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Novel Antiallergic and Antiinflammatory Agents. Part II: Synthesis and Pharmacology of TYB-2285 and its Related Compounds

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Abstract—A series of *m*-bis(glycoloylamino)benzene derivatives was synthesized by treatment of the corresponding *m*-diaminobenzene derivatives with glycoloyl chloride derivatives in pyridine. Hydrolysis of acetyl compounds gave hydroxy derivatives, from which other acyl derivatives could be synthesized. These compounds were tested in the rat PCA (passive cutaneous anaphylaxis) assay by oral administration. Benzonitrile derivatives (**4c**, **5c**, **6c**, **4h**, **5h**) exhibited notable inhibition in this assay. Compounds **5c** and **6c** also showed remarkable inhibition of eosinophil adhesion to TNF- (tumor necrosis factor) α-treated HUVEC (human umbilical vein endothelial cells) in the range of 10^{-8}–10^{-5} M. Compound **5c** is now under investigation in Japan as TYB-2285 (Figure 1) for asthma and atopic dermatitis in phase II clinical studies.

Introduction

In the previous paper[1], we reported that compounds **1** and **2** (Figure 1) inhibited the rat PCA (passive cutaneous anaphylaxis) reaction[2] (30 mg/kg, p.o.) and that they showed remarkable inhibition of eosinophil adhesion to TNF-(tumor necrosis factor) α-treated HUVEC (human umbilical vein endothelial cells)[3] in the concentration range of 10^{-8}–10^{-5} M. Recently, eosinophils have come to be thought of as contributing to the pathogenesis of allergic diseases such as asthma and atopic dermatitis. Eosinophils accumulate in the lungs and nasal airway after allergic challenge.[4–6] The initial phase in the process of eosinophil accumulation is eosinophil adhesion to endothelial cells.[7,8] For the purpose of the development of new antiallergic and antiinflammatory drugs for asthma and atopic dermatitis, we focused on eosinophil adhesion to the endothelial cell. Therefore, we synthesized new *m*-bis(glycoloylamino)-benzene derivatives[9] which have two active sites as do DSCG (disodium cromoglycate)[10] and Lodoxamide ethyl[11] (Figure 1). These compounds exhibit notable inhibition in the rat PCA assay[2] by oral administration. In addition, our compounds have unique effects, and in particular, compounds **4c**, **5c** and **6c**, showed a more marked inhibition of eosinophil adhesion to TNF-α-treated HUVEC[3] than did compounds **1** and **2**. Compound **5c** causes very unique effects. It inhibits the acute response (AR) and late response (LR) in naturally sensitized sheep.[12] In addition, it inhibits airway hyperresponsiveness (AHR). TYB-2285 (Figure 1) is now under investigation in Japan for asthma and atopic dermatitis in phase II clinical studies. In this paper, the synthesis structure–activity relationships and some pharmacological evaluations of this series compounds are described.

Chemistry

All the compounds (Table 1) were prepared from a commercially available acid chloride and *m*-phenylenediamine derivatives which were either commercially available or could be synthesized easily. Synthesis was carried out by General method A (Scheme 1). Compounds **4–13** ($R^1 = R^2$) were synthesized from *m*-phenylenediamine derivatives and 2.1–2.2 eq. acid chloride in high yields. These are symmetrical compounds, which are identified by ^{1}H NMR. Starting *m*-phenylenediamines (**3**) which were not commercially available, were

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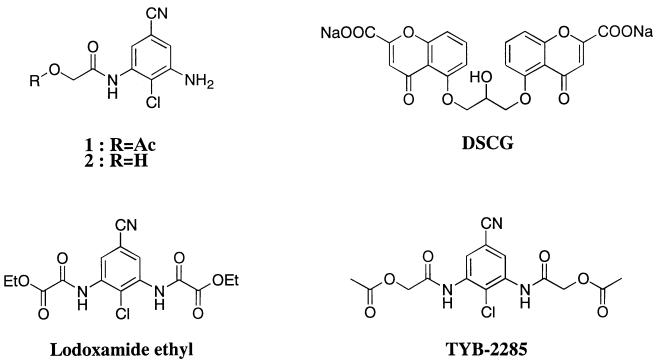


Figure 1. Structures of compounds **1** and **2**, DSCG, Lodoxamide ethyl and TYB-2285.

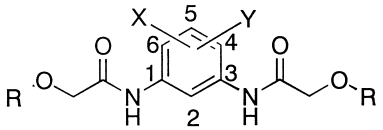
obtained from the corresponding *m*-dinitrobenzene derivatives by the method of Wright et al.[11] Hydroxyacetylamino derivatives (**6**) were synthesized from the corresponding acetoxyacetylamino derivatives (**5**) by hydrolysis in aqueous ammonia and methanol solution (General method B, Scheme 1). The methoxycarbonyl group of **5g** was not hydrolysed under these conditions. Propionyl, butyryl, isobutyryl, 2-acetoxybenzoyl and benzoyl derivatives (**7**, **9**, **10**, **11**, **12**) were synthesized by esterification of the corresponding hydroxy derivatives (**6**) (General method C, Scheme 1). 1,3-Diamino-4,6-dicarboxybenzene (**2j**) was synthesized by the method of Bogert et al.[13] from *m*-phenylenediamine. Compounds **14–20c** were synthesized from mono amide derivatives which were reported in the previous paper.[1] Compound **18c** was synthesized from silyl ether (**17c**) and acetoxyacetyl chloride. Other compounds were synthesized by General method D (Scheme 2). Piperidino, morpholino and methylsulfonyl derivatives were synthesized using a chloroacetyl derivative (**21c**). Chlorine atoms of its chloromethyl groups were substituted by secondary amine and thiomethyl groups easily (General method E, Scheme 3). All the compounds were determined by elementary analysis.

Results and Discussion

The effects of bis-amide derivatives in the rat PCA assay are shown in Table 1. The results of other compounds are listed in Table 2. In Table 1, where R is a hydrogen, methyl or lower acyl group, a series of compounds inhibited the PCA reaction by oral administration. Among those compounds, benzonitrile derivatives inhibited the PCA as strongly as ketotifen fumarate. Other compounds, which have $CONH_2$, COOMe, CF_3, or hydrogen atom as Y group, inhibited the PCA reaction slightly. When R are ethyl, phenyl, benzoyl groups, those compounds also showed a slight inhibition. Therefore, we investigated other benzonitrile compounds. The results are shown in Table 2. These compounds in which R^1 is different from R^2, also inhibited the rat PCA reaction. In the series of benzonitrile compounds shown in Tables 1 and 2, bigger R groups reduced activity in the rat PCA assay. In addition, compound **26c**, which has no oxygen atom at the α-position of the amide carbonyl group did not inhibit the rat PCA reaction. The result indicates that the oxygen atom at the α-position of the amide carbonyl group is important for inhibition of the rat PCA reaction. We then synthesized piperidino, morpholino and methanesulfonyl derivatives. However, these compounds showed no inhibition in the PCA assay by oral administration. Table 3 shows a comparison of compounds **4c**, **5c**, **4h** and **5h** in the PCA assay at a lower dose. All the compounds inhibit the PCA reaction in a dose dependent manner. The ED_{50} value of **5c** in this assay is 0.3 mg/kg p.o. It is clear that the compounds **4c** and **5c**, which have a chlorine atom at the 2-position, are more active than **4h** and **5h**.

