Charmm force field parameters for paromomycin

Charmm force field parameters[1,2] for paromomycin were combined from already existing parameters for sugar rings (`par_all22_prot.inp` Charmm file), lipids, amino alcohols (`par_all22_lipid.inp` Charmm file), and ribose (`par_all27_na.prm` Charmm file). Paromomycin was assumed in a fully protonated state, carrying a total charge of $+5e$ due to its five amino groups. Atomic partial charges were determined as ESP charges for paromomycin minimized using MP2 method and 6-31G* basis set. Necessary calculations were carried out with the Gaussian package[3]. The complete parameter set and Charmm topology files are listed below.

In order to evaluate the validity of the obtained parameters, an MD simulation of paromomycin in a box of 1600 TIP3P[4] water molecules was performed, and results were compared with the available experimental data. The system was neutralized with five Cl^- ions. Furthermore, four Na^+, and four Cl^- ions were added to mimic intracellular salt concentration of 150 mmol per liter. Simulations, corresponding to NPT ensemble with periodic boundary conditions, were performed with the use of NAMD package[5]. Electrostatic interactions were calculated using the Particle Mesh Ewald[6] summation method. The SHAKE[7] algorithm was applied for bonds involving hydrogen atoms, allowing for a time step of 2 fs. The collected data correspond to 300 ps production phase.

From the obtained trajectory several inter-proton distances, and distribution of ϕ/Ψ angles for sugar linkages were extracted. Their comparison with experimental NMR data obtained for neomycin[8] (apart from one 6' amino group, neomycin is identical to paromomycin) is presented in Table 1. To compare the MD derived ϕ/Ψ graphs (Figure 1) with the NMR data see the original paper[8].

