(m, 3 H), 6.6-6.9 (m, 3 H, ArH); MS (CI + NH_3), m/e 264 (M + 1). Anal. ($C_{16}H_{26}NO_2Cl$) C, H, N, Cl.

3-(Dipropylamino)-3,4-dihydro-2*H*-1-benzopyran-6-ol Hydrochloride (3b). The 6-methoxychromanamine **15** was O-demethylated by use of boron tribromide in dichloromethane as described for **5b**. Conversion to the HCl salt and recrystallization from ethanol-ether gave pure **16** (yield 70.8%): mp 190-192 °C; IR (KBr) 3125 cm^{-1} (OH), 2250 (NH^+); NMR ($CDCl_3$), free base, δ 0.9 (t, 6 H, 3'-CH_3), 1.5 (m, 4 H, 2'-CH_2), 2.5 (t, 4 H, 1'-CH_2), 2.8-3.5 (m, 3 H), 3.5-4.4 (m, 2 H), 6.3 (br, 1 H, OH), 6.4-6.8 (m, 3 H, ArH); MS (CI + NH_3), m/e 260 (M + 1). Anal. ($C_{15}H_{24}NO_2Cl$) C, H, N, Cl.

Estimation of pK_a Values. The negative logarithms of the compounds were determined by potentiometric titration as described by Albert and Serjeant.[22] For each compound three to four apparent pK_a values were determined.

Determination of 1-Octanol-Water Partition Coefficients. To obtain a measure of lipophilicity at physiological pH the 1-octanol-water distribution coefficients were determined at pH 7.4. The substances were dissolved in Na^+/K^+-phosphate buffer saturated with 1-octanol. After the mixture was shaken in a closed tube with 1-octanol saturated with phosphate buffer, the two phases were separated by centrifugation. The concentrations were determined by HPLC with electrochemical detection.[15] A 15-cm Nucleosil 5-C18 column was used for the separation.

Pharmacology. Determination of Metabolites of Dopamine. Female albino rats of a Wistar-derived strain (C.D.L., Groningen, The Netherlands) were used. The body weights of the rats varied from 180 to 220 g. The compounds were administered by intraperitoneal (ip) injection in a volume of 2.0 mL kg^{-1} of saline. After 1 h, during which time the behavioral effects were scored according the method of Costall et al.,[21] the rats were killed by cervical dislocation. The corpora striata were rapidly dissected, frozen on dry ice, and stored at -80 °C. Following weighing of the frozen samples, homogenization in 0.1 M perchloric acid, and centrifugation (3000-g, 7 °C, 15 min), the amounts of the metabolites HVA and DOPAC in the supernatants were determined according to the method of Westerink and Mulder[15] by use of purification on Sephadex G 10, separation on a reversed-phase (RP 18) HPLC column, and electrochemical detection.

Displacement of the Specific Binding of [^{3}H]-DP-5,6-ADTN in Rat Striatum. This assay which was performed with homogenized and washed membrane preparations from rat striatum tissue was carried out as described previously.[19] In each experiment the amount of [^{3}H]-DP-5,6-ADTN bound was determined in the absence (total) and presence (nonspecific) of 10^{-6} M (+)-butaclamol, the difference yielding specific [^{3}H]-DP-5,6-ADTN binding. The ability to compete with [^{3}H]-DP-5,6-ADTN was tested over a concentration range of 10^{-11}-10^{-4} M.

Displacement of the Specific Binding of [^{3}H]-N-0437 in Calf Striatal Membranes. The binding experiments were carried out according the procedure of Van der Weide et al.[20] Specific binding was defined as the difference in the amount of radioactivity in the absence or presence of 1 μM unlabeled N-0437. The ability to compete with [^{3}H]-N-0437 was tested over a concentration range of 10^{-11}-10^{-4} M.

Registry No. **3b**, 116005-03-9; **3b** (base), 116005-04-0; **5a**, 116004-97-8; **5a** (base), 116005-01-7; **5b**, 112960-16-4; **5b** (base), 112960-12-0; **6a**, 20351-79-5; **6b**, 5802-17-5; **8a**, 116004-85-4; **8b**, 116004-86-5; **10a**, 116004-87-6; **10a** (amine·HCl), 22406-62-8; **10b**, 116004-88-7; **10b** (amine·HCl), 22406-60-6; **11a**, 116004-89-8; *cis*-**11a**, 116004-90-1; **11b**, 116004-91-2; *cis*-**11b**, 116004-92-3; **12a**, 116025-07-1; **12b**, 116004-93-4; **13a**, 116004-94-5; **13a** (base), 116004-98-9; **13b**, 116004-95-6; **13b** (base), 116004-99-0; **14a**, 116004-96-7; **14a** (base), 116005-00-6; **14b**, 112960-15-3; **14b** (base), 112960-14-2; **15**, 116005-02-8; **15** (base), 110927-04-3; $ClCH_2COCl$, 79-04-9; n-C_3H_7I, 107-08-4; $C_2H_5CO_2H$, 79-09-4.

Retinobenzoic Acids. 1. Structure-Activity Relationships of Aromatic Amides with Retinoidal Activity

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Two types of aromatic amides, terephthalic monoanilides and (arylcarboxamido)benzoic acids, have been shown to possess potent retinoidal activities and can be classified as retinoids. The structure-activity relationships of these amides are discussed on the basis of differentiation-inducing activity on human promyelocytic leukemia cells HL-60. In generic formula 4 (X = NHCO or CONH), the necessary factors to elicit the retinoidal activities are a medium-sized alkyl group (isopropyl, *tert*-butyl, etc.) at the meta position and a carboxyl group at the para position of the other benzene ring. The bonding of the amide structure can be reversed, this moiety apparently having the role of locating the two benzene rings at suitable positions with respect to each other. Substitution at the ring position ortho to the amide group or N-methylation of the amide group caused loss of activity, presumably owing to the resultant change of conformation. It is clear that the mutual orientation of the benzylic methyl group(s) and the carboxyl group and their distance apart are essential factors determining the retinoidal activity. Among the synthesized compounds, 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid (Am80) and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid (Am580) were several times more active than retinoic acid in the assay. They are structurally related to retinoic acid, as is clear from the biological activity of the hybrid compounds (M2 and R2).

Retinoids are defined as "a class of compounds consisting of four isoprenoid units joined in head to tail manner.[1] All retinoids may be formally derived from a monocyclic parent compound (that is, retinol) ...". Biologically retinoids are substances that can elicit specific biological responses by binding to or activating a specific receptor or set of receptors.[2,3] Synthetic ligands, that is, synthetic retinoids, which have a better molecular fit to these putative receptors than retinoic acid does, may elicit stronger or more specific vitamin A activities than retinol or retinoic acid (**1**, Chart I).[4] The most important activities of retinoids are, certainly, the effects on the differentiation and proliferation of many types of cells.[5] The synthesis of potent new compounds with retinoidal activities should facilitate the application of retinoids to

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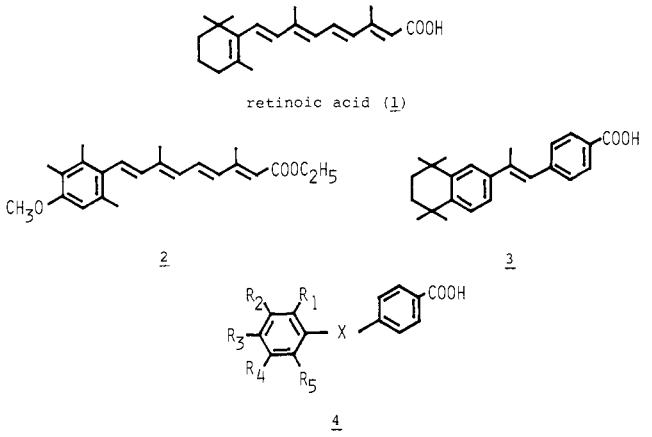
(2) Sporn, M. B.; Roberts, A. B.; Goodman, D. S., Eds. *The Retinoids*; Academic: Orlando, 1984.
(3) Sporn, M. B.; Roberts, A. B.; Roche, N. S.; Kagechika, H.; Shudo, K. *J. Am. Acad. Derm.* **1986**, *15*, 756.
(4) Shudo, K.; Kagechika, H. *Chemistry and Biology of Synthetic Retinoids*; Dawson, M. I., Okamura, W. H., Eds.; CRC: Boca Raton, FL, in press.
(5) Lotan, R. *Biochem. Biophys. Acta* **1980**, *605*, 33.

0022-2623/88/1831-2182$01.50/0

Chart I

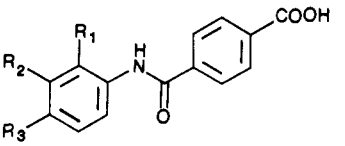


medicinal and chemotherapeutic areas[6] and also provide a useful method for the identification of the true retinoid receptor(s)[7] and the clarification of its role in cell biology. Interest in retinoids is also enhanced by the concurrent rapid progress of studies on tumor promoters (phorbol esters and teleocidins), many of whose activities are opposite to or in contrast with the biological activities of retinoids.[8,9]

So far, a number of compounds that show retinoidal activity have been reported. Among them, some compounds whose chemical structures are apparently superimposable on that of retinoic acid (**1**) have been found to be active in certain bioassays such as inhibition of papilloma formation by chemical carcinogens. Etretinate (**2**)[6] and the arotinoid **3**[10,11] are of particular interest. The former can be used clinically in the treatment of proliferative dermatological disease (psoriasis).[6] However, these compounds, as well as retinoic acid, have the clinical disadvantages of high toxicity (hypervitaminosis A) and long-lasting teratogenicity.[6] It is desirable to find new compounds that are more specific and can be eliminated promptly from the body.

Against this background, a series of new compounds with strong retinoidal activities has been found.[9,12] The generic structure is represented by **4**,[12] where the group X that links the two aromatic rings can be —NHCO—,[13] —CONH—,[14] —COCH=CH—,[15] —CH=CHCO—, —$COCH_2CO$—, epoxide, sulfonamide, ester, azo,[16] azoxy,

Table I. Differentiation-Inducing Activities of Monosubstituted Terephthalic Anilides



name	R_1	R_2	R_3	ED_{50},[a] M	rel act.[b]
retinoic acid				2.4×10^{-9} [c]	1
Am00	H	H	H	inactive[d]	
Am10	H	CH_3	H	inactive	
Am25	H	C_2H_5	H	inactive	
Am30	H	H	*i*-Pr	9.1×10^{-7}	9.8×10^{-4}
Am32	H	*i*-Pr	H	6.8×10^{-7}	1.3×10^{-3}
Am34	*i*-Pr	H	H	inactive	
Am38	H	Me_2N	H	inactive	
Am40	H	*t*-Bu	H	7.0×10^{-7}	3.2×10^{-3}
Am50	H	H	*t*-Bu	$>10^{-6}$ [d]	$<10^{-4}$
Am160	H	Ph	H	inactive	
Am162	H	c-C_6H_{11}	H	$>10^{-6}$	$<10^{-4}$
Am252	H	Br	H	inactive	

[a] ED_{50} values were calculated from NBT reduction assay data. Experiments were repeated more than three times in most cases. The values shown are representative ones or means (when more than five repetitions were done). This is also the case in the other tables. [b] The ratio of ED_{50} (a test compound) to ED_{50} (retinoic acid), both values having been obtained in concurrent experiments. This is also the case in the other tables. [c] The deviation (σ_{n-1}) of retinoic acid is estimated to be 1.8×10^{-9} M ($n = 90$). [d] "Inactive" means there was no activity at 10^{-6} M. "$>10^{-6}$ M" means there was slight activity at 10^{-6} M.

and so on, and R is a medium-sized alkyl group(s).[12] Such compounds have been named retinobenzoic acids. This paper describes in detail the aromatic amides with high retinoidal activity, laying emphasis on structure–activity relationships.

