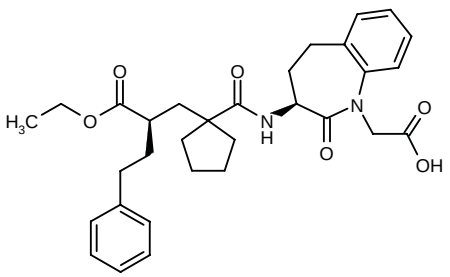
Drugs of the Future 2002, 27(1): 27-31

CCC: 0377-8282/2002

# SLV-306

*Antihypertensive*
*Treatment of Heart Failure*
*Neprilysin Inhibitor*
*Endothelin-Converting Enzyme Inhibitor*

2-[3(*S*)-[1-[2(*R*)-(Ethoxycarbonyl)-4-phenylbutyl]cyclopentan-1-ylcarboxamido]-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid



$C_{31}H_{38}N_2O_6$ Mol wt: 534.6492

CAS: 182821-27-8

EN: 242925

## Synthesis

SLV-306 is synthesized by acylation of 3(*S*)-amino-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-acetic acid *tert*-butyl ester (I) with 1-[2(*R*)-(ethoxycarbonyl)-4-phenylbutyl]cyclopentanecarboxylic acid (II) by means of methanesulfonyl chloride and triethylamine in dichloromethane to give the amide (III), which is then treated with trifluoroacetic acid in order to eliminate the *tert*-butyl ester group (1). Scheme 1.

The chiral intermediates amine (I) and acid (II) can be obtained as follows:

a) Bromination of 1-tetralone (IV) with $Br_2$ in methanol gives the 2-bromotetralone (V), which by reaction with hydroxylamine yields the corresponding oxime (VI). Isomerization of (VI) with polyphosphoric acid (PPA) at 80 °C affords the benzazepinone (VII), which is treated with potassium phthalimide (VIII) in DMF to provide the corresponding phthalimido derivative (IX). Reaction of (IX) with *tert*-butyl bromoacetate (X) by means of potassium *tert*-butoxide in DMF yields the benzazepine-1-acetic acid *tert*-butyl ester derivative (XI), which is treated with hot ethanolamine to eliminate the phthalimido group, yielding racemic amine (I). Finally, this racemate is submitted to optical resolution with L-(+)-tartaric acid to afford the chiral 3(*S*)-amino-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-acetic acid tert-butyl ester (I). Scheme 2.

b) Alkylation of diethyl malonate (XII) with 2-phenylethyl bromide (XIII) by means of potassium *tert*-butoxide in DMF gives diethyl 2-(2-phenylethyl)malonate (XIV), which is treated with KOH in ice-cooled water to afford the corresponding monoester monoacid (XV). The reaction of (XV) with formaldehyde in piperidine/water gives the acrylate (XVI), which is condensed with cyclopentanecarboxylic acid (XVII) by means of butyl lithium/diisopropylamine in THF to afford racemic (II). Finally, this racemate is submitted to optical resolution with L-(–)-α-methylbenzylamine to afford the chiral 1-[2(*R*)-(ethoxycarbonyl)-4-phenylbutyl]cyclopentanecarboxylic acid (II). Scheme 3.

## Description

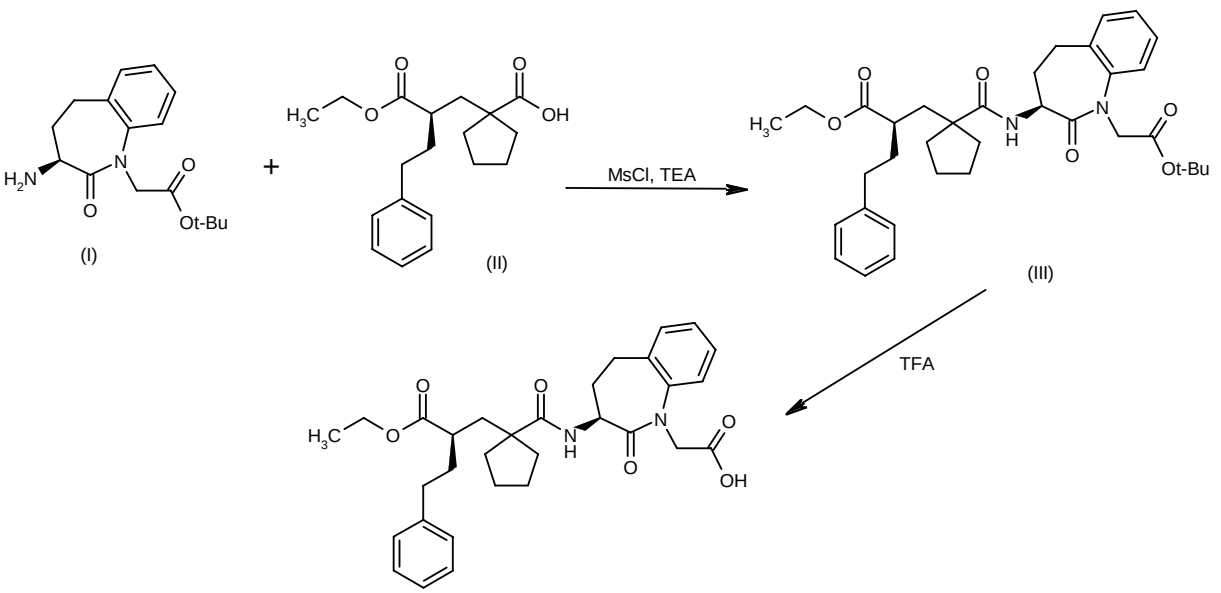
M.p. 71-4 °C; $[\alpha]_D^{20}$ –131.0° (c 0.5, MeOH).

