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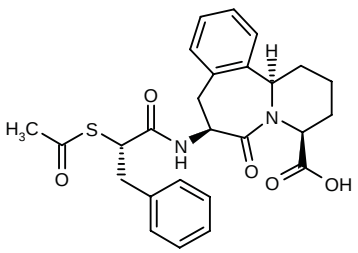
CCC: 0377-8282/2002

MDL-100240

Antihypertensive
Treatment of Heart Failure
ACE and NEP Inhibitor

M-100240

(4*S*,7*S*,12b*R*)-7-[2(*S*)-(Acetylsulfanyl)-3-phenylpropionamido]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-*a*][2]benzazepine-4-carboxylic acid



$C_{26}H_{28}N_2O_5S$

Mol wt: 480.5822

CAS: 142695-08-7

EN: 200002

Abstract

Arterial hypertension is the most common cardiovascular disease worldwide. Several therapeutic strategies are available for controlling the condition although they mainly target increased diastolic blood pressure. However, it now appears that the increased systolic blood pressure that may be present is an even greater risk. Thus, new strategies for controlling hypertension, and particularly systolic blood pressure, are being developed. One such strategy is dual inhibition of vasopeptidases. These agents suppress activity of both angiotensin-converting enzyme and neprilysin, resulting in increased vasodilating, natriuretic and antiproliferative effects of bradykinin, natriuretic peptides and adrenomedullin, which manifests as decreased vascular tone and reduced blood pressure. MDL-100240 is a dual vasopeptidase inhibitor that has shown potent vasodilating and hypotensive effects and has been chosen for further development as a treatment for hypertension and congestive heart failure.

Synthesis

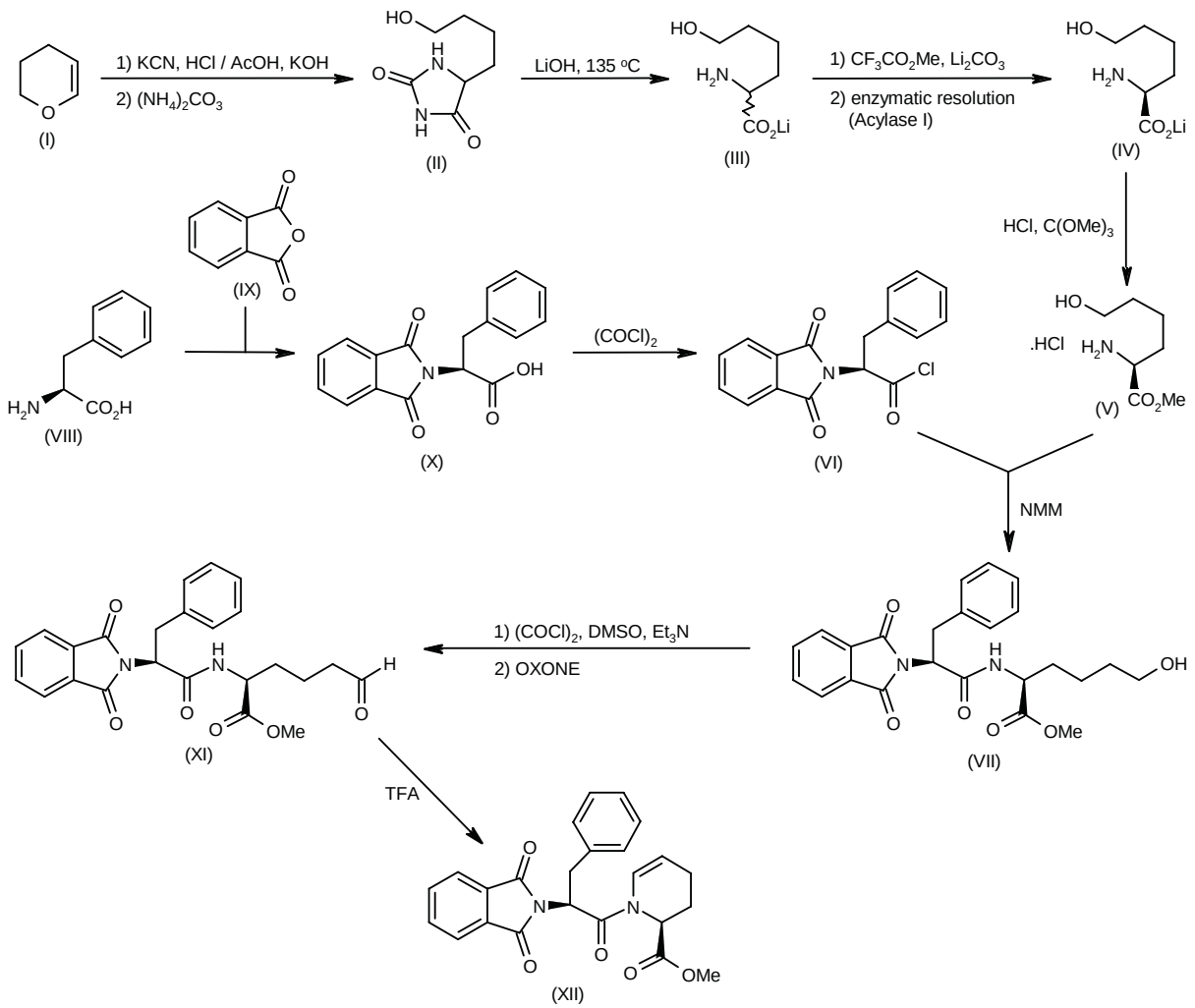
MDL-100240 can be synthesized by several related ways:

a) Reaction of 3,4-dihydro-2*H*-pyran (I) with potassium cyanide, HCl/HOAc and KOH in H_2O, followed by treatment with ammonium carbonate in H_2O provides hydantoin (II). Hydrolysis of compound (II) with LiOH in H_2O at 135 °C gives the racemic lithium salt (III), which by treatment with methyl trifluoroacetate and Li_2CO_3 in a refluxing mixture of BuOH/MeOH followed by enzymatic resolution with acylase I leads to the optically pure (*S*)-enantiomer (IV). Compound (IV) is converted into its corresponding methyl ester (V) using trimethyl orthoformate and HCl in refluxing MeOH (1, 2). The ester (V) is then coupled with *N*-phthaloyl-L-phenylalanine acid chloride (VI) by means of NMM in DMF/CH_2Cl_2 to provide the α-amino-ω-hydroxyhexanoic acid derivative (VII). Compound (VI) is prepared separately from L-phenylalanine (VIII) by reaction with phthalic anhydride (IX) in refluxing toluene (1) or DMF (2) to yield compound (X), which is treated with oxalyl chloride in refluxing toluene in the presence of DMF (1) or in DMF/CH_2Cl_2 (2). Oxidation of (VII) under Swern conditions – $(COCl)_2$, DMSO and Et_3N – followed by treatment with Oxone (potassium peroxymonosulfate) provides aldehyde (XI), which is then subjected to cyclization by means of TFA in CH_2Cl_2 to furnish the tetrahydropyridine derivative (XII) (1, 2). Scheme 1.

