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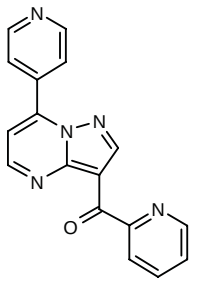
Ocinaplon

Rec INN

Treatment of Generalized Anxiety Disorder
$GABA_A$ Receptor Modulator

CL-273547

7-(4-Pyridyl)-3-(pyridin-2-ylcarbonyl)pyrazolo[1,5-*a*]pyrimidine
2-Pyridyl[7-(4-pyridyl)pyrazolo[1,5-*a*]pyrimidin-3-yl]methanone



$C_{17}H_{11}N_5O$
Mol wt: 301.31
CAS: 096604-21-6
EN: 174632

Abstract

Ocinaplon is a novel anxioselective agent indicated for the treatment of generalized anxiety disorder (GAD). The more traditional benzodiazepine anxiolytics work by potentiating the effects of GABA through their allosteric modulatory site at the $GABA_A$ receptor, the benzodiazepine (BZ) binding site (also known as omega receptor). Described as a nonsedative, nonbenzodiazepine agent, ocinaplon mimics the effects of benzodiazepines at this receptor site. Ocinaplon has proven effective as an anxiolytic agent despite showing a low affinity for binding at the BZ-site of the $GABA_A$ receptor. Therefore, ocinaplon can work to exhibit the full gamut of anxiolytic and anticonvulsant effects without producing the sedation and motor incoordination normally indicative of benzodiazepine administration. Ocinaplon is, therefore, described as a nonbenzodiazepine alternative to anxiolytic therapy, especially indicated in patients experiencing the commonly associated adverse events such as sedation and motor impairment.

Synthesis

Reaction of 4-acetylpyridine (I) with hot dimethylformamide dimethyl acetal (II) gives the enamino ketone (III), which is then condensed with (3-amino-1*H*-pyrazol-4-yl)(2-pyridyl)methanone (IV) in boiling acetic acid (1). Scheme 1.

Intermediate (IV), (3-amino-1*H*-pyrazol-4-yl)(2-pyridyl)methanone, is obtained by condensation of 3-oxo-3-(2-pyridyl)propionitrile (V) with dimethylformamide dimethyl acetal (II) to provide 2-(dimethylaminomethylene)-3-oxo-3-(2-pyridyl)propionitrile (VI), which is finally coupled with aminoguanidine nitrate (VII) by means of 10N NaOH in refluxing EtOH (2). Scheme 1.

Introduction

γ-Aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the mammalian CNS, and is involved in a wide range of physiological and psychological functions. GABA receptors can be classified into the ionotropic $GABA_A$ and the G-protein-coupled $GABA_B$ receptor subtypes, both of which are found throughout the brain. The ionotropic $GABA_A$ receptor is a hetero-oligomeric protein complex that consists of a GABA binding site coupled to an integral channel for chloride ion (Cl^-). Neuropharmacological and molecular research has helped to clarify the structure of this complex receptor site, potentiating the development of novel selective $GABA_A$ receptor ligands.

At least 19 different $GABA_A$ receptor subunits classified into 8 functionally distinct families have thus far been identified (6α, 3β, 3γ, 3ρ, 1δ, 1ε, 1π and 1ζ). Nevertheless, it is generally assumed that the majority of $GABA_A$ receptors exist in the CNS as a pentameric complex composed basically of 2α-, 2β- and 1γ-subunits, positioned around a water-filled ion-conducting pore, and, depending on their subunit composition, they exhibit distinct pharmacological and electrophysiological properties (3). Hence, the $GABA_A$ receptor is liable to display an enormous diversity, allowing for the development of novel specific drugs by establishing molecular targets for specific receptor subtype action.

