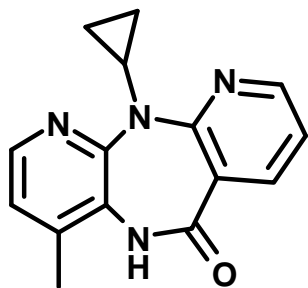
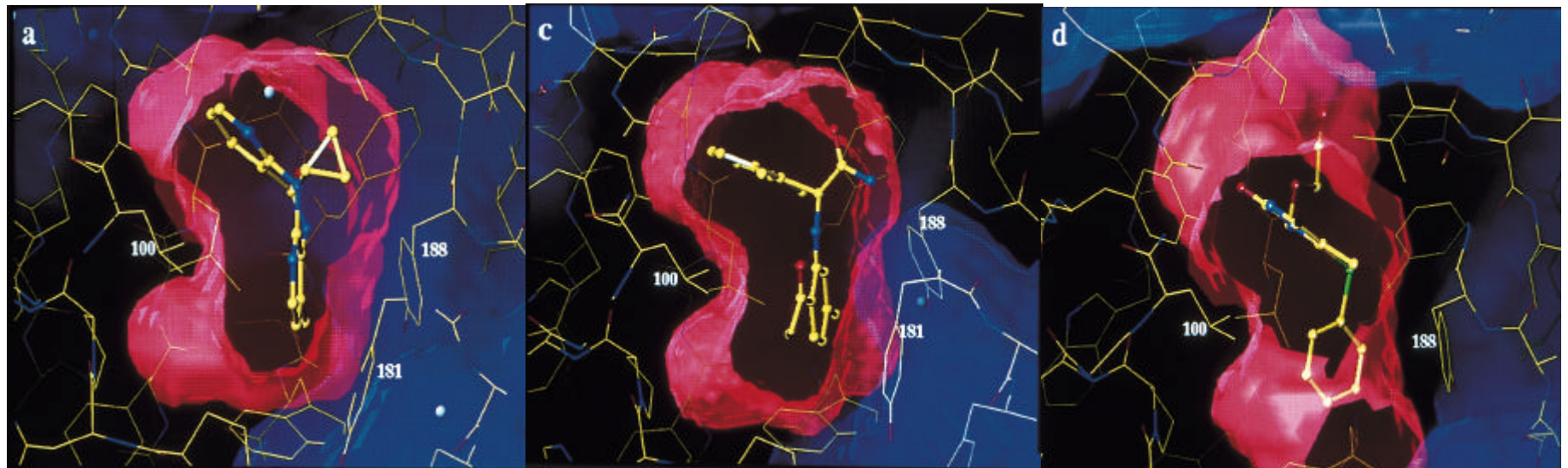
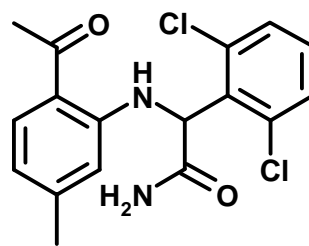


HIV-1 RT inhibited by structurally varied inhibitors

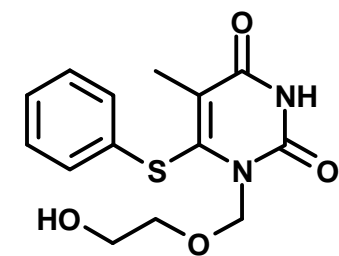
Nature Struct. Biol. Structure 293, 2(4), 1995



Nevirapine
 IC_{50} 0.08 μ M



α -APA
 IC_{50} 0.1 μ M



HEPT
 IC_{50} 17 μ M

Conclusions from these (and other) structures

- H-Bonds can be replaced by lipophilic interactions
- In the vast majority of cases involving drugs, induced fit is the consequence of hydrophobic interactions
 - This may be a reflection of their strength relative to H-bonds
- Good fit of a receptor around a ligand is normal
 - result of induced fit
 - does not imply no room for extra substituents
 - structural data often does not indicate obvious holes to fill
- Many different ligands can bind to same site
 - many ligands does not imply many binding sites
 - good news for patent busting
 - best series may be decided on another basis (ADME, selectivity)



Paradigm shifts

- Unexpected binding modes can result in a completely different SAR optimisation stratagem
- The relative importance of certain pharmacophoric groups can be usefully reassessed
- Specific hydrophobic interactions can yield large potency and selectivity gains
 - bulk properties (solubility, ADME) can be manipulated by introducing “non interactive” polar groups
- Interactive (protein binding groups) are not the same as functional groups (synthetic chemistry)



Implications for our modelling tools ?