Simultaneous cyclization and ester hydrolysis of compound (XII) with either trifluoromethanesulfonic acid/trifluoroacetic anhydride in CH_2Cl_2 (1-3) or trifluoromethanesulfonic acid (4), followed by reesterification with either bromodiphenylmethane and Cs_2CO_3 in DMF (2, 3) or diphenyldiazomethane (Ph_2CN_2) in CH_2Cl_2 (4), results in the ester (XIII). Removal of the phthaloyl moiety of compound (XIII) by treatment with hydrazine monohydrate in refluxing MeOH affords the amino derivative (XIV), which

L.A. Sorbera, R.M. Castañer, M. del Fresno, M. Bayés. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of Intermediate (XII)

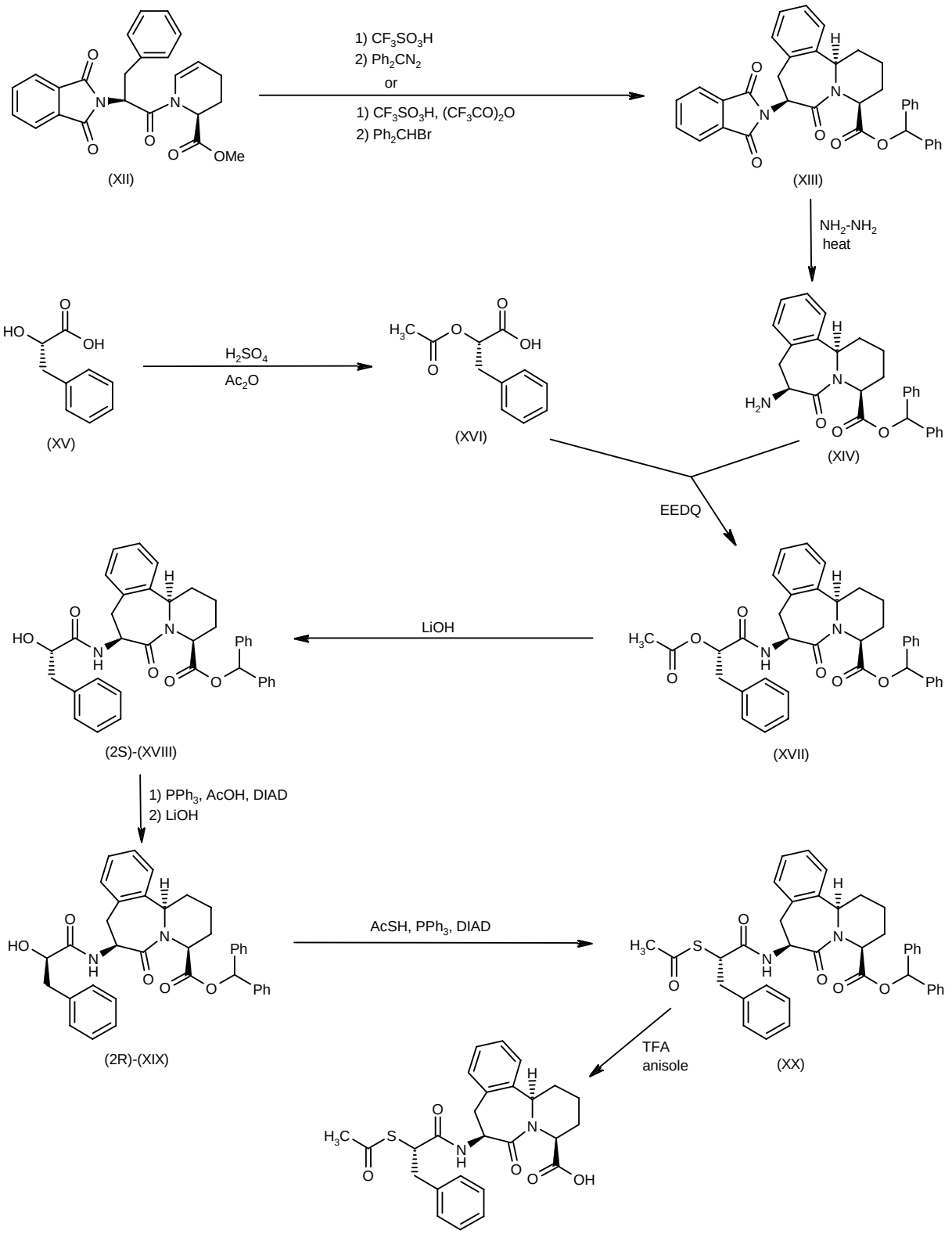


is coupled with (*S*)-3-phenyl-2-acetoxypropionic acid (XVI) – obtained by acetylation of (*S*)-3-phenyllactic acid (XV) with Ac_2O and H_2SO_4 – by means of EEDQ in CH_2Cl_2 to give amide (XVII). Deacetylation of (XVII) by saponification with LiOH in EtOH provides the hydroxyamide (2*S*)-(XVIII), which is then converted into its diastereomer (2*R*)-(XIX) by reaction with PPh_3, AcOH and DIAD in THF followed by treatment with LiOH in MeOH. Thioacetylation of (2*R*)-(XIX) by means of thioacetic acid, DIAD and PPh_3 in THF provides compound (XX), which is finally hydrolyzed at the diphenylmethyl group with TFA and anisole (2, 3). Scheme 2.

