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CCC: 0377-8282/99

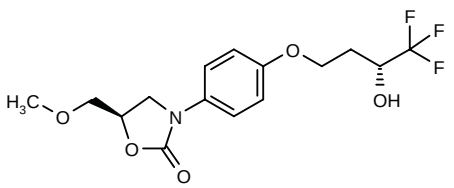
Befloxatone

Rec INN

Antidepressant
MAO-A Inhibitor

MD-370503

5(*R*)-(Methoxymethyl)-3-[4-[4,4,4-trifluoro-3(*R*)-hydroxybutoxy]phenyl]oxazolidin-2-one



$C_{15}H_{18}F_3NO_5$ Mol wt: 349.3100

CAS: 134564-82-2

EN: 186487

Synthesis

Befloxatone is obtained by condensation of 1,1,1-trifluoro-4-(tosyloxy)-2(*R*)-butanol (I) with 3-(4-hydroxyphenyl)-5(*R*)-(methoxymethyl)oxazolidin-2-one (II) by means of K_2CO_3 in hot DMF. (1, 2). Scheme 1.

Each of the two intermediates butanol (I) and oxazolidinone (II) can be prepared by two different methods:

1) Butanol (I):

1a) The reduction of 4,4,4-trifluoro-2-oxobutyric acid ethyl ester (III) with $NaBH_4$ in dichloromethane gives 4,4,4-trifluoro-2-hydroxybutyric acid ethyl ester (IV), which is hydrolyzed with NaOH in ethanol, yielding the corresponding acid (V). The optical resolution of (V) with 1(*S*)-phenylethylamine in hot ethanol affords the 3(*R*)-hydroxy enantiomer (VI) (1,3), which is reduced with $NaBH_4$ and BF_3 ethearate in THF to provide 4,4,4-trifluorobutane-1,3(*R*)-diol (VII). Finally, this compound is monotosylated by means of tosyl chloride and DMAP in pyridine to afford intermediate (I) (1). Scheme 2.

1b) The digestion of 4,4,4-trifluoro-3-hydroxybutyric acid ethyl ester (IV) with Novozym in a phosphate buffer gives the corresponding (*R*)-enantiomer (VIII), which is reduced with $NaBH_4$ in ethanol, yielding 4,4,4-trifluorobutane-1,3(*R*)-diol (VII) (4). Finally, this compound is monotosylated by means of tosyl chloride as before to give butanol (I) (2). Scheme 2.

2) Oxazolidinone (II):

2a) The reaction of 4-benzyloxyaniline (IX) with 1,4-dioxaspiro[4.5]decan-2(*S*)-ylmethyl methanesulfonate (X) by means of TEA at 140 °C gives 3-(4-benzyloxyphenylamino)propane-1,2(*R*)-diol (XI), which is cyclized with diethyl carbonate and sodium methoxide in refluxing toluene, yielding 3-(4-benzyloxyphenyl)-5(*R*)-(hydroxymethyl)oxazolidin-2-one (XII). The methylation of (XII) with dimethyl sulfate, NaOH and tetrabutylammonium bisulfate in hot toluene/water affords the corresponding methoxymethyl derivative (XIII). Finally, this compound is debenzylated by hydrogenation with H_2 over Pd/C in ethanol/dichloromethane to give oxazolidinone (II) (1). Scheme 3.

2b) The methylation of 4(*S*)-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane (XIV) with dimethyl sulfate and NaOH gives 4(*S*)-(methoxymethyl)-2,2-dimethyl-1,3-dioxolane (XV), which is hydrolyzed with hot aqueous HCl to 3-methoxypropane-1,2(*R*)-diol (XVI). The cyclization of (XVI) with diethyl carbonate by means of NaH affords 4(*S*)-(methoxymethyl)-1,3-dioxolan-2-one (XVII) (2, 5). The condensation of (XVII) with *N*-(4-benzyloxyphenyl)-carbamic acid methyl ester (XVIII) (obtained by reaction of 4-benzyloxyaniline (IX) with methyl chloroformate) by means of K_2CO_3 at 160 °C provides the protected oxazolidinone (XIII), which is finally debenzylated as before to give oxazolidinone (II) (2). Scheme 3.

Description

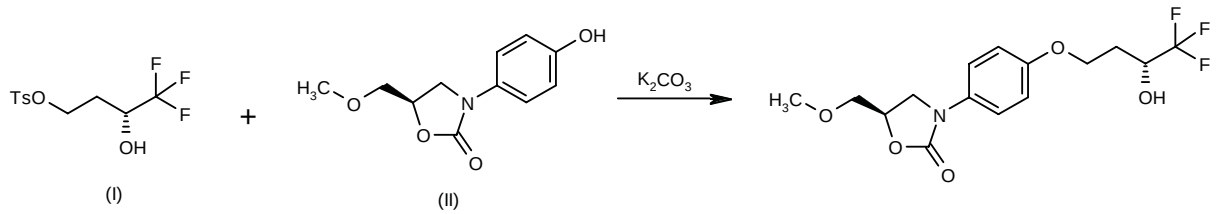
Crystals, m.p. 101 °C; $[\alpha]_D^{20}$ –11.5° (c 1, CH_2Cl_2) (1, 2).

