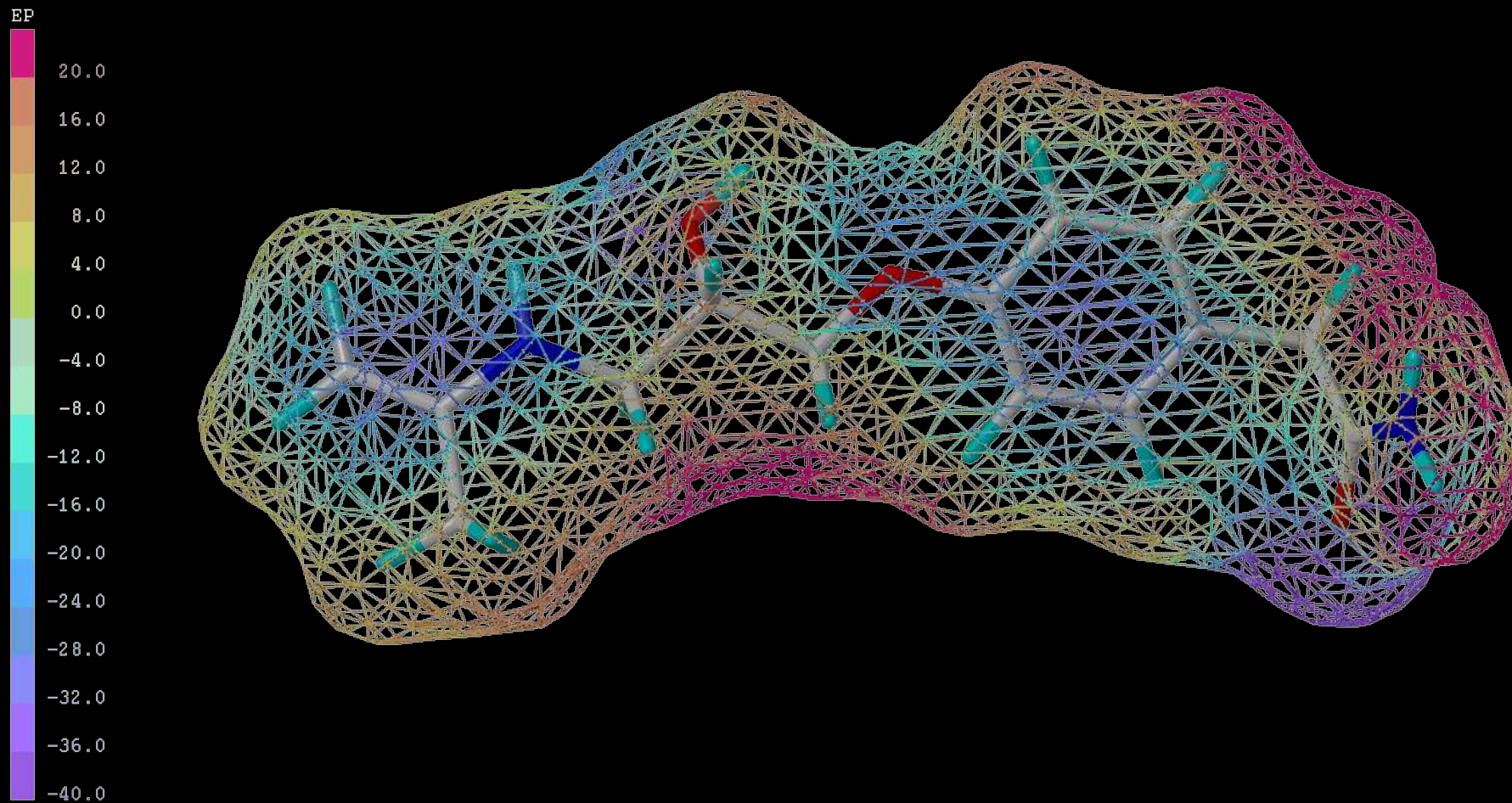
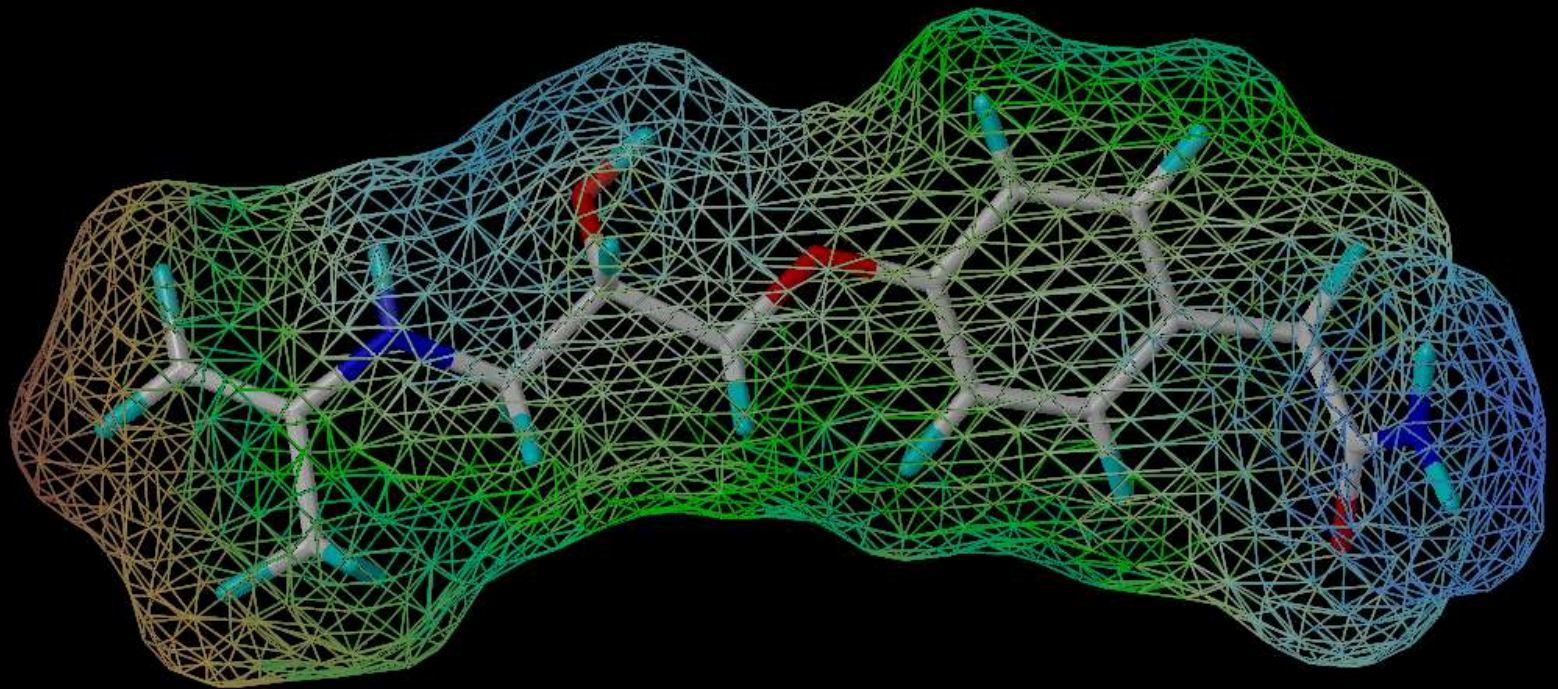


Elektrostatisches Potential

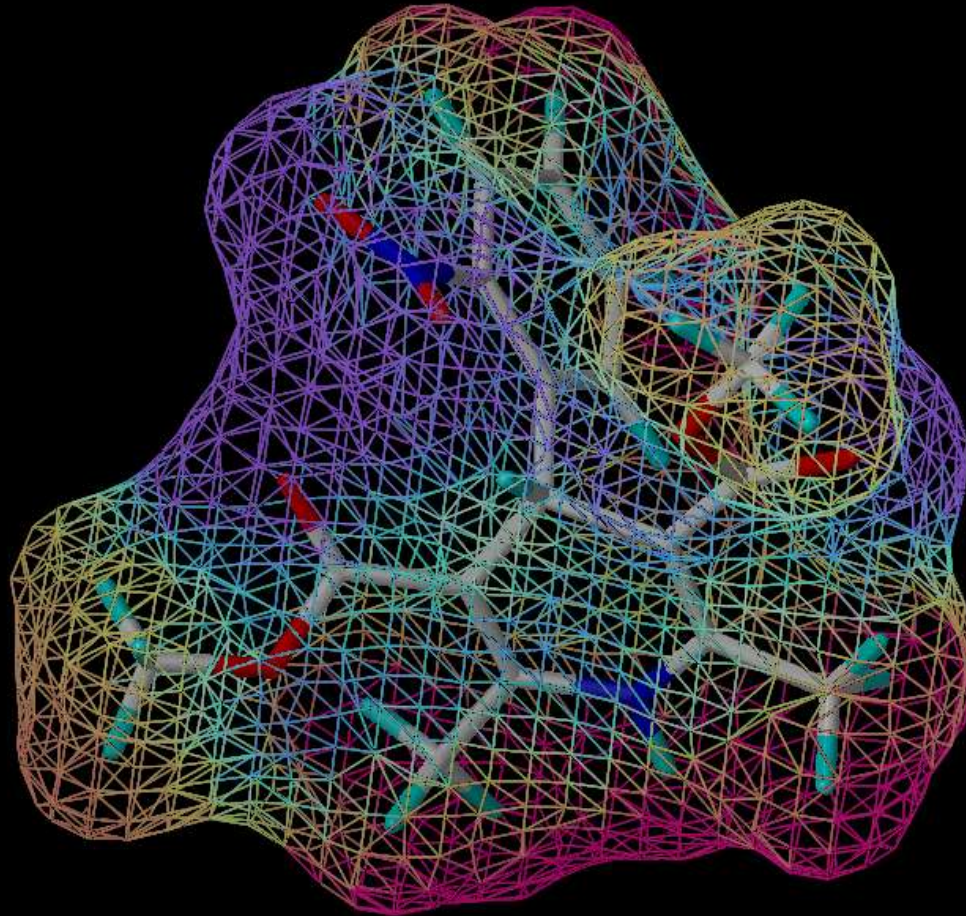


Lipophilie Potential

LP



Nifedipin: elektrostatisches Potential



Butanole: Lipophilie-Verteilung

LP

0.107

0.098

0.090

0.081

0.073

0.064

0.056

0.047

0.039

0.030

0.022

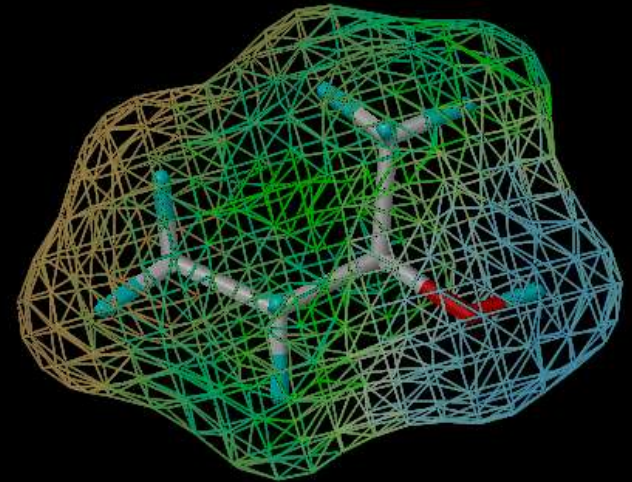
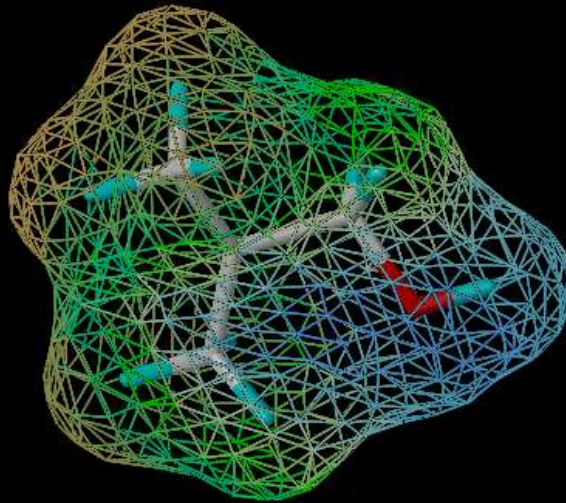
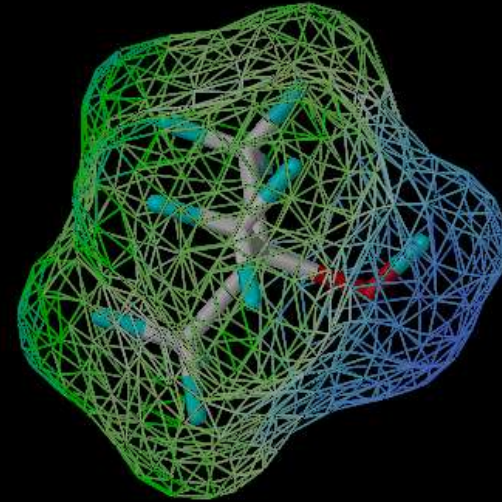
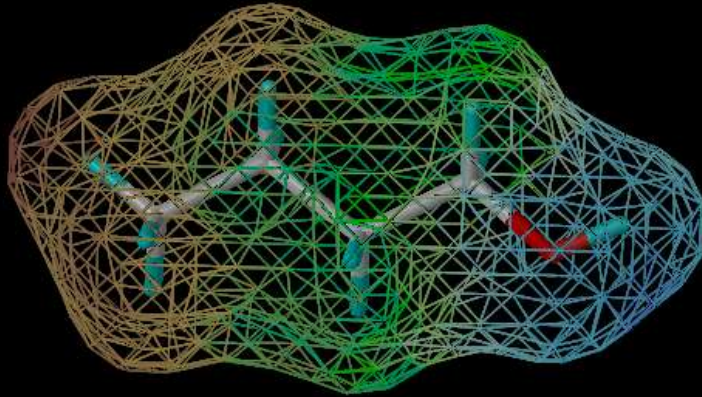
0.013

