Supplementary Material:

A molecular mechanics model for imatinib and imatinib:kinase binding

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Force field for imatinib and several analogues

The force field is presented below in the format appropriate for the Charmm simulation program [1]. Atom types, atom charges, and chemical bonding information are contained in a "topology file". Bond lengths and force constants, bond angle values and associated force constants, dihedral parameters and van der Waals parameters are all contained in a "parameter file".

References

[1] Brooks, B., Brooks III, C. L., Mackerell Jr., A. D., Nilsson, L., Petrella, R. J., Roux, B., Won, Y., Archontis, G., Bartels, C., Boresch, S., Caflisch, A., Caves, L., Cui, Q., Dinner, A. R., Feig, M., Fischer, S., Gao, J., Hodoscek, M., Im, W., Kuczera, K., Lazaridis, T., Ma, J., Ovchinnikov, V., Paci, E., Pastor, R. W., Post, C. B., Pu, J. Z., Schaefer, M., Tidor, B., Venable, R. M., Woodcock, H. L., Wu, X., Yang, W., York, D. M., , and Karplus, M. CHARMM: The biomolecular simulation program. *J. Comp. Chem. 30* (2009), 1545–1614.

Topology file: top_all27_imatinib.inp

```
* CHARMM topology for imatinib and its analogues
* Alexey Aleksandrov & Thomas Simonson, 2009
* Thomas.Simonson at polytechnique.edu
27  1

! ring E
MASS  201  CA1  12.0109997    C
MASS  202  CA2  12.0109997    C
MASS  203  HB1  1.00800002    H
MASS  204  HB2  1.00800002    H
MASS  205  NA1  14.0070000    N
! ring D
MASS  206 CR21  12.0109997    C
MASS  207 CR22  12.0109997    C
MASS  208 CR23  12.0109997    C
MASS  209 HR21  1.00800002    H
MASS  210 HR22  1.00800002    H
MASS  211 HR23  1.00800002    H
MASS  212 HR24  1.00800002    H
MASS  213 NR21  14.0070000    N
MASS  214 NR22  14.0070000    N
! ring C
MASS  215 CR31  12.0109997    C
MASS  216 CR32  12.0109997    C
MASS  217 HR31  1.00800002    H
MASS  218 HR32  1.00800002    H
MASS  219 NR30  14.0070000    N
! ring A
MASS  220 CR51  12.0109997    C
MASS  221 CR52  12.0109997    C
MASS  222 CR53  12.0109997    C
MASS  223 HR51  1.00800002    H
MASS  224 HR52  1.00800002    H
MASS  225 HR53  1.00800002    H
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MASS  226 NR51  14.0070000    N
MASS  227 NR52  14.0070000    N


! plain imatinib protonated at N36
RESI  IMA    1.0000
! Ring E ==========================
GROUP
ATOM    N7  NA1 -0.626
ATOM    C8  CA1  0.154
ATOM    H8  HB1  0.159
ATOM    C6  CA1  0.154
ATOM    H6  HB1  0.159
GROUP
ATOM    C9  CA2 -0.156
ATOM    H9  HB2  0.156
GROUP
ATOM   C10  CA2 -0.203
ATOM   H10  HB2  0.203
GROUP
ATOM    C5  CA2  0.000
! Ring D ==========================
GROUP
ATOM   C11 CR23 -0.079
ATOM   H44 HR23  0.079
GROUP
ATOM    C4 CR22  0.321
ATOM    N3 NR21 -0.738
ATOM   C12 CR22  0.161
ATOM   H45 HR22  0.160
ATOM    N1 NR21 -0.738
ATOM    C2 CR21  0.984
ATOM   N13 NR22 -0.845
ATOM   H14 HR24  0.401
! Ring C ==========================
ATOM   C15 CR31  0.294
```

```
GROUP
ATOM   C16 CR31  0.000
GROUP
