cell lines including six stomach adenocarcinomas, four osteosarcomas, three lung adenocarcinomas, a lung large-cell carcinoma, a lung squamous-cell carcinoma, and a colon adenocarcinoma. As summarized in Table I, CNDAC had potent cytotoxicity in 14 tumor cell lines with $IC_{50}$ values ranging from 0.04 to 6.8 μg/mL, but not against PC-13 lung large-cell carcinoma and QG-56 lung squamous-cell carcinoma. On the other hand, *ara*-C showed good cytotoxicity to only six of the cell lines (0.09–4.5 μg/mL) tested in this study. It is important to note that CNDAC shows a potent cytotoxicity in all tested the human stomach adenocarcinomas, the incidence of which is high in Japan.

In vivo antitumor activity of CNDAC and *ara*-C was also examined against intraperitoneally implanted mouse leukemia P388 ($10^6$ cells) in $CDF_1$ mice, with a dose of 100 mg/kg per day intraperitoneally given on days 1 and 5 from the day after tumor transplantation. The antitumor effects of CNDAC were measured by comparison of the median survival time of the treated group and that of an untreated group, with six $CDF_1$ female mice in each group. The survival time was greatly increased; the ratio of treated vs the control in median survival time was 183%, while that of *ara*-C was 163%. Median survival time of the untreated control group was 10.0 days. When a 20 mg/kg dose of CNDAC was administered intraperitoneally once each day on days 1–10, five out of six mice survived over 60 days ($T/C > 600\%$) after initial treatment (one mouse died at day 53). Although the optimal therapeutic schedule of CNDAC is not yet known, such excellent activity suggests that CNDAC is a promising agent for further evaluation for therapy of human cancer. Whether the mechanism responsible for its antitumor properties is related to the DNA-strand-breakage hypothesis is being studied. If CNDAC indeed acts as a "chemical X-ray", it would demonstrate a new approach for anticancer chemotherapy.

**Acknowledgment**. This investigation was supported in part by Grants-in-Aid for Cancer Research, Special Project Research on Cancer-Bioscience, and Scientific Research on Priority Areas from the Ministry of Education, Science, and Culture of Japan.

† This paper is dedicated to the memory of Professor Tohru Ueda, deceased September 19, 1990.

* Author to whom correspondence should be addressed.
‡ Hokkaido University.
§ Kanazawa University.

**Akira Matsuda,*,‡ Yuki Nakajima,‡ Atsushi Azuma‡ Motohiro Tanaka,§ Takuma Sasaki§**

*Faculty of Pharmaceutical Sciences*
*Hokkaido University*
*Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan*
*Cancer Research Institute*
*Kanazawa University*
*Takara-machi, Kanazawa 900, Japan*

*Received May 30, 1991*

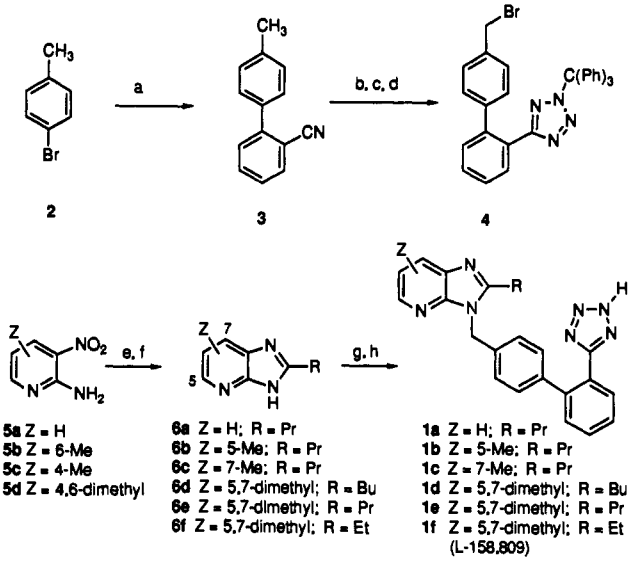
## Potent, Orally Active Imidazo[4,5-*b*]pyridine-Based Angiotensin II Receptor Antagonists

Angiotensin II is the principle pressor agent of the renin–angiotensin system (RAS). This system, a proteolytic cascade that regulates hemodynamics and water and electrolyte balance, can contribute to hypertensive states in man. The effects of the octapeptide angiotensin II (AII), which include vasoconstriction, stimulation of aldosterone synthesis and release, cardiac stimulation, and renal reabsorption of sodium, are mediated through specific membrane-bound receptors. Reducing AII levels with angiotensin converting enzyme (ACE) inhibitors such as captopril and enalapril has confirmed the therapeutic benefit of inhibiting the RAS in hypertension and heart failure.

