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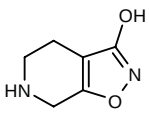
Gaboxadol

Prop INN

Treatment of Sleep Disorders
$GABA_A$ Receptor Agonist

Lu-02-030
MK-0928
THIP

4,5,6,7-Tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol



$C_6H_8N_2O_2$
Mol wt: 140,1412
CAS: 064603-91-4
CAS: 085118-33-8 (as monohydrochloride)
EN: 286075

Abstract

Approximately half of the U.S. adult population suffers from insomnia, with a higher incidence seen in the elderly. The benzodiazepines, sedative/hypnotic drugs which shorten sleep onset latency and increase sleep continuity, have been the standard treatment for insomnia. However, these agents also suppress REM and deep sleep and are associated with unwanted effects such as memory impairment, next-day residual sedation and alteration of hormonal secretion. Another pharmacotherapeutic option for the treatment of insomnia are the nonbenzodiazepines which are selective for the BZ1 or α1 subunit of $GABA_A$ receptors and have a reduced adverse event profile. However, no sedative/hypnotics effective against the spectrum of different insomnia complaints are as yet available, and researchers continue to search for compounds that can maintain sleep throughout the night while having an improved safety profile and a rapid onset of action. One nonbenzodiazepine to emerge that shows promise as a treatment for sleep disorders is the selective $GABA_A$ receptor agonist gaboxadol. Gaboxadol lengthens the duration of non-REM episodes and elevates slow-frequency components in EEGs within non-REM sleep, and, unlike benzodiazepine hypnotics, it increases sleep consolidation and intensity without inhibiting REM sleep. Gaboxadol is presently being evaluated in phase III trials for the treatment of insomnia.

Synthesis

The ethanolysis of 1-benzylpyrrolidin-2-one (I) with HCl in ethanol gives 4-(benzylamino)butyric acid ethyl ester (II), which is alkylated with ethyl bromoacetate (III) to yield the tertiary amine (IV). Cyclization of amine (IV) by means of sodium ethoxide affords 1-benzyl-3-hydroxy-1,2,5,6-tetrahydropyridine-4-carboxylic acid ethyl ester (V) (1), which by deprotection with H_2 over Pd/C in aqueous ethanol provides the debenzylated compound (VI). Condensation of compound (VI) with methyl chloroformate and K_2CO_3 in water gives the tetrahydropyridine-1,4-dicarboxylate derivative (VII), which by reaction with ethyleneglycol (VIII) and TsOH in refluxing benzene yields the cyclic ketal (IX). Treatement of ketal (IX) with hydroxylamine and NaOMe or KOH in methanol provides the carbohydroxamic acid (X), which is cyclized by means of either H_2SO_4, hot conc. HCl or $HClO_4$ to afford 3-hydroxy-4,5,6,7-tetrahydropyrido[4,3-*d*]oxazole-6-carboxylic acid methyl ester (XI). Finally, this compound is decarboxylated by means of HBr and glacial acetic acid and neutralized with triethylamine (1, 2). Scheme 1.

Introduction

According to the National Sleep Foundation, approximately 51% of the U.S. adult population suffers from insomnia, with a higher incidence seen in the elderly. Insomnia is the most common type of sleep disorder and is characterized by difficulties in falling asleep and/or maintaining sleep without interruptions. It can result in sleep deprivation, which may negatively affect the quality of life and even compromise safety in the workplace or while driving. Insomnia is considered a symptom rather than a disease or syndrome and it has been shown to be associated with other disorders, including depression, anxiety, gastrointestinal and cardiovascular problems (3-5).

