Anti-*Helicobacter pylori* Agents. An Update

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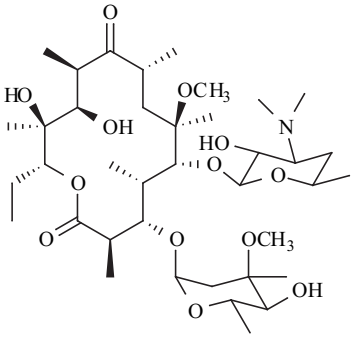
Abstract: *Helicobacter pylori* infection is the major causative factor of a number of gastric pathologies. Several classes of compounds have been identified as anti-*H. pylori* agents. Here we provide a review of anti-*H. pylori* compounds that have recently appeared in the literature, including the guanidino, antibiotics, acetamide, pyrazole and benzimidazole compounds.

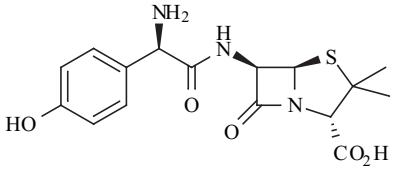
Keywords: *Helicobacter pylori*, gastric diseases, inhibitors, antibiotics.

INTRODUCTION

Helicobacter pylori is a Gram-negative bacterium isolated in 1982 by Warren and Marshall [1-3]. This microorganism colonizes the human gastric mucosa and damages epithelial cells by association and the release of cytotoxin. *H. pylori* is believed to be the principal cause of gastritis associated with peptic ulcer disease, is etiologically associated with chronic active-gastritis, mucosa-associated lymphoid tissue (MALT)-type gastric carcinoma and other gastric cancers, and has possible implications associated with gastric esophageal reflux disease (GERD) [4, 5]. There exists a variety of effective drugs for the treatment and eradication of *H. pylori* infection, including the antibiotics (β-lactams, macrolides and quinolones), bactericidal agents (bismuth salts), and antiprotozoal agents (metronidazole), that have been clinically useful in the elimination of the microorganism; however, drug resistance, side affects [6], and non-compliance [7] are common problems in the use of such drugs. Unfortunately, these antibacterial agents have to be used in combination therapy [8] and many have a wide bactericidal spectrum so that the elimination of *H. pylori* can produce an enhanced risk of resistance in other pathogenic bacteria responsible for more acute and detrimental systematic infectious diseases [9]. In addition, *H. pylori* offers the medicinal design chemist a hefty challenge of overcoming the unique parameters associated with its living environment. As a result, the need and challenge to produce new treatments for *H. pylori* infection has stimulated new research directed towards the design and discovery of novel structural leads possessing potent therapeutic efficacy without the risk of resistance and/or untoward effects. Here we do not attempt to provide the reader with a comprehensive review of all anti-*H. pylori* agents, instead we focus on some of the more exciting new leads in the area.



(**4**) Clarithromycin (CAM)
MIC - 0.057μg/mL



(**5**) Amoxicillin (AMPC)
MIC = 0.057μg/mL

Fig. (1). Drugs clinically useful in *H. pylori* therapy.

Guanidino Agents

Katsura and co-workers [10-12] have extensively studied the guanidino compounds as anti-*H. pylori* agents. They report the synthesis and activity of a series of furylthiazole derivatives among them, compound **1**, demonstrated a strong antimicrobial activity against *H. pylori* (Table I) [10]. In pursuing structure-activity relationship (SAR) studies in this series, new compounds were prepared substituting an aromatic group in place of the alicyclic portion of **1**. The resulting compounds, **2** and **3** (Table I) have showed great activity against *H. pylori* when compared with the known antibiotic clarithromycin (CAM) (**4**, Fig. **1**). These molecules are representative of the guanidino group of compounds, which also showed a degree of selectivity toward *H. pylori* in comparision with agents currently employed for eradication treatment, bismuth salicylate, metronidazole, and amoxillin (AMPC) (**5**, Fig.**1**) [12]. The investigators replaced the phenyl ring with a bioisoteric

