Conformationally Restricted Congeners of Hypotensive and Platelet Aggregation Inhibitors: 6-Aryl-5-methyl-4,5-dihydro-3(2*H*)-pyridazinones Derived from 5*H*-Indeno[1,2-*c*]pyridazine

Giorgio Cignarella,*† Daniela Barlocco,† Gerard A. Pinna,‡ Mario Loriga,‡ Odoardo Tofanetti,§ Mauro Germini,§ and Franca Sala§

Istituto Chimico Farmaceutico e Tossicologico, Università di Milano, Viale Abruzzi 42, 20131 Milano, Italy, Istituto di Chimica Farmaceutica e Tossicologica, Università di Sassari, Via Muroni 23/A, 07100 Sassari, Italy, and Boehringer Biochemia Robin, Research Laboratories, Via S. Uguzzone 5, 20126 Milano, Italy. *Received December 23, 1985*

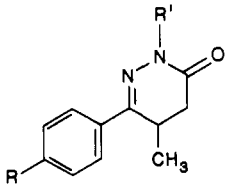
A number of 7-amino and 7-acylamino substituted 4,4a-dihydro-5*H*-indeno[1,2-*c*]pyridazin-3-ones have been synthesized as rigid congeners of hypotensive 6-aryl-5-methyl-4,5-dihydro-3(2*H*)-pyridazinones and tested as antihypertensive, antithrombotic, antiulcer, and antiinflammatory agents. Unlike the previously described 7-cyano derivative, which displayed only antiinflammatory action, the new series exhibited significant antihypertensive and antithrombotic properties. In this respect, the 7-amino (**2b**) and the 7-acetylamino (**2c**) derivatives were found to be the most potent and long lasting in reducing the blood pressure in spontaneously hypertensive rats and in protecting mice from the induction of thrombosis. These compounds, as well as the 7-(2-chloropropionyl) derivative **2d**, also exhibited antiinflammatory activity; in addition, **2c,d** were highly effective in inhibiting indomethacin-induced ulcers in the rat.

In recent years many papers have appeared dealing with the synthesis of 6-aryl-5-methyl-4,5-dihydro-3(2*H*)-pyridazinones (**1**), which display hypotensive,[1-3] platelet aggregation inhibiting,[3] and/or cardiotonic[4] effects.

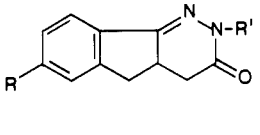
Our first attempts to embody one of the most potent hypotensive terms of the series (**1a**, R = CN) in the rigid structure of 7-cyano-4,4a-dihydro-5*H*-indeno[1,2-*c*]-pyridazin-3-one (**2a**) caused a complete loss of the hypotensive activity.[5] Conversely **2a** along with related compounds obtained by removal of the 7-substituent,[5] dehydrogenation of the pyridazinonic moiety,[6] and/or oxidation of the 9-CH_2 to 9-C=O[7] exhibited to various extents antiinflammatory, analgesic, and antipyretic properties.

Continuing our interest in derivatives of class **2**, we have now found that if the 7-cyano group of **2a** is replaced by amino or acetylamino groups the resulting compounds **2b** and **2c** display a potent blood pressure lowering effect on spontaneously hypertensive rats (SHR) and are also active as antithrombotic agents. However, unlike the case of the model compounds **1d–f**, methylation of **2b,c** at the 2-position (**2e,f**) or replacement of the acetyl with the 2-chloropropionyl group (**2d**) was detrimental for antihypertensive activity.

The synthesis of **2b–f** and their preliminary pharmacological evaluation are reported in this paper.



