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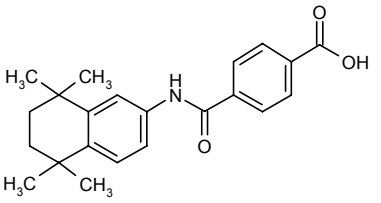
Tamibarotene

Prop INN

Leukemia Therapy
Retinoid RARα Agonist

AM-80
NSC-608000
TOS-80
Amnolake
Tamibaro™

4-[*N*-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-yl)carbamoyl]benzoic acid



$C_{22}H_{25}NO_3$
Mol wt: 351.4388
CAS: 094497-51-5
EN: 125711

Abstract

Acute promyelocytic leukemia (APL) is a form of acute myeloid leukemia (AML) caused by a specific chromosomal translocation: t(15;17). This translocation creates a fusion between the promyelocytic (PML) leukemia gene and the retinoic acid receptor α (RARα) gene to arrest the maturation of myeloid cells at the promyelocytic stage, leading to increased proliferation of promyelocytes. These accumulate in the bone marrow and peripheral blood, replacing normal blood cells. all-*trans*-Retinoic acid (ATRA) therapy targets the transforming activities of the PML-RARα fusion gene. Tamibarotene, a novel RARα agonist, was recently approved and launched in Japan for the treatment of relapsed or refractory APL. *In vitro*, it successfully induces PML differentiation and maturation, deterring PML proliferation. In *in vivo* studies, the compound demonstrated antitumor activity and good tolerability. Clinical investigations revealed its efficacy in APL patients who had relapsed from ATRA-induced complete remission, as well as a milder side effect profile compared to previous treatment. Tambarotene therefore represents a novel and promising therapy for APL.

Synthesis

Reaction of 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene (I) with HNO_3/H_2SO_4 gives 5,5,8,8-tetramethyl-2-nitro-5,6,7,8-tetrahydronaphthalene (II), which is reduced by means of H_2 over Pd/C in ethanol to yield 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2-amine (III). Condensation of compound (III) with terephthalic acid chloride monomethyl ester (IV) in pyridine affords the carboxamide (V), which is finally hydrolyzed at the methyl ester group with NaOH in ethanol/water (1). Scheme 1.

Introduction

Acute promyelocytic leukemia (APL) is a form of acute myeloid leukemia (AML) characterized by a deficiency in mature blood cells and an excess of immature cells called promyelocytes in the bone marrow and peripheral blood (2, 3). APL is associated in almost all cases with a translocation between chromosomes 15 and 17, symbolized as t(15;17). The translocation creates a PML (promyelocytic leukemia)-RARα (retinoic acid receptor α) fusion gene producing a chimeric protein that arrests the maturation of myeloid cells at the promyelocytic stage, leading to increased proliferation of promyelocytes (4-6).

The treatment of APL differs from that for all other forms of AML, and most APL patients are currently treated with all-*trans*-retinoic acid (ATRA) or arsenic trioxide alone or in combination with chemotherapy (7). ATRA therapy activates RAR and causes promyelocytes to differentiate and mature, deterring them from proliferating, and induces disease remission (8). The advent of ATRA

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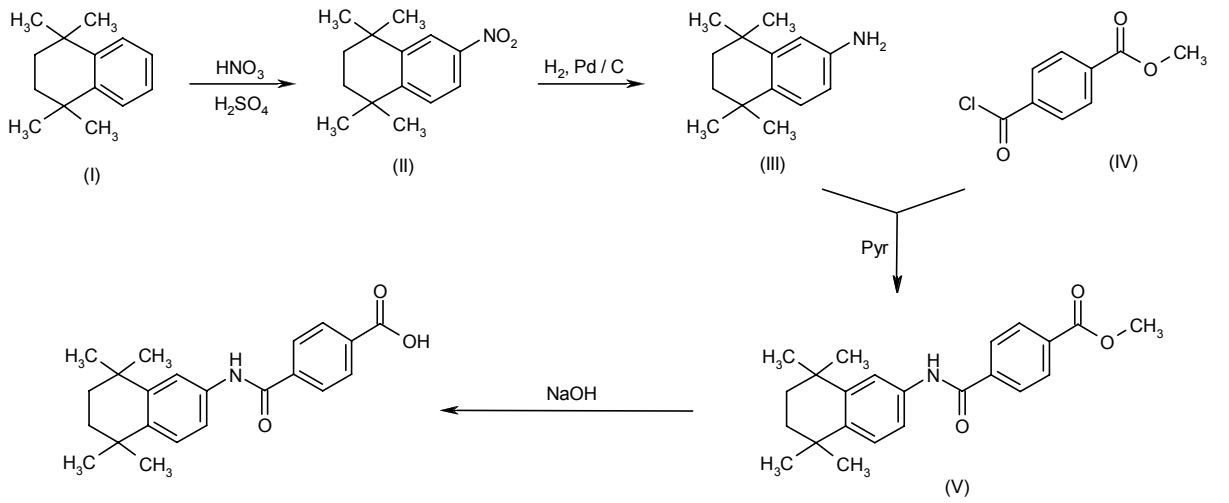
Scheme 1: Synthesis of Tamibarotene



therapy revolutionized the treatment of APL and markedly improved the prognosis.

