

# Supplementary information

## Are we ready to design oral PROTACs®?

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**Table S1:** Statistical results of the 2D descriptors in PROTAC-DB.

|                           | MW    | nC     | NAR     | PHI     | nHDon   | nHAcc   | TPSA(Tot) |
|---------------------------|-------|--------|---------|---------|---------|---------|-----------|
| <b>Number of values</b>   | 2258  | 2258   | 2258    | 2258    | 2258    | 2258    | 2258      |
| <b>Minimum</b>            | 533.6 | 27.00  | 1.000   | 7.357   | 1.000   | 9.000   | 101.2     |
| <b>25% Percentile</b>     | 851.8 | 43.00  | 4.000   | 13.83   | 3.000   | 15.00   | 209.1     |
| <b>Median</b>             | 970.1 | 49.00  | 4.000   | 17.05   | 4.500   | 18.00   | 239.0     |
| <b>75% Percentile</b>     | 1067  | 56.00  | 5.000   | 20.03   | 5.000   | 20.00   | 268.5     |
| <b>Maximum</b>            | 1963  | 96.00  | 9.000   | 42.27   | 11.00   | 38.00   | 460.1     |
| <b>Range</b>              | 1430  | 69.00  | 8.000   | 34.91   | 10.00   | 29.00   | 358.8     |
| <b>Mean</b>               | 972.9 | 49.52  | 4.484   | 17.32   | 4.539   | 17.70   | 240.0     |
| <b>Std. Deviation</b>     | 174.1 | 9.270  | 1.219   | 4.622   | 1.590   | 3.372   | 45.97     |
| <b>Std. Error of Mean</b> | 3.664 | 0.1951 | 0.02565 | 0.09727 | 0.03345 | 0.07096 | 0.9674    |

**Table S2:** Permeable PROTACs<sup>®</sup> introduced in the chemical space. Permeability values and their assesment methods. Caco-2: (AB: apical-basal, BA: basal-apical)

| Name      | Permeability (10 <sup>-6</sup> cm/s) | Permeability experiment | Permeability classification | Source   |
|-----------|--------------------------------------|-------------------------|-----------------------------|----------|
| ACBI1     | 2                                    | Caco-2                  | High                        | opnMe    |
| BI-0319   | 0.2                                  | Caco-2                  | Low                         | opnMe    |
| BI-3663   | 15.85                                | Caco-2                  | High                        | opnMe    |
| BI-4206   | 0.4                                  | Caco-2                  | Low                         | opnMe    |
| PROTAC-1  | 1.41                                 | PAMPA                   | High                        | Kihlberg |
| PROTAC-14 | 1.7 (AB), 14.1 (BA)                  | Caco-2                  | High                        | Skidmore |
| MZ4       | 0.60                                 | PAMPA                   | Low                         | Lokey    |
| MZ1       | 0.03                                 | PAMPA                   | Low                         | Lokey    |
| MZ3       | 0.01                                 | PAMPA                   | Low                         | Lokey    |
| MZP-61    | 0.30                                 | PAMPA                   | Low                         | Lokey    |
| MZP-55    | 0.16                                 | PAMPA                   | Low                         | Lokey    |
| CM09      | 0.01                                 | PAMPA                   | Low                         | Lokey    |
| CM11      | 0.008                                | PAMPA                   | Low                         | Lokey    |
| CMP98     | 0.00                                 | PAMPA                   | Low                         | Lokey    |
| AT3       | 0.01                                 | PAMPA                   | Low                         | Lokey    |
| AT6       | 0.00                                 | PAMPA                   | Low                         | Lokey    |
| AT2       | 0.00                                 | PAMPA                   | Low                         | Lokey    |

**Table S3:** Calculated 2D descriptors for highly permeable and bioavailable PROTACs<sup>®</sup> introduced in the chemical space.

| Name      | MW      | nC    | NAR  | PHI   | nHDon | nHAcc | TPSA(Tot) |
|-----------|---------|-------|------|-------|-------|-------|-----------|
| ARV-110   | 812.38  | 41.00 | 3.00 | 11.97 | 2.00  | 16.00 | 182.86    |
| ARV-471   | 723.99  | 45.00 | 4.00 | 9.88  | 2.00  | 9.00  | 96.43     |
| ACBI1     | 936.23  | 49.00 | 5.00 | 15.04 | 6.00  | 17.00 | 236.84    |
| BI-3663   | 917.93  | 44.00 | 4.00 | 15.56 | 4.00  | 22.00 | 244.47    |
| PROTAC-1  | 1034.24 | 50.00 | 5.00 | 19.04 | 4.00  | 22.00 | 264.87    |
| PROTAC-14 | 837.9   | 40.00 | 3.00 | 13.73 | 1.00  | 18.00 | 210.82    |