1a–f

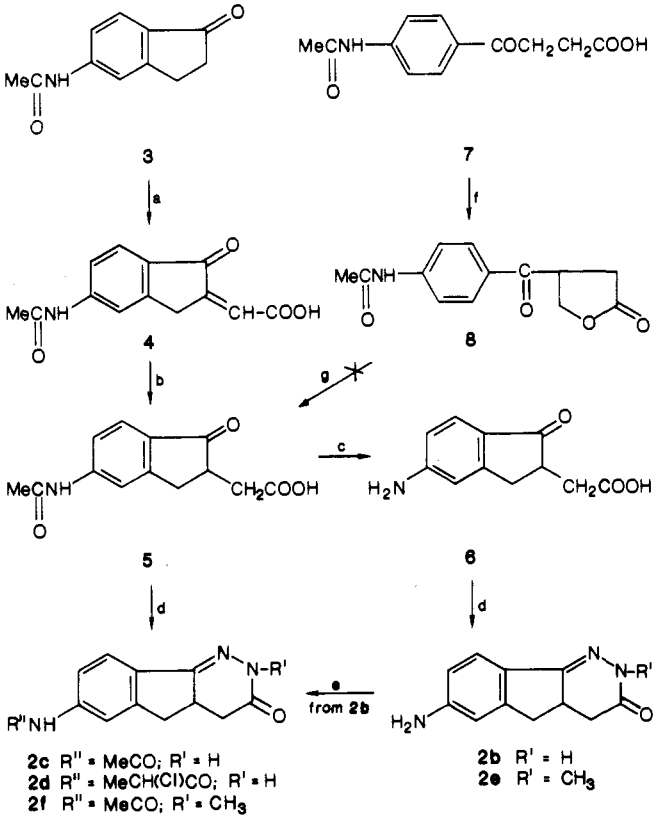


2a–f

R' = H; R = CN (**a**), NH_2 (**b**), $NHCOCH_3$ (**c**), $NHCOCH(Cl)CH_3$ (**d**)
R' = CH_3; R = NH_2 (**e**), $NHCOCH_3$ (**f**)

Chemistry. The synthesis of 7-(acetylamino)-4,4a-dihydro-5*H*-indeno[1,2-*c*]pyridazin-3-one (**2c**) was considered first. An attempted extension of the route followed for **2a**[5] starting from 3-[*p*-(acetylamino)benzoyl]propionic acid (**7**) was unsuccessful because of the failure to convert 3-[*p*-(acetylamino)benzoyl]-4-hydroxybutyric acid, in the form of lactone **8**, into the key intermediate 5-(acetylamino)-2,3-dihydro-1-oxo-1*H*-indene-2-acetic acid (**5**). Our second approach to **5** (see Scheme I) was devised starting from

Scheme I[a]



2c R" = MeCO; R' = H
2d R" = MeCH(Cl)CO; R' = H
2f R" = MeCO; R' = CH_3

2b R' = H
2e R' = CH_3

[a] (a) tartaric acid + $NaIO_4$; (b) Zn, AcOH; (c) 37% HCl; (d) R'$NHNH_2$, EtOH; (e) MeCH(Cl)COCl; (f) CH_2O, OH^-; (g) concd H_2SO_4 or PPA.

† Università di Milano.
‡ Università di Sassari.
§ Boehringer Biochemia Robin.

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Table I. Antihypertensive Activity[a]

compd	ED_{25},[b] mg/kg, po	AUC units[c]	rel act.[d]
2b	2.60	24350	0.74
2c	2.60[e]	17560	1.02
2d	10.00	27140	0.66
2e	15.50	36740	0.49
2f	15.00	31960	0.60
dihydralazine	0.72[f]	17940	1.00

[a] On conscious spontaneously hypertensive rats (SHR). [b] Dose that lowered the blood pressure by 25 mmHg (peak effect). [c] Areas under curves (see Figure 1). AUC are inversely proportional to activity. The test compounds were given orally in a dose of 12.5 mg/kg. [d] Relative activity based on dihydralazine (AUC dihydralazine/AUC compound). [e] In normotensive rats ED_{25} = 25 mg/kg. [f] In normotensive rats ED_{25} = 3.125 mg/kg.

the preformed bicyclic system of 5-(acetylamino)-1-indanone (**3**) in turn obtained by a known procedure from 5-acetylindan.[8] Reaction of **3** with tartaric acid and sodium periodate, under carefully controlled conditions, resulted in 5-(acetylamino)-2,3-dihydro-1-oxo-2-indanylideneacetic acid (**4**), which was reduced to **5** with zinc in acetic acid. Hydrolysis of **5** in refluxing hydrochloric acid resulted in the 5-amino derivative **6**. Condensation with hydrazine hydrate in refluxing ethanol smoothly converted **6** and **5** into the desired **2b** and **2c**, respectively, while a similar reaction with methylhydrazine led to **2e** and **2f**. Acylation of **2b** in toluene solution with 2-chloropropionyl chloride gave **2d**.

