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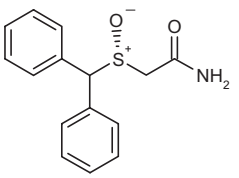
Armodafinil

Prop INN

Treatment of Excessive Sleepiness
α_1-Adrenoceptor Agonist

(–)-Modafinil
(*R*)-Modafinil
CEP-10952
CRL-40982
Nuvigil™

(–)-2-(*S*$_R$-1,1-Diphenylmethylsulfinyl)acetamide
(–)-2-(*S*$_R$-Benzhydrylsulfinyl)acetamide



$C_{15}H_{15}NO_2S$
Mol wt: 273.3511

CAS: 112111-43-0
EN: 135643

Abstract

Patients with obstructive sleep apnea/hypopnea syndrome (OSA/HS), narcolepsy and shift work sleep disorder (SWSD) can suffer from excessive sleepiness that greatly impairs their quality of life. The α_1-adrenoceptor agonist armodafinil ([*R*]-modafinil, Nuvigil™) has been demonstrated to improve wakefulness in these patients. Phase III studies of armodafinil in a total of 993 patients with OSA/HS, narcolepsy and SWSD showed that the compound enhances wakefulness without interfering with normal sleep. Armodafinil has also demonstrated efficacy when used as an adjunctive therapy in OSA/HS patients with residual excessive sleepiness after nasal continuous positive airway pressure (nCPAP) therapy. Armodafinil has been shown to provide higher and more sustained plasma concentrations, as well as superior effects on attention and wakefulness, compared to modafinil.

Synthesis

Armodafinil can be prepared by two approaches:

1) Condensation of diphenylmethanol (I) with 2-sulfanilacetic acid (II) in TFA gives 2-(diphenylmethylsulfanyl)acetic acid (III) which is esterified with ethanol by means of sulfuric acid to yield ethyl ester (IV). Oxidation of compound (IV) by means of H_2O_2 in methanol provides racemic 2-(diphenylmethylsulfinyl)acetic acid ethyl ester (V), which after hydrolysis with NaOH in ethanol/water affords the corresponding racemic acid (VI). Optical resolution can be achieved by two different ways, either by enantioselective crystallization of the salt of acid (VI) with (*S*)-(–)-α-methylbenzylamine (VII) to provide (*R*)-2-(diphenylmethylsulfinyl)acetic acid (VIII), which is finally methylated and treated with NH_4OH (1-3), or by reaction of acid (VI) with (*R*)-4-phenylthiazolidine-2-thione (IX) by means of DCC and DMAP in CH_2Cl_2 to yield the corresponding diastereomeric mixture of thiazolidinones (X) and (XI), which is separated by column chromatography and the desired diastereomer (XI) is finally treated with ammonia (4). Scheme 1.

2) By asymmetric oxidation of diphenylmethylsulfanyl)acetic acid (XII) (5) by means of cumene hydroperoxide in the presence of DIEA and catalysis of $Ti(OiPr)_4$/(*S*,*S*)-diethyl tartrate/water complex in toluene or AcOEt (6). Scheme 2.

Background

Sleep apnea is a sleep disorder in which breathing stops during 10 s or more, sometimes more than 300

