Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

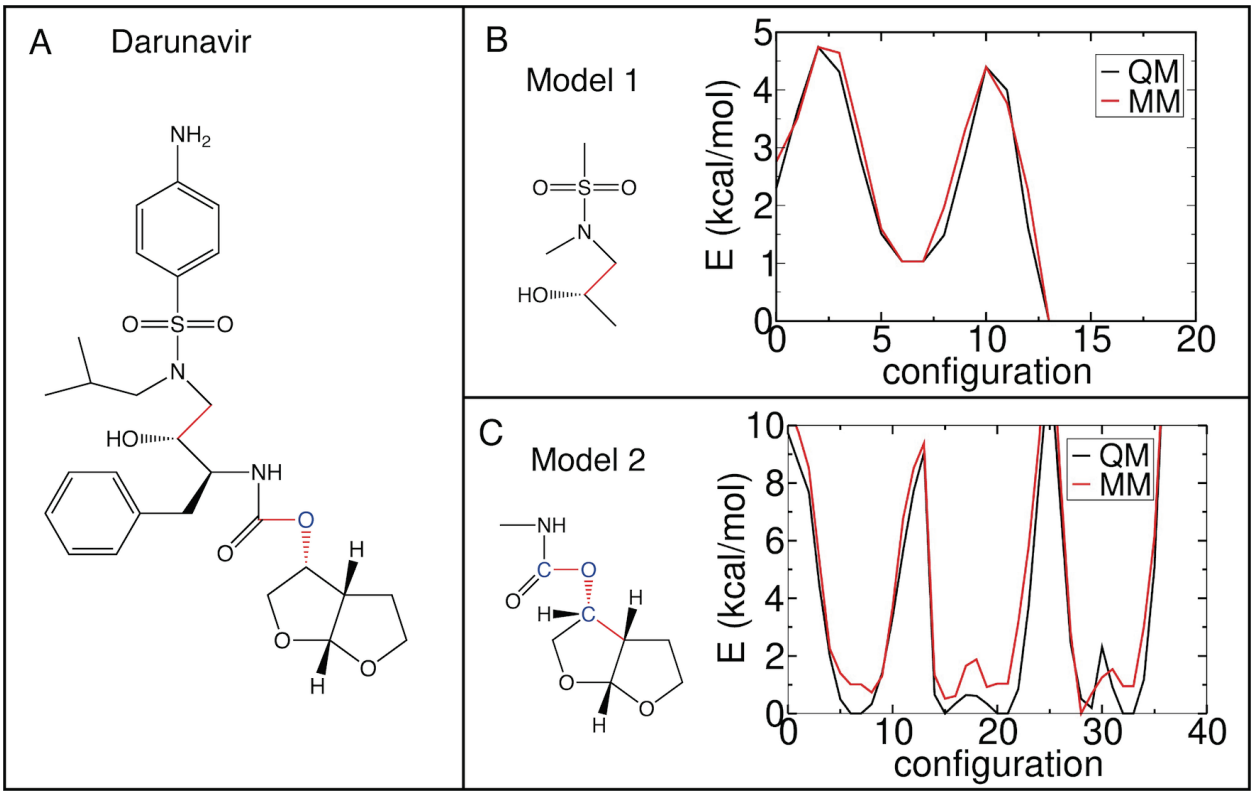

Figure S1. Parameterization of darunavir. A) Structure of darunavir. The bonds that involved dihedrals requiring optimization are shown in red. In addition, the blue colored oxygen indicates the center of the angle that required optimization. B) Model I and the corresponding fit of the dihedral scan. C) Model 2 and the corresponding fit of the dihedral scans. Atoms for which the angle parameter was fitted are shown in blue.

DRV parameter file:

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read param card flex append
* Parameters generated by analogy by
* CHARMM General Force Field (CGenFF) program version 2.2.0
*

! Penalties lower than 10 indicate the analogy is fair; penalties between 10
! and 50 mean some basic validation is recommended; penalties higher than
! 50 indicate poor analogy and mandate extensive validation/optimization.