Recently, it has been reported that eosinophil significantly relates to airway inflammation in asthma[14–16] and atopic dermatitis.[17] Therefore, we investigated the effect of these compounds on eosinophil adhesion to TNF-α-treated HUVEC. The results are shown in Table 4. Compounds **5c** and **6c** caused inhibition of eosinophil adhesion to TNF-α-treated HUVEC in the range of 10^{-8}–10^{-5} M. DSCG have no effect in the same range. Ketotifen fumarate showed no inhibition at less than 10^{-6} M, and neither did tranilast at less than 10^{-5} M. These concentrations are higher than the plasma concentrations of the drugs at their usual clinical doses. In comparison with DSCG, ketotifen fumarate and tranilast, compounds **5c** and **6c** inhibit at lower concentrations. Eosinophil adhesion to endothelial cells is the initial phase in the process of eosinophil accumulation. At the site of inflammation, cytokines such as TNF-α and interleukin-1 (IL-1), are released, and endothelial cells are activated. Recently, Tominaga et al.[3] showed that compounds **5c** and **6c** did not inhibit

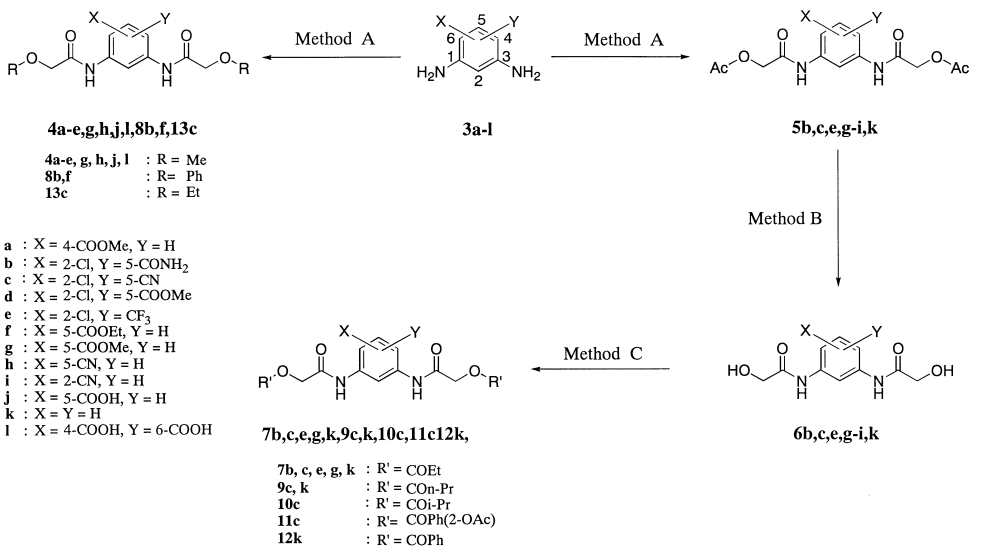
Table 1. Physical and pharmaceutical data of bisglycolic amide derivatives



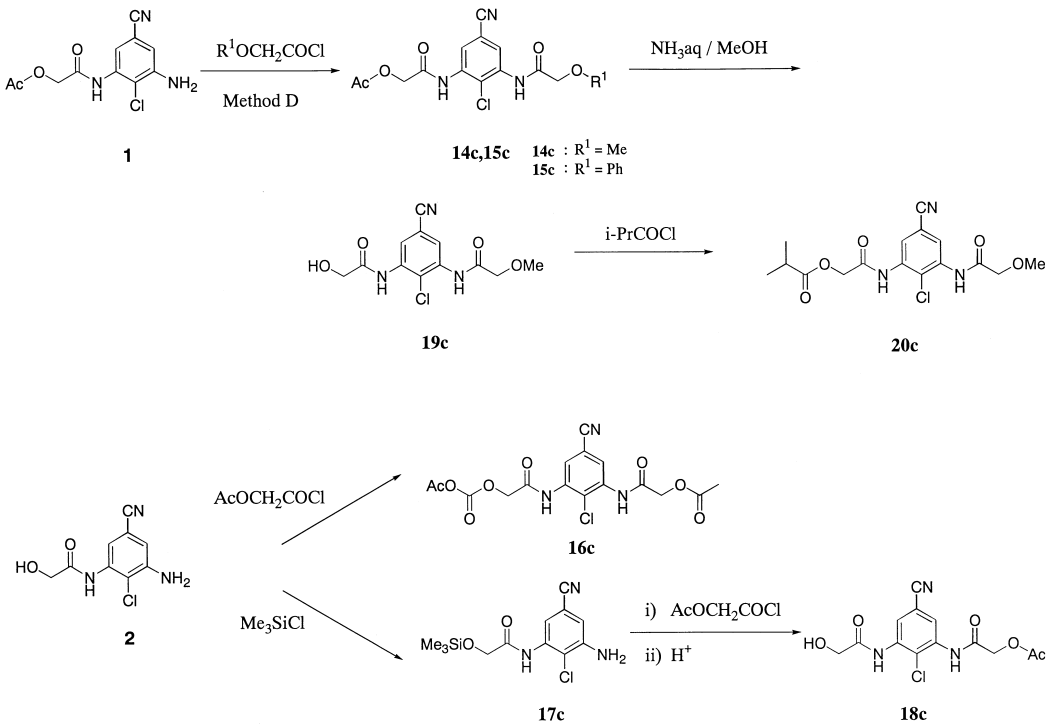
Compd no.	X	Y	R	mp (°C)	Formula	Yield (%)	Recryst. solvent[a]	PCA inhibition (%) 30 mg/kg p.o.
4a	4-COOEt	H	Me	90–91	$C_{15}H_{20}N_2O_5$	92	A	53
4b	2-Cl	5-$CONH_2$	Me	209	$C_{13}H_{16}N_3O_5Cl.1/2H_2O$	78	B	27
5b	2-Cl	5-$CONH_2$	Ac	216–218	$C_{15}H_{16}N_3O_7Cl$	53	C	ND
6b	2-Cl	5-$CONH_2$	H	254–257	$C_{11}H_{12}N_3O_5Cl$	67	C	ND
7b	2-Cl	5-$CONH_2$	COEt	195–198	$C_{17}H_{20}N_3O_7Cl$	90	D	NA
8b	2-Cl	5-$CONH_2$	Ph	250–251	$C_{23}H_{20}N_3O_5C$	61	C	ND
4c	2-Cl	5-CN	Me	173–174	$C_{13}H_{14}N_3O_4Cl$	59	B	70
13c	2-Cl	5-CN	Et	152–153	$C_{15}H_{18}N_3O_4Cl$	60	D	38
5c	2-Cl	5-CN	Ac	195	$C_{15}H_{14}N_3O_6Cl$	29	D	94
6c	2-Cl	5-CN	H	228 (Dec.)	$C_{11}H_{10}N_3O_4Cl$	62	D	77
7c	2-Cl	5-CN	COEt	141 (Dec.)	$C_{17}H_{18}N_3O_5Cl$	30	D	83
9c	2-Cl	5-CN	COnPr	143–144	$C_{19}H_{22}N_3O_6Cl$	48	D	91
10c	2-Cl	5-CN	COiPr	140–141	$C_{19}H_{22}N_3O_6Cl$	36	D	89
11c	2-Cl	5-CN	COPh(2-OAc)	166 (Dec.)	$C_{29}H_{22}N_3O_{10}Cl$	43	D	14
4d	2-Cl	5-COOMe	Me	162–164	$C_{14}H_{17}N_2O_6Cl$	77	D	NA
4e	2-Cl	5-CF_3	Me	160–162	$C_{13}H_{14}N_2O_4ClF_3$	70	D	NA
5e	2-Cl	5-CF_3	Ac	154–155	$C_{15}H_{14}N_2O_6ClF_3$	83	D	ND
6e	2-Cl	5-CF_3	H	285–287	$C_{11}H_{10}N_2O_4ClF_3$	78	D	ND
7e	2-Cl	5-CF_3	COEt	116–118	$C_{17}H_{18}N_2O_6Cl$	67	D	49
8f	5-COOEt	H	Ph	140–141	$C_{25}H_{24}N_2O_6$	62	D	NA
4g	5-COOMe	H	Me	140–141	$C_{14}H_{18}N_2O_6$	56	D	NA
5g	5-COOMe	H	Ac	195–197	$C_{16}H_{18}N_2O_8.1/4H_2O$	79	D	ND
6g	5-COOMe	H	H	222–225	$C_{12}H_{14}N_2O_6.1/4H_2O$	81	D	ND
7g	5-COOMe	H	COEt	167–168	$C_{18}H_{22}N_2O_8.1/4H_2O$	83	D	NA
4h	5-CN	H	Me	144 (Dec.)	$C_{13}H_{15}N_3O_4$	63	A	88
5h	5-CN	H	Ac	131 (Dec.)	$C_{15}H_{15}N_3O_6$	53	D	16
6h	5-CN	H	H	226–228	$C_{11}H_{11}N_3O_4.1/4H_2O$	71	D	ND
5i	2-CN	H	Ac	151–153	$C_{15}H15N_3O_6.1/4H_2O$	77	D	73
6i	2-CN	H	H	188–189	$C_{11}H_{11}N_3O_4$	70	D	ND
4j	5-COOH	H	Me	229 (Dec.)	$C_{13}H_{16}N_2O$	67	D	25
5k	H	H	Ac	150–151	$C_{16}H_{20}N_2O_6$	51	D	ND
6k	H	H	H	139–143	$C_{10}H_{12}N_2O_6.1/4H_2O$	82	D	ND
7k	H	H	COEt	130–132	$C_{16}H_{20}N_2O_6$	88	D	ND
12k	H	H	COPh	193–197	$C_{24}H_{20}N_2O_6$	95	D	ND
41	4-COOH	6-COOH	Me	281 (Dec.)	$C_{14}H_{16}N_2O_8.1/2H_2O$	24	E	NA
	ketotifen fumarate							91

