Drugs of the Future 2001, 26(7): 651-657

CCC: 0377-8282/2001

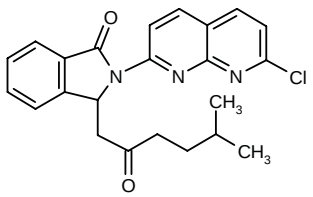
Pagoclone

Prop INN; USAN

Anxiolytic
GABA-A/BZD Site Partial Agonist

IP-456
RP-62955

(+)-2-(7-Chloro-1,8-naphthyridin-2-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one



$C_{23}H_{22}ClN_3O_2$ Mol wt: 407.9040

CAS: 133737-32-3
CAS: 150391-34-7 (as monohydrochloride)

EN: 162990

Synthesis

Pagoclone has been obtained by several related ways:

1) Condensation of 7-hydroxy-1,8-naphthyridin-2-amine (I) with phthalic anhydride (II) in refluxing acetic acid gives *N*-(7-hydroxy-1,8-naphthyridin-2-yl)phthalimide (III), which is treated with refluxing $POCl_3$ to yield the 7-chloro derivative (IV). Reduction of compound (IV) with KBH_4 in dioxane affords 2-(7-chloro-1,8-naphthyridin-2-yl)-3-hydroxyisoindolin-1-one (V) (1, 2), which is condensed with 5-methyl-2-hexanone (VI) by means of NaH in DMF to give (±)-2-(7-chloro-1,8-naphthyridin-2-yl)-3-(5-methyl-2-oxohexyl)isoindolin-1-one (VII) (racemic pagoclone) (3).The treatment of (VII) with NaOH in dioxane/water yields the racemic benzoic acid (VIII) (4-6). Optical resolution of racemic (VIII) by means of (+)-ephedrine (4, 5) or cinchonine (6, 7) affords the (+)-isomer (IX), which is finally cyclized to the chiral (+)-indolinone derivative pagoclone by means of $SOCl_2$ and imidazole in dichloromethane (4-7). Scheme 1.

2) The isoindolinone (VII) (racemic pagoclone) can also be obtained by reaction of isoindolinone (V) with $SOCl_2$ in DMF to provide 3-chloro-2-(7-chloro-1,8-naphthyridin-2-yl)isoindolin-1-one (X), which is condensed with 3-oxo-6-methylheptanoic acid ethyl ester (XI) by means of NaH in DMF to yield 2-[2-(7-chloro-1,8-naphthyridin-2-yl)-3-oxoisoindolin-1-yl]-6-methyl-3-oxoheptanoic acid ethyl ester (XII). Finally, this compound is decarboxylated to the indolinone (VII) by means of LiCl in refluxing DMSO/water (3) Scheme 2.

3) The racemic benzoic acid (VIII) can also be obtained by hydrolysis of the heptanoic ester (XII) with concentrated sulfuric acid to give the corresponding free acid (XIII), which is finally decarboxylated and hydrolyzed by means of NaOH in water (6, 7). Scheme 2.

4) The optical resolution of racemic pagoclone (VII) can also be performed by reaction with (–)-(1*R*,2*R*,3*S*,5*R*)-pinanediol (XIV) by means of PPTS in refluxing dichloroethane to give the ketal (XV) as a diastereomeric mixture separated by crystallization. Finally, hydrolysis of the desired diastereomer (XVI) with 12N HCl affords the (+)-enantiomer, pagoclone (8). Scheme 3.

