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Pharmacological and Pharmacokinetic Evaluation of EXP3312, an Orally-active Non-peptide Angiotensin II-Receptor Antagonist

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Abstract

EXP3312, 2-*n*-propyl-4-chloro-1-[(2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl)methyl]imidazole-5-carboxylaldehyde, is a non-peptide angiotensin II (AII) AT_1-receptor antagonist.

In the rabbit isolated aorta EXP3312 inhibited the contractile response to AII competitively with a pA_2 value of 8·24. In renal hypertensive rats EXP3312 reduced blood pressure with intravenous and oral ED30 values of 0·19 and 0·14 mg kg^{-1}, respectively. It also reduced blood pressure in frusemide-treated dogs when administered orally at 1 and 3 mg kg^{-1}. In rats and dogs, the absolute oral bioavailability of EXP3312 averaged 60 and 28%, respectively. When EXP3312 was administered intravenously to rats and dogs the plasma elimination half-lives were 1·20 and 2·52 h, respectively. In rats and dogs EXP3312 was metabolized to an active metabolite M1, 2-*n*-propyl-4-chloro-1-[(2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl)methyl]imidazole-5-carboxylic acid. M1 is about ten times more potent than EXP3312 in renal hypertensive rats; the intravenous ED30 value was 0·02 mg kg^{-1}. Because high plasma levels of M1 were found in rats after oral administration of EXP3312, it is likely that M1 contributes to the long duration of the antihypertensive effects of EXP3312 in renal hypertensive rats.

The results show that EXP3312 is a potent, orally active, competitive and selective AT_1-receptor antagonist and a potent antihypertensive agent; it is likely to be therapeutically useful in the treatment of hypertension and congestive heart failure.

Angiotensin II (AII) is the primary effector molecule of the renin-angiotensin system. An AII receptor antagonist would provide a direct approach to blocking the influence of the renin-angiotensin system. Highly potent and orally active non-peptide AII receptor antagonists, including losartan (Fig. 1), have been synthesized (Duncia et al 1992). The chemistry, pharmacology, pharmacokinetics, and toxicology of losartan have been reported by Wong et al (1991a,b). EXP3312, 2-*n*-propyl-4-chloro-1-[(2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl)methyl]imidazole-5-carboxylaldehyde, is a related analogue of losartan (Fig. 1). EXP3312 has been shown to have a high binding affinity for AII receptor binding sites in rat adrenal cortical tissues, with an IC50 value of 50 nM (DeNobel et al 1991), somewhat less than that of losartan (Wong et al 1991a). EXP3312, however, showed pronounced oral hypotensive potency exceeding that of losartan. In a manner similar to losartan, EXP3312 generated a more potent active carboxylic acid metabolite M1, 2-*n*-propyl-4-chloro-1-[(2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl)methyl]imidazole-5-carboxylic acid (Fig. 1). This paper describes the pharmacology and pharmacokinetics of EXP3312 in rats and dogs. The concentration–contractile response curve in-vitro for AII was also determined in the rabbit aorta.

Materials and Methods

Chemicals

Losartan, EXP3312 and M1 were synthesized by the Medicinal Chemistry group of the DuPont Merck Pharmaceutical Company. All organic solvents, buffer salts, and reagents were purchased from commercial sources and were of the highest quality available. Rat plasma from male Sprague–Dawley rats, containing EDTA, was purchased from Cocalico Biologicals (Reumstown, PA, USA).

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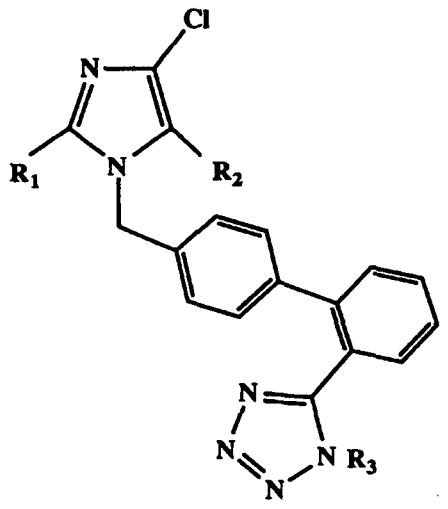
In-vitro rabbit aorta bioassay