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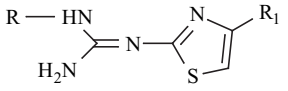
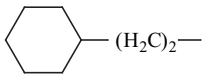
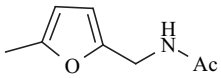
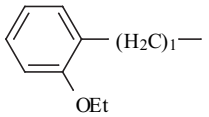
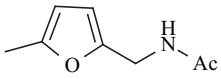
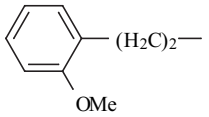
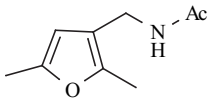
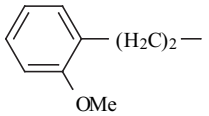
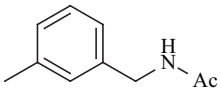
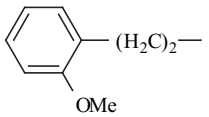
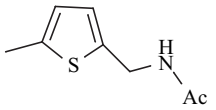
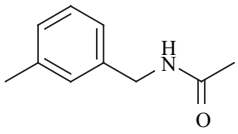
Table I. Guanidinothiazole Inhibitors and their Activities



Compd. n[o]	R	R_1	MIC (μg/mL)[a]	Ref.
1			0.069	10
2			0.026	12
3			0.046	12
6			0.017	13
7			0.0065	14
8			0.32	15

[a]MIC = Minimum inhibitory concentration

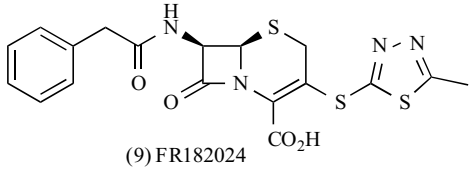
furan ring and introduced various alkyl substituents on the guanidine moiety. Analysis of the activity of the series of guanidine compounds indicated anti-*H. pylori* potency to be regulated by both the steric bulk and lipophilicity found in this area of the molecule, with benzyl and phenethyl moieties providing the optimal activity profiles [13]. Among the various compounds examined, 2-(2-methoxy-phenyl) ethyl derivative, **6**, exhibited the highest anti-*H. pylori* activity (Table I). The increased activity associated with the compounds containing the phenyl ring led to further investigations targeting a wide range of biaryl derivatives. Within the guanidinothiazole series, the pyridyl, thienyl and thiazolyl derivatives all showed potent anti-*H. pylori* activities. In particular, one compound, **7** exhibited the strongest activity with an anti-*H. pylori* potency of 3-10 times that of AMPC and CAM [14]. The results of the investigations showed that the aryl junction between the guanidinothiazole and acetamidomethyl moieties does not just act as a simple spacer, but instead plays an intricate structural role regulating the pharmacological character in this series of guanidino compounds.

Ishikawa and co-workers [15] have described a novel histamine H_2 receptor antagonist that includes a guanidinothiazole ring moiety in its chemical structure. The compound, FR145715 (**8**) exhibited a positive pharmacological profile as a structurally novel anti-ulcer agent, with a histamine-induced antagonist response three times as potent as ranitidine. In addition, **8** possessed cytoprotective properties when examined in several ulcer models. Although the antibacterial activity of **8** against *H. pylori* was revealed to be anywhere from 6 to 17 times less than AMPC and CAM, it was shown to be more potent than metronidazole, which is being prescribed clinically for eradication of *H. pylori*.

Antibiotics

In 1999, Yoshida and co-workers [16-18] reported the preliminary results of their examination of cephem derivatives as potential anti-*H. pylori* agents. Of the cephem derivatives tested, FR182024 (**9,** Fig. **2**) showed a promising profile that exhibited a therapeutic efficacy superior to AMPC and CAM, and a low potential for diarrhea associated with AMPC therapies [19, 20]. FR182024 contains a (5-methyl-1,3,4-thiadiazol-2-yl)-thio moiety at the 3-position of the cephem structure and a phenylacetamido group at the 7-position. Initial SAR studies with the cephem series of compounds show that various thio-heterocyclic groups in the 3-position produce derivatives with extremely high activity, especially those

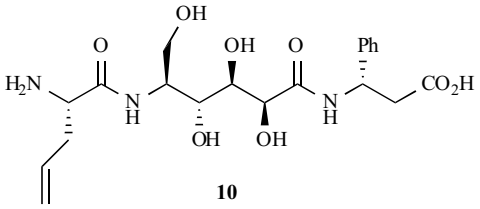
mono-heterocyclic compounds containing nitrogen and sulfur atoms.



