Studies on Antiulcer Agents. III.[1] Plausible Mechanism of Antisecretory Action of Ethyl 2-[(1*H*-Benzimidazol-2-yl)sulfinylmethyl]-4-dimethylamino-5-pyrimidinecarboxylate, an H^+/K^+-ATPase Inhibitor, Based on Its Reaction with Thiols

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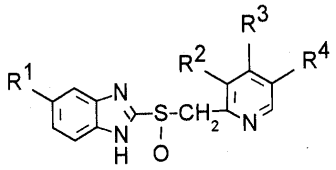
To explore the mechanism of the gastric antisecretion activity of ethyl 2-[(1*H*-benzimidazol-2-yl)sulfinylmethyl]-4-dimethylamino-5-pyrimidinecarboxylate (5), a potential H^+/K^+-ATPase inhibitor, in the acid compartment of parietal cells, its reaction with some alkylthiols in the presence of hydrochloric acid was investigated. Upon treatment with 2-mercaptoethanol under acidic conditions, 5 gave a characteristic 1 : 2 adduct, ethyl 4-[2-(2-hydroxyethyldithio)-1-(2-hydroxyethylthio)ethylidenamino]pyrimido[1,2-*a*]benzimidazole-3-carboxylate (6), instead of providing a disulfide of type 3, 2-(2-alkyldithiomethylpyridino)benzimidazolide, the product predicted to be formed according to the reaction mechanism of common H^+/K^+-ATPase inhibitors, such as omeprazole or lansoprazole, with mercaptans. With a large excess of 2-mercaptoethanol, 5 provided 2-(2-hydroxyethylthio)-1*H*-benzimidazole (8) and ethyl 4-dimethylamino-2-(2-hydroxyethyldithio)-5-pyrimidinecarboxylate (9) as well as 6. The transformation mechanisms and their implications are discussed.

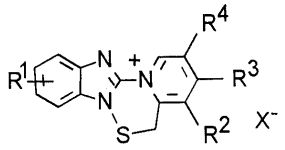
Key words antiulcer agent; proton pump inhibitor; pyrimidine derivative; antisecretory mechanism; pyrimido[1,2-*a*]benzimidazole derivative

Substituted benzimidazoles, such as omeprazole and lansoprazole, have attracted considerable attention as potential therapeutics for the treatment of peptic ulcers and severe hypersecretion in Zollinger–Ellison syndrome. Their pharmacological effect is ascribed to potent antisecretory action, which has been postulated to originate from irreversible covalent binding with a mercapto group of the gastric proton-pumping enzyme, H^+/K^+-ATPase, located in the apical membrane of the parietal cells.[2] This mechanism of action is supported by chemical evidence that the drugs are transformed into the intermediate cyclic sulfenamides (**1** and **2**) *via* the Smiles rearrangement in the presence of acid, followed by coupling with adequate thiols to form the ultimate nonsymmetric disulfides (**3** and **4**) (Chart 1).[3]

In our preceding paper, we showed that ethyl 2-[(1*H*-benzimidazol-2-yl)sulfinylmethyl]-4-dimethylamino-5-pyrimidinecarboxylate (**5**, MAZ-525), in which the pyridine moiety of omeprazole and lansoprazole is replaced with the ethyl 4-dimethylamino-5-pyrimidinecarboxylate function, is a potent H^+/K^+-ATPase inhibitor possessing an excellent mucosal protective activity upon



omeprazole : $R^1 = R^3 = OCH_3$
$R^2 = R^4 = CH_3$
lansoprazole : $R^1 = R^4 = H$
$R^2 = CH_3$, $R^3 = OCH_2CF_3$



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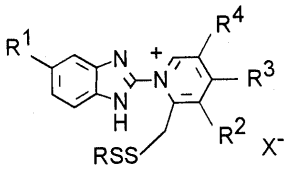

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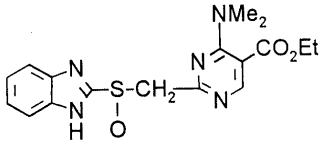

