Drugs of the Future 1999, 24(2): 133-140

CCC: 0377-8282/99

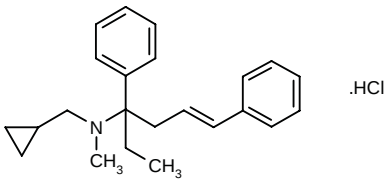
Igmesine Hydrochloride

Rec INNM

Antidepressant
Antidiarrheal
σ-Receptor Ligand

CI-1019
JO-1784

(+)-*N*-(Cyclopropylmethyl)-*N*-[1-ethyl-1,4-diphenyl-3(*E*)-butenyl]-*N*-methylamine hydrochloride



$C_{23}H_{29}N.ClH$ Mol wt: 355.95

CAS: 130152-35-1
CAS: 140850-73-3 (as free base)

EN: 185001

Synthesis

1) Racemic igmesine has been synthesized as follows: Alkylation of 2-phenylbutyric acid (I) with cinnamyl bromide (II) by means of butyl lithium in THF gives 2-ethyl-2,5-diphenyl-4-pentenoic acid (III), which is treated with sodium azide and phenyl dichlorophosphate in dichloromethane, yielding the corresponding azide (IV). The Curtius rearrangement of (IV) in refluxing toluene affords the isocyanate (V), which is reduced with $LiAlH_4/AlCl_3$ in THF to give *N*-(1-ethyl-1,4-diphenyl-3-butenyl)-*N*-metylamine (VI). The acylation of (VI) with cyclopropanecarbonyl chloride (VII) by means of triethylamine in dichloromethane yields the corresponding amide (VIII), which is finally reduced with $LiAlH_4/AlCl_3$ in THF/ethyl ether (1). Scheme 1.

2) Igmesine has been synthesized as follows: Hydrolysis of the already described isocyanate (V) with HCl in refluxing THF/water gives the corresponding amine (IX), which is submitted to optical resolution with L-(–)tartaric acid, yielding the (+)-isomer (+)-(IX). The acylation of (+)-(IX) with formic acid and carbonyldiimidazole (CDI) affords the expected formamide (+)-(X), which is reduced with $AlAl_3/LiAlH_4$ in THF/ethyl ether, giving (–)-*N*-(1-ethyl-1,4-diphenyl-3-butenyl)-*N*-metylamine (–)-(VI). The condensation of (–)-(VI) with cyclopropanecarbonyl chloride (VII) by means of triethylamine in dichloromethane yields the corresponding amide (+)-(VIII), which is finally reduced with $AlCl_3/LiAlH_4$ in THF/ethyl ether (1). Scheme 2.

