

Supporting Information

Few-Shot Learning for Low-Data Drug Discovery

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1 Few-Shot Learning on Tox21

1.1 SR-HSE (372 Actives and 6,095 Inactives)

Table S1: ROC-AUC and PR-AUC Scores for ML Models on TOX21 SR-HSE Target. Values are mean values with standard deviation over 20 rounds of testing. Best values are highlighted in bold text. The first column shows the composition of the support set as explained in text.

| TOX21 SR-HSE | Metric | RF | Graph Conv | SiameseNet | MatchingNet | ProtoNet | RelationNet |
|-----------------|---------|-------------------|-------------------|-------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| 10+/10- | ROC-AUC | 0.563 \pm 0.030 | 0.572 \pm 0.049 | 0.780 \pm 0.028 | 0.793 \pm 0.002 | 0.782 \pm 0.017 | 0.774 \pm 0.004 |
| | PR-AUC | 0.078 \pm 0.014 | 0.080 \pm 0.022 | 0.133 \pm 0.020 | 0.272 \pm 0.015 | 0.271 \pm 0.055 | 0.271 \pm 0.021 |
| 5+/10- | ROC-AUC | 0.546 \pm 0.035 | 0.565 \pm 0.047 | 0.777 \pm 0.067 | 0.778 \pm 0.002 | 0.772 \pm 0.013 | 0.791 \pm 0.003 |
| | PR-AUC | 0.074 \pm 0.013 | 0.085 \pm 0.020 | 0.117 \pm 0.034 | 0.266 \pm 0.012 | 0.278 \pm 0.045 | 0.280 \pm 0.031 |
| 1+/10- | ROC-AUC | 0.518 \pm 0.036 | 0.540 \pm 0.058 | 0.778 \pm 0.168 | 0.788 \pm 0.001 | 0.780 \pm 0.003 | 0.776 \pm 0.001 |
| | PR-AUC | 0.064 \pm 0.009 | 0.075 \pm 0.019 | 0.052 \pm 0.047 | 0.208 \pm 0.007 | 0.283 \pm 0.016 | 0.243 \pm 0.007 |
| 1+/5- | ROC-AUC | 0.515 \pm 0.044 | 0.503 \pm 0.061 | 0.801 \pm 0.162 | 0.775 \pm 0.002 | 0.773 \pm 0.005 | 0.789 \pm 0.001 |
| | PR-AUC | 0.064 \pm 0.010 | 0.064 \pm 0.013 | 0.064 \pm 0.041 | 0.235 \pm 0.017 | 0.270 \pm 0.018 | 0.229 \pm 0.005 |
| 1+/1- | ROC-AUC | 0.521 \pm 0.045 | 0.520 \pm 0.066 | 0.769 \pm 0.084 | 0.770 \pm 0.006 | 0.779 \pm 0.007 | 0.772 \pm 0.001 |
| | PR-AUC | 0.066 \pm 0.009 | 0.066 \pm 0.015 | 0.125 \pm 0.059 | 0.230 \pm 0.024 | 0.266 \pm 0.029 | 0.274 \pm 0.008 |

1.2 SR-MMP (918 Actives and 4,892 Inactives)

Table S2: ROC-AUC and PR-AUC Scores for ML Models on TOX21 SR-MMP Target. Values are mean values with standard deviation over 20 rounds of testing. Best values are highlighted in bold text. The first column shows the composition of the support set as explained in text.