0.005

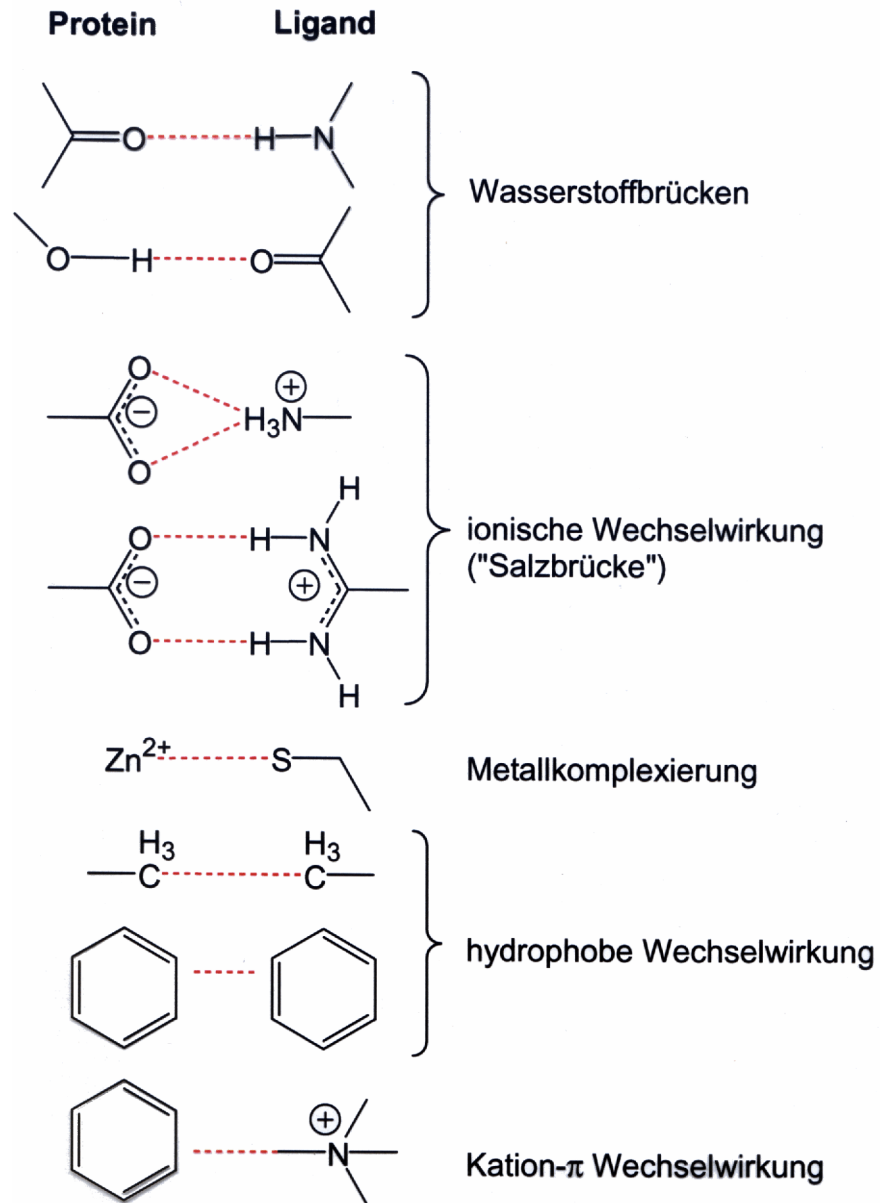
-0.004

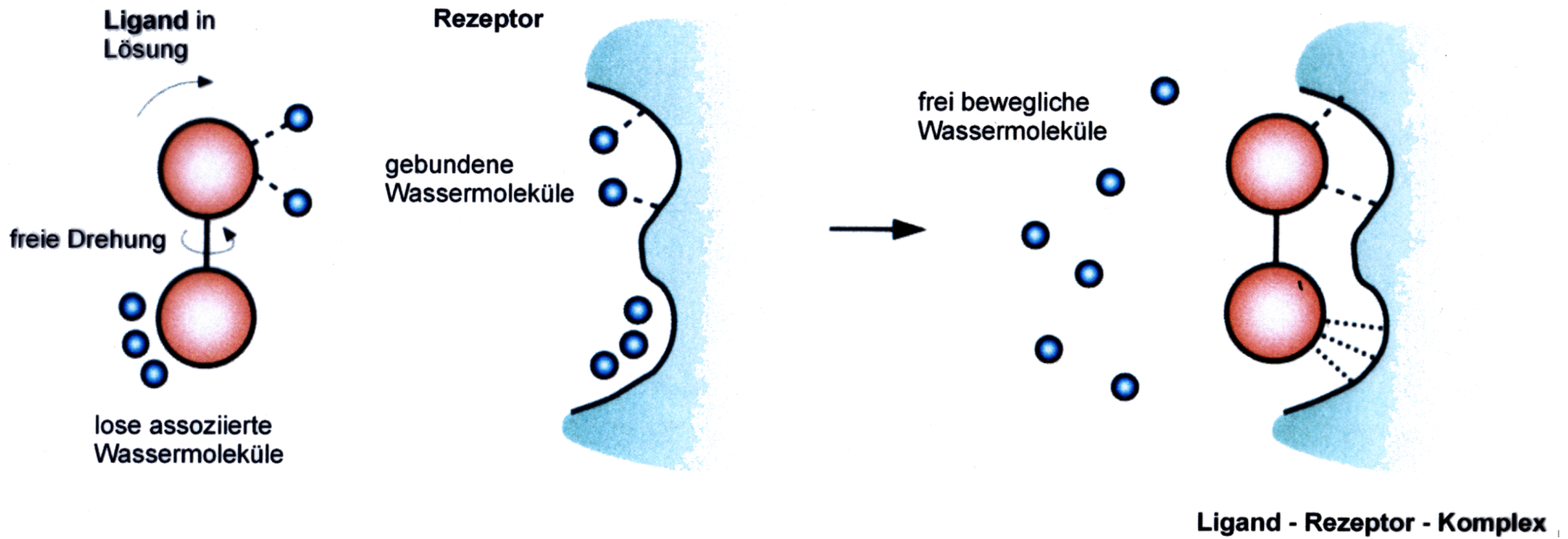
-0.012

-0.021



Protein-Ligand-Wechselwirkungen



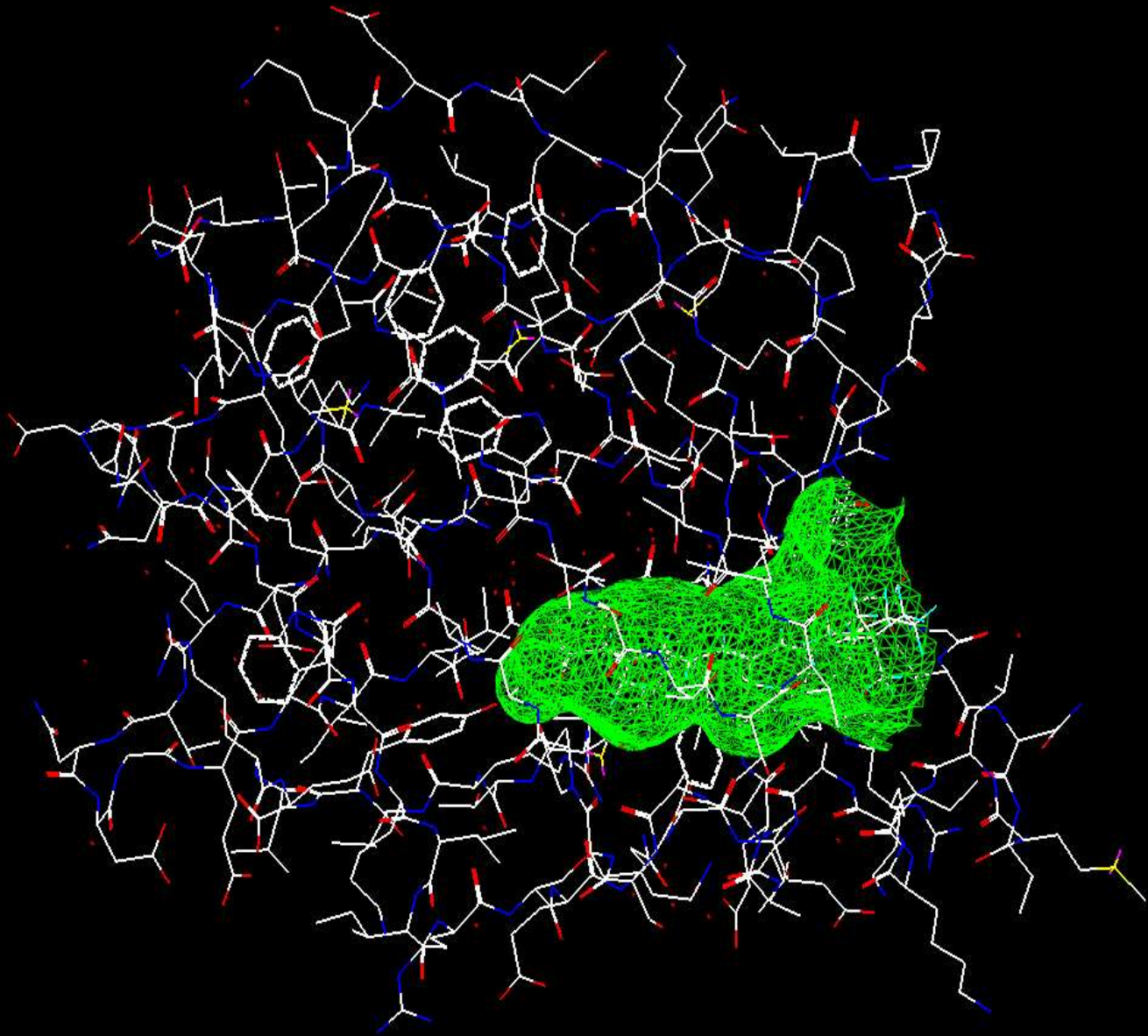


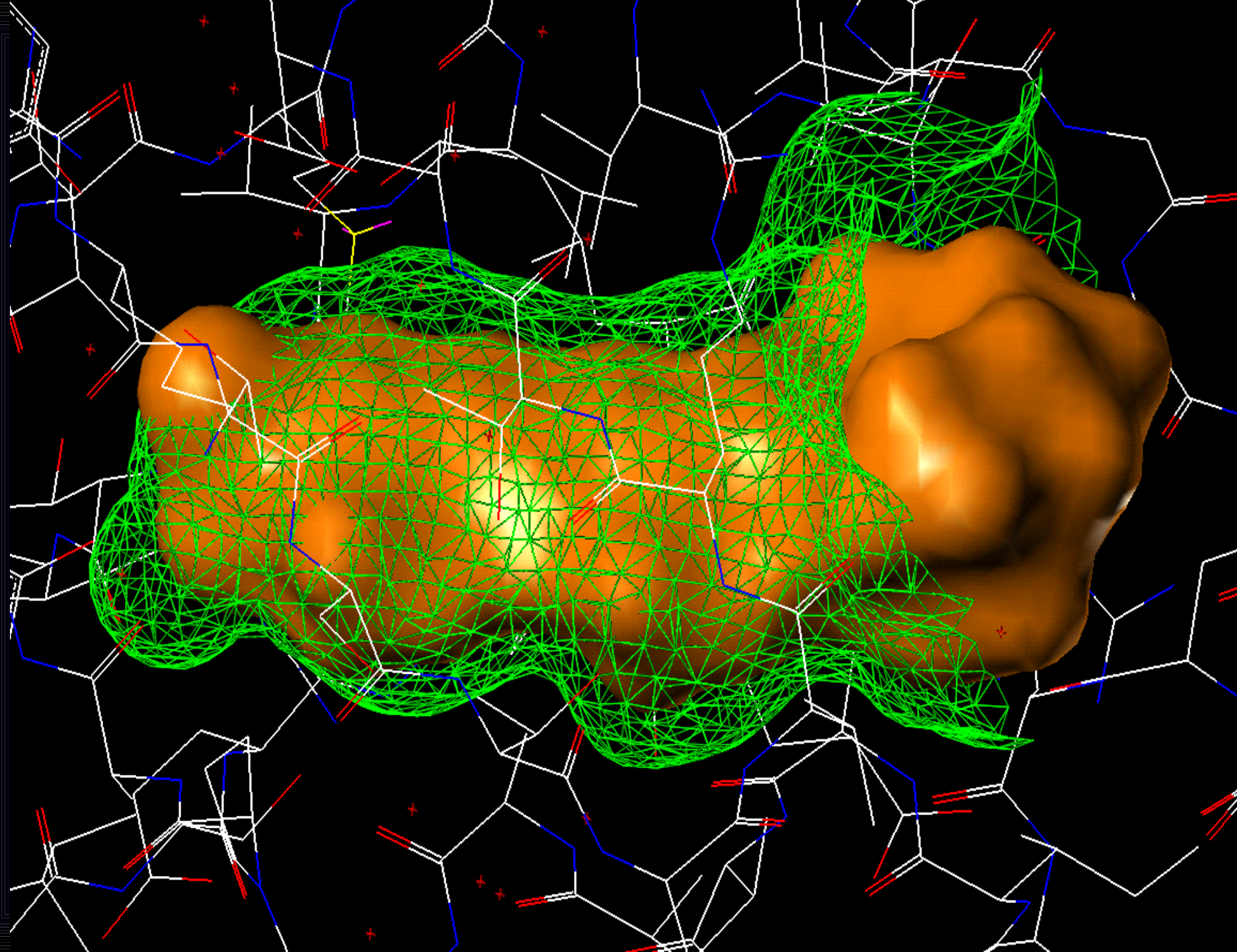
Basisgleichungen:

