Insights on the atropisomeric properties of Elagolix and its derivatives

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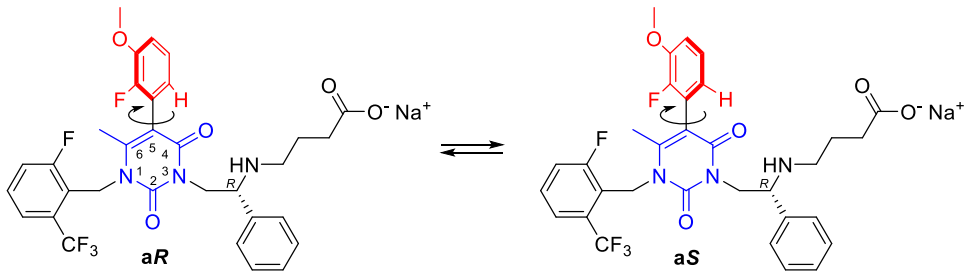
Elagolix is the first non-peptide orally active gonadotropin-releasing hormone (GnRH) antagonist, approved for the treatment of sex-hormone dependent diseases such as endometriosis[1] and uterine fibroids.[2] Chemically it is an uracil-based derivative having a stereocenter with (*R*)-configuration and 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 (see figure below).



After the recognition and characterization of the atropisomers of elagolix through spectroscopic, analytical, and theoretical techniques,[3] the design and synthesis of some analogues differently substituted at the 6- or 4-position of the uracil moiety were carried out. The increase of the steric hindrance and/or the modulation of the electronic factors at these positions were able to affect the atropisomeric properties of this class of derivatives.

Few new congeners showed atropisomeric interconversion rates higher than elagolix, which allowed their separation and analyses as single atropisomers.

These outcomes contributed to shed light on the structural determinants involved in the control of the spatial arrangement of the substituents within this molecular framework, useful for future development of derivatives with higher activity.

(1) Lamb, Y. N. *Drugs* **2018**, *78*, 1501.
(2) Muhammad, J.; Yusof, Y.; Ahmad, I.; Norhayati, M.N. *BMC Womens Health* **2022**, 22, 14.
(3) Ciceri, S.; Colombo, D.; Fassi, E.M.A.; Ferraboschi, P.; Grazioso, G.; Grisenti, P.; Iannone, M.; Castellano, C.; Meneghetti, F. *Molecules* **2023**, *28*, 3861.