## Introduction

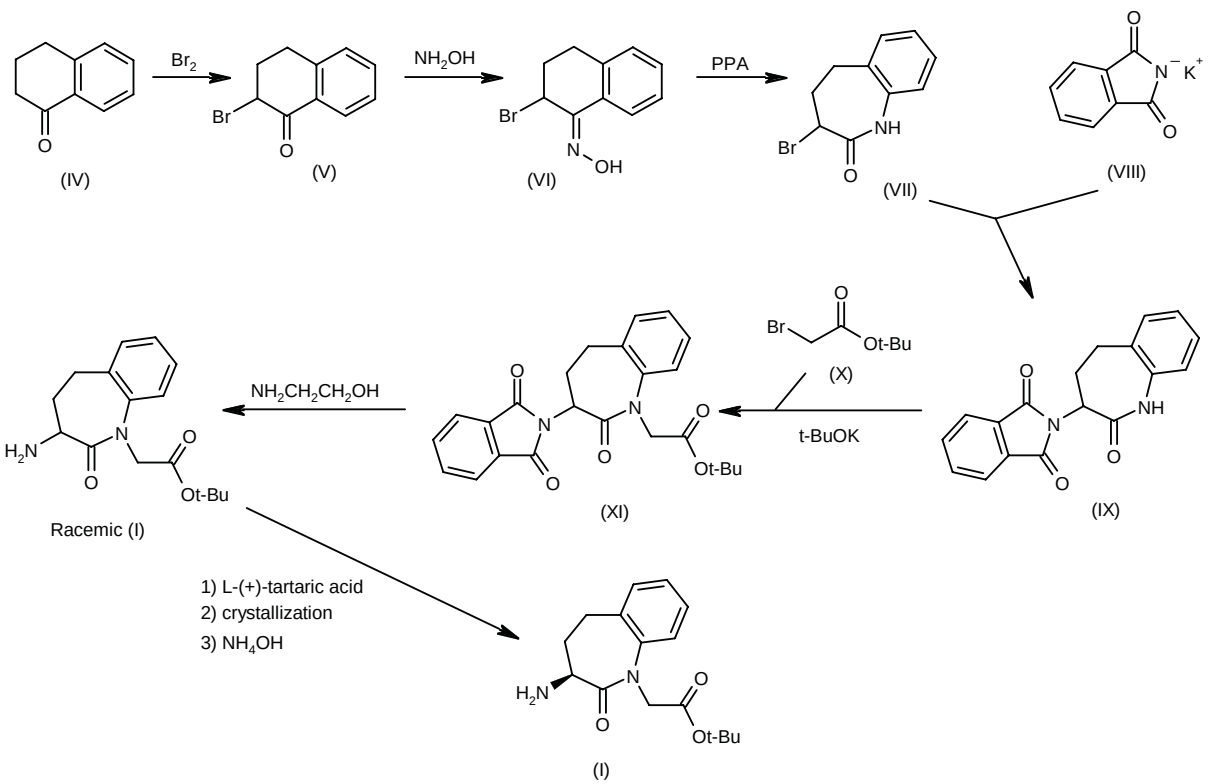
Arterial hypertension is the most prevalent cardiovascular condition in the world, affecting almost 691 million people. In the U.S. alone, 50 million individuals suffer from the condition. Hypertension is defined by WHO and the American Heart Association (AHA) as consistent systolic blood pressure (SBP) of 140 mmHg or higher and diastolic blood pressure (DBP) of 90 mmHg or higher and is chronic and preventable. It may be a primary disease or caused by other diseases. If hypertension is not controlled, it becomes a significant risk factor for several serious cardiovascular and renal conditions. One such condition is congestive heart failure, a progressive disorder of left ventricular myocardial remodeling which manifests as impaired cardiac function and circulatory congestion and is characterized as autonomic dysfunction, neurohormonal activation and overproduction of cytokines which all contribute to progressive circulatory failure. According to

