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The Quest for a Simple Bioactive Analog of Paclitaxel as a Potential Anticancer Agent

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CONSPECTUS: Paclitaxel (PTX), introduced into the clinic in 1991, has revealed itself as an effective antimicrotubule drug for treatment of a range of otherwise intractable cancers. Along with docetaxel (DTX) and in combination with other agents such as cisplatin, it has proven to be a first-line therapy. Unfortunately, PTX and DTX carry severe liabilities such as debilitating side effects, rapid onset of resistance, and rather complex molecular structures offering substantial challenges to ease of synthetic manipulation. Consequently, the past 15 years has witnessed many efforts to synthesize and test highly modified analogs based on intuitive structural similarity relationships with the PTX molecular skeleton, as well as efforts to mimic the conformational profile of the ligand observed in the macromolecular tubulin–PTX complex. Highly successful improvements in potency, up to 50-fold increases in IC50 have been achieved by constructing bridges between distal centers in PTX that imitate the conformer of the electron crystallographic binding pose. Much less successful have been numerous attempts to truncate PTX by replacing the baccatin core with simpler moieties to achieve PTX-like potencies and applying a wide range of flexible synthesis-based chemistries. Reported efforts, characterized by a fascinating array of baccatin substitutes, have failed to surpass the bioactivities of PTX in both microtubule disassembly assays and cytotoxicity measurements against a range of cell types. Most of the structures retain the main elements of the PTX C13 side chain, while seeking a smaller rigid bicycle as a baccatin replacement adorned with substituents to mimic the C2 benzoyl moiety and the oxetane ring. We surmise that past studies have been handicapped by solubility and membrane permeability issues, but primarily by the existence of an expansive taxane binding pocket and the discrepancy in molecular size between PTX and the pruned analogs. A number of these molecules offer molecular volumes 50−60% that of PTX, fewer contacts with the tubulin protein, severe mismatches with the PTX pharmacophore, lessened capacity to displace binding site waters contributing to ΔGbind and unanticipated binding poses. The latter is a critical drawback if molecular designs of simpler PTX structures are based on a perceived or known PTX binding conformation. We conclude that design and synthesis of a highly cytotoxic tubulin-assembly agent based on the paclitaxel pharmacophore remains an unsolved challenge, but one that can be overcome by focus on the architecture of the taxane binding site independent of the effective, but not unique, hand-in-glove match represented by the PTX–tubulin complex.

1. INTRODUCTION

The decade of the 1970s was bookended by two significant discoveries in the area of naturally occurring anticancer agents: the isolation and structural elucidation of the diterpenoid taxol (as it was then called), 1, in 1971,1 and its subsequent identification as a promoter of microtubule assembly in 1979.2 A personal account of these two events has recently been published.3 These discoveries led ultimately to the first clinical demonstration of the activity of taxol against ovarian cancer in 1989,4 its approval for treatment of ovarian and breast cancers by the FDA in 1991 and 1993, respectively, and its controversial name change to paclitaxel.5 Docetaxel (2)6 and cabazitaxel (3)7 are the only other taxanes currently in clinical use (Figure 1).

The mechanism of action of paclitaxel is intimately associated with its activity as a potent promoter of microtubule assembly and, thus, as an antimitotic agent,8,9 but it has also shown activity as a neuroprotective agent.10 Under physiological conditions the major therapeutic effect of taxol and taxol-like compounds is the slowing of tubulin dynamics rather than tubulin polymerization,9 and a recent publication has argued that its interference with intracellular trafficking on microtubules is probably its most important function.11 Since both of these effects depend on or are at least closely related to the ability of paclitaxel to bind to microtubules and to promote the polymerization of tubulin to microtubules, this activity remains the key to its overall effectiveness as an anticancer agent.

The numerous paclitaxel analogs in clinical trials12 and the vast majority of the analogs that have been evaluated retain the basic paclitaxel skeleton and differ in substituents on the ring system and on the side chain. This approach, while successful, begs the question “Is the paclitaxel skeleton essential for bioactivity? Is it possible that a simplified structure could be...
constructed with equal or even enhanced bioactivity compared with paclitaxel?" This Account lays out the options for such a structure and describes the progress made toward its synthesis. The selection of compounds for discussion has been limited to those prepared by total synthesis or those compounds prepared from paclitaxel or 10-deacetyl baccatin III designed to test the microtubule-bound conformation of the drug. This definition necessarily excludes the many thousands of analogs prepared by chemical modification of paclitaxel or 10-deacetyl baccatin III.