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Chart 1

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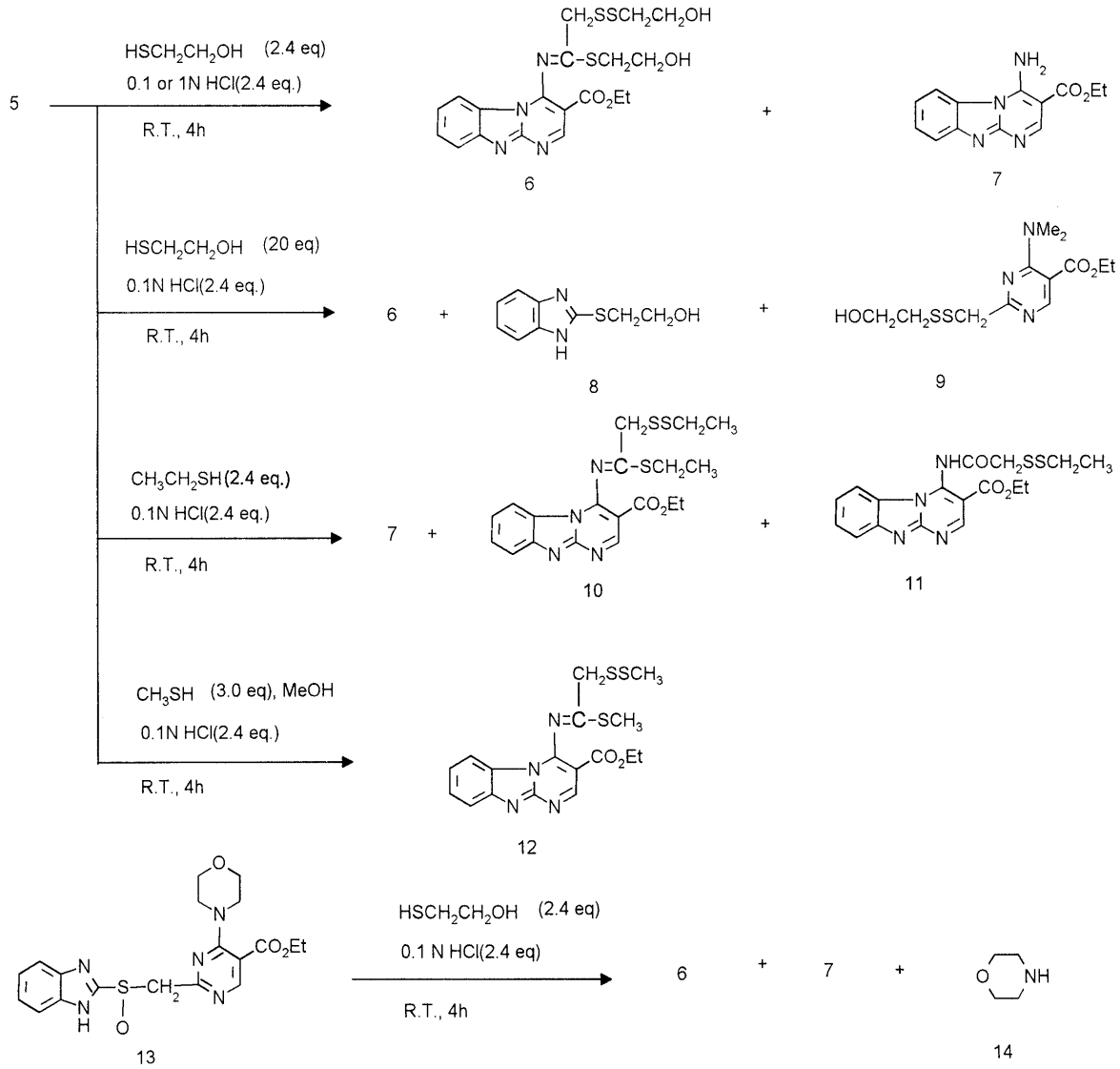


Chart 2

oral or parenteral administration.[4] In order to explore the mechanism of the antisecretory activity, we studied the reaction of **5** with some thiols in the presence of hydrochloric acid, as a model reaction of **5** in the acid compartment of parietal cells.

When **5** was treated with a mixture of 1 molar eq each of 2-mercaptoethanol and 0.1 N hydrochloric acid for several hours at room temperature, formation of an usual adduct, ethyl 4-[2-(2-hydroxyethyldithio)-1-(2-hydroxyethylthio)ethylidenamino]pyrimido[1,2-*a*]benzimidazole-3-carboxylate (**6**), yellow precipitate, was observed. The mass spectrum (MS) of **6** showed a peak at *m/z* 467 due to $(M+H)^+$, which was consistent with the incorporation of two 2-hydroxyethylthio groups and the loss of the dimethylamino moiety. The ^{1}H-NMR spectrum also displayed four methylene proton signals at δ 2.53, 3.36—3.43, 3.72 and 3.68—3.91, due to two hydroxyethylthio groups, in addition to the two protons at δ 3.88 and 4.07 due to the $C=NCH_2S-$ group. The ^{13}C-NMR spectrum gave similar information.

It is noteworthy that a rise of the pH value of the reaction mixture was observed at the end of the reaction. Therefore, more than 2 molar eq of both alkylthiol and hydrochloric acid were employed for the next reaction. Reaction conditions were set up on the basis of the results of a preliminary study (Chart 2). The reaction time was fixed 4 h based on the duration of the inhibitory effect of **5** on histamine-stimulated secretion in rats, and the reaction temperature was, for convenience, maintained at room temperature.

Thus, **5** was allowed to react with a mixture of 2.4 molar eq each of 2-mercaptoethanol and 0.1 N hydrochloric acid, affording **6** and its hydrolysis product, ethyl 4-aminopyrimido[1,2-*a*]benzimidazole-3-carboxylate (**7**), in 57 and 6% yields, respectively. The use of 1 N hydrochloric acid failed to improve the yield of **6** or **7**. With 20 molar eq of 2-mercaptoethanol, the reaction proceeded readily to give **6** as the major product in 66% yield, accompanied with 2-(2-hydroxyethylthio)-1*H*-benzimidazole (**8**) and ethyl 4-dimethylamino-2-(2-hydroxyethyldithiomethyl)-5-pyrimidinecarboxylate (**9**) in 25 and 8% yields, respectively. Formation of analogous substances corresponding to **8** and **9** has also been reported in the reaction of omeprazole with 2-mercaptoethanol under similar conditions.[5]

The reaction of **5** with a mixture of 2.4 molar eq each

of ethanethiol and 0.1 N hydrochloric acid provided not only ethyl 4-(2-ethyldithio-1-ethylthioethylidenamino)-pyrimido[1,2-*a*]benzimidazole-3-carboxylate (**10**), but also ethyl 4-(2-ethyldithioacetylamino)pyrimido[1,2-*a*]-benzimidazole-3-carboxylate (**11**), in which incorporation of one ethylthio group was observed in the ^{1}H-NMR spectrum, in 63 and 5.8% yields, respectively, together with 7 in 7.3% yield. The thiol component in this reaction could easily be replaced by methanethiol, giving the corresponding product, ethyl 4-(2-methyldithio-1-methylthioethylidenamino)pyrimido[1,2-*a*]benzimidazole-3-carboxylate (**12**), in 52% yield as yellow crystals. The ultraviolet (UV) spectra of **10** and **12** were almost identical with that of **6**.