In order to design the new active compounds (**4**), our guidelines were as follows: (1) The structure–activity relationships of chemical carcinogens, (dimethylamino)azobenzenes and (dimethylamino)stilbenes,[17] and aminofluorenes and heteroaromatic amines[18,19] suggest that the chemical moiety C=C can be replaced by N=C, N=N, and other nitrogen-containing structures. (2) A retinol analogue that does not possess the terminal cyclohexene ring can bind to opsin.[20] Similarly, the potent tumor promoter teleocidin has an important hydrophobic cyclic ring, but lyngbyatoxin has an open-chain hydrophobic group.[21] The cyclohexenyl ring of retinoic acid can be replaced by an acyclic group. (3) Moreover, the structure–activity relationships of teleocidin showed us that the amide bond is important for the fixation of the conformationally flexible structure.[22] (4) Our belief on drug design is that we should not be overrational in considering modifications of chemical structure.

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(7) Hashimoto, Y.; Kagechika, H.; Kawachi, E.; Shudo, K. *Jpn. J. Cancer Res.* **1988**, *79*, 473.
(8) Takagi, K.; Suganuma, M.; Kagechika, H.; Shudo, K.; Ninomiya, M.; Muto, Y.; Fujiki, H. *J. Cancer Res. Clin. Oncol.* **1988**, *114*, 221.
(9) Shudo, K. *Differentiation of Cancer Cells and Cancer Therapy*; Hozumi, M., Takaku, F., Eds.; Soft Science Publications: Tokyo, 1985; pp 189–196.
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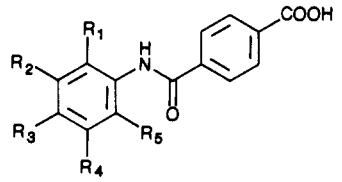
(21) Fujiki, H.; Suganuma, M.; Tahira, T.; Yoshioka, A.; Nakayasu, M.; Endo, Y.; Shudo, K.; Takayama, S.; Moore, R. E.; Sugimura, T. *Cellular Interactions by Environmental Tumor Promoters* Fujiki, H., Hecker, E., Moore, R. E.; Sugimura, T.; Weinstein, I. B., Eds.; Japan Scientific Societies Press; Tokyo/VNU Science Press: Utrecht, The Netherlands, 1984.
(22) (a) Endo, Y.; Shudo, K.; Itai, A.; Hasegawa, M.; Sakai, S. *Tetrahedron* **1986**, *42*, 5905. (b) Itai, A.; Kato, Y.; Tomioka, N.; Iitaka, Y.; Endo, Y.; Hasegawa, M.; Shudo, K.; Fujiki, H.; Sakai, S. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 3688.

Table II. Differentiation-Inducing Activities of Di- or Trisubstituted Terephthalic Anilides



name	R_1	R_2	R_3	R_4	R_5	ED_{50}, M	relative act.
retinoic acid						2.4×10^{-9}	1
Am20	H	Et	Et	H	H	2.6×10^{-7}	7.7×10^{-3}
Am55	H	*t*-Bu	H	*t*-Bu	H	3.6×10^{-8}	0.15
Am60	*i*-Pr	H	H	H	*i*-Pr	inactive	
Am62	*i*-Pr	H	H	*i*-Pr	H	inactive	
Am64	*i*-Pr	H	*i*-Pr	H	H	inactive	
Am66	H	*i*-Pr	H	*i*-Pr	H	3.8×10^{-8}	4.2×10^{-2}
Am68	H	*i*-Pr	*i*-Pr	H	H	2.1×10^{-9}	1.4
Am45	*t*-Bu	H	*t*-Bu	H	*t*-Bu	inactive	

Table III. Differentiation-Inducing Activities of Terephthalic Anilides with a Fused Alkyl Group

name[a]	ED_{50}, M	relative act.
retinoic acid	2.4×10^{-9}	1
Am68	2.1×10^{-9}	1.4
Am80	7.9×10^{-10} [b]	3.5
Am140	$>10^{-6}$	$<10^{-4}$
Am150	6.8×10^{-8}	5.9×10^{-2}

[a] Structures: see Figure 1. [b] The deviation (σ_{n-1}) of Am80 is estimated to be 1.1×10^{-10} M (n = 26).

In this study, the retinoidal activities of the aromatic amides were evaluated in terms of the potency to induce the differentiation of the human promyelocytic leukemia cell line HL-60 to mature granulocytes. This cell line was established by Gallo et al.[23] and is known to be induced to differentiate into mature monocytes by tumor promoters or vitamin D_3 and into mature granulocytes by retinoic acid.[24] This differentiation-inducing ability of retinoids is in good agreement with the results of other assays of retinoids.[4] As the marker of differentiation, morphological changes were examined after Wright-Giemsa staining and functional changes were measured by the Nitroblue tetrazolium (NBT) reduction assay.[25] The ED_{50} values of active compounds were calculated from the NBT reduction assay data and were in agreement with the activities estimated from the morphological changes.

Results

The biological activities of (*N*-phenylcarbamoyl)benzoic acid derivatives (**4**, X = -NHCO-), i.e. terephthalic monoanilides, are shown in Tables I-III. The simplest (nonsubstituted) terephthalic monoanilide Am00 was completely inactive at cconcentrations below 10^{-6} M in the assay system. However, the introduction of a bulky alkyl group, such as an isopropyl or a *tert*-butyl group, at the meta position (R_2) resulted in the appearance of differentiation-inducing activity (Table I). The compounds bearing such a bulky alkyl group at the ortho or para position have little or no activity. The effects of several alkyl groups at the meta position were compared. The substitution of a small alkyl group (methyl or ethyl) or a large alkyl group (cyclohexyl or phenyl was not effective. Moreover, the compound possessing a polar dimethylamino group (Am38) or a bromine atom (Am252) was inactive. Therefore, it seems to be important for the differentiation-inducing activity that a medium-sized and hydrophobic alkyl group (i.e., isopropyl or *tert*-butyl group) should exist at the meta position.

The effect of more than one (bulky) alkyl substituent is shown in Table II. All the compounds having an *o*-alkyl group are inactive, even when the *m*-alkyl group is also present. The compounds that have two medium-sized *m*-alkyl groups (Am55, Am66) are more active than the corresponding monosubstituted compounds by 1 order of magnitude. Interestingly, the compound Am68, which has two alkyl groups at the meta and para positions, showed stronger activity than Am66 or retinoic acid. The *p*-alkyl group, though itself having little or no effect on the activity, increases the activity very strongly when it coexists with the *m*-alkyl group (Am20, Am68).

One possible interpretation of this indirect effect of the *p*-alkyl group is a steric interaction between the two alkyl groups. Though isopropyl groups of Am32 or Am66 can rotate nearly freely, the two isopropyl groups in Am68 would interact strongly and their rotation would be restricted. They should exist in a restricted conformation where the four methyl groups face in opposite directions. Consequently, some conformationally more restricted compounds, where the two isopropyl groups of Am68 are linked to form a ring system (illustrated in Figure 1), were synthesized and their activities were compared. The four benzylic methyl groups of Am68 are fixed face to face in Am140. On the other hand, Am80 has four methyl groups facing away as expected in Am68. In Am150, a set of methyl groups lies outside the bicyclo ring. The activities of these compounds (shown in Table III) are very interesting. Am140, with no methyl group is inactive even at the concentration of 10^{-6} M. However, introduction of methyl groups at the bridgehead positions (Am150) restored strong activity. In fact, Am80 has the strongest differentiation-inducing activity of all the terephthalic anilides, being about 3.5 times more active than retinoic acid. From these results, it is clear that the direction of the methyl groups at the benzylic position is very important for the activity. Probably, the methyls at the meta position (C-8) are more important than those at the para position, since para-substituted anilides themselves did not affect the activity.

Next, the activities of (phenylcarboxamido)benzoic acid derivatives (**4**, X = -CONH-) were examined (Table IV). These compounds have reversed amide bonds, compared with the terephthalic monoanilides. Nevertheless, the structure-activity relationships, especially the effect of alkyl substituents, are very similar in both cases. Non-

(23) Collins, S. J.; Gallo, R. C.; Gallagher, R. E. *Nature (London)* **1977**, *270*, 347.
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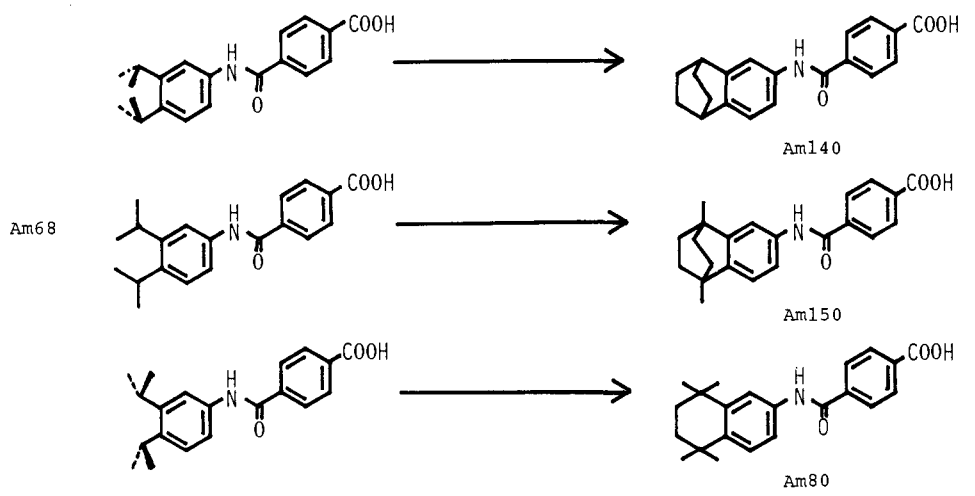
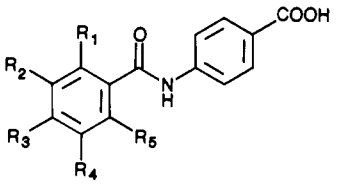
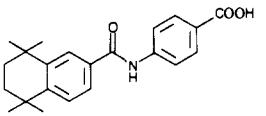


Figure 1.

Table IV. Differentiation-Inducing Activities of (Arylcarboxamido)benzoic Acids



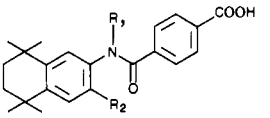
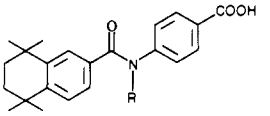
name	R_1	R_2	R_3	R_4	R_5	ED_{50}, M	rel act.
retinoic acid						2.4×10^{-9}	1
Am500	H	H	H	H	H	inactive	
Am540	H	*t*-Bu	H	H	H	$>10^{-6}$	$<10^{-4}$
Am550	H	H	*t*-Bu	H	H	$>10^{-6}$	$<10^{-4}$
Am555	H	*t*-Bu	H	*t*-Bu	H	4.8×10^{-8}	5.6×10^{-2}
Am568	H	*i*-Pr	*i*-Pr	H	H	6.8×10^{-8}	4.0×10^{-2}
Am580						3.4×10^{-10} (n = 12)	7.2

substitued (phenylcarboxamido)benzoic acid (Am500) is completely inactive. Introduction of a bulky alkyl group leads to the appearance of activity (Am540) and compounds possessing two alkyl groups (Am555 and Am568) are more active. In this case, also, Am580, corresponding to Am80, has the strongest activity and is about 7.2 times more active than retinoic acid.

