**Supplementary Information**

**Repurposing benzimidazole and benzothiazole derivatives as potential inhibitors of SARS-CoV-2: DFT, QSAR, molecular docking, molecular dynamics simulation, and *in-silico* pharmacokinetic and toxicity studies**

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**Table S1.** Energetic properties of the investigated compounds

|  |  |  |
| --- | --- | --- |
| **Compound****(Molecular formula)** | **Single point energy****(kcal/mol)** | **Dipole moment (D)** |
| Comp. 1 (C15H14N4O) | ₋5.4853×105 | 1.218 |
| Comp. 2 (C15H14N4O2) | ₋9.4927×105 | 0.969 |
| Comp. 3 (C15H14N4O) | ₋5.4834×105 | 1.560 |
| Comp. 4 (C12H10N4O) | ₋4.7525×105 | 1.276 |
| Comp. 5 (C15H13N3OS) | ₋7.6340×105 | 0.859 |
| Comp. 6 (C12H9N3OS) | ₋6.9031×105 | 0.930 |

**Table S2.** Quantum chemical parameters for the investigated compounds

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Compound** | **HOMO (eV)** | **LUMO (eV)** | **ΔE (eV)** | **χ (Pauling)** | **η (eV)** | **σ** | **μ (eV)** | **S** | **ω****(ev)** |
| Comp. 1 | ₋0.1948 | ₋0.0466 | 0.1482 | ₋0.1207 | 0.0741 | 13.49 | 0.1207 | 6.747 | 0.097 |
| Comp. 2 | ₋0.2001 | ₋0.0563 | 0.1438 | ₋0.1282 | 0.0719 | 13.90 | 0.1282 | 6.954 | 0.103 |
| Comp. 3 | ₋0.1425 | ₋0.0531 | 0.0894 | ₋0.0978 | 0.0447 | 22.37 | 0.0978 | 11.185 | 0.106 |
| Comp. 4 | ₋0.2044 | ₋0.0594 | 0.1382 | ₋0.1319 | 0.0725 | 13.79 | 0.1319 | 6.858 | 0.119 |
| Comp. 5 | ₋0.1506 | ₋0.1100 | 0.0406 | ₋0.1303 | 0.0203 | 49.26 | 0.1303 | 24.630 | 0.416 |
| Comp. 6 | ₋0.1992 | ₋0.0976 | 0.1016 | ₋0.1484 | 0.0508 | 19.68 | 0.1484 | 9.842 | 0.216 |

**Table S3.** Molecular interactions and binding energies of ligands with SARS-CoV-2 Mpro

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Sl. No. | Ligand | Receptor-Chain (A) | Interaction | Distance | E (kcal/mol) | Binding Energy ∆G (Autodock vina) |
| Comp. 1 | N1 7 | O LEU 287  | H-donor | 3.30 | -1.9 | ₋7.3 |
| N1 7 | OD1 ASP 289 | ionic | 3.56 | -1.7 |
| N2 10 | OD1 ASP 289 | ionic | 3.13 | -3.7 |
| N2 10 | OD2 ASP 289 | ionic | 3.77 | -1.0 |
| Comp. 2 | N3 11 | OG1 THR 199 | H-donor | 3.16 | -1.4 | ₋7.2 |
| N4 14 | O LEU 287 | H-donor | 3.32 | -1.6 |
| N1 7 | OD1 ASP 289 | ionic | 4.00 | -0.5 |
| N2 10 | OD1 ASP 289 | ionic | 3.04 | -4.2 |
| N2 10 | OD2 ASP 289 | ionic | 3.65 | -1.4 |
| N3 11 | OD1 ASP 289 | ionic | 3.91 | -0.7 |
| N3 11 | OD2 ASP 289 | ionic | 3.86 | -0.8 |
| Comp. 3 | N3 11 | OG1 THR 199 | H-donor | 3.16 | -1.4 | ₋7.1 |
| N4 14 | O LEU 287 | H-donor | 3.32 | -1.6 |
| Comp. 4 | N2 10 | OD1 ASP 289 | H-donor | 2.99 | -1.8 | ₋6.4 |
| C8 15 | O LEU 287 | H-donor | 3.62 | -1.4 |
| N2 10 | OD1 ASP 289 | ionic | 2.99 | -4.6 |
| N3 11 | OD1 ASP 289 | ionic | 3.84 | -0.9 |
| Comp. 5 | N2 1 | OG1 THR 199 | H-donor | 3.06 | -1.0 | ₋6.8 |
| Comp. 6 | N1 9 | O LEU 287 | H-donor | 2.94 | -4.2 | ₋5.9 |
| N2 11 | OG1 THR 199 | H-donor | 3.25 | -1.1 |
| N1 9 | OD1 ASP 289 | ionic | 3.19 | -3.3 |