An alternative mode of inhibiting AII is to antagonize its interaction with the receptor. Although peptide analogues of AII inhibit the action of AII by competitively binding to the receptor,[1] their prospects as clinical agents are limited due to short duration, poor oral bioavailability, and partial agonist activity.

Recently, nonpeptidic, orally active AII receptor antagonists, have been reported,[2] and one of these, 2-*n*-butyl-4-chloro-5-(hydroxymethyl)-1-[[2′-1*H*-tetrazol-5-yl)bi-

**Scheme I**[a]



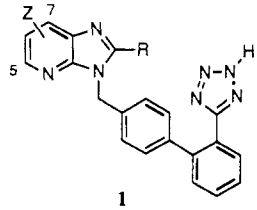

[a] Reagents: (a) $^t$BuLi, pentane–THF, −78 °C, 30 min; $ZnCl_2$–$Et_2O$, 25 °C, 2 h; 2-bromobenzonitrile, 2 mol % $Ni(PPh_3)_2Cl_2$, 25 °C, 18 h, (88%); (b) $Me_3SnN_3$, toluene, reflux, 24 h; dilute HCl, 25 °C; (c) $(Ph)_3CCl$, $Et_3N$, $CH_2Cl_2$, reflux, 1.5 h; (d) *N*-bromosuccinimide, 10 mol % dibenzoyl peroxide, $CCl_4$, reflux, 2 h; (e) $H_2$, (1 atm), 10% Pd–C (10 w/w %), MeOH; (f) butyric acid (**6a–c,e**), valeric acid (**6d**), or propionic acid (**6f**), polyphosphoric acid, 80–90 °C, 3–8 h (75–95%, 2 steps); (g) NaH, DMF, 25 °C, 20 min; **4**, 2–12 h (30–75 %); (h) $HCO_2H$, 25 °C, 12 h (85–95%).

(1) Khosla, M. C.; Smeby, R. R.; Bumpus, F. M. Structure Activity Relationship in Angiontensin II Analogs. In *Angiotensin*; Page, I. H., Bumpus, F. M., Eds.; Springer Verlag: Heidelberg, 1973; pp 126–161. Streeten, D. H. P.; Anderson, G. H. Angiotensin-Receptor Blocking Drugs. In *Clinical Pharmacology of Antihypertensive Drugs, Handbook of Hypertension*, Doyle, A. E., Ed.; Elsevier: New York, 1984; Vol. 5, pp 246–271. Bovy, P. R.; Blaine, E. H. Peptidic and Non-peptidic Angiotensin II Competitive Antagonists. *Current Cardiovascular Patents* **1989**, *1*, 2044–2056.

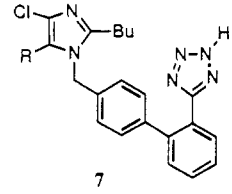
(2) Matsumura, K.; Hashimoto, N.; Furakawa, Y. U.S. patent 4,207,324, 1980. Furakawa, Y.; Kishimoto, S.; Nishikawa, K. U.S. patent 4,340,598, 1982. Furakawa, Y.; Kishimoto, S.; Nishikawa, K. U.S. patent 4,355,040, 1982. Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A. L.; Price, W. A.; Wells, G. J.; Wong, P. C.; Calabrese, J. C.; Timmermans, P. B. M. W. M. The Discovery of Potent Nonpeptide Angiotensin II Receptor Antagonists: A New Class of Potent Antihypertensives. *J. Med. Chem.* **1990**, *33*, 1312–1329. Weinstock, J.; Keenan, R. M.; Samanen, J.; Hempel, J.; Finkelstein, J. A.; Franz, R. G.; Gaitanopoulus, D. E.; Girard, G. R.; Gleason, J. G.; Hill, D. T.; Morgan, T. M.; Peishoff, C. E.; Aiyar, N.; Brooks, D. P.; Fredrickson, T. A.; Ohlstein, E. H.; Ruffolo, R. R., Jr.; Stack, E. J.; Sulpizio, A. C.; Weidley, E. F.; Edwards, R. M. 1-(Carboxybenzyl)imidazole-5-acrylic Acids: Potent and Selective Angiotensin II Receptor Antagonists. *J. Med. Chem.* **1991**, *34*, 1514–1517.

