Minimizing acidity in a series of aldose reductase inhibitors: the case of 2-fluoro-4-(1*H*-pyrrol-1-yl)phenol as a scaffold

M. Chatzopoulou*, V.J. Demopoulos
chatzom@pharm.auth.gr

Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece

Aldose reductase (ALR2) is a notorious enzyme mostly known for its participation in the polyol pathway of glucose metabolism. Targeting this pathway for the treatment of long-term diabetic complications has been the focus of studies in the past (1), and a number of aldose reductase inhibitors (ARIs) have been synthesized and clinically tested towards these pathologies. More recent studies also attribute a causative role of ALR2 in inflammatory pathologies and support the significance of this enzyme as a pharmacotherapeutic target (2). In the plethora of ARIs synthesized so far, two categories are the most studied, namely that of cyclic imides and carboxylic acid derivatives. However, a number of cyclic imide derivatives exhibited acute side effects and carboxylic acids presented with poor membrane permeation. In order to overcome the limitations of the two classic categories of ARIs, formerly, we have described a successful bioisosteric replacement of a carboxylic acid moiety with that of a 2,6-difluorophenol (3). 2,6-Difluorophenol has a pKa value of 7.12, therefore its derivatives could diffuse through membranes more adequately than their carboxylate counterparts. In the present work, we investigated the synthetic feasibility and ARI activity of aroylpyrroles bearing groups that are non-anionic in physiological pH such as the phenol, 2-fluorophenol, salicylaldoxime, nitroaldoxime, and 3,4-difluorophenyl moiety (Figure 1). The 2-fluorophenol derivative exhibited the most promising combination of activity and physicochemical properties, thus a further optimization of this structure was exploited. In the new series of compounds, a novel submicromolar ARI was discovered (IC_{50} = 0.443 μM) that was also the most selective inhibitor in this series (S.I. = 27) against the homologous enzyme aldehyde reductase. Physicochemical evaluation of this ARI, along with promising ex vivo data on sorbitol accumulation in rat lenses support the notion that this compound could be a successful lead compound for the synthesis of ARIs with minimum acidity.

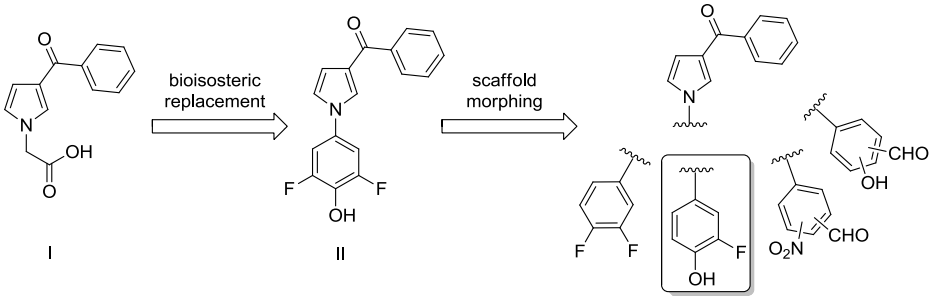

Fig. 1: Rationale for the design of aldose reductase inhibitors with minimized acidity

References

(1) P. Alexiou, K. Pegklidou, M. Chatzopoulou et al., Curr. Med. Chem. **2009**, 16, 734-752.
(2) M. Chatzopoulou, P. Alexiou, E. Kotsamasakou et al., Exp. Opin. Ther. Pat. **2012**, 22, 1303-1323.
(3) M. Chatzopoulou, E. Mamadou, M. Juskova et al., Bioorg. Med. Chem. **2011**, 19, 1426-1433.