$$\Delta G = \Delta H - T \Delta S$$

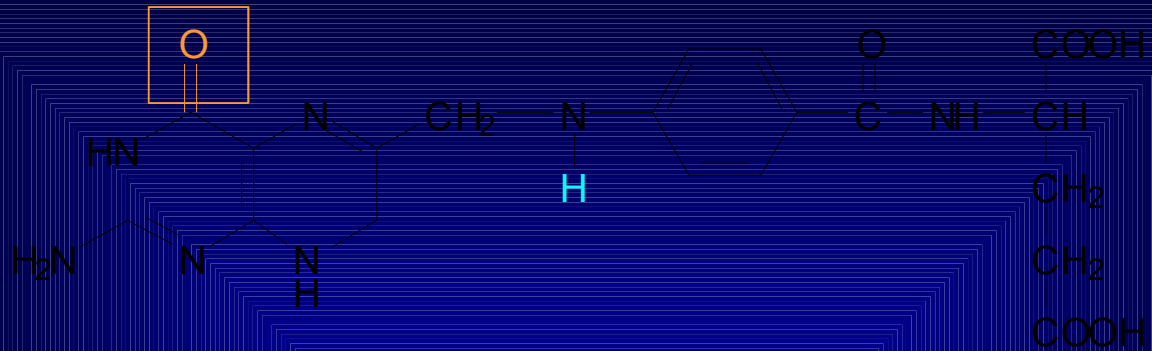
$$\Delta G = -RT \ln K_A$$

Retinol-bindendes Protein mit Bindungstasche

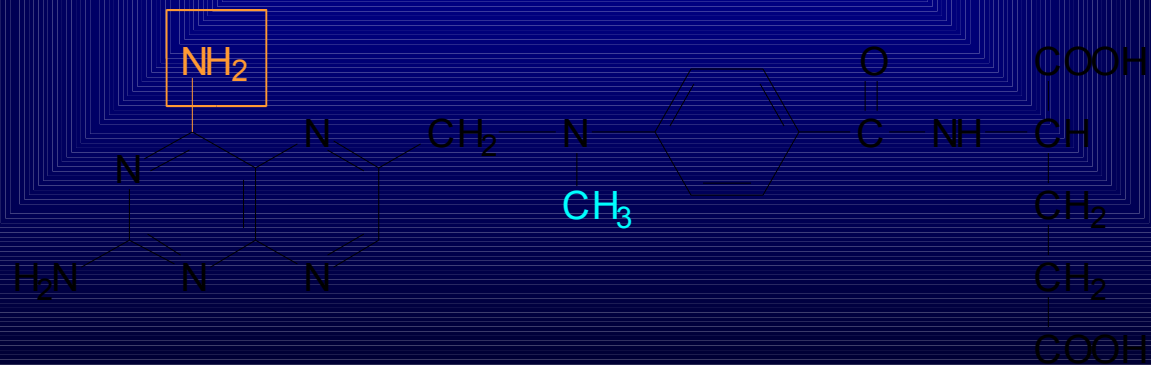




Komplementarität der Eigenschaften

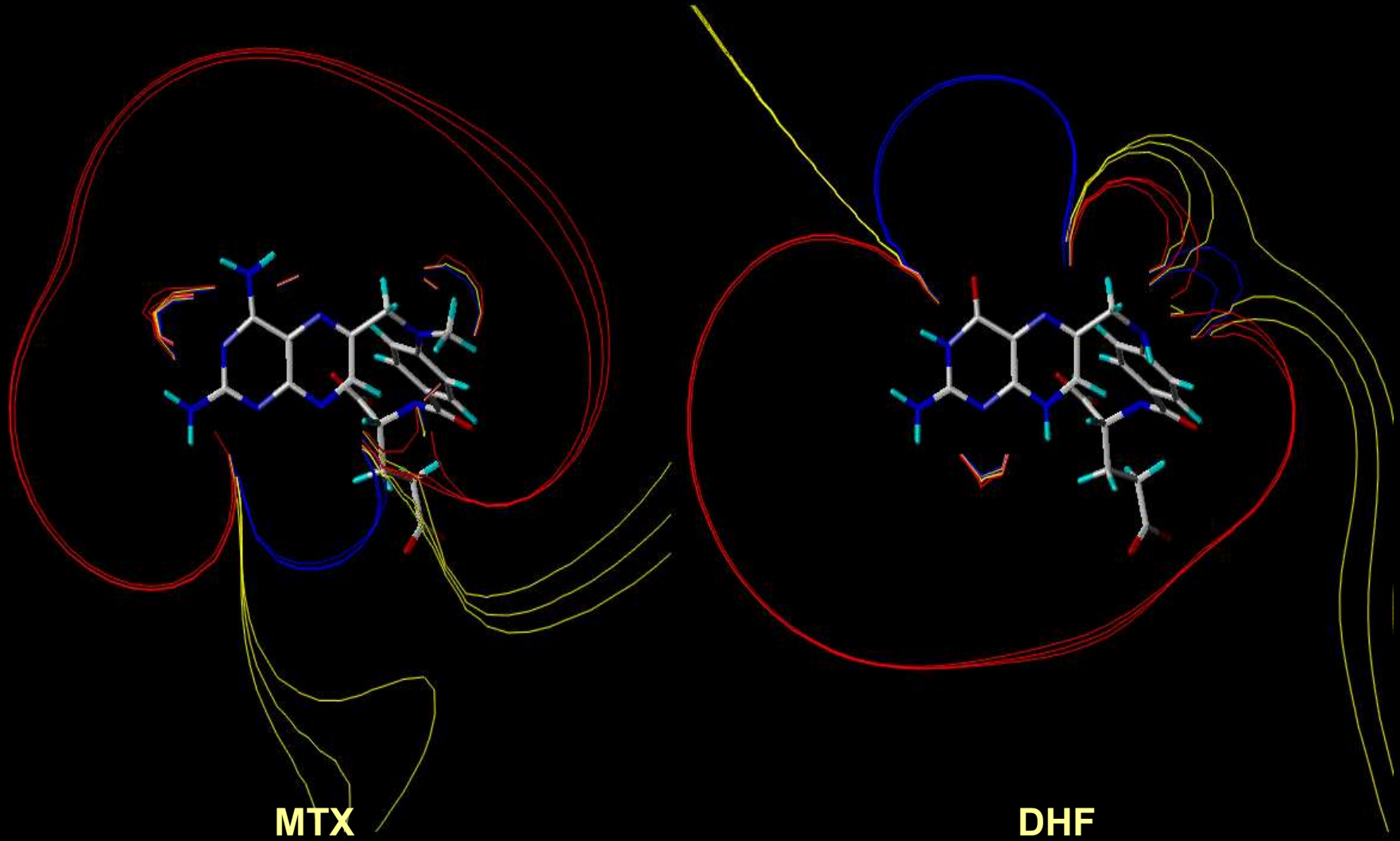


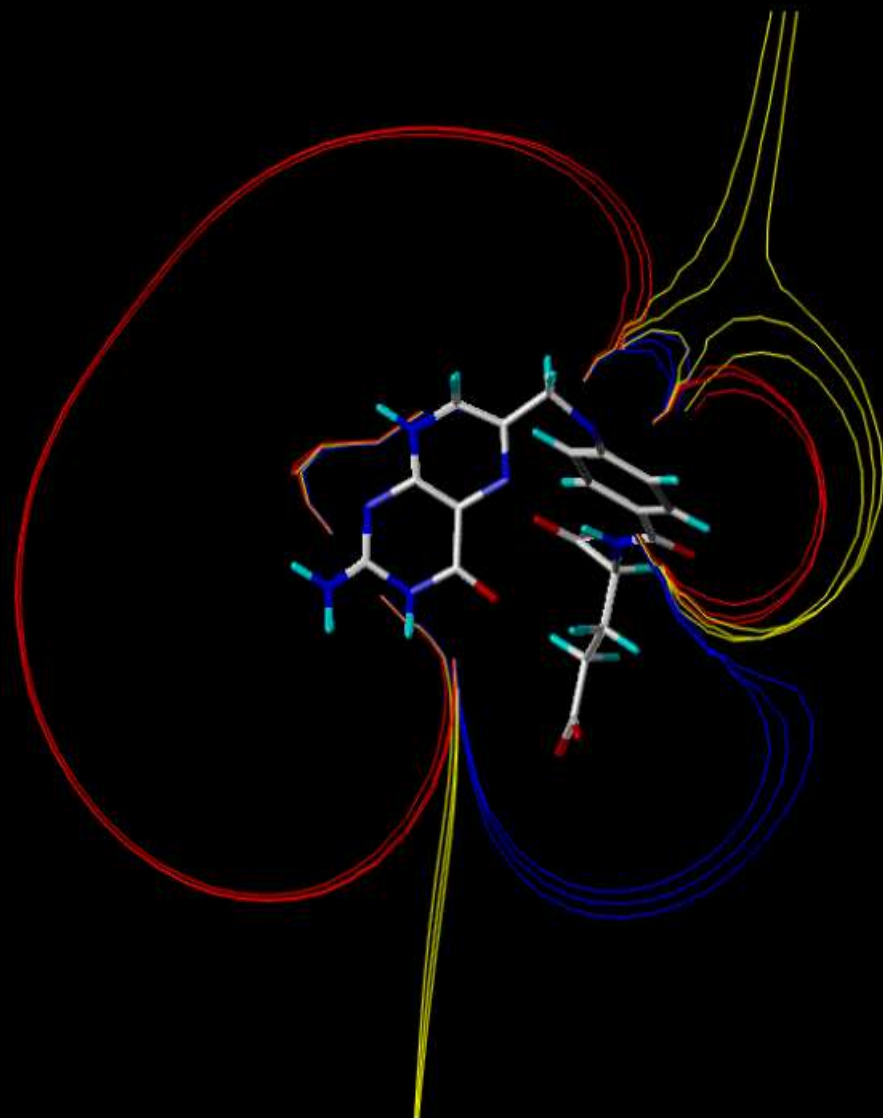
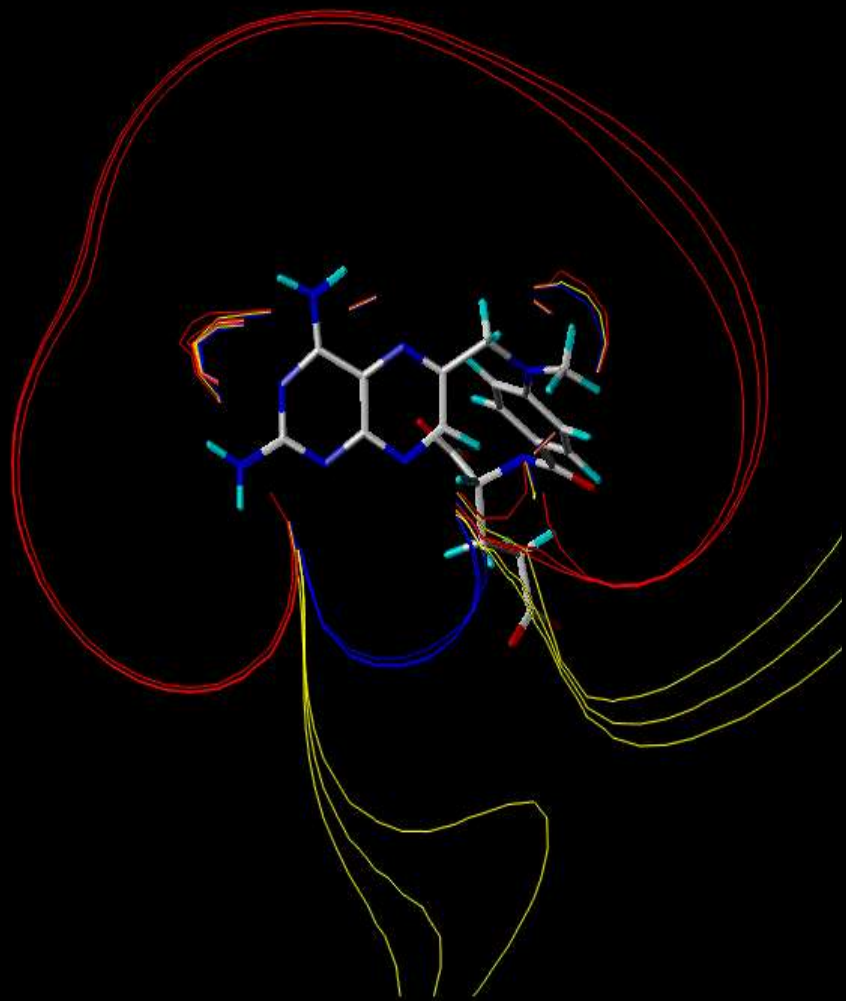
Substrat: Dihydrofolsäure (DHF)



