Articles

Novel Naphthalene Derivatives as Inhibitors of Human Immunoglobulin E Antibody Production†

Masaichi Hasegawa,* Kazuya Takenouchi, Katsushi Takahashi, Takahiro Takeuchi, Keiji Komoriya, Yasuhide Uejima, and Takashi Kamimura

Teijin Institute for Bio-Medical Research, 4-3-2 Asahigaoka, Hino, Tokyo 191, Japan

Received July 11, 1996⊗

A series of naphthalene derivatives with a variety of substituents at the 2-position was prepared in order to evaluate their suppressive effect on immunoglobulin E (IgE) antibody production by human peripheral blood mononuclear cells provoked with anti-CD40 antibody (α-CD40), interleukin-4 (IL-4), and interleukin-10 (IL-10). Compounds having a 1,4-phenylene spacer moiety tethered between the 2-naphthyl nucleus and anthranilic acid suppressed IgE antibody production *in vitro* in preference to that of IgG antibody without affecting cell viability. Deletion of the anthranilic acid moiety diminished the inhibitory activities. Changing the 2-naphthyl to a 1-naphthyl or phenyl nucleus led to no change in the potency, indicating that the aromatic group at this position is indispensable for the inhibitory activities. On the other hand, changing the 1,4-phenylene spacer to a 1,3-phenylene one resulted in reduced potency. Similarly, inhibitory activities were lost when the CO_2H moiety at the 2-position was moved to the 3- or 4-position on the terminal benzene. These observations suggest that the conformation around the anthranilic acid moiety affects the inhibitory activities toward IgE biosynthesis. 2-(4-(2-Naphthyloxy)benzamido)benzoic acid (**29**) seemed to be a more potent inhibitor of IgE production than of IgG production. Insertion of a methylene between the inter-phenylene and the amide moiety resulted in 2-((4-(2-naphthyloxy)phenyl)acetamido)benzoic acid (**31**), which provided a stronger inhibition of both IgE and IgG production, although the selectivity toward IgE was lower than that of **29**. Introduction of a benzyl group at the 6-position on the naphthalene ring considerably increased the inhibitory activity toward IgE production with an IC_{50} of 8.3 nM (**36**). The potency of **31** and **36** was retained when hydrocortisone or lipopolysaccharide was used instead of α-CD40 and IL-10 as costimulatory factors with IL-4, implying that these compounds may interfere with signal transduction between IL-4/IL-4 receptor cognition and genetic transcription that induce class-switching of immunoglobulin in B cells. These novel naphthalene derivatives are thus excellent candidates for further investigation with a view toward a therapeutic remedy against IgE-mediated allergic diseases.

Introduction

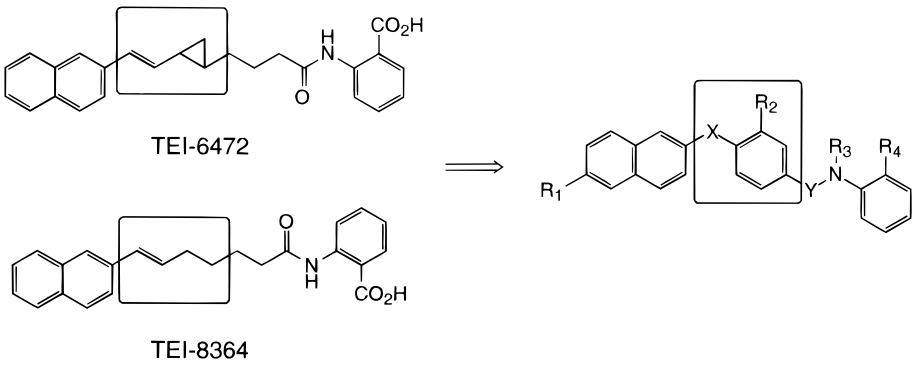
Allergies in humans are characterized by the appearance in serum and tissues of the immunoglobulin E isotype (IgE) directed toward specific environmental antigens.[1] Binding of antigens to specific IgE on mast cells or basophiles leads to the cross-linking of IgE receptors, resulting in cell activation and degranulation for the release of inflammatory mediators such as platelet-activating factor (PAF), leukotrienes, and histamine.[2] These mediators contribute to bronchoconstriction and recruitment of inflammatory cells such as leukocytes and lymphocytes. IgE-mediated allergic diseases, called atopy, include allergic rhinitis, ophthalmia, asthma, dermatitis, drug and food allergy, anaphylaxis, and hyper-IgE syndrome. The suppression of undesirable IgE-mediated inflammation and immune reactions is believed to be useful for treatment of atopic disorders. Although there are many antiallergic remedies such as histamine antagonists and mast cell stabilizers available on the market at present, they are not very effective against allergic disorders because they are unable to prevent immunization against an allergenic antigen. Recent research on suppressive agents of IgE biosynthesis has gained much attention because such agents may prevent immunization against the allergen.[1c] IgE production by mature B cells is regulated by various cytokines and adhesion molecules.[3] Soluble interleukin-4 (IL-4) receptor,[4] an IL-4 mutant protein,[5] interleukin-12 (IL-12),[6] interferon-γ (IFN-γ),[7] anti-lymphocyte function-associated antigen-1 (LFA-1) antibody,[8] anti-CD23 antibody,[9] interleukin-8 (IL-8),[10] and soluble IgE receptor[11] are known to suppress IgE production *in vitro* and/or *in vivo*. Surprisingly, anti-IgE antibodies down-regulate IgE biosynthesis by inducing apotosis in the B cells.[12] These agents are not, however, regarded as promising orally active ones owing to their polypeptide structure. Splatast, a low molecular weight antiallergic agent, was reported to suppress murine IgE production *in vitro* and *in vivo*.[13] It was reported to suppress IgE production by 56% at 2 μM in human B cells cultured with an antigen-specific T cell line. Nevertheless, the clinical effect of splatast on IgE

† A part of this study was presented at the AFMC International Medicinal Chemistry Symposium 95, Tokyo, Japan, Sept. 3−8, 1995 (PIT052), and at the AAAA&I (American Academy of Allergy, Asthma, and Immunology) International Conference, New York, NY, Feb. 24−March 1, 1995 (A345 and A346).

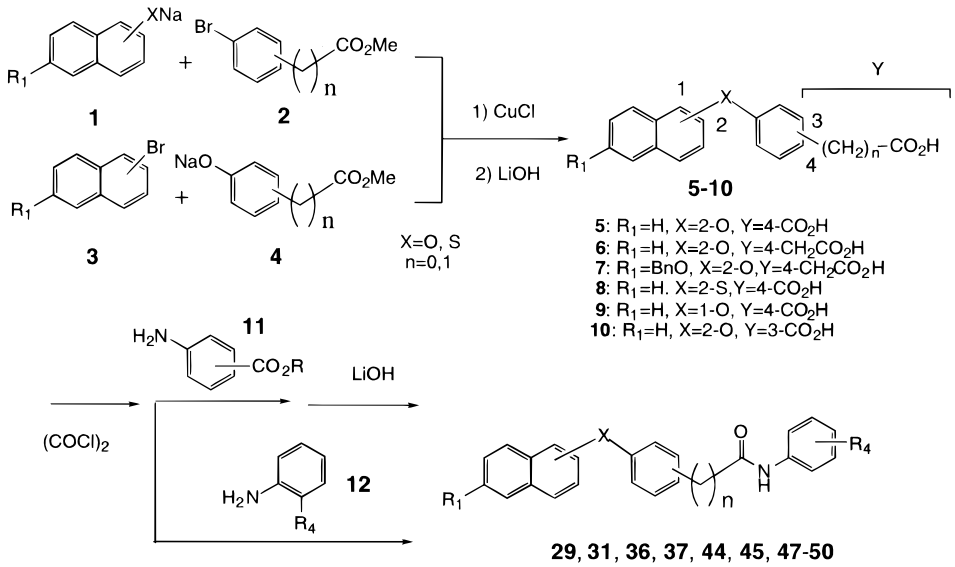
⊗ Abstract published in *Advance ACS Abstracts,* February 1, 1997.

S0022-2623(96)00504-3 CCC: $14.00

Scheme 1



Scheme 2



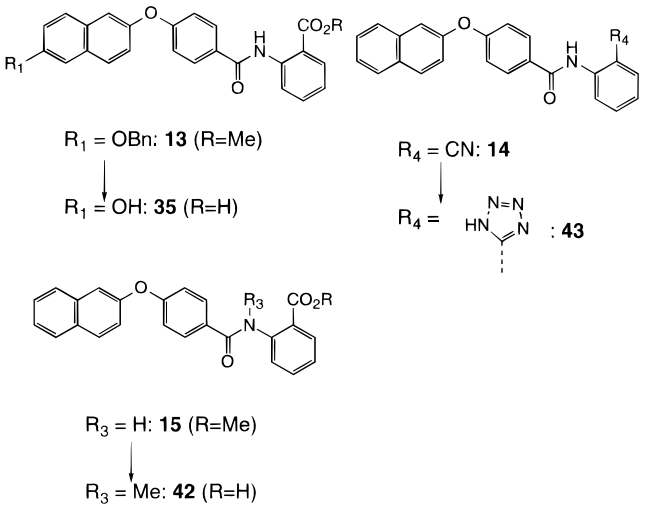
production seems obscure. It was also reported that disodium cromoglycate (DSCG) and its derivatives suppressed IgE biosynthesis *in vitro*.[14] Prostaglandin E_2 was reported to inhibit IL-4-induced IgE production in human peripheral blood mononuclear cells (PBMC),[7b] whereas it stimulated IgE production by murine splenocytes or B cells.[15] Hence, there are no orally active agents that are recognized to suppress the IgE level suitable for clinical use.

We previously demonstrated that (7*E*)-*N*-(2-carboxyphenyl)-8-(2-naphthyl)-5,6-*trans*-methano-7-octenamide L-lysine salt (TEI-6472), which was first discovered as an inhibitor of leukotriene biosynthesis, showed a suppressive effect on IgE antibody production by trinitrophenol (TNP)−keyhole limpet hemocyanin (KLH)-primed murine spleen cells.[16] Since the effect of TEI-6472 on IgE production was not considered to be optimal, we became interested in the structure−activity relationship (SAR) of a series of its analogues. However, the cyclopropane moiety impeded the accessible synthesis of analogues. Therefore, we opted for designing a new class of inhibitors of IgE production that had no cyclopropane moiety. Replacement of cyclopropane with simple methylene afforded TEI-8364, which showed IgE preferential inhibition of antibody biosynthesis in PBMC and tonsillar B cells, both stimulated with IL-4, IL-10,[17] and anti-CD40 antibody (α-CD40).[3d,18] However, the optimal effective dose was found to be more than 1 μM. In order to find a promising candidate for a human IgE-suppressive agent, we decided to change the ene-cyclopropane moiety of TEI-6472 into an inter-phenylene one, considering the homology of molecular rigidity (Scheme 1). This change in drug design was also favorable in view of the feasibility of preparing diverse new compounds. Here we report (1) the discovery of novel low molecular weight inhibitors of IgE production by PBMC provoked with α-CD40, IL-4, and IL-10 and (2) the first SAR studies on the inhibition of IgE biosynthesis.

Chemistry

Naphthalene derivatives were generally prepared as follows (Scheme 2): Sodium naphthoxide or naphthalenethiolate (**1**) was coupled with methyl bromobenzoate or methyl bromophenylacetate (**2**) with copper(I) chloride[19] followed by hydrolysis to give carboxylic acids **5**−**10**. The same reaction using naphthyl bromide derivative **3** and sodium phenoxide derivative **4** also afforded **5**−**10**. After the conversion of **5**−**10** to acyl chloride with $(COCl)_2$, condensation of the corresponding acyl chlorides with aniline derivative **12** provided amides **44** and **45**. When R was methyl in **11**, the products were treated with LiOH to give acids **29**, **31**, **36**, **37**, and **47**−**50** ($R_4 = CO_2H$). Compound **46**, having a benzene moiety instead of the naphthalene ring, was also prepared by the same procedure using sodium phenoxide instead of sodium naphthoxide. As shown in Scheme 3, benzyl ether **13** was hydrogenated followed by hydrolysis to give **35**. Nitrile **14** was converted to tetrazole derivative **43** with NaN_3 and NH_4Cl. Com-

Scheme 3



pound **42** was obtained from **15** by methylation with MeI and NaI followed by hydrolysis.

Scheme 4 shows the reactions for the preparation of **30**, **34**, **40**, **41**, and **51**: Sodium naphthoxide (**16**) and ethyl 3-(4-bromophenyl)cinnamate were condensed with CuCl followed by hydrogenation and hydrolysis to yield **17**, which was converted to **34** in the same manner as in Scheme 2. An attempt was made to invert the order of the amide moiety. Compound **16** was coupled with 4-nitrophenyl bromide and then hydrogenated over Pd/C to give 4-(2-naphthyloxy)aniline (**18**). Condensation of **18** and phthalic anhydride yielded **51**. Compound **16** and methyl 4-(bromomethyl)benzoate were condensed in alkali media without CuCl followed by hydrolysis to give **19**. Similar reaction of methyl 4-chloro-3-nitrobenzoate with **16** led to **20** in good yield because of the electron-attracting effect of NO_2. Compounds **19** and **20** were treated with methyl anthranilate followed by hydrolysis in the same manner as in Scheme 2 to provide **30** and **40**, respectively. Reduction of **5** with $LiAlH_4$ gave alcohol, which was converted to bromide **21** with CBr_4 and trioctylphosphine[20] and then coupled with methyl anthranilate with K_2CO_3 and NaI followed by hydrolysis to yield benzylamine derivative **41**.

As indicated in Scheme 5, methyl 4-(2-naphthyloxy)-phenylacetate (**22**) was alkylated with MeI and lithium diisopropylamide (LDA) followed by hydrolysis to afford **23**. Further methylation was accomplished by the reaction of the methyl ester of **23** with MeI and LDA followed by hydrolysis to yield **24**. Compounds **23** and **24** were then converted to **32** and **33**, respectively, as described above.

