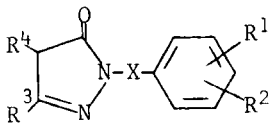
Chapter 7. Diuretics

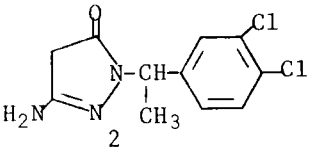
Robert L. Smith, Otto W. Woltersdorf, Jr. and Edward J. Cragoe, Jr.
Merck Sharp & Dohme Research Laboratories, West Point, Pa. 19486

The medical use of diuretics for edema and hypertension continues to grow more rapidly than the pharmaceutical industry in general. The most promising agents being generated in research are those with novel structures, unique modes of action and increased safety. Some valuable reviews of the field,[1-3] symposia[4] and medical perspectives[5-9] have been published. New insights have developed regarding the role of prostaglandins and related systems in kidney function and in the control of blood pressure.

1-Aralkyl-2-pyrazolin-5-ones (1) - In a search for a new chemical type of salidiuretic with high ceiling and long duration of action, a series of compounds of type 1 was discovered by Horstmann and colleagues.[10,11] Elucidation of the structure-activity (S/A) requirements[11,12] led to the



1



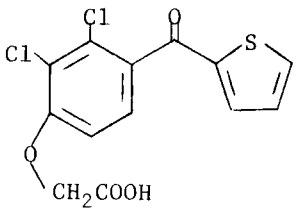
2

selection of 2 (Muzolimine, BAY g 2821) for detailed pharmacological and clinical study.[13,14] Compound 2 is amphoteric, forming soluble salts in acids and bases, and it is more lipophilic than furosemide. The tautomeric form and conformation of 2 were determined by X-ray analysis and quantum-chemical M.O. calculations. Electron density distribution was estimated with the aid of CNDO/2 calculations.[15] In dogs, 2 combines a high ceiling salidiuretic effect similar to furosemide with a somewhat longer duration of action. It was more potent than furosemide; p.o. doses of 0.1 to 3 mg/kg induced a linear increase in saliuresis, while glomular filtration rate (GFR) was unchanged and p-aminohippurate (PAH) clearance was increased.[16] The Na^+/K^+ ratio was somewhat higher than that of furosemide. In rats, 2 was less effective than furosemide, whereas, the duration of action was longer. Compound 2 reduced blood pressure in renal hypertensive dogs and in renal hypertensive and SH rats.[17] The drug appeared to work via inhibition of tubular reabsorption and not by increased filtration. Similar to furosemide, 2 inhibited sodium transport at the medullary portion of the ascending limb of Henle's loop;[18] however, unlike furosemide it acted only from the peritubular side. Apparently, 2 does not work by inhibition of renal Na^+-K^+-ATPase.[19] Studies using isolated frog skins showed that, on the serosal side, 2 increases the Na^+ permeability of the serosal membrane and decreases the active Na^+ transport capacity at the mucosal cell membrane.[20] In normal volunteers, the threshold dose of 2

ISBN 0-12-040513-X

was 10 mg p.o. and responses to doses up to 80 mg were log-linear. Excretion of Na^+ and Cl^- were as high with 30 mg of 2 as seen with 40 mg of furosemide; K^+ excretion was considerably lower.[21] Compound 2 was effective in chronic heart failure patients[22,23] and in those with varying degrees of renal insufficiency.[23-25] The primary site of action appeared to be the thick ascending limb of Henle's loop with possibly some proximal action.[22,26] Single p.o. doses of 40 mg of 2 produced little change in plasma renin, angiotensin II and aldosterone levels; Na^+ levels did not change but a marked decrease in K^+ levels occurred.[27] In patients with hepatogenic ascites, a combination of 2 with spironolactone was more effective than furosemide with spironolactone.[28]

Ticrynafen (3) - Numerous clinical studies[29-35] with 3 revealed its unique characteristics. Doses of 250 to 500 mg produced natriuresis and kaliuresis comparable to 50 mg hydrochlorothiazide. However, in contradistinction to hydrochlorothiazide, 3 induced a plasma urate decrease and bicarbonate increase. Although the drug bears a structural similarity to ethacrynic acid, it appears to act at a different site in the nephron. Instead of inhibiting Na^+ and Cl^- reabsorption in the thick ascending limb of the loop of Henle, it apparently acts primarily within the cortical distal nephron with some action in the proximal nephron.[31,37]