What are the consequences ?



The success of docking programs

- GOLD - validation 100 compounds 70% docked well (J. Mol. Biol. 727, 267, 1997)
- LUDI - validation on 80 compounds
- DOCK - validation on 10's compounds

A success ??

- Redocking a poor test of the algorithm
- Often more successful structures are polar
- Need docking and scoring functions



“the principle driving force of our algorithm (GOLD) is the identification of hydrogen binding interactions between ligand and protein.....(GOLD) is more likely to succeed if the ligand is polar”

Peter Willett in “development and validation of a GA algorithm for flexible docking”

“interestingly, several small molecules containing functional groups, frequently involved in protein-ligand interactions, do not associate in water. Acetic acid does not form a stable complex with guanidine in water. Simple amides do not associate”

Bohm (LUDI) in “molecular recognition for the design of new drugs ?”
Angew. Chem. 2588, 35, 1996.

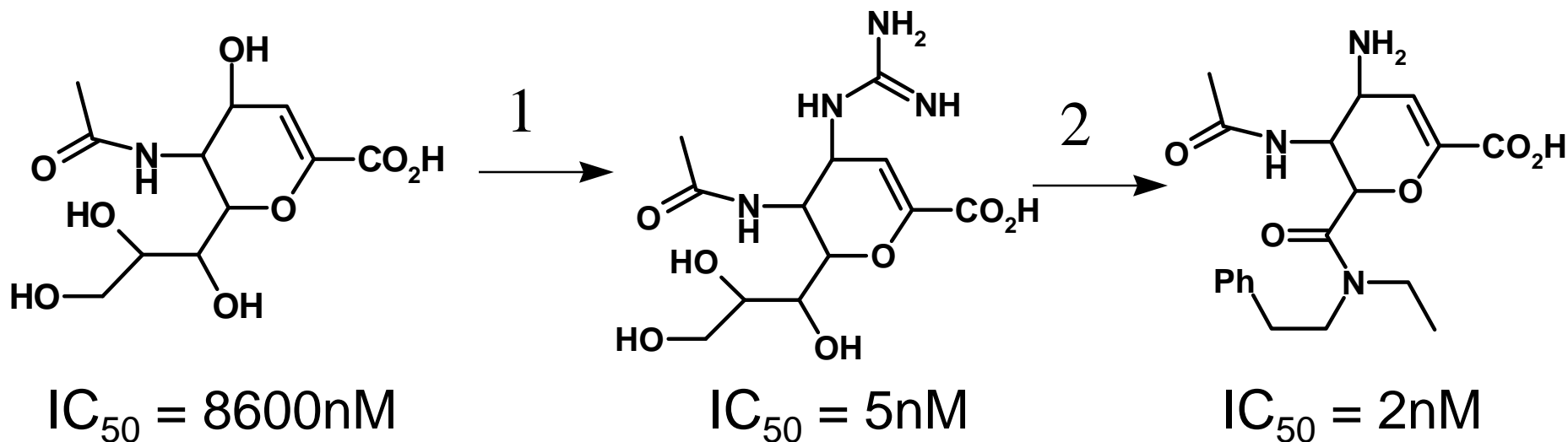


- Over emphasis upon polar interactions - especially H-bonds
 - some very biased (eg DOCK)
 - tends to suggest maintenance and/or addition of polar interactions
 - poor solubility and ADME properties
- Little account taken of induced fit
 - constrains thought about adding groups
 - makes overlay of “similar” molecules difficult
 - new intra-receptor bonds created upon ligand binding not considered