Introduction

Anxiety disorders are common worldwide and the U.S. Surgeon General has reported a 1-year prevalence of more than 16% in adults (18-54 years) (9). Anxiety is the pathological counterpart of fear and is manifested in mood, thinking, behavior and physiological activity. Symptoms can mimic other clinical conditions such as myocardial infarction, cardiac arrhythmia, hyperthyroidism and/or epilepsy. The numerous existing types of anxiety disorders are characterized by their different symptoms. They include generalized anxiety disorder (GAD), panic disorder, obsessive-compulsive disorder, acute stress disorder, posttraumatic stress disorder, social phobia and specific phobias. GAD is characterized by anxiety or worry that cannot be attributed to any factor. It is accompanied by multiple symptoms and lasts for more than 6 months. GAD has a 1-year prevalence of approximately 3%, a lifetime prevalence of 4.1-6.6% and almost 50% of all cases manifest in childhood or adolescence. Panic disorder presents as discrete episodes of

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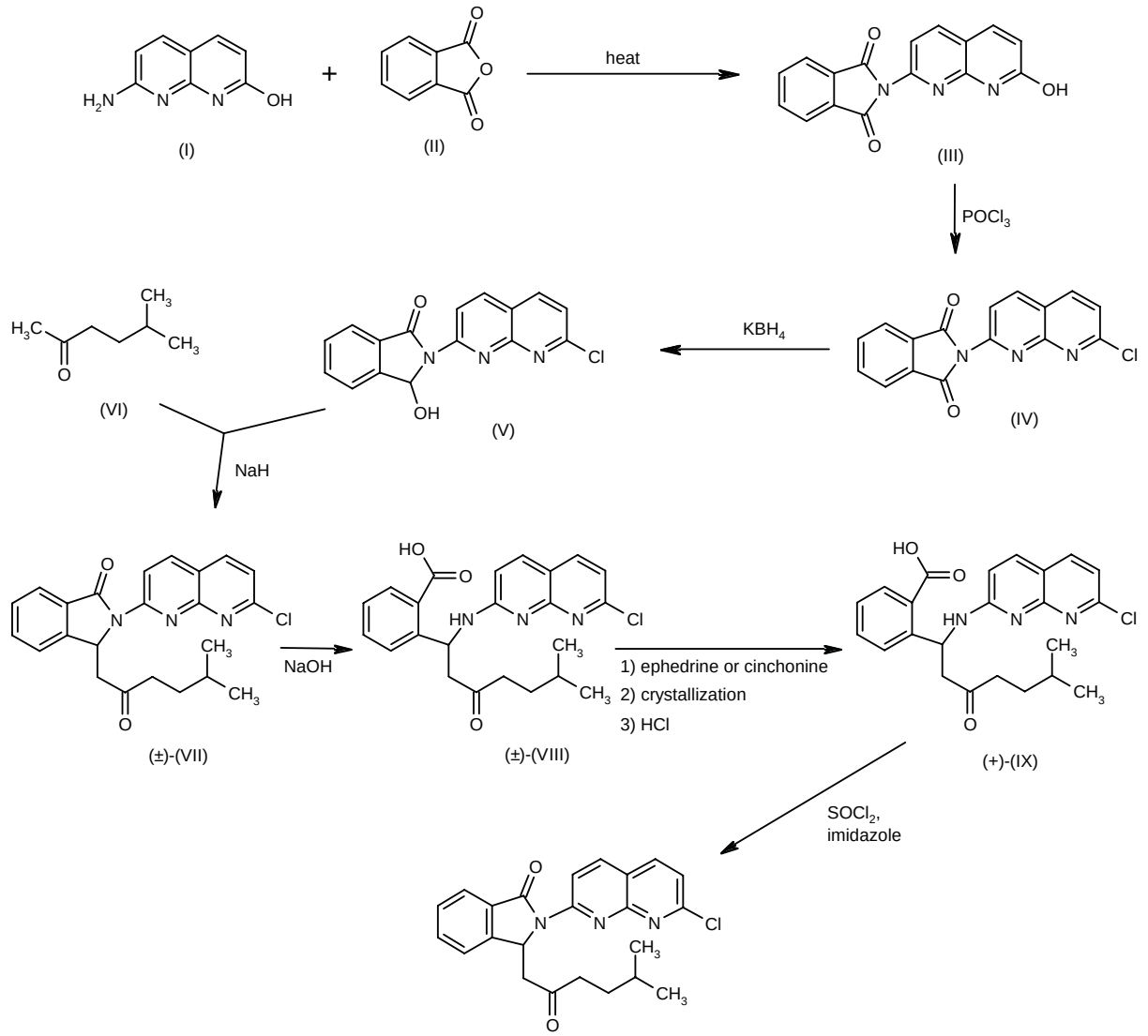
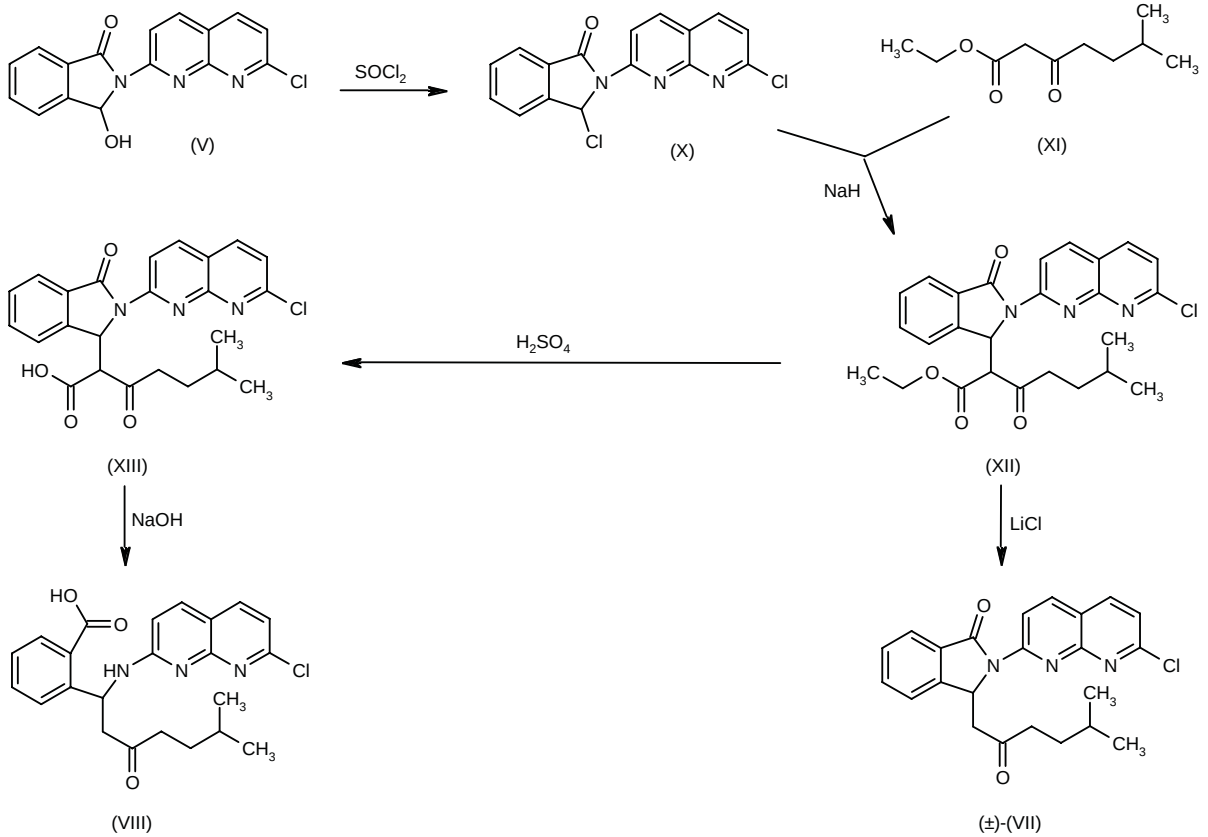
Scheme 1: Synthesis of Pagoclone

