 0.60 | 0.306 | 0.4 | 0.15 | 0.417 | Fu |
| BBB permeability | -1.719 | -1.63 | -3.89 | -2.65 | -1.6 | -1.85 | log BB |
| CNS permeability | -4.74 | -4.93 | -4.92 | -6.25 | -4.77 | -4.51 | logPS |
| Metabolism | CYP2D6 substrate | No | No | No  | No | No | No | Yes/No |
| CYP3A4 substrate | Yes | No | Yes  | No | No | Yes |
| CYP1A2 inhibitor | No | No | No  | No | No | No |
| CYP2C19 inhibitor | No | No | No | No | No | No |
| CYP2C9 inhibitor | No | No |  No  | No | No | No |
| CYP2D6 inhibitor | No | No | No | No | No | No  |
| CYP3A4 inhibitor | No | No | No  | No | No | No  |
| Excretion | Total clearance  | -0.373 | 0.216 | 0.701 | 0.539 | 0.318 | 0.365 | log ml/min/kg |
| Renal OCT2 substrate  | No | No | No  | No  | No | No | Yes/No |
| Toxicity  | AMES toxicity  | No | No | No  | No  | No | No |
| Max. tolerated dose(Human) | -2.677 | 0.678 | -0.267 | -0.62 | 0.43 | -3.05 | log mg/kg/day |
| hERG I inhibitor | No | No  | No | No | No | No  | Yes/No |
| Oral rat acute toxicity(LD50) | 3.08 | 2.471 | 2.545 | 2.659 | 2.49 | 3.10 | Mol/kg |
| Oral rat chronic toxicity(LOAEL) | 2.81 | 3.652 | 2.124 | 4.00 | 4.20 | 2.91 | log mg/kg\_bw/day |
| Hepatotoxicity | Yes | Yes  | Yes  | No | No | No | Yes/No |
| Skin sensitization | No | No  | No  | No | No | No |
| T.pyriformis toxicity | 0.285 | 0.285 | 0.285 | 0.285 | 0.285 | 0.285 | log µg/L |
| Minnow toxicity | 9.83 | 8.49 | 10.56 | 11.70 | 6.04 | 8.87 | log µg/L |
| Drug likeness | Lipinski | No | No | No | No | No | No | Yes/No |
| Bioactivity Score  | GPCR ligand | -2.38 | 0.25 | -3.90 | -3.73 | 0.11 | -2.22 |  |
| Ion channel modulator | -3.42 | -0.21 | -3.95 | -3.82 | -0.40 | -3.32 |
| Kinase inhibitor  | -3.44 | -0.48 | -3.96 | -3.85 | -0.24 | -3.33 |
| Nuclear receptor ligand | -3.13 | -0.20 | -3.95 | -3.79 | -0.04 | -3.06 |
| Protease inhibitor | -1.82 | 0.11 | -3.86 | -3.67 | -0.09 | -1.17 |
| Enzyme inhibitor  | -2.61 | 0.36 | -3.89 | -3.68 | 0.24 | -2.25 |