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# Novel Antiallergic Agents. Part I: Synthesis and Pharmacology of Pyrimidine Amide Derivatives

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**Abstract**—We have synthesized many pyrimidine amide derivatives. Novel pyrimidine bis-glycolic amide derivatives showed moderate inhibition in the rat passive cutaneous anaphylaxis (PCA) assay by oral administration. Among these compounds, 2,4-bis(methoxyacetylamino)-6-piperidinopyrirnidine (**2i**) exhibited significant inhibition. However the compound (**2i**) did not inhibit antigen-induced histamine or SRS-A release from lung fragments of the guinea-pig at less than $10^{-4}$ M. Derivatives of **2i** have also notable or moderate activity in the rat PCA assay. Compound **2h** which has no oxygen atom at the α-position of the amide carbonyl group and, compound **17** which has no amide carbonyl group, showed no inhibition in the rat PCA assay. We supposed that both the amide carbonyl group and the oxygen atom at α-position of the amide carbonyl group play an important role in inhibiting the rat PCA reaction. These pyrimidine bis-glycolic amide derivatives have a novel structure and unique activity which suggests they may be potentially useful in the treatment of allergic diseases. © 1998 Elsevier Science Ltd. All rights reserved.

## Introduction

Since the development of DSCG (disodium cromoglycate)[1] (Figure 1), many antiallergic drugs[2–5] have been developed for the treatment of various kinds of allergic diseases, such as asthma and atopic dermatitis. Most of these drugs inhibit the release of chemical mediators from the mast cell. Antagonists of leukotriene (LT) $C_4$, $D_4$,[6] platelet activating factor (PAF)[7] and thromboxane (TX) $A_2$,[8] and an inhibitor of $TXA_2$ synthetase[9] have also been developed. However, these antiallergic drugs have not necessarily lived up to expectations in the treatment of various kinds of allergic diseases, particularly in the treatment of bronchial asthma. In order to find compounds having improved antiallergic activity, we have investigated various pyrimidine bis-amide compounds such as oxamate, oxyacetamide and so on, which possess two active sites in their molecules, as does DSCG. We found that pyrimidine bis-glycolic amide compounds have a unique antiallergic activity. These compounds inhibited the rat passive cutaneous anaphylaxis (PCA)[10] reaction significantly by oral administration but showed no inhibition of antigen-induced histamine[11] or SRS-A[12] release from lung fragment of guinea-pig in vitro at less than $10^{-4}$ M. TYB-2285[13] (Figure 1), which is under investigation in Japan for asthma and atopic dermatitis in phase II clinical studies, also contains the same amide groups. In this paper, the synthesis, structure–activity relationship and pharmacological evaluations of this series compounds are described.

## Chemistry

All the compounds listed in Tables 1–4 were synthesized as below. Compounds **2–6a** were easily prepared by the method of Roth et al.[14,15] from 6-chloro-2,4-diaminopyrimidine (**1a**). On treatment with an alkyl oxalyl chloride (General method A), 2,4-diamino compounds **1–6a** were converted to dioxamate derivatives (**1b**, **2b–e**, **3c**,**d**, **4b**, **5c**, **6c**) in pyridine or dichloromethane with triethylamine. Oxamic acid (**2f**) was prepared by hydrolysis of compound **2b** in aqueous sodium hydroxide solution. Similarly, other amide compounds (**2h–o**, **3i**, **4i**, **7i**) were prepared by General method A as shown in

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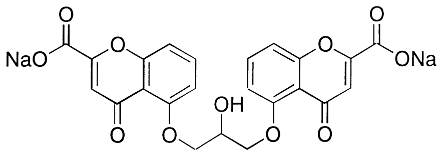
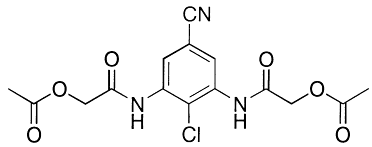


**DSCG**



**TYB-2285**

**Figure 1.** Structures of DSCG and TYB-2285.

Scheme 1 from 2,4-diamino compounds (**1–6a**, **7a**) by treatment with the corresponding acid chloride. Synthesis of compound **2g** was carried out by treatment with aceticformic anhydride prepared in situ. Compound **2p** was prepared by hydrolysis of **2o** using anhydrous ammonia methanol solution. Compounds **9**, **11** and **13** were prepared from the corresponding mono, di or triaminopyrimidine by treatment with methoxyacetyl chloride (Scheme 2). Bisalkylamino compounds **17–20** were synthesized from 2,4,6-trichloropyrimidine (**14**) via 2,4-dichloro-6-piperidinopyrimidine (**15**)[14] (Scheme 3). In the synthesis of **15** we used 2 mol of piperidine for 1 mol of **14**, and monopiperidinopyrimidines **15** and **16** were obtained. Compounds **17–20** were prepared by treatment of compound **15** with excess of amines such as 2-methoxyethylamine, 2-hydroxyethylamine, diethanolamine and morpholine.

## Results and Discussion

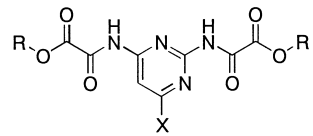
The rat PCA assay was used to evaluate antiallergic activity of synthesized compounds. The PCA is the most classic and popular allergic reaction. The mechanism of the PCA is very simple and is convenient for clarifying the drug mechanism. The results obtained in the p.o. rat PCA assay for oxamates and oxamic acid (i.v. 3 mg/kg, 5 min before challenge) are listed in Table 1. Inhibitory activities of antigen-induced histamine and SRS-A release from lung fragment of guinea-pig were also tested. All the compounds shown in Table 1 inhibited the histamine release from lung fragment of guinea-pig at $10^{-4}$ M as strongly as tranilast and amlexanox. But amlexanox showed stronger activity than the oxamates and tranilast in SRS-A release assay. Tranilast having inhibitory activities of histamine and SRS-A at $10^{-4}$ M, inhibited the rat PCA reaction. Saijo et al.[5] reported that amlexanox also inhibited the rat PCA reaction. Though compounds **2b**, **2c**, **3c**, **4b**, **5c** and **6c** inhibited the rat PCA reaction significantly at 30 mg/kg by oral administration, other oxamates (**2d**, **3d**, **2e**) showed no inhibition of the rat PCA reaction at 30 mg/kg by oral administration. In a single dose toxicity study of **2b** at 1200 mg/kg by oral administration, calcium oxalate was precipitated in the rat renal tubules.