Thus, these two types of aromatic amides have very similar structure–activity relationships. This is interesting considering the difference of their chemical characters, such as the electronic character of the aromatic rings and the pK_a values of the carboxyl group.

Though these amides, terephthalic anilides and (arylcarboxamido)benzoic acids, seem to be structurally different from retinoic acid, they are strong differentiation inducers and also show other retinoidal actions. The relation of these amides to retinoic acid was suggested by the observation of the differentiation-inducing activity of the hybrid compounds derived from retinoic acid and the aromatic amides, as illustrated in Figure 2. Compound R2 is constructed from the left half of retinoic acid and the right half of Am580, and compound M2 from the right half of retinoic acid and the left half of Am80. These hybrid compounds have significant activity to induce differentiation of HL-60 cells to mature granulocytes, though the activities are weaker. Compound F2, a nor (two carbon less) analogue of M2, is inactive. These results indicated that the aromatic amide compounds described above are structurally related to retinoic acid.

Table V. Substitution Effects in Am80 and Am580

name			ED_{50}, M	relative act.
retinoic acid			2.4×10^{-9}	1
				
Am80	R_1 = H	R_2 = H	7.9×10^{-10}	3.5
Am100	R_1 = H	R_2 = CH_3	3.5×10^{-7}	6.0×10^{-3}
Am110	R_1 = H	R_2 = NO_2	$>10^{-6}$	$<10^{-4}$
Am114	R_1 = H	R_2 = NH_2	5.6×10^{-7}	1.1×10^{-2}
Am118	R_1 = H	R_2 = Br	$>10^{-6}$	$<10^{-4}$
Am90	R_1 = CH_3	R_2 = H	$>10^{-6}$	$<10^{-4}$
				
Am580	R = H		3.4×10^{-10}	7.2
Am590	R = CH_3		$>10^{-6}$	$<10^{-4}$

The effects of substituents on Am80 and Am580 are summarized in Table V. A substituent ortho (C-3) to the amide N atom decreased the activity of Am80 by 2 or 3 orders of magnitude. This agreed with the results on a series of diisopropyl-substituted derivatives, that compounds having an isopropyl group at R_1 (ortho) are all inactive, even if a meta substituent exists. More interestingly, introduction of a methyl group at the amide N

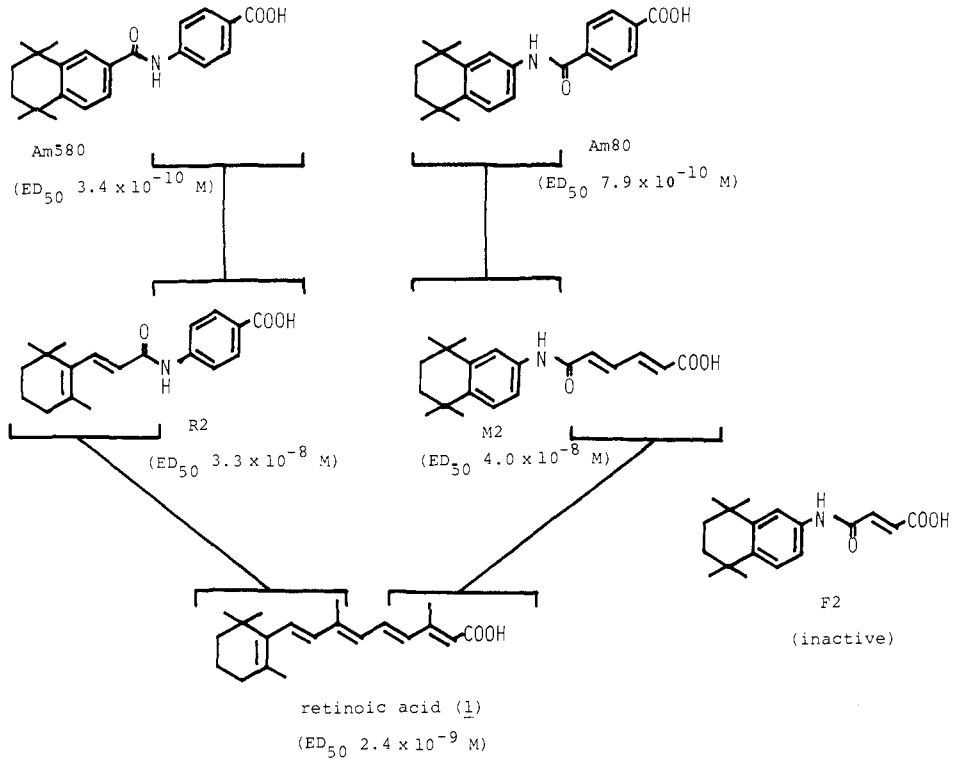


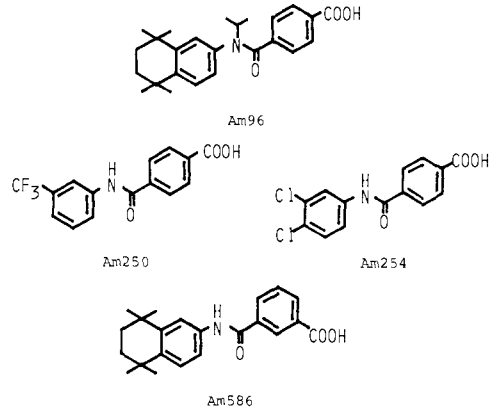
Figure 2.

atom of Am80 or Am580 (this gives the compounds named Am90 or Am590, respectively) resulted in a 10^4-fold reduction in activity. One possible reason is that the amide proton is necessary for the activity, and it is blocked in the compounds Am90 and Am590. The facts that inversion of the amide bond (Am80 vs Am580) causes little change in the activity and that the linking group X in general formula 4 can be further varied (ester, azo, etc.[12-16]) do not favor this idea. Another possible interpretation is a change of the conformation of the amide bonds. From the spectroscopic analysis, in fact, the amide bonds of the highly active amides Am80 and Am580 are trans, whereas in the inactive amides Am90 and Am590, the amide bond is cis. This is supported by X-ray crystallographic analysis. The results of conformational studies of the amide bonds will be published elsewhere.

Several related amide compounds have been prepared and their biological activities (HL-60) were tested. The structures of some of the compounds are shown in Table VI. Am70 and Am75 showed some activity, but the potency is lower. Similar results were obtained with Am570, Am572, and Am577. Am96 (Chart II), the *N*-isopropyl derivative of Am80, did not show any activity, like Am90 discussed above. The ortho-substituted isomer of Am80 (Am120) was also inactive. Naphthyl and tetrahydronaphthyl derivatives, without any methyl substituent, did not show any activity. Compounds substitued with 3-CF_3, 3-Br, or 3,4-Cl_2 (Am250, Am252, and Am254, respectively) were inactive.

When the carboxylic acid was transferred to the meta position, as in Am586, the activity was decreased more than 1000 times. When the carboxylic acid was modified to an ester, the activity in the assay decreased to about $^1/_{10}$ of that of the parent acid. Though HL-60 cells may not possess highly active metabolizing enzymes, a part of the ester may be hydrolyzed to the active acid which elicits the biological activity. Similar results were observed with several carboxamide derivatives. These ester or carboxamide derivatives may be effective prodrugs for in vivo experiments or clinical use.

Chart II

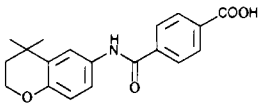
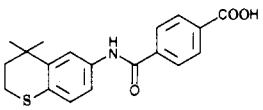
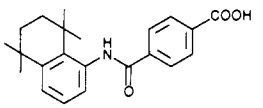
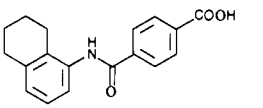
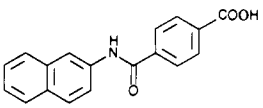
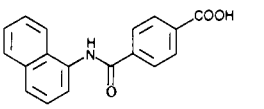
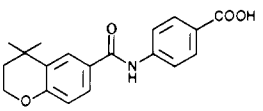
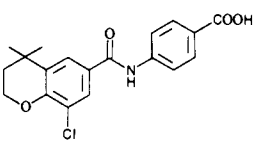
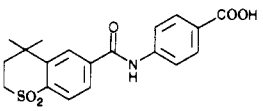


Discussion

The modulation of cell differentiation and proliferation by retinoids is the most important among various retinoidal actions.[2] For this activity, retinoic acid is believed to be the active form in living cells. In this study we report the cell-differentiation-inducing activity of aromatic amides. These amide compounds were structurally related to retinoic acid through their hybrid compounds (Figure 2). Other retinoidal activities have also been examined, especially those of Am80[13] and Am580,[14] which are representative strong inducers of differentiation of HL-60 cells. These include differentiation of mouse teratocarcinoma cells F9 (morphologically and functionally in terms of induction of plasminogen activator),[26] inhibition of the proliferation of mouse melanoma S91 cells,[26] and inhibition of the induction of ornithine decarboxylase by tumor promoters (TPA,[26] teleocidin[8]). The compounds also inhibit proliferation and keratinization of rat bladder cancer cell line BES20B[27] and keratinization of hamster tracheal

(26) Jetten, A. M.; Anderson, K.; Deas, M. A.; Kagechika, H.; Lotan, R.; Rearick, J. I.; Shudo, K. *Cancer Res.* **1987**, *47*, 3523.
(27) Kawachi, E.; Shudo, K. unpublished results.

Table VI. Differentiation-Inducing Activities of Some Amide Derivatives

name	structure	ED_{50}, M	rel act.
retinoic acid		2.4×10^{-9}	1
Am70		$>10^{-6}$	$<10^{-4}$
Am75		7.3×10^{-8}	5.1×10^{-2}
Am120		$>10^{-6}$	$<10^{-4}$
Am174		inactive	
Am170		inactive	
Am172		inactive	
Am570		8.0×10^{-7}	3.5×10^{-3}
Am572		7.5×10^{-8}	3.7×10^{-2}
Am577		inactive	

tissues.[26] Furthermore, some mechanistic studies have been done. The expression of *c-myc* gene, whose expression is enhanced in HL-60 cells, is suppressed prior to the differentiation of the cells by treatment by Am80, as by retinoic acid.[28] Am80 and Am580 enhance the binding of epidermal growth factor (EGF) to the cellular receptors in NRK cells.[3] Thus, the aromatic amides described here are not only inducers of differentiation of HL-60 cells but also modulators of differentiation and proliferation of various cells, probably by the same mechanism as retinoic acid. Therefore, they can be biologically classified as "retinoids".[3] Various benzoic acids having the general structure **4**, including the amide compounds, have similar retinoidal activities and may be comprehensively named "retinobenzoic acids". Am80 and Am580 are among the most active retinobenzoic acids.