The structure–activity relationships of paclitaxel have been investigated extensively and reviewed on several occasions. For the purposes of this Account, the major structural features necessary for activity are the C13 N-acyl-β-phenylisoserine side chain or some variation of it, an acyl group at C4, and the C2 benzoate group or some variation thereof. While the oxetane ring was originally thought to be essential for activity based on early results that ring-opened analogs were inactive, the cyclopropane analog and the D-seco analog reveal potency similar to paclitaxel in the stabilization of microtubules (Figure 2). Thus, the oxetane ring is no longer regarded as essential.

2. SIMPLIFIED ANALOGS DESIGNED WITHOUT THE ASSISTANCE OF THE STRUCTURE OF THE LIGAND–MT COMPLEX

One of the first attempts to design a simplified analog was made by Fuji and co-workers, who used molecular mechanics to calculate the distance between the C4 and C13 carbons of paclitaxel as 4.5 Å. This information was used to design 6a–6f (Figure 3), where the distance D, corresponding to the C4–C13 separation in paclitaxel, varied from 2.6 to 9.0 Å. None of these compounds showed any significant tubulin inhibitory activity, unsurprising given the flexible nature of the chain linking the side chain and the oxetane ring and the lack of a C2-benzoyl group equivalent.

A recent attempt to improve on Fuji’s structure was reported by Gao and co-workers, who conceived 7a and 7b (Figure 3). These compounds showed very weak inhibitory activity against microtubule disassembly, with IC50 values 200- and 120-fold larger than those for paclitaxel, and moderate antiproliferative activity with IC50 values 5–10-fold larger than those for paclitaxel in six different cell lines. They also showed the same pattern of activity as paclitaxel, with higher potency to paclitaxel-sensitive cell lines and reduced potency against paclitaxel-resistant cell lines.

A more complex structure 8b (Figure 4) was prepared by Botta and Corelli based on their finding that the lowest-energy conformation of the dimeric macrolactam 8a could be superimposed on a low energy conformation of paclitaxel. Synthesis of 8b was accomplished from 8a, but surprisingly both compounds had essentially the same activity against the B16-F10 murine melanoma cell line and were inactive in a tubulin assembly assay.

Three investigators developed simplified analogs containing bridged rings aimed at providing the structural rigidity of the baccatin III core of paclitaxel. Klar and co-workers synthesized a series of over 20 compounds from a borneol-like lead structure. Pyridyl derivative 9a (Figure 5) furnished the best tubulin-assembly activity, 13-fold more potent than paclitaxel at stabilizing microtubules. Its close analog 9b was evaluated in the NCI 60-cell line screen, but it proved much less active than paclitaxel, and the compounds were abandoned as cancer therapeutics. The reason for the discrepancy between microtubule stabilization and antiproliferative activities was not investigated, but it could be due in part to the lack of water-solubility or poor cell membrane penetration.
Frejd et al. designed 10 (Figure 5) based on comparative modeling of its spiro[6-hydroxybicyclo[2.2.2] octan-2-one-3,1'- cyclohex-3'-en]-2'-one core with the baccatin core of one of the X-ray structures of paclitaxel using MacroModel. The compound was inactive in an assay to determine microtubule stabilization. The authors concluded this was likely due to the lack of a 2-benzoate group.24

Analogs based on the adamantane core were prepared by Zeﬁrova and co-workers. The synthesis of 11a25 was followed by the synthesis and biological evaluation of 11b–13 (Figure 6). All four compounds were over a thousand-fold less cytotoxic than paclitaxel, but all likewise showed some level of tubulin polymerization activity as judged by the relative amount of tubulin pelleted after incubation with each substance.26,27

Vauzeilles and Beau prepared simplified compounds with the general structure 14 (Figure 7), where R represents one of seven substituted benzenes or one of three substituted benzyl groups. The structures were designed based on an overlay of the MM3* conformation of the β-L-glucurono-γ-lactone core of 14 with the taxane core of paclitaxel. The only analog to show any tubulin polymerization activity was 14d, but this was only very weakly active (IC50 90 μM) compared with paclitaxel's 0.5 μM response in the same assay.28