[a]A: EtOAc/Hexane; B: EtOH/EtOAc/Hexane; C: MeOH; D: EtOH; E: EtOH/H_2O.
ND, Not done.
NA, Not active.

the adhesion of neutrophil at the same range (10^{-8}–10^{-5} M). Eosinophil adhesion to TNF-α-treated HUVEC was blocked by mAb against VLA-4 (anti-VLA-4), but not by that against Mac-1 (anti-Mac-1). However neutrophil adhesion was blocked by anti-Mac-1, but not by anti-VLA-4.[3] These results suggest that compounds **5c** and **6c** might block the VIA-4/VCAM-1 pathway selectively. Abraham et al.[14] showed that treatment with a monoclonal antibody (mAb) against VLA-4 inhibited the late response (LR) and airway hyper-responsiveness (AHR). In fact, the compound **5c**, named TYB-2285, inhibits the acute response (AR) and the LR in naturally-sensitized sheep.[12] In addition, it inhibits the AHR. Sagara et al.[15] demonstrated that a mAb against VLA-4 inhibited the LR in sensitized guinea pigs by inhibiting migration of eosinophils into the airway. Bently et al.[16] reported that VCAM-1 expression increased in patients with asthma after antigen challenge.



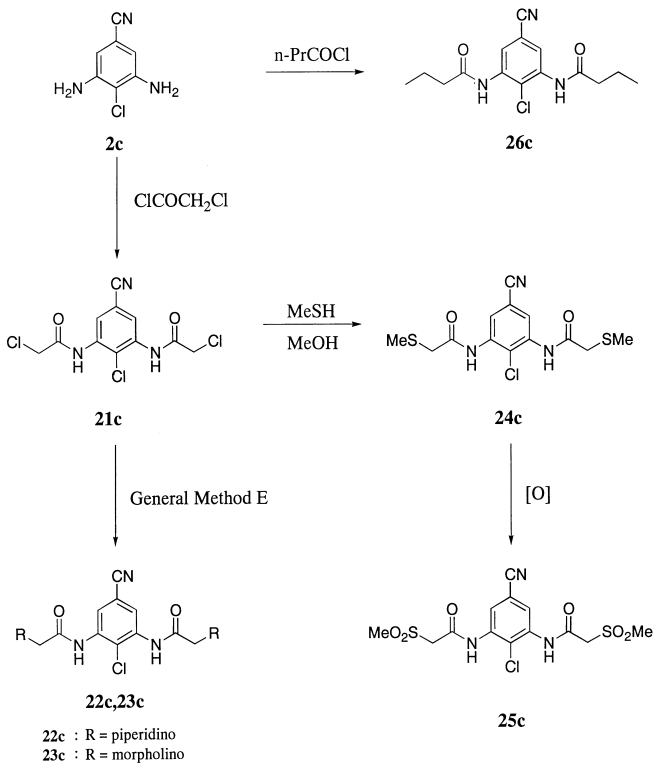
Scheme 1. Synthesis of bisglycolic amide derivatives.



Scheme 2. Synthesis of compounds **14c**, **15c**, **16c**, **18c**, **19c** and **20c**.

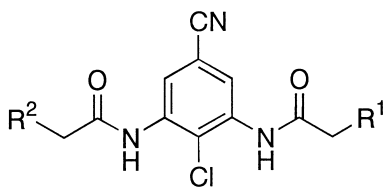
Groves et al.[17] showed that VCAM-1 was upregulated on dermal endothelium and dendritic cells in allergic contact dermatitis and atopic dermatitis patients. These results suggest that TYB-2285 may be suitable as a new type of antiallergic and antiinflammatory drug for treating allergic diseases such as asthma and atopic dermatitis.

Recently, Yasuda et al.[18] reported that anti-VLA-4 antibody, in combination with other anti-adhesion molecule antibodies, inhibited the PCA reaction. We speculate that TYB-2285 and its derivatives might inhibit the PCA reaction by a mechanism related with the inhibition of the VLA-4/VCAM-1 pathway. Further



Scheme 3. Synthesis of compounds **22c**–**26c**.

Table 2. Physical and pharmaceutical data of benzonitrile derivatives



Compd no.	R^1	R^2	mp (°C)	Formula	Yield (%)	Recryst. solvent[a]	PCA inhibition (%) 30 mg/kg p.o.
14c	OMe	OAc	159–160	$C_{14}H_{14}N_3O_5Cl$	85	A	92
15c	OPh	OAc	212–213	$C_{19}H_{16}N_3O_5Cl$	78	A	75
16c	OAc	$OCOCH_2OAc$	154–157	$C_{17}H_{16}N_2O_8Cl$	70	A	81
18c	OH	OAc	213–216	$C_{13}H_{12}N_3O_3Cl$	38	—[b]	95
19c	OH	OMe	160 (Dec.)	$C_{12}H_{12}N_3O_4Cl$	86	A	94
20c	OMe	$OCOCH(CH_3)_2$	119–120	$C_{16}H_{18}N_3O_5Cl$	72	A	89
22c	piperidino	piperidino	290 (Dec.)	$C_{21}H_{28}N_5O_2Cl$	84	B	ND
23c	morpholino	morpholino	296 (Dec.)	$C_{19}H_{24}N_5O_4Cl$	79	B	35
25c	SO_2Me	SO_2Me	204 (Dec.)	$C_{13}H_{14}N_3O_6S_2Cl$	44	C	NA
26c	Et	Et	200–201	$C_{15}H_{18}N_3O_2Cl$	53	C	NA

[a]A: EtOH; B: CH_3Cl/Toluene; C: MeOH.
[b]Not recryst.
ND, Not done.
NA, Not active.

Table 3. Effect of compounds in rat PCA assay

Compd no.	Inhibition (%) of rat PCA Dose (mg/kg p.o.)				
	30	10	3	1	(ED_{50})
4c	91**	84**	75**	52**	(0.3 mg/kg)
5c	93**	76**	52**		
4h	88**	79**	46*		
5h		16	6		
ketotifen[a]	91**	76**	35*	18	

[a]ketotifen fumarate.
* $p < 0.05$, ** $p < 0.01$ versus control.