BONDS
CG3C51 OG302   334.30     1.4110 ! drv1 , from CG3C51 OG301, penalty= 5

ANGLES
CG311  CG321  NG301    57.00    107.00 ! drv1 , from CG321 CG321 NG301, penalty= 0.6
CG3C52 CG3C51 OG302    58.00    106.50    8.00   2.56100 ! drv1 , from CG3C52 CG3C51 OG301, penalty= 0.5
CG3RC1 CG3C51 OG302    75.70    110.10 ! drv1 , from CG3RC1 CG3C51 OG303, penalty= 1
OG302  CG3C51 HGA1     45.90    108.50 ! drv1 , from OG301 CG3C51 HGA1, penalty= 0.5
CG2O6  NG2S1  CG311    60.00    120.00 ! drv1 , from CG2O6 NG2S1 CG321, penalty= 0.6
CG2O6  OG302  CG3C51   34.940   106.470 ! fftk optimized, original penalty 10

DIHEDRALS
OG2D1  CG2O6  NG2S1  CG311      4.0000  2   180.00 ! drv1 , from OG2D1 CG2O6 NG2S1 CG321, penalty= 0.6
OG2D1  CG2O6  NG2S1  CG311      0.9500  4     0.00 ! drv1 , from OG2D1 CG2O6 NG2S1 CG321, penalty= 0.6
OG302  CG2O6  NG2S1  CG311      4.0000  2   180.00 ! drv1 , from OG302 CG2O6 NG2S1 CG321, penalty= 0.6
OG302  CG2O6  NG2S1  CG311      0.9500  4     0.00 ! drv1 , from OG302 CG2O6 NG2S1 CG321, penalty= 0.6
NG2S1  CG2O6  OG302  CG3C51     2.7340  2   180.00 ! fftk optimized, original penalty 10
NG2S1  CG2O6  OG302  CG3C51     2.9150  4   180.00 ! fftk optimized, original penalty 10
NG2S1  CG2O6  OG302  CG3C51     0.4100  6     0.00 ! fftk optimized, original penalty 10
OG2D1  CG2O6  OG302  CG3C51     1.7310  2   180.00 ! fftk optimized, original penalty 10
OG2D1  CG2O6  OG302  CG3C51     2.9700  4     0.00 ! fftk optimized, original penalty 10
OG2D1  CG2O6  OG302  CG3C51     0.3980  6     0.00 ! fftk optimized, original penalty 10
CG321  CG311  CG311  OG311      0.1400  3     0.00 ! drv1 , from CG311 CG311 CG311 OG311, penalty= 0.6
CG311  CG311  CG321  CG2R61     0.0400  3     0.00 ! drv1 , from CG331 CG311 CG321 CG2R61, penalty= 1.5
CG311  CG311  CG321  NG301      0.1600  1   180.00 ! drv1 , from CG321 CG321 CG321 NG301, penalty= 4.6
CG311  CG311  CG321  NG301      0.3900  2     0.00 ! drv1 , from CG321 CG321 CG321 NG301, penalty= 4.6
CG331  CG311  CG321  NG301      1.315   1   180.00 ! fftk optimized, original penalty 4.9 (needed to improve next dihedral)
CG331  CG311  CG321  NG301      0.250   2     0.00 ! fftk optimized, original penalty 4.9 (needed to improve next dihedral)
CG331  CG311  CG321  NG301      1.306   4   180.00 ! fftk optimized, original penalty 4.9 (needed to improve next dihedral)
OG311  CG311  CG321  NG301      2.899   1   180.00 ! fftk optimized, original penalty 34.5
OG311  CG311  CG321  NG301      1.410   4   180.00 ! fftk optimized, original penalty 34.5
HGA1   CG311  CG321  NG301      0.1600  3     0.00 ! drv1 , from NG301 CG321 CG321 HGA2, penalty= 4
