PDEIV阻害剤を骨粗鬆症治療薬として開発するための基礎的研究

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1998 Fiscal Year Final Research Report Summary

Basic Studies for development of anti-osteoporosis drugs from PDEIV inhibitors.

Research Project

Project/Area Number

08838025

Research Category

Grant-in-Aid for Scientific Research (C)

Allocation Type

Single-year Grants

Section

一般

Research Field

老化(加齢)

Research Institution

Kanazawa University

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Keywords

Phosphodiesterase / PDEIV / Inhibitors / Osteoporosis / Therapeutic drugs / Targeting / Animal model / Walker256 / S

Research Abstract

We previously developed new xanthine derivatives having selective PDE IV inhibitory activity, and suggested that they exhibited osteoblastogenic and a1ti- osteoclastogenic actions. We attemped to further develop new anti-osteoporosis drugs arid osteoporosis animal model in the research project

and obtained the following results ;
1)A new heterocycle-condensed purine, 3 , 4-dipropyl-4, 5,7, 8-tetrahydro-3H-imidazo [l, 2-i]purin 5-one (XT-611), which shows selective and potent PDE IV inhibitory activity without emetic action, was developed according to the analysis of the structural and electronic properties of alkylxanthine derivatives.
2)Our developed compounds and other known PDE IV inhibitors showed significant anabolic actions in the in vitro and in viva experimental systems.
3)We newly developed an acidic peptide [(Asp)6], which was a good carrier of drug for bone targeting.
4)We showed that Walker256/S mammary carcinoma caused osteoporisis-like changes in rats and ectopically secreted LH-RH, resulting inhibition of sex hormone secretion and stopping the sex cycle. Then, this tumor may be a useful animal model for postmenopausal osteoprosis.

Research Products (12 results)

All Other

All Publications (12 results)

[Publications] Hiroyuki Sawanishi: "Selective inhibitors of cyclic AMP-specific phosphodiesterase:Heterocycl condensed purimes." J.Med.Chem.40. 3248-3253 (1997)

[Publications] Ken-ichi Miyamoto: "Reduction of bone Loss by clenbufylline, an inhibitor of phospho-diesterase 4." Biochem.Pharmacol.54. 613-617 (1997)

[Publications] Kanji Yamamoto: "Relationships between the structural and electronic properties of alkylxanthine derivatives and their inhibitory activity on PDE IV" Biol.Pharm.Bull.21. 356-359 (1998)

[Publications] Yoshihiro Waki: "Walker 256/S carcinosarcoma causes osteoprosis-like changes through production of luteinizing hormone-releasing hormone." Cancer Res.in press. (1999)

[Publications] Yoshihiro Waki: "Effects of XT-44,a phosphodiesterase 4 inhibitor, in osteoblastogenesis and osteoclastogenesis in culture and its therapeutic effects in rat." Jpn.J.Pharmacol.in press. (1999)

[Publications] Yoshihiro Waki: "Postmenopanse-like bone Loss by mammary carcinoma Walker 256/S which secretes lateinizing hormone-releasing hormone." Jpn.J.Pharomacol.in press. (1999)

[Publications] Hiroyuki Sawanishi, Hirokazu Suzuki, Shinya Yamamoto, Yoshihiro Waki, Shohei Kasugai, Keiichi Ohya, Nagao Suzuki, Ken-ichi Miyamoto, and Kenzo Takagi: "Selective inhibitors of cyclic AMP-specific phosphodiesterase : Heterocycle-condensed purines." J.Med.Chem.40(20). 3248-3253 (1997)

[Publications] Ken-ichi Miyamoto, Yoshihiro Waki, Takashi Horita, Shohei Kasugai, and Keiichi Ohya: "Reduction of bone loss by denbufylline, an inhibitor of phosphodiesterase 4." Biochem.Pharmacol. 54. 613-617 (1997)

[Publications] Kenji Yamamoto, Hiroyuki Sawanishi, And Ken-ichi Miyamoto: "Relationships between the structural and electronic properties of alkylzanthine derivatives and their inhibitory activity on PDEIV isoenzyme." Bio.Pharm.Bull. 21. 356-359 (1998)

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