(9) FR182024

Fig. (2). Cephem derivative.

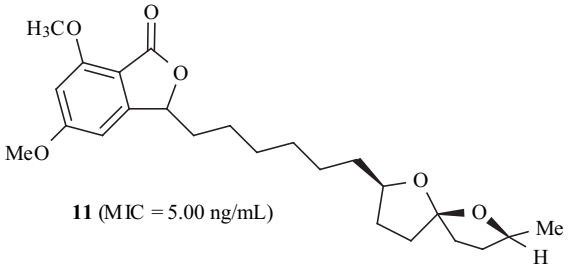
The pyloricidins A, B and C are naturally occurring antibiotics that have been shown to possess a high degree of antibacterial potency and selectivity against *H. pylori* [21, 22]. Investigation of the SAR for the terminal peptidic moiety of these compounds has been undertaken by Hasuoka and co-workers [23-25]. These researchers have prepared and tested a series of various amino acid substituted pyloricidin B and C derivatives. Interestingly, derivatives bearing α-D-, β- and γ-amino acids or peptide mimetics, exhibited a decreased anti-*H. pylori* activity, while derivatives bearing α-L-amino acids were found to maintain activity. Among those derivatives that were examined, the allylglycine derivative **10** (Fig. **3**) exhibited the most potent anti-*H. pylori* activity, with a MIC value of less than 0.006 μg/mL.



10

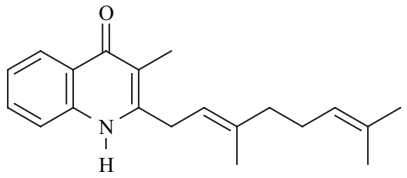
Fig. (3). Pyloricidin derivative.

Several new phthalide compounds, isolated from Phanerochaete velutina, have been shown to possess a significant degree of anti-*H. pylori* activity [26]. In particular, compound **11** (Fig. **4**) exhibited a high degree of activity that was extremely dependent on a variety of structural features. For example, while changes in the stereochemistry associated with the spiroketal has little effect on antibacterial activity, the diketone formed by ring opening exhibits a decreased potency of approximately 100-fold. The spiroketal moiety has also been found in quinolones isolated from *Pseudonocardia* sp. CL38489 [27]. Many quinolone derivatives have been reported with anti-microbial activities [28]. The quinolone derivative **12** (Fig. **5**) proved to be one of the most potent and promising anti-*H. pylori* compounds isolated.



11 (MIC = 5.00 ng/mL)

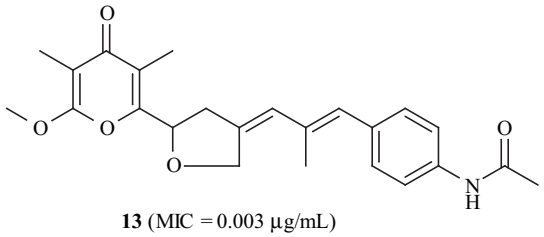
Fig. (4). Phthalide derivative.



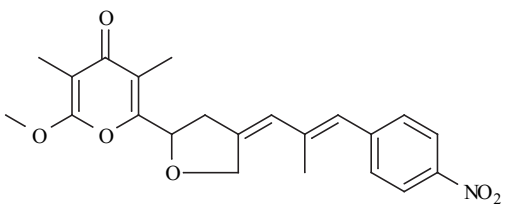
12 (MIC = 0.1 ng/mL)

Fig. (5). Quinolone compound.