ATOM   C17  CT3 -0.270
ATOM   H46   HA  0.090
ATOM   H47   HA  0.090
ATOM   H48   HA  0.090
GROUP
ATOM   C18 CR31 -0.162
ATOM   H49 HR31  0.162
GROUP
ATOM   C21 CR31 -0.264
ATOM   H51 HR31  0.201
ATOM   C19 CR31 -0.264
ATOM   H50 HR31  0.201
ATOM   C20 CR32  0.291
ATOM   N22 NR30 -0.801
ATOM   H23 HR32  0.367
ATOM   C24   CC  0.862
ATOM   O25    O -0.553
ATOM   C26   CA -0.040
! Ring B ==========================
GROUP
ATOM   C27   CA -0.115
ATOM   H52   HP  0.115
GROUP
ATOM   C28   CA -0.115
ATOM   H53   HP  0.115
GROUP
ATOM   C30   CA -0.115
ATOM   H54   HP  0.115
GROUP
ATOM   C31   CA -0.115
ATOM   H55   HP  0.115
GROUP
ATOM   C29   CA  0.000
```

```
! Ring A ==========================
GROUP
ATOM   N36 NR51 -0.668
ATOM    H1 HR51  0.490
ATOM   C37 CR52 -0.357
ATOM   H62 HR52  0.235
ATOM   H63 HR52  0.235
ATOM   H64 HR52  0.235
ATOM   C38 CR53 -0.167
ATOM   H65 HR53  0.264
ATOM   H66 HR53  0.264
ATOM   C35 CR53 -0.167
ATOM   H60 HR53  0.264
ATOM   H61 HR53  0.264
ATOM   C34 CR53 -0.161
ATOM   H58 HR53  0.187
ATOM   H59 HR53  0.187
ATOM   C39 CR53 -0.161
ATOM   H67 HR53  0.187
ATOM   H68 HR53  0.187
ATOM   N33 NR52 -0.550
ATOM   C32 CR52 -0.136
ATOM   H56 HR52  0.184
ATOM   H57 HR52  0.184
! ring E
BOND    N7   C8   N7   C6
BOND    C8   H8   C8   C9
BOND    C6   H6   C6   C5
BOND    C9   H9   C9  C10
BOND   C10  H10  C10   C5
BOND    C5   C4
! ring D
BOND    C4   N3   C4  C11
BOND    N3   C2
BOND   C12  H45  C12   N1  C12  C11
BOND    N1   C2
```

```
BOND    C2  N13
BOND   N13  H14  N13  C15
BOND   C11  H44
! ring C
BOND   C16  C17  C16  C18  C16  C15
BOND   C18  H49  C18  C19
BOND   C15  C21
BOND   C21  H51  C21  C20
BOND   C19  H50  C19  C20
BOND   C20  N22
BOND   N22  H23  N22  C24
BOND   C24  O25  C24  C26
BOND   C26  C27  C26  C31
BOND   C17  H46  C17  H47  C17  H48
! ring B
BOND   C27  H52  C27  C28
BOND   C28  H53  C28  C29
BOND   C29  C32  C29  C30
BOND   C30  H54  C30  C31
BOND   C31  H55
! ring A
BOND   N36   H1  N36  C37  N36  C38  N36  C35
BOND   C37  H62  C37  H63  C37  H64
BOND   C38  H65  C38  H66  C38  C39
BOND   C35  H60  C35  H61  C35  C34
BOND   C34  H58  C34  H59  C34  N33
BOND   C39  H67  C39  H68  C39  N33
BOND   N33  C32
BOND   C32  H56  C32  H57

! neutral imatinib
PRES NIMA   0.00
! Ring A ==========================
GROUP
ATOM   N36 NR51 -0.561
ATOM   C37 CR52 -0.271
```

```
ATOM   H62 HR52  0.146
ATOM   H63 HR52  0.146
ATOM   H64 HR52  0.146
ATOM   C38 CR53 -0.109
ATOM   H65 HR53  0.154
ATOM   H66 HR53  0.154
ATOM   C35 CR53 -0.109
ATOM   H60 HR53  0.154
ATOM   H61 HR53  0.154
ATOM   C34 CR53 -0.110
ATOM   H58 HR53  0.154
ATOM   H59 HR53  0.154
ATOM   C39 CR53 -0.110
ATOM   H67 HR53  0.154
ATOM   H68 HR53  0.154
ATOM   N33 NR52 -0.567
ATOM   C32 CR52 -0.127
ATOM   H56 HR52  0.147
ATOM   H57 HR52  0.147
DELETE ATOM H1

! demethylated at C16
PRES R2H   0.000
GROUP
ATOM   C16   CR31  -0.200
ATOM   H16   HR31   0.200
DELETE ATOM C17
DELETE ATOM H46
DELETE ATOM H47
DELETE ATOM H48
BOND H16 C16
ANGLE H16 C16 C15
