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CCC: 0377-8282/99

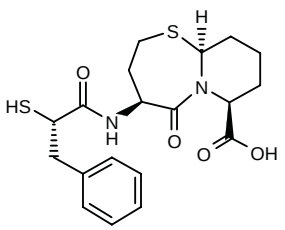
Omapatrilat

Prop INN

Antihypertensive
Treatment of Heart Failure
ACE Inhibitor
Neutral Endopeptidase Inhibitor

BMS-186716

(4*S*,7*S*,10a*S*)-5-Oxo-4-[3-phenyl-2(*S*)-sulfanylpropionamido]perhydropyrido[2,1-*b*][1,3]thiazepine-7-carboxylic acid



$C_{19}H_{24}N_2O_4S_2$ Mol wt: 408.542

CAS: 167305-00-2

EN: 218551

Synthesis

Omapatrilat has been obtained by two similar ways:

1) The condensation of *S*-acetyl-*N*-(benzyloxycarbonyl)-L-homocysteine (I) with 6-hydroxy-L-norleucine methyl ester (II) by means of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (WSC) and hydroxybenzotriazole (HOBT) in dichloromethane gives the corresponding dipeptide (III), which is oxidized with oxalyl chloride in dichloromethane, yielding the aldehyde (IV). The cyclization of (IV) by means of sodium methoxide and trifluoroacetic acid affords the perhydro-pyridothiazepinone (V), which is deprotected with trimethylsilyl iodide (TMS-I) in dichloromethane to give (VI) with a free amino group (1). The acylation of (VI) with 2(*S*)-(acetylsulfanyl)-3-phenylpropionic acid (VII) by means of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) in dichloromethane yields the corresponding amide (VIII), which is finally deprotected with NaOH in methanol and treated with HCl (1,2). Scheme 1.

2) The intermediates *S*-acetyl-*N*-(benzyloxycarbonyl)-L-homocysteine (I) and 6-hydroxy-L-norleucine (II) have been obtained as follows:

2a) The protection of 3-aminotetrahydrothiophen-2-one (IX) with *N*-(benzyloxycarbonyloxy)succinimide gives the expected carbamate (X), which is treated first with KOH and then with acetic anhydride, yielding *S*-acetyl-*N*-(benzyloxycarbonyl)-DL-homocysteine (XI). Finally, this compound is submitted to optical resolution with (S)-α-methylbenzylamine to afford intermediate (I) (1). Scheme 1.

2b) The alkylation of acetamidomalonic acid diethyl ester (XII) with 4-acetoxybutyl bromide (XIII) by means of NaH in DMF gives the alkylated ester (XIV), which by a decarboxylative saponification yields 6-acetoxy-DL-norleucine (XV). Optical resolution of (XV) by means of porcine kidney acylase/LiOH in water affords pure 6-hydroxy-L-norleucine (XVI), which is finally esterified with methanol/HCl to intermediate (II) (1). Scheme 1.

3) The condensation of 2(S)-phthalimido-4-(triphenylmethoxy)butyric acid (XVII) with 2(*S*)-amino-6,6-dimethoxyhexanoic acid methyl ester (XVIII) by means of BOP in methylene chloride gives the corresponding amide (XIX), which is treated with *p*-toluenesulfonic acid in methanol to eliminate the trityl group, yielding (XX) with a free hydroxy group. The reaction of (XX) with thioacetic acid by means of triphenylphosphine/diisopropyl azidodicarboxylate in THF affords the thioacetate (XXI), which is cyclized with sodium methoxide in methanol as before, giving the protected pyridothiazepinone (XXII). Finally, this compound is deprotected with hydrazine in methanol to afford the already reported intermediate (VI) (2). Scheme 2.

4) The intermediates 2(*S*)-phthalimido-4-(triphenylmethoxy)butyric acid (XVII) and 2(*S*)-amino-6,6-dimethoxyhexanoic acid methyl ester (XVIII) have been obtained as follows:

4a) The condensation of L-homoserine (XXIII) with phthalimide-*N*-carboxylic acid ethyl ester (XXIV) by means of Na_2CO_3 in water gives 4-hydroxy-2(*S*)-phthalimidobutyric acid (XXV), which is then treated with trityl chloride and triethylamine in chloroform to yield intermediate (XVII) (2). Scheme 2.