**Table S4.** Molecular interactions and binding energies of ligands with ACE2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Sl. No. | Ligand | Receptor chain (B) | Interaction | Distance | E (kcal/mol) | Binding Energy ∆G (Autodock vina) |
| Comp. 1 | N1 7 | OD1 ASP 494 | ionic | 3.41 | -2.3 | ₋7.5 |
| N2 10 | OD1 ASP 494  | ionic | 3.87 | -0.8 |
| 6-ring | CA ARG 671  | pi- pi | 3.98 | -0.9 |
| Comp. 2 | N4 14 | O VAL 672 | H-donor | 2.96 | -4.9 | ₋7.5 |
| 6-ring | N VAL 672 | pi- pi | 3.73 | -1.4 |
| Comp. 3 | N2 10 | OE2 GLU 495 | H-donor | 3.21 | -7.2 | ₋7.2 |
| N2 10 | OE2 GLU 495  | ionic | 3.21 | -3.2 |
| N3 11 | OE2 GLU 495 | ionic | 3.91 | -0.7 |
| 5-ring | CA ASP 494 | pi- pi | 3.55 | -1.2 |
| Comp. 4 | N2 10 | O VAL 672 | H-donor | 2.88 | -2.3 | ₋6.7 |
| N3 11 | O VAL 672 | H-donor | 3.03 | -5.2 |
| N4 14 | O HIS 493 | H-donor | 3.12 | -2.5 |
| Comp. 5 | N4 14 | O VAL 672 | H-donor | 2.96 | -4.9 | ₋7.2 |
| 6-ring | CA ARG 671  | pi- pi | 3.98 | -0.9 |
| N4 14 | O HIS 493 | H-donor | 3.12 | -2.5 |
| Comp. 6 | S1 7 | OE2 GLU 489 | H-donor | 4.41 | -0.4 | ₋6.4 |
| N3 13 | OH TYR 613 | H-donor | 3.15 | -3.8 |
| N2 11 | OE2 GLU 489 | ionic | 2.96 | -4.7 |
| N3 13 | OE2 GLU 489  | ionic | 3.03 | -4.3 |
| 5-ring | ND2 ASN 674  | pi- pi | 3.51 | -0.7 |

**Table S5.** Pharmacokinetic properties of the ligands

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ligand** | **GI absorption** | **BBB permeant** | **P-gp substrate** | **CYP1A2 inhibitor** | **CYP2C19 inhibitor** | **CYP2C9 inhibitor** | **CYP2D6 inhibitor** | **CYP3A4 inhibitor** | **Log *K*p (skin permeation)** |
| Comp. 1 | High | Yes | No | Yes | No | No | No | No | ₋5.58 cm/s |
| Comp. 2 | High | No | No | Yes | No | No | Yes | No | ₋5.86 cm/s |
| Comp. 3 | High | Yes | No | Yes | Yes | No | Yes | No | ₋5.50 cm/s |
| Comp. 4 | High | Yes | No | Yes | No | No | No | No | ₋5.66 cm/s |
| Comp. 5 | High | Yes | No | Yes | Yes | Yes | No | No | ₋4.98 cm/s |
| Comp. 6 | High | Yes | No | Yes | Yes | Yes | No | No | ₋5.14 cm/s |