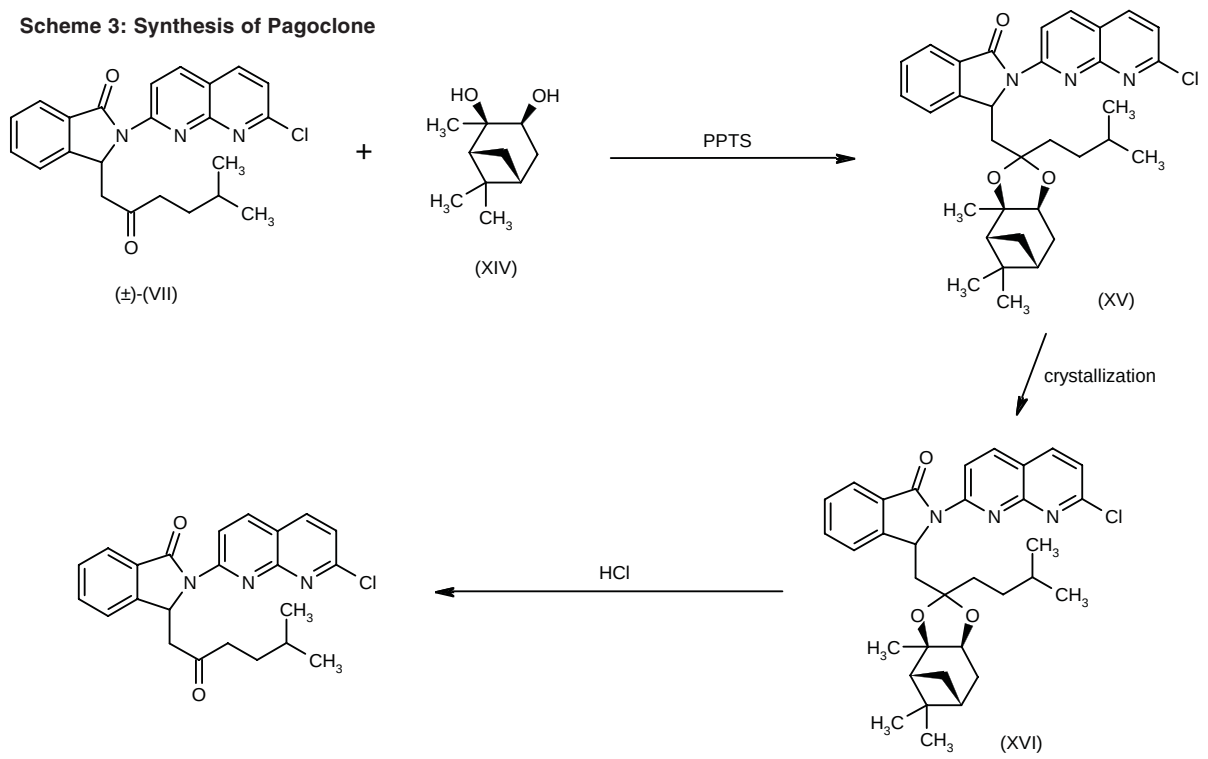


intense fear and is associated with multiple somatic and cognitive symptoms. The 1-year and lifetime prevalences for this disorder are 2 and 2-4%, respectively. Agoraphobia which has a 1-year prevalence of 5%, presents as a severe and pervasive fear of being unable to escape from certain situations (*e.g.*, airplanes), of being alone outside of one's home and/or of being in crowded places. Obsessive-compulsive disorder is recurrent and presents as repetitive, intrusive images or impulses leading to anxiety or distress (*i.e.*, obsessions) and/or repetitive and ritualistic behaviors or mental acts performed to relieve such anxiety (*i.e.*, compulsions). Obsessive-compulsive disorder usually begins in adolescence or young adulthood and has a 1-year prevalence of 2.4%. Acute stress disorder presents as anxiety and behavioral disturbances usually following a traumatic event. It is characterized by dissociation, flashbacks, hyperarousal and generalized anxiety. Posttraumatic stress disorder is similar to acute stress disorder only it is prolonged (more than 1 month) or of a delayed onset (symptoms present at least 6 months following the traumatic event); acute (1-3 months) and chronic (more than 3 months) subtypes exist. The 1-year prevalence of both acute stress and posttraumatic stress disorders is about 3.6%. Social phobias or social anxiety disorder is characterized by persistent and intense anxiety in social situations which is due to a fear of embarrassment or ridicule. It has a 1-year and lifetime prevalence of 7.9 and 13.3%, respectively. Specific phobias are characterized as a fear of a specific object(s) (*e.g.*, snakes, spiders) or situation(s) (*e.g.*,