Sialic acid to Zanamivir and Beyond

1. Nature 1993, 363, 418 "Rational design"
2. J. Med.Chem. 1998, 41, 787 Induced fit

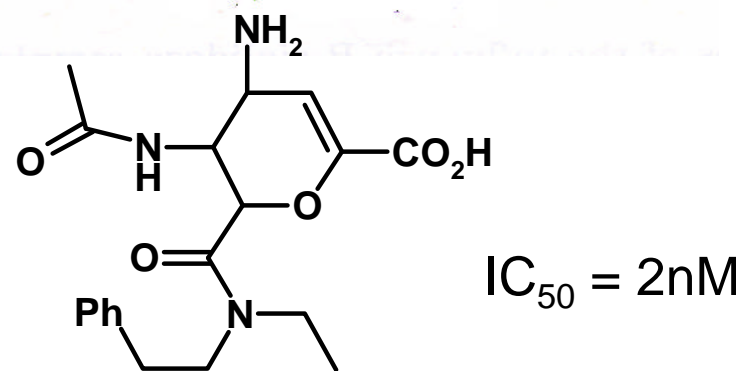
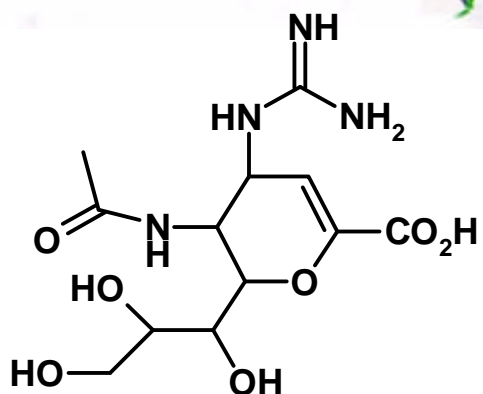
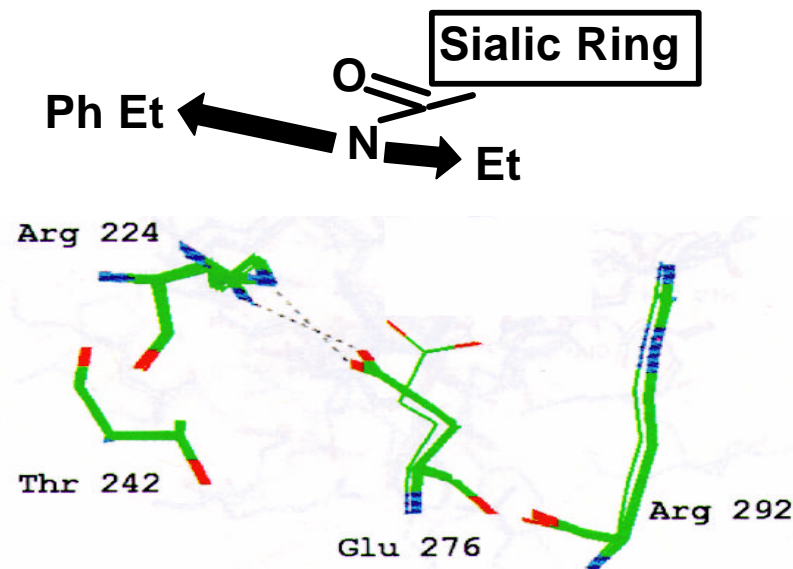
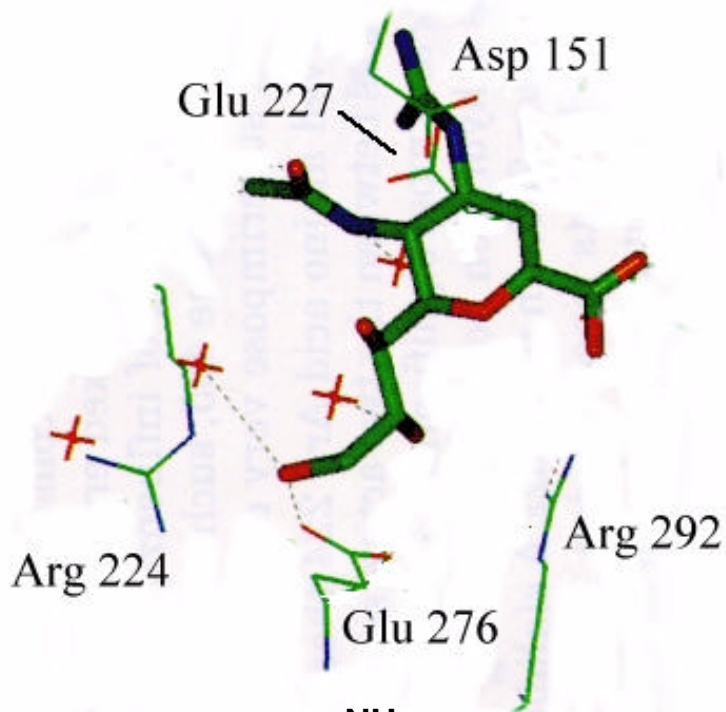