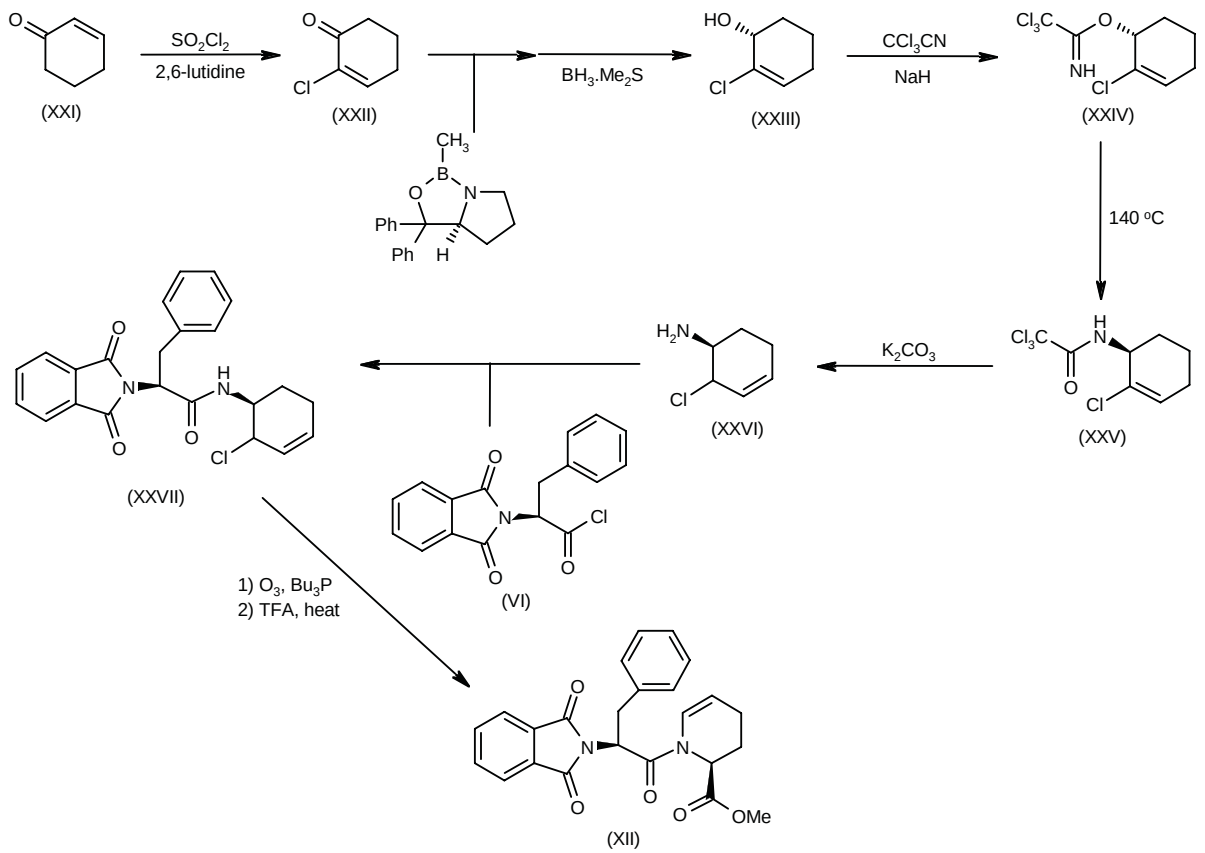
b) Treatment of 2-cyclohexenone (XXI) with SO_2Cl_2 and 2,6-lutidine in dichloromethane provides 2-chloro-2-cyclohexenone (XXII), which is reduced with (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]-oxazaborole and borane dimethyl sulfide complex in THF/MeOH giving (*R*)-2-chloro-2-cyclohexen-1-ol (XXIII). Reaction of (XXIII) with trichloroacetonitrile by means of NaH in diethyl ether gives the cyclohexenol derivative (XXIV), which is converted into acetamide (XXV) by heating at 140 °C in chlorobenzene. Hydrolysis of (XXV) with K_2CO_3 in water/methanol affords (*S*)-2-chloro-2-cyclohexen-1-amine (XXVI), which is then condensed with *N*-phthaloyl-L-phenylalanine acid chloride (VI) in ethyl acetate to yield amide (XXVII). Finally, ozonolysis of amide (XXVII) in CH_2Cl_2/MeOH, followed by reduction with tributylphosphine and treatment with TFA in refluxing CH_2Cl_2 provides the previously described intermediate (XII) (3). Scheme 3.

c) *N*-Phthaloyl-L-phenylalanine (X) is coupled to the racemic unsaturated amine (XXVIII) by means of EEDQ in dichloromethane to provide amide (XXIX), which is converted into a mixture of diastereomeric amides (XXX) by ozonolysis in CH_2Cl_2/MeOH, followed by reduction with dimethyl sulfide in pyridine and dehydration with TFA

Scheme 2: Synthesis of MDL-100240



Scheme 3: Synthesis of Intermediate (XII)



in refluxing CH_2Cl_2. Finally, chromatographic separation of this mixture by HPLC yields the previously described intermediate (XII) (4). Scheme 4.

d) Reaction of compound (XIV) with 2(*R*)-bromopropionic acid (XXXI) by means of EEDQ in CH_2Cl_2 affords amide (XXXII), which is treated with thioacetic acid and Cs_2CO_3 in DMF to give the protected thioacetate derivative (XX). Finally, the diphenylmethyl ester group of (XX) is removed by hydrolysis with TFA and anisole (5). Scheme 5.