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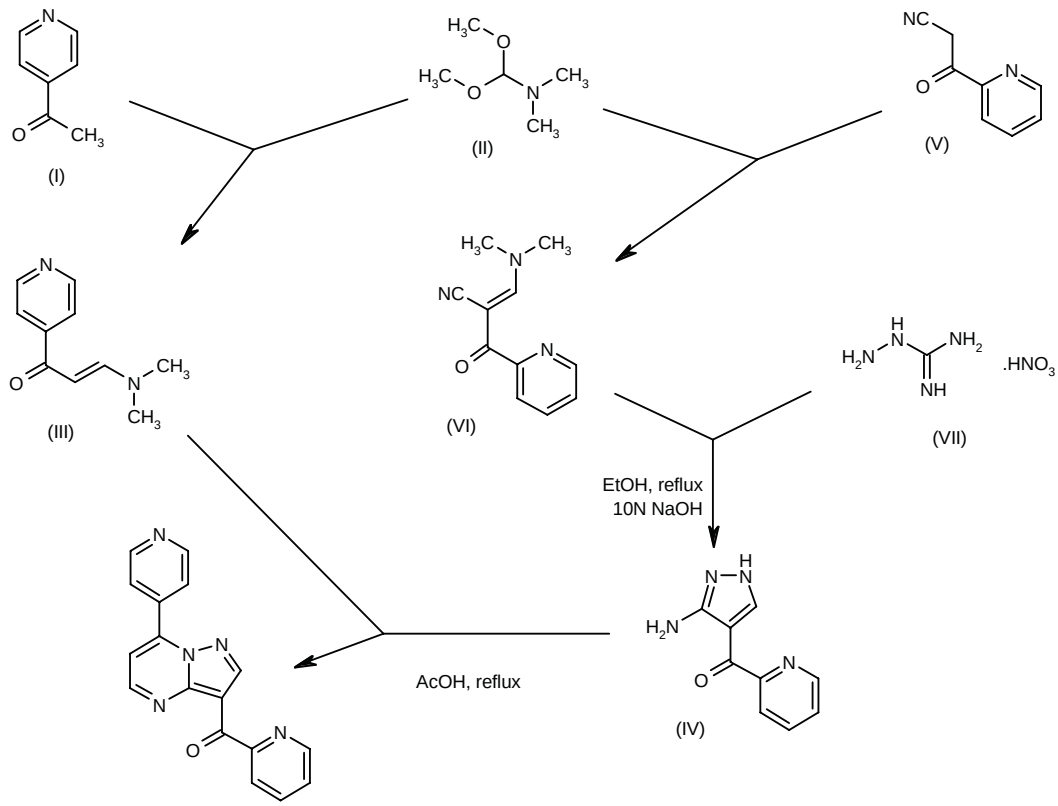
Scheme 1: Synthesis of Ocinaplon



In general, GABA works at receptor sites widely distributed across the brain to produce a plethora of inhibitory effects. In the CNS, GABA produces its inhibitory effect mainly via $GABA_A$ receptors by facilitating the Cl^- influx through the receptor-associated channel. This leads the neuron to a hyperpolarization state resulting in an increase in the firing threshold and therefore in a reduction in the probability of action potential initiation, thereby causing neuronal inhibition and of associated responses.

Pharmacological studies have indicated that the $GABA_A$ receptor is involved in the physiological and behavioral manifestation of anxiety, and is therefore a common target for designer anxiolytics, anticonvulsants and sedatives.

The binding affinity of GABA can be allosterically modulated by a wide variety of drugs that interact with distinct binding sites at the $GABA_A$ receptor complex (*e.g.*, benzodiazepines site, barbiturates site). Allosteric facilitation occurs when drugs bind to these sites, which allows the receptor to bend open. This change in molecular configuration allows an increase in GABA binding (*i.e.*, makes the receptor site more "sensitive" to circulating GABA).

Benzodiazepines have been indicated for antianxiety therapy since the 1960s, and are currently the mainstay of treatment in patients with anxiety. They comprise a large, well-known group of therapeutics displaying efficacy for this indication. Benzodiazepines act by enhancing the binding of GABA at its aforementioned endogenous receptor sites, which results in a potentiation of GABA's ability to increase conductance of Cl^- through the $GABA_A$ receptor-coupled channel. The benzodiazepine binding site has been specifically named the BZ (or ω) binding site.

While benzodiazepines are very effective in treating patients with anxiety, their usefulness has been limited due to their association with a plethora of unwanted side effects including ataxia, amnesia, tolerance development, abuse potential and concomitant sedation. Sedation is of particular concern in patients undergoing anxiolytic therapy within an active working population, and can make benzodiazepine therapy intolerable in severe cases. Therefore, the development of benzodiazepine receptor ligands with nonbenzodiazepine chemical structures are being developed in order to find a suitable receptor ligand that produces an anxiolytic effect without the unwanted

sedation. Interestingly, it has been demonstrated that the anxiolytic and sedative effects of benzodiazepines are differentially and respectively mediated by the α2 and α1 $GABA_A$ receptor subtypes (4, 5). These findings provide the rationale for a more anxioselective agent that could have a binding affinity for specific receptor subtypes involved in the anxiolytic but not sedative properties associated with general $GABA_A$ binding affinity. Thus, new perspectives are open for developing new drugs with an improved pharmacological profile based on their specificity for $GABA_A$ receptor subtypes.