| TOX21 SR-MMP | Metric | RF | Graph Conv | SiameseNet | MatchingNet | ProtoNet | RelationNet |
|-----------------|---------|-------------------|-------------------|-------------------|-------------------------------------|-------------------------------------|-------------------|
| 10+/10- | ROC-AUC | 0.679 \pm 0.047 | 0.654 \pm 0.068 | 0.860 \pm 0.025 | 0.844 \pm 0.005 | 0.845 \pm 0.015 | 0.842 \pm 0.007 |
| | PR-AUC | 0.296 \pm 0.052 | 0.270 \pm 0.066 | 0.371 \pm 0.029 | 0.511 \pm 0.017 | 0.510 \pm 0.032 | 0.496 \pm 0.023 |
| 5+/10- | ROC-AUC | 0.647 \pm 0.055 | 0.652 \pm 0.056 | 0.858 \pm 0.055 | 0.853 \pm 0.007 | 0.846 \pm 0.014 | 0.842 \pm 0.007 |
| | PR-AUC | 0.268 \pm 0.044 | 0.273 \pm 0.059 | 0.303 \pm 0.064 | 0.519 \pm 0.031 | 0.527 \pm 0.029 | 0.494 \pm 0.038 |
| 1+/10- | ROC-AUC | 0.613 \pm 0.063 | 0.587 \pm 0.081 | 0.876 \pm 0.068 | 0.842 \pm 0.002 | 0.849 \pm 0.005 | 0.844 \pm 0.002 |
| | PR-AUC | 0.236 \pm 0.054 | 0.221 \pm 0.050 | 0.158 \pm 0.124 | 0.444 \pm 0.005 | 0.508 \pm 0.025 | 0.470 \pm 0.011 |
| 1+/5- | ROC-AUC | 0.539 \pm 0.078 | 0.592 \pm 0.095 | 0.815 \pm 0.172 | 0.853 \pm 0.001 | 0.846 \pm 0.005 | 0.846 \pm 0.001 |
| | PR-AUC | 0.188 \pm 0.035 | 0.226 \pm 0.059 | 0.179 \pm 0.099 | 0.499 \pm 0.011 | 0.508 \pm 0.025 | 0.470 \pm 0.007 |
| 1+/1- | ROC-AUC | 0.580 \pm 0.060 | 0.572 \pm 0.128 | 0.845 \pm 0.055 | 0.851 \pm 0.008 | 0.847 \pm 0.003 | 0.840 \pm 0.004 |
| | PR-AUC | 0.209 \pm 0.034 | 0.219 \pm 0.075 | 0.311 \pm 0.084 | 0.511 \pm 0.037 | 0.506 \pm 0.018 | 0.471 \pm 0.022 |

1.3 SR-p53 (423 Actives and 6,351 Inactives)

Table S3: ROC-AUC and PR-AUC Scores for ML Models on TOX21 SR-p53 Target. Values are mean values with standard deviation over 20 rounds of testing. Best values are highlighted in bold text. The first column shows the composition of the support set as explained in text.

| TOX21 SR-p53 | Metric | RF | Graph Conv | SiameseNet | MatchingNet | ProtoNet | RelationNet |
|-----------------|---------|-------------------|-------------------|-------------------|-------------------------------------|-------------------------------------|-------------------|
| 10+/10- | ROC-AUC | 0.610 \pm 0.033 | 0.635 \pm 0.048 | 0.835 \pm 0.029 | 0.834 \pm 0.003 | 0.850 \pm 0.004 | 0.826 \pm 0.011 |
| | PR-AUC | 0.101 \pm 0.011 | 0.101 \pm 0.022 | 0.172 \pm 0.027 | 0.317 \pm 0.007 | 0.369 \pm 0.027 | 0.313 \pm 0.039 |
| 5+/10- | ROC-AUC | 0.614 \pm 0.033 | 0.614 \pm 0.054 | 0.848 \pm 0.060 | 0.842 \pm 0.003 | 0.852 \pm 0.009 | 0.834 \pm 0.002 |
| | PR-AUC | 0.102 \pm 0.014 | 0.098 \pm 0.023 | 0.151 \pm 0.045 | 0.323 \pm 0.014 | 0.358 \pm 0.042 | 0.291 \pm 0.028 |
| 1+/10- | ROC-AUC | 0.558 \pm 0.069 | 0.548 \pm 0.083 | 0.855 \pm 0.148 | 0.837 \pm 0.001 | 0.848 \pm 0.005 | 0.824 \pm 0.001 |
| | PR-AUC | 0.084 \pm 0.019 | 0.081 \pm 0.023 | 0.088 \pm 0.061 | 0.249 \pm 0.004 | 0.361 \pm 0.030 | 0.262 \pm 0.007 |
| 1+/5- | ROC-AUC | 0.548 \pm 0.070 | 0.582 \pm 0.088 | 0.805 \pm 0.154 | 0.833 \pm 0.001 | 0.840 \pm 0.005 | 0.822 \pm 0.001 |
| | PR-AUC | 0.083 \pm 0.022 | 0.093 \pm 0.028 | 0.076 \pm 0.057 | 0.283 \pm 0.012 | 0.310 \pm 0.023 | 0.257 \pm 0.003 |
| 1+/1- | ROC-AUC | 0.549 \pm 0.064 | 0.553 \pm 0.103 | 0.840 \pm 0.061 | 0.838 \pm 0.004 | 0.834 \pm 0.003 | 0.827 \pm 0.001 |
| | PR-AUC | 0.079 \pm 0.016 | 0.085 \pm 0.027 | 0.160 \pm 0.046 | 0.316 \pm 0.022 | 0.346 \pm 0.021 | 0.279 \pm 0.015 |