Scheme 2: Synthesis of Intermediates (VII) and (VIII)



Scheme 3: Synthesis of Pagoclone



storms, heights) and they have a 1-year prevalence of 8% (9).

Treatment of anxiety disorders usually consists of psychotherapy and/or drug therapy which typically includes benzodiazepines or antidepressants. Benzodiazepines are a large class of compounds that are fast-acting and relatively safe. They bind to benzodiazepine binding sites on the GABA-A receptor complex and exert agonistic actions. GABA-A receptors are distributed thoughout the CNS including the amygdala which is thought to play a significant role in the etiology of anxiety. Benzodiazepines are classified as short-, intermediate- or long-acting and have a broad spectrum of anxiolytic activity. However, these agents have become less popular because they can produce dependency, tolerance or withdrawal symptoms. Moreover, they are associated with adverse events such as sedation, psychomotor retardation, memory impairment, depression, emotional blunting and rebound anxiety (9). The result has been a major effort to find agents that may act via a different mechanism at the GABA-A/benzodiazepine receptor level that also show improved efficacy and safety profiles as compared to classic benzodiazepines. Those agents under development which act at the GABA/benzodiazepine receptor are shown in Table I (9).

The first nonbenzodiazepine compounds found were the cyclopyrrolones. Examples such as zopiclone and suriclone have been shown to have anxiolytic efficacy including sedation and anticonvulsant activity (10, 11). Recently, other compounds have been identified that possess a restricted efficacy as compared to benzodiazepines in that they cause little or no sedation or muscle relaxation at doses required to induce anxiolytic and anticonvulsant activity and they have a low potential to cause tolerance, withdrawal and physical dependence. Pagoclone, is one such novel member of the cyclopyrrolone family that appears to be a partial agonist at the GABA-A/benzodiazepam binding site. It has shown favorable anxiolytic efficacy and a good side effect profile and has been chosen for further development.

Pharmacological Actions

In vitro studies examining pagoclone binding to the benzodiazepine binding site on the GABA-A receptor in rat cerebrocortical membrane reported a K_i value of 0.98 nM. No difference was observed in the agent's ability to bind to the putative BZ_1 and the BZ_2 binding subtypes in rat cerebellum and hippocampus, respectively (12). Pago-clone appears to be a partial agonist since it displaced [^{3}H]-flunitrazepam binding to rat cortical membranes with an IC50 of 1.6 ± 0.2 nM, had no effect on [^{3}H]-muscimol binding to the GABA recognition site of the GABA/benzodiazepine receptor and enhanced [^{35}S]-TBPS binding to the picrotoxin site by 37% (13).

Further *in vitro* studies using rat cerebral cortex wild-type and natural mutant diazepam-insensitive receptors showed high affinity binding of pagoclone to the wild-type diazepam-sensitive sites (K_i = 0.3 nM) and markedly low affinity for the diazepam-insensitive sites (K_i = 3000 nM) (14).