0022-2623/91/1834-2919$02.50/0 

Table I. Angiotensin II Antagonist Activity of Imidazo[4,5-*b*]pyridines 1



1



7

| compd | Z | R | mp, °C | $IC_{50}$, nM[a] | iv $ED_{50}$, mg/kg[b] |
|---|---|---|---|---|---|
| 1a | H | *n*-Pr | 221–222 | 8 | |
| 1b | 5-methyl | *n*-Pr | 220–221 | 2 | 1.0 (0.95–1.2)[c] |
| 1c | 7-methyl | *n*-Pr | 136–139[e] | 1 | 0.14 (0.11–0.17)[d] |
| 1d | 5,7-dimethyl | *n*-Bu | 196–197[f] | 0.5 | 0.45 (0.29–0.7)[d] |
| 1e | 5,7-dimethyl | *n*-Pr | 166–168[f] | 0.3 | 0.087 (0.074–0.103)[d] |
| 1f (L-158,809) | 5,7-dimethyl | Et | 185–186[e] | 0.3 | 0.048 (0.042–0.054)[d] |
| 7a (DuP 753) | | $CH_2OH$ | | 50 | |
| 7b (EXP3174) | | $CO_2H$ | | 6 | |
| 8 | | Sar[1],Ile[8]-AII | | 0.2 | |

[a] Binding affinity (rabbit aorta); see ref 10b for experimental details. [b] Antihypertensive effect in rats – inhibition of AII-induced pressor responses; see ref 11. [c] Estimated range based on 56% inhibition of the AII pressor response in 2 rats at a dose 1 mg/kg. [d] 95% confidence limits, $n = 4$. [e] Hydrate. [f] Hemihydrate.

Table II. Comparison of the Iv and Oral Effects of L-158,809 on the Inhibition of AII-Induced Pressor Responses in Rats[a]

| iv | | po | |
|---|---|---|---|
| iv dose, mg/kg | % peak inhibition of pressor response[b] | po dose, mg/kg | % peak inhibition of pressor response[b] |
| 0.03 | 36 (±8) | 0.03 | 52 (±7) |
| 0.1 | 85 (±5) | 0.1 | 75 (±6) |
| 0.3 | 99 (±1)[c] | 0.3 | 92 (±2) |

[a] See ref 11 for experimental details. [b] Values represent mean (±SEM), ($n = 4$). [c] $n = 2$.

phenyl-4-yl]methyl]imidazole, DuP 753 (MK-954),[3a,b] is undergoing extensive clinical evaluation.[3c] This class of antagonists, which are devoid of agonist activity, contains an imidazole moiety which tolerates a variety of substituents at the 4- and 5-positions while maintaining high binding affinity to the AII receptor. This is further exemplified in reports of substituted benzimidazoles as AII antagonists.[4a–e] Herein we report highly potent imidazopyridine-based AII antagonists (1) which exhibit long duration of action upon oral administration to rats.[5]

The synthesis of 1a–f is illustrated in Scheme I. A nickel-catalyzed biaryl coupling reaction of the zinc derivative, prepared from bromide 2, with 2-bromobenzonitrile provided substituted biphenyl 3 in good yield.[6] Conversion of compound 3 to the trityl-protected tetrazole 4 was accomplished according to the published procedure.[7] Imidazo[4,5-*b*]pyridines 6a–f were prepared by reduction of 2-amino-3-nitropyridine derivatives 5a–d[8] to the corresponding diaminopyridines which were then condensed with an appropriate carboxylic acid in polyphosphoric acid.[9] The imidazopyridines 6a–f were then treated with NaH and 4 to give the coupled products (not shown), which were deprotected by treatment with protic acid to provide 1a–f. The regiochemistry of the alkylation of 6a–f could be verified by observation of a nuclear Overhauser

