3-(Arylacetylamino)-*N*-methylbenzamides: A Novel Class of Selective Anti-*Helicobacter pylori* Agents

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After chemical modification preceded by the random screening of our chemical library, a novel class of selective anti-*Helicobacter pylori* agents was generated. Consequently, the 3-(arylacetylamino)-*N*-methylbenzamides, which were quite easy to prepare, showed potent inhibitory activity against *Helicobacter pylori* but exhibited no inhibitory activity against other sorts of bacteria and fungi, e.g., *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, and *Candida albicans*. These compounds showed potent anti-*H. pylori* activity under acidic conditions, whereas amoxicillin and clarithromycin decreased activity. The 3-(3-arylpropionylamino)-*N*-methylbenzamides, 3-(aryloxyacetylamino)-*N*-methylbenzamides, and (3-methylcarbamoylphenyl)carbamic acid 1-arylmethyl esters also exhibited potent anti-*H. pylori* activity. Finally, we selected **7n** (BAS-118) as a candidate compound for further evaluation.

Introduction

Helicobacter pylori (*H. pylori*) is a Gram-negative microaerophilic bacterium which was isolated and identified first in the stomach of patients with gastritis and peptic ulcer.[1] Further investigations revealed that the bacterium is an important cause of gastritis, is responsible for the formation and recurrence of gastric and duodenal ulcers, and is closely related with gastric cancer.[2] Besides gastroduodenal disease, associations between *H. pylori* infection and other various extraintestinal pathologies have been reported.[3]

In the clinical setting, *H. pylori* is eradicated mainly by triple therapy which consists of a combination of two antibacterial agents with different mechanisms of action, which are selected from amoxicillin, clarithromycin, and metronidazole, and in a proton pump inhibitor. However, antibacterial agents used in this therapy show a broad and potent antibacterial spectrum; high dose and long-term administration are required for complete eradication. This therapy thus occasionally provokes side effects such as diarrhea, including pseudomembranous enterocolitis in serious cases. Therefore, the development of selective anti-*H. pylori* agents is demanded to avoid such drawbacks.

As selective anti-*H. pylori* agents, omeprazole and its sulfide derivative,[4] 2-(substituted guanidino)-4-(furyl or phenyl)thiazoles,[5] benzyloxyisoquinoline derivatives,[6] and FR145715[7] have been reported. Some natural products, e.g., phthalide compounds,[8] alkylquinolone derivatives,[9,10] cabreuvin,[11] and γ-pyrone compounds,[12] also have shown potent activity against and good selectivity for *H. pylori*. On the basis of their inhibitory activity on dihydroorotate dehydrogenase, *H. pylori*-selective pyrazole derivatives have been reported recently.[13]

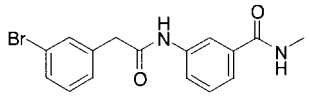

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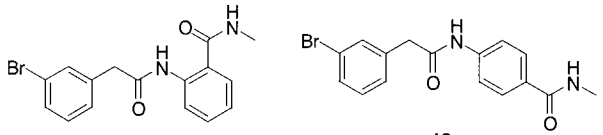
Figure 1. Hit compound from random screening.



12 **13**

Figure 2. Regioisomers of compound **1**.

To generate a new class of selective anti-*H. pylori* agents, we randomly screened our original chemical library. The selectivity for the other bacteria, e.g., *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, and *Candida albicans*, was investigated in some selected compounds. These investigations afforded several new classes of *H. pylori*-selective compounds. Among them, compound **1** (Figure 1) was most attractive because of its simple structure, synthetic easiness, stability under acidic conditions,[14] potent anti-*H. pylori* activity (MIC = 0.39 μg/mL), and excellent selectivity for other bacteria and fungi. We report herein the synthesis of derivatives of compound **1** and their structure−activity relationship.

Chemistry

Derivatives of the *N*-methylbenzamide moiety (**4a**−**g**) were prepared as described in Scheme 1a. (3-Bromophenyl)acetic acid **2** was treated with oxalyl chloride and a catalytic amount of DMF in CH_2Cl_2 to

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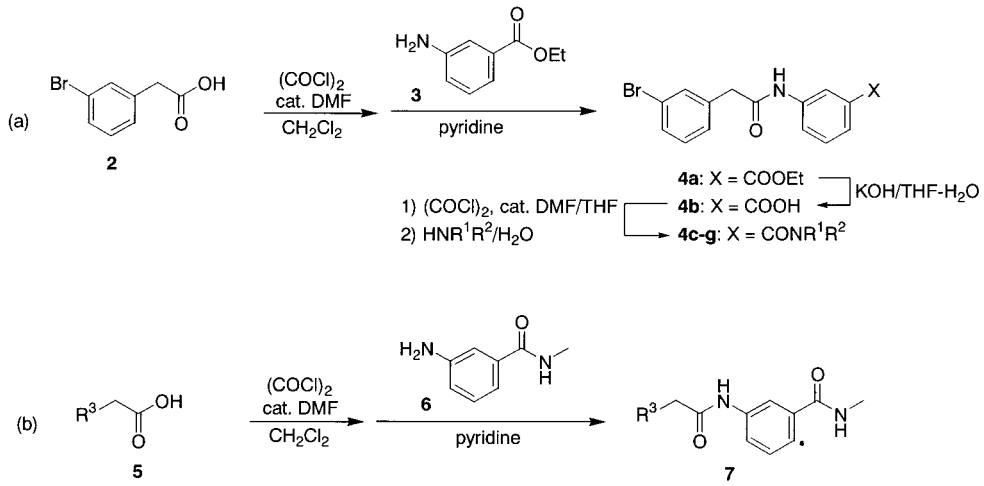
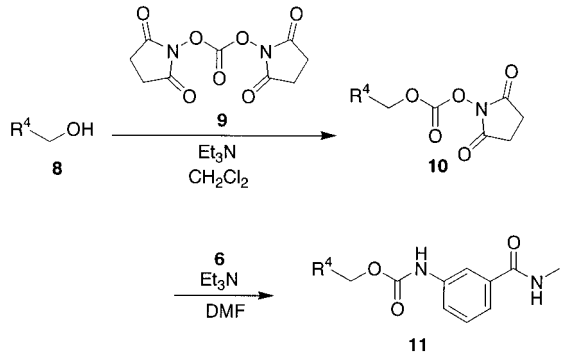
Scheme 1. Synthesis of Amide Derivatives



Scheme 2. Synthesis of Carbamate Derivatives



afford the corresponding acid chloride, which was allowed to react with 3-aminobenzoic acid ethyl ester **3** in the presence of pyridine to give the coupled product **4a**. The ester moiety in **4a** was then hydrolyzed, and the carboxylic acid obtained was converted to acid chloride, which was treated with amine derivatives to afford the amide derivatives **4c**−**g**. The *o*- and *p*-derivatives (**12** and **13** (Figure 2), respectively) were also prepared in a similar manner. The *N*-methylbenzamide derivative **7** was obtained in one step (Scheme 1b). Therefore, coupling of the arylacetic acid **5** with the commercially available 3-amino-*N*-methylbenzamide **6** via acid chloride yielded the desired product efficaciously.[15]

The method for the preparation of the carbamate derivative **11** is shown in Scheme 2. Treatment of the alcohol derivative **8** and di(*N*-succinimidyl) carbonate **9** in the presence of triethylamine in CH_2Cl_2 afforded the active ester **10**, which was allowed to react with the aniline derivative **6** to afford the carbamate derivative **11**.