2 Few-Shot Learning on MUV

2.1 MUV-832 (30 Actives and 14,637 Decoys)

Table S4: ROC-AUC and PR-AUC Scores for ML Models on MUV MUV-832 Target. Values are mean values with standard deviation over 20 rounds of testing. Best values are highlighted in bold text. The first column shows the composition of the support set as explained in text.

| MUV MUV-832 | Metric | RF | Graph Conv | SiameseNet | MatchingNet | ProtoNet | RelationNet |
|----------------|---------|---------------------------------|-------------------|-------------------|-------------------|-------------------|---------------------------------|
| 10+/10- | ROC-AUC | 0.824 \pm 0.068 | 0.753 \pm 0.073 | 0.608 \pm 0.019 | 0.720 \pm 0.043 | 0.585 \pm 0.041 | 0.566 \pm 0.050 |
| | PR-AUC | 0.069 \pm 0.047 | 0.006 \pm 0.004 | 0.001 \pm 0.000 | 0.005 \pm 0.001 | 0.004 \pm 0.003 | 0.003 \pm 0.001 |
| 5+/10- | ROC-AUC | 0.747 \pm 0.072 | 0.683 \pm 0.080 | 0.561 \pm 0.039 | 0.651 \pm 0.031 | 0.656 \pm 0.021 | 0.561 \pm 0.105 |
| | PR-AUC | 0.122 \pm 0.058 | 0.012 \pm 0.017 | 0.001 \pm 0.002 | 0.008 \pm 0.001 | 0.007 \pm 0.001 | 0.003 \pm 0.001 |
| 1+/10- | ROC-AUC | 0.601 \pm 0.060 | 0.556 \pm 0.076 | 0.722 \pm 0.136 | 0.615 \pm 0.026 | 0.607 \pm 0.014 | 0.683 \pm 0.010 |
| | PR-AUC | 0.035 \pm 0.034 | 0.007 \pm 0.009 | 0.003 \pm 0.004 | 0.004 \pm 0.001 | 0.006 \pm 0.000 | 0.007 \pm 0.000 |
| 1+/5- | ROC-AUC | 0.579 \pm 0.071 | 0.551 \pm 0.115 | 0.773 \pm 0.084 | 0.514 \pm 0.012 | 0.570 \pm 0.021 | 0.500 \pm 0.000 |
| | PR-AUC | 0.036 \pm 0.033 | 0.005 \pm 0.003 | 0.003 \pm 0.003 | 0.003 \pm 0.000 | 0.004 \pm 0.001 | 0.002 \pm 0.000 |
| 1+/1- | ROC-AUC | 0.582 \pm 0.089 | 0.567 \pm 0.155 | 0.768 \pm 0.079 | 0.496 \pm 0.028 | 0.517 \pm 0.010 | 0.577 \pm 0.011 |
| | PR-AUC | 0.039 \pm 0.038 | 0.006 \pm 0.009 | 0.005 \pm 0.003 | 0.003 \pm 0.000 | 0.005 \pm 0.001 | 0.004 \pm 0.000 |

