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-2,6-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 μM), **6** (3-(4-aminophenyl)-1,3-dimethylpyrrolidine-2,5-dione, K_i = 1.75 μM), **7** (3-(4-aminophenyl)-3-methylpyrrolidine-2,5-dione, K_i = 0.8 μM), and **8** (3-(4-aminophenyl)-3-ethylpyrrolidine-2,5-dione, K_i = 1.0 μM). Compound **15** (3-(4-aminophenyl)pyrrolidine-2,5-dione) proved unexpectedly difficult to prepare following standard methods and was only moderately inhibitory toward aromatase (IC_{50} = 20 μM). Compound **16** (3-(4-aminophenyl)-3-ethyl-1-methylpyrrolidine-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 μM, 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.[7] 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 synthesised[9] and evaluated pharmacologically[10] in 1951, and phensuximide (**3**, 1-methyl-3-phenylpyrrolidine-2,5-dione) and methsuximide (**4**, 1,3-dimethyl-3-phenylpyrrolidine-2,5-dione) 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

† Welsh School of Pharmacy, UWIST.
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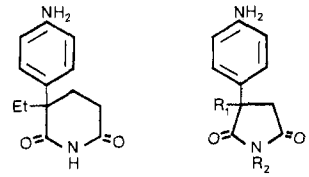
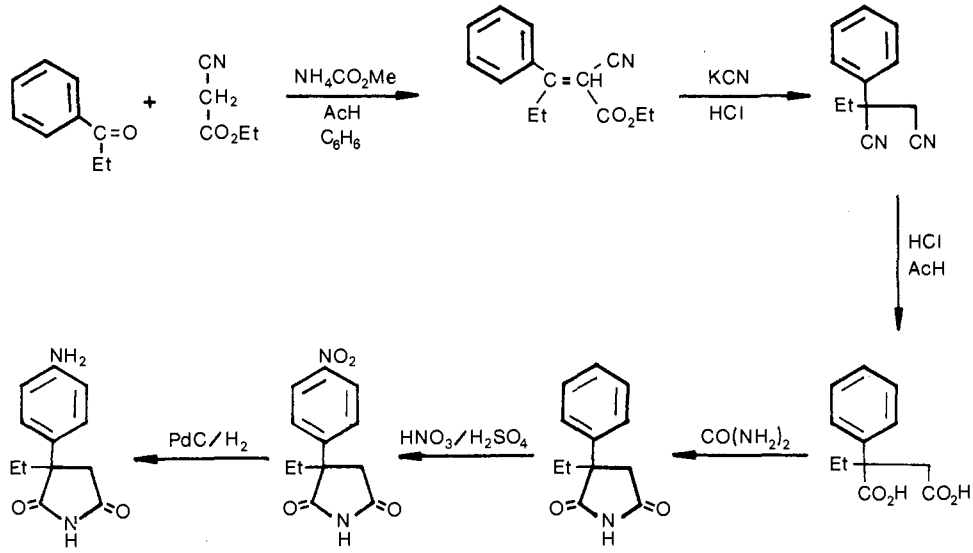
Table I. Summary of the (4-Aminophenyl)pyrrolidine-2,5-dione Analogues of Aminoglutethimide



no.	R_1	R_2	mp, °C	yield,[a] %	formula	anal. or ref
5	H	Me	165	82	$C_{11}H_{12}N_2O_2$	16
6	Me	Me	123–125	60	$C_{12}H_{14}N_2O_2$	16
7	Me	H	165–166.5	64	$C_{11}H_{12}N_2O_2$	27
8	Et	H	127–128	36	$C_{12}H_{14}N_2O_2$	28
15	H	H	171.5–173.5	90	$C_{10}H_{10}N_2O_2$	C, H, N
16	Et	Me	111–113	56	$C_{13}H_{16}N_2O_2$	C, H, N

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

Scheme I



acid (**9**) by this method gave **10** (3-phenylpyrrolidine-2,5-dione), 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 $NaHCO_3$ (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 K_2CO_3 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-(4-nitrophenyl)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 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).

