Synthesis and Antiinflammatory and Analgesic Properties of 2-Amino-1*H*-benzimidazole and 1,2-Dihydro-2-iminocycloheptimidazole Derivatives

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2-Amino-1*H*-benzimidazoles (3) and 1,2-dihydro-2-iminocycloheptimidazoles (4) were synthesized and evaluated for antiinflammatory and analgesic activities. The compounds in the series 3 were synthesized *via* phenylthioureas (6) or 2-chloro-1*H*-benzimidazole (12). Most of 4 were synthesized by two methods. One was the reaction of carbodiimides (14) with 2-amino-2,4,6-cycloheptatrien-1-one (method A). The other was the reaction of guanidines (15) with 2-chloro-2,4,6-cycloheptatrien-1-one (method B). Some of the compounds 3 and 4 exhibited potent antiinflammatory and analgesic activities when compared to timegadine (1) or tiaramide hydrochloride (HCl) (17). It was of interest that 1-(2-benzothiazolyl)-2-cyclohexylimino-1,2-dihydrocycloheptimidazole (4e) showed superior analgesic activity to timegadine or tiaramide HCl (ED_{50} = 1.7 mg/kg *p.o.* in the acetic acid-induced writhing test, ED_{30} = 14.0 mg/kg *p.o.* in Randall–Selitto method) in spite of no effect on prostaglandin E_2 synthesis.

Keywords 1,2-dihydro-2-iminocycloheptimidazole; 2-amino-1*H*-benzimidazole; antiinflammatory activity; analgesic activity; timegadine; 2-amino-4,5-dihydro-1*H*-imidazole

The acidic antiinflammatory agents exemplified by indomethacin or aspirin exert their activity through the inhibition of prostaglandin (PG) synthetases,[1] while clinically available basic antiinflammatory agents (*e.g.*, tiaramide hydrochloride, emorfazone) do not inhibit these synthetases.[2] Timegadine (**1**) which is a basic antiinflammatory agent has been reported to inhibit the PG synthetases and also to show an interesting pharmacological profile.[2,3]

In the preceding papers, we reported the synthesis and hypotensive activity of novel 2-arylamino-4,5-dihydro-1*H*-imidazoles (**2**).[4] Hence, we were interested in a common structure, namely the guanidine moiety, of the 2-aminoimidazole derivatives **2** and timegadine. We tested some of the compounds **2** for antiinflammatory activity. It was indicated that some of the tested compounds showed antiinflammatory activity. Particularly, 4,5-dihydro-2-[2-(3,4,5-trimethoxyphenoxy)phenylamino]-1*H*-imidazole (**2a**), which exhibited no hypotensive activity,[4a] inhibited carrageenin-induced paw edema in rats (30.6% at 100 mg/kg *p.o.*) and also exhibited analgesic activity in the acetic acid-induced writhing test in mice (ED_{50} = 50.1 mg/kg *p.o.*). Thus, we focused our attention on a cyclic guanidine group as a chemical structure for the design of new basic antiinflammatory agents.

On the basis of the above mentioned consideration we designed for 2-amino-1*H*-benzimidazoles (**3**) and 1,2-dihydro-2-iminocycloheptimidazoles (**4**) which possess a cyclic guanidine group in each structure. This design would be also supported by the fact that 2-aryl, 2-heteroaryl, and 2-alkylsulfonylbenzimidazoles showed antiinflammatory activity.[2a,5a]

This article describes the synthesis, pharmacology, and structure–activity relationships of 2-amino-1*H*-benzimidazoles **3** and 1,2-dihydro-2-iminocycloheptimidazoles **4**.