Hemmstoff: Methotrexat (MTX)

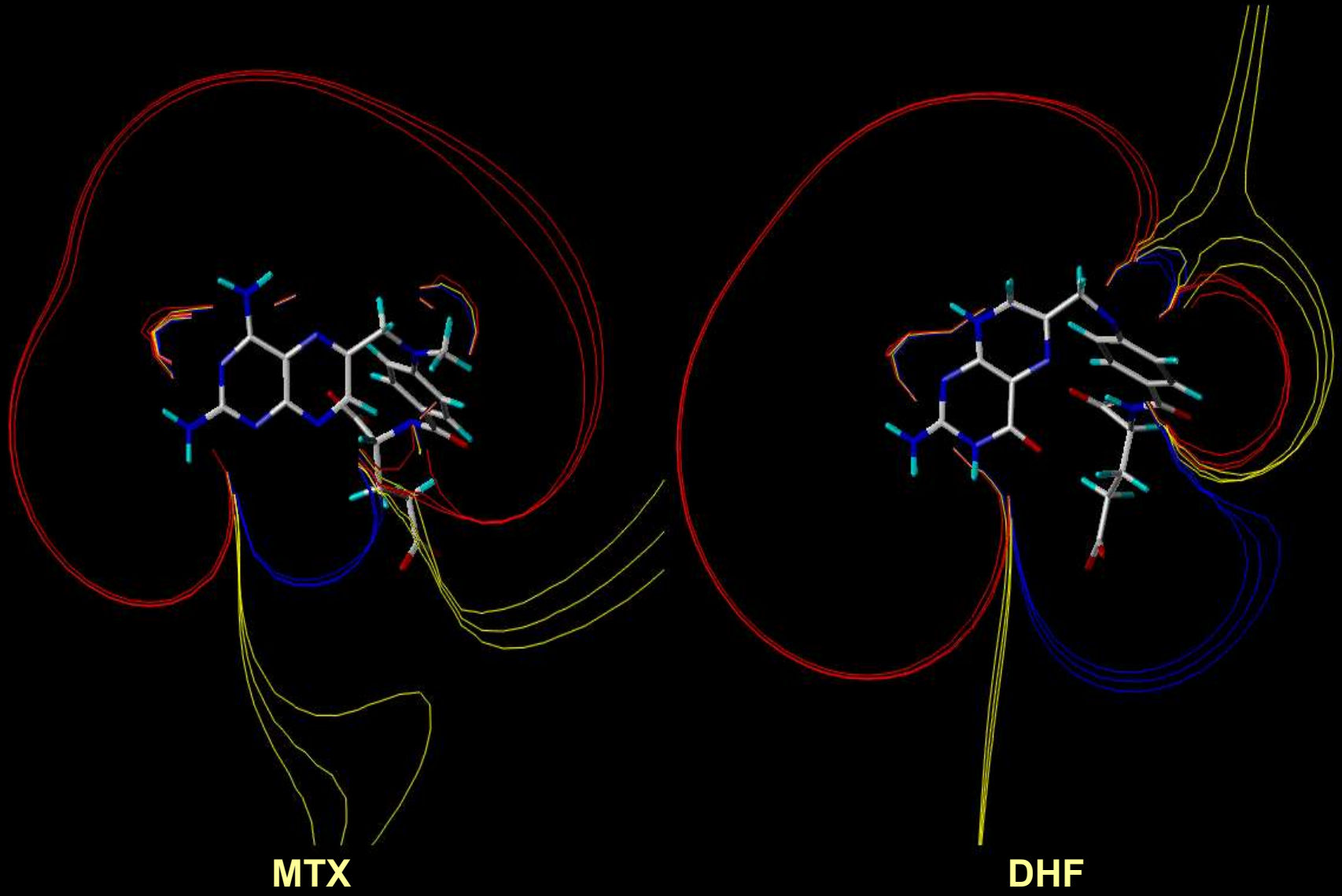
Elektrostatische Potentiale von MTX und DHF



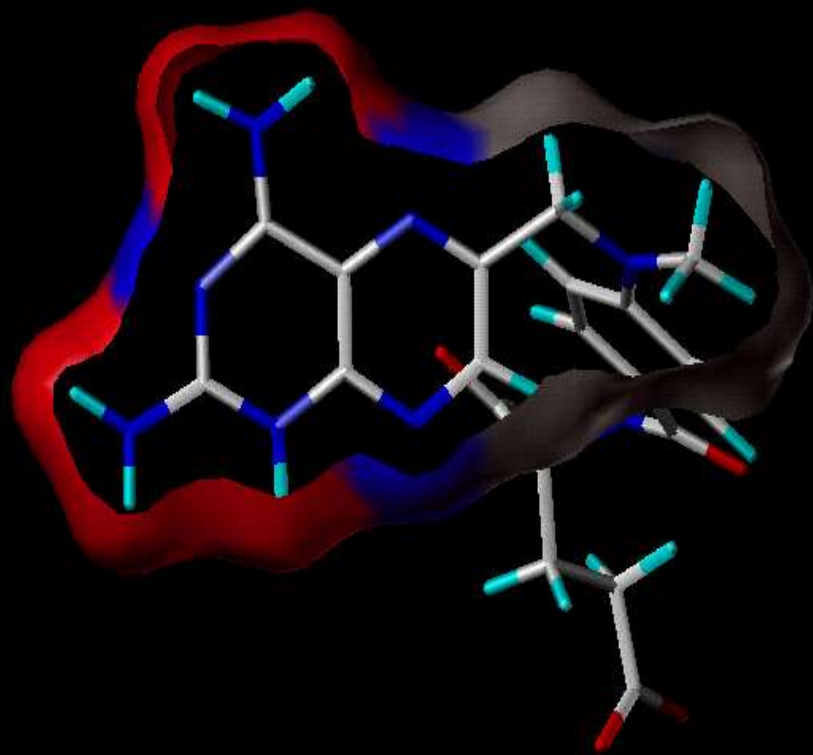


DHF

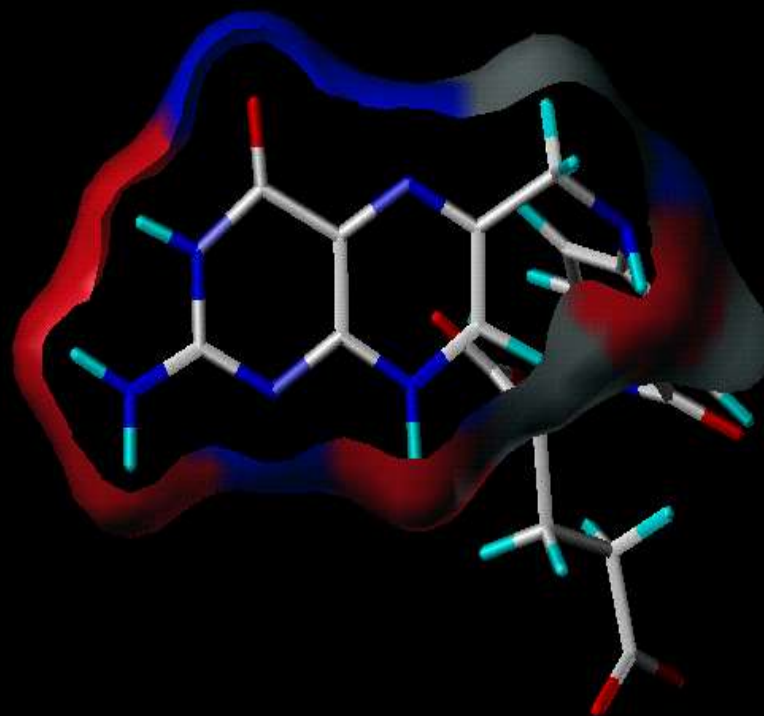
Elektrostatische Potentiale von MTX und DHF



Wasserstoffbrückenbindungs-muster

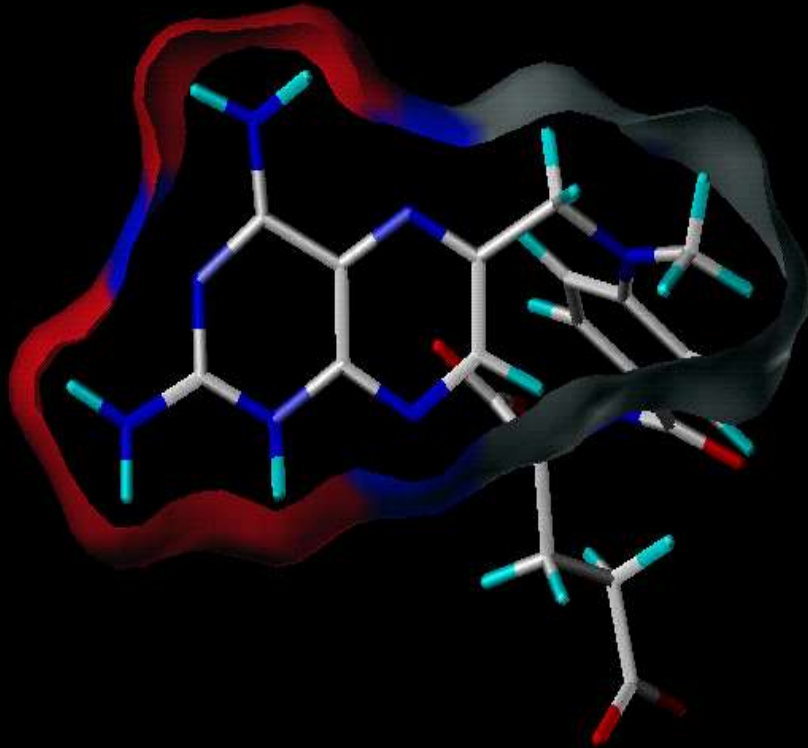


MTX

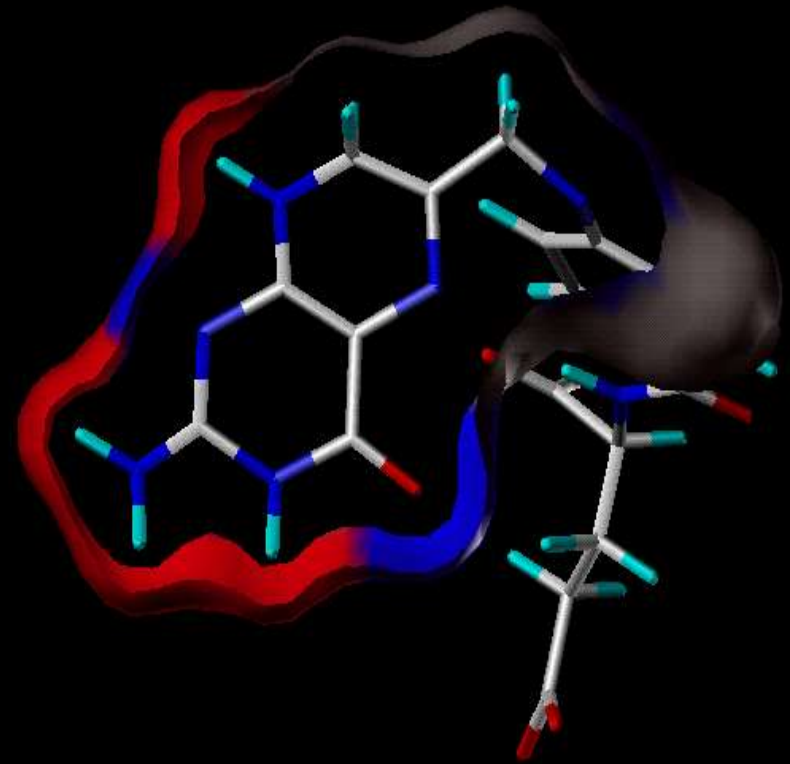


DHF

Wasserstoffbrückenbindungs-muster



MTX




DHF


Modelling bei unbekannter Zielstruktur


Kenntnis von:

