Supporting Information

Bringing clarity to the prediction of protein-ligand binding free energies via "blurring"

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GAFF Parameter Files for the Ligands (.frcmod)

Benzene:

remark goes here
MASS

BOND

ANGLE

DIHE

IMPROPER
ca-ca-ca-ha 1.1 180.0 2.0 General improper torsional angle
(2 general atom types)

NONBON

Benzofuran:

remark goes here
MASS

BOND

ANGLE

DIHE
cc-cd-ca-ca 1 2.550 180.000 2.000 same as X -c2-ca-X
cd-cc-os-ca 1 1.050 180.000 2.000 same as X -c2-os-X
ca-ca-cd-ha 1 2.550 180.000 2.000 same as X -c2-ca-X
ca-os-cc-h4 1 1.050 180.000 2.000 same as X -c2-os-X

IMPROPER
cd-h4-cc-os 1.1 180.0 2.0 Using default value
ca-cc-cd-ha 1.1 180.0 2.0 Using default value
ca-ca-ca-cd 1.1 180.0 2.0 Using default value
ca-ca-ca-ha 1.1 180.0 2.0 General improper torsional angle
(2 general atom types)
ca-ca-ca-os 1.1 180.0 2.0 Using default value

NONBON

Indene:

remark goes here
MASS

BOND

ANGLE

DIHE
c2-ce-ca-ca 1 2.550 180.000 2.000 same as X -c2-ca-X
ca-ca-ce-ha 1 6.650 180.000 2.000 same as X -c2-ce-X

IMPROPER
c3-ce-c2-ha 1.1 180.0 2.0 Using default value
c2-ca-ce-ha 1.1 180.0 2.0 Using default value
ca-ca-ca-ha 1.1 180.0 2.0 General improper torsional angle
(2 general atom types)
ca-ca-ca-ce 1.1 180.0 2.0 Using default value

NONBON

Isobutylbenzene:

remark goes here
MASS

BOND

ANGLE

DIHE

IMPROPER
ca-ca-ca-ha 1.1 180.0 2.0 General improper torsional angle
(2 general atom types)

NONBON

Indole:

remark goes here
MASS

BOND

ANGLE

DIHE
cc-cd-ca-ca 1 2.550 180.000 2.000 same as X -c2-ca-X
ca-ca-cd-ha 1 2.550 180.000 2.000 same as X -c2-ca-X

IMPROPER
ca-cc-na-hn 1.1 180.0 2.0 General improper torsional angle
(2 general atom types)
cd-h4-cc-na 1.1 180.0 2.0 Using default value
ca-cc-cd-ha 1.1 180.0 2.0 Using default value
ca-ca-ca-ha 1.1 180.0 2.0 General improper torsional angle
(2 general atom types)
ca-ca-ca-na 1.1 180.0 2.0 Using default value
ca-ca-ca-cd 1.1 180.0 2.0 Using default value

NONBON

n-butyl benzene:

remark goes here
MASS

BOND

ANGLE

DIHE

IMPROPER
ca-ca-ca-ha 1.1 180.0 2.0 General improper torsional angle
(2 general atom types)

NONBON

p-xylene:

remark goes here
MASS

BOND

ANGLE

DIHE

IMPROPER
ca-ca-ca-ha 1.1 180.0 2.0 General improper torsional angle

(2 general atom types)

NONBON

o-xylene:

remark goes here
MASS

BOND

ANGLE

DIHE

IMPROPER
ca-ca-ca-ha 1.1 180.0 2.0 General improper torsional angle
(2 general atom types)

NONBON

Coordinate files for the initial ligand poses:

Benzene:

```
@<TRIPOS>MOLECULE
BNZ
  12   12    1    0    0
SMALL
bcc


@<TRIPOS>ATOM
     1 C1        25.9610    5.3060    4.7870 ca      1 BNZ     -0.130000
     2 C2        26.3840    5.0360    3.4850 ca      1 BNZ     -0.130000
     3 C3        27.3330    5.8560    2.8760 ca      1 BNZ     -0.130000
     4 C4        27.8610    6.9450    3.5700 ca      1 BNZ     -0.130000
     5 C5        27.4390    7.2150    4.8710 ca      1 BNZ     -0.130000
     6 C6        26.4890    6.3950    5.4800 ca      1 BNZ     -0.130000
     7 H1        25.2190    4.6650    5.2620 ha      1 BNZ      0.130000
     8 H2        25.9710    4.1850    2.9430 ha      1 BNZ      0.130000
     9 H3        27.6630    5.6460    1.8590 ha      1 BNZ      0.130000
```

```
    10 H4        28.6030    7.5860    3.0940 ha       1 BNZ      0.130000
    11 H5        27.8510    8.0660    5.4130 ha       1 BNZ      0.130000
    12 H6        26.1590    6.6050    6.4970 ha       1 BNZ      0.130000
@<TRIPOS>BOND
    1    1    2 ar
    2    1    6 ar
    3    1    7 1
    4    2    3 ar
    5    2    8 1
    6    3    4 ar
    7    3    9 1
    8    4    5 ar
    9    4   10 1
   10    5    6 ar
   11    5   11 1
   12    6   12 1
@<TRIPOS>SUBSTRUCTURE
    1 BNZ         1 TEMP              0 ****  ****    0 ROOT
```

Benzofuran:

```
@<TRIPOS>MOLECULE
BZF
  15    16     1     0     0
SMALL
bcc


@<TRIPOS>ATOM
     1 O1        27.6870    6.1320    2.2450 os       1 BZF     -0.204200
     2 C2        28.4050    7.3130    2.4230 cc       1 BZF     -0.014900
     3 C3        28.2790    7.9020    3.6620 cd       1 BZF     -0.177200
     4 C3A       27.4020    7.0140    4.3330 ca       1 BZF     -0.106800
     5 C4        26.8980    7.0750    5.6280 ca       1 BZF     -0.083000
     6 C5        26.0380    6.0520    6.0410 ca       1 BZF     -0.149000
     7 C6        25.7030    5.0060    5.1680 ca       1 BZF     -0.113000
     8 C7        26.2250    4.9710    3.8690 ca       1 BZF     -0.121000
     9 C7A       27.0780    5.9950    3.4740 ca       1 BZF      0.058100
    10 H2        28.9740    7.6140    1.5470 h4       1 BZF      0.189000
    11 H3        28.7450    8.8190    4.0180 ha       1 BZF      0.165000
    12 H4        27.1650    7.8910    6.2980 ha       1 BZF      0.138000
    13 H5        25.6250    6.0680    7.0490 ha       1 BZF      0.133000
    14 H6        25.0320    4.2150    5.5020 ha       1 BZF      0.135000
    15 H7        25.9720    4.1640    3.1840 ha       1 BZF      0.150000
@<TRIPOS>BOND
    1    1    2 1
    2    1    9 1
    3    2    3 2
    4    2   10 1
    5    3    4 1
```

```
    6    3   11 1
    7    4    5 ar
    8    4    9 ar
    9    5    6 ar
   10    5   12 1
   11    6    7 ar
   12    6   13 1
   13    7    8 ar
   14    7   14 1
   15    8    9 ar
   16    8   15 1
@<TRIPOS>SUBSTRUCTURE
    1 BZF         1 TEMP              0 ****  ****    0 ROOT
```