Zanamivir

More selective
for A type virus

Sialidase inhibited by Zanamivir analogues

J. Med.Chem. 1998, 41, 787



Induced fit warning signs

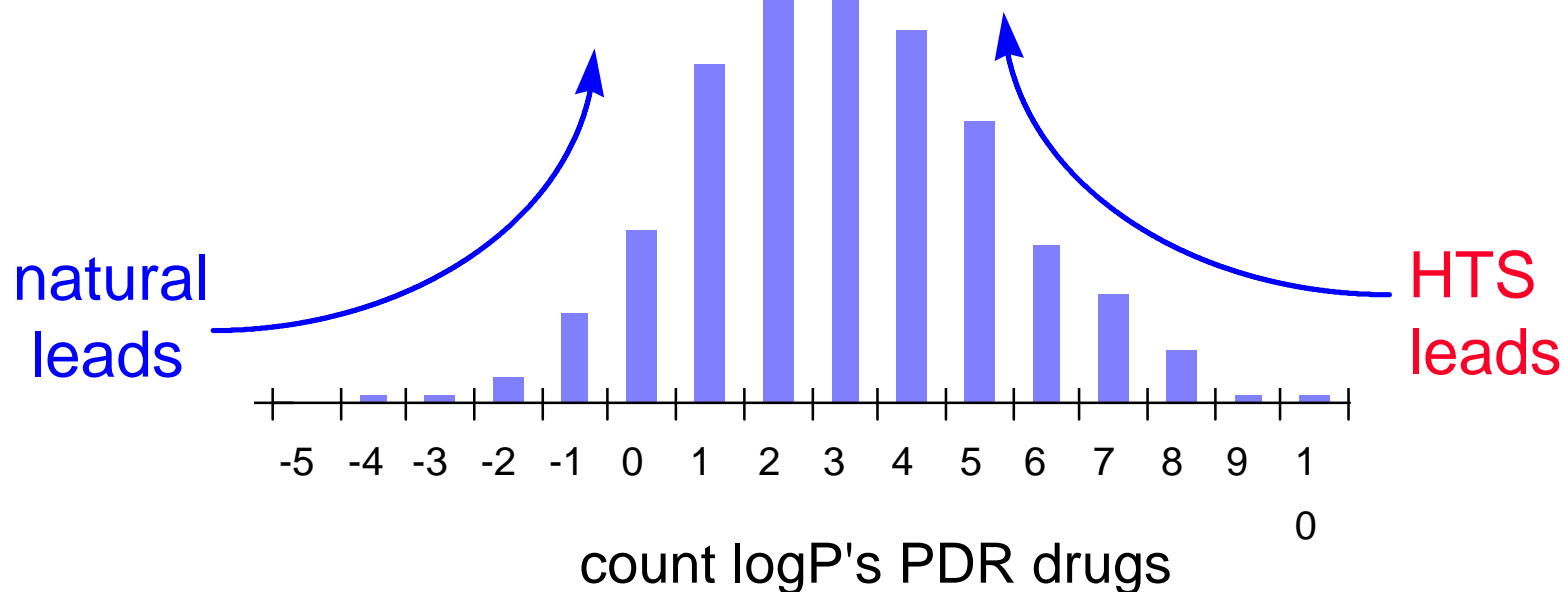
- Time dependent inhibition
 - enzyme kinetics, incubation time dependency
- Changes in CD, solubility, crystallinity of protein
- ‘Odd’ QSAR
 - similar molecules - non parallel QSAR
 - extreme dependency on small lipophilic group
- Very high % buried surface area of sample ligand in X-ray structure