4b) The condensation of 6-hydroxy-L-norleucine (XVI) with phthalimide (XXIV) as before gives 6-hydroxy-2(*S*)-phthalimidohexanoic acid (XXVI), which is esterified with methyl iodide/Cs_2CO_3 in DMF to yield the methyl ester (XXVII). The oxidation of (XXVII) with oxalyl

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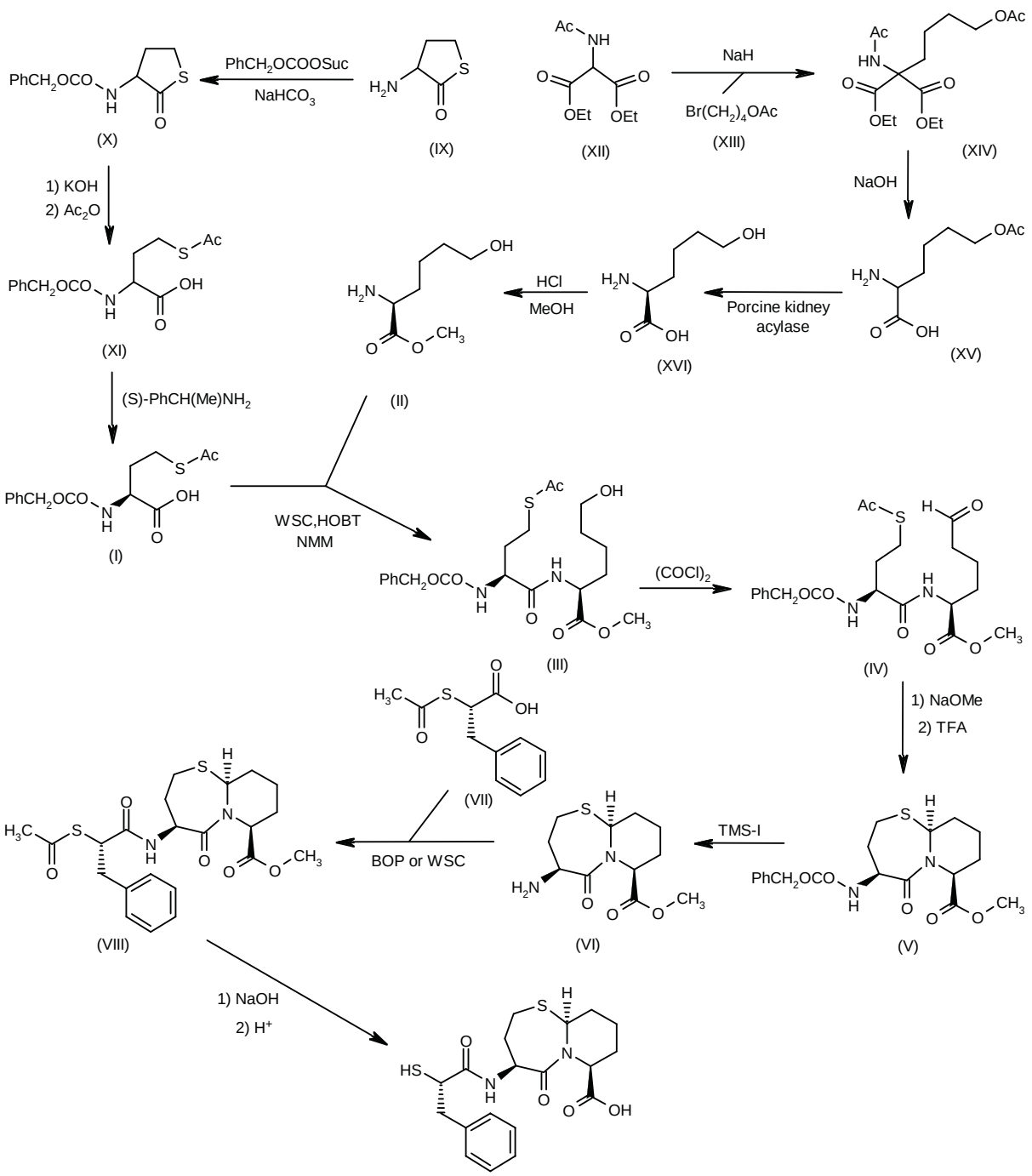
Scheme 1: Synthesis of Omapatrilat