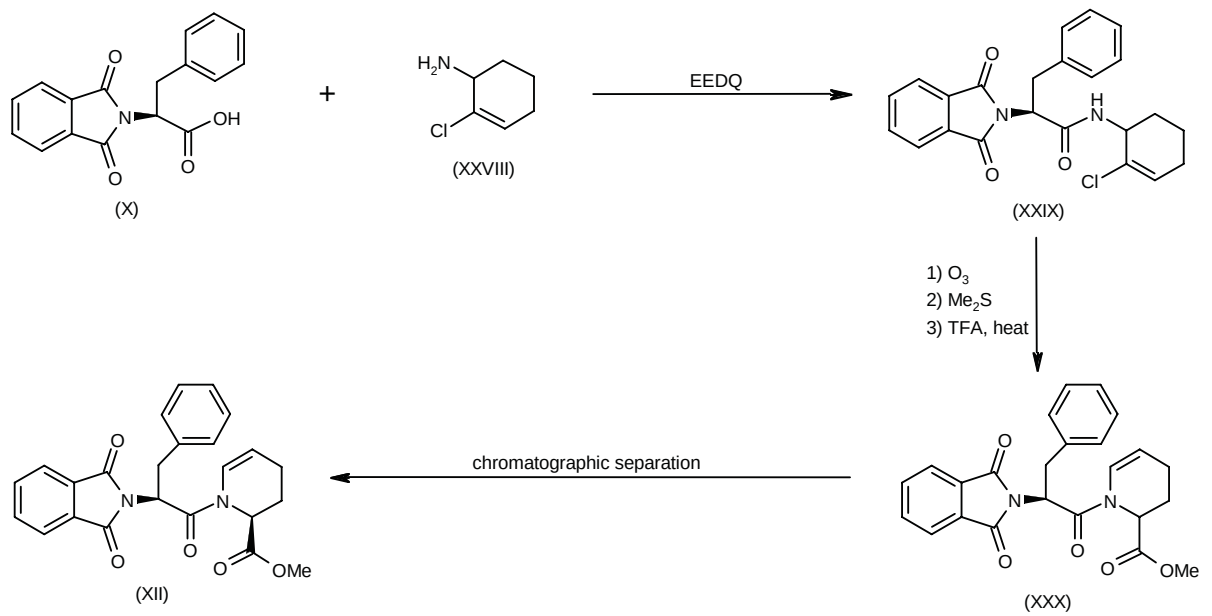
e) Treatment of *N*-phthaloyl-L-phenylalanine acid chloride (VI) with 2,6-dicyanopiperidine (XXXIII) – obtained by reaction of glutaric dialdehyde (XXXIV) with NaCN and ammonium chloride in water – by means of potassium *tert*-butoxide in ice/carbon tetrachloride gives the tetrahydropyridine derivative (XXXV), which is then subjected to cyclization with H_2SO_4 and trifluoroacetic acid anhydride to yield the benzazepine derivative (XXXVI). Hydrolysis of the cyano group of (XXXVI) with water yields the carboxylic acid (XXXVII), from which the desired diastereomer (XXXVIII) is separated by chromatography. Removal of the phthaloyl moiety of compound (XXXVIII) by treatment with hydrazine monohydrate and Et_3N in refluxing MeOH affords the amino derivative (XXXIX), which is then condensed with 2(*R*)-bromopropionic acid (XXXI) by means of *N*-hydroxysuccinimide (HOSu) and 1,3-dicyclohexylcarbodiimide (DCC) in THF resulting in amide (XL). Finally, MDL-100240 is obtained by reaction of (XL) with thioacetic acid and KOH in acetone (6). Scheme 6.

f) Treatment of acid chloride (VI) with ammonia provides amide (XLI), which by reaction with glutaric dialdehyde (XXXIV) in refluxing CH_2Cl_2 affords the pyridine derivative (XLII). Cyclization of (XLII) with either trifluoromethanesulfonic acid in CH_2Cl_2 or H_2SO_4 and trifluoroacetic acid anhydride yields the pyridobenzodiazepine derivative (XLIII), which is finally converted into intermediate (XXXVIII) by introduction of a carboxylic group by reaction with either H_2SO_4 and formic acid or H_2SO_4 and carbon monoxide (6). Scheme 6.

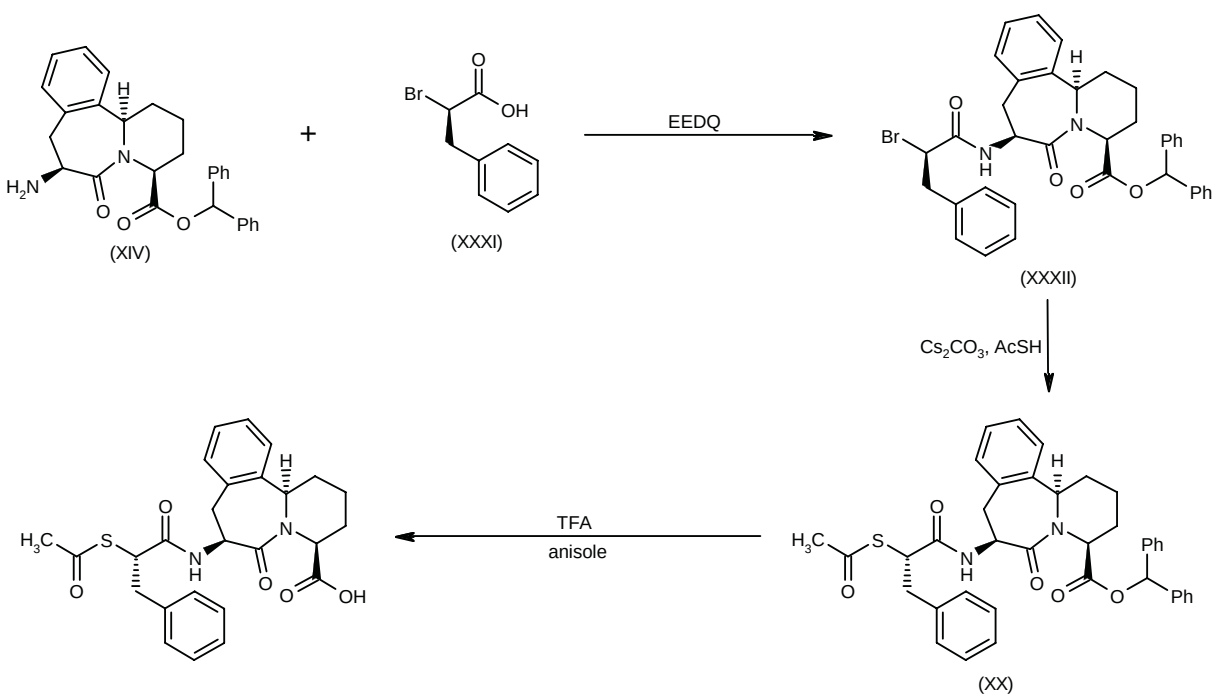
Introduction

Arterial hypertension is defined by the World Health Organization and the American Heart Association as