2-Naphthylmagnesium bromide[21] from **25** reacted with methyl 4-formylbenzoate to yield carbinol derivative **26**. Oxidation of **26** with pyridinium chlorochromate (PCC), followed by hydrolysis, gave ketone **27**. Reduction of **26** with triethylsilane in trifluoroacetic acid (TFA),[22] followed by hydrolysis, resulted in the formation of **28**. Condensation of **27** and **28** with methyl anthranilate followed by hydrolysis as described above afforded **39** and **38**, respectively (Scheme 6). Table 1 lists the analytical data of the major compounds **29**−**45**.

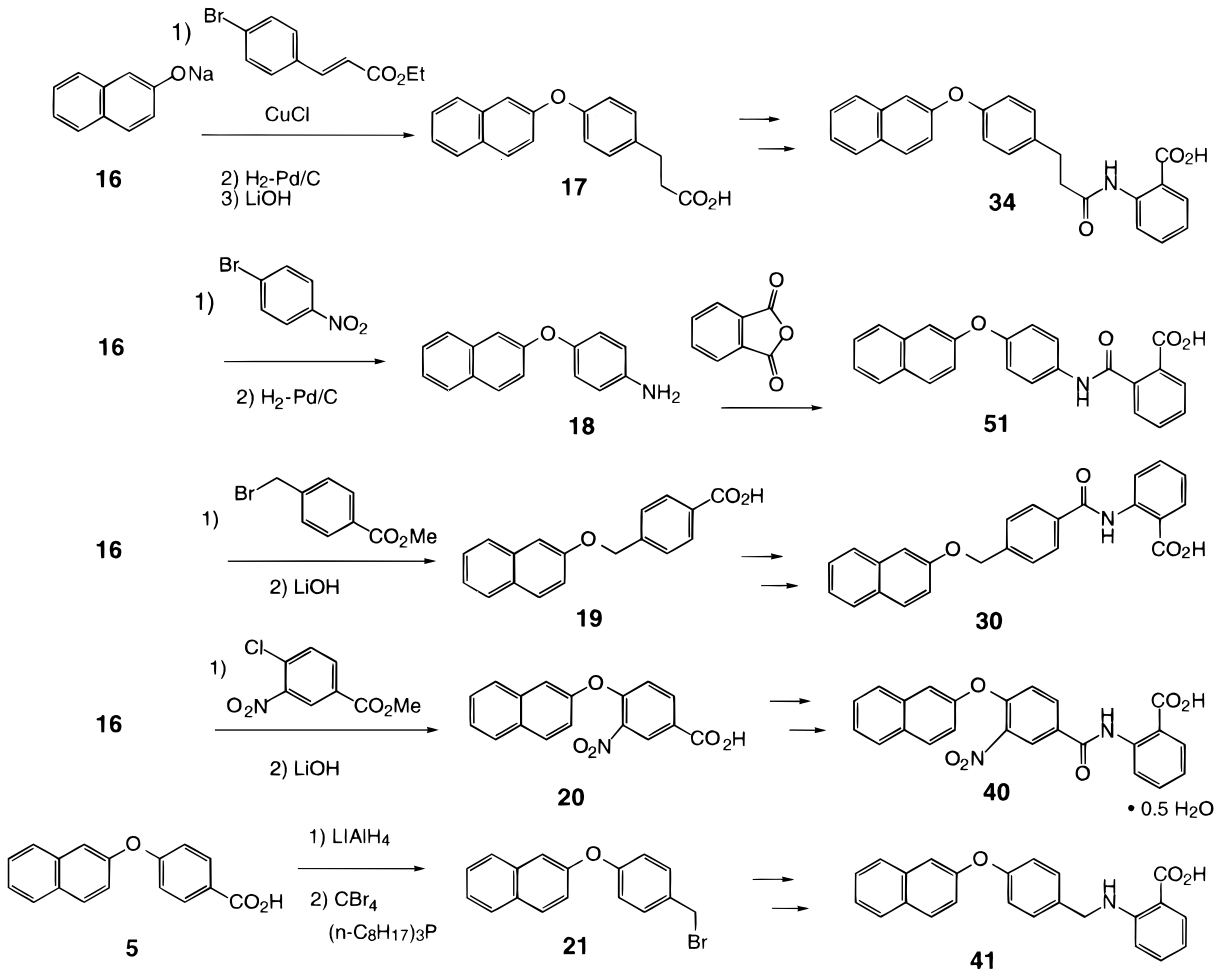
Results and Discussion

All the synthesized compounds were evaluated for *in vitro* inhibition of total IgE and IgG production by, and for their effect on the viability of, human PBMC. PBMC from healthy donors were cultured with α-CD40, IL-4, and IL-10 with or without the test compounds for 2 weeks.[18] IgE and IgG levels were determined by enzyme-linked immunosorbent assay (ELISA). Suppression (%) was calculated by the following mathematical equation: (level without compound − level with compound)/level without compound × 100. The results are summarized in Table 2, where they are expressed as suppression (%) of IgE production, IgG production, and cell viability by each compound tested at 3 μM. In these columns, a negative number of suppression (%) means enhancement of antibody biosynthesis or cell viability. The IC_{50} (μM) is also given for highly active compounds. For determination of cell viability, the alamar blue assay was performed as described in the instruction manual provided by the manufacturer. This assay includes an oxidation−reduction indicator that both fluoresces and changes color in response to chemical reduction of alamar blue resulting from cell growth and is generally used, like the MTT assay, to measure relative cytotoxicity of various compounds. Continued cell growth causes the redox indicator to change from the oxidized (nonfluorescent, blue) form to the reduced (fluorescent, red) form because cell growth maintains a reduced environment while inhibition of cell growth maintains an oxidized environment.

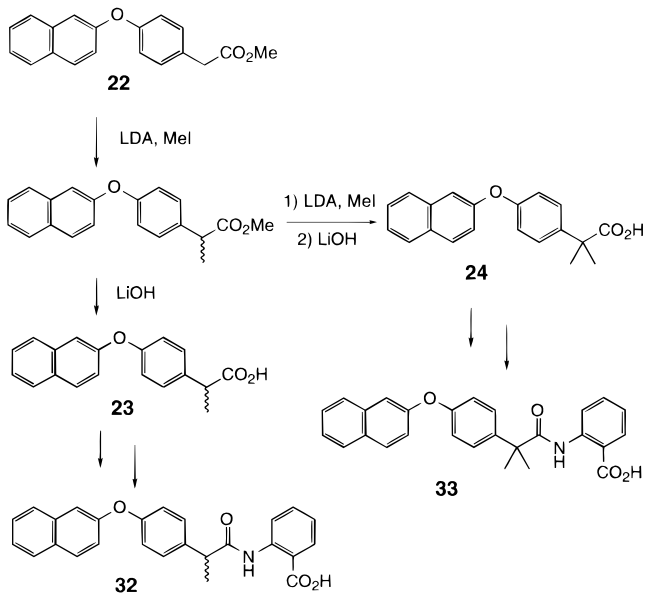
Table 2 lists the inhibitory activities of **29**−**45** toward IgE and IgG production and their effects on viability. Suppression of IgE production caused by the lead compound TEI-6472 was strong, with an IC_{50} of 1.9 μM toward PBMC, similar to the result found with TNP-KLH-primed mouse splenocytes.[16] The inhibition of immunoglobulin production was IgE selective in view of the minimal effect on the IgG. An attempt to alter the vinyl and cyclopropane moiety of TEI-6472 to 1,4-phenylene was successful from the results of 2-(4-(2-naphthyloxy)benzamido)benzoic acid (**29**) and 2-((4-(2-naphthyloxy)phenyl)acetamido)benzoic acid (**31**). Compound **29** seems to be a potent inhibitor of IgE production, with an IC_{50} of 1.3 μM, in preference to IgG production. The presence of a 3 μM concentration of **29** in the culture did not affect the cell viability. Insertion of the methylene between the inter-phenylene and the amide moiety resulted in **31**, which was found to be a 3 times more potent inhibitor of IgE ($IC_{50} = 0.6$ μM) than TEI-6472; however, it also suppressed IgG production ($IC_{50} = 4.3$ μM). It is quite interesting that the transfer of the methylene in **31** to the para position (**30**) eliminated the potency. Further extension of molecular size by insertion of an additional methylene moiety to give **34** diminished the activity. These results indicate that both the distance between naphthalene and anthranilic acid and the relative conformation of the internal phenylene moiety are responsible for the inhibitory activity. Compound **29** was thus selected as the second lead compound in view of its biological efficacy and synthetic efficiency.

Alteration of X to S (**37**), CH_2 (**38**), or CO (**39**) resulted in loss of activity, suggesting that oxygen in X may play an important role. Methylation and dimethylation of **31**, yielding **32** and **33**, respectively, considerably reduced the inhibitory effect. Steric hindrance of the methyl or dimethyl moiety in Y restricts the molecular conformation, which may influence the biological effect.

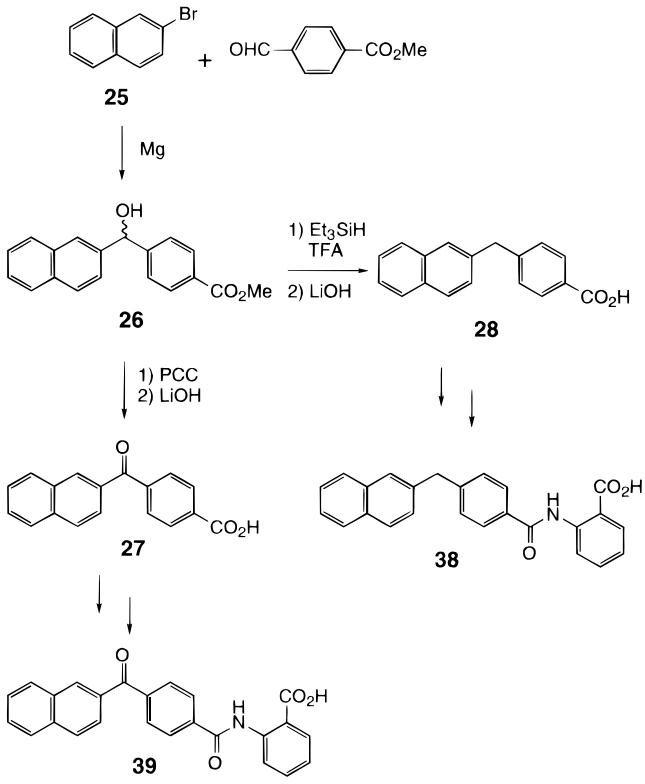
Scheme 4



Scheme 5

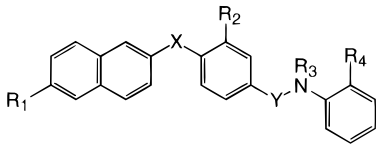


Scheme 6



Substitution of a hydroxy moiety at R_1 provided **35**, which maintained inhibitory activity comparable to that of **29**. It is of great interest, however, that the introduction of benzyloxy at the 6-position (R_1) on the naphthalene ring of **31**, affording **36**, resulted in a significant enhancement of IgE inhibitory activity ($IC_{50} = 8.3$ nM) together with a partial decrease in the cell viability. Similarly, introduction of NO_2 at R_2 (**40**) increased IgE inhibitory activity without much reduction in cell viability. Noteworthy is the fact that methylation of the

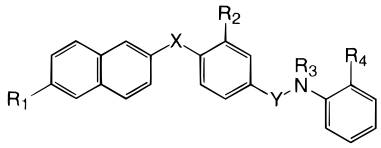
Table 1. Analytical Data of Naphthalene Derivatives



compd	R_1	X	R_2	Y	R_3	R_4	mp, °C	formula[a]
29	H	O	H	CO	H	CO_2H	213.0−213.5	$C_{24}H_{17}NO_4$
30	H	OCH_2	H	CO	H	CO_2H	218.5−219.0	$C_{25}H_{19}NO_4$
31	H	O	H	CH_2CO	H	CO_2H	173.5	$C_{25}H_{19}NO_4$
32	H	O	H	CHMeCO	H	CO_2H	185.0−185.5	$C_{26}H_{21}NO_4$
33	H	O	H	CMe_2CO	H	CO_2H	211.5−212.0	$C_{27}H_{23}NO_4$
34	H	O	H	$(CH_2)_2CO$	H	CO_2H	168.0−168.5	$C_{26}H_{21}NO_4$
35	OH	O	H	CO	H	CO_2H	250.5−251.0	$C_{24}H_{17}NO_5$
36	OBn	O	H	CH_2CO	H	CO_2H	210.0−210.5	$C_{32}H_{25}NO_5$
37	H	S	H	CO	H	CO_2H	238.5−239.0	$C_{24}H_{17}NO_3S$
38	H	CH_2	H	CO	H	CO_2H	221.0−222.0	$C_{25}H_{19}NO_3$
39	H	CO	H	CO	H	CO_2H	242.0−243.0	$C_{25}H_{17}NO_4$
40	H	O	NO_2	CO	H	CO_2H	241.0−242.0	$C_{24}H_{16}N_2O_6 \cdot {}^1/_2H_2O$
41	H	O	H	CH_2	H	CO_2H	194.5−195.5	$C_{24}H_{19}NO_3$
42	H	O	H	CO	Me	CO_2H	166.0−167.0	$C_{25}H_{19}NO_4$
43	H	O	H	CO	H	2-TET[b]	223.5−224.0	$C_{24}H_{17}N_5O_2$
44	H	O	H	CO	H	$CONH_2$	199.5−200.5	$C_{24}H_{18}N_2O_3$
45	H	O	H	CO	H	NH_2	204.5−206.5	$C_{23}H_{18}N_2O_2$

[a] C, H, N analyses were within ±0.4% of theoretical values. [b] 2-(1*H*-Tetrazol-5-yl).