Tamibarotene (AM-80), a novel RARα agonist developed by Nippon Shinyaku, was recently approved in Japan for the treatment of relapsed or refractory APL, and has been launched under the brand name Amnolake® (9).

Pharmacological Actions

The retinoid activity of tamibarotene was initially determined via the analysis of structure-activity relationships of a series of amides in human HL-60 promyelocytic leukemia cells. Tamibarotene was several times more active than retinoic acid, inducing significant differentiation of HL-60 cells to mature granulocytes (ED_{50} = 0.79 nM) (10).

Further studies in HL-60 cell sublines were carried out to determine selective receptor activity. Tamibarotene was found to be equivalent to the selective RAR agonist TTNPB in its ability to transactivate the RARα receptor (EC_{50} = 45 nM), but it was significantly less active at RARβ and RARγ receptors (EC_{50} = 235 and 591 nM, respectively); both compounds were inactive at retinoid X receptors (RXRs). Tamibarotene inhibited proliferation and induced HL-60 cell differentiation with efficacy comparable to TTNPB, and like TTNPB, it did not induce apoptosis, which was attributed to its lack of RXR-transactivating activity (11).

The dibenzodiazepine derivatives HX-600, HX-620 and HX-630 were shown to enhance the differentiation-inducing and antiproliferative effects of tamibarotene in HL-60 cells, which appeared to be due to their binding to the RXR site of RXR-RAR heterodimers (12-14).

Further studies described synergistic activity for diphenylamine derivatives in combination with tamibarotene, allowing retinoid activity to manifest at low concentrations. DA-011 and LGD-1069 both demonstrated dose-dependent synergism with tamibarotene; the percentage of differentiated cells (14%) induced by 0.1 nM tamibarotene was increased to 20%, 45% and 86%, respectively, in the presence of 1, 10 and 100 nM DA-011 (14, 15).

Although other studies (11) demonstrated that tamibarotene does not induce apoptosis, further studies have provided evidence to the contrary. In HL-60 cells, tamibarotene induced G1 arrest which was driven and enhanced by 3,5,3'-triiodo-L-thyronine (T_3). The cooperative action of T_3 was also evident on tamibarotene-induced expression of CD11b, a marker of differentiation, and tamibarotene-induced suppression of the antiapoptotic gene product Bcl-2 (16). Experiments in SK-BR-3 breast cancer cells revealed that tamibarotene inhibits growth, induces G1 arrest and stimulates apoptosis (17).

In hepatocellular carcinoma cell (HCC) lines, tamibarotene was shown to inhibit proliferation, which was associated with upregulation of insulin-like growth factor-binding protein-3 (IGFBP-3), a retinoid-responsive gene. The *in vivo* antitumor effect of tamibarotene was also investigated in athymic nude mice with intrahepatic spread of the HCC cell line JHH-7 following intrasplenic injection. Tamibarotene (8 mg/kg/day p.o.) significantly decreased the formation of tumor nodules on the liver surface (18).

To elucidate the genes responsible for tamibarotene-mediated differentiation of HL-60 cells, DNA microarray analysis was carried out. A total of 204 genes were found to be differentially modulated by ATRA and tamibarotene, including two components of the phosphatidylinositol 3-kinase (PI3-kinase)/Akt signal transduction pathway, the phosphatidylinositol 3-kinase β-catalytic subunit and ribosomal protein S6 kinase 1, which are related to the regu-

lation of cell proliferation and apoptosis. It was also demonstrated that application of PI3-kinase inhibitors mimics the effects of ATRA on HL-60 cell proliferation, suggesting that the concomitant use of tamibarotene and PI3-kinase inhibitors could broaden the therapeutic potential (19).

