Supporting Information

Farnesyltransferase - New Insights into the Zinc-Coordination Sphere Paradigm: Evidence for a Carboxylate-Shift Mechanism

*Sérgio F. Sousa, Pedro A. Fernandes, and Maria João Ramos**

REQUIMTE, Departamento de Química, Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre, 687, 4169-007 Porto, Portugal

* E-mail: mjramos@fc.up.pt

CRYSTALLOGRAPHIC STRUCTURES – FTASE

Distances between the Zinc Atom and the second Carboxylate oxygen from Asp297β (Zn-O_b)

(Structures with resolution > 2.50 Å not considered in the analysis – marked in red)

1. FTase Resting State (1 Zinc Thiolate Bond)

	PDB Code	Res. (Å)	Year	Distance Zn-O_b[i] (Å)	Other Possible Zinc Ligands[ii] / Distance (Å)	FTase Ligands
1	1FT1	2.25	1997	2.56	H_2O / 2.70	-

Average Value Zn-O_b (Å)	2.56

2. FTase Binary Complex (1 Zinc Thiolate Bond)

	PDB Code	Res. (Å)	Year	Distance Zn-O_b (Å)	Other Possible Zinc Ligands / Distance (Å)	FTase Ligands
1	1FPP	2.75	1998	2.03	-	FPP[iii]
2	1FT2	3.40	1998	3.05	-	FPP
3	1O1R	2.30	2003	2.35	H_2O / 2.56	GGPP[iv]
4	1O1S	2.30	2003	2.42	H_2O / 2.18	1NH[v]

Average Value Zn-O_b (Å)	2.39

3. FTase Ternary Complex (2 Zinc Thiolate Bonds)

	PDB Code	Res. (Å)	Year	Distance Zn-O_b (Å)	Other Possible Zinc Ligands / Distance (Å)	FTase Ligands
1	1QBQ	2.40	1999	2.45	S (Cys) / 2.48	HFP[vi] + CVIM
2	1D8D	2.00	2000	2.61	S (Cys) / 2.40	FII[vii] + KKKSKTKCVIM
3	1JCR	2.00	2001	2.53	S (Cys) / 2.41	FPP + CVFM
4	1JCS	2.20	2001	2.55	S (Cys) / 2.35	FII + TKCVFM

Average Value Zn-O_b (Å)	2.54

4. FTase Ternary Complex (1 Zinc Thiolate Bond)

	PDB Code	Res. (Å)	Year	Distance Zn-O_b (Å)	Other Possible Zinc Ligands / Distance (Å)	FTase Ligands
1	1JCQ	2.30	2001	2.67	Sc (L-739) / 2.36	FPP + L-739,750[viii]
2	1LD7	2.00	2002	2.61	N (U49) / 2.07	FPP + U66[ix]
3	1LD8	1.80	2002	2.53	N (U49) / 1.97	FPP + U49[x]
4	1MZC	2.00	2002	2.55	N (BNE) / 1.93	FPP + BNE[xi]

5	1N94	3.50	2002	2.77	-	HFP + TIN[xii]
6	1N95	2.30	2002	2.41	N (FTH) / 2.70	HFP + FTH[xiii]
7	1N9A	3.20	2002	2.44	-	HFP + FTI[xiv]
8	1NI1	2.30	2002	2.33	N (2C5) / 2.55	HFP + 2C5[xv]
9	1NL4	2.70	2003	2.30	N (FTL) / 2.35	HFP + FTL[xvi]
10	1O5M	2.30	2003	2.49	H_2O / 2.51	FPP + SCH66336[xvii]

Average Value Zn-O_b (Å)	2.51

5. FTase Product Complex (1 Zinc Thiolate Bond)

	PDB Code	Res. (Å)	Year	Distance Zn-O_b (Å)	Other Possible Zinc Ligands / Distance (Å)	FTase Ligands
1	1KZO	2.20	2002	2.42	H_2O / 2.67	FPP + Far-TKCVIM[xviii]
2	1KZP	2.10	2002	2.42	S (Far-KCVIM) / 2.66	Far-KCVIM
3	1O1T	2.10	2003	2.49	S (Far-KCVIM) / 2.70	Far-CVIM

