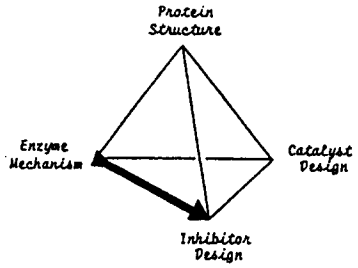
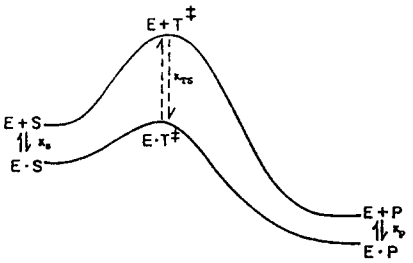
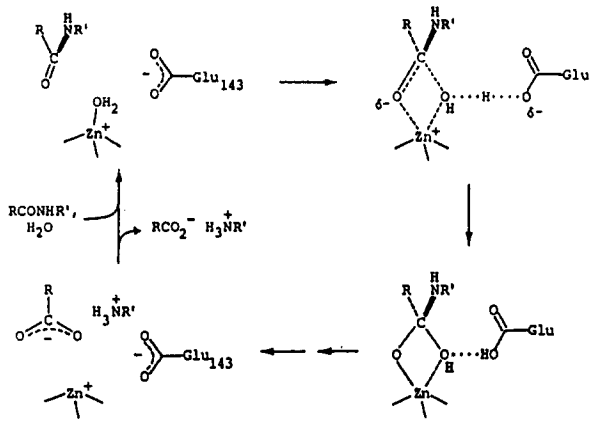
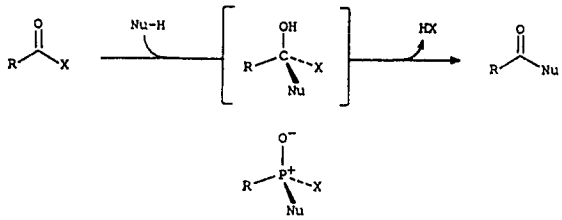
MECHANISM-DERIVED INHIBITOR DESIGN