Synthesis 1-(2-Methyl-4-quinolyl) and 1-(4-methoxy-

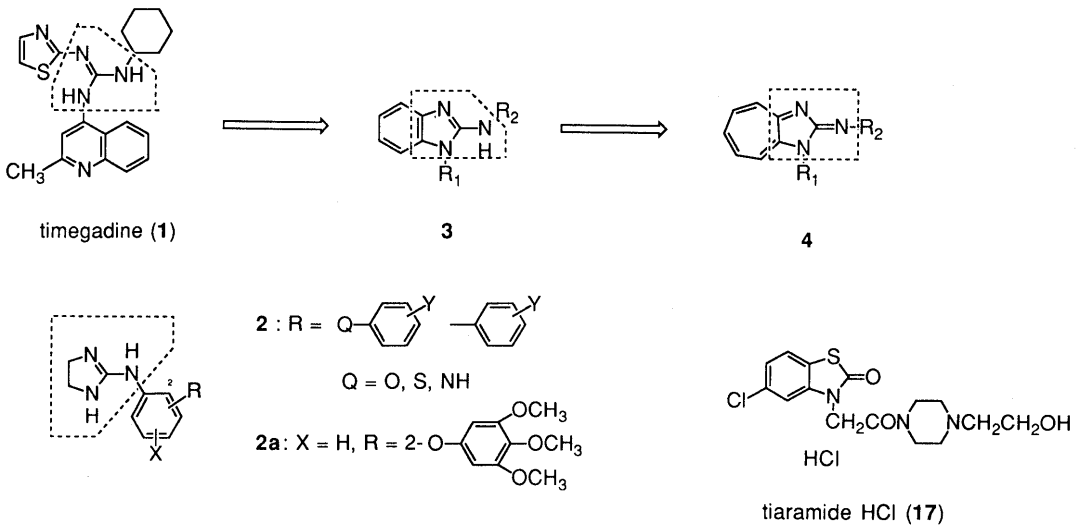


Chart 1

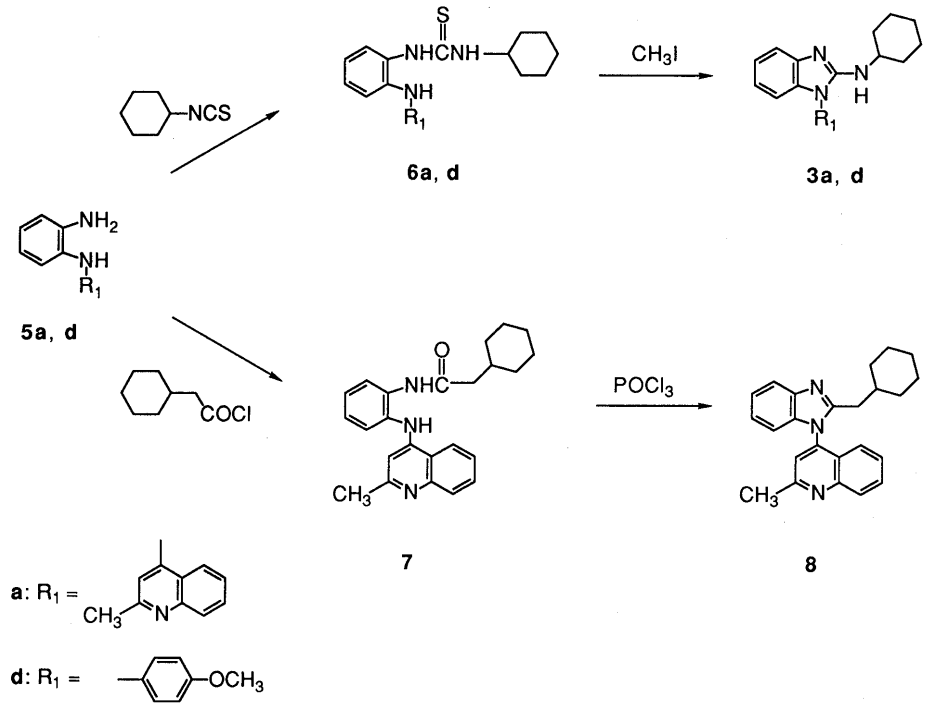


Chart 2

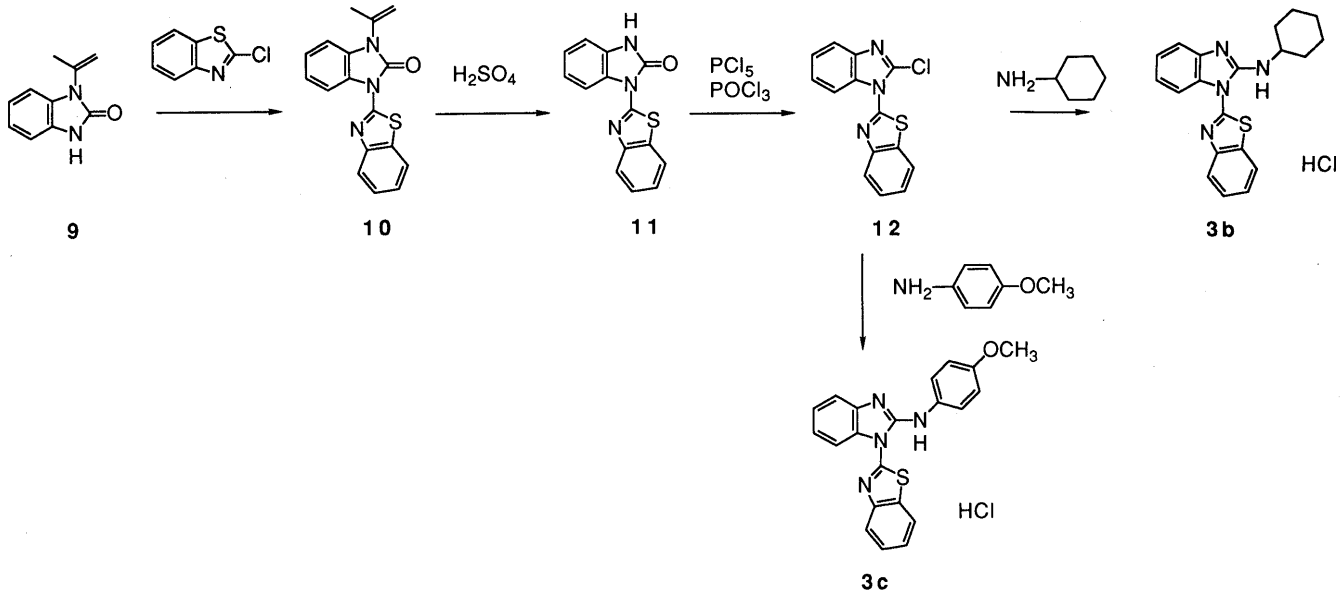


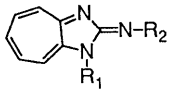
Chart 3

phenyl)-2-cyclohexylamino-1*H*-benzimidazole (**3a** and **3d**) were synthesized by methylation and subsequent cyclization of the thioureas (**6a** and **6d**), which were prepared by the reaction of the corresponding phenylenediamines (**5a** and **5d**) with cyclohexylisothiocyanate (Chart 2). 2-Cyclohexylmethyl-1-(2-methyl-4-quinolyl)-1*H*-benzimidazole (**8**) was synthesized by acylation of **5a** with cyclohexylacetyl chloride and subsequent cyclization by treatment with $POCl_3$ (Chart 2).

2-Amino-1-(2-benzothiazolyl)-1*H*-benzimidazoles (**3b** and **3c**) depicted in Chart 3 were synthesized *via* 1-(2-benzothiazolyl)-1,3-dihydro-2*H*-benzimidazol-2-one (**11**), which was prepared by the reaction of 1,3-dihydro-1-(2-propenyl)-2*H*-benzimidazol-2-one (**9**) with 2-chlorobenzothiazole in the presence of K_2CO_3 followed by depropenylation with dil. H_2SO_4. The benzimidazol-2-one **11** was then converted to the 2-chloro derivative (**12**) by chlorination with $POCl_3$ and PCl_5. The reaction of **12** with cyclohexylamine and *p*-anisidine afforded **3b** and **3c**, respectively.

The 1,2-dihydro-2-iminocycloheptimidazoles **4** synthesized in this study are listed in Table I. Most compounds **4** were prepared by two different methods, A and B, as shown in Chart 4. Method A involves the preparation of carbodiimides (**14**) by treatment of the corresponding ureas or thioureas (**13**) with PPh_3, CCl_4, and NEt_3 in CH_2Cl_2 and the successive reaction with 2-amino-2,4,6-cycloheptatrien-1-one in toluene (method A_1) or in the absence of

TABLE I. Physical Properties of 1,2-Dihydro-2-iminocycloheptimidazoles (**4**)



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No.	R_1	R_2	Form[a]	Method	Yield (%)	mp (°C) (Recryst. solvent)[b]	Formula	Analysis (%) Calcd (Found)		
								C	H	N
4a	2-Methyl-4-quinolyl	Cyclohexyl	F	A_2	31.9[c]	200—206 (IPA)	$C_{24}H_{24}N_4$	78.23 (78.38)	6.56 6.61	15.20 14.98)
4b	4-Pyridyl	Cyclohexyl	F	A_1	21.3	114—116.5 (H–IPE)	$C_{19}H_{20}N_4$	74.98 (75.67)	6.62 7.01	18.41 18.39)
4c	2-Pyridyl	Cyclohexyl	F	A_1	11.0	112—115 (H–IPE)	$C_{19}H_{20}N_4$	74.94 (74.88)	6.62 6.66	18.41 17.94)
4d	2-Thiazolyl	Cyclohexyl	F	A_1	15.7	135—137 (IPA)	$C_{17}H_{18}N_4S$	65.78 (66.11)	5.84 5.55	18.05 18.30)
4e	2-Benzothiazolyl	Cyclohexyl	F	A_1	8.5[d]	197—198 (C–IPA–M)	$C_{21}H_{20}N_4S$	69.97 (70.17)	5.59 5.52	15.54 15.68)
				B	16.7					
4f	1*H*-Benzimidazol-2-yl	Cyclohexyl	F	B	22.6[e]	207—208 (C–IPA)	$C_{21}H_{21}N_5$	73.44 (73.92)	6.16 6.18	20.39 20.59)
4g	Cyclohexyl	2-Methyl-4-quinolyl	HCl	A_2	4.6[c]	300 (dec.) (E–M)	$C_{24}H_{24}N_4$ ·HCl·H_2O	68.15 (67.79)	6.43 6.35	13.24 13.26)
4h	Cyclohexyl	2-Benzothiazolyl	F	A_1	4.5[d]	250 (dec.) (T)	$C_{21}H_{20}N_4S$	69.97 (70.09)	5.59 5.56	15.54 15.52)
4i	Cyclohexyl	1*H*-Benzimidazol-2-yl	F	B	3.2[e]	215 (dec.) (E–W)	$C_{21}H_{21}N_5$	73.44 (73.73)	6.16 6.13	20.39 20.67)
4j	2-Benzothiazolyl	iso-Propyl	F	A_1	10.1	201 (C–IPA)	$C_{18}H_{16}N_4S$	67.48 (67.85)	5.03 4.93	17.49 17.41)
4k	2-Benzothiazolyl	*tert*-Butyl	F	A_1	16.4	182—185 (A–EA)	$C_{19}H_{18}N_4S$	68.24 (68.39)	5.42 5.40	16.75 16.76)
4l	2-Benzothiazolyl	Cyclooctyl	F	A_2	7.1[f]	141—142 (IPE)	$C_{23}H_{24}N_4S$	71.10 (71.67)	6.23 6.36	14.42 14.34)
4m	Cyclooctyl	2-Benzothiazolyl	HCl	A_2	3.5[f]	296 (dec.) (EE)	$C_{23}H_{24}N_4S$ ·HCl·H_2O	62.36 (62.45)	6.14 5.84	12.65 12.69)
4n	Phenyl	Cyclohexyl	FA	A_2	37.0	123—126.5 (IPA)	$C_{20}H_{21}N_3$ ·$C_4H_4O_4$ ·1/2H_2O	67.27 (67.53)	6.12 6.36	9.81 9.45)
4o	4-Methoxyphenyl	Cyclohexyl	FA	A_2	49.6	104.5—107 (dec.) (A–IPA)	$C_{21}H_{23}N_3O$ ·$C_4H_4O_4$ ·1/2acetone	66.51 (66.05)	6.32 6.54	8.78 8.26)
4p	4-Methoxyphenyl	4-Methoxyphenyl	HCl	A_2	30.8	88—91 (E–EA)	$C_{22}H_{19}N_3O_2$ ·HCl·5/2H_2O	60.20 (60.32)	5.74 5.75	9.57 9.62)
4q	iso-Propyl	4-Methoxyphenyl	F	[g]	19.6	123—128 (IPA–IPE)	$C_{18}H_{19}N_3O$ ·1/10H_2O	73.25 (73.11)	6.54 6.48	14.24 13.95)
4r	Cyclohexyl	Cyclohexyl	F	A_2	34.7	104—106 (H)	$C_{20}H_{27}N_3$	77.63 (77.82)	8.79 8.43	13.58 13.64)

a) F = free base, FA = fumarate. *b*) A = acetone, C = chloroform, E = ethanol, EA = ethyl acetate, EE = diethyl ether, H = *n*-hexane, IPA = isopropanol, IPE = diisopropyl ether, M = methanol, T = toluene, W = water. *c*—*f*) Each pair of the corresponding regioisomers was afforded simultaneously in one reaction. *g*) See Experimental.