(3) (a) Chiu, A. T.; McCall, D. E.; Price, W. A.; Wong, P. C.; Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Wexler, R. R.; Yoo, S. E.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists. VII. Cellular and Biochemical Pharmacology of DuP 753, an Orally Active Antihypertensive Agent. *J. Pharmacol. Exp. Ther.* **1990**, *252*, 711–718. (b) Wong, P. C.; Price, W. A.; Chiu, A. T.; Duncia, J. V.; Carini, D. J.; Wexler, R. R.; Johnson, A. L.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists. XI. Pharmacology of EXP3174: An Active Metabolite of DuP 753, An Orally Active Antihypertensive Agent. *J. Pharmacol. Exp. Ther.* **1990**, *255*, 211–217. (c) Christen, Y.; Waeber, B.; Nussberg, J.; Porchet, M.; Borland, R. M.; Lee, R. J.; Maggon, K.; Shum, L.; Timmermans, P. B. M. W. M.; Brunner, H. R. Oral Administration of DuP 753, A Specific Angiotensin II Receptor Antagonist, to Normal Male Volunteers. *Circulation* **1991**, *83*, 1333–1342.

(4) (a) Chakravarty, P. K.; Camara, V. J.; Chen, A.; Marcin, L. M.; Greenlee, W. J.; Patchett, A. A.; Chang, R. S. L.; Lotti, V. J.; Siegl, P. K. S. Substituted Benzimidazoles as Novel Non-Peptide Angiotensin II Receptor Antagonists. *Book. of Abstracts* 200th National Meeting of the American Chemical Society, Washington, DC, Aug 26–31, 1990; Americal Chemical Society: Washington, DC, 1990; MEDI No. 90. (b) Chakravarty, P. K.; Camara, V. J.; Patchett, A. A.; Greenlee, W. J.; Walsh, T. F. Eur. Pat. Appl. 400,835, 1990. (c) Roberts, D. A.; Russell, S. T. Eur. Pat. Appl. 399,732, 1990. (d) Narr, B.; Bomhard, A.; Hauel, N.; van Meel, J.; Wienen, W.; Entzeroth, M. Eur. Pat. Appl. 392,317, 1990. (e) Carini, D. J.; Duncia, J. V.; Yoo, S.-E. U.S. Patent 4,880,804, 1989.

(5) Chakravarty, P. K.; Greenlee, W. J.; Mantlo, N. B.; Patchett, A. A.; Walsh, T. F. Eur. Pat. Appl. 400,974, 1990. Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D.; Chen, A.; Camara, V. J.; Chang, R. S. L.; Lotti, V. J.; Siegl, P. K. S.; Patchett, A. A.; Greenlee, W. J. Potent, Orally Active Imidazo[4,5-*b*]pyridine Angiotensin II Receptor Antagonists. *Book of Abstracts* 201st National Meeting of the American Chemical Society, Atlanta, GA, April 14–19, 1991; American Chemical Society: Washington, DC, 1991; MEDI No. 71. Roberts, D. A.; Ratcliffe, A. H.; Gibson, K. H.; Wood, R. Eur. Pat. Appl. 399,731, 1990. Herold, P.; Buhlmayer, P. Eur. Pat. Appl. 415,886, 1991. Kazutoshi, M.; Masayuki, M.; Naoki, Y.; Osamu, H.; Nobuyuki, M.; Hiroki, I.; Takashi, M.; Toshiyuki, M.; Sachiyuki, H.; Norio, M. Eur. Pat. Appl. 420,237, 1991. Oku, T.; Setoi, H.; Kayakirl, H.; Inoue, T.; Kuroda, A.; Katayama, A.; Hashimoto, M.; Satoh, S.; Tanaka, H. Eur. Pat. Appl. 426,021, 1991.