Indene:

```
@<TRIPOS>MOLECULE
DEN
  17    18     1     0     0
SMALL
bcc


@<TRIPOS>ATOM
     1 C1         27.8930    8.1940    4.3020 c3       1 DEN     -0.019900
     2 C2         28.2820    7.9480    2.8530 c2       1 DEN     -0.173200
     3 C3         27.7850    6.7910    2.3920 ce       1 DEN     -0.117200
     4 C4         26.3290    4.9370    3.4480 ca       1 DEN     -0.107000
     5 C5         25.6760    4.5490    4.6230 ca       1 DEN     -0.133000
     6 C6         25.7240    5.3600    5.7650 ca       1 DEN     -0.129000
     7 C7         26.4260    6.5710    5.7510 ca       1 DEN     -0.115000
     8 C8         27.0720    6.9450    4.5770 ca       1 DEN     -0.094300
     9 C9         27.0210    6.1420    3.4560 ca       1 DEN     -0.071800
    10 H11        28.7680    8.2500    4.9550 hc       1 DEN      0.074700
    11 H12        27.2920    9.1000    4.4130 hc       1 DEN      0.074700
    12 H22        28.8940    8.6500    2.2880 ha       1 DEN      0.142000
    13 H32        27.8990    6.3550    1.3970 ha       1 DEN      0.144000
    14 H4         26.2980    4.3140    2.5560 ha       1 DEN      0.134000
    15 H5         25.1250    3.6100    4.6490 ha       1 DEN      0.130000
    16 H6         25.2100    5.0460    6.6730 ha       1 DEN      0.130000
    17 H7         26.4660    7.2040    6.6370 ha       1 DEN      0.132000
@<TRIPOS>BOND
    1    1    2 1
    2    1    8 1
    3    1   10 1
    4    1   11 1
    5    2    3 2
    6    2   12 1
    7    3    9 1
    8    3   13 1
    9    4    5 ar
```

```
   10    4    9 ar
   11    4   14 1
   12    5    6 ar
   13    5   15 1
   14    6    7 ar
   15    6   16 1
   16    7    8 ar
   17    7   17 1
   18    8    9 ar
@<TRIPOS>SUBSTRUCTURE
    1 DEN         1 TEMP              0 ****  ****    0 ROOT
```

Isobutylbenzene:

```
@<TRIPOS>MOLECULE
I4B
  24    24     1     0     0
SMALL
bcc


@<TRIPOS>ATOM
     1 C1         27.2970    6.7760    3.4620 ca        1 I4B     -0.075300
     2 C2         27.2970    7.2570    4.7730 ca        1 I4B     -0.128500
     3 C3         26.5700    6.5980    5.7640 ca        1 I4B     -0.128500
     4 C4         25.8400    5.4530    5.4490 ca        1 I4B     -0.134000
     5 C5         25.8390    4.9680    4.1430 ca        1 I4B     -0.128500
     6 C6         26.5660    5.6270    3.1520 ca        1 I4B     -0.128500
     7 C1a        28.0920    7.4910    2.3770 c3        1 I4B     -0.036100
     8 C2a        27.2090    8.3350    1.4260 c3        1 I4B     -0.063700
     9 C3a        28.0620    8.9030    0.2710 c3        1 I4B     -0.091100
    10 C4a        26.5070    9.4890    2.1770 c3        1 I4B     -0.091100
    11 H2         27.8630    8.1520    5.0270 ha        1 I4B      0.131000
    12 H3         26.5710    6.9790    6.7850 ha        1 I4B      0.130000
    13 H4         25.2710    4.9390    6.2230 ha        1 I4B      0.130000
    14 H5         25.2690    4.0720    3.8950 ha        1 I4B      0.130000
    15 H6         26.5610    5.2420    2.1330 ha        1 I4B      0.131000
    16 H1a1       28.8520    8.1300    2.8340 hc        1 I4B      0.048200
    17 H1a2       28.6320    6.7410    1.7930 hc        1 I4B      0.048200
    18 H2a        26.4410    7.6880    0.9930 hc        1 I4B      0.050700
    19 H3a1       28.5350    8.0940   -0.2920 hc        1 I4B      0.034700
    20 H3a2       28.8470    9.5610    0.6530 hc        1 I4B      0.034700
    21 H3a3       27.4400    9.4750   -0.4210 hc        1 I4B      0.034700
    22 H4a1       27.2380   10.1470    2.6520 hc        1 I4B      0.034700
    23 H4a2       25.8390    9.1010    2.9500 hc        1 I4B      0.034700
    24 H4a3       25.9060   10.0850    1.4870 hc        1 I4B      0.034700
@<TRIPOS>BOND
         1    1    2 ar
    2    1    6 ar
    3    1    7 1
    4    2    3 ar
```

```
    5    2   11 1
    6    3    4 ar
    7    3   12 1
    8    4    5 ar
    9    4   13 1
   10    5    6 ar
   11    5   14 1
   12    6   15 1
   13    7    8 1
   14    7   16 1
   15    7   17 1
   16    8    9 1
   17    8   10 1
   18    8   18 1
   19    9   19 1
   20    9   20 1
   21    9   21 1
   22   10   22 1
   23   10   23 1
   24   10   24 1
@<TRIPOS>SUBSTRUCTURE
    1 I4B         1 TEMP              0 ****  ****    0 ROOT
```