Table 2. Inhibition of IgE and IgG Production by PBMC



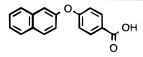
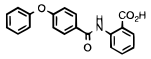
							suppression (%) at 3 μM (IC_{50}, μM)		
compd	R_1	X	R_2	Y	R_3	R_4	IgE production	IgG production	viability
TEI-6472							63.0 (1.88)	−0.5 (>10)	−2.6
29	H	O	H	CO	H	CO_2H	64.8 (1.3)	−16.9 (38)	−7.4
30	H	OCH_2	H	CO	H	CO_2H	−6.1	−16.1	NT[a]
31	H	O	H	CH_2CO	H	CO_2H	86.6 (0.6)	31.2 (4.3)	11.4
32	H	O	H	CHMeCO	H	CO_2H	8.7	−15.9	−2.1
33	H	O	H	CMe_2CO	H	CO_2H	−30.4	−5.4	−11.3
34	H	O	H	$(CH_2)_2CO$	H	CO_2H	8.5	−41.2	−2.9
35	OH	O	H	CO	H	CO_2H	76.6 (1.2)	−8.7 (>10)	5.2
36	OBn	O	H	CH_2CO	H	CO_2H	95.1 (0.0083)	91.7 (0.042)	58.2
37	H	S	H	CO	H	CO_2H	25.8	−2.8	NT
38	H	CH_2	H	CO	H	CO_2H	9.5	−21.1	−1.1
39	H	CO	H	CO	H	CO_2H	10.3	5.4	NT
40	H	O	NO_2	CO	H	CO_2H	93.0 (0.29)	36.9 (2.4)	19.1
41	H	O	H	CH_2	H	CO_2H	21.9	−4.5	−1.7
42	H	O	H	CO	Me	CO_2H	−27.7	10.1	−5.1
43	H	O	H	CO	H	2-TET[b]	−74.5	−18.7	−13.6
44	H	O	H	CO	H	$CONH_2$	8.6	10.8	7.3
45	H	O	H	CO	H	NH_2	31.6 (4.4)	3.3 (>10)	−9.3

[a] NT = not tested. [b] 2-(1*H*-Tetrazol-5-yl).

amide moiety (R_3 = Me, **42**) caused loss of activity. Therefore, the ability of a conformational change in the two benzene rings, which may prevent hydrogen bond formation, appears to be crucial for the suppressive activity toward IgE production. Carboxylic acid at R_4 of **29** was converted to tetrazole to give **43**. Although the tetrazole moiety is in general recognized as a bioisoster of CO_2H in view of its pK_a value,[23] it is quite intriguing that **43** caused enhancement of IgE production. These results demonstrate that the shape and the size of R_4 remarkably affect IgE production. Comparison of **44** with **29** showed that $CONH_2$ at R_4 should not be substituted for CO_2H, indicating that this hydrogen bond is responsible for the activity. It is unique that **45**, having an amino group at R_4, showed modest potency.

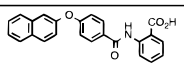
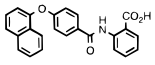
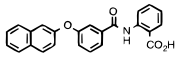
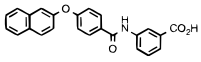
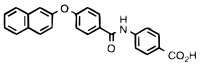
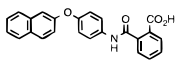
Table 3 lists the inhibitory activities toward IgE and IgG production and viability effect for the compounds having a partial structure of **29**. Compound **5**, lacking the anthranilic acid moiety, was inactive; this observation is consistent with the importance of this moiety, as described above. Conversion of the naphthalene ring into benzene (**46**) resulted in retention of the potency. However, further elimination of this benzene moiety or replacement of the benzene moiety with a cyclohexane one virtually abolished the potency (data not shown). These facts confirm that both the anthranilic acid

Table 3. Inhibition of IgE and IgG Production by PBMC for Compounds Having Partial Structure

Compnd	Structure	mp, °C	formula[a]	Suppression(%) at 3μM (IC50, μM) IgE	IgG	Viability
5		180.0-181.0°C	$C_{17}H_{12}O_3$	-4.6	-4.8	NT
46		197.0-197.5°C	$C_{20}H_{15}NO_4$	46.0 (3.28)	-1.8 (>10)	-1.4

[a] C, H, N analyses were within ±0.4% of theoretical values. NT = not tested.

Table 4. Inhibition by Isomers of **29** of IgE and IgG Production by PBMC

Compnd	Structure	mp, °C	formula[a]	Suppression(%) at 3μM (IC50, μM) IgE	IgG	Viability
29		213.0-213.5	$C_{24}H_{17}NO_4$	64.8(1.3)	-16.9 (38)	-7.4
47		217.5-218.5	$C_{24}H_{17}NO_4$	96.9 (1.57)	64.7 (2.32)	-6.5
48		180.0-181.0	$C_{24}H_{17}NO_4$	-26.2	-16.0	-23.6
49		278.0-279.0	$C_{24}H_{17}NO_4$	-29.6	2.5	-14.5
50		293.5-294.5	$C_{24}H_{17}NO_4$	6.4	24.4	-16.1
51		176.0-178.0	$C_{24}H_{17}NO_4$	-11.8	-23.1	1.5

[a] C, H, N analyses were within ±0.4% of theoretical values.

moiety and the benzene ring on the opposite side are essential for the inhibitory activities toward IgE biosynthesis.

Table 4 lists five isomers of **29** that were also studied as inhibitors of IgE production. 1-Substituted naphthalene isomer **47** was equally as active as **29**, indicating the importance of the aryloxy moiety on the left side as was shown by **46**. Rearrangement of **29** also gave the 1,3-oriented isomer **48**, which completely lost the activity. This implies that the shape of the molecule is also responsible for the inhibitory effect on IgE production. Transfer of carboxylic acid substituents to the 3- or 4-position (**49**, **50**) entirely eliminated the potency. Of great interest is the fact that inversion of the amide functionality (**51**) also resulted in loss of activity. These results strongly indicate that the anthranilic acid moiety, including its amide functionality, is a core moiety for the inhibitory activities. Reduction of the carbonyl moiety of the amide afforded **41**, which also showed absolutely no activity at all (Table 2). These facts strongly suggest that the carbonyl group in the amide is essential for the suppressive activity toward IgE biosynthesis.

The detailed mode of action of IgE inhibition is not understood. It is well known that IL-4 production by T cells plays a major role in the induction of IgE production by B cells.[4,5] α-CD40 is believed to be an equivalent

Table 5. Comparison of *in Vitro* Suppressive Effect on IgE production of **31** and **36**

	IgE production, IC_{50} (μM) human PBMC IL-4, α-CD40, IL-10	human PBMC IL-4, HC	mouse B cells IL-4, LPS
31	0.6	1.9	0.63
36	0.0083	NT[a]	0.012

[a] NT = not tested.

Table 6. Comparison of *in Vitro* Biological Data on **29**, **31**, **36**, and **30**

	production, IC_{50} (μM) IgE, human PBMC IL-4, α-CD40, IL-10	LTB_4, RBL-1 A23187	PGE_2, WI-38 A23187, IL-1α
29	1.3	0.4	10
31	0.6	0.7	10
36	0.0083	1.2	NT[a]
30	>3.0	NT	<1.0

[a] NT = not tested.

of the CD40 ligand expressed on the surface of T cells, which then costimulates B cells via CD40. These facts demonstrate that these compounds act on B cells. DSCG was reported to inhibit the Sμ to Sε deletional switch recombination and IgE synthesis in human B cells.[14] In addition, we previously reported that TEI-8364, having the inter-phenylene replaced with a hexenyl chain, affected B cell differentiation and IgE preferential class-switching.[18] Since TEI-8364 also possesses naphthalene and anthranilic acid moieties, the inhibitory mechanism of these compounds here may be the same as that of TEI-8364. Table 5 compares the *in vitro* suppressive effect on IgE production between **31** and **36**. When mouse spleen B cells were stimulated with IL-4 and lipopolysaccharide (LPS), **31** and **36** inhibited IgE synthesis comparably to the extent found in the original experiment using IL-4-, α-CD40-, and IL-10-treated human PBMC; for instance, **36** lowered IgE production with an IC_{50} of 0.012 μM. The same tendency was observed with **31** when IL-4 and hydrocortisone (HC) instead of IL-4, α-CD40, and IL-10 were added to cultures of human PBMC.[24] These data strongly suggest that compounds such as **31** or **36** may interfere with signal transduction between IL-4/IL-4 receptor cognition[25] and genetic transcription, which induce the class-switching of immunoglobulin in B cells to release IgE.[26]

Table 6 summarizes the effects of four compounds on the production of arachidonic acid metabolites. Since PGE_2 was reported to affect IgE synthesis,[7b,15] some of our representative compounds were evaluated for their suppressive effect on PGE_2 biosynthesis by human lung fibroblast WI-38 stimulated with interleukin-1α (IL-1α) and Ca^{2+} ionophore A23187.[27] Compounds **29** and **31** showed weak activity with an IC_{50} of 10 μM, whereas **30**, having little IgE inhibitory effect, was found to be a relatively strong inhibitor of PGE_2 production. These data demonstrate that PGE_2 does not play a pivotal role in the inhibition of IgE biosynthesis by these compounds. Although TEI-6472 was shown to be an inhibitor of IgE and LTB_4 biosynthesis, the relationship between IgE biosynthesis and LTB_4 seems obscure. Compounds **29**, **31**, and **36** exhibited a strong suppressive effect on LTB_4 production by rat basophilic leukemia cells (RBL-1) stimulated with A23187.[28] However,

the suppressive effect of these compounds on IgE production did not correlate with that on LTB_4 production.

Conclusion

We prepared a series of naphthyloxy-substituted benzamidobenzoic acids and related derivatives and conducted the structure−activity relationship studies on their inhibitory activities toward IgE biosynthesis. The results may be summarized as follows: (1) 2-(4-(2-Naphthyloxy)benzamido)benzoic acid (**29**) was found to have a suppressive activity for IgE in preference to that for IgG biosynthesis. (2) The presence of a 2-aryloxy group at the 4-position on the inter-phenylene was necessary for the inhibitory activity. (3) A spacer methylene between the amide and phenylene (**31**) enhanced the suppressive activity for IgE and IgG biosynthesis, whereas it weakened IgE class selectivity. (4) The anthranilic acid moiety was found to be a core moiety: The carboxylic acid and amide carbonyl could not be moved to another position and were not replaceable with other functional groups. (5) Placement of a benzyloxy group on the 6-position of the naphthalene ring (**36**) provided the optimal potency.

The efficacy of **31** and **36** was maintained when α-CD40 and IL-10 were replaced by HC or LPS as costimulatory factors with IL-4, implying that these compounds may act on IL-4 signal transduction to cause class-switching of immunoglobulin in B cells. No correlation between IgE production and LTB_4/PGE_2 production was observed in terms of suppressive effect.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a JEOL EX-270 Fourier transform spectrometer at 270 MHz (^1H) and 68 MHz (^{13}C), using tetramethylsilane as an internal standard. The abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. For TLC analysis, Merck precoated TLC (silica gel 60 F254, d = 0.25 mm) was used. Melting point determinations were performed on an electrothermal YANACO MP-S3 or METTLER FP62 apparatus. The FT-IR spectra were determined on a JASCO FT/IR-5300 in a KBr pellet. Purification by medium-pressure liquid chromatography was carried out on Daisogel IR-60 silica gel. Where analyses are indicated only by symbols of the elements, analytical results are within ±0.4% of the theoretical values. All nonaqueous reactions were carried out under an inert atmosphere except for hydrogenations, which were carried out under a hydrogen atmosphere. THF and ether were distilled from sodium benzophenone ketyl prior to use. CH_2Cl_2 was dried over CaH_2. Pyridine and MeOH were dried over molecular sieve 4A and molecular sieve 3A, respectively. The other commercially available reagents and solvents were used without further purification unless otherwise stated.

Biological Assay of *in Vitro* Effects of the Derivatives on IgE and IgG Production by and Viability of Human PBMC Stimulated with IL-4, IL-10, and α-CD40.[18] Human PBMC were obtained by the Ficoll-Paque (Pharmacia, Uppsala, Sweden) density gradient centrifugation technique. PBMC (final: 2×10^6 cells/mL) were cultured in triplicate in flat-bottomed 96-well plates (Falcon, NJ) in a final volume of 200 μL of RPMI 1640 supplemented with 10% fetal calf serum (FCS; Whittaker, ML), 2 mM glutamine, 50 units/mL penicillin, and 50 μg/mL streptomycin. IL-4 (0.1 μg/mL), IL-10 (0.2 μg/mL), and α-CD40 (2 μg/mL), with or without test compound, were added to the cultures on day 0. After 14 days, the culture medium was harvested, and human IgG and IgE levels in it were determined by enzyme-linked immunosorbent assays (ELISA). Suppression (%) was calculated by the following mathematical equation: (level without compound − level with compound)/level without compound × 100. After removal of the medium, alamar blue (Biosource, CA; 20 μL/well) was added to the cultures, and incubation was carried out for 2 h. Cell viability was measured by counting the number of fluorescent (viable) cells (excitation λ = 530 nm, emission λ = 590 nm). Suppression (%) was calculated as described above.

Biological Assay of *in Vitro* Effects of Derivatives on IgE Production by Human PBMC Stimulated with IL-4 and HC. HC (1 μM) was used instead of IL-10 and α-CD40 according to the same procedure as described above.

Biological Assay of *in Vitro* Effects of Derivatives on IgE Production by Mouse Spleen B Cells Stimulated with IL-4 and LPS. Mouse B cells were prepared by treating DBA/2 splenocytes with anti-mouse T cell serum (Cedarlane, Canada) followed by incubation with Low-Tox rabbit complement (Cedarlane, Canada). B cells were fractionated by gradient centrifugation and cultured in RPMI 1640 medium (the same as described above) supplemented with 10% FCS (Whittaker, ML) in 96-well plates. LPS (Sigma, MO) was added at a final concentration of 2 μg/mL. After incubation for 1 day, mouse IL-4 (Genzyme, MA) was added at a final concentration of 50 ng/mL. Cultures was continued for 6 days, and IgE levels in the media were measured by ELISA.

