Synthesis and Biochemical Evaluation of Analogues of Aminoglutethimide Based on Phenylpyrrolidine-2,5-dione

Michael J. Daly,*[†] Gareth W. Jones,[†] Paul J. Nicholls,[†] H. John Smith,[†] Martin G. Rowlands,[‡] and Michael A. Bunnett[‡]

Welsh School of Pharmacy, UWIST, Cardiff, CF1 3XF, United Kingdom, and Drug Development Section, Institute of Cancer Research, Sutton, Surrey SM2 5PX, United Kingdom. Received June 6, 1985

A series of (aminophenyl)pyrrolidine-2,5-diones has been prepared that bear structural similarities to aminoglutethimide (1, 3-(4-aminophenyl)-3-ethylpiperidine-2,5-dione). The inhibitory activity of these compounds was evaluated toward human placental aromatase and bovine adrenal cholesterol side chain cleavage (CSCC) enzyme assay systems. Selective, competitive inhibition of the aromatase enzyme system was demonstrated by 5 (3-(4-aminophenyl)-1-methylpyrrolidine-2,5-dione, $K_i = 1.75 \ \mu$ M), 6 (3-(4-aminophenyl)-1,3-dimethylpyrrolidine-2,5-dione, $K_i = 1.75 \ \mu$ M), 7 (3-(4-aminophenyl)-3-methylpyrrolidine-2,5-dione, $K_i = 0.8 \ \mu$ M), and 8 (3-(4-aminophenyl)-3-ethylpyrrolidine-2,5-dione, $K_i = 1.0 \ \mu$ M). Compound 15 (3-(4-aminophenyl)pyrrolidine-2,5-dione) proved unexpectedly difficult to prepare following standard methods and was only moderately inhibitory toward aromatase (IC₅₀ = 20 \ \muM). Compound 16 (3-(4-aminophenyl)-3-ethylpyrrolidine-2,5-dione) was weakly inhibitory toward testosterone aromatization and totally inactive toward androstenedione aromatization. These compounds were either weak or ineffective inhibitors of the CSCC enzyme systems, while 1 gave K_i values toward aromatase and CSCC enzymes of 0.68 and 14 μ M, respectively. The unsubstituted phenylpyrrolidinediones were inactive in either system, and the 4-nitrophenyl derivatives exhibited weak, nonselective inhibition, indicating the importance of the primary amine moiety for potent inhibition of aromatase activity.

Aminoglutethimide (1, 3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione) suppresses estrogen biosynthesis in postmenopausal women, thereby removing the stimulus for breast tumor growth, and is becoming increasingly used to treat hormone-dependent metastatic breast carcinoma.^{1,2} This action is mediated via inhibition of several cytochrome P-450 dependent steroidogenic enzyme systems, and the most potent action is directed toward the aromatase enzyme complex, which is responsible for the conversion of the androgens to estrogens.³ The other major site of action is inhibition of the cholesterol side chain cleavage (CSCC) enzyme, which converts cholesterol to pregnenolone.⁴ Inhibition of the CSCC enzyme system reduces adrenal hydrocortisone production, necessitating clinical replacement of this steroid to prevent the resulting reflex rise in adrenocorticotrophic hormone (ACTH) from overcoming adrenal suppression.⁵ Potent, selective inhibitors of aromatase may therefore be expected to possess clinical advantages over 1, since replacement hydrocortisone could be omitted from therapy if the activity of the CSCC enzyme is not inhibited. Preliminary clinical trials with 4-hydroxyandrostenedione, a selective type I inhibitor of aromatase,⁶ have shown promising results without replacement hydrocortisone therapy. The present report concerns the development of some selectively competitive type II, nonsteroidal inhibitors of aromatase, structurally related to aminoglutethimide.