Indole:

```
@<TRIPOS>MOLECULE
IND
  16    17     1     0     0
SMALL
bcc


@<TRIPOS>ATOM
     1 N1         28.5630    7.3530    3.2020 na       1 IND     -0.196400
     2 C2         28.3720    6.5850    2.0520 cc       1 IND     -0.109100
     3 C3         27.4350    5.6000    2.3200 cd       1 IND     -0.187200
     4 C4         26.1540    5.0890    4.4640 ca       1 IND     -0.082000
     5 C5         25.9840    5.5100    5.7880 ca       1 IND     -0.159000
     6 C6         26.7070    6.6040    6.2890 ca       1 IND     -0.113000
     7 C7         27.6110    7.2920    5.4710 ca       1 IND     -0.146000
     8 C8         27.7600    6.8520    4.1610 ca       1 IND     -0.047200
     9 C9         27.0580    5.7900    3.6750 ca       1 IND     -0.095800
    10 H1         29.1910    8.1450    3.3010 hn       1 IND      0.297700
    11 H2         28.9190    6.8040    1.1370 h4       1 IND      0.163000
    12 H3         27.0740    4.8440    1.6260 ha       1 IND      0.156000
    13 H4         25.5980    4.2410    4.0650 ha       1 IND      0.133000
    14 H5         25.2830    4.9830    6.4360 ha       1 IND      0.128000
    15 H6         26.5640    6.9200    7.3220 ha       1 IND      0.128000
    16 H7         28.1770    8.1420    5.8500 ha       1 IND      0.130000
@<TRIPOS>BOND
    1    1    2 1
```

```
    2    1    8 1
    3    1   10 1
    4    2    3 2
    5    2   11 1
    6    3    9 1
    7    3   12 1
    8    4    5 ar
    9    4    9 ar
   10    4   13 1
   11    5    6 ar
   12    5   14 1
   13    6    7 ar
   14    6   15 1
   15    7    8 ar
   16    7   16 1
   17    8    9 ar
@<TRIPOS>SUBSTRUCTURE
    1 IND         1 TEMP              0 ****  ****     0 ROOT
```

