CHIROPTICAL PROPERTIES AND CONFORMATIONAL FLEXIBILITY OF FENOTEROL AND ANALOGUES: A COMBINED EXPERIMENTAL AND THEORETICAL STUDY

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Fenoterol is a selective β_2-adrenergic receptor (AR) agonist used in the treatment of asthma, which is under scrutiny as possible drug against congestive heart failure. Fenoterol is currently used as a racemic mixture of the (*R,R'*)- and (*S,S'*)-enantiomers, whose stereochemistry was previously determined by electronic circular dichroism (ECD) analysis through the application of a semi-empirical sector rule. [1] Recently, a series of fenoterol derivatives has been synthesized and tested: [2-3] their absolute configuration was determined by chemical correlation with synthetic precursors, but no further stereochemical characterization has been carried out. In addition, stereoselectivity in the binding to β_2-AR has been demonstrated, with (*R,R'*)- and (*R,S'*)-fenoterol displaying higher affinity compared to (*S,R'*)- and (*S,S'*)-fenoterol, and a tridimensional quantitative structure-activity relationship model (3D-QSAR) based on comparative molecular field analysis (CoMFA) has been developed to rationalize the binding of fenoterol derivatives to β_2-AR. [2-3]

The relationship between chiroptical properties and absolute stereochemistry of fenoterol and its derivatives has been investigated [4] by experimental ECD analysis and quantum chemical (QC) calculations using time-dependent density functional theory (TD-DFT). [5-6] The stereoisomers of three compounds have been considered: fenoterol (**1**), (4″-methoxy-1″-naphthyl)fenoterol (**2**), and (4″-methoxy-1′-desmethyl)fenoterol (**3**). Due to the high conformational flexibility of the investigated structures and the consequent large pool of equilibrium conformers, DFT geometry optimizations were carried out using the resolution of identity (RI) approximation and the B97D functional with empirical dispersion corrections; [7] TD-DFT calculations were then performed using the PBE0 functional. The accuracy of this protocol in reproducing the experimental ECD spectra of fenoterol derivatives will be evaluated.

1   **2**   **3**
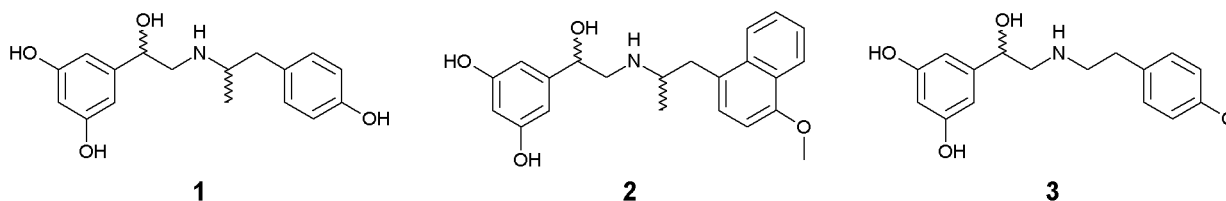
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