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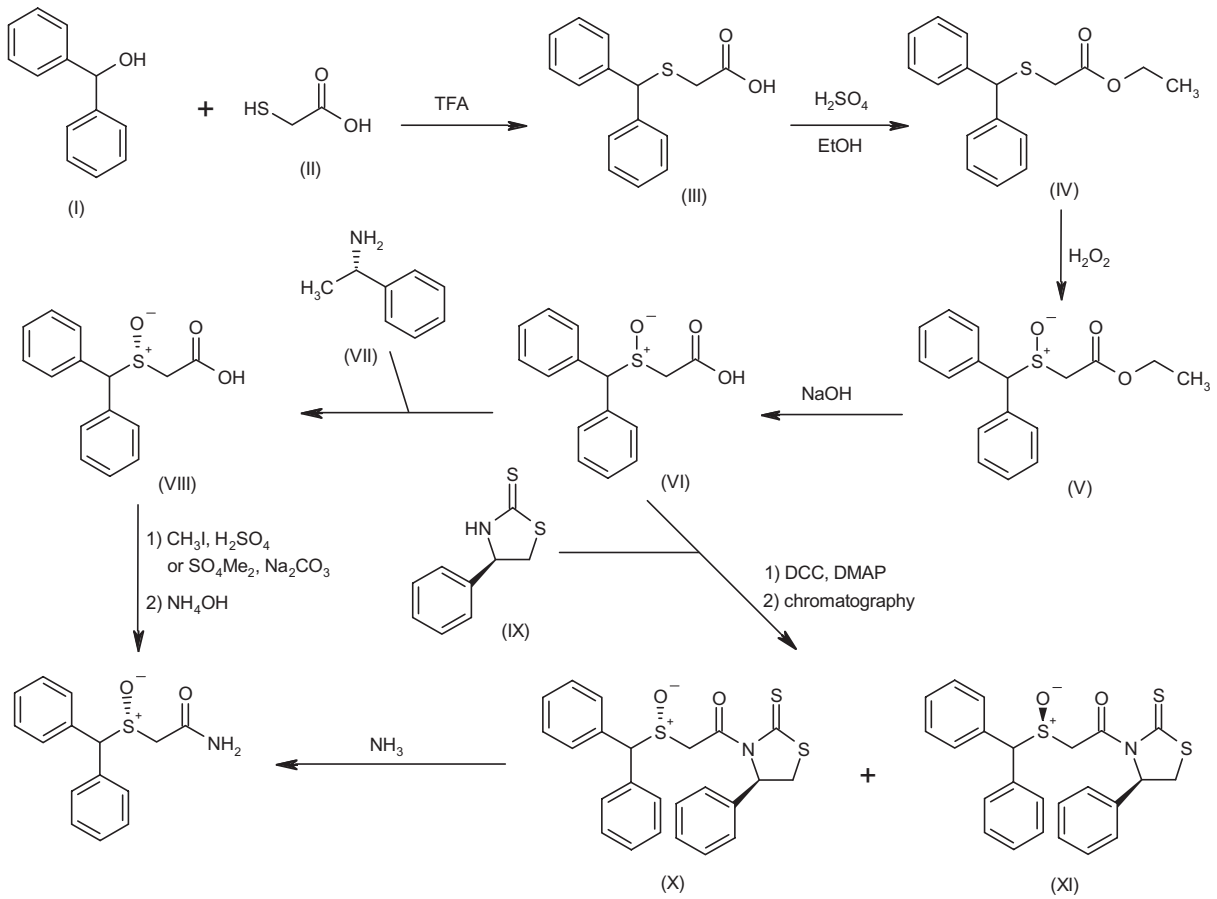
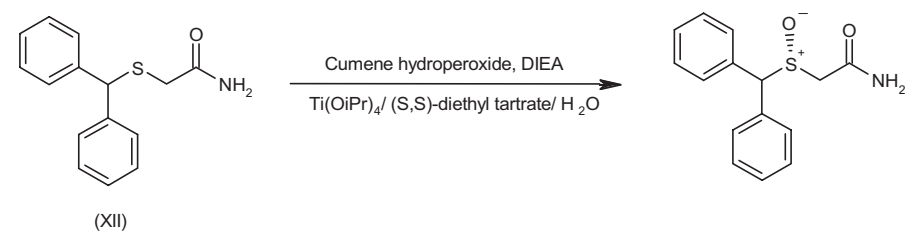
Scheme 1: Synthesis of Armodafinil



Scheme 2: Synthesis of Armodafinil



times a night. Symptoms of this disorder include excessive daytime sleepiness, loud snoring, observed episodes of breathing stoppage during sleep, followed by choking and gasping for breath, and awakening with a dry mouth, sore throat and/or morning headache. Obstructive sleep apnea occurs when the walls of the pharynx collapse on themselves and obstruct the flow of air. After 10-30 s without air, the person may rouse to a lighter level of sleep or brief wakefulness, allowing the muscles to regain their normal tone and breathing to return to normal. Patients with this type of apnea may experience pauses in breathing hundreds of times during the night, often without realizing it (7).

Narcolepsy is a chronic sleep disorder of neurological origin that can be described as an intrusion of rapid eye movement (REM) sleep into the waking state. The disorder is characterized by 4 classic symptoms: excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. Disturbed nighttime sleep, tossing and turning, nightmares, leg jerks and frequent awaken-

ings, as well as automatic behavior, or performing tasks and activities without recollection of the event, also occur in patients with narcolepsy. Patients with this disorder suffer irresistible sleep attacks that can last for 30 s to over 30 min, regardless of the amount of prior nighttime sleep. A person with narcolepsy can nod off while talking, driving, eating and working, making it a particularly distressing and potentially dangerous disorder (8).