(6) Negishi, E.; King, A. O.; Okukado, N. Selective Carbon-Carbon Bind Formation via Transition Metal Catalysts. 3. A Highly Selective Synthesis of Unsymmetrical Biaryls and Diarylmethanes by the Nickel- or Palladium-Catalyzed Reaction of Aryl- and Benzylzinc Derivatives with Aryl Halides. *J. Org. Chem.* **1977**, *42*, 1821.

(7) Aldrich, P. E., Duncia, J. V.; Pierce, M. E. U.S. patent 4,870,186, 1989.

(8) Compounds 5a and 5c were obtained from Aldrich Chemical Co. Compound 5b: Lappin, G. R.; Slezak, F. B. Some Derivatives of 3- and 5-Nitro-2-aminopyridines. *J. Am. Chem. Soc.* **1950**, *72*, 2806–2807 and references cited therein. Compound 5d: Batkowski, T.; Tomasik, D.; Tomasik, P. 3,5-Dinitro-2,4-lutidine. *Rocz. Chem.* **1969**, *43*, 481–486.

(9) Compare with: Dubey, P. K.; Ratnam, C. V. Synthesis and Spectra of 6-Bromo-2-alkyl-1H-imidazo[4,5-*b*]pyridines. *Indian J. Chem.* **1978**, *16B*, 531.

effect between the *N*-benzylic methylene protons and the α-protons of the 2-ethyl or propyl substituent.[10a]

Examination of the SAR of the imidazole containing AII antagonists[2,3] indicated that polar groups capable of hydrogen-bonding interactions at the 5-position of the imidazole enhanced binding affinity. It occurred to us that an imidazopyridine heterocycle could replace the imidazole of these compounds as it contains a common imidazole element and a pyridine nitrogen capable of mimicking the hydrogen-bond activity of the polar imidazole 5-substituent. Indeed, this modification resulted in potent AII antagonists (compounds **1a–f**). Evidence that the pyridine nitrogen atom of the imidazopyridine indeed enhances the binding affinity is provided as compounds **1** are at least 20-fold more potent than structurally similar benzimidazole counterparts.[4a]

The in vitro binding affinities of the compounds in Table I were determined by their ability to displace the specific binding ligand $^{125}$I-Sar$^1$,Ile$^8$-AII from receptors in the rabbit aorta membrane and are expressed as $IC_{50}$ values.[10b] Initial work on the structure–affinity relationship demonstrated that pyridine ring nitrogen placement, as found in the 3-substituted imidazo[4,5-*b*]pyridine isomer **1**, was important in order to obtain good binding affinity (data not shown). Further studies revealed that subtituents about the imidazo[4,5-*b*]pyridine ring had a significant effect on activity. From the $IC_{50}$ values shown in Table I, a 4- to 8-fold increase in binding affinity is seen upon methylation at either the 5- or 7-positions of the imidazopyridine (**1b,c** vs **1a**). This effect is additive, as the 5,7-dimethyl analogue **1e** is 26-fold more potent than **1a** ($IC_{50}$ = 0.3 vs 8 nM). Of note is that butyl, propyl, or ethyl substituents at the 2-position of the imidazopyridine have similar in vitro binding affinities (**1d–f**). Imidazopyridines **1b–f** show greater receptor binding affinity compared to DuP 753 (MK 954)[3a] and its metabolite, EXP3174.[3b]

In vivo potency of **1b–f** (Table I) was determined by assessing the inhibition of pressor responses to 0.1 μg/kg iv AII in conscious normotensive rats.[11] Compounds **1b–f** were potent in this assay, showing $ED_{50}$'s from 0.048–0.45 mg/kg for iv administration. The SAR indicates that in vivo potencies are more sensitive to substitution about the imidazopyridine ring than are the in vitro binding affinities. This is evident upon comparison of the 2-butyl and 2-ethyl analogues (**1d,f**), where a 1.6-fold difference of $IC_{50}$ values (0.5 vs 0.3 nM) is translated into a 10-fold difference in iv potencies ($ED_{50}$ = 0.45 vs 0.048 mg/kg). From this screening process the most potent compound, L-158,809, was chosen for more extensive studies.