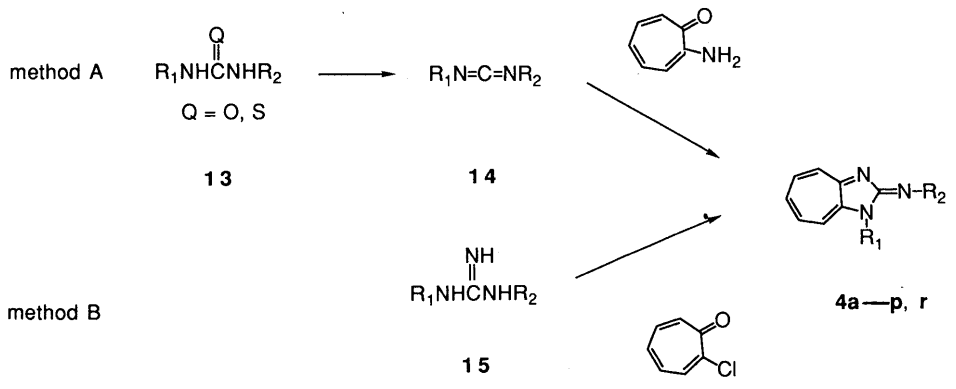


Chart 4

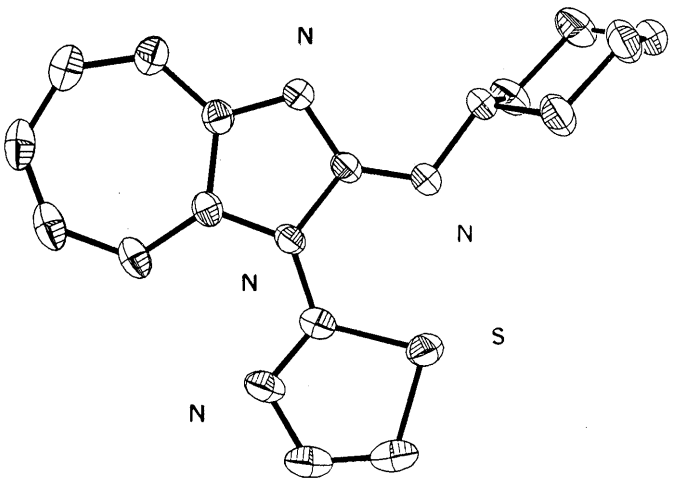


Fig. 1. Crystal Structure of **4d** Determined by X-Ray Crystallographic Analysis

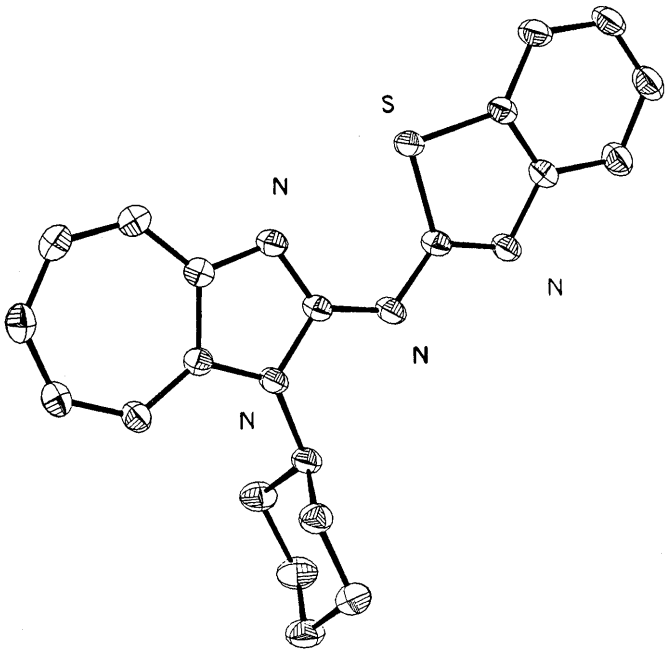
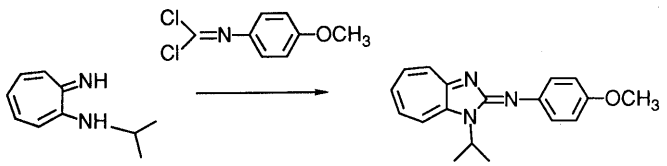


Fig. 2. Crystal Structure of **4h** Determined by X-Ray Crystallographic Analysis

solvent (method A_2). The starting ureas and thioureas **13** were prepared by the reaction of the corresponding amines with isocyanates or isothiocyanates. Method B comprises the reaction of guanidines (**15**) with 2-chloro-2,4,6-cycloheptatrien-1-one. In methods A and B, 1-heteroaryl or 1-aryl-2-alkylimino isomers (R_1 = heteroaryl or aryl, R_2 = alkyl) were predominantly afforded.

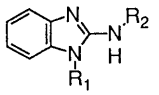
The correct positions of the two substituents (R_1 and R_2) in 2-cyclohexylimino-1-(2-thiazolyl)-, 2-(2-benzothiazolyl-imino)-1-cyclohexyl-, and 2-cyclohexylimino-1-phenyl-1,2-dihydrocycloheptimidazole (**4d**, **4h**, and **4n**) were determined by X-ray crystallographic analyses (Figs. 1 and 2, Table V). The structure of 1-(2-benzothiazolyl)-2-cyclohexylimino-1,2-dihydrocycloheptimidazole (**4e**), the regioisomer of **4h**, was confirmed by comparing the proton nuclear magnetic resonance (^{1}H-NMR), mass (MS), and ultraviolet (UV) spectra of **4e** with those of **4d** and **4n′** (the free base of **4n**). Namely, as shown in Table IV, the methine protons of the



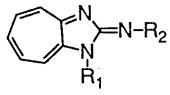
16 **4q**

Chart 5

TABLE II. Antiinflammatory and Analgesic Activities of 2-Amino-1*H*-Benzimidazoles (**3**), 1,2-Dihydro-2-iminocycloheptimidazoles (**4**), and Related Compound



3
free base or HCl



4
free base, HCl, or fumarate

No.	R_1	R_2	Carrageenin edema inhibition (%)[a] 100 mg/kg *p.o.*	AcOH writhing inhibition (%)[a] 3.2 mg/kg *p.o.*	32 mg/kg *p.o.*
3a	2-Methyl-4-quinolyl	Cyclohexyl	42.0	47.6[b]	54.7
3b	2-Benzothiazolyl	Cyclohexyl	I.A.		41.0
3c	2-Benzothiazolyl	4-Methoxyphenyl	I.A.		25.3
3d	4-Methoxyphenyl	Cyclohexyl	53.2		81.9
4a	2-Methyl-4-quinolyl	Cyclohexyl	52.2	I.A.	I.A.
4b	4-Pyridyl	Cyclohexyl	I.A.	65.3	
4c	2-Pyridyl	Cyclohexyl	I.A.	I.A.	
4d	2-Thiazolyl	Cyclohexyl	30.4	38.5	
4e	2-Benzothiazolyl	Cyclohexyl	31.0	54.6	78.0
4f	1*H*-Benzimidazol-2-yl	Cyclohexyl	47.2	I.A.	I.A.
4g	Cyclohexyl	2-Methyl-4-quinolyl	14.3	38.0	
4h	Cyclohexyl	2-Benzothiazolyl	16.0	48.5	
4i	Cyclohexyl	1*H*-Benzimidazol-2-yl	20.8	I.A.	
4j	2-Benzothiazolyl	iso-Propyl	27.7	14.7	
4k	2-Benzothiazolyl	*tert*-Butyl	I.A.	46.7	
4l	2-Benzothiazolyl	Cyclooctyl	I.A.	16.8	
4m	Cyclooctyl	2-Benzothiazolyl	I.A.	I.A.	
4n	Phenyl	Cyclohexyl	31.9	18.3	
4o	4-Methoxyphenyl	Cyclohexyl	54.3	I.A.	I.A.
4p	4-Methoxyphenyl	4-Methoxyphenyl	59.5	62.0	
4q	iso-Propyl	4-Methoxyphenyl	47.8	18.7	
4r	Cyclohexyl	Cyclohexyl	35.0	31.8	
8	—	—	I.A.		I.A.
Timegadine (**1**)			44.4	13.2	36.1
Tiaramide HCl (**17**)			34.0	30.1	51.1

a) I.A. = inactive. *b*) 10 mg/kg *p.o.*

cyclohexyl substituents in **4d**, **4e**, and **4n′** were observed at 4.15, 4.15, and 3.90 ppm, respectively, while that in **4h** was 4.85 ppm. In the MS spectra, **4d**, **4e**, and **4n′** showed the fragments ($M^+ - C_3H_7$) corresponding to the cleavage of the alkyl substituents, while **4h** showed the fragment ($M^+ - C_6H_{10}$). In UV spectra, the absorption bands of the longest wavelength were observed at 400 nm for **4d**, 401 nm for **4e**, and 395 nm for **4n′**, in contrast to 462 nm for **4h**.