Results and Discussion

Compounds **2b–f** have undergone evaluation of their antihypertensive, platelet aggregation inhibiting, antithrombotic, and antiinflammatory activities. Compounds **2b–d** were also tested as antiulcer agents.

The antihypertensive activity is reported in terms of doses that lowered by 25 mmHg (ED_{25}) the blood pressure of conscious spontaneously hypertensive rats (peak effect) and as units of area under the curve (AUC) for 0–6 h duration using dihydralazine as the reference drug. In vitro platelet aggregation experiments were performed using guinea pig platelet rich plasma (PRP), preincubated with the test compound at doses equimolar with respect to acetyl salicyclic acid (ASA), 66 μM. Aggregation was induced by either adenosine diphosphate (ADP), collagen, or thrombin. The antithrombotic activity in vivo was evaluated in the mouse by inducing death or paralysis of the hind limbs with a thrombotic mixture (collagen 200 μg/mL, adrenalin 200 μM), and it is reported as a percent protection vs. controls at doses equimolar to 20 mg/kg of ASA. The antiinflammatory activity is reported in terms of doses that inhibit by 50% (ED_{50}) the carrageenin-induced edema of the hind paw in rats. The antiulcer activity was evaluated in the rat by the indomethacin-induced ulcer model and reported in terms of doses that reduced by 50% the number and severity of gastric lesions. All test compounds induced a linear dose-dependent reduction of 20–50 mmHg in systolic blood pressure of SHR; the effect was rapid in onset and, in the case of **2c**, persisted for at least 6 h after medication (Figure 1). Though none of the compounds caused the sharp drop in blood pressure exhibited by dihydralazine, the relative activity of **2b** and **2c** in terms of AUC, respectively, approaches or equals that of the reference drug (Table I). Platelet aggregation inhibiting activity was displayed in the order

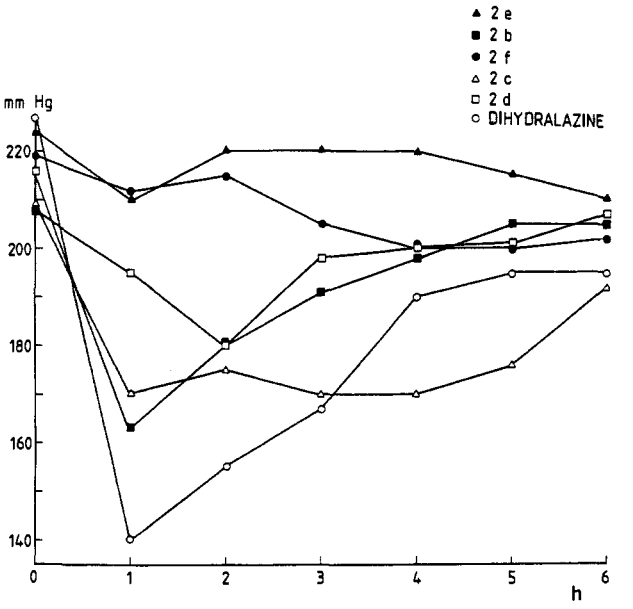

Figure 1. Time-dependent antihypertensive activity of **2b–f** and dihydralazine. Test compounds and reference drug are administered po at a single dose of 12.5 mg/kg to spontaneously hypertensive rats.

by **2c**, **2d**, and **2b** (Table II). However, the observed inhibition of the first phase curve suggests a mechanism of action different from that of ASA and NSAID. A hypothesis could be made that these compounds act through inhibition of cAMP phosphodiesterase, thereby elevating the cellular level of cAMP.[9] All test compounds displayed antithrombotic effects comparable with those of ASA, with **2b** and **2c** being the most potent. The latter compounds, as well as **2d**, also displayed antiinflammatory activity. Finally, the acylamino derivatives **2c,d** were found to be highly effective in inhibiting indomethacin-induced ulcers.