Biological Assay of *in Vitro* Effects of Derivatives on LTB_4 Production.[28] Rat basophile leukemia cell line RBL-1 (Dainippon Pharmaceutical Co., Japan) was maintained in Dulbecco's modified Eagle's medium containing FCS (10%). Cells were preincubated with or without test compounds for 10 min at 37 °C. Ca^{2+} ionophore A23187 was added at a final concentration of 2 μM. After incubation for 5 min, the reaction was stopped, and the culture media were harvested. The level of LTB_4 in the supernatant of the centrifuged medium was determined with an ELISA assay kit (Cayman & Amersham).

Biological Assay of *in Vitro* Effects of Derivatives on PGE_2 Production.[27] Human lung fibroblasts, WI-38 (Riken Cell Bank, Japan), were maintained in Dulbecco's modified Eagle's medium containing penicillin (50 units) and streptomycin (50 mg/mL) and supplemented with 10% FCS. Cell suspensions (200 μL, 2×10^5 cells/mL) were plated onto 96-well plates, and the cells were grown to confluence (4 days). Then they were starved with fresh medium minus serum but containing 0.5% bovine serum albumin (BSA) overnight. The medium was aspirated and replaced with that containing 0.5% BSA and interleukin-1α (IL-1α) (10 ng/mL) with or without test compound. The cells were then incubated overnight at 37 °C. PGE_2 released into the medium was determined with an ELISA assay kit (Cayman & Amersham).

4-(2-Naphthyloxy)phenylacetic Acid (6). General Procedure A.[19a] To a solution of 2-naphthol (28.83 g, 0.20 mol) in a mixture of dry benzene (400 mL) and dry MeOH (100 mL) was added NaOMe (28%, MeOH solution, 36.7 mL, 0.19 mol) at room temperature. The reaction mixture was stirred for 1 h at room temperature and then concentrated. A mixture of the residue, methyl 4-bromophenylacetate (45.8 g, 0.20 mol), and CuCl (5.94 g, 0.06 mol) in dry pyridine (500 mL) was heated at 120 °C with stirring for 86 h. After cooling, 5 N HCl (150 mL) was poured into the reaction mixture, and the products were extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated. Purification by silica gel column chromatography (hexane−EtOAc, 50:1−10:1) gave the methyl ester of the title compound (**22**, 27.4 g, 48%). A solution of this compound (26.7 g, 95 mmol) in MeOH−THF (175/350 mL) was treated with 4 N LiOH (119 mL, 0.48 mol) and stirred overnight at room temperature. The reaction mixture was acidified to pH 1 with 5 N HCl (95 mL) and stirred for 1 h at room temperature. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Recrystallization from CH_3CN afforded **6** (20.73 g, 78% yield) as a white prism: ^1H NMR ($CDCl_3$) δ 3.67 (s, 2 H), 7.04 (d, J = 8.6 Hz, 2 H), 7.24−7.34 (m, 4 H), 7.43 (dquint, J = 1.7, 6.9 Hz, 2 H), 7.71 (d, J = 8.9 Hz, 1 H), 7.81−7.85 (m, 2 H), 10.10 (s br, 1 H).

4-(Naphthyloxy)benzoic Acid (5). Methyl 4-hydroxybenzoate and 2-bromonaphthalene were treated instead of 2-naphthol and methyl 4-bromobenzoate, respectively, according to the same procedure as described in the preparation of

6 to afford **5** as a white solid in 20% yield: mp 180−181 °C; ^{1}H NMR ($CDCl_3$) δ 7.04−7.10 (m, 2 H), 7.25−7.29 (m, 1 H), 7.44−7.54 (m, 3 H), 7.76−7.79 (m, 1 H), 7.83−7.90 (m, 2 H), 8.07−8.12 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 115.9, 117.7, 120.5, 125.6, 125.7, 127.0, 127.5, 127.9, 130.6, 131.9, 134.2, 153.2, 161.2, 167.0. Anal. ($C_{17}H_{12}O_3$) C, H, N.

4-((6-(Benzyloxy)-2-naphthyl)oxy)phenylacetic Acid (7). Methyl 4-hydroxyphenylacetate and 6-(benzyloxy)-2-bromonaphthalene were treated instead of 2-naphthol and methyl 4-bromobenzoate, respectively, according to the same procedure as described in the preparation of **6** to afford **7** as a white solid: 8% yield: ^{1}H NMR (DMSO-d_6) δ 3.65 (s, 2 H), 5.18 (s, 2 H), 7.00 (d, J = 8.6 Hz, 2 H), 7.20−7.50 (m, 11 H), 7.64 (d, J = 9.6 Hz, 1 H), 7.71 (d, J = 8.9 Hz, 1 H).

4-(2-Naphthylthio)benzoic Acid (8). 2-Naphthalenethiol and ethyl 4-bromobenzoate were treated instead of 2-naphthol and methyl 4-bromobenzoate, respectively, according to the same procedure as described in the preparation of **6** to afford **8** as amber needles: 60% yield; ^{1}H NMR ($CDCl_3$) δ 7.23 (s, 2 H), 7.49−7.58 (m, 3 H), 7.81−7.96 (m, 5 H), 8.06 (d, J = 1.7 Hz, 1 H).

4-(1-Naphthyloxy)benzoic Acid (9). Methyl 4-hydroxybenzoate and 1-bromonaphthalene were treated instead of 2-naphthol and methyl 4-bromophenylacetate, respectively, according to the same procedure as described in the preparation of **6** to afford **9** as a white solid: 14% yield; ^{1}H NMR ($CDCl_3$) δ 6.94 (d, J = 7.6 Hz, 2 H), 7.06 (d, J = 6.3 Hz, 1 H), 7.35−7.55 (m, 3 H), 7.69 (d, J = 8.9 Hz, 1 H), 7.87 (d, J = 8.5 Hz, 1 H), 8.0−8.3 (m, 3 H).

3-(2-Naphthyloxy)benzoic Acid (10). Methyl 3-hydroxybenzoate and 2-bromonaphthalene were treated instead of 2-naphthol and methyl 4-bromophenylacetate, respectively, according to the same procedure as described in the preparation of **6** to afford **10** as a white solid: 52% yield; ^{1}H NMR ($CDCl_3$) δ 7.29 (dt, J = 9.0, 1.9 Hz, 2 H), 7.40−7.55 (m, 5 H), 7.72 (d, J = 7.5 Hz, 1 H), 7.83 (d, J = 7.2 Hz, 1 H), 7.90−8.00 (m, 2 H).

2-(4-(2-Naphthyloxy)benzamido)benzonitrile (14). To a suspension of **5** (264 mg, 1.0 mmol) in dry CH_2Cl_2 (5 mL) was added oxalyl chloride (140 mg, 1.1 mmol) followed by treatment with DMF (1 drop). After having been stirred for 2 h at 35 °C, the reaction mixture was concentrated. To a solution of the residue in dry CH_2Cl_2 (7 mL) was added a solution of anthranilonitrile (118 mg, 1.0 mmol) and triethylamine (111 mg, 1.1 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C; this was stirred for 4 h at 0 °C and then overnight at room temperature. The reaction mixture was poured onto water, and the products were extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (hexane−EtOAc, 20:1−5:1) gave **14** (263 mg, 72% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.15 (d, J = 8.9 Hz, 2 H), 7.18−7.30 (m, 2 H), 7.46−7.54 (m, 3 H), 7.61−7.69 (m, 2 H), 7.76−7.79 (m, 1 H), 7.85−7.96 (m, 4 H), 8.34 (s br, 1 H), 8.61 (d, J = 8.6 Hz, 1 H).

3-(4-(2-Naphthyloxy)phenyl)propanoic Acid (17). To a solution of 2-naphthol (1.44 g, 10 mmol) in dry benzene (20 mL) and dry MeOH (5 mL) was added NaOMe (28%, MeOH solution, 1.83 mL, 9.5 mmol) at room temperature. The reaction mixture was stirred for 1 h at room temperature and then concentrated. A mixture of the resultant solution, ethyl (*E*)-4-bromocinnamate (2.55 g, 10 mmol), and CuCl (0.3 g, 3 mmol) in dry pyridine (10 mL) was heated at 120 °C with stirring for 48 h. After cooling, 5 N HCl (150 mL) was poured into the reaction mixture, and the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Purification by silica gel column chromatography (hexane−EtOAc, 20:1) gave methyl (*E*)-3-(4-(2-naphthyloxy)phenyl)propenate (280 mg, 53%): ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3 H), 6.37 (d, J = 15.8 Hz, 1 H), 7.04−7.06 (m, 2 H), 7.24−7.28 (m, 1 H), 7.40−7.54 (m, 5 H), 7.68 (d, J = 15.8 Hz, 1 H), 7.72−7.76 (m, 1 H), 7.83−7.88 (m, 2 H).

To a solution of this compound (280 mg, 0.92 mmol) in EtOAc (5 mL) was added 10% Pd/C (10 wt %, 30 mg), and this was stirred for 6 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated to give the methyl ester of **17**. A solution of this compound (275 mg, 0.9 mmol) in MeOH−THF (5/10 mL) was treated with 4 N LiOH (2.2 mL, 9 mmol) and stirred overnight at room temperature. The reaction mixture was acidified to pH 1 with 5 N HCl (3 mL) and stirred for 1 h at room temperature. The mixture was poured onto water, and the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Recrystallization from hexane−benzene (3/2 mL) afforded **17** as pale yellow needles (219 mg, 83%): ^{1}H NMR ($CDCl_3$) δ 2.71 (t, J = 7.6 Hz, 2 H), 2.98 (t, J = 7.6 Hz, 2 H), 7.00 (d, J = 8.6 Hz, 2 H), 7.19−7.29 (m, 4 H), 7.36−7.47 (m, 2 H), 7.70 (d, J = 7.6 Hz, 1 H), 7.82 (d, J = 8.9 Hz, 2 H).

4-(2-Naphthyloxy)aniline (18). To a solution of 2-naphthol (1.44 g, 10 mmol) in dry DMF (10 mL) was added 60% NaH (60% in fossil oil, 400 mg, 10 mmol) at 0 °C. After this mixture had been stirred for 0.3 h, 4-bromonitrobenzene (2.02 g, 10 mmol) was introduced to it, and stirring was continued overnight at room temperature. The reaction mixture was poured onto water, and the products were extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc, 50:1−10:1) to give 4-(2-naphthyloxy)nitrobenzene as a white solid. To a solution of this compound (0.49 g, 1.85 mmol) in EtOAc (5 mL) was added 10% Pd/C (49 mg), and the resulting mixture was stirred overnight at room temperature under a hydrogen atmosphere. The mixture was filtered through Celite. Concentration of the filtrate gave **18** (423 mg, 97%) as a brown solid: ^{1}H NMR ($CDCl_3$) δ 3.62 (s br, 2 H), 6.72 (d, J = 8.9 Hz, 2 H), 6.94 (d, J = 8.6 Hz, 2 H), 7.15 (d, J = 2.3 Hz, 1 H), 7.22−7.26 (m, 1 H), 7.32−7.44 (m, 2 H), 7.64 (d, J = 7.9 Hz, 1 H), 7.79 (d, J = 8.9 Hz, 2 H).

4-((2-Naphthyloxy)methyl)benzoic Acid (19). To a solution of 2-naphthol (721 mg, 5.0 mmol) in DMF (5 mL) was added NaH (60% in fossil oil, 220 mg, 5.5 mmol). After the mixture had been stirred for 1 h at room temperature, methyl 4-(bromomethyl)benzoate was added to it, and stirring continued for 3.5 h at room temperature. The reaction mixture was poured onto water, and the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Recrystallization from MeOH gave the methyl ester of the title compound. A solution of this compound (1.06 g, 3.63 mmol) in MeOH−THF (8/15 mL) was treated with 4 N LiOH (9 mL, 36 mol) and stirred overnight. The reaction mixture was acidified to pH 1 with 5 N HCl (10 mL) and stirred for 20 min at room temperature. The mixture was washed with water, and the products were extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated. Recrystallization from CH_3CN afforded **19** (0.87 g) as a white needle in 55% yield: ^{1}H NMR ($CDCl_3$) δ 5.28 (s, 2 H), 7.20−7.27 (m, 2 H), 7.35 (dt, J = 2.0, 7.9 Hz, 1 H), 7.45 (dt, J = 1.3, 8.2 Hz, 1 H), 7.61 (d, J = 8.3 Hz, 2 H), 7.72 (d, J = 7.9 Hz, 1 H), 7.78 (d, J = 8.9 Hz, 2 H), 8.15 (d, J = 8.2 Hz, 2 H).

4-(2-Naphthyloxy)-3-nitrobenzoic Acid (20). Methyl 4-chloro-3-nitrobenzoate was treated instead of methyl 4-(bromomethyl)benzoate according to the same procedure as described in the preparation of **19** to give **20** as a white solid: 99% yield; ^{1}H NMR (DMSO-d_6) δ 7.20 (d, J = 8.9 Hz, 1 H), 7.41 (dd, J = 1.3, 6.0 Hz, 1 H), 7.50−7.60 (m, 2 H), 7.69 (d, J = 1.3 Hz, 1 H), 7.91 (m, 1 H), 7.98 (m, 1 H), 8.06 (d, J = 8.9 Hz, 1 H), 8.16 (dd, J = 2.0, 4.0 Hz, 1 H), 8.53 (d, J = 2.3 Hz, 1 H).