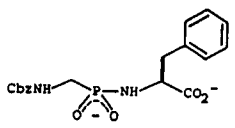




GENERAL BASE MECHANISM FOR ZINC PEPTIDASES

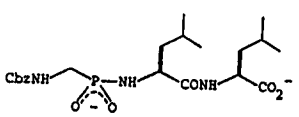






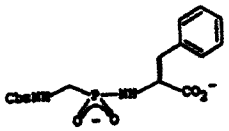
CbzGly^{P}Phe

K_i = 90 nM for carboxypeptidase A



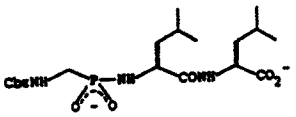
CbzGly^{P}LeuLeu

K_i = 9 nM for thermolysin



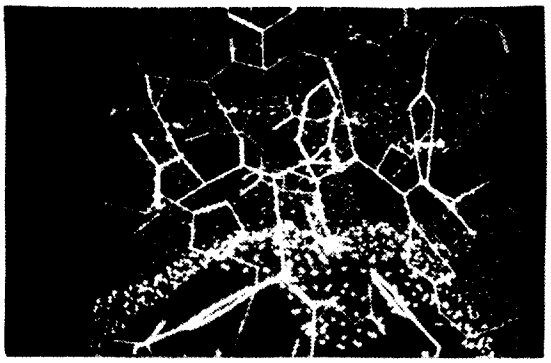
Cbz^{P}Phe

K_i = 90 nM for carboxypeptidase A



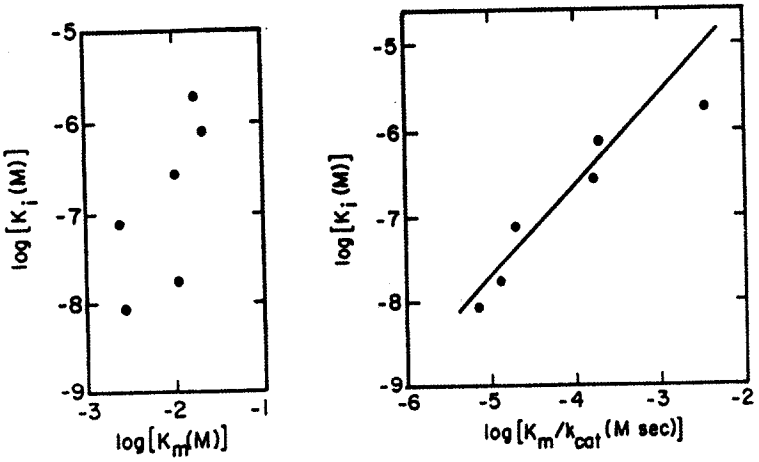
Cbz^{P}LeuLeu

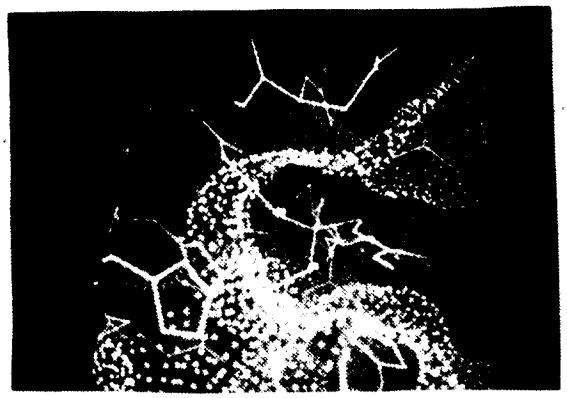
K_i = 9 nM for thermolysin

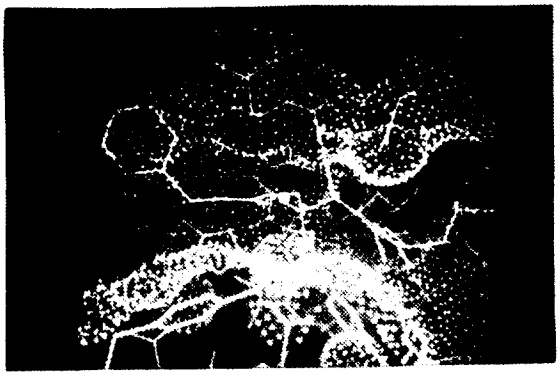


COMPARISON OF PHOSPHONATE AND PHOSPHONAMIDATE INHIBITORS OF THERMOLYSIN

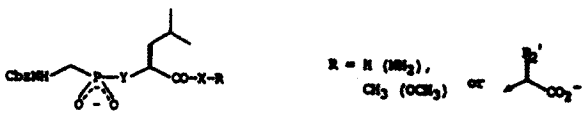