Therefore, several kinds of pyrimidine amide compounds other than the oxamates shown in Table 2 were investigated. Only compound **2i** showed significant inhibition in the rat PCA assay at 30mg/kg p.o., but **2i** exhibited no inhibition in histamine and SRS-A release assays at less than $10^{-4}$ M. The pyrimidine bis-glycolic amide derivatives shown in Table 3 also showed no inhibition of histamine and SRS-A release from lung fragment of guinea-pig at less than $10^{-4}$ M. Though they do not have antihistamine activity at less than $10^{-4}$ M, they inhibit the PCA reaction. But compounds **1i**, **3i**, **4i**, **7i**, **2m** and **2p** have less inhibitory activity than **2i** in this assay. Compounds **9**, **11** and **13** inhibit the rat PCA assay as strongly as **3i** and **4i**. Compounds **17–20** (shown in Table 5), which have no amide carbonyl group, exhibited no inhibition in the rat PCA assay. Taking the effect of compounds **2i**, **2h** and **17** in the PCA assay into consideration, both the amide carbonyl group and oxygen atom at the α-position of the amide carbonyl group are important to antiallergic activity. TYB-2285, which is being investigated in Japan for asthma and atopic dermatitis in phase II clinical studies also contains the same amide groups.

## Conclusion

In this study, we have investigated many pyrimidine amide derivatives. Pyrimidine-2,4-dioxamate showed notable inhibition in the rat PCA assay and inhibited antigen-induced histamine and SRS-A release firom lung fragment of guinea-pig as strongly as tranilast, but these compounds were metabolised to calcium oxalate, which precipitated in the rat renal tubules. 2,4-Bis-methoxyacetylaminopyrimidine derivatives showed notable inhibition on the rat PCA assay. But these compounds are not active against antigen-induced histamine and SRS-A release from lung fragment of guinea-pig at less than $10^{-4}$ M. 2,4-Bis(methoxyacethylamino)pyrimidine derivatives are novel, unique antiallergic compounds. We believe that both the amide carbonyl group and the oxygen atom at the α-position of the amide carbonyl group play an important role in inhibiting the rat PCA reaction. Further studies are required to determine the precise mechanism of these compounds.

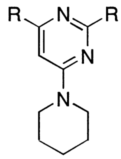
**Table 1.** Physical and pharmacological data of pyrimidine dioxamates



| Compd no. | R | X | mp (°C) | Yield (%) | Recryst. solvent[a] | Formula | Inhibition (%) of rat PCA 30 mg/kg p.o. | Inhibition (%) of release ($10^{-4}$ M) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Histamine | SRS-A |
| **1b** | Et | Cl | 172 | 63 | A | $C_{12}H_{13}N_4O_6Cl{\cdot}H_2O$ | 42 (200 mg/kg) | 24.5 | 46.6 |
| **2b** | Et | piperidino | 151–152 | 43 | A | $C_{17}H_{23}N_5O_6$ | 92 | 12.2 | 46.6 |
| **2c** | Me | piperidino | 147–148 | 42 | A | $C_{15}H_{19}N_5O_6{\cdot}H_2O$ | 86 | 32.1 | 50.0 |
| **3c** | Me | morpholino | 190–193 | 46 | B | $C_{14}H_{19}N_5O_7$ | 99 | 27.7 | 47.3 |
| **4b** | Et | OMe | 132–134 | 82 | C | $C_{13}H_{17}N_4O_7{\cdot}H_2O$ | 83 | 44.2 | 57.6 |
| **2d** | *n*-Pr | piperidino | 97–101 | 50 | A | $C_{19}H_{27}N5O_6$ | NE | 31.6 | 52.3 |
| **3d** | *n*-Pr | morpholino | 145–146 | 33 | A | $C_{18}H_{25}N_5O_7$ | NE | 29.8 | 50.0 |
| **2e** | $CH_2Ph$ | piperidino | 155–159 | 48 | A | $C_{27}H_{27}N_5O_6.1/2H_2O$ | NE | 26.5 | 48.6 |
| **5c** | Me | pyrrolidino | 161–162 | 43 | A | $C_{14}H_{17}N_5O_6.H_2O$ | 81 | 19.9 | 40.2 |
| **6c** | Me | homopiperidino | 130–135 | 64 | A | $C_{16}H_{21}N_5O_6$ | 77 | 26.3 | 49.2 |
| **2f** | H | piperidino | 167 (Dec.) | 54 | D | $C_{13}H_{15}N_5O_6$ | 100 (3 mg/kg, iv) | 20.5 | 43.2 |
| | ketotifen fumarate | | | | | | 96, 81 (10 mg/kg) | ND | ND |
| | tranilast | | | | | | 92 (200 mg/kg) | 33.2 | 26.7 |
| | amlexanox | | | | | | ND | 25.7 | 77.1 |

[a]A: EtOH; B: Dioxane; C: $EtOH/H_2O$; D: Not recryst.
NE, No effect.
ND, Not done.

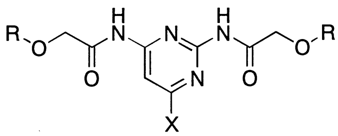
**Table 2.** Physical and pharmacological data of pyrimidine derivatives



| Compd no. | R | mp (°C) | Yield (%) | Recryst. solvent[a] | Formula | Rat PCA inhibition (%) 30 mg/kg p.o. |
|---|---|---|---|---|---|---|
| **2g** | NHCOH | 247 (Dec.) | 52 | A | $C_{11}H_{15}N_5O_2$ | 28 |
| **2h** | $NHCOCH_3$ | 280 (Dec.) | 69 | B | $C_{13}H_{19}N_5O_2$ | 23 |
| **2i** | $NHCOCH_2OMe$ | 159–160 | 72 | F | $C_{15}H_{23}N_5O_4$ | 81 |
| **2j** | NH2-Fu[b] | 148–150 | 36 | C | $C_{19}H_{19}N_5O_4 \cdot H_2O$ | 13 (ip) |
| **2k** | NHCOCH = CHAr[c] | 280 (Dec.) | 60 | D | $C_{27}H_{27}N_5O_2$ | 8 (200 mg/kg) |
| **2l** | $NHCOCH_2CH_2COOEt$ | 198–199 | 66 | E | $C_{21}H_5O_6$ | NE |

[a]A: EtOAc; B: EtOH/Pyridine; C: EtOH; D: Dioxane/EtOH; E: EtOH/EtOAc; F: Not recryst.
[b]2-Fu, 2-Furoyl.
[c]Ar, Ph-3,4-$(OMe)_2$.
NE, No effect.

