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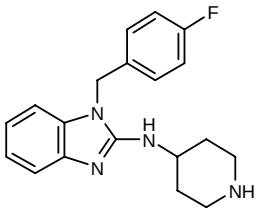
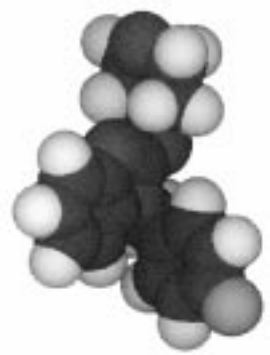
CCC: 0377-8282/98

Norastemizole

Antihistamine

1-(4-Fluorobenzyl)-2-(piperidinyl-4-amino)-1*H*-benzimidazole





$C_{19}H_{21}N_4F$ Mol wt: 324.40

CAS: 075970-99-9
EN: 209628

Synthesis

Norastemizole can be obtained in the following way as shown in scheme 1 (1, 2):

The synthesis is carried out by mild and selective palladium coupling of readily available 1-(4-fluorobenzyl)-2-chlorobenzimidazole (I) with 4-aminopiperidine dihydrochloride (II) to obtain norastemizole in 84% isolated yield. The synthesis is highly selective and involves a one-step process.

Description

White to off-white crystals, m.p. 218.4-219.2 °C.

Introduction

Antihistamines are among the most widely used drugs in the world. By blocking the actions of histamine on peripheral H_1 receptors, they provide relief to millions of patients from the symptoms of allergic rhinitis and the common cold. The first generation of these agents was introduced in the 1940s and these are now mostly used as over-the-counter combinations with analgesics and/or decongestants. Examples of this class are chlorpheniramine, diphenhydramine, promethazine and hydroxyzine. Despite their salutary therapeutic benefits and low cost, these drugs all have the disadvantages of causing sedation and drowsiness, which limits their full potential for many patients. They also cause anticholinergic side effects, such as dry mouth (3).

To overcome these problems, a second generation of nonsedating antihistamines was introduced during the last 20 years. The main drugs in this class are terfenadine (Seldane®), astemizole (Hismanal®), loratadine (Claritin®) and cetirizine (Zyrtec®) (4). They are also virtually devoid of anticholinergic actions. Most patients can use them during the day without loss of mental or physical performance (3, 5, 6). However, in the case of terfenadine and astemizole, the structural changes brought with them a potentially lethal side effect under certain circumstances. In the mid-1980s, reports began to appear of torsades de pointes (TdP), a polymorphic ventricular tachycardia associated with prolongation of the QT interval (7). This rhythm abnormality can cause syncope, and may even degenerate into ventricular fibrillation and cardiac arrest. Drugs that have been found to cause TdPs all delay cardiac repolarization, and thus prolong the QT interval, usually by blocking cardiac outward potassium channels. Examples include Class III antiarrhythmics (*e.g.*, sotalol and dofetilide), quinidine, probucol and ketoconazole. In the case of terfenadine and astemizole, the QT prolongation was found to be due to the parent drugs, whereas the metabolites had little or no cardiac effects (7, 8).

Under normal conditions, plasma concentrations after oral administration of terfenadine are low to undetectable due to extensive first-pass metabolism (9). The therapeutic benefits thus derive mostly from an active metabolite (fexofenadine), which has no significant effects on cardiac repolarization (7, 8). However, plasma concentrations of the parent compound can build up to critical levels if hepatic function is impaired by liver disease or by

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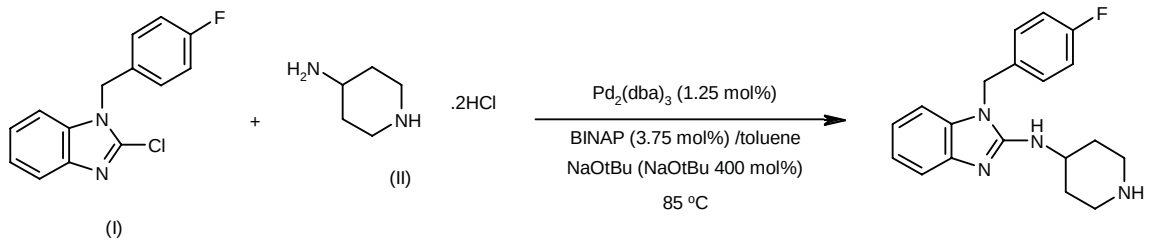
Scheme 1: Synthesis of Norastemizole



drugs, such as antifungals or macrolide antibiotics, which inhibit mixed function oxidase. Under these conditions, excessive QT prolongation can lead to life-threatening cardiac arrhythmias (7).