Aminoglutethimide is the 4-amino derivative of the sedative agent glutethimide (2, 3-ethyl-3-phenylpiperidine-2,6-dione) and was originally developed as an anticonvulsant.⁸ A series of structurally related anticonvulsants, based on phenylpyrrolidine-2,5-dione, were synthesised⁹ and evaluated pharmacologically¹⁰ in 1951, and phensuximide (3, 1-methyl-3-phenylpyrrolidine-2,5-dione) and methsuximide (4, 1,3-dimethyl-3-phenylpyrrolidine-2,5dione) were introduced for the therapy of petit mal and psychomotor epilepsy.¹¹ In the present work, we have introduced primary amine groups at the 4-phenyl position of a series of phenylpyrrolidine-2,5-diones, the compounds developed differing from aminoglutethimide by one methylene group in the heterocyclic ring and by alkyl substitution, as shown in Table I. This is analogous to the modification of glutethimide (2) to give aminoglutethimide (1), since 2 is not an inhibitor of aromatase, and the position of the primary amine moiety has been found to significantly influence the inhibitory profile of analogues of $1.^{12}$

Results and Discussion

Synthesis of Analogues. The 4-aminophenyl derivatives 3-(4-aminophenyl)-1-methylpyrrolidine-2,5-dione (5) and its 1,3-dimethyl analogue 6 were prepared directly from 3 and 4 as reported previously.¹³ 3-(4-Aminophenyl)-3-methylpyrrolidine-2,5-dione (7) and its 3-ethyl analogue 8 were synthesized as shown in Scheme I (acetophenone was utilized in place of propiophenone for the preparation of 7).

The cyanoacetate esters were prepared with ammonium acetate catalyst, added portionwise to improve the yield.¹⁴ High-temperature cyclization of succinic acids with urea can lead to problems of incomplete reaction, with the production of mixtures of starting material and imide products.¹⁵ Ring closure of phenylethane-1,2-dicarboxylic

- Camacho, A. M.; Cash, R.; Brough, A. J.; Wilroy, R. S. J. Am. Med. Assoc. 1967, 202, 20.
- (2) Santen, R. J.; Badder, E.; Leman, S.; Harvey, H.; Lipton, A.; Boucher, A. E.; Manni, A.; Rosen, H. Breast Cancer Res. Treat. 1982, 2, 375.
- (3) Chakraborty, J.; Hopkins, R.; Parke, D. V. Biochem. J. 1972, 130, 19P.
- (4) Cash, R.; Brough, A. J.; Cohen, M. N. P.; Satoh, P. S. J. Clin. Endocrinol. Metab. 1967, 27, 1239.
- (5) Santen, R. J.; Wells, S. A. Cancer 1980, 46, 1066.
- (6) Santen, R. J.; Brodie, A. M. H. Clin. Oncol. 1982, 1, 77.
- (7) Coombes, R. C.; Goss, P.; Dowsett, M.; Gazet, J-C.; Brodie, A. Lancet 1984, 1237.
- (8) Aguilar, J. A.; Martin, H. C. Can. Med. J. 1961, 84, 374.
- (9) Miller, C. A.; Long, L. M. J. Am. Chem. Soc. 1951, 73, 4895.
- (10) Chen, G.; Portman, R.; Ensor, C. R. J. Pharmacol. Exp. Ther. 1951, 103, 54.
- (11) Zimmerman, F. T. Arch. Neurol. Psychiat. 1951, 66, 156.
- (12) Foster, A. B.; Jarman, M.; Leung, C-S.; Rowlands, M. G.; Taylor, G. N. J. Med. Chem. 1983, 26, 50.
- (13) Scoular, I. T.; Nicholls, P. J.; Smith, H. J. Eur. J. Med. Chem. 1976, 11, 91.
- (14) Cragoe, E. J.; Robb, C. M.; Sprague, J. M. J. Org. Chem. 1950, 15, 381.

[†]Welsh School of Pharmacy, UWIST.

[‡]Drug Development Section, Institute of Cancer Research.

Table I. Summary of the (4-Aminophenyl)pyrrolidine-2,5-dione Analogues of Aminoglutethimide



^a Yield refers to catalytic hydrogenation, after crystallization from propan-2-ol.

Scheme I



acid (9) by this method gave 10 (3-phenylpyrrolidine-2,5dione), with a melting point (78–79 °C) that agreed with a reported value.¹⁶ However, the product appeared to be contaminated with starting material, since washing with NaHCO₃ (2% w/v) gave the pure imide, as shown by analytical and melting point data.^{9,17} Methylation of parent imides was performed by the method of El-Zanfally and co-workers,¹⁸ utilizing methyl iodide and dry K₂CO₃ in acetone.