Description

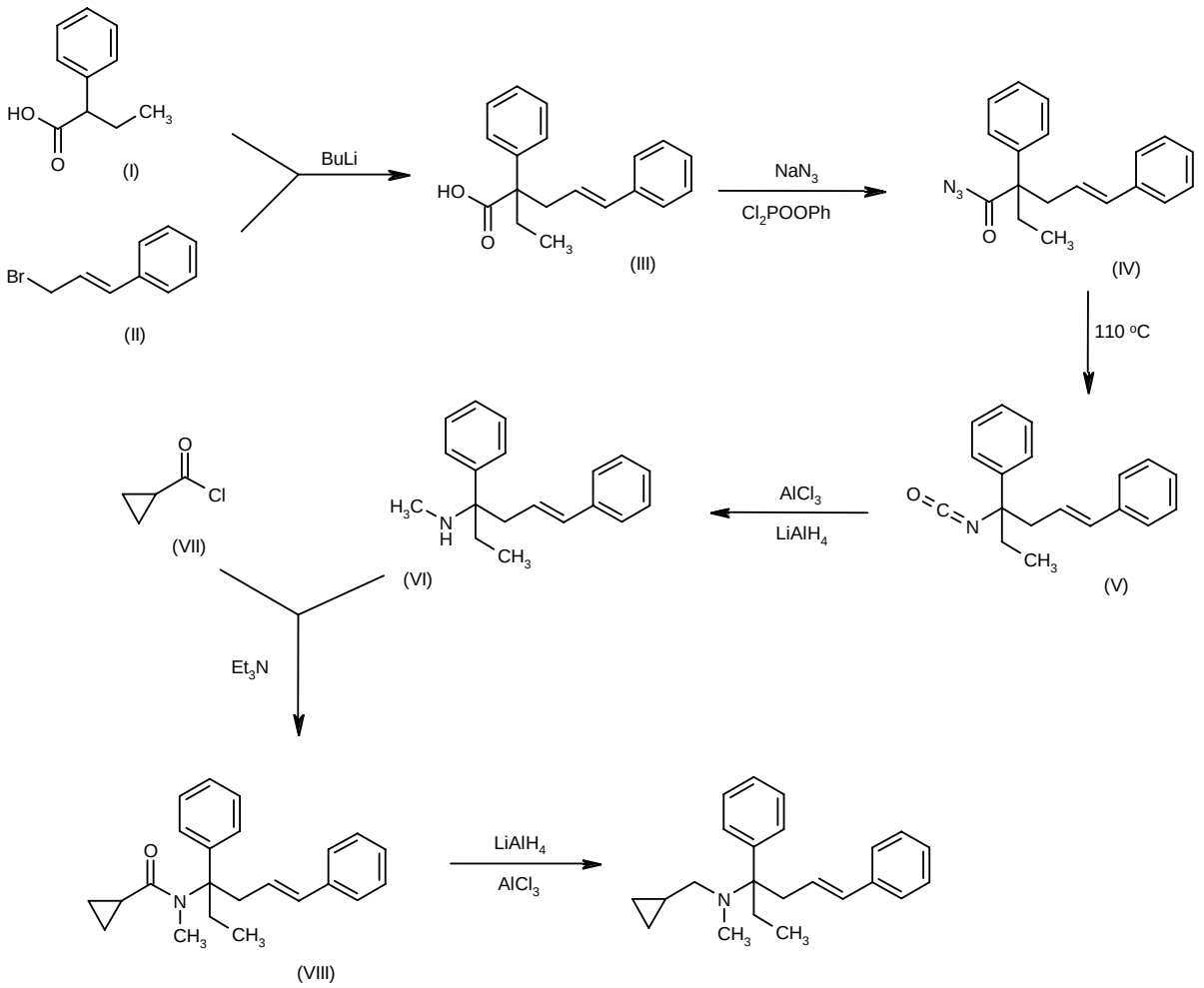
Racemic hemimaleate, m.p. 99-102 °C; (+)-isomer hydrochloride, m.p. 177 °C, $[\alpha]_D^{25}$ +49.7° (c 3, MeOH).

Introduction

The σ receptor was originally suggested to be a subtype of the μ receptor by Martin and coworkers (2) from results showing psychotomimetic effects of a σ ligand compound, SKF-10047, in the chronic spinal dog. However, this classification was discarded after studies demonstrated that the majority of the effects elicited by σ opiates are not abolished by the opiate antagonist naloxone (3, 4). σ Receptors were later considered to be phencyclidine (PCP) receptors due to their similar physiological effects and common binding properties. However, the unique pharmacology, binding profile, distribution and behavioral effects of selective σ compounds led to a separate classification of σ receptors as haloperidol-sensitive, nonopioid, non-PCP, high affinity (+)-SKF-10047 binding sites (5). σ Receptors are now recognized as a class of receptors with their own binding profile and local distribution distinct from the PCP and glutamate binding sites (3, 6-8). Discussion of the pharmacology, biochemistry and functionality of σ receptors continues (8) and has given rise to numerous hypotheses concerning the physiological role of these receptors. Moreover, recent investigation has yielded surprising new data prompting interesting questions about this enigmatic site.

L.A. Sorbera, J. Silvestre, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Racemic Igmesine



