PASSAGE OF IDEAS

MOLECULAR SIMILARITY

Electron Density Determines All Molecular Properties

BCP Properties Compactly Summarise The Electron Density

Geometrical Bond Lengths Correlate With BCP Properties - *on a small scale*

Can Bond Length Be Used As a Parameter To Investigate Molecular Properties And Activities?

QSAR

Which Region Of The Molecular Electron Density Should We Examine?

- ***Global Property***
  - **-Lipophilicity**
- ***Site Specific Property***
  - **-Acidity, Toxicity**

Hansch Analysis

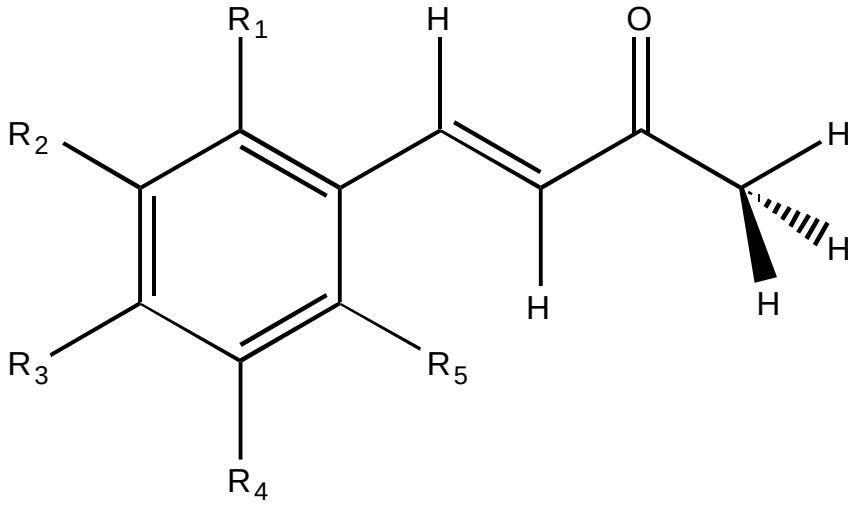
$$\mathbf{Log(1/C) = a\ LogP + b\ \sigma + c}$$

$$\mathbf{Log(1/C) = a\ LogP + b\ \beta + c}$$

Where :

β depends upon the *choice of bonds*

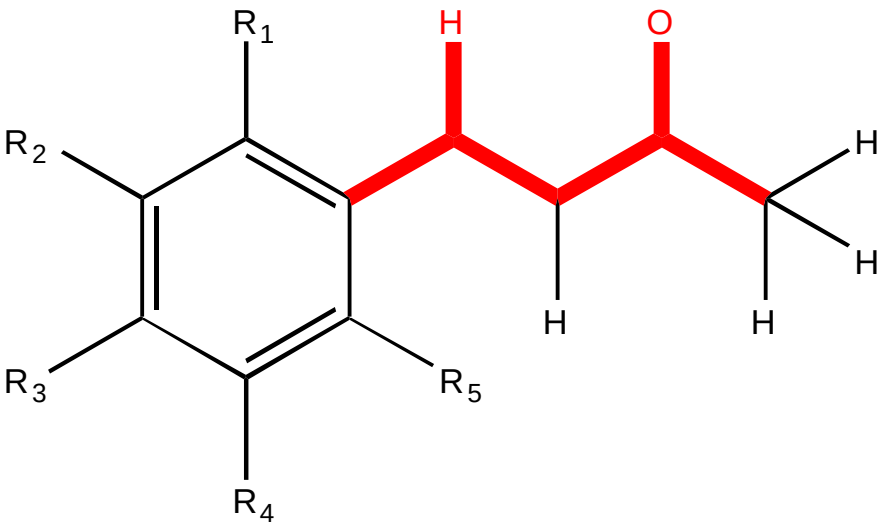
Experimental Results Determine the Composition of Parameter b