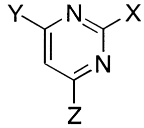
**Table 3.** Physical and pharmacological data of pyrimidine bisamide compounds



| Compd no. | X | R | mp (°C) | Yield (%) | Recryst. solvent[a] | Formula | Rat PCA inhibition (%) 30 mg/kg p.o. |
|---|---|---|---|---|---|---|---|
| **2i** | piperidino | Me | 159–160 | 72 | F | $C_{15}H_{23}N_5O_4$ | 81 |
| **3i** | morphorino | Me | 189–191 | 86 | F | $C_{14}H_{21}N_5O_5$ | 68 |
| **4i** | OMe | Me | 168–169 | 45 | A | $C_{11}H_{16}N_4O_5$ | 51 |
| **1i** | Cl | Me | 143 (Dec.) | 28 | B | $C_{10}H_{13}N_4O_4Cl$ | 72 |
| **7i** | H | Me | 171 (Dec.) | 46 | A | $C_{10}H_{14}N_4O_4$ | 53 |
| **2m** | piperidino | Et | 147–148 | 78 | C | $C_{17}H_{27}N_5O_4$ | 40 |
| **2n** | piperidino | Ph | 192–193 | 66 | A | $C_{25}H_{27}N_5O_4$ | 11 |
| **2o** | piperidino | Ac | 249 (Dec.) | 25 | E | $C_{17}H_{23}N_5O_6$ | NE |
| **2p** | piperidino | H | 197–198 | 89 | F | $C_{13}H_{19}N_5O_4$ | 67 |

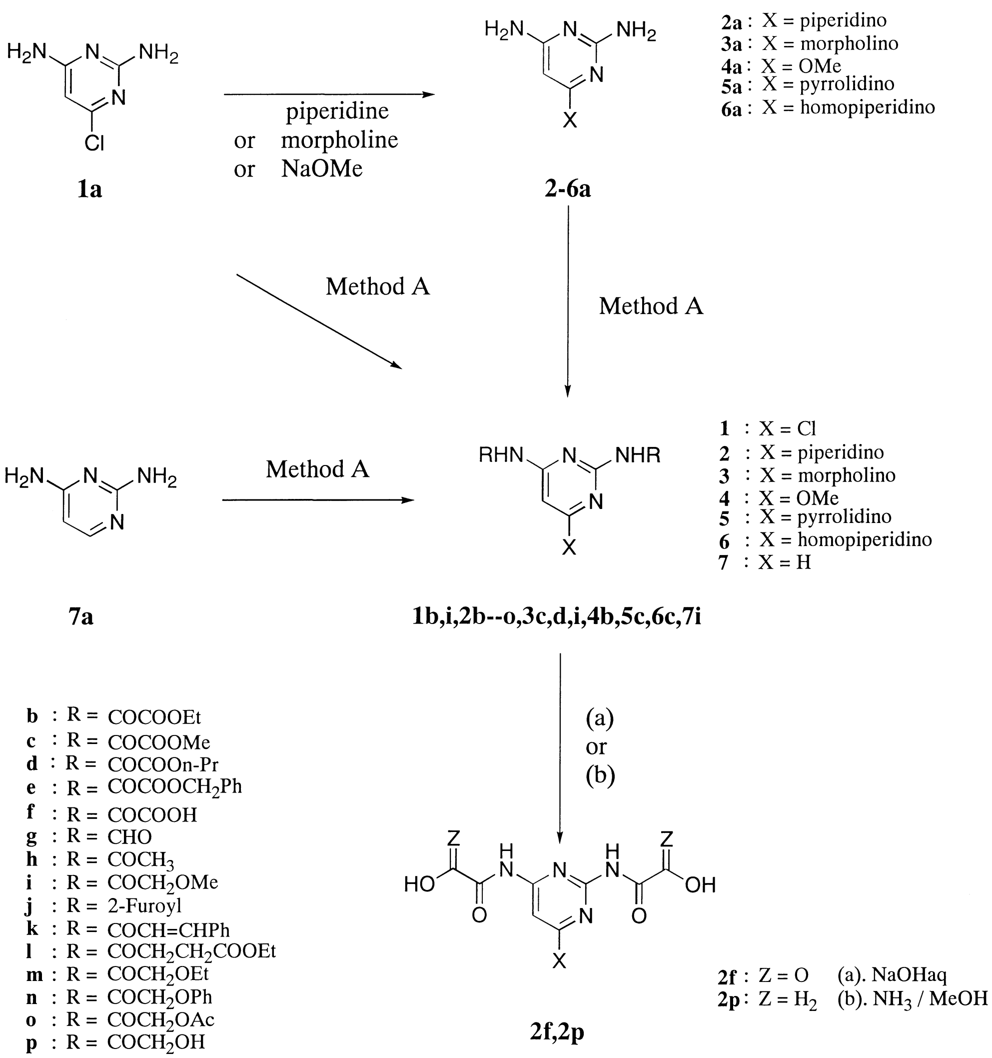
[a]A: EtOH; B: EtOAc/Hexane; C: EtOH/$H_2O$; D: EtOH; E: Dioxane; F: Not recryst.
NE, No effect.

**Table 4.** Physical and pharmacological data of pyrimidine derivatives



| Compd no. | X | Y | Z | mp (°C) | Yield (%) | Recryst. solvent[a] | Formula | PCA inhibition (%) 30 mg/kg p.o. |
|---|---|---|---|---|---|---|---|---|
| **9** | $NHCOCH_2OMe$ | H | H | 135–137 | 88 | A | $C_7H_9N_3O_2$ | 40 |
| **11** | H | $NHCOCH_2OMe$ | $NHCOCH_2OMe$ | 110–112 | 38 | B | $C_{10}H_{14}N_4O_4$ | 62 |
| **13** | $NHCOCH_2OMe$ | $NHCOCH_2OMe$ | $NHCOCH_2OMe$ | 205 (Dec.) | 31 | C | $C_{13}H_{19}N_5O_6$ | 56 |

[a]A: EtOAc; B: EtOAc/Hexane; C: EtOH.



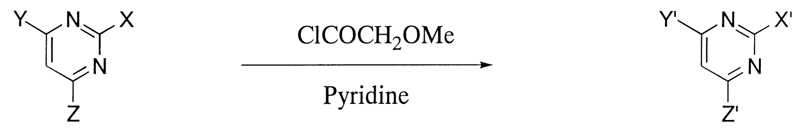

**Scheme 1.** Synthesis of pyrimidine oxamates, oxamic acid and amide derivatives.

## Experimental

Melting points were determined with a Mettler capillary melting-point apparatus (Model FP 61) and were uncorrected. $^{1}H$ NMR spectra were recorded on a Varian FT80A 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.