4-(2-Naphthyloxy)benzyl Bromide (21).[20] To a suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in dry THF (10 mL) was added a solution of **5** (264 mg, 1.0 mmol) in dry THF (5 mL) at 0 °C. The mixture was stirred for 3 h at room temperature and poured into ether (30 mL) and saturated Na_2SO_4 solution (30 mL). The products were extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residual mixture was chromatographed on silica gel (using hexane−EtOAc, 3:1) to afford 4-(2-naphthyloxy)-benzyl alcohol (239 mg, 95% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.70 (s, 2 H), 7.07 (d, J = 8.6 Hz, 2 H), 7.24−7.28 (m, 1 H), 7.31 (d, J = 2.6 Hz, 1 H), 7.36−7.49 (m, 4 H), 7.70 (d, J = 7.6 Hz, 1 H), 7.81−7.85 (m, 2 H).

Tri-*n*-octylphosphine (708 mg, 1.91 mmol) was added to a solution of 4-(2-naphthyloxy)benzyl alcohol (239 mg, 0.95 mmol) and CBr_4 (633 mg, 1.91 mmol) in dry ether (5 mL) at room temperature, and the resulting mixture was stirred for 40 min at room temperature. Water was poured into the reaction mixture, and the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (hexane−EtOAc, 50:1) gave **21** (300 mg, 100% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.61 (s, 2 H), 7.02−7.06 (m, 2 H), 7.23−7.26 (m, 2 H), 7.35−7.49 (m, 4 H), 7.71−7.74 (m, 1 H), 7.82−7.86 (m, 2 H).

2-(4-(2-Naphthyloxy)phenyl)propionic Acid (23). *n*-BuLi (1.66 M in hexane, 0.72 mL, 1.2 mmol) was added to a solution of diisopropylamine (121 mg, 1.2 mmol) in THF (5 mL) at −70 °C. After the mixture stirred at −70 °C for 1 h, a solution of **22** (292 mg, 1.0 mmol) in THF (3 mL) was added to the reaction mixture followed by stirring for 1.5 h at −70 °C. The reaction mixture was treated with MeI (170 mg, 1.2 mmol) and stirred for 2 h at −70 °C. It was allowed to warm to −10 °C. Stirring was continued until the reaction was completed. The resulting reaction was quenched with saturated NH_4Cl, and the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The resultant mixture was purified by column chromatography on silica gel (hexane−EtOAc, 100:1−20:1) to give the methyl ester of **23** as a pale yellowish oil (226 mg, 74% yield). A solution of this compound (138 mg, 0.45 mmol) in MeOH−THF (4/8 mL) was treated with 4 N LiOH (1.1 mL, 4.5 mmol) and stirred overnight at room temperature. The reaction mixture was acidified to pH 1 with 5 N HCl (2 mL) and stirred for 30 min at room temperature. The mixture was poured onto water, and the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Purification by silica gel column chromatography (hexane−EtOAc−AcOH, 100:100:1) gave **23** as a foam (103 mg) in a total 58% yield from **22**: ^{1}H NMR ($CDCl_3$) δ 1.53 (d, J = 7.3 Hz, 3 H), 3.76 (q, J = 7.3 Hz, 1 H), 7.03 (d, J = 8.6 Hz, 2 H), 7.23−7.33 (m, 4 H), 7.43 (dquint, J = 1.6, 6.9 Hz, 2 H), 7.71 (d, J = 7.6 Hz, 1 H), 7.80−7.85 (m, 2 H).

2-Methyl-2-(4-(2-naphthyloxy)phenyl)propionic Acid (24). To a solution of diisopropylamine (92 mg, 0.91 mmol) in THF (5 mL) was added *n*-BuLi (1.66 M in hexane, 0.55 mL, 0.91 mmol) at −70 °C. After the mixture had been stirred at −70 °C for 0.5 h, a solution of the methyl ester of **23** (233 mg, 0.76 mmol) in THF (3 mL) was added to the reaction mixture followed by stirring for 1 h at −70 °C. The reaction mixture was then treated with MeI (130 mg, 0.91 mmol) and stirred for 2 h at −70 °C. It was allowed to warm to −15 °C, and stirring was continued at this temperature for 2 h. The resulting reaction was subsequently quenched with saturated NH_4Cl; then the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (hexane−EtOAc, 100:1−50:1) to give the methyl ester of **24** (194 mg, 80% yield) as a pale yellow oil. A solution of this compound (248 mg, 0.77 mmol) in MeOH−THF (4/8 mL) was treated with 4 N LiOH (1.9 mL, 7.7 mmol) and stirred overnight at room temperature. The reaction mixture was acidified to pH 1 with 5 N HCl and stirred for 45 min at room temperature. The mixture was poured onto water, and the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Purification by silica gel column chromatography (hexane−EtOAc−AcOH, 100:100:1) gave **24** (203 mg) as a white solid in a total 69% yield from the methyl ester of **23**: ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 6 H), 7.03 (d, J = 8.9 Hz, 2 H), 7.24−7.28 (m, 1 H), 7.34−7.49 (m, 5 H), 7.72 (d, J = 8.9 Hz, 1 H), 7.81−7.85 (m, 2 H).

Methyl 4-(Hydroxy(2-naphthyl)methyl)benzoate (26).[21] A mixture of Mg (0.53 g, 22 mmol) in dry THF (20 mL) was heated at 50 °C with stirring. To the mixture was added a solution of 2-bromonaphthalene (4.14 g, 20 mmol) in THF (20 mL) over a period of 1 h. The reaction mixture was heated to reflux with stirring for 3 h. After cooling to room temperature, it was treated with methyl 4-formylbenzoate (2.95 g, 18 mmol) and stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl, and the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Purification by silica gel column chromatography (hexane−EtOAc, 10:1−5:1) gave **26** (4.67 g, 89%) as a slightly yellowish liquid: ^{1}H NMR ($CDCl_3$) δ 2.38 (d, J = 3.6 Hz, 1 H), 3.90 (s, 3 H), 6.05 (d, J = 3.3 Hz, 1 H), 7.39−7.53 (m, 5 H), 7.79−7.86 (m, 4 H), 8.01 (d, J = 8.6 Hz, 2 H).

4-(2-Naphthoyl)benzoic Acid (27). To a solution of **26** (496 mg, 1.70 mmol) in dry CH_2Cl_2 was added pyridinium chlorochromate (PCC) (0.55 g, 2.5 mmol), and the mixture was stirred for 2 h at room temperature. The reaction mixture was filtered on short-pass column chromatography on silica gel using CH_2Cl_2 as an eluent. A mixture of ether (10 mL) and hexane (10 mL) was poured into the concentrated filtrate. The precipitate was collected on the filter to afford the methyl ester of **27** (312 mg, 63%). A solution of this compound (290 mg, 1.0 mmol) in MeOH−THF (2/4 mL) was treated with 4 N LiOH (2.5 mL, 10 mmol) and stirred overnight at room temperature. The reaction mixture was acidified to pH 1 with 5 N HCl and stirred for 30 min at room temperature. The mixture was poured onto water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Recrystallization from CH_3CN gave **27** (191 mg, total 43% yield from **26**) as a white crystal: ^{1}H NMR ($CDCl_3$) δ 7.55−7.68 (m, 2 H), 7.92−8.00 (m, 6 H), 8.25−8.28 (m, 3 H).

4-(2-Naphthylmethyl)benzoic Acid (28).[22] To a solution of **26** (292 mg, 1.0 mmol) in CF_3CO_2H (1.2 mL) was added triethylsilane (349 mg, 3.0 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was poured onto aqueous $NaHCO_3$, and the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Purification by silica gel column chromatography (using hexane−EtOAc, 30:1, as an eluent) gave the methyl ester of **28** (250 mg, 90%) as a white solid. A solution of this compound (249 mg, 0.9 mmol) in MeOH−THF (3/6 mL) was treated with 4 N LiOH (2.3 mL, 9.0 mmol) and stirred overnight. The reaction mixture was acidified to pH 1 with 5 N HCl and stirred for 30 min at room temperature. The mixture was poured onto water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Recrystallization from CH_3CN gave **28** (196 mg, total 75% yield from **26**) as a white crystal: ^{1}H NMR ($CDCl_3$) δ 4.21 (s, 2 H), 7.25−7.35 (m, 3 H), 7.42−7.49 (m, 2 H), 7.64 (s, 1 H), 7.76−7.83 (m, 3 H), 8.03 (d, J = 8.3 Hz, 2 H).

Preparation of 2-((4-(2-Naphthyloxy)phenyl)acetamido)benzoic Acid (31). General Procedure B. To a solution of **6** (19.49 g, 70 mmol) in CH_2Cl_2 (350 mL) was added oxalyl chloride (9.8 g, 77 mmol) dropwise at room temperature. After the addition of DMF (10 drops), stirring was continued for 1 h at 35 °C. The reaction mixture was concentrated, and to a solution of the residue in dry CH_2Cl_2 (200 mL) was added a solution of methyl anthranilate (10.6 g, 70 mmol) and triethylamine (7.8 g, 77 mmol) in dry CH_2Cl_2 (200 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and then overnight at room temperature. After the reaction mixture had been poured onto water, the products were extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (hexane−EtOAc, 20:1−5:1) gave the methyl ester of **31** (23.5 g, 57 mmol) as a yellow liquid. A solution of this compound (23.5 g, 82%) in MeOH/THF (100/200 mL) was treated with 4 N LiOH (71 mL, 290 mmol) and stirred overnight at room temperature. The reaction mixture was acidified to pH 1 with 5 N HCl and stirred for 30 min at room temperature. The mixture was poured onto water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Recrystallization from CH_3CN gave **31** (10.0 g, total 37% yield from **6**) as white needles: mp 173.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.80 (s, 2 H), 7.04 (t, J = 7.6 Hz, 1 H), 7.09−7.14 (m, 2 H), 7.21−7.29 (m, 2 H), 7.34−7.45 (m, 4 H), 7.54−7.65 (m, 2 H), 7.76 (d, J = 8.6 Hz, 2 H), 8.07 (dd, J = 1.7, 7.9 Hz, 1 H), 8.76 (dd, J = 1.0, 8.6

Hz, 1 H), 10.74 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 43.8, 113.4, 116.4, 119.1, 119.6, 119.9, 122.7, 124.7, 126.6, 127.0, 127.6, 129.7, 130.0, 130.1, 131.0, 131.3, 133.9, 134.0, 140.7, 154.7, 155.5, 169.3, 169.6; IR (neat) 2922, 1671, 1586, 1505, 1451, 1402, 1296, 1250, 1227, 1165, 1088, 963, 754 cm^{-1}. Anal. ($C_{25}H_{19}NO_4$) C, H, N.

2-(4-(2-Naphthyloxy)benzamido)benzoic Acid (29). Following the same procedure as described for the preparation of **31**, but using **5** instead of **6**, compound **29** was prepared via **15** as while needles recrystallized from CH_3CN in 74% yield: mp 213.0−213.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.16−7.25 (m, 3 H), 7.36 (dd, J = 2.3, 8.9 Hz, 1 H), 7.45−7.68 (m, 4 H), 7.87−8.08 (m, 6 H), 8.69 (d, J = 7.6 Hz, 1 H), 12.15 (br s, 1 H), 13.75 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 115.4, 116.5, 118.1, 119.9, 120.1, 122.8, 125.3, 126.8, 127.2, 127.7, 129.2, 129.4, 130.3, 130.4, 131.2, 133.9, 134.3, 141.2, 153.1, 160.2, 164.0, 170.0; IR (KBr) 1663, 1611, 1505, 1393, 1302, 1223, 1173, 847, 748, 685, 530, 469 cm^{-1}. Anal. ($C_{24}H_{17}NO_4$) C, H, N.

2-(4-((2-Naphthyloxy)methyl)benzamido)benzoic Acid (30). Following the same procedure as described for the preparation of **31**, but using **19** instead of **6**, compound **30** was prepared as white granules recrystallized from CH_3CN in 51% yield: mp 218.5−219.0 °C; ^{1}H NMR ($CDCl_3$) δ 5.28 (s, 2 H), 7.17−7.45 (m, 5 H), 7.63−7.80 (m, 6 H), 8.07 (d, J = 8.6 Hz, 2 H), 8.15 (dd, J = 1.7, 7.9 Hz, 1 H), 8.95−8.99 (m, 1 H), 11.90 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 68.6, 107.4, 116.5, 118.7, 119.9, 122.9, 123.7, 126.4, 126.7, 127.2, 127.4, 127.5, 127.9, 128.6, 129.4, 131.3, 134.0, 134.1, 134.3, 141.1, 141.2, 141.3, 156.0, 164.4, 170.0. Anal. ($C_{25}H_{19}NO_4$) C, H, N.

2-(2-(4-(2-Naphthyloxy)phenyl)propionamido)benzoic Acid (32). Following the same procedure as described for the preparation of **31**, but using **23** instead of **6**, compound **32** was prepared as white needles recrystallized from CH_3CN in 36% yield: mp 185.0−185.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.48 (d, J = 6.9 Hz, 3 H), 3.88 (q, J = 6.9 Hz, 1 H), 7.04−7.14 (m, 3 H), 7.28 (dd, J = 2.3, 8.9 Hz, 1 H), 7.39−7.59 (m, 6 H), 7.80 (d, J = 7.6 Hz, 1 H), 7.90 (dd, J = 1.3, 7.6 Hz, 1 H), 7.95 (d, J = 8.2 Hz, 2 H), 8.52 (d, J = 7.6 Hz, 1 H), 11.28 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 18.5, 47.2, 114.0, 116.5, 119.3, 119.9, 120.0, 122.9, 125.1, 126.9, 127.3, 127.9, 129.5, 130.1, 130.4, 131.4, 134.2, 134.4, 136.5, 141.2, 154.7, 155.9, 169.8, 172.8. Anal. ($C_{26}H_{21}NO_4$) C, H, N.