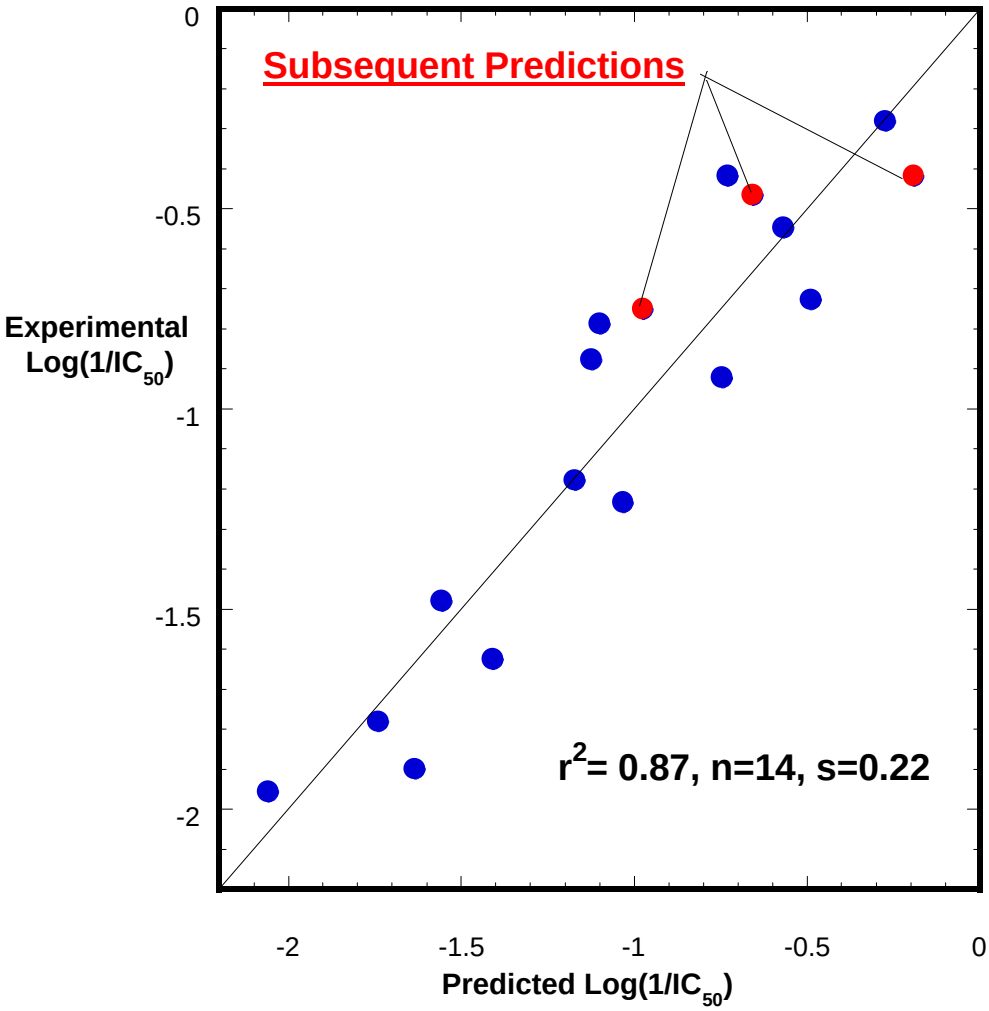
Substituted Phenylbut-1-en-3-ones[1]

MOLECULE	IC50μM
C_6F_5	1.9
3-$NO_2C_6H_4$	2.6
3-Br-4-F C_6H_3	2.6
4-Br C_6H_4	2.9
3-(F_3C) C_6H_4	3.5
5-Br C_6H_4	5.3
4-$NO_2C_6H_4$	5.6
4-FC C_6H_4	6.1
4-Me C_6H_4	7.5
4-Cl C_6H_4	8.3
4-(MeS) C_6H_4	15
C_6H_5	17
2,4-$(MeO)_2$ C_6H_4	30
3-OH-4(MeO) C_6H_4	42
4-(OH) C_6H_4	60
4-(MeO) C_6H_4	79
4-(Me_2N) C_6H_4	90

1.Ducki, S.; Hadfield, J. A.; Hepworth, L. A.; Lawrence, N. J.; Liu, C. Y.; McGown, A. T. *Bioorg. Med. Chem.Lett.* **1997**, *7*, **3091-3094.**