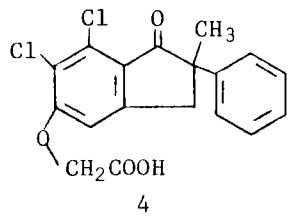


3

Compound 3 also exhibited a significant kaliuretic effect. The drug markedly affected either the reabsorptive or the secretory flux of urate in the proximal tubule; profound uricosuria was produced. This effect is independent of any proximal natriuretic effect of the agent.[31,36,38] Studies in hypertensive patients over periods up to six weeks showed that single daily doses of 250 mg of 3 were less antihypertensive than 50 mg of hydrochlorothiazide. However, when this dose was given twice daily, the antihypertensive effects of the two drugs were similar except that the onset of action of 3 was later than that of hydrochlorothiazide.[39-41]

It is interesting to note that some analogs of 3 wherein the 2-thienyl moiety is replaced by an aryl group have been reported recently. Biological data on the p-fluorophenyl analog in animals closely paralleled that of 3.[42]

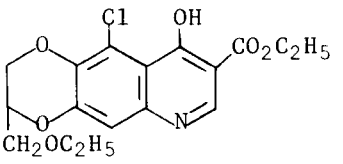
Indanones - The S/A relationships of the indanyloxyacetic acid diuretics have been further elucidated.[43,44] MK-196 (4) exhibits potent salidiuretic effects in rats, dogs and chimpanzees[43,45] and is uricosuric in chimpanzees[45-47] and rats.[48] It is antihypertensive in SH rats and in renal hypertensive African green monkeys.[45] Micropuncture studies in rats indicated that the drug acts primarily in the loop of Henle and collecting duct.[49,50] Single and multiple p.o. doses (14 days) of 10 and 20 mg of 4 were compared with



4

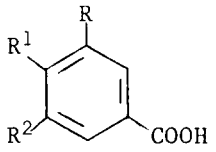
40 mg of furosemide in normal volunteers.[51-53] The 10 mg dose of 4 produced slightly less salidiuresis and the 20 mg dose more than 40 mg of furosemide over a 24 hr. period. Neither dose of 4 caused any increase in plasma urate levels, while furosemide caused urate retention. The high dose of 4 produced a temporary uricosuria. In mildly hypertensive patients, a 10 mg or 15 mg p.o. daily dose of 4 for one month produced a hypotensive effect as great or greater than that of 50 mg of hydrochlorothiazide.[54]

Quincarbate (5) - A novel class of 1,4-dioxino[2,3-g]quinolines was discovered and shown to possess potent salidiuretic properties.[55] Detailed S/A studies revealed 5 to be the most active member of the series.[56,57] In the Lipschitz rat assay, the p.o. salidiuretic potency of 5 was much greater than that of furosemide or hydrochlorothiazide. The Na^+/K^+ ratio and high ceiling effects of 5 were similar to furosemide, but the dose-response curve was flatter. 5 was highly effective in dogs and man, weakly effective in rhesus monkeys and inactive in mice and hamsters. The site of action is unknown; mechanisms involving carbonic anhydrase inhibition and aldosterone antagonism have been excluded. Preliminary clinical data indicate p.o. doses as low as 5 mg are effective.[56,57]



5

Sulfonamide Diuretics - This class continues to be the most widely used of all the diuretics; therefore, the medicinal chemical investigation of this chemical type has continued. The S/A relationships developed by Feit and Nielson in the 3-sulfamoylbenzoic acid series (6) have been both extensive and provocative. After studying the structural requirements of R and R^1



