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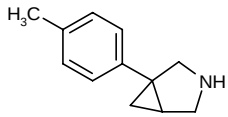
Bicifadine*

Prop INN; USAN

Nonopioid Analgesic
Norepinephrine Transporter Inhibitor
Serotonin Transporter Inhibitor
NMDA Antagonist

DOV-220075
CL-220075 (as hydrochloride)
MCV-4147 (as hydrochloride)
NIH-9542 (as hydrochloride)

(±)-1-(4-Methylphenyl)-3-azabicyclo[3.1.0]hexane



$C_{12}H_{15}N$
Mol wt: 173.2575

CAS: 071195-57-8

CAS: 066504-75-4 (as hydrochloride)

EN: 321976

Abstract

Although a multitude of agents have been developed and marketed for pain management, an effective treatment for chronic pain has not yet been found. Opioid analgesics have been used for thousands of years to treat pain. However, they are not effective in the treatment of all types of chronic pain and can be associated with adverse events, tolerance and dependency. The development of nonopioid therapeutics remains a priority for researchers in the search for effective long-term therapy of chronic pain states. The 1-phenyl-3-azabicyclo[3.1.0]hexane bicifadine is a particularly attractive novel nonopioid analgesic. This NMDA antagonist, which is also an inhibitor of both the norepinephrine and serotonin transporters, was shown to have a non-narcotic profile and potent analgesic activity *in vivo*. The clinical efficacy of bicifadine has also been demonstrated as a treatment for postoperative dental pain, postbunionectomy pain and chronic lower back pain. Bicifadine is undergoing phase III clinical development for the treatment of acute pain and chronic lower back pain.

Synthesis

Bicifadine can be prepared by several different ways:

1) The esterification and bromination of 4-methylphenylacetic acid (I) by successive treatment with $SOCl_2$, *N*-bromosuccinimide/HBr and methanol gives 2-bromo-2-(4-methylphenyl)acetic acid methyl ester (II), which is condensed with methyl acrylate by means of NaH and EtOH in ether to yield *cis*-1-(4-methylphenyl)cyclopropane-1,2-dicarboxylic acid dimethyl ester (III). Hydrolysis of diester (III) with KOH and HCl in refluxing EtOH affords the corresponding diacid (IV), which by reaction with urea in refluxing xylene provides 1-(4-methylphenyl)cyclopropane-1,2-dicarboximide (V). Finally, this compound is reduced with sodium bis(2-methoxyethoxy)-aluminum hydride in refluxing benzene (1, 2) or with BH_3-THF in THF (2). Scheme 1.

2) Reaction of methyl ester (II) with acrylonitrile by means of NaH and MeOH in ether gives *cis*-2-cyano-1-(methoxycarbonyl)-1-(4-methylphenyl)cyclopropane (VI), which by reductive cyclization with borane in THF results in 1-(4-methylphenyl)-3-azabicyclo[3.1.0]hexan-2-one (VII). Finally, this compound is reduced with sodium bis(2-methoxyethoxy)aluminum hydride as before (1). Scheme 1.

3) By reaction of 3-(4-methylphenyl)-3-pyrroline with methylene iodide and powdered copper in benzene in a molar ratio of 1:2:4 (1). Scheme 1.

Introduction

Pain, either acute or chronic, is defined as an unpleasant sensory and emotional experience that is associated with the potential for real acute or ongoing tissue damage. It is an extremely complex process that involves

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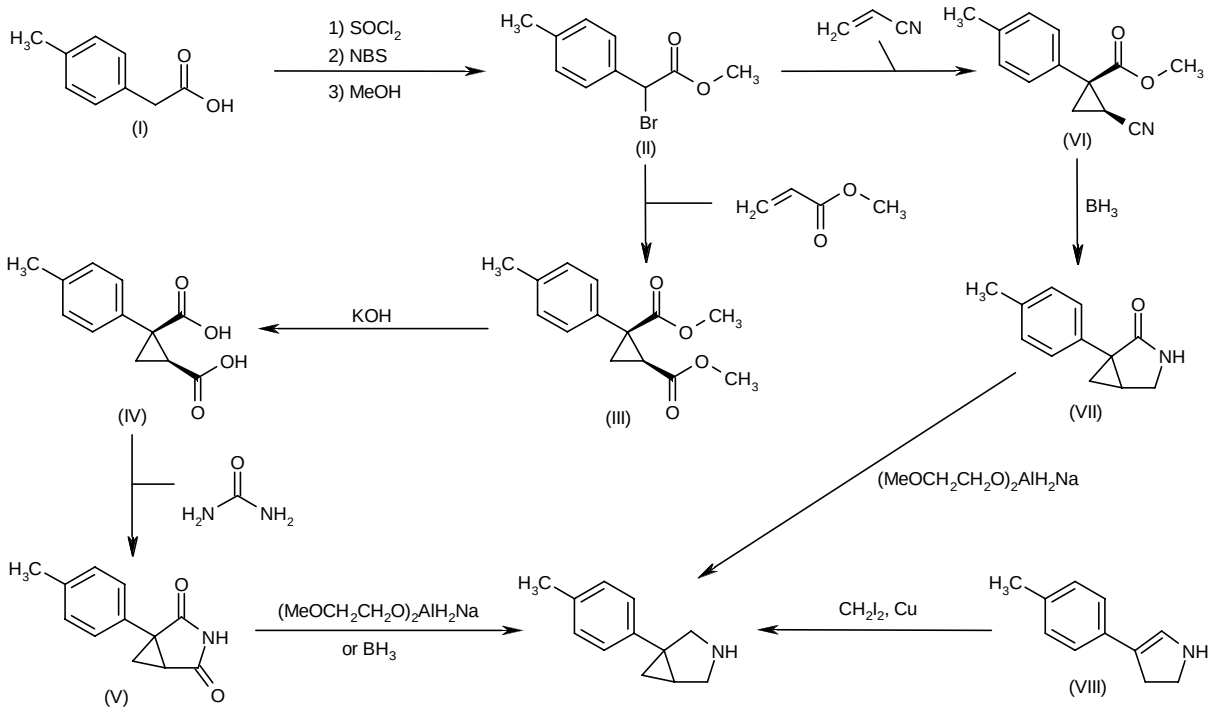
Scheme 1: Synthesis of Bicifadine