The psychostimulating agent modafinil (Provigil®) is currently used to treat patients with daytime sleepiness associated with narcolepsy, and the drug may also be useful in the treatment of attention deficit hyperactivity disorder (ADHD), depression and cocaine dependence. Both enantiomers of modafinil are pharmacologically active, but (*R*)-modafinil (armodafinil, Nuvigil™) has an apparent steady-state oral clearance 3-fold less than that of (*S*)-modafinil and shows a longer half-life compared to the racemate. Armodafinil is undergoing regulatory review at the FDA for use in improving wakefulness in patients with excessive sleepiness associated with narcolepsy, shift work sleep disorder (SWSD) and obstructive sleep apnea/hypopnea syndrome (OSA/HS) (9).

Preclinical Pharmacology

A rat model predictive of human sleep patterns was used to compare the wake-promoting activities of armodafinil and *d*-methamphetamine. Male WKY rats subjected to a 12/12 light/dark cycle received armodafinil (30, 100 or 300 mg/kg i.p.), *d*-methamphetamine (1 mg/kg i.p.) or vehicle and were monitored for 30 h. The total cumulative sleep loss on armodafinil was 44 ± 4 min at 30 mg/kg, 85 ± 8 min at 100 mg/kg and 254 ± 11 min at 300 mg/kg, as compared to 109 ± 9 min for *d*-methamphetamine and 22 ± 4 min for vehicle. Total cumulative sleep loss was maximal 2, 3 and 9 h, respectively, after injection of 30, 100 and 300 mg/kg armodafinil, compared to 4 and 1 h, respectively, after injection of *d*-methamphetamine and vehicle. At doses (1 and 100 mg/kg i.p.) producing a comparable enhancement of wakefulness, armodafinil was not associated with the hyperthermia, increased locomotor activity or acute rebound hypersomnolence observed with *d*-methamphetamine (10).

Clinical Studies

The effects of a single dose of armodafinil (100, 150, 200 or 300 mg) on wakefulness and the ability to maintain attention were investigated in 107 healthy male volunteers subjected to 28 h of acute sleep loss. Armodafinil significantly improved wakefulness, as measured by the Maintenance of Wakefulness Test (MWT) for sleep latency, at all doses administered. In addition, the ability to maintain attention, as determined by the Psychomotor

Table I: Clinical studies of armodafinil (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized Double-blind	Armodafinil, 100 mg Armodafinil, 150 mg Armodafinil, 200 mg Armodafinil, 300 mg Modafinil, 200 mg Placebo	107	All armodafinil dose levels significantly improved wakefulness and the ability to maintain attention in healthy volunteers after a period of acute sleep loss	11
Narcolepsy, Sleep apnea	Randomized Double-blind Pooled/meta-analysis	Armodafinil, 150 mg/d x 12 wks (n=406) Armodafinil, 250 mg/d x 12 wks (n=181) Placebo (n=406)	993	Armodafinil was well tolerated and showed efficacy in improving attention and episodic memory in patients with obstructive sleep apnea/hypopnea syndrome, narcolepsy or shift work sleep disorder	12-14
Sleep apnea	Randomized Double-blind Multicenter	Armodafinil, 150 mg o.d. x 12 wks (n=129) Placebo (n=130)	259	Armodafinil improved measures of wakefulness, fatigue and quality of episodic memory in patients with obstructive sleep apnea/hypopnea syndrome	15
Sleep apnea	Randomized Double-blind Multicenter	Armodafinil, 150 mg o.d. x 12 wks Armodafinil, 250 mg o.d. x 12 wks Placebo	392	Armodafinil was well tolerated and improved the ability of patients with obstructive sleep apnea/hypopnea syndrome and residual sleepiness to sustain wakefulness	16
Sleep disorder	Randomized Double-blind Multicenter	Armodafinil, 50 mg on d 1 → 100 mg on d 2 → 150 mg x 12 wks Placebo	254	Improvements in sleep latency, episodic secondary memory and attention were observed in patients with chronic shift work sleep disorder treated with armodafinil	17
Sleep disorder	Randomized Double-blind	Armodafinil, 150 mg o.d. x 12 wks (n=65) Armodafinil, 250 mg o.d. x 12 wks (n=67) Placebo (n=64)	326	Armodafinil significantly improved wakefulness, memory, attention and fatigue in patients with excessive sleepiness	18

Vigilance Task (PVT) median reaction time and number of lapses, was also improved by all doses of armodafinil relative to placebo. Abdominal pain and nausea were the most frequent adverse events. The same dose of armodafinil (200 mg) produced higher and more sustained plasma concentrations than modafinil, as well as more sustained attention and wakefulness postdosing (11). The results of this study and those that follow are summarized in Table I.

