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Fluticasone Furoate

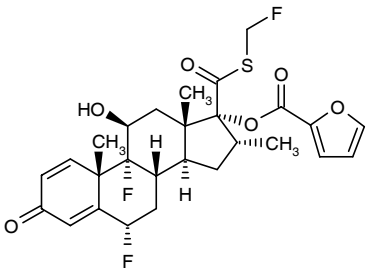
Glucocorticoid Receptor Agonist
Intranasal Corticosteroid

Prop INNM; USAN

685698
698
GW-685698
GW-685698X

6α,9α-Difluoro-17α-(furan-2-ylcarbonyloxy)-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17-carbothioic acid *S*-(fluoromethyl) ester

InChI=1/C27H29F3O6S/c1-14-9-16-17-11-19(29)18-10-15(31)6-7-24(18,2)26(17,30)21(32)12-25(16,3)27(14,23(34)37-13-28)36-22(33)20-5-4-8-35-20/h4-8,10,14,16-17,19,21,32H,9,11-13H2,1-3H3/t14-,16+,17+,19+,21+,24+,25+,26+,27+/m1/s1



$C_{27}H_{29}F_3O_6S$
Mol wt: 538.5768

CAS: 397864-44-7

EN: 317132

Abstract

Allergic rhinitis is characterized by symptoms (*e.g.*, frequent or repetitive sneezing, runny or congested nose, pruritus of the nose, eyes and throat) that are the result of complex allergen-driven mucosal inflammation mediated by resident/infiltrating inflammatory cells, inflammatory mediators and cytokines. Thus, strategies for the treatment of allergic rhinitis have focused on targeting various levels of the inflammatory cascade. Intranasal corticosteroids are becoming an increasingly popular first-line therapy for allergic rhinitis. They target the allergic inflammation which contributes to the late-stage symptom of nasal congestion and they can be used prophylactically to prevent early-phase responses to allergens. Fluticasone furoate exhibits enhanced affinity for the glucocorticoid receptor, potent preclinical antiinflammatory activity and efficacy in patients with seasonal allergic rhinitis. Fluticasone furoate has been submitted for regulatory approval for the treatment of allergic rhinitis and is undergoing phase II development for asthma and chronic obstructive pulmonary disease (COPD).

Synthesis

Fluticasone furoate is synthesized by the following method:

The starting 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid (I) is converted to the analogous carbothioic acid (II) via activation with carbonyl diimidazole, followed by reaction with hydrogen sulfide gas (1). The α-hydroxyl group of (II) is then selectively acylated with 2-furoyl chloride (III) to give the 17-furoate ester (IV) (2, 3). Finally, condensation of thioacid (IV) with bromofluoromethane under basic conditions provides the target fluoromethyl thioester (2-4). Scheme 1.

Background

Allergic rhinitis, also known as allergic rhinoconjunctivitis, is an inflammation of the mucus membranes in response to an airborne antigen and is characterized by frequent or repetitive sneezing, runny or congested nose and pruritus of the nose, eyes and throat. Other possible symptoms include headache, impaired smell, postnasal drip, conjunctival symptoms, sinusitis and other complicating respiratory symptoms. More than 115 million people are estimated to suffer from allergic rhinitis according to the World Allergy Organization. The condition is estimated to affect 10-20% of the general population and is considered the sixth most prevalent chronic disease (5-7).

Allergic rhinitis is generally classified into three groups: seasonal, perennial and occupational. However, distinction among the three often proves difficult. Therefore, a different classification system has been pro-