Table 4. Effect of compounds on eosinophil adhesion to TNF-α-treated HUVEC

Compd no.	Percentage of cell adhesion Concentration of test compounds			
	10^{-8} M	10^{-7} M	10^{-6} M	10^{-5} M
5c	78*	58**	52**	32**
6c	54**	25***	16***	5***
ketotifen[a]			NA	49**
DSCG			NA	NA
tranilast		NA	22**	38*

[a]ketotifen fumarate.
NA, Not active.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus control (%) adhesion of eosinophils to TNF-α-treated HUVEC in the absence of test compounds.

studies are required to determine the precise mechanism of these compounds.

Conclusion

We have synthesized a number of bis-glycolylacetylaminobenzene derivatives and investigated their pharmacological activity. Among them, 3,5-bis(glycolylacetylamino)benzonitrile derivatives showed antiallergic activity in the PCA assay at 30 mg/kg p.o. and marked inhibition of eosinophil adhesion to TNF-α-treated HUVEC in the range of 10^{-8}–10^{-5} M. One of the compounds, 3,5-bis(acetoxyacetylamino)-4-chlorobenzonitrile (**5c**), named TYB-2285, is now being investigated in Japan for asthma and atopic dermatitis in phase II clinical studies.

Experimental

Melting points were determined with a Mettler capillary melting-point apparatus (Model FP 61) and uncorrected. ^{1}H NMR spectra were recorded on a Varian FT 80A spectrometer or a Varian Gemini-200 spectrometer using TMS as an internal standard. ^{13}C NMR were recorded on a Varian XL-300 spectrometer using TMS as an internal standard. Elemental analyses were performed at Kyoto University and TOYOBO analytical center. All starting materials were commercially available unless otherwise noted.

Passive cutaneous anaphylaxs (PCA) assay. Male Wistar rats (weighing about 200 g) were passively sensitized by intradermal injection of 0.1 mL of a solution of rat antiserum to egg albumin in each of two sites (four sites in total) at both sides of the dorsal median line. After 48 h, each rat was challenged by injecting a mixture (1 mL) of egg albumin and Evans blue solution via the tail vein to induce passive cutaneous anaphylaxis (PCA). Thirty minutes after the challenge, the rats were sacrificed to take the bluing region, and the amount of pigment from the bluing region was measured by the method of Katayama et al.[19] Test compounds were orally administrered to the rats (six rats/group) at a dose of 3 mg/kg 30 min before the antigen challenge.

Eosinophil adhesion to TNF-α-treated HUVEC. CSFE-labeled eosinophils (1×10^5 cells/well) were layered over HUVEC prestimulated with TNF-α. After 20 min of incubation, unbound cells were removed by plate inversion in RPMI-1640 for 30 min at room temperature. After adding 0.3% Triton X to the adherent cells, the intensity of fluorescence was measured using an automated microplate fluorometer with 485/22 nM excitation and a 530/25 nM emission filter. HUVEC were incubated with each compound for 6 h during treatment with 100 U/mL TNF-α, and were washed before the adhesion assay. Eosinophils were also preincubated for 20 min with each compound, and were then recoincubated with HUVEC in the presence of compounds. For the experiments evaluating the compounds, the percentage of control was calculated according to the following formula:

Percentage of control = (the percentage adhering to 100 U/mL of TNF-α-treated HUVEC in the presence of compounds − the percentage adhering to untreated HUVEC)/(the percentage adhering to 100 U/mL of TNF-α-treated HUVEC in the absence of compounds − the percentage adhering to untreated HUVEC).

General method A. Ethyl 2,4-bis(methoxyacetylamino) benzoate (4a). Methoxyacetyl chloride (4.0 mL) was added dropwise to a solution of ethyl 2,4-diaminobenzoate (3.6 g) in pyridine (80 mL) at room temperature. The mixture was stirred at room temperature for 3 h. Thereafter, pyridine was distilled off under reduced pressure. Water was added to the residue, and the resulting mixture was extracted with chloroform. The organic layer was washed with water and saturated

sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The resulting solids were recrystallized from ethyl acetate/hexane to give 6.0 g of **4a**; mp 90–91 °C. ^{1}H NMR (DMSO-d_6) δ: 11.50 (1H, s), 10.12 (1H, s), 8.86 (1H, d, J = 2 Hz), 7.91 (1H, d, J = 6 Hz), 7.55 (1H, dd, J = 6 Hz and J = 2 Hz), 4.28 (2H, q, J = 7 Hz), 4.00 (1H, s), 3.42 (1H, s), 3.34 (3H, s), 1.32 (3H, t, J = 7 Hz). Anal. calcd for $C_{15}H_{20}N_2O_6$: C, 55.55; H, 6.22; N, 8.64, found: C, 55.57; H, 6.24; N, 8.64.

Compounds **4b–e**, **g**, **h**, **j–l**, **5b**, **c**, **e**, **g–i**, **8b**, **8f**, **13c** and **26c** were prepared in the same manner as **4a** (General method A).

3,5-Bis(methoxyacetylamino)-4-chlorobenzamide hemihydrate (4b). From 3,5-diamino-4-chlorobenzamide (2.8 g) and methoxyacetyl chloride (3.0 mL): 4.0 g of **4b**; mp 209 °C. ^{1}H NMR (DMSO-d_6) δ: 9.43 (1H, s), 8.11 (2H, s), 7.98 (1H, s), 7.40 (1H, s), 4.06 (4H, s), 3.42 (6H, s). Anal. calcd for $C_{13}H_{16}N_3O_5Cl{\cdot}1/2H_2O$: C, 46.09; H, 5.06; N, 12.40; Cl, 10.47, found: C, 45.84; H, 5.16; N, 12.29; Cl, 10.47.

3,5-Bis(acetoxyacetylamino)-4-chlorobenzamide (5b). From 4-chloro-3,5-diaminobenzamide (5.6 g) and acetoxyacetyl chloride (7.2 mL): 6.2 g of **5b**; mp 216–218 °C; ^{1}H NMR (DMSO-d_6) δ: 9.79 (2H, s), 7.98 (2H, s), 7.95 (2H, s), 7.35 (1H, s), 4.70 (4H, s), 2.11 (6H, s). Anal. calcd for $C_{15}H_{16}N_3O_7Cl$: C, 46.70; H, 4.18; N, 10.89, found: C, 46.65; H, 4.28; N, 10.71.

3,5-Bis(phenoxyacetylamino)-4-chlorobenzamide (8b). From 4-chloro-3,5-diaminobenzamide (2.4 g) and phenoxyacetyl chloride (4.0 mL): 3.6 g of **8b**; mp 250–251 °C. ^{1}H NMR (DMSO-d_6) δ: 9.89 (2H, s), 8.08 (2H s), 7.99 (1H, s), 7.60–6.80 (11H, m), 4.78 (4H, s). Anal. calcd for $C_{23}H_{20}N_3O_5Cl$: C, 60.86; H, 4.48; N, 9.26, found: C, 60.82; H, 4.50; N, 9.29.

3,5-Bis(methoxyacetylamino)-4-chlorobenzonitrile (4c). From 4-chloro-3,5-diaminobenzonitrile (3.3 g) and methoxyacetyl chloride (4.0 mL): 5.1 g of **4c**; mp 173–174 °C. ^{1}H NMR (DMSO-d_6) δ: 9.50 (2H, s), 8.11 (2H, s), 4.07 (4H, s), 3.41 (6H, s). Anal. calcd for $C_{13}H_{14}N_3O_4Cl$: C, 50.09; H, 4.53; N, 13.48; Cl, 11.37, found: C, 50.11; H, 4.34; N, 13.50; Cl, 11.47.