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

[a] Each value represents the mean of two determinations (variability <10%)

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

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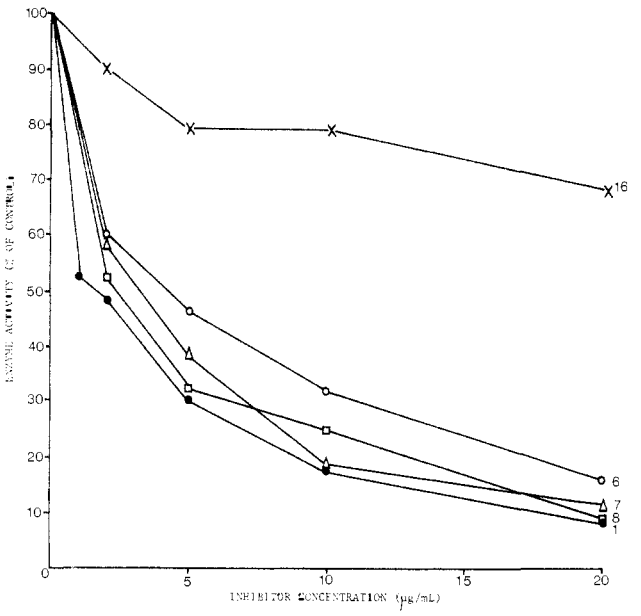

Figure 1. Inhibitory effect of aminoglutethimide (1) and the (4-aminophenyl)pyrrolidine-2,5-dione derivatives 6–8 and 16 toward aromatase activity from human term placenta, utilizing testosterone (1.5 μM) as the substrate. Each point represents a duplicate reading (variability <10%).

Table III. Inhibition of Androgen Aromatization

no.	compd	testosterone[a] IC_{50}, μM	testosterone[a] K_i, μM	androstenedione[b] 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	ND[c]	10.2

[a] Substrate concentration 1.5 μM (K_m = 0.13 μM). [b] Substrate concentration 0.25 μM (K_m = 55 nM). [c] ND, 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 μg/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 μM,[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 plots[22] 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.

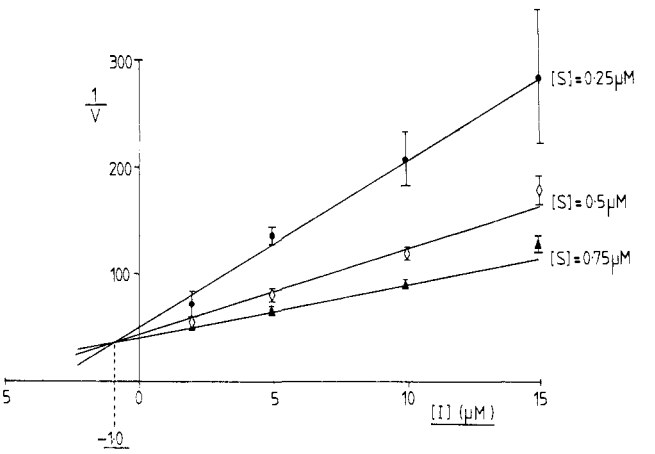

Figure 2. Dixon plot determined for 8. Velocity (v) is expressed as micromoles of testosterone aromatized per minute per milligram of protein. Each point represents the mean of four determinations ± standard error of the mean.

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-(4-aminophenyl)-3-ethyl-1-methylpyrrolidine-2,5-dione (16) was only weakly inhibitory against testosterone aromatization and possessed no activity toward either androstenedione 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 man[25] 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'

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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 $NaHCO_3$ solution (2%) until effervescence ceased. The ether layer was washed with water (2 × 50 mL), dried (Na_2SO_4), and evaporated to give a white crystalline solid which crystallized from ether to give **10** as white crystals: mp 90–91 °C (lit.[9,17] mp 88–90 °C, 90 °C); IR ν_{max} 3240 (N-H str), 1790, 1780 (C=O), 1692, 1728 (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. ($C_{10}H_9NO_2$) C, H, N.

3-(4-Nitrophenyl)pyrrolidine-2,5-dione (11). Compound **10** (6 g, 0.034 mol) was added portionwise to fuming HNO_3 (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. ($C_{10}H_8N_2O_4$) 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, NH_2), 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. ($C_{10}H_{10}N_2O_2$) C, H, N.

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 CO_2. 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 (Me_2SO) δ 2.44 (m, 2 H, CH_2CH_2CO, J = 7 Hz), 2.98 (m, 2 H, CH_2CO, 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. ($C_9H_{10}N_2O_3$) 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 (Me_2SO) δ 2.22 (m, CH_2CH_2CO, J_{HaHb} = 18 Hz, CH_2CH_2CO, J = 7 Hz), 4.72 (s, 2 H, NH_2), 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. ($C_9H_{12}N_2O$) C, H, N.

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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.

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Thromboxane Synthetase Inhibitors and Antihypertensive Agents. 1. *N*-[(1*H*-Imidazol-1-yl)alkyl]aryl Amides and *N*-[(1*H*-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 processes[2] as well as chemically because of their challenging structural requirements.

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