Over recent years, safety concerns with second-generation antihistamines have prompted the development of their metabolites as safer and equally or more effective alternatives. In 1996, after an unusually rapid development program which was actively encouraged by the FDA, the first of these third-generation agents, fexofenadine (Allegra®), the active metabolite of terfenadine, gained regulatory approval. Meanwhile, despite escalating labelling restrictions and warnings, cases of drug-associated arrhythmias continued to be reported in patients receiving terfenadine and astemizole. With the availability of a safer alternative in fexofenadine, the benefits of terfenadine no longer outweighed the risks, and in 1997, it was withdrawn from the market at the request of the FDA (10).

Two additional third-generation antihistamines are also in advanced clinical development, norastemizole and descarboethoxyloratadine (DCL), which are the active metabolites of astemizole and loratadine, respectively. These agents are at least as effective as their parent compounds and may offer significant advantages in terms of both safety and efficacy. Because they are not subject to further metabolism, they also offer more predictable plasma levels and less interpatient variability. This monograph describes the clinical and preclinical profile of norastemizole.

Pharmacological Actions

The preclinical pharmacology of norastemizole and astemizole are summarized in Table I. Intrinsic potency and selectivity for receptor subtypes were determined by competitive radioligand binding studies in isolated receptor preparations (11). Norastemizole inhibited binding of [^{3}H]-pyrilamine to guinea pig cerebellum membranes with an IC_{50} of 4.1 nM. By comparison, astemizole had about 13 times less affinity for H_1 receptors. Neither compound showed appreciable affinity for H_2 or H_3 receptors at concentrations up to 10 μM. In preparations of cloned human muscarinic receptors, norastemizole showed only weak affinity for M_2 and M_3 receptors (IC_{50} = 2380 nM and 1350 nM, respectively). Its affinity for M_1 receptors was about 27 times less than that for H_1 receptors.

Norastemizole relaxed guinea pig tracheal strips precontracted with histamine with an IC_{50} value around 30 nM (12). It was 300-1000 times less potent against carbachol-induced contractions, showing that it has little or no functional antimuscarinic activity. Norastemizole also displayed potent activity against histamine-induced contractions in guinea pig ileum (12). The mean IC_{50} was

Table I: Summary of the preclinical pharmacology of astemizole and norastemizole.

	Astemizole	Norastemizole
Radioligand binding		
H_1 receptors (guinea pig cerebellum)	IC_{50} = 54.8 nM	IC_{50} = 4.1 nM
M_1 receptors (cloned human)	IC_{50} = 900 nM	IC_{50} = 110 nM
Relaxation of guinea pig tracheal pigs		
Histamine-induced contractions	Not determined	IC_{50} = 30 nM
Carbachol-induced contractions	Not determined	IC_{50} = 10,000 nM
Relaxation of histamine-induced contractions in guinea pig ileum	IC_{50} = 0.84 nM	IC_{50} = 0.022 nM
Guinea pig wheal and flare model		
Effective dose	1 mg/kg, p.o.	0.05 mg/kg, p.o.
Onset of action	30-60 min	15-30 min
Duration of action	>120 min	>120 min

0.022 nM. In comparison, astemizole had an IC_{50} of 0.84 nM in this system and was thus 39-fold less potent than norastemizole.

In vivo antihistamine activity was assessed using the guinea pig wheal and flare model (12). Guinea pigs were challenged with various doses of histamine injected intradermally at a matrix of sites (balanced Latin square design) on the shaved laterodorsal skin at various times after administration of the test substance. Each guinea pig's wheal and flare responses were quantitated by measuring the area of extravasation of Evans blue dye which had been previously administered intravenously. Norastemizole had a rapid onset of action, showing activity 15-30 min after oral administration. Maximum activity was achieved between 30 and 60 min and did not decline up to 120 min. Relative potency was estimated against ascending doses of histamine given 60 min after an oral dose of the test substance. Norastemizole, at 0.05 mg/kg, showed similar activity to astemizole at 1 mg/kg and fexofenadine at 7.5 mg/kg. It was thus 20 times more potent than astemizole, and 150 times more potent than fexofenadine. The actions of norastemizole were specific for histamine, as bradykinin-induced extravasation of the Evans blue dye was unaffected.

The risk of cardiac side effects was assessed by monitoring effects on ECG intervals in conscious dogs (13). Norastemizole had no effects on the ECG when administered either orally or intravenously at 3 mg/kg (60-fold greater than the therapeutic dose in guinea pigs). In contrast, astemizole produced marked QT prolongation at 3 mg/kg i.v. No effects were seen after oral administration of astemizole, which probably reflects its low oral bioavailability. Norastemizole, therefore, has no cardiac liability in this model. Previous studies in guinea pigs (14, 15) have demonstrated that norastemizole not only possessed up to 39-fold more potent antihistamine activity than astemizole, but also caused no ECG changes at 20- to 60-fold higher doses than those at which astemizole produced significant prolongation of the QT interval.

