It was notable that furosemide, a high-celing diuretic, showed weaker diuretic activy and lower urinary ratio (Na^+/K^+) than compound 18, and increased the severity of glycerol-induced acute renal failure. They are unsuitable characters for a diuretic. In conclusion, we identified that 8-(dicyclopropylmethyl)-1,3-dipropylxanthine (18, KF-15372) is the most potent and selective adenosine A_1 receptor antagonist reported to date. The physiological role of adenosine A_1 receptors in the kidney and detailed pharmacological activities of 18 are under active study in our laboratories and will be reported in due course.

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Design of a Well-Absorbed Renin Inhibitor

Renin is the first and rate-limiting enzyme in the well-known renin–angiotensin cascade that produces the pressor hormone angiotensin II, thus inhibition of this enzyme could lead to the introduction of a new class of antihypertensive agents.[1] Orally active inhibitors of angiotensin converting enzyme (ACE), the second enzyme in the cascade, have been demonstrated clinically efficacious for controlling hypertension,[2] however an orally active, and hence therapeutically useful, renin inhibitor has yet to be developed. In order to become a viable drug, an orally active renin inhibitor must possess two attributes. It must be absorbed from the gastrointestinal tract into the systemic circulation and it must elicit a dose-related lowering of blood pressure when given orally in a pharmacologic model. Although a number of claims of oral activity for renin inhibitors have appeared in the literature,[3-5] the majority of these claims are based solely upon blood pressure effects observed following oral administration, and absorption is not addressed.[3] In one case an inhibitor was described as orally active only upon the basis of measurement of changes in plasma renin activity.[4] Bioavailability was determined in rats for one renin inhibitor and found to be low.[5]

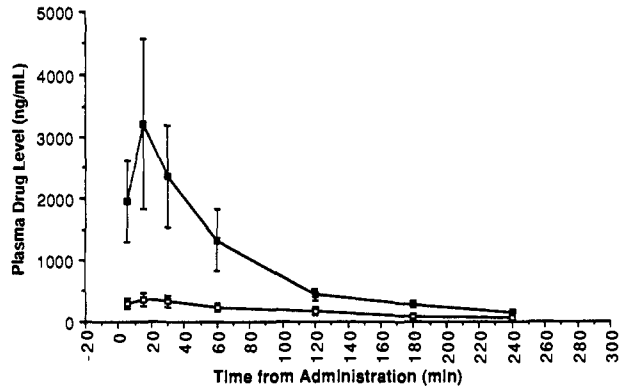

Figure 1. Plasma drug levels from a 10 mg/kg i.d. dose of inhibitor 4 in anesthetized, salt-depleted cynomolgus monkeys ($n = 4$). Points are designated as follows: arterial samples (□) and portal vein samples (■).

We have previously described a series of renin inhibitors that incorporated a C-terminal oxazolidinone. These compounds possessed both high hydrophilicity and excellent intravenous efficacy, but exhibited low bioavailability in monkey and rat models when dosed via the intraduodenal route.[6] The low systemic drug levels were attributed to extensive first pass hepatic uptake followed by biliary excretion.[7] These inhibitors contained histidine at the P_2 site.[8] Since it is known that the presence of polar or potentially ionizable groups can augment biliary excretion,[9] we reasoned that it was the presence of the basic imidazole of the histidine residue that was responsible for the low bioavailability. This report describes the results from a study in which substitution of other groups in place of the imidazole was shown to have profound effects upon intestinal absorption.

The structures of the compounds described are shown in Table I. We have previously shown in another series of renin inhibitors that other heterocycles could replace the histidine imidazole without loss in potency against purified human renal renin at pH 6.0.[10] This was largely the case in the current series with the exception of compound 3, incorporating 1-methylhistidine, which was 7-fold less potent than the parent histidine-containing inhibitor 1[6] in the purified renin assay. In the more physiologically relevant plasma renin assay conducted at pH 7.4, only inhibitor 4, containing (4-thiazolyl)Ala, showed good activity (6-fold loss in potency compared to 1) while the other compounds were 16-fold to 45-fold less potent than 1.