Scheme 4: Synthesis of Intermediate (XII)



Scheme 5: Synthesis of MDL-100240



Scheme 6: Synthesis of MDL-100240

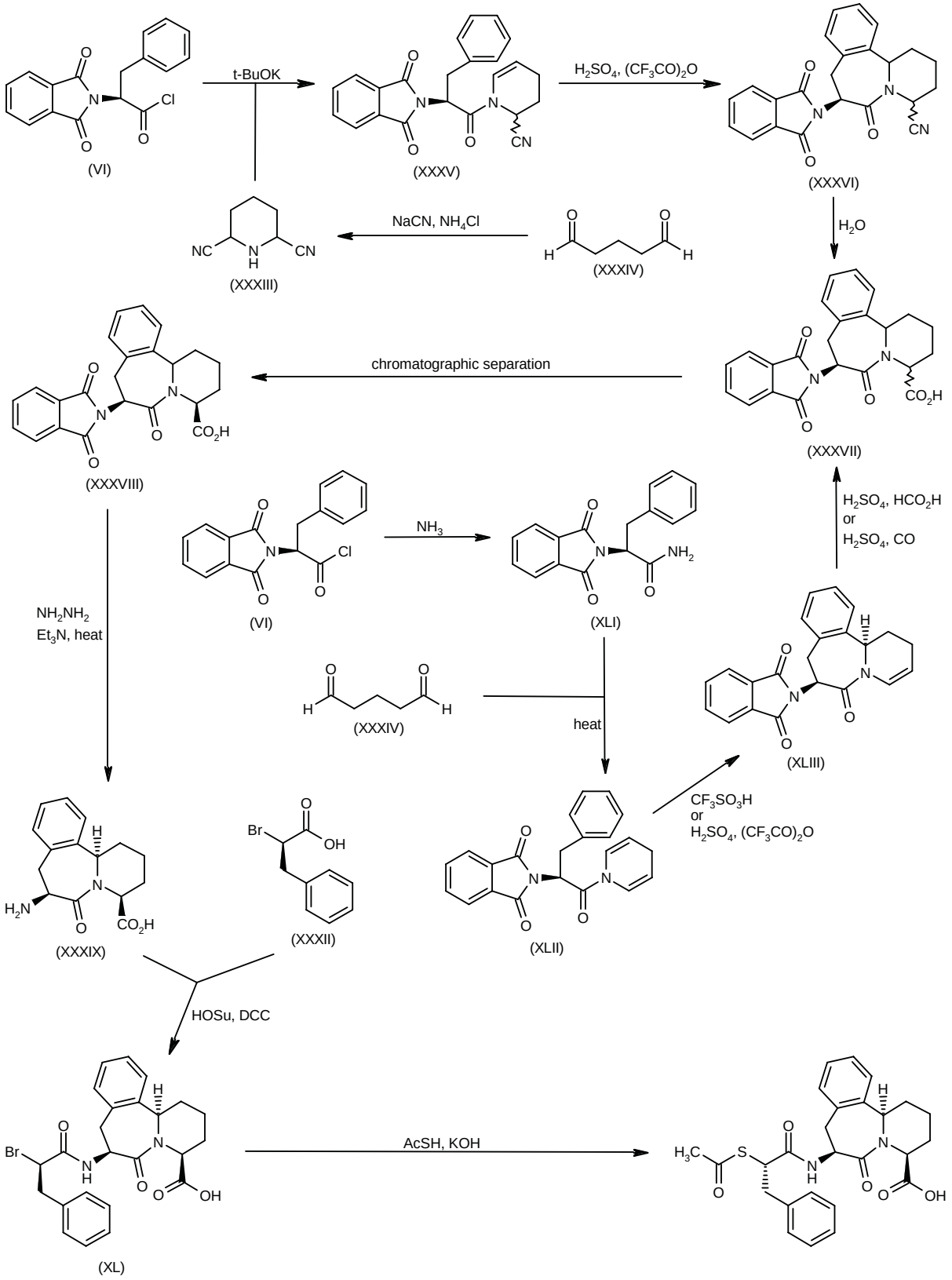
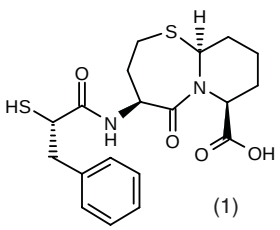
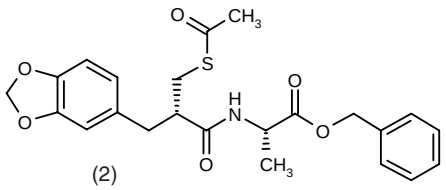


Table I: Dual vasopeptidase inhibitors in development (from Prous Science Integrity®).

Drug Name	Source	Phase
1. Omapatrilat	Bristol-Myers Squibb	Preregistered
2. Fasidotril	Bioprojet/Lilly	II
3. MDL-100240	Aventis Pharma	II
4. Z-13752A/GW-660511X	Zambon/GlaxoSmithKline	II
5. E-4030	Eisai	Preclinical


(1)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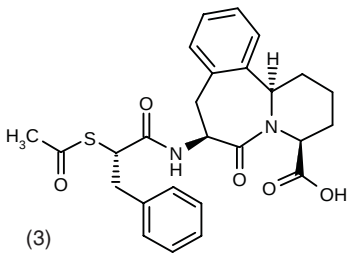
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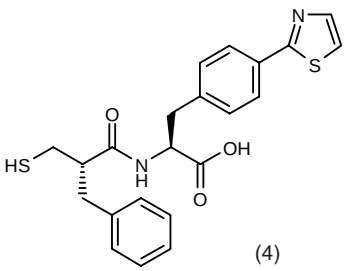
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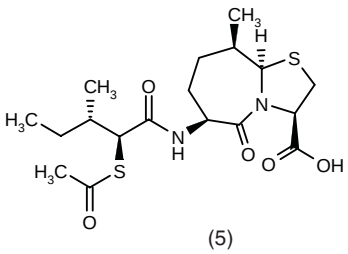
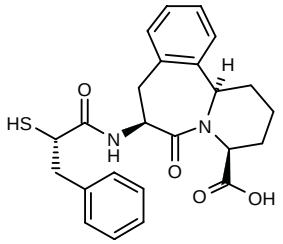

(5)

consistent systolic blood pressure (SBP) of 140 mmHg or higher and diastolic blood pressure (DBP) of 90 mmHg or higher. Arterial hypertension may be a primary or secondary disease and it is chronic but preventable. It is the most common cardiovascular condition in the world with as many as 691 million people suffering from the condition. If hypertension is not controlled, it becomes a significant risk factor for several serious cardiovascular (*i.e.*, congestive heart failure) and renal pathologies (7).