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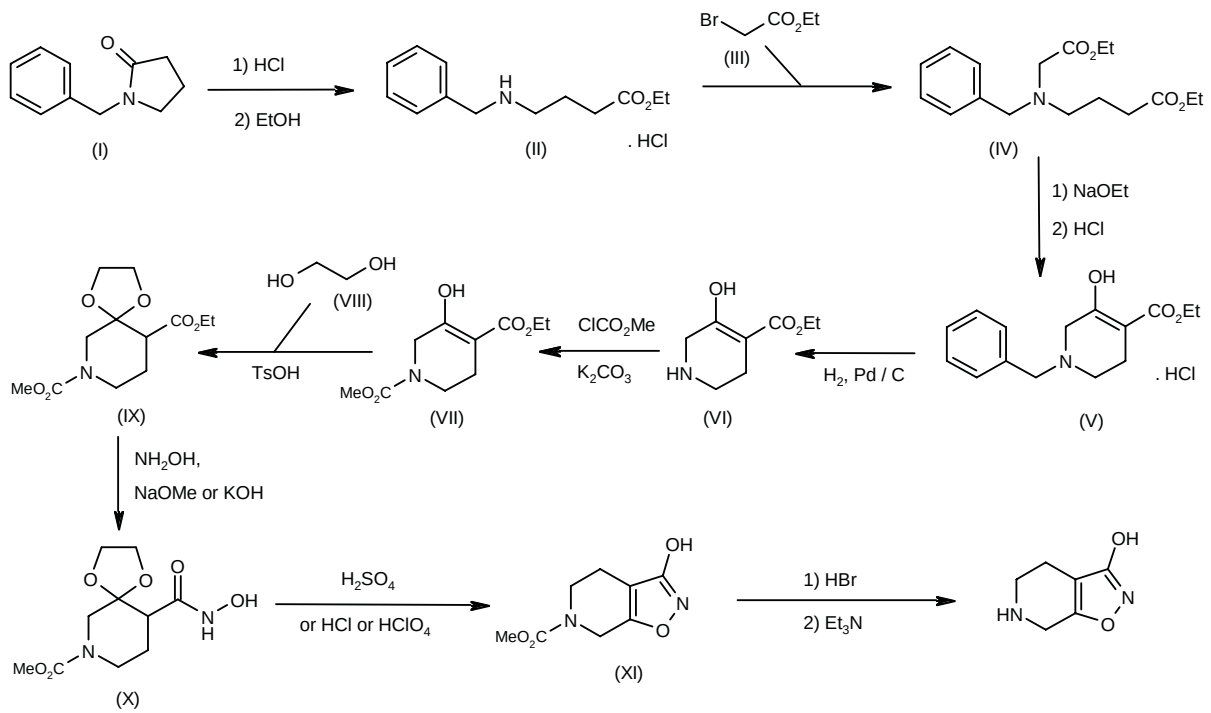
Scheme 1: Synthesis of Gaboxadol



The most widely used sedative/hypnotic drugs are the benzodiazepines. These agents act by modulating the major inhibitory neurotransmitter GABA through allosteric interactions with $GABA_A$ receptors to potentiate responses to GABA. $GABA_A$ receptors are transmembrane ligand-gated chloride ion channels containing specific binding sites for GABA and other distinct allosteric modulatory binding sites, such as those for benzodiazepines. Benzodiazepines bind to all 5 subunits of the $GABA_A$ chloride channel, thus increasing GABA release and ultimately dampening neuronal activity. These agents have been shown to shorten sleep onset latency and increase sleep continuity. However, they also suppress REM and deep sleep and it is well established that benzodiazepines are associated with unwanted effects such as memory impairment and next-day residual sedation. In addition, benzodiazepines are thought to alter hormonal secretions, *i.e.*, they inhibit cortisol and growth hormone (GH) release and stimulate prolactin secretion. In the late 1980s, another class of drugs known as nonbenzodiazepines were described that are selective for the BZ1 or α1 subunit of $GABA_A$ receptors and exhibit a reduced adverse event profile. However, to date, there are no sedative/hypnotics which are effective against the spectrum of different insomnia complaints. Thus, researchers continue to search for compounds possessing an improved safety profile and a rapid onset of action, while maintaining sleep throughout the night (6-11).

One nonbenzodiazepine that shows promise as a treatment for insomnia is the selective $GABA_A$ receptor agonist gaboxadol (Lu-02030, THIP), which exerts its effects on sleep in a manner that differs from other $GABA_A$ modulators. Gaboxadol lengthens the duration of non-REM episodes and elevates slow-frequency (< 8 Hz) components in the EEG within non-REM sleep. Unlike benzodiazepine hypnotics, gaboxadol increases sleep consolidation and intensity without inhibiting REM sleep, and its effects appear to be sustained during chronic treatment (12-14). Gaboxadol was therefore chosen for further development as a treatment for insomnia.