Inhibitors 1–5 were administered intraduodenally to anesthetized rats.[11] Plasma drug levels were determined by a renin inhibition assay[12] from samples taken from both

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(11) Inhibitors 1–5 are not active against rat renin ($IC_{50} \geq 7.5\ \mu M$).

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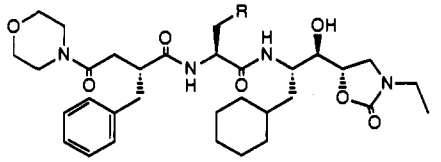
Table I. Renin Inhibitors Containing Heterocycle-Substituted Alanine Residues at the P_2 Histidine Site



no.	R	log P^a pH 6.5	log P^a pH 7.4	solubility, mM pH 7.4	IC_{50}, nM purified pH 6.5[b]	IC_{50}, nM plasma pH 7.4[c]
1	imidazol-4-yl (His)[d]	1.90	2.20	4.2	0.99	1.3
2	pyrazol-3-yl	2.52	2.49	3.7	1.1	21
3	1-methylimidazol-4-yl	2.01	2.16	3.2	7.4	58
4	thiazol-4-yl	2.82	2.83	0.71	0.60	8.1
5	thiophen-2-yl	3.59	3.59	0.10	1.5	43

[a] Octanol/water. [b] Purified human renal renin. [c] Human plasma renin. [d] See ref 6.

Table II. Plasma Levels of Renin Inhibitors Given Intraduodenally to Anesthetized Rats[a]

	plasma levels, ng/mL[b]			
	10 min		30 min	
no.[c]	systemic	portal	systemic	portal
1	55 ± 29	280 ± 80	34 ± 20[d]	390 ± 140[d]
2	6.7 ± 2.3	28 ± 16[e]	7.0 ± 2.0	58 ± 23
3	93 ± 34	950 ± 710	43 ± 17	350 ± 230
4	320 ± 100[e]	1900 ± 700[e]	300 ± 50[f,g]	1100 ± 500[g]
5	340 ± 60[h]	810 ± 70[f]	160 ± 30[h]	570 ± 230

[a] 10 mg/kg i.d. dose. [b] Mean ± SE, $n = 3$. [c] See Table I for structures. [d] $n = 5$. [e] Differs significantly from value for 1 ($P \leq 0.05$). [f] Differs significantly from value for 1 ($P \leq 0.005$). [g] $n = 6$. [h] Differs significantly from value for 1 ($P \leq 0.01$).

the systemic and portal circulation at 10 and 30 min, and the results are shown in Table II. Compound 1 was absorbed across the intestine as shown by its portal drug levels but the systemic levels indicated that it was extensively extracted by the liver. Inhibitor 3, incorporating a basic imidazole but lacking the potentially reactive imidazole NH functionality, showed a similar profile while compound 2, which contains the potentially reactive NH functionality but on a less basic heterocycle, was significantly less well absorbed across the intestine than 1. Inhibitors 4 and 5, which employ heterocycles that are both less reactive and less basic, each gave both portal and systemic drug levels that were significantly higher than were observed for 1.[13]

Anesthetized, salt-depleted cynomolgus monkeys[14] were dosed at 10 mg/kg intraduodenally with inhibitor 4. The drug level–time profiles for both systemic and portal circulation are shown in Figure 1. Peak plasma levels were observed early in the experiment (380 ± 110 ng/mL, systemic; 3200 ± 1400 ng/mL, portal, $n = 4$) and declined steadily, with 62 ± 35 ng/mL being present in the 4-h systemic samples. The integrated area under the curve for the systemic plasma levels (AUC_{0-4h} = 39 100 ± 8600 (ng/mL)min) is among the highest yet reported for any renin inhibitor, however first-pass hepatic extraction limits the amount of drug that reaches the systemic circulation. Upon oral administration to conscious, salt-depleted monkeys at the same dose, similarly high, but more variable, systemic plasma levels were observed (AUC_{0-4h} = 71 600 ± 37 500 (ng/mL)min, $n = 2$).