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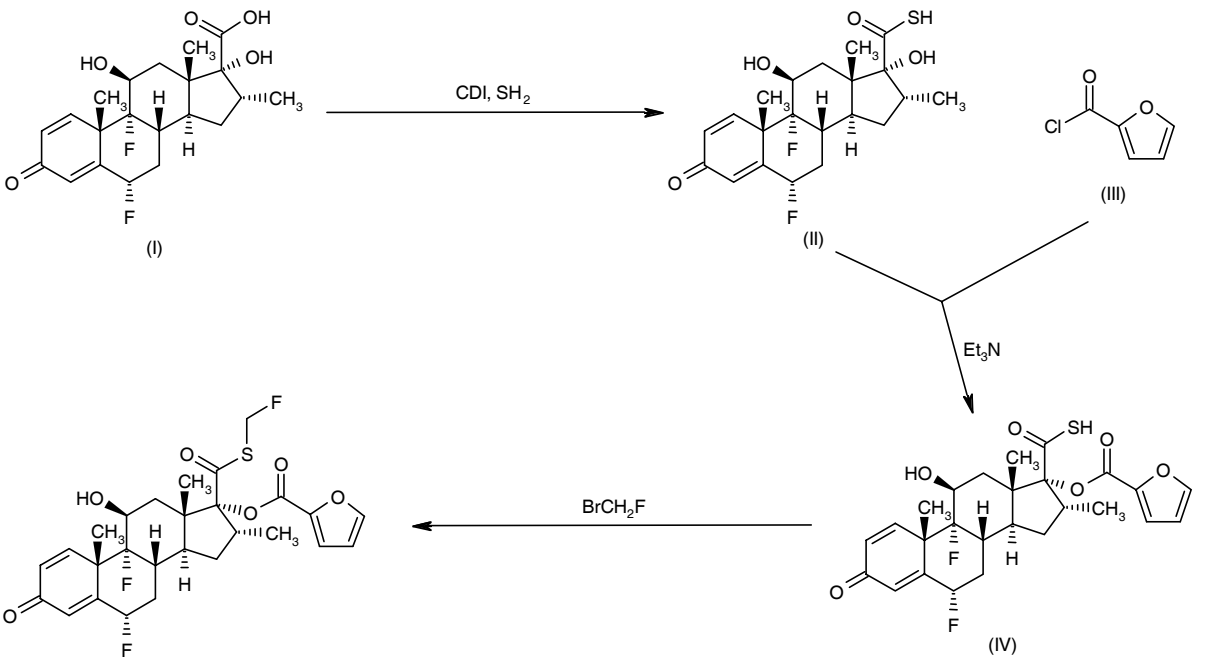
Scheme 1: Synthesis of Fluticasone Furoate



posed by the Allergic Rhinitis and its Impact on Allergy (ARIA) group and the World Health Organization (WHO). This system employs symptoms, quality-of-life parameters, duration and severity, and includes the following allergic rhinitis subgroups: intermittent (*i.e.*, symptoms present for 4 days/week or less than 4 weeks/year) mild (*i.e.*, sleep or daily activities not affected, no troublesome symptoms observed); intermittent moderate to severe (*i.e.*, associated with abnormal sleep, impairment of daily activities and/or other troublesome symptoms); persistent mild; and persistent moderate to severe (5, 8).

The symptoms of allergic rhinitis are the result of complex allergen-driven mucosal inflammation which involves resident and infiltrating inflammatory cells, inflammatory mediators (*e.g.*, histamine, prostaglandins, leukotrienes, tryptase) and cytokines (*e.g.*, IL-1β, TNF-α, IL-4, IL-5, IL-10, TGF-β, RANTES, eotaxin, GM-CSF). Strategies for the treatment of allergic rhinitis have therefore focused on intervening at various levels of the inflammatory cascade. The most common therapies include H_1 antihistamines to block histamine release, intranasal corticosteroids to suppress nasal inflammation and nonsteroidal antiinflammatory drugs (NSAIDs) to inhibit the release of allergic mediators from mast cells (5, 9, 10).

Intranasal corticosteroids in particular are becoming increasingly popular as first-line therapies for allergic rhinitis, especially for those patients with moderate to severe symptoms or in those with perennial allergic rhinitis with predominately nasal symptoms. Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex and are involved in many physiological processes, including inflammation, immune responses, stress responses, carbohydrate metabolism, protein catabolism, electrolyte homeostasis and behavior, among others. The class includes both glucocorticoids and mineralocorticoids, although corticosteroid is often used synonymously for glucocorticoid. In allergic rhinitis, these hormones target allergic inflammation which contributes to the late-stage symptom of nasal congestion. They can be used prophylactically to prevent early-phase responses to allergens and they effectively relieve sneezing, rhinorrhea and congestion. Several intranasal corticosteroids are currently undergoing clinical development for the treatment of allergic rhinitis, as shown in Table I (5, 9, 10).