Liganden:
Substrate
Inhibitoren
Agonisten
Antagonisten

Modelling



 Pharmacophor
Mapping

 Molekülfeld-
Analyse

 Pseudo-
Rezeptoren

 QSAR

Vorhersage

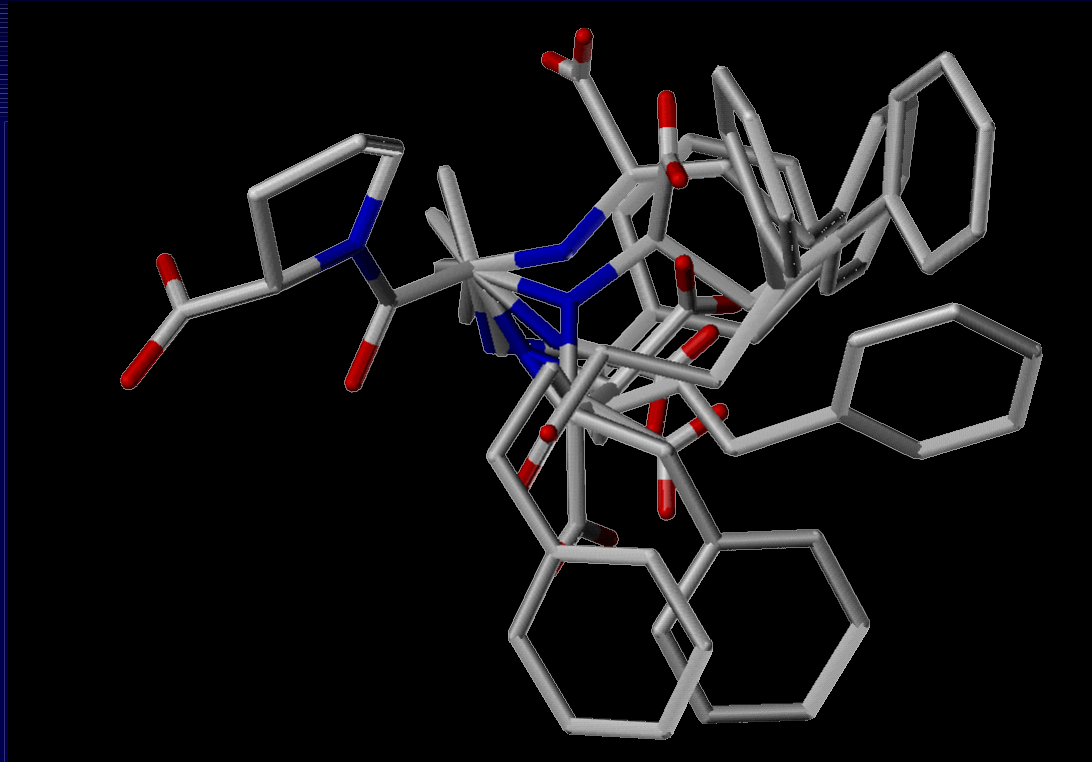
 Pharmakophor
 Geometrie

 Aktivitätswerte

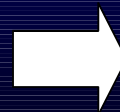

 Design

QSAR

Pharmakophor Mapping

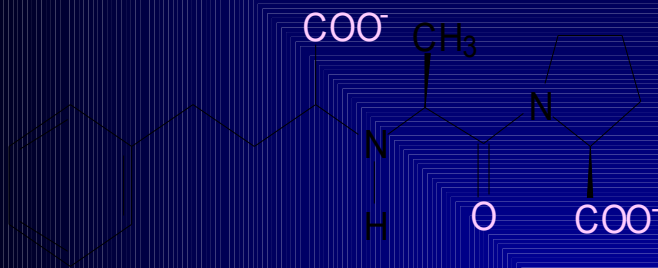


räumliche Anordnung
der essentiellen Gruppen

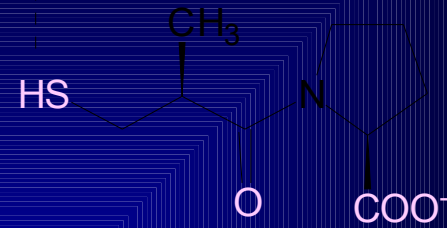


Vergleich der Konformationen
verschiedener Liganden

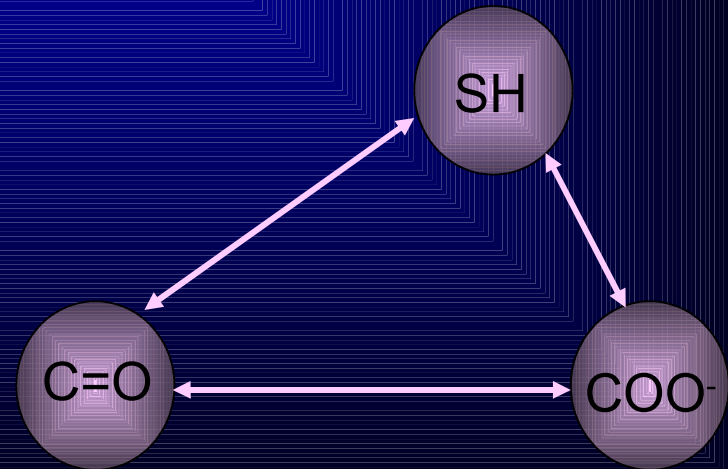
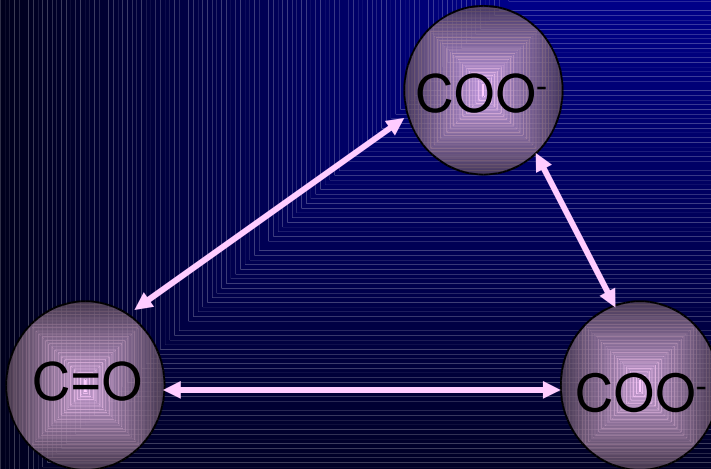
Pharmakophor Mapping



Enalaprilat

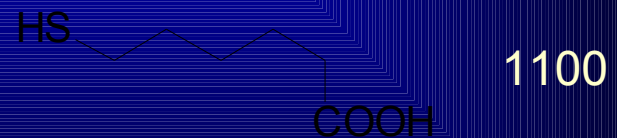
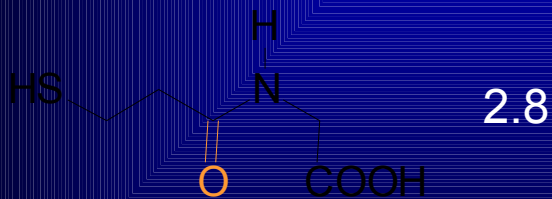
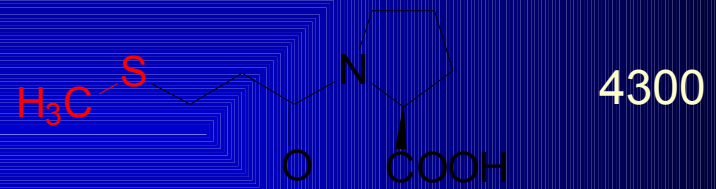
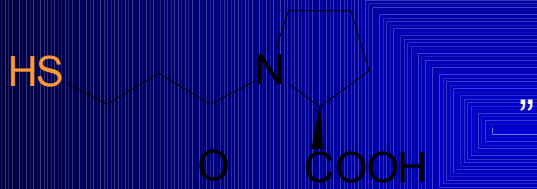
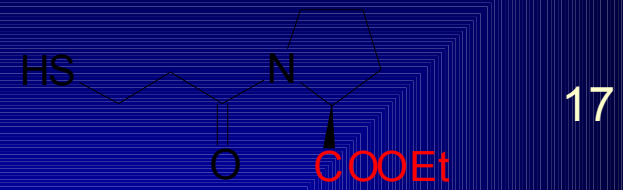
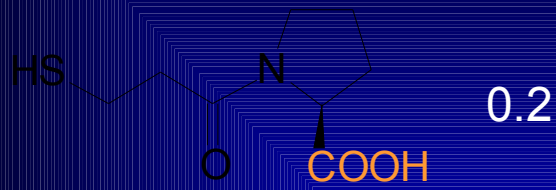


Captopril



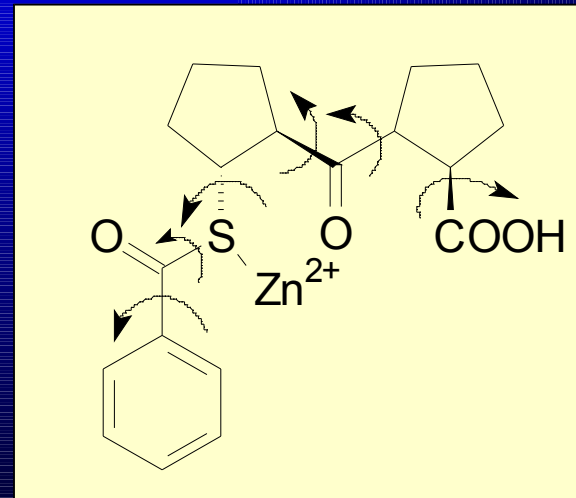
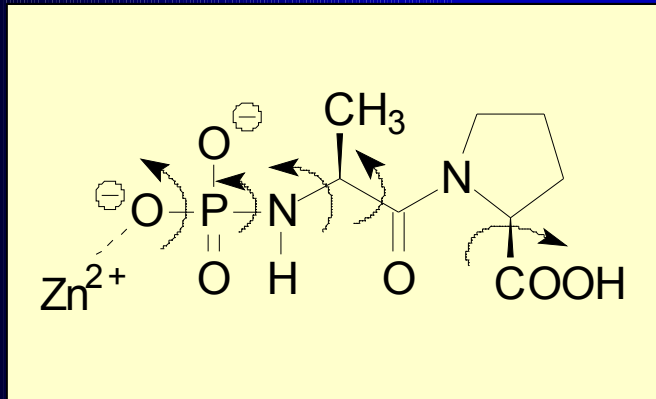
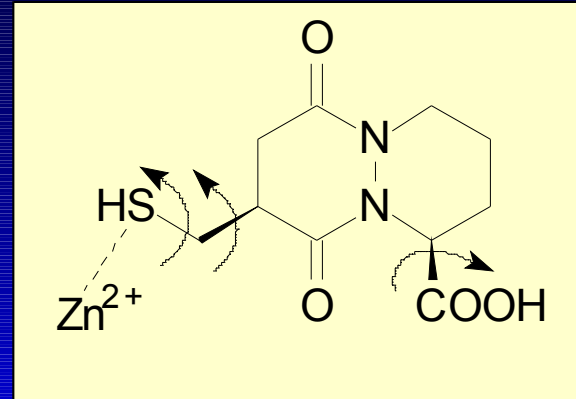
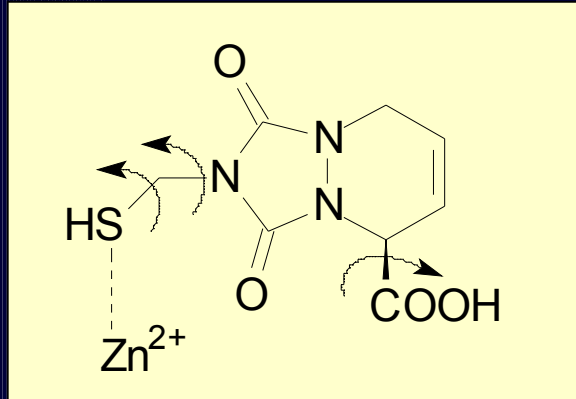
Hemmwirkung gegenüber ACE

IC₅₀ (μM)