3,5-Bis(ethoxyacetylamino)-4-chlorobenzonitrile (13c). From 4-chloro-3,5-diaminobenzonitrile (3.3 g) and ethoxyacetyl chloride (4.8 mL): 4.0 g of **13c**; mp 152–153 °C; ^{1}H NMR (DMSO-d_6) δ: 9.45 (2H, s), 8.15 (2H, s), 4.10 (4H, s), 3.60 (4H, q, J = 7 Hz), 1.21 (6H, t, J = 7 Hz). Anal. calcd for $C_{15}H_{18}N_3O_4Cl$: C, 53.02; H, 5.34; N, 12.37; Cl, 10.43, found: C, 53.15; H, 5.33; N, 12.51; Cl, 10.43.

3,5-Bis(acetoxyacetylamino)-4-chlorobenzonitrile (5c). From 4-chloro-3,5-diaminobenzonitrile (67 g) and acetoxyacetyl chloride (95 mL): 43 g of **5c**; mp 195 °C. ^{1}H NMR (DMSO-d_6) δ: 9.94 (2H, s), 4.73 (4H, s), 2.10 (6H, s). ^{13}C NMR (DMSO-d_6) δ: 170.09 (s), 166.73 (s), 136.42 (s), 125.90 (s), 125.07 (d), 117.69 (s), 109.89 (s), 62.47 (t), 20.58 (t). Anal. calcd for $C_{15}H_{14}N_3O_6Cl$: C, 48.99; H, 3.92; N, 11.43; Cl, 9.64, found: C, 49.05; H, 3.84; N, 11.49; Cl, 9.50.

Methyl 3,5-bis(methoxyacetylamino)-4-chlorobenzoate (4d). From methyl 4-chloro-3,5-diaminobenzoate dihydrochloride (1.1 g) and methoxyacetyl chloride (0.8 mL): 1.1 g of **4d**; mp 162–164 °C. ^{1}H NMR (DMSO-d_6) δ: 9.41 (2H, s), 8.28 (2H, s), 4.07 (4H, s), 3.85 (3H, s), 3.43 (6H, s). Anal. calcd for $C_{14}H_{17}N_2O_6Cl$; C, 48.78; H, 4.97; N, 8.13; Cl, 10.28, found: C, 48.73; H, 5.10; N, 8.13; Cl, 10.13.

3,5-Bis(methoxyacetylamino)-4-chlorobenzotrifluoride (4e). From 4-chloro-3,5-diaminobenzotrifluoride (4.2 g) and methoxyacetyl chloride (4.0 mL): 5.0 g of **4e**; mp 160–162 °C. ^{1}H NMR (DMSO-d_6) δ: 9.50 (2H, s), 8.08 (2H, s), 4.08 (4H, s), 3.41 (6H, s). Anal. calcd for $C_{13}H_{14}N_2O_4ClF_3$: C, 44.02; H, 3.98; N, 7.90; Cl, 9.99; F, 16.07, found: C, 44.17; H, 3.97; N, 7.95; Cl, 9.87; F, 15.99.

3,5-Bis(acetoxyacetylamino)-4-chlorobenzotrifluoride (5e). From 4-chloro-3,5-diaminobenzotrifluoride (4.2 g) and acetoxyacetyl chloride (5.6 mL): 6.8 g of **5e**; mp 154–155 °C ^{1}H NMR (DMSO-d_6) δ: 9.92 (2H, s), 7.94 (2H, s), 4.73 (4H, s), 2.12 (6H, s). Anal. calcd for $C_{15}H_{14}N_2O_6ClF_3$: C, 43.86; H, 3.44; N, 6.82, found: C, 43.77; H, 3.32; N, 6.82.

Ethyl 3,5-bis(phenoxyacetylamino)benzoate (8f). From ethyl 3,5-diaminobenzoate dihydrochloride (2.5 g) and phenoxyacetyl chloride (3.0 mL): 2.1 g of **8f**; mp 140–141 °C. ^{1}H NMR (DMSO-d_6) δ: 10.32 (2H, s), 8.31 (1H, dd, J = 2 Hz and J = 2 Hz), 8.01 (2H, d, J = 2 Hz), 7.95–6.75 (10H, m), 4.69 (4H, s), 4.29 (2H, q, J = 7 Hz), 1.30 (3H, t, J = 7 Hz). Anal. calcd for $C_{25}H_{24}N_2O_6Cl$: C, 66.95; H, 5.39; N, 6.25, found: C, 66.97; H, 5.38; N, 6.25.

Methyl 3,5-bis(methoxyacetylamino)benzoate (4g). From methyl 3,5-diaminobenzoate dihydrochloride (7.2 g) and methoxyacetyl chloride (6.0 mL): 5.2 g of **4g**; mp 140–141 °C. ^{1}H NMR (DMSO-d_6) δ: 10.06 (2H,s), 8.78 (1H, dd, J = 2 Hz and J = 2 Hz), 8.00 (2H, d, J = 2 Hz), 3.98 (4H, s), 3.82 (3H, s), 3.36 (6H, s). Anal. calcd for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.85; N, 9.03, found: C, 54.12; H, 5.85; N, 9.00.

Methyl 3,5-bis(acetoxyacetylamino)benzoate 1/4 hydrate (5g). From methyl 3,5-diaminobenzoate (8.3 g) and acetoxyacetyl chloride (11.9 mL): 14.6 g of **5g**; mp 195–197 °C. ^{1}H NMR (DMSO-d_6) δ: 10.25 (2H, s), 8.14

(1H, dd, $J=2$ Hz and $J=2$ Hz), 7.92 (2H, d, $J=2$ Hz), 4.16 (4H, s), 3.82 (3H, s), 2.11 (6H, s) Anal. calcd for $C_{16}H_{18}N_2O_8 \cdot 1/4H_2O$: C, 51.82; H, 5.03; N, 7.55, found: C, 51.98; H, 4.91; N, 7.61.

3,5-Bis(methoxyacetylamino)benzonitrile (4h). From 3,5-diaminobenzonitrile (4.4 g) and methoxyacetyl chloride (6.0 mL): 4.3 g of **4h**; mp 144 °C. ^{1}H NMR (DMSO-d_6) δ: 10.06 (2H, s), 8.30 (1H, dd, $J=2$ Hz and $J=2$ Hz), 7.75 (2H, d, $J=2$ Hz), 4.00 (4H, s), 3.36 (6H, s). Anal. calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15, found: C, 56.24; H, 5.54; N, 15.21.

3,5-Bis(acetoxyacetylamino)benzonitrile 1/4 hydrate (5h). From 3,5-diaminobenzonitrile (5.9 g) and acetoxyacetyl chloride (9.5 mL): 7.2 g of **5h**; mp 131 °C (Dec.). ^{1}H NMR (DMSO-d_6) δ: 10.38 (2H, s), 8.10 (1H, dd, $J=2$ Hz and $J=2$ Hz), 7.65 (2H, d, $J=2$ Hz), 4.62 (4H, s), 2.09 (6H, s). Anal. calcd for $C_{15}H_{15}N_3O_6 \cdot 1/4H_2O$: C 53.33; H, 4.62; N, 12.44, found: C, 53.28; H, 4.55; N, 13.37.

2,6-Bis(acetoxyacetylamino)benzonitrile (5i). From 2,6-diaminobenzonitrile (9.3 g) and acetoxyacetyl chloride (24 mL): 18.0 g of **5i**; mp 151–153 °C. ^{1}H NMR (DMSO-d_6) δ: 10.25 (2H, s), 7.85–7.40 (3H, m), 4.66 (4H, s), 2.11 (6H, s). Anal. calcd for $C_{15}H_{15}N_3O_6$: C, 54.05; H, 4.54; N, 12.61, found: C, 54.03; H, 4.56; N, 12.57.

3,5-Bis(methoxyacetylamino)benzoic acid (4j). From 3,5-diaminobenzoic acid (6.1 g) and methoxyacetyl chloride (8.0 mL): 8.0 g of **4j**; mp 229 °C (Dec.). ^{1}H NMR (DMSO-d_6) δ: 12.87 (1H, s), 9.92 (2H, s), 8.32–8.17 (1H, m), 8.04–7.90 (2H, m), 3.97 (4H, s), 3.35 (6H, s). Anal. calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46; found: C, 52.82; H, 5.45; N, 9.60.