Introduction

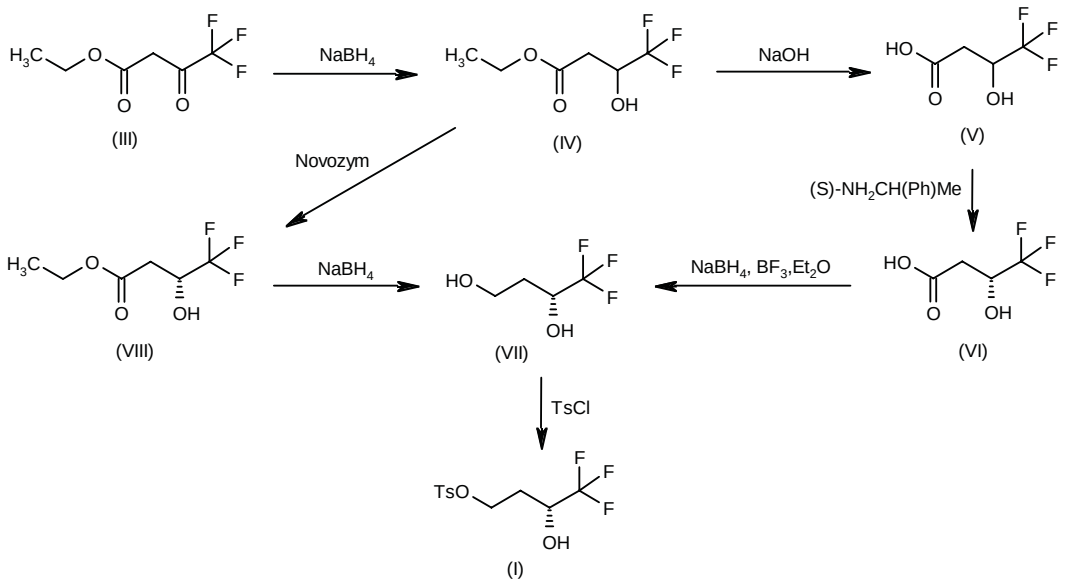
Depression is a very common illness that is associated with substantial morbidity and mortality. There are various forms of depressive disorders. Three of the most prevalent types are major depression, dysthymia and bipolar disorder, formerly called manic-depressive illness. According to data presented by the Global Burden of Disease study, a worldwide epidemiological study by the

X. Rabasseda, L.A. Sorbera, J. Castañer. P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Befloxatone



Scheme 2: Synthesis of Intermediate (I)



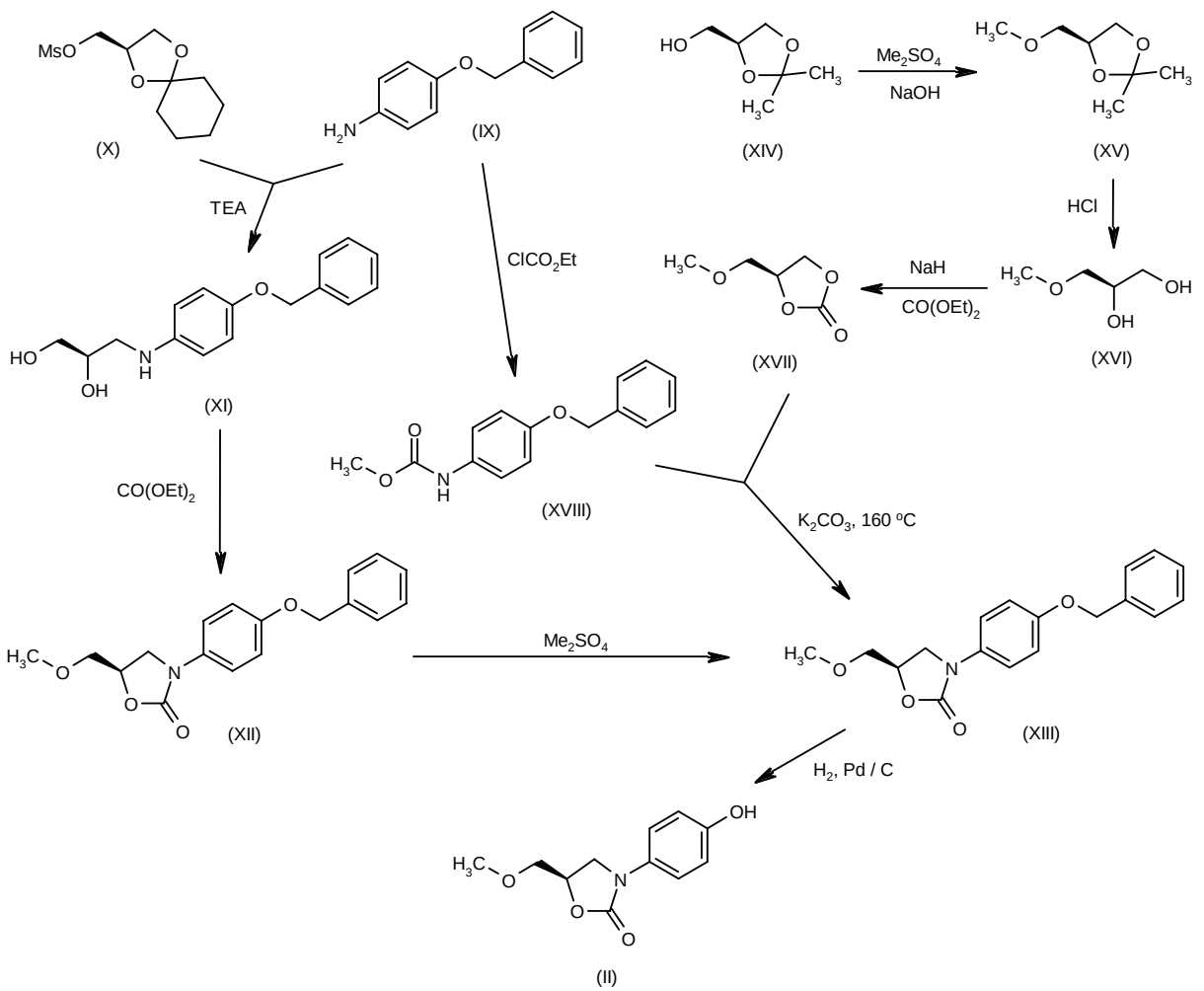
World Health Organization, the World Bank and Harvard University, unipolar major depression and bipolar disorder were the leading and sixth causes, respectively, of disability worldwide in 1990, with 340 million people suffering from major depressive disorders. The etiology of depression is unknown, but it may represent an interaction between psychological and biochemical mechanisms rather than a single factor. The symptoms appear to be mediated through alterations in levels of some central neurotransmitters, although it is unknown whether this is the cause of the disorder.