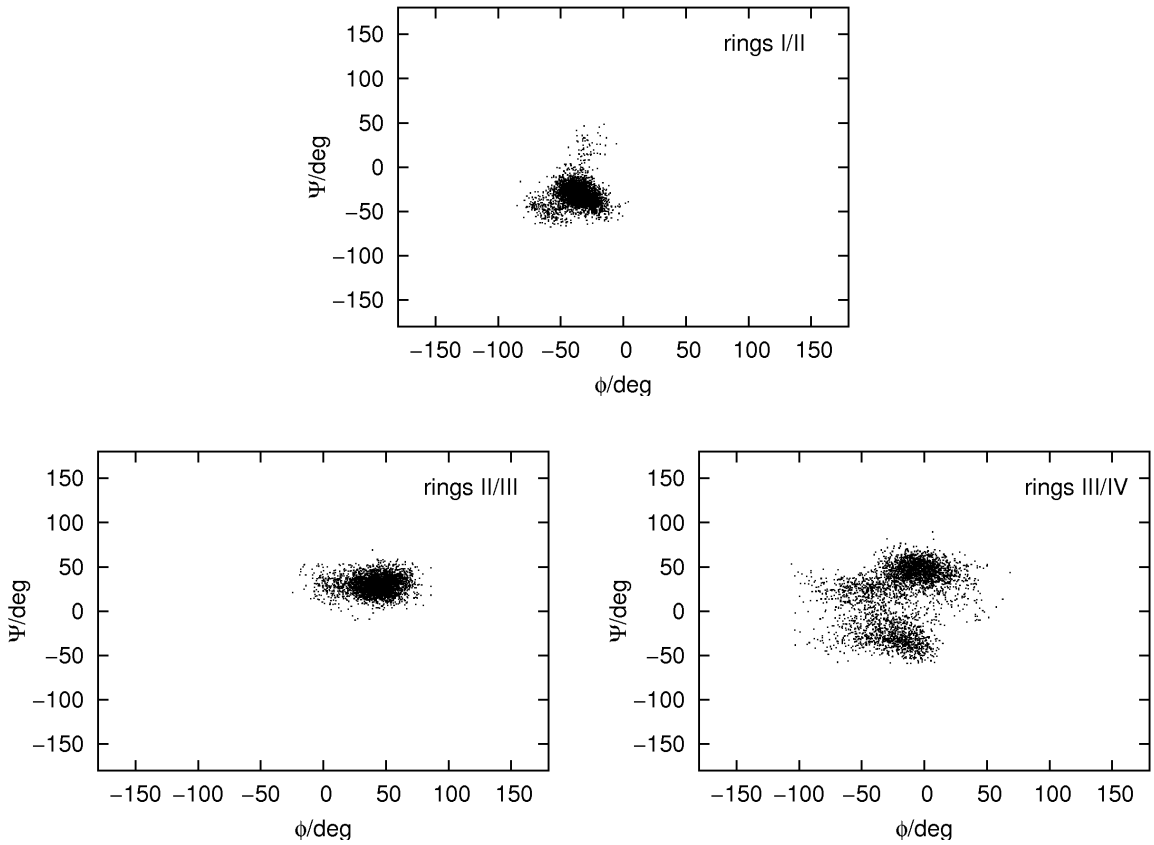

Figure 1: Distributions of ϕ and Ψ angles for paromomycin sugar linkages obtained from MD simulation, showing good agreement with experimental data[8].

protons	d_{sym}[Å]	d_{exp}[Å]
H11 – H33	4.15(0.24)	>3.5
H11 – H24	2.28(0.22)	2.5
H11 – H25	3.29(0.24)	3.0
H11 – H35	4.45(0.63)	3.0
H11 – H32	3.34(0.35)	3.6
H11 – H34	4.15(0.24)	>3.5
H31 – H24	4.50(0.11)	>4.0
H31 – H25	2.57(0.23)	2.3
H31 – H26	3.38(0.26)	3.6
H32 – H26	4.58(0.29)	3.3
H31 – H34	3.26(0.21)	3.2
H41 – H33	2.33(0.22)	2.6
H41 – H32	4.31(0.33)	3.1
H41 – H34	3.96(0.67)	3.9

Table 1: Simulated (paromomycin) and NMR[8] (neomycin) inter-proton distances.

