ELAGOLIX AND ITS DERIVATIVES: ANALYTICAL AND THEORETICAL INVESTIGATIONS OF THEIR ATROPISOMERIC PROPERTIES

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Among the Gonadotropin Releasing Hormone (GnRH) modulators [1], elagolix represents a breakthrough being the first non-peptide orally active GnRH-antagonist approved for the treatment of sex-hormone dependent diseases such as endometriosis [2] and uterine fibroids [3]. Chemically, it is an uracil-based derivative having a stereocenter with (*R*)-configuration and an additional source of chirality, called atropisomerism, arising from a restricted rotation around a C-C bond due to steric hindrance involving the *o*-fluorine of the 5-aryl group with the methyl and the carbonyl oxygen at 6- and 4-position of the uracil moiety, respectively (Figure 1).[4]

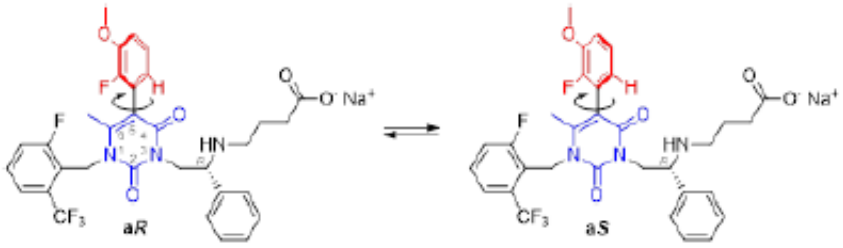

Figure 1: Chemical structure of elagolix: the hindrance to rotation about the single bond is indicated by the black arrow.

Since atropisomerism occurs *via* a time/temperature-dependent bond rotation causing a conformational instability, it is very important to be considered in drug discovery and development processes.[5]

Herein, we will focus on the investigation of the elagolix conformational stability, through spectroscopic, analytical, and theoretical techniques, and of few new analogues differently substituted at the 6- or 4-position of the uracil moiety. These derivatives showed atropisomeric interconversion rates lower than elagolix, allowing their separation and the analyses as single atropisomers.

Overall, these outcomes contributed to clarify the structural determinants involved in the control of the spatial arrangement of the substituents within this molecular framework, useful for future development of single atropisomers with higher selectivity.

References

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