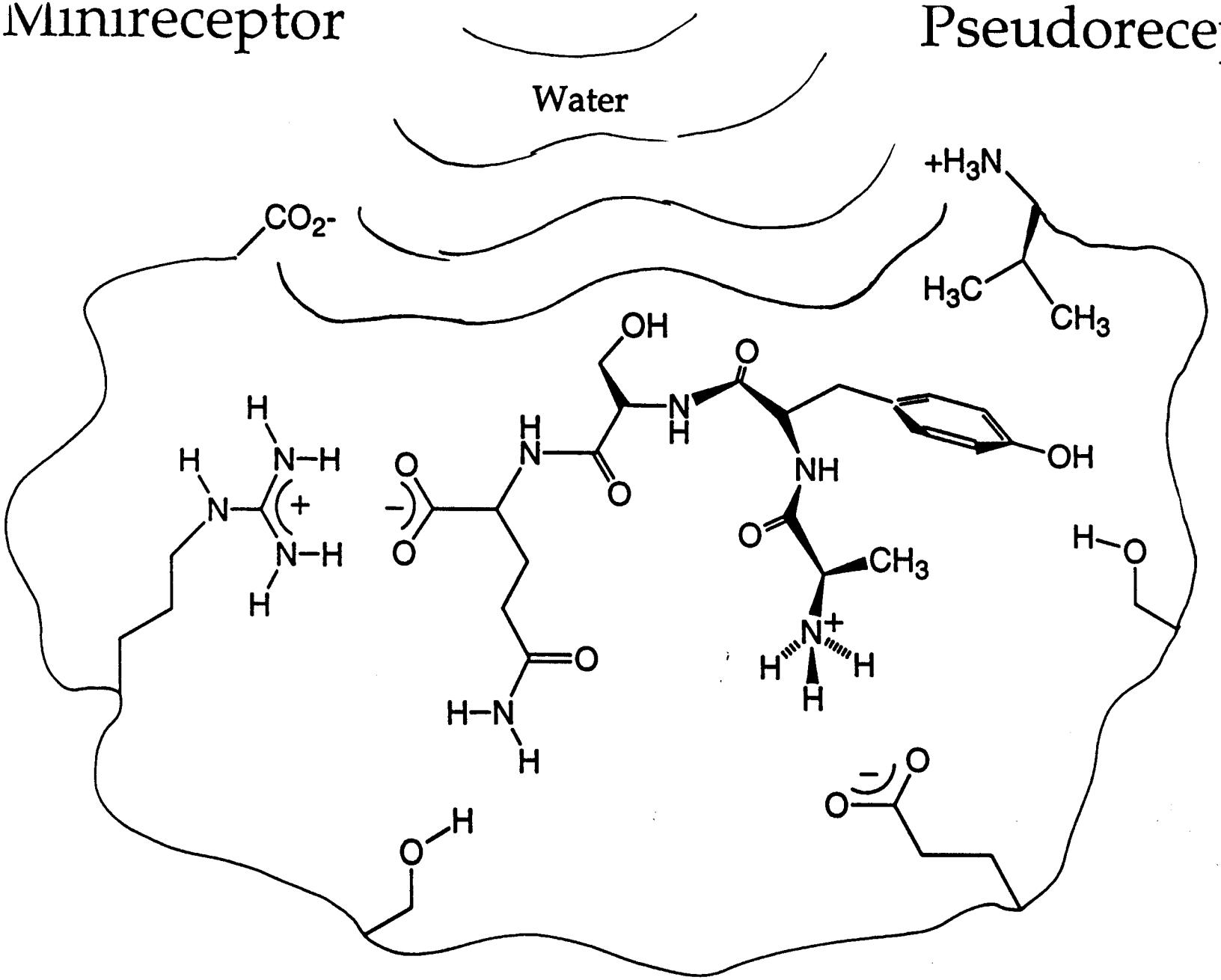
Minireceptor

Pseudoreceptor



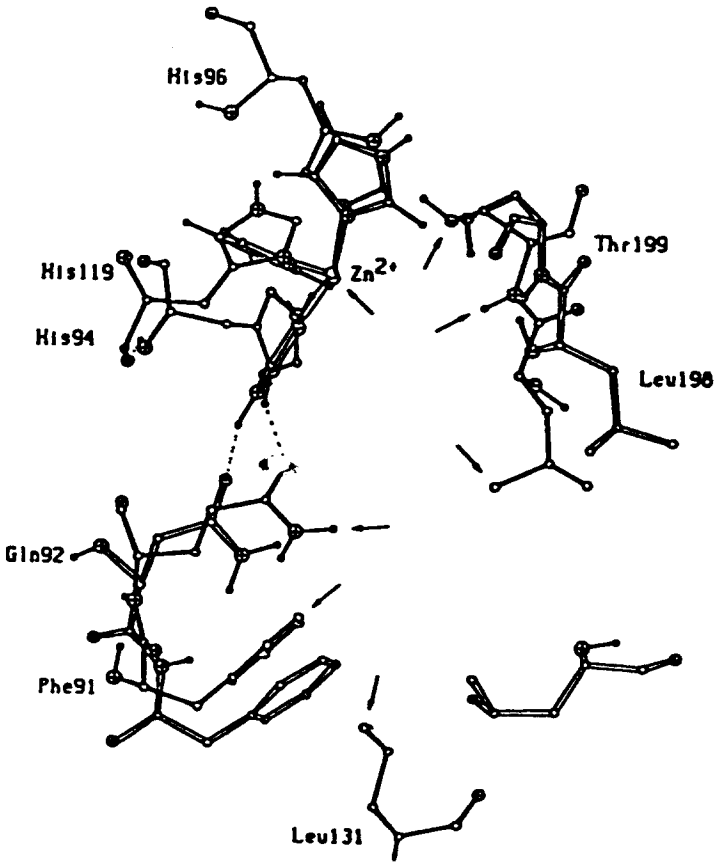
Pseudoreceptors and Minireceptors

- Flexible comparison of pharmacophore elements
- Mechanistic insights
- Selectivity by evaluating multiple receptors or subtypes
- $\Delta E_{bind}(rel)$ ($\Delta G_{bind}(rel)$ via Free Energy Perturbation
- 3-D searches as for enzyme X-ray structures
- *De novo* design

Minireceptor Enzyme Validation