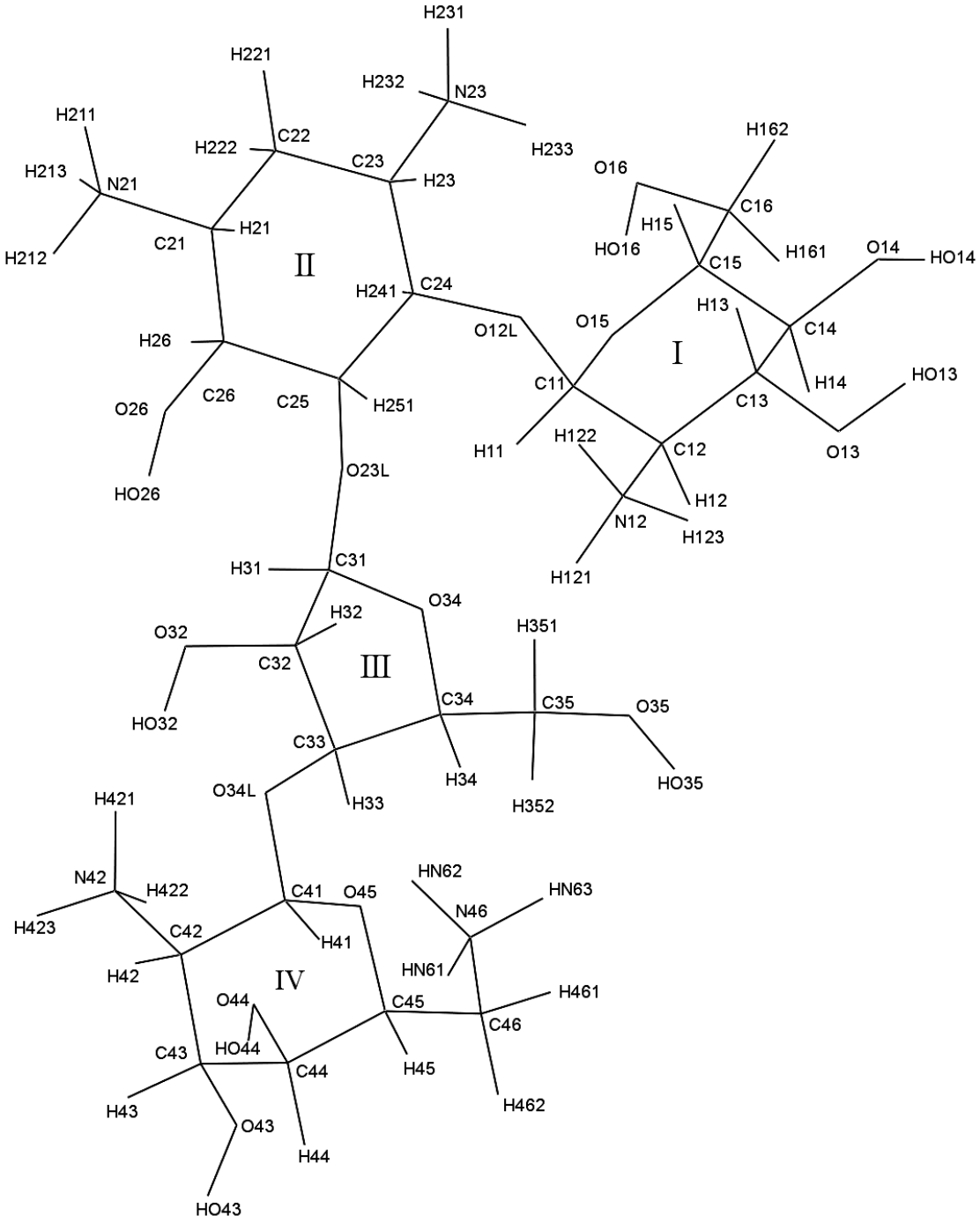

Figure 2: Numbering of paromomycin atoms, as they appear in the Charmm topology file.