n-butyl benzene:

```
@<TRIPOS>MOLECULE
N4B
  24    24     1     0     0
SMALL
bcc


@<TRIPOS>ATOM
     1 C1         27.5030    7.0450    3.9350 ca        1 N4B     -0.075300
     2 C2         26.8940    7.0570    5.1920 ca        1 N4B     -0.129000
     3 C3         26.0750    6.0000    5.5870 ca        1 N4B     -0.128500
     4 C4         25.8600    4.9250    4.7270 ca        1 N4B     -0.134000
     5 C5         26.4670    4.9060    3.4720 ca        1 N4B     -0.128500
     6 C6         27.2870    5.9630    3.0780 ca        1 N4B     -0.129000
     7 C1a        28.3980    8.2010    3.5090 c3        1 N4B     -0.038100
     8 C2a        27.6080    9.4730    3.1170 c3        1 N4B     -0.073400
     9 C3a        26.6610    9.2820    1.9070 c3        1 N4B     -0.082400
    10 C4a        27.4130    8.9860    0.5930 c3        1 N4B     -0.092100
    11 H2         27.0580    7.8950    5.8690 ha        1 N4B      0.130500
    12 H3         25.6020    6.0160    6.5690 ha        1 N4B      0.130000
    13 H4         25.2200    4.0990    5.0350 ha        1 N4B      0.130000
    14 H5         26.3000    4.0660    2.7990 ha        1 N4B      0.130000
    15 H6         27.7560    5.9410    2.0960 ha        1 N4B      0.130500
    16 H1a1       29.0660    8.4500    4.3370 hc        1 N4B      0.047700
    17 H1a2       29.0450    7.8940    2.6840 hc        1 N4B      0.047700
    18 H2a1       27.0190    9.8020    3.9760 hc        1 N4B      0.041200
    19 H2a2       28.3150   10.2770    2.8960 hc        1 N4B      0.041200
    20 H3a1       25.9470    8.4810    2.1100 hc        1 N4B      0.043200
    21 H3a2       26.0790   10.1980    1.7750 hc        1 N4B      0.043200
    22 H4a1       28.1460    9.7690    0.3830 hc        1 N4B      0.031700
```

```
    23 H4a2      27.9300    8.0270    0.6400 hc       1 N4B      0.031700
    24 H4a3      26.7080    8.9470   -0.2400 hc       1 N4B      0.031700
@<TRIPOS>BOND
    1    1    2 ar
    2    1    6 ar
    3    1    7 1
    4    2    3 ar
    5    2   11 1
    6    3    4 ar
    7    3   12 1
    8    4    5 ar
    9    4   13 1
   10    5    6 ar
   11    5   14 1
   12    6   15 1
   13    7    8 1
   14    7   16 1
   15    7   17 1
   16    8    9 1
   17    8   18 1
   18    8   19 1
   19    9   10 1
   20    9   20 1
   21    9   21 1
   22   10   22 1
   23   10   23 1
   24   10   24 1
@<TRIPOS>SUBSTRUCTURE
    1 N4B        1 TEMP            0 ****  ****    0 ROOT
```

p-xylene:

```
@<TRIPOS>MOLECULE
PXY
  18    18     1     0     0
SMALL
bcc


@<TRIPOS>ATOM
     1 C1         26.6430    6.1260    4.7030 ca       1 PXY     -0.082300
     2 C2         26.7880    5.6320    3.4060 ca       1 PXY     -0.127000
     3 C3         27.2620    6.4580    2.3880 ca       1 PXY     -0.127000
     4 C4         27.5950    7.7860    2.6570 ca       1 PXY     -0.082300
     5 C5         27.4510    8.2810    3.9550 ca       1 PXY     -0.127000
     6 C6         26.9770    7.4540    4.9730 ca       1 PXY     -0.127000
     7 C1a        26.1260    5.2180    5.8050 c3       1 PXY     -0.052800
     8 C4a        28.1110    8.6780    1.5410 c3       1 PXY     -0.052800
     9 H2         26.5300    4.5970    3.1850 ha       1 PXY      0.130000
    10 H3         27.3710    6.0630    1.3790 ha       1 PXY      0.130000
    11 H5         27.7080    9.3150    4.1790 ha       1 PXY      0.130000
```

```
    12 H6        26.8690    7.8520    5.9810 ha       1 PXY      0.130000
    13 H1a1      26.0600    5.7460    6.7590 hc       1 PXY      0.043200
    14 H1a2      26.7920    4.3620    5.9370 hc       1 PXY      0.043200
    15 H1a3      25.1310    4.8430    5.5550 hc       1 PXY      0.043200
    16 H4a1      28.3020    9.6920    1.8980 hc       1 PXY      0.043200
    17 H4a2      29.0430    8.2790    1.1350 hc       1 PXY      0.043200
    18 H4a3      27.3800    8.7350    0.7310 hc       1 PXY      0.043200
@<TRIPOS>BOND
    1    1    2 ar
    2    1    6 ar
    3    1    7 1
    4    2    3 ar
    5    2    9 1
    6    3    4 ar
    7    3   10 1
    8    4    5 ar
    9    4    8 1
   10    5    6 ar
   11    5   11 1
   12    6   12 1
   13    7   13 1
   14    7   14 1
   15    7   15 1
   16    8   16 1
   17    8   17 1
   18    8   18 1
@<TRIPOS>SUBSTRUCTURE
    1 PXY         1 TEMP              0 ****  ****    0 ROOT
```