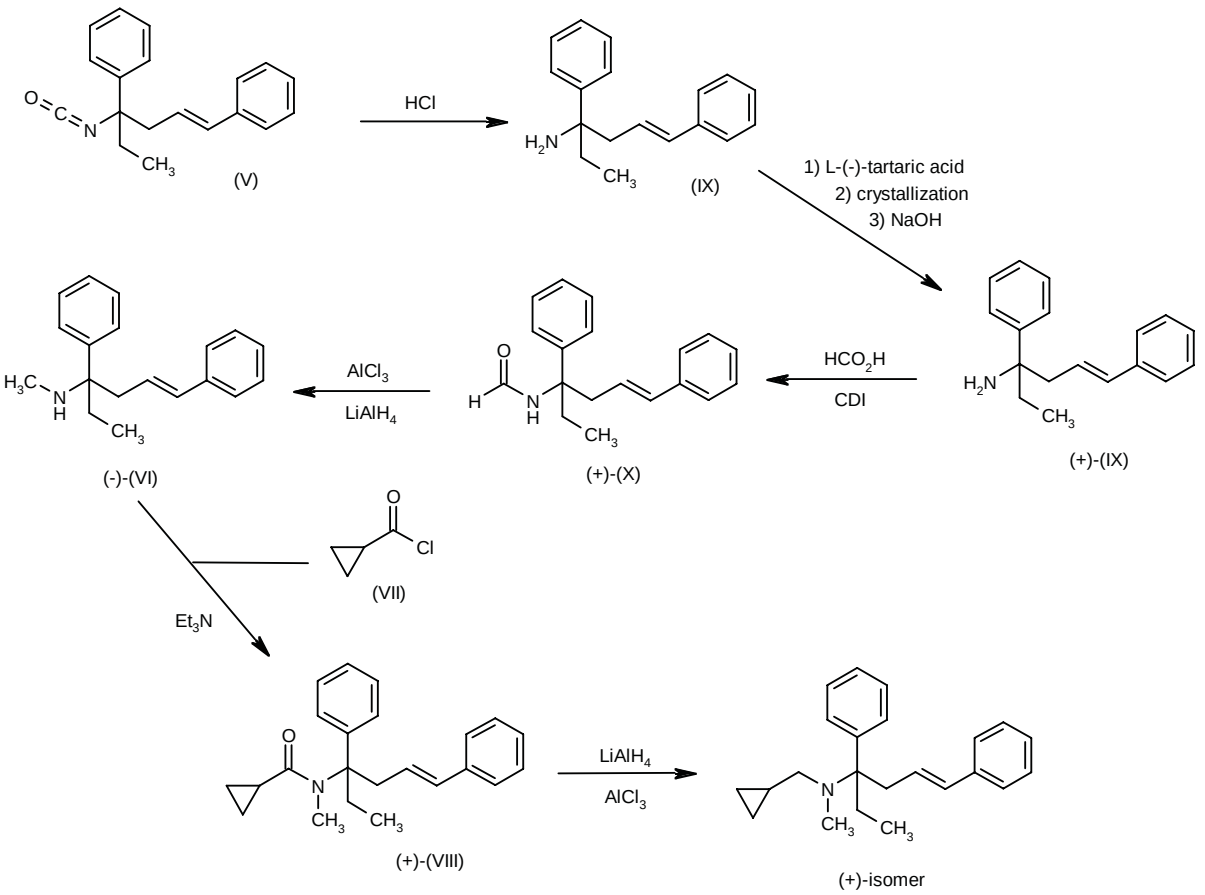
σ Receptors are widely distributed throughout the body, including the liver (9), myenteric plexus (10), gastrointestinal tract (11), spleen (12), peripheral blood leukocytes (13), brain (3, 14, 15) and endocrine tissues (16, 17). However, the cellular and subcellular locations of these binding sites are controversial. Studies suggest that sigma binding sites are preferentially located in the membrane of the endoplasmic reticulum (18, 19). Additional studies describe a presynaptic location in which the receptors are coupled to ion channels (20).

Although σ receptors have been shown to be involved in various CNS and peripheral disorders, the biological role of the σ receptor remains unclear. It has been identified as a P450 isoenzyme, a participant in the inositol triphosphate signaling cascade, a target for intracellular Ca^{2+}-dependent endogenous ligands, and recently, as a type of sterol isomerase (21). The σ receptor has been implicated in immunological responses, motor disorders, psychosis and neuroprotection (8, 18), modulation of endocrine function (22) and brain sterol synthesis (18, 21).

Strictly speaking, the σ binding site cannot yet be classified as a receptor since no endogenous ligands have been identified. Several candidates have been proposed to be endogenous ligands of σ receptors, including progesterone (22, 23), the cerebral peptides neuropeptide Y and peptide YY (24-26) and the Zn^{2+} ion (27). However, controversy over the endogenous ligand continues (5, 28, 29).