Charmm topology file for paromomycin with all its amino groups ionized (a total charge of $+5e$). For atom numbering see Figure 2.

```
*>>>>>> CHARMM topology file <<<<<<
27 1
MASS      9   HN5    1.00800  H
MASS     11   HN7    1.00800  H
MASS     12   HN8    1.00800  H
MASS     33   CN7   12.01100  C
MASS     34   CN7B  12.01100  C
MASS     37   CN8   12.01100  C
MASS     38   CN8B  12.01100  C
MASS     76   ON5   15.99900  O
MASS     78   ON6B  15.99900  O
MASS    201   HCL    1.00800  H
MASS    202   HAS    1.00800  H
MASS    203   HOS    1.00800  H
MASS    211   CTS   12.01100  C
MASS    221   ON5P  15.99900  O
MASS    222   OHS   15.99900  O
MASS    223   OES   15.99900  O
MASS    231   NH3L  14.00700  N

AUTO ANGLES DIHE

RESI PARO  5.00
ATOM C21   CN8     0.44
ATOM H21   HN8     0.12
ATOM N21   NH3L   -0.77
ATOM H211  HCL     0.45
ATOM H212  HCL     0.45
ATOM H213  HCL     0.45
ATOM C22   CN7    -0.70
ATOM H221  HN7     0.24
ATOM H222  HN7     0.23
ATOM C23   CN8     0.32
ATOM H23   HN8     0.11
ATOM N23   NH3L   -0.64
ATOM H231  HCL     0.42
ATOM H232  HCL     0.42
ATOM H233  HCL     0.42
ATOM C24   CN7     0.10
ATOM H241  HN7     0.15
ATOM C25   CN8    -0.06
ATOM H251  HN8     0.14
ATOM C26   CN7     0.05
ATOM H26   HN7     0.12
ATOM O26   ON5P   -0.63
```

```
ATOM HO26  HN5     0.48
ATOM O12L  ON5P   -0.46
ATOM C11   CTS     0.32
ATOM H11   HAS     0.14
ATOM C15   CTS     0.03
ATOM H15   HAS     0.05
ATOM O15   OES    -0.46
ATOM C12   CTS    -0.10
ATOM H12   HAS     0.18
ATOM N12   NH3L   -1.04
ATOM H121  HCL     0.53
ATOM H122  HCL     0.53
ATOM H123  HCL     0.53
ATOM C13   CTS     0.57
ATOM H13   HAS     0.00
ATOM O13   OHS    -0.63
ATOM HO13  HOS     0.45
ATOM C14   CTS    -0.03
ATOM H14   HAS     0.12
ATOM O14   OHS    -0.59
ATOM HO14  HOS     0.46
ATOM C16   CTS     0.36
ATOM H161  HAS     0.01
ATOM H162  HAS     0.07
ATOM O16   OHS    -0.68
ATOM HO16  HOS     0.45
ATOM O23L  ON5P   -0.45
ATOM C34   CN7     0.32
ATOM H34   HN7     0.11
ATOM O34   ON6B   -0.64
ATOM C31   CN7B    0.67
ATOM H31   HN7     0.04
ATOM C32   CN7B    0.16
ATOM H32   HN7     0.09
ATOM O32   ON5    -0.66
ATOM HO32  HN5     0.50
ATOM C33   CN7    -0.27
ATOM H33   HN7     0.19
ATOM HO35  HN5     0.48
ATOM O35   ON5    -0.66
ATOM C35   CN8B    0.05
ATOM H351  HN8     0.03
ATOM H352  HN8     0.08
ATOM O34L  ON5P   -0.39
ATOM C41   CTS     0.49
ATOM H41   HAS     0.04
ATOM C45   CTS    -0.16
ATOM H45   HAS     0.19
```

```
ATOM O45   OES    -0.34
ATOM C42   CTS     0.06
ATOM H42   HAS     0.13
ATOM N42   NH3L   -0.55
ATOM H421  HCL     0.38
ATOM H422  HCL     0.38
ATOM H423  HCL     0.38
ATOM C43   CTS     0.06
ATOM H43   HAS     0.13
ATOM O43   OHS    -0.63
ATOM HO43  HOS     0.49
ATOM C44   CTS     0.17
ATOM H44   HAS     0.15
ATOM O44   OHS    -0.62
ATOM HO44  HOS     0.46
ATOM C46   CTS     0.12
ATOM H461  HAS     0.11
ATOM H462  HAS     0.15
ATOM N46   NH3L   -0.56
ATOM HN61  HCL     0.40
ATOM HN62  HCL     0.40
ATOM HN63  HCL     0.40

BOND C21  C22       C22  C23       C23  C24      N46  HN62
BOND C21  H21       C22  H221      C22  H222     N42  H423
BOND C23  H23       C24  H241      N21  H213
BOND C25  H251      C24  C25       N23  H233
BOND C26  H26       C26  O26       O26  HO26
BOND C21  N21       N21  H211      N21  H212
BOND C23  N23       N23  H231      N23  H232
BOND C25  O23L      C25  C26       C12  C11
BOND C24  O12L      C26  C21       C14  O14
BOND C11  O12L      C11  H11       C11  O15
BOND C12  H12       C12  C13       C13  H13
BOND C13  O13       O13  HO13      C13  C14
BOND O14  HO14      C14  C15       C15  H15
BOND C16  H161      C16  O16       O16  HO16
BOND C12  N12       N12  H121      N12  H122
BOND C31  O23L      C14  H14       C34  O34
BOND C31  C32       C32  C33       C33  C34
BOND C31  H31       C15  C16       C35  H352
BOND C32  O32       O32  HO32      C32  H32
BOND C33  H33       C16  H162      C44  O44
BOND C34  H34       C34  C35       C46  H462
BOND C35  O35       O35  HO35      C35  H351
BOND C33  O34L      C15  O15       N46  HN63
BOND C41  O34L      N12  H123      C44  H44
BOND C41  H41       C41  O45       C41  C42
```

```
BOND C42  H42       C42  C43       C43  H43
BOND C43  O43       O43  HO43      C43  C44
BOND O44  HO44      C44  C45       C45  H45
BOND C46  H461      C46  N46       N46  HN61
BOND C45  O45       O34  C31       C45  C46
BOND C42  N42       N42  H421      N42  H422
```