6

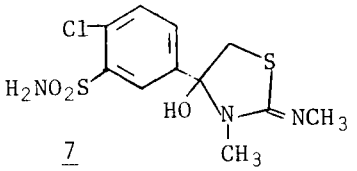
R	R^1	R^2	6
$n\text{-}C_4H_9NH$-	C_6H_5O-	H_2NO_2S-	a
$C_6H_5CH_2NH$-	C_6H_5O-	CH_3O_2S-	b
$C_6H_5CH_2NH$-	C_6H_5CO-	CH_3O_2S-	c
$C_6H_5CH_2O$-	C_6H_5CO-	HCONH	d
$(CH_2)_4N$-	C_6H_5O-	H_2NO_2S-	e

which led to the highly potent loop diuretic bumetanide (6a), their current work has focused on R^2. Compounds in which R^2 is mesyl[58] (such as 6b and 6c) or even formamido[59] (6d) are about 1/10 as potent as 6a in standard dog assays. More recently, this study has been extended to include replacements for carboxy, including alkoxymethyl, alkylthiomethyl, aminomethyl and substituted-aminomethyl. Some of these compounds were equipotent with 6a.[60]

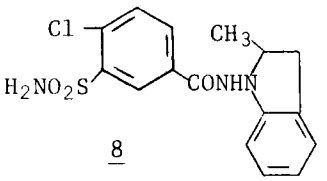
Merkel and co-workers have found an analog of 6 (6e, piretanide) that

is more potent in rats than 6a. The dose-related effects of 6e, furosemide and 6a on urine and electrolyte were similar; however, the slope of the dose-response excretion pattern of 6 was flatter than those of furosemide and 6a.[61]

Compound 7 (tizolemide, HOE 740) represents an outstanding example of a series of basic sulfonamide diuretics. P.O. studies in rats at 50 mg/kg showed tizolemide to have salidiuretic effects superior to those of hydrochlorothiazide and chlorthalidone and to have the long duration of action characteristic of chlorthalidone.[62,63]



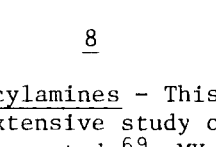
7



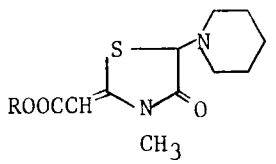
8

A report on the pharmacology of indapamide (8) indicates that it has a salidiuretic potency in normal, acidotic, alkalotic and SH rats equal to trichlormethiazide.[64] Clinical studies have confirmed the antihypertensive activity of this drug.[65,66]

Salicylamines - This novel class of diuretics has been disclosed[67,68] and an extensive study of the structural requirements for salidiuretic activity reported.[69] MK-447 (9) was selected for intensive pharmacological evaluation. It was more effective than furosemide in producing saluresis and diuresis in rats, dogs and chimpanzees. In subdiuretic doses, 9 was antihypertensive in SH rats. The antihypertensive effect was reduced by indomethacin which suggests that it is prostaglandin-mediated. Compound 9 was antihypertensive in diuretic doses in renal hypertensive dogs.[70] The drug stimulated the biosynthesis of PGE_2 from arachidonate in ram seminal vesicular microsomes, in intact mouse ovaries and in rat kidney slices. The anti-inflammatory properties of 9 were demonstrated by its effect in reducing carrageenan-induced foot edema in rats and the croton oil-induced swelling in mouse ears. Depression of PGG_2 levels was suggested as contributing to the antiinflammatory effect of 9.[71,72] A study in human volunteers at 6.25, 25 and 100 mg p.o. revealed a dose-related diuresis and saliuresis with minimal kaliuresis indicating that 9 is a potent high ceiling diuretic.[73]



9



No.	R
10	C_2H_5
11	H

Etozolin (10) was reported a number of years ago;[74] however, only recently has a disclosure of the salidiuretic and choleretic S/A relationships of the chemical series appeared. In addition, its pharmacology, site of action, toxicity and metabolism in laboratory animals and man have been published.[75]

The corresponding carboxylic acid (11,

etozolinic acid), which is a major metabolite of 10, is reported to be somewhat more active and less toxic than 10.[76]

Prostaglandins (PGs) - A comprehensive review[77] examining the actions postulated for the major renal prostaglandins (PGE_2, $PGF_{2\alpha}$, PGD_2 and PGA_2) in the regulation of blood pressure, renal blood flow (RBF) and renal sodium and water excretion was published in mid-1976. This brief review focuses on the highlights gleaned from recent investigations of the intrarenal transport, the sites and modes of metabolism and the pharmacological and physiological functions of renal PGs. Their interrelationships with other regulators of kidney function including diuretic agents are also considered.

