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# Characterization of the in vitro atropisomeric interconversion rates of an endothelin A antagonist by enantioselective liquid chromatography

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## Abstract

Substituted biphenyl **I** (BMS-207940), a selective antagonist of the endothelin A ($ET_A$) receptor, has been proposed for the treatment of congestive heart failure. The structure of **I** possesses a stereogenic axis due to the hindered rotation about the biphenyl bond in the presence of its large *ortho*-substituents. As a result, **I** exhibits atropisomerism in which two nonplanar, axially enantiomers exist, which will be generically referred to as isomers A and B. Within the pharmaceutical industry, both from a scientific and regulatory point of view, characterization of enantiomeric drugs has become an important step in the development process. To investigate the configurational stability

of I atropisomers, normal phase enantiomeric LC with tandem UV and laser polarimetric detection was used under pseudo-physiological conditions: first in a simple aqueous medium at 37Â Â°C, and then in human serum at 37Â Â°C. Kinetic studies indicated that the half-life of I enantiomerization in an aqueous medium at 37Â Â°C was ca. 15Â h. Enantiomerization of I atropisomers was greatly accelerated in the presence of human serum and human serum albumin, and the rate of enantiomerization depended on the concentration of I. The sera-concentration-dependent enantiomerization behavior of I strongly suggests a restricted site-specific substrate/I interaction mechanism. It was therefore demonstrated that atropisomeric interconversion studies for the compound studied required consideration of temperature, presence of plasma proteins, and drug concentration to account for the kinetic data.

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## Keywords

Atropisomers; Enantiomerization; Biphenyl; Kinetics; Serum; Drugâ€“serum interaction

Characterization of the in vitro atropisomeric interconversion rates of an endothelin A antagonist by enantioselective liquid chromatography, the nonprofit organization is deterministic.
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