2.2 MUV-846 (30 Actives and 14,681 Decoys)

Table S5: ROC-AUC and PR-AUC Scores for ML Models on MUV MUV-846 Target. Values are mean values with standard deviation over 20 rounds of testing. Best values are highlighted in bold text. The first column shows the composition of the support set as explained in text.

| MUV MUV-846 | Metric | RF | Graph Conv | SiameseNet | MatchingNet | ProtoNet | RelationNet |
|----------------|---------|-------------------------------------|-------------------------------------|-------------------|-------------------|-------------------|-------------------|
| 10+/10- | ROC-AUC | 0.876 \pm 0.048 | 0.849 \pm 0.045 | 0.594 \pm 0.024 | 0.715 \pm 0.048 | 0.719 \pm 0.036 | 0.482 \pm 0.035 |
| | PR-AUC | 0.115 \pm 0.053 | 0.025 \pm 0.019 | 0.001 \pm 0.000 | 0.022 \pm 0.012 | 0.003 \pm 0.001 | 0.001 \pm 0.000 |
| 5+/10- | ROC-AUC | 0.833 \pm 0.042 | 0.754 \pm 0.065 | 0.555 \pm 0.056 | 0.453 \pm 0.024 | 0.560 \pm 0.033 | 0.549 \pm 0.047 |
| | PR-AUC | 0.088 \pm 0.055 | 0.038 \pm 0.029 | 0.001 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 |
| 1+/10- | ROC-AUC | 0.676 \pm 0.104 | 0.656 \pm 0.123 | 0.711 \pm 0.104 | 0.437 \pm 0.026 | 0.490 \pm 0.017 | 0.556 \pm 0.008 |
| | PR-AUC | 0.024 \pm 0.031 | 0.012 \pm 0.012 | 0.001 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 |
| 1+/5- | ROC-AUC | 0.661 \pm 0.093 | 0.690 \pm 0.124 | 0.688 \pm 0.171 | 0.388 \pm 0.011 | 0.441 \pm 0.012 | 0.500 \pm 0.000 |
| | PR-AUC | 0.039 \pm 0.034 | 0.014 \pm 0.013 | 0.001 \pm 0.001 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 |
| 1+/1- | ROC-AUC | 0.624 \pm 0.123 | 0.642 \pm 0.159 | 0.647 \pm 0.094 | 0.518 \pm 0.029 | 0.456 \pm 0.025 | 0.490 \pm 0.008 |
| | PR-AUC | 0.031 \pm 0.040 | 0.011 \pm 0.010 | 0.009 \pm 0.021 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 |

2.3 MUV-852 (29 Actives and 14,622 Decoys)

Table S6: ROC-AUC and PR-AUC Scores for ML Models on MUV MUV-852 Target. Values are mean values with standard deviation over 20 rounds of testing. Best values are highlighted in bold text. The first column shows the composition of the support set as explained in text.

| MUV MUV-852 | Metric | RF | Graph Conv | SiameseNet | MatchingNet | ProtoNet | RelationNet |
|----------------|---------|-------------------------------------|-------------------------------------|-------------------|-------------------|-------------------|-------------------|
| 10+/10- | ROC-AUC | 0.790 \pm 0.048 | 0.803 \pm 0.054 | 0.574 \pm 0.019 | 0.647 \pm 0.035 | 0.639 \pm 0.052 | 0.515 \pm 0.042 |
| | PR-AUC | 0.137 \pm 0.086 | 0.010 \pm 0.004 | 0.001 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.001 |
| 5+/10- | ROC-AUC | 0.787 \pm 0.041 | 0.779 \pm 0.031 | 0.612 \pm 0.031 | 0.564 \pm 0.033 | 0.592 \pm 0.032 | 0.453 \pm 0.026 |
| | PR-AUC | 0.130 \pm 0.093 | 0.021 \pm 0.023 | 0.001 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 |
| 1+/10- | ROC-AUC | 0.665 \pm 0.103 | 0.654 \pm 0.156 | 0.741 \pm 0.129 | 0.556 \pm 0.020 | 0.591 \pm 0.022 | 0.594 \pm 0.008 |
| | PR-AUC | 0.036 \pm 0.044 | 0.007 \pm 0.005 | 0.001 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.003 \pm 0.000 |
| 1+/5- | ROC-AUC | 0.639 \pm 0.145 | 0.607 \pm 0.168 | 0.665 \pm 0.126 | 0.485 \pm 0.020 | 0.523 \pm 0.017 | 0.500 \pm 0.000 |
| | PR-AUC | 0.052 \pm 0.062 | 0.007 \pm 0.006 | 0.001 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 |
| 1+/1- | ROC-AUC | 0.621 \pm 0.114 | 0.674 \pm 0.174 | 0.673 \pm 0.099 | 0.462 \pm 0.014 | 0.506 \pm 0.020 | 0.510 \pm 0.008 |
| | PR-AUC | 0.034 \pm 0.050 | 0.007 \pm 0.005 | 0.006 \pm 0.011 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 |

