NEW DIRECTIONS IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE ANALOGS OF LULIBERIN

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At the present time, the possibility has been shown of using highly active analogs of luliberin in clinical medicine. At the same time, traditional methods of obtaining such preparations by combining the most effective modifications [1] do not always lead to the desired result. We have considered some new directions in the synthesis of these compounds: the preparation of cyclic analogs and analogs with a shortened amino acid sequence. Eleven compounds have been synthesized:

H-Ser-Tyr-*D*-Ala-Leu-Arg-Pro-NHEt (1)
H-Pro-Ser-Tyr-*D*-Ala-Leu-Arg-Pro-NHEt (2)
Z-*D*-Phe-Pro-Ser-Tyr-*D*-Ala-Leu-Arg-Pro-NHEt (3)
H-*D*-Pro-Ser-Tyr-*D*-Ala-Leu-Arg-Pro-NHEt (4)
pGlu-Ser-Tyr-*D*-Ala-Leu-Arg-Pro-NHEt (5)
BOC-Phe-Ser-Tyr-*D*-Ala-Leu-Arg-Pro-NHEt (6)
H-Pro-Gly-Ser-Tyr-*D*-Ala-Leu-Arg-Pro-NHEt (7)
H-Pro-Ser-Tyr-*D*-Ala-Leu-Arg-OH (8)
H-Pro-Gly-Pro-*D*-Phe-Pro-Ser-Tyr-*D*-Ala-Leu-Arg-OH (9)
—Pro-Ser-Tyr-*D*-Ala-Leu-Arg— (10)
—Pro-*D*-Phe-Pro-Ser-Tyr-*D*-Ala-Leu-Arg-Pro-Gly— (11)

In biological trials, the influence of the analogs on ovulation [1] and on the action of chorionic gonadotropin (CG) on the ovaries and uterus of sexually immature rats were evaluated [2]. It was found that the peptides (1), (2), (9), and (11) possessed a comparatively high antiovulatory activity and compounds (1), (3), (5), (6), (7), and (11), in addition, stimulated the course of the ovulation processes. In the tests with CG, the agonist analogs caused a strong inhibitory effect, while the antagonists showed no such action. It is interesting to note that some compounds (2 and 10) potentiated the action of CG to a considerable degree. As special investigations showed, the analog (1) strongly accelerated the estrous cycle of the rat, which passed through its phases completely in 3–10 h (while the control took 4–5 days). The results of the biological trials of the cyclic analogs and their linear precursors confirmed the hypothesis of the quasicyclic structure of the "biologically active" conformation of luliberin and the influence of the spatial orientation of the amide bond in the ring of pyroglutamic acid on the agonistic or antagonistic activity.

The promising nature of the synthesis of cyclic analogs and of analogs with shortened amino acid sequences has been shown for the first time. The results obtained indicate the possibility of using these compounds as contraceptive agents. A new direction of the preparation of luliberin antagonists (analogs of type 9) has been developed.

LITERATURE CITED

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