DeltaDelta Neural Networks for Lead Optimization of Small Molecule Potency
Supplementary Information

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```python
import torch
import torch.nn as nn
import torch.nn.functional as F
from torch.autograd import Variable


def weights_init(m):
    """
    Xavier weight init.
    """
    if isinstance(m, nn.Conv3d) or isinstance(m, nn.Linear):
        torch.nn.init.xavier_normal(m.weight.data)
        if m.bias is not None:
            m.bias.data.fill_(0)


class DeltaDeltaG(nn.Module):
    """
    Delta-delta G simple prototype.
    """
    def __init__(self, input_channels=16):
        super(DeltaDeltaG, self).__init__()
        self.conv1 = nn.Conv3d(input_channels, 32, kernel_size=3)
        self.conv2 = nn.Conv3d(32, 32, kernel_size=3)
        self.max1 = nn.MaxPool3d(3)

        self.conv3 = nn.Conv3d(32, 3, kernel_size=3)
        self.lin1 = nn.Linear(192, 1, bias=False)
        self.dp1 = nn.Dropout(p=.5)
        self.apply(weights_init)

    def forward_once(self, x):
        x = F.relu(self.conv1(x))
        x = F.relu(self.conv2(x))
        x = self.max1(x)

        x = F.relu(self.conv3(x))
        x = x.view(x.shape[0], -1)
        return x

    def forward(self, x0, x1):
        d1 = self.forward_once(x0)
        d2 = self.forward_once(x1)
        diff = self.dp1(d1 - d2)
        return self.lin1(diff)
```

Listing 1: Two-legged three-dimensional convolutional neural network architecture used in this study. Weights are fixed in both legs, and a difference in latent space (representing difference in binding) is then performed.

Supplementary Table 1: Descriptive information regarding the complexes taken from Wang *et al.* and Mobley *et al.*

Target	**PDB Id.**	**# ligands**	**Affinity range (kcal / mol)**
BRD4	(a)	8	4.46 [a]
BACE	4DJW	36	3.5
CDK2	1H1R	16	4.2
JNK1	2GMX	21	3.4
MCL1	4HW3	42	4.2
P38	3FLY	34	3.8
PTP1B	2QBS	23	5.1
Thrombin	2ZFF	11	1.7
TYK2	4GIH	16	4.3

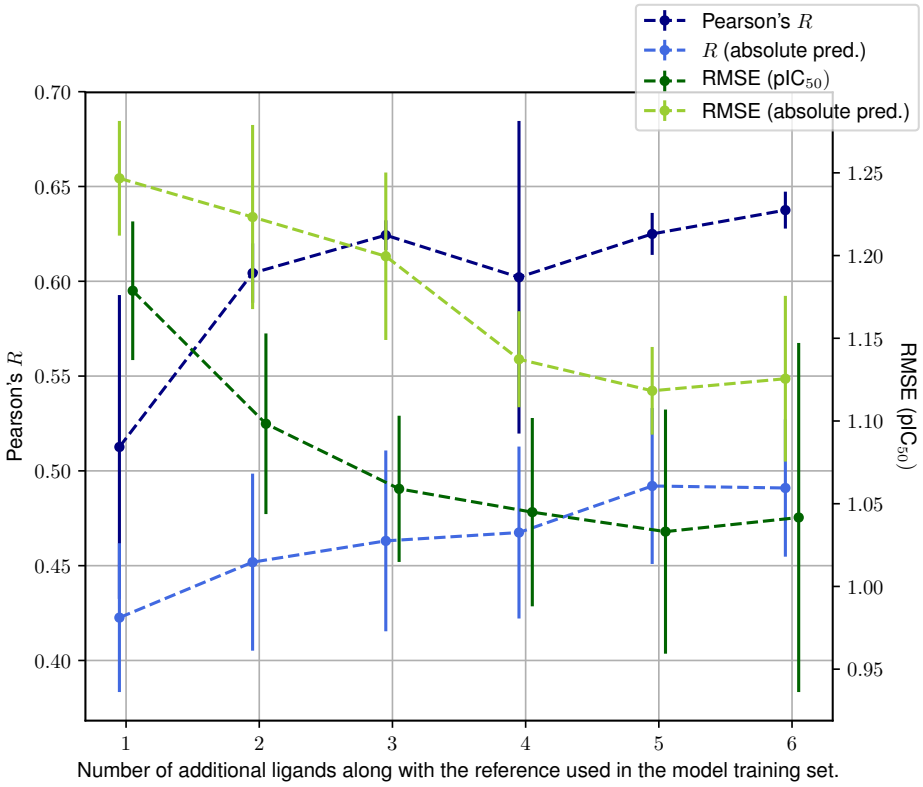
[a]Complexes taken from github.com/MobleyLab/benchmarksets, with experimental and FEP validation provided in several publications [3, 4]

Supplementary Table 2: Descriptive information regarding the series from Janssen R&D.