Results and Discussion

First, transformation of the *N*-methylbenzamide moiety was examined, the results of which are summarized in Table 1. The *N*-methyl derivative **1** showed potent anti-*H. Pylori* activity, while the *N*-ethyl derivative **4e** showed less potent activity. The unsubstituted benzamide derivative **4c** and the *N*,*N*-dimethyl derivative **4d** showed much less activity. Other amide derivatives, e.g., the hydroxamic acid **4f** and its *O*-methyl ester **4g**, also showed less potent activity. The benzoic acid derivative **4b** and its ethyl ester **4a** were not active. Alternatively, we also prepared the *o*- and *p*-substituted *N*-methylbenzamide derivatives (**12** and **13**, respectively) which did not show any anti-*H. pylori* activity (MIC > 50 μg/mL). Accordingly, only the *m*-substituted *N*-methylbenzamide derivative **1** was shown to have potent anti-*H. pylori* activity.

Table 1. SAR of Benzamide Moiety

no.	X	MIC (μg/mL)
1	$CONHCH_3$	0.39
4a	$COOCH_2CH_3$	>100
4b	COOH	>100
4c	$CONH_2$	100
4d	$CON(CH_3)_2$	25
4e	$CONHCH_2CH_3$	3.12
4f	CONHOH	12.5
4g	$CONHOCH_3$	12.5
	clarithromycin	0.05

Table 2. SAR of Phenylacetamide Moiety

no.	R^3	MIC (μg/mL)
7a	Ph	1.56
7b	3-F-Ph	3.12
7c	2-Cl-Ph	3.12
7d	3-Cl-Ph	0.39
7e	4-Cl-Ph	0.78
1	3-Br-Ph	0.39
7f	4-Br-Ph	0.78
7g	3-Me-Ph	0.39
7h	3-MeO-Ph	0.78
7i	$3\text{-}PhCH_2O\text{-}Ph$	0.78
7j	$3\text{-}NO_2\text{-}Ph$	3.12
7k	3-OH-Ph	6.25

Second, the effects of substituents on the phenyl ring in the phenylacetamide moiety were investigated (Table 2). Regarding the position of substituents, the anti-*H. pylori* activity of the 2-chloro compound **7c** was less potent; hence, the 3- and 4-chloro compounds (**7d** and **7e**, respectively) showed similar potent activity. Regarding the bromo-substituted compounds, the 3-and 4-substituted compounds (**1** and **7f**, respectively) also showed similar anti-*H. pylori* activity. Therefore, the effects of substituents are represented here by the results of the 3-substituted derivatives.[16] Small substituents, e.g., hydrogen (**7a**) and fluorine (**7b**), showed less potent anti-*H. pylori* activity. Among large substituents, the lipo-

Table 3. SAR of Arylacetamide and Other Amide Derivatives

no.	R^3	MIC (μg/mL)
7l	cyclohexyl	12.5
7m	1-naphthyl	0.10
7n	2-naphthyl	0.05
7o	3-benzothienyl	0.10
7p	3,4-methylendioxyphenyl	0.78
7q	3-indolyl	0.78
7r	benzyl	12.5
7s	2-MeO-benzyl	0.78
7t	phenoxy	3.12
7u	2,3-Cl_2-phenoxy	0.39
7v	1-naphthoxy	0.10
7w	2-naphthoxy	0.39

Table 4. SAR of Carbamate Derivatives

no.	R^4	MIC (μg/mL)
11a	4-Me-Ph	0.10
11b	4-Cl-Ph	0.20
11c	2,6-Cl_2-Ph	0.20
11d	1-naphthyl	0.05
11e	2-naphthyl	0.10

philic substituents, e.g., methyl (**7g**) and methoxy (**7h**), exhibited good activity; however, the activity of polar substituents, e.g., nitro (**7j**), and hydrophilic substituents, e.g., hydroxyl (**7k**), was less potent. A very large and lipophilic benzyloxy group (**7i**) also showed potent activity.

Other aromatic rings were also investigated (Table 3). The 1-naphthyl and 2-naphthylacetamide derivatives (**7m** and **7n**, respectively) showed quite potent anti-*H. pylori* activity which was comparable to that of clarithromycin (see Table 1). Among heteroaryl rings, the lipophilic rings, e.g., benzothiophene (**7o**), afforded similar potency; however, more hydrophilic rings, e.g., the 3,4-methylenedioxyphenyl and indolyl derivatives (**7p** and **7q**, respectively), exhibited less potent activity. Nevertheless, the cyclohexylacetamide derivative **7l** showed very much less potent activity despite its lipophilic property. This result indicates that the flat structure would be essential for potent anti-*H pylori* activity in this area.

The 3-phenylpropionylamide derivatives were also prepared (Table 3). Although the phenyl derivative **7r** showed less potent activity, introduction of the lipophilic methoxy group at its 2-position (**7s**) improved activity. In the case of aryloxyacetamide derivatives (**7t**−**w**), more lipophilic compounds showed potent anti-*H. pylori* activity. Among them, the 1-naphthoxyacetamide derivative **7v** afforded quite potent anti-*H. pylori* activity.

In consideration of the structure−activity relationship (SAR) of the amide derivatives that introduction of lipophilic substituents increased activity, the carbamate derivatives were prepared and some of active compounds are summarized in Table 4. In the case of the benzyl carbamate derivatives, compounds bearing lipophilic substituents, e.g., methyl and chlorine, exhibited potent anti-*H. pylori* activity (**11a**−**c**). In this case, the 1-naphthylmethyl and 2-naphthylmethyl derivatives (**11d** and **11e**, respectively) showed quite potent anti-*H. pylori* activity, too.

SARs described so far are summarized as follows. Regarding the methylamide moiety, only the *m*-substituted methylamide compound showed potent activity. On the contrary, substituents of the arylalkylamide moiety were widely acceptable; especially, the lipophilic flat structure afforded quite potent anti-*H. pylori* activity.

Table 5. Anti-*H. pylori* Activity under Acidic Conditions

	MIC (μg/mL)		
compound	pH 7.0	pH 6.0	pH 5.0
amoxicillin	0.031	0.125	0.50
clarithromycin	0.063	0.50	2.0
7m	0.125	0.125	0.125
7n	0.063	0.063	0.063
7o	0.25	0.25	0.25

Selectivity for *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, and *Candida albicans* was evaluated by the agar hole method to several active compounds. None of the tested compounds (**1**, **4e**−**g**, **7a**−**h**, **7m**, and **7n**) showed antibacterial and antifungal activity against any of the tested organisms at a concentration of 1000 μg/mL. Although the inhibition mechanism against *H. pylori* remains unknown at present, the potent inhibitory activity against and complete selectivity for *H. pylori* of the above mentioned compounds are quite important points for a drug with fewer side effects.