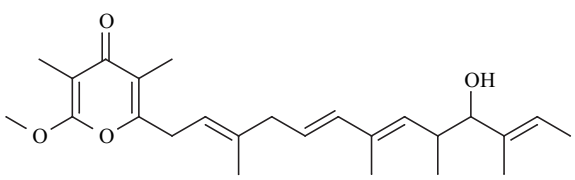
Several other natural products have been reported to possess a significant degree of activity against *H. pylori*. N-acetyl aureothamine (**13**), a γ-pyrone derivative, was isolated from a culture of *Streptomyces netropsis*. This N-acetyl aureothamine exhibited extensive anti-*H. pylori* activity as shown by the MIC value in Fig. **6**. Other γ-pyrone compounds were tested for activity included aureothin (**14**) [29] and actinopyrone A (**15**) [30]. Actinopyrone A proved to be one of the most potent anti-*H. pylori* compounds tested showing an activity of over 250-fold that of AMPC [31]. Another antibiotic, YM-181741, a benz[a]anthraquinone compound **16** (Fig. **6**), isolated from a culture broth of *Streptomyces* sp. Q57219, exhibits a weaker anti-*H. pylori* activity when compared with AMPC and CAM, but a better selectivity in that it is inactive against many other Gram-positive and Gram-negative bacteria [32].



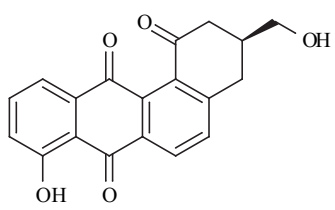
13 (MIC = 0.003 μg/mL)



14 (MIC = 0.00078 μg/mL)



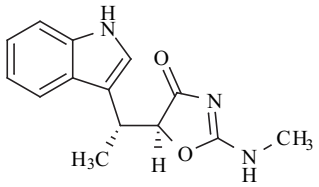
15 (MIC = 0.0001 μg/mL)



16 (MIC = 0.2 μg/mL)

Fig. (6). γ-pyrone and anthraquinone derivatives.

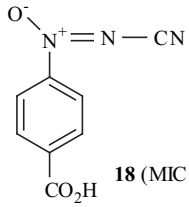
Indolmycin [33] (**17**, Fig. **7**), isolated from an African strain of *Streptomyces albus*, is an effective anti-Staphylococci compound whose mechanism of activity lies in the ability to inhibit bacterial tryptophanyl-tRNA synthetase [34]. Compound **17** has also been shown to possess potent anti-*H. pylori* activity, but with no significant antibacterial effect on many common aerobic and anaerobic bacteria [35]. Recently, Hasuoka and co-workers [36] have described what appears to be a practical stereoselective synthesis for the large-scale production of **17** [37, 38], which should allow for extensive SAR analyses.



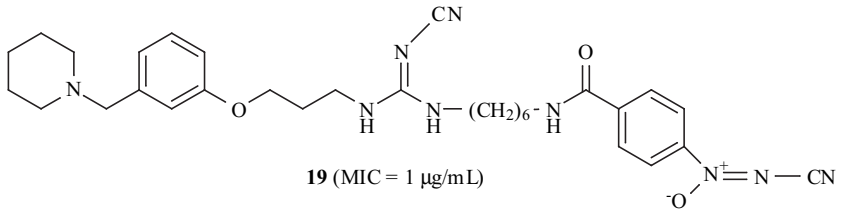
17 (MIC = 0.016 μg/mL)

Fig. (7). Structure of indolmycin.

Calvatic acid (**18**, Fig. **8**), an antibiotic isolated from *Calvatia lilacina*, has also been shown to exhibit potent anti-*H. pylori* activity [39]. Sorba and co-workers [40] have already exploited the calvatic acid structure to design novel compounds where an antisecretory pharmacophore and the anti-*H. pylori* activity have been joined within a single molecule. To date, the most active in this series is compound **19** (Fig. **8**), which has been shown to possess a MIC higher than metronidazole, but lower than calvatic acid.