The discovery of the efficacy of irreversible monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants in the 1950s had a significant impact on the development of modern biological psychiatry. In the early 1960s, the tricyclic antidepressants were the first drugs of choice for the treatment of depressive illness. In order to avoid some of the side effects of tricyclic antidepressants newer drugs, termed second-generation antidepressants, began to reach the market in the 1970s. During the last 15 years there have been important advances in the field of antidepressant research, which have led to the introduction of a number of selective 5-HT and noradrenaline reuptake inhibitors and two reversible MAOIs.

Considerable efforts are now being made to improve antidepressant therapy. Thus, serotonin receptor (5-HT_{1A}, 5-$HT_{1B/1D}$, 5-HT_{2C} and 5-HT_7) modulators, corticotropin-releasing factor receptor antagonists, substance P antagonists, α_2-adrenoceptor antagonists and cortisol-lowering agents are being actively investigated with the aim of obtaining novel treatment modalities for patients suffering from depression.

MAO [EC 1.4.3.4], an enzyme located mainly in the outer mitochondrial membrane of neurons, glial and other cells, catalyzes the oxidative deamination of neurotransmitters and xenobiotic amines (6, 7). There are two major MAO isoforms: MAO-A, which prefererentially deaminates serotonin (5-HT) and norepinephrine (NE), and MAO-B, which preferentially deaminates phenylethylamine and benzylamine. Dopamine and tyramine are substrates for both forms of MAO (8-10). MAO-A inhibitors exert their therapeutic effect by preventing the

Scheme 3: Synthesis of Intermediate (II)



degradation of NE, thus increasing synaptic NE concentrations.

The first generation of MAO inhibitors (isocarboxazid, tranylcypromine sulfate, phenelzine and nialamide) nonselectively and irreversibly blocked both MAO isoforms. In spite of their antidepressant activity, the popularity of MAOIs decreased in the early 1960s due to a number of drawback, most importantly their adverse interactions with a number of drugs and certain foods, particularly those rich in tyramine (11, 12).

Over the last 20 years, research efforts have been aimed at developing new MAO inhibitors with selective, reversible and more short-lasting effects. These efforts have resulted in the launch of three reversible MAO-A inhibitors: moclobemide, tetrindol and toloxatone. The chemical structures of selected reversible MAO-A inhibitors launched and under development are shown in Table I. One such compound under development, befloxatone, was selected from a series of oxazolidinone derivatives as a potent, competitive and selective MAO-A inhibitor with potential antidepressant properties.

Pharmacological Actions

Biochemical profile

Befloxatone is a potent, reversible and selective MAO-A inhibitor in rat and in human tissues that specifically interacts with the flavin adenine dinucleotide (FAD) cofactor of the enzyme and with specific amino acids of the active site (13). Befloxatone exhibits nanomolar inhibitory activity against MAO-A in rat brain homogenates (K_i = 2-2.5 nM) as well as in heart, liver and

Table I: MAO-A inhibitors launched and under development (Prous Science Ensemble database).