**Histamine and SRS-A release assay.** Male Hartley guinea-pigs weighing about 400 g were passively sensitized by an i.v. injection of guinea-pig anti BSA serum. Two days after the injection, the guinea-pigs were sacrificed by bleeding from femoral arteries. The lungs were removed and fragmented with a tissue chopper. The suspended lung fragments were distributed into individual tubes and suspended in Tyrode's solution. To the solution was added test compound and BSA. It was incubated at 37 °C for 15 min. After the removal of fragmentation, histamine and SRS-A were assayed, respectively, by the method of May et al.[11] and by biological methods using isolated guinea-pig ileum as described elsewhere.

**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

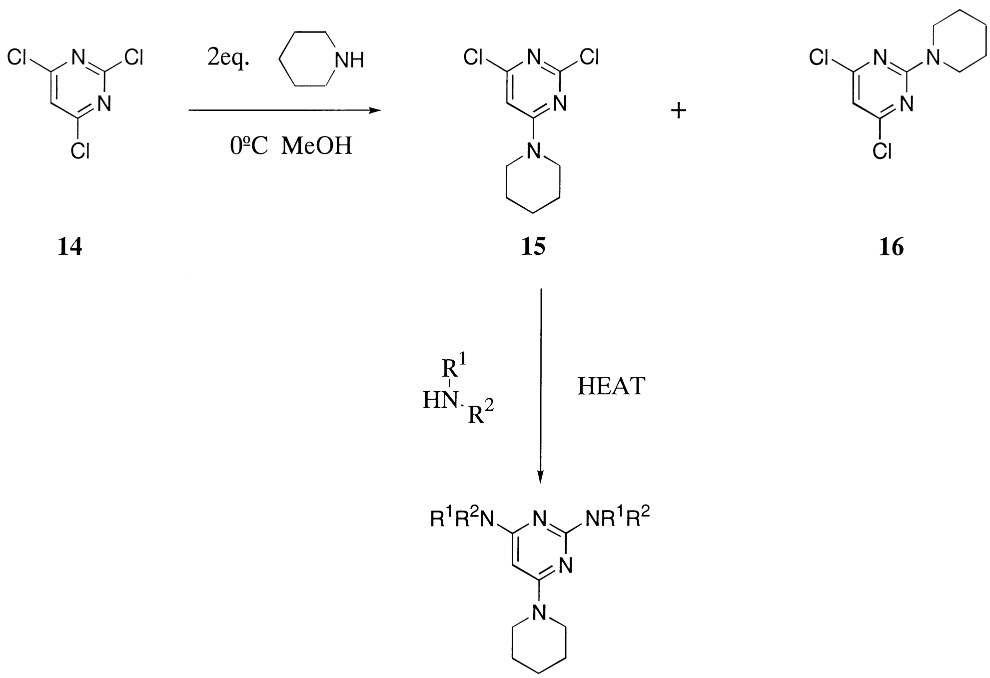


**8,10,12** → **9,11,13**

**8** : X = $NH_2$, Y = Z = H
**10** : X = H, Y = Z = $NH_2$
**12** : X = Y = Z = $NH_2$

**9** : X' = $NHCOCH_2OMe$, Y' = Z' = H
**11** : X' = H, Y' = Z' = $NHCOCH_2OMe$
**13** : X' = Y' = Z' = $NHCOCH_2OMe$

**Scheme 2.** Synthesis of compounds **9**, **11** and **13**.



**14** **15** **16**

**17-20**

**17** : $R^1$ = $CH_2CH_2OMe$, $R^2$ = H
**18** : $R^1$ = $CH_2CH_2OH$, $R^2$ = H
**19** : $R^1$ = $R^2$ = $CH_2CH_2OH$
**20** : $NR^1R^2$ = morpholino

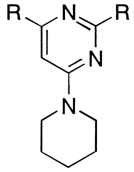
**Scheme 3.** Synthesis of compounds **17–20**.

total) at both sides of dorsal median line. After 48 hr, 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 blueing region, and the amount of pigment from the blueing region was measured by the method of Katayama et al.[16] Test compounds were orally administrated to the rats (six in total) in a dose of 30 mg/kg 30 min before the antigen challenge.

Compounds (**2–7a**) were prepared by the method in the literature.[14]

**General method A. Diethyl 6-chloropyrimidine 2,4-dioxamate monohydrate (1b).** Ethyl oxalyl chloride (6.0 g) was added dropwise to a solution of 6-chloro-2,4-diaminopyrimidine (2.9 g) in pyridine (20 mL) at room temperature. The mixture was stirred at room temperature for 2 hr. Thereafter, pyridine was distilled off under reduced pressure. Water and ethyl acetate were added to

**Table 5.** Physical and pharmacological data of 2,4,6-triaminopyrimidine derivatives




| Compd no. | R | mp (°C) | Yield | Recryst. solvent[a] | Formula | Rat PCA inhibition (%) 30 mg/kg p.o. |
|---|---|---|---|---|---|---|
| **17** | $NHCH_2CH_2OMe$ | 136–138 | 75 | A | $C_{15}H_{27}N_5O_2 \cdot C_4H_4O_4$ | NE |
| **18** | $NHCH_2CH_2OH$ | 196–197 | 26 | B | $C_{13}H_{23}N_5O_2 \cdot C_2H_2O_2 \cdot H_2O$ | NE |
| **19** | $N(CH_2CH_2OH)_2$ | 99–103 | 29 | B | $C_{17}H_{31}N_5O_4$ | NE |
| **20** | morpholino | 217–218 | 77 | C | $C_{17}H_{27}N_5O_2$ | ND |

[a]A: EtOH; B: EtOAc; C: EtOH/$H_2O$.
NE, No effect.
ND, Not done.

the residue. The organic layer was washed with water and then saturated in sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate. All solvent was distilled off under reduced pressure. The resulting crude solids were recrystallized from ethanol to give 4.6 g of **1b**; mp 172 °C. $^1$H NMR (DMSO-$d_6$) δ 11.40 (2H, s), 7.69 (1H, s), 4.27 (4H, q, $J$ = 8 Hz), 1.30 (3H, t, $J$ = 8 Hz), 1.27 (3H, t, $J$ = 8 Hz). Anal. calcd for $C_{12}H_{13}N_4O_6Cl \cdot H_2O$: C, 39.73; H, 4.17; N, 15.45; Cl, 9.78, found: C, 39.73; H, 4.13; N, 15.41; Cl, 9.83.

Compounds **1i**, **2b–e**, **2g–o**, **3c**, **3d**, **3i**, **4b**, **4i**, **5c**, **6c**, **7i**, **9**, **11** and **13** were prepared in the same manner as **1b** (General method A).