Demonstration that endogenous renomedullary PGs most likely enter the tubular fluid at a site in the loop of Henle has been achieved by Oates and colleagues[78] using the stop-flow technique in anesthetized dogs. Neither the influx mechanism nor a determination as to whether PG influx and efflux occur at the same loop site could be made from the experimental data. However, the latter served to substantiate the proposed intrarenal origin of urinary PGs.[79] Furthermore, the identified PG entry site provided support for the hypothesis[79] that PGs elaborated in the medulla, the renal site of maximal PG synthetic capacity,[80] can enter the lumen. They are subsequently transported via the tubular fluid to possible sites of action in the cortex, the renal tissue richest in degradative enzymes[80] but limited in ability to form PGs.[80,81] Whether PGs in tubular fluid influence kidney function remains to be established.

Recent studies[82] on 9-keto PG reductase (9-KPGR) preparations isolated from rabbit and human kidneys have shown that the loop diuretics, ethacrynic acid and furosemide, and the potent PG synthetase inhibitor, indomethacin, inhibit 9-KPGR. At drug concentrations of 5×10^{-4}M, ethacyrnic acid, indomethacin and furosemide reduced rabbit renal 9-KPGR activity by 79%, 76% and 30%, respectively. Human renocortical 9-KPGR, although found to be less sensitive to inhibition than the rabbit enzyme, was inhibited similarly by ethacrynic acid, indomethacin and furosemide. In both species, ethacrynic acid was markedly more inhibitory than furosemide; interestingly, thiazide diuretics were without significant effect. These observations, coupled with the known ability of ethacrynic acid and furosemide to inhibit 15-hydroxy-PG dehydrogenase (15-HPGDH),[83] the major renocortical deactivating enzyme, led Stone and Hart[82] to suggest that blockade of 9-KPGR and 15-HPGDH may contribute to the therapeutic effects elicited by ethacrynic acid and furosemide in man since modulation of the PGE_2 to $PGF_{2\alpha}$ ratio is thought to exert an important influence on renal function.[84]

Weber et al[85] recently obtained the first definitive evidence that renal 9-KPGR is under the control of NaCl intake by examining the effects of low and high sodium diets on urinary sodium ($U_{Na}V$), urine volume (UV), PGE_2 and $PGF_{2\alpha}$ excretion, plasma renin activity (PRA) and renal 9-KPGR activity in cross-bred rabbits. At high NaCl (2.5 g/100 g diet) intake, $U_{Na}V$ was nine times but UV, only twice, that at low NaCl (0.25 g/100 g

diet) intake. PRA decreased from 12.9 to 1.8 $ngml^{-1}h^{-1}$ in going from the low to high NaCl diet. At low NaCl intake, daily urinary excretions of PGE_2 and $PGF_{2\alpha}$ were 1.9 and 2.1 µg, respectively, giving a 1:1.1 ratio of PGE_2 to $PGF_{2\alpha}$; 9-KPGR activity was found to be 0.61 ± 0.07 and 0.1 ± 0.01 nM $PGF_{2\alpha}$ formed $min^{-1}mg^{-1}$ in the cortex and medulla, respectively. At high NaCl intake, 9-KPGR activity increased three-fold in the cortex and two-fold in the medulla; daily urinary excretion of PGE_2 decreased to 0.53 µg, whereas, that of $PGF_{2\alpha}$ (2.43 µg) remained essentially unchanged, giving a 1:4.6 ratio of PGE_2 to $PGF_{2\alpha}$. Based on these results, Weber and co-workers proposed the intriguing concept that renal 9-KPGR is intimately involved in adjusting the activity of the renin-angiotensin system and distal nephron function in response to NaCl ingestion and, accordingly, may play a pivotal role in the regulation of NaCl and water balance. Indeed, such a mechanism may be operative in man, particularly in disease states such as Bartter's syndrome in which changes in the PGE_2 to $PGF_{2\alpha}$ ratio have been observed[86] to accompany variations in sodium and volume homeostasis.

