**Supplementary Information**

**ABBV-744 and Onalespid as Potential Inhibitors of SARS-CoV-2 main Protease Enzyme: A Promising Therapeutics in COVID-19?**

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**Table S1**. The considered compounds for the input library.

|  |  |  |
| --- | --- | --- |
| **Entry**  | **Compounds Name** | **SMILES TEXT** |
| 1 | AC-55541 | c1(c2c(c(=O)[nH]n1)cccc2)[C@H](NC(=O)c1ccccc1)C(=O)N/N=C(/c1cccc(c1)Br)\C |
| 2 | ABBV-744 | c1(c2c(c(=O)n(c1)C)[nH]c(c2)C(=O)NCC)c1cc(ccc1Oc1c(cc(cc1C)F)C)C(C)(C)O |
| 3 | 4EGI-1 | C1=CC=C(C(=C1)CC(=NNC2=NC(=CS2)C3=CC(=C(C=C3)Cl)Cl)C(=O)O)[N](=O)[O-] |
| 4 | 4E2RCat | O=C(O)c1cc(c2ccc(/C=C\3/SC(=S)N(Cc4ccccc4)C3=O)o2)ccc1Cl |
| 5 | 4E1RCat | O=C1/C(=C\c2ccc(c3ccc([N](=O)[O])cc3)o2)/C=C(c2ccccc2)N1c1ccc(C(=O)O)cc1 |
| 6 | 1-Deoxynojirimycin | C1C(C(C(C(N1)CO)O)O)O |
| 7 | Zotatifin | c1(c2c(cc(n1)OC)O[C@@]1([C@]2([C@@H]([C@@H]([C@H]1c1ccccc1)CN(C)C)O)O)c1ccc(cc1)C#N)OC |
| 8 | XL413 | C1CC(NC1)C2=NC3=C(C(=O)N2)OC4=C3C=C(C=C4)Cl |
| 9 | Verapamil | CC(C)C(CCCN(C)CCC1=CC(=C(C=C1)OC)OC)(C#N)C2=CC(=C(C=C2)OC)OC |
| 10 | Valproic acid | CCCC(CCC)C(=O)O |
| 11 | Tomivosertib | c1(=O)n2c(c(cc1Nc1ncnc(c1)N)C)C(=O)NC12CCCCC1 |
| 12 | Ternatin\_4 | [C@@H]1(C(=O)N[C@H]([C@H](CC)C)C(=C)N([C@@H](C)C(=O)N([C@@H](CC(C)C)C(=O)N[C@H](C(=O)N([C@H](C(=O)N2CCCC[C@@H]2C(=O)N1)C)C)C[C@@H](C)C=C)C)C)[C@@H](C(C)C)O |
| 13 | Siramesine | C1CN(CCC12C3=CC=CC=C3CO2)CCCCC4=CN(C5=CC=CC=C54)C6=CC=C(C=C6)F |
| 14 | silmitasertib | C1=CC(=CC(=C1)Cl)NC2=NC3=C(C=CC(=C3)C(=O)O)C4=C2C=CN=C4 |
| 15 | Sapanisertib | CC(C)N1C2=NC=NC(=C2C(=N1)C3=CC4=C(C=C3)OC(=N4)N)N |
| 16 | RVX-208 | c1c(cc(c2c1nc([nH]c2=O)c1cc(c(c(c1)C)OCCO)C)O)OC |
| 17 | Ruxolitinib | C1CCC(C1)C(CC#N)N2C=C(C=N2)C3=C4C=CNC4=NC=N3 |
| 18 | RS-PPCC | c1ccccc1[C@@]1(CCN(CC1)C[C@H]1C[C@]1(C(=O)OC)c1ccc(cc1)C)O |
| 19 | Rimcazole | CC1CN(CC(N1)C)CCCN2C3=CC=CC=C3C4=CC=CC=C42 |
| 20 | Ribavirin | C1=NC(=NN1C2C(C(C(O2)CO)O)O)C(=O)N |
| 21 | Rapamycin | CC1CCC2CC(C(=CC=CC=CC(CC(C(=O)C(C(C(=CC(C(=O)CC(OC(=O)C3CCCCN3C(=O)C(=O)C1(O2)O)C(C)CC4CCC(C(C4)OC)O)C)C)O)OC)C)C)C)OC |
| 22 | Quercetin | C1=CC(=C(C=C1C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O)O |