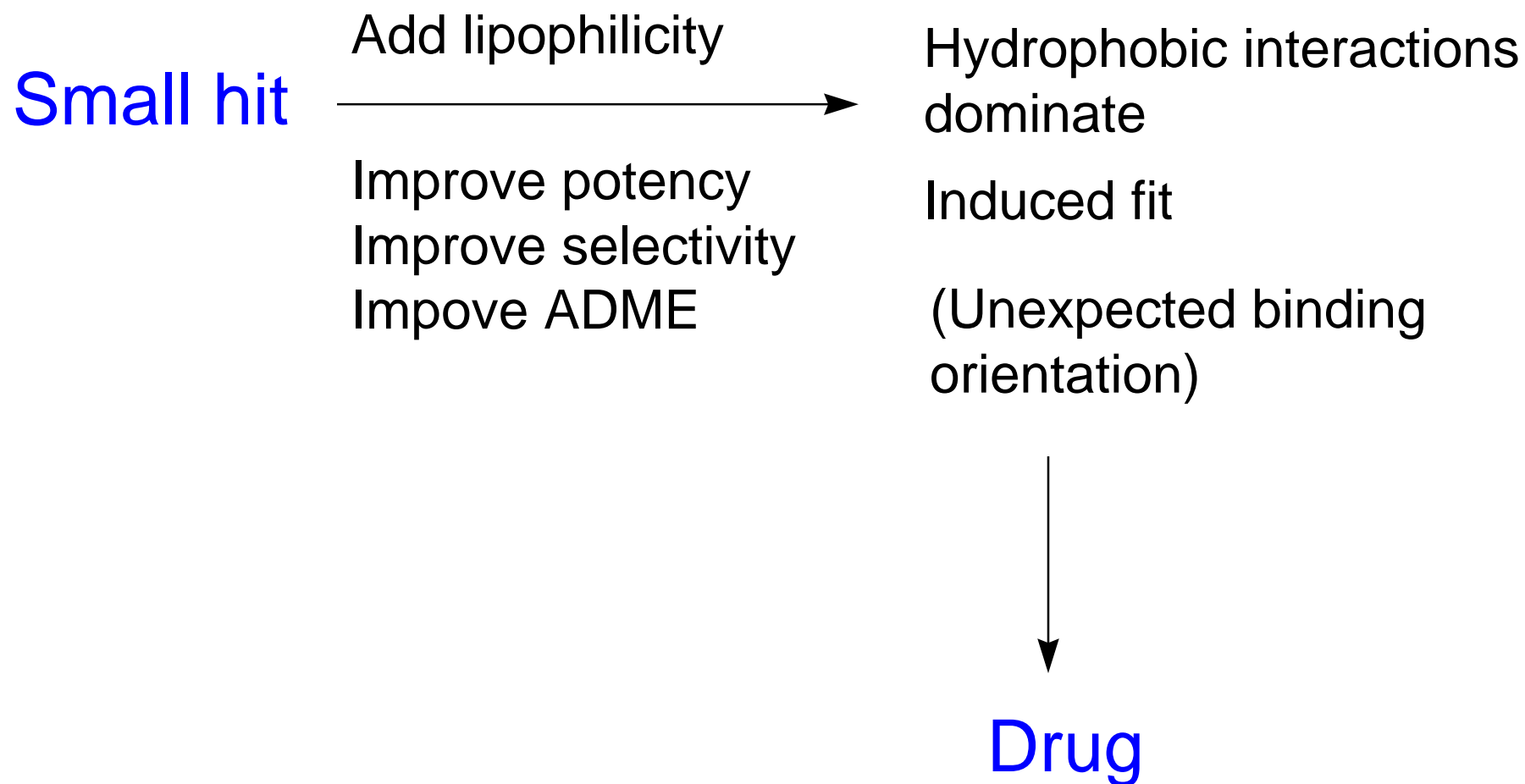
Challenges of drug-design

remove polar gps
increase affinity
add lipophilicity
optimise ADME

remove non-specific fat
maintain specific hydrophobic
contacts
introduce polar gps
optimise ADME



Journey from small 'hit' to a drug



Specific hydrophobic interactions are required

- Activity often increases with lipophilicity
 - 2 to 3 fold per CH_2 . Compounds 'unhappy' in water.
- Introduction of additional lipophilicity can give much greater affinity increase
 - good fit, induced fit, displaced water

Too much non productive hydrophobicity - poor ADME



Summary

- **Specific hydrophobic interactions important**
 - often dominate or replace polar interactions
 - important for potency & selectivity
- **Induced-fit common**
 - especially with drug-like molecules (ADME)
 - overlay of ‘similar’ molecules difficult
 - paradigm shifts in understanding - new series
- **Modelling tools**
 - over emphasise H-bonds
 - can lead to poor bulk properties (eg solubility)
 - inflexibility of active-site models a major problem



Holistic drug design

- Focus upon the whole process
 - solubility, ADME and interaction with target
- Realistic expectations of modelling tools
 - awareness of strengths and weaknesses
 - especially where selectivity is a major issue
- Measurement and observation crucial
 - not replaced by software and databases

Experimentation, insight and luck still essential



Acknowledgement

- Andy Davis
 - Dept. Physical and Metabolic Sciences

Simon J. Teague, Andy M. Davis
Angew. Chem. Int. Ed. Engl. 1999, 38, 736-749

“Hydrogen bonding, hydrophobic interactions and failure of the rigid receptor hypothesis”