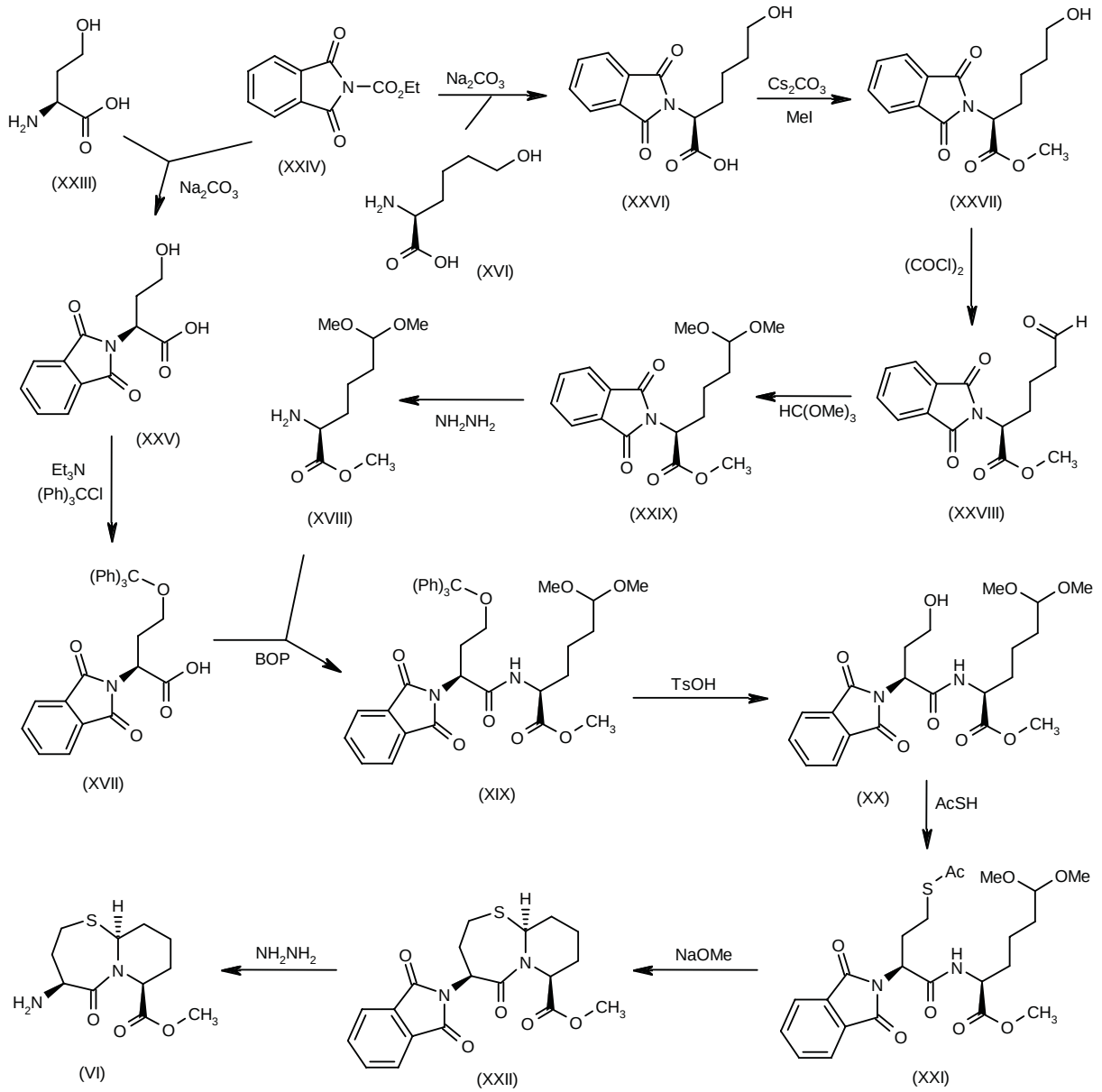


chloride in dichloromethane affords aldehyde (XXVIII), which is treated with trimethyl orthoformate/*p*-toluenesulfonic acid to give the dimethylketal (XXIX). Finally, this compound is deprotected with hydrazine in methanol, yielding intermediate (XVIII) (2). Scheme 2.

Description

White solid, m.p. 218-20 °C (decomp.), $[\alpha]_D$ –78.9° (c 0.46, DMF) (1); crystals, m.p. 216-7 °C (decomp.), $[\alpha]_D$ –72.6° (c 0.28, DMF) (2).

Scheme 2: Synthesis of Intermediate (VI)



Introduction

Three zinc-dependent cell-surface vasopeptidases are known to play an important role in the production and metabolism of vasoactive peptides, and thus to be involved in the pathophysiology of hypertension, left ventricular hypertrophy, heart failure and the progression of renal failure. Angiotensin-converting enzyme (ACE) is responsible for the production of angiotensin II, a vasoconstrictor octapeptide. Endothelin-converting enzyme (ECE) catalyzes the conversion of the inactive big endothelin-1 into the more potent vasoconstrictor endothelin-1. Neutral endopeptidase (NEP) degrades the atrial natriuretic peptide, which induces diuresis, natriuresis and vasodilatation.