With regard to the other three pairs of isolated regioisomers (**4a** *vs.* **4g**, **4f** *vs.* **4i**, and **4l** *vs.* **4m**), the similar spectral features were observed in ^{1}H-NMR and MS spectra. Therefore, the structures of these pairs and also other compounds **4** could be possibly identified by extending the spectral features observed in the pair of **4e** and **4h**.

The reaction of 7-imino-*N*-isopropyl-1,3,5-cyclohepta-

TABLE III. Pharmacological Data of Selected Compounds

No.	Antiinflammatory activity[a]				Analgesic activity[a]		
	Carrageenin edema inhibition (%)		Adjuvant arthritis inhibition (%) 32 mg/kg *p.o.*		AcOH writhing inhibition ED_{50} mg/kg *p.o.*	Randall–Selitto method ED_{30} mg/kg *p.o.*	PG E_2 synthesis inhibition[a] IC_{50} (μM)
	32 mg/kg *p.o.*	100 mg/kg *p.o.*	Inj. paw	Noninj. paw			
3a	12.5	42.0	41.5	41.3	9.2	65.2	1.2
3d	N.T.	53.2	I.A.	I.A.	(81.9%)[b]	>100	N.T.
4e	21.4	31.0	I.A.	I.A.	1.7	14.0	>100[d]
4p	32.7	59.5	I.A.	I.A.	(62.0%)[c]	>100	>100
Timegadine (**1**)	31.1	44.4	64.1	67.3	44.9	37.4	3.7
Tiaramide HCl (**17**)	6.0	34.0	I.A.	I.A.	18.4	34.2	>1000
			(ED_{50} > 500 mg/kg *p.o.*)				

a) N.T. = not tested. I.A. = inactive. *b*) Inhibition (%) at 32 mg/kg *p.o.* *c*) Inhibition (%) at 3.2 mg/kg *p.o.* *d*) Data of the hydrochloride of **4e**.

trien-1-ylamine (**16**) with 4-methoxyphenylcarbonimidic dichloride gave 1-isopropyl-2-(4-methoxyphenylimino) derivative (**4q**) (Chart 5).

Antiinflammatory, Analgesic, and PG E_2 Synthesis Inhibitory Activities 2-Amino-1*H*-benzimidazoles **3a**—**d**, 1,2-dihydro-2-iminocycloheptimidazoles **4a**—**r**, and the related compound **8** were tested for antiinflammatory activity (carrageenin-induced paw edema in rats) and for analgesic activity (acetic acid-induced writhing in mice). The results are listed in Table II, along with the data of timegadine **1** and tiaramide hydrochloride (HCl) (**17**) (Chart 1).

2-Cyclohexylamino-1-(2-methyl-4-quinolyl)-1*H*-benzimidazole **3a**, which we first designed in this study by using timegadine as a lead compound, exhibited potent antiinflammatory and analgesic activities. As shown in compound **8**, replacing the amino group at the 2-position of benzimidazole in **3a** with a methylene resulted in complete loss in both activities. The subsequent study in searching for an alternative to the quinolyl group revealed that a 4-methoxyphenyl (**3d**) was effective in terms of its increase of potency. These results suggest that the cyclic form of a guanidine such as 2-aminobenzimidazole may exert antiinflammatory and analgesic activities similarly to the guanidine moiety in timegadine, while the quinolyl group is not necessarily essential.

On the basis of these findings, we subsequently designed 1,2-dihydro-2-iminocycloheptimidazole derivatives **4** for further exploration. The activities of 1-(2-methyl-4-quinolyl)-, 1-(2-benzothiazolyl)-, and 1-(4-methoxyphenyl)-2-cyclohexylimino-1,2-dihydrocycloheptimidazole (**4a**, **4e**, and **4o**), which correspond to **3a**, **3b**, and **3d**, were first investigated. The results disclosed that the above compounds exhibited antiinflammatory activity, however, only **4e** had potent analgesic activity superior to timegadine or tiaramide HCl. 2-(2-Methyl-4-quinolylimino) and 2-(2-benzothiazolylimino) derivatives (**4g** and **4h**) showed inferior antiinflammatory activity compared to their regioisomers **4a** and **4e**, but **4g** acquired analgesic activity which its isomer did not exhibit. To obtain more effective compounds we continued further modifications of the substituents R_1 and R_2 in the structure of **4**.

Substitution of the 1-position in the cycloheptimidazole nucleus of **4** with a hydrophilic heterocycle such as 4- and 2-pyridyl groups (**4b** and **4c**) resulted in the loss of antiinflammatory activity. 2-Thiazolyl (**4d**) sustained antiinflammatory activity but decreased analgesic activity in comparison with **4e**. Compounds (**4f** and **4i**) having 2-benzimidazole as the substituents R_1 and R_2, respectively, exhibited no analgesic activity. Replacement of the cyclohexyl group in **4e** with isopropyl, *tert*-butyl, and cyclooctyl groups (**4j**, **4k**, and **4l**) lost or decreased antiinflammatory and analgesic activities. It seemed to be necessary for exhibiting both activities that the alkyl group in the imino moiety had suitable lipophilicity and/or steric bulk. Among the compounds having a phenyl group either or both at R_1 and R_2, bis(4-methoxyphenyl) derivative (**4p**) exhibited the highest potency in both antiinflammatory and analgesic activities in the series of compounds **4**. Finally dicyclohexyl derivative (**4r**) was shown to be not so potent as **4p**.

Four compounds, **3a**, **3d**, **4e**, and **4p**, were selected for further evaluation of antiinflammatory activity on adjuvant arthritis in rats, analgesic activity in the Randall–Selitto method, and inhibitory activity against PG E_2 synthesis in a sheep seminal vesicle. The results are listed in Table III.

Compound **3a** inhibited adjuvant arthritis and PG E_2 synthesis, and it is pharmacological profiled as a timegadine-like antiinflammatory agent. On the other hand, **4e** showed no effect on adjuvant arthritis and also no effect on PG E_2 synthesis. However, its analgesic activities in the Randall–Selitto method and the acetic acid-induced writhing test indicated it to be potent and superior to timegadine and tiaramide HCl. The mechanism in exhibiting potent analgesic activities has not yet been elucidated.

Experimental

The melting points were determined on a capillary melting point apparatus (MEL-TEMP) and are uncorrected. The infrared (IR) spectra were measured on a Shimadzu IR-408 spectrometer. The ^{1}H-NMR spectra were recorded on JEOL JNM-PMX60, Varian EM-390, and Hitachi R-90H spectrometers using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, br = broad, d = doublet, q = quartet, dd = double doublet, sep = septet, m = multiplet. The MS spectra were recorded on JEOL JMSD300 and Hitachi M-80 mass spectrometers. The UV spectra were measured on a Hitachi-228 spectrophotometer.