Because cardiovascular diseases represent a significant global burden, twice that of cancer, research has focused intensely on developing 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 (7, 8).

Several strategies have been devised to treat arterial 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, calcium channel blockers and potassium channel activators have also shown efficacy in the treatment of hypertension and heart failure (7, 8).

Currently available therapies for the treatment of arterial hypertension target the increased DBP. However, it has recently become evident that increased SBP may present an even greater risk than increased DBP. Thus, researchers are looking for new strategies that can better control SBP, reduce risk factors, improve treatment for heart failure and be effective in a more diverse population of hypertensive subjects. One strategy to control hypertension and heart failure that has been shown to be especially effective in controlling SBP involves the inhibition of 2 zinc-dependent cell-surface vasopeptidases, ACE (EC 3.4.15.1) and neprilysin (neutral endopeptidase, NEP; EC 3.4.24.11). ACE and NEP are 2 enzymes belonging to the zinc-containing metalloprotease family that are involved in the biosynthesis and/or activation of peptides mediating cardiovascular and renal function. ACE is responsible for the production of angiotensin II, the active octapeptide responsible for many physiological effects including vasoconstriction, stimulation of aldosterone release and renal absorption of sodium. NEP degrades atrial natriuretic peptide (ANP), a 28-amino-acid peptide that induces diuresis, natriuresis and vasodilation. Simultaneous inhibition of ACE and NEP would result in an attenuation of activity of the renin-angiotensin system and enhancement of vasodilating, natriuretic and antiproliferative effects of bradykinin, natriuretic peptides and adrenomedullin, which manifests as decreased vascular tone and reduced blood pressure. These effects would be potentially effective in the treatment of hypertension and congestive heart failure, as well as angina, renal insufficiency and glaucoma. Several dual vasopeptidase inhibitors that are currently under development for the treatment of arterial hypertension and/or heart failure are shown in Table I (7, 8).



[I]

MDL-100240, the orally active thioester prodrug of MDL-100173 [I], is a novel, potent dual vasopeptidase inhibitor that has balanced inhibitory activity against ACE and NEP. It has shown promising vasodilating and hypotensive effects beneficial to the cardiovascular system. MDL-100240 has been selected for further development as a treatment for arterial hypertension and congestive heart failure.

Pharmacological Actions

MDL-100173 equipotently inhibited ACE from rabbit lung (K_i = 0.11 nM) and NEP from rat kidney (K_i = 0.08 nM). The thioester prodrug MDL-100240 was less potent in inhibiting ACE from rabbit lung with a Ki value of 27 nM, possibly due to contamination with inhibitory thiol. MDL-100240 was effective in inhibiting ACE and NEP activities *ex vivo* in liver, kidney, brain and gut homogenates obtained from rats treated with the agent at a dose of 3 mg/kg i.p. (5, 9).

The ability of MDL-100173 and MDL-100240 to inhibit ACE and NEP activity *in vivo* was also demonstrated in several studies. Both agents (3 mg/kg i.p.) successfully suppressed angiotensin I-induced pressor responses by 75-80% in anesthetized rats, indicating inhibition of ACE; effects occurred within 15-30 min of dosing and were sustained for a minimum of 2 h. In addition, treatment of anesthetized rats with MDL-100240 (10 mg/kg i.v.) was found to enhance the effects of infused ANP(99-126) (0.1 μg/kg/min) on blood pressure and diuresis, and the effects of infused bradykinin (1 μg/kg/min) on blood pressure, indicating successful inhibition of NEP by the agent (9).

MDL-100240 was also shown in 4-day experiments to exert effects on vasoactive peptide (*e.g.*, angiotensin I and II, bradykinin, ANP, endothelin-1 [ET-1] and big ET-1) responses in conscious rats. The agent (3 mg/kg bolus followed by 3 mg/kg/h infusion on days 3 and 4) in vehicle-treated animals caused a slight but significant decrease in mean arterial blood pressure (MAP; –5 ± 2 mmHg), in addition to inducing tachycardia (41 ± 12 beats/min), increasing renal (17 ± 3%) and mesenteric (13 ± 4%) flows and increasing renal (23 ± 4%) and mesenteric (19 ± 5%) vascular conductances. Moreover, MDL-100240 completely inhibited angiotensin I (250 pmol/kg i.v. bolus on days 1-4)-induced hypertension, bradycardia and reductions in renal mesenteric and hindquarter vascular conductances, but had no effect on angiotensin II (125 pmol/kg bolus on days 1-4)-induced pressor, bradycardic or hindquarter vasoconstrictor effects. MDL-100240 did, however, enhance overall renal and mesenteric vasoconstrictor responses to angiotensin II. Administration of MDL-100240 to animals treated with bradykinin (3 nmol/kg) resulted in a reduction in bradykinin-induced tachycardia and an enhancement of renal, mesenteric and hindquarter vasodilator responses; bradykinin continued to cause significant hypotension in the presence of MDL-100240. The hypotensive effects of ANP (500 pmol/kg on days 1-4) were enhanced by MDL-100240 and promoted a delay in hindquarter vasoconstriction. Administration of MDL-100240 significantly attenuated big ET-1 (250 pmol/kg)-induced pressor effects but had no effect on bradycardic and renal, mesenteric and hindquarter vasodilator responses seen with big ET-1 alone. MDL-100240 had no effect on the initial and subsequent pressor and bradycardic actions of ET-1, although it enhanced renal and mesenteric vasoconstrictor effects (10).