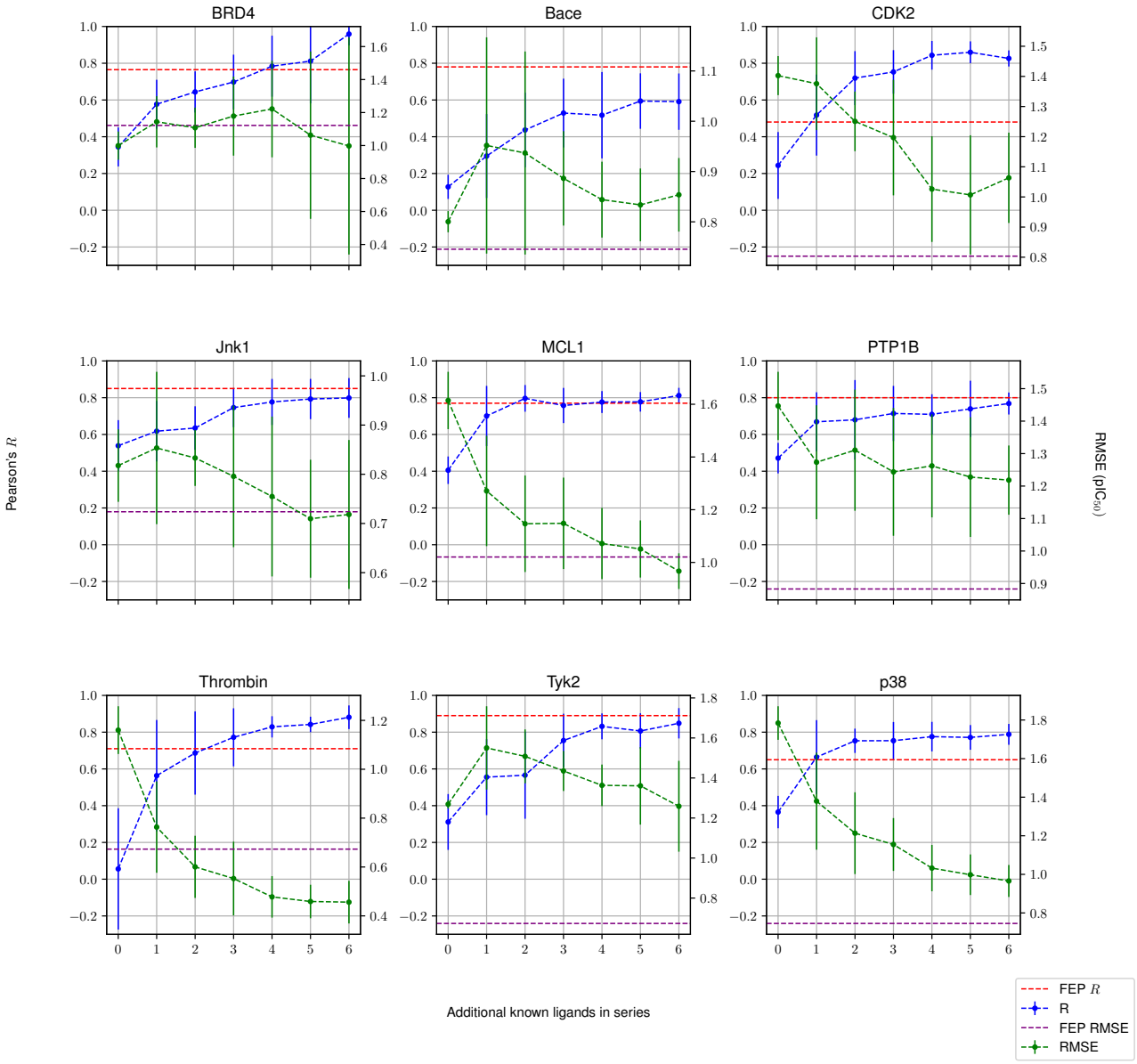
Target	**Set no.**	**# ligands**	**Affinity range (pIC_{50})**
PDE2	1	900	5.78
PDE2	2	303	4.66
PDE2	3	278	3.86
PDE3	1	218	3.57
PDE3	2	48	1.85
PDE3	3	65	2.02
PDE10	1	166	3.22
PDE10	2	270	3.18
PDE10	3	216	2.39
ROS1	-	165	3.39
BACE	-	229	3.89

Supplementary Table 3: Rules defined for the 3-dimensional descriptors described in this work.

