Screening of a sulfonamide library by supercritical fluid chromatography-mass spectrometry (SFC-MS)

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❑ Introduction

High-throughput synthesis (HTS) techniques allow pharmaceutical chemists to readily produce more and more new drug candidates. To achieve the quality and safety requirements expected for new drug compounds, analysts need new analytical methods capable of quick, highly-efficient separations as well as characterization of all compounds and impurities.

Until recently High Performance Liquid Chromatography coupled to Mass Spectrometry (HPLC-MS) has been preferentially used for this purpose. However Supercritical Fluid Chromatography coupled to Mass Spectrometry (SFC-MS) appears more and more as a complementary technique for HT analysis. Orthogonality between these two chromatographic techniques may allow the detection by SFC-MS of impurities missed by HPLC analysis due to co-elution.

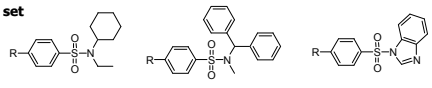
The aim of this work is to evaluate the ability of SFC-MS for screening and purification of a small library of neutral and basic sulfonamides. A goal of the study of these libraries is to define a set of properties-based rules allowing prediction of the suitability of the technique for a given compound.

❑ Objectives

- Explore the chemical space covered by SFC
- Identify correlations between retention times and analytes' physico-chemical properties
- Ideally: design a generic SFC method

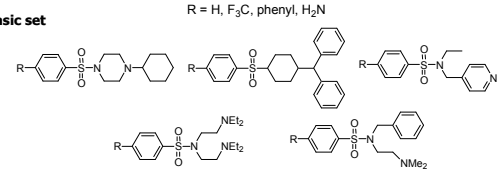
■ The library

- **Neutral set**



R = H, F_3C, phenyl, H_2N

- **Basic set**



R = H, F_3C, phenyl, H_2N

❑ Design of the compounds

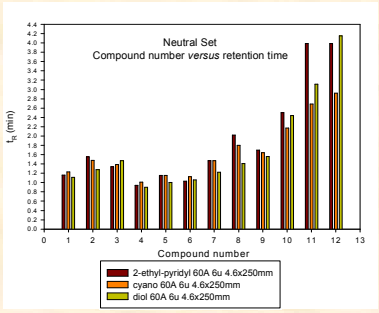
- Why sulfonamides?
  - easily synthesized
  - widely used in medicinal applications
- Follow Lipinski's rule of five
- Broad range of logP and pKa

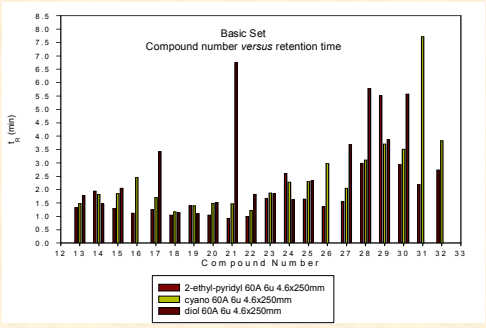
❑ Columns

- 2-ethyl-pyridyl (2-EP) 4.6x250mm 60A 6u
- cyano 4.6x250mm 60A 6u
- diol 4.6x250mm 60A 6u

❑ Methods

- Neutral set: isocratic 20% and 10% MeOH
- Basic set: isocratic 20% and 10% MeOH +0.1% v/v diethylamine (DEA)





❑ Results

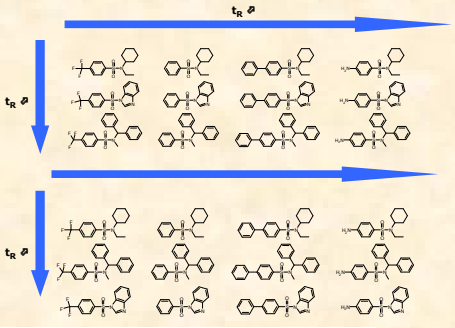
- All neutral compounds eluted in less than 5min on the three columns
- No specificity
- Trends correlating structures and retention times
- BUT: no correlations between retention times and logP, logD and pKa

❑ Results

- 2-EP and cyano: all basic compounds eluted in less than 8min provided use of DEA
- Diol column: most basic compounds not eluted in 10min
- No specificity
- Trends correlating structures and retention times
- BUT: no correlations between retention times and logP, logD and pKa

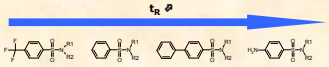
❑ Trends

- 2-EP and cyano columns
- Diol column



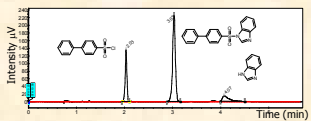
❑ Trends

- 2-EP, cyano and diol columns



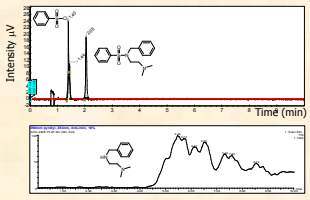
❑ Purification evaluation

- All neutral compounds resolved from starting material on 2-Ep column using 10% MeOH isocratic elutioneluted in less than 5min on the three columns



❑ Purification evaluation

- Basic compounds resolved from starting material on 2-EP column using 10% MeOH + 0.1% DEA
- BUT: some starting amines very badly eluted ⇒ no stacked injection allowed



■ Conclusion and future work

- SFC suitable for analysis of neutral and basic compounds provided basic additive (DEA) is used
- Starting amines of basic set badly eluted from any column

} ⇒ This could raise issues for preparative chromatography

- Clear trends linking structures and retention, but no correlation between retention and physico-chemical properties ⇒ try other retention parameter (logk) and molecular descriptors
- Design, synthesise and analyse acidic set

■ Acknowledgements

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