Another analog with two fused five-membered rings was evaluated by Shintani et al., who found that the small molecule designated GS-164 (15) (Figure 7) had a similar tubulin-assembly effect at 40 μM to that of paclitaxel at 5 μM. GS-164 had however at least 1000-fold less growth inhibitory potency than paclitaxel in a series of cell lines.29 It was also found to have activity as a neuroprotective agent.30

Roussi et al. prepared analogs based on a cholic acid precursor (Figure 8). The key cis A–B ring junction provides a U-shaped conformation similar to that of baccatin III. None of the analogs showed inhibitory activity against microtubule disassembly. Compounds 16a and 16c did reveal weak cytotoxicity to KB cells (IC50’s 2.7 and 7.2 μM, respectively), while 16b was not cytotoxic. It showed modest inhibition of microtubule assembly; the opposite of that from paclitaxel!31

Howarth et al. synthesized protected 17a−17d (Figure 8) based on the hypothesis that paclitaxel behaves as a GTP mimic, with the baccatin III core acting as the guanosine part of GTP and the side chain representing a triphosphate. The deprotected derivative was not prepared, but the protected analogs were weakly cytotoxic against the colon cancer cell line SW480.32 No results of microtubule disassembly assays were reported.

3. THE SOLUTION AND MICROTUBULE-BOUND CONFORMATIONS OF PACLITAXEL

As noted earlier, the bioactivity of paclitaxel is closely linked to its ability to bind to microtubules and stabilize them, leading to mitotic arrest.35–38 It has been presumed that the design of a simple bioactive analog of paclitaxel is likely to be successful if the resulting structure possesses a 3D shape closely matching the microtubule-bound conformation of paclitaxel. In this context, the determination of conformation becomes a matter of prime importance. The major conformational variations among candidube tubulin-binding structures are in the C13 side...
chains as illustrated by Figure 9. For additional details, see the Supporting Information.

Various conformationally constrained taxoids have challenged the proposed polar hydrophobic collapse and nonpolar poses. Georg prepared bridged analogs 18a and 18b (Figure 10) as a test of the “hydrophobic collapse” conformation, but neither demonstrated tubulin-assembly activity, providing indirect evidence that the bound state is unlike this conformation.42

A series of macrocyclic taxanes was prepared by Ojima to test his proposed common pharmacophore for paclitaxel and the epothilones.43 Bridged compound 19 (Figure 11) gave an IC50 value of 0.39 μM against human breast cancer cells (MDA-435yLCC6-WT) and 37% tubulin polymerization vs paclitaxel. This is a reversal of the pattern found in most of the other compounds discussed herein; with good tubulin polymerization activity but weaker activity against cells. This could mean that 19 operates by a different mechanism against cells than paclitaxel. A later paper reported the synthesis of 19 and a large number of similar congeners with differing ring sizes, but 19 was the most active in the series.44

Two nontaxoids, 20 and 21 (Figure 12), were also prepared by Ojima to test the common pharmacophore concept.45 Both compounds showed only micromolar cytotoxicities against four different cell lines and no tubulin assembly activity. It would appear that the limited cytotoxic activities arise by a mechanism of action different from that of paclitaxel.

Ojima also prepared bridged 22 (Figure 13) and some related compounds based on the X-ray crystallographic structure of paclitaxel. Compound 22 was the most cytotoxic (IC50 0.067 μM, LCC6-WT human breast cancer cells) compared with 0.004 μM for paclitaxel, but no tubulin assembly data were reported. Thus, the mechanism of action was not established.46

These results, taken together, indicate that the activities of bridged paclitaxels vary widely with the nature of the bridging linker, but that none of the proposed models are capable of guiding the synthesis of constrained analogs with activity superior to paclitaxel itself.