CG311  CG311  NG2S1  CG2O6      1.8000  1     0.00 ! drv1 , from CG311 CG311 NG2S1 CG2O1, penalty= 3.5
CG321  CG311  NG2S1  CG2O6      1.8000  1     0.00 ! drv1 , from CG321 CG311 NG2S1 CG2O1, penalty= 3.5
HGA1   CG311  NG2S1  CG2O6      0.0000  1     0.00 ! drv1 , from HGA1 CG311 NG2S1 CG2O1, penalty= 3.5
CG311  CG321  NG301  CG321      1.4200  1   180.00 ! drv1 , from CG321 CG321 NG301 CG321, penalty= 0.6
CG311  CG321  NG301  CG321      0.8200  2     0.00 ! drv1 , from CG321 CG321 NG301 CG321, penalty= 0.6
CG311  CG321  NG301  CG321      1.0200  3     0.00 ! drv1 , from CG321 CG321 NG301 CG321, penalty= 0.6
CG311  CG321  NG301  SG3O2      0.1000  1     0.00 ! drv1 , from CG321 CG321 NG301 SG3O2, penalty= 0.6
CG311  CG321  NG301  SG3O2      0.7000  2     0.00 ! drv1 , from CG321 CG321 NG301 SG3O2, penalty= 0.6
CG311  CG321  NG301  SG3O2      0.1000  3     0.00 ! drv1 , from CG321 CG321 NG301 SG3O2, penalty= 0.6
OG302  CG3C51 CG3C52 OG3C51     0.2000  3     0.00 ! drv1 , from OG301 CG3C51 CG3C52 OG3C51, penalty= 0.5
OG302  CG3C51 CG3C52 HGA2       0.1950  3   180.00 ! drv1 , from OG301 CG3C51 CG3C52 HGA2, penalty= 0.5
OG302  CG3C51 CG3RC1 CG3C52     1.4340  1   180.00 ! fftk optimized, original penalty 15
OG302  CG3C51 CG3RC1 CG3C52     1.1010  2     0.00 ! fftk optimized, original penalty 15
OG302  CG3C51 CG3RC1 CG3C52     2.8370  3   180.00 ! fftk optimized, original penalty 15
OG302  CG3C51 CG3RC1 CG3RC1     0.4500  2     0.00 ! drv1 , from OG303 CG3C51 CG3RC1 CG3RC1, penalty= 1
OG302  CG3C51 CG3RC1 CG3RC1     0.9000  6     0.00 ! drv1 , from OG303 CG3C51 CG3RC1 CG3RC1, penalty= 1
OG302  CG3C51 CG3RC1 HGA1       0.1500  3     0.00 ! drv1 , from OG303 CG3C51 CG3RC1 HGA1, penalty= 1
CG3C52 CG3C51 OG302  CG2O6      1.3950  1     0.00 ! fftk optimized, original penalty 76.9
CG3C52 CG3C51 OG302  CG2O6      1.4090  2   180.00 ! fftk optimized, original penalty 76.9
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CG3C52 CG3C51 OG302 CG2O6   1.4190 3   0.00 ! fftk optimized, original penalty 76.9
CG3C52 CG3C51 OG302 CG2O6   0.0480 4   0.00 ! fftk optimized, original penalty 76.9
CG3C52 CG3C51 OG302 CG2O6   0.6610 6   0.00 ! fftk optimized, original penalty 76.9
CG3RC1 CG3C51 OG302 CG2O6   2.6000 2   180.00 ! fftk optimized, original penalty 78
CG3RC1 CG3C51 OG302 CG2O6   1.8070 3   180.00 ! fftk optimized, original penalty 78
CG3RC1 CG3C51 OG302 CG2O6   0.6970 4   0.00 ! fftk optimized, original penalty 78
HGA1   CG3C51 OG302 CG2O6   0.0000 3   0.00 ! drv1 , from HGA2 CG321 OG302 CG2O6, penalty= 65, not optimized because kphi = 0.0

