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IN VITRO SUSCEPTIBILITY OF *HELICOBACTER PYLORI* TO TRIFLUOROMETHYL KETONES

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Abstract: Heteroaromatic trifluoromethyl ketones (TFMK's) showed strong inhibitory activity against *Helicobacter pylori*. The MIC_{50} observed for 2-trifluoroacetonylbenzoxazole (**1**) is 20-fold more active than metronidazole and is only twice as high as that of clarithromycin. The inhibitory mode of TFMK's on Hp growth was not related to inhibition of urease.

Helicobacter pylori (Hp) is well recognized to be involved in the pathogenesis of peptic ulceration and gastric carcinogenesis, and effective treatment is an important therapeutic goal.[1] In 1994, the National Institute of Health Consensus Conference on Hp published a report that all ulcer patients with Hp infection should be treated with antimicrobial agents in addition to gastric antisecretory drugs.[2] However, the optimal protocol for eradication has not been established. A variety of drugs with susceptibility for Hp, such as antibiotics (amoxicillin and clarithromycin), bactericidal agents (bismuth), proton pump inhibitors (omeprazole), and antiprotozoal agents (metronidazole), have been effective in the clinic. However, the increase in antimicrobial resistance is an especially pertinent problem. Therefore, the development of a new class of inhibitors of Hp is of importance.[3] Recently, we have found that some trifluoromethylketones (TFMK's) can exert *in vitro* inhibitory activity against Hp, while they have been proven to inhibit the action of a variety of serine esterase, juvenile hormone esterase, or mammalian carboxylesterases.[4]

In this paper we report the inhibition of Hp by a variety of heteroaromatic and aromatic TFMK's, most of them previously synthesized in our laboratory.[5] To our knowlege this is the first report on the screening of TFMK's for activity against Hp.

Typical compounds that inhibit the growth of Hp are shown in the Table where the degree of inhibitory activity is expressed as half the minimum inhibitory concentration (MIC) value.[6] The compound exhibiting the highest inhibitory potency was 2-trifluoroacetonylbenzoxazole (**1**). In an effort to further define this inhibitory activity, a series of structurally similar compounds were tested, determining the importance of the benzoxazole and the trifluoromethyl ketone moieties. The replacement of the benzoxazole residue of **1** with other aromatic or heteroaromatic rings resulted in diminished potency, indicating that the benzazole derivatives were more active than either benzene or azole derivatives. Removal of the methylene of **1**, that is **4**, significantly diminished the potency, and **1** was 14 times more potent than the corresponding non-fluorinated analog (**5**), indicating the possibility that the trifluoromethyl ketone moiety is necessary for the potency.

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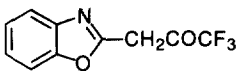
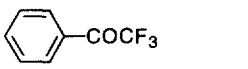
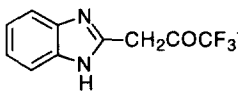
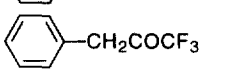
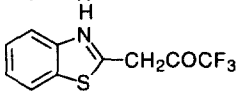
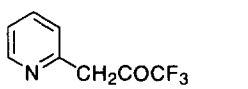
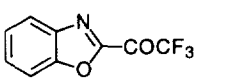
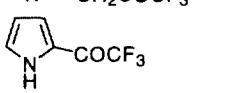
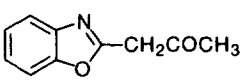
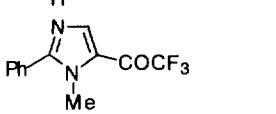
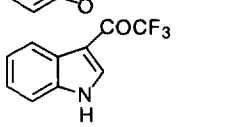
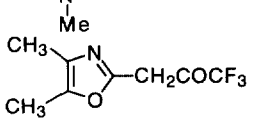
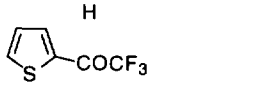
Table *In vitro* susceptibility of *H. pylori* to trifluoromethyl ketones

Compd No.	Compound	MIC_{50} (μg/mL)	Compd No.	Compound	MIC_{50} (μg/mL)
1		3.6	8		> 100
2		52	9		> 100
3		70	10		> 100
4		> 100	11		> 100
5		51	12		> 100
6		12	13		> 100
7		53		Metronidazole	74
				Clarithromycin	1.9
				Erythromycin	1.8

As the bactericidal activity of TFMK's was suspected to be related to the inhibition of urease activity of Hp,[1] we examined the inhibitory activity of TFMK's against Jack bean urease.[7] However, the inhibitory action of TFMK's against the growth of Hp was unrelated to the urease activity.

In conclusion we were able to find the compound (**1**), which showed potent inhibitory activity against Hp, as a candidate for further investigation. The extensive structure-activity relationship, including the killing mechanism of the bactericidal activity, in this type of compound will be reported in due course.

References and Notes

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6. The MIC value was determined for each compound by a broth microdilution method using Hp (ATCC43504) according to the following literature: Numao, N.; Iwahori, A.; Hirota, Y.; Sasatsu, M.; Kondo, I.; Onimura, K.; Sampe, R.; Yamane, S.; Itoh, S.; Katoh, T.; Kobayashi, S. *Biol. Pharm. Bull.* **1997**, 20, 800.
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