On the other hand, treatment of ethyl 2-[(1*H*-benzimidazol-2-yl)sulfinylmethyl]-4-morpholino-5-pyrimidinecarboxylate (**13**)[6] with 2-mercaptoethanol under analogous conditions, as well as resulting in the production of **6** and **7**, furnished morpholine (**14**) in 69% yield, by elimination from the 4-position of the pyrimidine nucleus. The result suggested that eliminated dimethylamine caused the rise of pH value of the reaction mixture observed in the reaction of **5** and 2-mercaptoethanol.

For the purpose of structural assignment of the products, several chemical manipulations were performed (Chart 3). Hydrolysis of **6** in 1 N ethanolic hydrochloric acid gave **7** in 22% yield, and the production of **7** was observed even in a run with 0.1 N hydrochloric acid (detected by thin layer chromatography). Furthermore, hydrolysis of **7** and **11** in 5 N hydrochloric acid gave the same product, 4-hydroxypyrimido[1,2-*a*]benzimidazole-3-carboxylic acid (**15**). The elemental analysis of **15** indicated the formula $C_{11}H_7N_3O_3$. Also, the ^{1}H-NMR spectrum of **15** supported the disappearance of the ethoxy group of **7**. The data indicated that the amino and ethoxycarbonyl groups attached to **7** were converted into hydroxy and carboxylic acid groups, respectively. Based on the above findings and the fact that omeprazole also yielded the Smiles rearrangement products under similar conditions, compounds **6**, **7**, **10**, **11**, **12** and **15** were assumed to have a pyrimido[1,2-*a*]benzimidazole ring system in common. Structural identification of **7**, **8** and **15** was accomplished by comparison of their spectral properties with those of authentic specimens synthesized according to the reported method.[7] Cyclization of 2-amino-1*H*-benzimidazole (**16**) with ethyl ethoxymethylenecyanoacetate afforded **7** in 64% yield, and hydrolysis of ethyl 4-hydroxypyrimido[1,2-*a*]benzimidazole-3-carboxylate (**17**) gave **15** in 85% yield. Additionally, **8** was identical with the substance prepared by alkylation of 2-mercapto-1*H*-benzimidazole with 2-bromoethanol in the presence of potassium carbonate in dimethylformamide (DMF). On the other hand, an X-ray crystallographic study proved **10** to be ethyl 4-(2-ethyldithio-1-ethylthioethylidenamino)pyrimido[1,2-*a*]benzimidazole-3-carboxylate, which led to the determination of structures **6** and **12**, and implied the conversion of **6** into **7** by hydrolysis.

A plausible pathway for the formation of pyrimido[1,2-*a*]benzimidazoles is illustrated in Chart 4. The process resembles that of omeprazole, which is structurally similar.[3a] The reaction is initiated by protonation at the N(1) atom of the benzimidazole nucleus, giving the cationic intermediate (**19**), which then undergoes nucleophilic attack by the N(1) atom of the pyrimidine nucleus to form the cationic spiro intermediate (**20**). The intermediate **20** undergoes cleavage of the C–S bond to afford the labile sulfenic acid (**21**), followed by coupling with thiol to afford a nonsymmetric disulfide (**22**). Subsequently, the intermediate **22** is further attacked by another alkylthio anion, due to the strong electron-withdrawing effect of the ethoxycarbonyl group, to form the dihydropyrimidine