- Simulate active site of Human Carbonic Anhyrase (2. Å resolution) with four potent docked sulfonamide inhibitors and the program YAK

- Nine residues targeted including the catalytic Zn

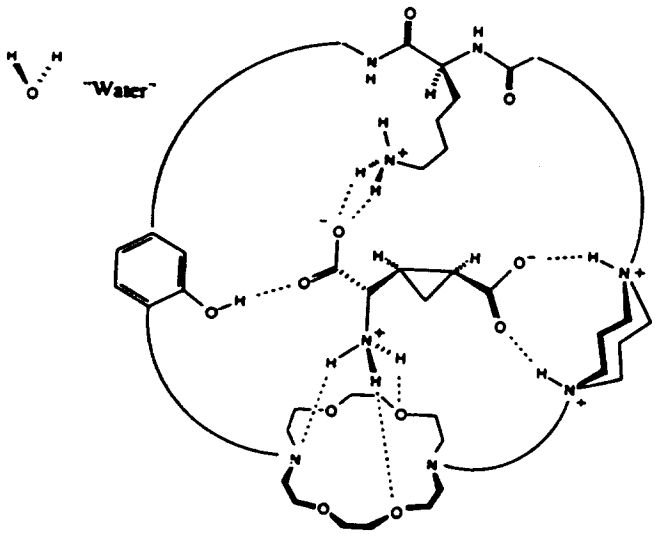


- Five of nine residues sited within 0.7 Å of X-ray positions; mean deviation for all nine 1.7 Å. For Thermolysin and 3 phosphorimidate inhibitors, average deviation of 1.3 Å for 12 AA side chains

