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CCC: 0377-8282/99

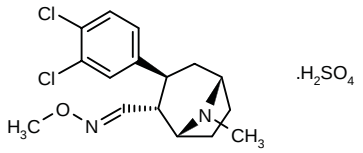
Brasofensine Sulfate

Prop INNM

Antiparkinsonian
Dopamine Reuptake Inhibitor

BMS-204756
NS-2214

(*E*)-(1*R*,2*R*,3*S*,5*S*)-3-(3,4-Dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carbaldehyde *O*-methyloxime sulfate (1:1) salt



$C_{16}H_{20}Cl_2N_2O.H_2O_4S$ Mol wt: 425.3308

CAS: 171655-92-8
CAS: 173830-14-3 [as maleate salt (1:1)]
CAS: 173830-20-1 (as monohydrochloride)
CAS: 173830-18-7 (as disulfate salt)
CAS: 173830-17-6 (as monofumarate salt)
CAS: 173830-15-4 [as citrate (1:1)]
CAS: 171655-91-7 (as free base)

EN: 224675

Synthesis

Synthesis of brasofensine: The hydrolysis of (1*R*,2*R*,3*S*,5*S*)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester (I) with refluxing 1M HCl gives the corresponding hydroxy acid (II), which is dehydrated with refluxing $POCl_3$ and treated with methanol to the unsaturated methyl ester (III). The reaction of (III) with 3,4-dichlorophenylmagnesium bromide in ether yields a mixture of (1*R*,2*S*,3*S*,5*S*)- and (1*R*,2*R*,3*S*,5*S*)-3-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl esters (V) and (VI), respectively. Enantiomer (V) is isomerized to (VI) by treating the mixture with sodium methoxide in refluxing methanol. The reduction of (VI) with $LiAlH_4$ in ethyl ether gives (1*R*,2*R*,3*S*,5*S*)-[3-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octan-2-yl]methanol (VII), which is oxidized with oxalyl chloride in dichloromethane, affording aldehyde (VIII). Finally, this compound is treated with methoxyammonium chloride and Na_2CO_3 in methanol, giving brasofensine as an oil. Several salts of brasofensine were obtained by addition of the acid to a solution of brasofensine in ethanol and recrystallization from either water or isopropanol (1). Scheme 1.

Synthesis of 8-[^{11}C-methyl]-brasofensine: The demethylation of the previously described intermediate (VI) by means of 2,2,2-trichloroethyl chloroformate in refluxing toluene gives the expected ester (IX), which is protected with di-*tert*-butyl dicarbonate in THF, affording (1*R*,2*R*,3*S*,5*S*)-8-(*tert*-butoxycarbonyl)-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester (X). The reduction of (X) with $LiAlH_4$ in ethyl ether gives (1*R*,2*R*,3*S*,5*S*)-8-(*tert*-butoxycarbonyl)-[3-(3,4-dichlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octan-2-yl]methanol (XI), which is oxidized with oxalyl chloride in dichloromethane, affording the aldehyde (XII). The reaction of (XII) with methoxyammonium chloride and Na_2CO_3 in methanol gives the *O*-methyloxime (XIII), which is deprotected with trifluoroacetic acid in dichloromethane, yielding (1*R*,2*R*,3*S*,5*S*)-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane-2-carbadehyde *O*-methyloxime (XIV) (1). Finally, this compound is methylated with [^{11}C]-methyl iodide in DMSO at 130 °C (2). Scheme 2.

Description

White crystals: sulfate, m.p. 161-3 °C; disulfate, m.p. 84-7 °C; maleate, m.p. 140-2 °C; citrate, m.p. 143-4 °C; malonate, m.p. 116-8 °C; fumarate, m.p. 158-9 °C; hydrochloride, m.p. 74-5 °C (1).

Introduction

The pharmacological treatment of Parkinson's disease has improved in recent years, thanks to a better understanding of how to use existing drugs as well as the introduction of newer agents. Current pharmacological treatment of Parkinson's disease is shown in Table I and