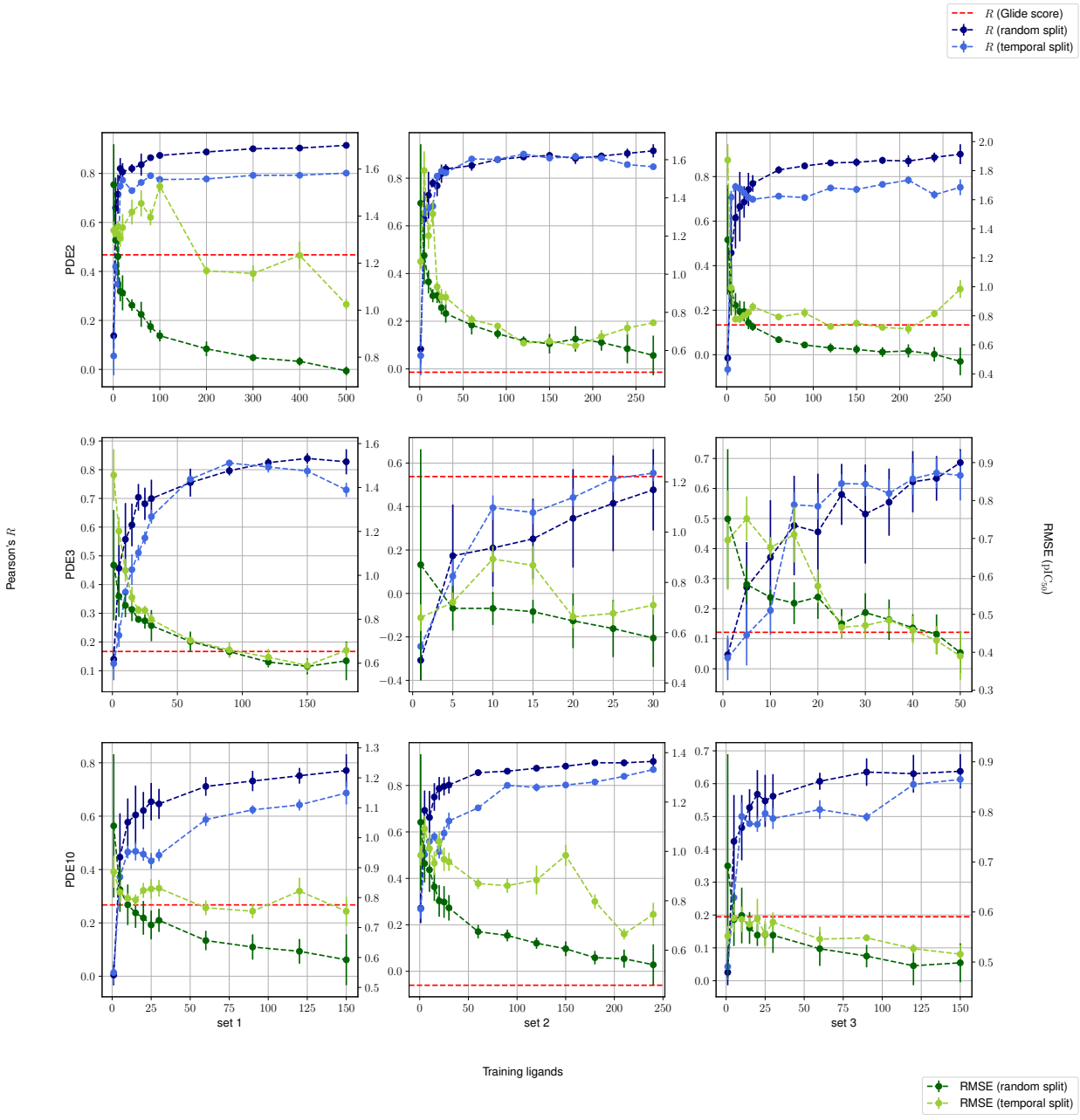
Property	**Rule**
Hydrophobic	Aliphatic or aromatic C
Aromatic	Aromatic C
Hydrogen bond acceptor	Acceptor 1 H-bond or S Spherical N Acceptor 2 H-bonds or S Spherical O Acceptor 2 H-bonds S
Hydrogen bond donor	Donor 1 H-bond or Donor S Spherical H with either O or N partner
Positive ionizable	Gasteiger positive charge
Negative ionizable	Gasteiger negative charge