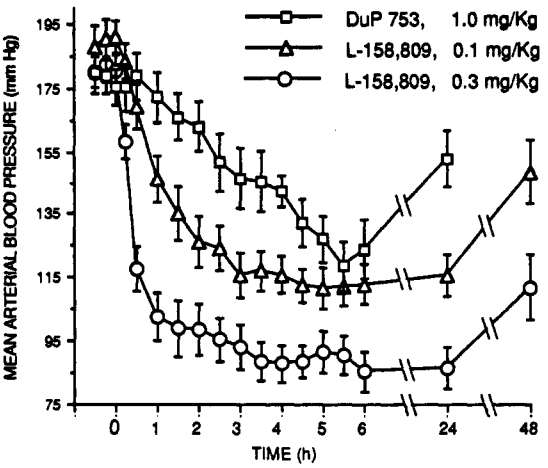



**Figure 1.** Effects of L-158,809 (0.1 mg/kg, $n$ = 6 and 0.3 mg/kg, $n$ = 3) and DuP 753 (1.0 mg/kg, $n$ = 4) on blood pressure in the coarcted rat after oral administration. Values represent the means ± SEM.

Scatchard analysis of $^{125}$I-Sar$^1$,Ile$^8$-AII binding indicated that L-158,809 interacted in a competitive manner with the AII receptor (rabbit aorta). In rat adrenal cortical cells, L-158,809 (2 nM) shifted the concentration–response curve for AII-induced aldosterone release to the right without altering the maximal response (data not shown). The calculated $_pA_2$ value of 10.5 confirmed that L-158,809 is an extremely potent antagonist without agonist activity. Similar to DuP 753, L-158,809 is highly selective for the $AT_1$ receptor and shows little affinity for the $AT_2$ receptor found in rat brain.[12]

As shown in Table II, L-158,809 exhibited a dose-related inhibition of AII-induced pressor responses in conscious normotensive rats upon intravenous and oral administration. The duration of action was excellent, as the inhibitory effect was still evident at 24 h after a single dose of 0.1 mg/kg iv or 0.3 mg/kg po. L-158,809 is potent upon oral administration, having an $ED_{50}$ of 0.026 mg/kg; and the po/iv $ED_{50}$ ratio of greater than unity indicates that it is well adsorbed. The specificity of the antihypertensive effect of L-158,809 in conscious normotensive rats is evidenced, since at these doses it produces no observable alterations of the basal heart rate or mean arterial blood pressure and does not inhibit the pressor response produced by the α-adrenergic agonist, methoxamine.

The antihypertensive effect of L-158,809 was evaluated in coarcted hypertensive conscious rats.[13] L-158,809

(10) (a) Products arising from alkylation at N1 or N4 were also distinguishable by the expected nuclear Overhauser effects. (b) Protocol for binding assay in rabbit aorta membrane: Rabbit aorta membranes were prepared as described in Chang, R. S.; Lotti, V. J.; Chen, T. B. *Biochem. Biophys. Res. Commun.* **1988**, *151*, 1213. For $^{125}$I-Sar$^1$,Ile$^8$-AII binding assays, 10 μL of buffer (for total binding), Sar$^1$,Ile$^8$-AII (1 μM) (for nonspecific binding) or test compounds (for displacement), and 10 μL of $^{125}$I-Sar$^1$,Ile$^8$-AII (26-46 pM) were added to duplicate or triplicate tubes. Receptor membranes (250 μL) were added to each tube to initiate binding reaction. The reaction mixtures were incubated for 90 min. The reaction was terminated by filtration under reduced pressure through glass-fiber GF/B filters and washed immediately 4 times with 4 mL of ice-cold Tris-HCl (pH 7.4) containing 0.15 M NaCl. The radioactivity trapped in the filters was counted by using a γ counter. The $IC_{50}$ values are inhibitor concentrations which give 50% displacement of specifically bound $^{125}$I-Sar$^1$,Ile$^8$-AII.