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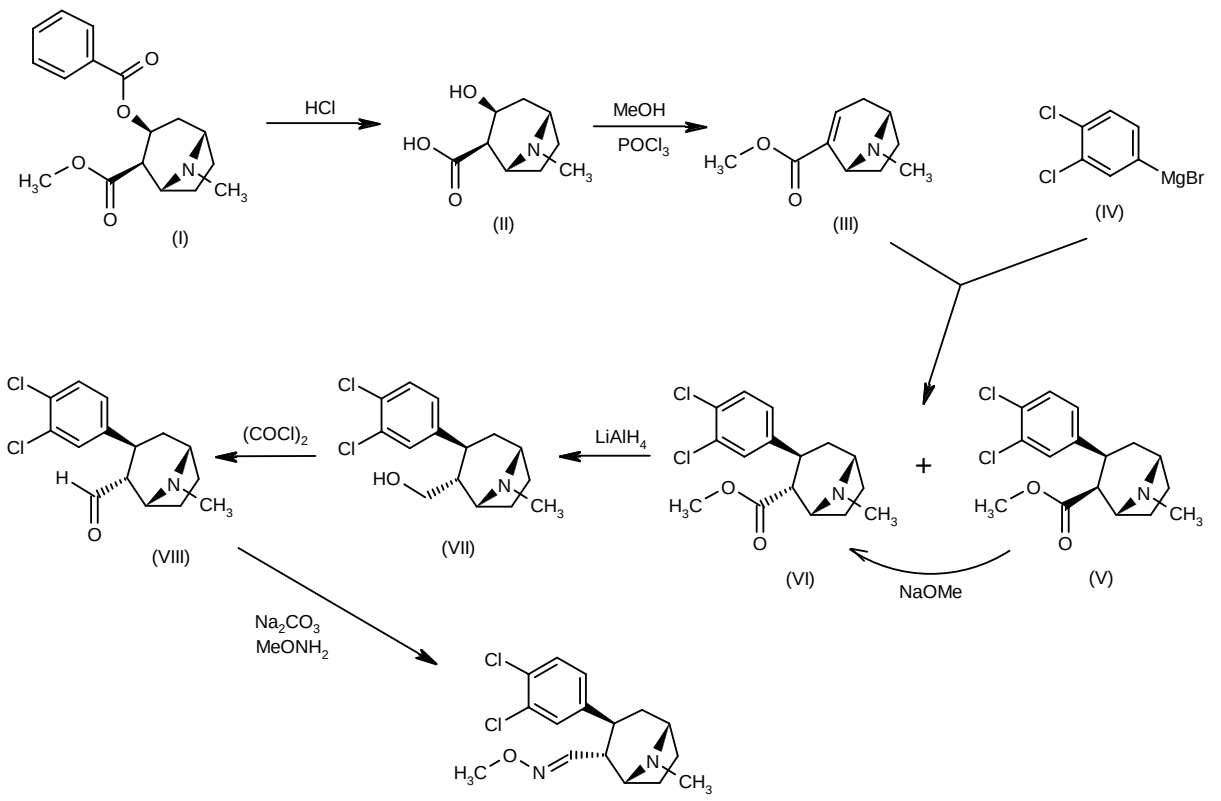
Scheme 1: Synthesis of Brasofensine



therapeutic approaches under investigation for the treatment of Parkinson's disease are presented in Table II.

During the last few years there has been a growing interest in the therapeutic possibilities of dopamine reuptake inhibition for the treatment of neurological and psychiatric disorders. Dopamine is known to be released into the synaptic cleft in order to stimulate postsynaptic dopaminergic receptors. The removal of dopamine occurs normally by a reuptake mechanism into presynaptic terminals. Inhibition of this uptake produces an enhancement of the physiological dopaminergic activity.

Cocaine has been described to have dopamine reuptake-inhibiting properties. Research efforts have focused on the design of cocaine analogs with selective dopamine reuptake-inhibiting properties and low toxicity/dependence liability. Thus, several attempts were made to synthesize cocaine analogs (3-13), but due to stimulant effects their potential as therapeutic agents was limited. More recently, a new class of cocaine congeners possessing 3-substituted aldoxime groups in the endo-α-configuration has been reported to include dopamine reuptake inhibitors with a low toxicity/side effect profile. From this series, NS-2214 (brasofensine) was selected for further development (1, 2).

Pharmacological Actions

In vitro, brasofensine was shown to inhibit dopamine reuptake in striatal synaptosomes (IC_{50} = 0.003 μM), as well as noradrenaline reuptake in hippocampal synaptosomes and serotonin reuptake in cortical synaptosomes (IC_{50} = 0.0013 and 0.013 μM, respectively) (1). It was effective at low doses in mouse, rat and monkey models of parkinsonism, and appeared to be more effective than known dopamine reuptake inhibitors such as nomifensine, diclofensine and GBR-12909. Furthermore, the long duration of action of brasofensine (approx. 24 h) indicates the potential for once-daily dosing (14).

