

Chemical Shift Correlations in Drug Discovery - Methods and Applications

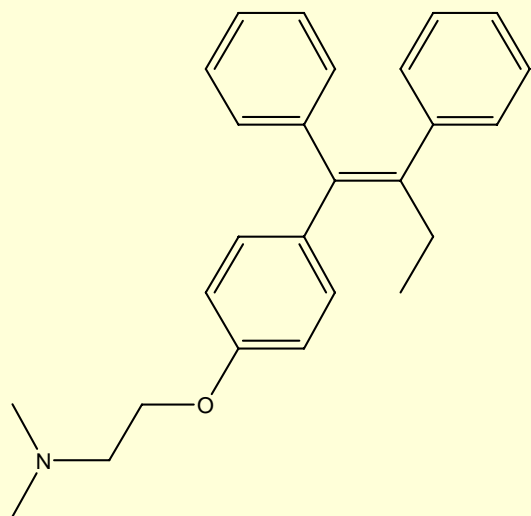
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Research

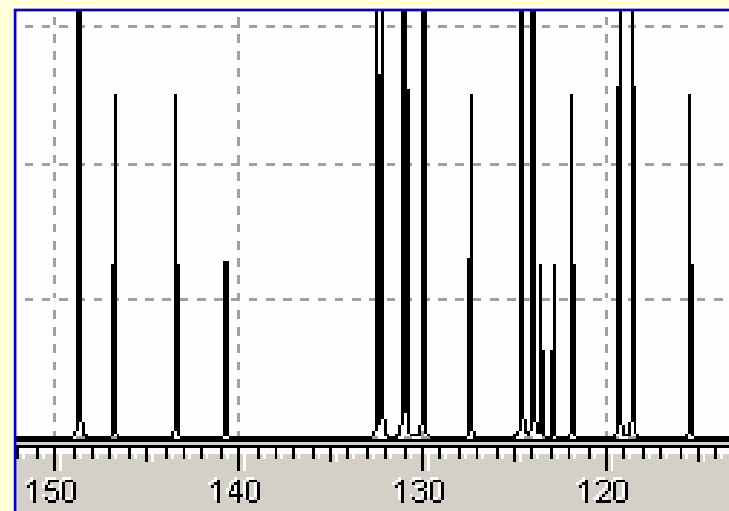
Introduction

- **Structure-Activity Relationship (SAR)**

- ▶ Based on the idea that there is a correlation between the structure of a molecule and its activity