Although the renin-angiotensin system has been established as a prime target for cardiovascular disease therapy, the search for a new generation of drugs is being actively pursued with the aim of further decreasing cardiovascular morbidity and mortality. A new therapeutic strategy has been planned based on the design of compounds that are able to inhibit two or more endothelial cell peptidases (3).

Table I: Structures of dual and triple vasopeptidase inhibitors in development (from Prous Science Ensemble database).

Dual NEP/ACE inhibitors

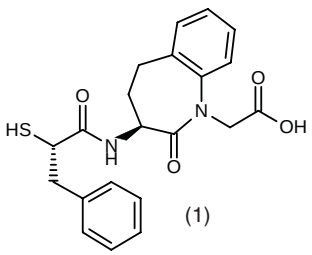
1. BMS-182657
   (Bristol-Myers Squibb)
2. ER-32935
   (Eisai)
3. Fasidotril
   (Bioprojet)
4. MDL-100240
   (Hoechst Marion Roussel)
5. Omapatrilat
   (Bristol-Myers Squibb)
6. Sampatrilat
   (Roberts, licensed from Pfizer)
7. Z-13752A
   (Zambon)

Dual NEP/ECE inhibitors

8. SLV-306
   (Solvay)

Triple NEP/ACE/ECE inhibitors

9. CGS-26582
   (Novartis)
10. SA-6817
    (Santen)
11. Sch-54470
    (Schering-Plough)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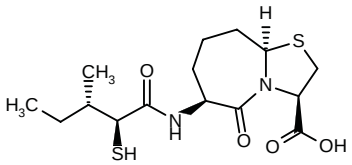
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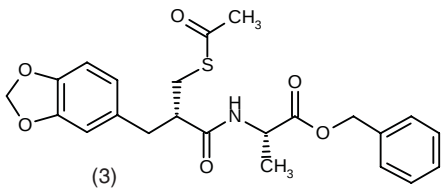
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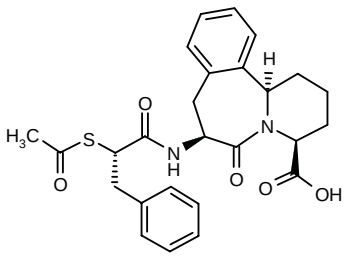
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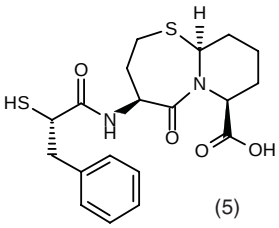
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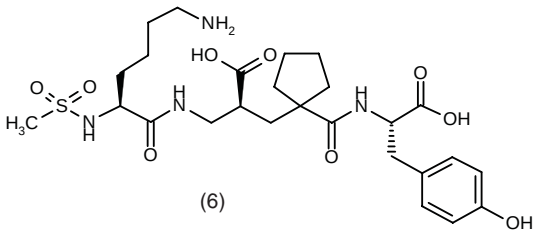
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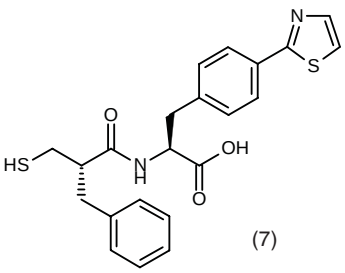
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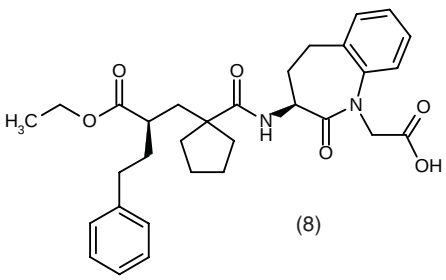
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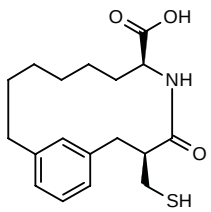
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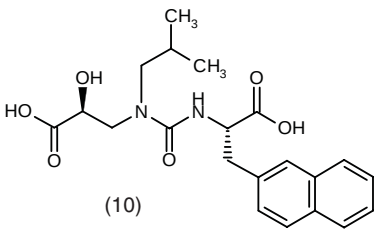
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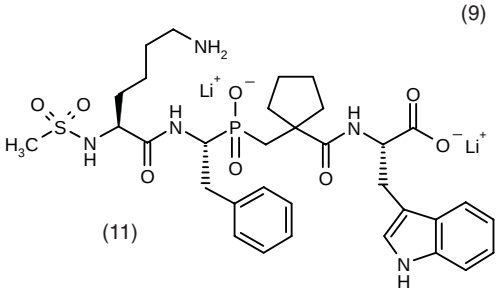
(11)