Finally, anti-*H. pylori* activity under acidic conditions was evaluated.[17] Activity of amoxicillin and clarithromycin at pH 5.0 was 16−32 times less potent than that at pH 7.0, whereas MIC values of compounds **7m**, **7n**, and **7o** did not change under acidic conditions (Table 5). These results suggest that the above mentioned compounds would show potent anti-*H. pylori* activity in stomach.

Conclusions

After chemical modification preceded by the random screening of our chemical library, a novel class of selective anti-*Helicobacter pylori* agents was generated. Consequently, the 3-(arylacetylamino)-*N*-methylbenzamides, which were quite easy to prepare, showed potent inhibitory activity against *H. pylori* but showed no inhibitory activity against other sorts of bacteria and fungi, e.g., *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, and *Candida albicans*. These compounds showed potent anti-*H. pylori* activity under acidic conditions, whereas amoxicillin and clarithromycin decreased activity. Finally, we selected **7n** as a candidate compound for further evaluation. Details on the microbiological features of **7n** (BAS-118) will be reported soon.

Experimental Section

General. All ^{1}H NMR spectra taken at 300 MHz were measured on a Bruker ARX-300 or DPX-300 instrument and are reported in parts per million from internal tetramethylsilane. IR spectra were recorded on a JASCO FT/IR-5300 instrument; absorptions are reported in cm^{-1}. Most of reagents were purchased from Tokyo Chemical Industry and were used without further purification. A clinically isolated *Helicobacter pylori* strain 31A was kindly provided from Microorganism Department, First Laboratory of Bacteria, Tokyo Metropolitan Research Laboratory of Public Health. Regarding other bacteria and fungi, the following standard strains were used: *Bacillus subtilis* ATCC6633, *Staphylococcus aureus* 209P ATCC6538P, *Escherichia coli* MCI2195, *Pseudomonas aeruginosa* MCI2197, *Bacteroides fragilis* MCI2173, and *Candida albicans* MCI2202. Brain-heart infusion and yeast extract

were purchased from Difco Laboratories. Fetal bovine serum, Neutrient agar, and potato dextrose agar were purchased from Upstate Biotechnology, Eiken, and Nissui, respectively.

3-[2-(3-Bromophenyl)acetylamino]benzoic Acid Ethyl Ester (4a). To a solution of (3-bromophenyl)acetic acid **2** (2.88 g, 13.4 mmol) in CH_2Cl_2 (30 mL) were added oxalyl chloride (1.79 g, 14.1 mmol) and two drops of DMF, and the resulting solution was stirred for 1 h at room temperature. The solution was then cooled to 0 °C, and 3-aminobenzoic acid ethyl ester **3** (2.21 g, 13.4 mmol) and pyridine (2.70 mL, 33.5 mmol) were added. After the mixture was stirred at room temperature overnight, the solvent was removed and water (50 mL) was added to the residue. The resulting mixture was acidified by the addition of 2 N HCl, and the precipitates formed were collected by filtration and were then washed with water. After drying in vacuo, AcOEt (20 mL) was added to the precipitates; the mixture was dissolved under reflux conditions. Hexane (10 mL) was then added at that temperature, and the mixture was cooled to room temperature. The crystals formed were filtered and were then washed with the solvent (50% AcOEt in hexane) to afford the titled compound (3.57 g, yield 74%): mp 140 °C; IR (KBr) 3279, 1713, 1671, 1593, 1557; ^{1}H NMR ($CDCl_3$) 1.38 (t, J = 4.2 Hz, 3 H), 3.72 (s, 2 H), 4.36 (d, J = 4.2 Hz, 2 H), 7.10−7.55 (m, 6 H), 7.79 (d, J = 8.7 Hz, 1 H), 7.85−7.95 (m, 2 H). Anal. ($C_{17}H_{16}BrNO_3$) C, H, N.

3-[2-(3-Bromophenyl)acetylamino]benzoic Acid (4b). To a solution of the ester **4a** (1.65 g, 4.56 mmol) in THF (15 mL) was added a KOH solution (0.60 g of KOH in 2 mL of water, 9.12 mmol). After the resulting solution was stirred at 60 °C for 11 h, water (20 mL) was added; subsequently, THF was removed under reduced pressure. This water solution was then acidified by the addition of 2 N HCl solution, and the precipitates formed were filtered and were then washed with water to afford the titled compound (1.42 g, yield 93%): mp 249−250 °C; IR (KBr) 3272, 1692, 1663, 1591, 1537; ^{1}H NMR (DMSO-d_6) 3.66 (s, 2 H), 7.20−7.40 (m, 4 H), 7.53 (s, 1 H), 7.60 (d, J = 7.8 Hz, 1 H), 7.73 (d, J = 7.8 Hz, 1 H), 8.19 (s, 1 H), 10.33 (s, 1H), 12.83 (s, 1 H). Anal. ($C_{15}H_{12}BrNO_3$) C, H, N, Br.

3-[2-(3-Bromophenyl)acetylamino]-*N*,*N*-dimethylbenzamide (4d). To a solution of the benzoic acid derivative **4b** (167 mg, 0.50 mmol) in THF (5 mL), oxalyl chloride (67 mg, 0.53 mmol) and one drop of DMF were added. The resulting solution was then stirred for 1 h at room temperature, and 50% dimethylamine solution in water (0.45 mL, 5.0 mmol) was added. After being stirred for 4 h at room temperature, the mixture was extracted with AcOEt. Combined extracts were washed with saturated NaCl solution and were then dried over $MgSO_4$. Filtration of the drying agent and removal of the solvents yielded the crude product, which was purified by recrystallization from an AcOEt (1.5 mL) and hexane (1.5 mL) mixture, to give the desired compound (112 mg, yield 62%): mp 119−120 °C; IR (KBr) 1678, 1613, 1588, 1557; ^{1}H NMR (DMSO-d_6) 2.90 (s, 3 H), 2.96 (s, 3 H), 3.68 (s, 2 H), 7.06 (d, J = 7.8 Hz, 1 H), 7.25−7.41 (m, 3 H), 7.47 (m, 1 H), 7.53−7.60 (m, 2 H), 7.68 (s, 1 H), 10.30 (s, 1 H). Anal. ($C_{17}H_{17}BrN_2O_2$) C, H, N, Br.

3-[2-(3-Bromophenyl)acetylamino]-*N*-ethylbenzamide (4e): mp 155 °C; IR (KBr) 3329, 3268, 1665, 1640, 1549; ^{1}H NMR (DMSO-d_6) 1.11 (t, J = 6.9 Hz, 3 H), 3.29 (m, 2 H), 3.67 (s, 2 H), 7.20−7.40 (m, 3 H), 7.47 (d, J = 8.1 Hz, 1 H), 7.49 (d, J = 8.1 Hz, 1 H), 7.56 (s, 1 H), 7.75 (d, J = 8.4 Hz, 1 H), 8.00 (s, 1 H), 8.41 (t, J = 5.1 Hz, 1 H), 10.32 (s, 1 H). Anal. ($C_{17}H_{17}BrN_2O_2 \cdot 0.1H_2O$) C, H, N.