2.4 MUV-858 (29 Actives and 14,745 Decoys)

Table S7: ROC-AUC and PR-AUC Scores for ML Models on MUV MUV-858 Target. Values are mean values with standard deviation over 20 rounds of testing. Best values are highlighted in bold text. The first column shows the composition of the support set as explained in text.

| MUV MUV-858 | Metric | RF | Graph Conv | SiameseNet | MatchingNet | ProtoNet | RelationNet |
|----------------|---------|-------------------------------------|-------------------------------------|-------------------|-------------------------------------|-------------------|-------------------|
| 10+/10- | ROC-AUC | 0.609 \pm 0.079 | 0.644 \pm 0.071 | 0.533 \pm 0.031 | 0.545 \pm 0.057 | 0.539 \pm 0.041 | 0.489 \pm 0.052 |
| | PR-AUC | 0.004 \pm 0.003 | 0.003 \pm 0.001 | 0.001 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.001 \pm 0.000 |
| 5+/10- | ROC-AUC | 0.573 \pm 0.070 | 0.598 \pm 0.054 | 0.529 \pm 0.036 | 0.446 \pm 0.036 | 0.562 \pm 0.026 | 0.469 \pm 0.026 |
| | PR-AUC | 0.011 \pm 0.013 | 0.003 \pm 0.002 | 0.001 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 |
| 1+/10- | ROC-AUC | 0.537 \pm 0.058 | 0.556 \pm 0.052 | 0.527 \pm 0.162 | 0.405 \pm 0.009 | 0.488 \pm 0.014 | 0.477 \pm 0.008 |
| | PR-AUC | 0.005 \pm 0.008 | 0.003 \pm 0.001 | 0.000 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 |
| 1+/5- | ROC-AUC | 0.534 \pm 0.065 | 0.550 \pm 0.071 | 0.514 \pm 0.140 | 0.440 \pm 0.016 | 0.482 \pm 0.014 | 0.500 \pm 0.000 |
| | PR-AUC | 0.005 \pm 0.008 | 0.003 \pm 0.002 | 0.001 \pm 0.001 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 |
| 1+/1- | ROC-AUC | 0.521 \pm 0.065 | 0.505 \pm 0.069 | 0.558 \pm 0.103 | 0.554 \pm 0.017 | 0.526 \pm 0.014 | 0.437 \pm 0.014 |
| | PR-AUC | 0.002 \pm 0.001 | 0.003 \pm 0.001 | 0.002 \pm 0.001 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 |

2.5 MUV-859 (24 Actives and 14,722 Decoys)

Table S8: ROC-AUC and PR-AUC Scores for ML Models on MUV MUV-859 Target. Values are mean values with standard deviation over 20 rounds of testing. Best values are highlighted in bold text. The first column shows the composition of the support set as explained in text.