interrelated neurotransmitter and neuromodulator systems in ascending and descending spinal pathways and supraspinal sites. It is estimated that 45% of the U.S. population will seek medical assistance for persistent pain at some point during their lives, including almost 25 million and between 75 and 80 million individuals suffering from acute and chronic pain, respectively. The most common form is chronic back pain, affecting nearly 31 million individuals. In addition, 70-90% of patients with advanced cancer, 60% of all HIV-positive individuals, 80% of patients with end-stage AIDS and 25 million migraine sufferers experience significant pain. These rates do not even begin to include individuals diagnosed with any one of the numerous chronic pain conditions, such as rheumatoid arthritis, angina pectoris and postherpetic neuralgia, particularly prevalent in the older population (3).

The primary goal of the treatment of pain is analgesia to improve the quality of life of the individual. Although hundreds of agents have been developed and marketed for pain management, there is still no effective treatment for chronic pain. The American Pain Foundation estimates that only 1 in 4 patients receives proper treatment for pain. This is due in part to the fact that patients experience differential responses to drugs depending on the type of nerve and tissue damage evident in their underlying pain condition (3).

Opioid analgesics, or opiates, have been used for thousands of years to treat pain. This class of agents produces potent analgesic effects by activating mu, delta or kappa opioid receptors. These receptors normally regulate nociception, mood and responses to stress by interacting with endogenous endorphins. However, these agents are not effective in the treatment of all types of chronic pain and there are many disadvantages associated with long-term opioid therapy, including adverse events, tolerance and dependency. Thus, the development of nonopioid therapeutics remains a priority for researchers in the search for effective long-term therapy of chronic pain states (3-6).

Numerous nonopioid analgesics with various mechanisms of action have been discovered and have been marketed or are under development. These agents include nonsteroidal antiinflammatory drugs (NSAIDs), cyclooxygenase type 2 (COX-2) inhibitors, nitric oxide synthase (NOS) inhibitors, superoxide dismutase mimetics, GABA receptor agonists, phospholipase A_2 (PLA_2) inhibitors, ion channel modulators, cannabinoids, nociceptin receptor antagonists, antidepressants and histamine antagonists, among others (3). The 1-(substituted-phenyl)-3-azabicyclo[3.1.0]hexane bicifadine (DOV-220075) is a particularly attractive nonopioid analgesic. It is an inhibitor of both the norepinephrine and serotonin transporters and an NMDA antagonist with a non-narcotic profile. Bicifadine was shown to have potent analgesic activity *in vivo* and was chosen for further development for the treatment of pain (2, 7).

Pharmacological Actions

An *in vitro* study examining the interaction between the [^{3}H]-imipramine binding site and the 5-hydroxytryptamine (5-HT, serotonin) transporter complex in human platelets showed that bicifadine was a preferential blocker of [^{3}H]-5-HT uptake (8).

Bicifadine was shown to reverse abnormal (3-legged) gait in rats with inflamed paws (ED_{50} = 18 mg/kg p.o.) more potently than aspirin (ED_{50} = 74 mg/kg p.o.) and codeine (ED_{50} = 51 mg/kg p.o.), and it exhibited marked analgesic activity in the inflamed rat paw pressure threshold test (ED_{50} = 11 *vs.* 150 and 43 mg/kg p.o., respectively, for aspirin and codeine) and the mouse writhing assay (ED_{50} = 13 *vs.* 29 and 9 mg/kg p.o., respectively). Comparison of the oral therapeutic indices in rats of bicifadine (LD_{50} = 370 mg/kg p.o.) with other compounds revealed that bicifadine compared favorably to aspirin (LD_{50} = 1466 mg/kg p.o.) and was significantly better than codeine, pentazocine and propoxyphene (LD_{50} = 252, 246 and 55 mg/kg p.o., respectively) (2, 7).

