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Additive free preparative chiral SFC separations of 2,2-dimethyl-3-aryl-propanoic acids

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ABSTRACT

A series of racemic 2,2-dimethyl-3-aryl-propanoic acids were resolved by chiral supercritical fluid chromatography (SFC) without the use of an acidic additive, trifluoroacetic acid (TFA). The use of additive-free protic methanol as co-solvent in CO_2 was expanded to successfully resolve other series of carboxylic acid containing racemates. Large-scale SFC of racemic acid **4**, 3-(1-(4-fluorophenyl)-1*H*-indazol-5-yl)-2,2-dimethyl-3-phenylpropanoic acid, in methanol without TFA as additive on both Chiralpak AD-H and Chiralcel OJ-H will be discussed, along with impact on throughput and solvent consumption. Investigation of co-solvent effect on peak sharpening of acid racemate **20**, 2-(2-chloro-9-fluoro-5*H*-chromeno[2,3-b]pyridin-5-yl)-2-methylpropanoic acid, without TFA further indicated that methanol in CO_2 provided improved peak shape compared with isopropanol (IPA) and acetonitrile. Finally, we discuss the resolution of basic aromatic chiral amines without the addition of basic additives such as diethylamine (DEA) and application of this protocol for the large-scale SFC separation of weakly basic indazole-containing racemate **14**, methyl 3-(1*H*-indazol-5-yl)-2,2-dimethyl-3-phenylpropanoate, in methanol without DEA.

1. Introduction

Glucocorticoid receptor (GR) is a member of the steroid family of nuclear hormone receptors that is involved in modulating a variety of immunological and metabolic signaling pathways upon glucocorticoid binding [1,2]. A series of 2,2-dimethyl-3-aryl-propanoic acid derivatives were developed as novel GR modulators [3–6] in which the chirality of each individual enantiomer had significant impact on biological activity, metabolism and toxicity. Thus, preparation of optically pure enantiomers from these compounds became an essential requirement and played an important role in the program's progression. For large-scale chiral purification, preparative HPLC requires large amounts of solvent with a long cycle time, resulting in a low throughput and extended evaporation time after separations [7,8]. In addition, chiral HPLC typically requires TFA as an additive in the mobile phase of heptane/alcohols to sharpen peaks and resolve acidic compounds [9,10]. Although using TFA in chiral analyses of acidic compounds is not a major concern, it should be avoided in preparative mode. TFA has the potential to cause compound degradation, transesterification, if esters are present in the compound that is being subjected to chiral separation or ester formation of acidic compounds when methanol (MeOH) is used as co-solvent. In addition, the removal of TFA by evaporation is problematic on a preparative scale.

Supercritical fluid chromatography (SFC) has been successfully applied to both analytical chiral purity assessment and preparative chiral resolution to provide enantiomerically pure compounds [11–14]. Attributes of this technology are faster method development cycle, readiness in scale-up, higher throughput and reduced solvent consumption. As a general practice, MeOH with acidic and/or basic additives have been predominantly used in chiral SFC for resolving acidic racemates [15–19]. Analytical analysis of aromatic chiral acids by SFC with water as a neutral additive and the replacement of acid additives (e.g. TFA, formic acid, acetic acid) in MeOH has been demonstrated [20–23]. However, successful large-scale separations of chiral acids and bases using SFC technology has been limited [24–26], since the effect of acid additives are dependent on the nature of analytes and SFC separation conditions. This article will discuss applications of preparative chiral SFC in separating 2,2-dimethyl-3-aryl-propanoic acids and the extended structurally similar series of racemic acids in methanol without the need for TFA as an additive. This unique capability will be demonstrated in large-scale chiral SFC separation of racemic acid **4**. Co-solvent effect on peak sharpening without TFA was investigated