A search in the Prous Science Ensemble database reveals that several such dual- and triple-action vasopeptidase inhibitors are under development. Dual inhibitors of ACE and NEP include omapatrilat (Bristol-Myers Squibb) in phase III trials for hypertension and in phase II for heart failure; sampatrilat (Pfizer, licensed to Roberts), MDL-100240 (Hoechst Marion Roussel) and fasidotril (Bioprojet), all in phase II; Z-13752A (Zambon) in phase I; and ER-32935 (Eisai) and BMS-182657 (Bristol-Myers Squibb) in preclinical testing. Dual-action NEP and ECE inhibitors include SLV-306 (Solvay), which is in phase I clinical trials as a potential treatment for heart failure. At least three triple-action ACE, ECE and NEP inhibitors have been reported to be in preclinical testing: Sch-54470 (Schering-Plough), SA-6817 (Santen) and CGS-26582 (Novartis). The structures of dual and triple vasopeptidase inhibitors are shown in Table I, and their enzyme inhibitory activity is summarized in Table II.

Table II: Inhibition of vasopeptidases in vitro *(from Prous Science MFLine database).*

Compound	Parameter	ACE[a]	NEP[b]	ECE	Ref.
Dual NEP/ACE inhibitors					
BMS-182657	IC_{50}	10.5*	7.93*		20-23
ER-32935	K_i	1.8[c]	8.5		24
Fasidotril	K_i	215[d]	13.7[c]		25
MDL-100240	K_i	110	0.08		26
Omapatrilat	IC_{50}	5.0	8.0		1
Sampatrilat	IC_{50}	3.0	15.0		27
Z-13752A	IC_{50}	3.2	1.8		27
Dual NEP/ECE inhibitors					
SLV-306[#]	K_i		0.4[f]		28
	IC_{50}			1029[f]	28
Triple NEP/ACE/ECE inhibitors					
CGS-26582	IC_{50}	175[f]	4.0[f]	620[g]	29, 30
SA-6817	K_i	15.0	4.4		31
	IC_{50}			910[f]	31
Sch-54470	IC_{50}	2.6[h]	90.0*[f]	70.0[h]	32, 33

[a]Rabbit lung enzyme except when otherwise indicated. [b]Rat kidney enzyme except when otherwise indicated. [c]Rat lung enzyme. [d]Human kidney enzyme. [e]Human recombinant enzyme. [f]Enzyme source not reported. [g]Pig aorta enzyme. [h]Guinea pig lung enzyme. *Mean value from different experiments using the same method. [#]Data refer to KC-12615, the active metabolite of SLV-306.

In the search for dual vasopeptidase (metalloprotease) inhibitors with beneficial cardiovascular effects, scientists at Bristol-Myers Squibb synthesized a series of mercaptoacetyl-based fused heterocyclic dipeptide compounds and selected one of them, BMS-186716 (omapatrilat), for clinical development (1).

Pharmacological Actions

The pharmacological activity of omapatrilat has been characterized. The compound exhibited nanomolar potency against both neutral endopeptidase and ACE *in vitro* (K_i = 9 and 6 nmol/l, respectively), as well as potent and long-lasting inhibition of the angiotensin I-induced pressor response in rats after i.v. or oral administration and in monkeys after oral administration. Orally administered omapatrilat showed potent and long-lasting antihypertensive effects in low-, normal- and high-renin rat models of hypertension, and it significantly potentiated urinary sodium, ANP and cGMP excretion in response to exogenous ANP in monkeys (1, 4, 5).

The long-term effects of omapatrilat were assessed in cardiomyopathic hamsters with progressive heart failure, and were compared to those of placebo and the ACE inhibitor captopril. The compounds were administered at doses producing maximum ACE inhibition, being 200 μmol/kg/day in the case of omapatrilat and 750 μmol/kg/day for captopril. Compounds were administered to cardiomyopathic hamsters in the initial stages of left ventricular dilation, and hemodynamic parameters were measured and left ventricular volume was determined *ex vivo*; normal age-matched hamsters served as controls. Omapatrilat and captopril were administered at the same doses in another study to determine survival. The increase in urinary ANP, improvements in left ventricular preload and remodeling and survival were significantly superior in animals treated with the dual NEP/ACE inhibitor as compared to the ACE inhibitor or placebo. These findings indicate the possibility of increased survival in heart failure patients treated with the dual inhibitor omapatrilat (6).