Toxicity

In vivo analysis of the pharmacological effects of tamibarotene was carried out in a number of experimental animals. Subcutaneous administration of tamibarotene to mice at doses of 0.1, 1.0, 10 and 50 mg/kg was not associated with changes in general behavior or clinical condition and did not induce mortality for up to 7 days after dosing. Further doses of 1, 10 and 50 mg/kg did not produce anticonvulsant or proconvulsant effects, although the two higher doses did induce a significant increase in sleeping time. Administration of tamibarotene produced some analgesic effects in mice, with a weak effect in the tail clip test and a significant effect in the writhing test. There were no significant alterations in locomotor activity in mice or body temperature in rats. Studies in beagle dogs revealed that the drug administered s.c. or i.v. at doses of 1, 10 and 50 mg/kg had no notable effect on the cardiovascular system, although there was some evidence of respiratory stimulation. Tamibarotene had no effect on gastrointestinal motility in mice and did not affect urine volume or electrolyte excretion in rats (20).

Pharmacokinetics and Metabolism

The major metabolites of i.v. tamibarotene were examined in rats. More than 15 metabolites were detected, although neither glucuronide nor sulfate conjugates were present. The 7 major biliary metabolites were identified as 6-hydroxy-tamibarotene (M-3), 7-hydroxy-tamibarotene (M-4), 6-oxo-tamibarotene (M-5), unchanged drug (M-0) and the taurine conjugates of M-3 (M-1), M-4 (M-2) and M-0 (M-6) (21).

The pharmacokinetic profile of tamibarotene was studied in rats after topical application and s.c. administration of [^{14}C]-labeled drug. Topical application (0.1% ointment) produced very different results in animals with normal skin and stripped skin. In rats with normal skin, administration of tamibarotene via an occlusive dressing resulted in undetectable levels of radioactivity in blood or plasma. In contrast, in stripped skin rats, plasma radioactivity peaked at 2 h postdose and exhibited a half-life of 5.5 h. Absorption was approximately 6 times greater than in normal skin rats, as 54.7% of the dose of radioactivity was excreted. Following s.c. administration (1 mg/kg), the maximum concentration of radioactivity in blood was attained at 1-2 h, with a half-life of 4-5 h. Biliary excretion was approximately 80% of the dose, and enterohepatic circulation was estimated to be 36.5%. Systemic distribution was evident, especially in the liver, adrenal gland and kidney. Two major metabolic pathways were postulated in rats: 6- or 7-hydroxylation to yield hydroxy-tamibarotene, leading to the formation of oxo-tamibarotene, and hydrolysis of the carboxamide bond to yield tetrahydrotetramethylnaphthalenylamine and terephthalic acid. Furthermore, tamibarotene was susceptible to the formation of taurine conjugates. A high proportion of total radioactivity in plasma was comprised of unchanged drug, whereas low levels were detected in urine and bile (22, 23) (see Table I).

Table I: Tamibarotene excretion after single administration in different animal models (from Prous Science Integrity®).

Animal (dose)	FR(0-24) (%)	FR(0-48) (%)	UR(0-24) (%)	UR(0-48) (%)
Male mice (1 mg/kg sc)	69.3	72.1	24.5	25.9
Male mice (1 mg/kg top)	14.9	20.7	4.7	7.2
Male rats (1 mg/kg sc)	50.2	78.6	9.6	10.6
Female rats (1 mg/kg sc)	32.0	67.6	12.3	15.5
Male rats (1 mg/kg top)	33.2	43.8	6.3	7.4
Male rabbits (1 mg/kg top)	4.3	10.2	4.1	6.1
Male dogs (1 mg/kg sc)	23.0	43.4	1.6	2.3
Male dogs (1 mg/kg top)	0.2	0.4	0.02	0.03

FR: total radioactivity recovered from feces expressed as percent of dose administered; UR: total radioactivity recovered from urine expressed as percent of dose administered. Data from Refs. 21-23, 25.

Consecutive tamibarotene dosing (s.c.) was also assessed in rats. Administration of [^{14}C]-labeled drug (0.2 mg/kg) once a day for 24 days did not alter t_{max} or C_{max} of blood radioactivity compared to single doses, suggesting little accumulation in the blood. Cumulative excretion was not different from single doses; radioactivity at 168 h after the final dose was 6.7% and 89.1%, respectively, in the urine and feces. In most tissues, the concentration of radioactivity at 24 h after each dose reached a steady state within 24 doses. Accumulation and delayed elimination of radioactivity were observed, especially in the adrenal gland, fat, skin and epididymis (24) (see Table I).

The analysis of placental transfer and excretion into milk after administration of [^{14}C]-tamibarotene was performed in pregnant or nursing rats. Plasma radioactivity in the dam and fetus was detectable at low levels following topical administration (10 mg/kg) to pregnant rats with normal skin on the 12th day of pregnancy. In pregnant rats with stripped skin, fetal radioactivity levels following doses of 1 and 10 mg/kg were one-third of the maternal plasma level. Radioactivity was detected in the fetus after s.c. administration (1 mg/kg) on the 12th and 19th day of pregnancy, which peaked at 4 h after dosing, and levels were reported to be one-fourth and one-half of the respective maternal plasma levels. High levels of radioactivity were detected in fetal liver. Subcutaneous adminis-

tration of radiolabeled tamibarotene (1 mg/kg) to lactating rats revealed 94 times greater radioactivity in the milk compared to the plasma (25).