Force field parameters used for paromomycin, with standard Charmm potential energy terms.

```
ATOM PROPERTIES

  #  ATOM     N (EFF)    RADIUS

   9 HN5     -0.0460     0.2245
  11 HN7     -0.0220     1.3200
  12 HN8     -0.0280     1.3400
  33 CN7     -0.0200     2.2750
  34 CN7B    -0.0200     2.2750
  37 CN8     -0.0560     2.0100
  38 CN8B    -0.0560     2.0100
  76 ON5     -0.1521     1.7700
  78 ON6B    -0.1521     1.7700
 201 HCL     -0.0460     0.2245
 202 HAS     -0.0220     1.3200
 203 HOS     -0.0460     0.2245
 211 CTS     -0.0200     2.2750
 221 ON5P    -0.1521     1.7700
 222 OHS     -0.1521     1.7700
 223 OES     -0.1521     1.7700
 231 NH3L    -0.2000     1.8500

BOND PARAMETERS
!V(bond) = Kb(b - b0)**2
!Kb: kcal/mole/A**2
!b0: A
  #   B O N D           Kb         bO
  1  CN7  - HN7        309.0     1.111
  2  CN7  - CN7        222.5     1.529
  3  CN7B - HN7        309.0     1.111
  4  CN7B - CN7        222.5     1.460
  5  CN7B - CN7B       200.0     1.450
  6  CN8  - HN8        309.0     1.111
  7  CN8  - CN7        222.5     1.516
 10  CN8B - HN8        309.0     1.111
 11  CN8B - CN7        222.5     1.512
 13  ON5  - HN5        545.0     0.960
 15  ON5  - CN7B       428.0     1.400
```

17	ON5	- CN8B	428.0	1.420
18	ON6B	- CN7	240.0	1.480
19	ON6B	- CN7B	260.0	1.420
20	CTS	- HAS	335.6	1.100
21	CTS	- CTS	325.5	1.507
22	ON5P	- HN5	545.0	0.960
23	ON5P	- CN7	385.3	1.417
24	ON5P	- CN7B	385.3	1.417
25	ON5P	- CN8	385.3	1.417
26	ON5P	- CTS	385.3	1.417
27	OHS	- HOS	546.4	0.960
28	OHS	- CTS	384.1	1.407
29	OES	- CTS	385.3	1.417
30	NH3L	- CN8	261.0	1.510
31	NH3L	- HCL	410.0	1.040
32	NH3L	- CTS	261.0	1.510

BOND ANGLE PARAMETERS
!V(angle) = Kt(Theta - T0)**2
!Kt: kcal/mole/rad**2
!T0: degrees

#	A N G L E	Kt	TO
1	HN7 - CN7 - HN7	35.50	109.0000
4	HN8 - CN8B - HN8	35.50	109.0000
6	CN7 - ON5P - HN5	57.55	109.1722
7	CN7 - CN7 - HN7	40.00	108.0000
8	CN7 - CN7B - HN7	34.53	110.1000
9	CN7 - CN8 - HN8	34.53	110.1000
10	CN7 - CN8B - HN8	34.53	110.1000
11	CN7 - CN8 - CN7	58.35	113.6000
12	CN7B - ON5 - HN5	57.50	109.0000
13	CN7B - CN7 - HN7	34.53	110.1000
14	CN7B - CN7B - HN7	33.40	110.1000
16	CN7B - CN7 - CN7	60.00	100.0000
17	CN7B - CN7B - CN7	110.00	96.0000
19	CN7B - ON6B - CN7	110.00	115.0000
21	CN8 - CN7 - HN7	34.50	110.1000
29	CN8 - ON5P - CN7B	92.59	111.5092
30	CN8 - CN7 - CN8	58.35	113.6000
32	CN8B - ON5 - HN5	57.50	106.0000