Rabbit aortic helical strips were prepared and mounted in tissue baths containing oxygenated (95% O_2–5% CO_2) Krebs bicarbonate solution at 37°C as described previously (Wong et al 1990a). A cumulative concentration–contractile response curve for AII was obtained for each tissue before and after 15 min incubation with EXP3312. The analog contraction signal was recorded with a Grass force-displacement transducer (Grass Instrument Co., Quincy, MA, USA) connected to a Grass polygraph (Grass Instrument Co.) and analysed with a digital computer (Buxco Electronics, Inc., Sharon, CT, USA). Responses were expressed as a percentage of the maximal AII contractile response. To measure the potency of EXP3312, the pA_2 of EXP3312 was derived from the Schild plot, as described by Kenakin (1987). Concentration–contractile response curves for noradrenaline and KCl were also determined in the presence or absence of EXP3312 at 10 μM to determine the specificity of this antagonist.

Effects in pithed rats

Rats, 300–400 g, were anaesthetized, cannulated and pithed as previously described (Wong et al 1990a). The carotid artery and the jugular vein were cannulated for arterial pressure measurement and intravenous administration of drugs, respectively. Blood pressure was measured using a Gould pressure trans-



Compound	R_1	R_2	R_3
Losartan	n-C_4H_9	CH_2OH	K
EXP3174	n-C_4H_9	COOH	H
EXP3312	n-C_3H_7	CHO	H
M1	n-C_3H_7	COOH	H

FIG. 1. The chemical structures of losartan, EXP3174, EXP3312 and M1.

ducer (Model: P23ID, Gould Inc., Oxnard, CA, USA) coupled to a Grass polygraph (Grass Instrument Co.) and analysed with a digital computer (Buxco Electronics, Inc.). Both diastolic blood pressure and heart rate (HR) were recorded. Fifteen minutes before injection of AII, the animal was pre-treated with vehicle (a mixture of $NaHCO_3$ and dextrose). Dose–pressor response curves for AII were generated as described previously (Wong et al 1990a). Only one full dose–response curve was obtained for each rat.

Effects in conscious renal hypertensive rats

The renal hypertensive rats were prepared by a complete ligation of the left renal artery as described previously (Wong et al 1990a). Six days after the ligation, the animals were surgically prepared with carotid arterial and jugular venous catheters 18–24 h before the experiments (Wong et al 1990a). Blood pressure and HR were monitored as described above. Mean arterial pressure (MAP) was determined as the sum of diastolic blood pressure and one third of the pulse pressure. In the first series of experiments, conscious renal hypertensive rats were dosed with cumulative intravenous injections of EXP3312 or M1 and captopril at 3 mg kg^{-1}. In the second series, conscious renal hypertensive rats were dosed orally with the vehicle or EXP3312 at 0·3 to 10 mg kg^{-1} and the experiment was monitored for 3 h. In the third series, conscious renal hypertensive rats were dosed orally with the vehicle or EXP3312 at 1 mg kg^{1} and the experiment was monitored for 24 h. The intravenous and oral doses (ED30) of EXP3312 that reduced MAP by 30 mmHg were calculated by linear regression. EXP3312 was dissolved in a mixture of sodium $NaHCO_3$ and dextrose.

Effects in conscious normotensive dogs

Mongrel dogs of either sex were surgically prepared with a vascular access port (a chronic catheter device which can be connected to a pressure transducer for measurement of blood pressure) as described previously (Wong et al 1990b, 1991b). To elevate plasma renin activity frusemide (10 mg kg^{-1}) was administered intramuscularly 18 h before the experiment and intravenously 2 h before the experiment, as described previously (Wong et al 1991b). EXP3312 at 1 and 3 mg kg^{-1} or vehicle (a mixture of $NaHCO_3$ and dextrose) was given orally by gavage in frusemide-treated dogs. MAP was recorded as described above.

Animal dosing for pharmacokinetic studies

Rat. Male Sprague–Dawley CD rats (250–300 g) were cannulated as previously described (Wong et al 1993). Groups of four rats each were administered an oral dose of 10 mg kg^{-1} or an intravenous dose of 3 mg kg^{-1} of EXP3312 formulated in a mixture of poly(ethylene glycol) 400, water and ethanol (40:50:10, v/v). Blood samples (1 mL) obtained by cardiac puncture were collected 5, 10, 15, 30 and 45 min pre-dose, and 1, 2, 3, 4, 6, 8 and 10 h post-dose (4 rats per time point) into vacutainer tubes containing EDTA. Plasma was separated from blood cells by centrifugation, and stored frozen at − 20°C until analysed.