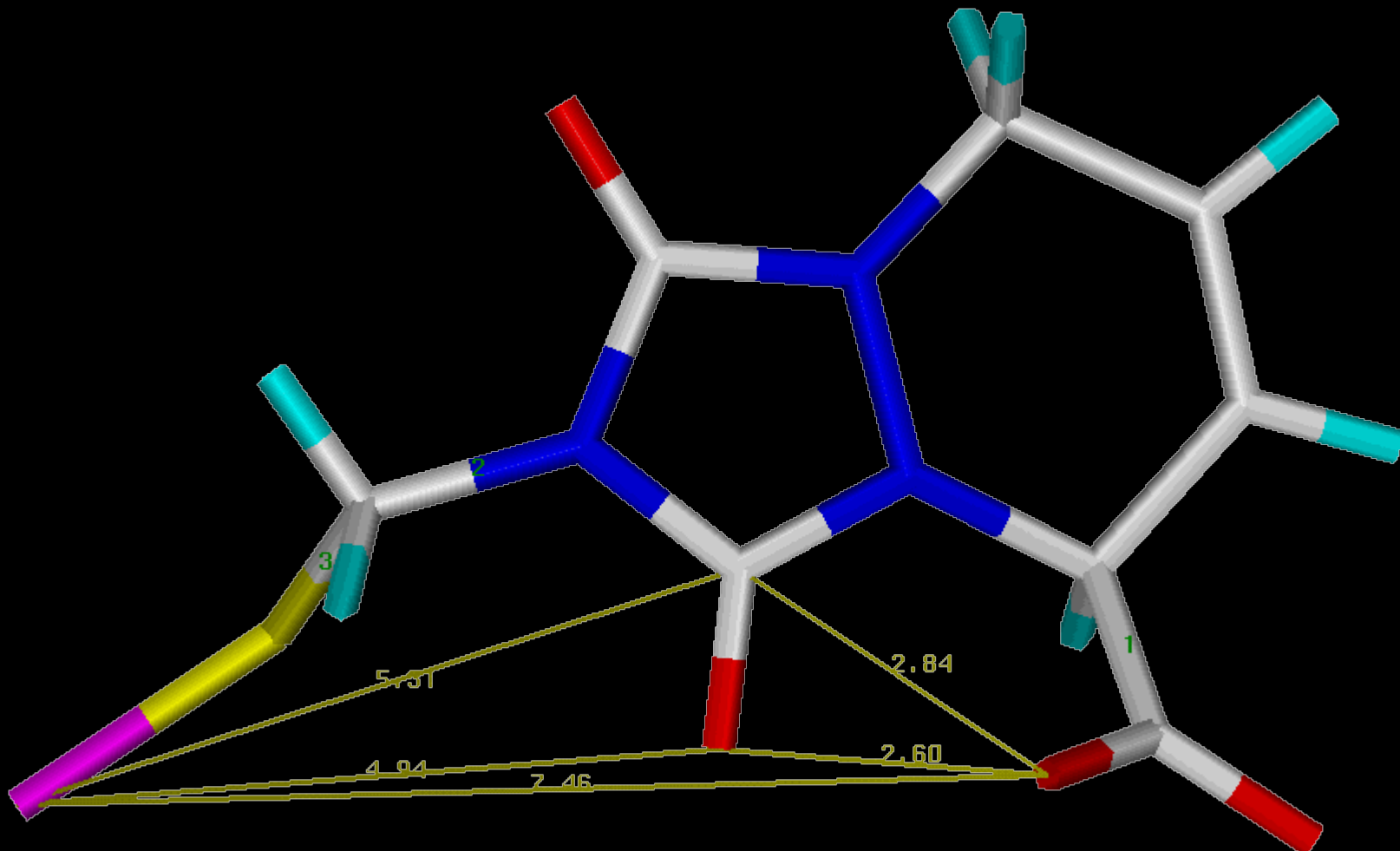


Carboxylat-Gruppe, Zink-Bindungsgruppe, Carbonylgruppe sind essentiell

Beispiel: ACE-Hemmer



MOLE



3

1

5.31

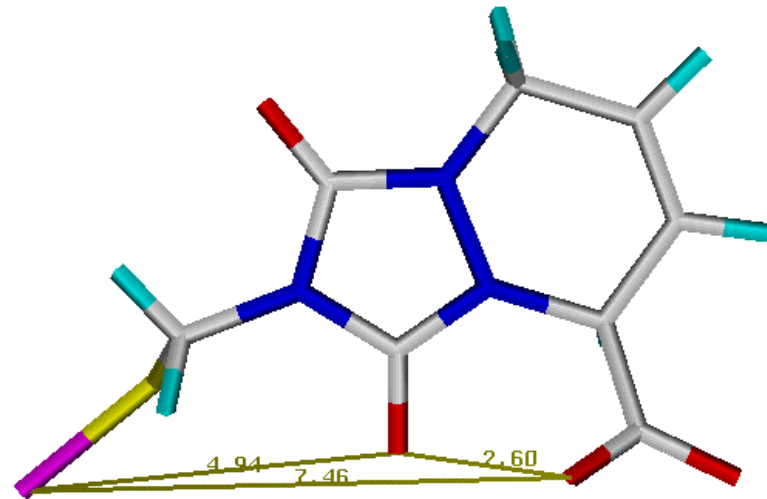
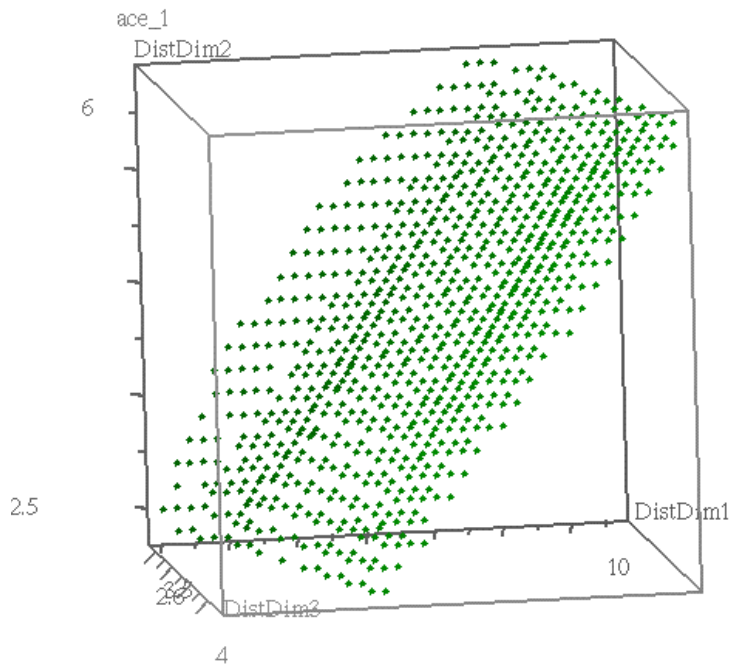
2.84

4.94

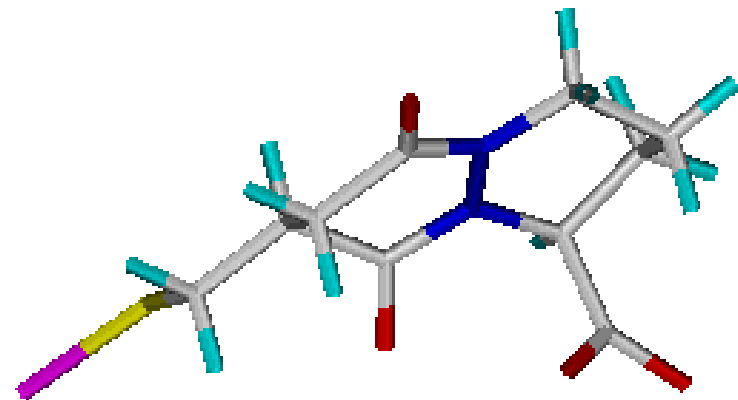
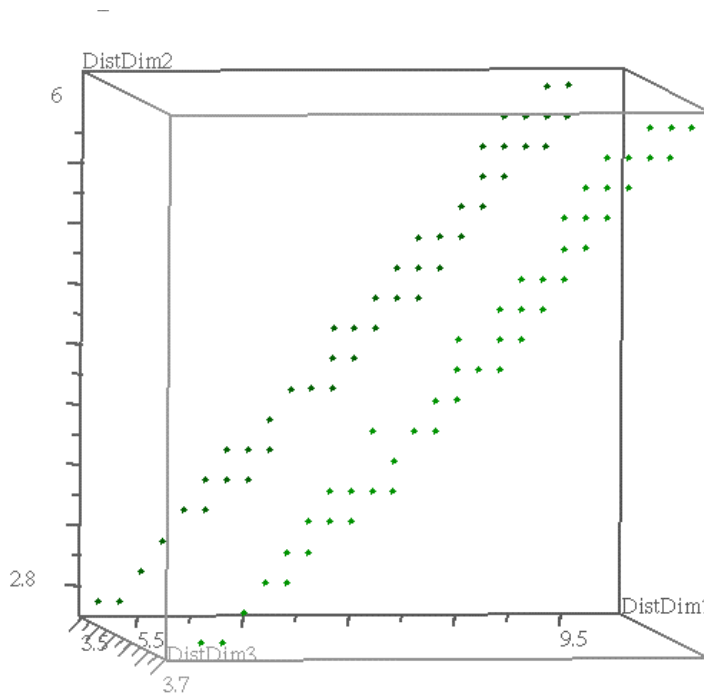
7.46

2.60

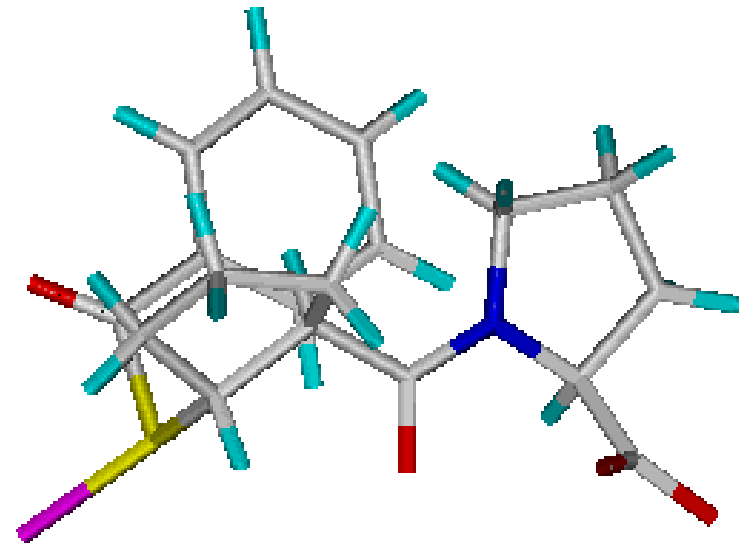
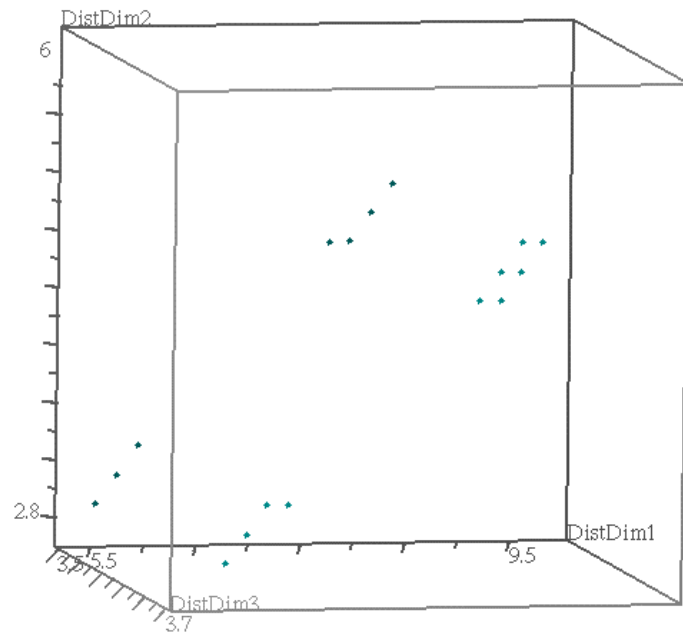
Mögliche Abstände der pharmakophoren Gruppen



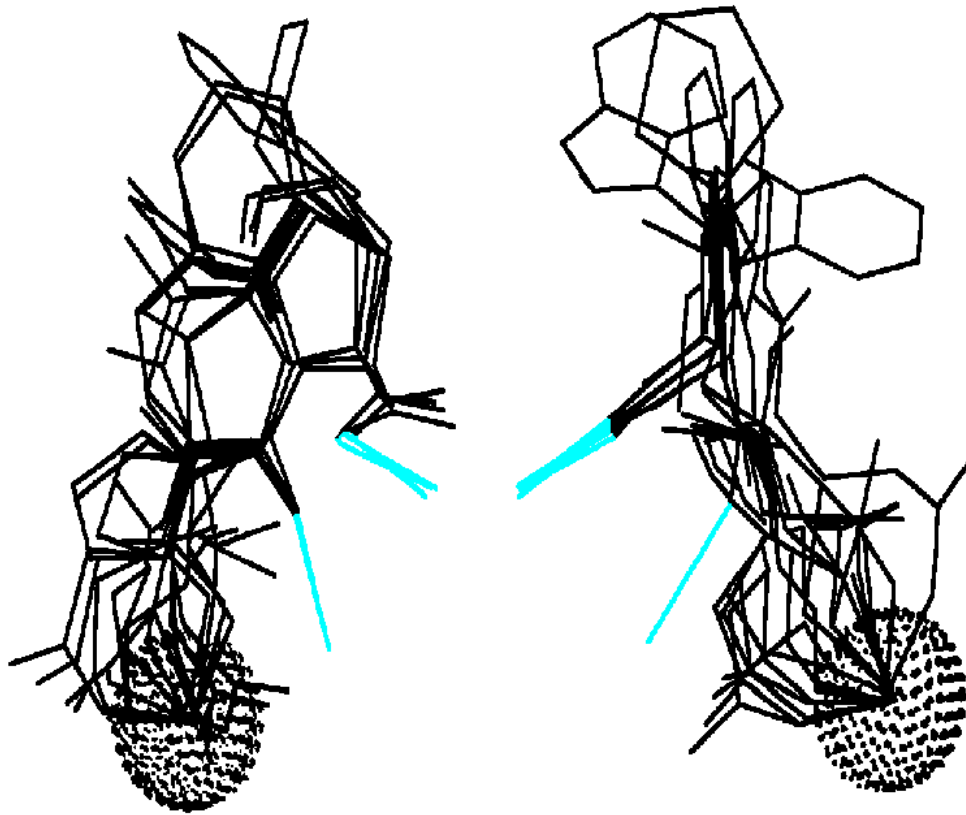
Mögliche Abstände der pharmakophoren Gruppen (2 Derivate)



Mögliche Abstände der pharmakophoren Gruppen (4 Derivate)



Überlagerung aller Derivate



Modelling bei bekannter 3D-Struktur

Kenntnis von:

Liganden
und
Struktur von
Ligand-Protein-
Komplexen

Modelling



Ligand
Docking



Analyse der
Bindungstasche



Virtuelles
Screening

Vorhersage



Aktivitätswerte

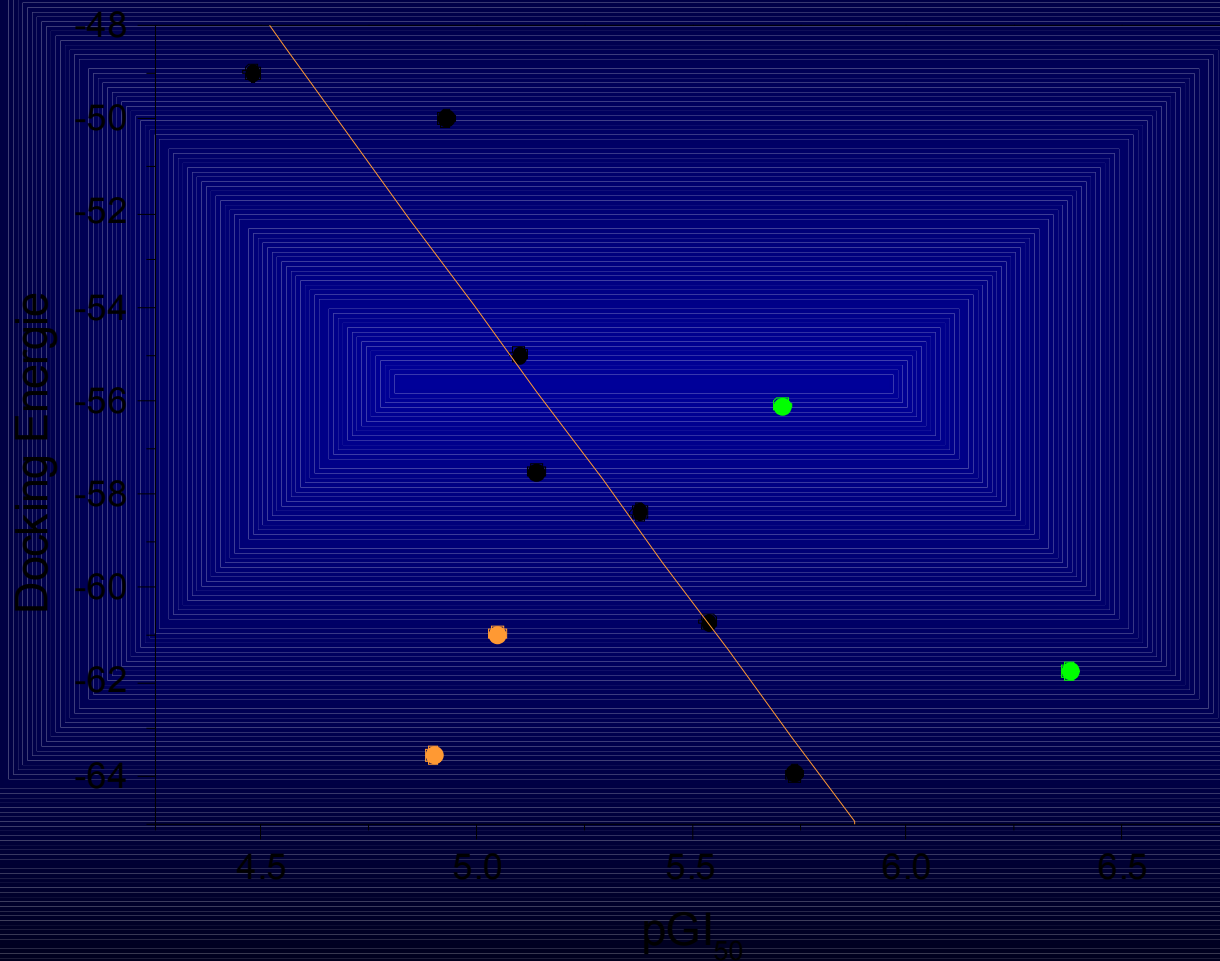


Design



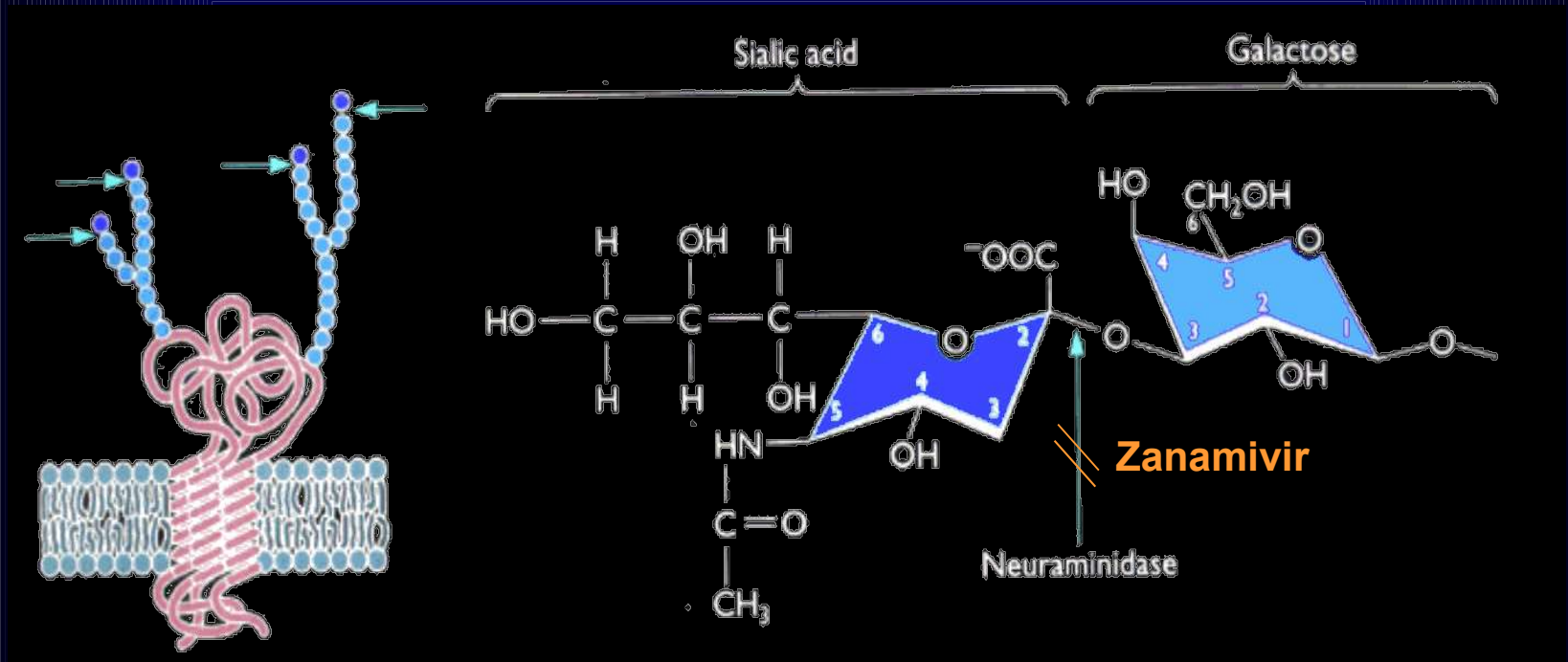
Identifizierung
wichtiger
Aminosäuren

Docking von Liganden

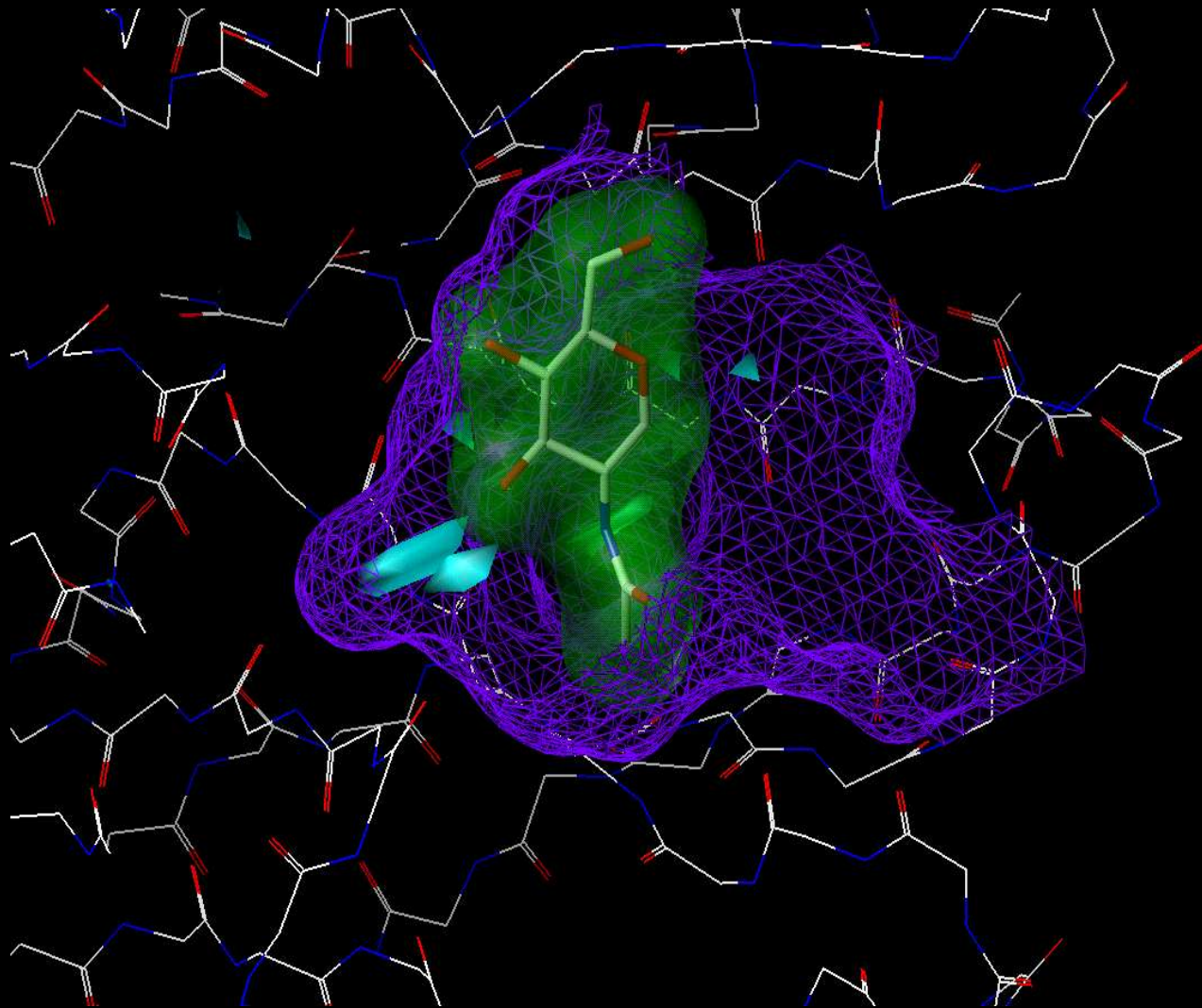


Antivirale Wirkstoffe

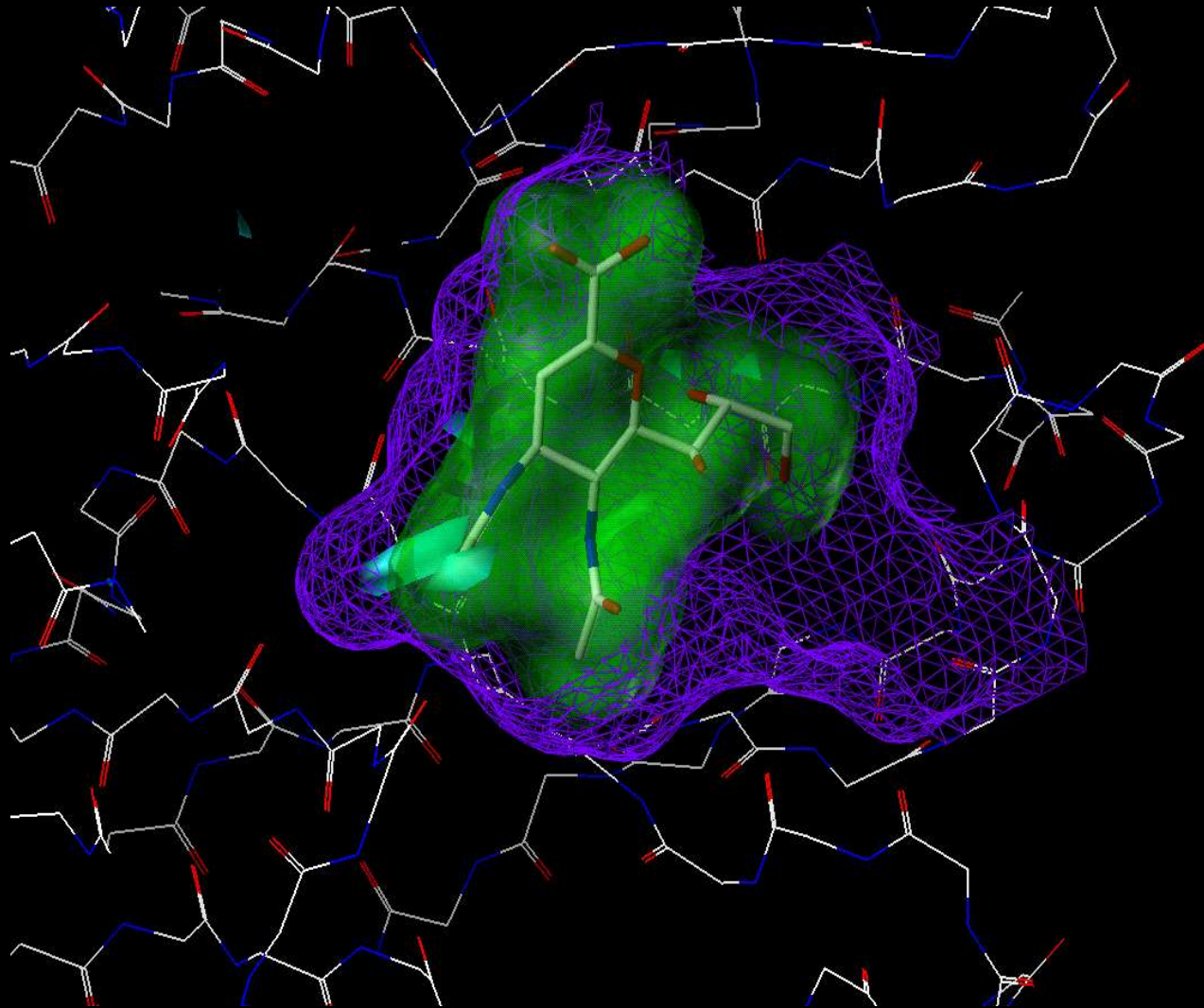
Neuraminidase-Hemmstoffe