The anxiolytic efficacy of pagoclone was also demonstrated in several behavioral models. Mice treated with the agent were protected from pentylenetetrazole-induced seizures with an ID_{50} value of 0.21 mg/kg p.o. obtained. The agent was concluded to have restricted anticonvulsant activity as compared to diazepam and activity resembling the partial agonist CGS-9896. Pagoclone did not protect against convulsions induced by agents acting on the chloride channel (picrotoxin) or glycine receptor (strychnine) or which involved several pathways (maximal electroshock), but was effective against isoniazid (ED_{50} = 0.26 mg/kg p.o.)-, bicuculline (ED_{50} = 0.087 mg/kg p.o.)- and 3-mercaptopropionic acid (ED_{50} = 2.6 mg/kg p.o.)-induced convulsions in mice. Pagoclone was also effective in a modified Geller-Seifter conflict paradigm model, the elevated plus maze test (minimal effective dose [MED] = 0.33 mg/kg p.o. for both models) and the Vogel water lick conflict test (MED = 0.1 mg/kg p.o.) in rats. Pagoclone was 6 times more effective than diazepam in antagonizing discriminative stimulus effects of pentylenetetrazole (ED_{50} = 0.28 *vs.* 1.77 mg/kg p.o.). Moreover, pagoclone displayed very little activity (ED_{50} = > 50 mg/kg p.o.) in tests of sedative (barbiturate- or alcohol-induced sedation tests in mice and electrocorticographic studies in rats) or myorelaxant (inclined screen test in rats and grasping test in mice) effects and showed little capacity to induced physical dependence (12, 13, 15, 16).

In other behavioral studies in rodents, pagoclone exhibited MED values of 0.63 and 1.0 mg/kg p.o.in the elevated plus-maze and conflict tests in rats, respectively. In tests evaluating inhibition of PTZ-induced seizures in rats, induction of ataxia in mice and interaction with ethanol in mice, pagoclone demonstrated ED_{50} values of 0.66, 93 and >800 mg/kg p.o., respectively (17).

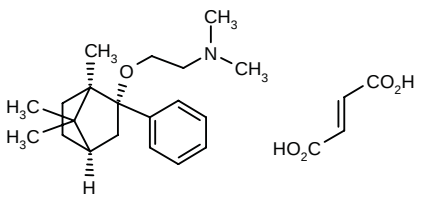
A study comparing the effects of the full agonist suriclone (3, 10 and 30 mg/kg i.p.) and pagoclone (3, 10 and 30 mg/kg i.p.) on body temperature in mice provided more evidence that pagoclone is a partial agonist at the benzodiazepine binding site. Suriclone produced significant, dose-dependent hypothermia (3-4 °C with doses of 10 and 30 mg/kg), an effect blocked by flumazenil (10 mg/kg). The low dose of pagoclone (3 mg/kg) had no effect on body temperature although 10 and 30 mg/kg significantly decreased body temperatures a maximum of 1-1.5 °C. Results showed that the effects of suriclone on body temperature were similar to other benzodiazepine full agonists while pagoclone was much less effective, with only the higher doses producing a reduction in temperature that was only a third of that seen with the full agonist (18).

Clinical Studies

A single-blind study using [^{11}C]-flumazenil positron emission tomography (PET) conducted in 6 healthy male

Table I: Drugs acting on benzodiazepine and other GABA receptors in development for anxiety (Prous Drug R&D Backgrounders database).

Drug Name	Company	Mechanism of Action	Status
1. Deramciclane fumarate	Egis/Orion/Pharmacia	GABA reuptake inhibitor and 5-HT_2 antagonist	Phase III
2. Pagoclone	Aventis/Interneuron/Pfizer	GABA-A/BZD site partial agonist	Phase III
3. Gidazepam	Russan Acad. Med. Sci.	GABA/BZD site agonist	Phase II
4. NGD-91-3*	Neurogen/Pfizer	GABA receptor partial agonist	Phase II
5. NS-2710 (ME-3127)	NeuroSearch/Meiji Seika/Ferrer	GABA-A/BZD site agonist	Phase II
6. Ro-46-2153*	Roche	GABA-A/BZD site partial agonist	Phase I
7. AC-5216	Dainippon	GABA-A/BZD site agonist	Preclinical
8. Co-2-6749 (GMA-839)	CoCensys/Wyeth-Ayerst	GABA-A receptor modulator	Preclinical
9. D14	Univ. degli Studi di Firenze	GABA-A/BZD site ligand	Preclinical
10. DAA-1097	Nihon Nohyaku/Taisho	GABA-A/BZD site agonist	Preclinical
11. L-838417	Merck & Co.	GABA-A/BZD subtype-specific agonist/antagonist	Preclinical
12. SX-4699	Dainippon	BZD receptor ligand	Preclinical