IMPROPERS

END
RETURN

DRV str file:

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* Toppar stream file generated by
* CHARMM General Force Field (CGenFF) program version 2.2.0
* For use with CGenFF version 4.0
*

read rtf card append
* Topologies generated by
* CHARMM General Force Field (CGenFF) program version 2.2.0
* using valence-based bond orders
*
36 1

! "penalty" is the highest penalty score of the associated parameters.
! Penalties lower than 10 indicate the analogy is fair; penalties between 10
! and 50 mean some basic validation is recommended; penalties higher than
! 50 indicate poor analogy and mandate extensive validation/optimization.

RESI DRV                0.000 ! param penalty=  78.000 ; charge penalty=  11.514
GROUP           ! CHARGE   CH_PENALTY
ATOM N1     NG2S3  -0.838 !    0.000
ATOM N2     NG301  -0.487 !    4.554
ATOM N3     NG2S1  -0.337 !    4.160
ATOM C1     CG2R61  0.054 !    0.000
ATOM C2     CG2R61 -0.110 !    0.000
ATOM C3     CG2R61 -0.110 !    0.000
ATOM C4     CG2R61  0.121 !    0.000
ATOM C5     CG2R61 -0.110 !    0.000
ATOM C6     CG2R61 -0.110 !    0.000
ATOM C7     CG321   0.083 !    1.971
ATOM C8     CG311  -0.079 !    3.623
ATOM C9     CG331  -0.270 !    2.182
ATOM C10    CG331  -0.270 !    2.182
ATOM C11    CG321   0.093 !   11.081
ATOM C12    CG311   0.139 !   11.514
ATOM C13    CG311   0.072 !    2.768
ATOM C14    CG2O6   0.224 !    7.919
ATOM C15    CG3C51  0.134 !    9.490
ATOM C16    CG3C52  0.017 !    2.505
ATOM C17    CG3RC1  0.069 !    0.050
ATOM C18    CG3C52  0.020 !    0.000
ATOM C19    CG3C52 -0.179 !    4.082
ATOM C20    CG3RC1  0.035 !    4.787
ATOM C21    CG321  -0.184 !    2.105
ATOM C22    CG2R61 -0.117 !    0.000
ATOM C23    CG2R61 -0.108 !    0.000
ATOM C24    CG2R61 -0.115 !    0.000
ATOM C25    CG2R61 -0.108 !    0.000
ATOM C26    CG2R61 -0.117 !    0.000
ATOM C27    CG2R61 -0.006 !    0.330
ATOM O1     OG2P1  -0.360 !    0.000
ATOM O2     OG2P1  -0.360 !    0.000
ATOM O3     OG311  -0.652 !    1.725
ATOM O4     OG2D1  -0.389 !    3.162
ATOM O5     OG302  -0.200 !    9.329
ATOM O6     OG3C51 -0.343 !    0.158
ATOM O7     OG3C51 -0.342 !    0.000
ATOM S      SG3O2   0.540 !    0.042
ATOM H1     HGP4    0.382 !    0.000
ATOM H2     HGP4    0.382 !    0.000
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ATOM H3     HGR61   0.115 !    0.000
ATOM H4     HGR61   0.115 !    0.000
ATOM H5     HGR61   0.115 !    0.000
ATOM H6     HGR61   0.115 !    0.000
ATOM H7     HGA2    0.090 !    0.000
ATOM H8     HGA2    0.090 !    0.000
ATOM H9     HGA1    0.090 !    0.300
ATOM H10    HGA3    0.090 !    0.000
ATOM H11    HGA3    0.090 !    0.000