Launched

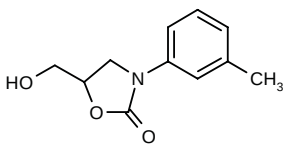
1. Toloxatone
   Humoryl
   Sanofi-Synthélabo (1984)
2. Moclobemide
   Manerix
   Roche (1990)
3. Tetrindol
   Center of Chemistry of Drugs (Moscow (1992)

Clinical Trials

4. Befloxatone
   Sanofi-Synthélabo

Preclinical

5. 2614W94
   Krenitsky Pharmaceuticals
6. Glycinamide derivative
   AstraZeneca
7. KP9
   Krenitsky Pharmaceuticals
8. SL-650477*,[1]
   Sanofi-Synthélabo
9. T-794
   Tanabe Shinyaku; Taisho
10. UR-1827[2]
    Ube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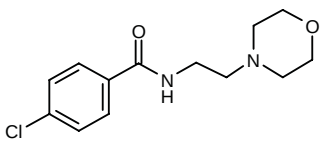
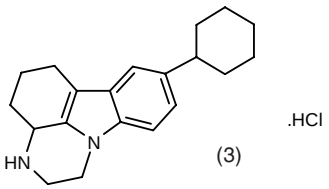
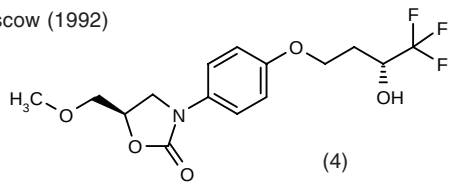
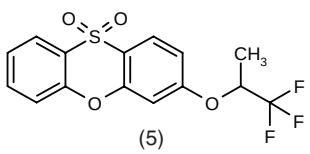
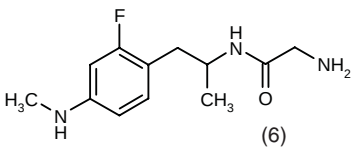
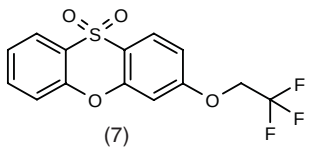

(2)


.HCl
(3)


(4)


(5)


.CH_3CO_2H
(6)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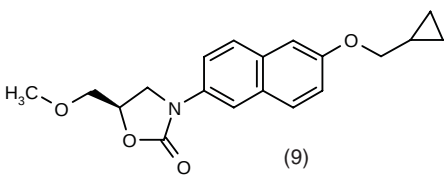
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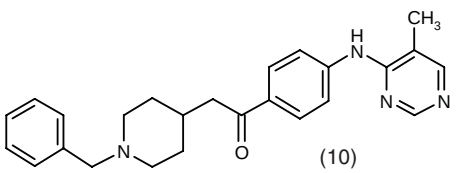
(10)

*Structure not yet detected. [1]Reversible mixed MAO-A/MAO-B inhibitor. [2]Also acetylcholinesterase inhibitor and norepinephrine uptake inhibitor; potentially useful in the treatment of cognitive dysfunction and depressive syndromes in humans with Alzheimer's disease.

Table II: Inhibitory activities for selected reversible MAO-A inhibitors (Prous Science MFLine® database).

Compound	K_i (μM) MAO-A	MAO-B	Enzyme source	$K_{i_{MAO-B}}/K_{i_{MAO-A}}$ Selectivity index	Ref.
Befloxatone	0.002[a]	0.35[a]	Rat brain	175	14
Moclobemide	11.5	>100	Rat brain	>8.7	14
Pirlindole	0.24[b]	NA	Rat brain	–	42
Toloxatone	1.63	39	Rat brain	23.9	14
Tetrindole	0.40	110	Rat brain	244	43

[a]Mean from different experiments using similar methodology; [b]IC_{50} (μM); NA: not active.

intestine from rats and humans (K_i = 1.9-3.6 nM), and is more potent than other reversible MAO-A inhibitors including moclobemide, pirlindole, toloxatone and tetrindole (Table II). Selectivity for MAO-A over MAO-B in vitro varies from 269 to 920, depending on tissue and species, and is maintained *ex vivo* (14). Kinetic experiments indicated that befloxatone inhibits deamination of [^{14}C]-5-HT (MAO-A substrate) and [^{14}C]-phenylethylamine (MAO-B substrate) in a full competitive manner, with K_i values of 2 and 150 nM, respectively (14). Binding studies with [^{3}H]-befloxatone in rat brain sections and homogenates indicate that the compound labels with high affinity (K_d = 1.3 nM) a single population of sites with the pharmacological characteristics and regional distribution of MAO-A (15, 16). The specificity of befloxatone is demonstrated by its lack of affinity (up to 10 μM) for a large variety of receptor sites including noradrenergic, dopaminergic, serotonergic, muscarinic, histaminergic and opioid receptors, L-type Ca^{2+} channels and sigma sites. Moreover, beflotaxone does not interact with monoamine reuptake systems in synaptosomes from rat striatum, cortex or hypothalamus and does not modify the activities of benzylamine oxidase or diamine oxidase in rat heart and ileum, respectively, or succinate and pyruvate dehydrogenase (14).