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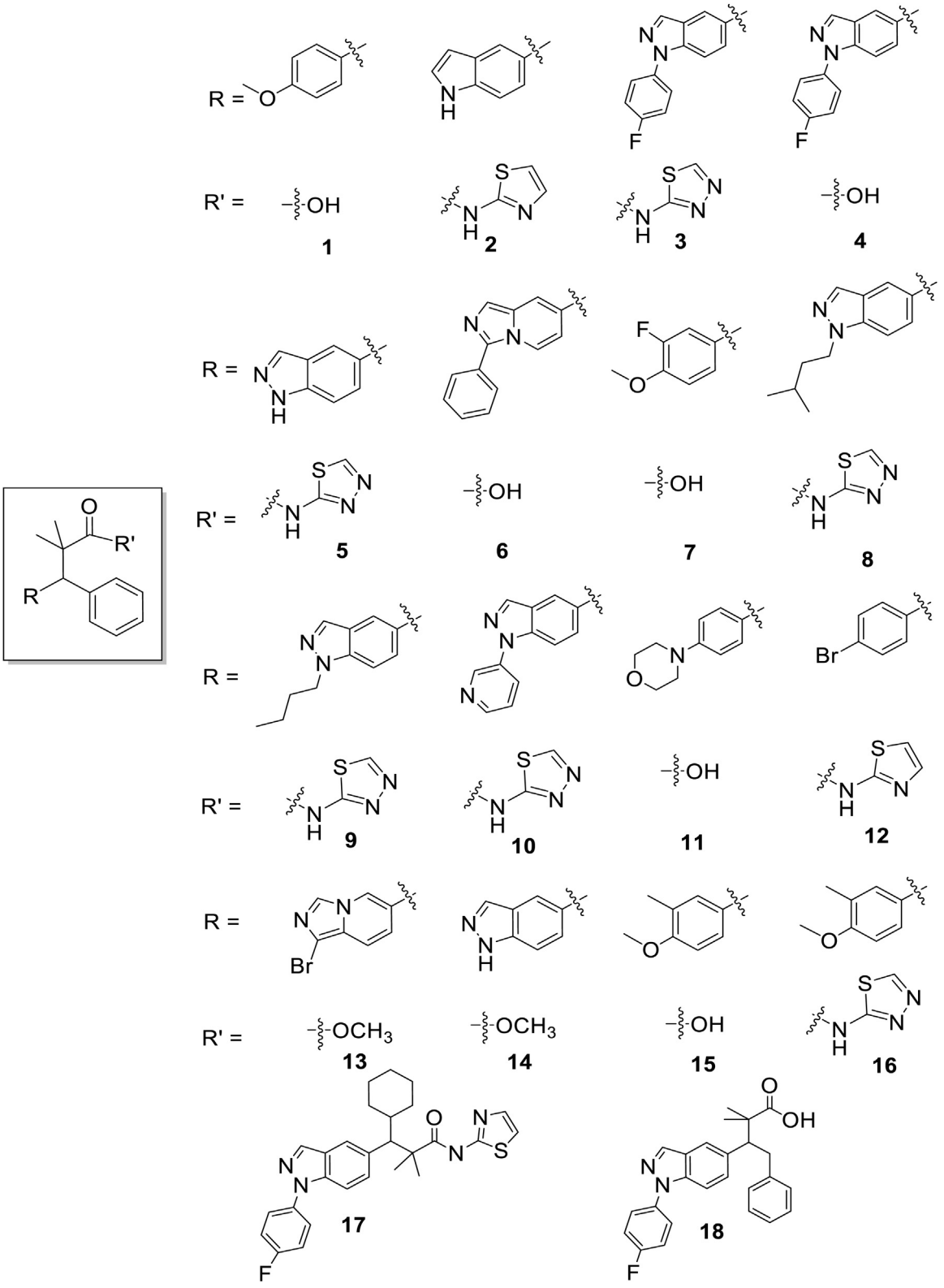

Fig. 1. 2,2-dimethyl-3-aryl-propanoic acids and their derivatives.

with the racemic acid **20**. Chiral SFC of aromatic chiral amines in MeOH without basic additive will also be presented. MeOH in CO_2 without DEA and the resulting impact on throughput and solvent consumptions will be discussed in the context of large-scale SFC of weakly basic racemate **14**. Structural effects on retention of these propanoic acids and derivatives will be discussed.