Pharmacokinetics and Metabolism

[^{14}C]-Radiolabeled omapatrilat was administered to male beagle dogs at a dose of 200 mg p.o. or 50 mg i.v. over a 15-min infusion period. Blood samples were collected for up to 96 h postdosing, and urine and feces were collected for up to 168 h. Mean recovery in the urine and feces of radioactivity was 63.8 and 24.3%, respectively, for oral dosing; respective values for i.v. dosing were 73.8 and 17.3%. Excretion of radioactivity in the urine was nearly complete within 48 h of drug administration by either route. Mean C_{max} for free and radiolabeled omapatrilat was 11.2 and 18.8 μg/ml, respectively, by the i.v. route and 1.6 and 31.7 μg/ml for oral dosing. Median t_{max} for free and radiolabeled omapatrilat was 0.2 and 0.2 h, respectively, by the i.v. route and 0.8 and 0.2 h after oral dosing. Mean AUC for free and radiolabeled omapatrilat was 2.3 and 24.6 μg.h/ml, respectively, by the i.v. route and 1.1 and 303 μg.h/ml after oral administration. Oral absorption was determined to be approximately 90% and oral bioavailability was approximately 13%, indicating that considerable first-pass metabolism takes place in this species. All of the major metabolites, which accounted for about 70% of the radioactivity eliminated in urine, were identified. The major metabolic pathways of omapatrilat in dogs included mixed disulfide formation, *S*-methylation, sulfoxidation of the *S*-methyl metabolite, glucuronidation of the parent carboxyl group and cleavage of the amide bond (7).

Several articles have been published describing HPLC/positive ion electrospray mass spectrometry methods for determination of omapatrilat and its metabolites in pharmacokinetic/metabolic studies (8-10).

Clinical Studies

The 24-h hormonal effects on the plasma angiotensin II/angiotensin I ratio of a single dose of omapatrilat (10 mg), a dual NEP/ACE inhibitor, and of fosinopril (20 mg), an ACE inhibitor, were compared in 9 mildly sodium-depleted healthy subjects. Peak and AUC values for the plasma Ang II/Ang I ratio and for Ang II were similar with both compounds, with significant inhibition of ACE achieved in both cases 24 h postdosing. The

Box 1: Blood pressure-lowering effects of omapatrilat in healthy volunteers (14) [from Prous Science CSLine database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Healthy normotensive volunteers (n = 36)
Treatments[1]	Omapatrilat (O), 10 mg/d x 10 d (n = 6) O25 mg/d x 10 d (n = 6) O50 mg/d x 10 d (n = 6) O75 mg/d x 10 d (n = 6) Placebo (P) x 10 d (n = 12)
Results	BP peak (mean change) at day 1 (mmHg): O10 (–7.6) < O25 (–17.6) = O50 (–17.9) ≤ O75 (–18.7) BP trough (mean change) at day 1 (mmHg): O10 (–0.1) < O25 (–3.5) < O50 (–12.5) = O75 (–12.0) BP peak (mean change) at day 10 (mmHg): O10 (–11.0) < O25 (–19.2) = O50 (–14.1) < O75 (–24.3) BP trough (mean change) at day 10 (mmHg): O10 (–6.8) < O25 (–8.3) = O50 (–8.8) < O75 (–13.3)
Conclusions	Omapatrilat dose-dependently lowered MAP. This antihypertensive effect was related to NEP and ACE inhibition by omapatrilat.

[1]Na 6 g/d was administered 4 d prior to dosing for all treatment groups.

decrease in mean blood pressure at peak was similar for both active drugs, and both differed significantly from placebo. Urinary ANP also increased with omapatrilat, but not with fosinopril, and a mild natriuretic effect was observed. The increase in plasma active renin was inhibited by fosinopril, but not by omapatrilat. The antihypertensive effect of a single dose of the NEP/ACE inhibitor was shorter lasting than that of the ACE inhibitor. Thus, at the same level of ACE inhibition, the activity of the dual NEP/ACE inhibitor omapatrilat and that of the ACE inhibitor fosinopril are biologically different (11, 12).