The hypotensive effects of MDL-100173 and MDL-100240 have been demonstrated in several *in vivo* studies involving spontaneously hypertensive rats (SHR) and desoxycorticosterone acetate (DOCA)-salt hypertensive rats. MDL-100240 potently and significantly lowered blood pressure following oral administration (30 mg/kg) *in vivo* in both SHR and DOCA-salt rats (3). A further detailed study using these 2 hypertensive rat models in addition to high-renin renovascular hypertensive rats (*i.e.*, rats subjected to the 2 kidney, 1 clip Goldblatt method) also showed the hypotensive, diuretic and natriuretic efficacy of MDL-100173 (10 and 20 mg/kg i.v.). In comparison to captopril (5 and 10 mg/kg i.v.) which significantly lowered blood pressure only in the renovascular and SHR models and had no effect on urine, ANP or sodium excretion, MDL-100173 significantly lowered blood pressure and increased urinary excretion of ANP in all 3 models and significantly elevated diuresis and natriuresis in the SHR and DOCA-salt rats. Both agents were found to increase plasma renin activity (11).

Several studies have shown the efficacy of MDL-100240 in the (mREN2) 27 transgenic rat (TGRen2) model of severe arterial hypertension in which the mouse *REN2* gene is inserted into the rat genome, resulting in severe cardiovascular damage and enhanced tissue synthesis of angiotensin II. In one study, the activity of MDL-100240 (3 mg/kg/h i.v. infusion for 32 h) and enalaprilat (3 mg/kg/h i.v. infusion for 32 h) were compared. Both agents significantly lowered blood pressure and caused regional vasodilation (*i.e.*, mesenteric and hindquarter) over the first 8 h of infusion, although MDL-100240 was significantly more potent in lowering blood pressure than enalaprilat (–54 ± 9 *vs.* –38 ± 4 mmHg) due to a significantly greater decrease in cardiac index as compared to enalaprilat. In contrast to the effects of enalaprilat which were reduced between 8 and 24 h after the start of infusion, the antihypertensive effects of MDL-100240 were sustained regardless of the recovery of cardiac index.

This sustained effect of the agent was due to stimulation of further mesenteric and hindquarter vascular bed vasodilation. Infusion of the bradykinin B_2 receptor antagonist Hoe-140 (1 mg/kg i.v.) starting 24 h after the onset of enalaprilat and MDL-100240 infusion did not attenuate or suppress the effects of either agent, suggesting that the antihypertensive effects of these agents were not due to inhibition of bradykinin degradation, but instead were via suppression of angiotensin II production (12).

The effects of MDL-100240 (40 mg/kg by gavage) were also compared to ramipril (5 mg/kg by gavage) in 5-week-old TGRen2 rats. After 4 weeks of treatment, both agents significantly lowered blood pressure (174 ± 6 and 166 ± 5 mmHg for MDL-100240 and ramipril, respectively, *vs.* 255 ± 15 mmHg for placebo) and attenuated left ventricular hypertrophy (2.71 ± 0.22 and 2.36 ± 0.2 mg/g body weight, respectively, *vs.* 3.73 ± 0.25 mg/g for placebo) as compared to placebo. Aortic dilatation and mesenteric arteriole hypertrophy were significantly prevented and plasma aldosterone and creatinine levels were significantly decreased as compared to placebo in rats treated with MDL-100240 or ramipril. Treatment with both agents resulted in a significant decrease in tension responses of endothelium-free aortic rings *in vitro* to phenylephrine, KCl and ET-1. Plasma ANP levels were 11 and 2.4% higher in MDL-100240- and ramipril-treated rats, respectively, as compared to placebo, although results were not significant; cGMP levels were unaffected by either treatment. Examination of vascular metalloproteinase (MMP-1, MMP-2 and MMP-9) content via zymography showed that while ramipril treatment significantly increased only MMP-1 levels (145 ± 17 *vs.* 109 ± 18 arbitrary units [AU]), MDL-100240 significantly increased MMP-1 (160 ± 42 *vs.* 109 ± 18 AU), MMP-2 (190 ± 60 *vs.* 121 ± 47 AU) and MMP-9 (163 ± 45 *vs.* 100 ± 30 AU) as compared to untreated TGRen2 rats. The differential effects of the agents were further demonstrated when infusion of the bradykinin B_2 receptor antagonist icatibant (0.5-3 mg/kg via osmotic minipump starting at 4 weeks) was shown to significantly attenuate the blood pressure-lowering effect of MDL-100240 but not ramipril. These results suggest that the antihypertensive effect of MDL-100240 may, in part, involve enhancement of bradykinins (13-15).

A study using rats with chronic heart failure following experimental myocardial infarction has reported the efficacy of MDL-100240 (63 mol/kg p.o. b.i.d. for 4 weeks starting 1 week after infarction). Treatment resulted in significant decreases in atrial and ventricular hypertrophy, lung edema and left ventricular end diastolic pressure (LVEDP) as compared to placebo; MDL-100240 treatment also resulted in increased plasma renin activity and a reduction in plasma ANP. In comparison, although treatment with captopril (46 mol/kg p.o. b.i.d.) increased plasma renin activity and reduced plasma ANP in a manner similar to MDL-100240, it only reduced lung edema, with no effects on atrial and ventricular hypertrophy or LVEDP seen. Mean arterial blood pressure, heart rate and body weight were not altered by treatment with either agent (16).