A recent comparative investigation[87] of the renal responses to intrarenal infusions of PGE_2 (0.4 µg $Kg^{-1}min^{-1}$) and PGD_2 (0.4-0.8 µg $Kg^{-1}min^{-1}$) in the anesthetized dog revealed that, whereas, both PGs produced substantial and comparable increases in total RBF and renal venous PRA, only PGE_2 caused a marked diuresis and natriuresis. Further, GFR was not affected by PGE_2 but was reduced significantly by PGD_2 except when the latter was administered at a lower dose (0.04 µg $Kg^{-1}min^{-1}$). The failure of PGD_2 to alter electrolyte and fluid excretion rates concomitantly with the observed, induced renal vasodilation is counter to the results reported in a recent abstract.[89] Furthermore, this behavior is rather surprising since most renal vasodilators, with the exception of secretin,[88] produce a salidiuresis which accompanies elevation of RBF.[90,91] Nonetheless, Bolger et al[87] conclude that PGD_2 of intrarenal origin is likely to be involved primarily in the control of kidney hemodynamics and not in fluid and electrolyte regulation.

While investigating the unilateral ureteral-obstructed rabbit model of hydronephrosis, Needleman and colleagues[92] succeeded in unmasking the presence of TXA_2 synthetase and its potent constrictile product, thromboxane A_2 (TXA_2), in the ureteral-obstructed kidney but not in the contralateral normal kidney. This discovery marks the entry of TXA_2 into the realm of renal PGs. Both arachidonic acid (AA) and the endoperoxide PGH_2 were readily metabolized to TXA_2 by microsomal fractions of homogenates derived from the hydronephrotic kidney. Employing [^{14}C]-AA in this preparation, the percentages of radioactivity converted to PGE_2, $PGF_{2\alpha}$, PGD_2 and TXA_2 (measured as TXB_2) were 15%, 10%, 5% and 2.5-3%, respectively. These workers believe that the potential role of TXA_2 in ureteral obstruction, if TXA_2 is produced in other species, may be in altering regional blood flow to non-functioning kidney locales or in decreasing total RBF to a non-functioning kidney in a pathological situation.

The effect of decreased release of endogenous renal PGs on $U_{Na}V$ has been examined by Kirschenbaum and Stein[93] in conscious dogs undergoing a

water diuresis. Intravenous administration of either of two PG synthetase inhibitors, meclofenamate (2 mg Kg^{-1}) and RO 20-5720 (1 mg Kg^{-1}), failed to alter GFR, UV, U_KV, mean arterial pressure or renal plasma flow but elicited a four-fold increase in $U_{Na}V$ resulting primarily from a rise in U_{Na}. These data suggest that inhibition of intrarenal PG synthesis in the conscious dog is associated with a natriuresis without a change in UV or U_KV during water diuresis and, therefore, may indicate that the observed $U_{Na}V$ increase resulted from diminished sodium reabsorption at a site(s) beyond the distal tubule. These investigators were tempted to suggest that a decrease in local PGE release is associated with a commensurate diminution in collecting-duct sodium reabsorption. The tenability of this suggestion is suspect in view of recent studies by Stokes and Kokko[94] in rabbits and Ganguli et al[95] in rats which strongly suggest that endogenous PGE_2 inhibits sodium reabsorption in the collecting tubule.

In conclusion, although notable strides have been achieved in this challenging area of research since the initial discovery of medullin, the full consequences of renal PG involvement in kidney function are yet to be fully delineated and understood.