In vivo in a marmoset model of MPTP-induced parkinsonism, brasofensine at doses of 0.1-2.5 mg/kg p.o. caused a dose-dependent increase in locomotor activity

Scheme 2: Synthesis of Brasofensine

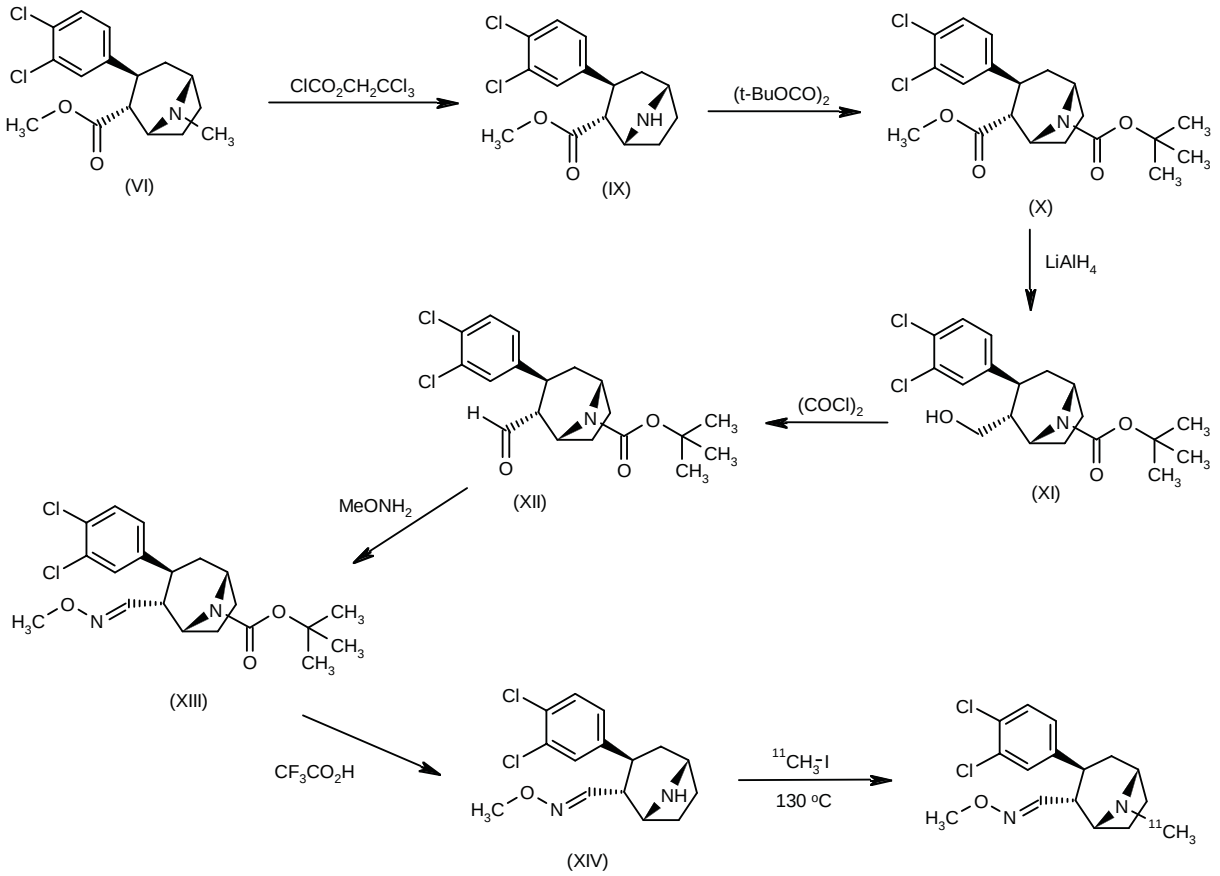


Table I: Pharmacological treatment of Parkinson's disease (from Prous Science Ensemble database).

	Manufacturer	Year of introduction
Dopamine precursors		
Levodopa	Roche	1969
Levodopa/carbidopa[1]	DuPont Pharm.	1972
Levodopa/benserazide[1]	Roche	1973
Droxidopa	Sumitomo	1989
MAO-B inhibitors		
Selegiline HCl	Orion; Asta Medica	1981
Zydis[2] selegiline HCl	Elan Pharma	1998
COMT inhibitors		
Tolcapone	Roche	1997 (withdrawn)
Entacapone	Orion	1998
Dopamine agonists		
Amantadine HCl	Novartis	1964
Apomorphine HCl	Britannia	—
Bromocriptine mesilate	Novartis	1975
Pergolide mesilate	Lilly	1989
Cabergoline	Pharmacia & Upjohn	1993
Pramipexole HCl	Boehringer Ingelheim	1997
Ropinirole HCl	SmithKline Beecham	1997
Anticholinergics[3]		
Procyclidine HCl	Glaxo Wellcome	1951
Benztropine mesylate	Merck & Co.	1954
Biperiden HCl	Knoll	1954
Orphenadrine HCl	3M Pharm.; Yamanouchi	1955

[1]Peripheral decarboxylase inhibitor. [2]Instantly dissolving technology from R.P. Scherer. [3]Used to relieve mild tremor but do not improve akinesia.

Table II: Therapeutic approaches under investigation for the treatment of Parkinson's disease (from Prous Science Ensemble database).