Pharmacological Actions

Gaboxadol has been shown to bind to all $GABA_A$ receptor subtypes with relatively low selectivity, but the functional activity resulting from binding is dependent on the subunit composition of the $GABA_A$ receptor. Table I summarizes the *in vitro* pharmacological profile of gaboxadol compared with the endogenous ligand GABA, and its functional and binding selectivity at the major human $GABA_A$ receptor subunit combinations. Studies have reported that gaboxadol is a partial agonist at α1- or α3β2/3γ2-containing receptors, a full agonist at α5β2/3γ2S-containing receptors and a superagonist with maximum responses 60% greater than GABA at α4β3δ-containing receptors. The activity of gaboxadol was

Table I: In vitro pharmacological profile of gaboxadol compared to GABA (from Prous Science Integrity®).

Compound	Inhibition of neuronal activity[a]	Functional (F) and binding (B) selectivity [d]			
		α1βxγx	α2βxγx	α3βxγx	α5βxγx
GABA	131.8[b] (13)	F: 7.9-30 (15-17)	F: 3.98 (15)	F: 11-208 (15, 16)	F: 2-24 (16)
	20.41[c] (13)	B: 0.021-0.077 (15)	B: 0.023 (15)	B: 0.50 (15)	B: 0.0088 (15)
Gaboxadol	6.76[b] (13)	F: 143-358 (15, 16)	F: 117-203 (15, 17)	F: 233-499 (15-17)	F: 28-339 (16)
	4.46[c] (13)	B: 0.27-1.62 (15)	B: 0.37 (15)	B: 0.166 (15)	B: 0.047 (15)

[a] Functional activity in intact cortical tissue (IC_{50}, μM; wedge preparation assay) in the absence ([b]) or presence ([c]) of the GABA reuptake inhibitor tiagabine. [d]Functional (induction of ionic currents [EC_{50}, μM] and binding selectivity (displacement of [^{3}H]-muscimol [K_i, μM]) assays evaluated in cells transfected with human recombinant $GABA_A$ receptor α (1, 2, 3 and 5), β and γ subunits. References in parentheses.

characterized in *in vitro* experiments using rat cortical wedge preparations containing a variety of subunit assemblies (*e.g.*, α1, β2, β3 and γ2S abundant in the neocortex, together with lower levels of α2, α3, α4, α5, γ3 and δ) where inhibition of spontaneous activity was assessed, and in *Xenopus* oocytes expressing human α1β3γ2S, α5β3γ2 or α5β3γ3 $GABA_A$ receptors. Gaboxadol was shown to have the greatest full agonist potency at α5β3γ2 (EC_{50} = 40 μM; E_{max} = 99%) and α5β3γ3 (EC_{50} = 29 μM; E_{max} = 93%) subunits expressed in oocytes. The full agonist activity observed with gaboxadol in the cortical wedge preparations was about 40-50 times more potent (EC_{50} = 6.8 μM) than that observed in oocytes expressing α1β3γ2S. When compared to benzodiazepine-site agonists such as diazepam, flunitrazepam, lorazepam, indiplon, zaleplon and zolpidem, which exerted only weak inhibitory effects on spontaneous activity in the cortical wedge preparation, gaboxadol was much more potent; ethanol did not potentiate the effects of gaboxadol. Together, these results suggest that extrasynaptic receptors may play an important role in the full agonist activity of gaboxadol in intact tissue and that gaboxadol may interact with a receptor population that is insensitive to benzodiazepines (15-20).

Results from a study using Sf9 cells expressing human α1β2γ2S $GABA_A$ receptors provided evidence that gaboxadol (0.01-50 mM) exerts both inhibitory and agonist effects. Treatment with gaboxadol at concentrations of 0.005-1 mM increased peak whole-cell currents. The EC_{50} values for peak whole-cell currents obtained in cells treated with gaboxadol alone or in combination with diazepam (1 μM) were 154 and 53 μM, respectively. The initial rate of current delay was increased when supersaturating gaboxadol concentrations (10-50 mM) were used, with an off current evoked when gaboxadol was removed. These results indicate that gaboxadol has an inhibitory effect at supersaturating concentrations. Mean currents stimulated by 10-20 mM gaboxadol over the first 4 s were increased in the presence of diazepam (1 μM) although diazepam had no effect on the 4-s mean current evoked by 50 mM gaboxadol (21).