| 23 | PS3061 | [C@@H]1(C(=O)N[C@@H](CC(C)C)C(=O)N([C@H](C(=O)N[C@H](C(=O)N([C@H](C(=O)O[C@@H](C(=O)N[C@H](C(=O)N1C)CC(C)C)CCC#N)C)C)CC(C)C)Cc1cn(c2c1cccc2)Cc1ccc(cc1)Br)C)CC(C)C |
| 24 | Progestrone | CC(=O)C1CCC2C1(CCC3C2CCC4=CC(=O)CCC34C)C |
| 25 | Ponatinib | CC1=C(C=C(C=C1)C(=O)NC2=CC(=C(C=C2)CN3CCN(CC3)C)C(F)(F)F)C#CC4=CN=C5N4N=CC=C5 |
| 26 | Pioglitazone | CCC1=CN=C(C=C1)CCOC2=CC=C(C=C2)CC3C(=O)NC(=O)S3 |
| 27 | Pimozide | C1CN(CCC1N2C3=CC=CC=C3NC2=O)CCCC(C4=CC=C(C=C4)F)C5=CC=C(C=C5)F |
| 28 | PF-846 | c1c2c(ncc1)n(nn2)c1ccc(cc1)C(=O)N([C@H]1CNCCC1)c1c(cccn1)Cl |
| 29 | Pepstatin | CC(C)CC(C(CC(=O)O)O)NC(=O)C(C)NC(=O)CC(C(CC(C)C)NC(=O)C(C(C)C)NC(=O)C(C(C)C)NC(=O)CC(C)C)O |
| 30 | PD-144418 | CCCN1CCC=C(C1)C2=CC(=NO2)C3=CC=C(C=C3)C.C(=O)(C(=O)O)O |
| 31 | PB28 | c12c(cccc1OC)[C@@H](CCC2)CCCN1CCN(CC1)C1CCCCC1 |
| 32 | Pazopanib | CC1=C(C=C(C=C1)NC2=NC=CC(=N2)N(C)C3=CC4=NN(C(=C4C=C3)C)C)S(=O)(=O)N.Cl |
| 33 | onalespib | CC(C)C1=CC(=C(C=C1O)O)C(=O)N2CC3=C(C2)C=C(C=C3)CN4CCN(CC4)C |
| 34 | Olanzapine | CC1=CC2=C(NC3=CC=CC=C3N=C2S1)N4CCN(CC4)C |
| 35 | Nitazoxanide | CC(=O)OC1=CC=CC=C1C(=O)NC2=NC=C(S2)[N+](=O)[O-] |
| 36 | Nafamostat | C1=CC(=CC=C1C(=O)OC2=CC3=C(C=C2)C=C(C=C3)C(=N)N)N=C(N)N |
| 37 | MZ1 | N1=C(c2c(n3c([C@@H]1CC(=O)NCCOCCOCCOCC(=O)N[C@H](C(C)(C)C)C(=O)N1C[C@H](C[C@H]1C(=O)NCc1ccc(cc1)c1scnc1C)O)nnc3C)sc(c2C)C)c1ccc(cc1)Cl |
| 38 | Mycophenolic acid | CC1=C2COC(=O)C2=C(C(=C1OC)CC=C(C)CCC(=O)O)O |
| 39 | ML240 | c1c2c(ccc1)nc(n2c1nc(c2c(n1)c(ccc2)OC)NCc1ccccc1)N |
| 40 | Minoxidil | C1CCN(CC1)C2=NC(=N)N(C(=C2)N)O |
| 41 | Midostaurin | c12c3c(c4c5c1n(c1c2cccc1)[C@@]1([C@@H]([C@@H](C[C@H](n5c2c4cccc2)O1)N(C(=O)c1ccccc1)C)OC)C)C(=O)NC3 |
| 42 | Metformin | CN(C)C(=N)N=C(N)N |
| 43 | merimepodib | COC1=C(C=CC(=C1)NC(=O)NC2=CC=CC(=C2)CNC(=O)OC3CCOC3)C4=CN=CO4 |
| 44 | Luminespib | CCNC(=O)C1=NOC(=C1C2=CC=C(C=C2)CN3CCOCC3)C4=CC(=C(C=C4O)O)C(C)C |
| 45 | Lovastatin | CCC(C)C(=O)OC1CC(C=C2C1C(C(C=C2)C)CCC3CC(CC(=O)O3)O)C |
| 46 | Loratadine | CCOC(=O)N1CCC(=C2C3=C(CCC4=C2N=CC=C4)C=C(C=C3)Cl)CC1 |
| 47 | Lisinopril | C1CC(N(C1)C(=O)C(CCCCN)NC(CCC2=CC=CC=C2)C(=O)O)C(=O)O |