Bicifadine was generally inactive in the high-intensity rat tail-flick and mouse hot-plate models. It showed no physical dependence liability when administered as an s.c. pellet or using an incremental i.p. dosing schedule. No morphine-like physical dependence was observed and little tolerance developed in studies in rhesus monkeys administered the agent over 40 days. Bicifadine did not exhibit any antiinflammatory activity and it did not inhibit prostaglandin synthetase *in vitro* (7, 9-11).

Clinical Studies

The analgesic efficacy of bicifadine (75 and 150 mg p.o.) against postoperative pain was demonstrated in a single-dose, double-blind, placebo- and aspirin (650 mg p.o.)-controlled, parallel-group study conducted in 100 patients with moderate to severe postoperative abdominal or orthopedic pain. Bicifadine was well tolerated. Adverse events reported were minor and included diaphoresis, drowsiness, dizziness and a “high” feeling. The majority of these adverse events were seen in patients on the higher dose of bicifadine. Significant analgesia was observed in patients administered 150 mg bicifadine or aspirin compared to placebo and 75 mg bicifadine. No significant difference was observed between the 75-mg bicifadine dose and placebo (12).

A double-blind, randomized, placebo-controlled, single-dose phase II trial in 752 patients compared the analgesic efficacy and safety of bicifadine (200, 400 or 600 mg p.o.) with placebo and codeine (60 mg p.o.) in the treatment of moderate to severe postoperative dental pain (*i.e.*, surgical removal of impacted third molars). Both active agents were well tolerated, with no serious adverse events, nausea and emesis being the most common. A significant, dose-dependent increase in summary measures of efficacy (Sum of Pain Relief and Intensity Difference [SPRID], Sum of Pain Intensity Difference [SPID], Total Pain Relief [TOTPAR]) was observed in patients receiving bicifadine compared to placebo. In addition, a significant, time-related increase in pain relief was observed in patients administered 400 and 600 mg of bicifadine. Maximum effects were observed within 2-3 h of dosing and were sustained for the 6-h examination period. Maximal effect scores for the doses of 200 and 400 mg were similar to those observed for codeine, while the effects observed with the dose of 600 mg were significantly greater (13).

A double-blind, randomized, placebo-controlled, single-dose phase III trial in 540 patients compared the analgesic efficacy and safety of bicifadine (200, 400 or 600 mg p.o.) with placebo and tramadol (100 mg p.o.) in the treatment of moderate to severe postoperative dental pain. Both bicifadine and tramadol were well tolerated, with no serious adverse events observed. Nausea and emesis were the most common adverse events reported, with the highest frequency in the 600-mg bicifadine group. Overall, however, bicifadine was associated with a lower frequency of adverse events. A significant overall effect on SPRID, SPID and TOTPAR scores was noted in patients receiving bicifadine as compared to placebo and significant time-related pain relief was observed at all doses of bicifadine. Maximum effects were seen within 1 h of dosing and were sustained for the 12-h examination period. Maximal effect scores for the 400- and 600-mg doses of bicifadine were comparable to those obtained for tramadol (14).

A pivotal, multicenter, double-blind, randomized, placebo-controlled phase III trial in about 480 outpatients with moderate to severe acute pain following bunionectomy has been initiated to determine the safety and efficacy of 3 doses of bicifadine over a 5-day period. This trial is using tramadol as an active control and the primary efficacy endpoint is the SPRID score. Secondary endpoints include time to use of rescue medication, clinical global evaluations and other measures of analgesia (15).

Two pivotal, multicenter, double-blind, randomized, placebo-controlled phase III trials have been initiated in patients with chronic lower back pain to determine the safety and efficacy of bicifadine for up to 1 year. Primary efficacy endpoints include changes in pain severity ratings by the patient, measures of functional disability and patients’ global impression of change. Secondary endpoints are changes in these measures at several time points prior to the end of treatment, the rate of discontinuation due to lack of efficacy, time to use of rescue medication and other analgesia-related rating scales. One study will assess the effects of 3 doses of bicifadine over 3 months, and patients who complete this study will be eligible to enter a follow-up study with up to 1 year of additional treatment (16). The other pivotal trial was initiated in December and will enroll approximately 1,550 patients, 1,050 of whom will be entered directly and randomized to receive either bicifadine 400 mg b.i.d. or appropriate analgesic treatment selected by the investigator. In addition, approximately 500 patients who have

completed 12 weeks of treatment in the above trial or the confirmation trial currently planned for later in the year will be enrolled to received bicifadine 400 mg b.i.d. (17).

In March 2004, DOV Pharmaceutical and the FDA reached an agreement on a plan for the balance of the phase III bicifadine program necessary to submit an NDA for both acute pain and chronic lower back pain. An NDA filing is predicted for 2006. Controlled-release formulations of the agent are being developed under a joint venture between DOV and Elan. Bicifadine continues to undergo phase III development with a total of 7 trials planned to evaluate its safety and efficacy as a treatment for acute pain and chronic lower back pain (16, 17).

Source

DOV Pharmaceutical, Inc. (US); licensed from Wyeth Pharmaceuticals (US).

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