Pharmacokinetics and Metabolism

Norastemizole interacts to a much lesser extent with the mixed function oxidase which is mainly responsible for the metabolism of astemizole. Microsomal cDNA-derived CYP3A4 was prepared from a human lymphoblastoid cell line (h3A4/OR) and assayed by conversion of testosterone to its 6-beta-hydroxylated metabolite. Norastemizole was only a weak inhibitor of the enzyme, with an IC_{50} of 195 μM, compared to 7 μM for astemizole. In human microsome preparations, only 5-10% of norastemizole was metabolized during a 30-min incubation at concentrations from 5-100 μM. In contrast, astemizole was metabolized to a much greater extent (22-55%) under the same conditions (Sepracor, data on file).

Toxicokinetic studies in dogs have shown that the extent of systemic drug exposure during oral administration of norastemizole for 28 days was roughly proportional to doses between 5 and 20 mg/kg/day. No significant differences in drug exposure were found between Days 1 and 28 at 5 or 10 mg/kg/day. However, values of 20 mg/kg/day at Day 28 were about double those on Day 1, indicating that the drug has the potential to accumulate at higher doses. Comparison of the pharmacokinetics of norastemizole and astemizole in rats showed that norastemizole had better oral bioavailability (18% *vs.* 3%) and a longer terminal elimination half-life (17.7 *vs.* 10.8 h) (Sepracor, data on file).

Pharmacokinetics have been determined in human volunteers after single oral doses of 6.4 and 12.8 mg (16). Systemic bioavailability, as measured by the area under the curve (AUC), was roughly proportional to dose. Peak plasma levels were attained between 50 and 60 min, and elimination half-life averaged 165 h (*i.e.*, approximately 1 week). The long half-life is probably mainly due to the large volume of distribution which has previously been reported for astemizole and its metabolites (17, 18).

Toxicology

Norastemizole is generally well tolerated in dogs. The highest no-effect dose in 28-day studies has been determined to be 10 mg/kg/day. Dose-limiting side effects were generally nonspecific and included sporadic emesis and diarrhea. In the rat, 10 mg/kg/day was also found to be the highest no-effect dose in 6-month studies. Higher doses were associated with an increase in the frequency, but not the severity, of a spontaneous inflammatory cardiomyopathy which is commonly found at background levels in these Spague-Dawley rats. There were no signs of similar effects in other species, and this finding is therefore considered to be rat-specific and of no clinical relevance. No ECG changes were observed at any time in any of these studies (Sepracor, data on file).

Clinical Studies

Two studies have been conducted in normal human volunteers to determine the efficacy of norastemizole against histamine-induced wheal and flare (16, 19). This model is currently considered to be the most reliable way of evaluating the pharmacodynamic activity of H_1 receptor antagonists. Marked suppression of the wheal and flare response was observed with single oral doses of norastemizole of 6.4-100 mg. Clinically significant therapeutic effects were observed as early as 30 min after administration, even after the lowest dose. Maximum effects (up to 100% suppression at the higher doses) were attained with each dose between 1 and 4 h and persisted for at least 24 h. The maximum suppression obtained with the lowest dose (6.4 mg) was around 60%.

In most, but not all studies, astemizole has been shown to have a significantly slower onset of action than the other second-generation nonsedating antihistamines (3, 5, 6, 20, 21). In routine use, maximum efficacy is not

usually attained until after about 1 week of chronic administration and loading regimens of 3 times the standard dose are often used for the first few days to a week in an attempt to shorten the delay (5, 6, 20). The relatively rapid onset of action of norastemizole should be an advantage in providing immediate symptomatic relief and achieving steady levels of prophylaxis for both acute and chronic allergy sufferers.

No clinically significant changes in heart rate or in ECG intervals were observed with norastemizole in the above studies. A separate study was also undertaken in 381 normal subjects to confirm the absence of any cardiac electrophysiological effects. Norastemizole was administered as a single oral dose on two consecutive days at 5, 20 or 62.5 mg. No change was seen in either heart rate, PR, QRS or QT intervals (22). The results of these three studies demonstrate that norastemizole shows no signs of cardiac toxicity, even at multiples of the therapeutic dose.

Norastemizole is potentially an important new addition to the class of third-generation antihistamines. It offers significant advantages over the second-generation parent compound astemizole in terms of potency, safety and onset and duration of action.

Manufacturer

Sepracor, Inc. (US); collaboration and license agreement with Janssen Pharmaceutica NV (BE).

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