| MUV MUV-859 | Metric | RF | Graph Conv | SiameseNet | MatchingNet | ProtoNet | RelationNet |
|----------------|---------|-------------------------------------|-------------------------------------|-------------------|-------------------|-------------------------------------|-------------------------------------|
| 10+/10- | ROC-AUC | 0.539 \pm 0.077 | 0.517 \pm 0.057 | 0.499 \pm 0.018 | 0.516 \pm 0.042 | 0.513 \pm 0.041 | 0.398 \pm 0.053 |
| | PR-AUC | 0.003 \pm 0.005 | 0.001 \pm 0.000 | 0.001 \pm 0.000 | 0.001 \pm 0.000 | 0.001 \pm 0.000 | 0.001 \pm 0.000 |
| 5+/10- | ROC-AUC | 0.538 \pm 0.066 | 0.515 \pm 0.067 | 0.492 \pm 0.020 | 0.464 \pm 0.023 | 0.510 \pm 0.024 | 0.481 \pm 0.052 |
| | PR-AUC | 0.002 \pm 0.001 | 0.002 \pm 0.001 | 0.000 \pm 0.000 | 0.001 \pm 0.000 | 0.001 \pm 0.000 | 0.005 \pm 0.004 |
| 1+/10- | ROC-AUC | 0.517 \pm 0.081 | 0.504 \pm 0.060 | 0.539 \pm 0.109 | 0.446 \pm 0.015 | 0.522 \pm 0.011 | 0.427 \pm 0.014 |
| | PR-AUC | 0.002 \pm 0.001 | 0.002 \pm 0.000 | 0.000 \pm 0.000 | 0.001 \pm 0.000 | 0.002 \pm 0.000 | 0.001 \pm 0.000 |
| 1+/5- | ROC-AUC | 0.524 \pm 0.064 | 0.527 \pm 0.057 | 0.426 \pm 0.121 | 0.480 \pm 0.013 | 0.453 \pm 0.013 | 0.500 \pm 0.000 |
| | PR-AUC | 0.002 \pm 0.001 | 0.002 \pm 0.002 | 0.000 \pm 0.000 | 0.002 \pm 0.000 | 0.001 \pm 0.000 | 0.002 \pm 0.000 |
| 1+/1- | ROC-AUC | 0.517 \pm 0.064 | 0.499 \pm 0.061 | 0.455 \pm 0.072 | 0.504 \pm 0.016 | 0.522 \pm 0.009 | 0.406 \pm 0.014 |
| | PR-AUC | 0.002 \pm 0.001 | 0.002 \pm 0.001 | 0.001 \pm 0.000 | 0.002 \pm 0.000 | 0.002 \pm 0.000 | 0.001 \pm 0.000 |

3 Few-Shot Learning on DUD-E GPCR Subset

Table S9: ROC-AUC and PR-AUC Scores for ML Models on DUD-E GPCR adrb2 Target. Values are mean values with standard deviation over 20 rounds of testing. Best values are highlighted in bold text. The first column shows the composition of the support set as explained in text.

| DUD-E GPCR adrb2 | Metric | RF | Graph Conv | SiameseNet | MatchingNet | ProtoNet | RelationNet |
|---------------------|---------|-------------------|-------------------|-------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| 10+/10- | ROC-AUC | 0.969 \pm 0.018 | 0.914 \pm 0.038 | 0.998 \pm 0.000 | 1.000 \pm 0.000 | 1.000 \pm 0.000 | 0.998 \pm 0.001 |
| | PR-AUC | 0.806 \pm 0.103 | 0.311 \pm 0.099 | 0.963 \pm 0.014 | 0.986 \pm 0.002 | 0.997 \pm 0.001 | 0.991 \pm 0.002 |
| 5+/10- | ROC-AUC | 0.948 \pm 0.022 | 0.875 \pm 0.043 | 0.998 \pm 0.005 | 0.996 \pm 0.000 | 1.000 \pm 0.000 | 0.998 \pm 0.001 |
| | PR-AUC | 0.729 \pm 0.088 | 0.230 \pm 0.102 | 0.959 \pm 0.047 | 0.982 \pm 0.003 | 0.996 \pm 0.001 | 0.985 \pm 0.001 |
| 1+/10- | ROC-AUC | 0.842 \pm 0.055 | 0.748 \pm 0.072 | 0.998 \pm 0.001 | 0.999 \pm 0.000 | 0.998 \pm 0.000 | 0.998 \pm 0.000 |
| | PR-AUC | 0.339 \pm 0.135 | 0.099 \pm 0.056 | 0.909 \pm 0.117 | 0.975 \pm 0.002 | 0.966 \pm 0.009 | 0.974 \pm 0.000 |
| 1+/5- | ROC-AUC | 0.842 \pm 0.088 | 0.744 \pm 0.080 | 0.998 \pm 0.000 | 0.995 \pm 0.000 | 0.996 \pm 0.000 | 0.997 \pm 0.000 |
| | PR-AUC | 0.339 \pm 0.142 | 0.095 \pm 0.059 | 0.913 \pm 0.131 | 0.953 \pm 0.005 | 0.993 \pm 0.001 | 0.917 \pm 0.005 |
| 1+/1- | ROC-AUC | 0.776 \pm 0.122 | 0.731 \pm 0.088 | 0.998 \pm 0.001 | 0.996 \pm 0.000 | 0.997 \pm 0.000 | 0.998 \pm 0.000 |
| | PR-AUC | 0.227 \pm 0.180 | 0.058 \pm 0.032 | 0.909 \pm 0.052 | 0.981 \pm 0.003 | 0.982 \pm 0.006 | 0.964 \pm 0.002 |