Four randomized, double-blind, placebo-controlled studies were conducted to support the filing of an NDA for armodafinil. These phase III studies evaluated the benefits of armodafinil for the treatment of excessive sleepiness associated with OSA/HS, narcolepsy and SWSD. In these studies, patients received 150 or 250 mg of armodafinil once daily or placebo for 12 weeks. A total of 993 patients with excessive sleepiness participated in the studies, which included 601 patients with OSA/HS, 174 patients with narcolepsy and 216 patients with SWSD. Overall, all patient populations receiving armodafinil showed significantly improved wakefulness as compared to placebo. In addition, narcolepsy and OSA/HS patients showed significant improvements in fatigue on armodafinil compared to placebo. These effects were associated with improvements in the quality of episodic secondary memory of all patients, as well as in the power of attention in patients with narcolepsy and SWSD. The wakefulness later in the day produced by armodafinil therapy was not found to interfere with patients' normal nighttime sleep schedule. Armodafinil was generally well tolerated, with headache, nausea, dizziness, insomnia and anxiety being the most frequent adverse events (9, 12-14).

The efficacy and safety of armodafinil were assessed in two multicenter, double-blind, randomized, placebo-controlled trials in 392 and 259 patients with OSA/HS who had residual excessive sleepiness despite stable nasal continuous positive airway pressure (nCPAP) therapy. Armodafinil (150 or 250 mg once daily) was administered for 12 weeks as adjunctive therapy to nCPAP in this multicenter, randomized, double-blind, placebo-controlled trial. Wakefulness, as measured by the MWT, showed significant improvement on armodafinil at final visit compared to placebo. Armodafinil therapy also led to improved clinical condition on the Clinical Global Impression of Change (CGI-C), improved subjective wakefulness on the Epworth Sleepiness Scale (ESS) and reduced fatigue on the Brief Fatigue Inventory (BFI). Clinical benefit lasted from week 4 until the end of the studies. Armodafinil was associated with improvement or no difference compared to placebo with respect to quality of episodic memory, speed of memory or attention. Nighttime sleep and nCPAP therapy were not affected by treatment with armodafinil. The most frequently reported adverse events were headache, nausea, diarrhea, insomnia, dizziness and anxiety (15, 16).

Improvements in sleep latency, memory and attention were observed in patients with chronic SWSD treated with armodafinil in a 12-week, multicenter, randomized, double-blind, placebo-controlled study. The trial included 254 patients who took armodafinil on nights they worked a night shift or participated in a laboratory night shift. Doses of armodafinil were 50 mg on the first night, 100 mg on the second and third nights, and 150 mg thereafter. Sleep latencies during laboratory night shifts were significantly lengthened with armodafinil compared with placebo. Clinical Global Impression of Improvement (CGI-I) was improved in more armodafinil-treated patients and patient-reported sleepiness was reduced compared to placebo. Cognitive function tests revealed improvements in episodic secondary memory and power and the continuity of attention with armodafinil. The drug was well tolerated, headache, nausea, nasopharyngitis and anxiety being the most common adverse events (17).

Another double-blind, randomized, placebo-controlled trial evaluated the efficacy of armodafinil (150 or 250 mg once daily) in 326 patients with excessive sleepiness associated with narcolepsy over 12 weeks. Armodafinil treatment was associated with significant improvement compared to baseline in mean sleep latency on the MWT and in the percentage of patients showing improvement on the CGI-C compared to placebo. The quality of episodic memory, the power of attention, the ESS and fatigue measured on the BFI all improved on armodafinil. These parameters improved early in the day and the beneficial effect was maintained throughout the day. Armodafinil did not adversely affect nighttime sleep and the treatment was generally well tolerated (18).

Source

Cephalon, Inc. (US).

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