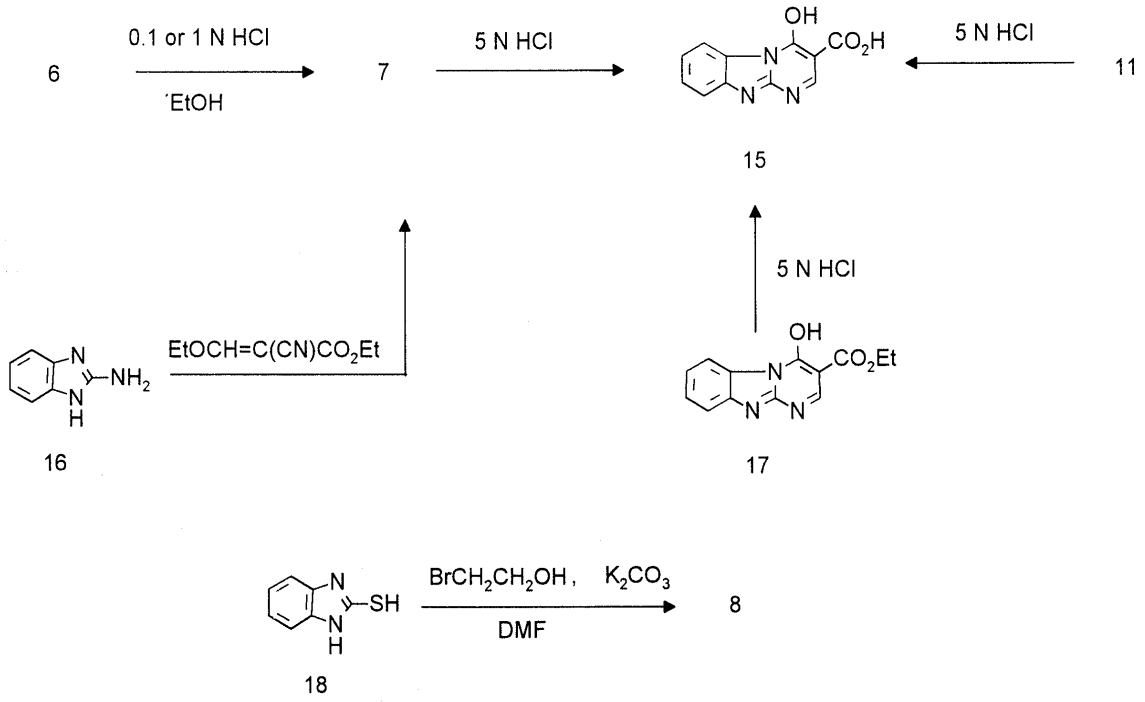


Chart 3

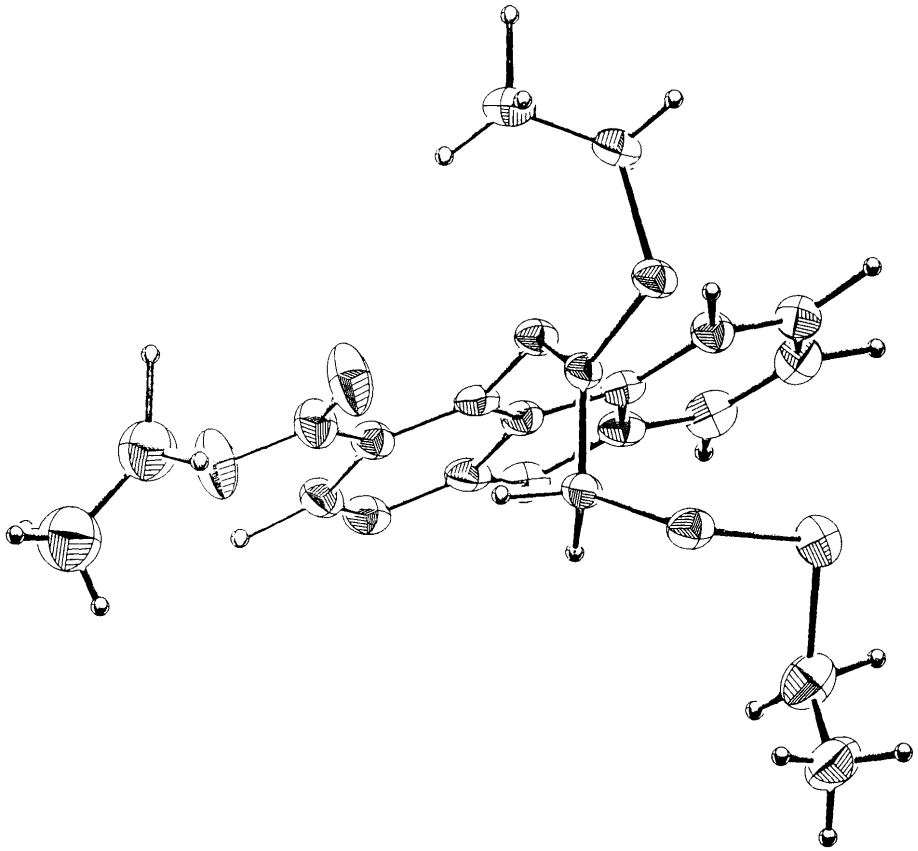


Fig. 1

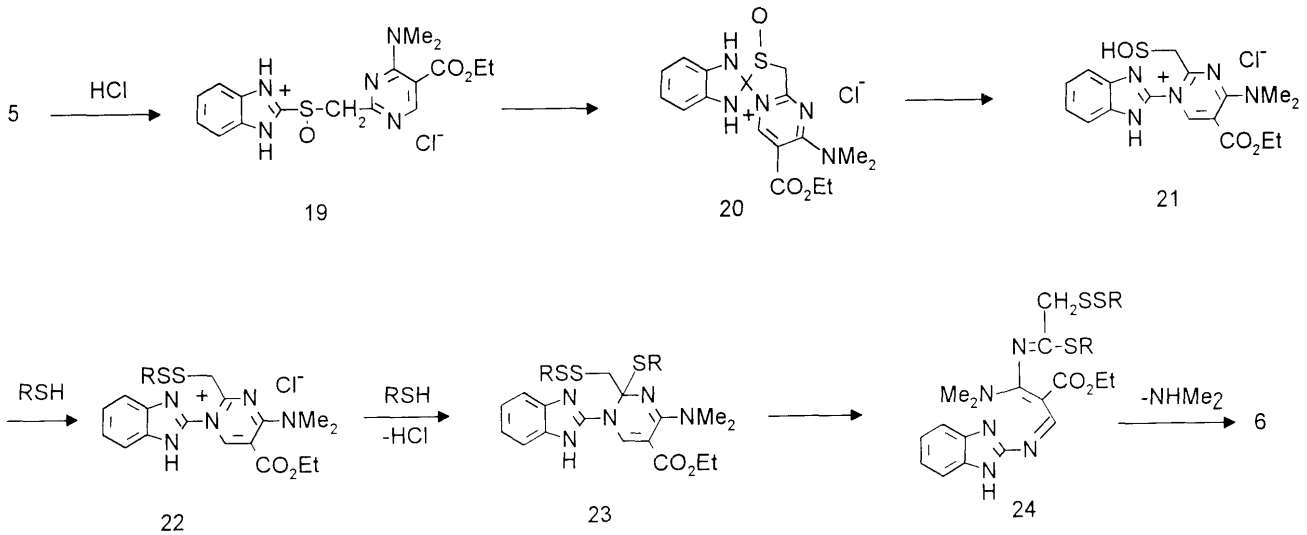
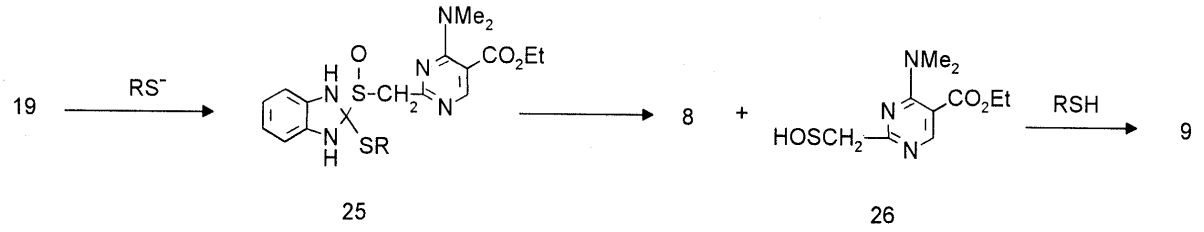