Early on, the existence of multiple σ receptor sites was suspected (8) and recent evidence strongly suggests the presence of more than two subtypes of σ receptors (18, 30). At least two subtypes, σ_1 and σ_2, have been identified and pharmacologically characterized (31), with the σ_1 site having a high affinity for (+)-isomers of benzomorphans (*e.g.*, (+)-pentazocine), haloperidol and ditolylguanidine (DTG), and the σ_2 site showing a slight preference for the (–)-isomers of benzomorphans in

Scheme 2: Synthesis of Igmesine



addition to high affinity for haloperidol and DTG. The σ_1 receptor has been recently cloned (32, 33). Although the σ_2 receptor shares many pharmacological, distributional and biochemical properties with σ_1 and other putative mammalian σ receptors, due to the lack of selective, high-affinity radioligands it has not yet been purified (18).

Several σ receptor agonists (*e.g.*, SKF-10047; DTG; pentazocine) and antagonists (*e.g.*, 3-PPP; rimcazole) have been developed (23) which have enabled the further elucidation of the function of sigma receptors. A number of these compounds are under preclinical development (*e.g.*, AZ-21666; L-687384; SA-4503) or are currently undergoing clinical trials for the treatment of disorders, including psychosis, neuronal injury and toxicity, anxiety, depression and intestinal disorders. Thus, LU-28-179, a selective σ_2 ligand, has anxiolytic-like effects and is in phase I clinical trials. Igmesine, a σ_1 ligand, has antidepressant effects and is in phase II clinical trials. Table I shows the affinity of the σ receptor subtypes of selected compounds which preferentially act as ligands for σ binding sites.

Pharmacological Actions

Igmesine has been reported to be a potent and selective ligand for brain and gastrointestinal σ binding sites with no affinity for PCP binding sites (15). Using igmesine, numerous advances have been made to further clarify and reveal central and peripheral effects attributed to σ receptor binding. Studies have revealed central actions of igmesine, including antiamnesic, antidepressant and stress-reducing or antianxiety properties in the rat, potentiation of acetylcholine release and NMDA responses from rat hippocampal slices, neuroprotective effects from focal and global cerebral ischemia and trimethyltin exposure in mice, gerbils and rats, and modulation of centrally mediated immune function (34-43).

Igmesine binding to σ receptors has been shown to result in inhibition of intestinal secretion and diarrhea *in vitro* and *in vivo* in rats (44-48). The majority of antidiarrheal agents in use are opiate derivatives that slow intestinal motility and secretion, with treatment frequently resulting in diarrhea due to impairment of water and

Table I: Affinities of selected σ receptor ligands (data from Prous Science MFLine database).

Compound	Parameter	σ_1[a]	σ_2[b]	σ Receptors	Material	Ref.
Amiodarone	K_i	1.4			Liver, Guinea pig	21
	K_i	2.1			Brain, Guinea pig	21
AZ-21666	K_i	4.3[NS]	0.77[NS]		NS	59
Azidopamil	K_i	42.0			Liver, Guinea pig	32
	K_i	58.0			Brain, Guinea pig	32
DTG	IC_{50}	36.0	52.0		Brain, Rat	60, 61
	K_i	14.0			Liver, Guinea pig	32
	K_i	19.0			Brain, Guinea pig	33
	IC_{50}			253.0[c]	Brain, Rat	15
E-5842	K_i	4.0			Brain, Guinea pig	62
	K_i		220[e]		Brain, Rat	62
Haloperidol	IC_{50}	0.65	17.0		Brain, Rat	60, 61
	K_i	0.2			Liver, Guinea pig	32
	K_i	0.2			Brain, Guinea pig	32
	IC_{50}			5.0[c]	Brain, Rat	6
	IC_{50}			2.0[d]	Brain, Rat	6
Igmesine	K_i	75.0[NS]	>1000[NS]		NS	49
	IC_{50}			39.0[c]	Brain, Rat	15
L-687384	IC_{50}	0.26	12.0		Brain, Rat	60, 61
LU-28-179	IC_{50}	17.0	0.12		Brain, Rat	60, 61
Pentazocine	K_i	1.7			Liver, Guinea pig	32
	K_i	1.5			Brain, Guinea pig	32
	IC_{50}			286[c]	Brain, Rat	6
	IC_{50}			25.0[d]	Brain, Rat	6
(+)-Pentazocine	IC_{50}	3.0	2100		Brain, Rat	60, 61
(–)-Pentazocine	IC_{50}	8.9	29.0		Brain, Rat	60, 61
(+)-3-PPP	K_i	6.0			Liver, Guinea pig	32
	K_i	7.0			Brain, Guinea pig	32
	IC_{50}			49.0[c]	Brain, Rat	6
	IC_{50}			32.0[d]	Brain, Rat	6
Progesterone	K_i	260			Liver, Guinea pig	32
	K_i	338			Brain, Guinea pig	32
Rimcazole	IC_{50}	690	180		Brain, Rat	60, 61
	IC_{50}			2649[c]	Brain, Rat	15
SA-4503	IC_{50}	17.0[NS]	1800[NS]		NS	63
(+)-SKF-10047	K_i	41.0			Liver, Guinea pig	32
	K_i	41.0			Brain, Guinea pig	32
	IC_{50}			75.0[c]	Brain, Rat	6
	IC_{50}			365[d]	Brain, Rat	6
Trifluoperazine	K_i	15.0[g]			Liver, Guinea pig	32
	K_i	21.0[g]			Brain, Guinea pig	32