3-[2-(3-Bromophenyl)acetylamino]-*N*-hydroxybenzamide (4f): mp 184−186 °C (dec); IR (KBr) 3314, 3231, 1663, 1632, 1582, 1535; ^{1}H NMR (DMSO-d_6) 3.68 (s, 2 H), 7.25−7.60 (m, 6 H), 7.75 (d, J = 6.9 Hz, 1 H), 7.98 (s, 1 H), 9.01 (s, 1 H), 10.33 (s, 1 H), 11.12 (s, 1 H). Anal. ($C_{15}H_{13}BrN_2O_3 \cdot 0.1H_2O$) C, H, N.

3-[2-(3-Bromophenyl)acetylamino]-*N*-methoxybenzamide (4g): mp 166 °C; IR (KBr) 3299, 3187, 1659, 1611, 1595, 1560; ^{1}H NMR (DMSO-d_6) 3.69 (s, 5 H), 7.22−7.60 (m, 6 H), 7.77 (s, 1 H), 8.00 (s, 1 H), 10.37 (s, 1 H), 11.69 (s, 1 H). Anal. ($C_{16}H_{15}BrN_2O_3$) C, H, N, Br.

2-[2-(3-Bromophenyl)acetylamino]-*N*-methylbenzamide (12): mp 134 °C; IR (KBr) 3339, 1674, 1651, 1589, 1524; ^{1}H NMR (DMSO-d_6) 2.75 (d, J = 4.5 Hz, 2 H), 3.71 (s, 2 H), 7.11 (dd, J = 7.5 Hz, 7.5 Hz, 1 H), 7.20−7.35 (m, 2H), 7.40−7.55 (m, 2H), 7.54 (m, 1H), 7.65 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1 H), 8.65 (d, J = 4.5 Hz, 1 H), 11.34 (s, 1H). Anal. ($C_{16}H_{15}BrN_2O_2$) C, H, N, Br.

4-[2-(3-Bromophenyl)acetylamino]-*N*-methylbenzamide (13): mp 245 °C; IR (KBr) 3260, 1669, 1634, 1599, 1570, 1537, 1507; ^{1}H NMR (DMSO-d_6) 2.73 (d, J = 4.5 Hz, 3 H), 3.67 (s, 2 H), 7.20−7.35 (m, 2H), 7.44 (m, 1 H), 7.53 (m, 1 H), 7.62 (d, J = 8.4 Hz, 2 H), 7.76 (d, J = 8.4 Hz, 2 H), 8.30 (d, J = 4.5 Hz, 1 H), 10.38 (s, 1H). Anal. ($C_{16}H_{15}BrN_2O_2$) C, H, N, Br.

3-[2-(3-Chlorophenyl)acetylamino]-*N*-methylbenzamide (7d). (3-Chlorophenyl)acetic acid (192 mg, 1.13 mmol) was dissolved in CH_2Cl_2 (8 mL), and oxalyl chloride (0.10 mL, 1.18 mmol) and one drop of DMF were added to the solution. After the mixture was stirred for 1 h at room temperature, 3-amino-*N*-methylbenzamide **6** (167 mg, 1.13 mmol) and pyridine (0.19 mL, 2.31 mmol) were added, and the resulting solution was then stirred at room temperature overnight. Subsequently, the solvent was evaporated under reduced pressure; water (10 mL) and 2 N HCl (1 mL) were added to the residue. The crystals formed were filtered and were then washed with water. After drying in vacuo, these crystals were added to AcOEt (6 mL). Subsequently, the mixture was heated under reflux for 10 min. The mixture was cooled to room temperature, and the crystals were collected by filtration and were then washed with AcOEt to give the desired compound (233 mg, yield 68%): mp 165−166 °C; IR (KBr) 3324, 1642, 1593, 1555; ^{1}H NMR (DMSO-d_6) 2.76 (d, J = 4.5 Hz, 3 H), 3.68 (s, 2 H), 7.25−7.42 (m, 5 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.74 (d, J = 7.8 Hz, 1 H), 8.02 (dd, J = 1.8 Hz, 1.8 Hz, 1 H), 8.36 (d, J = 4.5 Hz, 1 H), 10.31 (s, 1 H). Anal. ($C_{16}H_{15}ClN_2O_2$) C, H, N, Cl.

3-[2-(3-Bromophenyl)acetylamino]-*N*-methylbenzamide (1): mp 176−178 °C; IR (KBr) 3324, 3254, 1642, 1591, 1554; NMR (DMSO-d_6) 2.76 (d, J = 4.5 Hz, 3 H), 3.68 (s, 2 H), 7.27−7.41 (m, 3 H), 7.45−7.50 (m, 2 H), 7.56 (s, 1 H), 7.75 (d, J = 8.0 Hz, 1 H), 8.03 (s, 1 H), 8.42 (d, J = 4.5 Hz, 1 H), 10.35 (s, 1 H). Anal. ($C_{16}H_{15}BrN_2O_2$) C, H, N, Br.

3-[2-(3-Bromophenyl)acetylamino]benzamide (4c): mp 202 °C; IR (KBr) 3378, 3295, 1659, 1624, 1586, 1534; ^{1}H NMR (DMSO-d_6) 3.67 (s, 2 H), 7.20−7.60 (m, 7 H), 7.76 (d, J = 9.3 Hz, 1 H), 7.94 (s, 1 H), 8.03 (s, 1 H), 10.33 (s, 1 H). Anal. ($C_{15}H_{13}BrN_2O_2$) C, H, N, Br.

***N*-Methyl-3-(phenylacetylamino)benzamide (7a):** mp 140−142 °C; ^{1}H NMR (DMSO-d_6) 2.75 (d, J = 4.5 Hz, 3 H), 3.63 (s, 2 H), 7.22−7.48 (m, 7 H), 7.74 (m, 1 H), 8.01 (s, 1 H), 8.37 (d, J = 4.5 Hz, 1 H), 10.30 (s, 1 H). Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

3-[2-(3-Fluorophenyl)acetylamino]-*N*-methylbenzamide (7b): mp 147−148 °C; IR (KBr) 3314, 1661, 1636, 1587, 1530; ^{1}H NMR (DMSO-d_6) 2.76 (d, J = 4.2 Hz, 3 H), 3.69 (s, 2 H), 7.08 (dd, J = 5.7 Hz, 5.7 Hz, 1 H), 7.14 (d, J = 7.5 Hz, 2 H), 7.38 (m, 2 H), 7.47 (d, J = 8.1 Hz, 1 H), 7.74 (d, J = 8.1 Hz, 1 H), 8.02 (s, 1 H), 8.35 (d, J = 4.2 Hz, 1 H), 10.30 (s, 1 H). Anal. ($C_{16}H_{15}FN_2O_2$) C, H, N, F.

3-[2-(2-Chlorophenyl)acetylamino]-*N*-methylbenzamide (7c): mp 211−212 °C; IR (KBr) 3268, 1659, 1642, 1586, 1535; ^{1}H NMR (DMSO-d_6) 2.77 (d, J = 3.6 Hz, 3 H), 3.85 (s, 2 H), 7.25−7.55 (m, 6 H), 7.74 (d, J = 7.5 Hz, 1 H), 8.04 (s, 1 H), 8.36 (d, J = 3.6 Hz, 1 H), 10.34 (s, 1 H). Anal. ($C_{16}H_{15}ClN_2O_2$) C, H, N.