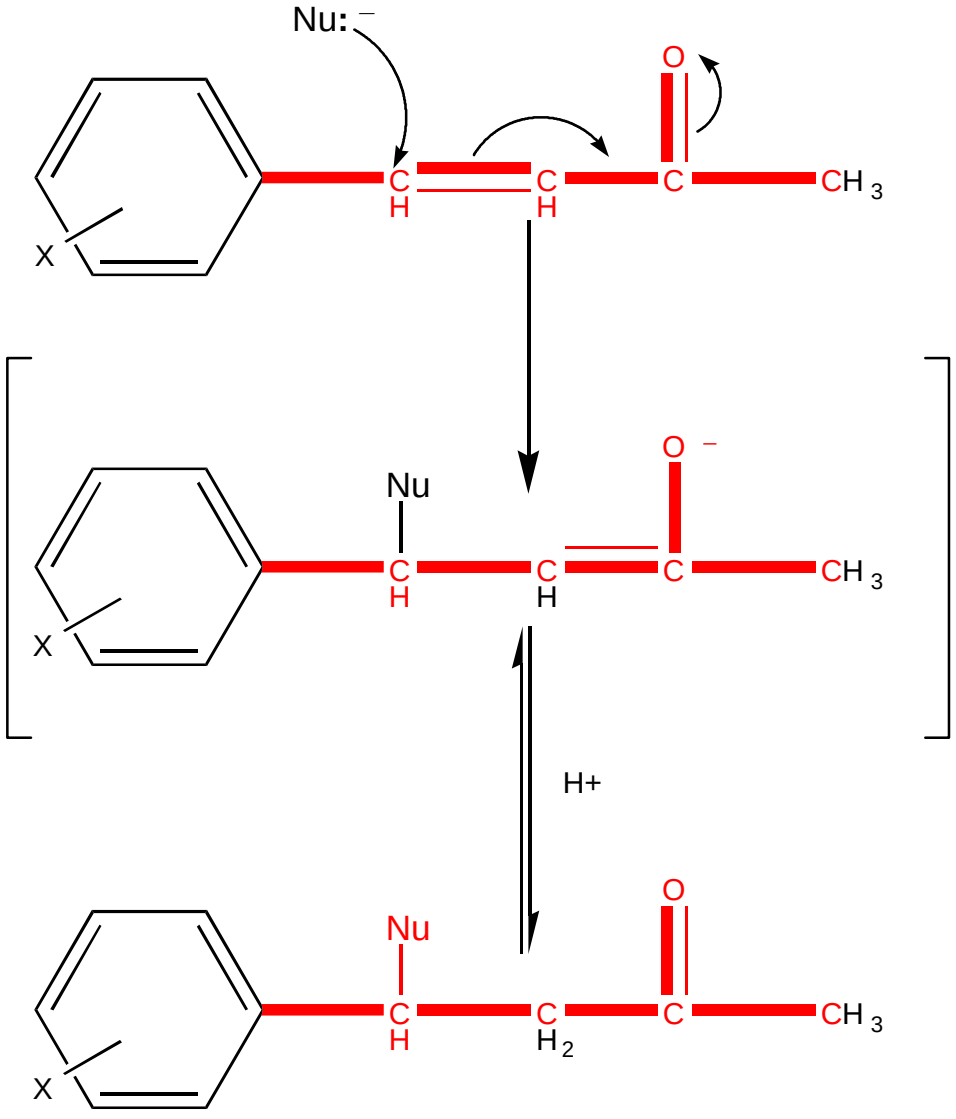


Predicted Log(1/IC $_{50}$) vs. Experimental Log(1/IC $_{50}$)