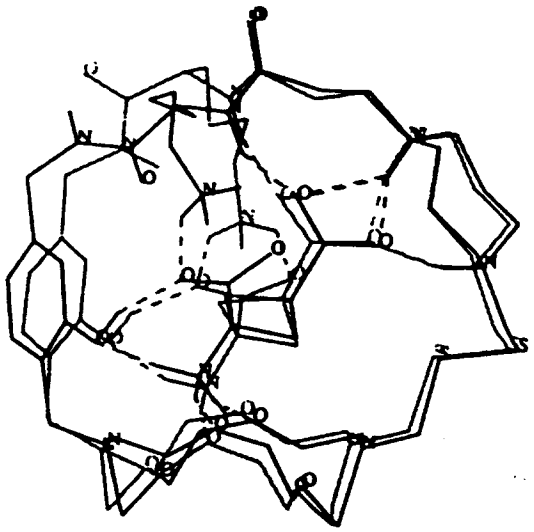
(Snyder, J.P.; Rao, S.N., Koehler, K.F.; Vedani, A. in "3D QSAR in Drug Design," Ed. H. Kubinyi, ESCOM, Leiden, 1993, pp 336-354)

NMDA Agonists Glutamic Acid Receptors

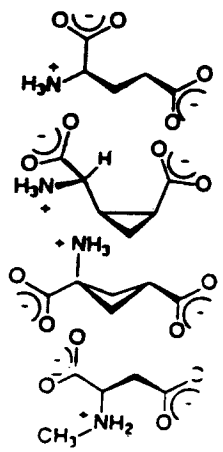
Schematic representation of the pseudoreceptor constructed around SRS-CPG. Curved lines correspond to molecular spacers between the key binding groups.



Comparison of the AMBER optimized *cis*-2,4-MG pseudoreceptor complexes before and after the F transformation MGA → S-GLU → MGA.



Comparison of experimental and predicted free energies of binding for NMDA agonists relative to (S)-glutamic acid: $\Delta\Delta G_{binding}$ ($\Delta G_{agonist}$ - $\Delta G_{S\text{-}GLU}$). kcal/mol, 277°K



	Ki(μM)	$^{277}\Delta G_{exp}$	$\Delta\Delta G_{exp}$	$\Delta\Delta G_{calc}$ H_2O	$\Delta\Delta G_{calc}$ $DE(\Delta r)$
S-Glu	0.036	1.8	0.0		
R-Glu	2.7	-0.55	2.4	16.9	1.8
SRS	0.009	2.6	-0.76	-2.0	-1.9
RSR	0.055	1.6	0.23	-3.1	-0.9
SSR	0.15	1.0	0.79	9.2	2.8
RRS	1.7	-0.29	2.1	4.4	0.1
MGA	0.052	1.6	0.20	—	1.4
NMDA	3.3	-0.66	2.5	—	1.3

(Snyder, J.P.; Rao, S.N., Koehler, K.F.; Pellicciari, R. in "Trends in Receptor Research," Eds. P. Angeli, U. Gulini, W. Quaglia, Elsevier, 1992, pp 367-403)

Taxol and Taxotere

- Isolated in limited quantities from the Western Yew tree and related species

- Exciting antitumor lead in early clinical trials:

  Drug refractory, advanced ovarian cancer
  Metastatic breast cancer
  Non-small cell lung cancer
  Head and neck cancer

- Unique mechanism of antimitotic action: promotes assembly and stability of microtubules

- Total synthesis in 1994:

  R. Holton et al, *J.Am.Chem.Soc.* **1994**, *116*, 1597
  K.C. Nicolaou et al, *Nature* **1994**, Feb. 17, 631

- Considerable SAR available

- No simple and bio-effective analogs known

Receptor Building and Design Templating

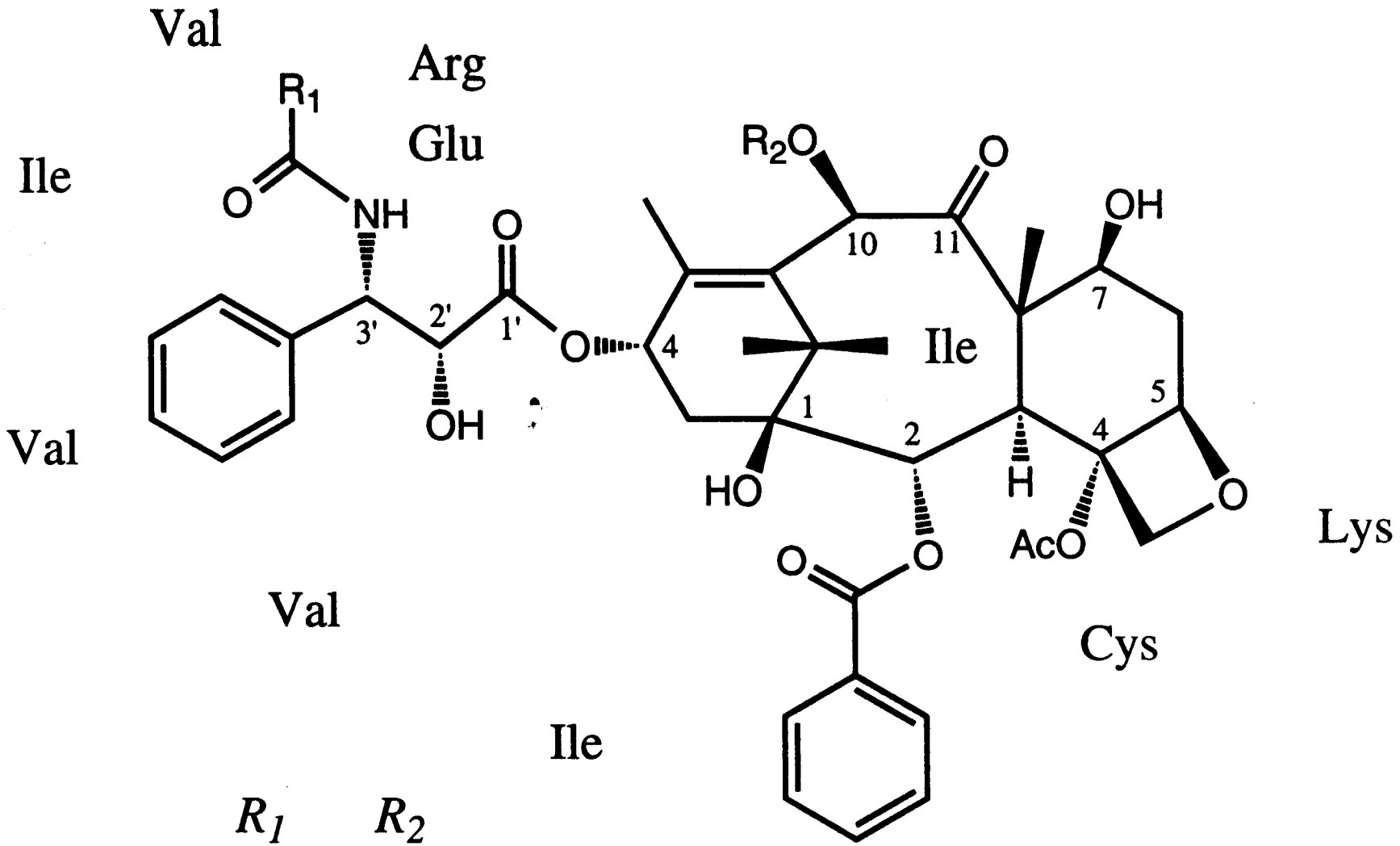
- Use taxotere/taxol conformations believed to be bioactive (Williams et al, *Tetrahedron* 1993, *49*, 6545; *Can. J. Chem.* 1994, *72*, 252)