ANGLE H16 C16 C18
DIHE H16 C16 C15 C21
DIHE H16 C16 C15 N13
DIHE H16 C16 C18 C19
```

```
DIHE H16 C16 C18 H49

! methylated at C28
PRES R1M   0.000
GROUP
ATOM   C28   CA   0.00
GROUP
ATOM   C281  CT3 -0.27
ATOM   H28A  HA   0.09
ATOM   H28B  HA   0.09
ATOM   H28C  HA   0.09
DELETE ATOM H53
BOND C281 C28
BOND C281 H28A C281 H28B C281 H28C
ANGLE H28A C281  C28
ANGLE H28B C281  C28
ANGLE H28C C281  C28
ANGLE H28A C281 H28B
ANGLE H28A C281 H28C
ANGLE H28B C281 H28C
ANGLE C281  C28  C27
ANGLE C281  C28  C29
DIHE  C281  C28  C27  C26
DIHE  C281  C28  C27  H52
DIHE  C281  C28  C29  C30
DIHE  C281  C28  C29  C32
DIHE  H28A C281  C28  C27
DIHE  H28A C281  C28  C29
DIHE  H28B C281  C28  C27
DIHE  H28B C281  C28  C29
DIHE  H28C C281  C28  C27
DIHE  H28C C281  C28  C29

! chlorinated at C28
PRES R1CL   0.000
GROUP
```

```
ATOM   C28   CA   -0.010
ATOM   CL1  CLA    0.010
DELETE ATOM H53
BOND CL1  C28
ANGLE CL1  C28  C29
ANGLE CL1  C28  C27
DIHE  CL1  C28  C27  C26
DIHE  CL1  C28  C27  H52
DIHE  CL1  C28  C29  C30
DIHE  CL1  C28  C29  C32

! nytrogen at C9
PRES X1N   0.000
GROUP
ATOM   N7  NA1  -0.632
ATOM   C8  CA1   0.328
ATOM   H8  HB1   0.204
ATOM   C6  CA1   0.203
ATOM   H6  HB1   0.163
ATOM   N9  NA1  -0.632
ATOM  C10  CA2   0.203
ATOM  H10  HB2   0.163
DELETE ATOM C9
DELETE ATOM H9
BOND N9  C8  N9  C10
ANGLE  N9   C8   N7
ANGLE  N9   C8   H8
ANGLE  N9  C10   C5
ANGLE  N9  C10  H10
ANGLE  C8   N9  C10
DIHE   N9   C8   N7   C6
DIHE   N9  C10   C5   C6
DIHE   N9  C10   C5   C4
DIHE   N7   C8   N9  C10
DIHE   H8   C8   N9  C10
DIHE   C8   N9  C10   C5
```

```
DIHE   C8   N9  C10  H10

END
```

Parameter file: par_all27_imatinib.inp

```
BONDS
NR51   HR51   550.30  0.9940 ! rA
NR51   CR52   297.50  1.4290
NR51   CR53   259.80  1.4190
CR52   HR52   429.80  1.0800
CR53   HR53   378.50  1.0910
CR53   CR53   316.90  1.4820
CR53   NR52   359.00  1.3880
NR52   CR52   359.80  1.4260

CR52   CA     341.60  1.4940 ! rA - rB

CLA    CA     407.80  1.7540 ! rB

NR30   CC     380.80  1.3910 ! rB - rC
CC     CA     430.70  1.4650

CR31   HR31   449.40  1.0800 ! rC
CR31   CR31   476.10  1.3630
CR31   CR32   453.20  1.3730
CR32   NR30   424.90  1.4120
NR30   HR32   590.60  1.0030
CT3    CR31   350.60  1.5120

CR22   CR22   524.80  1.3480 ! rC - rD
CR21   NR22   428.50  1.3930
NR22   HR24   586.70  1.0090
NR22   CR31   288.90  1.4130
CR22   CR21   398.30  1.3890

CR22   HR22   487.60  1.0770 ! rD
CR22   NR21   556.30  1.2920
CR22   CR23   452.70  1.3470
NR21   CR21   487.50  1.3290
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```
CR23    HR23    458.90  1.0760

CA2     CR22    349.10  1.4500 ! rD -- rE

NA1     CA1     519.50  1.3000 ! rE
CA1     HB1     451.00  1.0770
CA1     CA2     460.80  1.3600
CA2     HB2     452.90  1.0760
CA2     CA2     479.30  1.3560

NA1     CA2     392.20  1.2800

ANGLES
NR51    CR52    HR52     59.10   104.50 ! rA
HR52    CR52    HR52     50.30   111.90
NR51    CR53    HR53     49.30   102.70