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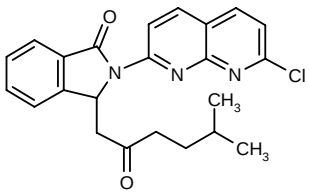

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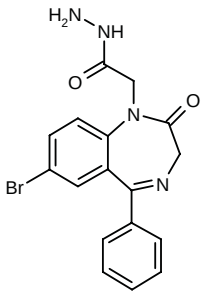

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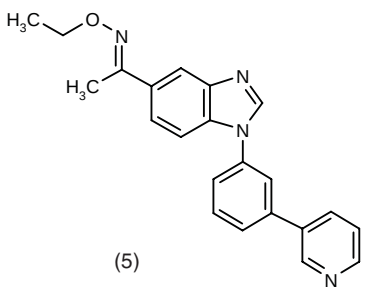

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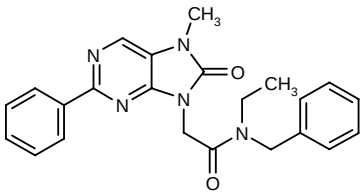

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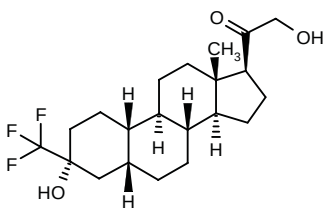

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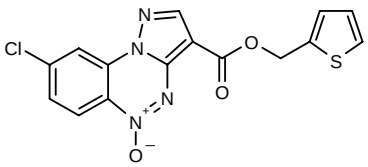

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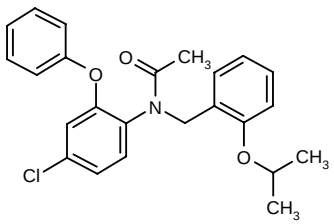

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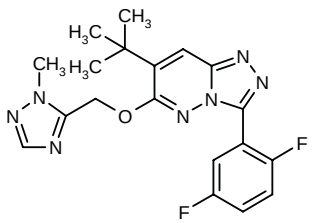

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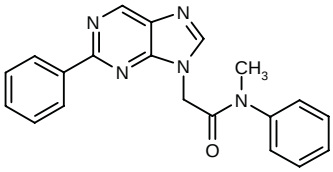

(12)

*Structure not yet detected.

Box 1: Receptor occupancy of pagoclone compared to lorazepam (19) [Prous Science Integrity].

Design	Randomized, single-blind, comparative clinical study
Population	Healthy volunteers (n = 6)
Treatments	Pagoclone, 0.4 mg p.o. Lorazepam, 1 mg p.o.
Results	GABA-benzodiazepine receptor occupancy in frontal cortex, change: P (14.7) > L (5.6) No statistically significant differences in impairment of saccadic eye movements between the two treatments
Conclusions	Pagoclone resulted in a greater level of GABA-benzodizepine receptor occupancy than lorazepam, but no differences in saccadic eye movements were observed

Box 2: Sleep effects of pagoclone compared to zopiclone (20) [Prous Science Integrity database].

Design	Randomized, double-blind, comparative, placebo-controlled, multicenter, crossover clinical study
Population	Healthy volunteers (n = 6)
Treatments	Pagoclone, 100 μg p.o. s.d. Zopiclone, 7.5 mg p.o. s.d. Placebo
Results	Both pagoclone and zopiclone reduced sleep onset latency and increased perceived sleep quality Zopiclone increased stage 2 sleep and decreased awakenings
Conclusions	Pagoclone 100 mg showed slight sleep-promoting efects but did not produce the typical hypnotic effects observed after zoplicone