Mechanism of action	Manufacturer	Status
Dopamine reuptake inhibitors		
Brasofensine (NS-2214)	NeuroSearch; Bristol-Myers Squibb	Phase II
Dopamine agonists		
TV-1203	Teva	Phase II
Dopamine D_1 agonists		
ABT-431	Abbott	Phase II
	CeNeS	Research
Dopamine D_2 agonists		
BAM-1110[1]	Nippon Shoji; Maruko; Tokyo Tanabe	Phase II
N-0923 transdermal patch	Discovery Therapeutics; Yoshitomi	Phase II
PNU-95666E	Pharmacia & Upjohn	Phase I
Nicotinic acetylcholine agonists		
SIB-1508Y	Sibia Neurosciences	Phase II
SIB-1765F	Sibia Neurosciences	Preclinical
MAO-B inhibitors		
Lazabemide HCl (Pakio)[2]	Roche	NDA filed
Rasagiline mesylate (TVP-1012)[3]	Teva	Phase III
SL-34.0026	Synthelabo	Phase I
Adenosine A_{2A} antagonists		
KW-6002	Kyowa Hakko	Phase II
Sch-58261	Schering-Plough	Preclinical
Neuroprotective agents		
Riluzole[5]	Rhône-Poulenc Rorer	Phase III
OPC-14117[6]	Otsuka	Phase II
MIF[7]	NIH	Preclinical
Neurotrophic agents[4]		
NeuroCell-PD[8]	Diacrin; Genzyme Tissue Repair	Phase II/III
Neurturin[9]	Genentech	Preclinical
OP-1[10]	Creative BioMolecules	Preclinical
Neurophilin ligands		
NIL-A	Guilford; Amgen	Preclinical
	Vertex	Research
δ-Opioid agonists		
SNC-80[11]	Glaxo Wellcome; NIH	Preclinical
5-HT_{2C} antagonists		
SB-205553[12]	SmithKline Beecham	Research
Gene therapy		
AAV-based therapy[13]	Cell Genesys	Research
ProSavin[14]	Oxford BioMedica	Preclinical
Cell therapy		
hRPE-GM[15]	Theracell; Emory University	Preclinical
Spheramine[16]	Titan	Preclinical
Stem cell-derived dopaminergic neurons	NeuralSTEM	Preclinical

[1]Also dopamine D_1 agonist. [2]Also under development for Alzheimer's disease (as Tempium). [3]Also under development for Alzheimer's disease. [4]See also MAO-B inhibitors and adenosine A_{2A} antagonists. [5]Launched in 1995 for amyotrophic lateral sclerosis (as Rilutek). [6]Also under development for AIDS-related dementia. [7]Macrophage migration-inhibitory factor. [8]Porcine neural cell product. [9]Protein which is homologous to GDNF. [10]Small-molecule neurotrophic agent. [11]A dopaminergic mechanism, mediated via dopamine D_1 receptors, is suggested to be involved. [12]Suggested to be useful in reducing the dose of dopamine replacement therapy. [13]Delivery of genes responsible for the production of levodopa using an adenovirus-associated viral gene delivery system. [14]Genes are transferred to brain cells using LentiVector technology. [15]Dopaminergic human retinal pigmented epithelial cells attached to gelatin microcarriers for intrastriatal transplantation. [16]Microcarriers coated with dopamine-producing natural human cells.

and a dose-dependent decrease in disability scores (alertness, reaction to stimuli, checking movements, attention and eye movements, posture, balance/coordination and vocalization) (1).

In a similar model, common marmosets were treated for 5 days with MPTP (2.0 mg/kg s.c.) and then with L-dopa/carbidopa (12.5 + 12.5 mg/kg p.o. b.i.d.) until the appearance of dyskinesias. Several months thereafter, animals were administered L-dopa/carbidopa for 2 days followed by brasofensine (0.5 mg/kg p.o.) for 11 days. Title compound effectively reversed MPTP-induced akinesia in this model and, in contrast to L-dopa, brasofensine did not produce concomitant dyskinesia, stereotypy or hyperactivity. Brasofensine relieved akinesia more effectively than tremor, and animals treated with the compound suffered some weight loss (approx.10%) during the treatment period. These findings support the utility of brasofensine in the early treatment of Parkinson's disease (15).

Clinical Studies

Brasofensine has been evaluated in safety and tolerability studies in parkinsonian patients, with satisfactory results. Various clinical efficacy studies are currently underway: an international, multicenter efficacy study in 150 levodopa-naive patients, as well as combination therapy studies in levodopa-treated patients in stable phase or who are suffering fluctuations (dyskinesia or on-off phenomena). Phase II proof-of-principle studies are expected to be completed in early 1999 (16).

Source

NeuroSearch A/S (DK); licensed to Bristol-Myers Squibb Co. (US) for development and marketing worldwide except in Scandinavia and the Baltic countries (17).

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