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

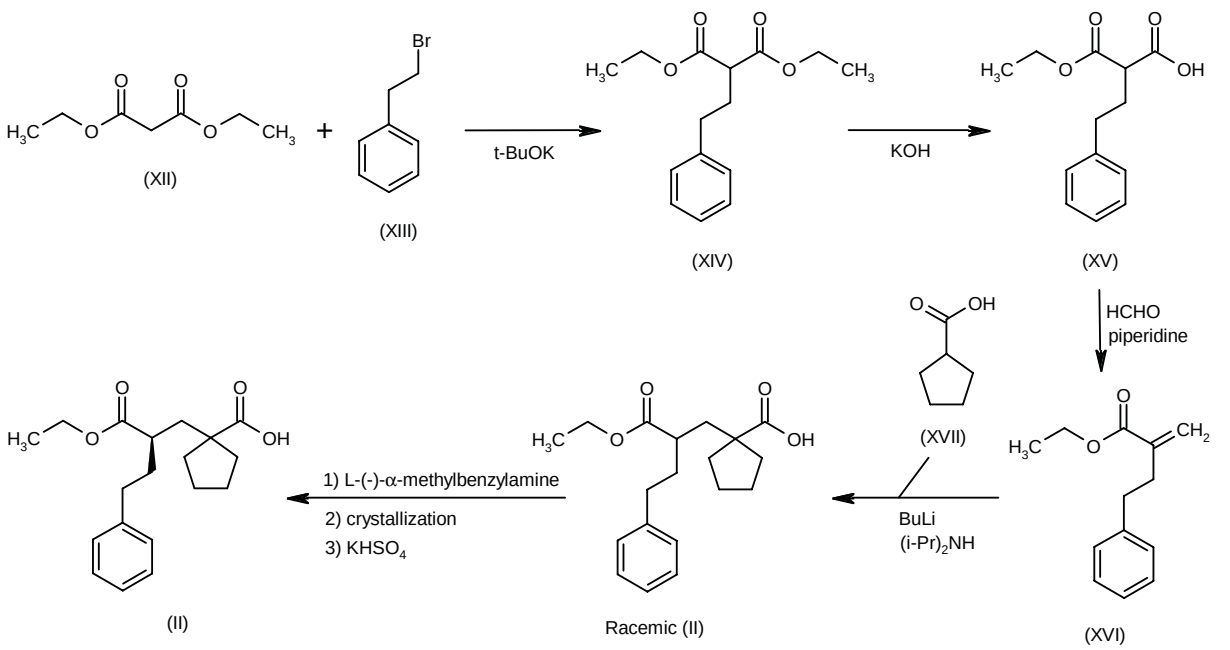
**Scheme 1: Synthesis of SLV-306**




**Scheme 2: Synthesis of Intermediate (I)**



**Scheme 3: Synthesis of Intermediate (II)**




the AHA, approximately 4.7 million individuals in the U.S. have congestive heart failure with as many as 550, 000 new cases diagnosed annually (2, 3).

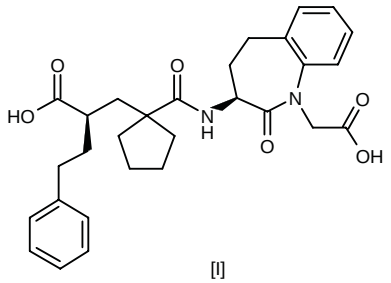
The global burden of cardiovascular diseases is now double that of cancer and is expected to significantly increase over the next two decades (2). Thus, significant efforts are being made to develop safe and more effective agents to control hypertension and treat heart failure. The main goal of the treatment of hypertension is to reduce the overall risk of coronary heart disease. Thus, treatment of hypertension is an essential component of the treatment of heart failure.