18 (MIC = 0.016 μg/mL)

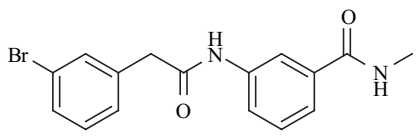


19 (MIC = 1 μg/mL)

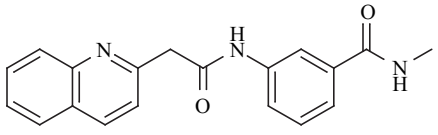
Fig. (8). Calvatic acid and its derivative.

Arylacetamides

In 2001, Ando and co-workers [41] reported the discovery of a new class of *H. pylori*-selective compounds from the random screening of established chemical libraries. Among the compounds found, compound **20** (Fig. **9**) was particularly attractive in that it afforded a relatively simple structure possessing good acid stability, potent activity, and excellent selectivity. In attempting to improve the activity, derivatives of compound **20** were synthesized. SAR studies demonstrated that substitution of N-methylbenzamide moiety with N-ethyl, N,N-dimethyl, hydroxamic acid, and benzoic acid, and its ethyl ester produced a series of compounds with decreased anti-*H. pylori* activities. In addition, substitution on the phenyl ring with 3-chloro and 3-bromo atoms provided derivatives with an activity comparable with the parent compound **20**. Interestingly, it was the substitution of the aromatic rings that produced the most active derivative. The 2-naphtylacetamide derivative **21** (Fig. **9**) exhibited an anti-*H. pylori* activity comparable with that of CAM.



20 (MIC = 0.39 μg/mL)



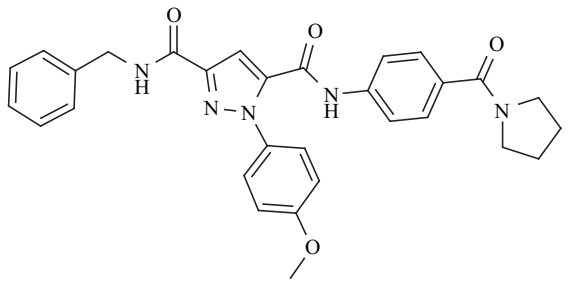
21 (MIC = 0.05 μg/mL)

Fig. (9). Arylacetamide compounds.

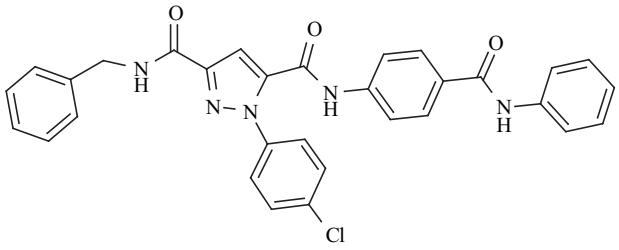
Pyrazoles and Benzimidazoles

As with many other organisms, inhibition of the *de novo* pyrimidine pathway in *H. pylori* is an attractive target for antibacterial drug design. Coperland and co-workers [42] reported their discovery of a new class of pyrazole compounds that inhibit dihydroorotate dehydrogenase (DHOase), a key enzyme in the *de novo* biosynthesis of pyrimidine [43, 44]. In particular, compound **22** (Fig. **10**), along with several analogs [42, 45], were shown to be selective inhibitors of *H. pylori*, with little or no activity towards other Gram-negative and Gram-positive bacteria. In addition, the compounds were inactive against human cell lines. Investigation into the SAR of these pyrazole compounds using parallel synthesis resulted in an extremely active compound, **23** (Fig. **10**) [46]. In general, the SAR studies showed that the 4-chlorophenyl substituent is typically favored over the 4-methoxyphenyl (**23** vs. **22**).