R = H or



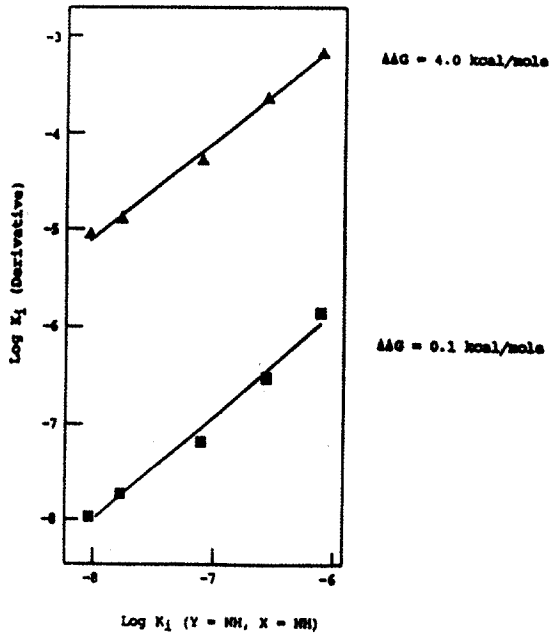


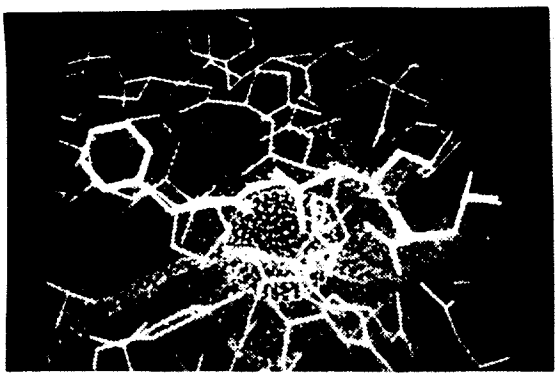


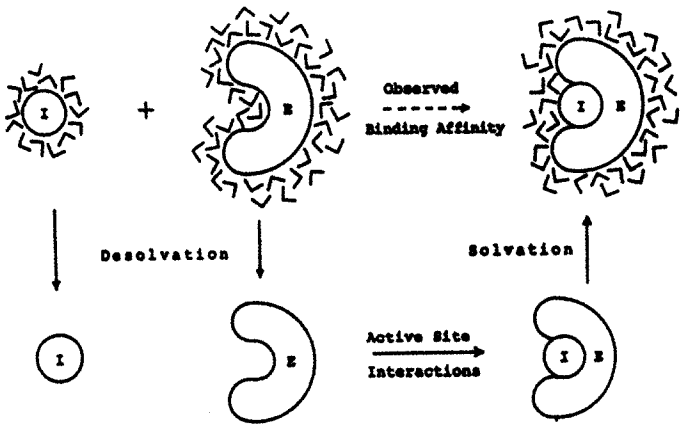
COMPARISON OF PHOSPHONAMIDE AMIDE AND ESTER INHIBITORS OF THERMOLYSIN



▲ Y = O, X = NH ■ Y = CH_2, X = NH

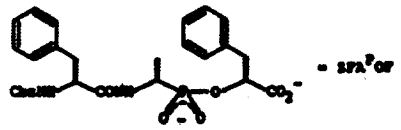


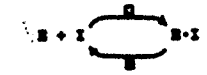


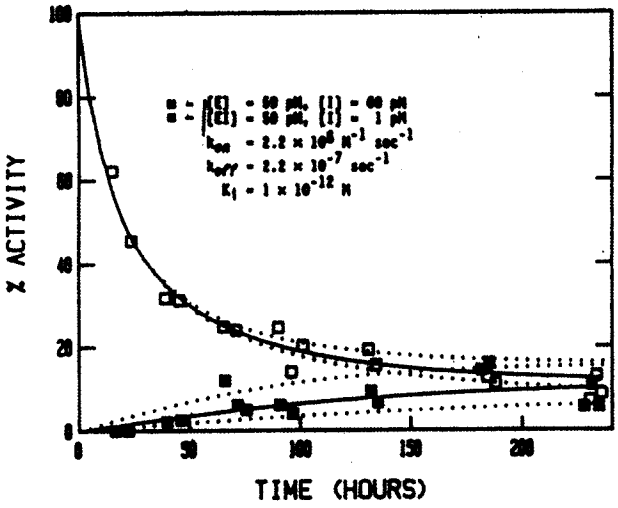


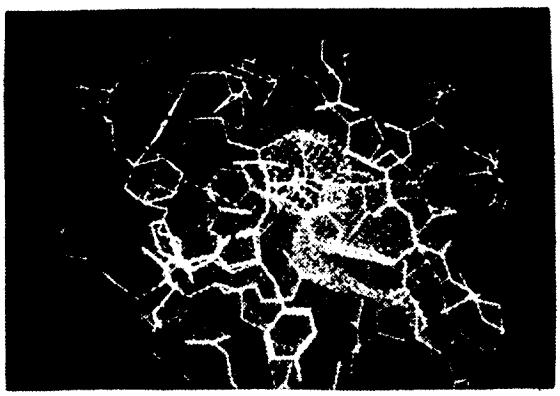
Differences in observed binding affinity are due to differences in:

Solvation of inhibitors
Conformational properties of inhibitors
Active site interactions
Direct: H-bonding/van der Waals/dipolar effects
Indirect: Lewis basicity of oxyanion/carbonyl