Metallic	Mg, Zn, Mn, Ca or Fe
Excluded volume	All atom types



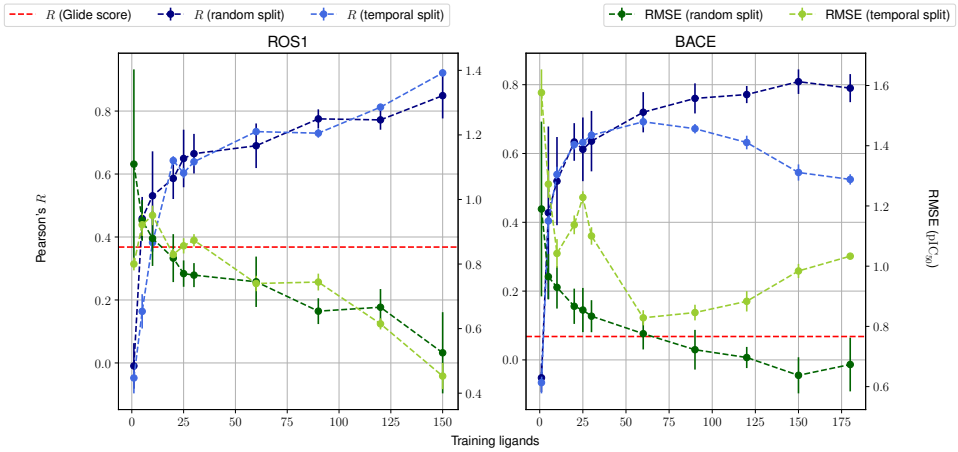
Supplementary Figure 1: Average Pearson's correlation coefficient R and RMSE (± 1 standard deviation) based on 25 independent runs on the BindingDB protein-ligand validation sets, with varying number of ligands in training and test and comparison against an identically-trained absolute binding affinity predictor.