***N*^{1}-Cyclohexyl-*N*^{2}-[2-(2-methyl-4-quinolylamino)phenyl]thiourea (6a)** A solution of *N*-(2-methyl-4-quinolyl)-1,2-phenylenediamine[6] (**5a**, 2.00 g) and cyclohexylisothiocyanate (1.13 g) in EtOH (17.3 ml) was refluxed for 1.5 h and cooled to room temperature. The precipitated powder was collected by filtration and washed with EtOH to afford **6a** (1.92 g, 61.4%) as crystals: mp 191—192 °C (from EtOH). *Anal.* Calcd for $C_{23}H_{26}N_4S$:

C, 70.73; H, 6.71; N, 14.35. Found: C, 70.49; H, 6.89; N, 14.60. IR (Nujol): 3400—3100, 1590, 1570 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.8—1.9 (10H, m, $(CH_2)_5$), 2.33 (3H, s, CH_3), 3.95 (1H, m, NCH), 6.27 (1H, s, aromatic H), 7.05—7.85 (8H, m, aromatic H and NH), 8.23 (1H, d, J=6 Hz, aromatic H), 8.47 (1H, br s, NH), 8.67 (1H, br s, NH). MS m/z: 390 (M^+), 357, 291.

N^1-Cyclohexyl-N^2-[2-(4-methoxyphenylamino)phenyl]thiourea (6d) **6d** was prepared in a similar manner for **6a**, 72.3%, and used without purification in the following step. IR (Nujol): 3430, 3340—3150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.8—2.15 (10H, m, $(CH_2)_5$), 3.80 (3H, s, CH_3), 4.2 (1H, m, NCH), 5.71 (1H, br s, NH), 5.81 (1H, br s, NH), 6.65—7.3 (8H, m, aromatic H), 7.37 (1H, br s, NH).

2-Cyclohexylamino-1-(2-methyl-4-quinolyl)-1*H*-benzimidazole (3a) A suspension of **6a** (1.81 g) and CH_3I (0.40 ml) in EtOH (18.1 ml) was refluxed for 5 h and cooled with ice-water. The precipitated crystals were collected by filtration, dissolved in hot MeOH, and neutralized with methanolic NaOH (0.19 g). The resulting solution was concentrated *in vacuo* and the residue was suspended in water. The insoluble powder was collected by filtration and recrystallized from EtOH–MeOH to afford **3a** (1.06 g, 64.2%) as colorless crystals: mp 242—243.5 °C. *Anal.* Calcd for $C_{23}H_{24}N_4$: C, 77.50; H, 6.79; N, 15.72. Found: C, 77.75; H, 6.93; N, 15.59. IR (Nujol): 3250, 1605, 1565 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.65—2.35 (10H, m, $(CH_2)_5$), 2.73 (3H, s, CH_3), 4.0 (1H, m, NCH), 4.15 (1H, br s, NH), 6.55—8.3 (9H, m, aromatic H). MS m/z: 356 (M^+), 273.

2-Cyclohexylamino-1-(4-methoxyphenyl)-1*H*-benzimidazole (3d) **3d** was prepared in a similar manner for **3a**, 57.0%, colorless crystals: mp 143—144 °C (from *n*-hexane–AcOEt). *Anal.* Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.96; H, 7.08; N, 13.02. IR (Nujol): 3400, 1615, 1600, 1555, 1245 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.85—2.25 (10H, m, $(CH_2)_5$), 3.90 (3H, s, CH_3), 3.9 (1H, m, NCH), 3.95 (1H, br s, NH), 6.75—7.6 (8H, m, aromatic H). MS m/z: 321 (M^+), 239.

4-[2-[(Cyclohexylacetyl)amino]phenylamino]-2-methylquinoline (7) Cyclohexylacetyl chloride (3.29 g) was added dropwise to a stirred suspension of *N*-(2-methyl-4-quinolyl)-1,2-phenylenediamine[6] (**5a**, 4.25 g) and pyridine (5.39 g) in CH_2Cl_2 (42.5 ml) under ice cooling over 30 min. The resulting mixture was stirred at the same temperature for 2.5 h and concentrated *in vacuo*. The residue was triturated with water and filtered. The obtained solid was partitioned between $CHCl_3$ and 5% NaOH. The $CHCl_3$ layer was washed with brine, dried, and evaporated *in vacuo* to afford **7** (5.39 g, 84.7%) as a crude solid, which was used without purification for the following reaction. IR (Nujol): 3400, 3300, 1640, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.55—1.85 (11H, m, cyclohexyl H), 2.14 (2H, d, J=7 Hz, $COCH_2$), 2.47 (3H, s, CH_3), 6.43 (1H, s, aromatic H), 7.05—8.0 (10H, m, aromatic H and 2NH).

2-Cyclohexylmethyl-1-(2-methyl-4-quinolyl)-1*H*-benzimidazole (8) A solution of **7** (3.82 g) and $POCl_3$ (2.85 ml) in $CHCl_3$ (38 ml) and pyridine (40 ml) was refluxed for 11 h and evaporated *in vacuo*. The residue was partitioned between aqueous NaOH and $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried, evaporated *in vacuo*, and chromatographed ($CHCl_3$–MeOH) over silica gel to afford **8** (0.95 g, 26.1%) as yellow crystals: mp 185—187.5 °C (from AcOEt). *Anal.* Calcd for $C_{24}H_{25}N_3$: C, 81.09; H, 7.09; N, 11.82. Found: C, 80.86; H, 6.95; N, 11.84. IR (Nujol): 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.55—2.1 (11H, m, cyclohexyl H), 2.50 (1H, d, J=6.5 Hz, C<u>H</u>–⬡), 2.53 (1H, d, J=7.5 Hz, C<u>H</u>–⬡), 2.83 (3H, s, CH_3), 6.75 (1H, dd, J=7, 2 Hz, aromatic H), 6.95—7.85 (7H, m, aromatic H), 8.11 (1H, d, J=8.5 Hz, aromatic H). MS m/z: 355 (M^+), 272.

1-(2-Benzothiazolyl)-1,3-dihydro-3-(2-isopropenyl)-2*H*-benzimidazol-2-one (10) A suspension of 1,3-dihydro-1-(2-isopropenyl)-2*H*-benzimidazol-2-one[7] (**9**, 523 mg), 2-chlorobenzothiazole (509 mg), and K_2CO_3 (601 mg) in *N*,*N*-dimethylformamide (DMF) (2.6 ml) was stirred at 120 °C for 2.5 h, cooled, and partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was washed with brine, dried, and evaporated *in vacuo* to afford **10** (540 mg, 58.6%) as a colorless powder: mp 140—141 °C (from diisopropyl ether). *Anal.* Calcd for $C_{17}H_{13}N_3OS$: C, 66.43; H, 4.26; N, 13.67. Found: C, 66.25; H, 4.09; N, 13.66. IR (Nujol): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, d, J=1 Hz, CH_3), 5.28 (1H, s, C=CH), 5.43 (1H, q, J=1 Hz, C=CH), 7.05—7.55 (5H, m, aromatic H), 7.75—8.0 (2H, m, aromatic H), 8.65—8.85 (1H, m, aromatic H). MS m/z: 307 (M^+), 267, 225.

1-(2-Benzothiazolyl)-1,3-dihydro-2*H*-benzimidazol-2-one (11) A mixture of **10** (0.48 g), H_2SO_4 (0.32 ml), H_2O (0.32 ml), EtOH (3.4 ml), and CH_2Cl_2 (3.0 ml) was stirred under reflux for 13 h, cooled, and filtered to afford **11** (0.38 g, 91.2%) as colorless needles: mp 302—304 °C (from EtOH). *Anal.* Calcd for $C_{14}H_9N_3OS$: C, 62.91; H, 3.39; N, 15.72. Found: C, 62.78; H, 3.75; N, 15.70. IR (Nujol): 3200, 3150, 1730 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 7.05—7.6 (5H, m, aromatic H), 7.85—8.1 (2H, m, aromatic H), 8.4—8.6 (1H, m, aromatic H), 11.0 (1H, br, NH). MS m/z: 267 (M^+), 225.

1-(2-Benzothiazolyl)-2-chloro-1*H*-benzimidazole (12) A mixture of **11** (286 mg), $POCl_3$ (5.3 ml), and PCl_5 (335 mg) was refluxed for 9 h and evaporated *in vacuo*. The residue was partitioned between 2.5% NaOH and CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried, evaporated *in vacuo*, and chromatographed ($CHCl_3$) over silica gel to afford **12** (46 mg, 15.4%) as a colorless powder: mp 124.5 °C (dec.) (from diisopropyl ether). *Anal.* Calcd for $C_{14}H_8ClN_3S$: C, 58.85; H, 2.82; N, 14.71. Found: C, 58.72; H, 3.10; N, 14.03. IR (Nujol): 1515, 1495 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.15—8.15 (8H, m, aromatic H). MS m/z: 285 (M^+), 250.