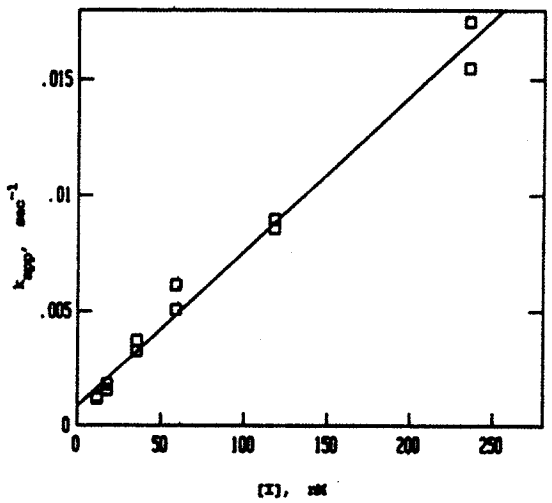






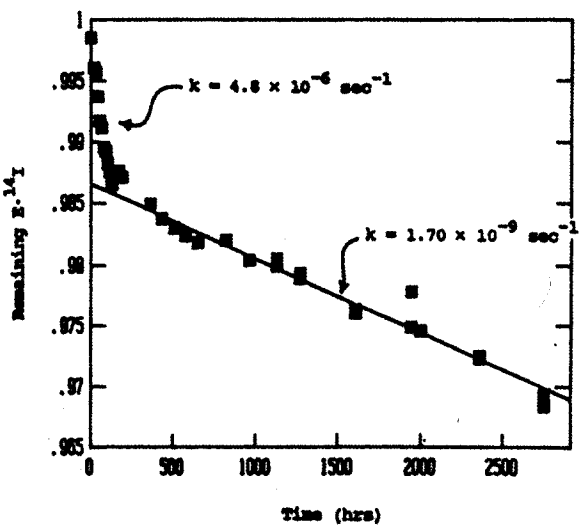


DISSOCIATION OF Cbz-Phe-Val^{P}-(O)Phe
Determination of k_{on}



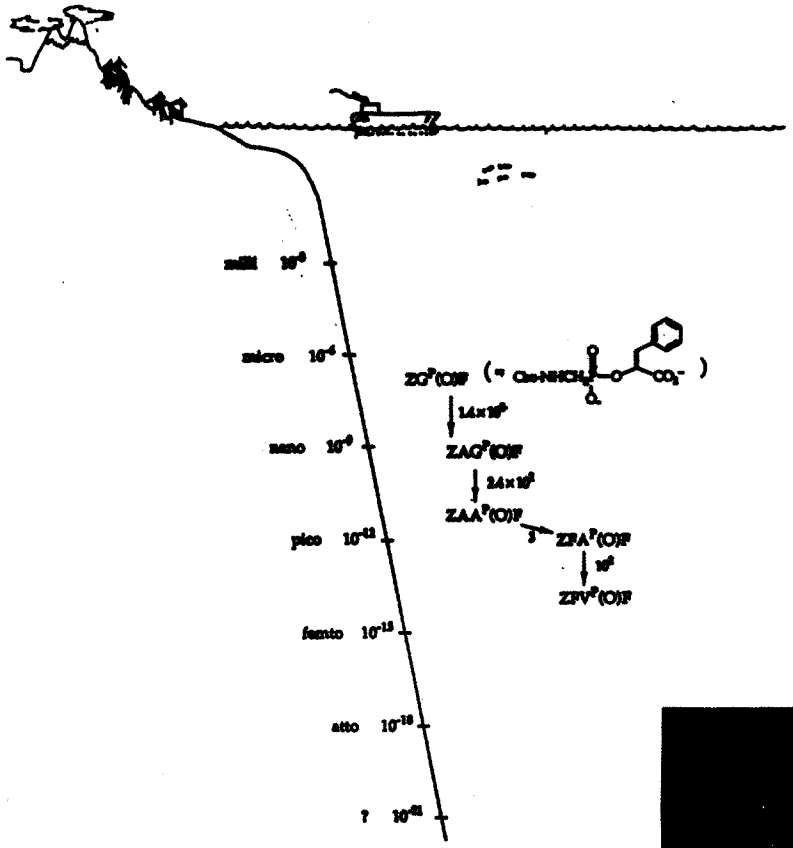
If $k_{on} = 1.8 \times 10^{8}\ M^{-1}\ sec^{-1}$, $K_i = 10$ nM $\Rightarrow$ $k_{off} = 1.8 \times 10^{-9}\ sec^{-1}$
$t_{1/2}$ for dissociation = 14.6 years

