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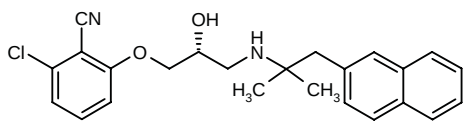
NPS-2143

Treatment of Osteoporosis
Calcilytic

SB-262470

2-Chloro-6-[3-[1,1-dimethyl-2-(2-naphthyl)ethylamino]-2(*R*)-hydroxypropoxy]benzonitrile



$C_{24}H_{25}ClN_2O_2$
Mol wt: 408.9265
CAS: 284035-33-2
CAS: 324523-20-8 (as monohydrochloride)
EN: 270642

Abstract

Efforts to discover new treatments for osteoporosis led to the identification of the potent and selective, small-molecule calcium receptor antagonist NPS-2143. NPS-2143 is the prototype calcilytic drug, designed to act on calcium receptors on the surface of parathyroid glands, stimulating the release of the body's own stores of native parathyroid hormone (PTH). In osteopenic ovariectomized rats, daily oral administration of NPS-2143 resulted in moderate but sustained increases in plasma PTH levels and marked increases in bone formation and resorption, with no net bone gain or loss. The combination of NPS-2143 and estrogen increases bone formation and density to a greater extent than either agent alone. These results suggest that NPS-2143 may be useful in the treatment of established osteoporosis.

Synthesis*

NPS-2143 can be obtained by coupling 2-chloro-6-[2(*R*)-oxiranylmethoxy]benzonitrile (I) with 1,1-dimethyl-2-(2-naphthyl)ethylamine (II) in ethanol at 50-60 °C (1). Scheme 1.

Intermediates (I) and (II) can be obtained as follows:

a) Treatment of 2-chloro-6-fluorobenzonitrile (III) with 18-crown-6 and potassium acetate in refluxing acetonitrile, followed by hydrolysis with NaOH in H_2O provides 3-chloro-2-cyanophenol (IV), which is then condensed with 3-nitrobenzenesulfonic acid (2*R*)-2-oxiranylmethyl ester (V) in DMF by means of NaH to furnish 2-chloro-6-[2(*R*)-oxiranylmethoxy]benzonitrile (I).

b) Treatment of 2-(aminomethyl)naphthalene (VI) with 2,4,6-triphenylpyrylium tetrafluoroborate in EtOH, followed by the reaction of the resulting compound dissolved in DMSO with the sodium salt obtained by treatment of 2-nitropropane (VII) with NaH in MeOH, gives the nitro derivative (VIII). Finally, reduction of the nitro group of (VIII) by hydrogenation over Ni Raney in EtOH yields 1,1,-dimethyl-2-(2-naphthyl)ethylamine (II).

Introduction

Osteoporosis is a major health problem affecting about 5 million women and 1.5 million men in the U.S., with an even larger number having decreased bone mineral density. Osteoporosis leads to osteoporotic fractures, which in 1995 cost the U.S. $13.8 billion (2). Most of the agents presently used in the treatment of osteoporosis (*e.g.*, vitamin D, hormone replacement therapy, bisphosphonates) prevent bone resorption but do not increase bone formation. In contrast, parathyroid hormone stimulates bone formation. A recent clinical trial has shown that, in postmenopausal women with prior vertebral fractures, a segment of parathyroid hormone (1-34) decreased the risk of new fractures and increased bone mineral density (3). One of the disadvantages to the clinical use of parathyroid hormone is that it has to be injected.

Parathyroid secretion is regulated by the extracellular calcium-sensing receptor, which is expressed at several sites including parathyroid cells. This G-protein-coupled receptor is sensitized by calcimimetics to reduce the lev-

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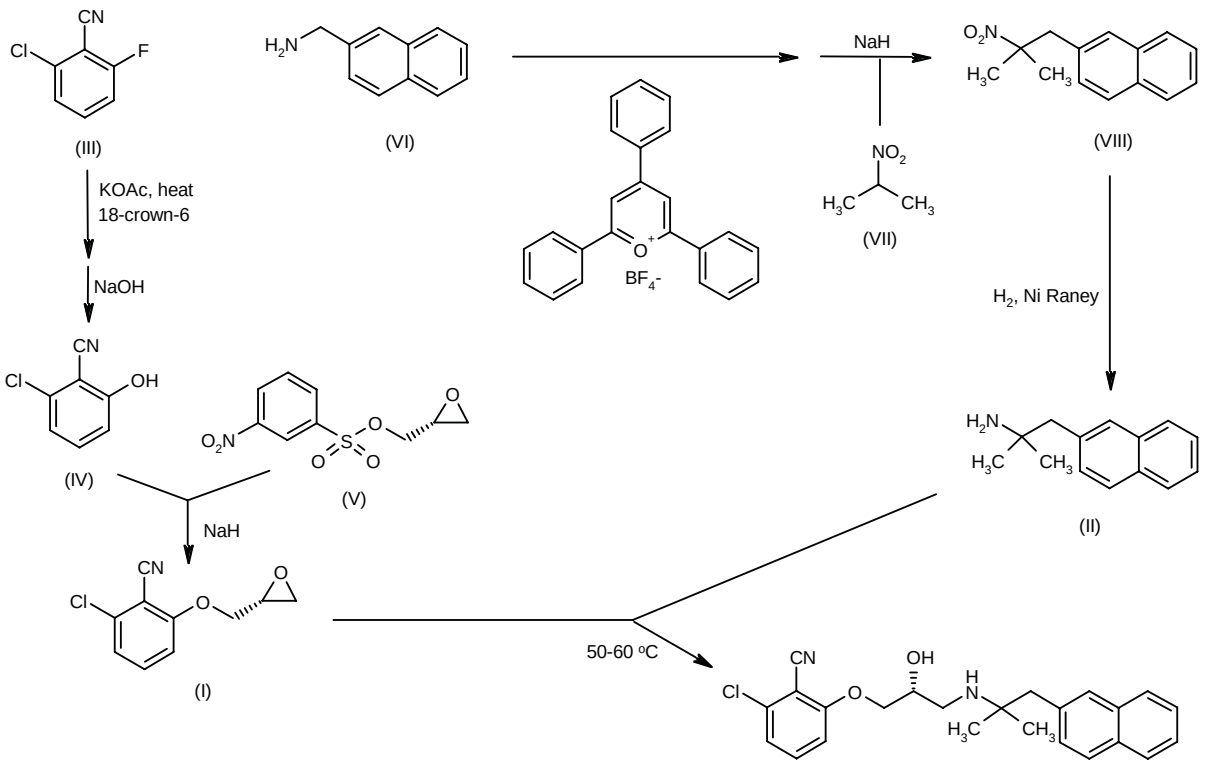
Scheme 1: Synthesis of NPS-2143