These data indicated that replacement of the 7-cyano group of **2a** by a NH_2 (**2b**) or $NHCOCH_3$ (**2c**) induced a significant antihypertensive activity accompanied by both antithrombotic and antiinflammatory action. However, concomitant alkylation at the N-2 position (**2e** and **2f**) led to scarcely active compounds.

The pharmacological results presently available on compounds **2a–f** deserve some comments regarding the structural and biological analogies between derivatives **1** and **2**. Taking into account that **2a–f** have as counterparts compounds **1a–f**, reportedly potent hypotensive and platelet aggregation inhibiting agents,[1-3] only two out of five derivatives (**2b**, **2c**) were found to exhibit a pharmacological profile somewhat comparable to that of the corresponding **1**. Although the small number of the compounds **2** tested does not allow any definite hypothesis, it appears reasonable to assume that embodying the freely rotating phenyl ring of **1** into the rigid quasi-planar structure **2** could involve not only modifications of absorption and/or metabolism but also substantial differences in drug–receptor interactions. Consequently, the antihypertensive activity of **2b,c** is more likely to reside in peculiar structural features of the indenopyridazinonic framework rather than in structural analogies with the arylpyridazinones **1**.

The finding that the acetylamino derivative **2c** also manifested potent antiulcer properties, at least in one experimental model, induced us to select this compound for further biological investigation in order to better understand the mechanism involved in the antihypertensive,

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Table II. Other Biological Activities

compd	LD_{50}, mg/kg mouse (os)	antithrombotic[a] activity (mouse)	antiaggregation activity in vitro[b] [ADP], 0.5 μM revers	[ADP], 0.5 μM irrevers	[thrombin], 0.625 IU/mL		[collagen], 0.8 μg/mL	antiinflammatory[c] activity (rat) ED_{50}, mp/kg, po	antiulcer[d] activity (rat) ED_{50}, mg/kg, po
2b	308	87	31	66	44[e]	34[f]	58	40.8 ± 13.1	100
2c	1000	100	45	81	95	100	73	160.5 ± 46.5	0.3
2d	1000	62	48	40	84	83	60	155.2 ± 26.5	0.3
2e	750	58	7	33	36	37	26	inactive	NT[g]
2f	1000	50	4	23	5	37	40	inactive	NT
ASA	1100[h]	44	0	100	0	0	75	145.0 ± 74.0	

[a] Protection vs. controls %: dose equimolar to ASA 20 mg/kg. [b] Guinea pig PRP is used. The compounds are tested at 66 μM (see Experimental Section). Inhibition vs. controls %. Mean of five experiments: SD not indicated is <20%. [c] Carrageenin paw edema test: dose that inhibits the swelling of paw by 50%. [d] Dose that reduced by 50% the indomethacin-induced gastric lesions, assessed on an arbitrary scale. [e] Value calculated after 2 min. [f] Value calculated after 4 min. [g] Not tested. [h] See ref 16.

antithrombotic, antiaggregating, and antiulcer activities. In the meantime, a structure–activity study has been undertaken aiming at the synthesis of analogues of **2c** having a more selective pharmacological profile.

Experimental Section

Chemistry. Melting points were determined with a Büchi 510 capillary melting point apparatus and are uncorrected. The elemental analyses (C, H, N, and Cl) for the new substances were within ±0.4% of the theoretical values. IR spectra were recorded on an Acculab-Beckamn spectrophotometer. NMR spectra were recorded on a Hitachi Perkin-Elmer R 600 FT spectrophotometer, with tetramethylsilane as an internal standard.

5-(Acetylamino)-2,3-dihydro-1-oxo-2-indanylideneacetic Acid (4). To an ice-cooled solution of 11.3 g of sodium metaperiodate in 1.3 mL of concentrated sulfuric acid and 75 mL of water, a solution of 8 g of tartaric acid in 20 mL of water was added. After 10 min the ice bath was removed and the mixture was stirred for 30 min at room temperature. Then, in the following order, 5 g (0.026 mol) of 5-(acetylamino)-1-indanone (**3**),[8] 9.5 g of NaOH in 86.5 mL of water, and 75 mL of EtOH were added. A yellow precipitate appeared almost immediately. After 17 h at room temperature the solid was filtered off and resuspended in water. The resulting basic suspension was acidified with 3 N HCl, and the yellow microcrystalline precipitate was isolated by filtration and dried overnight at 60 °C to give 3.88 g (60%) of **4**: mp 255–258 °C dec. Anal. ($C_{13}H_{11}NO_4$) C, H, N.