3-[2-(4-Chlorophenyl)acetylamino]-*N*-methylbenzamide (7e): mp 163−164 °C; IR (KBr) 3279, 1663, 1640, 1588, 1535; ^{1}H NMR (DMSO-d_6) 2.76 (d, J = 3.9 Hz, 3 H), 3.66 (s, 2 H), 7.35−7.42 (m, 5 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.75 (d, J =

7.8 Hz, 1 H), 8.02 (dd, J = 1.5 Hz, 1.5 Hz, 1 H), 8.36 (d, J = 3.9 Hz, 1 H), 10.30 (s, 1 H). Anal. ($C_{16}H_{15}ClN_2O_2 \cdot 0.3H_2O$) C, H, N.

3-[2-(4-Bromophenyl)acetylamino]-*N*-methylbenzamide (7f): mp 165−166 °C; IR (KBr) 3283, 1665, 1642, 1588, 1534; ^{1}H NMR (DMSO-d_6) 2.77 (d, J = 4.5 Hz, 3 H), 3.64 (s, 2 H), 7.23−7.40 (m, 3 H), 7.40−7.58 (m, 3 H), 7.75 (d, J = 7.8 Hz, 1 H), 8.01 (s, 1 H), 8.37 (d, J = 4.5 Hz, 1 H), 10.30 (s, 1 H). Anal. ($C_{16}H_{15}BrN_2O_2 \cdot 0.5H_2O$) C, H, N.

***N*-Methyl-3-[2-(3-methylphenyl)acetylamino]benzamide (7g):** mp 131 °C; IR (KBr) 3299, 1659, 1634, 1586, 1530; ^{1}H NMR (DMSO-d_6) 2.29 (s, 3 H), 2.76 (d, J = 4.5 Hz, 3 H), 3.60 (s, 2 H), 7.06 (d, J = 6.9 Hz, 1 H), 7.09−7.22 (m, 3 H), 7.36 (dd, J = 7.8 Hz, 7.8 Hz, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.75 (d, J = 7.8 Hz, 1 H), 8.02 (s, 1 H), 8.35 (d, J = 4.5 Hz, 1 H), 10.26 (s, 1 H). Anal. ($C_{17}H_{18}N_2O_2$) C, H, N.

3-[2-(3-Methoxyphenyl)acetylamino]-*N*-methylbenzamide (7h): mp 104−106 °C; ^{1}H NMR (DMSO-d_6) 2.76 (d, J = 4.5 Hz, 3 H), 3.60 (s, 2 H), 3.73 (s, 3 H), 6.81 (m, 1 H), 6.89−6.92 (m, 2 H), 7.23 (m, 2 H), 7.35 (m, 1 H), 7.47 (m, 1 H), 7.76 (m, 1 H), 8.02 (s, 1 H), 8.38 (m, 1 H), 10.28 (s, 1 H). Anal. ($C_{17}H_{18}N_2O_3$) C, H, N.

3-[2-(3-Benzyloxyphenyl)acetylamino]-*N*-methylbenzamide (7i): mp 150 °C; IR (KBr) 3302, 1661, 1634, 1586, 1530; ^{1}H NMR (DMSO-d_6) 2.76 (d, J = 4.5 Hz, 3 H), 3.61 (s, 2 H), 5.09 (s, 2 H), 6.91 (dd, J = 7.8 Hz, 7.8 Hz, 2 H), 7.01 (s, 1 H), 7.27 (dd, J = 7.8 Hz, 7.8 Hz, 1 H), 7.25−7.52 (m, 7 H), 7.74 (d, J = 7.8 Hz, 1 H), 8.02 (s, 1 H), 8.36 (d, J = 4.5 Hz, 1 H), 10.27 (s, 1 H). Anal. ($C_{23}H_{22}N_2O_3$) C, H, N.

***N*-Methyl-3-[2-(3-nitrophenyl)acetylamino]benzamide (7j):** mp 139 °C; IR (KBr) 3322, 3250, 1665, 1640, 1555, 1524; ^{1}H NMR (DMSO-d_6) 2.76 (d, J = 4.5 Hz, 3 H), 3.86 (s, 2 H), 7.37 (dd, J = 7.8 Hz, 7.8 Hz, 1 H), 7.49 (d, J = 7.8 Hz, 1 H), 7.64 (dd, J = 8.1 Hz, 8.1 Hz, 1 H), 7.75 (d, J = 8.1 Hz, 1 H), 7.80 (d, J = 8.1 Hz, 1 H), 8.03 (s, 1 H), 8.13 (d, J = 8.1 Hz, 1 H), 8.24 (s, 1 H), 8.37 (d, J = 4.5 Hz, 1 H), 10.39 (s, 1 H). Anal. ($C_{16}H_{15}N_3O_4$) C, H, N.

3-[2-(3-Hydroxyphenyl)acetylamino]-*N*-methylbenzamide (7k): mp 188−189 °C; ^{1}H NMR (DMSO-d_6) 3.52 (s, 2 H), 6.62 (m, 1 H), 6.72−6.75 (m, 2 H), 7.08 (m, 1 H), 7.32−7.37 (m, 2 H), 7.51 (d, J = 6.9 Hz, 1 H), 7.76 (d, J = 7.8 Hz, 1 H), 7.92 (s, 1 H), 8.02 (s, 1 H), 9.34 (s, 1 H), 10.25 (s, 1 H). Anal. ($C_{16}H_{16}N_2O_3$) C, H, N.

3-(2-Cyclohexylacetylamino)-*N*-methylbenzamide (7l): mp 183 °C; IR (KBr) 3293, 1657, 1640, 1588, 1535; ^{1}H NMR (DMSO-d_6) 0.99 (m, 2 H), 1.03−1.38 (m, 3 H), 1.55−1.90 (m, 6 H), 2.19 (d, J = 7.0 Hz, 2 H), 2.76 (d, J = 4.5 Hz, 3 H), 7.34 (dd, J = 7.8 Hz, 7.8 Hz, 1 H), 7.45 (d, J = 7.8 Hz, 1 H), 7.74 (d, J = 7.8 Hz, 1 H), 8.01 (s, 1 H), 8.34 (d, J = 4.5 Hz, 1 H), 9.95 (s, 1 H). Anal. ($C_{16}H_{22}N_2O_2$) C, H, N.

***N*-Methyl-3-[2-(1-naphthyl)acetylamino]benzamide (7m):** mp 201−202 °C; IR (KBr) 3274, 1657, 1640, 1588, 1532; ^{1}H NMR (DMSO-d_6) 2.75 (d, J = 4.5 Hz, 3 H), 4.16 (s, 2 H), 7.36 (dd, J = 8.1 Hz, 8.1 Hz, 1 H), 7.40−7.60 (m, 5 H), 7.74 (d, J = 7.8 Hz, 1 H), 7.84 (d, J = 7.8 Hz, 1 H), 7.97 (d, J = 7.8 Hz, 1 H), 8.03 (s, 1 H), 8.35 (d, J = 7.8 Hz, 1 H), 8.37 (d, J = 4.5H z, 1 H), 10.44 (s, 1 H). Anal. ($C_{20}H_{18}N_2O_2$) C, H, N.