Chart 4

intermediate (**23**). The intermediate **23** is converted into a benzimidazole (**24**) by cleavage of the C–N bond in the dihydropyrimidine moiety, then produces the final product **6** by ring-closure, which involves the displacement of the dimethylamino group by the N(1) atom in the benzimidazole nucleus.

The pathway to **8** and **9** is illustrated in Chart 5. The cationic center in **19** might be subjected to nucleophilic attack of the hydroxyethylthio anion predominantly rather than that of the N(1) atom in the pyrimidine nucleus, because 2-mercaptoethanol was employed in a large excess. The resulting dihydrobenzimidazole intermediate (**25**), after cleavage of the C–S bond, gives **8** and a sulfenic acid (**26**). The labile intermediate **26** immediately reacts with 2-mercaptoethanol to give **9**.

In conclusion, thiol sites are known to exist on the enzyme H^+/K^+-ATPase,[8] and therefore, the two transformation mechanisms of **5** can be thought of as



R=CH_2CH_2OH

Chart 5

models of the reaction in the acid compartment of parietal cells. However, the cleavage of **5** into **8** and **9** is probably a minor process, since it occurs only in the presence of a large excess of thiol. It is interesting that **5** has a capability to react with two thiol sites, irrespective of whether the reaction proceeds through the Smiles rearrangement or cleavage.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded in a Nujol mull on a Hitachi 270-30 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were taken with a Bruker AC250 instrument using tetramethylsilane as an internal standard. MS were obtained with a JEOL JMS-LX2000 liquid chromatograph-mass spectrometer using a flow injection system. UV spectra were recorded with a Hitachi 150-20 spectrophotometer.

Reaction of Ethyl 2-[(1*H*-Benzimidazol-2-yl)sulfinylmethyl]-4-dimethylamino-5-pyrimidinecarboxylate (5) with 2-Mercaptoethanol in Hydrochloric Acid Solution 1) Compound **5** (4.0 g, 0.0107 mol) was added to a solution of 2-mercaptoethanol (2.0 g, 0.0257 mol) in 0.1 N hydrochloric acid (257 ml), and the solution was stirred for 4 h at room temperature. The resulting precipitates were filtered off, washed successively with water and CH_2Cl_2, and recrystallized from DMF to give ethyl 4-[2-(2-hydroxyethyldithio)-1-(2-hydroxyethylthio)ethylidenamino]pyrimido-[1,2-*a*]benzimidazole-3-carboxylate (**6**) (2.9 g, 57%) as yellow needles. mp 173—174 °C. IR cm^{-1}: 3300—3500 (OH), 1720 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.34 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.53 (2H, m, SCH_2), 3.72 (2H, m, SCH_2), 3.36—3.48 (2H, m, $SC\underline{H}_2CH_2O$), 3.68—3.91 (2H, m, $SC\underline{H}_2CH_2O$), 3.88 (1H, d, J=15.1 Hz, CH), 4.07 (1H, d, J=15.1 Hz, CH), 4.29 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 4.71 (1H, t, J=5.4 Hz, OH), 5.15 (1H, t, J=5.4 Hz, OH), 7.40 (1H, t, J=7.1 Hz, aromatic H), 7.57 (1H, t, J=7.1 Hz, aromatic H), 7.84 (2H, t, J=7.8 Hz, aromatic H), 9.00 (1H, s, C2-H). ^{13}C-NMR (DMSO-d_6) δ: 14.0 (CH_3), 34.3 (CH_2), 40.5 (CH_2), 43.4 (CH_2), 59.2 (CH_2), 60.9 (CH_2), 97.0 (C), 115.9 (CH), 117.3 (CH), 119.0 (CH), 126.3 (CH), 127.1 (C), 144.4 (C), 151.1 (C), 153.7 (C), 156.9 (CH), 163.2 (C), 180.0 (CO). UV $\lambda_{max}^{acetonitrile}$ nm (ε): 222 (17460), 271 (170540), 367 (3690). MS m/z: 467 $(M+H)^+$. *Anal.* Calcd for $C_{19}H_{22}N_4O_4S_3$: C, 48.91; H, 4.75; N, 12.01. Found: C, 49.00; H 4.60; N, 11.79. The filtrate was neutralized with a 5% aqueous $NaHCO_3$ solution and then extracted with $CHCl_3$. The organic layer was separated, dried over Na_2SO_4 and evaporated under reduced pressure. The oily product was triturated with AcOEt to give a solid. The solid was collected by filtration and recrystallized from DMF–H_2O to give ethyl 4-aminopyrimido[1,2-*a*]benzimidazole-3-carboxylate (**7**) (0.16 g, 6%) as colorless crystals. mp 296—297 °C.[6] IR cm^{-1}: 3050—3300 (NH_2), 1696 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.36 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 4.31 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 7.40 (1H, t, J=7.4 Hz, aromatic H), 7.55 (1H, t, J=7.4 Hz, aromatic H), 7.78 (1H, d, J=8.2 Hz, aromatic H), 8.46 (1H, d, J=8.2 Hz, aromatic H), 8.83 (1H, s, aromatic H), 8.95 (2H, br, NH_2). MS m/z: 257 $(M+H)^+$. *Anal.* Calcd for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.86. Found: C, 61.06; H, 4.60; N, 21.95.