els of parathyroid hormone, which is useful in the treatment of hyperparathyroid hormone conditions. Calcilytic agents inhibit the calcium-sensing receptor and increase the levels of parathyroid hormone (4). NPS-2143 is the first substance shown to be calcilytic.

Pharmacological Actions

In vitro

Calcimimetics were developed prior to the calcilytic agent NPS-2143. This development used HEK 293 cells engineered to express the human parathyroid Ca^{2+} sensing receptor, which are referred to as HEK 293 4.0-7 cells. In these cells, increasing the extracellular Ca^{2+} concentration led to increases in intracellular Ca^{2+} concentrations. This response was inhibited by NPS-2143 with an IC_{50} of 43 nM. The intracellular Ca^{2+} concentration was also increased with the calcimimetic NPSR-467, and this response was also inhibited by NPS-2143 (5).

NPS-2143 was found to be selective for the calcium-sensing receptor, as it did not inhibit the thapsigargin-induced release of calcium from intracellular cells or the movement of calcium through calcium channels. NPS-2143 was also selective for the calcium-sensing receptor over other G-protein-coupled receptors. Thus, even at a much higher concentration (3 μM), NPS-2143 did not affect responses of HEK cells mediated by purinergic, thrombin and bradykinin receptors. NPS-2143 also had no effect on metabotropic glutamate receptor or $GABA_B$ receptor-mediated responses (5).

Primary cultures of bovine parathyroid cells secrete parathyroid hormone under normocalcemic conditions, and this secretion was augmented by NPS-2143 with an EC_{50} of 41 nM. Increasing extracellular calcium or NPSR-467 inhibited parathyroid hormone secretion, and these effects were reversed by NPS-2143 (5). After these eloquent experiments demonstrated that NPS-2143 stimulates parathyroid hormone secretion *in vitro*, it was of interest to know whether the effect could be observed *in vivo*.

In vivo

In anesthetized rats, the intravenous infusion of NPS-2143 (0.1 μmol/kg/min) increased plasma parathyroid hormone levels 4- to 5-fold (5). The next step in the development of NPS-2143 was testing in animal models of osteoporosis.

Osteopenic rats

Ovariectomized rats develop osteopenia (reduced bone mineral density). In these rats, the induction of hypocalcemia by infusion of the calcium chelator EGTA raised the circulating parathyroid hormones to levels that were sufficient to stimulate bone formation (6). Subsequently, the effects of NPS-2143 were studied in ovariectomized rats.

After oral administration of NPS-2143 (100 μmol/kg), the peak plasma concentration of about 175 ng/ml was observed after 2 h. The level was maintained at 125 ng/ml for 8 h but became undetectable at 24 h (< 10 ng/ml) (7). This is a much more sustained elevation of plasma parathyroid hormone than that observed when parathyroid hormone is injected subcutaneously. Hyperparathyroidism is associated with bone loss and abnormal bone histology, but this was not observed with NPS-2143 treatment.

Female rats had a 15% reduction in bone mineral density at the lumbar spine and proximal tibia and 24% reduction at the distal femur 3 months after ovariectomy. Although daily administration of NPS-2143 (100 μmol/kg p.o.) did increase plasma parathyroid hormone, it did not affect bone mineral density. Subsequent analysis showed that the compound was increasing bone turnover by increasing both bone formation and bone resorption. These results were disappointing, since they suggested that NPS-2143 alone would not be useful in the treatment of osteopenia (7).

More encouraging results, however, were obtained when NPS-2143 was combined with an antiresorption agent. The estrogen 17β-estradiol (0.01 mg/kg/90 days s.c.) alone prevented bone resorption, causing an increase in the cancellous bone area in osteopenic rats. The combination of 17β-estradiol and NPS-2143 increased cancellous bone area to a greater extent than 17β-estradiol alone. The combination also increased bone formation rate and bone mineral density to a greater extent than either agent alone (7).

There have been reports of calcium receptors on both osteoclasts and osteoblasts. However, it appears that the effects of NPS-2143 are mediated via parathyroid hormone secretion and not osteoclasts or osteoblast, since it had no direct effects on osteoblasts or osteoclasts *in vitro* (7).

The calcium sensing receptor is present at sites other than the parathyroid gland, and the effects of NPS-2143 at these sites remain to be investigated.

Source

Codeveloped by NPS Pharmaceuticals, Inc. (US) and GlaxoSmithKline plc (GB).

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