Average Value Zn-O_b (Å)	2.44

[i] O_b refers to the Asp297β carboxylate oxygen located at a larger distance from zinc.
[ii] In addition to Asp297β, Cys299β, and His362β.
[iii] FPP – Farnesyl diphosphate, a 15-carbons isoprenoid, the natural substrate of FTase.
[iv] GGPP – Geranylgeranyl diphosphate, a 20-carbons isoprenoid, the natural substrate of GGTase I.
[v] 1NH – a 24-carbons Isoprenoid Analog.
[vi] HFP – α-hydroxyfarnesylphosphonic acid, a 15-carbons FPP analog.
[vii] FII – a 17-carbons FPP analog.
[viii] L-739,750 – a peptidomimetic FTase inhibitor.
[ix] U66 –FTase inhibitor compound 66.
[x] U49 – FTase inhibitor compound 49.
[xi] BNE – FTase inhibitor compound 33A.
[xii] TIN – Aryl tetrahydropyridine inhibitor of FTase.
[xiii] FTH – Aryl tetrahydropyridine inhibitor of FTase.
[xiv] FTI – Aryl tetrahydropyridine inhibitor of FTase.
[xv] 2C5 – Imidazole and Cyanophenyl containing inhibitor of FTase.
[xvi] FTL – Imidazole-containing biphenyl inhibitor of FTase.
[xvii] SCH66336 – Tricyclic FTase Inhibitor.
[xviii] Far-TKCVIM, Far-KCVIM, and Far-CVIM refer to farnesylated peptides at the Cysteine residue.

Summary

	Number of Zinc-Thiolate Bonds	Average Distance Zn-O_b (Å)
FTase Resting State	1	2.56
FTase Binary Complex	1	2.39
FTase Ternary Complex	2	2.54
FTase Ternary Complex	1	2.51
FTase Product Complex	1	2.44
All Structures	-	2.49

STATIONARY POINTS

- Smaller Model -

```
Minimum 1

C -0.7134  2.0176 -3.6496
C -0.2176  1.2685 -2.4248
O  1.0058  1.2623 -2.0816
O -1.1482  0.6081 -1.7358
H  1.9361 -2.9304  0.7900
C  0.9265 -3.1140  1.1670
S -0.3411 -2.7216 -0.1911
C  2.0806  2.0952  2.0505
N  1.1801  1.6339  3.0205
C  1.6873  1.5152  0.8589
C  0.2799  0.7993  2.4093
N  0.5670  0.7098  1.1029
Zn -0.4184 -0.4154 -0.2565
O -2.3170 -0.5759  0.9037
H -2.2640 -1.5654  0.8342
H -3.0990 -0.2161  0.4391
H  0.8169 -4.1734  1.4147
H  0.7509 -2.5130  2.0646
H  2.0718  1.6153 -0.1444
```

H 2.8856 2.7736 2.2794
H -0.5453 0.3114 2.9017
H 1.1857 1.8775 4.0019
H 0.1002 2.5895 -4.1018
H -1.5363 2.6862 -3.3712
H -1.1081 1.2993 -4.3786