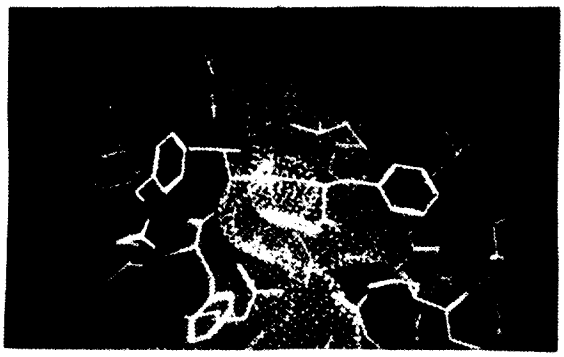
DISSOCIATION OF Cbz-Phe-Val^{P}-(O)Phe

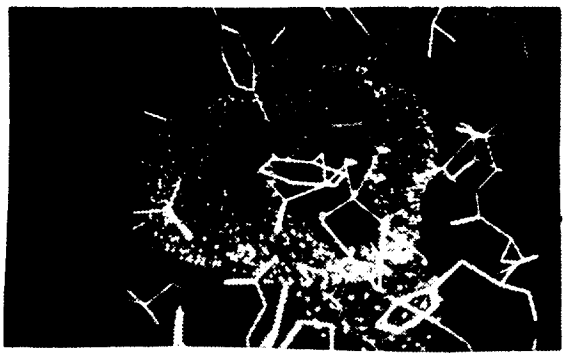


$$K_i = \frac{k_{off}}{k_{on}} = 11\ nM$$

Inhibition of Carboxypeptidase A

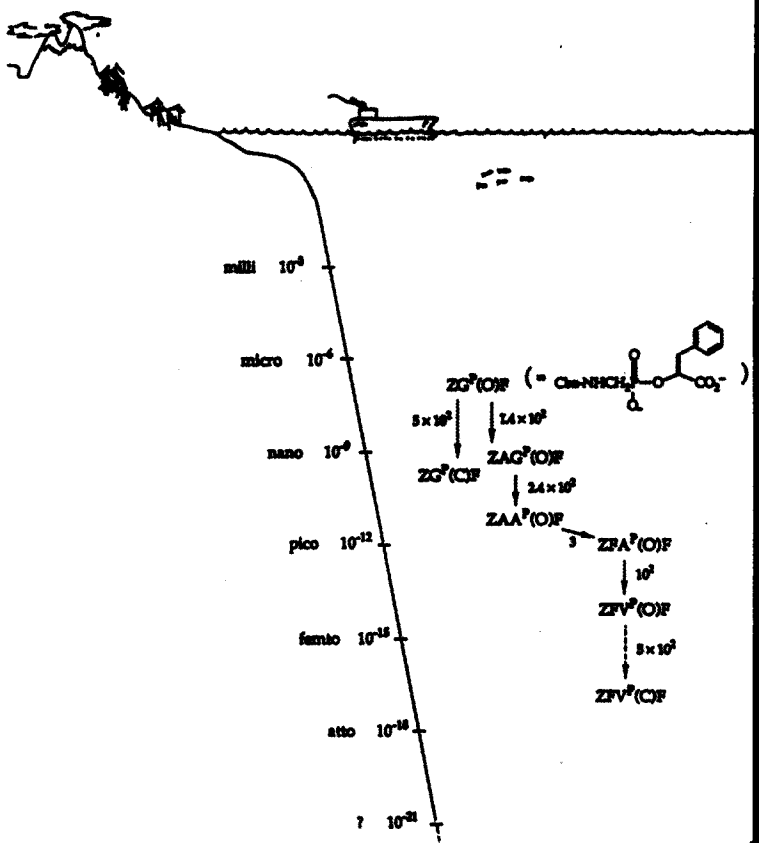




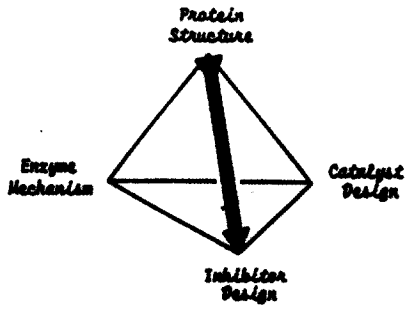


Inhibition of Carboxypeptidase A

How far down can it go?



STRUCTURE-DERIVED INHIBITOR DESIGN



Strategies for Enzyme Inhibitor Design

Mechanism-Derived

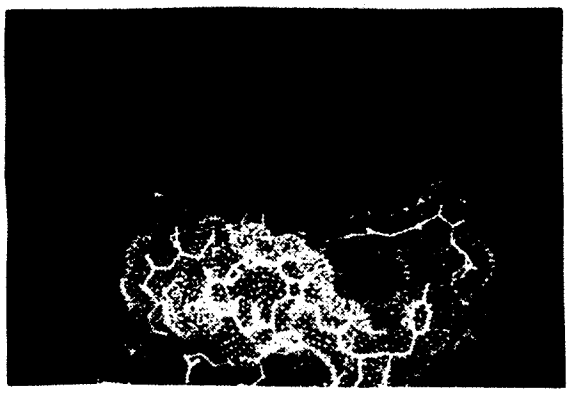
Information required:
- Structure of enzyme substrate
- Mechanism of enzymatic transformation

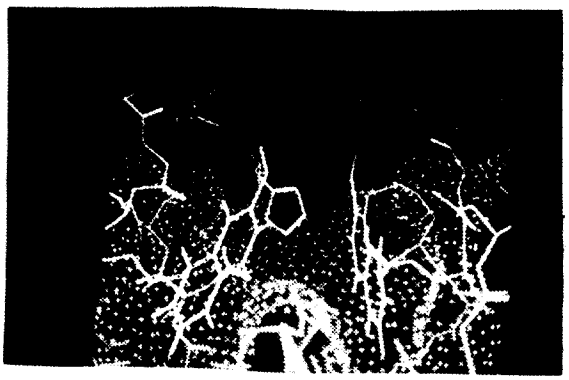
Types of inhibitors:
- Transition-state or multisubstrate analogs
- Suicide inhibitors

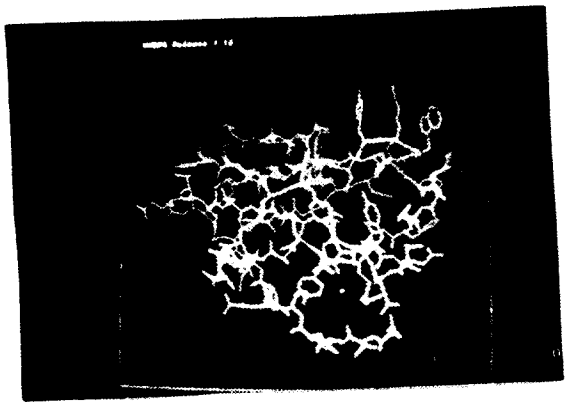
Structure-Derived

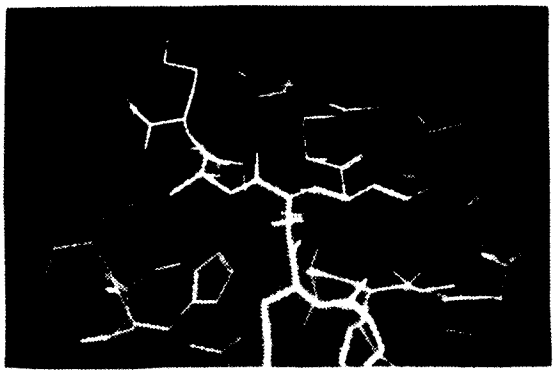
Information required:
- 3-Dimensional structure of protein ligand
- 3-Dimensional structure of protein binding site