NR51    CR53    CR53     49.90   111.50
HR51    NR51    CR52     45.70   107.60
HR51    NR51    CR53     35.50   116.60
CR52    NR51    CR53     44.30   112.30
CR53    NR51    CR53     21.20   116.70
CR53    CR53    HR53     42.80   113.60
CR53    CR53    NR52     57.40   112.00
HR53    CR53    HR53     43.10   113.50
CR53    NR52    CR53     27.10    80.40
CR53    NR52    CR52     40.30   105.10
HR53    CR53    NR52     54.00   114.90
NR52    CR52    HR52     55.60   109.10

NR52    CR52    CA       73.50   111.10 ! rA - rB
CR52    CA      CA       49.60   117.60
HR52    CR52    CA       53.80   111.00

CR22    NR21    CR21     61.30   119.40 ! rB
CR22    CR23    CR22     64.10   113.30
CR22    CR23    HR23     37.80   123.80
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HR22    CR22    NR21     43.60   115.90
HR22    CR22    CR23     46.00   120.80
NR21    CR22    CR23     47.60   122.90
NR21    CR21    NR21     66.30   127.70
NR21    CR21    NR22     94.10   118.10
CR21    NR22    HR24     49.70   124.80
CLA     CA      CA       64.60   118.00

CR32    NR30    CC       39.80   121.90 ! rB - rC
HR32    NR30    CC       10.10   115.50
NR30    CC      O        94.00   126.70
NR30    CC      CA       62.50   112.50
CC      CA      CA       93.30   113.10
O       CC      CA      107.40   125.20

CT3     CR31    CR31     54.60   132.50 ! rC
HA      CT3     CR31     50.70   109.90
CR31    CR31    HR31     33.60   125.50
CR31    CR31    CR31     66.40   134.20
CR31    CR31    CR32     34.40   135.50
CR31    CR32    CR31     62.60   127.90
CR31    CR32    NR30     63.50   130.10
HR31    CR31    CR32     48.30   124.40
CR32    NR30    HR32     63.60   111.10
HR32    NR30    HR32     46.40   101.90

CR21    NR22    CR31     80.50   122.20 ! rC - rD
NR22    CR31    CR31     78.50   124.90
HR24    NR22    CR31     72.80   115.40

CA1     CA2     CR22     52.60   116.80 ! rD - rE
CA2     CA2     CR22     23.70   118.70
CA2     CR22    NR21     75.40   116.80
CA2     CR22    CR23     39.50   125.00

NA1     CA1     HB1      52.20   115.90 ! rE
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```
NA1     CA1     CA2     104.40   124.70
CA1     NA1     CA1       5.20   118.70
CA1     CA2     HB2      41.90   120.00
CA1     CA2     CA2      21.90   116.60
HB1     CA1     CA2      43.00   119.30
CA2     CA2     HB2      42.10   120.20
CA2     CA2     CA2      70.10   117.60

NA1     CA1     NA1     166.50   130.10
CA1     NA1     CA2      22.90   115.80
NA1     CA2     HB2      63.50   118.50
NA1     CA2     CA2     134.90   122.90

DIHEDRALS
HB1     CA1     NA1     CA1      6.60   2  180.0 ! rE
CA1     CA2     CA2     CA2      5.30   2  180.0
CA1     CA2     CA2     HB2      3.20   2  180.0
CA2     CA1     NA1     CA1      4.60   2  180.0
HB2     CA2     CA1     NA1      3.70   2  180.0
HB2     CA2     CA1     HB1      3.00   2  180.0
CA2     CA2     CA1     NA1      4.20   2  180.0
CA2     CA2     CA1     HB1      4.60   2  180.0