Extensive SAR studies of the prodrug, omeprazole (**24**) [47] have led Kühler and co-workers [48] in the design of a new class of anti-*H. pylori* agents based on modification of **24**. Modifications have included the replacement of the pyridine nitrogen with carbon, substitution of the -SO- group with -O-, -NH- or -CH_2-, as well as alteration of the benzimidazole. Using a number of different quantitative structure-activity relationship (QSAR) methods on the pharmacological data provided by these derivatives resulted in the design and synthesis of compound **25** (Fig. **11**). Further SAR experiments established that the 3-position of the phenyl ring could tolerate a large amount of 'chemical bulk' such as *iso*-Bu, -$(CH_2CH_2O)_3CH_3$, and -$(CH_2CH_2O)_5CH_3$. A variety of groups, including



22 (MIC = 0.25 μg/mL)

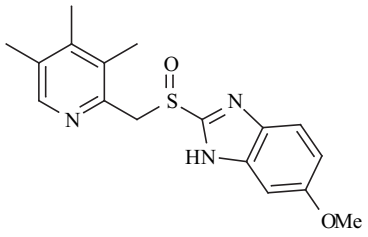


23 (MIC = 0.125 μg/mL)

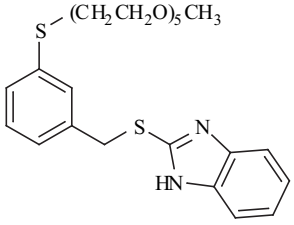
Fig. (10). Pyrazole derivatives as DHOase Inhibitors.

carbamates, amides, and sulfonamides [49], were substituted into the 3-position and examined for potential anti-*H. pylori* activity. The phenyl carbamate derivative, **26** (Fig. **11**) exhibited the most potent bactericidal activity, and also displayed low MIC values against a rather broad range of *H. pylori* strains, including those resistant to metronidazole and CAM.

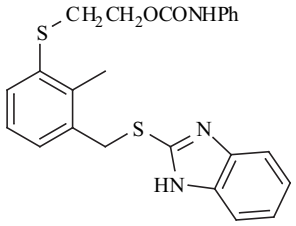
but one of many factors that must be taken into consideration of an agent's potential clinical efficacy. In addition, an effective agent would be able to penetrate the mucosal layer of the stomach, it would possess a significant stability to the acid environment [55] and it would be effective against both dividing and dormant cells [56]. As a result, the standard anti-*H. pylori* MIC data obtained from *in*



24 Omeprazole



25 (MBC = 0.96 μg/mL)



26 (MBC = 1 μg/mL, MIC = 0.25 μg/mL)

Fig. (11). Benzimidazole compounds as *H. pylori* inhibitors.

CONCLUSION AND PROSPECTIVES

H. pylori infection is widespread throughout the global population and has been associated with gastric diseases gastritis, peptic ulcer diseases, and gastric cancers. Although eradication of *H. pylori* can be achieved with a variety of currently available antibiotic regimens, the problems associated with acquired drug resistance in *H. pylori*, has produced much concern. Currently, research efforts are aimed at the design and discovery of novel agents that possess the bactericidal potency and selectivity needed to effectively combat *H. pylori* infection. It is evident from the reports cited, that the discovery of a variety of novel guanidino, antibiotic, acetamide, pyrazole and benzimidazole compounds have recently provided new avenues for anti-*H. pylori* drug design. However, there are not yet any reports of the anticipated drug discovery based on the exploitation of *H. pylori* genomic data. *H. pylori* is one of the bacteria whose complete sequence data is available in the public domain [50-53]. Huynen and coworkers [54] have used comparative genomics to predict a variety of proteins specific to *H. pylori*. Many of these proteins are believed to be outer membrane proteins important to host colonization, and thus have the potential to serve as good drug targets. Unfortunately, there exist many hurdles to overcome before target specific drug design of anti-*H. pylori* agents becomes a viable route for the production of clinically useful agents. This is best illustrated by the wide range of agents that are effective against *H. pylori in vitro*, yet have little clinical utility. In the case of *H. pylori*, the antibacterial activity is *vitro* testing may not provide sufficient information to validate agents as leads for pursuing rational drug design. Nevertheless, with the rapidly advancing technologies associated with DNA microarrays, proteomics, structural genomics, and high-throughput screening, it is likely that a variety of new specific *H. pylori* drug targets will be identified and exploited for the design of new drugs [57].

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