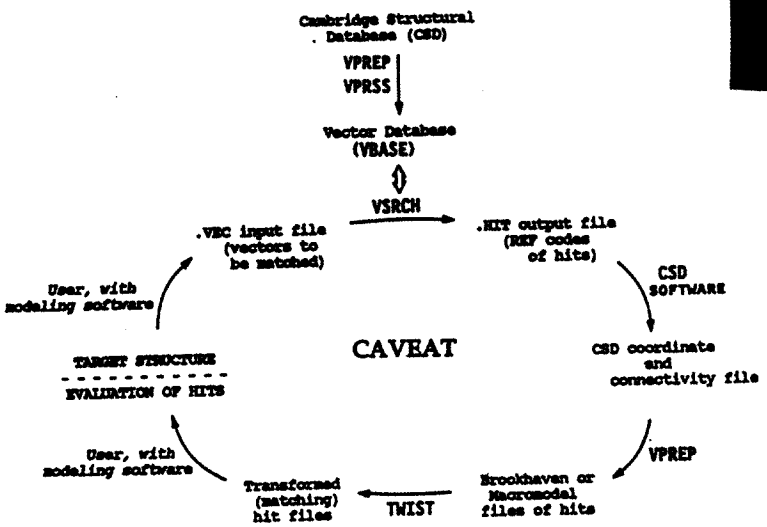
Type of inhibitors:
- Mimics of known ligands
- De novo inventions

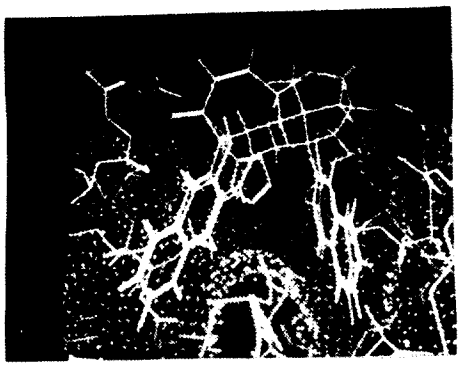


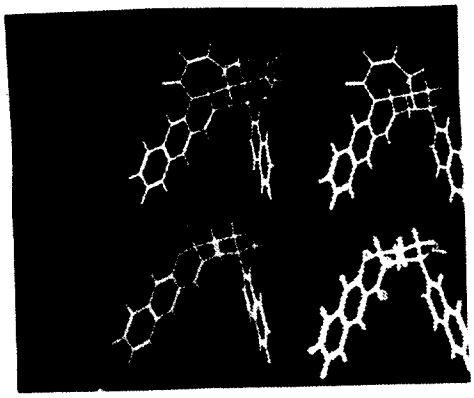


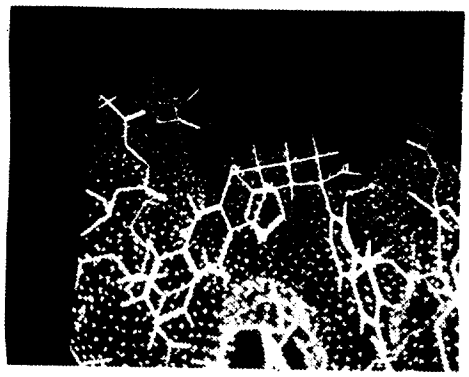


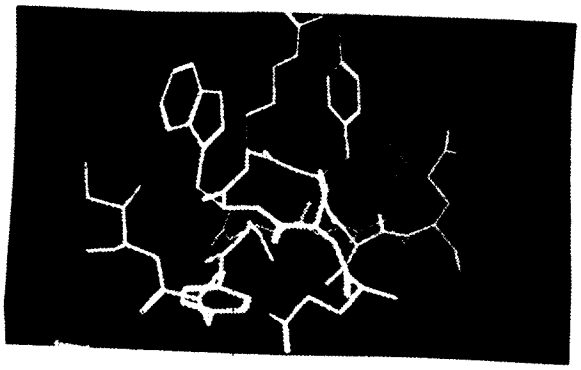


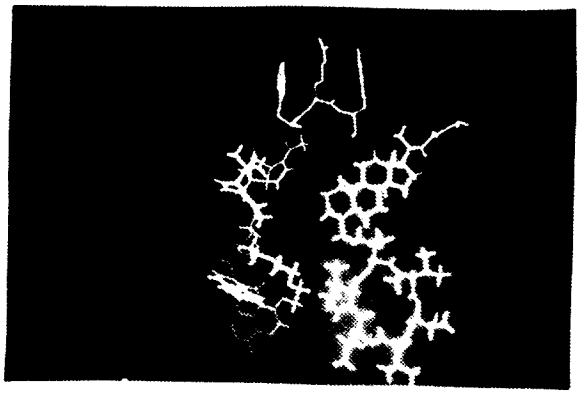

Cambridge Structural Database (CSD)
VPREP
VPRSS
Vector Database (VBASE)
VSRCH
.VEC input file (vectors to be matched)
.HIT output file (REF codes of hits)
CSD SOFTWARE
User, with modeling software
CAVEAT
CSD coordinate and connectivity file
TARGET STRUCTURE
EVALUATION OF HITS
VPREP
User, with modeling software
Transformed (matching) hit files
TWIST
Brookhaven or Macromodel files of hits