subjects, provided *in vivo* evidence that pagoclone is a partial agonist at the GABA/benzodiazepine receptor. Subjects were orally administered either pagoclone (03.4 mg) or the full agonist, lorazepam (1 mg), 90 min prior to injection of [^{11}C]-flumazenil (370 MBq). Those subjects given pagoclone showed higher GABA/benzodiazepine receptor occupancy in the frontal cortex as compared to lorazepam-treated subjects (14.7 ± 5.7 *vs.* 5.6 ± 5.2); similar results were obtained in the thalamus and cerebellum. In lorazepam-treated subjects, increasing occupancy was associated with increasing plasma lorazepam concentrations, a relationship not observed with pagoclone. No significant differences were observed between treatment groups and impairment of saccadic eye movements in 4 of 6 subjects. However, 1 lorazepam-treated subject displayed a higher level of impairment while the remaining pagoclone-treated subject showed only a low level of impairment. Thus, the higher receptor occupancy seen with pagoclone was not associated with a greater impairment of saccadic eye movements, which is consistent with the hypothesis that pagoclone is a partial agonist at the GABA/benzodiazepine receptor (19) (Box 1).

Results from a double-blind, placebo-controlled, crossover study revealed that pagoclone (100 μg p.o.) had no significant effects on sleep architecture but significantly decreased sleep onset latency and increased perceived quality of sleep. Sleep parameters were assessed using home sleep recordings (Medilog ambulatory system) and the St. Mary's Hospital and Leeds sleep questionnaires given the morning after. In contrast, zopiclone (7.5 mg p.o.) improved most subjective measures and increased sleep efficiency, stage 2 sleep and REM latency and reduced wakenings and sleep onset latency when the same subjects were examined 11 months before. Although pagoclone produced slight sleep promoting effects, it did not exhibit those changes observed with typical hypnotics such as zopiclone (20) (Box 2).

The efficacy and safety of pagoclone (0.15, 0.3 or 0.6 mg/day) were demonstrated in a multicenter, randomized, placebo-controlled study conducted in 227 outpatients with DSM-IV panic disorder with or without agoraphobia. A greater reduction in the mean number of panic attacks was observed after 8 weeks of treatment with pagoclone as compared to placebo with significant differences observed at the 0.3 mg/day dose (mean decrease from baseline of 3.9 *vs.* 2.3 attacks). A significant reduction in HAM-A total scores was observed after 8-weeks of treatment with the 0.15 and 0.30 mg/day pagoclone doses in those patients with high baseline levels of anxiety (HAM-A scores of at least 18). No significant differences in incidence of adverse events, laboratory parameters, ECG or vital signs were observed between pagoclone and placebo groups. In addition, no differences were observed between placebo- and pagoclone-treated patients on the Stanford Sleepiness Scale or on the Rickels Withdrawal checklist indicating no clinically significant daytime sedative effects or withdrawal symptoms for the agent (21) (Box 3).

Box 3: Efficacy and safety of pagoclone in the treatment of panic disorder with or without agarophobia (21) [Prous Science Integrity database].

Design	Randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Patients with panic disorder with or without agoraphobia (n = 277)
Treatments	Pagoclone, 0.15 mg/d p.o. x 8 wks Pagoclone, 0.3 mg/d p.o. x 8 wks Pagoclone, 0.6 mg/d p.o. x 8 wks Placebo
Results	No panic attacks, change @ 8 wks: P0.3 (–3.9) > Pl (2.3) [$p = 0.02$] Hamilton Rating Scale for Anxiety score reduction rate @ 8 wks in patients wirh baseline HAM-A score ≥ 18: P0.15 ~ P0.3 > Pl [$p = 0.04$]
Conclusions	Pagoclone reduced panic attacks and appeared to reduce symptoms of generalized anxiety

The efficacy and safety of pagoclone are currently being investigated in a phase III clinical trial in patients with panic disorder and a phase II trial in patients with GAD (22).

Manufacturer

Discovered by Aventis Pharma SA (FR); licensed to Interneuron Pharmaceuticals, Inc. (US), who licensed the product to Pfizer, Inc. (US).

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