1-(2-Benzothiazolyl)-2-cyclohexylamino-1*H*-benzimidazole Hydrochloride (3b) A solution of **12** (622 mg) and cyclohexylamine (648 mg) in EtOH (6.2 ml) was refluxed for 3 h and concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ and 5% NaOH. The $CHCl_3$ layer was washed with brine, dried, evaporated *in vacuo*, and chromatographed (toluene–AcOEt) over silica gel to afford colorless crystals, which were converted to the hydrochloride in the usual manner to afford **3b** (345 mg, 41.2%) as a colorless powder: mp 207—215 °C (from AcOEt–EtOH). *Anal.* Calcd for $C_{20}H_{20}N_4S \cdot HCl$: C, 62.41; H, 5.24; H, 14.56. Found: C, 61.84; H, 5.55; N, 14.37. IR (Nujol): 2700—2100, 1660, 1600, 1540 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.0—2.3 (10H, m, $(CH_2)_5$), 4.05 (1H, m, NCH), 7.3—7.9 (6H, m, aromatic H), 7.9—8.5 (2H, m, aromatic H), 9.4 (1H, br, NH). MS m/z: 348 (m^+), 266.

1-(2-Benzothiazolyl)-2-(4-methoxyphenylamino)-1*H*-benzimidazole Hydrochloride (3c) **3c** was prepared in a similar manner for **3b**, 22.8%, a colorless powder: mp 200—202.5 °C (from Et_2O). *Anal.* Calcd for $C_{21}H_{16}N_4OS \cdot HCl \cdot 1.8H_2O$: C, 56.92; H, 4.32; N, 12.64. Found: C, 57.18; H, 4.38; N, 12.81. IR (Nujol): 2800—2000, 1670, 1640, 1550 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.80 (3H, s, CH_3), 4.4 (2H, br s, 2NH), 7.05 (2H, d, J=9 Hz, aromatic H), 7.2—7.75 (7H, m, aromatic H), 8.05—8.3 (3H, m, aromatic H). MS m/z: 372 (M^+), 357.

N^1-(2-Benzothiazolyl)-N^2-cyclohexylthiourea (13b) A solution of 2-aminobenzothiazole (100 g) in a mixture (200 ml) of toluene and DMF was added dropwise to a stirred suspension of 60% NaH in a mixture (300 ml) of toluene and DMF under ice cooling in an atmosphere of N_2, and then cyclohexylisothiocyanate (103.4 g) was added dropwise. The resulting mixture was stirred at room temperature for 2 h and poured into a mixture of ice and water. The resulting mixture was adjusted to pH 7.0 with conc. HCl. The precipitate was collected by filtration and recrystallized from $CHCl_3$–MeOH to afford **13b** (139.8 g, 72.2%) as a colorless powder: mp 218—219 °C. *Anal.* Calcd for $C_{14}H_{17}N_3S_2$: C, 57.70; H, 5.88; N, 14.42. Found: C, 57.79; H, 6.04; N, 14.43. IR (Nujol): 3200, 3050, 1570 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.0—2.2 (10H, m, $(CH_2)_5$), 4.2 (1H, m, NCH), 7.0—8.0 (4H, m, aromatic H), 9.9 (1H, m, NH), 11.8 (1H, m, NH). MS m/z: 291 (M^+), 150.

The following thioureas (**13a**, **13c**, and **13d**) were prepared from 4-aminopyridine or 2-aminobenzothiazole and the corresponding isothiocyanates in a similar manner for **13b**.

N^1-Cyclohexyl-N^2-(4-pyridyl)thiourea (**13a**): 88.3%, a colorless powder: mp 159—160 °C (from EtOH–*n*-hexane). *Anal.* Calcd for $C_{12}H_{17}N_3S$: C, 61.24; H, 7.28; N, 17.85. Found: C, 61.35; H, 7.62; N, 17.76. IR (Nujol): 3200, 1600, 1580 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.0—2.2 (10H, m, $(CH_2)_5$), 4.10 (1H, m, NCH), 7.60 (2H, dd, J=7, 1 Hz, aromatic H), 8.0 (1H, br d, J=8 Hz, NH), 8.31 (2H, dd, J=7, 1 Hz, aromatic H), 9.55 (1H, m, NH). MS m/z: 235 (M^+), 206, 202.

N^1-(2-Benzothiazolyl)-N^2-isopropylthiourea (**13c**): 35.2%, a colorless powder: mp 202—204 °C (from $CHCl_3$–MeOH). *Anal.* Calcd for $C_{11}H_{13}N_3S_2$: C, 52.56; H, 5.21; N, 16.72. Found: C, 52.37; H, 5.43; N, 16.69. IR (Nujol): 3150, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.37 (6H, d, J=6 Hz, $2CH_3$), 4.48 (1H, m, NCH), 7.15—8.1 (4H, m, aromatic H), 9.8 (1H, m, NH), 11.9 (1H, m, NH).

N^1-(2-Benzothiazolyl)-N^2-cyclooctylthiourea (**13d**): 88.7%, a colorless powder: mp 196—198.5 °C (from diisopropyl ether). *Anal.* Calcd for $C_{16}N_{21}N_3S_2$: C, 60.15; H, 6.63; N, 13.15. Found: C, 60.43; H, 6.90; N, 13.04. IR (Nujol): 3250, 1575 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.4—2.2 (14H, m, $(CH_2)_7$), 4.25 (1H, m, NCH), 7.2—8.0 (4H, m, aromatic H), 10.15 (1H, m, NH), 11.8 (1H, m, NH). MS m/z: 319 (M^+), 150.

The other known ureas and thioureas (**13**) used in this study were prepared according to the literature.[8]

Guanidines (**15**) were prepared according to the literature.[9]

Preparation of 1,2-Dihydro-2-iminocycloheptimidazoles (4). Method A_1: 1-(2-Benzothiazolyl)-2-cyclohexylimino-1,2-dihydrocycloheptimidazole (4e) and 2-(2-Benzothiazolylimino)-1-cyclohexyl-1,2-dihydrocycloheptimidazole (4h) A solution of **13b** (41.0 g), PPh_3 (44.3 g), NEt_3 (17.1 g), and CCl_4 (26.0 g) in CH_2Cl_2 (450 ml) was stirred at room temperature in