5-(Acetylamino)-2,3-dihydro-1-oxo-1*H*-indene-2-acetic Acid (5). A stirred mixture of **4** (5 g, 0.02 mol), 40 mL of acetic acid, 15 mL of water, and 3.7 g of zinc dust was heated on a steam bath for 0.5 h, then filtered and diluted with water (300 mL). The cooled solution was extracted 3 times with ether (100 mL); the organic layer was dried with sodium sulfate, and the solvent was evaporated. The residue was recrystallized from absolute ethanol to give **5** (2.8 g, 55%): mp 178–180 °C. Anal. ($C_{13}H_{13}NO_4$) C, H, N.

5-Amino-2,3-dihydro-1-oxo-1*H*-indene-2-acetic Acid (6). A suspension of **5** (5 g, 0.02 mol) in 20 mL of concentrated HCl was refluxed for 15 min. After dilution with 100 mL of water and cooling at 5 °C the mixture was brought to pH 4 by means of Na_2CO_3 and the product was filtered off. The solid thus isolated was washed with water and dried to give **6** as a microcrystalline product (2.9 g, 70%): mp 192–194 °C. Anal. ($C_{11}H_{11}NO_3$) C, H, N.

7-(Acetylamino)-4,4a-dihydro-5*H*-indeno[1,2-*c*]pyridazin-3-one (2c). A solution of **5** (5 g, 0.020 mol) and hydrazine hydrate (1.1g, 0.022 mol) in 100 mL of ethanol was refluxed for 2 h. After cooling, the product was filtered off, washed with ethanol, and dried to give **2c** (3.68 g, 75%): mp 315 °C. Anal. ($C_{13}H_{13}N_3O_2$) C, H, N.

Following the same procedure, **6** gave **2b** (76%): mp 235 °C dec. Anal. ($C_{11}H_{11}N_3O$) C, H, N.

7-(2-Chloropropionyl)amino-4,4a-dihydro-5*H*-indeno[1,2-*c*]pyridazin-3-one (2d). Chloropropionyl chloride (4.22 g, 0.033 mol) was added dropwise to a solution of **2b** (5.5 g, 0.027 mol) in 75 mL of absolute toluene. The mixture was then stirred under reflux for 6 h, cooled, and filtered. The solid thus isolated was washed first with toluene and then with 5% $NaHCO_3$ solution to give **2d** (7.48 g, 95%): mp 250 °C dec. Anal. ($C_{14}H_{14}ClN_3O_2$) C, H, N, Cl.

2-Methyl-7-(acetylamino)-4,4a-dihydro-5*H*-indeno-[1,2-*c*]pyridazin-3-one (2f). A solution of **5** (5.0 g, 0.020 mol) and methylhydrazine (0.92 g, 0.02 mol) in 100 mL of EtOH was refluxed for 4 h. After cooling, the product was filtered off. The pale-yellow solid thus obtained was washed with ethanol and dried to give **2f** (4.1 g, 79%): mp 255 °C dec. Anal. ($C_{14}H_{15}N_3O_2$) C, H, N.

Following the same procedure, **6** gave **2e** (60%): mp 190–192 °C. Anal. ($C_{12}H_{13}N_3O$) C, H, N.

4-[*p*-(Acetylamino)benzoyl]-2(3*H*)-dihydrofuranone (8). To a stirred solution of 3-[*p*-(acetylamino)benzoyl]propanoic acid (7 g, 0.021 mol) in 0.5 N NaOH (50 mL, 0.025 mol) 37% formaldehyde (1.7 mL, 0.023 mol) was added. After 2 h at room temperature, the mixture was acidified with concentrated HCl (3 mL) and stirred for an additional 12 h. The product that separated was filtered off, washed with water, and recrystallized from MeOH to give **8** (2.6 g, 50%): mp 156 °C. Attempted conversion of **8** into **5** by short heating in 96% H_2SO_4 or in PPA resulted in tar formation.