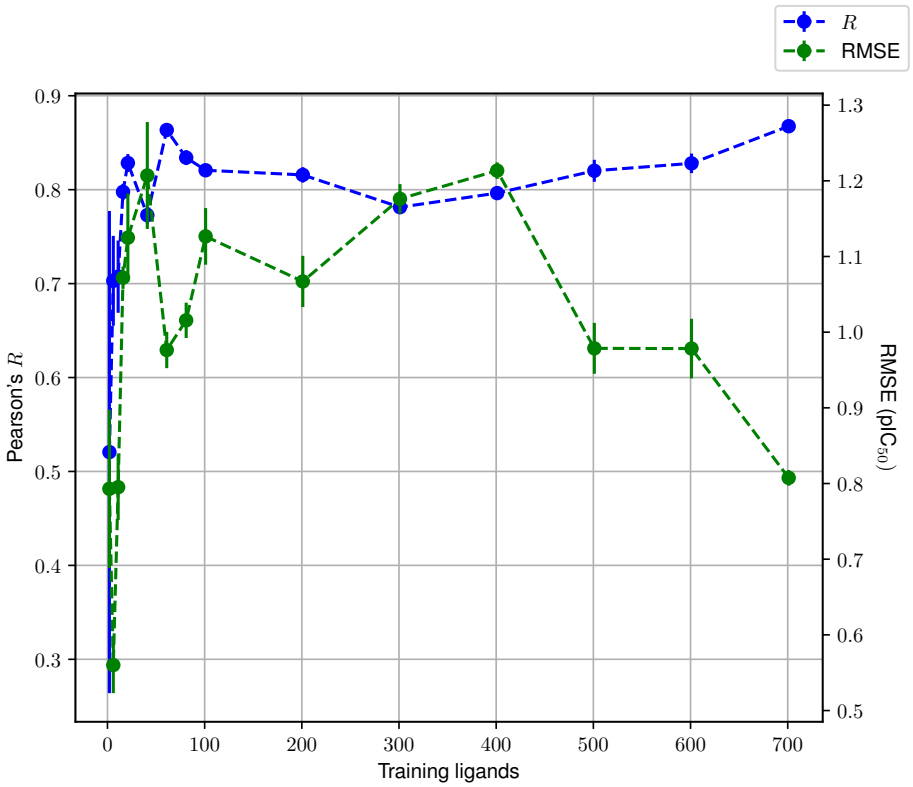
Supplementary Figure 2: Average Pearson's correlation coefficient R and RMSE (± 1 standard deviation) based on 25 independent runs on the Schrödinger dataset [1] and BRD4 inhibitor series [2] with reference reported FEP performance. For the BRD4 series, an average FEP performance between two studies was taken for reference [3, 4].



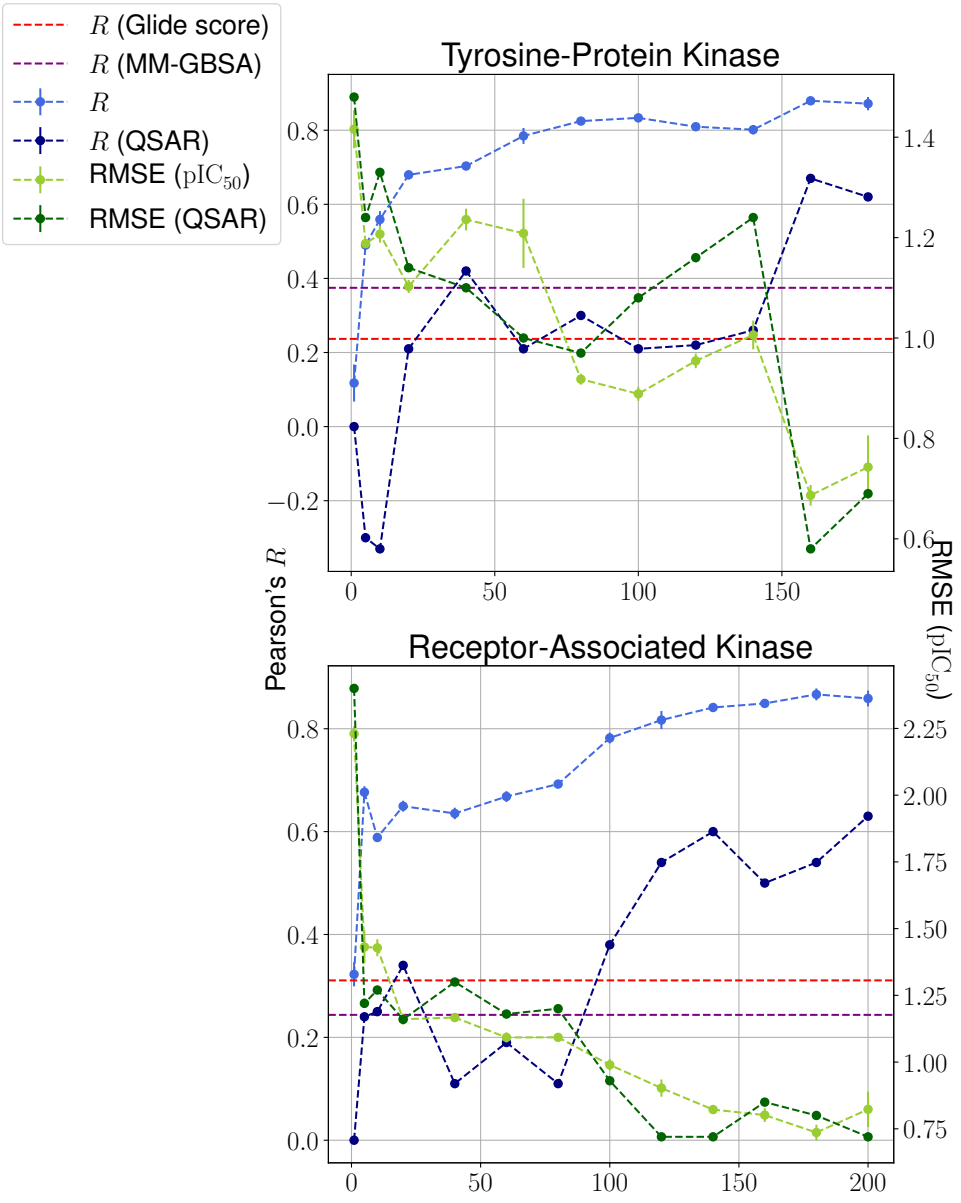
Supplementary Figure 3: Average Pearson's correlation coefficient R and RMSE (± 1 standard deviation) based on 25 independent runs on the Janssen PDE sets, using both a random and a temporal split and a Glide score baseline.



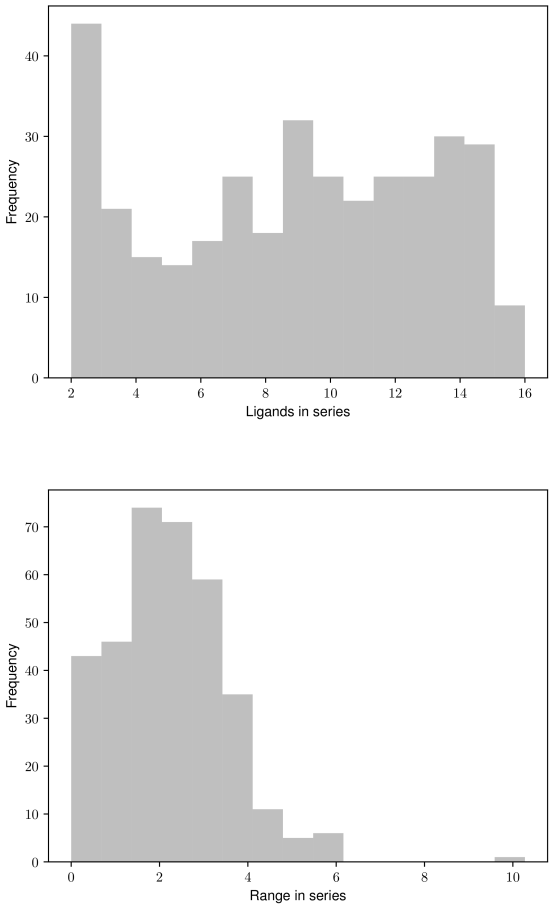
Supplementary Figure 4: Average Pearson's correlation coefficient R and RMSE (± 1 standard deviation) based on 25 independent runs on the Janssen ROS1 and BACE sets, using both a random and a temporal split and a Glide score baseline.



Supplementary Figure 5: Pearson's correlation coefficient R and RMSE (± 1 standard deviation) based on 25 independent runs on the Janssen PDE2 first set using a chemical similarity based split.



Supplementary Figure 6: Average Pearson's correlation coefficient R and RMSE (± 1 standard deviation) based on 5 independent runs on the Biogen Tyrosine-Protein Kinase and Receptor-Associated Kinase sets, using temporal split and with MM-GBSA, Glide score, and a random forest QSAR model (MACCS + ECFP4 + rdkit descriptors) as baselines.



Supplementary Figure 7: Histograms of available ligands and range per congeneric series in the BindingDB database.

References

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