***N*-Methyl-3-[2-(2-naphthyl)acetylamino]benzamide (7n):** mp 175−176 °C; IR (KBr) 3393, 1655, 1634, 1588, 1530; ^{1}H NMR (DMSO-d_6) 2.76 (d, J = 4.5 Hz, 3 H), 3.83 (s, 2 H), 7.37 (dd, J = 7.8 Hz, 7.8 Hz, 1 H), 7.40−7.55 (m, 4 H), 7.77 (d, J = 8.4 Hz, 1 H), 7.81−7.96 (m, 4 H), 8.04 (s, 1 H), 8.36 (d, J = 4.5 Hz, 1 H), 10.37 (s, 1 H). Anal. ($C_{20}H_{18}N_2O_2$) C, H, N.

3-[2-(3-benzo[*b*]thienyl)acetylamino]-*N*-methylbenzamide (7o): mp 194 °C; IR (KBr) 3285, 1663, 1636, 1588, 1532; ^{1}H NMR (DMSO-d_6) 2.75 (d, J = 4.2 Hz, 3 H), 3.94 (s, 2 H), 7.32−7.53 (m, 4 H), 7.61 (s, 1 H), 7.76 (d, J = 6.9 Hz, 1 H), 7.91 (d, J = 7.2 Hz, 1 H), 7.98 (d, J = 7.2 Hz, 1 H), 8.04 (s, 1 H), 8.35 (d, J = 4.2 Hz, 1 H), 10.40 (s, 1 H). Anal. ($C_{18}H_{16}N_2O_2S$) C, H, N, S.

3-[2-(5-Benzo[1,3]dioxolyl)acetylamino]-*N*-methylbenzamide (7p): mp 174−175 °C; IR (KBr) 3337, 3291, 1659, 1634, 1586, 1530, 1505; ^{1}H NMR (DMSO-d_6) 2.76 (d, J = 4.5 Hz, 3 H), 3.55 (s, 2 H), 5.98 (s, 2 H), 6.74−6.93 (m, 3 H), 7.36 (dd, J = 7.8 Hz, 7.8 Hz, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.75 (d, J = 7.8 Hz, 1 H), 8.01 (s, 1 H), 8.35 (d, J = 4.5 Hz, 1 H), 10.20 (s, 1 H). Anal. ($C_{17}H_{16}N_2O_4$) C, H, N.

3-[2-(3−1*H*-Indolyl)acetylamino]-*N*-methylbenzamide (7q): mp 168−169 °C; IR (KBr) 3382, 3287, 1655, 1636, 1588, 1555, 1528; ^{1}H NMR (DMSO-d_6) 2.73 (d, J = 4.5 Hz, 3 H), 3.72 (s, 2 H), 6.96 (dd, J = 7.5 Hz, 7.5 Hz, 1 H), 7.05 (dd, J = 7.8 Hz, 7.8 Hz, 1 H), 7.24 (s, 1 H), 7.27−7.38 (m, 2 H), 7.43 (d, J = 7.8 Hz, 1 H), 7.59 (d, J = 7.8 Hz, 1 H), 7.75 (d, J = 8.7 Hz, 1 H), 8.00 (s, 1 H), 8.32 (d, J = 4.5 Hz, 1 H), 10.18 (s, 1 H), 10.88 (s, 1 H). Anal. ($C_{18}H_{16}N_3O_2$) C, H, N.

***N*-Methyl-3-(3-phenylpropionylamino)benzamide (7r):** mp 142−143 °C; IR (KBr) 3295, 1657, 1613, 1593, 1545; ^{1}H NMR (DMSO-d_6) 2.62 (t, J = 7.8 Hz, 2 H), 2.75 (d, J = 4.5 Hz, 3 H), 2.90 (t, J = 7.8 Hz, 2 H), 7.10−7.40 (m, 6 H), 7.44 (d, J = 7.5 Hz, 1 H), 7.72 (d, J = 7.5 Hz, 1 H), 7.99 (s, 1 H), 8.33 (d, J = 4.5 Hz, 1 H), 10.00 (s, 1 H). Anal. ($C_{17}H_{18}N_2O_2$) C, H, N.

3-[3-(2-Methoxyphenyl)propionylamino]-*N*-methylbenzamide (7s): mp 150 °C; IR (KBr) 3297, 1658, 1644, 1550; ^{1}H NMR (DMSO-d_6) 2.56 (t, J = 7.2 Hz, 2 H), 2.75 (d, J = 3.9 Hz, 3 H), 2.85 (t, J = 7.2 Hz, 2 H), 3.78 (s, 3 H), 6.84 (dd, J = 7.5 Hz, 7.5 Hz, 1 H), 6.93 (d, J = 7.5 Hz, 1 H), 7.05−7.20 (m, 2 H), 7.26 (dd, J = 8.1 Hz, 8.1 Hz, 1 H), 7.34 (d, J = 8.1 Hz, 1 H), 7.72 (d, J = 8.1 Hz, 1 H), 7.99 (s, 1 H), 8.38 (d, J = 3.9 Hz, 1 H), 9.67 (s, 1 H). Anal. ($C_{18}H_{20}N_2O_3$) C, H, N.

***N*-Methyl-3-(2-phenoxyacetylamino)benzamide (7t):** mp 131 °C; IR (KBr) 3378, 3283, 1669, 1640, 1588, 1535; ^{1}H NMR (DMSO-d_6) 2.75 (d, J = 4.5 Hz, 3 H), 4.69 (s, 2 H), 6.63−7.01 (m, 3 H), 7.22−7.40 (m, 3 H), 7.50 (d, J = 7.8 Hz, 1 H), 7.77 (d, J = 7.8 Hz, 1 H), 8.05 (s, 1 H), 8.36 (d, J = 4.5 Hz, 1 H), 10.18 (s, 1 H). Anal. ($C_{16}H_{16}N_2O_3$) C, H, N.

3-[2-(2,3-Dichlorophenoxy)acetylamino]-*N*-methylbenzamide (7u): mp 192−193 °C; IR (KBr) 3385, 3291, 1692, 1644, 1547; ^{1}H NMR (DMSO-d_6) 2.77 (d, J = 4.5 Hz, 3 H), 4.91 (s, 2 H), 7.08 (d, J = 8.1 Hz, 1 H), 7.20−7.45 (m, 3 H), 7.52 (d, J = 7.8 Hz, 1 H), 7.74 (d, J = 8.7 Hz, 1 H), 8.05 (s, 1 H), 8.42 (d, J = 4.5 Hz, 1 H), 10.34 (s, 1 H). Anal. ($C_{16}H_{14}Cl_2N_2O_3$) C, H, N.

***N*-Methyl-3-[2-(1-naphthoxy)acetylamino]benzamide (7v):** mp 194 °C; IR (KBr) 3405, 3304, 1696, 1638, 1541; ^{1}H NMR (DMSO-d_6) 2.75 (d, J = 4.2 Hz, 3 H), 4.92 (s, 2 H), 6.92 (d, J = 7.8 Hz, 1 H), 7.33−7.62 (m, 6 H), 7.79 (d, J = 8.1 Hz, 1 H), 7.88 (m, 1 H), 8.08 (s, 1 H), 8.31 (m, 1 H), 8.41 (d, J = 4.2 Hz, 1 H), 10.36 (s, 1 H). Anal. ($C_{20}H_{18}N_2O_3 \cdot 0.1H_2O$) C, H, N.