The structure–activity relationships of the aromatic amides can be summarized as follows: (1) In the generic formula 4, a medium-sized alkyl group such as an isopropyl or a *tert*-butyl group at the meta position (R_2) is necessary for the activity. The activity is greatly diminished when the alkyl group is smaller or larger, or when the substitution position is ortho or para. (2) The orientation of this alkyl group is an important factor. Conformational restriction of alkyl groups by a ring system or the presence of a *p*-alkyl group increases the activity, and Am80 and Am580 are several times more active than retinoic acid. (3) The carboxyl group at the para position of the other benzene ring is also necessary. (4) The binding position of the intervening amide moiety can be reversed. Our other studies have shown that the group can be replaced with an ester, sulfonamide, azo, azoxy, or α,β-unsaturated ketone group.[12-16] The structure–activity relationships, especially the effect of alkyl substitutions are very similar in the two types of aromatic amides and also resemble that of azobenzenecarboxylic acids (X = —N=N— in **4**) or stilbenecarboxylic acids (X = —C=C— in **4**).[16] The results and the activities of hybrid compounds derived from Am80 (or Am580) and retinoic acid indicated that retinobenzoic acids including amide compounds and retinoic acid are agonists with respect to each other. This is also supported by the fact that some retinobenzoic acids have the same activities as retinoic acid in various assays. (5) Methyl substitution at the amide N atom of Am80 and Am580 always diminished the activity. From the spectroscopic studies, this can be attributed to the differences of conformation. The highly active secondary amides, Am80 and Am580, have trans amide bonds. On the other hand, nearly inactive tertiary amides, Am90 and Am590, have cis amide bonds. This large difference of amide conformation results in a change of the whole molecular structure and especially of the distance between the two essential groups for the activity, the *m*-alkyl group and the *p*-carboxyl group. The intervening group X, though it can be varied, must have a role in locating the two essential groups at the proper positions. The diminished activities resulting from ortho substitution are also explained by this notion. The bulky groups at the ortho position would cause distortion of the amide bond torsion angle or a change of the stereochemistry of the single bond adjacent to the amide bond (s-cis or s-trans structure of Ar–CO or Ar–NH), leading to a significant change of the molecular structure. Taking into account the discussion under (2) above, the most important factors for the activity are the orientation and the distance between the dimethyl group on the benzylic carbon and the carboxylic acid. Elucidation of the critical three-dimensional structure is in progress.

Thus, the activities of the retinoidal amides are strictly related to their structures. This result indicates that the action of retinobenzoic acids or retinoids is very specific and results from binding to a specific receptor(s). At present, the identity of the true retinoid-binding protein (receptor) is not clear[2] (though some candidates have been proposed[7,29,30]) and the mechanism of action is not understood, though it should be related to fundamental biological phenomena. Since Am80 and Am580 are chemically more stable to light, heat, oxidation, etc., and more easily prepared than retinoic acid derivatives, they should be powerful tools for the isolation of specific receptor(s)[7] and the elucidation of retinoidal action.

Furthermore, the chemical and physical characteristics of the amide compounds are very different from those of retinoic acid or other conventional retinoids so far known. One disadvantage of conventional retinoids from the

(28) Hashimoto, Y.; Kagechika, H.; Kawachi, E.; Shudo, K. *Chem. Pharm. Bull.* **1987**, *35*, 3190.

(29) (a) Petkovich, M.; Brand, N. J.; Krust, A.; Chambon, P. *Nature (London)* **1987**, *330*, 444. (b) Brand, N.; Petkovich, M.; Krust, A.; Chambon, P.; de The, H.; Marchio, A.; Tiollais, P.; Dejean, A. *Nature (London)* **1988**, *332*, 850.

(30) Giguere, V.; Ong, E. S.; Segui, P.; Evans, R. M. *Nature (London)* **1987**, *330*, 624.

clinical viewpoint is their strong toxicity, which may be partially caused by their high hydrophobicity. The new retinoidal amides are definitely more polar and should exhibit quite different pharmacokinetic behavior. In fact, clearance from animals is faster (data not shown). Am80 and Am580, having potent retinoidal activities and different chemical properties from conventional retinoids, may well prove to be clinically useful in the fields of dermatology and oncology.

Experimental Section

Cells and Culture. The human promyelocytic leukemia cells HL-60 were supplied by Prof. F. Takaku (Faculty of Medicine, University of Tokyo) and have been maintained in continuous suspension culture. The cells are cultured in plastic flasks in RPMI1640, supplemented with 5% fetal calf serum (FCS) and antibiotics (penicillin G and streptomycin), in a humidified atmosphere of 5% CO_2 in air at 37 °C.

Test compounds were dissolved in ethanol at 0.2 mM and added to the cells (about 8×10^4 cells/mL), while the final ethanol concentration was kept at less than 0.5%. Control cells were given the same volume of ethanol. A positive control, retinoic acid, was always assayed at the same time. The cells were incubated for 4 days and stained with Wright-Giemsa. Differential counts were then performed under a light microscope on a minimum of 200 cells. Nitroblue tetrazolium (NBT) reduction was assayed as described.[25] Cells were incubated for 20 min at 37 °C in RPMI1640 medium (5% FCS) and an equal volume of phosphate-buffered saline (PBS) containing NBT (0.2%) and 12-*O*-tetradecanoylphorbol 13-acetate (TPA; 200 ng/mL). The percentage of cells containing blue-black formazan was determined on a minimum of 200 cells. The results of these two evaluations were always in good agreement.

The assays of test compounds were performed at least three times. ED_{50} values of active compounds were calculated from the NBT reduction assay data. Relative activities were calculated as the ratio of ED_{50} of the test compound to ED_{50} of retinoic acid obtained in concurrent experiments.

General Procedure for Terephthalic Anilides. Terephthalic acid monomethyl ester chloride (1 mmol) was added to a solution of (alkyl-substituted) aniline (1 mmol) in dry benzene (20 mL) and pyridine (1 mL) and stirred at room temperature over several hours. Then the mixture was poured into water and extracted with AcOEt. The organic layer was washed successively with 2 N HCl, H_2O, 1 N $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$. After evaporation, the crude mixture was purified by silica gel column chromatography or recrystallization to give terephthalanilic acid methyl ester. The ester was hydrolyzed with 2 N NaOH (10 equiv) in EtOH at room temperature. The mixture was acidified with 2 NHCl and then extracted with AcOEt. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. After the removal of the solvent, the crude product was recrystallized to give terephthalic monoanilide.

4-[(3-Isopropylphenyl)carbamoyl]benzoic Acid (Am32). Condensation of *m*-isopropylaniline and terephthalic acid monomethyl ester chloride gave methyl 4-[(3-isopropylphenyl)carbamoyl]benzoate (Am33), which was hydrolyzed to Am32 (80.8%). *m*-Isopropylaniline was prepared from isopropylbenzene (38%) by means of the Goralski reaction.[31] Am33: colorless flakes (from CH_2Cl_2–*n*-hexane); mp 104–106 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, 6 H, J = 7 Hz), 2.94 (hep, 1 H, J = 7 Hz), 3.97 (s, 3 H), 7.06 (d, 1 H, J = 7.5 Hz), 7.31 (t, 1 H, J = 7.5 Hz), 7.45–7.55 (m, 2 H), 7.80 (br s, 1 H), 7.94 (d, 2 H, J = 8 Hz), 8.16 (d, 2 H, J = 8 Hz). Anal. ($C_{18}H_{19}NO_3$) C, H, N. Am32: colorless prisms (from AcOEt–*n*-hexane), mp 103–105 °C; ^1H NMR (100 MHz, $CDCl_3$–DMSO-d_6) δ 1.28 (d, 6 H, J = 8 Hz), 2.92 (hep, 2 H, J = 8 Hz), 7.00 (d, 1 H, J = 7 Hz), 7.27 (t, 1 H, J = 7 Hz), 7.5–7.7 (m, 2 H), 7.99 (d, 2 H, J = 8.5 Hz), 8.14 (d, 2 H, J = 8.5 Hz), 9.18 (br s, 1 H). Anal. ($C_{17}H_{17}NO_3$) C, H, N.

4-[(2,4,6-Tri-*tert*-butylphenyl)carbamoyl]benzoic Acid (Am45). Terephthalic acid monomethyl ester chloride (400 mg, 2 mmol) was added to a solution of 2,4,6-tri-*tert*-butylaniline (261 mg, 1 mmol) and a catalytic amount of 4-dimethylaminopyridine in 6 mL of pyridine, and the mixture was stirred at 130 °C for 5 h and then at room temperature overnight. After the removal of the solvent, the residue was diluted with AcOEt. The organic layer was washed successively with 2 N HCl (three times), 1 N $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$. After evaporation, the crude product was purified by silica gel column chromatography to give methyl 4-[(2,4,6-tri-*tert*-butylphenyl)carbamoyl]benzoate (Am146), which was hydrolyzed to Am45. Am46: colorless prisms (from CH_2Cl_2–*n*-hexane), mp >300 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 1.34 (s, 9 H), 1.41 (s, 18 H), 3.97 (s, 3 H), 7.44 (s, 2 H), 7.46 (br s, 1 H), 7.96 (d, 2 H, J = 8 Hz), 8.17 (d, 2 H, J = 8 Hz). Anal. ($C_{27}H_{37}NO_3$) C, H, N. Am45: colorless prisms (from CH_3OH–benzene); ^1H NMR (100 MHz, CD_3OD) δ 1.34 (s, 9 H), 1.41 (s, 18 H), 7.49 (s, 2 H), 8.06 (d, 2 H, J = 8 Hz), 8.18 (d, 2 H, J = 8 Hz); MS, M^+ 409.

4-[(3,5-Di-*tert*-butylphenyl)carbamoyl]benzoic Acid (Am55). Condensation of 3,5-di-*tert*-butylaniline and terephthalic acid monomethyl ester chloride gave methyl 4-[(3,5-di-*tert*-butylphenyl)carbamoyl]benzoate (Am56, 87.2%), which was hydrolyzed to Am55 (86.3%). 3,5-Di-*tert*-butylaniline was prepared from *p*-di-*tert*-butylbenzene, as follows. A mixture of *p*-di-*tert*-butylbenzene (10 g, 52.6 mmol) and AcCl (4.2 g, 53.5 mmol) in 100 mL of dry $ClCH_2CH_2Cl$ was added to the suspension of $AlCl_3$ (8 g, 60.2 mmol) in 150 mL of dry $ClCH_2CH_2Cl$ at 0 °C and was stirred for 1.5 h. The mixture was poured into ice water and extracted with CH_2Cl_2. The organic layer was washed successively with H_2O, 1 N $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$. After evaporation, the crude mixture was separated by silica gel column chromatography to give 2,5-di-*tert*-butylacetophenone (23.4%), 3,5-di-*tert*-butylacetophenone (20.8%), and *p*-*tert*-butylacetophenone (23.1%). 3,5-Di-*tert*-butylacetophenone (170 mg, 0.73 mmol) and H_2NOH·HCl (70 mg, 1 mmol) were dissolved in 3 mL of EtOH and 0.5 mL of pyridine and then refluxed for 30 min. After concentration, the residue was diluted with CH_2Cl_2. The organic layer was washed successively with H_2O, 2 N HCl, H_2O, 1 N $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$. After evaporation, the crude oxime (106 mg, 58.6%) was obtained. To a solution of this oxime (66 mg, 0.27 mmol) in 3 mL of dry ether, 0.03 mL of $SOCl_2$ (0.42 mmol) was added dropwise at −10 °C. After 1 h, the mixture was poured into H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated to give 3,5-di-*tert*-butylacetanilide (45 mg, 68.2%), which was hydrolyzed to give 3,5-di-*tert*-butylaniline. 3,5-Di-*tert*-butylacetoanilide: colorless prisms (from CH_2Cl_2–*n*-hexane); ^1H NMR (100 MHz, $CDCl_3$) δ 1.30 (s, 18 H), 2.16 (s, 3 H), 7.16 (t, 1 H, J = 2 Hz), 7.33 (d, 2 H, J = 2 Hz), 7.12 (br s, 1 H). Am56: colorless needles (from CH_2Cl_2–*n*-hexane), mp 215.5–216 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 1.34 (s, 18 H), 3.97 (s, 3 H), 7.24 (t, 1 H, J = 2 Hz), 7.49 (d, 2 H, J = 2 Hz), 7.80 (br s, 1 H), 7.92 (d, 2 H, J = 8 Hz), 8.14 (d, 2 H, J = 8 Hz). Anal. ($C_{23}H_{29}NO_3$) C, H, N. Am55: colorless flakes (from AcOEt–*n*-hexane), mp 271–272 °C; ^1H NMR (100 MHz, CD_3OD) δ 1.36 (s, 18 H), 7.25 (t, 1 H, J = 2 Hz), 7.59 (d, 2 H, J = 2 Hz), 7.98 (d, 2 H, J = 8.5 Hz), 8.14 (d, 2 H, J = 8.5 Hz). Anal. ($C_{22}H_{27}NO_3$) C, H, N.