Transition State 1

C -0.6384 1.9984 -3.5901
C -0.3074 1.1644 -2.3705
O 0.8979 0.9152 -2.0143
O -1.3186 0.6702 -1.6683
H 1.9799 -2.9557 0.5609
C 0.9995 -3.1255 1.0136
S -0.3618 -2.6985 -0.2400
C 2.0844 2.1131 2.0745
N 1.0887 1.7523 2.9926
C 1.7548 1.4800 0.8902
C 0.1974 0.9242 2.3591
N 0.5812 0.7432 1.0880
Zn -0.3662 -0.3946 -0.2842
O -2.2452 -0.5561 1.0530
H -2.1516 -1.5397 0.9430
H -3.0179 -0.2139 0.5596
H 0.8909 -4.1852 1.2609
H 0.9024 -2.5285 1.9254
H 2.2288 1.5033 -0.0779
H 2.9027 2.7658 2.3291
H -0.6907 0.5022 2.8011
H 1.0294 2.0544 3.9558
H 0.2659 2.4554 -3.9983
H -1.3709 2.7707 -3.3295
H -1.0969 1.3557 -4.3521

Minimum 2

N 1.3136 0.0227 0.5252
C 1.9846 -0.3173 1.7060
C 3.3456 -0.3036 1.4651
N 3.4884 0.0463 0.1168
C 2.2437 0.2354 -0.4229
Zn -0.6676 0.1395 0.1452
O -1.0089 -1.5204 -1.2800
C -1.4106 -2.2205 -0.2579

```
O -1.3855 -1.6530  0.9211
C -1.9244 -3.6291 -0.4210
S -1.7442  2.0733 -0.3175
C -0.6076  3.3913  0.4488
H -0.7161  3.3931  1.5365
H -0.9307  4.3565  0.0498
H  0.4371  3.2177  0.1757
H  1.4557 -0.5522  2.6153
H  4.1846 -0.5078  2.1093
H  2.0023  0.4869 -1.4510
H  4.3610  0.1373 -0.3862
H -1.7290 -4.2129  0.4826
H -1.4699 -4.1033 -1.2949
H -3.0111 -3.5951 -0.5750
O  0.3252  0.5638 -2.6645
H -0.3089  1.2806 -2.4337
H -0.1366 -0.3006 -2.5733
```

Transition State 2

```
C -1.3072  2.0602 -3.2534
C -0.7992  1.1248 -2.1848
O  0.4444  0.7289 -2.1796
O -1.5904  0.6599 -1.2603
H  1.9543 -2.9213  1.2311
C  0.8814 -3.1307  1.2518
S  0.0930 -2.7398 -0.4343
C  1.9310  2.0291  2.4147
N  0.6206  1.8729  2.8818
C  2.0030  1.2885  1.2500
C -0.0631  1.0607  2.0159
N  0.7580  0.6910  1.0158
Zn  0.1822 -0.4983 -0.5177
O -2.6659 -0.0245  1.1275
H -2.8567 -0.9811  1.0884
H -2.5143  0.3215  0.2123
H  0.7248 -4.1985  1.4278
H  0.4020 -2.5593  2.0516
H  2.8361  1.1559  0.5790
H  2.6673  2.6284  2.9237
H -1.1072  0.7627  2.0843
H  0.2305  2.2924  3.7152
H -0.4883  2.6627 -3.6542
H -2.1003  2.6998 -2.8555
H -1.7308  1.4657 -4.0737
```

Minimum 3

C -1.9077 1.7145 -3.0600
C -1.1000 0.8903 -2.0901
O 0.1844 0.7624 -2.2061
O -1.6829 0.2544 -1.0991
H 1.4751 -2.5059 1.7883
C 1.0529 -3.2266 1.0818
S 1.1737 -2.5894 -0.7068
C 1.7214 1.6663 2.7791
N 0.3502 1.9354 2.8570
C 1.8764 0.8433 1.6810
C -0.2905 1.2911 1.8305
N 0.6200 0.6201 1.0991
Zn 0.3154 -0.5217 -0.5456
O -3.1153 1.0803 0.9419
H -3.9761 0.6892 1.1723
H -2.7621 0.7374 0.0711
H 1.6330 -4.1527 1.1230
H 0.0118 -3.4385 1.3402
H 2.7750 0.4074 1.2746
H 2.4385 2.0647 3.4773
H -1.3672 1.3122 1.6584
H -0.1072 2.5104 3.5519
H -1.2496 2.3051 -3.7003
H -2.5961 2.3697 -2.5147
H -2.5125 1.0452 -3.6849