HB2     CA2     CA2     HB2      4.80   2  180.0
CA2     CA2     CA2     HB2      4.00   2  180.0

CR22    CA2     CA1     NA1      6.80   2  180.0 ! rD - rE
CR22    CA2     CA1     HB1      4.50   2  180.0
CR22    CA2     CA2     CA2      1.80   2  180.0
CR22    CA2     CA2     HB2      3.50   2  180.0
CR22    CR23    CR22    CA2      4.90   2  180.0
HR23    CR23    CR22    CA2      4.70   2  180.0
CR21    NR21    CR22    CA2      2.90   2  180.0
NR21    CR22    CA2     CA1      0.30   1    0.0
NR21    CR22    CA2     CA1      1.10   2  180.0
NR21    CR22    CA2     CA2      0.00   1    0.0
NR21    CR22    CA2     CA2      1.70   2  180.0
```

```
CR23   CR22   CA2    CA1      0.10   1    0.0
CR23   CR22   CA2    CA1      1.30   2  180.0
CR23   CR22   CA2    CA2      0.40   1    0.0
CR23   CR22   CA2    CA2      0.90   2  180.0

CR22   CR23   CR22   HR22     2.10   2  180.0 ! rD
CR22   CR23   CR22   NR21     3.20   2  180.0
CR21   NR21   CR22   HR22    11.40   2  180.0
CR21   NR21   CR22   CR23     9.30   2  180.0
NR21   CR21   NR21   CR22     3.70   2  180.0
HR23   CR23   CR22   HR22     3.20   2  180.0
HR23   CR23   CR22   NR21     3.40   2  180.0

NR22   CR31   CR31   CT3      4.10   2  180.0 ! rC - rD
CR22   CR21   NR21   CR22     4.10   2  180.0
NR22   CR21   NR21   CR22     6.60   2  180.0
HR22   CR22   CR22   HR22     4.90   2  180.0
HR22   CR22   CR22   CR23     6.80   2  180.0
CR21   CR22   CR22   HR22     6.60   2  180.0
CR21   CR22   CR22   CR23     6.00   2  180.0
NR21   CR21   CR22   CR22     2.50   2  180.0
NR21   CR21   CR22   HR22     0.80   2  180.0
NR22   CR21   CR22   CR22     2.70   2  180.0
NR22   CR21   CR22   HR22     3.00   2  180.0
CR22   CR23   CR22   CR22     6.30   2  180.0
HR23   CR23   CR22   CR22     4.00   2  180.0
CR31   CR31   NR22   CR21     0.80   2  180.0
CR31   CR31   NR22   HR24     1.00   2  180.0
HR24   NR22   CR21   CR22     1.50   2  180.0
HR24   NR22   CR21   NR21     1.50   2  180.0
CR31   NR22   CR21   CR22     0.70   2  180.0
CR31   NR22   CR21   NR21     0.70   2  180.0
NR22   CR31   CR31   CR31     2.10   2  180.0
HR31   CR31   CR31   NR22     1.90   2  180.0
CR32   CR31   CR31   NR22     1.90   2  180.0
```

```
HR31    CR31    CR31    HR31     1.90   2  180.0 ! rC
HR31    CR31    CR31    CR31     3.60   2  180.0
CR31    CR31    CR31    CR31     2.90   2  180.0
CR31    CR32    CR31    CR31     2.50   2  180.0
CR31    CR32    CR31    HR31     3.80   2  180.0
NR30    CR32    CR31    CR31     5.10   2  180.0
NR30    CR32    CR31    HR31     5.90   2  180.0
CR32    CR31    CR31    CR31     3.70   2  180.0
CR32    CR31    CR31    HR31     5.90   2  180.0
HR32    NR30    CR32    CR31     3.50   2  180.0
CR31    CR31    CT3     HA       0.10   3    0.0
HR31    CR31    CR31    CT3      3.50   2  180.0
CR31    CR31    CR31    CT3      4.10   2  180.0

CC      NR30    CR32    CR31     0.60   2  180.0 ! rB - rC
O       CC      NR30    CR32     1.40   2  180.0
O       CC      NR30    HR32     2.10   2  180.0