References

1. P. Y. D. Wong, Pharm. J., 215, 433 (1975).
2. W. Rupp, Arzneim.-Forsch., 27 (1), 289 (1977).
3. A. Lant, Practitioner, 219, 519 (1977).
4. Symposium on the Pharmacology of Diuretics, J. Clin. Pharmacol., 17, 618-680 (10 part 2), (1977).
5. D. G. Vidt, Postgrad. Med., 59 (5), 143 (1976).
6. R. H. Maffly, J. Am. Med. Assoc., 235, 2526 (1976).
7. R. W. Gifford, Jr., J. Am. Med. Assoc., 235, 1890 (1976).
8. W. Modell in Drugs of Choice, 1976-1977, W. Modell, Ed., C. V. Mosby Co., St. Louis, Mo., 1976, p. 92.
9. A. B. Schwartz, Nephrology for the Practicing Physician, Grune & Stratton, New York, N.Y., 1975.
10. E. Möller, K. Meng, E. Wehinger and H. Horstmann, U.D. Patents 3,949,083, April 6, 1976; 3,952,008, April 20, 1976; 3,957,814, May 18, 1977; 3,978,077, August 31, 1976; 4,002,641, January 11, 1977; 4,032,646, June 28, 1977.
11. J. Castañer, Drugs of the Future, 2, 387 (1977).
12. H. Horstmann, E. Moller, E. Wehinger and K. Meng, Abstr. Pap., Am. Chem. Soc., 174th Meet. MEDI 19 (1977).
13. Brit. Pharmacop. Comm. Appr. Names (Suppl. 7) 2 (1977).
14. E. Möller, H. Horstmann, K. Meng and D. Loew, Experientia, 33, 382 (1977).
15. E. Möller, H. Horstmann and K. Meng, Pharmatherapeutica, 1, 540 (1977).
16. D. Loew and K. Meng, Naunyn-Schmedeberg's Arch. Pharmacol., 297 (Suppl. 2), R38 (1977).
17. K. Meng, D. Loew, K. Stoepel and F. Hoffmeister, Curr. Med. Res. Opin., 4, 555 (1977).
18. D. Loew and K. Meng, Pharmatherapeutica, 1, 333 (1977).

19. H. J. Kramer, Pharmatherapeutica, 1, 353 (1977).
20. A. Dorge, R. Rick and E. V. Arnim, Pharmatherapeutica, 1, 341 (1977).
21. D. Lowe, Curr. Med. Res. Opin., 4, 455 (1977).
22. K. J. Berg, S. Jorstad and A. Tromsdal, Pharmatherapeutica, 1, 319 (1977).
23. P. Fauchald and E. Lind, Pharmatherapeutica, 1, 409 (1977).
24. G. Hoppeseyler, A. Heissler, M. Coppencastrop, M. Schindler, P. Schollmeyer and W. Ritter, Pharmatherapeutica, 1, 422 (1977).
25. A. Röckel, Curr. Med. Res. Opin., 4, 574 (1977).
26. M. Mussche and N. Lameire, Curr. Med. Res. Opin., 4, 462 (1977).
27. E. Schnurr, H. Kuppers, K. Wiesen and B. Grabensee, Pharmatherapeutica, 1, 415 (1977).
28. F. Heinrich, D. Loew and J. Dycka, Curr. Med. Res. Opin., 4, 706 (1977).
29. G. Lemieux, A. Kiss, A. Gougoux and P. Vinay, J. Clin. Chem. Clin. Biochem., 14, 306 (1976).
30. K. Lau, R. M. Stote, M. Goldberg and Z. S. Agus, Clin. Sci. Mol. Med., 53, 379 (1977).
31. T. H. Steele, D. R. Prasad and O. G. Reese, Wis. Med. J., 76, S54 (1977).
32. A. K. Jain, F. G. McMahon, R. Vargas and J. R. Ryan, Clin. Pharmacol. Ther., 21, 107 (1977).
33. P. Bessin, J. Bonnet, M. F. Malin, Abstr. Pap., Am. Chem. Soc., 174th Meet. MEDI 5 (1977).
34. A. R. Maass, R. M. Stote, I. B. Snow, R. Erickson, Abstr. Pap., Am. Chem. Soc., 174th Meet. MEDI 6 (1977).
35. O. G. Reese, Jr. and T. H. Steele, Am. J. Med., 60, 973 (1976).
36. D. R. Prasad, I. M. Weiner and T. H. Steele, J. Pharmacol. Exp. Ther., 200, 58 (1977).
37. K. Lau, R. Stote, M. Goldberg and Z. S. Agus, Clin. Res., 24, 405A (1976).
38. G. Lemieux, A. Kiss, P. Vinay and A. Gougoux, Kidney Int., 12, 104 (1977).
39. M. Nemati, M. C. Kyle, E. D. Freis, J. Amer. Med. Assoc., 237, 652 (1977).
40. A. Gillies, G. Morgan and T. Morgan, Aust. N. Z. Med. Med., 7, 443 (1977).
41. R. Vargas, A. Jain, J. Ryan, F. G. McMahon, Clin. Pharmacol. Ther., 21, 119 (1977).
42. P. H. Jones, D. S. Bariana, A. K. L. Fung, Y. C. Martin, J. Kynel and A. Lall, Ger. Offen. 2,642,879, April 7, 1977.
43. O. W. Woltersdorf, Jr., S. J. deSolms, E. M. Schultz and E. J. Cragoe, Jr., J. Med. Chem., 20, 1400 (1977).
44. S. J. deSolms, O. W. Woltersdorf, Jr., E. J. Cragoe, Jr., L. S. Watson and G. M. Fanelli, Jr., J. Med. Chem., 21, in press (1978).
45. L. S. Watson, G. M. Fanelli, H. F. Russo, C. S. Sweet, C. T. Ludden and A. Scriabine, in New Antihypertensive Drugs, A. Scriabine and C. S. Sweet, Eds., Spectrum Publications, Inc., Holliswood, N. Y., 1976, p. 307.
46. G. M. Fanelli, Jr., D. L. Bohn, A. Scriabine and K. H. Beyer, Jr., J. Pharmacol. Exp. Ther., 200, 402 (1977).