The search for anxiolytics chemically unrelated to benzodiazepines, but with continued action at the $GABA_A$ receptor, has led to the development of drugs that either selectively bind to specific $GABA_A$ receptor subtypes and/or show different efficacies at $GABA_A$ receptors. Ocinaplon is a new drug candidate designed specifically to relieve anxiety without sedation in this way. In this regard, it has been suggested that drugs with partial agonist activity at the $GABA_A$ BZ site receptor may cause benzodiazepine-like effects with less of the associated side effects. Such drugs would be expected to maintain their anxiolytic and anticonvulsive properties, but would not produce sedation or psychomotor disturbances. Ocinaplon is one such partial agonist that has been strategically designed to have benzodiazepine-like qualities without the associated adverse effects.

Pharmacological Actions

Ocinaplon is a chemically unique molecule, with a distinctive pharmacological profile of activity. Its BZ (benzodiazepine ω) receptor subtype specificity allows it to work selectively at the $GABA_A$ receptor to produce antianxiety effects, but without the undesirable effects normally associated with benzodiazepine administration. Ocinaplon therefore addresses a significant unmet need in the field of anxioselective treatment.

The anxiolytic-like effects of ocinaplon have been demonstrated in different studies using a variety of animal models and species (6-9). However, it binds to the benzodiazepine omega receptor with low affinity, showing an IC_{50} of 2 μM by the displacement of [^{3}H]-flunitrazepam, and does not stimulate *t*-butyl bicyclophosphorothionate (TBPS) binding to the same degree as diazepam (6), indicating a reduced potential for causing concomitant sedation. The *in vitro* $GABA_A$ BZ site receptor affinities and *in vivo* anxiolytic-like effects of ocinaplon and similar compounds are summarized in Tables I and II, respectively.

Results from behavioral drug discrimination testing in rats have shown that ocinaplon can be established as a discriminnative stimulus. Besides, benzodiazepines such as triazolam, but not other drugs acting on receptors other than the $GABA_A$ BZ site receptor, were able to substitute for ocinaplon in this behavioral test (8). Hence, it was concluded that ocinaplon and benzodiazepines share a common underlying mechanism of action.

Table I: In vitro *$GABA_A$ BZ-site receptor affinities of ocinaplon and other selected compounds (from Prous Science Integrity®).*

	$GABA_A$ BZ-site receptor affinity[a]		
Compound	IC_{50} (nM)	K_i (nM)	Ref.
AC-5216	>1000[b]	–	13
Alprazolam	–	10.4-11.2[b]	14
Diazepam	4.90-28.0	4.90-18.8	15-22
Flunitrazepam	1.40-2.10	–	23
Flurazepam	–	14.0-17.0	18
Lorazepam	–	0.10-0.13	18
Ocinaplon	2000	–	8
Pagoclone	1.60	0.41-0.98	21, 24
RWJ-51204	–	0.18-0.37[b]	14
SL-65.1498	–	6.80-117[b]	25

[a]Receptor affinities evaluated in rat brain tissues by the displacement of [^{3}H]-flunitrazepam except where otherwise indicated. [b]Displacement of [^{3}H]-flumazenil.

Table II: In vivo *anxiolytic-like effects of ocinaplon and other selected GABA BZ-site receptor modulators (from Prous Science Integrity®).*

	Anxiolytic-like activity[a] MED (mg/kg p.o.)	
Compound	Vogel conflict test	EPM test
AC-5216	0.30 (26)	–
Alprazolam	2.00-8.10[b,c] (27, 28)	1.00[c] (27)
Chlordiazepoxide	–	3.00 (14)
Clorazepate Dipotassium	10.0 (25)	10.0 (25)
Diazepam	5.0-10.0 (16, 21, 25, 26, 29)	3.00-20.0 (14, 21, 25, 31)
Flunitrazepam	–	–
Flurazepam	–	–
Lorazepam	3.00 (30)	0.30-1.00 (14, 25)
Ocinaplon	3.10 (7)	–
Pagoclone	0.10-0.33 (21, 30)	0.63 (21)
RWJ-51204	0.10 (14)	0.10 (14)
SL-65.1498	10.0 (25)	3.00 (25)

[a]Anxiolytic activity evaluated in the Vogel conflict test or in the elevated plus-maze test in rats after oral administration, except where otherwise indicated. [b]Evaluated in the Geller-Seifter conflict test. [c]Intraperitoneal drug administration. References in parentheses.