Two other conformations for the tubulin-bound structure of paclitaxel have been proposed. The T-taxol structure was initially identified by one of us by mapping to the electron crystallographic density.41 The related rotational echo double resonance (REDOR)-taxol structure was proposed by Ojima in 200540 based on initial REDOR experiments reported in 2000 by Bane et al.47 The structure was modified48 by a second set of REDOR NMR data49 and by modeling the structure in a reshaped 1JFF tubulin structure.50 T-taxol and REDOR-taxol differ considerably in the C13 side chain conformations leading to alternative orientations of the C2′ hydroxyl group and the two terminal phenyl moieties emanating from C3′. These deviations furnish a molecular volume for the REDOR conformer that is ~15 Å3 larger than the T-taxol conformer. The two conformations have been compared by Ojima48 and by Snyder51−53 with significantly different conclusions. High

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**Figure 9.** Conformations of paclitaxel: (a) nonpolar,36−38 (b) polar collapsed,37,39 (c) extended,37,38 (d) REDOR taxol,40 (e) T-taxol.41

**Figure 10.** Bridged analogs presumed to mimic the “hydrophobic collapse” conformation of paclitaxel.

**Figure 11.** Bridged paclitaxel analog mimicking the “common pharmacophore” conformation of paclitaxel.

**Figure 12.** Nontaxoid analogs to mimic the “common pharmacophore” conformation of paclitaxel.

**Figure 13.** Bridged analog that mimics the X-ray structure of paclitaxel (22).
level density functional calculations suggest the T-taxol conformation to be 5–7 kcal/mol more stable than the REDOR form.\textsuperscript{53} Despite the differences, the general outline of the microtubule-bound conformation is clear enough to allow the design of simplified analogs with a somewhat common overall shape.

Experimental validation of the taxol binding conformation, or a closely related form, was provided by a series of REDOR NMR experiments on labeled paclitaxels. The first analysis in 2000 employed the labeled paclitaxel 23,\textsuperscript{47} while a second set of REDOR measurements was performed on labeled 24 and 25 (Figure 14).\textsuperscript{49} These studies led to the assignment of intermolecular distances shown in 26 and 27 (Figure 15).\textsuperscript{49}

Intermolecular 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.\textsuperscript{49} Both the T-taxol and the REDOR-taxol conformations are consistent with the REDOR NMR data, although neither set of distances predict the T-taxol and the REDOR-taxol conformations are consistent with the electron crystallographic T-taxol/tubulin structures\textsuperscript{41,56} as being the best models of the tubulin-bound conformation of paclitaxel. The question remains, is it possible to construct compounds that retain paclitaxel’s bioactivity with the same basic shape but with much less structural complexity?

### 4. SIMPLE COMPOUNDS BASED ON THE MICROTUBULE-BOUND CONFORMATION OF PACLITAXEL

Bridged bicycles 31–34 (Figure 17) were prepared by Ganesh et al. as an attempt to design bioactive compounds based on the T-taxol conformation.\textsuperscript{57} All had similar antiproliferative activities, with IC_{50} values in the 10–18 \mu M range against the A2780 cell line, as opposed to 0.02 \mu M for paclitaxel. All were able to promote tubulin assembly and stabilize the resulting microtubules to cold-induced disassembly at a dose of 30 \mu M, compared with paclitaxel’s IC_{50} of 0.4 \mu M. Thus, these compounds exhibit definite but weak tubulin-assembly activity as well as antiproliferative activity.

Compound 32 was modeled into the \beta-tubulin paclitaxel-binding site and shown to be able to adopt a conformation similar to T-taxol with the C-4 and C-13 side chains matching closely. The C-2 benzoyl phenyl ring overlapped that of

![Figure 14. Labeled paclitaxels used for REDOR internuclear distance determinations.](image)

![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-CD3 acetate, and C3'phenyl (p-F).](image)

![Table 1. Comparison of Predicted and Observed Internuclear Distances (Å) for Microtubule-Bound Paclitaxel](table)

![Figure 16. Constraining paclitaxel analogs with equal or better potency than paclitaxel.](image)
Unbridged 35 was the best mimic of the REDOR-taxol conformation, with IC₅₀ values of 3.8–8.3 μM against a panel of four non-drug-resistant cell lines; paclitaxel had IC₅₀ values of 0.002–0.05 μM when tested against the same cell lines. Compound 35 showed weak binding to tubulin, as determined by displacement of the fluorescent paclitaxel analog Flutax-2 with an estimated binding constant of 50–100 μM. Bridged 36 was inactive to all cell lines except the A2780 ovarian cancer line, where it furnished an IC₅₀ of 15 μM against the A2780 ovarian cancer cell line. These values compare with 0.015 μM for paclitaxel in the same assay. Interestingly the open-chain alkaloid 38 was almost as potent as the bridged alkaloid 37, indicating that bridging in this molecular system has no significant effect on activity.