Table S10: ROC-AUC and PR-AUC Scores for ML Models on DUD-E GPCR cxcr4 Target. Values are mean values with standard deviation over 20 rounds of testing. Best values are highlighted in bold text. The first column shows the composition of the support set as explained in text.

| DUD-E GPCR cxcr4 | Metric | RF | Graph Conv | SiameseNet | MatchingNet | ProtoNet | RelationNet |
|---------------------|---------|-------------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| 10+/10- | ROC-AUC | 0.994 \pm 0.005 | 0.965 \pm 0.020 | 0.570 \pm 0.028 | 0.801 \pm 0.030 | 0.631 \pm 0.045 | 0.858 \pm 0.014 |
| | PR-AUC | 0.938 \pm 0.043 | 0.697 \pm 0.134 | 0.014 \pm 0.002 | 0.085 \pm 0.022 | 0.107 \pm 0.020 | 0.133 \pm 0.038 |
| 5+/10- | ROC-AUC | 0.968 \pm 0.019 | 0.927 \pm 0.062 | 0.525 \pm 0.038 | 0.693 \pm 0.025 | 0.685 \pm 0.130 | 0.679 \pm 0.019 |
| | PR-AUC | 0.794 \pm 0.141 | 0.626 \pm 0.188 | 0.031 \pm 0.012 | 0.029 \pm 0.003 | 0.122 \pm 0.054 | 0.096 \pm 0.010 |
| 1+/10- | ROC-AUC | 0.866 \pm 0.086 | 0.828 \pm 0.108 | 0.520 \pm 0.087 | 0.764 \pm 0.021 | 0.684 \pm 0.032 | 0.734 \pm 0.018 |
| | PR-AUC | 0.380 \pm 0.140 | 0.361 \pm 0.162 | 0.039 \pm 0.066 | 0.066 \pm 0.027 | 0.041 \pm 0.009 | 0.108 \pm 0.009 |
| 1+/5- | ROC-AUC | 0.874 \pm 0.081 | 0.781 \pm 0.094 | 0.520 \pm 0.084 | 0.707 \pm 0.082 | 0.590 \pm 0.087 | 0.700 \pm 0.007 |
| | PR-AUC | 0.417 \pm 0.092 | 0.347 \pm 0.111 | 0.050 \pm 0.082 | 0.079 \pm 0.037 | 0.045 \pm 0.017 | 0.063 \pm 0.005 |
| 1+/1- | ROC-AUC | 0.833 \pm 0.088 | 0.689 \pm 0.150 | 0.545 \pm 0.040 | 0.593 \pm 0.034 | 0.732 \pm 0.022 | 0.496 \pm 0.010 |
| | PR-AUC | 0.375 \pm 0.124 | 0.174 \pm 0.151 | 0.091 \pm 0.102 | 0.041 \pm 0.008 | 0.104 \pm 0.012 | 0.035 \pm 0.005 |