| 48 | JQ1 | N1=C(c2c(n3c([C@@H]1CC(=O)OC(C)(C)C)nnc3C)sc(c2C)C)c1ccc(cc1)Cl |
| 49 | INK-128 | c1(c2c(ncn1)n(nc2c1ccc2c(c1)nc(o2)N)C(C)C)N |
| 50 | Indomethacin | CC1=C(C2=C(N1C(=O)C3=CC=C(C=C3)Cl)C=CC(=C2)OC)CC(=O)O |
| 51 | Ifenprodil | CC(C(C1=CC=C(C=C1)O)O)N2CCC(CC2)CC3=CC=CC=C3 |
| 52 | Hydroxychloroquine | CCN(CCCC(C)NC1=C2C=CC(=CC2=NC=C1)Cl)CCO |
| 53 | Haloperidol | C1CN(CCC1(C2=CC=C(C=C2)Cl)O)CCCC(=O)C3=CC=C(C=C3)F |
| 54 | H-89 | c1c(c2c(cc1)cncc2)S(=O)(=O)NCCNC/C=C/c1ccc(cc1)Br |
| 55 | E-52862 | c1ccc2c(c1)cc(cc2)n1nc(cc1C)OCCN1CCOCC1 |
| 56 | dextromethorphan | CN1CCC23CCCCC2C1CC4=C3C=C(C=C4)OC |
| 57 | dBET6 | C1(=N[C@@H](c2n(c3c1c(c(s3)C)C)c(nn2)C)CC(=O)NCCCCNC(=O)COc1c2c(ccc1)C(=O)N(C2=O)[C@H]1C(=O)NC(=O)CC1)c1ccc(cc1)Cl |
| 58 | DBeQ | c1c2c(ccc1)c(nc(n2)NCc1ccccc1)NCc1ccccc1 |
| 59 | Daunorubicin | CC1C(C(CC(O1)OC2CC(CC3=C2C(=C4C(=C3O)C(=O)C5=C(C4=O)C(=CC=C5)OC)O)(C(=O)C)O)N)O |
| 60 | CPI-0610 | c1(ccc(cc1)C1=N[C@H](c2c(c3c1cccc3)c(no2)C)CC(=O)N)Cl |
| 61 | compound\_10 | c1c(cc(c(c1)OC)S(=O)(=O)Nc1ccc(cc1)O)c1sc(nc1C)NC(=O)C(C)(C)C |
| 62 | compound\_2 | c1c2cccc1[C@@H](C)OC(=O)[C@H]1CCCN(N1)C(=O)[C@@H](NC(=O)[C@H](C(C)C)NC(=O)[C@@H]([C@@H](CC/C=C/2)OC)C)C |
| 63 | cloperastine | C1CCN(CC1)CCOC(C2=CC=CC=C2)C3=CC=C(C=C3)Cl |
| 64 | Clemastine | CC(C1=CC=CC=C1)(C2=CC=C(C=C2)Cl)OCCC3CCCN3C |
| 65 | Chloramphenicol | C1=CC(=CC=C1C(C(CO)NC(=O)C(Cl)Cl)O)[N+](=O)[O-] |
| 66 | CB5083 | c1(ccccc1)CNc1c2c(nc(n1)n1c(cc3c1cccc3C(=O)N)C)CCOC2 |
| 67 | carbetapentane | CCN(CC)CCOCCOC(=O)C1(CCCC1)C2=CC=CC=C2 |
| 68 | Captopril | CC(CS)C(=O)N1CCCC1C(=O)O |
| 69 | Camostat | CN(C)C(=O)COC(=O)CC1=CC=C(C=C1)OC(=O)C2=CC=C(C=C2)N=C(N)N |
| 70 | Birvudine | C1C(C(OC1N2C=C(C(=O)NC2=O)C=CBr)CO)O |
| 71 | BD1008 | CN(CCC1=CC(=C(C=C1)Cl)Cl)CCN2CCCC2 |
| 72 | Bafilomycin A1 | CC1CC(=CC=CC(C(OC(=O)C(=CC(=CC(C1O)C)C)OC)C(C)C(C(C)C2(CC(C(C(O2)C(C)C)C)O)O)O)OC)C |
| 73 | Azithromycin | CCC1C(C(C(N(CC(CC(C(C(C(C(C(=O)O1)C)OC2CC(C(C(O2)C)O)(C)OC)C)OC3C(C(CC(O3)C)N(C)C)O)(C)O)C)C)C)O)(C)O |
| 74 | AZ3451 | c1c(ccc(c1)C#N)NC(=O)c1ccc2c(c1)nc(n2[C@H](C)C1CCCCC1)c1cc2c(cc1Br)OCO2 |
| 75 | Apicidin | CCC(C)C1C(=O)N2CCCCC2C(=O)NC(C(=O)NC(C(=O)N1)CC3=CN(C4=CC=CC=C43)OC)CCCCCC(=O)CC |