Nitration and hydrogenation of the parent imides was performed as described previously,¹³ with the reaction time for nitration reduced to 2 h. Nitration of 10 by this method failed to give isolatable products, presumably due to mixed isomer formation, a similar difficulty having been reported for the nitration of glutethimide.¹² The attempted alternative route to the required nitrated derivative 11 (3-(4nitrophenyl)pyrrolidine-2,5-dione) by nitration of 9 followed by ring closure of the product (4-nitrophenyl)ethane-1,2-dicarboxylic acid (12) with urea led to decarboxylation and the production of 13 (3-(4-nitrophenyl)propionamide), presumably due to the electron-withdrawing effect of the nitro group. This difficulty has previously been reported,¹⁹ but the reaction product was

Table II. Inhibition of Bovine Adrenal CSCC Enzyme^a

no.	compd	% inhibn of bovine adrenal CSCC enzyme (inhibitor concn 50 µg/mL)
1	aminoglutethimide	83
5	1-methyl analogue	30
6	1,3-dimethyl analogue	30
7	3-methyl analogue	0
8	3-ethyl analogue	38
15	1,3-unsubstituted analogue	30
16	3-ethyl-1-methyl analogue	0

^aEach value represents the mean of two determinations (variability <10%)

not characterized. The amide formed in this reaction was hydrogenated to give the primary amine derivative 14 (3-(4-aminophenyl)propionamide) for testing in the assay procedures. The successful preparation of the required 4-nitro derivative 11 was eventually achieved by treatment of 10 with fuming nitric acid at -40 °C,²⁰ although the product obtained differed in its physical properties compared with previously published data.¹⁹ This product was then successfully hydrogenated to 15 (3-(4-aminophenyl)pyrrolidine-2,5-dione).

Enzyme Inhibitory Assay Procedure. The analogues prepared were tested for their inhibitory activity against

⁽¹⁵⁾ Naps, M.; Johns, I. R. J. Am. Chem. Soc. 1940, 62, 2450.

⁽¹⁶⁾ Magarian, E.; Becker, G. W.; Diamond, L. J. Pharm. Sci. 1973, 62, 325.

⁽¹⁷⁾ Ramart-Lucas, M.; Papadakis, M. Z. Ann. Chim. 1932, 18, 51.

⁽¹⁸⁾ El-Zanfally, S.; Khalifa, M.; Abou-Zeid, Y. M. J. Pharm. Sci. 1968, 57, 2176.

⁽¹⁹⁾ Lange, J.; Lapsewicz, J. Acta. Pol. Pharm. 1978, 35, 289.

⁽²⁰⁾ Kornet, M. J., Crider, A. M.; Magarian, E. O. J. Med. Chem. 1977, 20, 405.



Figure 1. Inhibitory effect of aminoglutethimide (1) and the (4-aminophenyl)pyrrolidine-2,5-dione derivatives 6–8 and 16 toward aromatase activity from human term placenta, utilizing testosterone $(1.5 \ \mu M)$ as the substrate. Each point represents a duplicate reading (variability <10%).

Table III. Inhibition of Androgen Aromatization

		test tero	os- ne ^a	andros- tene-
no.	compd	IC ₅₀ , μ Μ	$K_{i}, \mu M$	dione ^σ IC ₅₀ , μM
1	aminoglutethimide	6.13	0.68	8.3
5	1-methyl analogue	16.6	1.75	10.04
6	1,3-dimethyl analogue	15.66	1.75	10.04
7	3-methyl analogue	12.5	0.8	10.04
8	3-ethyl analogue	13.5	1.0	8.4
15	1,3-unsubstituted analogue	20.0	\mathbf{ND}^{c}	10.2

^aSubstrate concentration 1.5 μ M ($K_m = 0.13 \mu$ M). ^bSubstrate concentration 0.25 μ M ($K_m = 55 n$ M). ^cND, not determined.

the CSCC and aromatase enzymes as described previously.¹² In addition, the most effective inhibitors of testosterone aromatization were further evaluated for their ability to inhibit the aromatization of androstenedione, since this may be the preferred substrate for the enzyme.²¹ Table II shows the percentage inhibition of the CSCC enzyme obtained at the highest concentration of inhibitor employed (50 μ g/mL), compared with aminoglutethimide.

All six (4-aminophenyl)pyrrolidine-2,5-diones were either weak or ineffective inhibitors of the CSCC enzyme, and 50% inhibition was not obtained. Under similar assay conditions, 1 has an IC_{50} of 30 μ M,¹² this value referring to the concentration of inhibitor required to reduce enzyme activity to 50% of the control value at the concentration of substrate employed.

Figure 1 expresses the activity of four of the 4-aminophenyl compounds against the aromatization of testosterone, compared with aminoglutethimide.