47. G. M. Fanelli, Jr., D. L. Bohn and A. G. Zacchei, J. Pharmacol. Exp. Ther., 200, 413 (1977).
48. R. McKenzie, T. Knight and E. J. Weinman, Proc. Soc. Exp. Biol. Med., 153, 202 (1976).
49. M. L. Kauker, Fed. Proc., 35, 224 (1976).
50. M. L. Kauker, J. Pharmacol. Exp. Ther., 200, 81 (1977).
51. B. T. Emmerson, L. Thompson and K. Mitchell, J. Clin. Chem. Biochem., 14, 286 (1976).
52. K. F. Tempero, G. Hitzenberger, Z. E. Dziewanowska, H. Halkin and G. H. Besselaar, Clin. Pharmacol. Ther., 19, 116 (1976).
53. Z. E. Dziewanowska, K. F. Tempero, F. Perret, G. Hitzenberger and G. H. Besselaar, Clin. Res., 24, 253A (1976).
54. K. F. Tempero, J. A. Vedin, C. E. Wilhelmsson, P. Lund-Johansen, C. Vorburger, C. Moerlin, H. Aaberg, W. Enenkel, J. Bolognese and Z. E. Dziewanowska, Clin. Pharmacol. Ther., 21, 119 (1977).
55. T. A. C. Boschman and J. G. Korsloot, U.S. Patent 3,865,832, February, 1975.
56. J. van Dijk and J. Hartog and T. A. C. Boschman, J. Med. Chem., 19, 982 (1976).
57. T. A. C. Borschman, J. van Dijk and J. Hartog, 5th Intern. Symp. Med. Chem., Paris, July (1976).
58. P. W. Feit and O. B. T. Nielson, J. Med. Chem., 19, 402 (1976).
59. P. W. Feit and O. B. T. Nielson, J. Med. Chem., 20, 1687 (1977).
60. P. W. Feit and O. B. T. Nielson, Abstr. Pap., Am. Chem. Soc. 174th Meet. MEDI 2 (1977).
61. W. Merkel, D. Bormann, D. Mania, R. Muschaweck and M. Hropot, Eur. J. Med. Chem., 11, 399 (1976).
62. H-J. Lang, B. Knabe and R. Muschaweck, Abstr. Pap., Am. Chem. Soc. 174th Meet. MEDI 3 (1977).
63. Hoechst A.G. Belg. Pat. 850,451, January, 1976.
64. Y. Suzuki, Y. Hamaguchi and I. Yamagami, Nippon Yakurigaku Zasshi, 73, 321 (1977).
65. G. Gragnoli, F. Puccetti, R. Nami, I. Tanganelli, F. Favilli and E. Betti, Minerva Med., 68, 749 (1977).
66. P. Turner, G. N. Volans and H. J. Rogers, Curr. Med. Res. Opin., 4, 596 (1977).
67. E. J. Cragoe, Jr. and E. M. Schultz, U.S. Patents 3,794,734, February, 1974; 3,928,624, December, 1975 and 4,029,816, June, 1977.
68. E. M. Schultz and E. J. Cragoe, Jr., U.S. Patents 3,809,721, May, 1974; 3,864,401, February, 1975; 3,979,361, September, 1976 and 4,044,153, August, 1977.
69. R. L. Smith, G. E. Stokker and E. J. Cragoe, Jr., Abstr. Pap., Am. Chem. Soc. 174th Meet. MEDI 7 (1977).
70. A. Scriabine, L. S. Watson, H. R. Russo, C. T. Ludden, C. S. Sweet, G. M. Fanelli, Jr., N. Bohidar and C. A. Stone, Fed. Proc., 37, 921 (1978).
71. F. A. Kuehl, Jr., J. L. Humes, R. W. Egan, E. A. Ham, G. C. Beveridge and C. G. Van Arman, Nature, 265, 170 (1977).
72. F. A. Kuehl, Jr., R. W. Egan, J. L. Humes, G. C. Beveridge and G. C. Van Arman, New Biochemical Aspects of Prostaglandins and Thromboxans, Academic Press, N. Y., (1978).