**Table S2**. The 43 generated compounds using Phase virtual screening.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Entry** | **Compounds Name** | **Num Sites Matched** | **Matched Ligand Sites** | **PhaseScreenScore** |
| 1 | 4E1RCat | 4 | A(-) A(3) D(-) D(-) D(5) R(9) R(10) | 1.462 |
| 2 | 4E2RCat | 4 | A(4) A(2) D(-) D(-) D(6) R(9) R(-) | 1.376 |
| 3 | Pimozide | 4 | A(1) A(-) D(-) D(2) D(-) R(7) R(10) | 1.351 |
| 4 | silmitasertib | 4 | A(1) A(4) D(-) D(-) D(5) R(9) R(-) | 1.321 |
| 5 | H-89 | 4 | A(2) A(1) D(5) D(-) D(-) R(-) R(9) | 1.295 |
| 6 | Tomivosertib | 4 | A(3) A(2) D(-) D(-) D(8) R(11) R(-) | 1.237 |
| 7 | PF-846 | 4 | A(1) A(-) D(6) D(-) D(-) R(10) R(12) | 1.229 |
| 8 | 4EGI-1 | 4 | A(1) A(3) D(-) D(-) D(5) R(9) R(-) | 1.214 |
| 9 | CB5083 | 4 | A(2) A(-) D(-) D(5) D(7) R(11) R(-) | 1.212 |
| 10 | Azithromycin | 4 | A(3) A(7) D(16) D(13) D(-) R(-) R(-) | 1.179 |
| 11 | Lisinopril | 5 | A(3) A(-) D(6) D(8) D(9) R(12) R(-) | 1.161 |
| 12 | Pazopanib | 5 | A(1) A(3) D(-) D(7) D(6) R(13) R(-) | 1.159 |
| 13 | RVX-208 | 4 | A(1) A(4) D(8) D(-) D(-) R(15) R(-) | 1.126 |
| 14 | AC-55541 | 4 | A(3) A(-) D(8) D(-) D(-) R(13) R(14) | 1.092 |
| 15 | compound\_10 | 5 | A(-) A(6) D(9) D(8) D(7) R(12) R(-) | 1.073 |
| 16 | dBET6 | 4 | A(10) A(-) D(13) D(12) D(-) R(22) R(-) | 1.068 |
| 17 | Indomethacin | 4 | A(3) A(1) D(5) D(-) D(-) R(11) R(-) | 1.066 |
| 18 | Ribavirin | 5 | A(1) A(6) D(9) D(12) D(10) R(-) R(-) | 1.017 |
| 19 | Zotatifin | 4 | A(6) A(1) D(-) D(8) D(-) R(15) R(-) | 1.014 |
| 20 | Pioglitazone | 4 | A(2) A(4) D(-) D(-) D(6) R(10) R(-) | 0.999 |
| 21 | Hydroxychloroquine | 4 | A(-) A(2) D(-) D(4) D(3) R(10) R(-) | 0.998 |
| 22 | CPI-0610 | 4 | A(1) A(2) D(6) D(-) D(-) R(11) R(-) | 0.988 |
| 23 | merimepodib | 4 | A(5) A(2) D(-) D(8) D(-) R(-) R(13) | 0.934 |
| 24 | Daunorubicin | 5 | A(6) A(4) D(13) D(-) D(12) R(-) R(20) | 0.911 |
| 25 | Birvudine | 5 | A(4) A(3) D(-) D(8) D(7) R(11) R(-) | 0.822 |
| 26 | RS-PPCC | 4 | A(1) A(2) D(-) D(-) D(4) R(8) R(-) | 0.816 |
| 27 | Chloramphenicol | 4 | A(1) A(3) D(5) D(-) D(-) R(9) R(-) | 0.74 |
| 28 | Sapanisertib | 5 | A(1) A(4) D(-) D(6) D(8) R(12) R(-) | 0.737 |
| 29 | INK-128 | 5 | A(3) A(4) D(-) D(8) D(6) R(11) R(-) | 0.737 |
| 30 | Mycophenolic acid | 5 | A(6) A(3) D(-) D(7) D(8) R(13) R(-) | 0.722 |
| 31 | ML240 | 5 | A(1) A(4) D(5) D(6) D(-) R(10) R(-) | 0.692 |
| 32 | onalespib | 4 | A(-) A(3) D(4) D(-) D(5) R(10) R(-) | 0.687 |
| 33 | Ifenprodil | 5 | A(2) A(1) D(-) D(4) D(3) R(-) R(7) | 0.674 |
| 34 | Bafilomycin A1 | 4 | A(1) A(4) D(11) D(-) D(12) R(-) R(-) | 0.658 |
| 35 | Quercetin | 6 | A(2) A(4) D(10) D(8) D(9) R(15) R(-) | 0.56 |
| 36 | DBeQ | 4 | A(1) A(-) D(-) D(3) D(4) R(7) R(-) | 0.508 |
| 37 | compound\_2 | 4 | A(4) A(6) D(9) D(7) D(-) R(-) R(-) | 0.49 |
| 38 | ABBV-744 | 5 | A(4) A(1) D(7) D(-) D(5) R(13) R(-) | 0.488 |
| 39 | Luminespib | 5 | A(4) A(5) D(-) D(8) D(7) R(13) R(-) | 0.461 |
| 40 | 1-Deoxynojirimycin | 5 | A(3) A(1) D(8) D(7) D(5) R(-) R(-) | 0.444 |
| 41 | Captopril | 4 | A(2) A(1) D(-) D(5) D(4) R(-) R(-) | 0.419 |
| 42 | Pepstatin | 5 | A(7) A(3) D(11) D(16) D(12) R(-) R(-) | 0.378 |
| 43 | MZ1 | 5 | A(7) A(8) D(16) D(-) D(13) R(26) R(-) | 0.357 |