Apparent K_i values were subsequently determined by Dixon plots²² for potent inhibitors of testosterone aromatization, as shown in Figure 2. Regression lines were calculated by least-squares analysis.

Table III shows the inhibition of the aromatase enzyme by the (4-aminophenyl)pyrrolidinediones against both androgen substrates.



⁽²²⁾ Dixon, M. Biochem. J. 1953, 55, 170.



Figure 2. Dixon plot determined for 8. Velocity (v) is expressed as micromoles of testosterone aromatized per minute per milligram of protein. Each point represents the mean of four determinations \pm standard error of the mean.

Table IV. Extent of Inhibition of the CSCC and Aromatase Enzymes by the Propionamide Derivatives^a

no.	compd	% inhibn of the CSCC enzyme (inhibitor concn 50 µg/mL)	% inhibn of the aromatase enzyme (inhibitor concn 20 μg/mL)
13	4-nitro derivative	28	8
14	4-amino derivative	19	38

 a Each value represents the mean of two determinations (variability $<\!10\%)$

Four analogues were strong inhibitors of aromatase, with IC_{50} and K_i values similar to that of 1, although 3-(4aminophenyl)-3-ethyl-1-methylpyrrolidine-2,5-dione (16) was only weakly inhibitory against testosterone aromatization and possessed no activity toward either and rostenedione aromatization or the side-chain cleavage of cholesterol. None of the parent aryl ring unsubstituted phenylpyrrolidine-2,5-diones were inhibitors in either assay system, and their 4-nitrophenyl derivatives were weak, nonselective inhibitors. These results suggest that the primary amine moiety is a positive requirement for potent inhibitory action toward aromatase, as found previously for analogues of 1 utilizing both enzyme systems.¹² The straight-chain propionamide derivatives 13 and 14 were weak inhibitors of testosterone aromatization, with some activity against the CSCC enzyme, as shown in Table IV. These results further indicate that a rigid heterocyclic ring system may also be important for aromatase inhibition.

The ability to selectively inhibit the aromatization of both androgens, as demonstrated by the (4-aminophenyl)pyrrolidinediones 5–8, implies that these agents may be effective aromatase inhibitors in vivo. The activity of the CSCC enzyme is not strongly inhibited by these agents, indicating that replacement glucocorticoid may not be required during such therapy. Studies in rats,²³ dogs,²⁴ and man²⁵ have indicated that both **3** and **4** are extensively N-demethylated in vivo to 3-phenylpyrrolidine-2,5-dione (10) and 3-methyl-3-phenylpyrrolidine-2,5-dione, respectively. The 4-aminophenyl derivatives lacking the *N*methyl group may therefore prove to be more pharmacologically effective aromatase inhibitors in vivo than their *N*-methyl derivatives. An assessment of these agents'

 ⁽²³⁾ Nicholls, P. J.; Orton, T. C. Br. J. Pharmacol. 1972, 45, 48.
(24) Dudley, K. H.; Bius, D. L.; Waldrop, C. Drug Metab. Disp.,

^{1974, 2, 113.}

⁽²⁵⁾ Karch, S. B. J. Am. Med. Assoc. 1973, 223, 1463.

ability to lower estrogen levels in laboratory animals is being pursued at the present time.

Experimental Section

All reagents and solvents were general purpose or analytical reagent grade. Proton NMR spectra (90 MHz) were determined in a Perkin-Elmer R32 spectrometer. Chemical shifts are reported in δ , parts per million, downfield from internal tetramethylsilane. Melting points were determined on an Electrothermal apparatus and are corrected. Infrared spectra were determined in KBr disks, unless otherwise stated, on either a Perkin-Elmer 681 Infrared spectrophotometer, or a Perkin-Elmer 357 Grating Infra-red spectrophotometer. Phenylethane-1,2-dicarboxylic acid (9) was purchased from the Aldrich Chemical Co., Gillingham, Dorset, U.K.