o-xylene:

```
@<TRIPOS>MOLECULE
OXE
  18    18     1     0     0
SMALL
bcc


@<TRIPOS>ATOM
     1 C1        27.1800    7.4890    4.4750 ca       1 OXE     -0.078300
     2 C2        27.6450    6.9130    3.2830 ca       1 OXE     -0.078300
     3 C3        27.3150    5.5880    2.9830 ca       1 OXE     -0.127000
     4 C4        26.5320    4.8380    3.8580 ca       1 OXE     -0.132000
     5 C5        26.0710    5.4090    5.0400 ca       1 OXE     -0.132000
     6 C6        26.3940    6.7290    5.3460 ca       1 OXE     -0.127000
     7 C11       27.5150    8.9290    4.8400 c3       1 OXE     -0.051800
     8 C21       28.5030    7.7040    2.3040 c3       1 OXE     -0.051800
     9 H3        27.6710    5.1310    2.0600 ha       1 OXE      0.130000
    10 H4        26.2800    3.8060    3.6160 ha       1 OXE      0.130000
    11 H5        25.4580    4.8250    5.7260 ha       1 OXE      0.130000
```

```
   12 H6        26.0280    7.1660    6.2750 ha       1 OXE      0.130000
   13 H111      27.0660    9.2110    5.7960 hc       1 OXE      0.043367
   14 H112      28.5950    9.0630    4.9260 hc       1 OXE      0.043367
   15 H113      27.1390    9.6160    4.0790 hc       1 OXE      0.043367
   16 H211      29.4250    8.0380    2.7850 hc       1 OXE      0.043367
   17 H212      28.7790    7.0990    1.4380 hc       1 OXE      0.043367
   18 H213      27.9630    8.5810    1.9410 hc       1 OXE      0.043367
@<TRIPOS>BOND
   1    1    2 ar
   2    1    6 ar
   3    1    7 1
   4    2    3 ar
   5    2    8 1
   6    3    4 ar
   7    3    9 1
   8    4    5 ar
   9    4   10 1
  10    5    6 ar
  11    5   11 1
  12    6   12 1
  13    7   13 1
  14    7   14 1
  15    7   15 1
  16    8   16 1
  17    8   17 1
  18    8   18 1
@<TRIPOS>SUBSTRUCTURE
   1 OXE         1 TEMP              0 ****  ****    0 ROOT
```

Table SI.1. Experimental binding free energies along with the Glide SP and Glide XP docking scores obtained for the top hits from the standard docking protocol.[1-3] The receptor structures were prepared with the Protein Preparation Wizard utility of the Schrodinger 2013-2 Suite using Epik state penalties.[1, 4] Protonation states were assigned via PROPKA at pH 7.0.[5, 6] Hydrogen positions were optimized with the OPLS 2005 force field.[7, 8] Docking was carried out using the Standard Precision (SP) and Extra Precision (XP) algorithms of Glide version 5.9. Experimental free energy of binding values are in kcal/mol.

PDB	Ligand	Exp. ΔG_{bind}	Glide SP Score for the top hit	Glide XP Score for the top hit
181L	benzene	-5.2	-5.67	-5.00
182L	2,3-benzofuran	-5.5	-6.93	-6.85
183L	indene	-5.1	-7.39	-7.25
184L	i-Butyl benzene	-6.5	-7.72	-7.61
185L	indole	-4.9	-6.75	-5.96
186L	n-Butyl benzene	-6.7	-7.03	-7.32
187L	p-xylene	-4.7	-6.71	-6.36
188L	o-xylene	-4.6	-6.75	-6.34

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