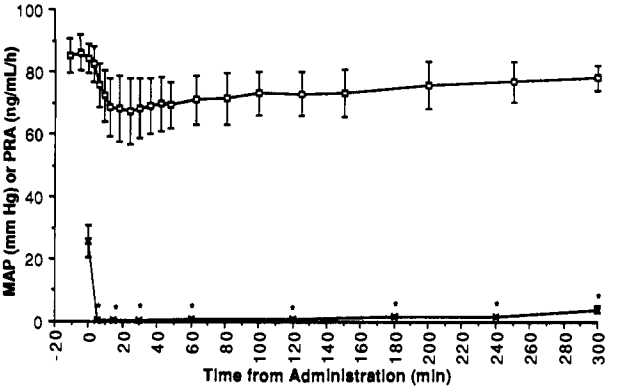


Figure 2. Effects of a 10 mg/kg i.d. dose of inhibitor 4 in anesthetized, salt-depleted cynomolgus monkeys ($n = 4$). Results are shown as mean ± SE and were considered significantly different from $T = 0$, if $P \leq 0.005$ (*). MAP = mean arterial pressure (□). PRA = plasma renin activity (×).

Table III. Enzyme Specificity

	% inhibition[a]			
no.[b]	cathepsin D[c]	cathepsin D[d]	pepsin[e]	pepsin[f]
1	2	nd[g]	2	nd[g]
4	93[h]	100[i]	57	26

[a] At 1×10^{-5} M. [b] See Table I for structures. [c] Bovine, pH 3.0. [d] Human, pH 3.0. [e] Porcine, pH 2.0. [f] Human, pH 2.0. [g] Not determined. [h] 28% inhibition at 1×10^{-7} M. [i] 40% inhibition at 1×10^{-7} M.

The blood pressure data from the intraduodenal monkey experiments are shown in Figure 2. Hypotension was observed, but disappointingly, the blood pressure response was not statistically significant even though peak plasma drug levels were 94 ± 27 times the IC_{50} value (IC_{50} monkey plasma, pH 7.4 = 5.9 nM). This moderate hypotensive activity remains unexplained (similar blood pressure responses were observed during the oral experiments, results not shown). Plasma renin activity (PRA) was almost completely suppressed for the duration of the experiments.

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(13) While this work was in progress, another renin inhibitor incorporating (4-thiazolyl)Ala was reported. This compound gave slightly higher plasma levels than those reported for 4 when dosed orally in marmosets at 30 mg/kg. Hiwada, K.; Kokubu, T.; Muneta, S.; Morisawa, Y.; Yabe, Y.; Koike, H.; Iijima, Y. *Hypertension* **1988**, *11*, 708. A second renin inhibitor incorporating (4-thiazolyl)Ala was recently reported. This compound gave lower plasma levels than those reported for 4 when dosed orally in marmosets at 10 mg/kg. Kokubu, T.; Hiwada, K.; Murakami, E.; Muneta, S.; Kitami, Y.; Salmon, P. F. *Hypertension* **1990**, *15*, 909.

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Dissociation between blood pressure and PRA has been observed by others[15] and one explanation is that a renin inhibitor must affect both circulating and tissue renin in order to elicit a blood pressure response. Thus one possibility for the low level of efficacy is that inhibitor 4 is binding to some other enzyme and is unable to reach the appropriate site of action. As seen in Table III, substitution of the thiazole for the imidazole decreased the inhibitor's specificity toward renin.[10,16]

It has been demonstrated by us[6,17] and others[18] that increasing a renin inhibitor's hydrophilicity can also lead to an improvement in efficacy. Conversely, in the present series of inhibitors, it is the more lipophilic compounds, as measured by partition coefficient and solubility (Table I), that result in superior absorption. The results reported herein clearly demonstrate that modification of the P_2 site of a molecular weight 700 peptide-based renin inhibitor can significantly improve both absorption from the gastrointestinal tract and passage through the liver into the systemic circulation. Studies currently underway are directed toward improving the efficacy of this series of renin inhibitors.

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Book Reviews

Handbook of Natural Products Data. Volume 1. Diterpenoid and Steroidal Alkaloids. Edited by Atta-ur-Rahman. Elsevier, Amsterdam, 1990. vii + 962 pp. 17.5 × 24.5 cm. ISBN 0-444-88173-5. $353.75.