(11) Protocol for in vivo testing in conscious rats: Male Sprague-Dawley rats (300–400 gm) were instrumented with arterial and venous catheters for recording blood pressure and administration of test compounds, respectively. In the conscious state, pressor responses to a submaximal dose of AII (0.1 μg/kg iv) or methoxamine (50 μg/kg iv) were recorded before and following intravenous and oral administration of test compounds. The vehicles were saturated $NaHCO_3$ (15%), saline (35%), and distilled water (50%) for iv and 1 N NaOH–0.5% methocel (10:90) suspension for po administration. Data are expressed as percent inhibition of the AII response at each dose. The duration of action is expressed as the time until the peak response falls below 30% for a single bolus dose of the drug. Potency ($ED_{50}$ value) is expressed as the dose required to elicit a 50% peak inhibition.

(12) Chang, R. S. L.; Lotti, V. J. Two Distinct Angiotensin II Receptor Binding Sites in Rat Adrenal Revealed by New Selective Nonpeptide Ligands. *Mol. Pharmacol.* **1990**, *37*, 347–351. Bumpus, F. M.; Catt, K. J.; Chiu, A. T.; DeGasparo, M.; Goodfriend, T.; Husain, A.; Peach, M. J.; Taylor, D. G., Jr.; Timmermans, P. B. M. W. M. Nomenclature for Angiotensin Receptors: A Special Report of the Nomenclature Committee of the Council for High Blood Pressure Research. *Hypertension* **1991**, *17*, 720.

produced a dose-related reduction in mean arterial blood pressure when administered orally (Figure 1). At single doses of 0.1 and 0.3 mg/kg po, L-158,809 reduced the mean arterial blood pressure to normotensive levels (~60 and ~80 mmHg), with a duration of action exceeding 24 h. The onset of action occurred within 30 min, and the maximal response was measured at approximately 3 h. DuP 753 (1.0 mg/kg po) was more than 10-fold less potent and produced a maximal decrease in blood pressure at approximately 6 h (Figure 1). At the end of the protocol, iv bolus injections of 1.0 or 0.6 mg/kg enalaprilat were used to confirm the renin dependence of blood pressure in these animals, and the effect of these large doses was similar to response levels produced by L-158,809 at 0.3 mg/kg po. A hypotensive effect of L-158,809 or DuP 753 was not observed in normotensive rats with normal renin levels.

In summary, imidazo[4,5-*b*]pyridine analogues **1** represent an important new class of AII antagonists. The biological profile of L-158,809 (**1f**) indicates it to be a highly potent and specific antagonist of AII both in vitro and in vivo. The excellent selectivity, potency, duration of action, and oral absorption of L-158,809 suggests it to be a useful tool in assessing the therapeutic value of AII receptor antagonism as well as the diverse roles of the RAS.

**Acknowledgment.** We would like to thank Dr. Salah Kivlighn for his input on the presentation of in vitro data and Dr. Lawrence Colwell for FAB-mass spectrometry services.

**Registry No.** **1a**, 135145-91-4; **1b**, 135145-92-5; **1c**, 135145-93-6; **1d**, 135145-94-7; **1e**, 135145-95-8; **1f**, 135145-96-9; **2**, 106-38-7; **3**, 114772-53-1; **4**, 133051-88-4; **5a**, 4214-75-9; **5b**, 21901-29-1; **5c**, 6635-86-5; **5d**, 22934-23-2; **6a**, 68175-09-7; **6b**, 135145-97-0; **6c**, 133239-98-2; **6d**, 133052-13-8; **6e**, 135070-89-2; **6f**, 133240-06-9; angiotensin II, 11128-99-7; 2-bromobenzonitrile, 2042-37-7; butyric acid, 107-92-6; valeric acid, 109-52-4; propionic acid, 79-09-4.

(13) The protocol for aortic coarction of the rats is described: Sweet, C. S.; Columbo, J. M.; Gaul, S. L. Central Antihypertensive Effects of Inhibitors of the Renin-Angiotensin System in Rats. *Am. J. Physiol.* **1976**, *231*, 1794 and references cited therein.

* Author to whom correspondence should be addressed.
† Exploratory Chemistry.
‡ Department of Pharmacology.