Ex vivo experiments showed that orally administered befloxatone induced a reversible and dose-dependent inhibition of MAO-A in the rat brain (ED_{50} = 0.06 mg/kg)

Table III: Pharmacological profile of befloxatone (Prous Science MFLine® database) (20).

In vivo tests	ED_{50} (mg/kg p.o.)
Potentiation of L-5-HTP-induced tremors (mice)	0.21
Potentiation of L-dopa-induced behavior (mice)	0.66
Potentiation of PEA-induced stereotypies (mice)	58.0
Beavioral tests	
Reduction of immobility in the forced swimming test (rats)	0.1*
Reduction of escape failures on helpless behavior (rats)	0.03*
Prevention of reserpine-induced hypothermia (mice)	0.29
Prevention of reserpine-induced ptosis (mice)	0.26
Prevention of reserpine-induced akinesia (mice)	0.061
Suppression of REMS/total sleep ratio (rats)	4.83

and duodenum (ED_{50} = 0.025 mg/kg (14). Befloxatone exhibited reversible activity both *in vitro*, where the 100-fold dilution of brain homogenate samples resulted in a complete recovery of MAO-A activity, and *ex vivo*, where complete recovery of the enzymatic activity was achieved 24 h after a single oral dose of 0.75 mg/kg (14). High levels of [^{3}H]-befloxatone binding were found in locus ceruleus, interpeduncular nucleus, dorsal raphe, habenula and nucleus of the solitary tractus, and moderate levels were found in cerebral cortex, limbic and extrapyramidal system.

In rat whole brain, beflotaxone (0.001-0.75 mg/kg p.o.) increased endogenous levels of NE, DA and 5-HT and decreased the levels of their metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyacetic acid (5-HIAA), with a maximal effect at 1-2 h. Studies on the effects of befloxatone on extracellular DA, NE and 5-HT content in striatum and frontal cortex, as well as on the firing rate of monoaminergic neurons in the substantia nigra, locus ceruleus and dorsal raphe, were done in order to investigate the compound's effects on brain monoaminergic transmission. Befloxatone (0.75 mg/kg i.p.) increased extracellular levels of DA in striatum (+300%) and increased extracellular NE in frontal cortex (+100%). It also decreased MAO-A in a selective and reversible manner, with a maximal effect (–99%) 1 h after administration, and decreased DOPAC (–65%), homovanillic acid (–65%) and 5-HIAA (–25%) 2 h after administration. Befloxatone had no effect on extracellular 5-HT, which was in contrast to the increases in tissue concentrations observed in whole brain and striatum. At a dose of 1 mg/kg i.p., befloxatone reduced the firing rate of monoaminergic neurons in the locus ceruleus (40%) and dorsal raphe (100%), but had no effect (up to 10 mg/kg i.p.) on firing rate in the substantia nigra. Experimental evidence indicates that the reduction in firing rates produced by befloxatone is a result of increased stimulation of both inhibitory α_2-adrenergic and 5-HT_{1A} somatodenditric autoreceptors produced by elevated synaptic levels of NE and 5-HT (17). Moreover, short-term administration of befloxatone (0.75 mg/kg/day for 2 days) reduced the firing activity of 5-HT neurons, followed by recovery after 21 days of sustained administration (18). This sequence of events correlated well with the delayed onset of action of MAOIs in major depression.

Behavioral tests

The MAO-A inhibitory activity of befloxatone was confirmed *in vivo*. Befloxatone potentiated 5-HPT-induced tremor in rats and mice (ED_{50} = 0.15 and 0.21 mg/kg p.o., respectively), levodopa-induced behavior in mice (ED_{50} = 0.66 mg/kg p.o.) and, only at high doses (ED_{50} = 58 mg/kg), phenylethylamine-induced stereotypies (Table III). The potent MAO-A inhibitory activity correlated with rapid and extensive brain penetration (19) and with the drug's ability to enhance catecholamine release in vivo, strongly suggesting potential antidepressant activity.

The activity of befloxatone was evaluated in several animal models thought to be predictive of antidepressant activity in humans (15) (Tables III and IV). In the forced swimming test and learned helplessness paradigm in rats, the activity of befloxatone was observed at very low doses (MED = 0.1 and 0.03 mg/kg p.o., respectively) and was superior to that of reference compounds such as moclobemide (75- to 166-fold less potent). Befloxatone was also able to reverse reserpine-induced hypothermia, ptosis and akinesia in mice (ED_{50} = 0.29, 0.26 and 0.061 mg/kg p.o., respectively) at doses 5-fold lower than those

Table IV: Antidepressant activity (immobility reduction) in the forced swimming test of selected reversible MAO-A inhibitors (Prous Science MFLine® database).