Prof. Atta-ur-Rahman of the H.E.J. Research Institute of Chemistry, University of Karachi, has embarked on an ambitious project involving the systematic tabulation of all known natural products, together with information on their sources, molecular formulas, melting points, and spectral characteristics. This volume represents the first installment and lists data for 971 diterpenoid and steroidal alkaloids reported until the end of 1988.

To achieve this compilation, Prof. Atta-un-Rahman has relied on more than a dozen assistants, all of whom are devoid of doctoral degrees. The relative lack of experience of the compilation team with the subject matter makes itself apparent even upon cursory inspection of this compendium. The structures are not uniformly drawn within a structural series. For example, for the steroidal alkaloids, the stereochemistry of the angular hydrogens is sometimes indicated by either thick or dotted lines, or by simply straight lines which carry no stereochemical overtones. In some other instances the angular hydrogens are just completely ignored. The five-membered ring D is sometimes drawn as a symmetrical pentagon, and at others as an asymmetrical cycle with the base either at the top or at the bottom. One can only conclude that the original literature drawings were copied by the individual members of the team without much thought toward internal uniformity or consistency.

Each alkaloid entry is duly accompanied by at least one literature reference. But it was decided to ignore accents, cedillas, and the like. The result is that Cavé becomes Cave, Döpke becomes Dopke and Şener becomes Sener. Of course, such a policy simplifies the compilers' job, but it fails to do justice to the names of the authors quoted.

Another difficulty is that the compilers have not tried to assess the literature critically and have made no attempts to correct or amend publications in the light of general knowledge or of later developments. For instance, 3-*N*-methylholarrhimine is spelled 3-*N*-methylholarrhimin simply because it appeared as such in the German literature, whereas holarrhimine is spelled correctly with an "e" at the end because it was described in English-language publications. Interestingly, the related alkaloid holarrhidine is nowhere cited.

The perfect exemplar of alkaloid compilation and tabulation to have appeared over the years has been authored by Cavé, Leboeuf, and Guinaudeau and has covered the aporphinoid alkaloids. It has appeared at intervals in the Journal of Natural Products. Any new listing of alkaloids should try to emulate this series for its consistency, accuracy, reliability, and thoroughness. The present *Handbook of Natural Products Data* unfortunately falls short of such a degree of excellence.

It should be added, however, that the project is worthwhile and deserves to be continued, provided that much greater dedication to high standards is applied. The present handbook and its future companions would then become a useful complement to the recently published Dictionary of Alkaloids by I. W. Southon and J. Buckingham, published by Chapman and Hall.

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Organic Chemistry of Drug Synthesis. Vol 4. By Daniel Lednicer and Lester A. Mitscher with Gunda I. Georg. John Wiley and Sons, Inc., New York. 1990. xiii + 253 pp. 16 × 24 cm. ISBN 0-471-85548-0. $44.95.

The fourth volume of this series summarizes syntheses of drugs given a United States Adopted Name between 1983 and 1987. Arrangement of 11 chapters is by chemical class (aliphatic/alicyclic; monocyclic aromatics; polycyclic aromatics and reduced relatives; steroids; five- and six-membered heterocycles; five- and six-membered benzofused heterocycles; bicyclic fused heterocycles; β-lactam antibiotics; and twenty pages devoted to miscellaneous heterocyclic species). A bioactivity cross index, a cumulative index for volumes 1–4, references mainly in the 1980s, and comments on biological activity are provided. Many syntheses are derived from the patent literature.

These concise summaries can serve as a good starting point for chemists entering the medicinal chemical arena, but as pointed out by Alfred Burger actual syntheses by which drugs are produced are "not often divulged by the industrial chemists and engineers" (*J. Med. Chem.* 1990, *33*, 2061). Information presented could be useful as a partial source of lecture material utilized in honors courses in medicinal chemistry at the undergraduate level both in pharmacy schools and in chemistry departments. This volume is of less value to practicing synthetic chemists well-grounded in