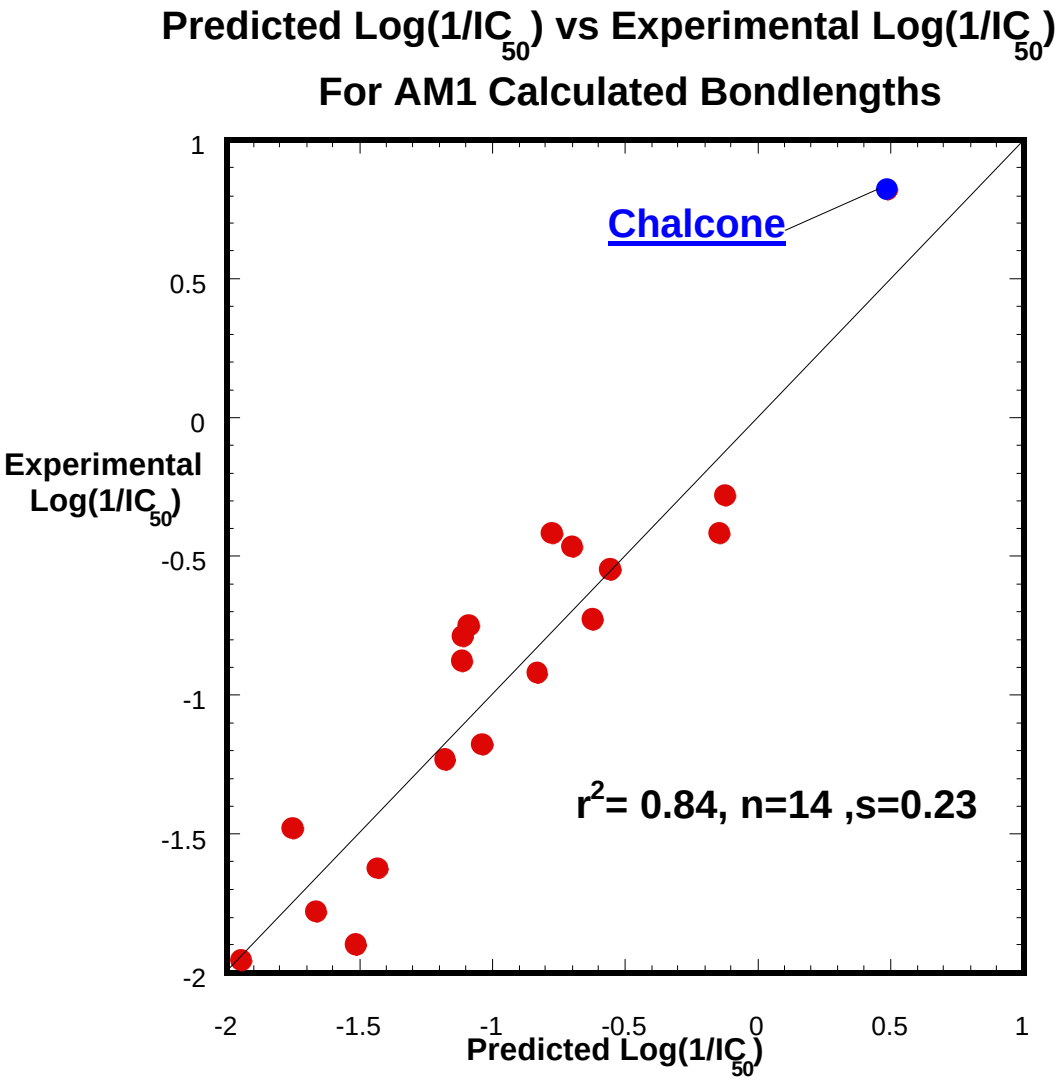
Michael Addition

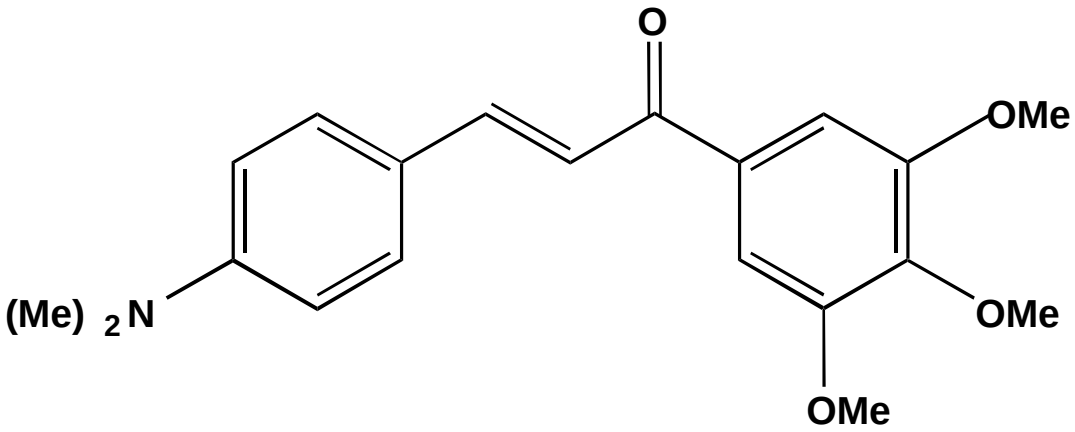
- **Suspected mode of action[1,2]**
- ***Active Centre* supports the hypothesis**