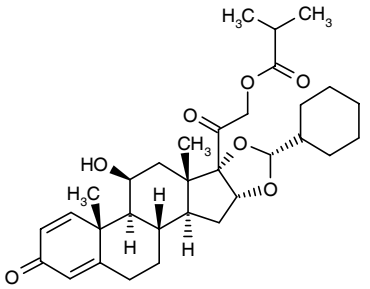
Fluticasone furoate (variously known as GW-685698, GW-685698X, 685698 or 698; preregistered in the U.S. as Allermist™ and in the E.U. as Avamys®) is one such novel, topically active glucocorticoid that exhibits enhanced affinity for the glucocorticoid receptor. The agent has shown potent preclinical antiinflammatory activity and was chosen for further development for the treatment of allergic rhinitis, as well as asthma and chronic obstructive pulmonary disease (COPD) (5, 11-13).

Preclinical Pharmacology

Analysis of the X-ray crystal structure of fluticasone furoate interacting with the glucocorticoid receptor showed that the agent fully occupies a lipophilic pocket in the receptor, and hydrogen bond interactions were evident through the 3-keto (with Gln570 and Arg611) and the 11β-hydroxy (with Asn564) groups. Further studies were

Table I: Intranasal corticosteroids under clinical development for the treatment of allergic rhinitis (from Prous Science Integrity®).

Drug	Source	Phase
1. Ciclesonide[1]	Altana Pharma	R-2006
2. Fluticasone furoate	GlaxoSmithKline	Prereg.
3. NS-126[2]	Nippon Shinyaku	III



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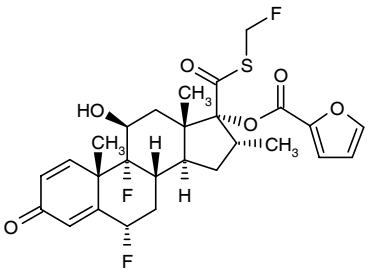

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[1]Launched for asthma in 2005. [2]Structure not available.

performed to determine the binding affinity of fluticasone furoate for the human lung glucocorticoid receptor. Results revealed a fast association and slow dissociation, with a relative receptor affinity (RRA) of 2989 ± 135 (*vs.* 100 ± 5 for dexamethasone as reference). The RRA of fluticasone furoate was significantly enhanced compared to clinically available corticosteroids, including mometasone furoate (2244 ± 142), fluticasone propionate (1775 ± 130), beclometasone-17-monopropionate (1345 ± 125), ciclesonide active principle (1212) and budesonide (855). No instability or chemical modification of fluticasone furoate was observed in lung tissue (11, 12).

The efficacy of fluticasone furoate was determined in several *in vitro* and *in vivo* glucocorticoid receptor assays. Experiments using human lung epithelial A549 cells showed that the agent causes rapid (< 20 min) translocation of the glucocorticoid receptor into the nucleus and exhibits approximately 2 times greater affinity for these cells as compared to fluticasone propionate. Fluticasone furoate also bound with high affinity to human plasma protein (99.4%) and was selective for the glucocorticoid receptor over the progesterone, androgen, mineralocorticoid and estrogen receptors. It exhibited potent antiinflammatory activity. Fluticasone furoate was more potent in stimulating alkaline phosphatase secretion driven by an ELAM promoter containing NF-κB sites in tumor necrosis factor (TNF)-treated A549 cells (IC_{50} = 25 pM) as compared to budesonide (IC_{50} = 185 pM), ciclesonide active principle (IC_{50} = 185 pM), mometasone furoate (IC_{50} = 40 pM) and fluticasone propionate (IC_{50} = 33 pM). In addition, it more effectively stimulated TNF release from lipopolysaccharide (LPS)-treated peripheral blood mononuclear cells (PBMCs) as compared to budesonide, ciclesonide active principle and fluticasone propionate (IC_{50} = 0.15 nM *vs.* 5.6, 4.1 and 0.24 nM, respectively). Moreover, low-dose fluticasone furoate administration *in vivo* (100 μg intranasally) to rats subjected to ovalbumin challenges to induce lung inflammation markedly prevented lung eosinophilia (13).