Several strategies have been devised to treat hypertension and/or heart failure. These include modulation of the renin-angiotensin system which plays a key role in regulating blood pressure and electrolyte and fluid balance (*e.g.*, inhibitors of angiotensin converting enzyme [ACE], ACE2, renin and antagonism of angiotensin II and aldosterone). In addition, inhibitors of vasopeptidase, calcium channel blockers and potassium channel activators have also shown efficacy in the treatment of hypertension and heart failure (2, 3).

Two other attractive approaches to controlling hypertension and heart failure involve the inhibition of neprilysin (neutral endopeptidase; NEP) and antagonism of endothelin. NEP is an enzyme belonging to the zinc-containing metalloproteases family of enzymes which is responsible for the degradation of atrial natriuretic peptide (ANP), a 28 amino acid peptide that induces diuresis, natriuresis and vasodilation. Thus, inhibition of NEP results in an enhancement of the effects of ANP which would be potentially effective in the treatment of hypertension and congestive heart failure as well as angina, renal insufficiency and glaucoma (2, 3).

Another interesting approach to controlling hypertension and heart failure is antagonism of endothelin, a 21 amino acid peptide that is the most potent and long-acting endogenous vasoconstrictor isolated to date. The peptide is known to have mitogenic, vasoconstrictor and bronchoconstrictor effects and has been found in aortic endothelium, neurons, vascular smooth muscle and gastric mucosa. Four endothelin isopeptides (endothelin-1, -2, -3 and -4) and 2 receptor subtypes ($ET_A$ and $ET_B$) have been identified. Endothelin-1 is considered to be a key mediator of the pathophysiology of cardiovascular disease and antagonism of this peptide has the potential to be a beneficial treatment of cardiovascular conditions. In particular, treatment with endothelin converting enzyme (ECE) inhibitors which block the synthesis of endothelin-1 from big endothelin-1 (its precursor) is one such approach to control hypertension and heart failure.

Inhibition of both the synthesis of the vasoconstrictor endothelin-1 and the degradation of vasodilator substances such as ANP presents an interesting and novel strategy for treatment of cardiovascular conditions. SLV-306 is a novel orally active dual-action endopeptidase inhibitor that inhibits both NEP and ECE and thus possesses promising vasodilatory and hypotensive effects that would be beneficial on the cardiovascular system.



[I]

SLV-306 has been selected for further development as a treatment for hypertension and heart failure.

## Pharmacological Actions

KC-12615 [I], the active metabolite of SLV-306, was shown to potently inhibit both NEP ($K_i$ = 0.400 nM) and ECE ($IC_{50}$ = 1.29 μM) in *in vitro* enzyme assays (4, 5). Moreover, SLV-306 has been shown to selectively inhibit a novel target known as human soluble endopeptidase (hSEP) (6).

The diuretic and natriuretic activities of SLV-360 and its metabolite were demonstrated in an *in vivo* study involving conscious rats under neurolept-analgesia following i.v. saline loading. Significant dose-dependent increases in diuresis and natriuresis were observed following i.v. administration of KC-12615 (+300 μl with 0.1 mg/kg and +620 μl with 3 mg/kg as compared to controls within 10 min of volume loading) and after oral administration of SLV-360 (+410 μl at 10 mg/kg and +570 μl at 100 mg/kg as compared to controls within 20 min of volume loading (4, 5).

The antihypertensive and diuretic effects of KC-12615 (30 mg/kg i.v.) and SLV-360 (10 mg/kg i.v.) were demonstrated in in vivo experiments using DOCA-salt hypertensive rats. SBP and DBP were reduced –18.8 ± 4.7 and –17.6 ± 9.3 mmHg, respectively, following KC-12615 administration and 15 and 20%, respectively, following SLV-360 treatment. A significant increase in diuresis (3.8 ± 1.9 *vs.* 1.2 ± 0.4 ml/rat in controls) was observed within 40 min of infusion of the metabolite. Moreover, pretreatment of anesthetized rats with KC-12615 (10 mg/kg i.v.) or SLV-360 (10 mg/kg intraduodenal) significantly and potently attenuated (KC-12615: maximum SBP = 165.8 ± 19.7 *vs.* 189.4 ±7.9 mmHg in controls; SLV-360: maximum SBP = 137.8 ± 20.7 *vs.* 161.2 ± 24.4 in controls) the increase in blood pressure due to infusion of big endothelin (0.5 nmol/kg i.v.) (4).