CA      CC      NR30    CR32     3.40   2  180.0
CA      CC      NR30    HR32     0.50   2  180.0
CA      CA      CC      NR30     1.20   2  180.0
CA      CA      CC      O        1.20   2  180.0
HP      CA      CA      CC       3.30   2  180.0
CA      CA      CA      CC       5.90   2  180.0

CLA     CA      CA      HP       3.00   2  180.0 ! rB
CLA     CA      CA      CA       3.00   2  180.0
CLA     CA      CA      CR52     3.00   2  180.0

NR52    CR53    CR53    HR53     0.10   3    0.0 ! rA - rB
CR52    CA      CA      CA       4.70   2  180.0
CR52    CA      CA      HP       4.80   2  180.0
CA      CA      CR52    NR52     0.30   3    0.0
CA      CA      CR52    HR52     0.20   3    0.0
CA      CR52    NR52    CR53     0.70   3    0.0
HR52    CR52    NR52    CR53     0.00   3    0.0
CT3     CA      CA      CR52     4.70   2  180.0
```

```
HR52   CR52   NR51   HR51     0.10   3    0.0 ! rA
HR52   CR52   NR51   CR53     0.10   3    0.0
HR53   CR53   NR51   HR51     0.10   3    0.0
HR53   CR53   NR51   CR52     0.10   3    0.0
HR53   CR53   NR51   CR53     0.00   3    0.0
CR53   CR53   NR51   HR51     0.10   3    0.0
CR53   CR53   NR51   CR52     0.20   3    0.0
CR53   CR53   NR51   CR53     0.10   3    0.0
CR53   NR52   CR53   CR53     0.30   3    0.0
CR53   NR52   CR53   HR53     0.20   3    0.0
HR53   CR53   CR53   NR51     0.10   3    0.0
HR53   CR53   CR53   HR53     0.10   3    0.0
NR52   CR53   CR53   NR51     0.20   3    0.0
CR52   NR52   CR53   CR53     0.50   3    0.0
CR52   NR52   CR53   HR53     0.10   3    0.0

CA1    NA1    CA1    NA1      3.00   2  180.0
CA1    CA2    CA2    NA1      3.00   2  180.0
NA1    CA1    NA1    CA2      3.00   2  180.0
HB1    CA1    NA1    CA2      3.00   2  180.0
CA1    NA1    CA2    CA2      3.00   2  180.0
CA1    NA1    CA2    HB2      3.00   2  180.0
NA1    CA2    CA2    CR22     3.00   2  180.0

IMPROPER

NONBONDED
CR51    0.000000  -0.070000     1.9924 ! rA
CR52    0.000000  -0.080000     2.0600
CR53    0.000000  -0.055000     2.1750
HR51    0.000000  -0.046000     0.2245
HR52    0.000000  -0.030000     1.3582
HR53    0.000000  -0.030000     1.3582
NR51    0.000000  -0.200000     1.8500
NR52    0.000000  -0.200000     1.8500
```

```
CR31    0.000000  -0.070000     1.9924 ! rC
CR32    0.000000  -0.070000     1.9924
HR31    0.000000  -0.030000     1.3582
HR32    0.000000  -0.046000     0.2245
NR30    0.000000  -0.200000     1.8500

CR21    0.000000  -0.070000     1.9924 ! rD
CR22    0.000000  -0.070000     1.9924
CR23    0.000000  -0.070000     1.9924
HR21    0.000000  -0.030000     1.3582
HR22    0.000000  -0.030000     1.3582
HR23    0.000000  -0.030000     1.3582
HR24    0.000000  -0.046000     0.2245
NR21    0.000000  -0.200000     1.8500
NR22    0.000000  -0.200000     1.8500

CA1     0.000000  -0.070000     1.9924 ! rE
CA2     0.000000  -0.070000     1.9924
HB1     0.000000  -0.030000     1.3582
HB2     0.000000  -0.030000     1.3582
NA1     0.000000  -0.200000     1.8500
```