Pharmacokinetics and Metabolism

The metabolism of fluticasone furoate was examined in human hepatocytes. The agent was rapidly metabolized via cleavage of the 17β-fluoromethylthioester, yielding a 17β-carboxylic acid derivative which retained the furoate ester moiety; no metabolism to fluticasone was observed. This primary metabolite was found to be more than 1,000-fold less active in functional glucocorticoid receptor assays (11).

Clinical Studies

The efficacy of intranasal fluticasone furoate (once daily for 8 days) was demonstrated in a single-center, randomized, single-blind, placebo-controlled, crossover study conducted in 59 adult males suffering from seasonal allergic rhinitis (SAR). At the end of each 8-day treatment period, participants were subjected to two 4-h allergen (grass pollen) challenges (at 1-5 h after the last dose followed by a second challenge at 22-26 h) in the Vienna challenge chamber model. Treatment with fluticasone furoate attenuated seasonal rhinitis symptoms, with improvements seen in total nasal symptom scores (TNSS; reductions of 4.14 and 3.63 points after the first and second challenge, respectively), global symptom scores, nasal secretions, eye symptom scores and nasal airflow. The effects of the agent at each endpoint were sustained for 24 h (14, 15).

A randomized, double-blind, placebo-controlled study in 641 subjects with SAR examined the safety and efficacy of once-daily intranasal fluticasone furoate (50, 100, 200 or 400 μg) for 2 weeks in improving both ocular and nasal symptoms. Treatment resulted in significant decreases in subject-rated daily reflective TNSS (*i.e.*, sum of nasal congestion, itching, rhinorrhea and sneezing scores on a 0-3-point scale), the primary endpoint. The least squared mean change from baseline (9.5-9.6 points) was –3.50, –3.84, –3.19 and –4.02 for the respec-

tive doses *versus* –1.83 for placebo. The respective changes in predose instantaneous total nasal symptom score (iTNSS) were –2.74, –3.03, –2.57 and –3.36 *versus* –1.15 for placebo. Significant reductions in the reflective total ocular symptom score (rTOSS; *i.e.*, sum of eye itching/burning, tearing/watering and redness on a 0-3-point scale; baseline: 5.9-6.3) were obtained on all doses of fluticasone furoate (–1.93, –2.08, –1.92 and –2.43, respectively, *vs.* –1.34 for placebo). Fluticasone furoate at doses of 100-400 μg also gave significantly greater reductions in predose iTOSS compared to placebo and the low fluticasone furoate dose; least squared mean change in this score from baseline (5.8-6.2 points) was –1.79, –1.60 and –2.06, respectively, for the 100-, 200- and 400-μg fluticasone furoate groups *vs.* –1.05 and –1.42 for the placebo and 50-μg dose groups, respectively. The overall response to therapy (combined ratings of moderately or significantly improved) for all doses were significantly better than for placebo (53%, 52%, 49% and 59%, respectively, *vs.* 28%). The incidence of adverse events (24-29%) and 24-h urinary free cortisol excretion rates were similar for all treatment groups and there was a low incidence of abnormal laboratory parameters reported for all groups. A dose of 100 μg fluticasone furoate once daily was recommended for phase III studies (16, 17).

GlaxoSmithKline has filed for U.S. and E.U. approval for intranasal fluticasone furoate (Allermist™ and Avamys®, respectively) to treat the symptoms of SAR and perennial allergic rhinitis (PAR). Fluticasone furoate continues to undergo phase III development for the treatment of the symptoms of PAR (18-24) and SAR (24-28) and vasomotor rhinitis (29, 30), and phase II trials are also under way for the treatment of asthma (31) and COPD.

Source

GlaxoSmithKline (GB, US).

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