ATOM H12    HGA3    0.090 !    0.000
ATOM H13    HGA3    0.090 !    0.000
ATOM H14    HGA3    0.090 !    0.000
ATOM H15    HGA3    0.090 !    0.000
ATOM H16    HGA2    0.090 !    0.000
ATOM H17    HGA2    0.090 !    0.000
ATOM H18    HGA1    0.090 !    0.300
ATOM H19    HGP1    0.419 !    0.000
ATOM H20    HGA1    0.090 !    0.175
ATOM H21    HGP1    0.322 !    0.000
ATOM H22    HGA1    0.090 !    2.500
ATOM H23    HGA2    0.090 !    0.025
ATOM H24    HGA2    0.090 !    0.025
ATOM H25    HGA1    0.090 !    0.000
ATOM H26    HGA2    0.090 !    0.000
ATOM H27    HGA2    0.090 !    0.000
ATOM H28    HGA2    0.090 !    0.000
ATOM H29    HGA2    0.090 !    0.000
ATOM H30    HGA1    0.090 !    0.050
ATOM H31    HGA2    0.090 !    0.000
ATOM H32    HGA2    0.090 !    0.000
ATOM H33    HGR61   0.115 !    0.000
ATOM H34    HGR61   0.115 !    0.000
ATOM H35    HGR61   0.115 !    0.000
ATOM H36    HGR61   0.115 !    0.000
ATOM H37    HGR61   0.115 !    0.000
            ! Bond order
BOND N1   C1   ! 1
BOND N1   H1   ! 1
BOND N1   H2   ! 1
BOND N2   C7   ! 1
BOND N2   C11  ! 1
BOND N2   S    ! 1
BOND N3   C14  ! 1
BOND N3   H21  ! 1
BOND N3   C13  ! 1
BOND C1   C2   ! 2
BOND C1   C6   ! 1
BOND C2   C3   ! 1
BOND C2   H3   ! 1
BOND C3   C4   ! 2
BOND C3   H4   ! 1
BOND C4   C5   ! 1
BOND C4   S    ! 1
BOND C5   C6   ! 2
BOND C5   H5   ! 1
BOND C6   H6   ! 1
BOND C7   C8   ! 1
BOND C7   H7   ! 1
BOND C7   H8   ! 1
BOND C8   C9   ! 1
BOND C8   C10  ! 1
BOND C8   H9   ! 1
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BOND C9   H10  ! 1
BOND C9   H11  ! 1
BOND C9   H12  ! 1
BOND C10  H13  ! 1
BOND C10  H14  ! 1
BOND C10  H15  ! 1
BOND C11  C12  ! 1
BOND C11  H16  ! 1
BOND C11  H17  ! 1
BOND C12  C13  ! 1
BOND C12  O3   ! 1
BOND C12  H18  ! 1
BOND C13  C21  ! 1
BOND C13  H20  ! 1
BOND C14  O4   ! 2
BOND C14  O5   ! 1
BOND C15  C16  ! 1
BOND C15  C20  ! 1
BOND C15  H22  ! 1
BOND C15  O5   ! 1
BOND C16  O6   ! 1
BOND C16  H23  ! 1
BOND C16  H24  ! 1
BOND C17  C20  ! 1
BOND C17  O7   ! 1
BOND C17  H25  ! 1
BOND C17  O6   ! 1
BOND C18  C19  ! 1
BOND C18  H26  ! 1
BOND C18  H27  ! 1
BOND C18  O7   ! 1
BOND C19  C20  ! 1
BOND C19  H28  ! 1
BOND C19  H29  ! 1
BOND C20  H30  ! 1
BOND C21  C27  ! 1
BOND C21  H31  ! 1
BOND C21  H32  ! 1
BOND C22  C23  ! 2
BOND C22  C27  ! 1
BOND C22  H33  ! 1
BOND C23  C24  ! 1
BOND C23  H34  ! 1
BOND C24  C25  ! 2
BOND C24  H35  ! 1
BOND C25  C26  ! 1
BOND C25  H36  ! 1
BOND C26  C27  ! 2
BOND C26  H37  ! 1
BOND O1   S    ! 2
BOND O2   S    ! 2
BOND O3   H19  ! 1
IMPR N1    H2    H1    C1
IMPR C14   N3    O4    O5

END
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