33	CN8B - CN7 - HN7	34.50	110.1000
35	CN8B - CN7 - CN7	45.00	110.0000
39	ON5 - CN7B - HN7	60.00	109.5000
41	ON5 - CN8B - HN8	45.90	108.8900
43	ON5 - CN7B - CN7	90.00	108.0000
45	ON5 - CN8B - CN7	75.70	110.1000
47	ON5 - CN7B - CN7B	80.00	108.4000
50	ON6B - CN7 - HN7	45.20	107.2400

```
 51  ON6B - CN7B - HN7      45.20  107.2400
 52  ON6B - CN7  - CN7     100.00  110.0000
 53  ON6B - CN7B - CN7B     90.00  106.0000
 55  ON6B - CN7  - CN8B     90.00  108.2000
 56  HCL  - NH3L - CN8      33.00  109.5000
 57  HCL  - NH3L - HCL      41.00  109.5000
 58  HAS  - CTS  - HAS      36.82  106.1784
 59  CTS  - ON5P - CN7      92.59  111.5092
 60  CTS  - NH3L - HCL      33.00  109.5000
 61  CTS  - CTS  - HAS      42.91  109.7502
 62  CTS  - OHS  - HOS      57.55  109.1722
 63  CTS  - CTS  - CTS     167.35  110.6156
 64  CTS  - OES  - CTS      92.59  111.5092
 65  ON5P - CN7  - HN7      52.51  109.3850
 66  ON5P - CN7B - HN7      52.51  109.3850
 67  ON5P - CN8  - HN8      52.51  109.3850
 68  ON5P - CN7  - CN7     112.21  107.6019
 69  ON5P - CN8  - CN7     112.21  107.6019
 70  ON5P - CN7  - CN7B    112.21  107.6019
 71  ON5P - CN7B - CN7B    112.21  107.6019
 72  ON5P - CN7  - CN8     112.21  107.6019
 73  ON5P - CN7B - ON6B     37.44  112.1882
 74  ON5P - CTS  - HAS      62.25  106.4025
 75  ON5P - CTS  - CTS     169.03  108.3759
 76  OHS  - CTS  - HAS      52.51  109.3850
 77  OHS  - CTS  - CTS     112.21  107.6019
 78  OES  - CTS  - HAS      62.25  106.4025
 79  OES  - CTS  - CTS     169.03  108.3759
 80  OES  - CTS  - ON5P     37.44  112.1882
 83  NH3L - CN8  - HN8      52.51  109.3850
 84  NH3L - CN8  - CN7     112.21  107.6019
 85  NH3L - CTS  - HAS      52.51  109.3850
 86  NH3L - CTS  - CTS     112.21  107.6019

DIHEDRAL ANGLE PARAMETERS
!V(dihedral) = Kc(1 + cos(n(chi) - delta))
!Kchi: kcal/mole
!n: multiplicity
!delta: degrees
   #   T O R S I O N                Kc         n     delta

   1  X    - CN8  - CN7  - X        0.20       3     0.0000
   3  X    - ON5P - CTS  - X        0.00       1     0.0000
   4  X    - NH3L - CN8  - X        0.10       3     0.0000
   5  X    - NH3L - CTS  - X        0.10       3     0.0000
   6  HN7  - CN7  - CN7  - HN7      0.20       3     0.0000
   7  HN7  - CN7B - CN7  - HN7      0.20       3     0.0000
   8  HN7  - CN7B - CN7B - HN7      0.00       3     0.0000
```