4-[(3,4-Diisopropylphenyl)carbamoyl]benzoic Acid (Am68). Condensation of 3,4-diisopropylaniline and terephthalic acid monomethyl ester chloride gave methyl 4-[(3,4-diisopropylphenyl)carbamoyl]benzoate (Am69, 61.6%), which was hydrolyzed to Am68 (75.3%). 3,4-Diisopropylaniline was prepared from o-diisopropylbenzene by nitration (HNO_3–H_2SO_4 in AcOH, 81.6%) followed by catalytic hydrogenation (10% Pd–C in EtOH, 83.0%). 3,4-diisopropylnitrobenzene: pale yellow oil; ^1H NMR (100 MHz, $CDCl_3$) δ 1.20 (d, 6 H, J = 7 Hz), 1.29 (d, 6 H, J = 7 Hz), 3.33 (hep, 2 H, J = 7 Hz), 7.38 (d, 1 H, J = 8.5 Hz), 7.99 (dd, 1 H, J = 2, 8.5 Hz), 8.10 (d, 1 H, J = 2 Hz). 3,4-Diisopropylaniline: pale colored needles; ^1H NMR (100 MHz, $CDCl_3$) δ 1.37 (d, 12 H, J = 7 Hz), 3.31 (hep, 2 H, J = 7 Hz), 3.74 (br s, 2 H), 6.70 (dd, 1 H, J = 2, 8 Hz), 6.76 (d, 1 H, J = 2 Hz), 7.20 (d, 1 H, J = 8 Hz). Am69: colorless flakes (from CH_2Cl_2–*n*-hexane), mp 137.5–138 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, 6 H, J = 7 Hz), 1.26 (d, 6 H, J = 7 Hz), 3.25 (hep, 1 H, J = 7 Hz), 3.29 (hep, 1 H, J = 7 Hz), 3.96 (s, 3 H), 7.27 (d, 1 H, J = 8.5 Hz), 7.45 (d, 1 H, J = 2 Hz), 7.50 (dd, 1 H, J = 2, 8.5 Hz), 7.77 (br s,

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1 H), 7.93 (d, 2 H, J = 8.5 Hz), 8.15 (d, 2 H, J = 8.5 Hz); IR (KBr) 1660, 1715 cm^{-1}. Anal. ($C_{21}H_{25}NO_3$) C, H, N. Am68: colorless needles (from AcOEt–n-hexane), mp 220.5–221.5 °C; ^1H NMR (100 MHz, $CDCl_3$–DMSO-d_6) δ 1.25 (d, 6 H, J = 7 Hz), 1.27 (d, 6 H, J = 7 Hz), 3.25 (hep, 1 H, J = 7 Hz), 3.29 (hep, 1 H, J = 7 Hz), 7.23 (d, 1 H, J = 9 Hz), 7.59 (d, 1 H, J = 2 Hz), 7.60 (dd, 1 H, J = 2, 9 Hz), 8.00 (d, 2 H, J = 9 Hz), 8.13 (d, 2 H, J = 9 Hz), 9.34 (br s, 1 H); IR (KBr) 1650, 1679 cm^{-1}. Anal. ($C_{20}H_{23}NO_3$) C, H, N.

4-[(4,4-Dimethyl-6-chromanyl)carbamoyl]benzoic Acid (Am70). Condensaton of 6-amino-4,4-dimethylchromane and terephthalic acid monomethyl ester chloride gave methyl 4-[(4,4-dimethyl-6-chromanyl)carbamoyl]benzoate (Am71, 85.8%), which was hydrolyzed to Am70 (99.3%). 6-Amino-4,4-dimethylchromane was prepared as follows. A solution of 3 mL of HNO_3 in 9 mL of Ac_2O was added to a solution of 4,4-dimethylchromane[32] (64.35 g) in 8 mL of Ac_2O at 0 °C over 10 min, and the mixture was stirred for 50 min. The mixture was poured into 200 mL of saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. After evaporation, the crude mixture was purified by silica gel column chromatography to give 4,4-dimethyl-6-nitrochromane (2.81 g, 50.5%) and 4,4-dimethyl-8-nitrochromane (2.00 g, 36.0%). 4,4-Dimethyl-6-nitrochromane was hydrogenated to 6-amino-4,4-dimethylchromane as usual (10% Pd–C in EtOH, 48.0%). 4,4-Dimethyl-6-nitrochromane: pale yellow prisms (from n-hexane), mp 76.5–77 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 1.39 (s, 6 H), 1.87 (t, 2 H, J = 6 Hz), 4.28 (t, 2 H, J = 6 Hz), 6.82 (d, 1 H, J = 10 Hz), 7.96 (dd, 1 H, J = 3, 10 Hz), 8.19 (d, 1 H, J = 3 Hz). 6-Amino-4,4-dimethylchromane: pale brown oil; ^1H NMR (100 MHz, $CDCl_3$) δ 1.31 (s, 6 H), 1.82 (t, 2 H, J = 6 Hz), 3.14 (br s, 2 H), 4.06 (t, 2 H, J = 6 Hz), 6.3–6.65 (m, 3 H). Am71: pale yellow needles (from benzene–n-hexane), mp 129–130 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 1.35 (s, 6 H), 1.84 (t, 2 H, J = 5 Hz), 3.95 (s, 3 H), 4.20 (t, 2 H, J = 5 Hz), 6.77 (d, 1 H, J = 9 Hz), 7.24 (dd, 1 H, J = 2, 9 Hz), 7.59 (d, 1 H, J = 2 Hz), 7.89 (d, 2 H, J = 9 Hz), 7.92 (br s, 1 H), 8.11 (d, 2 H, J = 9 Hz); IR (Kbr) 1675, 1715 cm^{-1}. Anal. ($C_{20}H_{21}NO_4$) C, H, N. Am70: pale yellow prisms (from AcOEt–n-hexane), mp 230.5–231.5 °C; ^1H NMR (100 MHz, $CDCl_3$–DMSO-d_6) δ 1.35 (s, 6 H), 1.84 (t, 2 H, J = 5 Hz), 4.17 (t, 2 H, J = 5 Hz), 6.73 (d, 1 H, J = 9 Hz), 7.38 (dd, 1 H, J = 3, 9 Hz), 7.69 (d, 1 H, J = 3 Hz), 7.97 (d, 2 H, J = 9 Hz), 8.11 (d, 2 H, J = 9 Hz), 9.32 (br s, 1 H); IR (KBr) 1675, 1720 cm^{-1}. Anal. ($C_{19}H_{19}NO_4 \cdot {}^2/_3H_2O$) C, H, N.

4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic Acid (Am80). 2,5-Dimethyl-2,5-hexanediol (50 g, 0.34 mol) was added to 400 mL of concentrated HCl at 0 °C with vigorous stirring, and HCl gas was passed through this solution for 15 min. The precipitates were collected and dissolved in CH_2Cl_2. The organic layer was washed with H_2O until the aqueous layer showed pH ca. 7 and dried over $MgSO_4$. The solvent was removed to leave 2,5-dichloro-2,5-dimethylhexane, which was placed in a sealed tube (highly volatile). A mixture of 2,5-dichloro-2,5-dimethylhexane (27 g, 0.15 mol) and $AlCl_3$ (2.0 g, 14 mmol) in 600 mL of dry benzene was reflexed for 24 h and then poured into 1 L of ice-cooled 1 N HCl. The organic layer was washed successively with H_2O, 1 N Na_2CO_3, H_2O, and brine and dried over $MgSO_4$. After the removal of the solvent, the residue was distilled under vacuum to give 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (22.7 g, 81.9%). A mixture of 2.5 mL of HNO_3 and 4 mL of H_2SO_4 was added to 1,2,3,4-tetrahydro-1,1.4,4-tetramethylnaphthalene (5.305 g, 28.17 mmol) at −10 °C. After 1 h the mixture was poured into ice water and extracted with CH_2Cl_2. The organic layer was washed 1 N NaOH, H_2O, and brine and dried over $MgSO_4$. After evaporation, the crude product was recrystallized to give 1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-nitronaphthalene (49.9%). This nitro compound was hydrogenated by the usual method (10% Pd–C in EtOH, 48.0%). Condensation of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine and terephthalic acid monomethyl ester chloride gave methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)caramoyl]benzoate (Am81, 86.7%), which was hydrolyzed to Am80. 1,2,3,4-Tetrahydro-1,1,4,4-tetramethyl-6-nitronaphthalene: colorless flakes (from CH_3OH), mp 71–72 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 1.30 (s, 6 H), 1.32 (s, 6 H), 1.57 (s, 4 H), 7.41 (d, 1 H, J = 8 Hz), 7.94 (dd, 1 H, J = 2, 8 Hz), 8.15 (d, 1 H, J = 2 Hz). Anal. ($C_{14}H_{19}NO_2$) C, H, N. 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine: colorless needles (from n-hexane), mp 72–73 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 1.23 (s, 6 H), 1.25 (s, 6 H), 1.64 (s, 4 H), 2.6–3.2 (br s, 2 H), 6.51 (dd, 1 H, J = 3, 8 Hz), 6.62 (d, 1 H, J = 3 Hz), 7.07 (d, 1 H, J = 8 Hz). Anal. ($C_{14}H_{21}N$) C, H, N. Am81: colorless needles (from CH_2Cl_2–n-hexane), mp 211–212 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 1.29 (s, 6 H), 1.31 (s, 6 H), 1.72 (s, 4 H), 3.95 (s, 3 H), 7.29 (d, 1 H, J = 8 Hz), 7.46 (dd, 1 H, J = 2, 8 Hz), 7.64 (d, 1 H, J = 2 Hz), 8.00 (d, 2 H, J = 8 Hz), 8.13 (d, 2 H, J = 8 Hz); IR (KBr) 1640, 1715 cm^{-1}. Anal. ($C_{23}H_{27}NO_3 \cdot {}^1/_8H_2O$) C, H, N. Am80: colorless prisms (from AcOEt–n-hexane), mp 231–232 °C; ^1H NMR (100 MHz, CD_3OD) δ 1.28 (s, 6 H), 1.30 (s, 6 H), 1.71 (s, 4 H), 7.29 (d, 1 H, J = 8 Hz), 7.46 (dd, 1 H, J = 2, 8 Hz), 7.63 (d, 1 H, J = 2 Hz), 8.00 (d, 2 H, J = 8 Hz), 8.12 (d, 2 H, J = 8 Hz); IR (KBr) 1645, 1690 cm^{-1}. Anal. ($C_{22}H_{25}NO_3$) C, H, N.