1,3-Bis(acetoxyacetylamino)benzene (5k). From *m*-phenylenediamine (21.6 g) and acetoxyacetyl chloride (56 mL): 36.1 g of **5k**; mp 150–151 °C. ^{1}H NMR (DMSO-d_6) δ: 10.04 (2H, s), 7.93–7.80 (1H, m), 7.30–7.15 (3H, m), 4.61 (4H, s), 2.12 (6H, s). Anal. calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.09, found: C, 54.52; H, 5.16; N, 9.08.

4,6-Bis(methoxyacetylamino)-*m*-phthalic acid hemihydrate (4l). From 4,6-diamino-*m*-phthalic acid (5.4 g) and methoxyacetyl chloride (5.5 mL): 2.5 g of **4l**; mp 277 °C (Dec.). ^{1}H NMR (DMSO-d_6) δ: 12.00 (2H, s), 9.92 (1H, s), 8.63 (1H, s), 4.02 (4H, s), 3.42 (6H, s). Anal. calcd for $C_{14}H_{16}N_2O_8 \cdot 1/2H_2O$: C, 48.14; 4.91; N, 8.02, found: C, 48.12; H, 4.86; N, 8.02.

3,5-Bis(butyrylamino)-4-chlorobenzonitrile (26c). From **3c** (3.4 g) and butyryl chloride (4.6 mL): 3.3 g of **26c**; mp 200–201 °C. ^{1}H NMR (DMSO-d_6) δ: 9.67 (2H, s). 7.93 (2H, s), 2.37 (4H, t, $J=7$ Hz), 1.62 (4H, m), 0.94 (6H, t, $J=7$ Hz). Anal. calcd for $C_{15}H_{18}N_3O_2Cl$: C, 58.54; H, 5.89; N, 13.65; Cl, 11.52, found: C, 58.37; H, 5.83; N, 13.54; Cl, 11.46.

General method B. 3,5-Bis(hydroxyacetylamino)-4-chlorobenzamide (6b). To a solution of **5b** (0.8 g) in methanol (100 mL) was added dropwise 28% aqueous ammonia (10 mL). The mixture was stirred at room temperature for 2 h. Thereafter, the solvent was distilled off under reduced pressure. The resulting solids were recrystallized from ethanol to give 0.4 g of **6b**; mp 254–257 °C. ^{1}H NMR (DMSO-d_6) δ: 9.45 (2H, s), 8.30 (2H, s), 7.97 (1H, s), 7.40 (1H, s), 6.10 (2H, t, $J=4$ Hz) 4.08 (4H, d, $J=4$ Hz). Anal. calcd for $C_{11}H_{12}N_3O_5Cl$: C, 43.79; H, 4.01; N, 13.93, found: C, 43.89; H, 4.21; N, 13.85.

Compounds **6c**, **e**, **g–i** and **k** were prepared in the same manner as **6b** (General method B).

3,5-Bis(hydroxyacetylamino)-4-chlorobenzonitrile (6c). From **5c** (27 g): 13 g of **6c**; mp 228 °C (Dec.). ^{1}H NMR (DMSO-d_6) δ: 8.27 (2H, s), 7.85 (2H, s), 4.70 (4H, s), 3.30 (2H, s). Anal. calcd for $C_{11}H_{10}N_3O_4Cl$: C, 46.58; H, 3.55; N, 14.81; Cl, 12.50, found: C, 46.57; H, 3.73; N, 14.81; Cl, 12.24.

3,5-Bis(hydroxyacetylamino)-4-chlorobenzotrifluoride (6e). From **7c** (4.1 g): 2.1 g of **6e**; mp 285–287 °C. ^{1}H NMR (DMSO-d_6) δ: 7.94 (2H, s), 8.29 (2H, s), 4.07 (4H, s). Anal. calcd for $C_{11}H_{10}N_2O_4ClF_3$: C, 40.45; H, 3.09; N, 8.58, found: C, 40.50; H, 3.06; N, 8.55.

Methyl 3,5-bis(hydroxyacetylamino)benzoate 1/4 hydrate (6g). From **5g** (8.0 g): 5.0 g of **6g**); mp 222–225 °C. ^{1}H NMR (DMSO-d_6) δ: 9.86 (2H, s), 8.23 (1H, dd, $J=2$ Hz), 8.02 (2H, d, $J=2$ Hz), 5.54 (2H, t, $J=5$ Hz), 3.96 (4H, d, $J=5$ Hz) 3.81 (3H, s) Anal. calcd for $C_{12}H_{14}N_2O_6 \cdot 1/4H_2O$: C, 50.26; H, 5.10; N, 9.77, found: C, 50.54; H, 4.95; N, 9.85.

3,5-Bis(hydroxyacetylamino)benzonitrile 1/4 hydrate (6h). From **5h** (2.3 g): 1.2 g of **6h**; mp 226–228 °C. ^{1}H NMR (DMSO-d_6) δ: 9.94 (2H, s), 8.35 (1H, dd, $J=2$ Hz and $J=2$ Hz), 7.79 (2H, d, $J=2$ Hz), 5.60 (2H, s), 3.99 (4H, s). Anal. calcd for $C_{11}H_{11}N_3O_4 \cdot 1/4H_2O$: C, 52.07; H, 4.57; N, 16.56, found: C, 52.28; H, 4.50; N, 16.76.

2,6-Bis(hydroxyacetylamino)benzonitrile (6i). From **5i** (6.7 g): 3.8 g of **6i**; mp 188–189 °C. ^{2}H NMR (DMSO-d_6) δ: 9.60 (2H, s), 7.61 (3H, m), 6.12 (2H, s), 4.02 (4H, s). Anal. calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86, found: C, 53.69; H, 4.45; N, 16.85.

1,3-Bis(hydroxyacetylamino)benzene 1/4 hydrate (6k). From **5k** (30.0 g): 18.1 g of **6k**; mp 139–143 °C. ^{1}H NMR (DMSO-d_6) δ: 10.54 (2H, s), 8.04–7.90 (1H, m),

7.45–7.00 (3H, m), 5.52 (2H, t, $J=6$ Hz), 3.94 (4H, d, $J=6$ Hz). Anal. calcd for $C_{10}H_{12}N_2O_4 \cdot 1/4H_2O$: C, 52.51; H, 5.55; N, 12.25, found: C, 52.62; H, 5.59; N, 12.29.

General method C. 3,5-Bis(propionyloxyacetylamino)-4-chlorobenzamide (7b). Propionyl chloride (0.3 mL) was added dropwise to a solution of the compound **6b** (0.56 g) in pyridine (15 mL) at room temperature. The mixture was stirred at room temperature for 1 h. Thereafter, pyridine, was distilled off reduced pressure to remove the solvent. Water was added to the residue. The resulting solids were filtered and recrystallized from ethanol to give 0.6 g of **7b**; mp 195–198 °C. ^{1}H NMR (DMSO-d_6) δ: 9.79 (2H, s), 7.99 (1H, s), 7.96 (2H, s), 7.39 (1H, s), 4.72 (4H, s), 2.42 (4H, q, $J=7$ Hz), 1.08 (6H, t, $J=7$ Hz). Anal. calcd for $C_{17}H_{20}N_3O_7Cl$: C, 49.34; H, 4.87; N, 10.15, found: C, 49.10; H, 5.00; N, 10.03.

Compounds **7c**, **e**, **g**, **k**, **9c**, **10c**, **11c** and **12k** were prepared in the same manner as **7b** (General method C).