Dog. In a cross-over design, three male beagle dogs (8–10 kg) were administered EXP3312 3 mg kg^{-1} intravenously and 10 mg kg^{-1} orally. There was a washout period of at least one week between dosing days. Intravenous doses were administered into the cephalic vein. Blood samples (2 mL) were obtained 5, 10, 15, 30 and 45 min at pre-dose and 1, 2, 3, 4, 6, 8, 10 and 12 h post-dose by repeated puncture of the jugular vein and were collected into tubes containing EDTA. Plasma was separated from blood cells by centrifugation, and stored frozen at − 20°C until analysed.

Sample analyses

Plasma samples, with added internal standard, were applied to Bondelute octyl cartridges (Analytichem International, Harbor City, CA, USA) previously pre-washed with methanol and water. The cartridges were then washed with water and the compounds of interest were eluted with 2 × 0·5 mL methanol. Samples were evaporated to dryness under nitrogen, reconstituted with mobile phase and analysed by HPLC. The coefficients of variation for the intra- and inter-day precision of the assay were less than 10% for concentrations ranging from 0·020 to 10·0 μg mL^{-1}. The detection limit was 20 ng mL^{-1} using 0·5 mL plasma for extraction. The extraction recovery was greater than 90% in the above concentration range.

The plasma concentration–time data were used to determine the bioavailability and pharmacokinetic parameters by standard model-independent methods as described previously (Wong et al 1993).

HPLC conditions

EXP3312, the carboxylic acid metabolite M1, and the internal standard were detected by HPLC with UV detection. Separation was achieved on a C8 column (250 × 4·6 mm, 5 μm; Zorbax, Mac Mod); the mobile phase was 0·1 M phosphoric acid-acetonitrile-water (31:49:20, v/v) delivered at a flow rate of 1·5 mL min^{-1}. The HPLC system consisted of a Perkin-Elmer series 4 pump, an ISS-100 autosampler (Perkin-Elmer), and a Spectroflow 783 programmable absorbance detector (ABI Applied Biosystems, Foster City, CA, USA) set at 254 nm.

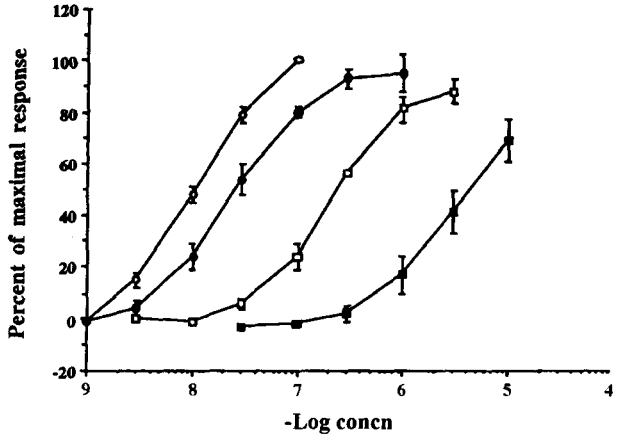


FIG. 2. Effects of EXP3312 on the log concentration–contractile response curves for angiotensin II in the rabbit aorta. Values represent the mean ± s.e.m. (n = 7). (○) Control, (●) EXP3312 0·01 μM, (□) EXP3312 0·1 μM and (■) EXP3312 1 μM.

Plasma concentrations were calculated from the ratio of the peak height of EXP3312 to that of the internal standard, with reference to a standard curve. A Nelson Analytical 4400 Chromatography Data System (Xtrchrom software, version 7·2, Nelson Analytical, Cupertino, CA, USA) was used to record chromatograms and integrate peak heights.

Results and Discussion

Pharmacology

Two major AII receptor subtypes, AT_1 and AT_2, have been defined pharmacologically with selective ligands, losartan and PD123177 or CGP 42112A (for reviews see Wong et al 1992; Timmermans et al 1993). Similar to losartan, EXP3312 is a selective AT_1-receptor ligand and has a high binding affinity for the AT_1-receptor subtype in the rat adrenal cortex, with an IC50 of 50 nM (DeNoble et al 1991). As expected from a selective AT_1-receptor antagonist, EXP3312 is very potent in blocking the contractile and pressor responses to AII in the rabbit isolated aorta and pithed rats, respectively. It does not appear to have AII-like agonistic effects in-vitro or in-vivo.