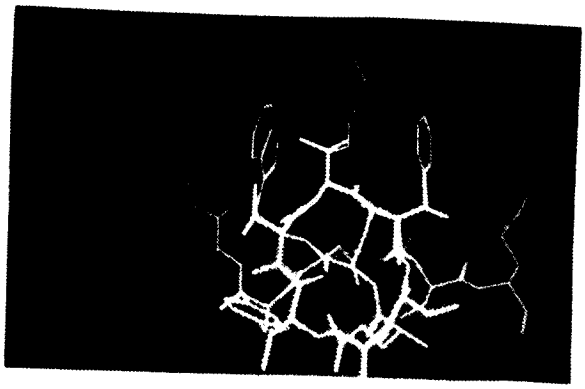


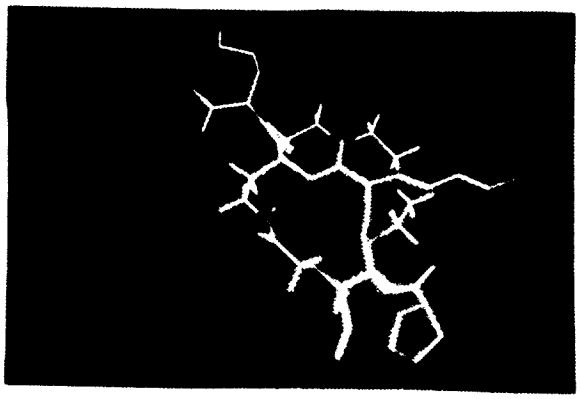


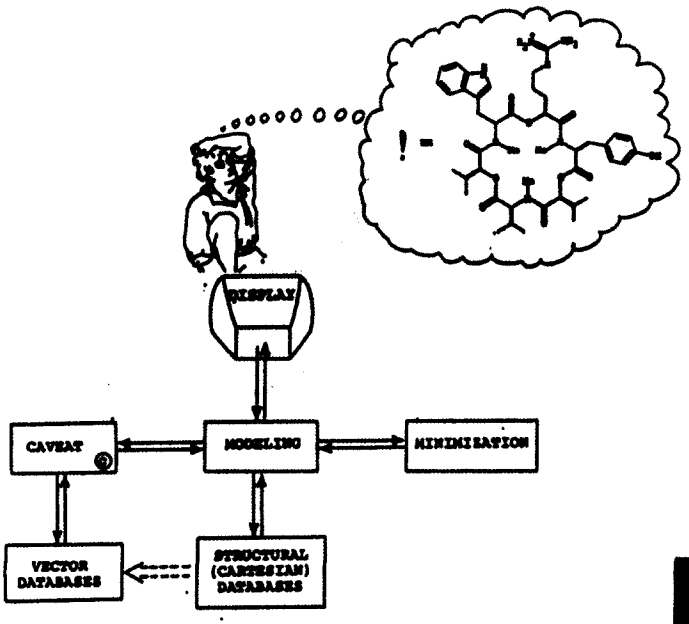


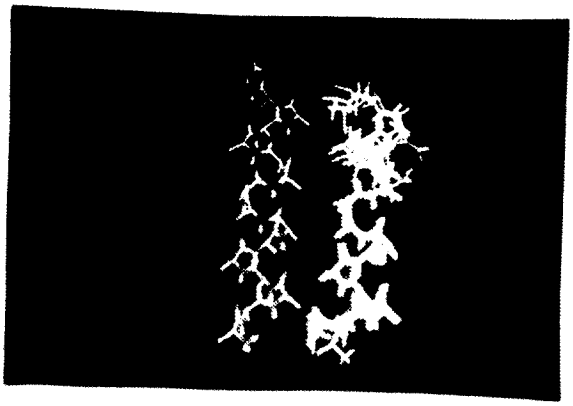


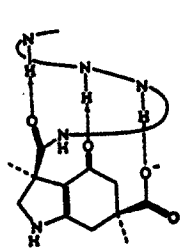


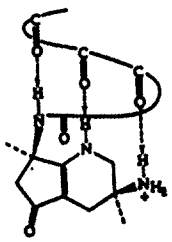


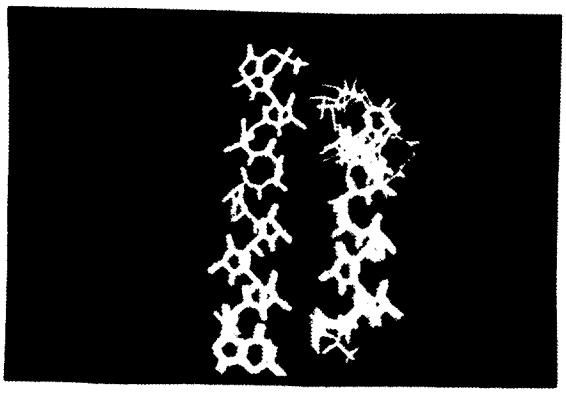


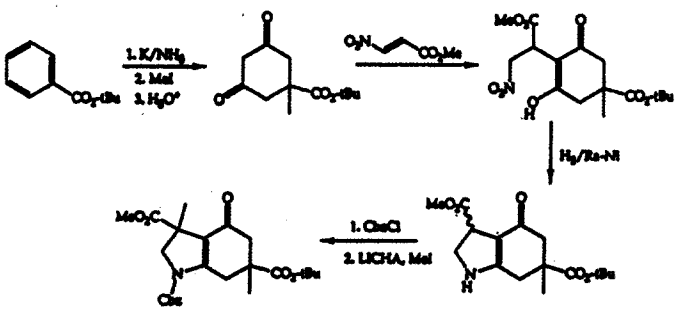

DISPLAY
CAVEAT
MODELING
MINIMIZATION
VECTOR DATABASES
STRUCTURAL (CARTESIAN) DATABASES

