ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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GnRH Antagonists: The Promise of Treating Sex-Hormone-Related Diseases

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Title: Spiroindoline Derivatives for Use as Gonadotropin-Releasing Hormone Receptor Antagonists

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Disease Area: Sex-hormone-related diseases in both men and women **Biological Target:** Gonadotropin-Releasing Hormone Receptor (GnRH)

Summary: The invention in this patent application relates to spiroindoline derivatives represented generally by formula (I), which are gonadotropin-releasing hormone (GnRH) receptor antagonists. These compounds may potentially be useful for the treatment of many sex-hormone-related diseases in both men and women, including but not limited to endometriosis, uterine leiomyoma (fibroids), gonadal steroid-dependent neoplasia such as cancers of the prostate, breast, and ovary, premenstrual syndrome, benign prostatic hypertrophy, contraception, infertility, and assisted reproductive therapy such as in vitro fertilization.

Gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone releasing hormone (LHRH), is a decapeptide (pGiu-His-Trp-Ser-Tyr-Giy-LeuArg-Pro-Giy-NH2) that is released from the hypothalamus. GnRH plays a key role in human reproduction. It stimulates the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. LH is responsible for the regulation of gonadal steroid production in both genders and late ovarian follicle development and ovulation in female mammals, and FSH regulates spermatogenesis in males and early follicular development in females.

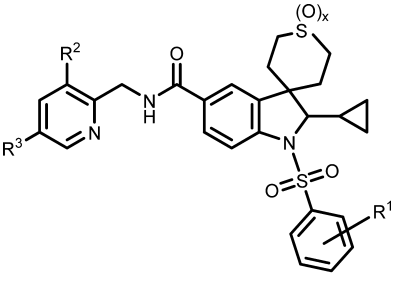
Considerable research activities were dedicated to the development of synthetic GnRH agonists and antagonists, particularly in the fields of endometriosis, uterine leiomyoma (fibroids), prostate cancer, breast cancer, ovarian cancer, prostatic hyperplasia, assisted reproductive therapy, and precocious puberty.

GnRH agonists bind to the GnRH receptor on the pituitary gonadotrophic cells to induce the synthesis and release of gonadotropins. This results in excessive release of FSH and LH, which is referred to as flare-up. Their chronic administration reduces the release of gonadotropin from the pituitary and results in the down-regulation of the receptor and subsequent suppression of the production of sex steroidal hormone. Examples of GnRH agonists include the decapeptide leuprorelin (pGiu-His-Trp-Ser-Tyr-D-Leu-LeuArg-Pro-NHEt).

GnRH antagonists suppress gonadotropins and offer several advantages, including the lack of side effects associated with the flare up seen under GnRH agonist treatments. Several peptidic antagonists with low histamine release potential were reported; however, they exhibited limited clinical use because of their low oral bioavailabilities.

The discovery of nonpeptidic GnRH antagonists was the subject of intensive research for more than 15 years and resulted in the identification of several candidates. However, none of them has succeeded so far to reach the market. Therefore, there is still an unmet need for the development of effective small molecule compounds that are active as GnRH antagonists to be used as medications to treat sex-hormone-related conditions. The spiroindoline derivatives described by the inventors in this patent application aim to fulfill such unmet need.

Important Compound Classes:



Formula (I)

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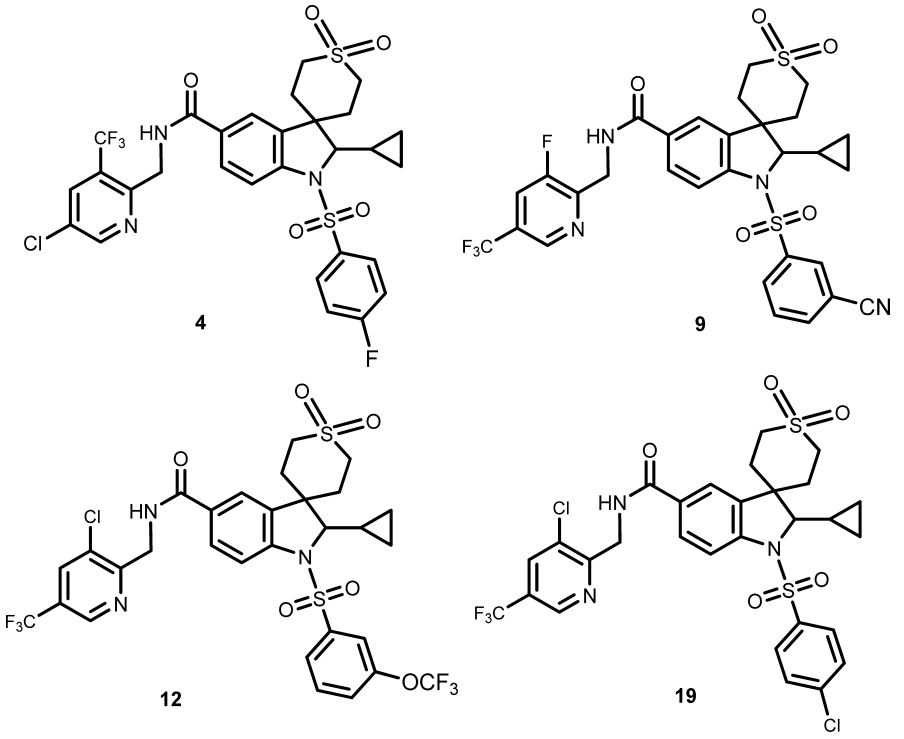
Key Structures: The inventors reported the structures and methods of synthesis for 20 examples of formula (I) including the following four compounds. The compounds were prepared as racemic mixtures and each was resolved into two enantiomers using chiral column chromatography methods.



Biological Assay:

- Receptor binding assay using radiolabeled buserelin
- Tag-lite receptor binding assay
- IP-One HTRF assay
- In vivo pharmacokinetics in rats
- LH suppression in the ovariectomized rat

Biological Data: The inventors reported the data from the IP-One HTRF assay with buserelin for 19 examples of formula (I) including their resolved enantiomers; the data for the representative examples **4**, **9**, **12**, and **13** (above) are listed in the following table:

Potency in IP-One HTRF assay with buserelin (at EC_{80}) stimulation			
Compound	Potency: IC_{50} μM	Compound	Potency: IC_{50} μM
4 (enantiomer 1)	0.0033	**4** (enantiomer 2)	4.08
9 (enantiomer 1)	0.107	**9** (enantiomer 2)	2.31
12 (enantiomer 1)	0.068	**12** (enantiomer 2)	4.21
19 (enantiomer 1)	9.35	**19** (enantiomer 2)	0.0055

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Copperman, A. B.; Benadiva, C. *Reprod. Biol. Endocrinol.* **2013**, *11*, 20.

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Notes

The authors declare no competing financial interest.