However, discrimination was difficult to establish and maintain, giving ocinaplon the classification of a weak discriminative stimulus. The authors concluded that the weak discriminative stimulus effect is the result of a reduced affinity for ocinaplon binding at the BZ ω receptor site. While ocinaplon binds poorly to the benzodiazepine receptor, the discrimination stimulus effect of ocinaplon is terminated following addition of the benzodiazepine receptor antagonist flumazenil (Ro 15-1788), further supporting the benzodiazepine-like action of ocinaplon (8). Overall, these studies have shown that while ocinaplon has many actions that are likened to benzodiazepine administration, it also remains distinct in that it is a weak discriminative stimulus and lacks the high receptor potency indicative of benzodiazepine anxiolytics. Pharmacological data point to the selective interaction of ocinaplon at the $GABA_A$ ω receptor subtype.

Early studies with ocinaplon demonstrated that the drug produces its anxiolytic effects at doses much lower than those that induce sedation. The anxiolytic potential of ocinaplon was measured in its ability to increase punished responding in both rats and monkeys. Punished responding testing is a common method for testing a drug's anxiolytic properties and has been shown to be related to clinical activity in humans. Punished responding rates were shown to be increased by both ocinaplon and benzodiazepine administration. Increases in punished responding rates were dose-dependent, and the oral minimal effective dose (MED) was determined to be 3.1 mg/kg and 4.0 mg/kg in rats and primates, respectively (6, 7), doses 20-55 times lower than those producing sedation and muscle incoordination (differences in dose depend on the model used to test anxiolytic action). These results were compared with benzodiazepine administration, where the effective dose approximates the dose needed to produce unwanted side effects. It is thought that this ability to produce the wanted effects of the drug without the concomitant sedation and muscle incoordination is due to ocinaplon's low binding affinity for the GABA-A receptor. Ocinaplon was also shown to be 15 times less likely to potentiate the effects of alcohol when compared with the commonly administered benzodiazepine, diazepam (6).

Ocinaplon's anxiolytic-like effects were also demonstrated in pigeons in a punished responding conflict procedure. Results showed that oral doses of ocinaplon 10 mg/kg and 30 mg/kg were both effective in increasing levels of punished responding and did not affect unpunished responding in this paradigm. Benzodiazepine receptor antagonist administration was associated with a reversal of this effect in punished pigeons, with the increased response rate being attenuated following addition of flumazenil (8). These results confirmed previous reports of ocinaplon's ability to increase punished responding in rats and nonhuman primates (6, 9).

Ocinaplon was also shown to antagonize the discriminative stimulus effects produced by administration of the convulsant drug pentylenetetrazole in a dose-dependent fashion. Antagonism of this discriminative effect is said to be predictive of an anxiolytic effect in humans; however, claims to this nature have been questioned by some investigators (9). Likewise, ocinaplon has been shown to reduce pentylenetetrazole- and bicuculline-induced convulsions in rats. These anticonvulsant effects are similar to those observed following benzodiazepine administration (6).

Furthermore, ocinaplon has been shown to cause significantly less motor incoordination than diazepam (demonstrated via horizontal ambulation and rod-walking ability in rats). Ocinaplon administration is also associated with a decreased potentiation of the effects of alcohol (shown by loss of righting and amnesic liability measures in rats) (6). The reduction of these preclinical adverse events indicates the reduced potential for adverse events to occur in human trials.

Overall, the results of these preclinical studies showed that ocinaplon is an effective anxiolytic agent in animal models of anxiety, but is not associated with the side effects commonly experienced by benzodiazepine-treated animals.

Pharmacokinetics

The pharmacokinetic profile of ocinaplon was determined in a number of animal studies. Oral administration of single-dose radioactive [^{14}C]-ocinaplon 90 mg in healthy male volunteers showed ocinaplon to be rapidly absorbed (t_{max} = 1.1 h), and eliminated ($t_{1/2}$ = 0.8 h). Ocinaplon was extensively metabolized, with up to 12 potential metabolites observed in the urine; 42% of the radioactive ocinaplon dose was excreted in urine within the first 6 h, with less than 1% being excreted as ocinaplon. The AUC of ocinaplon represented 5.4% of total radioactivity (10).