Spectrum



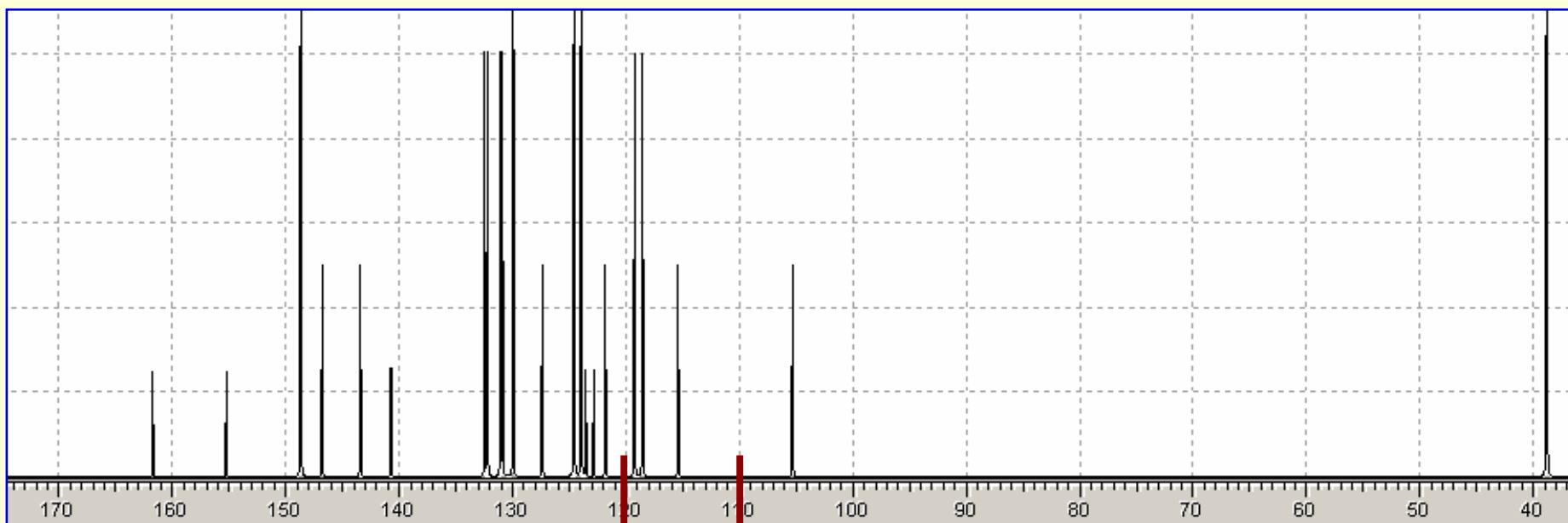
SAR

SDAR

Activity and Properties

Sample Data Set

Predicted ^{13}C NMR Spectrum of TPL₂ Compound



10 ppm spectral "bin"

Methods

- **Optimization**

- ▶ **Data Collection**

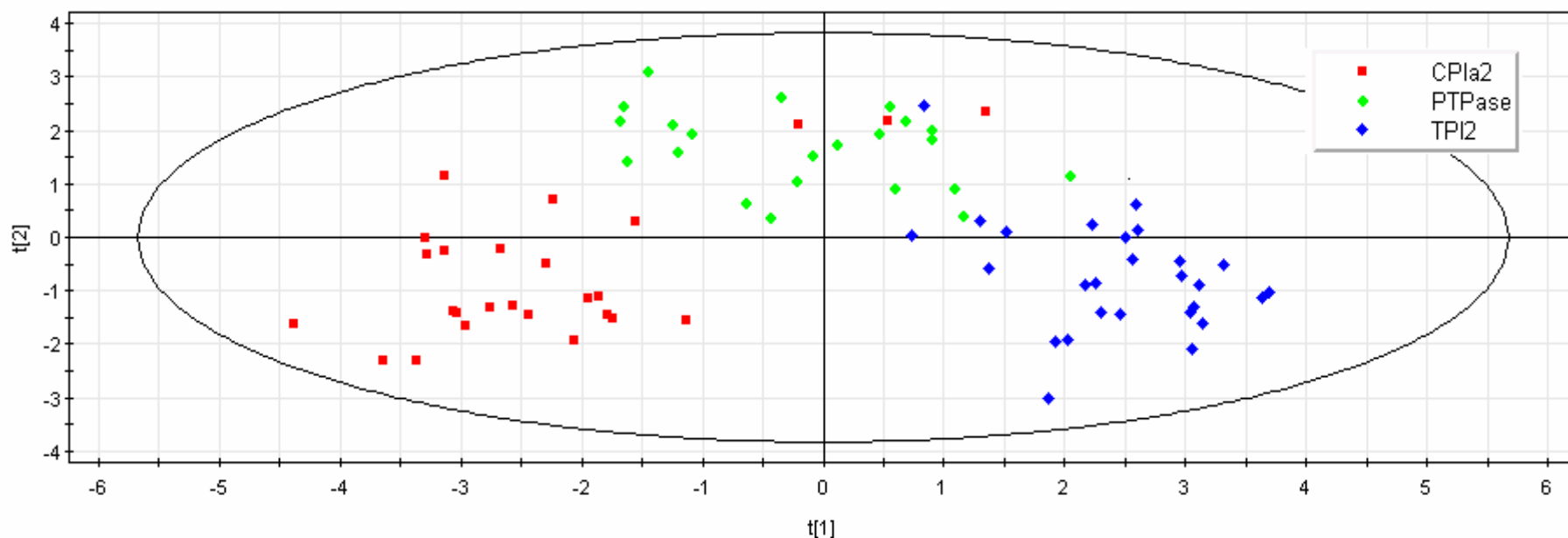
- Analyze and compare various NMR Spectra (^{13}C , DEPT, ^1H) for predictive quality
 - Compare various “bin” sizes (ex: 20ppm vs. 10ppm vs. 1ppm)
 - Observe differences between experimental spectra and predicted spectra

- ▶ **Data Analysis (Simca-P 10.5)**

- Optimal parameters determined via comparison of R^2 and Q^2 values, as well as visual correlations displayed by the scores plot