**Diethyl 6-piperidinopyrimidine 2,4-dioxamate (2b)**. From 2,4-diamino-6-piperidinopyrimidine (4.2 g) and ethyl oxalyl chloride (5.6 mL): 6.2 g; mp 151–152 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.90 (1H, s), 10.16 (1H, s), 6.95 (1H, s), 4.27 (2H, q, $J$ = 7 Hz), 4.23 (2H, q, $J$ = 7 Hz), 3.70–3.15 (4H, m), 1.80–1.20 (6H, m), 1.30 (3H, t, $J$ = 7 Hz ), 1.23 (3H, t, $J$ = 7 Hz). $^{13}$C NMR (DMSO-$d_6$) δ: 162.7, 161.7, 160.1, 157.7, 156.7, 155.7, 86.1, 62.7, 61.5, 44.9, 25.2, 24.0, 13.8. Anal. calcd for $C_{17}H_{23}N_5O_6$: C, 51.90; H, 5.89; N, 17.80, found: C, 52.16; H, 5.85; N, 17.89.

**Dimethyl 6-piperidinopyrimidine 2,4-dioxamate (2c).** From 2,4-diamino-6-piperidinopyrimidine (5.8 g) and methyl oxalyl chloride (7.7 g): 6.1 g; mp 147–148 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.88 (1H, s), 10.17 (1H, s), 6.84 (1H, s), 5.83 (3H, m), 3.77 (3H, s), 3.70–3.15 (4H, m), 1.77–1.25 (6H, m). Anal. calcd for $C_{15}H_{19}N_5O_6$: C, 49.31; H, 5.24: N, 19.17, found: C, 49.20; H, 5.21; N, 19.23.

**Dimethyl 6-morpholinopyrimidine 2,4-dioxamate (3c).** From 2,4-diamino-6-morpholinopyrimidine (150 g) and methyl oxalyl chloride (160 mL): 130 g; mp 190–193 °C. $^1$H NMR ($CDCl_3$) δ: 9.45 (1H, S), 9.05 (1H, s), 7.23 (1H, s), 3.95 (6H, s), 3.80–3.50 (8H, m). Anal. calcd for $C_{14}H_{17}N_5O_7$: C, 45.78; H, 4.67; N, 19.07, found: C, 45.79; H, 4.68; N, 18.80.

**Diethyl 6-methoxypyrimidine 2,4-dioxamate monohydrate (4b).** From 2,4-diamino-6-methoxypyrimidine (3.8 g) and ethyl oxalyl chloride (9.8 g): 8.8 g; mp 132–134 °C. $^1$H NMR (DMSO-$d_6$) δ: 11.30 (1H, s), 10.60 (1H, s), 7.03 (1H, s), 4.29 (4H, q, $J$ = 7 Hz), 3.87 (3H, s), 3.33 (2H, s, $H_2O$), 1.30 (3H, t, $J$ = 7 Hz), 1.25 (3H, t, $J$ = 7 Hz). Anal. calcd for $C_{13}H_{16}N_4O_7 \cdot H_2O$: C, 43.58; H, 5.06; N, 15.64, found: C, 43.75; H, 4.85; N, 15.89.

**Di-*n*-propyl 6-piperidinopyrimidine 2,4-dioxamate (2d).** From 2,4-diamino-6-piperidinopyrimidine (5.8 g) and *n*-propyl oxalyl chloride (9.8 g): 6.3 g; mp 97–101 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.88 (1H, s), 10.15 (1H, s), 6.95 (1H, s), 4.18 (2H, q, $J$ = 7 Hz), 4.12 (2H, q, $J$ = 7 Hz), 3.65–3.20 (4H, m), 1.90–1.10 (10H, m), 0.90 (3H, t, $J$ = 7 Hz), 0.84 (3H, t, $J$ = 7 Hz). $^{13}$C NMR (DMSO-d$_6$) δ 162.77 (s), 161.89 (s, s), 160.25 (s), 157.55 (s), 156.73 (s), 155.73 (s), 86.17 (s), 68.00 (s), 66.88 (s), 45.01 (t, t), 25.30 (2t), 24.03 (t), 21.39 (2t), 10.24 (q), 10.16 (q). Anal. calcd for $C_{19}H_{27}N_5O_6$: C, 54.15; H, 6.46; N, 16.62, found: C, 54.36; H, 6.30; N, 16.77.

**Di-*n*-propyl 6-morpholinopyrimidine 2,4-dioxamate (3d).** From 2,4-diamino-6-morpholinopyrimidine (5.9 g) and *n*-propyl oxalyl chloride (9.8 g): 8.3 g; mp 145–146 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.96 (1H, s), 10.26 (1H, s), 6.94 (1H, s), 4.18 (2H, q, $J$ = 7 Hz), 4.10 (2H, q, $J$ = 7 Hz), 3.75–3.30 (8H, m), 1.64 (4H, m), 0.94 (3H, t, $J$ = 7 Hz), 0.84 (3H, t, $J$ = 7 Hz). Anal. calcd for $C_{18}H_{25}N_5O_7$: C, 51.06; H, 5.95; N, 16.54, found: C, 51.11; H, 5.79; N, 16.50.

**Dibenzyl 6-piperidinopyrimidine 2,4-dioxamate hemihydrate (2e).** From 2,4-diamino-6-piperidinopyrimidine (5.8 g) and benzyl oxalyl chloride (12.5 g): 9.2 g; mp 155–159 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.96 (1H, s), 10.30 (1H, s), 7.46–7.15 (10H, m), 6.92 (1H, s), 5.28 (2H, s), 5.21 (2H, s), 3.60–3.35 (4H, m), 1.68–1.30 (6H, m). Anal. calcd for $C_{27}H_{27}N_5O_6 \cdot 1/2H_2O$: C, 61.59; H, 5.36; N, 13.30, found: C, 61.79; H, 5.22; N, 13.32.

**Dimethyl 6-pyrrolidinopyrimidine 2,4-dioxamate (5c).** From 2,4-diamino-6-pyrrolidinopyrimidine (5.4 g) and methyl oxalyl chloride (5.8 mL): 7.2 g; mp 161–162 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.86 (1H, s), 10.10 (1H, s), 6.18 (1H, s), 3.82 (3H, s), 3.78 (3H, s), 3.52–3.10 (4H, m), 2.10–1.70 (4H, m). Anal. calcd for $C_{14}H_{17}N_5O_7 \cdot H_2O$: C, 47.86; H, 4.88; N, 19.93, found: C, 47.82; H, 4.76; N, 19.90.