2-(2-Methyl-2-(4-(2-naphthyloxy)phenyl)propionamido)benzoic Acid (33). Following the same procedure as described for the preparation of **31**, but using **24** instead of **6**, compound **33** was prepared as white needles recrystallized from CH_3CN in 65% yield: mp 211.5−212.0 °C; ^{1}H NMR (DMSO-d_6) δ 1.61 (s, 6 H), 7.07 (d, J = 8.6 Hz, 2 H), 7.11 (t, J = 7.3 Hz, 1 H), 7.28 (dd, J = 1.6, 8.9 Hz, 1 H), 7.40−7.52 (m, 5 H), 7.58 (dt, J = 1.7, 6.9 Hz, 1 H), 7.80 (d, J = 7.9 Hz, 1 H), 7.90−7.97 (m, 3 H), 8.62 (d, J = 8.6 Hz, 1 H), 11.25 (br s, 1 H), 13.62 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 26.6, 47.5, 113.7, 115.6, 118.8, 119.2, 119.7, 122.4, 124.8, 126.6, 127.0, 127.6, 127.8, 129.8, 130.1, 131.1, 133.9, 134.2, 139.8, 141.3, 154.4, 155.3, 169.9, 175.3. Anal. ($C_{27}H_{23}NO_4$) C, H, N.

2-(3-(4-(2-Naphthyloxy)phenyl)propionamido)benzoic Acid (34). Following the same procedure as described for the preparation of **31**, but using **17** instead of **6**, compound **34** was prepared as white needles recrystallized from CH_3CN in 62% yield: mp 168.0−168.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.78 (t, J = 7.9 Hz, 2 H), 3.09 (t, J = 7.9 Hz, 2 H), 6.97−7.02 (m, 2 H), 7.12 (dt, J = 1.0, 7.3 Hz, 1 H), 7.20−7.27 (m, 4 H), 7.41 (dquint, J = 1.3, 6.9 Hz, 2 H), 7.57−7.68 (m, 2 H), 7.80 (d, J = 8.9 Hz, 2 H), 8.10 (dd, J = 1.7, 7.9 Hz, 1 H), 8.76 (dd, J = 1.0, 8.6 Hz, 1 H), 10.87 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 29.9, 39.0, 113.1, 116.4, 118.7, 119.0, 119.5, 119.9, 122.5, 124.7, 126.6, 127.0, 127.6, 129.6, 129.9, 130.0, 130.2, 131.0, 133.9, 134.0, 136.1, 140.7, 154.6, 154.8, 169.5, 170.4. Anal. ($C_{26}H_{21}NO_4$) C, H, N.

2-(4-((6-Hydroxy-2-naphthyl)oxy)benzamido)benzoic Acid (35). Compound **7** was converted to **13** by reaction with methyl anthranilate in the same procedure as described for the preparation of **31**. A solution of **13** (1.35 g, 2.7 mmol) in THF (50 mL) was hydrogenated in the presence of 10% Pd/C (330 mg) at room temperature. Stirring overnight, filtration through Celite, and concentration provided the methyl ester of **35** (1.04 g, 2.5 mmol). A solution of this compound (1.04 g, 2.5 mmol) in MeOH−THF (40/40 mL) was treated with 4 N LiOH solution (8 mL, 32 mmol) and stirred overnight at room temperature. The reaction mixture was acidified to pH 1 with 5 N HCl and stirred for 30 min at room temperature. The mixture was then poured onto water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Recrystallization from CH_3CN gave **35** (784 mg, total 73% yield from **13**) as a white crystal: mp 250.5−251.0 °C; ^{1}H NMR (DMSO-d_6) δ 7.05−7.20 (m, 6 H), 7.24 (s, 1 H), 7.60 (dt, J = 2.0, 9.0 Hz, 1 H), 7.74 (dd, J = 9.0, 13.0 Hz, 2 H), 7.95 (d, J = 8.9 Hz, 2 H), 8.03 (dd, J = 1.7, 8.0 Hz, 1 H), 8.28 (d, J = 9.0 Hz, 1 H), 9.70 (s, 1 H), 12.2 (br s, 1 H), 13.7 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 108.8, 116.2, 116.4, 117.4, 119.4, 119.8, 120.5, 122.8, 128.2, 128.4, 128.7, 128.8, 129.3, 131.3, 132.0, 134.3, 141.2, 150.3, 155.0, 160.9, 164.0, 170.0. Anal. ($C_{24}H_{17}NO_5$) C, H, N.

2-((4-((6-(Benzyloxy)-2-naphthyl)oxy)phenyl)acetamido)benzoic Acid (36). Following the same procedure as described for the preparation of **31**, but using **7** instead of **6**, compound **36** was prepared as pale yellow granules recrystallized from CH_3CN in 56% yield: mp 210.0−210.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.74 (s, 2 H), 5.20 (s, 2 H), 7.02 (d, J = 8.6 Hz, 2 H), 7.12 (t, J = 7.3 Hz, 1 H), 7.20−7.27 (m, 2 H), 7.30−7.58 (m, 10 H), 7.75 (d, J = 8.9 Hz, 1 H), 7.83 (d, J = 8.9 Hz, 1 H), 7.95 (dd, J = 1.3, 7.9 Hz, 1 H), 8.50 (d, J = 7.9 Hz, 1 H), 12.0 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 43.8, 69.3, 107.5, 114.2, 116.4, 118.6, 119.4, 119.8, 120.2, 122.7, 127.7, 127.8, 127.9, 128.4, 128.6, 128.8, 129.2, 129.7, 130.9, 131.0, 131.2, 134.0, 136.9, 140.7, 152.7, 155.5, 156.0, 169.3, 169.6. Anal. ($C_{32}H_{25}NO_5$) C, H, N.

2-(4-(2-Naphthylthio)benzamido)benzoic Acid (37). Following the same procedure as described for the preparation of **31**, but using **8** instead of **6**, compound **37** was obtained as white needles recrystallized from 2-propanol in 76% yield: mp 238.5−239.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.15 (t, J = 7.6 Hz, 1 H), 7.34 (d, J = 8.6 Hz, 2 H), 7.49−7.65 (m, 4 H), 7.80−7.92 (m, 5 H), 8.04 (s, 1 H), 8.13 (dd, J = 2.0, 8.3 Hz, 1 H), 8.93 (d, J = 8.3 Hz, 1 H), 11.84 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 116.6, 119.9, 122.9, 126.9, 127.0, 127.6, 127.7, 128.0, 128.4, 129.2, 129.5, 129.6, 131.2, 132.2, 132.3, 132.4, 133.4, 134.2, 141.0, 141.7, 164.0, 170.0. Anal. ($C_{24}H_{17}NO_3S$) C, H, N.

2-(4-(2-Naphthylmethyl)benzamido)benzoic Acid (38). Following the same procedure as described for the preparation of **31**, but using **28** instead of **6**, compound **38** was obtained as white needles recrystallized from CH_3CN in 79% yield: mp 221.0−222.0 °C; ^{1}H NMR ($CDCl_3$) δ 4.22 (s, 2 H), 7.15 (t, J = 8.3 Hz, 1 H), 7.24−7.50 (m, 5 H), 7.63−7.69 (m, 2 H), 7.77−7.83 (m, 3 H), 7.96 (d, J = 8.6 Hz, 2 H), 8.14 (dd, J = 1.7, 7.9 Hz, 1 H), 8.96 (d, J = 7.9 Hz, 1 H), 11.80 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 40.9, 116.3, 119.8, 122.8, 125.5, 126.1, 126.8, 127.3, 127.4, 127.5, 128.1, 129.3, 131.2, 131.6, 132.3, 132.4, 133.1, 134.3, 138.1, 141.2, 145.7, 164.4, 169.8. Anal. ($C_{25}H_{19}NO_3$) C, H, N.

2-(4-(2-Naphthoyl)benzamido)benzoic Acid (39). Following the same procedure as described for the preparation of **31**, but using **27** instead of **6**, compound **39** was prepared as pale yellow needles recrystallized from CH_3CN in 62% yield: mp 242.0−243.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.18−7.24 (m, 1 H), 7.58−7.70 (m, 3 H), 7.92−8.01 (m, 6 H), 8.17 (d, J = 8.6 Hz, 3 H), 8.28 (s, 1 H), 8.99 (d, J = 8.3 Hz, 1 H), 12.04 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 116.9, 120.1, 123.3, 125.1, 127.1, 127.3, 127.7, 128.5, 128.8, 129.7, 130.1, 131.3, 131.8, 131.9, 133.7, 134.2, 134.3, 134.9, 137.5, 140.3, 140.6, 140.8, 164.0, 169.9, 195.2. Anal. ($C_{25}H_{17}NO_4$) C, H, N.

2-(3-Nitro-4-(2-naphthyloxy)benzamido)benzoic Acid Hemihydrate (40). Following the same procedure as described for the preparation of **31**, but using **20** instead of **6**, compound **40** was prepared as a white solid recrystallized from CH_3CN in 33% yield: mp 241.0−242.0 °C; ^{1}H NMR (DMSO-d_6) δ 7.24 (t, J = 7.2 Hz, 1 H), 7.34 (d, J = 8.5 Hz, 1 H), 7.43 (dd, J = 2.6, 4.5 Hz, 1 H), 7.50−7.60 (m, 2 H), 7.60−7.70 (m, 2 H), 7.95 (dd, J = 8.1, 14.6 Hz, 2 H), 8.06 (dd, J = 7.6, 8.0 Hz, 2 H), 8.20−8.25 (m, 1 H), 8.60−8.70 (m, 2 H), 12.3 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 115.9, 117.5, 119.9, 120.6, 120.7, 121.0, 123.8, 125.2, 126.0, 127.3, 127.7, 128.1, 129.8, 131.0,

131.5, 133.8, 134.1, 134.6, 140.6, 140.7, 152.7, 152.9, 162.4, 170.2. Anal. ($C_{24}H_{16}N_2O_6 \cdot 0.5H_2O$) C, H, N.

2-((4-(2-Naphthyloxy)benzyl)amino)benzoic Acid (41). To a solution of **21** (313 mg, 1.0 mmol) in dry DMF (3 mL) were added methyl anthranilate (151 mg, 1.0 mmol), K_2CO_3 (207 mg, 1.5 mmol), and NaI (225 mg, 1.5 mmol) at room temperature. The reaction mixture was heated at 120 °C with stirring overnight. Water was poured into the reaction mixture, and the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (hexane−EtOAc, 100:1−50:1) gave the methyl ester of **41** (222 mg, 58%). A solution of this compound (220 mg, 0.57 mmol) in MeOH−THF (3/6 mL) was treated with 4 N LiOH solution (1.4 mL, 5.7 mmol) and stirred overnight at room temperature. The reaction mixture was acidified to pH 1 with 5 N HCl and stirred for 30 min at room temperature. The mixture was poured onto water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Recrystallization from CH_3CN gave **41** (166 mg, total 44% yield from **21**) as a pale yellow crystal: mp 194.5−195.5 °C; ^{1}H NMR ($CDCl_3$) δ 4.46 (s, 2 H), 6.66 (t, J = 8.6 Hz, 2 H), 7.02−7.14 (m, 2 H), 7.23−7.54 (m, 7 H), 7.70 (d, J = 7.6 Hz, 1 H), 7.76−7.92 (m, 3 H), 7.99 (d, J = 7.9 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 600 MHz) δ 45.9, 112.3, 114.2, 114.3, 115.4, 119.1, 119.5, 120.3, 125.7, 127.5, 127.7, 128.3, 129.6, 130.4, 130.9, 132.4, 133.5, 134.5, 135.0, 135.3, 151.1, 155.1, 156.2, 170.9. Anal. ($C_{24}H_{19}NO_3$) C, H, N.

2-(*N*-Methyl-4-(2-naphthyloxy)benzamido)benzoic Acid (42). To a solution of **29** (77 mg, 0.20 mmol) in CH_2Cl_2 and MeOH (3/3 mL) was added (trimethylsilyl)diazomethane (in hexane, 2 M) with stirring at room temperature until the color of the reaction mixture turned yellow. After concentration, a solution of the residue (**15**) in THF (5 mL) was treated with MeI (86 mg, 0.60 mmol) and NaH (60% in fossil oil, 12 mg, 0.30 mmol) at room temperature. Stirring was continued for 4.5 h at room temperature. The reaction mixture was poured onto water, and the products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (hexane−EtOAc, 3:1−2:1) gave the methyl ester of **42** (42 mg, 51% yield) as colorless liquid. A solution of this compound (42 mg, 0.10 mmol) in MeOH−THF (2/4 mL) was treated with 4 N LiOH (0.3 mL, 1.2 mmol) and stirred for 2.5 h at room temperature and for 2.5 h at 50 °C. The reaction mixture was acidified to pH 1 with 5 N HCl and stirred for 30 min at room temperature. The mixture was poured onto water, and the products were extraced with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. Ether was added to the residue, and the resulting solid was collected to give **42** (total 28% yield from **29**, 22 mg) as a white solid: mp 166.0−167.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.45 (s, 3 H), 6.79 (br s, 1 H), 7.13−7.57 (m, 10 H), 7.67 (d, J = 6.9 Hz, 1 H), 7.79 (d, J = 7.6 Hz, 2 H), 7.90−8.00 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 37.7, 114.2, 117.5, 119.7, 125.0, 126.7, 127.0, 127.3, 127.6, 129.1, 129.9, 130.0, 130.1, 130.2, 130.9, 131.3, 132.8, 132.9, 133.8, 144.2, 153.8, 157.2, 166.7. Anal. ($C_{25}H_{19}NO_4$) H, N; C: calcd, 75.6; found, 75.1.

1-(4-(2-Naphthyloxy)benzamido)-2-(1*H*-tetrazol-5-yl)-benzene (43). A suspension of **14** (109 mg, 0.3 mmol), NH_4Cl (48 mg, 0.9 mmol), and NaN_3 (59 mg, 0.9 mmol) in dry DMF (3 mL) was heated with stirring at 80 °C for 24 h. The reaction mixture was poured onto iced aqueous HCl. The products were extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Recrystallization from CH_3CN yielded **43** (92 mg, 75%) as a colorless crystal: mp 223.5−224.0 °C; ^{1}H NMR (CD_3OD) δ 7.15−7.21 (m, 2 H), 7.27−7.35 (m, 2 H), 7.43−7.53 (m, 3 H), 7.57−7.63 (m, 1 H), 7.78−8.01 (m, 4 H), 8.14−8.19 (m, 2 H), 8.76−8.81 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 114.1, 115.7, 118.3, 120.5, 122.4, 124.5, 125.6, 127.1, 127.6, 128.0, 128.9, 129.4, 130.0, 130.6, 130.7, 132.1, 134.2, 137.5, 153.4, 160.6, 164.6. Anal. ($C_{24}H_{17}N_5O_2$) C, H, N.