4-[Methyl(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic Acid (Am90). NaH (60%; 30 mg, 0.75 mmol) was washed twice with 1 mL of n-hexane and suspended in 2 mL of dry DMF. A solution of Am80 (100 mg, 0.28 mmol) in 2 mL of dry DMF was added to this suspension at room temperature, and the mixture was stirred for 30 min. To this yellow solution was added 0.5 mL (large excess) of CH_3I. After 30 min, the solvent and excess CH_3I were removed under vacuum. The residue was diluted with AcOEt, washed with H_2O, and dried over $MgSO_4$. After evaporation, the crude product was purified by silica gel column chromatography to give methyl 4-[methyl-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoate (Am91, 83.3%), which was hydrolyzed to Am90 as usual. Am91: colorless prisms (from CH_2Cl_2–n-hexane), mp 117–118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 6 H), 1.21 (s, 6 H), 1.55–1.60 (m, 4 H), 3.49 (s, 3 H), 3.86 (s, 3 H), 6.72 (br s, 1 H), 6.89 (dd, 1 H, J = 2.5, 8.5 Hz), 7.19 (d, 1 H, J = 8.5 Hz), 7.31 (d, 2 H, J = 8 Hz), 7.81 (d, 2 H, J = 8 Hz); IR (KBr) 1625, 1720 cm^{-1}. Anal. ($C_{24}H_{29}NO_3$) C, H, N. Am90: colorless flakes (from AcOEt–n-hexane), mp 217–219 °C; ^1H NMR (100 MHz, CD_3OD) δ 0.98 (s, 6 H), 1.21 (s, 6 H), 1.60 (s, 4 H), 3.48 (s, 3 H), 6.82 (d, 1 H, J = 2 Hz), 7.01 (dd, 1 H, J = 2, 8 Hz), 7.27 (d, 1 H, J = 8 Hz), 7.32 (d, 2 H, J = 8 Hz), 7.81 (d, 2 H, J = 8 Hz); IR (KBr) 1635, 1685 cm^{-1}. Anal. ($C_{23}H_{27}NO_3$) C, H, N. C, H, N.

4-[(5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)carbamoyl]benzoic Acid (Am100). $AlCl_3$ (300 mg, 2.25 mmol) was added portionwise to a solution of 2,5-dichloro-2,5-dimethylhexane (5.0 g, 27.3 mmol; see the section on Am80) in 15 mL of dry toluene at 0 °C. After 1 h, the dark solution was poured into ice water and then extracted with ether. The organic layer was washed successively with H_2O, 1 N Na_2CO_3, H_2O, and brine and dried over $MgSO_4$. After the removal of the solvent, the crude product was distilled to give 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene (4.44 g, 80.4%). 5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylamine was prepared from this hydrocarbon by nitration (HNO_3–H_2SO_4 in AcOH) followed by catalytic hydrogenation (10% Pd–C in EtOH, 62.1%). Condensation of 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylamine and terephthalic acid monomethyl ester chloride gave methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)carbamoyl]benzoate (Am101), which was hydrolyzed to Am100. 1,2,3,4-Tetrahydro-1,1,4,4,6-pentamethylnaphthalene: colorless prisms (from CH_3OH), mp 33.5–34 °C; bp_4 88–90 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 1.30 (s, 12 H), 1.71 (s, 4 H), 2.30 (s, 3 H), 6.8–7.3 (m, 3 H). 1,2,3,4-Tetrahydro-1,1,4,4,6-pentamethyl-7-nitronaphthalene: colorless leaflets (from EtOH), mp 150.5–152 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 1.30 (s, 12 H), 1.71 (s, 4 H), 2.56 (s, 3 H), 7.19 (s, 1 H), 7.93 (s, 1 H). Am101: colorless needles (from CH_2Cl_2–n-hexane), mp 175.5–176 °C. Anal. ($C_{24}H_{29}NO_3$) C, H, N. Am100: colorless needles (from AcOEt–n-hexane), mp 258–259 °C; ^1H NMR (400 MHz, CD_3OD) δ 1.27 (s, 6 H), 1.28 (s, 6 H), 1.71 (s, 4 H), 2.24 (s, 3 H), 7.23 (s, 1 H), 7.26 (s, 1 H), 8.04 (d, 2 H, J = 8 Hz), 8.15 (d, 2 H, J = 8 Hz). Anal. ($C_{23}H_{29}NO_3$) C, H, N.

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4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-nitro-2-naphthalenyl)carbamoyl]benzoic Acid (Am110). To a solution of Am80 (60 mg, 0.17 mmol) in 6 mL of trifluoromethanesulfonic acid (TFSA) was added KNO_3 (18 mg, 0.18 mmol) at 0 °C. After 15 min, the mixture was poured into ice water and extracted with AcOEt. The organic layer was washed with H_2O until the aqueous layer showed pH ca. 7 and dried over $MgSO_4$. The solvent was removed to give Am110 (qy). Am110: yellow needles (from AcOEt–*n*-hexane), mp 265–266 °C; ^1H NMR (400 MHz, CD_3OD) δ 1.35 (s, 6 H), 1.36 (s, 6 H), 1.78 (s, 4 H), 8.06 (d, 2 H, J = 8 Hz), 8.15 (s, 1 H), 8.18 (d, 2 H, J = 8 Hz), 8.39 (s, 1 H). Anal. ($C_{22}H_{24}N_2O_5$) C, H, N.

4-[(3-Amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic Acid (Am114). Am110 was hydrogenated on 10% Pd–C in EtOH by the usual method to give Am114. Am114: colorless prisms (from AcOEt–CH_3OH), mp 268–269 °C; ^1H NMR (400 MHz, CD_3OD) δ 1.32 (s, 6 H), 1.34 (s, 6 H), 1.77 (s, 4 H), 7.42 (s, 1 H), 7.43 (s, 1 H), 8.13 (d, 2 H, J = 8.5 Hz), 8.17 (d, 2 H, J = 8.5 Hz).

4-[(3-Bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic Acid (Am118). A mixture of 2,5-dichloro-2,5-dimethylhexane (2.0 g, 10.9 mmol; see the section on Am80) and $AlCl_3$ (160 mg, 1.20 mmol) in 5.7 mL of dry bromobenzene was heated at 60–70 °C for 3 h. The dark solution was poured into ice water and extracted with CH_2Cl_2. The organic layer was washed successively with H_2O, 1 N Na_2CO_3, H_2O, and brine and dried over $MgSO_4$. After the removal of the solvent, the residue was distilled under vacuum to give 6-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (1.4 g, 48.3%). This bromide (2.15 g, 8.04 mmol) was added portionwise to a solution of KNO_3 (800 mg, 7.92 mmol) in 20 mL of concentrated H_2SO_4 at 0 °C. The mixture was stirred for 2 h and then poured into ice water and extracted with CH_2Cl_2. The organic layer was washed successively with H_2O, 1 N $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$. After evaporation, the crude product was purified by silica gel column chromatography to give 6-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-7-nitronaphthalene (16.3%), 6-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-5,7-dinitronaphthalene (11.2%), 1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6,7-dinitronaphthalene (7.9%), and starting material (50.2%). Fe (300 mg, 5.45 mmol) was added to a solution of 6-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-7-nitronaphthalene (323 mg, 1.04 mmol) in 10 mL of AcOH, and the mixture was heated at 100 °C for 2 h. After filtration, the AcOH solution was diluted with CH_2Cl_2 and H_2O. The organic layer was washed with 2 N NaOH, H_2O, and brine and dried over $MgSO_4$. After evaporation, the crude product was purified by silica gel column chromatography to give 6-amino-7-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (160 mg, 54.8%). Condensation of this amine and terephthalic acid monomethyl ester chloride gave methyl 4-[(3-bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoate (Am119, 81.3%), which was hydrolyzed to Am118. 6-Bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene: colorless oil; bp_3 120–123 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 1.25 (s, 12 H), 1.67 (s, 4 H), 7.1–7.5 (m, 3 H). 6-Bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-7-nitronaphthalene: colorless plates (from *n*-hexane), mp 167.5–168 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 1.29 (s, 12 H), 1.70 (s, 4 H), 7.58 (s, 1 H), 7.80 (s, 1 H). Anal. ($C_{10}H_{18}BrNO_2$) C, H, N. 6-Amino-7-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene: pale brown solid; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 6 H), 1.23 (s, 6 H), 1.63 (s, 4 H), 3.4–4.2 (br s, 2 H), 6.70 (s, 1 H), 7.30 (s, 1 H). Am119: colorless needles (from CH_3OH); ^1H NMR (60 MHz, $CDCl_3$) δ 1.26 (s, 6 H), 1.33 (s, 6 H), 1.68 (s, 4 H), 3.91 (s, 3 H), 7.37 (s, 1 H), 7.86 (d, 2 H, J = 9 Hz), 8.08 (d, 2 H, J = 9 Hz), 8.26 (s, 1 H), 8.37 (s, 1 H). Am118: colorless needles (from AcOEt–*n*-hexane), mp 251.5–252 °C; ^1H NMR (400 MHz, CD_3OD) δ 1.29 (s, 6 H), 1.30 (s, 6 H), 1.72 (s, 4 H), 7.59 (s, 1 H), 7.64 (s, 1 H), 8.05 (d, 2 H, J = 8 Hz), 8.15 (d, 2 H, J = 8 Hz). Anal. $C_{22}H_{24}BrNO_3$) C, H, N.

4-[(5,8-Ethano-5,6,7,8-tetrahydro-5,8-dimethyl-2-naphthalenyl)carbamoyl]benzoic Acid (Am150). 1,4-Dimethylcyclohexane (50 g, 0.45 mol) and *tert*-butyl chloride (163 g, 1.76 mol) were dissolved in 200 mL of CH_2Cl_2. $AlCl_3$ (1.56 g) was added to this solution at 0 °C, and after 20 min, 4.66 g of $AlCl_3$ (total 46.8 mmol) was added. After a further 20 min, the mixture was diluted with CH_2Cl_2 and H_2O. The organic layer was washed with H_2O until the aqueous layer showed pH ca. 7 and dried over $MgSO_4$. After the removal of the solvent, the residue was distilled under vacuum to give 1,4-dichloro-1,4-dimethylcyclohexane (9.5 g, 11.7%). This dichloride (6.22 g, 34.3 mmol) was dissolved in 137 mL of dry benzene. $AlCl_3$ (0.45 g, 3.38 mmol) was added to this solution, and the mixture was refluxed for 24 h. The mixture was poured into ice water. The organic layer was washed successively with H_2O, 1 N Na_2CO_3, H_2O, and brine and dried over $MgSO_4$. After the removal of the solvent, the residue was distilled to give 1,4-ethano-1,2,3,4-tetrahydro-1,4-dimethylnaphthalene (3.86 g, 60.4%). 1,4-Ethano-1,2,3,4-tetrahydro-1,4-dimethylnaphthalene was nitrated by HNO_3–H_2SO_4 in CH_3NO_2 (reflux, 3 h, 86.5%) and then hydrogenated on 10% Pd–C in EtOH (84.2%) as usual to give 5,8-ethano-5,6,7,8-tetrahydro-5,8-dimethyl-2-naphthylamine. Condensation of this amine and terephthalic acid monomethyl ester chloride gave methyl 4-[(5,8-ethano-5,6,7,8-tetrahydro-5,8-dimethyl-2-naphthalenyl)carbamoyl]benzoate (Am151, 50%), which was hydrolyzed to Am150 (45.8%). 1,4-Ethano-1,2,3,4-tetrahydro-1,4-dimethylnaphthalene: colorless oil; bp_6 111–115 °C. 1,4-Ethano-1,2,3,4-tetrahydro-1,4-dimethyl-6-nitronaphthalene: colorless prisms (from CH_3OH), mp 61.5–62 °C. Anal. ($C_{14}H_{17}NO_2$) C, H, N. Am151: colorless prisms (from CH_2Cl_2–*n*-hexane), mp 187–188 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 1.2–1.8 (m, 14 H), 3.98 (s, 3 H), 7.20 (d, 1 H, J = 2 Hz), 7.30 (dd, 1 H, J = 2, 8 Hz), 7.50 (d, 1 H, J = 8 Hz), 7.81 (br s, 1 H), 7.91 (d, 2 H, J = 9 Hz), 8.15 (d, 2 H, J = 9 Hz). Anal. ($C_{23}H_{25}NO_3$) C, H, N. Am150: colorless prisms (from AcOEt–*n*-hexane), mp 225 °C; ^1H NMR (100 MHz, DMSO-d_6) δ 1.2–1.7 (m, 14 H), 7.20 (d, 1 H, J = 2 Hz), 7.30 (dd, 1 H, J = 2, 8 Hz), 7.40 (d, 1 H, J = 8 Hz), 7.80 (br s, 1 H), 8.00 (d, 2 H, J = 9 Hz), 8.20 (d, 2 H, J = 9 Hz). Anal. ($C_{22}H_{23}NO_3$) C, H, N.