**Dimethyl 6-homopiperidinopyrimidine 2,4-dioxamate (6c).** From 2,4-diamino-6-homopiperidinopyrimidine (6.2 g) and methyl oxalyl chloride (5.8 mL): 7.3 g mp 130–135 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.84 (1H, s), 10.13 (1H, s), 6.82 (1H, s), 3.80 (3H, s), 3.75 (3H,s), 3.65–3.25 (4H, m), 1.85–1.50 (8H, m). Anal. calcd for $C_{16}H_{21}N_5O_6$: C, 50.66; H, 5.58; N, 18.46, found: C, 50.78; H, 5.49; N, 18.41.

**2,4-Bis(formylamino)-6-piperidinopyrimidine (2g).** The mixture of acetic anhydride (11.4 mL) and formic acid (4.5 mL) was stirred at 60 °C for 2 h. After cooling, 2,4-diaminopyrimidine (5.8 g) was added to the solution at room temperature. The mixture was stirred at room temperature for 2 h. The resulting crystals were filtered and washed with water. After drying, the solids were recrystallized from ethyl acetate to give 3.9 g of **2g**; mp 247 °C (Dec.). $^1$H NMR (DMSO-$d_6$) δ: 10.30 (1H, s), 10.17 (1H, s), 9.35 (1H, s), 9.20 (1H, s), 5.82 (1H, s), 3.65–3.30 (4H, m), 1.78–1.25 (6H, m). Anal. calcd for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10, found: C, 52.97; H, 6.04; N, 28.36.

**2,4-Bis(acetylamino)-6-piperidinopyrimidine (2h).** From 2,4-diamino-6-piperidinopyrimidine (5.8 g) and acetyl chloride (4.5 mL): 5.7 g; mp 280 °C (Dec.). $^1$H NMR (DMSO-$d_6$) δ: 10.05 (1H, s), 9.50 (1H, s), 7.10 (1H, s), 3.60–3.20 (4H, m), 2.22 (3H, s), 2.08 (3H, s), 1.70–1.35 (6H, m). Anal. calcd for $C_{13}H_{19}N_5O_2$: C, 56.30; H, 6.91; N, 25.25, found: C, 56.47; H, 6.89; N, 25.23.

**2,4-Bis(methoxyacetylamino)-6-piperidinopyrimidine (2i).** From 2,4-diamino-6-piperidinopyrimidine (5.0 g) and methoxyacetyl chloride (5.0 mL) 2.7 g; mp 159–160 °C. $^2$H NMR (DMSO-$d_6$) δ: 9.55 (1H, s), 9.48 (1H, s), 7.05 (1H, s), 4.20 (2H, s), 4.05 (2H, s), 3.53 (4H, s), 3.35 (3H, s), 3.32 (3H, s), 1.60 (6H, s). Anal. calcd for $C_{15}H_{23}N_5O_4$: C, 53.40; H, 6.87; N, 20.76, found: C, 53.46; H, 6.72; N, 20.81.

**2,4-Bis(2-furoylamino)-6-piperidinopyrimidine monohydrate (2j).** From 2,4-diamino-6-piperidinopyrimidine (5.4 g) and 2-furoyl chloride (6.0 mL): 4.1 g; mp 148–150 °C. $^1$H NMR ($CDCl_3$) δ: 9.33 (1H, s), 8.47 (1H, s), 7.50–7.21 (5H, m), 6.51–6.40 (2H, m), 3.72–3.46 (4H, m), 1.75–1.42 (6H, m). Anal. calcd for $C_{19}H_{19}N_5O_4 \cdot H_2O$: C, 57.14; H, 5.30; N, 17.54, found: C, 57.41; H, 5.33; N, 17.58.

**2,4-Bis(3,4-dimethoxycinnamoylamino)-6-piperidinopyrimidine (2k).** The mixture of 3,4-dimethoxycinnamic acid (10.1 g) and thionyl chloride (8.0 mL) was stirred at 55 °C for 30 min. Thereafter thionyl chloride was distilled off under reduced pressure. The solution of 2,4-diamino-6-piperidinopyrimidine (4.3 g) in pyridine (200 mL) was added to the resulting crystals. The mixture was stirred at room temperature overnight. Thereafter, to the solution was added triethylamine (6.8 mL), and pyridine was distilled off under reduced pressure. The resulting crystals were filtered and washed water, and recrystallized from dioxane/ethanol to give **2k**; mp 237–240 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.17 (1H, s), 9.77 (1H, s), 7.67–6.85 (11H, m), 3.80 (12H, s), 3.57 (4H, s), 1.60 (6H, s). Calcd for $C_{31}H_{35}O_6$: C, 64.91; H, 6.15; N, 12.21, found: C, 64.90; H, 6.14; N, 12.15.

**2,4-Bis(ethylsuccinylamino)-6-piperidinopyrimidine (2l).** From 2,4-diamino-6-methoxypyrimidine (5.8 g) and ethyl succinyl chloride (9.0 mL): 8.9 g; mp 198–199 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.15 (1H, s), 9.64 (1H, s), 7.08 (1H, s), 4.04 (4H, q, $J = 7$ Hz), 3.75–3.35 (4H, m), 3.10–2.30 (8H, m), 1.80–1.30 (6H, m), 1.18 (6H, t, $J = 7$ Hz). Calcd for $C_{21}H_{31}N_5O_6$: C, 56.11; H, 6.95; N, 15.58, found: C, 56.17; H, 7.00; N, 15.38.

**2,4-Bis(methoxyacetylamino)-6-morpholinopyrimidine (3i).** From 2,4-diamino-6-morpholinopyrimidine (5.0 g) and methoxyacetyl chloride (5.0 mL): 7.5 g; mp 189–191 °C. $^1$H NMR (DMSO-$d_6$) °: 8.73 (1H, s), 8.48 (1H, s), 7.22 (1H, s), 4.05 (2H, S), 3.97 (2H, s), 3.68 (8H, m), 3.47 (3H, s), 3.45 (3H, s). Anal. calcd for $C_{14}H_{21}N_5O_5$: C, 49.55; H, 6.24; N, 20.64, found: C, 49.62; H, 6.20; N, 20.66.

**2,4-Bis(methoxyacetylamino)-6-methoxypyrimidine (4i).** From 2,4-diamino-6-methoxypyrimidine (3.8 g) and methoxyacetyl chloride (6.0 mL): 3.8 g; mp 168–169 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.02 (2H, s), 7.05 (1H, s), 4.26 (2H, s), 4.06 (2H, s), 3.87 (3H, s), 3.34 (6H, s). Anal. calcd for $C_{11}H_{16}N_4O_5$: C, 46.48; H, 5.67; N, 19.71, found: C, 46.69, H, 5.72; N, 19.98.