TABLE IV. IR, ^{1}H-NMR, and MS Spectral Data for the Compounds **4**

No.	R_1	R_2	Form[a]	IR (Nujol) cm^{-1} C=N	^{1}H-NMR δ (*J*, Hz) (solvent)	MS (*m/z*)
4a	2-Methyl-4-quinolyl	Cyclohexyl	F	1640	($CDCl_3$) 0.9—2.1 (10H, m), 2.80 (3H, s), 3.95 (1H, m, NCH), 5.94 (1H, dd, 9, 1), 6.67 (1H, m), 6.90 (1H, m), 7.27 (1H, s), 7.50 (4H, m), 7.75 (1H, m), 8.15 (1H, d, 9)	368 (M^+) 325 ($M^+-C_3H_7$)
4b	4-Pyridyl	Cyclohexyl	F	1650	($CDCl_3$) 1.0—1.9 (10H, m), 3.90 (1H, m, NCH), 6.50 (1H, d, 10), 6.7 (1H, m), 6.95 (1H, d, 10), 7.1—7.4 (2H, m), 7.43 (2H, dd, 7, 1.5), 8.78 (2H, dd, 7, 1.5)	304 (M^+) 261 ($M^+-C_3H_7$)
4c	2-Pyridyl	Cyclohexyl	F	1645	($CDCl_3$) 1.0—2.0 (10H, m), 3.90 (1H, m, NCH), 6.2—7.5 (6H, m), 7.9 (2H, m), 8.5 (1H, m)	304 (M^+) 261 ($M^+-C_3H_7$)
4d[c]	2-Thiazolyl	Cyclohexyl	F	1660	($CDCl_3$) 1.3—2.1 (10H, m), 4.15 (1H, m, NCH), 7.15 (1H, d, 4), 6.7—7.6 (4H, m), 7.65 (1H, d, 4), 9.15 (1H, d, 10)	310 (M^+) 267 ($M^+-C_3H_7$)
4e[c]	2-Benzothiazolyl	Cyclohexyl	F	1675	($CDCl_3$) 1.3—2.1 (10H, m), 4.15 (1H, m, NCH), 6.7—7.0 (1H, m), 7.2—7.6 (5H, m), 7.8—8.0 (2H, m), 9.35 (1H, d, 10)	360 (M^+) 317 ($M^+-C_3H_7$)
4f	1*H*-Benzimidazol-2-yl	Cyclohexyl	F	1650	(DMSO-d_6) 1.1—2.2 (10H, m), 4.16 (1H, m, NCH), 7.00 (2H, dd, 6, 4), 7.52 (2H, dd, 6, 4), 7.95 (1H, m), 8.2 (3H, m), 10.28 (1H, d, 10.5), 12.8 (1H, br)	343 (M^+) 300 ($M^+-C_3H_7$)
4g	Cyclohexyl	2-Methyl-4-quinolyl	HCl	1630	($CDCl_3$) 1.2—2.9 (10H, m), 3.00 (3H, s), 4.85 (1H, m, NCH), 7.3—8.2 (8H, m), 8.48 (1H, dd, 9, 1), 8.70 (1H, dd, 9, 1)	368 (M^+) 286 ($M^+-C_6H_{10}$)
4g'	(The free base of **4g**)[b]			1610	($CDCl_3$) 1.2—2.9 (10H, m), 2.73 (3H, s), 4.78 (1H, m, NCH), 7.0—7.9 (8H, m), 8.02 (1H, dd, 9, 1), 8.28 (1H, dd, 9, 1)	368 (M^+) 285 ($M^+-C_6H_{11}$)
4h[c]	Cyclohexyl	2-Benzothiazolyl	F	1605	(DMSO-d_6) 1.15—2.8 (10H, m), 4.85 (1H, m, NCH), 7.05—8.3 (9H, m)	360 (M^+) 278 ($M^+-C_6H_{10}$)
4i	Cyclohexyl	1*H*-Benzimidazol-2-yl	F	1620	(DMSO-d_6) 1.2—2.7 (10H, m), 4.95 (1H, m, NCH), 5.55 (1H, br), 7.0—7.9 (9H, m)	343 (M^+) 261 ($M^+-C_6H_{10}$)
4j	2-Benzothiazolyl	iso-Propyl	F	1675	($CDCl_3$) 1.36 (6H, d, 6), 4.39 (1H, sep, 6, NCH), 6.7—7.1 (1H, m), 7.2—7.7 (5H, m), 7.8—8.2 (2H, m), 9.38 (1H, d, 9)	320 (M^+) 305 (M^+-CH_3)
4k	2-Benzothiazolyl	*tert*-Butyl	F	1675	($CDCl_3$) 1.55 (9H, s), 6.90 (1H, m), 7.15—7.6 (5H, m), 7.8—8.0 (2H, m), 9.38 (1H, d, 10)	334 (M^+) 319 (M^+-CH_3)
4l	2-Benzothiazolyl	Cyclooctyl	F	1670	($CDCl_3$) 1.3—2.1 (14H, m), 4.28 (1H, m, NCH), 6.85 (1H, m), 7.1—7.55 (5H, m), 7.7—8.0 (2H, m), 9.25 (1H, d, 10)	388 (M^+) 317 ($M^+-C_5H_{11}$)
4m	Cyclooctyl	2-Benzothiazolyl	HCl	1600	(DMSO-d_6) 1.3—2.2 (14H, m), 5.22 (1H, m, NCH), 7.2—8.0 (4H, m), 8.1—8.8 (5H, m)	388 (M^+) 278 ($M^+-C_8H_{14}$)
4n	Phenyl	Cyclohexyl	FA	1650	(DMSO-d_6) 1.0—2.05 (10H, m), 4.00 (1H, m, NCH), 6.50 (2H, s), 7.1—8.2 (10H, m), 8.8 (2H, br s)	303 (M^+) 260 ($M^+-C_3H_7$)
4n'[c]	(The free base of **4n**)[b]			1635	($CDCl_3$) 1.0—2.0 (10H, m), 3.90 (1H, m, NCH), 6.32 (1H, d, 9), 6.45—7.65 (9H, m)	303 (M^+) 260 ($M^+-C_3H_7$)
4o	4-Methoxyphenyl	Cyclohexyl	FA	1640	(DMSO-d_6) 0.95—2.1 (10H, m), 3.86 (1H, s), 4.0 (1H, m, NCH), 6.45 (2H, s), 6.9—8.35 (11H, m)	333 (M^+) 290 ($M^+-C_3H_7$)
4o'	(The free base of **4o**)[b]			1630	($CDCl_3$) 0.85—2.1 (10H, m), 3.83 (3H, s), 4.00 (1H, m, NCH), 6.33 (1H, br d, 9), 6.45—7.55 (8H, m)	333 (M^+) 290 ($M^+-C_3H_7$)
4p	4-Methoxyphenyl	4-Methoxyphenyl	HCl	1635	(DMSO-d_6) 3.75 (3H, s), 3.88 (3H, s), 6.95 (2H, d, 9), 7.25 (2H, d, 9), 7.2—8.65 (9H, m), 10.4 (1H, br s)	357 (M^+) 342 (M^+-CH_3)
4q	iso-Propyl	4-Methoxyphenyl	F	1635	($CDCl_3$) 1.60 (6H, d, 7), 3.78 (3H, s), 5.15 (1H, sep, 7, NCH), 6.6—7.45 (9H, m)	293 (M^+) 251 ($M^+-C_3H_6$) 236 ($M^+-C_3H_6-CH_3$)
4r[c]	Cyclohexyl	Cyclohexyl	F	1635	($CDCl_3$) 0.95—2.7 (20H, m), 3.87 (1H, m), 4.37 (1H, m), 6.35—7.3 (5H, m)	309 (M^+) 227 ($M^+-C_6H_{10}$) 184 ($M^+-C_6H_{10}-C_3H_7$) 145 ($M^+-C_6H_{10}\times 2$)

a) F = free base, FA = fumarate. *b*) The free bases were obtained from the corresponding hydrochlorides or fumarates in a usual manner. **4g'**: mp 155—167 °C (dec.) (from diisopropyl ether). *Anal.* Calcd for $C_{24}H_{24}N_4$: C, 78.23; H, 6.56; N, 15.20. Found: C, 78.05; H, 6.40; N, 15.21. **4n'**: mp 126—130.5 °C (from *n*-hexane–diisopropyl ether). *Anal.* Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.44; H, 7.23; N, 14.06. **4o'**: mp 135—141 °C (from *n*-hexane). *Anal.* Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 76.05; H, 7.04; N, 12.16. *c*) UV λ_{max} (EtOH) nm (log ε): **4d**: 400 (4.17), 308 (4.27), 255 (4.15), 227 (4.31); **4e**: 401 (4.17), 315 (4.28), 268 (4.27), 217 (4.58); **4h**: 462 (4.44), 298 (4.56), 240 (4.51); **4n'**: 395 (4.25), 248 (4.43); **4r**: 396 (4.21), 254 (4.41).

an atmosphere of N_2 for 3.5 h and concentrated *in vacuo*. The residue was triturated with Et_2O. The extract was evaporated *in vacuo* to afford crude N^1-(2-benzothiazolyl)-N^2-cyclohexylcarbodiimide (**14b**) quantitatively as an oil, which was used without purification for the following reaction. IR (film): 2100 cm^{-1}. **14b** was not further characterized.

A mixture of the carbodiimide (**14b**, 40.0 g) and 2-amino-2,4,6-cycloheptatrien-1-one[10] (18.2 g) in toluene (100 ml) was stirred at 80 °C for 13 h. After cooling, the reaction mixture was suspended in Et_2O. The solution and insoluble material were separated by filtration. The solution was evaporated *in vacuo* and chromatographed (toluene–AcOEt (9 : 1))

over silica gel to afford **4e** (4.6 g) as red needles. The insoluble material was chromatographed (toluene–AcOEt (9 : 1)) over basic alumina to afford **4h** (2.45 g) as reddish purple crystals. The physical data of **4e** and **4h** are listed in Tables I and IV.

