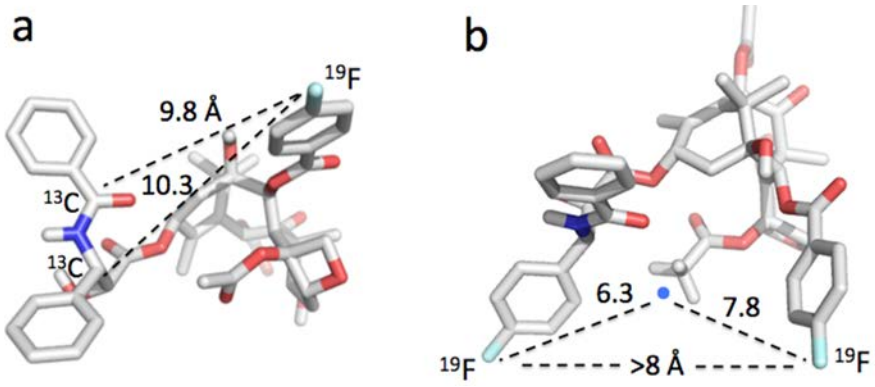
Internuclear distances determined by REDOR NMR were compared with those predicted by the major conformers depicted in Figure 9, with the results shown in Table 1.[49] Both the T-taxol and the REDOR-taxol conformations are consistent with the REDOR NMR data, although neither set of

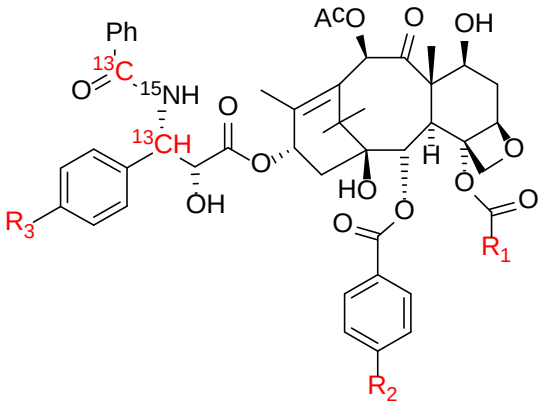


26 **27**

FIGURE 15. Internuclear distances among centers in microtubule-bound paclitaxel from REDOR NMR. a) C2-benzoyl (*p*-F) to the C3' carbon and the C(=O) carbon of the benzamide; b) C2-benzoyl (*p*-F), C4-CD_3 acetate and C3'-phenyl (*p*-F).

distances in **26** and **27** are able to resolve the C13/C2'OH conformational issue.[51]

TABLE 1. Comparison of predicted and observed internuclear distances for microtubule-bound paclitaxel[a]



Distances (Å)	Polar	Non-polar	REDOR PTX	T-Taxol	Expt
R^1-R^2	**7.9**	**8.0**	**7.6**	**7.9**	**7.8**
R^1-R^3	**5.9**	7.2	**6.1**	**6.6**	**6.3**
R^2-R^3	4.6	**12.5**	**13.1**	**12.2**	**>8**
R^2-^{13}CH	**9.6**	8.5	**9.5**	**9.9**	**10.3**
R^2-^{13}CO	**10.4**	6.2	**9.9**	**9.1**	**9.8**

[a]Numbers in bold agree with the REDOR data within ± 0.8 Å

Additional powerful support for the taxol binding conformation was provided by the synthesis of bridged paclitaxels locked into conformations designed to mimic those of T-taxol (Figure 16).[54] Two of these bridged analogs, **28** and **29**, which best matched the T-taxol conformation showed enhanced activity compared with paclitaxel. Compound **28** (IC_{50} 0.30 nM, A2780 ovarian cancer cells) was 22-fold more cytotoxic than paclitaxel (IC_{50} 6.6 nM) and also approximately double the tubulin-assembly