Pharmacokinetic profiles of tamibarotene were studied in dogs, mice and rabbits. After topical application of [^{14}C]-labeled tamibarotene (0.1% ointment) to mice and rabbits with normal skin, plasma levels peaked at 8 and 12 h after application, respectively. Percutaneous absorption was below 2% of dose for dogs, 34% for mice and 23% for rabbits. Plasma levels peaked at 1, 4 and 4 h after s.c. dosing (1 mg/kg) in mice, dogs and rabbits, with respective half-lives of 2.4, 7.2 and 4.1 h. Urinary and fecal excretion was 3.5% and 94.7% of the dose in dogs, 27.0% and 73.2% of the dose in mice and 43.5% and 45.6% of the dose in rabbits, respectively. Unchanged tamibarotene was present in high amounts in the plasma and bile or feces of all animal species tested except in rat bile, where the compound was predominantly detected in the form of its taurine conjugate (M-6). *In vivo* plasma protein binding of [^{14}C]-tamibarotene and/or its radioactive metabolites was reported to be > 98% in rats and dogs after s.c. administration. Assessment of plasma protein binding was also carried out *in vitro* and was found to be over 99% in rats, dogs and humans. Binding to human serum albumin was not affected by diazepam, digoxin or warfarin. Examination of human samples taken from phase II and III clinical trials revealed that fecal excretion was the major elimination route, and hydroxylation and taurine conjugation of unchanged and hydroxy-tamibarotene also occurred (26) (see Table I).

Clinical Studies

The rapid development of resistance to ATRA is caused by a progressive decrease in plasma drug concentration and/or an increased expression of cytoplasmic retinoid-binding proteins (CRABP). As tamibarotene displays low affinity for CRABP, it was evaluated in a phase II study in APL patients who had relapsed after ATRA-induced complete remission (CR). Twelve patients received tamibarotene (6 mg/m^2/day p.o.), and 6 patients achieved a CR at days 20-52. Toxicity was minimal and less than with prior ATRA therapy. Adverse events included hyperlipidemia and dryness of skin and lips. Interestingly, 1 patient who had been refractory to initial induction chemotherapy achieved a CR on tamibarotene (27).

A pilot study wad conducted by Japanese investigators in 19 APL patients who had relapsed after ATRA-induced CR. Eleven patients (58%) achieved CR between days 20 and 58. Furthermore, analysis of PML-RARα immunostaining as an indication of PML morphological differentiation revealed a close correlation with clinical effect, as patients whose blasts were sensitive to tamibarotene despite a poor response to ATRA (n=3) achieved CR (28).

Tamibarotene was administered to 2 patients with relapsed APL following previous ATRA treatment and produced a gradual resolution of pancytopenia in both patients, with no evidence of elevated or differentiated leukemia cells in the bone marrow. Tamibarotene treatment alone also resulted in CR in both patients, on days 52 and 38 of treatment. CR was associated with PML gene rearrangement and abolition of the t(15;17) translocation, although PML-RARα chimeric messenger RNA was still detected (29).

A multicenter study was conducted in APL patients who had relapsed after CR induced by ATRA. Patients received tamibarotene (6 mg/m^2/day p.o.) until CR was achieved. Of 24 evaluable patients, 14 (58%) achieved CR. Adverse events included 1 case of retinoic acid syndrome, 1 case of hyperleukocytosis, 9 cases of xerosis, 8 cases of cheilitis, 16 cases of hypertriglyceridemia and 15 cases of hypercholesterolemia, although all were generally milder than with ATRA, which all patients had received previously (30, 31).

The long-term clinical outcomes of these 14 patients who achieved a second CR on tamibarotene were also reported. Four patients relapsed within 6 months despite subsequent consolidation chemotherapy. Six patients underwent HLA-matched allogeneic bone marrow transplantation (BMT) and 4 of 8 patients who did not receive BMT are alive without relapse for more than 49 months. The PML-RARα fusion transcript was undetectable by reverse transcriptase-polymerase chain reaction in all surviving patients (32).

Nippon Shinyaku recently announced the launch in Japan of tamibarotene as Amnolake® for the treatment of relapsed or refractory APL (9).

Source

Nippon Shinyaku Co., Ltd. (JP) (under license from Toko Pharmaceutical Ind. Co., Ltd.).

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