Method A_2: 2-Cyclohexylimino-1,2-dihydro-1-(2-methyl-4-quinolyl)cycloheptimidazole (4a) and 1-Cyclohexyl-1,2-dihydro-2-(2-methyl-4-quinolylimino)cycloheptimidazole Hydrochloride (4g) A mixture of N^1-cyclohexyl-N^2-(2-methyl-4-quinolyl)carbodiimide[3] (3.54 g) and 2-amino-2,4,6-cycloheptatrien-1-one[10] (1.62 g) was stirred at 80 °C for 2.5 h and chromatographed (toluene–AcOEt) over basic alumina. The first eluate was evaporated *in vacuo* to afford **4a** (1.57 g) as orange-colored crystals. The second eluated was evaporated *in vacuo* and the residue was chromatographed ($CHCl_3$–MeOH) over silica gel. The obtained free base was converted to hydrochloride in the usual manner. The hydrochloride was recrystallized from EtOH–MeOH to afford **4g** (0.25 g) as an orange-colored powder. The physical data of **4a** and **4g** are listed in Table I and IV.

The following carbodiimides (**14**) were prepared from the corresponding thioureas **13** in a similar manner for **14b**, and used without purification for the following reaction.

N^1-Cyclohexyl-N^2-(4-pyridyl)carbodiimide (14a) **14a** was prepared quantitatively from **13a**. IR (film): 2150 cm^{-1}.

N^1-(2-Benzothiazolyl)-N^2-isopropylcarbodiimide (14c) **14c** was prepared in 36.0% yield from **13c**. IR (film): 2100 cm^{-1}.

N^1-(2-Benzothiazolyl)-N^2-cyclooctylcarbodiimide (14d) **14d** was prepared quantitatively from **13d**. IR (film): 2100 cm^{-1}.

N^1-Cyclohexyl-N^2-(4-methoxyphenyl)carbodiimide (14e) **14e** was prepared in 69.6% yield from N^1-cyclohexyl-N^2-(4-methoxyphenyl)-thiourea.[8a] IR (film): 2120 cm^{-1}.

The other known carbodiimides **14** used in this report were prepared according to the literature.[8b,11]

Method B: 1-(1*H*-Benzimidazol-2-yl)-2-cyclohexylimino-1,2-dihydrocycloheptimidazole (4f) and 2-(1*H*-Benzimidazol-2-ylimino)-1-cyclohexyl-1,2-dihydrocycloheptimidazole (4i) A mixture of N^1-(1*H*-benzimidazol-2-yl)-N^2-cyclohexylguanidine[9a] (3.0 g), 2-chloro-2,4,6-cycloheptatrien-1-one[12] (1.64 g), and K_2CO_3 (1.62 g) in toluene (3 ml) and DMF (1 ml) was stirred at 100 °C for 10 h, poured into ice water, and extracted with $CHCl_3$. The extract was washed with brine, dried, evaporated *in vacuo*, and chromatographed ($CHCl_3$–MeOH) over silica gel. The first eluate was evaporated *in vacuo* and chromatographed (toluene–AcOEt) over basic alumina. The obtained crude solid was recrystallized from $CHCl_3$–isopropanol to afford **4f** (0.91 g) as red crystals. The second eluate was evaporated *in vacuo* and chromatographed (toluene–AcOEt) over basic alumina. The obtained crude oil was crystallized from diisopropyl ether and recrystallized from EtOH–water to afford **4i** (0.13 g) as a dark purple powder. The physical data of **4f** and **4i** are listed in Tables I and IV.

Compounds **4** prepared by methods A_1, A_2, and B are listed in Table I and their spectral data are listed in Table IV.

1,2-Dihydro-1-isopropyl-2-(4-methoxyphenylimino)cycloheptimidazole (4q) A solution of 4-methoxyphenylcarbonimidic dichloride[13] (939 mg), 7-imino-*N*-isopropyl-1,3,5-cycloheptatrien-1-amine[14] (**16**, 649 mg), and NEt_3 (1.20 g) in 1,2-dichloroethane (10 ml) was stirred at room temperature for 3 h and under reflux for 10 h. The reaction mixture was partitioned between 2.5% NaOH and CH_2Cl_2. The CH_2Cl_2 layer was washed with brine, dried, evaporated *in vacuo*, and chromatographed (CH_2Cl_2–MeOH) over silica gel. The eluate was evaporated *in vacuo* and the residue was recrystallized from Et_2O–iso-PrOH to afford **4q** (0.23 g) as a dark red powder. The physical data are listed in Tables I and IV.

X-Ray Crystallography Crystal data of **4d**, **4h**, and **4n′** (the free base of **4n**) are listed in Table V.

Lattice constants and intensity data were measured using graphite-monochromated CuK_α ($\lambda = 1.54178$ Å) radiation on a Rigaku AFC-5 diffractometer. Unique reflections with $F_O \geqq 3\sigma_F$ were obtained using the 2θ–ω scanning method within $5° \leqq 2\theta \leqq 130°$. The structures were solved by MULTAN 78 based on direct methods and refined. The ORTEP drawings of **4d** and **4h** are shown in Figs. 1 and 2.

Carrageenin-Induced Paw Edema in Rats The experiment was done according to the method of Winter *et al.*[15] with five male Sprague–Dawley rats weighing 175—225 g per group, starved for 24 h beforehand. One hour after the oral administration of test compounds, 0.1 ml of 1% λ-carrageenin was injected subcutaneously into the plantar surface of the right hind paw. After another 3 h, the volume of the edema was measured.

Acetic Acid-Induced Writhing in Mice A modification of the method of Koster *et al.*[16] was used. The test compounds were administered orally to male ddY mice weighing 27—35 g. Groups of ten animals starved for 24 h were used at each dose. One hour later, 0.2% AcOH solution was injected intraperitoneally in a volume of 0.2 ml/10 g of body weight to induce writhing. After 3 min, the animals were observed for 10 min and the writhings were counted.

TABLE V. Crystal Data of **4d**, **h**, and **n′**

	4d	**4h**	**4n′**[a]
Formula	$C_{17}H_{18}N_4S$	$C_{21}H_{20}N_4S$	$C_{20}H_{21}N_3$
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$	$C2/c$
Cell dimension a (Å)	13.731 (1)	13.568 (2)	18.177 (6)
b (Å)	8.925 (1)	11.351 (2)	11.991 (1)
c (Å)	6.902 (1)	13.910 (3)	17.854 (6)
α (°)	111.94 (1)		
β (°)	87.92 (1)	118.48 (2)	119.74 (3)
γ (°)	98.87 (2)		
V (Å^3)	775.0 (2)	1883.0 (6)	3379 (2)
Density (g cm^{-3})	$D_x = 1.330$	$D_c = 1.272$	$D_c = 1.193$
Number of formula units Z	2	4	8
Total number of unique reflections ($F_O \geqq 3\sigma_F$)	1944	2728	1953
Final R value	0.054	0.044	0.060

a) The free base of **4n**.

Adjuvant Arthritis in Rats Adjuvant arthritis was produced in female Sprague–Dawley rats weighing 160—230 g according to the methods of Pearson[17a] and Newbould[17b] with the injection of a suspension of *Mycobacterium tuberculosis* (0.5 mg) in liquid paraffin (0.05 ml) into the plantar surface of the right hind paw. Groups of ten animals were used at each dose. Test compounds were orally administered once a day for 23 d, starting on the day following injection of the adjuvant. The assessment of the severity of the disease was performed by measuring the swelling of the injected and the noninjected hind paws.

Randall–Selitto Method The pain threshold was measured on the inflammed paw of male Sprague–Dawley rats weighing 155—210 g in groups of ten animals at each dose, according to the procedure of Randall and Selitto.[18] Induction of the edema was obtained by injection of 0.1 ml of a 5% suspension of yeast into the plantar surface of the right hind paw of each rat starved for 24 h. Two hours later, test compounds were orally administered. After another 1 h, the pain threshold was measured.

Inhibition of PG E_2 Synthesis A modification of the method of Matsuda *et al.*[19] was used. The reaction mixture consisted of microsomal enzyme from sheep seminal vesicle, 1 mM epinephrine, 2 mM glutathione, 100 mM Tris–HCl, pH 7.6, and a test compound in a total volume of 200 μl. The reaction was started by the addition of 10 μM [^{14}C]arachidonic acid, performed at 37 °C for 5 min, and stopped by the addition of 1 N HCl (50 μl). Prostaglandins were extracted with AcOEt, and the AcOEt layer was dried with N_2 gas, dissolved in MeOH (40 μl), and 4 μl of the solution was applied to a thin-layer plate (Merck, Kieselgel 60 F_{254}). The solvent of the chromatography was a mixture of AcOEt and AcOH (100 : 2). The PG E_2 fraction was scraped out. Scintillation solution was added, and the decrease of the radioactivity by the compound was estimated.

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