**Table S6.** Drug-likeliness properties of the ligands

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ligand** | **Lipinski** | **Ghose** | **Veber** | **Egan** | **Muegge** | **Bioavailability Score** |
| Comp. 1 | Yes; 0 violation | Yes | Yes | Yes | Yes | 0.55 |
| Comp. 2 | Yes; 0 violation | Yes | Yes | Yes | Yes | 0.55 |
| Comp. 3 | Yes; 0 violation | Yes | Yes | Yes | Yes | 0.55 |
| Comp. 4 | Yes; 0 violation | Yes | Yes | Yes | Yes | 0.55 |
| Comp. 5 | Yes; 0 violation | Yes | Yes | Yes | Yes | 0.55 |
| Comp. 6 | Yes; 0 violation | Yes | Yes | Yes | Yes | 0.55 |

**Table S7.** Medicinal properties of the ligands

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ligand** | **PAINS** | **Brenk** | **Lead-likeness** | **Synthetic accessibility** |
| Comp. 1 | 1 alert: hzone\_phenol\_A | 1 alert: imine\_1 | Yes | 2.56 |
| Comp. 2 | 1 alert: hzone\_phenol\_A | 1 alert: imine\_1 | Yes | 2.65 |
| Comp. 3 | 0 alert | 1 alert: imine\_1 | Yes | 2.62 |
| Comp. 4 | 0 alert | 1 alert: imine\_1 | No; 1 violation: MW<250 | 2.91 |
| Comp. 5 | 0 alert | 1 alert: imine\_1 | No; 1 violation: XLOGP3>3.5 | 2.91 |
| Comp. 6 | 1 alert: hzone\_furan\_A | 1 alert: imine\_1 | No; 2 violations: MW<250, XLOGP3>3.5 | 3.01 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ligand** | **Log *P*o/w****(iLOGP)** | **Log *P*o/w****(XLOGP3)** | **Log *P*o/w****(WLOGP)** | **Log *P*o/w****(MLOGP)** | **Log *P*o/w****(SILICOS-IT)** | **Consensus Log *P*o/w** |
| Comp. 1 | 1.33 | 3.30 | 2.91 | 2.18 | 2.80 | 2.51 |
| Comp. 2 | 1.39 | 3.05 | 2.53 | 1.63 | 2.62 | 2.25 |
| Comp. 3 | 1.53 | 3.41 | 2.83 | 2.18 | 3.10 | 2.61 |
| Comp. 4 | 0.61 | 2.84 | 2.41 | 1.16 | 2.50 | 1.90 |
| Comp. 5 | 2.67 | 4.30 | 3.56 | 2.60 | 4.22 | 3.47 |
| Comp. 6 | 1.86 | 3.73 | 3.14 | 1.58 | 3.62 | 2.79 |

 **Table S8.** Lipophilicity of the ligands

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ligand** | **Molecular weight** | **Num. heavy atoms** | **Num. arom. heavy atoms** | **Fraction Csp3** | **Num. rotatable bonds** | **Num. H-bond acceptors** | **Num. H-bond donors** | **Molar Refractivity** | **TPSA** |
| Comp. 1 | 266.30 g/mol | 20 | 15 | 0.07 | 3 | 3 | 3 | 80.40 | 73.30 Å² |
| Comp. 2 | 282.30 g/mol | 21 | 15 | 0.07 | 4 | 4 | 3 | 82.09 | 82.53 Å² |
| Comp. 3 | 266.30 g/mol | 20 | 15 | 0.07 | 4 | 3 | 2 | 80.06 | 62.30 Å² |
| Comp. 4 | 226.23 g/mol | 17 | 14 | 0.00 | 3 | 3 | 2 | 65.84 | 66.21 Å² |
| Comp. 5 | 283.35 g/mol | 20 | 15 | 0.07 | 4 | 3 | 1 | 83.59 | 74.75 Å² |
| Comp. 6 | 243.28 g/mol | 17 | 14 | 0.00 | 3 | 3 | 1 | 69.36 | 78.66 Å² |