The compounds proved to be relatively insoluble in water even as salts, leading to an important discovery for their tubulin assembly activity. The initial good tubulin assembly activity was subsequently reinterpreted to be a false positive due to light scattering by insoluble substances. Determination of tubulin assembly activity by the alternative method of observing DAPI fluorescence (4′,6-diamidino-2-phenylindole) failed to detect significant tubulin polymerization.

The failure of bridged 37 to show significantly increased activity compared with open chain 38 is in telling contrast with the case of the bridged A-nor-taxol 40 with at least 20-fold improved antiproliferative activity compared with its unbridged precursor 39 (Figure 20). The reasons for these differences are not well understood at present.

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**6. SUMMARY AND CONCLUSIONS**

A summary of the structures and bioactivities of the compounds discussed is provided in the Supporting Information, Table S1. Attempts made to date to design simplified mimics of paclitaxel with bioactivities similar to those of paclitaxel have so far not been completely successful. None of the mimics combines significant activity in cells with significant tubulin-assembly activity. In terms of cell-based activity, the simple analogs 7a and 7b are the most potent, with activities ranging from 3.5- to 7.7-fold less potent than paclitaxel in three different cell lines. This substantial activity is unlikely due to tubulin-assembly, however, since these compounds are 120–200-fold less potent than paclitaxel, and most of the remaining compounds are at least 100-fold less potent. Compounds 20 and 35 are exceptions with potencies only 1–2 orders of magnitude less than paclitaxel against drug-resistant cell lines.

The situation for tubulin-polymerization activity is more complex, since different papers report the results in different ways. In sum, the only really active analogs are Klar’s pentacyclic compounds, of which 9a and 9b are good examples. These compounds appear to be more potent tubulin polymerization agents than paclitaxel, although the data were determined in an unusual way, and paclitaxel appears to be less active under these conditions than might have been expected.

The final point to note is that efforts to lock some of the simple compounds into the electron crystallographic taxol-tubulin conformation do not appear to improve bioactivity. In fact, it can be reduced. Bridged 36 is significantly less active than the similar but unbridged 35, while bridged 37 and its...
The reasons for the failure to develop simple bioactive tubulin-assembly promoters based on the T-taxol-tubulin structure and the related REDOR pharmacophore are not completely clear, since the structural target was highly successful in the design of bridged paclitaxel derivatives with improved activity. There may be several reasons for this. One impediment for the simplification mimics is likely to be their high insolvency and possibly poor membrane penetration, which presumably reduces their cellular uptake and their ability to encounter tubulin. Second, several important factors most certainly center around differences in molecular size, in particular, as it relates to the large taxane binding pocket and the discrepancy between the 3D space occupied by taxol and the simplified ligands. The latter not only access fewer contact anchor points, but it is likely they only poorly match key pharmacophore elements as indicated in Figure 21. There is little chance that 7a and 7b, two of the most active truncated paclitaxel analogs to date, can employ the same set of contacts with tubulin, implying that if they bind to the taxane binding pocket, they must certainly adopt a significantly different binding pose. Alternatively, as argued above, these compounds may likely find a binding nest somewhere else on the protein. Consequently, using the paclitaxel binding conformation or pharmacophore in the design phase for such significantly pruned agents would be misleading. This contrasts with bridged analogs like 28–30, which retain the full baccatin core and are constrained closely to the paclitaxel binding conformation.

A third barrier to promoting tubulin assembly is likewise related to molecular size. The volume of T-taxol solved in 1JFF is 831 Å³, while those for the active truncated taxanes discussed herein (7a and 7b) are only 376 and 391 Å³, respectively, a little under half the volume. Compounds 9a and 9b, which promote potent tubulin polymerization but fail to kill cells, likewise occupy only 60–65% of the volume presented by paclitaxel. Ligand occupation of tubulin protein clefts displaces water molecules into the microtubule lumen contributing to the free energy of binding (ΔG) via −TΔS. This term can be significant for many taxanes. Small molecules, however, carry a reduced capacity to dislodge water molecules from the same pockets. Thus, even if favorable geometries might be achieved by truncated taxanes, a combination of fewer ligand protein contacts, alternative binding poses, and an entropy disadvantage for reduced subcavities may well limit the extent of potency equivalency relative to the taxanes, epothilones, and other agents known to bind the taxane site. The design and synthesis of a highly cytotoxic tubulin-assembly agent based on the paclitaxel pharmacophore thus remains an, as yet, unsolved challenge.