Pharmacology. Antihypertensive Activity. Experiments were performed on unanesthetized SH rats (Charles River) weighing 150–200 g. Rats, 12 h fasted, were warmed at 33 °C in a heating chamber for 30 min prior to blood pressure determination. Groups of 6 animals/dose were employed. Systolic blood pressure was measured by the tail-cuff method, utilizing a tail plethismographic apparatus W + W BP Recorder 8002. Test compounds were suspended in 1% methylcellulose and administered in a volume of 10 mL/kg by gavage at dose levels of 1.56, 3.125, 6.25, 12.5, and 25 mg/kg. Systolic blood pressure was recorded every hour for 6 h after drug administration. ED_{25} values were calculated from the log dose–response curves. Dihydralazine was used as standard drug.

Hypotensive Activity. Experiments were performed on unanesthetized Sprague-Dawley male rats (Charles River), weighing 150–200 g, 12 h fasted, following the methodology above reported for antihypertensive activity. Compound **2c** was administered at doses of 6.25, 12.5, and 25 mg/kg po. Dihydralazine was used as the standard drug at doses of 0.78, 1.56, 3.125, and 6.25 mg/kg po.

Platelet Aggregation Inhibiting Activity in Vitro. The determination was carried out by the method described by Born and Cross.[10] Male crossbreed guinea pigs weighing 350–500 g, 18 h fasted, were used. Under sodium pentobarbital narcosis blood was taken from the abdominal aorta and was rendered nonclotting by adding a 3.8% (w/v) sodium citrate solution (final volume ratio 1:10). A plasma rich in platelets was then obtained as supernatant by centrifuging. Aggregation was triggered by adding (a) ADP at doses ranging form 0.25 to 2 μM/mL, (b) collagen (from equine tendon) at doses ranging from 0.8 to 2.4 μg/mL, or (c) thrombin at doses ranging from 0.312 to 1.25 IU/mL. Incubation of the platelets with the test compounds was carried out for 10 min at room temperature at a dose equimolar to the minimal dose of ASA

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(11) Wong, L. T.; Zawidzka, Z.; Thomas, B. H. *Pharm. Res. Commun.* **1978**, *10*, 939.

(66 μM dissolved in CH_3CO_2Na, 0.3 M), which completely inhibits platelet aggregation. The inhibiting action was expressed as percent inhibition by comparing the aggregation curve of the test compound with that of the control.

Antithrombotic Activity in Vivo. The determination was carried out by a modification of the method of Minno and Silver.[12] Male Swisse mice weighing 20–30 g were divided into three groups of 10. Groups 1 and 2 were treated with test compounds and the reference drug (ASA), respectively, both dissolved in 1% hydroxymethylcellulose and orally administered in a volume of 50 mL/kg. The dose of the test compound was equimolar to that of ASA (20 mg/kg). One hour after medication, groups 1 and 2, along with group 3 (controls), received a thrombotic mixture (fetal bovine collagen, 200 μg/mL, and adrenaline, 200 μM) in a volume of 10 mL/kg administered iv in the tail (before injection animals were warmed at 27 °C for 30 min). Death of the animals or paralysis of the hind limbs for more than 15 min was considered as a thrombotic effect. The antithrombotic activity was characterized as percent protection (%P) by relating the number of the thrombotic effects in group 1 (treated) to those of group 3 (controls), according to the formula $\%P = [(N_c - N_t)/N_c] \times 100$. The protection of the test compound was then compared to that of the reference drug (group 2).

Antiinflammatory Activity. The activity was determined in the carrageenin-induced edema of the rat paw by a modification of the method of Winter et al.[13] Male Sprague-Dawley rats weighing 130–150 g, 18 h fasted, were randomly divided into groups of eight. Each test compound was suspended in 1% carboxymethylcellulose and administered by gavage, with controls receiving the vehicle only. One hour after medication 0.1 mL of 1% carrageenin in normal sterile saline was injected into the plantar tissue of the right hind paw. Paw volume was measured by a plethysmometer at time intervals of 0, 1, and 3 h after induction of inflammation. Mean percentages of edema inhibition were calculated at the third hour, according to the formula % inhibition = $[(\Delta V_c - \Delta V_t)/\Delta V_c] \times 100$ where ΔV_c and ΔV_t were the increase in paw volume for control and treated animals, respectively.