2-(4-(2-Naphthyloxy)benzamido)benzamide (44). To a suspension of **5** (132 mg, 0.50 mmol) in dry CH_2Cl_2 (5 mL) was added oxalyl chloride (70 mg, 0.55 mmol) followed by treatment with DMF (1 drop). After the reaction mixture had been stirred for 2 h at 35 °C, it was concentrated. To a solution of the residue in dry CH_2Cl_2 (7 mL) was added a solution of 2-aminobenzamide (68 mg, 0.5 mmol) and triethylamine (56 mg, 0.55 mmol) in dry CH_2Cl_2 (5 mL). It was stirred overnight at room temperature. The reaction mixture was poured onto water, and the products were extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was recrystallized from CH_3CN to afford **44** (144 mg, 75%) as white crystals: mp 199.5−200.5 °C; ^{1}H NMR ($CDCl_3$) δ 5.66 (br s, 1 H), 6.22 (br s, 1 H), 7.09−7.16 (m, 3 H), 7.29−7.30 (m, 1 H), 7.42−7.61 (m, 5 H), 7.74−7.77 (m, 1 H), 7.84−7.90 (m, 2 H), 8.01−8.06 (m, 2 H), 8.87 (dd, J = 1.3, 8.9 Hz, 1 H), 12.22 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 115.2, 118.2, 119.1, 120.0, 120.1, 122.5, 125.2, 126.7, 127.2, 127.7, 128.7, 129.3, 129.4, 130.2, 130.3, 132.5, 133.9, 140.2, 153.2, 160.0, 163.7, 171.2. Anal. ($C_{24}H_{18}N_2O_3$) C, H, N.

2-(4-(2-Naphthyloxy)benzamido)aniline (45). To a suspension of **5** (132 mg, 0.50 mmol) in dry CH_2Cl_2 (5 mL) was added oxalyl chloride (70 mg, 0.55 mmol) followed by treatment with DMF (1 drop). The reaction mixture was concentrated after having been stirred for 2 h at 35 °C. A solution of the residue in dry CH_2Cl_2 (7 mL) was added to a solution of 1,2-phenylenediamine (162 mg, 1.5 mmol) and triethylamine (56 mg, 0.55 mmol) in dry CH_2Cl_2 (5 mL) over a period of 3 min. After having been stirred overnight at room temperature, the reaction mixture was poured onto water, and the products were extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane−EtOAc, 3:1−2:1) to afford **45** (35 mg, 20%) as a pale yellow solid: mp 204.5−206.5 °C; ^{1}H NMR (DMSO-d_6) δ 4.98 (br s, 2 H), 6.69 (t, J = 7.9 Hz, 1 H), 6.87 (d, J = 7.9 Hz, 1 H), 7.06 (t, J = 7.9 Hz, 1 H), 7.25 (d, J = 8.9 Hz, 3 H), 7.43 (dd, J = 2.6, 8.9 Hz, 1 H), 7.54−7.64 (m, 3 H), 7.96 (d, J = 8.9 Hz, 1 H), 8.05 (d, J = 8.9 Hz, 1 H), 8.08−8.15 (m, 3 H), 9.73 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 114.9, 116.1, 116.2, 117.8, 120.0, 123.3, 125.2, 126.5, 126.7, 126.8, 127.2, 127.7, 129.5, 130.1, 130.2, 130.3, 133.9, 143.2, 153.6, 159.5, 164.5. Anal. ($C_{23}H_{18}N_2O_2$) C, H, N.

2-(4-Phenoxybenzamido)benzoic Acid (46). Following the same procedure as described for the preparation of **31**, but using 4-(phenyloxy)benzoic acid instead of **6**, compound **46** was prepared as white needles recrystallized from CH_3CN in 48% yield: mp 197.0−197.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.12−7.26 (m, 6 H), 7.42−7.50 (m, 2 H), 7.65 (t, J = 8.6 Hz, 1 H), 7.97 (d, J = 8.9 Hz, 2 H), 8.05 (dd, J = 1.7, 7.9 Hz, 1 H), 8.69 (d, J = 7.9 Hz, 1 H), 12.13 (br s, 1 H), 13.77 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 116.26, 116.37, 117.74, 119.75, 122.79, 124.55, 128.97, 129.29, 130.28, 131.25, 134.29, 141.24, 155.26, 160.31, 163.94, 170.5. Anal. ($C_{20}H_{15}NO_4$) C, H, N.

2-(4-(1-Naphthyloxy)benzamido)benzoic Acid (47). Following the same procedure as described for the preparation of **31**, but using **9** instead of **6**, compound **47** was prepared as white needles recrystallized from CH_3CN in 37% yield: mp 217.5−218.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.00 (t, J = 7.2 Hz, 1 H), 7.11 (d, J = 8.9 Hz, 2 H), 7.18 (d, J = 8.0 Hz, 1 H), 7.34 (t, J = 8.3 Hz, 1 H), 7.50−7.61 (m, 3 H), 7.82 (d, J = 8.2 Hz, 1 H), 7.90−8.10 (m, 5 H), 8.64 (d, J = 8.3 Hz, 1 H), 12.2 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 115.5, 117.1, 118.4, 121.3, 121.6, 123.6, 124.6, 126.2, 126.6, 126.8, 128.1, 129.4, 129.9, 130.7, 131.4, 134.7, 141.0, 150.8, 160.4, 163.5, 170.9. Anal. ($C_{24}H_{17}NO_4$) C, H, N.

2-(3-(2-Naphthyloxy)benzamido)benzoic Acid (48). Following the same procedure as described for the preparation of **31**, but using **10** instead of **6**, compound **48** was prepared as a white solid in 43% yield: mp 180.0−181.0 °C; ^{1}H NMR (DMSO-d_6) δ 7.01 (t, J = 7.4 Hz, 1 H), 7.20−7.40 (m, 3 H), 7.40−7.55 (m, 3 H), 7.58 (t, J = 7.9 Hz, 1 H), 7.69 (s, 1 H), 7.85 (d, J = 7.6 Hz, 1 H), 7.92 (d, J = 1.7 Hz, 1 H), 7.95 (s, 1 H), 8.00 (d, J = 8.9 Hz, 1 H), 8.05 (d, J = 8.6 Hz, 1 H), 8.62 (d, J = 7.9 Hz, 1 H), 12.1 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 114.1, 117.5, 118.5, 119.8, 121.8, 121.9, 122.0, 123.5, 125.0, 126.7, 127.2, 127.7, 130.0, 130.3, 130.5, 130.9, 131.4, 133.9, 137.4, 140.8, 154.1, 157.1, 163.3, 170.6. Anal. ($C_{24}H_{17}NO_4$) C, H, N.

3-(4-(2-Naphthyloxy)benzamido)benzoic Acid (49). Following the same procedure as described for the preparation of **31**, but using **5** instead of **6** and methyl 3-aminobenzoate instead of methyl anthranilate, compound **49** was prepared in 48% yield as a white crystal (recrystallized from CH_3CN−2-propanol, 1:5): mp 278.0−279.0 °C; ^{1}H NMR (DMSO-d_6) δ 7.19 (d, J = 8.6 Hz, 2 H), 7.35 (dd, J = 2.3, 8.6 Hz, 1 H), 7.43−7.56 (m, 4 H), 7.67 (d, J = 7.3 Hz, 1 H), 7.87 (d, J = 7.6 Hz, 1 H), 7.96 (d, J = 7.6 Hz, 1 H), 8.01−8.08 (m, 4 H), 8.41 (s, 1 H), 10.37 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 115.1, 117.8, 120.0, 121.1, 124.4, 125.2, 126.8, 127.2, 127.7, 128.8, 129.4, 130.0, 130.2, 130.3, 131.2, 133.9, 139.4, 153.4, 159.8, 164.8, 167.2. Anal. ($C_{24}H_{17}NO_4$) C, H, N.

4-(4-(2-Naphthyloxy)benzoic Acid (50). Following the same procedure as described for the preparation of **31**, but using **5** and methyl 4-aminobenzoate instead of **6** and methyl anthranilate, respectively, compound **50** was prepared in 65% yield as a white crystal: mp 293.5−294.5 °C; ^{1}H NMR (DMSO-d_6) δ 7.19 (d, J = 8.6 Hz, 2 H), 7.35 (d, J = 8.9 Hz, 1 H), 7.46−7.56 (m, 3 H), 7.86−8.06 (m, 9 H), 10.46 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 115.1, 117.7, 119.4, 119.7, 120.0, 125.2, 125.4, 126.8, 127.2, 127.7, 129.3, 130.2, 130.3, 130.6, 130.7, 133.9, 143.3, 153.3, 159.9, 165.1, 166.9. Anal. ($C_{24}H_{17}NO_4$) C, H, N.

2-((4-(2-Naphthyloxy)phenyl)aminocarbonyl)benzoic Acid (51). To a solution of **18** (37 mg, 0.157 mmol) in dry CH_2Cl_2 (5 mL) was added phthalic anhydride (23.5 mg, 0.157 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was poured onto water, and the products were extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was recrystallized from CH_3CN to afford **51** (29 mg, 48%) as light brown needles: mp 176.0−178.0 °C; ^{1}H NMR (DMSO-d_6) δ 7.11 (d, J = 8.8 Hz, 2 H), 7.29−7.31 (m, 2 H), 7.40−7.49 (m, 2 H), 7.55−7.60 (m, 2 H), 7.66 (d, J = 7.3 Hz, 1 H), 7.75 (d, J = 9.3 Hz, 2 H), 7.82 (d, J = 7.8 Hz, 1 H), 7.89 (t, J = 6.8 Hz, 2 H), 7.95 (d, J = 8.3 Hz, 1 H), 10.39 (br s, 1 H), 13.01 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 112.3, 119.2, 119.8, 121.2, 124.6, 126.6, 127.0, 127.6, 127.7, 129.3, 129.5, 130.0, 131.6, 133.9, 135.7, 138.8, 151.5, 155.4, 167.2, 167.4. Anal. ($C_{24}H_{17}NO_4$) C, H, N.

Acknowledgment. The authors wish to thank Dr. Toshiaki Harada and Dr. Atsuo Hazato for helpful discussions. We also acknowledge Dr. Takashi Kawamura, Ms. Atsuko Mizumoto, and Mr. Naoki Hase for their technical support.

References

(1) (a) Backer, V.; Ulric, C. S.; Wendelboe, D.; Bach-Mortensen, N.; Hansen, K. K.; Laursen, E. M.; Dirksen, A. Distributions of Serum IgE in Children and Adolescents Aged 7 to 16 years in Copenhagen, in Relation to Factors of Importance. *Allergy* **1992**, *47*, 484−489. (b) Tollerund, D. J.; O'Connor, G. T.; Sparrow, D.; Weiss, S. T. Asthma, Hay Fever, and Phlegm Production Associated with Distinct Patterns of Allergy Skin Test Reactivity, Eosinophilia, and Serum IgE Levels. *Am. Rev. Respir. Dis.* **1991**, *144*, 776−781. (c) Ishizaka, K. Regulation of IgE Biosynthesis. *Adv. Immunol.* **1989**, *47*, 1−44.

(2) (a) MacDonald, S. M.; Rafnar, T.; Langdon, J.; Lichtenstein, L. M. Molecular Identification of an IgE-Dependent Histamine-Releasing Factor. *Science* **1995**, *269*, 688−690. (b) Blank, U.; Ra, C.; Miller, L.; White, K.; Metzger, H.; Kinet, J.-P. Complete Structure and Expression in Transfected Cells of High Affinity IgE Receptor. *Nature* **1989**, *337*, 187−189. (c) Schroeder, J. T.; Kagey-Sobotka, A.; Lichtenstein, L. M. The Role of Basophiles in Allergic Inflammation. *Allergy* **1995**, *50*, 463−472.

(3) (a) Powrie, F.; Coffman, R. L. Cytokine Regulation of T-Cell Function: Potential for Therapeutic Intervention. *Immunol. Today* **1993**, *14*, 270−274. (b) Zhang, K.; Clark, E. A.; Saxon, A. CD40 Stimulation Provides an IFN γ-Independent and IL-4 Dependent Differentiation Signal Directly to Human B Cells for IgE Production. *J. Immunol.* **1991**, *146*, 1836−1842. (c) Gascan, H.; Gauchat, J. F.; Aversa, G.; Vlasselear, P. V.; De Vries, J. E. Anti-CD40 Monoclonal Antibodies or CD4+T Cell Clones and IL-4 Induce IgG_4 and IgE Switching in Purified Human B Cells via Different Signaling Pathways. *J. Immunol.* **1991**, *147*, 8−13. (d) Uejima, Y.; Takahashi, K.; Komoriya, K.; Kurozumi, S.; Ochs, H. D. Effect of Interleukin-10 on anti-CD40-and-Interleukin-4-Induced Immunoglobulin E Production by Human Lymphocytes. *Int. Arch. Allergy Immunol.* **1996**, *110*, 225−232. (e) Bonnefoy, J.-Y.; Lecoanet-Henchoz, S.; Aubry, J.-P.; Gauchat, J.-F.; Graber, P. CD23 and B-cell Activation. *Curr. Opin. Immunol.* **1995**, *7*, 355−359. (f) Nonoyama, S.; Hollenbaugh, D.; Aruffo, A.; Ledbetter, J. A.; Ochs, H. D. B Cell Activation via CD-40 is Required for Specific Antibody Production by Antigen-Stimulated Human B Cells. *J. Exp. Med.* **1993**, *178*, 1097−1102. (g) Hollenbaugh, D.; Ochs, H. D.; Noelle, R. J.; Ledbetter, J. A.; Aruffo, A. The Role of CD40 and Its Ligand in the Regulation of the Immune Response. *Immunol. Rev.* **1994**, *138*, 23−37.