In the rabbit aorta, EXP3312 (10^{-8} to 10^{-6} M) shifted the concentration–contractile response curve for AII parallel and to the right in a concentration-dependent manner (Fig. 2). The pA_2 of EXP3312 was 8·24 ± 0·02 (n = 7), which was similar to that of losartan (8·48). The inhibitory effect of EXP3312 on the response to AII appears to be specific because it had minimal effects on the concentration–contractile response curves for noradrenaline and KCl (n = 9 for both, data not shown).

Similarly, in the pithed rat, EXP3312 at intravenous doses of 1 to 10 mg kg^{-1} caused a rightward shift of the log dose–pressor response curves for AII in a dose-dependent manner (Fig. 3). EXP3312 at 10 mg kg^{-1} intravenous did not significantly alter the dose-response curves for vasopressin or noradrenaline, suggesting selective AII antagonism (Fig. 3).

To examine the antihypertensive efficacy of EXP3312, its effect on blood pressure and HR were studied in renal artery-ligated rats. As shown in Fig. 4, cumulative intravenous injections of EXP3312 (n = 4) caused a dose-dependent decrease in MAP. At 3 mg kg^{-1} given intravenously,

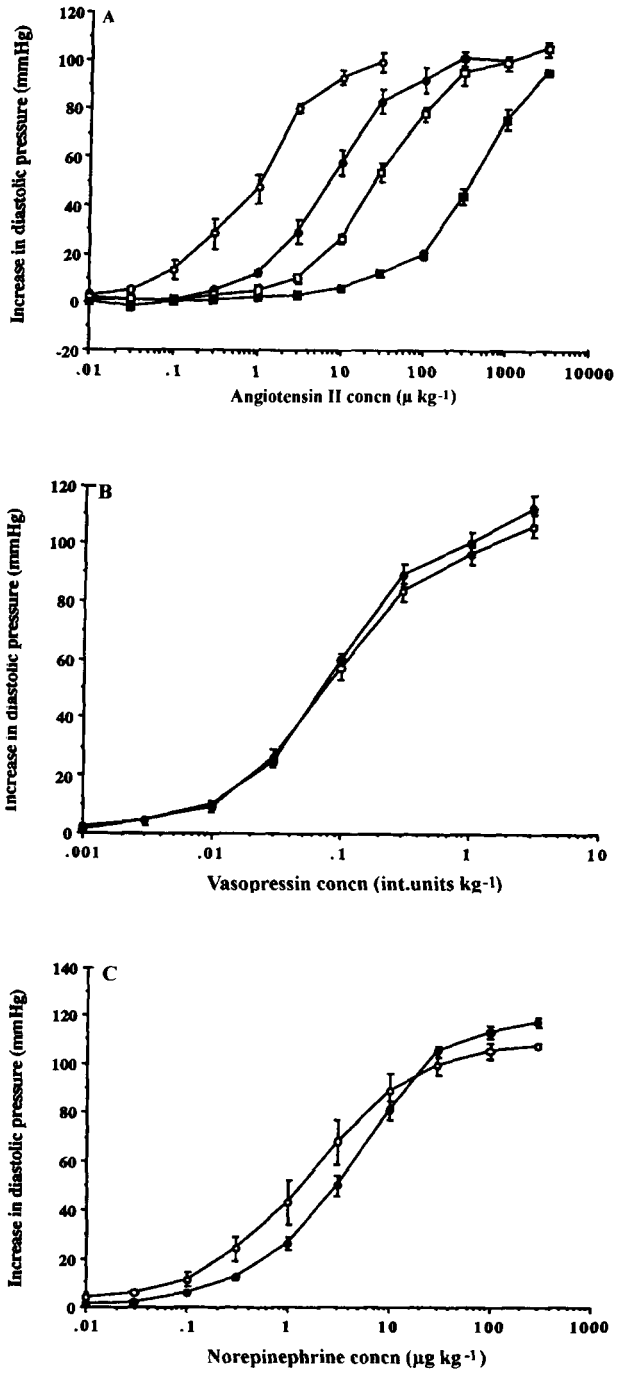


FIG. 3. Effects of intravenous saline vehicle and EXP3312 on the log dose–pressor response curves for A, angiotensin II; B, vasopressin and C, noradrenaline in the pithed rat. Values represent the mean ± s.e.m. (n = 4–5). (○) Control, (●) EXP3312 1 mg kg^{-1} intravenous, (□) EXP3312 3 mg kg^{-1} intravenous and (■) EXP3312 10 mg kg^{-1} intravenous.