[a]Data refers to displacement of [^{3}H]-(+)-pentazocine except when specified. [b]Data refers to displacement of [^{3}H]-DTG with "cold" σ_1 ligands except when specified. [c]Displacement of [^{3}H]-(+)-SKF-10047. [d]Displacement of [^{3}H]-(+)-3-PPP. [e]Displacement of [^{3}H]-ifenprodil. NS = not specified.

intestinal electrolyte transit. An agent such as igmesine, which specifically inhibits intestinal hypersecretion, could therefore be a more attractive antidiarrheal candidate. Additional studies have demonstrated differential effects with low and high doses of igmesine on NMDA responses from dorsal hippocampus pyramidal neurons, suggesting the presence of two σ receptor subtypes in the CNS (30). In fact, igmesine was found to be a highly selective ligand for the σ_1 receptor while lacking significant affinity for the σ_2 receptor, with K_i values of 75 nM and > 1000 nM, respectively (49).

Investigations using igmesine to elucidate σ binding site function eventually led to the conclusion that the compound has significant therapeutic potential, and recent work has focused on the development of the agent as an antidepressant and an inhibitor of colonic and intestinal hypersecretion.

Several studies have unsuccessfully attempted to identify the mechanism of action of igmesine. One study showed that direct modulation of the monoaminergic system is not involved. The effects of igmesine were compared to those of fluoxetine, imipramine and

clomipramine using synaptosomes from rat whole brain cortex to examine norepinephrine and serotonin uptake and from rat striata to examine dopamine uptake. Although igmesine was the most potent agent tested at σ_1 sites (K_i = 75 nM), followed by fluoxetine (K_i = 764 nM), imipramine (K_i = 856 nM) and clomipramine (K_i = 940 nM), it only weakly inhibited norepinephrine, serotonin and dopamine neuronal uptake (K_i = 637, 719 and 1168 nM, respectively). The other agents were more potent in inhibiting norepinephrine (K_i = 7, 3 and 156 nM, respectively) and serotonin (K_i = 7, 3 nM and 18 nM, respectively); dopamine was only weakly inhibited by these agents (K_i = 2832-4367 nM) (49).

Similarly, *in vivo* studies in rats have confirmed that igmesine, administered at behaviorally active doses, does not alter norepinephrine, dopamine or serotonin uptake or synthesis in brain stem, hippocampus, striata or cortex. Moreover, igmesine does not affect monoamine synthesis in norepinephrine-enriched brain stem, indicating that the agent does not have α_2-antagonistic activity. No significant affinity of igmesine for monoamine oxidases A or B were observed (50).

Results from *in vivo* studies in which cerebrospinal fluid was collected from the medial prefrontal cortex (MPFC) or striatum of igmesine-treated rats (32 mg/kg i.p.) demonstrated that extracellular norepinephrine and serotonin levels in the MPFC were increased by 63 and 33%, respectively; no effects on striatal or MPFC serotonin levels were observed. These results suggest that igmesine alters extracellular accumulation of norepinephrine and dopamine in the rat brain (51).

In vivo studies in CD-1 mice have also compared the antidepressant properties of igmesine with those of the standard antidepressants, desipramine and sertraline (30 mg/kg i.p.), using the tail-suspension test in which cumulative duration of immobility and average power of movement were measured. Igmesine at doses of 30 and 100 mg/kg i.p. significantly decreased immobility in a manner similar to desipramine and sertraline. Moreover, comparable antidepressant activity, including increased wheel rotations, was observed when normotensive rats were administered 32 and 64 mg/kg i.p. igmesine prior to the behavioral despair swim test of Porsolt. The effects of igmesine were not due to stimulation-like activity, since a significant decrease in locomotor activity was observed in nonacclimated rats and no effect or only a slight increase in activity was observed with the high dose in acclimated rats administered the agent (16, 32 and 64 mg/kg i.p.) (52).

