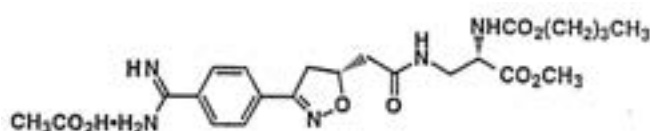


Chiral separation of multifunctional complex drug compounds

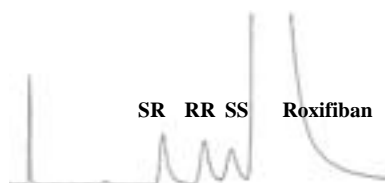
New drug compounds often contain several functional groups. This means that they are not easily classified, i.e. if they are acidic, basic or ampholytic. In addition they may also contain several stereogenic centers. When developing a method on **CHIRAL-AGP**, the Method Development Schemes are very useful, even for multifunctional compounds. Below are two examples of compounds with many functionalities as well as with two stereogenic centers.

Roxifiban

(*J.Chrom. A*, 844 (1999) 171-179, R.C. Williams et al)



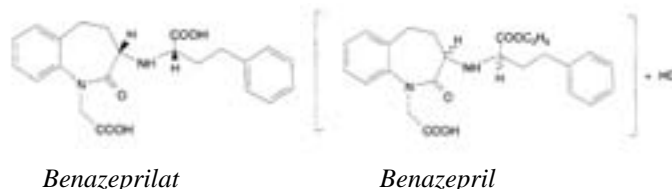
Roxifiban contains many different nonprotolytic functionalities together with a basic benzimidazole group with a pKa of 11. This protolytic group is the most important to consider when developing a method. When analyzing the structure, it can be described as a hydrophilic amine. In the Method Development Scheme the starting mobile phase for hydrophilic amines is 5% 2-propanol in 10 mM sodium phosphate buffer pH 7.0. The compound has two stereogenic centers and is developed as a single stereoisomer in the RS configuration, which means that the RR and SS diastereoisomers and the SR enantiomer are possible impurities. In the article an experimental design study was used in order to optimize the different variables for the separation of the four isomers. However, the optimized mobile phase was found to be the starting mobile phase for hydrophilic amines in the Method Development Scheme, see figure below.



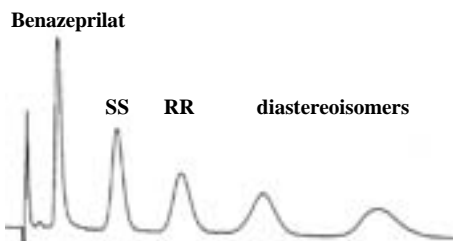
Column: **CHIRAL-AGP** 100x4.0 mm
 Mobile phase: 5% 2-propanol in 10 mM sodium phosphate buffer pH 7.0

Benazepril

(*J.Chrom. A*, 818 (1998) 53-60, R.Cirilli et al)



Benazepril contains different nonprotolytic functionalities, as well as an acidic group. This protolytic function is the most important group in order to determine the method development strategy. Benazepril is a strong acid. In the Method Development Scheme the starting mobile phase for strong acids is 10 mM sodium phosphate buffer pH 7.0. Depending on the result obtained with this mobile phase, optimization is carried out using variables as pH, organic modifier and buffer. Benazepril contains two stereogenic centers. A further complication in this analysis is that benazepril is administered as the (S,S)-configuration and hydrolyzed in vivo to its active dicarboxylic acid metabolite, benazeprilat. Benazepril's enantiomer and the diastereoisomeric pair of enantiomers are potential impurities, as well as the dicarboxylic acid. In the article an extensive investigation of mobile phase parameters was carried out. An optimized mobile phase was found (see figure below). By characterizing benazepril as a strong acid and following the Method Development Scheme for strong acids, it would also have been possible to develop a similar optimal mobile phase.



Column: **CHIRAL-AGP** 100x4.0 mm
 Mobile phase: 7.5% 2-propanol in 60 mM potassium phosphate buffer pH 4.0

When developing a method for a multifunctional complex compound on the **CHIRAL-AGP** column, look for protolytic functions. Decide which protolytic group might decide the character of the compound. Then test the corresponding starting mobile phase from the Method Development Scheme. If the compound contains protolytic groups of different character, in addition you may have to test another starting mobile phase corresponding to the other protolytic function. Another possibility is to test the three starting mobile phases in the Method Development Scheme in an unprejudiced way, in order to find the best route for method development.

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