Compound	MED (mg/kg)	Administration route	Animal	Ref.
Befloxatone	0.1	p.o.	Rats	20
Moclobemide	7.5	p.o.	Rats	20
	>30	i.p.	Mice	44
Pirlindole	5.0	i.p.	Rats	42
Toloxatone	256[a]	i.p.	Mice	45
Tetrindole	1.0	p.o.	Mice	46

[a]Single effective dose (mg/kg i.p.). MED = minimum effective dose.

Box 1: Effects of single- and multiple-dose befloxatone on psychomotor performance and memory in healthy volunteers (21) [Prous Science CSline database].

Design	Double-blind, placebo-controlled, randomized, crossover clinical study
Population	Healthy subjects (n = 12)
Treatments	Befloxatone (B), 5 mg p.o. s.d. B, 10 mg p.o. s.d. B, 5 mg p.o. b.i.d. x 6 d B, 10 mg p.o. o.d. x 6 d Placebo (P)
Results	Continuous performance task at d 8 (%): B5bid (98.3) ≥ P (97.6) ≥ B10od (96.9) Digit symbol substitution test change at d 6, 3 h postdose: P (112.7) ≥ B5bid (109.1) ≥ B10od (103.9) Total reaction time change at d 8 (ms): B5bid (98.3) ≥ P (97.6) = B10od (97.6) Short-term memory at d 8, normal: B5bid (9.2) ≥ B10bid (9.0) = P (9.0); divided: P (6.3) ≥ B5bid (6.2) ≥ B10bid (6.1)
Conclusions	Daily befloxatone did not appear to cause sedative or amnestic effects likely to interfere with activities of everyday

required for moclobemide (20). Befloxatone, in contrast to moclobemide and fluoxetine, exhibited significant activity (at 1 and 2 mg/kg i.p.) in the elevated plus maze, a test considered predictive for anxiolytic activity, indicating a wide spectrum of potential therapeutic indications ranging from anxiety disorders to major depression in humans. Like other clinically active antidepressant drugs, befloxatone dose-dependently (0.25-16 mg/kg p.o.) increased REM sleep latency and decreased REM sleep duration (ED_{50} = 4.83 for reduction of the relative REMS/total sleep) without affecting wakefulness and NREM (20). Befloxatone (0.15-1.5 mg/kg p.o.), like other reversible MAO-A inhibitors such as moclobemide and brofaromine, did not potentiate the pressor effect of orally administered tyramine (12 mg/kg). In contrast, the irreversible MAOIs produced a marked potentiation under the same conditions.

Toxicity

Befloxatone at doses of 0.15-150 mg/kg p.o. did not produce adverse effects such as stereotypy, aggression or fighting in mice. Mild, nonsignificant hypomotility was produced with the highest doses (100 and 200 mg/kg). Befloxatone did not induce sedative or stimulant activity up to 200 mg/kg, was devoid of anticholinergic activity and did not induce lethality in mice up to 400 mg/kg p.o. (20). Only a slight and transient decrease in blood pressure was observed after a dose of 10 mg/kg i.v. These data indicate that befloxatone is safe and has no side effects at effective doses in tests predictive of antidepressant activity.

Clinical Studies

Results from a single- and multiple-dose randomized, double-blind, placebo-controlled, comparative crossover clinical trial in 12 healthy young (20-25 years) subjects showed that befloxatone did not cause significant detrimental effects which could interfere with everyday life activities. Subjects, treated for 3 periods of 8 days separated by a washout period of at least 5 days, received a single oral dose of befloxatone (5 or 10 mg) on day 1 followed by multiple doses on day 3-8 of either once-daily befloxatone (10 mg in the a.m.) plus placebo (p.m.) or befloxatone (5 mg) or placebo twice-daily. Objective examination of memory (working memory, immediate and delayed free recall of word list, dual coding and face recognition), vigilance (continuous performance task and digit symbol substitution) and subjective assessment of mood and sleep according to visual analog scales and the Leeds Sleep Evaluation Questionnaire showed that both dosage schedules did not adversely affect vigilance or information processing. Short- and long-term memory were also not altered and no sleep disturbances or sedation were noted. It was concluded that befloxatone is safe to administer to depressed outpatients (21) (Box 1).

Single-dose befloxatone (5, 10 and 20 mg p.o.) treatment had no effects on psychomotor performance at 2, 4 and 8 h postdosing, according to results of a randomized, double-blind, 5-way crossover study in 15 healthy young males (22) (Box 2). Similar safety profiles were obtained from 9 other randomized, double- or single-blind, placebo-controlled studies in 168 healthy subjects given single doses of up to 160 mg or repeated doses of up to 80 mg/day for 7 days. Treatment resulted in dose-dependent reductions in plasma 3,4-dihydroxyphenylglycol (DHPG) levels which peaked at 2-4 h and were maintained for 24 h or more with doses of equal to or more than 10 mg (23) (Box 3).

