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Drugs of the Future

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Drugs of the Future

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Drugs of the Future

Drugs of the Future is a monthly publication designed to provide in monograph form information on new drugs from their first phases of development up to their marketing.

An Information Update section appears monthly providing the most recent information available on drugs whose monographs were published in the same-numbered issue of previous volumes. Drug information in this section can be consulted by developmental phase or alphabetical order.

Articles on topical fields, presented by leading specialists, explore the innovative areas of drug research and highlight the mechanisms by which drugs act, relating chemical structures to specific biological activities.

Drugs of the Future

Drugs of the Future is published monthly. A pharmacostructural index appears annually in the December issue. Cumulative chemical formula and general indices are published separately and mailed to subscribers in January.

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Calendar year subscription price for Volume 22, 1997 is US $ 975. Airmail additional (optional): America $ 70, Asia $ 120, Europe $ 40.Back volumes are available in book form, offering an Encyclopedia of drugs in various stages of research, continuously updated as new information becomes available.

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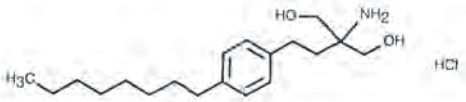
FTY720

Immunosuppressant

2-Amino-2-[2-(4-octylphenyl)ethyl]-1,3-propanediol hydrochloride



$C_{19}H_{33}NO_2.HCl$ Mol wt: 343.94

CAS: 162359-56-0

EN: 210392

Synthesis

The Friedel-Crafts condensation of phenethyl acetate (I) with octanoyl chloride (II) by means of $AlCl_3$ in dichloroethane gives 2-(4-octanoylphenyl)ethyl acetate (III), which is reduced with triethylsilane in TFA to afford 2-(4-octylphenyl)ethyl acetate (IV). The deprotection of (IV) with sodium ethoxide in ethanol gives 2-(4-octylphenyl)ethanol (V), which is treated with methanesulfonyl chloride followed by sodium iodide in refluxing 2-butanone yielding 2-(4-octylphenyl)ethyl iodide (VI). The condensation of (VI) with diethylacetamidomalonate (VII) by means of sodium ethoxide in ethanol/THF gives diethyl 2-acetamido-2-[2-(4-octylphenyl)ethyl]malonate (VIII), which is reduced with $LiAlH_4$ in THF and treated with acetic anhydride in pyridine to afford 2 - acetamido - 2 - (acetoxymethyl) - 4 - (4 - octylphenyl)-butyl acetate (IX). The hydrolysis of (IX) with lithium hydroxide in refluxing methanol/water gives 2-amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol (X), which is finally treated with HCl in diethyl ether (1, 2). Scheme 1.

Description

White crystalline powder, m.p. about 260 °C (decomp.).

Introduction

With the remarkable progress in immunology including the discovery of various cytokines, T-cell receptors and intercellular adhesion molecules, it has now become possible to elucidate the mechanism of immune response at cellular and molecular levels. During the research on immunoregulatory mechanism, cyclosporin A (CsA), a fungus cyclic peptide from *Trichoderma polysporum*, was found to suppress immune responses by inhibiting production of interleukin-2 (IL-2) in antigen-stimulated helper T-cells (3, 4). Since its first clinical use as an immunosuppressant, CsA has contributed greatly in preventing acute rejection in human organ transplantations. Recently, tacrolimus (TRL, FK506), a novel macrolide from *Streptomyces tsukubaensis*, was reported to have 10- to 100-fold more potent immunosuppressive activity than CsA (5-7). Similar to CsA, TRL inhibits antigen-induced T-cell proliferation by inhibiting IL-2 production in helper T-cells. Although CsA and TRL bind to different proteins, termed cyclophilin and FKBP, respectively, both cyclophilin/CsA and FKBP/TRL complexes inhibit phosphatase activity of calcineurin which activates nuclear factor in activated T-cells (NF-AT) involved in the promotion of IL-2 gene transcription (8). Since CsA and TRL have almost the same mechanism of action, these drugs show quite similar side effects, such as renal and liver toxicities (9). CsA- or TRL-based multiple drug therapy with steroids or other immunosuppressants such as azathioprine and mizoribine is widely used in order to reduce the side effects of individual immunosuppressants in human organ transplantations (10, 11). However, the concomitant use of CsA and TRL is contraindicated because of their similar side effects based on the mechanism of action. Thus, a novel immunosuppressant should not only be highly safe but also possess a mechanism of action distinct from CsA and TRL in order to allow concomitant administration with them.

For the above reasons, Yoshitomi Pharmaceutical Industries Ltd. began research on immunosuppressive substances from the products of vegetative wasp with Professor Tetsuro Fujita of Kyoto University (currently, Profesor of Setsunan University) and Taito Co., Ltd. In the culture broth of *Isaria sinclairii*, we isolated myriocin (ISP-I) and mycestericins, which have a potent immunosuppressive activity *in vitro* (12, 13). Chemical modification of myriocin (12-14) led to a synthetic compound, 2-amino-2-[2-(4-octylphenyl)-ethyl]propane-1,3-diol hydrochloride (FTY720) (2) that has more potent immunosuppressive activity and less toxicity compared to myriocin (1, 2, 14-16).

Kenji Chiba, Kunitomo Adachi. Research Laboratories, Yoshitomi Pharmaceutical Industries, Ltd., 3-7-25 Koyata, Iruma-shi, Saitama 358, Japan.

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