Gaboxadol has been shown in several rodent models to increase non-REM sleep and decrease wakefulness, acting in a manner distinct from benzodiazepine agonist modulators of $GABA_A$ receptors. When gaboxadol (4 mg/kg i.p.) was administered to rats at light onset, non-REM sleep was significantly promoted, with elevations observed in the rate of rise and maximal levels of delta activity within non-REM sleep episodes (12).

Repeated administration of gaboxadol (3 mg/kg i.p. once daily at dark onset for 5 days) was also shown to increase sleep maintenance and intensity. Gaboxadol-treated rats had more non-REM sleep, longer episodes of non-REM sleep and higher levels of slow-wave activity in EEGs within non-REM sleep episodes as compared to placebo; treatment did not alter REM sleep. These effects were present during the entire 5-day treatment period. Following cessation of gaboxadol administration, sleep patterns of gaboxadol- and placebo-treated rats were not significantly different. Thus, treatment with gaboxadol does not promote tolerance, nor does its withdrawal result in sleep disturbances in this model (14).

Results from a study conducted in rats suggest that gaboxadol may reduce waking via alterations in hypothalamic orexinergic tone. Microdialysis perfusion with the agent (100 μM) into the orexinergic hypothalamus during the light cycle significantly decreased wakefulness and increased non-REM sleep without altering REM sleep (22).

Sedation can be induced via stimulation of sleep-promoting cells in the ventrolateral preoptic nucleus (VLPO) and by inhibiting the ascending arousal tuberomammillary nucleus (TMN). A study using nonlesioned and VLPO-lesioned rats and examining brains 3 h post-dosing demonstrated that gaboxadol (5 mg/kg s.c. during the dark cycle) promotes sleep behavior and Fos induction in the sleep-promoting cells of the VLPO. Treatment with gaboxadol was shown to increase slow-wave sleep (SWS-1) and paradoxical sleep in nonlesioned rats as compared to vehicle-treated nonlesioned rats and gaboxadol-treated VLPO-lesioned rats, where decreases in SWS-1 and paradoxical sleep and increases in waking were noted. Fos immunoreactivity was observed in the VLPO but not the TMN of gaboxadol-treated nonlesioned rat brains, in contrast to vehicle-treated nonlesioned rats and gaboxadol-treated VLPO-lesioned rats, which exhibited Fos immunoreactivity in the TMN but not the VLPO. It was concluded that, unlike other $GABA_A$ receptor

modulators, gaboxadol activates the endogenous sleep system (23).

Another study also conducted in rats compared the sleep-promoting effects of long-term gaboxadol (5 mg/kg s.c. once daily during the light cycle for 3 weeks) administration with zolpidem (10 mg/kg s.c. once daily during the light cycle for 3 weeks), with results showing differential activity for the agents. Throughout the treatment period, gaboxadol-treated rats displayed a sustained decrease in waking and increases in SWS-1 and SWS-2; gaboxadol had no effects on paradoxical sleep. On the other hand, treatment with zolpidem suppressed paradoxical sleep throughout the entire treatment period and decreased waking and increased SWS-1 only during the first week of administration; zolpidem had no effect on waking during weeks 2 and 3 of the treatment period. Thus, in contrast to zolpidem, gaboxadol did not induce tolerance upon chronic treatment (24).

Further studies have provided additional evidence for the differential actions of gaboxadol as compared to other $GABA_A$ receptor modulators. Benzodiazepine and benzodiazepine-site agonists are known to impair motor performance, effects which are potentiated by ethanol. Using the rat rotarod model, it was found that gaboxadol, flunitrazepam, zolpidem and indiplon caused dose-dependent motor impairment. A comparison of the motor impairment with gaboxadol and other $GABA_A$ receptor complex modulators in this test in rats is shown in Table II. Importantly, while coadministration of ethanol (1 g/kg) did not potentiate the effects of gaboxadol, supraadditive effects were observed with all other agents. A time-dependent tolerance to motor impairment was noted for gaboxadol (7.9 mg/kg) and zolpidem (1.25 mg/kg) following 30-day dosing. However, when administered together, no cross-tolerance was observed between zolpidem and gaboxadol in a 31-day tolerance test, indicating that the agents interact with different receptor populations (25-30).