SLV-306 was also shown to be effective in several *in vivo* models of chronic heart failure. A study using rats with chronic heart failure due to aortic stenosis showed that SLV-360 (30 mg/kg/day for 12 weeks) treatment significantly reduced cardiac hypertrophy (heart weight: 1.8 *vs.* 2.3 g) and pulmonary congestion (lung weight: 1.9 *vs.* 3.1 g) as compared to untreated control rats. In addition, treated animals displayed a significant reduction (26 ± 18%) in the proportion of myosin V3 in pressure overloaded ventricles as compared to the increased expression observed in controls (42 ± 6 *vs.* 15 ± 7% in sham-operated animals) (5).

Similar efficacy was observed in three studies using genetically cardiomyopathic rats (SHHF/Mcc-facp), adriamycin-induced cardiomyopathic rabbits or dogs subjected to rapid cardiac pacing and aortic stenosis. Chronic SLV-360 treatment (30 mg/kg/day for 5 months in rats, 4 weeks in rabbits and 8 days in dogs) administered during the development of heart failure in all three models resulted in the following beneficial effects: significant diuresis and natriuresis and related reductions in edema (*i.e.*, a decrease in the lung weight:body weight ratio), improvements in cardiac function and hemodynamics (*i.e.*, decreases in cardiac filling pressure and total vascular resistance and an increase in cardiac output), a reduction in cardiac remodeling (*i.e.*, decreased heart weight:body weight ratio) and an improvement in neurohormonal activity (*i.e.*, decreases in plasma renin activity and aldosterone secretion, increases in plasma ANP and urinary cGMP) (7).

The efficacy of SLV-360 as a treatment for coronary heart disease was further supported from results of an *in vitro* study examining the effects of KC-12615 (1, 10 or 100 μM) on ECE-dependent big endothelin-1-induced vasoconstriction of human resistance arteries. Arteries were isolated from gluteal biopsies from patients with coronary heart disease with normal left ventricular ejection fractions. A dose-dependent decrease in big endothelin-induced vasoconstriction was observed in arteries incubated with the metabolite for 30 min; a significant response was obtained with the 100 μM concentration of KC-12615 (8).

## Clinical Studies

The efficacy of SLV-360 as a treatment for hypertension has been demonstrated in a phase II study conducted in hypertensive patients. Treatment with oral SLV-360 was safe and well tolerated and resulted in a significant reduction in both SBP and DBP. SLV-360 was also shown to improve hormone and hemodynamic parameters in an exploratory study involving patients with congestive heart failure (6).

SLV-360 continues to undergo phase II testing for the treatment of hypertension and congestive heart failure (9).

## Manufacturer

Solvay SA (BE).

## References

1. Waldeck, H., Höltje, D., Messinger, J., Antel, J., Wurl, M., Thormählen, D. (Kali-Chemie AG). *Benzazepin-, benzoxazepin- and benzothiazepin-N-acetic acid-derivs., their preparation and*

*their pharmaceutical compsns.* CA 2172354, EP 0733642, JP 1996269011, US 5677297.

2. Prous Science Drug R&D Backgrounders: *Arterial hypertension (online publication).* Updated Dec 24, 2001.

3. Prous Science Drug R&D Backgrounders: *Heart failure (online publication).* Updated Jan 3, 2002.

4. Meil, J., Wurl, M., Thormählen, D., Rose, H. *Pharmacology of the active metabolite of SLV 306, a mixed inhibitor of NEP and ECE.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.22.

5. Meil, J., Rupp, H., Thormählen, D., Rose, H. *In-vivo results with SLV 306 an orally active inhibitor of NEP and ECE.* Naunyn-Schmied Arch Pharmacol 1998, 358(1, Suppl. 2): Abst P 52.25.

6. *Proof of principle demonstrated in phase II studies for novel cardiology candidate therapeutic.* DailyDrugNews.com (Daily Essentials) September 18, 2001.

7. Thormahlen, D., Udvary, E., Rozsa, S., Papp, J.G., Tovofic, S. *Activity of SLV 306, a dual inhibitor of NEP and ECE-1, in animal models of chronic heart failure.* 6th Int Conf Endothelin (Oct 10-13, Montreal) 1999, Abst 180.

8. Seed, A., Hillier, C., Berry, C., Johnston, F., Petrie, M., McMurray, J.J.V. *Evidence that a novel orally active NEP/ECE inhibitor blocks the vasoconstrictor response to big endothelin in human resistance arteries.* J Am Coll Cardiol 2001, 37(2, Suppl. A): 237A.

9. *Pipeline.* Solvay Web Site January 14, 2002.