3-Phenylpyrrolidine-2,5-dione (10). Phenylethane-1,2-dicarboxylic acid (9; 19.4 g, 0.1 mol) was heated with urea (12 g, 0.3 mol) at 180–200 °C for 30 min. The residue crystallized from methanol to give 10 (10.5 g, 60% based on 9), as a white, crystalline material: mp 79–81 °C (lit.¹⁶ mp 79–81 °C). Further purification was carried out by dissolving the crystals in ether and washing with NaHCO₃ solution (2%) until effervescence ceased. The ether layer was washed with water (2 × 50 mL), dried (Na₂SO₄), and evaporated to give a white crystalline solid which crystallized from ether to give 10 as white crystalline solid which crystallized from ether to give 10 as white crystalline solid which crystallized from ether to give 10 as white crystalline solid which crystallized from ether to give 10 as white crystalline solid which crystallized from ether to give 10 as white crystalline solid which crystallized from ether to give 10 as white crystalline solid which crystallized from ether to give 10 as white crystalline solid which crystallized from (C=O) cm⁻¹; ¹H NMR δ 2.8 (1 H, dd, Ha, J_{HbHa} = 18 Hz, J_{HxHa} = 6 Hz), 3.16 (1 H, dd, Hb, J_{HaHb} = 18 Hz, J_{HxHb} = 9 Hz), 4.02 (1 H, dd, Hx, J_{HaHx} = 6 Hz, J_{HbHx} = 9 Hz), 7.28 (5 H, s, Ar H), 9.37 (1 H, s, NH). Anal. (C₁₀H₉NO₂) C, H, N.

3-(4-Nitrophenyl)pyrrolidine-2,5-dione (11). Compound 10 (6 g, 0.034 mol) was added portionwise to fuming HNO₃ (25 mL) at -40 °C over 20 min. The resulting solution was then poured, with vigorous stirring, into ice/water (300 mL), producing a white solid. Crystallization of the solid from EtOH gave white crystals of 11 (4.74 g, 63% based on 10): mp 148–150 °C (lit.¹⁹ mp 131–133 °C); ν_{max} 3310 (N–H str), 1783, 1718 (C==O), 1515, 1350 (N–O) cm⁻¹; ¹H NMR δ 2.86 (1 H, dd, Ha, J_{HbHa} = 18 Hz, J_{HxHa} = 6 Hz), 3.20 (1 H, dd, Hb, J_{HaHb} = 18 Hz, J_{HxHb} = 9 hz), 4.38 (1 H, dd, Hx, J_{HaHx} = 6 Hz, J_{HbHx} = 9 Hz), 7.63 (2 H, d, Ar H, J = 9 Hz), 8.19 (2 H, d, Ar H, J = 9 Hz), 11.46 (s, 1 H, NH). Anal. (C₁₀-H₈N₂O₄) C, H, N.

3-(4-Aminophenyl)pyrrolidine-2,5-dione (15). Compound 11 (2 g, 0.09 mol) was dissolved in EtOAc (50 mL) and shaken with gaseous H_2 and 10% Pd/C (0.2 g) until uptake of gas was complete (650 mL). The flask was cooled, the mixture filtered, and the solvent removed. The residue was crystallized from EtOH to give 15 as a pale orange solid (1.54 g, 90% based on 11): mp

171.5–173.5 °C; IR ν_{max} 3490, 3310 (N–H str), 1763, 1708 (C==O), 1265 (C–N str) cm⁻¹; ¹H NMR δ 2.56 (1 H, dd, Ha, J_{HbHa} = 18 Hz, J_{HxHa} = 6 Hz), 3.03 (1 H, dd, Hb, J_{HaHb} = 18 Hz, J_{HxHb} = 9 Hz), 3.84 (1 H, dd, Hx, J_{HaHx} = 6 Hz, J_{HbHx} = 9 Hz), 4.41 (2 H, s, NH₂), 6.47 (2 H, d, Ar H, J = 9 Hz), 6.83 (2 H, d, Ar H, J = 9 Hz), 11.12 (1 H, s, NH). Anal. (C₁₀H₁₀N₂O₂) C, H, N. **3-(4-Nitrophenyl)propionamide (13).** The diacid 9 was

3-(4-Nitrophenyl)propionamide (13). The diacid **9** was nitrated as described previously.¹³ The attempted ring closure of the product **12** (4 g, 0.167 mol) by fusion with molten urea at 170 °C led to charring and the production of CO₂. Extraction of the residue with chloroform (2 × 25 mL), removal of the solvent, and crystallization of the residue from EtOH gave **13** (1.09 g, 33% based on **12**) as light brown crystals: mp 175–176 °C (lit.²⁶ mp 175–176 °C); IR ν_{max} 3440 (amide N–H), 2850, 2940 (alkane C–H), 1660 (C=O), 1505, 1350 (N–O) cm⁻¹; ¹H NMR (Me₂SO) δ 2.44 (m, 2 H, CH₂CH₂CO, J = 7 Hz), 2.98 (m, 2 H, CH₂CO, J = 7 Hz), 6.84 (br s, 1 H, NH), 7.34 (br s, 1 H, NH), 7.53 (d, 2 H, Ar H, J = 9 Hz), 8.19 (d, 2 H, Ar H, J = 9 Hz). Anal. (C₉H₁₀N₂O₃) C, H, N.