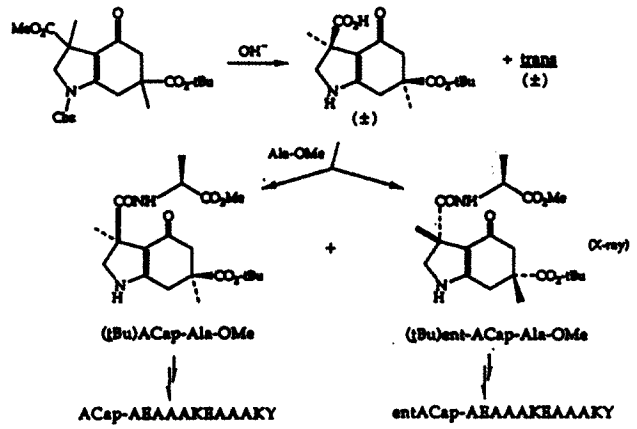


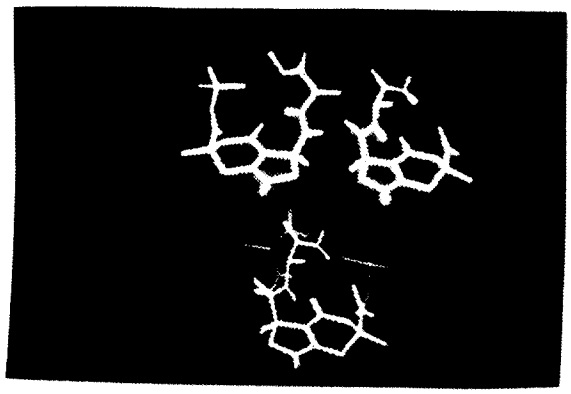


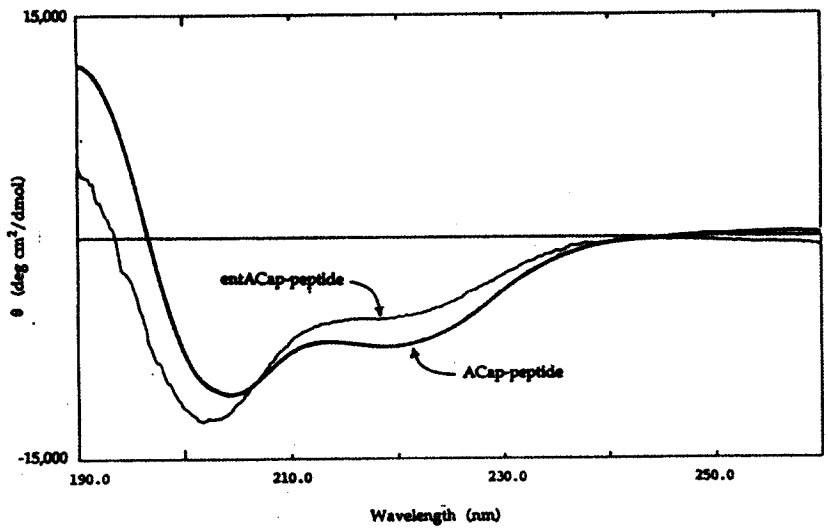





1. K/NH3
2. MeI
3. H3O+
O2N
CO2Me
MeO2C
H2/Ra-Ni
1. ClsCl
2. LiCHA, MeI


OH⁻
+ trans
(±)
Ala-OMe
+
(X-ray)
(tBu)ACap-Ala-OMe
(tBu)ent-ACap-Ala-OMe
ACap-AEAAAKEAAAKY
entACap-AEAAAKEAAAKY




15,000
-15,000
θ (deg cm²/dmol)
entACap-peptide
ACap-peptide
190.0
210.0
230.0
250.0
Wavelength (nm)