 **Table S9.** Physicochemical properties of the ligands

**Table S10.** Toxicity data of the ligands

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ligand** | **AMES toxicity** | **Max. tolerated dose (human)** | **hERG I inhibitor** | **hERG II inhibitor** | **Oral Rat Acute Toxicity (LD50)** | **Oral Rat Chronic Toxicity (LOAEL)** | **Hepatotoxicity** | **Skin Sensitisation** | **T. Pyriformis toxicity** | **Minnow toxicity** |
| Comp. 1 | Yes | ₋0.318 | No | Yes | 2.749 | 1.887 | No | No | 0.403 | 3.366 |
| Comp. 2 | No | ₋0.298 | No | Yes | 2.426 | 1.885 | No | No | 0.506 | 2.812 |
| Comp. 3 | Yes | ₋0.034 | No | Yes | 2.457 | 1.659 | No | No | 0.929 | 2.37 |
| Comp. 4 | Yes | ₋0.719 | No | No | 2.848 | 1.537 | No | No | 0.576 | 2.523 |
| Comp. 5 | Yes | ₋0.011 | No | Yes | 2.469 | 1.417 | No | No | 1.544 | 1.81 |
| Comp. 6 | No | ₋0.184 | No | No | 2.723 | 1.022 | No | No | 1.088 | 1.962 |

**Table S11.** Water solubility of the ligands

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Sl. No. |  | Comp. 1 | Comp. 2 | Comp. 3 | Comp. 4 | Comp. 5 | Comp. 6 |
| 1 | Log *S* (ESOL) | -3.93 | -3.78 | -3.93 | -3.44 | -4.60 | -4.11 |
| Solubility | 3.15e-02 mg/ml ; 1.18e-04 mol/l | 4.72e-02 mg/ml ; 1.67e-04 mol/l | 3.13e-02 mg/ml ; 1.17e-04 mol/l | 8.15e-02 mg/ml ; 3.60e-04 mol/l | 7.17e-03 mg/ml ; 2.53e-05 mol/l | 1.89e-02 mg/ml ; 7.77e-05 mol/l |
| Class | Soluble | Soluble | Soluble | Soluble | Moderately soluble | Moderately soluble |
| 2 | Log *S* (Ali)  | -4.51 | -4.45 | -4.40 | -3.89 | -5.58 | -5.07 |
| Solubility | 8.14e-03 mg/ml ; 3.06e-05 mol/l | 1.00e-02 mg/ml ; 3.55e-05 mol/l | 1.06e-02 mg/ml ; 4.00e-05 mol/l | 2.92e-02 mg/ml ; 1.29e-04 mol/l | 7.40e-04 mg/ml ; 2.61e-06 mol/l | 2.05e-03 mg/ml ; 8.44e-06 mol/l |
| Class | Moderately soluble | Moderately soluble | Moderately soluble | Soluble | Moderately soluble | Moderately soluble |
| 3 | Log *S* (SILICOS-IT) | -5.39 | -5.12 | -5.70 | -4.79 | -5.76 | -4.85 |
| Solubility | 1.09e-03 mg/ml ; 4.10e-06 mol/l | 2.13e-03 mg/ml ; 7.55e-06 mol/l | 5.29e-04 mg/ml ; 1.99e-06 mol/l | 3.64e-03 mg/ml ; 1.61e-05 mol/l | 4.97e-04 mg/ml ; 1.75e-06 mol/l | 3.42e-03 mg/ml ; 1.41e-05 mol/l |
| Class | Moderately soluble | Moderately soluble | Moderately soluble | Moderately soluble | Moderately soluble | Moderately soluble |