- Larger Model -

Minimum 1

N -2.4843 -6.3557 0.1750
C -2.2287 -4.8949 0.1737
C -3.3701 -4.1932 0.9233
O -4.5426 -4.2721 0.5609
C -2.1058 -4.3006 -1.2353
C -1.5612 -2.8643 -1.2390
O -1.4922 -2.1379 -0.1967
O -1.1767 -2.4142 -2.4314
H -1.7904 -6.8111 -0.3803
H -3.3885 -6.5537 -0.2000
H -1.2551 -4.7580 0.7118
H -1.4342 -4.9064 -1.8784
H -3.0868 -4.2817 -1.7590

```
N -3.0448 -3.4883  2.0969
C -3.9492 -2.4592  2.6428
C -3.3900 -1.0361  2.6280
O -3.2890 -0.3824  3.6569
H -2.0627 -3.3499  2.2905
H -4.9277 -2.4587  2.1117
H -4.1647 -2.7555  3.6912
N -3.1331 -0.4214  1.3640
C -2.5896  0.9711  1.3353
C -3.6808  2.0145  1.0325
O -3.4165  3.1988  0.8551
C -1.3825  1.1112  0.4004
S -1.7634  1.2879 -1.5057
H -2.7111 -1.0412  0.6777
H -2.2129  1.2371  2.3627
H -0.7114  0.2429  0.5173
H -0.8299  2.0409  0.6418
N -5.0493  1.6454  1.1097
C -6.0804  2.4296  0.3693
C -6.3288  3.7603  1.0834
O -6.7183  4.7388  0.4896
C -7.4203  1.6703  0.3312
C -7.2835  0.3053 -0.2608
C -7.2286  0.1395 -1.6466
C -7.1886 -0.8115  0.5726
C -7.0418 -1.1186 -2.2014
C -6.9878 -2.0764  0.0390
C -6.8973 -2.2251 -1.3519
O -6.6828 -3.4340 -1.9522
H -5.2152  0.6614  1.0344
H -5.7319  2.6130 -0.6802
H -6.1573  3.7972  2.1711
H -7.8502  1.6007  1.3517
H -8.1442  2.2641 -0.2625
H -7.3206  1.0151 -2.2998
H -7.2623 -0.6934  1.6608
H -6.9936 -1.2448 -3.2883
H -6.8716 -2.9421  0.7050
H -6.4044 -4.0442 -1.2777
N  2.3947 -1.5560  3.5689
C  1.8915 -2.6568  2.7067
C  0.7929 -3.4117  3.4449
O -0.3226 -3.5552  2.9979
C  2.9839 -3.6477  2.2810
C  4.1317 -2.9359  1.5609
O  4.6193 -3.3535  0.4945
O  4.6023 -1.8456  2.0518
H  3.2327 -1.1965  3.1200
H  2.6490 -1.9289  4.4616
H  1.4762 -2.1566  1.7967
H  1.0478 -3.8481  4.4257
```