The role for σ receptors in the pathophysiology of depression was further demonstrated using two rat models. When olfactory bulbectomized rats were treated with low doses of igmesine (200 μg/kg/day) for 3 weeks, the decrease in NMDA responses normally evident in this model of depression were not observed; high doses of igmesine were not as effective. Moreover, long-term treatment with the σ agonist igmesine or DTG increased the sensitivity of σ receptors, while long-term treatment with the σ antagonist haloperidol decreased receptor sensitivity. Similarly, during pregnancy a decreased sensitivity of σ receptors was observed, with 10-fold higher doses of DTG required to elicit NMDA responses. This attenuated sensitivity of σ receptors was most probably due to the high circulating levels of the σ antagonist progesterone. In the postpartum period, when progesterone levels fall and there is an increase in incidence of depressive episodes, σ receptors became highly sensitive, with increased responses to DTG observed (53).

Recent studies continue to examine the antidiarrheal properties of igmesine. Igmesine was shown to dose-dependently suppress vasointestinal peptide (0.1 mg/min)-induced jejunal hypersecretion *in vivo* in rats (ED_{50} = 178 mg/kg). Responses to igmesine (1 mg/kg) were abolished by i.v. administration of tetrodotoxin (5 mg/kg), cyclosomatostatin (1 mg/kg) and the σ antagonist BMY-14802 (1 mg/kg) (54). In addition, igmesine (1 mg/kg i.p.) significantly attenuated IL-1β (5 μg/kg i.p.)-induced colonic hypersecretion, while loperamide was ineffective. The somatostatin receptor antagonist anti-SRIF (10 μg/kg i.p.) effectively blocked the effects of igmesine, suggesting that somatostatin release may be involved in igmesine's inhibition of hypersecretion. Furthermore, these results indicate that σ and somatostatin receptors, but not opiate receptors, may be involved in the mechanism of action of igmesine (55).

Clinical Studies

Following a preliminary phase II, open-label study which demonstrated improvement in 31 severely depressed inpatients within 1 week after igmesine treatment, a 6-week, double-blind, placebo-controlled trial was undertaken. This study enrolled 348 inpatients and outpatients with Major Depressive Disorder (DSM-IV) from several countries who were administered igmesine (25 or 100 mg/day), fluoxetine (20 mg/day) or placebo. No significant differences were seen in scores from the 17-item Hamilton Depression Rating Scale (HAM-D) between treatment groups when results from outpatients and inpatients were analyzed together. However, when results of all outpatients from each country receiving igmesine (25 mg) were separated from those of inpatients, a significant 3.35-point greater decrease in HAM-D scores was observed as compared to the placebo group. These results suggest that hospitalization may contribute to the negative results. Few adverse effects, the majority being gastrointestinal in origin, were observed and patients treated with 25 mg igmesine had a slightly lower incidence of side effects (50%) as compared to patients receiving 100 mg igmesine (62%), fluoxetine (66%) or placebo (53%) (56).

A randomized, double-blind, placebo-controlled crossover study investigated the effect of igmesine treatment on basal and prostaglandin E_2 (PGE_2)-induced jejunal secretion in 16 healthy volunteers in which jejunal absorption of water and electrolytes was monitored using a three-lumen, open-segment perfusion method.

Subjects received orally either a 25-mg capsule of igmesine followed by a placebo 24 h later in randomized order or two 100-mg capsules of igmesine or placebo. PGE_2 (5 μM) was infused 90 min after igmesine or placebo administration to stimulate intestinal secretion and blood samples were taken 90-270 min following igmesine treatment. Both basal and PGE_2-induced net secretion of water and electrolytes were significantly inhibited in subjects given 200 mg igmesine, with inhibition maintained for 3 h; no effect was observed in subjects given the 25-mg dose. Plasma concentrations of igmesine at 90 min after administration were 26 ± 3 and 282 ± 74 μg/l for 25 and 200 mg igmesine, respectively. These results suggest that investigation of the efficacy of igmesine treatment in chronic diarrhea is also warranted (57).

Igmesine is in phase II trials for the treatment of depressive disorder (58).

Manufacturer

Jouveinal SA (FR); Warner-Lambert Co. (US).

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