9	HN8	- CN8	- CN7	- HN7	0.20	3	0.0000
11	HN8	- CN8B	- CN7	- HN7	0.20	3	0.0000
14	CN7	- CN7B	- CN7B	- HN7	0.20	3	0.0000
16	CN7	- ON6B	- CN7B	- HN7	0.00	3	0.0000
17	CN7B	- CN7	- CN7	- HN7	0.20	3	0.0000
18	CN7B	- CN7B	- CN7	- HN7	0.20	3	0.0000
20	CN7B	- ON6B	- CN7	- HN7	0.20	3	0.0000
21	CN7B	- ON5P	- CN8	- HN8	0.28	3	0.0000
23	CN7B	- CN7B	- CN7	- CN7	0.00	6	0.0000
25	CN7B	- ON6B	- CN7	- CN7	0.00	6	180.0000
26	CN7B	- ON5P	- CN8	- CN7	-0.85	-1	0.0000
31	CN8	- ON5P	- CN7B	- HN7	0.28	3	0.0000
32	CN8	- ON5P	- CN7B	- CN7B	-0.85	-1	0.0000
35	CN8B	- CN7	- CN7	- HN7	0.20	3	0.0000
40	CN8B	- CN7	- CN7	- CN7B	0.20	4	180.0000
43	ON5	- CN7B	- CN7	- HN7	0.20	3	0.0000
44	ON5	- CN7B	- CN7B	- HN7	0.00	3	0.0000
45	ON5	- CN8B	- CN7	- HN7	0.20	3	0.0000
49	ON5	- CN7B	- CN7	- CN7	0.00	3	0.0000
50	ON5	- CN8B	- CN7	- CN7	0.20	-4	180.0000
58	ON6B	- CN7	- CN7	- HN7	0.20	3	180.0000
59	ON6B	- CN7B	- CN7B	- HN7	0.20	3	0.0000
60	ON6B	- CN7B	- CN7B	- CN7	0.40	6	0.0000
61	ON6B	- CN7	- CN7	- CN7B	0.00	3	0.0000
67	ON6B	- CN7B	- CN7B	- ON5	0.00	3	0.0000
68	HAS	- CTS	- CTS	- HAS	0.00	-1	0.0000
71	HOS	- OHS	- CTS	- HAS	0.00	-1	0.0000
74	CTS	- ON5P	- CN7	- HN7	0.28	3	0.0000
75	CTS	- ON5P	- CN7	- CN7	-0.85	-1	0.0000
78	CTS	- ON5P	- CN7	- CN7B	-0.85	-1	0.0000
81	CTS	- ON5P	- CN7	- CN8	-0.85	-1	0.0000
84	CTS	- CTS	- CTS	- HAS	0.00	-1	0.0000
87	CTS	- OES	- CTS	- HAS	0.00	-1	0.0000
90	CTS	- CTS	- CTS	- CTS	-1.07	-1	0.0000
93	CTS	- OES	- CTS	- CTS	-0.85	-1	0.0000
96	ON5P	- CN7	- CN7	- HN7	0.17	3	0.0000
97	ON5P	- CN7B	- CN7B	- HN7	0.17	3	0.0000
98	ON5P	- CN7B	- CN7B	- CN7	-1.20	-1	0.0000
101	ON5P	- CN7	- CN7	- CN8B	-1.20	-1	0.0000
104	ON5P	- CN7B	- CN7B	- ON5	-4.94	-1	0.0000
107	ON5P	- CN7	- CN7	- ON6B	-4.94	-1	0.0000
110	ON5P	- CTS	- CTS	- HAS	0.17	3	0.0000
111	ON5P	- CTS	- CTS	- CTS	-1.20	-1	0.0000
114	OHS	- CTS	- CTS	- HAS	0.00	-1	0.0000
117	OHS	- CTS	- CTS	- CTS	-1.91	-1	0.0000
120	OHS	- CTS	- CTS	- OHS	-4.94	-1	0.0000
123	OES	- CTS	- CTS	- HAS	0.00	-1	0.0000
126	OES	- CTS	- CTS	- CTS	-1.20	-1	0.0000

```
129  OES  - CTS  - CTS  - OHS     -3.80       -1     0.0000
135  NH3L - CN8  - CN7  - HN7      0.00       -1     0.0000
138  NH3L - CTS  - CTS  - HAS      0.00       -1     0.0000
141  NH3L - CTS  - CTS  - CTS     -1.91       -1     0.0000
144  NH3L - CTS  - CTS  - ON5P    -4.94       -1     0.0000
147  NH3L - CTS  - CTS  - OHS     -4.94       -1     0.0000
150  NH3L - CTS  - CTS  - OES     -3.80       -1     0.0000
154  HN5  - ON5  - CN7B - HN7      0.00        3     0.0000
155  HN5  - ON5P - CN7  - HN7      0.17        3     0.0000
156  HN5  - ON5  - CN8B - HN8      0.00        3     0.0000
160  HN5  - ON5  - CN7B - CN7      0.30       -3     0.0000
162  HN5  - ON5  - CN8B - CN7      1.33       -1     0.0000
165  HN7  - CN7B - CN7  - CN7      0.20        3     0.0000
167  HN8  - CN8B - CN7  - CN7      0.20        3     0.0000
171  HN5  - ON5  - CN7B - CN7B     0.00       -6   180.0000
177  CN7  - ON6B - CN7B - CN7B     0.00        6     0.0000
181  HN5  - ON5P - CN7  - CN8      1.05       -1     0.0000
187  CN7B - ON6B - CN7  - CN8B     2.00        3     0.0000
202  HN8  - CN8B - CN7  - ON6B     0.20        1     0.0000
203  CN8  - ON5P - CN7B - ON6B     0.19       -1     0.0000
206  ON5  - CN8B - CN7  - ON6B     3.40        1   180.0000
207  HOS  - OHS  - CTS  - CTS      1.05       -1     0.0000
210  HN7  - CN7B - CN7  - ON5P     0.17        3     0.0000
211  CN7  - ON6B - CN7B - ON5P     0.19       -1     0.0000
214  CN7B - CN7B - CN7  - ON5P    -1.20       -1     0.0000
217  ON5  - CN7B - CN7  - ON5P    -4.94       -1     0.0000
220  CTS  - OES  - CTS  - ON5P     0.19       -1     0.0000
```

References

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