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H  3.3964 -4.1811  3.1603
H  2.5489 -4.4276  1.6271
N  8.7657 -3.2256 -1.3799
C  7.4296 -2.5824 -1.3228
C  6.5406 -3.2556 -2.3513
O  5.5008 -2.7712 -2.7545
C  7.4753 -1.0491 -1.5035
O  8.3534 -0.4243 -0.6131
H  9.2477 -3.0590 -0.5226
H  9.2929 -2.8344 -2.1328
H  6.9750 -2.8258 -0.3208
H  6.8548 -4.2399 -2.7365
H  7.8588 -0.7603 -2.4982
H  6.4551 -0.6147 -1.3906
H  8.0441 -0.6175  0.2776
N  5.2182  5.1185  0.6526
C  3.7009  5.1216  0.5965
C  3.2057  3.7239  1.0270
O  2.4715  3.5684  1.9722
C  3.1785  5.5078 -0.8007
C  1.6959  5.6480 -0.7502
C  1.1185  6.8626 -0.3703
C  0.8752  4.5618 -1.0670
C -0.2576  6.9872 -0.2738
C -0.5025  4.6562 -0.9613
C -1.0720  5.8741 -0.5515
O -2.4077  6.0640 -0.4195
H  5.5629  5.9930  0.3089
H  5.5850  4.3728  0.0859
H  3.3046  5.8849  1.3249
H  3.6353  6.4675 -1.1212
H  3.4727  4.7550 -1.5607
H  1.7564  7.7244 -0.1445
H  1.3182  3.6140 -1.3990
H -0.7099  7.9400  0.0249
H -1.1287  3.7649 -1.1843
H -2.8429  5.2183 -0.4624
N  3.8165  2.6459  0.2573
C  4.0644  1.3741  1.0080
C  5.2250  1.5603  1.9860
O  5.7830  2.6305  2.1382
C  4.4105  0.2249  0.0646
C  3.3152 -0.1976 -0.8259
N  3.4403 -1.3443 -1.6307
C  2.0229  0.2674 -1.0451
C  2.2630 -1.5384 -2.2889
N  1.3826 -0.5781 -1.9564
H  3.3020  2.4841 -0.5875
H  3.1638  1.0765  1.6134
H  5.5351  0.6710  2.5643
H  5.3221  0.4406 -0.5418
```

H 4.6980 -0.6687 0.7405
H 4.2820 -1.9373 -1.7126
H 1.4962 1.1012 -0.6137
H 2.0779 -2.3564 -2.9654
Zn -0.5899 -0.4873 -2.3779
O -0.8076 -0.9035 -4.4563
H -1.1819 -1.8024 -4.2866
H -1.3274 -0.3800 -5.0925
O 7.1463 -1.1237 1.7282
H 6.2119 -1.3840 1.6118
H 7.5529 -1.7472 2.3183
H 5.5161 4.9928 1.6024

Minimum 3

N -2.1531 -6.4635 0.1160
C -1.9094 -5.0027 0.0416
C -3.1059 -4.2872 0.6889
O -4.2388 -4.3294 0.2113
C -1.7068 -4.4973 -1.3936
C -1.2094 -3.0605 -1.4620
O -1.0338 -2.3081 -0.4395
O -0.9700 -2.5388 -2.6653
H -1.4010 -6.9469 -0.3283
H -3.0119 -6.6982 -0.3364
H -0.9712 -4.8186 0.6274
H -0.9735 -5.1233 -1.9453
H -2.6448 -4.5461 -1.9867
N -2.8859 -3.6161 1.9013
C -3.8767 -2.6744 2.4563
C -3.3561 -1.2384 2.5488
O -2.8642 -0.7832 3.5686
H -1.9327 -3.5015 2.2187
H -4.8267 -2.7039 1.8773
H -4.1244 -3.0322 3.4778
N -3.5988 -0.3781 1.4313
C -3.0296 0.9986 1.4035
C -4.1084 2.0299 1.0278
O -3.8411 3.1602 0.6421
C -1.7628 1.1087 0.5467
S -2.0223 1.0184 -1.3877
H -3.5615 -0.8354 0.5431
H -2.7242 1.2725 2.4510
H -1.0493 0.3124 0.8280
H -1.2815 2.0920 0.7098
N -5.4737 1.7291 1.2956
C -6.5446 2.3990 0.5006
C -6.9364 3.7052 1.1949