3,5-Bis(propionyloxyacetylamino)-4-chlorobenzonitrile (7c). From **6c** (1.7 g) and proionyl chloride (1.3 mL): 1.2 g of **7c**; mp 141 °C (Dec.). ^{1}H NMR (DMSO-d_6) δ: 9.93 (2H, s), 7.97 (2H s), 4.75 (4H, s), 2.43 (4H, q, $J=7$ Hz), 1.09 (6H, t, $J=7$ Hz). Anal. calcd for $C_{17}H_{18}N_3O_6Cl$: C, 51.59; H, 4.58; N, 10.62; Cl, 8.96, found: C, 51.62; H, 4.64; N, 10.53; Cl, 8.82.

3,5-Bis(butyryloxyacetylamino)-4-chlorobenzonitrile (9c). From **6c** (2.8 g) and butyryl chloride (2.3 mL), 2.3 g of **9c**; mp 143–144 °C. ^{1}H NMR (DMSO-d_6) δ: 9.93 (2H,s), 7.98 (2Hs), 4.75 (4H,s), 2.40 (4H, q, $J=7$ Hz), 1.60 (4H, m), 0.94 (6H, t, $J=7$ Hz). Anal. calcd for $C_{19}H_{22}N_3O_6Cl$: C, 53.84; H, 5.23; N, 9.91, found: C, 53.62; H, 5.28; N, 9.98.

3,5-Bis(isobutyryloxyacetylamino)-4-chlorobenzonitrile (10c). From **6c** (2.8 g) and isobutyryl chloride (2.6 mL): 2.8 g of **10c**; mp 140–141 °C. ^{1}H NMR (DMSO-d_6) δ: 9.92 (2H, s), 7.99 (2H, s), 4.75 (4H, s), 2.85–2.45 (2H, m), 1.14 (12H, d, $J=8$ Hz),. Anal. calcd for $C_{19}H_{22}N_3O_6Cl$: C, 53.84; H, 5.23; N, 9.91, found: C, 53.59; H, 5.29; N, 9.92.

3,5-Bis(2-acetoxybenzoyloxyacetylamino)-4-chlorobenzonitrile (11c). From **6c** (2.8 g) and 2-acetoxybenzoyl chloride (4.4 g): 2.6 g of **11C**; mp 166 °C (Dec). ^{1}H NMR (DMSO-d_6) δ: 10.08 (2H, s), 8.25–7.10 (10H, m), 5.00 (4H, s), 2.27 (6H, s). Anal. calcd for $C_{29}H_{22}N_3O_{10}Cl$: C, 57.29; H, 3.65; N, 6.91, found: C, 57.01; H, 3.63; N, 6.89.

3,5-Bis(propionyloxyacetylamino)-4-chlorobenzotrifluoride (7e). From **7d** (1.2 g) and propionyl chloride (0.67 mL): 1.0 g of **7e**; mp 116–118 °C. ^{1}H NMR (DMSO-d_6) δ: 9.92 (2H, s), 7.93 (2H, s), 4.76 (4H, s), 2.44 (4H, q, $J=8$ Hz), 1.09 (6H, t, $J=8$ Hz). Anal. calcd for $C_{17}H_{18}N_2O_6ClF_3$: C, 46.53; H, 4.13; N, 6.38, found: C, 46.79; H, 4.22; N, 6.38.

Methyl 3,5-bis(propionyloxyacetylamino)benzoate 1/4 hydrate (7g). From **6g** (2.1 g) and propionic anhydride (5 mL): 2.5 g of **7g**; mp 167–168 °C. ^{1}H NMR (DMSO-d_6) δ: 10.26 (2H, s), 8.12 (1H, dd, $J=2$ Hz and $J=2$ Hz), 7.91 (2H, d, $J=2$ Hz), 4.72 (4H, s), 3.87 (3H, s), 2.41 (4H, q, $J=8$ Hz), 1.06 (6H, t, $J=8$ Hz). Anal. calcd for $C_{18}H_{22}N_2O_8.1/4H_2O$: C, 54.20; H, 5.68; N, 7.02, found: C, 54.41; 5.47; N, 7.13.

1,3-Bis(propionyloxyacetylamino)benzene (7k). From **6k** (2.2 g) and propionyl chloride (1.9 m): 3.0 g of **7k**; mp 130–132 °C. ^{1}H NMR (DMSO-d_6) δ: 10.01 (2H, s), 7.88 (1H, m), 7.35–7.15 (3H, m), 4.60 (4H, s), 2.40 (4H, q, $J=7$ Hz), 1.05 (6H, t, $J=7$ Hz). Anal. calcd for $C_{16}H_{20}N_2O_6$: C, 57.14; H, 5.99; N, 8.33, found: C, 57.04; H, 6.01; N, 8.35.

1,3-Bis(benzoyloxyacetylamino)benzene 1/4 hydrate (12k). From **6k** (2.2 g) and benzoyl chloride (2.6 g): 4.2 g of **12k**; mp 193–197 °C. ^{1}H NMR (DMSO-d_6) δ: 10.18 (2H, s), 8.22–7.05 (14H, m), 4.89 (4H, s). Anal. calcd for $C_{24}H_{20}N_2O_6$ $1/4H_2O$: C, 65.97; H; 4.73; N, 6.41, found: C, 66.09; H, 4.71; N, 6.61.

General method D. 3-(Acetoxyacetylamino)-4-chloro-5-(methoxyacetylamino)benzonitrile (14c). Methoxyacetyl chloride (1.0 mL) was added dropwise to a solution of 3-acetoxyacetylamino-5-amino-4-chlorobenzonitrile (2.7 g) in pyridine (50 mL) at room temperature. The mixture was stirred for 1 h at room temperature. Thereafter, the solvent was distilled off under reduced pressure. To the residue was added water and resulting solids were washed with water. The solids were recrystallized from ethanol to give 2.1 g of **14c**; mp 159–160 °C. ^{1}H NMR (DMSO-d_6) δ: 9.85 (1H, s), 9.64 (1H, s), 8.12 (1H, d, $J=2$ Hz), 7.97 (1H, d, $J=2$ Hz), 4.75 (2H, s), 4.08 (2H, s), 3.43 (3H, s), 2.13 (3H, s). Anal. calcd. for $C_{14}H_{14}N_3O_5Cl$: C, 49.50; H, 4.15; N, 12.37, found: C, 49.30; H, 4.12; N, 12.33.

Compounds **15c** and **16c** were prepared in the same manner as **14c** (General method D). In the case of **16c**, 2 equiv. acid chloride were used.

3-(Acethoxyacetylamino)-4-chloro-5-phenoxyacetylaminobenzonitrile (15c). From 3-acetoxyacetylamino-5-amino-4-chlorobenzonitrile (2.7 g) and phenoxyacetyl chloride (1.5 mL): 3.1 g of **15**; mp 212–213 °C. ^{1}H NMR (DMSO-d_6) δ: 9.96 (1H, s), 9.82 (1H, s), 8.09 (1H, d, $J=3$ Hz), 7.99 (1H, d, $J=3$ Hz), 7.52–6.82 (5H, m), 4.80 (2H, s), 4.76 (3H, s), 2.12 (3H, s). Anal. calcd for

$C_{19}H_{16}N_3O_5Cl$: C, 56.80; H, 4.01; N, 10.46, found: C, 56.73; H, 4.08; N, 10.47.

3-(Acetoxyacetylamino)-5-[(acetoxyacetoxy)acetylamino]-4-chlorobenzonitrile (16c). From 3-amino-4-chloro-5-(hydroxyacetylamino)benzonitrile (2.3 g) and acetoxyacetyl chloride (2.4 mL): 3.0 g of **16c**; mp 154–157 °C. ^{1}H MMR (DMSO-d_6) δ: 9.98 (1H, s), 7.97 (2H, s), 4.85 (2H, s), 4.77 (2H, s), 4.74 (2H, s), 2.13 (3H, s), 2.13 (3H, s). Anal. calcd for $C_{17}H_{16}N_3O_8Cl$: C, 47.96; H, 3.79; N, 9.87, found: C, 47.75; H, 3.77; N, 9.90.