- Taxotere surrounded by 11 amino acid side chains in accord with 31 β-tubulin N-terminal AA's (Rao et al *J. Biol Chem.* **1994**, *269*, 3132) and known taxane SAR

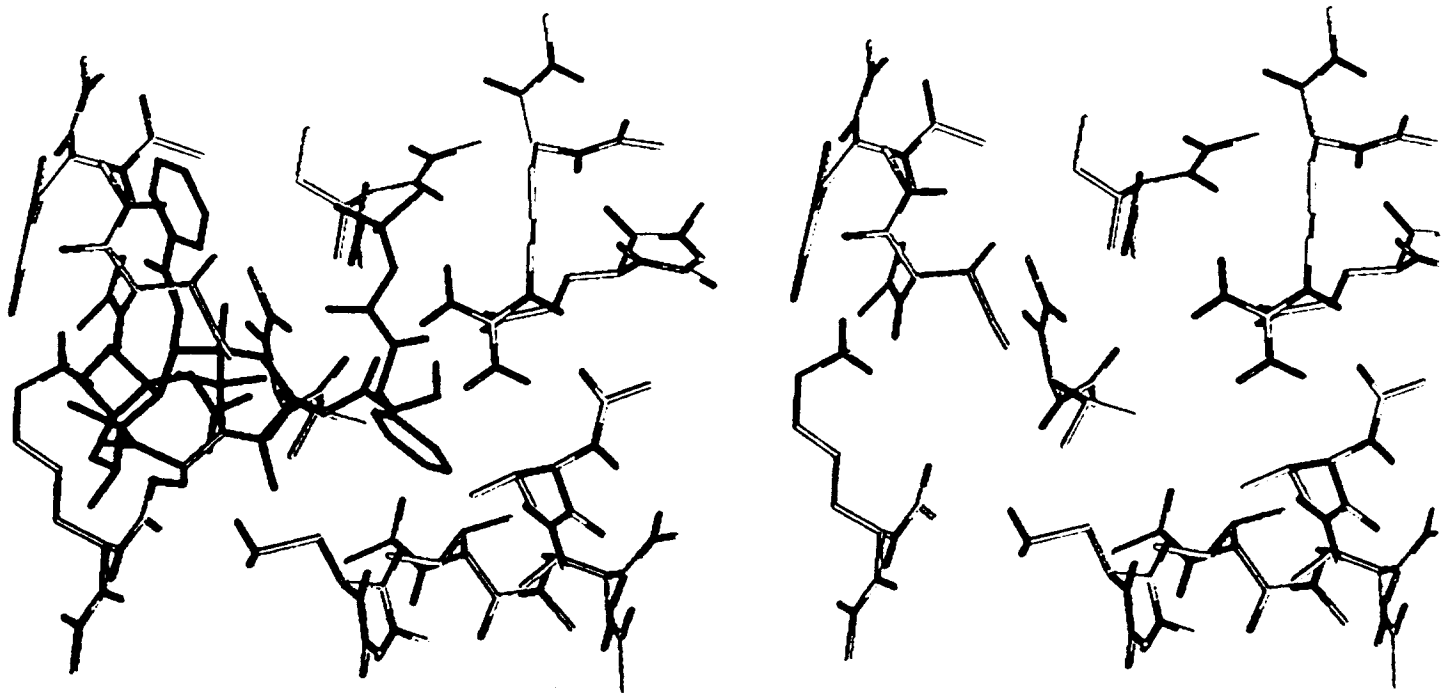
- AA's linked and resulting *pseudoreceptor* optimized with the AMBER force field