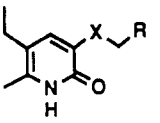
**Nathan B. Mantlo,*,† Prasun K. Chakravarty,† Debra L. Ondeyka,† Peter K. S. Siegl,‡ Raymond S. Chang,‡ Victor J. Lotti,‡ Kristie A. Faust,‡ Tsing-Bau Chen,‡ Terry W. Schorn,‡ Charles S. Sweet,‡ Scott E. Emmert,‡ Arthur A. Patchett,† William J. Greenlee†**

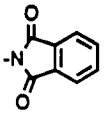
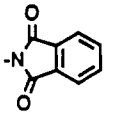
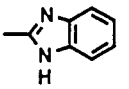
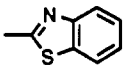
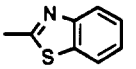
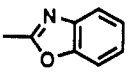
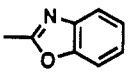
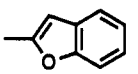
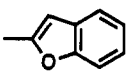
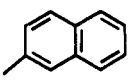
*Exploratory Chemistry*
*Merck Sharp and Dohme Research Laboratories*
*Rahway, New Jersey 07065*
*Department of Pharmacology*
*Merck Sharp and Dohme Research Laboratories*
*West Point, Pennsylvania 19486*
*Received May 1, 1991*

## 2-Pyridinone Derivatives: A New Class of Nonnucleoside, HIV-1-Specific Reverse Transcriptase Inhibitors

The development of potent and effective antiviral drugs for the control of human immunodeficiency virus type 1 (HIV-1) infection is one of the more pressing goals of contemporary medicinal chemistry. The unique nature of the replication cycle of retroviruses, such as HIV-1, offers a variety of potential areas for chemotherapeutic intervention.[1] One particularly important target is the viral reverse transcriptase (RT). Nucleoside analogues, including 3′-azidothymidine (AZT) and dideoxyinosine (ddI), which inhibit the process of reverse transcription are clinically useful drugs for the treatment of HIV-1 infection.[2] However, the utility of these nucleoside analogues is limited by the emergence of resistant viral strains[3] and by serious clinical side effects[4] which may be related

Table I. Inhibition of HIV-1 RT by 2-Pyridinones: Aromatic and Heterocyclic Derivatives



| no. | X | R | $IC_{50}$, nM[a] |
|---|---|---|---|
| 1 | NH |  | 30 |
| 2 | $CH_2$ |  | 3700 |
| 3 | NH |  | 6400 |
| 4 | NH |  | 350 |
| 5 | $CH_2$ |  | 370 |
| 6 | NH |  | 210 |
| 7 | $CH_2$ |  | 22 |
| 8 | NH |  | 235 |
| 9 | $CH_2$ |  | 77 |
| 10 | NH |  | 440 |

[a] The HIV-1 RT assay using rC·dG as template primer was carried out in a reaction mixture (50 μL) containing 55 mM Tris-HCl (pH 8.2), 30 mM KCl, 30 mM $MgCl_2$, 1 mM dithiothreitol (DTT), 1 mg/mL bovine serum albumin (BSA), 20 μg/mL $rC \cdot dG_{(12-18)}$ (Pharmacia), 50 μM EGTA, 8 μM [$^3$H]dGTP, 0.01% (v:v) Triton X-100, and 0.9 nM recombinant HIV-1 RT. The remainder of the procedure was performed as previously described.[9] The concentration that produced 50% inhibition ($IC_{50}$) is stated as the mean of at least three experiments.

(1) Mitsuya, H.; Yarchoan, R.; Broder, S. Molecular Targets for AIDS Therapy. *Science (Washington, D.C.)* **1990**, *249*, 1533-1544.
(2) Fischl, M. A.; et al. The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex. *New Engl. J. Med.* **1987**, *317*, 185-191. Butler, K. M.; et al. Dideoxyinosine in Children with Symptomatic Human Immunodeficiency Virus Infection. *New Engl. J. Med.* **1991**, *324*, 137-144.
(3) Larder, B. A.; Darby, G.; Richman, D. D. HIV with Reduced Sensitivity to Zidovudine (AZT) Isolated During Prolonged Therapy. *Science (Washington, D.C.)* **1989**, *243*, 1731-1734. Larder, B. A., Kemp, S. D. Multiple Mutations in HIV-1 Reverse Transcriptase Confer High-Level Resistance to Zidovudine (AZT). *Science (Washington, D.C.)* **1989**, *246*, 1155-1158.

0022-2623/91/1834-2922$02.50/0 