2) Compound **5** (2.0 g, 0.0054 mol) was allowed to react with 2-mercaptoethanol (1.0 g, 0.0129 mol) in 1 N hydrochloric acid (12.8 ml) under the same conditions as described above. The precipitates were recrystallized from DMF to give **6** (1.3 g, 52%). The filtrate was neutralized with a 5% aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with water and brine, then dried over Na_2SO_4 and the solvent was removed under reduced pressure to give an oil. The crude product was purified by column chromatography on silica gel with $CHCl_3$–EtOH (20 : 1) to provide **7** (0.16 g, 7.2%).

3) Compound **5** (4.0 g, 0.0107 mol) was treated with 2-mercaptoethanol (16.7 g, 0.214 mol) in 0.1 N hydrochloric acid (257 ml) for 4 h with stirring at room temperature. The precipitates were collected by filtration and recrystallized from DMF to give **6** (3.3 g, 66%). The filtrate was neutralized with a 5% aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with water and brine, then dried over Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography on silica gel with $CHCl_3$–EtOH (20 : 1) afforded ethyl 4-dimethylamino-2-(2-hydroxyethyldithiomethyl)-5-pyrimidinecarboxylate (**9**) (0.23 g, 8%) as an oil. IR cm^{-1}: 3100—3600 (OH), 1720 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.29 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.74 (2H, t, J=6.5 Hz, SCH_2), 3.02 (6H, s, $N(CH_3)_2$), 3.59 (2H, q, J=6.5 Hz, OCH_2), 4.00 (2H, s, SCH_2), 4.27 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 4.87 (1H, t, J=5.5 Hz, OH), 8.48 (1H, s, aromatic H). MS m/z: 288 $(M+H)^+$. *Anal.* Calcd for $C_{12}H_{19}N_3O_3S_2 \cdot HCl$: C, 40.73; H, 5.70; N, 11.87. Found: C, 40.76; H, 5.47; N, 11.67. The remaining aqueous solution was concentrated under reduced pressure at 30—40 °C, and the resulting residue was extracted with EtOH–$CHCl_3$ (1 : 1). The solution was dried over Na_2SO_4 and concentrated to give an oil. The crude product was purified by column chromatography on silica gel with $CHCl_3$–EtOH (10 : 1), and recrystallized from AcOEt to give 2-(2-hydroxyethylthio)-1*H*-benzimidazole (**8**) (0.36 g, 25%) as colorless prisms. mp 129—130 °C. IR cm^{-1}: 2700—3200 (OH and NH). ^{1}H-NMR (DMSO-d_6) δ: 3.36 (2H, t, J=6.0 Hz, SCH_2), 3.70 (2H, t, J=6.0 Hz, $C\underline{H}_2OH$), 5.13 (1H, br s, OH), 7.10 (2H, m, aromatic H), 7.35 (1H, brs, aromatic H), 7.49 (1H, br s, aromatic H), 12.52 (1H, s, NH). MS m/z: 200 $(M+H)^+$. *Anal.* Calcd for $C_9H_{10}N_2OS$: C, 55.65; H, 5.19; N, 14.42. Found: C, 55.81; H, 4.92; N, 14.51.

Reaction of 5 with Ethanethiol in 0.1 N Hydrochloric Acid A mixture of **5** (3.0 g, 0.0080 mol) and ethanethiol (1.5 g, 0.024 mol) in 0.1N hydrochloric acid (257 ml) was stirred vigorously for 4 h at room temperature. The precipitates were filtered off, washed with water and isopropyl ether, and dried. The crude product was purified by column chromatography on silica gel with $CHCl_3$–MeOH (20 : 1), and recrystallized from MeOH–isopropyl ether to give ethyl 4-(2-ethyldithio-1-ethylthioethylidenamino)pyrimido[1,2-*a*]benzimidazole-3-carboxylate (**10**) (1.6 g, 46%) as yellow needles. mp 113—115 °C. IR cm^{-1}: 1715 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.3 Hz, $SCH_2C\underline{H}_3$), 1.41 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 1.49(3H, t, J=7.4 Hz, $SCH_2C\underline{H}_3$), 2.42 (2H, q, J=7.4 Hz, $SC\underline{H}_2CH_3$), 3.19—3.41 (2H, m, $SC\underline{H}_2CH_3$), 3.58 (1H, d, J=14.8 Hz, SCH_2), 3.75 (1H, d, J=14.8 Hz, SCH_2), 4.36 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 7.37 (1H, t, J=8.4 Hz, aromatic H), 7.55 (1H, t, J=7.4 Hz, aromatic H), 7.71 (1H, d, J=8.3 Hz, aromatic H), 7.97 (1H, d, J=8.2 Hz, aromatic H), 9.25 (1H, s, C2-H). ^{13}C-NMR ($CDCl_3$) δ: 13.4 (CH_3), 13.8 (CH_3), 14.2 (CH_3), 26.4 (CH_2), 32.2 (CH_2), 44.4 (CH_2), 61.1 (CH_2), 96.5 (C), 115.7 (CH), 119.8 (CH), 122.1 (CH), 126.4 (CH), 127.4 (C), 144.8 (C), 151.4 (C), 154.1 (C), 156.9 (CH), 163.5 (C), 179.3 (CO). UV $\lambda_{max}^{acetonitrile}$ nm (ε): 368 (3630), 271 (44970), 222 (16920). MS m/z: 435 $(M+H)^+$. *Anal.* Calcd for $C_{19}H_{22}N_4O_2S_3$: C, 52.51; H, 5.10; N, 12.89. Found: C, 52.80; H, 5.15; N, 12.60. The aqueous filtrate was neutralized with 5% aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with water and brine, then dried over Na_2SO_4 and the solvent was removed under reduced pressure. The