General Procedure for (Arylcarboxamido)benzoic Acids. Alkyl-substituted benzoic acid (1 mmol) was dissolved in 5 mL of $SOCl_2$ with one drop of DMF at 0 °C and stirred for 30 min. The $SOCl_2$ was removed under vacuum, and the crude acid chloride was dissolved in 10 mL of pyridine. Methyl *p*-aminobenzoate (1.1 mmol) and a catalytic amount of 4-(dimethylamino)pyridine were added to this solution, and the mixture was heated at 60 °C for 2 h. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed successively with 2 N HCl (twice), 1 N $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$. After evaporation, the crude product was purified to give methyl (arylcarboxamido)benzoate. This ester was hydrolyzed to the acid by a usual method (aqueous NaOH/EtOH).

4-[(3,5-Di-*tert*-butylphenyl)carboxamido]benzoic Acid (Am555). Condensation of 3,5-di-*tert*-butylbenzoic acid and methyl *p*-aminobenzoate gave methyl 4-[(3,5-di-*tert*-butylphenyl)carboxamido]benzoate (Am556, 63.2%), which was hydrolyzed to Am555 (76.7%). 3,5-Di-*tert*-butylbenzoic acid was prepared from 3,5-di-*tert*-butylacetophenone by means of the haloform reaction.[33] Am556: colorless needles (from CH_2Cl_2–*n*-hexane); ^1H NMR (100 MHz, $CDCl_3$) δ 1.37 (s, 18 H), 3.92 (s, 3 H), 7.66 (br s, 3 H), 7.74 (d, 2 H, J = 8.5 Hz), 7.90 (br s, 1 H), 8.06 (d, 2 H, J = 8.5 Hz). Anal. ($C_{23}H_{29}NO_3$) C, H, N. Am555 colorless prisms (from AcOEt–*n*-hexane), mp 267–268 °C; ^1H NMR (100 MHz, CD_3OD) δ 1.39 (s, 18 H), 7.68 (t, 1 H, J = 2 Hz), 7.79 (d, 2 H, J = 2 Hz), 7.84 (d, 2 H, J = 8 Hz), 8.02 (d, 2 H, J = 8 Hz). Anal. ($C_{22}H_{27}NO_3$) C, H, N.

4-[(4,4-Dimethyl-6-chromanyl)carboxamido]benzoic Acid (Am570). Methyl 4-[(8-chloro-4,4-dimethyl-6-chromanyl)-carboxamido]benzoate (300 mg, 0.8 mmol; Am573, see the section of Am572) and AcONa (329 mg, 4 mmol) were dissolved in 30 mL of AcOH and hydrogenated on 10% Pd–C (600 mg) for 4.5 h. After filtration and dilution (60 mL of H_2O), it was basified by adding 1 N $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. The crude product was purified by recrystallization to give methyl 4-[(4,4-dimethyl-6-chromanyl)carboxamido]benzoate (Am571, 96.0%), which was hydrolyzed to Am570 (96.0%). Am571: colorless prisms (from benzene–*n*-hexane), mp 172 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 1.39 (s, 6 H), 1.88 (t, 2 H, J = 6 Hz), 3.92 (s, 3 H), 4.26 (t, 2 H,

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J = 6 Hz), 6.84 (d, 1 H, J = 3 Hz), 7.91 (br s, 1 H), 8.05 (d, 2 H, J = 8.5 Hz); IR (KBr) 1670, 1695 cm^{-1}. Anal. ($C_{20}H_{21}NO_4 \cdot {}^1/_8H_2O$) C, H, N. Am570: colorless needles (from AcOEt–*n*-hexane), mp 243–245 °C; ^{1}H NMR (100 MHz, CD_3OD) δ 1.40 (s, 6 H), 1.87 (t, 2 H, J = 5 Hz), 4.26 (t, 2 H, J = 5 Hz), 6.82 (d, 1 H, J = 8 Hz), 7.68 (dd, 1 H, J = 3, 8 Hz), 7.80 (d, 2 H, J = 8 Hz), 7.97 (d, 1 H, J = 3 Hz), 8.00 (d, 2 H, J = 8 Hz); IR (KBr) 1655, 1680 cm^{-1}. Anal. ($C_{19}H_{19}NO_4$) C, H, N.

4-[(8-Chloro-4,4-dimethyl-6-chromanyl)carboxamido]benzoic Acid (Am572). Condensation of 8-chloro-4,4-dimethylchromane-6-carboxylic acid and methyl *p*-aminobenzoate gave methyl 4-[(8-chloro-4,4-dimethyl-6-chromanyl)carboxamido]benzoate (Am573, 66.0%), which was hydrolyzed to Am572 (qy). 8-Chloro-4,4-dimethylchromane-6-carboxylic acid was prepared from 4,4-dimethylchroman-6-yl methyl ketone[32] by means of the haloform reaction[33] (58%). 8-Chloro-4,4-dimethylchlomane-6-carboxylic acid: colorless needles (from AcOEt–*n*-hexane), mp 218–219 °C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.36 (s, 6 H), 1.88 (t, 2 H, J = 5.5 Hz), 4.35 (t, 2 H, J = 5.5 Hz), 7.80 (d, 1 H, J = 2 Hz), 7.89 (d, 1 H, J = 2 Hz), 7.91 (br s, 1 H); IR (KBr) 1670 cm^{-1}. Anal. ($C_{12}H_{13}ClO_3$) C, H, N. Am573: colorless prisms (from benzene–*n*-hexane), mp 175 °C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.40 (s, 6 H), 1.91 (t, 2 H, J = 6 Hz), 3.92 (s, 3 H), 4.40 (t, 2 H, J = 6 Hz), 7.64 (d, 1 H, J = 2.5 Hz), 7.70 (d, 2 H, J = 9 Hz), 7.79 (d, 1 H, J = 2.5 Hz), 7.82 (br s, 1 H), 8.05 (d, 2 H, J = 9 Hz); IR (KBr) 1655, 1710 cm^{-1}. Anal. ($C_{20}H_{20}ClNO_4 \cdot {}^1/_4H_2O$) C, H, N. Am572: colorless needles (from AcOEt–*n*-hexane), mp 275–276 °C; ^{1}H NMR (100 MHz, CD_3OD) δ 1.41 (s, 6 H), 1.91 (t, 2 H, J = 5 Hz), 4.36 (t, 2 H, J = 5 Hz), 7.78 (d, 2 H, J = 8.5 Hz), 7.82 (d, 1 H, J = 3 Hz), 7.92 (d, 1 H, J = 3 Hz), 7.99 (d, 2 H, J = 8.5 Hz); IR (KBr) 1660, 1690 cm^{-1}. Anal. ($C_{19}H_{18}ClNO_4$) C, H, N.

4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic Acid (Am580). Condensation of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoic acid and methyl *p*-aminobenzoate gave methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoate (Am581, 96.6%), which was hydrolyzed to Am580 (77.2%). 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthoic acid was prepared from 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene by acetylation ($AcCl/AlCl_3/ClCH_2CH_2Cl$, 80.4%) followed by haloform reaction[33] (84.5%). 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthoic acid: colorless needles (from CH_2Cl_2–*n*-hexane), mp 177–179.5 °C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.30 (s, 6 H), 1.32 (s, 6 H), 1.72 (s, 4 H), 7.38 (d, 1 H, J = 8 Hz), 7.81 (dd, 1 H, J = 2, 8 Hz), 8.05 (d, 1 H, J = 2 Hz). Anal. ($C_{15}H_{20}O_2$) C, H, N. Am581: colorless needles (from CH_2Cl_2–*n*-hexane), mp 206–207 °C; ^{1}H NMR (100 MHz, CD_3OD) δ 1.32 (s, 6 H), 1.36 (s, 6 H), 1.76 (s, 4 H), 3.90 (s, 3 H), 7.45 (d, 1 H, J = 9 Hz), 7.68 (dd, 1 H, J = 2, 9 Hz), 7.84 (d, 2 H, J = 9 Hz), 7.92 (d, 1 H, J = 2 Hz), 8.00 (d, 2 H, J = 9 Hz); IR (KBr) 1653, 1710 cm^{-1}. Anal. ($C_{23}H_{27}NO_3$) C, H, N. Am580: colorless needles (from AcOEt–*n*-hexane), mp 265–267 °C; ^{1}H NMR (100 MHz, CD_3OD) δ 1.33 (s, 6 H), 1.36 (s, 6 H), 1.76 (s, 4 H), 7.47 (d, 1 H, J = 8 Hz), 7.70 (dd, 1 H, J = 2, 8 Hz), 7.84 (d, 2 H, J = 8.5 Hz), 7.94 (d, 1 H, J = 2 Hz), 8.02 (d, 2 H, J = 8.5 Hz); IR (KBr) 1655, 1678 cm^{-1}. Anal. ($C_{22}H_{25}NO_3$) C, H, N.

4-[Methyl(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic Acid (Am590). N-Methylation of Am580, as described in the section on Am90, gave methyl 4-[methyl(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoate (Am591, 90.8%), which was hydrolyzed to Am590 (85.8%). Am591: colorless prisms (from CH_2Cl_2–*n*-hexane), mp 148.5–150 °C; ^{1}H NMR (100 MHz, CD_3OD) δ 0.96 (s, 6 H), 1.21 (s, 6 H), 1.60 (s, 4 H), 3.51 (s, 3 H), 3.87 (s, 3 H), 7.0–7.3 (m, 3 H), 7.22 (d, 2 H, J = 8.5 Hz), 7.90 (d, 2 H, J = 8.5 Hz); IR (KBr) 1636, 1710 cm^{-1}. Am590: colorless needles (from AcOEt–*n*-hexane), mp 249.5–250 °C; ^{1}H NMR (100 MHz, CD_3OD) δ 0.96 (s, 6 H), 1.21 (s, 6 H), 1.60 (s, 4 H), 3.51 (s, 3 H), 7.12 (d, 2 H, J = 8.5 Hz), 7.2–7.3 (m, 3 H), 7.90 (d, 2 H, J = 8.5 Hz); IR (KBr) 1615, 1724 cm^{-1}. Anal. ($C_{23}H_{27}NO_3$) C, H, N.

Muconic Acid Mono(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)amide (M2). Condensation of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine and muconic acid monomethyl ester chloride gave the methyl ester of M2 (M1, 79.2%), which was hydrolyzed to M2 (qy), according to the general method for terephthalic anilides. M1: pale yellow flakes (from CH_2Cl_2–*n*-hexane), mp 203.5–205 °C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.28 (s, 6 H), 1.29 (s, 6 H), 1.69 (s, 4 H), 3.80 (s, 3 H), 6.0–6.5 (m, 2 H), 7.1–7.6 (m, 5 H); IR (KBr) 1675, 1720 cm^{-1}. Anal. ($C_{20}H_{25}NO_3 \cdot {}^1/_8H_2O$), C, H, N. M2: pale yellow prisms (from AcOEt–*n*-hexane), mp 249–251.5 °C; ^{1}H NMR (100 MHz, CD_3OD) δ 1.26 (s, 6 H), 1.28 (s, 6 H), 1.71 (s, 4 H), 6.0–6.6 (m, 2 H), 7.1–7.7 (m, 5 H). Anal. ($C_{19}H_{23}NO_3 \cdot {}^1/_8H_2O$) C, H, N.