3-Amino-4-chloro-5-(trimethylsiloxyacetylamino)benzonitrile (17c). Triethylamine (2.8 mL) was added to a solution of 3-amino-4-chloro-5-(hydroxyacetylamino) benzonitrile (2.3 g) in tetrahydrofuran (100 mL). Trimethylsilyl chloride (2.5 mL) was added dropwise to the mixture at room temperature. The mixture was stirred at room temperature for 20 h. Thereafter, the solvent was distilled off reduced pressure. The resulting solids were filtered and washed with water. The solids were recrystallized from ethyl acetate/hexane to give 2.0 g of **17c**; mp 132–133 °C. ^{2}H NMR (DMSO-d_6) δ: 9.22 (1H, 8), 7.68 (1H, d, $J=2$ Hz), 6.90 (1H, d, $J=2$ Hz), 5.97 (2H, s), 4.19 (2H, s), 0.20 (9H, s).

3-(Acetoxyacetylamino)-4-chloro-5-(hydroxyacetylamino) benzonitrile (18c). Acetoxyacetyl chloride (0.5 mL) was added dropwise to a solution of the compound **1** (1.5 g) in dichloromethane (100 mL) at room temperature. The mixture was stirred at room temperature for 2 h. Thereafter, the solvent was distilled off under reduced pressure. The residue was dissolved in a small amount of methanol, and water (10 mL) and 1N-HCl aq (1 mL) were added to the solution. The mixture was stirred at room temperature. The resulting solids were filtered and washed with water, ethanol and then diethylether to give 0.6 g of **18c**: mp 213–216 °C. ^{2}H NMR (DMSO-d_6) δ: 9.97 (1H, s), 9.52 (2H, s), 8.29 (1H, d, $J=2$ Hz), 7.90 (1H, d, $J=2$ Hz), 6.16 (1H, t, $J=5$ Hz), 4.74 (2H, s), 4.04 (2H, d, $J=5$ Hz), 2.13 (3H, s). Anal. calcd for $C_{13}H_{12}N_3O_2Cl$: C, 47.94; H, 3.71; N, 12.90, found: C, 47.74; H, 3.77; N, 12.98.

4-Chloro-3-(hydroxyacetylamino)-5-(methoxyacetylamino) benzonitrile (19c). The compound **19c** was prepared in the same manner as **6b** from **14c** (0.4 g). The resulting solids were recrystallized from ethanol to give 0.3 g of **19c**; mp 160 °C (Dec.). ^{1}H NMR (DMSO-d_6) δ: 9.48 (2H, s), 8.30 (1H, d, $J=2$ Hz), 8.03 (1H, d, $J=2$ Hz), 6.10 (1H, s), 4.06 (4H, s), 3.42 (3H, s). Anal. calcd for $C_{12}H_{12}N_3O_4CL$: C, 48.42; H, 4.06; N, 14.12, found: C, 48.18; H, 4.08; N, 14.02.

4-Chloro-3-(isobutylryloxyacetylamino)-5-(methoxyacetylamino)benzonitrile (20c). The compound **20c** was prepared in the same manner as **7b** from 4-chloro-3-hydroxyacetylamino-5-methoxyacetylaminobenzonitrile (0.9 g) and isobutyryl chloride (0.35 mL). The resulting solids were recrystallized from ethanol to give 0.8 g of **20c**; mp 119–120 °C. ^{1}H NMR (DMSO-d_6) δ: 9.19 (2H, s), 8.09 (1H, d, $J=2$ Hz), 7.99 (1H, d, $J=2$ Hz), 4.75 (2H, s), 4.06 (2H, s), 3.90 (3H, s), 2.60 (1H, q, $J=7$ Hz), 1.14 (6H, d, $J=7$ Hz). Anal. calcd for $C_{16}H_{18}N_3O_5$ Cl: C, 52.25; H, 4.93; N, 11.43, found: C, 52.33; H, 4.87; N, 11.44.

3,5-Bis(chloroacetylamino)-4-chlorobenzonitrile (21c). To a solution of 3,5-diamino-4-chlorobenzonitrile (5.50 g) in acetic acid was added chloroacetyl chloride (6.3 mL) at room temperature. The mixture was stirred at room temperature for 1 h. The resulting solids were filtered and washed with water. The solid recrystallized from ethyl acetate/hexane to give 5.3 g of **21c**; mp 231 °C (Dec.). ^{1}H NMR (DMSO-d_6) δ: 10.10 (2H, s), 7.89 (2H, s), 4.36 (4H, s).

General method E. 3,5-Bis(piperidinoacetylamino)-4-chlorobenzonitrile (22c). The mixture of the compound **21c** (3.2 g) in piperidine (50 mL) was stirred at 100 °C for 2 h. Thereafter, piperidine was distilled off under reduced pressure. The residue was extracted with chloroform and the organic layer was washed with water. The organic layer was dried over anhydrous sodium sulfate. The solvent was distilled under reduced pressure. The resulting solids were recrystallized from chloroform/methanol to give 2.6 g of **22c**; mp 290 °C (Dec.). ^{1}H NMR (DMSO-d_6) δ: 10.20 (1H, s), 8.55 (2H, s), 3.15 (4H, s), 2.70–2.40 (8H, m), 1.80–1.40 (12H, m). Anal. calcd for $C_{21}H_{28}N_5O_2Cl$: C, 60.35; H, 6.75; N, 16.76; Cl, 8.48, found: C, 60.35; H, 6.82; N, 16.83; Cl, 8.38.

Compound **23c** was prepared in the same manner as **22c** (General method E).

3,5-Bis(morpholinoacetylamino)-4-chlorobenzonitrile (23c). From **21c** (3.9 g) and morpholine (50 mL): 4.0 g of **23c**; mp 290 °C (Dec.). ^{1}H NMR ($CDCl_3$) δ: 10.05 (1H, s), 8.57 (2H, s), 3.60 (8H, m), 3.20 (4H, s), 2.66 (8H, m). Anal. calcd for $C_{19}H_{24}N_5O_4Cl$: C, 54.09; H, 5.73; N, 16.60; Cl, 8.40, found: C, 53.83; H, 5.72; N, 16.71; Cl, 8.36.

3,5-Bis(methylthioacetylamino)-4-chlorobenzonitrile (24c). To a solution of the compound **21c** (3.2 g) and triethylamine (6.2 mL) in DMF (40 mL) was added dropwise 30% methylmercaptane methanol solution (3.0 mL) at room temperature. Thereafter, the mixture was stirred at room temperature for 3 h. Thereafter, water (150 mL) was added to the mixture. The resulting solids were filtered and washed with water. The solids were recrystallized from ethanol to give 2.7 g of **24c**; mp

183–184 °C. ^{1}H NMR ($CDCl_3$) δ: 9.50 (2H, s), 8.50 (2H, s), 3.40 (4H, s), 2.20 (6H, s).

3,5-Bis(methylsulfonylacetylamino)-4-chlorobenzonitrile (25c). To a solution of the compound **24c** (2.3 g) and in chloroform (250 mL) was added dropwise *m*-chloroperbenzoic acid (5.1 g) in chloroform (150 mL) at room temperature. The mixture was refluxed for 4 h. After cooling, the precipitate was filtered off. The organic layer was washed with water and dried over anhydrous sodium sulfate. Chloroform was distilled off under reduced pressure. The resulting solids were recrystallized from methanol to give 1.2 g of **25c**; mp 204 °C (Dec.). ^{1}H NMR (DMSO-d_6) δ: 10.25 (2H, s), 8.05 (2H, s), 4.45 (4H, s), 3.13 (6H, s). Anal. calcd for $C_{13}H_{14}N_3O_6S_2Cl$: C, 38.28; H, 3.46 N, 10.30; Cl, 8.69; S, 15.72, found: C, 38.29; H, 3.46; N, 10.40; Cl, 8.67; S, 15.67.

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