EXP3312 reduced blood pressure to a normotensive level. Captopril at 3 mg kg^{-1} at the end did not lower MAP further, suggesting that EXP3312 at 3 mg kg^{-1} caused a maximum blockage of the vasoconstrictor influence of the renin-angiotensin system. The calculated intravenous ED30 for EXP3312 is 0·19 mg kg^{-1}, which is four times more potent

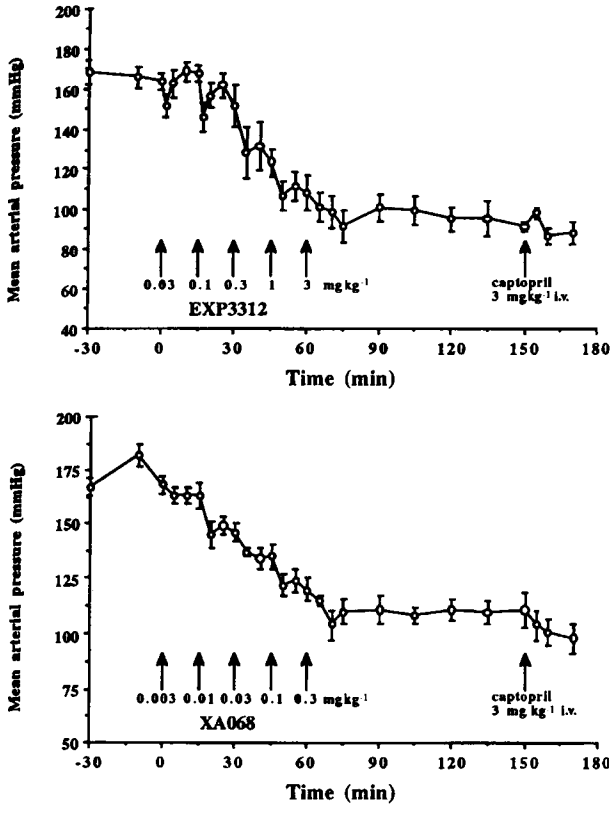


FIG. 4. Effect of intravenous EXP3312 (A) and M1 (B) on mean arterial pressure in conscious renal hypertensive rats. Values represent the mean ± s.e.m. (n = 4–5).

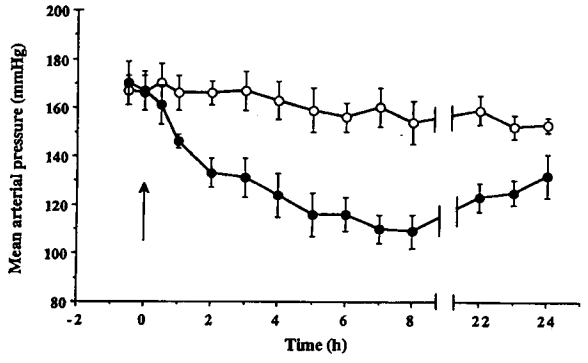


FIG. 5. Effects of oral EXP3312 on mean arterial pressure in conscious renal hypertensive rats. Values represent the mean ± s.e.m. (n = 6–9). (○) Control, (●) EXP3312 1 mg kg^{-1} oral.

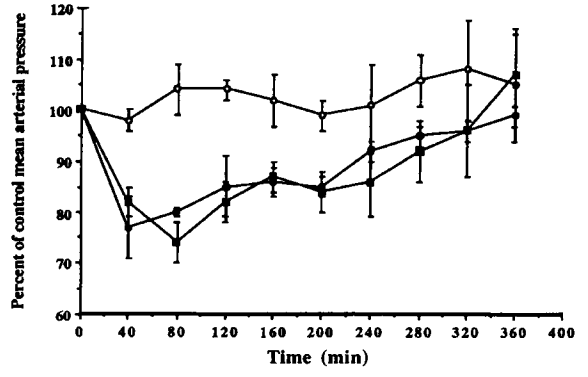


FIG. 6. Effects of oral EXP3312 on mean arterial pressure (expressed as percentage of control mean arterial pressure) in conscious frusemide-treated dogs. Basal values of mean arterial pressure in the dogs treated with the vehicle and EXP3312 at 1 and 3 mg kg^{-1} were 111 ± 6, 107 ± 5 and 114 ± 4 mmHg, respectively. Values represent the mean ± s.e.m. (n = 4–8). (○) vehicle, (●) EXP3312 1 mg kg^{-1} oral and (■) EXP3312 3 mg kg^{-1} oral.