Pharmacokinetics

The pharmacokinetics of MDL-100173 and MDL-100240 have been reported in a study validating 2 novel methods based on HPLC with ultraviolet absorbance detection at 200 nm, which detect unchanged MDL-100240 and free MDL-100173 or total MDL-100173 (following incubation of plasma with dithioreitol) levels in plasma. Both methods offered quantification of the compounds over the range of 25-1000 ng/ml. The overall extraction efficacies from dog plasma of unchanged MDL-100240 and free MDL-100173 using the first method were 79 and 86%, respectively, and the extraction efficacy from dog plasma of total MDL-100173 using the second method was 75%. Using these methods, it was reported that the plasma half-lives for MDL-100240 and free MDL-100173 obtained following i.v. administration of MDL-100240 (12.5 mg/kg) to male beagles were 0.04 and 0.1 h, respectively; the terminal elimination half-life for total MDL-100173 was 35.7 h. The AUC value obtained for total MDL-100173 was almost 10-fold higher than the sum of the AUC values for MDL-100240 and unconjugated MDL-100173. Similar results were obtained following i.v. (12.5 mg/kg) and oral (25 mg/kg) dosing of rats and dogs with MDL-100240. While MDL-100240 and unconjugated MDL-100173 plasma levels decreased rapidly following i.v. and oral administration (*i.e.*, detectable for only 1-2 h postdosing), total MDL-100173 was detected for 24-72 h postdosing. In dogs, the AUC values for total MDL-100173 were 28 and 67 times greater than the AUC for unconjugated MDL-100173 after oral and i.v. administration, respectively. The bioavailability of MDL-100240 based on total MDL-100173 was 9.97 and 45.7% in rats and dogs, respectively. The half-lives for unconjugated MDL-100173 and total radioactivity following i.v. administration of [^{14}C]-labeled MDL-100240 were 0.3 and 9.2 h in rats, respectively, and 0.2 and 31.1 h in dogs, respectively. Rats excreted 66 and 27% of the dose in feces and urine following i.v. administration, while dogs excreted 69 and 22%, respectively. These results suggest that significant biliary excretion may be evident following i.v. administration of MDL-100240 (17, 18).

A study involving first an open, 1-period, single-dose phase to characterize ACE inhibition after an i.v. infusion of MDL-100240 (12.5 mg) followed by a 3-group, parallel, randomized, double-blind phase to examine the bioavailability of MDL-100240 (2.5, 10 or 20 mg/day p.o.) after repeated dosing for 8 days, was conducted in 12 healthy male volunteers. Oral administration of 10 and 20 mg MDL-100240 resulted in similar ACE inhibition on days 1 and 8. Repeated dosing with 2.5 mg resulted in trough plasma ACE inhibition which increased from 33 to 44% after the final dose on day 8. The oral bioavailability of MDL-100240 was estimated to be 85% which was not significantly different from 100%. An accumulation ratio of 112% at steady state and a $t_{1/2}$ value of 0.31 days or 7.5 h were estimated (19).

Table II: Clinical studies of MDL-100240 (from Prous Science Integrity®).

Subjects	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind	Placebo iv → MDL-100240, 1.56 mg iv over 20 min → 6.25 mg iv over 20 min → 25 mg iv over 20 min (n=4) Placebo iv → MDL-100240, 3.13 mg iv over 20 min → 12.5 mg iv over 20 min → 50 mg iv over 20 min (n=4)	8	MDL-100240 induced a dose-dependent and long-lasting ACE blockade. Pressor responses to exogenous angiotensin I challenges were inhibited and the baroreceptor reflex in the presence of exogenous angiotensin II did not change. The magnitude and time course of the inhibition of the pressor responses to exogenous angiotensin I challenges were dose-dependent for both systolic and diastolic blood pressures, while the effects of angiotensin II remained unaffected	20
Healthy volunteers	Randomized, crossover	MDL-100240, 6.25 mg iv on a high-sodium diet MDL-100240, 6.25 mg iv on a low-sodium diet MDL-100240, 25 mg iv on a high-sodium diet MDL-100240, 25 mg iv on a low-sodium diet	12	MDL-100240 had a favorable hemodynamic, endocrine and renal profile in healthy subjects with a fall in blood pressure preserving renal hemodynamics and increasing urinary volume, atrial natriuretic peptide levels and cyclic GMP excretion	21

Clinical Studies

The safety and effects of MDL-100240 (1.56, 3.13, 6.25, 12.5, 25 and 50 mg i.v.) on vasopressor responses to exogenous angiotensin I and II challenges (i.v. bolus starting at 10 ng/kg) were examined in a randomized, double-blind, placebo-controlled, dose-escalation study involving 8 healthy males. Treatment with MDL-100240 was well tolerated and resulted in rapid, sustained and dose-dependent inhibition of plasma ACE (at 24 h postdosing: >70% with 12.5 mg or greater; about 50% with 3.13 and 6.25 mg; and about 30% with 1.56 mg). SBP and DBP responses to exogenous angiotensin I were dose-dependently inhibited in MDL-100240-treated subjects; response to angiotensin II challenges was unaffected by MDL-100240 treatment. Transient (3 h) decreases in mean supine blood pressure were seen with doses of 3.13 mg or greater and at 24 h or earlier with the 25- and 50-mg doses, although these decreases were not significant (20) (Table II).

A randomized, double-blind, placebo-controlled, crossover study involving 12 healthy volunteers with high (280 mmol/day) and low (80 mmol/day) sodium intake examined the endocrine and renal effects of single-dose MDL-100240 (6.25 and 25 mg i.v. over 20 min). Treatment with the agent decreased supine SBP during both high (8 and 4 mmHg 2 h after the high and low dose, respectively) and low (8 mmHg at 1-2 h after the high dose and –3 mmHg 4-6 h after the low dose) sodium intake; treatment did not alter DBP or heart rate. Treatment during both high and low sodium intake was also associated with a rapid and dose-related reduction in plasma ACE (71 and 85% at 8 h postdosing with the low and high doses, respectively), a decrease in plasma angiotensin II levels and an increase in plasma renin activity. Although plasma ANP levels were not affected by treatment, urinary ANP excretion dose-dependently increased; urinary GMP excretion was significantly increased from 0 to 8 h during high sodium intake and with the high dose of MDL-100240. Effective renal plasma flow and glomerular filtration were unaffected by treatment. However, urinary flow rate significantly increased during the first 2 h postdosing with either dose. In contrast to potassium excretion which remained stable, sodium excretion tended to increase from 0 to 4 h postdosing ($p = 0.07$) and uric acid excretion increased. Proximal and distal fractional sodium reabsorption was not affected by the agent. MDL-100240 was concluded to be safe with good tolerability. Four subjects, of whom 3 were in the low-sodium group, experienced a total of 6 episodes of symptomatic orthostatic hypotension (a decrease in SBP of 20 mmHg or more). Seven episodes of headache were seen in the group receiving MDL-100240 as compared to 3 in placebo. One case of diarrhea was reported (21) (Table II).

MDL-100240, being developed for the treatment of high blood pressure and congestive heart failure, advanced into phase IIb dose-finding trials for hypertension in 2001. Regulatory submissions in the U.S. and E.U. are expected in 2003 (22).

Source

Aventis Pharma AG (DE).

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