- AA's capped and resulting *minireceptor* optimized with AMBER

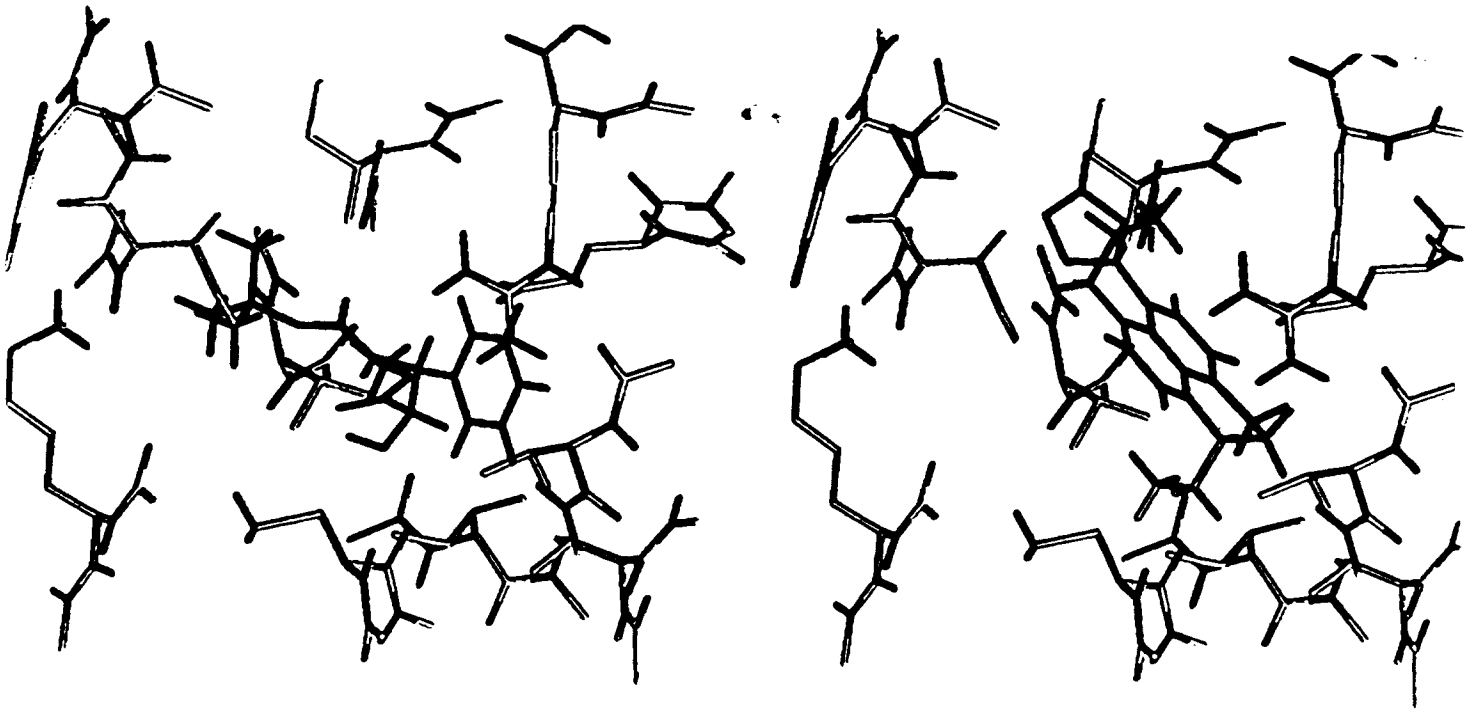
- Evacuated taxotere cavity searched with the *de novo* design tool LEAPFROG (Tripos)