2. Ducki, S. Anticancer Drugs from traditional Chinese Herbs. *PhD. Thesis* **1997 UMIST.**

AM1 Calculations

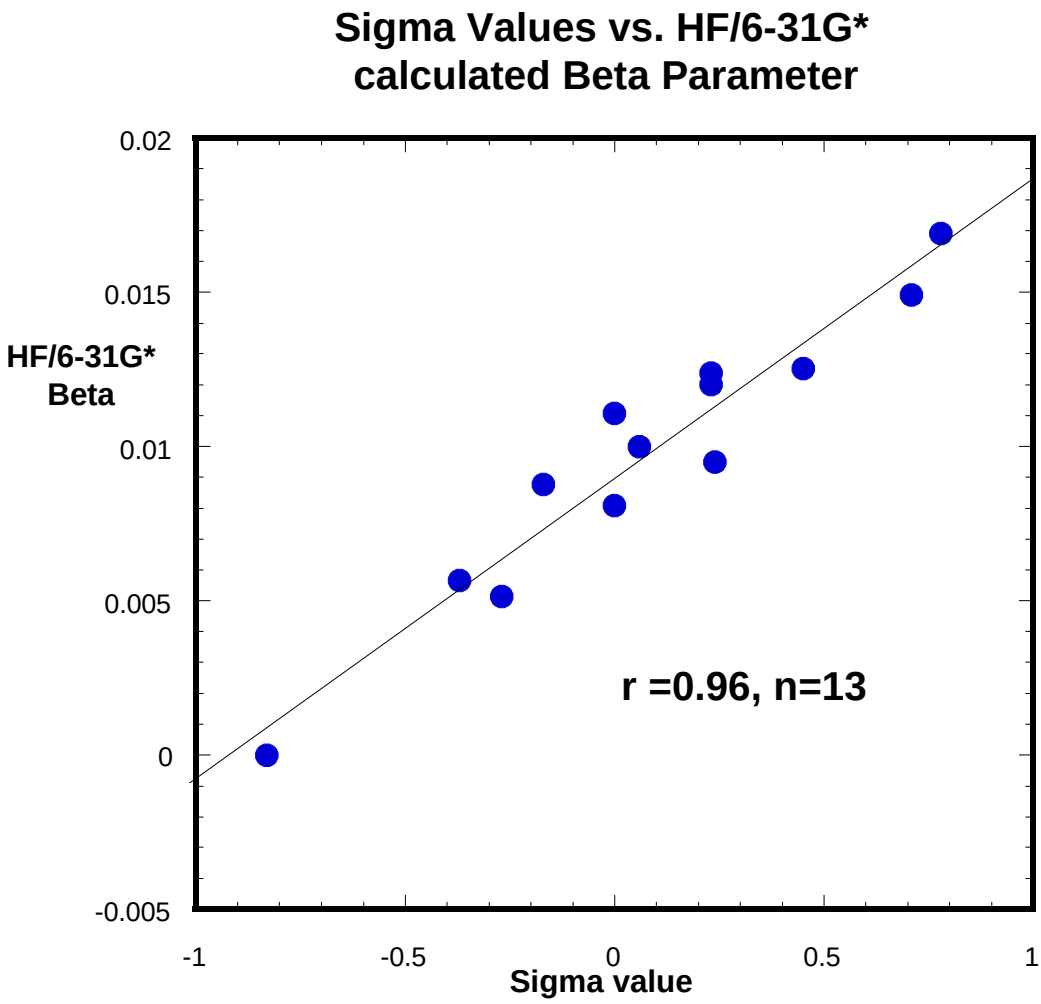




Substituted Chalcone IC_{50} = 0.15μM

Sigma Constants

- **not constant**
- **different for differing systems**
- **can be difficult to obtain**



We Are Measuring The Effect Any Particular Substituent Has On This Very System

Concluding Remarks

- **Reproduce/Predict Activity**
  - **Using *Ab Initio* Methods**

- **AM1 Calculations Feasible**
  - **Potential for Large Molecules**

- **Provide Information About the Site and Mechanism of Activity**

- **The Parameter β is Comparable to the σ Constant**
  - **System Specific**