***N*-Methyl-3-[2-(2-naphthoxy)acetylamino]benzamide (7w):** mp 174 °C; IR (KBr) 3382, 3275, 1672, 1638, 1588, 1557, 1534; ^{1}H NMR (DMSO-d_6) 2.75 (d, J = 4.5 Hz, 3 H), 4.82 (s, 2 H), 7.22−7.58 (m, 6 H), 7.78−7.95 (m, 4 H), 8.09 (s, 1 H), 8.40 (d, J = 4.5 Hz, 1 H), 10.28 (s, 1 H). Anal. ($C_{20}H_{18}N_2O_3$) C, H, N.

(3-Methylcarbamoylphenyl)carbamic Acid 4-Methylbenzyl Ester (11a). To a solution of 4-methylbenzyl alcohol (307 mg, 2.52 mmol) and di(*N*-succinimidyl) carbonate **9** (966 mg, 3.77 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (0.70 mL, 5.03 mmol), and the resulting solution was stirred for 4 h at room temperature. Water (20 mL) was then added, and the water layer was extracted with CH_2Cl_2. Combined extracts were washed with saturated NaCl, saturated $NaHCO_3$, saturated NaCl, 2 N HCl, and saturated NaCl successively, and they were then dried over $MgSO_4$. Filtration of the drying agent and removal of the solvents yielded the intermediate, which was dissolved in DMF (2 mL), and 3-amino-*N*-methylbenzamide **6** (341 mg, 2.27 mmol) and triethylamine (0.35 mL, 2.52 mmol) were added. After the mixture was stirred at room temperature overnight, the insoluble solid was filtered. The filtrate was then added to water (15 mL), and the precipitates formed were filtered and were then washed with water. After drying, this crude product was added to AcOEt (8 mL), and the resulting suspension was refluxed for 10 min. The mixture was then cooled to room temperature,

and crystals were filtered and washed with AcOEt to afford the desired compound (182 mg, yield 27%): mp 167−168 °C; IR (KBr) 3322, 1738, 1622, 1557; ^{1}H NMR (DMSO-d_6) 2.28 (s, 3 H), 2.74 (d, J = 4.6 Hz, 3 H), 5.09 (s, 2 H), 7.17 (d, J = 7.9 Hz, 2 H), 7.23−7.42 (m, 4 H), 7.54 (d, J = 6.5 Hz, 1 H), 7.91 (s, 1 H), 8.31 (d, J = 4.6 Hz, 1 H), 9.82 (s, 1 H). Anal. ($C_{17}H_{18}N_2O_3$) C, H, N.

(3-Methylcarbamoylphenyl)carbamic acid 4-chlorobenzyl ester (11b): mp 155−156 °C; IR (KBr) 3351, 3299, 1734, 1624, 1557; ^{1}H NMR (DMSO-d_6) 2.74 (d, J = 4.5 Hz, 3 H), 5.14 (s, 2 H), 7.25−7.43 (m, 6 H), 7.55 (d, J = 8.3 Hz, 1 H), 7.91 (s, 1 H), 8.32 (d, J = 4.5 Hz, 1 H), 9.88 (s, 1 H). Anal. ($C_{16}H_{15}ClN_2O_3$) C, H, N, Cl.

(3-Methylcarbamoylphenyl)carbamic acid 2,6-dihlorobenzyl ester (11c): mp 219−220 °C; IR (KBr) 3380, 3241, 1717, 1651, 1562; ^{1}H NMR (DMSO-d_6) 2.74 (d, J = 4.3 Hz, 3 H), 5.35 (s, 2 H), 7.25−7.60 (m, 6 H), 7.92 (s, 1 H), 8.35 (d, J = 4.3 Hz, 1 H), 9.92 (s, 1H). Anal. ($C_{16}H_{14}Cl_2N_2O_3$) C, H, N, Cl.

(3-Methylcarbamoylphenyl)carbamic acid 1-naphthylmethl ester (11d): mp 228−229 °C; IR (KBr) 3353, 3285, 1730, 1626, 1555; ^{1}H NMR (DMSO-d_6) 2.76 (d, J = 4.4 Hz, 3 H), 5.64 (s, 2 H), 7.30−7.45 (m, 2 H), 7.50−7.70 (m, 5 H), 7.90−8.03 (m, 3 H), 8.12 (d, J = 7.6 Hz, 1 H), 8.38 (d, J = 4.4 Hz, 1 H), 9.87 (s, 1 H). Anal. ($C_{20}H_{18}N_2O_3$) C, H, N.

(3-Methylcarbamoylphenyl)carbamic acid 2-naphthylmethl ester (11e): mp 157−158 °C; IR (KBr) 3314, 1699, 1642, 1589, 1539; ^{1}H NMR (DMSO-d_6) 2.76 (d, J = 4.8 Hz, 3 H), 5.32 (s, 2 H), 7.23−7.42 (m, 2 H), 7.42−7.60 (m, 4 H), 7.82−7.98 (m, 5 H), 8.32 (d, J = 4.8 Hz, 1 H), 9.90 (s, 1 H). Anal. ($C_{20}H_{18}N_2O_3$) C, H, N.

Measurement of Anti-*H. pylori* Activity. A *H. pylori* strain 31A was grown in a liquid medium (5 mL) containing brain-heart infusion broth with 10% fetal bovine serum in a test tube on a shaker under slightly aerobic conditions (5% O_2, 10% CO_2, 85% N_2) at 37 °C for 48 h. This culture was then inoculated to brain-heart infusion broth containing 10% fetal bovine serum at a ratio of 5%, and the 10% DMSO solution of a test compound was added at a ratio of 10%. The 10% DMSO solution was used as the reference test. Cultivation was carried out under slightly aerobic conditions described above at 37 °C for 48 h by shaking, and growth of *H. pylori* was then examined. Antibacterial activity was recorded as the lowest concentration at which the compound exhibited bacterial growth inhibition (minimum inhibitory concentration: MIC).

Anti-*H. pylori* Activity under Acidic Conditions. The liquid media aforementioned was adjusted to pH 7.0, 6.0, and 5.0 by addition of HCl and NaOH solution,[18] and anti-*H. pylori* activity was evaluated in a manner similar to the measurement method of the above normal condition.

Measurement of Antibacterial Activity except for *Bacteroides fragilis*. The Neutrient agar containing 0.5% of yeast extract (10 mL), in which 10^6−10^7 CFUs of test bacteria were inoculated, was poured onto a plate. After caking, a hole (4 mm diameter) was made with a pipe of stainless steel. Subsequently, 50 μL of the 10% DMSO solution of a test compound (1000 μg/mL) was added to the hole. The 10% DMSO solution was used as the reference solution. After being allowed to stand for 1 h at 8 °C to diffuse a test compound into the medium, the agar was incubated at 37 °C for 18 h. Antibacterial activity was confirmed by the formation of an inhibitory zone.

Measurement of Anti-*Bacteroides fragilis* Activity. The anti-*Bacteroides fragilis* activity was evaluated in a manner similar to the method described above except for the incubation method. After the diffusion of a test compound, the plate was placed in a pot for anaerobic bacteria cultivation. The interior of the pot was modified to anaerobic conditions by using a gas pack (BBL Microbiology Systems), and the medium was incubated at 37 °C for 18 h.