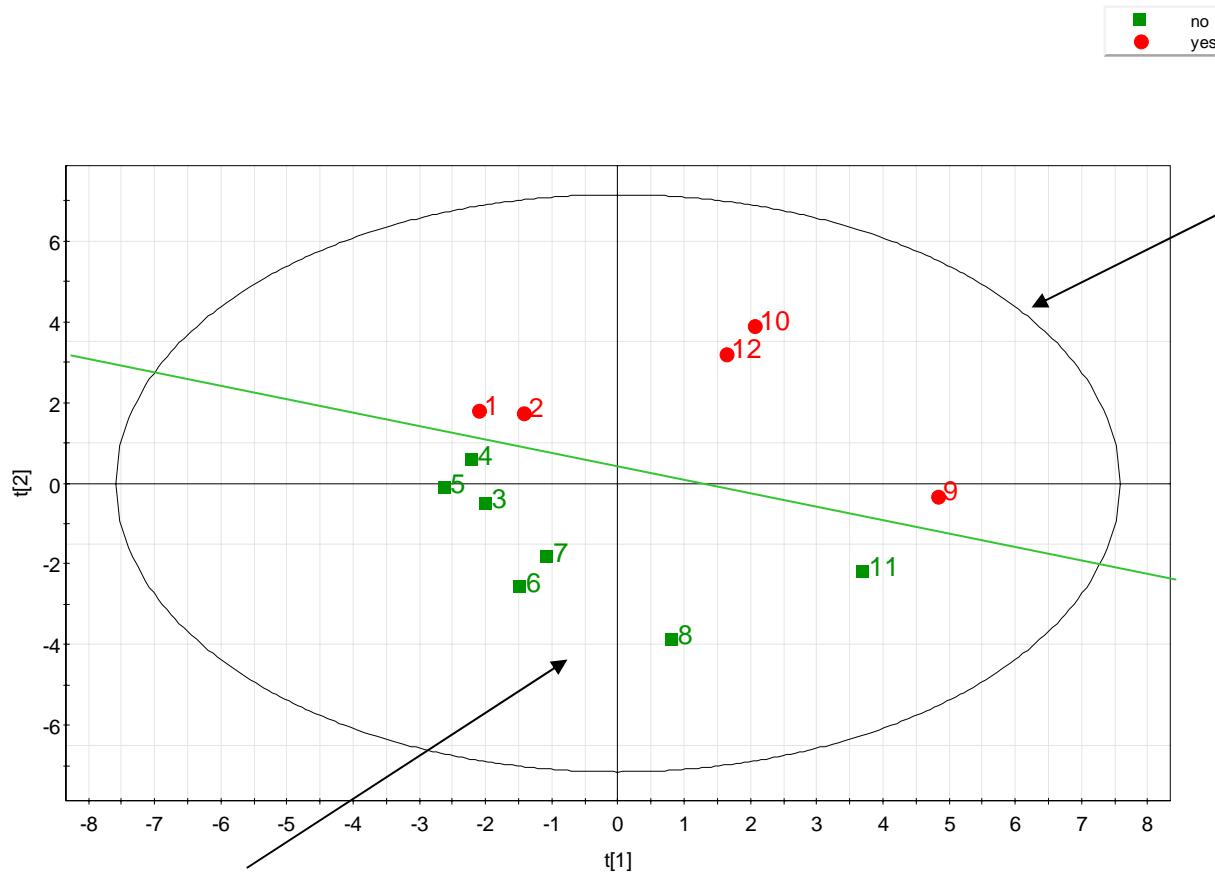
Results within a broad set of compounds (three distinct lead series)

Scores Plot



- **Three distinct groups that correlate with biochemical activity**
 - ▶ There is enough similarity within the groups, but enough variation between the groups for classification
 - ▶ We can use these results to suggest when a particular compound might have activity against two distinct protein targets

Results within a specific chemical lead series



(toxicity in red)

We can use these results to discriminate properties of individual compounds within the series

(no toxicity in green)

Ellipse: Hotelling T2 (0.95)

SIMCA-P+ 10.5 - 4/1/2005 3:08:05 PM

Conclusions

- **Optimization**

- ▶ Predicted data is often easier to interpret and leads to more accurate correlation plots due to lack of impurities introduced by experimental samples
- ▶ Smaller bins are not necessarily better for this type of analysis
- ▶ One type of spectrum is no better than the other (i.e. ^1H vs. ^{13}C); each spectrum sheds light on different aspects of the molecule contributing to an overall understanding of the inherent electrostatic and 3-D features

- **Results**

- ▶ It is possible to visually separate compound groups via NMR techniques and Multivariate methods
- ▶ Often, a molecule's placement on the scores plot not only depends on the features it has, but just as importantly, the features it does NOT have

Acknowledgements

- I wish to thank my colleagues and management in **Chemical Technologies and Chemical and Screening Sciences at Wyeth Research** for their interest in this project