(4) (a) Sato, T. A.; Widmer, M. B.; Finkelman, F. D.; Madani, H.; Jacobs, C. A.; Grabstein, K. H.; Maliszewski, C. R. Recombinant Soluble Murine IL-4 Receptor Can Inhibit or Enhance IgE Responses *in Vivo*. *J. Immunol.* **1993**, *150*, 2717−2723. (b) Garrone, P.; Djossou, O.; Galizzi, J.-P.; Banchereau, J. A. Recombinant Extracellular Domain of the Human Interleukin 4 Receptor Inhibits the Biological Effects of Interleukin 4 on T and B Lymphocytes. *Eur. J. Immunol.* **1991**, *21*, 1365−1369. (c) Rentz, H.; Enssle, K.; Lauffer, L.; Kurrle, R.; Galfand, E. W. Inhibition of Allergen-Induced IgE and IgG_1 Production by Soluble IL-4 Receptor. *Int. Arch. Allergy Immunol.* **1995**, *106*, 46−54.

(5) (a) Carballido, J. M.; Schols, D.; Namikawa, R.; Zurawski, S.; Zurawski, G.; Roncarolo, M.-G.; de Vries, J. E. IL-4 Induces Human B Cell Maturation and IgE Synthesis in Scid-hu Mice. Inhibition of Ongoing IgE Production by *In Vivo* Treatment with an IL-4/IL-13 Receptor Antagonist. *J. Immunol.* **1995**, *155*, 4162−4170. (b) Aversa, G.; Punnonen, J.; Cocks, B. G.; Malefyt, R. de W.; Vega, F., Jr.; Zurawski, S. M.; Zurawski, G.; de Vries, J. E. An Interleukin 4 (IL-4) Mutant Protein Inhibits both IL-4 or IL-13-Induced Human Immunoglobulin G_4 (IgG_4) and IgE Synthesis and B Cell Proliferation: Support for a Common Component Shared by IL-4 and IL-13 Receptors. *J. Exp. Med.* **1993**, *178*, 2213−2218.

(6) (a) Kiniwa, M.; Gately, M.; Gubler, U.; Chizzonite, R.; Fargeas, C.; Delespesse, G. Recombinant Interleukin-12 Suppresses the Synthesis of Immunoglobulin E by Interleukin-4 Stimulated Human Lymphocytes. *J. Clin. Invest.* **1992**, *90*, 262−266. (b) Morris, S. C.; Madden, K. B.; Adamovicz, J. J.; Gause, W. C.; Hubbard, B. R.; Gately, M. K.; Finkelman, F. D. Effects of IL-12 on *in Vivo* Cytokine Gene Expression and Ig Isotype Selection. *J. Immunol.* **1994**, *152*, 1047−1056.

(7) (a) Boguniewicz, M.; Jaffe, H. S.; Izu, A.; Sullivan, M. J.; York, D.; Geha, R. S.; Leung, D. Y. M. Recombinant γ Interferon in Treatment of Patients with Atopic Dermatitis and Elevated IgE Level. *Am. J. Med.* **1990**, *88*, 365−370. (b) Péne, J.; Rousset, F.; Briére, F.; Chretien, I.; Bonnefoy, J.-Y.; Spits, H.; Yokota, T.; Arai, N.; Banchereau, J.; De Vries, J. E. IgE Production by Normal Human Lymphocytes Is Induced by Interleukin 4 and Suppressed by Interferon γ and α and Prostaglandin E_2. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 6880−6884.

(8) Tanaka, Y.; Takahashi, A.; Arai, I.; Inoue, T.; Higuchi, S.; Otomo, S.; Watanabe, K.; Habu, S.; Nishimura, T. Prolonged Inhibition of an Antigen-Specific IgE Response *in Vivo* by Monoclonal Antibody Against Lymphocyte Function-Associated Antigen-1. *Eur. J. Immunol.* **1995**, *25*, 1555−1558.

(9) Flores-Romo, L.; Shields, J.; Humbert, Y.; Graber, P.; Aubry, J. P.; Gauchat, J. F.; Ayala, G.; Allet, B.; Chavez, M.; Bazin, H. Inhibition of an *in vivo* Antigen-Specific IgE Response by Antibodies to CD23. *Science* **1993**, *261*, 1038−1041.

(10) (a) Kimata, H.; Yoshida, A.; Ishioka, C.; Lindley, I.; Mikawa, H. Interleukin-8 (IL-8) Selectivity Inhibits Immunoglobulin E Production Induced by IL-4 in Human B Cells. *J. Exp. Med.* **1992**, *176*, 1227−1231. (b) Kimata, H.; Lidley, I.; Furusho, K. Selective Inhibition of Spontaneous IgE and IgG_4 Production by Interleukin-8 in Atopic Patients. *Blood* **1995**, *85*, 3191−3198.

(11) (a) Yanagihara, Y.; Kajiwara, K.; Ikizawa, K.; Koshio, T.; Okumura, K.; Ra, C. Recombinant Soluble Form of the Human High-affinity Immunoglobulin E (IgE) Receptor Inhibits IgE Production through Its Specific Binding to IgE-Bearing B cells. *J. Clin. Invest.* **1994**, *94*, 2162−2165. (b) Naito, K.; Hirama, M.; Okuyama, K.; Ra, C. Soluble Form of the Human High-Affinity Receptor for IgE Inhibits Recurrent Allergic Reaction in a Novel Mouse Model of Type I Allergy. *Eur. J. Immunol.* **1995**, *25*, 1631−1637.

(12) (a) Stadler, B. M.; Stämpfli, M. R.; Miescher, S.; Rudolf, M.; Vogel, M. Cloning of Human Anti-IgE Autoantibodies and Their Role in the Regulation of IgE Synthesis. *Int. Arch. Allergy Immunol.* **1995**, *107*, 48−50. (b) Stämpfli, M. R.; Miescher, S.; Aebischer, I.; Zürcher, A. W.; Stadler, B. M. Inhibition of Human IgE Synthesis by anti-IgE Antibodies Requires Divalent Recognition. *Eur. J. Immunol.* **1994**, *24*, 2161−2167. (c) Haak-Frendscho, M.; Robbins, K.; Lyon, R.; Shields, R.; Hooley, J.; Schoenhoff, M. Administration of an anti-IgE Antibody Inhibits CD23 Expression and IgE Production in Vivo. *Immunology* **1994**, *82*, 306−313.

(13) (a) Yanagihara, Y.; Kiniwa, M.; Ishizawa, K.; Yamaya, H.; Shida, T.; Matsuura, N.; Koda, A. Suppression of IgE Production of IPD-1151T (Suplatast Tosilate), a New Dimethylsulfonium Agent: (1) Regulation of murine IgE response. *Jpn. J. Pharmacol.* **1993**, *61*, 23−30. (b) Yanagihara, Y.; Kiniwa, M.; Ishizawa, K.;

Yamaya, H.; Shida, T.; Matsuura, N.; Koda, A. Suppression of IgE production by IPD-1151T (Suplatast Tosilate), a New Dimethylsulfonium Agent: (2) Regulation of Human IgE response. *Jpn. J. Pharmacol.* **1993**, *61*, 31−39. (c) Koda, A.; Yanagihara, Y.; Matsuura, N. IPD-1151T: A Prototype Drug for IgE Antibody Synthesis Modulation. *Agents Actions* **1991**, *34* (Suppl.), 369−378.

(14) (a) Loh, R. K. S.; Jabara, H. H.; Geha, R. S. Disodium Cromoglycate Inhibits Sμ to Sϵ Deletional Switch Recombination and IgE Synthesis in Human B cells. *J. Exp. Med.* **1994**, *180*, 663−671. (b) Kimata, H.; Yoshida, A.; Ishioka, C.; Mikawa, H. Disodium Cromoglycate (DSCG) Selectivity Inhibits IgE Production and Enhances IgG_4 Production by Human B cells in vitro. *Clin. Exp. Immunol.* **1991**, *84*, 395−399. (c) Kimata, H.; Mikawa, H. Nedocromil Sodium Selectively Inhibits IgE and IgG_4 Production in Human B Cells Stimulated with IL-4. *J. Immunol.* **1993**, *151*, 6723−6732.

(15) (a) Ohmori, H.; Hikida, M.; Takai, T. Prostaglandin E_2 as a Selective Stimulator of Antigen-Specific IgE Response in Murine Lymphocytes. *Eur. J. Immunol.* **1990**, *20*, 2499−2503. (b) Roper, R. L.; Phipps, R. P. Prostaglandin E_2 and cAMP Inhibit B Lymphocyte Activation and Simultaneously Promote IgE and IgG_1 Synthesis. *J. Immunol.* **1992**, *149*, 2984−2991.

(16) (a) Ohmori, H.; Hazato, A.; Kato, Y.; Kurozumi, S. Naphthalene Derivatives That Selectively Inhibit an Antigen Specific IgE Response in Murine Lymphocytes. *Int. J. Immunopharmacol.* **1990**, *12*, 333−336. (b) Ohmori, H.; Kishimoto, T.; Hikida, M.; Hazato, A.; Kurozumi, S. Suppression of IgE Antibody Response in Mice by a Naphthalene Derivative, TEI-6472. *Int. J. Immunopharmacol.* **1993**, *15*, 573−579.

(17) Malisan, F.; Briére, F.; Bridon, J.-M.; Harindranath, N.; Mills, F. C.; Max, E. E.; Banchereau, J.; Martinez-Valdez, H. Interleukin-10 Induces Immunoglobulin G Isotype Switch Recombination in Human CD40-Activated Naive B Lymphocytes. *J. Exp. Med.* **1996**, *183*, 937−947.

(18) Uejima, Y.; Takahashi, K.; Komoriya, K.; Kurozumi, S.; Ochs, H. D. Suppression of Human Immunoglobulin E Antibody Production by a New Naphthalene Derivative. *Immunopharmacology* **1995**, *30*, 167−176.

(19) (a) Williams, A. L.; Kinney, R. E.; Bridger, R. F. Solvent-Assisted Ullmann Ether Synthesis. Reactions of Dihydric Phenols. *J. Org. Chem.* **1967**, *32*, 2501−2505. (b) Yeager, G. W.; Schissel, D. N. A Convenient Method for the Preparation of 4-Aryloxyphenols. *Synthesis* **1991**, 63−68. (c) Ungnade, H. E. The Chemistry of the Diaryl Ethers. *Chem. Rev.* **1946**, *38*, 405−446 and references cited therein.

(20) Hooz, J.; Gilani, S. S. H. A Rapid, Mild Procedure for the Preparation of Alkyl Chlorides and Bromides. *Can. J. Chem.* **1968**, *46*, 86−87.

(21) Gilman, H.; St. John, N. B.; Schulz, F. α-Naphthoic Acid. *Organic Syntheses*; Wiley: New York, 1966; Collect. Vol. II, pp 425−427.

(22) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. Silane Reductions in Acidic Media. II. Reductions of Aryl Aldehydes and Ketones with Trialkylsilanes in Trifluoroacetic Acid. A Selective Method for Converting the Carbonyl Group to Methylene. *J. Org. Chem.* **1973**, *38*, 2675−2681.

(23) Lieber, E.; Patinkin, S. H.; Tao, H. H. The Comparative Acidic Properties of Some 5-Substituted Tetrazoles. *J. Am. Chem. Soc.* **1951**, *73*, 1792−1795.

(24) Jabara, H. H.; Loh, R.; Ramesh, N.; Vercelli, D.; Geha, R. S. Sequential Switching from μ to ϵ via γ4 in Human B cells Stimulated with IL-4 and Hydrocortisone. *J. Immunol.* **1993**, *151*, 4528−4533.

(25) Yanagihara, Y.; Ikizawa, K.; Kajiwara, K.; Koshio, T.; Basaki, Y.; Akiyama, Y. Functional Significance of IL-4 Receptor on B Cells in IL-4 Induced Human IgE Production. *J. Allergy Clin. Immunol.* **1995**, *96*, 1145−1151.

(26) (a) Karnitz, L. M.; Abraham, R. T. Cytokine Receptor Signaling Mechanisms. *Curr. Opin. Immunol.* **1995**, *7*, 320−326. (b) Patti, M. E.; Sun, X. J.; Bruening, J. C.; Araki, E.; Lipes, M. A.; White, M. F.; Kahn, C. R. 4PS/Insulin Receptor Substrate (IRS-2) is the Alternative Substrate of the Insulin Receptor in IRS-1 Deficient Mice. *J. Biol. Chem.* **1995**, *270*, 24670−24673. (c) Fenghao, X.; Saxon, A.; Nguyen, A.; Ke, Z.; Diaz-Sanchez, D.; Nel, A. Interleukin 4 Activates a Signal Transducer and Activator of Transcription (Stat) Protein Which Interacts with an Interferon-γ Activation Site-Like Sequence Upstream of the Iϵ Exon in the Human B Cell Line. Evidence for the Involvement of Janus Kinase 3 and Interleukin-4 Stat. *J. Clin. Invest.* **1995**, *96*, 907−914.

(27) Lin, L.-L.; Lin, A. Y.; Dewitt, D. L. Interleukin-1α Induces the Accumulation of Cytosolic Phospholipase A_2 and the Release of Prostaglandin E_2 in Human Fibroblasts. *J. Biol. Chem.* **1992**, *267*, 23451−23454.

(28) Jakschik, B. A.; Lee, L. H.; Shuffer, G.; Parker, C. W. Arachidonic Acid Metabolism in Rat Basophilic Leukemia (RBL-1) Cells. *Prostaglandins* **1978**, *16*, 733−748.

JM9605041