The pharmacokinetic profile of ocinaplon was further tested in fasted and nonfasted healthy male volunteers following single-dose oral administration of ocinaplon 60 mg. Investigators employed a 2-way crossover design to test the pharmacokinetics of ocinaplon before and after a high-fat breakfast. C_{max} and AUC values were shown to be significantly decreased in the presence of food, and the tmax was significantly longer following a high-fat breakfast although the presence of food did not significantly alter $t_{1/2}$ (11).

Clinical Studies

Over 140 healthy volunteers participated in a total of 7 double-blind, placebo-controlled phase I studies following oral administration of ocinaplon. Toxicity data from these studies showed that ocinaplon was well tolerated at the doses studied. There was no evidence of sedative or muscular side effects in this population.

Investigators then studied the efficacy and tolerability of immediate-release ocinaplon in a phase II randomized, double-blind, placebo-controlled trial. A total of 60

patients with a diagnosis of generalized anxiety disorder (GAD) were assigned to receive ocinaplon 90 mg/kg t.i.d. (n=31) or placebo (n=29) for 4 weeks. Hamilton Anxiety Scale (HAM-A) scores were adopted as the primary outcome measure in this study, while patient self-rating and Clinical Global Impression Scale scores were used as secondary measures of anxiolytic function. Results showed that immediate-release ocinaplon is a safe and highly effective anxiolytic in patients with GAD. A significant decrease in a number of anxiety measures was shown over the 4-week period (reductions in HAM-A scores of 6.3 and 14.2 in placebo and ocinaplon recipients, respectively). There was a significant between-group difference in these scores. Significant reductions in patient- and clinician-assessed anxiety levels were also established following ocinaplon administration. Some reductions were noted after only 1 week of therapy (a much shorter period than reported results for benzodiazepine treatments). Ocinaplon was therefore shown to have a more rapid onset of action when compared to traditional anxiolytic agents. Ocinaplon was shown to produce these effects without producing sedation or muscle relaxation, moving investigators to classify ocinaplon as an effective anxioselective agent (7).

A second phase II study was designed to calculate the efficacy of controlled-release ocinaplon in 117 male and female GAD patients (12). The controlled-release formulation was tested in order to confirm results from the first phase II study, as well as to test the effectiveness of the new, slow release preparation that potentially allowed for improved bioavailability and a more favorable dosing schedule. Patients received ocinaplon 120 mg b.i.d. or 60 mg t.i.d. for 14 days. HAM-A scores were the primary outcome measure, although Patient Rating Scale (PRS) and Clinical Global Impression Scale (CGI) scores were once again used as secondary outcomes. Mean baseline HAM-A score was 32 in these patients, indicating a high level of anxiety prior to study onset. Ocinaplon was shown to induce a statistically significant decrease in HAM-A scores following 14 days of administration when compared with placebo. PRS and CGI scores were also significantly decreased in both treatment groups. The ocinaplon 120 mg b.i.d. dosing regimen was more effective than the 60 mg t.i.d. schedule, producing reductions of 15.6 and 14.3 points from baseline in HAM-A scores, respectively. Placebo recipients showed a 9.5 point decrease in HAM-A scores (nonsignificant). The efficacy of ocinaplon was said to be at least comparable to that exhibited following benzodiazepine administration (12).

Ocinaplon was well tolerated by patients in this study, with adverse events rates of 7.7%, 7.7% and 10.3% reported by placebo, ocinaplon 120 mg and ocinaplon 60 mg recipients. There were no serious adverse events reported by any patients across all treatment groups. Of particular note was the fact that sedation and muscular incoordination rates were comparable between treatment and placebo groups. Ocinaplon was also associated with a reduced tendency for physical dependence, a feature normally characteristic of benzodiazepine administration. In addition, patients receiving ocinaplon did not experience rebound anxiety following treatment cessation. Overall, ocinaplon exhibited a more favorable tolerability profile when compared with traditional anxiolytic agents and comparable to that reported by placebo recipients.

Source

Discovered by Wyeth (US); licensed to Elan Corporation, plc (IE); developed in a joint venture with DOV Pharmaceutical, Inc. (US).

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