than losartan (ED30 = 0·8 mg kg^{-1}, Wong et al 1991a). The acid metabolite M1 given cumulatively intravenously also reduced MAP in a dose-dependent manner (Fig. 4) with a calculated intravenous ED30 of 0·02 mg kg^{-1}. M1 is about 10 times more potent than EXP3312 in reducing blood pressure in renal hypertensive rats.

Given orally, EXP3312 also reduced blood pressure dose-dependently at 0·3–3 mg kg^{-1} (n = 5 to 6 per dose, data not shown). The calculated oral ED30 for EXP3312 is 0·14 mg kg^{-1}. The oral potency of EXP3312 in renal hypertensive rats is about 4-fold better than that of losartan (ED30 = 0·6 mg kg^{-1}; Wong et al 1991a). When given orally at 1 mg kg^{-1} (n = 6), EXP3312 produced an antihypertensive effect of 24 h duration (Fig. 5) and did not alter HR (data not shown). In addition, compared with the vehicle-treated group, EXP3312 given orally at 1 and 3 mg kg^{-1} reduced MAP for about 6 h in frusemide-treated dogs (Fig. 6).

Pharmacokinetics

After intravenous administration of 3 mg kg^{-1} EXP3312 in rats, the plasma levels declined rapidly in a monophasic fashion with a terminal elimination half-life of 1·20 h (Table 1 and Fig. 7). The systemic clearance was 2·24 L h^{-1} kg^{-1} and the volume of distribution at the steady state was 1·44 L kg^{-1}. After a 10 mg kg^{-1} oral dose in rats, EXP3312 was rapidly absorbed with maximum plasma levels of 2·68 μg mL^{-1} detected after 0·25 h. The terminal half-life after oral administration was 1·80 h and the oral bioavailability was 60%. The high bioavailability and the fact that the systemic clearance of EXP3312 from plasma after an intravenous dose was similar to the hepatic blood flow, suggest that presystemic metabolism was not extensive in rats. The high clearance is probably extrahepatic in the system. Similar to losartan, EXP3312 is also metabolized to an active carboxylic acid metabolite M1. A significant amount of M1 was observed in plasma after both intravenous and oral administration. The oxidation of aldehyde to carboxylic acid might occur in the lung or the blood. The T_{max} values were 0·50 and 2·0 h after intravenous and oral administration, respectively. The mean peak plasma levels of M1 after 10 mg kg^{-1} oral administration was 20·52 μg mL^{-1}, which was much higher than that of the parent compound EXP3312 (2·69 μg mL^{-1}). The elimination half-lives of M1 after intravenous and oral administration in rats were 2·29 and 2·70 h, respectively, longer than those of the parent compound EXP3312. The AUC value of M1 were 14 to 44·5-fold greater than those of the parent compound EXP3312 in rats after intravenous and oral administration, respectively. It is likely that M1 contributes to the long duration of the antihypertensive effect of EXP3312 in renal hypertensive rats.

In dogs, plasma levels declined in a monophasic fashion with a terminal elimination half-life of 2·52 h (Table 2 and Fig. 8) after an intravenous dose of 3 mg kg^{-1} of EXP3312. The

Table 1. Pharmacokinetic parameters of EXP3312 and the carboxylic acid metabolite M1 in rats.

	Intravenous (3 mg kg^{-1})	Oral (10 mg kg^{-1})
EXP3312		
C_{max} ($\mu g\ mL^{-1}$)	–	2·68
T_{max} (h)	–	0·25
AUC ($\mu g\ h\ mL^{-1}$)	1·34	2·69
t½ (h)	1·20	1·80
Vd_{ss} ($L\ kg^{-1}$)	1·44	–
CL ($L\ h^{-1}\ kg^{-1}$)	2·24	–
F (%)	–	60
M1		
C_{max} ($\mu g\ mL^{-1}$)	5·50	20·52
T_{max} (h)	0·50	2·00
AUC ($\mu g\ h\ mL^{-1}$)	18·70	80·11
t½ (h)	2·29	2·70
$AUC_{M1}/AUC_{EXP3312}$	13·96	44·51

Table 2. Pharmacokinetic parameters of EXP3312 and the carboxylic acid metabolite M1 in dogs.