Antiulcer Activity. Indomethacin Ulcer. The technique described by Lee et al.[14] was employed. Male Albino rats of Sprague-Dawley strain, weighing 180–250 g, in groups of eight, were housed in individual cages and fasted for 24 h having free access to water. The test compounds were administered by gavage immediately after indomethacin (15 mg/kg, ip), while the control group received distilled water only. Five hours later animals were sacrificed and their stomachs excised and opened along the greater curvature. The number of severity of lesions were observed with a 10 × wide-field binocular microscope and evaluted with the method proposed by Moron et al.[15]

Registry No. **2b**, 103422-53-3; **2c**, 103422-54-4; **2d**, 103602-83-1; **2e**, 103794-16-7; **2f**, 103794-15-6; **3**, 58161-35-6; **4**, 103602-84-2; **5**, 103422-85-1; **6**, 103422-62-4; **8**, 95355-15-0; 3-[*p*-(acetylamino)benzoyl]propanoic acid, 5473-15-4.

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Synthesis and Antihypertensive Activity of 4-(Cyclic amido)-2*H*-1-benzopyrans

Valerie A. Ashwood, Robin E. Buckingham, Frederick Cassidy, John M. Evans,* Erol A. Faruk, Thomas C. Hamilton, David J. Nash, Geoffrey Stemp, and Kenneth Willcocks

Beecham Pharmaceuticals, Research Division, Medicinal Research Centre, The Pinnacles, Harlow, Essex, CM19 5AD England.
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The synthesis and antihypertensive activity of a series of novel 4-(cyclic amido)-2*H*-1-benzopyran-3-ols, administered orally to conscious spontaneously hypertensive rats, are described. The effects of lactam ring size, the presence of heteroatoms in the lactam ring, substitution at C(2) and C(3), relative stereochemistry at C(3) and C(4), and aromatic substitution pattern on the blood pressure lowering activity of this series have been determined. The key compound **2** from this work [BRL 34915; (±)-6-cyano-3,4-dihydro-2,2-dimethyl-*trans*-4-(2-oxopyrrolidin-1-yl)-2*H*-1-benzopyran-3-ol] has been resolved, and antihypertensive activity was found to reside primarily in the (-) enantiomer. The key step in the preparation of this class of compounds is the action of a cyclo amidic anion on an appropriate epoxide. Another approach, involving a cyclization step to the lactam was found to be more convenient in certain cases, particularly in forming the cis analogue of compound **2**. Compound **2** has been shown to possess a novel mechanism of action, and it has been selected for progression to the clinic.

During the preparation of a series of substituted *trans*-4-amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols and their evaluation as antihypertensive agents[1,2] it was discovered that introduction of a carbonyl group α to the C(4) nitrogen atom enhanced antihypertensive potency. This paper therefore describes the synthesis of a novel series of (cyclic amido)-2*H*-1-benzopyrans[3] and their effects on blood pressure in the spontaneously hypertensive rat (SHR). Included for comparison are *trans*-6-cyano-3,4-dihydro-2,2-dimethyl-4-pyrrolidin-1-yl-2*H*-1-benzopyran-3-ol (**1**; see Table I), the lead compound from the earlier work[1], and the calcium slow-channel blocker nifedipine. These (cyclic amido)benzopyranols have been shown to exert their antihypertensive action by a novel mechanism[4] in vascular smooth muscle involving the opening of potassium channels.

Chemistry. Convenient starting materials for the synthesis of the *trans*-4-(cyclic amido)-2*H*-1-benzopyran-3-ols shown in Tables I–III are the (±)-*trans*-3-bromo-3,4-dihydrobenzopyran-4-ols **52** or the corresponding (±)-epoxides **53** (Scheme I; only relative stereochemistry is shown). These compounds, with the exception of **8**, **9**,

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