# A new class of GnRH receptor modulators endowed with atropisomerism

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Among the Gonadotropin Releasing Hormone (GnRH) receptor modulators, 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 and uterine fibroids. 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.

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 lower than elagolix, which allowed their separation and analyses as single atropisomers. The chemical and physical characterization together with the outcomes of the ongoing biological tests will be useful for future development of derivatives with higher selectivity.

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