```
O -7.5231  4.5874  0.6129
C -7.7959  1.5085  0.3969
C -7.4957  0.1955 -0.2506
C -7.3732  0.1114 -1.6403
C -7.3208 -0.9500  0.5277
C -7.0501 -1.0912 -2.2505
C -6.9796 -2.1601 -0.0613
C -6.8346 -2.2262 -1.4538
O -6.5037 -3.3770 -2.1099
H -5.6639  0.7553  1.4242
H -6.1676  2.6198 -0.5321
H -6.6734  3.8198  2.2589
H -8.2408  1.3490  1.4006
H -8.5653  2.0477 -0.1920
H -7.5235  1.0094 -2.2512
H -7.4502 -0.9011  1.6159
H -6.9494 -1.1526 -3.3399
H -6.8085 -3.0474  0.5623
H -6.1814 -3.9970 -1.4651
N  2.3335 -1.4546  3.6499
C  1.9345 -2.5823  2.7682
C  0.8610 -3.4112  3.4620
O -0.2107 -3.6611  2.9560
C  3.1050 -3.4961  2.3794
C  4.2296 -2.7072  1.7027
O  4.7893 -3.0940  0.6615
O  4.6066 -1.5868  2.2096
H  3.1600 -1.0381  3.2297
H  2.5829 -1.8145  4.5494
H  1.5216 -2.1060  1.8446
H  1.0910 -3.8038  4.4671
H  3.5203 -4.0052  3.2716
H  2.7471 -4.2998  1.7078
N  8.9358 -2.8716 -1.1089
C  7.6038 -2.2185 -1.1383
C  6.7920 -2.8590 -2.2487
O  5.7995 -2.3475 -2.7304
C  7.6727 -0.6828 -1.2831
O  8.4732 -0.0785 -0.3101
H  9.3482 -2.7373 -0.2106
H  9.5247 -2.4618 -1.8039
H  7.0735 -2.4794 -0.1783
H  7.1199 -3.8429 -2.6231
H  8.1401 -0.3762 -2.2358
H  6.6470 -0.2484 -1.2511
H  8.0978 -0.2963  0.5489
N  4.9843  5.4303  0.3798
C  3.4698  5.3223  0.3456
C  3.0813  3.9336  0.8979
O  2.3743  3.8061  1.8680
C  2.9124  5.5527 -1.0721
```

```
C  1.4246  5.6209 -1.0195
C  0.7891  6.8341 -0.7406
C  0.6576  4.4751 -1.2478
C -0.5920  6.9035 -0.6665
C -0.7248  4.5152 -1.1629
C -1.3527  5.7369 -0.8656
O -2.6975  5.8797 -0.7699
H  5.2628  6.2985 -0.0333
H  5.3979  4.6714 -0.1348
H  3.0261  6.1144  1.0133
H  3.3139  6.5025 -1.4840
H  3.2400  4.7517 -1.7664
H  1.3850  7.7396 -0.5806
H  1.1486  3.5259 -1.4963
H -1.0901  7.8558 -0.4500
H -1.3114  3.5852 -1.3195
H -3.0994  5.0170 -0.7864
N  3.7544  2.8427  0.2037
C  4.1093  1.6538  1.0431
C  5.3042  1.9805  1.9371
O  5.7844  3.0966  1.9992
C  4.4691  0.4478  0.1781
C  3.3852 -0.0128 -0.7055
N  3.5879 -1.0264 -1.6607
C  2.0328  0.2903 -0.7708
C  2.3985 -1.3066 -2.2666
N  1.4334 -0.5217 -1.7433
H  3.2356  2.5778 -0.6126
H  3.2563  1.3633  1.7171
H  5.7160  1.1518  2.5405
H  5.3955  0.6293 -0.4166
H  4.7326 -0.4153  0.9038
H  4.4819 -1.5019 -1.8553
H  1.4494  0.9767 -0.1804
H  2.2439 -2.0396 -3.0551
Zn -0.5423 -0.6558 -1.9219
O  7.1426 -0.8062  1.9586
H  6.2146 -1.0777  1.8151
H  7.5375 -1.4236  2.5628
H  5.2990  5.3980  1.3319
O  1.0800 -3.0367 -4.2983
H  0.9686 -3.3042 -5.2275
H  0.2124 -2.9881 -3.8121
```