A study using pentylenetetrazol (PTZ)-kindled mice reported that while diazepam (0.16-1.3 mg/kg i.p. 30 min before PTZ) and alfaxalone (5-30 mg/kg i.p. 15 min before PTZ) exerted potent anticonvulsant effects and suppressed the development of kindling, gaboxadol (1-41 mg/kg s.c. 30 min before PTZ) had no anticonvulsant or antiepileptogenic effects. These results suggest that gaboxadol binds to different sites at the $GABA_A$ receptor complex (31).

Table II: Induction of motor impairment (ED_{50}, mg/kg) by gaboxadol compared with other $GABA_A$ receptor complex modulators with hypnotic properties in the rat rotarod test (from Prous Science Integrity®).

Compound	Motor impairment
Diazepam	1.70-7.10 i.p. (24-27)
Ethanol	1600 i.p. (23)
Gaboxadol	6.40 s.c. (23)
Flunitrazepam	4.63 i.p. (23)
Indiplon	0.58 s.c. (23)
Triazolam	0.50 i.p. (28)
Zolpidem	0.56 s.c. (23)

References in parentheses.

Pharmacokinetics

The pharmacokinetics of gaboxadol (10 and 20 mg i.m.) were examined in 6 healthy volunteers and 3 beagle dogs. A linear 1-compartment open model described the time course of gaboxadol serum concentrations, with maximum levels rapidly achieved at 15 and 10 min post-dosing in humans and dogs, respectively. Experiments in dogs demonstrated efficient absorption from injection sites (F = 0.94 ± 0.16). High interindividual variability in pharmacokinetic parameters was observed in both species and was not related to dose, indicating first-order kinetics (32).

Clinical Studies

A double-blind, randomized, placebo-controlled study conducted in 10 young (22-31 years old) healthy volunteers examined the effects of gaboxadol (20 mg p.o. 30 min before bedtime) on nocturnal sleep. Gaboxadol significantly increased SWS as compared to placebo by about 25 min; stage 3 (49.8 ± 26.8 min *vs.* 38.6 ± 20.1 min) and stage 4 (30.5 ± 21.6 min *vs.* 17.6 ± 12.9 min) sleep was also significantly longer in gaboxadol-treated subjects. In addition, according to spectral analysis of EEGs within non-REM sleep, significant elevations in the lower frequencies (< 8 Hz) and reductions in spindle frequency ranges (about 10-16 Hz) were observed in gaboxadol-treated subjects. These results suggest that treatment with gaboxadol promoted deep non-REM sleep without effecting REM sleep (33).

Gaboxadol (15 mg p.o. 30 min before bedtime) proved effective in influencing nocturnal sleep without altering hormonal secretion in a randomized, double-blind, placebo-controlled study in 10 healthy elderly (61-78 years old) subjects. Treatment with the agent did not alter levels of ACTH, cortisol, prolactin or GH. However, it significantly decreased perceived sleep latency (115.5 ± 11.2 min *vs.* 23.5 ± 13.1 min), elevated self-estimated total sleep time (7.5 ± 0.8 min *vs.* 6.8 ± 0.9 min) and increased sleep efficiency via reductions in intermittent wakefulness (49.8 ± 34.9 min *vs.* 67 ± 29.9 min), and increased low-frequency activity within EEGs during non-REM sleep as compared to placebo. REM sleep was not disrupted by the agent (34).

Because daytime naps are known to decrease the quality of sleep during subsequent nights, a randomized, double-blind, placebo-controlled, crossover study in 10 healthy young males (21-32 years old) examined the effects of gaboxadol (20 mg p.o. 30 min before bedtime) on postnap (nap at 1600-1800 h on the day of dosing) nocturnal sleep. The nap was shown to prolong sleep

latency, reduce total sleep time and SWS and attenuate delta, theta and alpha activity in EEGs during non-REM sleep. Treatment with gaboxadol tended to shorten nap-induced increases in sleep latency and significantly decreased intermittent wakefulness, increased total sleep time and SWS and enhanced delta and theta activity in non-REM sleep. Moreover, treatment with gaboxadol increased subjective sleep quality (35).

A multicenter, randomized, double-blind phase III study has been initiated to examine the safety and efficacy of gaboxadol for the treatment of insomnia. The trial plans to enroll about 650 patients with primary insomnia in an outpatient setting (36). Gaboxadol continues to undergo phase III testing for the treatment of sleep disorders (37).

Sources

H. Lundbeck A/S (DK); licensed to Merck & Co. (US).

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