	Intravenous (3 mg kg^{-1})	Oral (10 mg kg^{-1})
EXP3312		
C_{max} ($\mu g\ mL^{1}$)	N/A	1·48
T_{max} (h)	N/A	0·25
AUC ($\mu g\ h\ mL^{-1}$)	4·25	3·95
t½ (h)	2·52	3·45
Vd_{ss} ($L\ kg^{-1}$)	1·26	N/A
CL ($L\ h^{-1}\ kg^{-1}$)	0·71	N/A
F (%)	N/A	28
M1		
C_{max} ($\mu g\ mL^{-1}$)	1·58	0·79
T_{max} (h)	0·25	0·50
AUC ($\mu g\ h\ mL^{-1}$)	1·28	1·86
t½ (h)	0·83	1·84
$AUC_{M1}/AUC_{EXP3312}$	0·30	0·47

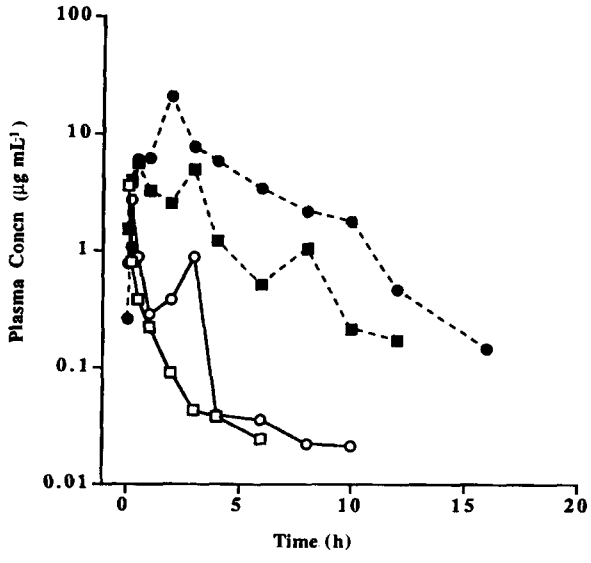


FIG. 7. Plasma levels of EXP3312 and M1 in rats after intravenous (3 mg kg^{-1}) and oral (10 mg kg^{-1}) administration of EXP3312 (n = 4). (□) EXP3312 intravenous, (○) EXP3312 oral, (■) M1 intravenous and (●) M1 oral.

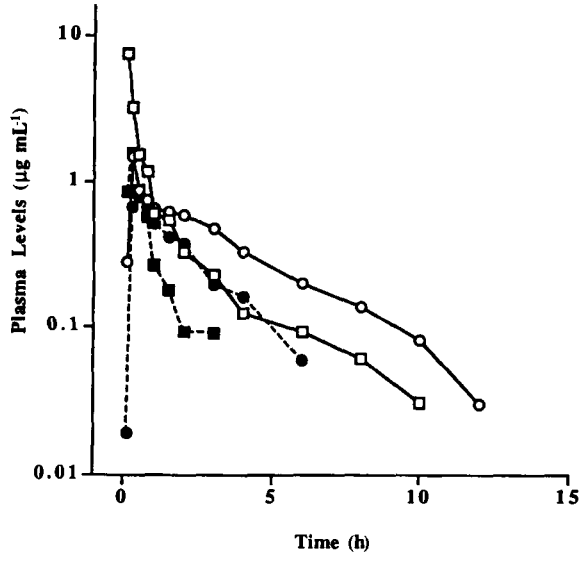


FIG. 8. Plasma levels of EXP3312 and M1 in dogs after intravenous (3 mg kg^{-1}) and oral (10 mg kg^{-1}) administration of EXP3312 (n = 3). (□) EXP3312 intravenous, (○) EXP3312 oral, (■) M1 intravenous and (●) M1 oral.