**2,4-Bis(methoxyacetylamino)-6-chloropyrimidine (1i).** From 2,4-diamino-6-chloropirimidine (5.8 g) and methoxyacetyl chloride (8.0): 3.2 g; mp 142–144 °C (Dec.). $^1$H NMR (DMSO-$d_6$) δ: 10.62 (1H, s), 10.42

(1H, s), 7.69 (1H, s), 4.21 (2H, s), 4.12 (2H, s), 3.32 (6H, s). Anal. calcd for $C_{10}H_{13}N_4O_4Cl$: C, 41.61; H, 4.54; N, 19.41; Cl, 12.28, found: C, 41.34; H, 4.36; N, 19.79; Cl, 12.55.

**2,4-Bis(methoxyacetylamino)pyrimidine (7i).** From 2,4-diaminopyrimidine (4.4 g) and methoxyacetyl chloride (8.0 mL): 4.7 g; mp 168–170 °C (Dec.). $^1$H NMR (DMSO-$d_6$) δ: 10.29 (1H, s), 10.09 (1H, s), 8.49 (1H, d, $J$ = 5 Hz), 7.73 (1H, d, $J$ = 5 Hz) 4.22 (2H, s), 4.12 (2H, s), 3.35 (3H, s), 3.32 (3H, s). Anal. calcd for $C_{10}H_{14}N_4O_4$: C, 47.24; H, 5.55; N, 22.04, found C, 47.01; H, 5.34; N, 21.77.

**2,4-Bis(ethoxyacetylamino)-6-piperidinopyrimidine (2m).** From 2,4-diamino-6-piperidinopyrimidine (5.6 g) and ethoxyacetyl chloride (7.0 mL): 8.3 g; mp 146–148 °C. $^1$H NMR ($CDCl_3$) δ: 8.72 (1H, s), 8.48 (1H, s), 7.22 (1H, s), 4.10 (2H, s), 4.00 (2H, s), 3.62 (2H, q, $J$ = 7 Hz), 3.58 (2H, q, $J$ = 7 Hz), 3.55 (4H, s), 1.62 (6H, s), 1.30 (3H, t, $J$ = 7 Hz), 1.28 (3H, t, $J$ = 7 Hz). Anal. calcd for $C_{17}H_{27}N_5O_4$: C, 55.87; H, 7.45; N, 19.17, found: C, 55.99; H, 7.52; N, 19.22.

**2,4-Bis(phenoxyacetylamino)-6-piperidinopyrimidine (2n).** From 2,4-diamino-6-piperidinopyrimidine (5.1 g) and phenoxyacetyl chloride (8.0 mL): 8.1 g; mp 192–193 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.15 (1H, s), 9.92 (1H, s), 7.45–6.60 (11H, m), 5.03 (2H, s), 4.80 (2H, s), 3.53 (4H, s), 1.55 (6H, s). Anal. calcd for $C_{25}H_{27}N_5O_4$: C, 65.06; H, 5.90; N, 15.18, found: C, 65.20; H, 5.61; N, 14.98.

**2,4-Bis(acetoxyacetylamino)-6-piperidinopyrimidine (2o).** From 2,4-diamino-6-piperidinopyrimidine (9.7 g) and acetoxyacetyl chloride (12 mL): 4.9 g; mp 248–249 °C (Dec.). $^1$H NMR (DMSO-$d_6$) δ: 10.30 (1H, s), 10.00 (1H, s), 7.00 (1H, s), 5.00 (2H, s), 4.72 (2H, s), 3.55 (4H, s), 2.10 (6H, s), 1.60 (6H, s). Anal. calcd for $C_{17}H_{23}N_5O_6$: C, 47.24; H, 5.55; N, 22.04, found: C, 47.01; H, 5.34; N, 21.77.

**2-Methoxyacetylaminopyrimidine (9).** Methoxyacetyl chloride (4.8 mL) was added dropwise to a solution of 2-aminopyrimidine (4.8 g) in pyridine (100 mL) at room temperature. The mixture was stirred at room temperature for 2 h. Thereafter, pyridine was distilled off under reduced pressure to remove the solvent. To the residue were added water and chloroform. The organic layer was washed with water, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting crude crystals were recrystallized from ethyl acetate to give 7.3 g of **9**; mp 135–137 °C. $^1$H NMR (DMSO-$d_6$) d: 9.20 (1H, s), 8.62 (2H, d, $J$ = 5 Hz), 7.03 (1H, dd, $J$ = 5 Hz and $J$ = 5 Hz), 4.14 (2H, s), 3.50 (3H, s). Anal. calcd for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14, found: C, 50.27; H, 5.18; N, 25.26.

**4,6-Bis(methoxyacetylamino)pyrimidine (11).** Methoxyacetyl chloride (6.0 mL) was added dropwise to a solution of 4,6-diaminopyrimidine hemisulfate (4.8 g) in pyridine (80 mL) at room temperature. The mixture was stirred at room temperature for 16 h and then at 80 °C for 1 h. Thereafter, pyridine was distilled off under reduced pressure. To the residue was added water and chloroform. The organic layer was washed with water and then with aqueous saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting crude crystals were recrystallized from ethyl acetate/hexane to give 2.9 g of **11**; mp 110–112 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.28 (2H, s), 8.73 (1H, s), 8.53 (1H, s), 4.06 (4H, s), 3.34 (6H, s). Anal. calcd for $C_{10}H_{14}N_4O_4$: C, 47.24; H, 5.55; N, 22.04, found: C, 47.53; H, 5.55; N, 22.14.

**2,4,6-Tris(methoxyacetylamino)pyrimidine (13).** Methoxyacetyl chloride (9.0 mL) was added dropwise to a solution of 2,4,6-triaminopyrimidine (3.8 g) in pyridine (80 mL) at room temperature. Then the mixture was stirred at 80 °C for 2 h. Thereafter, pyridine was distilled off under reduced pressure. To the residue was added water and chloroform. The organic layer was washed with water and then with aqueous saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the resulting crude crystals were recrystallized from ethanol to give 2.9 g of **13**; mp 110–112 °C. $^1$H NMR (DMSO-$d_6$) δ: 10.10 (2H, s), 9.86 (1H, s), 4.24 (2H, s), 4.09 (4H, s), 3.37 (6H, s), 3.28 (3H, s). Anal. calcd for $C_{13}H_{19}N_5O_6$: C, 45.75; H, 5.61; N, 20.52, found: C, 45.55; H, 5.53; N, 20.25.