73. M. B. Affrime, D. T. Lowenthal, G. Onesti, P. Busby, C. Swartz and B. Lei, Clin. Pharmacol. Ther., 21, 97 (1977).
74. G. Satzinger, Justus Liebig's Ann. Chem., 665, 150 (1963).
75. Elkapin® (Etozolin, GO 687), Arzneim.-Forsch., 27 (II), 1741 (1977).
76. G. Satzinger, M. Herrmann and K-O. Vollmer, U.S. Patent 3,971,794, July, 1976.
77. R. J. Anderson, T. Berl, K. M. McDonald and R. W. Schrier, Kidney Int., 10, 205 (1976).
78. W. M. Williams, J. C. Frölich, A. S. Nies and J. A. Oates, ibid, 11, 256 (1977).
79. J. C. Frölich, T. W. Wilson, B. J. Sweetman, M. Smigel, A. S. Nies, K. Carr, J. T. Watson and J. A. Oates, J. Clin. Invest., 55, 763 (1975).
80. K. Crowshaw and J. Z. Szlyk, Biochem. J., 116, 421 (1970).
81. C. Larsson and E. Änggard, Eur. J. Pharmacol., 21, 30 (1973).
82. K. J. Stone and M. Hart, Prostaglandins, 12, 197 (1976).
83. R. V. Patak, B. K. Mookerjee, C. J. Bentzel, P. E. Hysert, M. Babej and J. B. Lee, ibid, 10, 649 (1975).
84. K. U. Malik and J. C. McGiff, Circ. Res., 36, 599 (1975).
85. P. C. Weber, C. Larsson and B. Scherer, Nature, 266, 65 (1977).
86. J. R. Gill, J. C. Frölich, R. E. Bowden, A. A. Taylor, H. R. Keiser, H. W. Seyberth, J. A. Oates and F. C. Bartter, Am. J. Med., 61, 43 (1976).
87. P. M. Bolger, G. M. Eisner, P. T. Shea, P. W. Ramwell and L. M. Slotkoff, Nature, 267, 628 (1977).
88. G. R. Marchand, K. A. Hubel and H. E. Williamson, Proc. Soc. Exp. Biol. Med., 139, 1356 (1972).
89. O. Oelz, B. J. Sweetman, J. A. Oates, A. S. Nies and J. L. Data, Pharmacologist, 18, 163 (1976).
90. P. G. Baer and L. G. Navar, Kidney Int., 4, 12 (1973).
91. T. M. Daugharty, L. J. Belleau, J. A. Martino and L. E. Earley, Am. J. Physiol., 215, 1442 (1968).
92. A. R. Morrison, K. Nishikawa and P. Needleman, Nature, 267, 259 (1977).
93. M. A. Kirschenbaum and J. H. Stein, J. Clin. Invest., 57, 517 (1976).
94. J. B. Stokes and J. P. Kokko, ibid, 59, 1099 (1977).
95. M. Ganguli, L. Tobian, S. Azar and M. O'Donnell, Circ. Res., 40, I-135 (1977).