obtained oil was chromatographed on silica gel with $CHCl_3$–EtOH (20 : 1) to give **7** (0.15 g, 7%), **10** (0.5 g, 14%) and ethyl 4-(2-ethyldithioacetylamino)pyrimido[1,2-*a*]benzimidazole-3-carboxylate (**11**) (0.18g, 5.8%) which was recrystallized from MeOH. mp 140—141 °C. IR cm^{-1}: 2900—3100 (NH), 1710, 1630 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.28 (6H, t, J=7.2 Hz, $OCH_2\underline{CH_3}$ and $SCH_2\underline{CH_3}$), 2.81 (2H, q, J=7.2 Hz, $SC\underline{H_2}CH_3$), 3.84 (2H, s, $COCH_2$), 4.20 (2H, q, J=7.2 Hz, $OC\underline{H_2}CH_3$), 7.44 (1H, m, aromatic H), 7.59 (2H, m, aromatic H), 8.54 (1H, s, aromatic H), 8.88 (1H, d, J=8.3 Hz, aromatic H), 12.50—14.50 (1H, br, NH). ^{13}C-NMR (DMSO-d_6) δ: 14.2 (CH_3), 14.3 (CH_3), 31.4 (CH_2), 46.9 (CH_2), 60.3 (CH_2), 103.5 (C), 112.2 (CH), 118.0 (CH), 122.7 (CH), 126.5 (C), 126.6 (CH), 131.7 (C), 147.9 (C), 149.2 (C), 156.5 (CH), 164.4 (CO), 176.7 (CO). MS m/z: 391 $(M+H)^+$. *Anal.* Calcd for $C_{17}H_{18}N_4O_3S_2$: C, 52.29; H, 4.65; N, 14.35. Found: C, 52.36; H, 4.41; N, 14.29.

Reaction of 5 with Methanethiol in 0.1 N Hydrochloric Acid Compound **5** (3.7 g, 0.01 mol) was added to a mixture of 30% methanolic methanethiol (4.8 g, 0.03 mol) and 0.1 N hydrochloric acid (240 ml) and the mixture was stirred for 4 h at room temperature. It was neutralized with 5% $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was recrystallized from $CHCl_3$–diethyl ether to give ethyl 4-(2-methyldithio-1-methylthioethylidenamino)pyrimido[1,2-*a*]benzimidazole-3-carboxylate (**12**) (2.1 g, 52%) as yellow needles. mp 151—152 °C. IR cm^{-1}: 1710 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.33 (3H, t, J=7.1 Hz, $OCH_2\underline{CH_3}$), 2.20 (3H, s, SCH_3), 2.69 (3H, s, SCH_3), 3.92 (1H, d, J=15.3 Hz, SCH_2), 4.07 (1H, d, J=15.3 Hz, SCH_2), 4.27 (2H, q, J=7.1 Hz, $OC\underline{H_2}CH_3$), 7.40 (1H, t, J=7.2 Hz, aromatic H), 7.57 (1H, t, J=7.2 Hz, aromatic H), 7.81 (1H, d, J=8.1 Hz, aromatic H), 7.86 (1H, d, J=8.1 Hz, aromatic H), 9.09 (1H, s, C_2-H). ^{13}C-NMR ($CDCl_3$) δ: 14.3 (CH_3), 15.2 (CH_3), 22.6 (CH_3), 43.5 (CH_2), 61.3 (CH_2), 96.7 (C), 115.7 (CH), 120.1 (CH), 122.3 (CH), 126.6 (CH), 127.5 (C), 145.0 (C), 151.6 (C), 154.4 (C), 157.1 (CH), 163.7 (C), 179.9 (CO). UV $\lambda_{max}^{acetonitril}$ nm (ε): 366 (3780), 271 (49300), 222 (18260). MS m/z: 407 $(M+H)^+$. *Anal.* Calcd for $C_{17}H_{18}N_4O_2S_3$: C, 50.22; H, 4.46; N, 13.78. Found: C, 50.33; H, 4.43; N, 13.70.