With the knowledge surveyed here, we project that a potentially more fruitful approach would focus on exploitation of the properties of the taxane binding pocket alone and ignore perceived or observed paclitaxel conformations. It is worth noting that the taxoid site is home to not only PTX but also the epothilones, discodermolide, dicyostatin, and eleutherobin and sarcodictyin A. While fully confirmed structures of the corresponding tubulin complexes are not known, a reasonable binding hypothesis recognizes that a subset of pharmacophore elements might be shared by these molecules as proposed for PTX and epothilone but that each structure likewise utilizes a separate set of pharmacophore points dictated by a combination of individual structure and available conformations. In addition, the large tubulin binding cavity most likely accommodates different ligands in slightly different subsites. This implies that the remaining unoccupied space can house both highly ordered and less tightly bound waters that contribute differently to each ligand binding profile. Consequently, a potentially effective strategy for designing novel and easily prepared scaffolds to mimic the biological effects of PTX might employ two complementary substrategies. First, a fragment-based approach has the capacity to identify and exploit novel sets of pharmacophore anchor points associated with unique binding poses. Second, exploration of the water network surrounding a bound ligand with tools such as Watermap or SZMAP and GAMEPLAN offers opportunities to take advantage of enhanced binding free energy contributions by solvent manipulation. This one–two structure-based ligand optimization process and, others like it, may well overcome the limitations of the more intuitive PTX-based approaches of the past.

Figure 21. Comparison of interatomic distances (Å) for taxol and 7a with the same C13-side chain conformation: (a) taxol (pdb code 1JFF) with distances from the C13 phenyl ring centroids and C3 to the oxetane oxygen; (b) compound 7a with similar distances to the spirocyclic oxetane oxygen.

**ASSOCIATED CONTENT**

Supporting Information

A discussion of the C13 side chain conformations of paclitaxel and a table summarizing the structures and bioactivities of all the compounds discussed. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

Biographies

David G. I. Kingston was born in London, England, and received his B.A. and Ph.D. degrees (Lord Todd and D. W. Cameron) from Cambridge University in 1960 and 1964, respectively. After postdoctoral appointments at M.I.T. and Cambridge, he moved to SUNY Albany in 1966 and then to Virginia Tech in 1971, where he is currently a University Distinguished Professor of Chemistry and Director of the Virginia Tech Center for Drug Discovery. He has...
worked extensively on the chemistry, microtubule binding, and nanoparticle delivery of paclitaxel. He has carried out conservation and drug discovery in Suriname and Madagascar, and he is currently using ethnobotany to search for antimalarial agents from plants. He is a recipient of the Research Achievement Award of the American Society of Pharmacognosy and the ACS Ernest Guenther Award for the Chemistry of Natural Products, and is a member of the National Advisory Council for Complementary and Alternative Medicine. He also serves as one of several lay pastors in his local church.

James P. Snyder was born in Seattle, WA, USA, and received his B.S. and Ph.D. degrees from St. Martin’s College and Cornell Universities, respectively, followed by postdoctoral fellowships at the Friedrich-Alexander and Columbia Universities. The subsequent road passed through university appointments, industrial research, and back to the university again: Yeshiva University (New York City), University of Copenagen (Denmark), Merck Sharp and Dohme (New Jersey), Searle Pharmaceuticals (Chicago), IRBM (Institute for Research in Molecular Biology, Rome, Italy), and Emory University (Atlanta, Georgia), where he is currently Director of Bistoructural Research. The same path has crossed chemical, structural, theoretical, biological, and biochemical boundaries that have been projected into a palette of multidisciplinary parallel investigations and a course for undergraduates that links our daily lives to the root fundamentals of science: “Chemistry Biology and Molecular Modeling”. He still rides his yellow scooter to work daily through the hills and dales of Atlanta.

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