The results from a study of the effects of single oral doses of omapatrilat (2.5-500 mg) in healthy men have been reported. NEP activity was measured by the plasma and urinary concentrations of atrial natriuretic peptide (ANP) and its second messenger, cyclic guanosine monophosphate (cGMP), while ACE activity, along with plasma renin activity, was used to measure the drug's effects on the renin-angiotensin system. Urinary excretion of ANP increased dose-dependently following drug administration, although plasma ANP concentrations did not appear to vary from baseline. Urinary excretion and plasma concentrations of cGMP increased, indicating NEP inhibition. Plasma renin activity increased and serum ACE activity decreased, indicating effective ACE inhibition; this effect lasted for 24 h after dosing. These results demonstrated omapatrilat to be a potent and long-acting inhibitor of NEP and ACE activity in humans (13).

In a phase I double-blind, placebo-controlled clinical trial, omapatrilat was administered daily for 10 days to 36 normotensive volunteers at doses of 10, 25, 50 or 75 mg. Salt intake was limited to 6 g/day for the 4 days preceding the study and throughout the dosing period. On day 1 of dosing, supine cuff mean arterial pressure (MAP) decreased (as peak effect) by 7.6 ± 3.9, 17.6 ± 8.4, 17.9 ± 10.0 and 18.7 ± 3.7 mmHg at doses of 10, 25, 50 and 75 mg, respectively; the respective decreases in MAP as 24-h trough effect were 0.1 ± 9.8, 3.5 ± 8.6, 12.5 ± 8.6 and 12.0 ± 10.0 mmHg. MAP (as peak effect) on day 10 decreased by 11.0 ± 5.9, 19.2 ± 6.6, 14.1 ± 9.8 and 24.3 ± 6.2 mmHg, respectively, and (as trough effect) by 6.8 ± 7.1, 8.3 ± 4.7, 8.8 ± 13.4 and 13.3 ± 10.5 mmHg, respectively. Omapatrilat inhibited plasma neutral endopeptidase, as seen by elevations in urinary ANP and plasma cGMP, and serum ACE was inhibited significantly over a period of 24 h following administration at all dose levels. Plasma renin activity was inhibited in a dose-dependent fashion. The superior antihypertensive activity observed with omapatrilat in this group of healthy volunteers was attributed to the dual inhibition of two vasopeptidases, neutral endopeptidase and ACE (14) (Box 1).

The acute hemodynamic effects of administering omapatrilat were evaluated in 113 patients with heart failure (NYHA class II-IV) and LVEF of ≤ 40%. Study participants were randomized to treatment with placebo or one of several doses of omapatrilat (1, 2.5, 5, 10, 25 or 50 mg), and were monitored hemodynamically for 24 h thereafter. Baseline hemodynamics were similar in all treatment groups, with mean pulmonary capillary wedge pressure (PCW) of 23.4 mmHg and mean cardiac index (CI) of 2.2 l/min/m^2. PCW decreased dose-dependently in subjects receiving omapatrilat, with decreases ranging from –3.8 mmHg at the lowest dose to –8.1 mmHg at the highest dose. Cardiac index increased by 0.2 l/min/m^2 at the highest dose, but was unchanged at the lowest one. Mean arterial pressure also decreased in a dose-dependent fashion, ranging from –2.5 mmHg at the 2.5-mg dose to –15.2 mmHg at the 50-mg dose. Omapatrilat was well tolerated, with more frequent reports of adverse events by subjects in the placebo group than by those administered the active drug (15) (Box 2).

The results from a double-blind, randomized pilot study demonstrated that once-daily administration of omapatrilat for 3 months was an effective therapy for chronic heart failure. Eighteen male patients (NYHA class II-III) received omapatrilat at doses of 2.5, 5 or 10 mg/day.

Box 2: Acute hemodynamic effects of omapatrilat in heart failure (15) [from Prous Science CSLine database].

Design	Double-blind, randomized clinical study
Population	Patients with heart failure (NYHA Class II-IV; LVEF ≤ 40%) (n = 113)
Treatments	Omapatrilat (O), 1, 2.5, 5, 10, 25 or 50 mg (n = 80) Placebo (P) (n = 33)
Results[1]	Baseline hemodynamics were similar among all groups: mean pulmonary capillary wedge pressure (PCWP) = 23.4 mmHg; cardiac index (CI) = 2.2 l/min/m^2 PCWP change (mmHg): P (–1.8) < 02.5 (–3.8) < O10 (–5.2) < O25 (–7.5) < O50 (–8.1) [O25, O50 *vs.* P, p <0.05] CI change (l/min/m^2): P (0) = O2.5 (0) < O10 (+0.1) = O25 (+0.1) < O50 (+0.2) MAP change (mmHg): P (–2.5) ≥ O2.5 (–2.7) > O10 (–7.5) ≥ O25 (–8.0) > O50 (–15.2) [O25, O50 *vs.* P, p <0.05] Stroke volume index change (ml/beats/min): P (–1.6) < O2.5 (+0.1) < O10 (+0.6) < O25 (+2.9) > O50 (+2.1) [O25, O50 *vs.* P, p <0.05] Heart rate change (beats/min): P (+4.8) > O2.5 (+0.6) > O10 (–0.1) > O25 (–3.3) < O50 (+0.3) [O25 *vs.* P, p <0.05]
Conclusions	Omapatrilat was well tolerated with fewer reported adverse events than placebo

[1]Hemodynamic indices are expressed as mean change from baseline 4 h after dosing.