The pharmacodynamics and pharmacokinetics of single-dose befloxatone (10 mg p.o.) were assessed in 12 healthy elderly (65-73 years) subjects in a randomized, placebo-controlled, double-blind, 3-way crossover study in which befloxatone was also compared to amitriptyline (50 mg). No indications of sedation were observed in

Box 2: Effects of single-dose befloxatone on psychomotor performance and memory in healthy volunteers (22) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, comparative, crossover clinical study
Population	Healthy elderly subjects (n = 15)
Treatments	Befloxatone (B), 5 mg p.o. B, 10 mg p.o. B, 20 mg p.o. Amitriptyline (A), 50 mg p.o. Placebo (P)
Results	Critical flicker function change at 4 h postdosing (Hz): B10 (–0.4) = P (–0.4) ≥ A (–2.9) ≥ B5 (–0.2) = B20 (–0.2) Continuous reaction task at 4 h postdosing (ms): A (–36) > B5 (–5) ≥ P (–3) ≥ B20 (–2) ≥ B10 (–1) Digit symbol substitution test change at 4 h postdosing (n): A (–7) ≥ B20 (–4) ≥ P (–3) = B10 (–3) ≥ B5 (–1) Delayed free recall test at 4 h postdosing (n): A (–4.5) > B5 (–1.4) ≥ P (–1.2) ≥ B20 (–1) ≥ B10 (–0.5)
Conclusions	Befloxatone at 10 mg has no sedative or amnestic effects likely to interfere with activities of everyday

Box 3: Clinical pharmacology of befloxatone summarized from 9 studies in healthy subjects (23) [Prous Science CSline database].

Design	Randomized, placebo-controlled, double-blind, single-blind clinical studies
Population	Healthy subjects. Since some studies were crossover, each subject was counted according to the different doses received
Treatments	Befloxatone (B), 1-80 mg/d p.o. up to 160 mg s.d. Placebo (P)
Withdrawals	B: 3/272 (1.1%) P: 2/143 (1.4%)
Adverse events	B: 84/272 (30.8%) P: 27/143 (18.6%)
Results	Befloxatone induced a dose-related decrease in free plasma DHPG, with significant inhibition (40%) at doses of ≥ 2.5 mg and maximum inhibition (80%) at doses of ≥ 10 mg, peaking at 2-4 h and lasting 24 h or more with ≥ 10 mg Befloxatone did not have detrimental sedative, amnestic or psychomotor effects, even in elderly subjects and when administered with alcohol did not increase impairment over that seen with alcohol alone
Conclusions	Based on the information obtained, befloxatone appears to be a safe and potent selective MAO-A inhibitor without potential for inducing detrimental effects on the CNS

EEG profiles from befloxatone-treated subjects and β waves significantly increased (12-40 Hz) as compared to placebo and amitriptyline groups. Befloxatone significantly reduced DHPG plasma levels by 84.6% as compared to only 29% and 21.5% in the amitriptyline and placebo groups, respectively. Befloxatone was concluded to be safe since a similar incidence of mild to moderate side effects such as drowsiness (7.7%) and vomiting (7.7%) were observed in both placebo and befloxatone-treated groups; drowsiness (64.5%), impaired concentration (15.4%) and palpitations (7.7%) were reported in amitriptyline-treated subjects. The pharmacokinetic parameters obtained for befloxatone were similar to those reported for healthy young subjects, indicating that no dose adjustment is warranted in elderly subjects (24) (Box 4).

Several studies have reported very little interaction of befloxatone with other agents. Befloxatone (20 mg once daily for 10 days) in combination with ethanol (0.5 or 0.8 g/kg on days 6, 8 and 10) was shown to have no detrimental effects on psychomotor performance in healthy subjects in a randomized, double-blind, placebo-controlled study (25) (Box 5).

A single-blind, placebo-controlled study in 10 healthy male subjects showed only slight interactions between oral befloxatone (20 mg once daily) and tyramine. Subjects were given befloxatone after a meal containing increasing daily tyramine doses (up to 400 or 600 mg) until a dose was obtained that would increase systolic blood pressure (SBP) by at least 30 mmHg (Tyr 30). Befloxatone treatment was shown to significantly increase Tyr 30 (290 ± 105 *vs.* 1340 ± 422 mg in placebo).