Analyse der Bindungstasche: Neuraminidase mit gebundenem Liganden



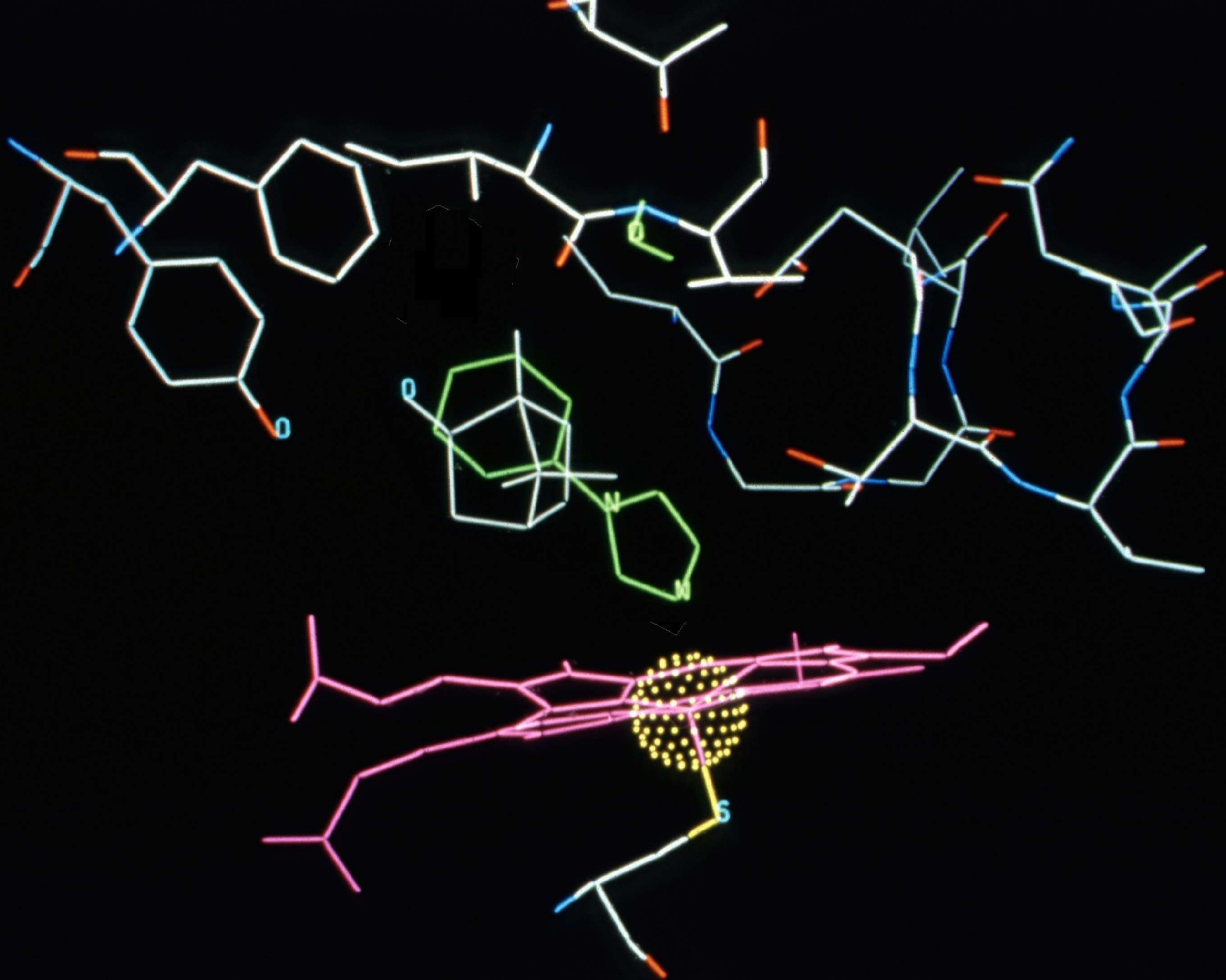
Analyse der Bindungstasche: Neuraminidase mit gebundenem Zanamivir

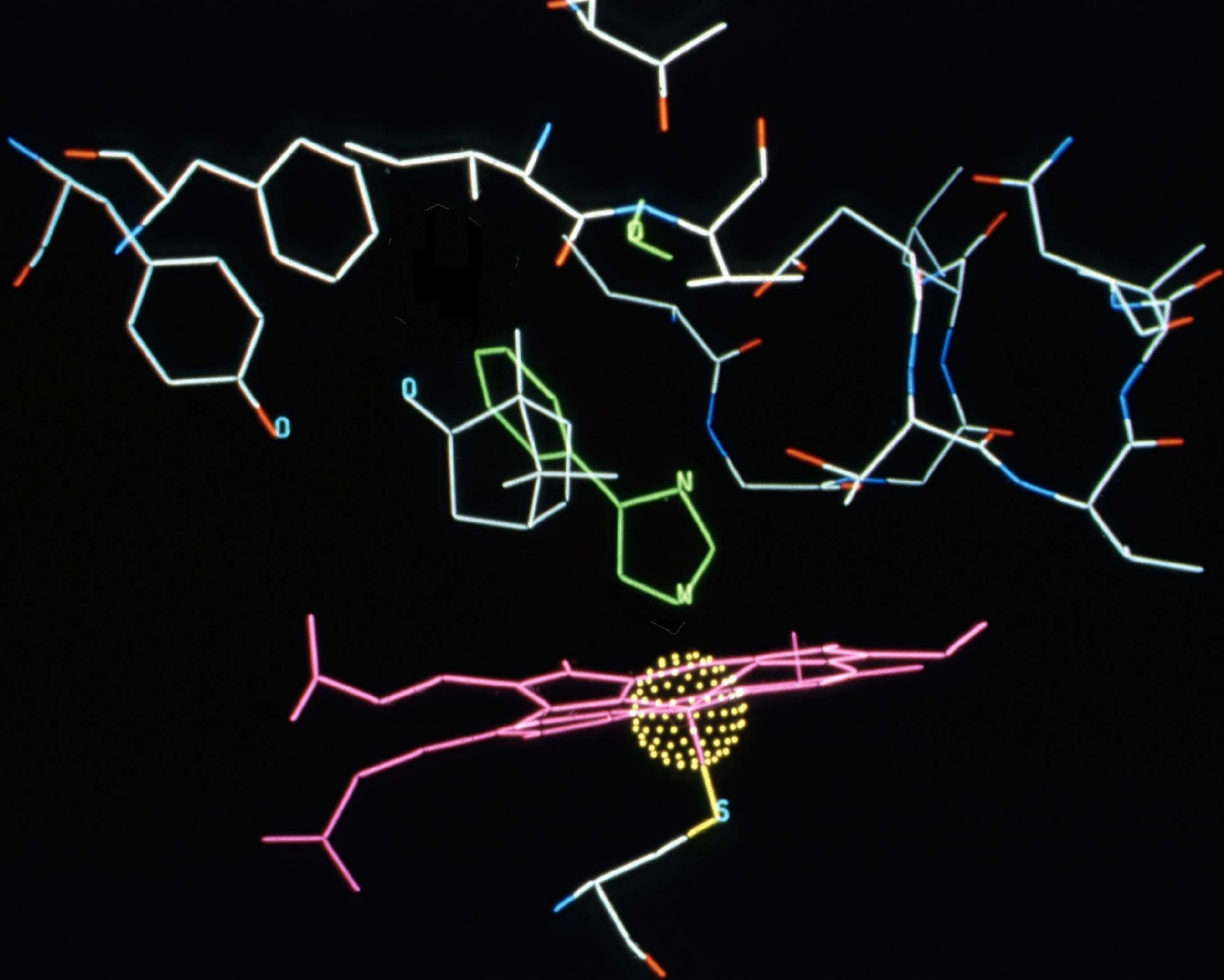


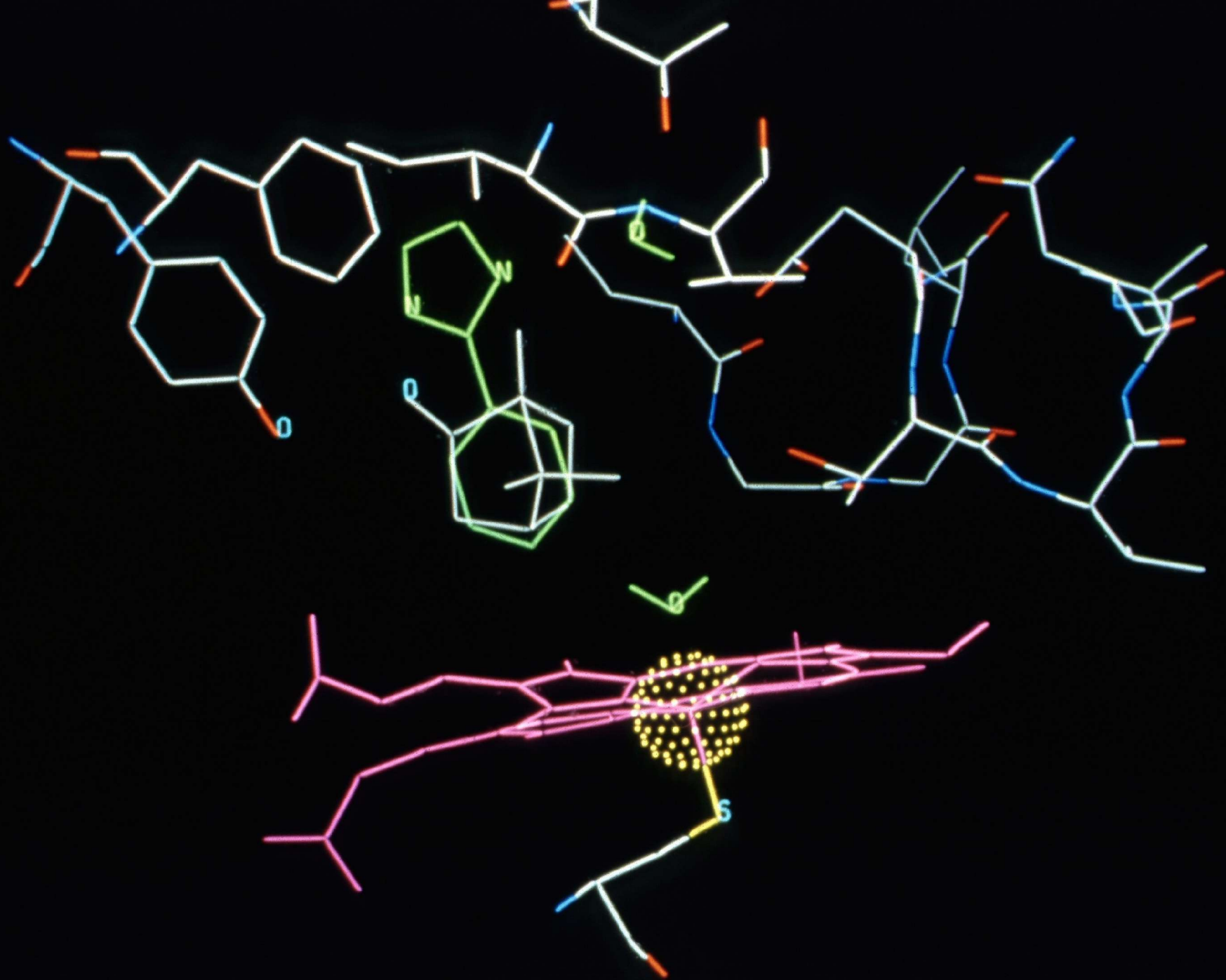
Grenzen: alternative Bindungsmodi

Beispiel:

Phenylimidazole als Inhibitoren
von Cytochrom aus *E. coli*









**Auf dem Weg zu neuen
Arzneistoffen...**

**...sind computergestützte Verfahren
wertvolle Werkzeuge**