	R_1	R_2
Taxol	Ph	Ac
Taxotere	t-BuO	H



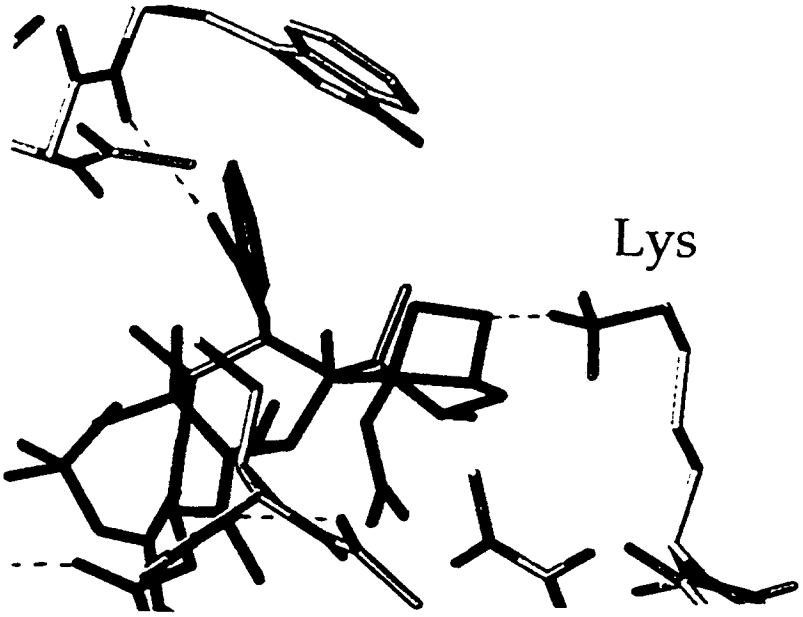
Taxol/Taxotere capped minireceptor showing taxotere optimized interactions (left); receptor cavity (right)



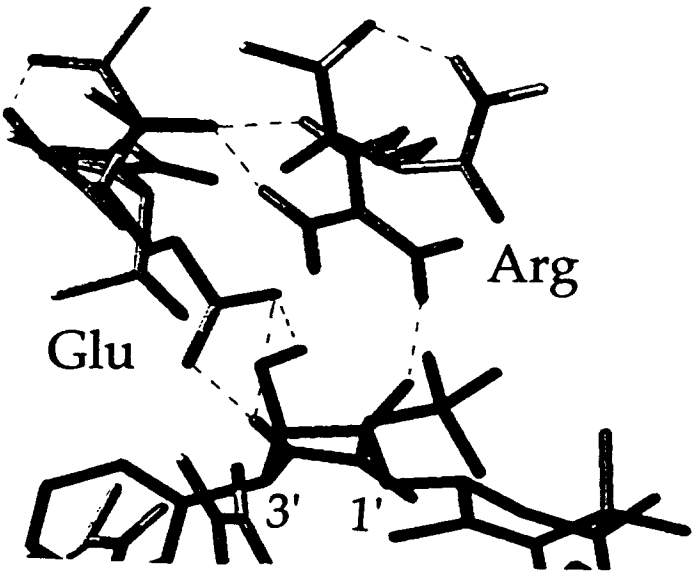
Minireceptor binding two Leapfrog generated ligands derived from *de novo* design

Taxol/Taxotere capped minireceptor; Key interactions between side chains and three important ligand centers

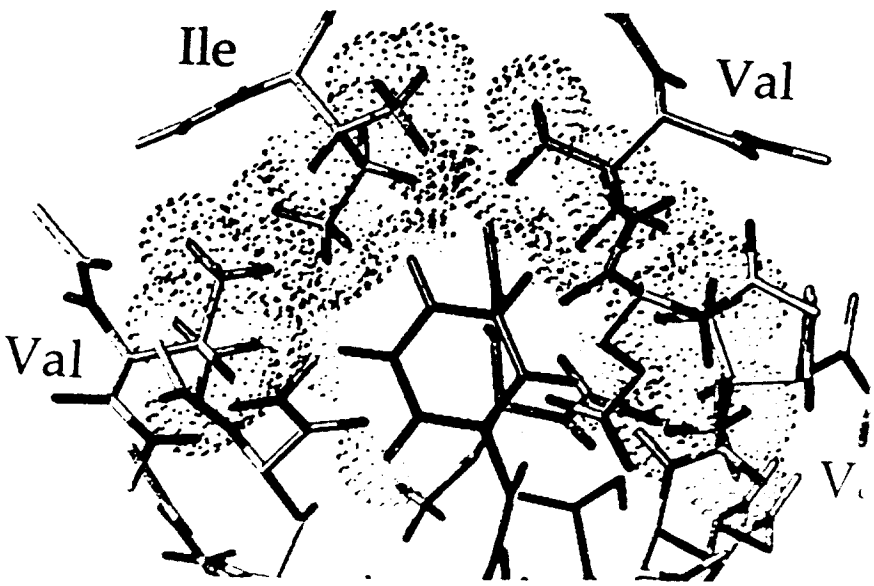
H-bond between Lys and O of oxetane ring