Box 4: Pharmacokinetics and safety of befloxatone in the elderly (24) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, comparative, crossover clinical study
Population	Healthy elderly subjects (n = 14)
Treatments	Befloxatone (B), 10 mg p.o. Amitriptyline (A), 50 mg p.o. Placebo (P)
Adverse events	B: 3/13 (23.1%) [headache 2/13 (15.4%), drowsiness 1/13 (7.7%), vomiting 1/13 (7.7%)] A: 10/13 (76.9%) [drowsiness 8/13 (61.5%), impaired concentration 2/13 (15.4%), palpitations 1/13 (7.7%)] P: 4/12 (33.3%) [headache 3/12 (25%), drowsiness 1/13 (7.7%), vomiting 1/13 (7.7%)]
Results	DHPG plasma level maximal decrease (%): B (–84.6) > A (–29) ≥ P (–21.5) EEG total power at all times: B = A = P EEG relative δ power at 7.5 h. B (–220%) > A (88.6%) EEG relative β power at 7.5 h: A (–34.8%) > B (30.9%) [$p < 0.05$]
Conclusions	A single dose of 10 mg p.o. of befloxatone is safe in the elderly and has MAO-A inhibitory activity and an EEG profile of a nonsedative antidepressant that does not require dose adjustment

Box 5: Befloxatone and ethanol interaction in healthy volunteers (25) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Healthy subjects
Treatments	Befloxatone (B), 20 mg p.o. x 10 d + ethanol (E), 0.5 mg/kg 2 h after befloxatone on day 6, 8 or 10 B, 20 mg p.o. x 10 d + ethanol, 0.8 mg/kg 2 h after befloxatone on day 6, 8 or 10 B, 20 mg p.o. x 10 d + placebo 2 h after befloxatone on day 6, 8 or 10
Results	Ethanol produced a dose-related impairment of CCT, body sway, CRT, divided attention and memory after 1-2 h Multiple doses of befloxatone 20 mg at steady state had no detrimental effects on performance as compared to placebo
Conclusions	No significant interaction was found between befloxatone and ethanol

Box 6: Safety and pharmacodynamics of befloxatone after fluoxetine withdrawal in healthy subjects (27) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Healthy subjects (n = 41)
Treatments	Fluoxetine (F), 40 mg o.d. x 7 d → 20 mg o.d. x 9 d → Befloxatone (B), 2.5 mg o.d. x 5 d F, 40 mg o.d. x 7 d → 20 mg o.d. x 9 d → B, 5 mg o.d. x 5 d F, 40 mg o.d. x 7 d → 20 mg o.d. x 9 d → B, 10 mg o.d. x 5 d F, 40 mg o.d. x 7 d → 20 mg o.d. x 9 d → B, 20 mg o.d. x 5 d F, 40 mg o.d. x 7 d → 20 mg o.d. x 9 d → Placebo o.d. x 5 d
Results	Subjective psychometric evaluation scales did not change after switching to all doses of befloxatone and were not significantly different from placebo Plasma 5-HIAA levels after switching to all doses of befloxatone were not different from placebo Neurological examination remained normal after switching to all doses of befloxatone
Conclusions	Despite the long half-life of fluoxetine and its active metabolites, befloxatone can be administered with caution after discontinuation of fluoxetine

Box 7: Safety and pharmacodynamics of befloxatone after imipramine withdrawal in healthy subjects (28) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Healthy subjects (n = 25)
Treatments	Imipramine (I), 25 mg o.d. x 5 d → 25 mg b.i.d. x 5 d → 25 mg t.i.d. x 6 d → Befloxatone (B), 10 mg o.d. x 5 d I, 25 mg o.d. x 5 d → 25 mg b.i.d. x 5 d → 25 mg t.i.d. x 6 d → Placebo (P) o.d. x 5 d
Adverse events	Symptomatic postural hypotension: B, 4/12 (33.3%); P, 1/12 (8.3%)
Results	There were no differences between placebo and befloxatone regarding subjective psychometric evaluation scales, platelet serotonin and plasma 5-HIAA levels; neurological examinations were normal
Conclusions	Direct switch from imipramine to befloxatone did not cause "serotonin syndrome". Thus, a washout period between discontinuation of tricyclic antidepressants and starting befloxatone administration could be avoided

However, the SBP AUC values for befloxatone and placebo were not significantly different. Results demonstrated that dietary restrictions are not necessary when befloxatone is given at doses up to 20 mg once daily after a standard meal (containing about 40 mg tyramine) (26).

Two randomized, double-blind, placebo-controlled, parallel-group studies in 41 healthy young males examined befloxatone (2.5, 5, 10 or 20 mg) treatment following fluoxetine (40 mg for 7 days and 20 mg for 9 days) or imipramine (25 mg o.d. for 5 days followed by b.i.d. for 5 days and t.i.d. for 6 days) withdrawal. The trials did not report any clinically significant changes in safety profiles, which included body temperature, hemodynamics and ECG, or in neurological examinations. In addition, subjective psychometric evaluations of befloxatone-treated subjects were not significantly different from placebo. Since no evidence of "serotonin syndrome" was observed, the studies concluded that washout periods prior to befloxatone administration were not required following fluoxetine or imipramine withdrawal. However, it was recommended that befloxatone be administered with caution following fluoxetine withdrawal in depressive patients (27, 28) (Boxes 6 and 7).

Other studies in healthy volunteers, including elderly patients, gave similar results (29-40).

Befloxatone is in phase III trials in Europe and the U.S. as an antidepressant. It is also being tested in preliminary clinical studies for several other indications, including smoking cessation (41).

Manufacturer

Sanofi-Synthélabo (FR).

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