Fumaric Acid Mono(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)amide (F2). Condensation of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine and fumaric acid

Table VII

code name	mp, °C	crystal form	solvent	formula
Am00	>300	colorless prisms	AcOEt–*n*-hexane	$C_{14}H_{11}NO_3$
Am10	288–289	colorless prisms	AcOEt–*n*-hexane	$C_{15}H_{13}NO_3$
Am20	259.5–260.5	colorless needles	AcOEt–*n*-hexane	$C_{18}H_{19}NO_3 \cdot {}^1/_8H_2O$
Am25	280–281	colorless flakes	AcOEt–CH_3OH	$C_{16}H_{15}NO_3$
Am30	>300	colorless needles	EtOH–AcOEt	$C_{17}H_{17}NO_3$
Am34	269.5–271	colorless needles	AcOEt–*n*-hexane	$C_{17}H_{17}NO_3$
Am38	250–251	pale brown leaflets	AcOEt–*n*-hexane	$C_{16}H_{16}N_2O_3$
Am40	201–202	colorless prisms	AcOEt–CH_3OH	$C_{18}H_{19}NO_3$
Am50	293–294	colorless prisms	CH_3OH–benzene	$C_{18}H_{19}NO_3$
Am60	>300	colorless needles	AcOEt–*n*-hexane	$C_{20}H_{23}NO_3 \cdot {}^1/_4H_2O$
Am62	230–231.5	colorless flakes	AcOEt–*n*-hexane	$C_{20}H_{23}NO_3$
Am64	244.5–246	colorless prisms	AcOEt–*n*-hexane	$C_{20}H_{23}NO_3 \cdot {}^1/_4H_2O$
Am66	256.5–258.5	colorless needles	AcOEt–*n*-hexane	$C_{20}H_{23}NO_3$
Am75	214–215	colorless prisms	AcOEt–*n*-hexane	$C_{19}H_{19}NO_3S$
Am96	182–183	colorless prisms	AcOEt–*n*-hexane	$C_{25}H_{31}NO_3$
Am120	297–298	colorless prisms	AcOEt–*n*-hexane	$C_{22}H_{25}NO_3$
Am140	>300	colorless prisms	AcOEt	$C_{20}H_{19}NO_3$
Am160	>300	colorless prisms	AcOEt–*n*-hexane	$C_{20}H_{15}NO_3$
Am162	237–237.5	colorless flakes	AcOEt–*n*-hexane	$C_{20}H_{21}NO_3$
Am170	>300	colorless prisms	EtOH–AcOEt	$C_{18}H_{13}NO_3 \cdot {}^1/_8H_2O$
Am172	>300	pale brown flakes	EtOH–AcOEt	$C_{18}H_{13}NO_3$
Am174	303–303.5	colorless needles	AcOEt–*n*-hexane	$C_{18}H_{17}NO_3$
Am250	281.5–282.5	colorless prisms	AcOEt–*n*-hexane	$C_{15}H_{10}F_3NO_3$
Am252	>300	colorless prisms	AcOEt–*n*-hexane	$C_{14}H_{10}BrNO_3$
Am254	>300	colorless prisms	AcOEt–*n*-hexane	$C_{19}H_9Cl_2NO_3$
Am500	295–296	colorless needles	AcOEt–*n*-hexane	$C_{14}H_{11}NO_3 \cdot {}^1/_8H_2O$
Am540	233–234	colorless prisms	AcOEt–*n*-hexane	$C_{18}H_{19}NO_3$
Am550	270–271	colorless flakes	AcOEt–*n*-hexane	$C_{18}H_{19}NO_3$
Am568	227–228	colorless prisms	CH_3OH	$C_{20}H_{23}NO_3 \cdot {}^1/_4H_2O$
Am577	293–294	colorless needles	AcOEt–*n*-hexane	$C_{19}H_{19}NO_5S$
Am586	213.5–214.5	colorless prisms	AcOEt–*n*-hexane	$C_{22}H_{25}NO_3$

monoethyl ester chloride gave the ethyl ester of F2 (F1, 80.2%), which was hydrolyzed to F2 (84.3%). F1: colorless flakes (from CH_2Cl_2–*n*-hexane), mp 147–148.5 °C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.27 (s, 6 H), 1.29 (s, 6 H), 1.33 (t, 3 H, J = 7 Hz), 1.68 (s, 4 H), 4.28 (q, 2 H, J = 7 Hz), 6.92 (d, 1 H, J = 16 Hz), 7.07 (d, 1 H, J = 16 Hz), 7.26 (d, 1 H, J = 9 Hz), 7.38 (dd, 1 H, J = 2, 9 Hz), 7.49 (d, 1 H, J = 2 Hz); IR (KBr) 1679, 1710 cm^{-1}. Anal. ($C_{20}H_{27}NO_3$) C, H, N. F2: colorless prisms (from AcOEt–*n*-hexane), mp 236.5–237 °C; ^{1}H NMR (100 MHz, $CDCl_3$–DMSO-d_6) δ 1.27 (s, 6 H), 1.29 (s, 6 H), 1.68 (s, 4 H), 6.84 (d, 1 H, J = 15 Hz), 7.21 (d, 1 H, J = 15 Hz), 7.23 (d, 1 H, J = 8 Hz), 7.45 (dd, 1 H, J = 2, 8 Hz), 7.67 (d, 1 H, J = 2 Hz). Anal. ($C_{18}H_{23}NO_3$) C, H, N.

4-[[2-(2,6,6-Trimethylcyclohexenyl)ethylene]carboxamido]benzoic Acid (R2). Condensation of β-cyclocitrylideneacetic acid chloride and methyl *p*-aminobenzoate gave methyl 4-[[2-(2,6,6-trimethylcyclohexenyl)ethylene]carboxamido]benzoate (R1, 87.8%), which was hydrolzyed to R2 (90%), according to the general method for (arylcarboxamido)benzoic acids. R1: colorless oil; ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.09 (s, 6 H), 1.3–1.7 (m, 4 H), 1.78 (s, 3 H), 1.9–2.1 (m, 2 H), 3.91 (s, 3 H), 5.93 (d, 1 H, J = 16 Hz), 7.51 (d, 1 H, J = 16 Hz), 7.69 (d, 2 H, J = 8 Hz), 8.00 (d, 2 H, J = 8 Hz). R2: colorless prisms (from AcOEt–*n*-hexane), mp 235–237 °C; ^{1}H NMR (100 MHz, CD_3OD) δ 1.13 (s, 6 H), 1.4–1.8 (m, 4 H), 1.84 (s, 3 H), 1.9–2.2 (m, 2 H), 6.16 (d, 1 H, J = 15 Hz), 7.26 (d, 1 H, J = 15 Hz), 7.74 (d, 2 H, J = 8.5 Hz), 7.98 (d, 2 H, J = 8.5 Hz). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

Other Compounds. Other compounds were prepared according to the general procedures in conventional ways. Their melting points and solvents for recrystallization are summarized in Table VII.

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Registry No. Am00, 16777-78-9; Am10, 116232-85-0; Am20, 102121-10-8; Am25, 116232-86-1; Am30, 102121-11-9; Am32, 102121-12-0; Am33, 102121-13-1; Am34, 102121-14-2; Am38, 116232-87-2; Am40, 102121-16-4; Am45, 116232-88-3; Am46, 116233-11-5; Am50, 116232-89-4; Am55, 116232-90-7; Am56, 116233-12-6; Am60, 102121-17-5; Am62, 102121-19-7; Am64, 102121-21-1; Am66, 102121-23-3; Am68, 102121-25-5; Am69, 102121-26-6; Am70, 109140-02-5; Am71, 109140-01-4; Am75, 109140-05-8; Am80, 94497-51-5; Am81, 94497-53-7; Am90, 110383-33-0; Am91, 102121-51-7; Am96, 116232-91-8; Am100, 116232-92-9; Am101, 116263-41-3; Am110, 116232-93-0; Am114, 116232-94-1; Am118, 116232-95-2; Am119, 116233-21-7; Am120, 116232-96-3; Am140, 116232-97-4; Am150, 116232-98-5; Am151, 116233-24-0; Am160, 116232-99-6; Am162, 102121-27-7; Am170, 116233-00-2; Am172, 116233-01-3; Am174, 116233-02-4; Am250, 116233-03-5; Am252, 116233-04-6; Am254, 116233-05-7; Am500, 582-80-9; Am540, 104182-35-6; Am550, 116233-06-8; Am555, 104182-40-3; Am556, 116233-25-1; Am568, 104182-41-4; Am570, 116233-07-9; Am571, 116233-27-3; Am572, 116233-08-0; Am573, 116233-26-2; Am577, 116233-09-1; Am580, 102121-60-8; Am581, 102121-59-5; Am586, 116233-10-4; Am590, 116193-58-9; Am591, 116233-28-4; F1, 116233-31-9; F2, 104182-38-9; M1, 116233-29-5; M2, 116233-30-8; R1, 116233-33-1; R2, 116233-32-0; *m*-isopropylaniline, 5369-16-4; terephthalic acid monomethyl ester chloride, 7377-26-6; 2,4,6-tri-*tert*-butylaniline, 961-38-6; 3,5-di-*tert*-butylaniline, 2380-36-1; *p*-di-*tert*-butylbenzene, 1012-72-2; 2,5-di-*tert*-butylacetophenone, 2040-08-6; 3,5-di-*tert*-butylacetophenone, 1756-31-6; *p*-*tert*-butylacetophenone, 943-27-1; 3,5-di-*tert*-butylacetophenone oxime, 101449-10-9; 3,5-di-*tert*-butylacetoanilide, 37055-54-2; 3,4-diisopropylaniline, 116233-13-7; o-diisopropylbenzene, 577-55-9; 3,4-diisopropylnitrobenzene, 116233-14-8; 6-amino-4,4-dimethylchromane, 109139-99-3; 4,4-dimethylchromane, 40614-27-5; 4,4-dimethyl-6-nitrochromane, 109139-98-2; 4,4-dimethyl-8-nitrochromane, 116233-15-9; 2,5-dimethyl-2,5-hexanediol, 110-03-2; 2,5-dichloro-2,5-dimethylhexane, 6223-78-5; 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene, 6683-46-1; 1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-nitronaphthalene, 102121-55-1; 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine, 92050-16-3; 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethylnaphthalene, 6683-48-3; 1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl-7-nitronaphthalene, 116233-16-0; 5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthylamine, 116233-17-1; bromobenzene, 108-86-1; 6-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene, 27452-17-1; 6-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-7-nitronaphthalene, 116233-18-2; 6-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-5,7-dinitronaphthalene, 116233-19-3; 1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6,7-dinitronaphthalene, 81864-04-2; 1,4-dimethylcyclohexane, 589-90-2; 1,4-dichloro-1,4-dimethylcyclohexane, 35951-37-2; 1,4-ethano-1,2,3,4-tetrahydro-1,4-dimethylnaphthalene, 67060-31-5; 1,4-ethano-1,2,3,4-tetrahydro-1,4-dimethyl-6-nitronaphthalene, 116233-22-8; 8-chloro-4,4-dimethylchromane-6-carboxylic acid, 109140-12-7; 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoic acid, 103031-30-7; fumaric acid monoethyl ester chloride, 26367-48-6; β-cyclocitrylideneacetic acid chloride, 69258-08-8; 3,5-di-*tert*-butylbenzoic acid, 16225-26-6; methyl *p*-aminobenzoate, 619-45-4; 6-amino-7-bromo-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene, 116233-20-6; 5,8-ethano-5,6,7,8-tetrahydro-5,8-dimethyl-2-naphthylamine, 116233-23-9; 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylacetate, 17610-21-8; muconic acid monomethyl ester chloride, 41967-17-3.