**2,4-Bis(hydroxyacetylamino)-6-piperidinopyrimidine (2p).** The compound **2o** was suspended in 15% ammonia methanol solution (150 mL), and the mixture was stirred at 50–60 °C for 4 h. After the reaction mixture allowed to cool, the resulting crystals were separated by filtration and washed with methanol to give 4.9 g of **2p**; mp 196–198 °C. $^1$H NMR (DMSO-$d_6$) δ: 7.07 (1H, s), 4.13 (2H, s), 4.00 (2H, s), 3.52 (4H, s), 3.48 (2H, s), 1.57 (6H, s). Anal. calcd for $C_{13}H_{19}N_5O_4$: C, 50.48; H, 6.19; N, 22.64, found: C, 50.52; H, 6.24; N, 22.50.

**6-Piperidinopyrimidine-2,4-dioxamic acid trihydrate (2f).** To the mixture of diethyl 6-piperidinopiyrimidine-2,4-dioxamate (23.6 g) in water (500 mL) was added 1N sodium hyroxide solution (150 mL) at 0 °C. The solution was stirred for 20 min at the same temperature. To the solution was added dropwise 0.2N hydrochloric acid at 0 °C. The resulting solids were filtered and washed with water. After drying, crude solids were dissolved in DMSO (80 mL) and methanol (1000 mL) was added to the solution. The resulting crystals were washed with methanol and water and dried under reduced pressure to give 10.9 g of **2f**; mp 167 °C (Dec.). $^1$H NMR (DMSO-$d_6$) δ: 10.60 (1H, s), 9.90 (1H, s), 7.00 (1H, s), 3.50 (4H, s), 1.57 (6H, s). Anal. calcd for $C_{13}H_{15}N_5O_6{\cdot}3H_2O$: C, 39.90; H, 5.41; N, 17.90, found: C, 39.66; H, 5.21; N, 18.20.

**2,4-Dichloro-6-piperidinopyrimidine (15).** Piperidine (39.5 mL) was added dropwise to a solution of 2,4,6-trichloropyrimidine (36.9 g) in methanol (100 mL) at 0 °C for 4 h. The mixture was stirred at room temperature overnight, and piperidine was distilled off. Water was added to the residue. The resulting crystals were filtered and washed with water. The crystals were recrystallized from hexane to give 32.7 g of **15**; mp 87–88 °C. $^1$H NMR ($CDCl_3$) δ: 6.42 (1H, s), 3.88–3.50 (4H, m), 1.95–1.35 (6H, m). $^{13}$C NMR ($CDCl_3$) δ: 162.7, 160.1, 159.7, 99.6, 45.7, 25.5, 24.2.

**4,6-Dichloro-2-piperidinopyrimidine (16).** After recrystalization of **15**, hexane was distilled off under reduced pressure. Hexane was added to the residue to give crystals. The crystals were washed with hexane to give 8.1 g of **16**; mp 73–74 °C. $^1$H NMR ($CDCl_3$) δ: 6.50 (1H, s), 4.05–3.45 (4H, m), 1.90–1.35 (6H, m). $^{12}$C NMR ($CDCl_3$) δ: 161.5, 160.4, 107.0, 45.1, 25.7, 24.6.

**2,4-Bis(2-methoxyethylamino)-6-piperidinopyrimidine hemifumarate (17).** The mixture of 2,4-dichloro-6-piperidinopyrimidine (11.7 g) and 2-methoxyethylamine (25 mL) in ethyleneglycol (50 mL) was stirred at 180 °C for 4 h. After cooling, chloroform and water were added to the solution. The organic layer was washed with water, and dried over sodium sulfate. Chloroform was distilled off under reduced pressure to remove the solvent. The residue was distilled to give oily free base (15.0 g) of **17** at 225–240 °C/0.07 mmHg. To this oil methanol and fumaric acid (5.6 g) were added. Methanol was distilled off under reduced pressure. The resulting solids were recrystallied from ethanol to give 15.9 g of **17**; mp 136–138 °C; $^1$H NMR ($CDCl_3$) δ: 12.30 (2H, s), 8.25–7.75 (2H, m), 6.82 (2H, s), 4.93 (1H, s), 3.70–3.05 (18H, m), 1.62 (6H, m). Anal. calcd for $C_{15}H_{27}N_5O_2{\cdot}C_4H_4O_4$: C, 53.63; H, 7.34; N, 16.46, found: C, 53.49; H, 7.38; N, 16.30.

**2,4-Bis(2-hydroxyethylamino)-6-piperidinopyrimidine hemifumarate monohydrate (18).** The mixture of 2,4-dichloro-6-piperidinopyrimidine (7) (23.2 g) and monoethanolamine (50 mL) was refluxed for 2.5 h. After cooling, sodium carbonate solution and chloroform were added to the solution. The organic layer was washed with water and dried with calcium carbonate. Chloroform was distilled off under reduced pressure. To the residue ethyl acetate and diethylether were added. The resulting solids were filtered to give free base of **18** (17.8 g). To a solution of this base in methanol was added fumaric acid (7.3 g). Methanol was distilled off under pressure to remove solvent. The resulting solids were recrystallized from methanol/water to 9.3 g of **18**; mp 196–197 °C. $^1$H NMR (DMSO-$d_6$) δ: 6.50 (1H, s), 6.6.40–6.25 (2H, m), 5.25–4.76 (8H, m), 3.60–3.00 (12H, m), 1.82–1.23 (6H, m). Anal. calcd for $C_{13}H_{23}N_5O_2{\cdot}$-$H_2O{\cdot}C_2H_2O_2$: C, 50.41; H, 7.62; N, 19.60, found C, 50.60; H, 7.47; N, 19.66.

Compounds **19** and **20** were prepared in the same manner as **18**.

**2,4-Bis(diethanolamino)-6-piperidinopyrimidine (19).** From 2,4-dichloro-6-piperidinopyrimidine (11.7 g) and diethanolamine (50 m): 5.4 g; mp 99–102 °C. $^1$H NMR ($CDCl_3$) δ: 5.02 (1H, s), 4.95–4.45 (4H, m), 4.00–3.10 (20H, m), 1.85–1.37 (6H, m). Anal. calcd for $C_{17}H_{31}N_5O_2$: C, 55.26; H, 8.46; N, 18.96, found: C, 54.96, H, 8.66; N, 18.87.

**2,4-Dimorpholino-6-piperidinopyrimidine (20).** From 2,4-dichloro-6-piperidinopyrimidine (5.8 g) and morpholine (20 mL): 6.4 g; mp 217–218 °C. $^1$H NMR ($CDCl_3$) δ: 5.07 (1H, s), 3.85–3.55 (12H, m), 3.55–3.25 (8H, m), 1.72–1.43 (6H, m). Anal. calcd for $C_{17}H_{27}N_5O_2$: C, 61.24; H, 8.16; N, 21.00, found: C, 61.04, H, 8.26; N, 21.03.

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