systemic clearance was 0·71 L h^{-1} kg^{-1} and the volume of distribution at the steady state was 1·26 L kg^{-1} in dogs. After a 10 mg kg^{-1} oral dose of EXP3312, the maximum plasma level of 1·48 $\mu g\ mL^{-1}$ was detected after 0·25 h. The terminal half-life after oral administration was 3·45 h and the oral bioavailability was 28%. The carboxylic acid metabolite M1 was also observed in dog plasma. The T_{max} values were 0·25 and 0·50 h after intravenous and oral administration, respectively. The mean peak plasma level of M1 after 10 mg kg^{-1} oral administration was 0·79 $\mu g\ mL^{-1}$. The elimination half-lives of M1 after intravenous and oral administration were 0·83 and 1·84 h, respectively, which were shorter than those of the parent compound EXP3312. The plasma level of M1 was much less than that of the parent compound. This is similar to losartan, because low levels of its acid metabolite EXP3174 are found in dogs at pharmacologically relevant doses (Christ et al 1994). The relative low bioavailability in dogs could be a result of incomplete absorption or of metabolism in the gut; because the systemic clearance was smaller than the hepatic blood flow, hepatic metabolism could be ruled out.

In summary, this study indicates that EXP3312 is a potent, orally active, competitive and selective AT_1-receptor antagonist and a potent antihypertensive agent. As losartan was shown to be effective for the treatment of hypertension and congestive heart failure (Wong et al 1991a; Timmermans et al 1993), it is likely that EXP3312 will also be therapeutically useful in these disorders.

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References

Christ, D. D., Wong, P. C., Wong, Y. N., Hart, S. D., Quon, C. Y., Lam, G. N. (1994) The pharmacokinetics and pharmacodynamics of the angiotensin II receptor antagonist losartan potassium (DuP 753/MK 954) in the dog. J. Pharmacol. Exp. Ther. 268: 1199–1205

DeNoble, V. J., DeNoble, K. F, Spencer, K. R., Chiu, A. T., Wong, P. C., Timmermans, P. B. M. W. M. (1991) Non-peptide angiotensin II receptor antagonist and angiotensin converting enzyme inhibitor: effect on a renin-induced deficit of a passive avoidance response in rats. Brain Res. 561: 230–235

Duncia, J. A., Carini, D. J., Chiu, A. T., Johnson, A. L., Price, W. A., Wong, P. C., Wexler, R. R., Timmermans, P. B. M. W. M. (1992) The discovery of DuP 753, a potent, orally active non-peptide angiotensin II receptor antagonist. Med. Res. Rev. 12: 149–191

Kenakin, T. P. (1987) Pharmacologic Analysis of Drug–Receptor Interactions, New York: Raven Press.

Timmermans, P. B. M. W. M., Wong, P. C., Chiu, A. T., Herblin, W. F., Benfield, P., Carini, D. J., Lee, R. J., Wexler, R. R., Saye, J. M., Smith, R. D. (1993) Angiotensin II receptors and angiotensin II receptor antagonists. Pharmacol. Rev. 45: 205–251

Wong, P. C., Price, W. A., Chiu, A. T., Carini, D. J., Duncia, J. V., Wexler, R. R., Johnson, A. L., Timmermans, P. B. M. W. M.(1990a) Non-peptide angiotensin II receptor antagonists: studies with EXP9270 and DuP 753· Hypertension 15: 823–834

Wong, P. C., Price, W. A., Chiu, A. T., Carini, D. J., Duncia, J. V., Wexler, R. R, Johnson, A. L., Timmermans, P. B. M. W. M. (1990b) Non-peptide angiotensin II receptor antagonists. VIII. Characterization of functional antagonism displayed by DuP 753, an orally active antihypertensive agent. J. Pharmacol. Exp. Ther. 252: 719–725

Wong, P. C., Barnes, T. B., Chiu, A. T., Christ, D. D., Duncia, J. V., Herblin, W. F., Timmermans, P. B. M. W. M. (1991a) Losartan (DuP 753), an orally-active non-peptide angiotensin II receptor antagonist. Cardiovasc. Drug Rev. 9: 317–339

Wong, P. C., Hart, S. D., Duncia, J. V., Timmermans, P. B. M. W. M. (1991b) Non-peptide angiotensin II receptor antagonists. Studies with DuP 753 and EXP3174 in dogs. Eur. J. Pharmacol. 202: 323–330

Wong, P. C., Chiu, A. T., Duncia, J. V., Herblin, W. F., Timmermans, P. B. M. W. M. (1992) Angiotensin II receptor antagonists and receptor subtypes. Trends Endocrinol. Metab. 3: 211–217

Wong, Y. N., Burcham, D. L., Huang, S.-M., Quon, C. Y. (1993) Metabolism and disposition of EXP631–a novel antidepressant analgesic. Biopharm. Drug Dispos. 14: 519–531