3-(4-Aminophenyl)propionamide (14). Compound 13 (1 g, 0.0051 mol) was hydrogenated by the general method described.¹³ Crystallization from EtOH (95%) gave 14 (170 mg, 20% based on 13) as light brown crystals: mp 136.5–137 °C; IR ν_{max} 3400 (N–H primary amine) 1695 (C=O) cm⁻¹; ¹H NMR (Me₂SO) δ 2.22 (m, CH₂CH₂CO, J_{HaHb} = 18 Hz, CH₂CH₂CO, J = 7 Hz), 4.72 (s, 2 H, NH₂), 6.45 (2 H, d, Ar H, J = 9 Hz), 6.82 (2 H, d, Ar H, J = 9 Hz), 6.66 (br s, 1 H, HNH), 7.18 (s, 1 H, HNH). Anal. (C₉H₁₂N₂O) C, H, N.

Acknowledgment. This investigation was supported by grants from the Medical Research Council (to the Institute of Cancer Research) and the Cancer Research Campaign (to both Institutes), from SERC (to M.D.), the Tenovus Cancer Charity and the T. J. Jones Memorial Fund (to G.J.), and from Ciba-Geigy Ltd., Horsham, U.K. (to P.N.).

Registry No. 5, 59512-13-9; **6**, 59512-15-1; **7**, 91351-05-2; **8**, 91567-07-6; **9**, 635-51-8; **10**, 3464-18-4; **11**, 32856-95-4; **12**, 21021-53-4; **13**, 98953-18-5; **14**, 38710-60-0; **15**, 32856-49-8; **16**, 99948-56-8; urea, 57-13-6; adrenal CSCC enzyme, 37292-81-2; aromatase, 9039-48-9.

- (27) Woods, G. F.; Heying, T. L.; Schwartzman, L. H.; Grenell, S. M.; Gasser, W. F.; Rowe, E. W.; Bolgiano, N. C. J. Org. Chem. 1954, 19, 1290.
- (28) British Patent 875023, Ciba-Geigy, 1961.

Thromboxane Synthetase Inhibitors and Antihypertensive Agents. 1. N-[(1H-Imidazol-1-yl)alkyl]aryl Amides and N-[(1H-1,2,4-Triazol-1-yl)alkyl]aryl Amides

William B. Wright, Jr.,* Jeffery B. Press,*¹ Peter S. Chan, Joseph W. Marsico, Margie F. Haug, Judy Lucas, Jess Tauber, and Andrew S. Tomcufcik

CNS—Cardiovascular Disease Research Section, Medical Research Division of American Cyanamid Co., Lederle Laboratories, Pearl River, New York 10965. Received December 14, 1984

The title compounds were prepared to investigate their potential as thromboxane synthetase inhibitors as well as antihypertensive agents. Imidazoles VIII and triazoles X were prepared to examine the effects of aromatic substitution, chain length, and heterocycle substitution upon biological activity. Imidazoles VIII and triazoles X were thromboxane synthetase inhibitors that did not inhibit prostacyclin formation. The most interesting thromboxane synthetase inhibitors prepared were 4-chloro-, 4-(trifluoromethyl)-, and 4-bromobenzamide derivatives of (1*H*-imidazol-1-yl)alkylamines with C_5-C_8 alkyl chains separating the heterocycle from the amide moiety, while the most active antihypertensive agents were 3- or 4-chloro, -bromo, or -(trifluoromethyl)benzamides with C_3 alkyl chains. The best thromboxane synthetase inhibitors in this study were up to 10 times more potent than the standard, dazoxiben (UK 37,248).

Prostaglandins (PGs) have been the subject of intense research efforts both biologically because of their ubiquitous role in physiological processes² as well as chemically because of their challenging structural requirements.

⁽²⁶⁾ Taverne, H. J. Recl. Trav. Chim. Pays-Bas 1915, 16, 255.