Box 3: Long-term hemodynamic effects of omapatrilat in heart failure (17) [from Prous Science CSLine database].

Design	Randomized, double-blind clinical study
Population	Patients with heart failure (NYHA Class II-IV, EF < 40%) (n = 42)
Treatments	Omapatrilat (O), 2.5-40 mg/d x 3 months
Results	Heart rate change: -2.8 [p <0.05] Ejection fraction change: 5.7 [p <0.01] Urinary volume (ml/24h) change: 351 [p <0.01] Urinary sodium (mEq/24h) change: 23 [p <0.01]
Conclusions	Long-term treatment with omapatrilat was associated with improved clinical status and cardiac function by afterload reduction, diuresis, natriuresis and neuroendocrine status; higher doses tended to exert a greater effect on some variables

Omapatrilat treatment resulted in reductions in heart rate, mean systolic and diastolic pressure and end-systolic pressure. In addition, ventriculoarterial coupling was improved, subendocardial viability score increased and a reduction in myocardial oxygen demand was observed in treated patients. No alterations in cutaneous blood flow were observed, but the forearm hyperemic response increased (16).

In a randomized, double-blind study of omapatrilat in heart failure, 42 patients were treated for 3 months with the compound, administered as once-daily doses of 2.5, 5, 10, 20 or 40 mg. Patients were assessed at baseline and after 3 months of treatment, and data for all doses was pooled. Clinical status and cardiac function improved in omapatrilat-treated patients, as seen by afterload reduction, diuresis, natriuresis and improved neuroendocrine status. The higher doses appeared to provide greater therapeutic benefit in some of these parameters (17) (Box 3).

A randomized, double-blind, multicenter trial has evaluated the efficacy of omapatrilat in 369 patients with heart failure. The compound was administered once daily for 12 weeks; the first 190 patients received doses of 2.5, 5 or 10 mg, and the last 179 patients received doses of 2.5, 20 or 40 mg. Heart rate showed a tendency to decrease with omapatrilat, and ejection fraction improved in a dose-dependent fashion. Arterial pressure decreased in a dose-related manner, while cardiac index remained unchanged. The combined incidence of death, hospitalization or cointervention for heart failure was 34% with 2.5 mg omapatrilat and 19% with 40 mg omapatrilat. Based on the sustained benefit obtained in this patient group, further study of omapatrilat as a potential replacement for

Box 4: Efficacy of omapatrilat in heart failure (18) [from Prous Science CSLine database].

Design	Double-blind, randomized, multicenter clinical study
Population	Patients with heart failure (NYHA Class II-IV, EF ≤ 40%, PCWP ≥ 15 mmHg and CI ≤ 3.0 l/min/m^2 (n = 369)
Treatments	Omapatrilat (O), 2.5, 5, 10, 20 or 40 mg/d x 12 wk
Results[1]	PCWP trough at wk 12, change (mmHg): O2.5 (–2.8) < O5 (–4.7) ≥ O10 (–4.8) ≤ O20 (-4.1) ≤ O40 (–4) PCWP peak at wk 12, change (mmHg): O2.5 (–5.8) < O5 (–8.7) = O10 (–8.7) O20 (–7.8) < O40 (–8.2) [O20, O40 *vs.* O2.5, p <0.05] EF improvement rate: O2.5 (23-25%) ≥ O40 (22-27%) Arterial pressure decreased dose-dependently. Incidence of death, hospitalization or cointervention was 34% with O2.5 and 19% with O40
Conclusions	Omapatrilat provided long-term benefit in heart failure and may potentially replace ACE inhibitors in this indi-

[1]Hemodynamic indices are expressed as mean change from baseline 4 h after dosing.

ACE inhibitors in the setting of heart failure appears to be warranted (18) (Box 4).

Omapatrilat is in phase II trials for the treatment of heart failure and phase III for the treatment of hypertension (19).

Manufacturer

Bristol-Myers Squibb Co. (US).

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