Reaction of Ethyl 2-[(1*H*-Benzimidazol-2-yl)sulfinylmethyl]-4-morpholino-5-pyrimidinecarboxylate (13) with 2-Mercaptoethanol in 0.1 N Hydrochloric Acid A mixture of **13** (4.2 g, 0.010 mol) and 2-mercaptoethanol (1.9 g, 0.024 mol) in 0.1 N hydrochloric acid (240 ml) was stirred for 4 h at room temperature. The resulting precipitates were filtered off, washed with water and CH_2Cl_2, and recrystallized from DMF to give **6** (3.0 g, 64%). The aqueous filtrate was neutralized with a 5% aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was washed with AcOEt and then recrystallized from DMF–H_2O to give **7** (0.12 g, 5%). The aqueous layer was adjusted to pH 5. After evaporation of the solvent, the resulting residue was treated with a 30% aqueous KOH solution (10 ml) and extracted with CH_2Cl_2 (100 ml). The organic layer was separated, then dried over Na_2SO_4 and evaporated under reduced pressure to yield morpholine (**14**) (0.6 g, 69%) as an oil. IR cm^{-1}: 3000—3500 (NH). ^{1}H-NMR (DMSO-d_6) δ: 2.65 (1H, s, NH), 2.90 (4H, m, $C\underline{H_2}NC\underline{H_2}$), 3.70 (4H, m, $C\underline{H_2}OC\underline{H_2}$).

Ethyl 4-Aminopyrimido[1,2-*a*]benzimidazole-3-carboxylate (7) 1) Compound **6** (0.5 g, 0.00107 mol) was added to a mixture of 1 N hydrochloric acid (20 ml) and EtOH (4 ml), and the solution was allowed to stand for 4 h at room temperature. The solution was neutralized with a 5% aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with water and brine, and dried over Na_2SO_4. After evaporation of the solvent, the solid was purified by column chromatography on silica gel with $CHCl_3$–EtOH (10 : 1) to give **7** (0.06 g, 22%).

2) A mixture of 2-amino-1*H*-benzimidazole (**16**) (1.3 g, 0.01 mol) and ethyl ethoxymethylenecyanoacetate (1.7 g, 0.01 mol) was heated at 120 °C for 1 h with stirring. The resulting solid was recrystallized from DMF to give **7** (1.6 g, 62%) as a powder.

4-Hydroxypyrimido[1,2-*a*]benzimidazole-3-carboxylic Acid (15) Compound **7** (0.5 g, 0.002 mol) in 5 N hydrochloric acid was heated for 3 h at 100 °C with stirring. After cooling, the pH value of the solution was adjusted to 6. The precipitates were washed with water and recrystallized from DMF to give **15** (0.25 g, 55%). mp 284—286 °C. IR cm^{-1}: 2500—3200 (OH), 1725 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 7.47 (1H, m, aromatic H), 7.62 (2H, m, aromatic H), 8.49 (1H, d, J=7.9 Hz, aromatic H), 8.78 (1H, s, C2-H), 11.00—14.50 (2H, br, OH and CO_2H). Compound **11** and ethyl 4-hydroxypyrimido[1,2-*a*]benzimidazole-3-carboxylate (**17**)[7] were treated under similar condition to give **15** in 60 and 68% yields, respectively.

2-(2-Hydroxyethylthio)-1*H*-benzimidazole (8) A mixture of 2-mercapto-1*H*-benzimidazole (**18**) (1.5 g, 0.01 mol), K_2CO_3 (1.9 g, 0.014 mol) and 2-bromoethanol (1.3 g, 0.01 mol) in DMF (15 ml) was heated at 60 °C for 3 h with stirring. The solution was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with $CHCl_3$ and the extract was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the crude product was recrystallized from EtOH–isopropyl ether to give **8** (1.2 g, 60%).

X-Ray Crystallographic Analysis of 10 Data Collection: A crystal (yellow prism) of $C_{19}H_{22}N_4O_2S_3$ having approximate dimension of 0.22 × 0.20 × 0.30 mm was used for analysis. All measurements were made on a Rigaku AFC5R diffractometer with graphite-monochromated MoK_α radiation (I=0.71069 Å). Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 24 carefully centered reflections in the range of $18.48 < 2\theta < 22.77°$, corresponded to a monoclinic cell with the following dimensions: a=8.061(2) Å, b=19.054(6) Å, c=14.551(5) Å, b=105.20(2)°, V=2157(1) Å^3.

For Z=4 and F.W.=434.59, the calculated density is 1.338 g/cm^3. Based on the systematic absences, of $h01 : h+1 \neq 2n$, $0k0 : k \neq 2n$, and the successful solution and refinement of the structure, the space group was determined to be $P2_1/n$.

The data were collected at a temperature of 23±1 °C using the w–$2q$ scan technique.

Scans of $(1.30+0.30\tan\theta)°$ were made at a speed of 4.0°/min (in omega).

Data Reduction: Of the 4072 reflections which were collected, 3780 were unique (R_{mt}=0.027). The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection, indicating crystal and electronic stability (no decay correction was applied). The linear absorption coefficient for MoK_α is 3.5 cm^{-1}. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement: The structure was solved by direct methods.[9] The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 1575 observed reflections ($I > 3.00s(I)$) and 243 variable parameters and converged with unweighted agreement factors of: $R = \sum \| F_O| - |F_C \| / \sum |F_O| = 0.052$ and $R_w = [\sum w(|F_O| - |F_C|)^2 / \sum wF_O^2)]^{1/2} = 0.056$.

The maximum and minimum peaks on the final difference Fourier map corresponded to 0.41 and $-0.29\,e^-$/Å, respectively. Neutral atom scattering factors were taken from Cromer and Waber.[10] Anomalous dispersion effects were included in F_{calc},[11] and the values for $\Delta f'$ and $\Delta f''$ were those of Cromer.[12] All calculations were performed using the TEXSAN[13] crystallographic software of Molecular Structure Corporation.

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