Measurement of Anti-*Candida albicans* Activity. The anti-*Candida albicans* activity was evaluated in a manner similar to the measurement method of antibacterial activity except for the medium (potato dextrose agar) and incubation conditions (at 27 °C for 24 h).

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References

(1) Marshall, B. J.; Warren, J. R. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* **1984**, *8390*, 1311−1315.

(2) Calam, J. *Helicobacter pylori*. *Eur. J. Clin. Invest.* **1994**, *24*, 501−510.

(3) Gasbarrini, A.; Franceschi, F.; Armuzzi, A.; Ojetti, V.; Candelli, M.; Sanz Torre, E.; De Lorenzo, A.; Anti, M.; Pretolani, S.; Gasbarrini, G. Extradigestive manifestations of *Helicobacter pylori* gastric infection. *Gut* **1999**, *45* (Suppl I), I9−I12.

(4) (a) Sjöström, J.-E.; Fryklund, J.; Kühler, T.; Larsson, H. In Vitro Antibacterial Activity of Omeprazole and Its Selectivity for *Helicobacter* spp. Are Dependent on Incubation Conditions. *Antimicrob. Agents Chemther.* **1996**, *40*, 621−626. (b) Sjöström, J.-E.; Kühler, T.; Larsson, H. Basis for the Selective Antibacterial Activity In Vitro of Proton Pump Inhibitors against *Helicobacter* spp. *Antimicrob. Agents Chemther.* **1997**, *41*, 1797−1801.

(5) (a) Katsura, Y.; Nishino, S.; Tomishi, T.; Sakane, K.; Matsumoto, Y.; Ishikawa, H.; Takasugi, H. Anti-*Helicobacter pylor*i agents. 2. Structure activity relationships in a new series of 2-alkylguanidino-4-furylthiazoles. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1307−1312. (b) Katsura, Y.; Nishino, S.; Ohno, M.; Sakane, K.; Matsumoto, Y.; Morinaga, C.; Ishikawa, H.; Takasugi, H. Anti-*Helicobacter pylor*i agents. 3. 2-[(Arylalkyl)guanidino]-4-furylthiazoles. *J. Med. Chem.* **1999**, *42*, 2920−2926. (c) Katsura, Y.; Tomishi, T.; Inoue, Y.; Sakane, K.; Matsumoto, Y.; Morinaga, C.; Ishikawa, H.; Takasugi, H. Anti-*Helicobacter pylor*i agents. 4. 2-(Substituted guanidino)-4-phenylthiazoles and Some Structurally Rigid Derivatives. *J. Med. Chem.* **2000**, *43*, 3315−3321.

(6) Yoshida, Y.; Barrett, D.; Azami, H.; Morinaga, C.; Matsumoto, Y.; Takasugi, H. Discovery of a novel benzyloxyisoquinoline derivative with potent anti-*Helicobacter pylori* activity. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1897−1902. (b) Yoshida, Y.; Barrett, D.; Azami, H.; Morinaga, C.; Matsumoto, S.; Matsumoto, Y.; Takasugi, H. Studies on Anti-*Helicobacter pylori* Agents. Part 1: Benzyloxyisoquinoline Derivatives. *Bioorg. Med. Chem.* **1999**, *7*, 2647−2666.

(7) Ishikawa, H.; Ito, H.; Higaki, M.; Higaki, M.; Matsumoto, Y.; Kamimura, T.; Katsura, Y.; Tomishi, T.; Inoue, Y.; Takasugi, H.; Tomoi, M.; Krakowka, S.; Yoshida, K. FR145715, a novel histamine H_2 receptor antagonist, with specific anti-*Helicobacter pylori* activities. *Eur. J. Pharm.* **1999**, *378*, 299−310.

(8) Dekker, K. A.; Inagaki, T.; Gootz, T. D.; Kaneda, K.; Nomura, E.; Sakakibara, T.; Sakemi, S.; Sugie, Y.; Yamauchi, Y.; Yoshikawa, N.; Kojima, Y. CJ-12,954 and Its Congeners, New Anti-*Helicobacter pylori* Compounds Produced by *Phanerochaete velutina*: Fermentation, Isolation, Structure Elucidation and Biological Activities. *J. Antibiot.* **1997**, *50*, 833−839.

(9) Dekker, K. A.; Inagaki, T.; Gootz, T. D.; Huang, L. H.; Kojima, Y.; Kohlbrenner, W. E.; Matsunaga, Y.; McGuirk, P. R.; Nomura, E.; Sakakibara, T.; Sakemi, S.; Suzuki, Y.; Yamauchi, Y.; Kojima, N. New Quinolone Compounds from *Pseudonocardia* sp. with Selective and Potent Anti-*Helicobacter pylori* Activity: Taxonomy of Producing Strain, Fermentation, Isolation, Structure Elucidation and Biological Activities. *J. Antibiot.* **1998**, *51*, 145−152.

(10) Hamasaki, N.; Ishii E.; Tominaga, K.; Tezuka, Y.; Nagaoka, T.; Kadota, S.; Kuroki, T.; Yano, I. Highly Selective Antibacterial Activity of Novel Alkyl Quinolone Alkaloids from a Chinese Herbal Medicine, Gosyusyu (Wu-Chu-Yu), against *Helicobacter pylori In Vitro*. *Microbiol. Immunol.* **2000**, *44*, 9−15.

(11) Ohsaki, A.; Takashima, J.; Chiba, N.; Kawamura, M. Microanalysis of a selective potent anti-*Helicobacter pylori* compound in a Brazilian medicinal plant, *Myroxylon puruiferum* and the activity of analogues. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1109−1112.

(12) Taniguchi, M.; Watanabe, M.; Nagai, K.; Suzumura, K.; Suzuki, K.; Tanaka, A. γ-Pyrone Compounds with Selective and Potent Anti-*Helicobacter pylori* Activity. *J. Antibiot.* **2000**, *53*, 844−847.

(13) Copeland, R. A.; Marcinkeviciene, J.; Haque, T. S.; Kopcho, L. M.; Jiang, W.; Wang, K.; Ecret, L. D.; Sizemore, C.; Amsler, K.

A.; Foster, L.; Tadesse, S.; Combs, A. P.; Stern, A. M.; Trainor, G. L.; Slee, A.; Rogers, M. J.; Hobbs, F. *Helicobacter pylori*-selective Antibacterials Based on Inhibition of Pyrimidine Biosynthesis. *J. Biol. Chem*. **2000**, *275*, 33373−33378.

(14) One of drawbacks of amoxicillin and clarithromycin is decomposition under acidic conditions, which leads to decrease of antibacterial activity in the stomach.

(15) Workup of the reaction mixture followed by recrystallization afforded a pure product in most cases.

(16) Anti-*H. pylori* activity of 4-F, 4-Me, 4-MeO, 4-NO_2, and 4-OH derivatives was similar to that of corresponding 3-substituted derivatives **7b**, **7g**, **7h**, **7j**, and **7k**, respectively.

(17) Brain-heart infusion broth containing 10% fetal bovine serum, which was used in usual screening, showed pH 7.2−7.3.

(18) Addition of phosphate buffer to the broth influenced the growth of *H. pylori*.

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