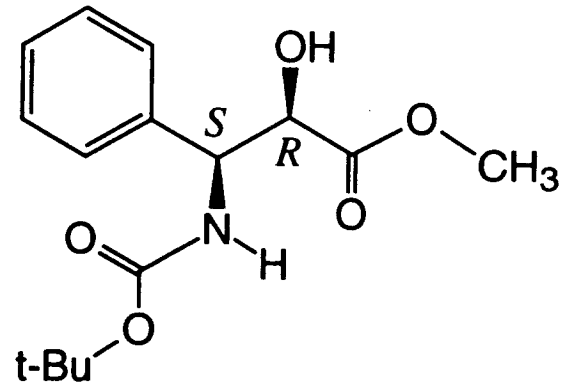


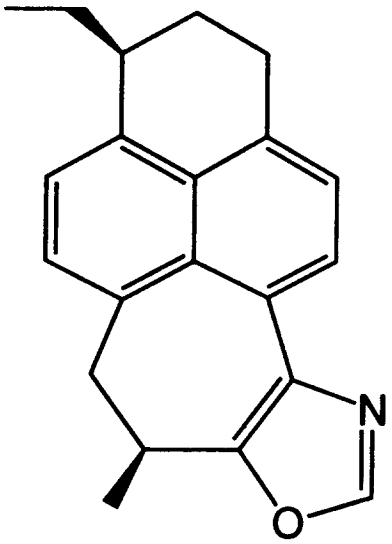
H-bonds between Glu/Arg and the hydrophilic groups on the C1'-C3' side chain of taxotere



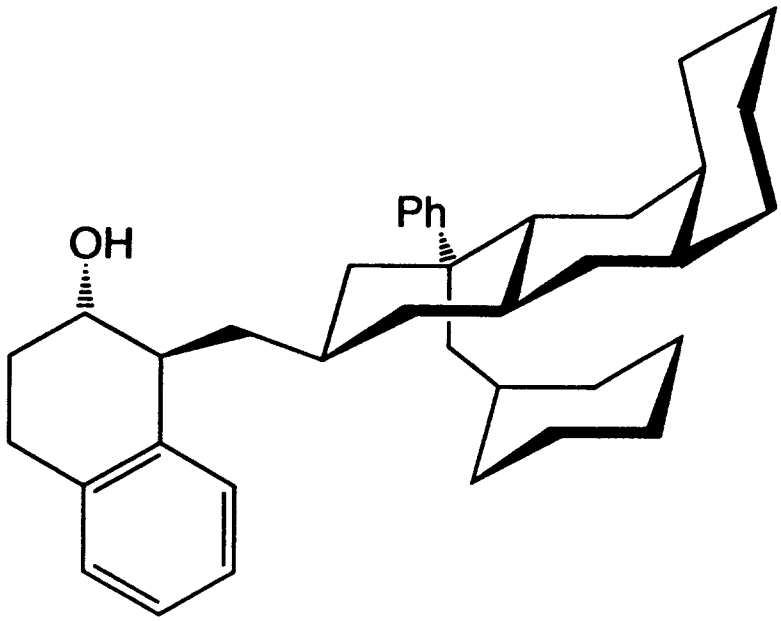
Hydrophobic pocket for Phenyl at C3' (Ile and 3 Val's)







LeapFrog Structures (Cramer, Tripos)



Conclusions

- o Mini- and pseudoreceptor construction facile and realistic
- o Semiquantitative prediction possible
- o Unique 3-D molecular design feasible
- o GrowMol design* and database screening underway

* Bohacek, R.S.; McMartin, C. *J.Am.Chem.Soc.* **1994**, *116*, 5560)

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