**Table S3**. Docking-based High Throughput Virtual Screening (HTVS) work flow.

|  |  |  |
| --- | --- | --- |
| **Entry** | **Compounds name** | **Glide GScore** |
| 1 | Pimozide | -7.25 |
| 2 | RS-PPCC | -6.74 |
| 3 | 4E2RCat | -6.69 |
| 4 | Daunorubicin | -6.64 |
| 5 | 4E1RCat | -6.24 |
| 6 | onalespib | -6.23 |
| 7 | Lisinopril | -6.22 |
| 8 | ML240 | -6.16 |
| 9 | compound\_10 | -6.03 |
| 10 | INK-128 | -6.02 |
| 11 | ABBV-744 | -5.97 |
| 12 | AC-55541 | -5.31 |
| 13 | RVX-208 | -5.56 |
| 14 | RS-PPCC | -5.81 |
| 15 | dBET6 | -5.90 |
| 16 | Pioglitazone | -5.77 |
| 17 | CB5083 | -5.76 |
| 18 | PF-846 | -5.58 |
| 19 | DBeQ | -5.52 |
| 20 | Captopril | -5.50 |
| 21 | Ribavirin | -5.42 |
| 22 | Pioglitazone | -5.41 |
| 23 | Tomivosertib | -5.35 |

**Table S4**. Docking-based Standard Precision (SP) Screening work flow.

|  |  |  |
| --- | --- | --- |
| **Entry** | **Compounds name** | **Glide GScore** |
| 1 | ABBV-744 | -8.19 |
| 2 | dBET6 | -7.84 |
| 3 | CB5083 | -7.35 |
| 4 | Pimozide | -7.34 |
| 5 | AC-55541 | -7.28 |
| 6 | Tomivosertib | -7.31 |
| 7 | Daunorubicin | -7.20 |
| 8 | RS-PPCC | -6.67 |
| 9 | onalespib | -6.90 |
| 10 | RS-PPCC | -6.52 |
| 11 | Lisinopril | -6.61 |
| 12 | Pimozide | -6.49 |

**Table S5**. Docking-based Extra Precision (XP) Screening work-flow.

|  |  |  |
| --- | --- | --- |
| Entry | Compounds name | Glide\_XP\_GScore |
| 1 | **Daunorubicin** | **-9.33** |
| 2 | **Onalespib** | **-8.21** |
| 3 | **ABBV-744** | **-7.79** |
| 4 | dBET6 | -7.53 |
| 5 | RS-PPCC | -6.30 |