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SYNTHESIS OF A PIPERIDINOMETHYLTHIOPHENE DERIVATIVE AS H_2-ANTAGONIST WITH INHIBITORY ACTIVITY AGAINST HELICOBACTER PYLORI

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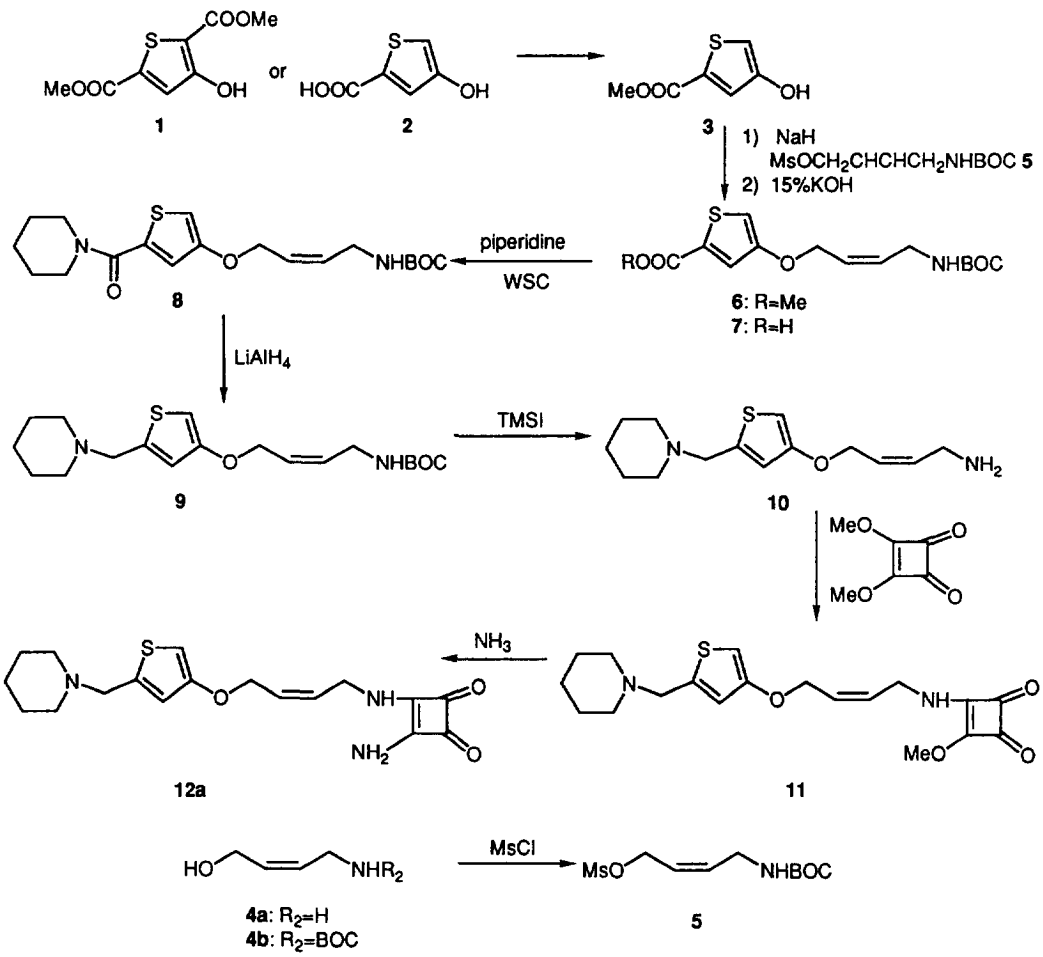
Abstract: Piperidinomethylthiophene derivatives **12** were synthesized, which showed a potent H_2 antagonistic activity together with a moderate inhibitory activity against *Helicobacter pylori*.

H_2 antagonists such as cimetidine, ranitidine and roxatidine have been clinically used as antiulcer drugs.[2] They are very effective against peptic ulcers based on anti-acid activity. However, one of the current issues concerning H_2 antagonist is the high incidence of ulcer recurrence after the discontinuation of H_2 antagonistic drugs.[3] Recently it has become a popular hypothesis that this ulcer recurrence relates to the existence of *Helicobacter pylori* in the stomach.[4] Prevention of *Helicobacter pylori* is said to reduce the recurrence of ulcer. In order to prevent ulcers together with their recurrence we planned to synthesize a H_2 antagonist with inhibitory activity against *Helicobacter pylori*. We synthesized piperidinomethylthiophene derivatives **12** in an attempt to obtain both H_2 antagonistic activity and inhibitory activity against *Helicobacter pylori*. We thought the compound containing sulfur would be effective to increase antimicrobial activity.

Synthesis was started with 5-hydroxy-2-thenoic acid methyl ester **3**, which was prepared from the diester **1**[5] treated with LiI in aqueous dimethylsulfoxide in 40% yield or from the hydroxyacid **2**[6] (prepared from the diester **1** by treatment with 2*N* sodium hydroxide and then diluted sulfuric acid) treated with methyl chloroformate, followed by addition of sodium methoxide in methanol in 82% yield. Treatment of **3** with NaH in DMF, followed by the addition of 4-(*t*-butoxycarbonylamino)-2-*cis*-buten-1-ol O-mesylate **5** at room temperature for 3h yielded the ester **6**, mp 48-49°C, in 79% yield. The mesylate **5** was easily prepared in quantitative yield from the alcohol **4b**[7] by treatment with mesyl chloride and triethylamine. The alcohol **4b** was synthesized from 4-amino-2-*cis*-buten-1-ol **4a** by treatment with dibutyldicarbonate in 96% yield.
Hydrolysis of the ester **6** with 15% KOH in methanol afforded the acid **7** (100% yield), which was converted to the amide **8** , mp49-53°C, in 87% yield by amidation with piperidine in the presence of WSC [1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrogen chloride] in methylene chloride at room temperature over night.

Chart 1 Synthesis of piperidinomethylthiophene derivative **12a**



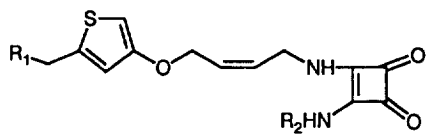
Reduction of **8** with $LiAlH_4$ in THF at room temperature for 6h yielded the amine **9** in 81% yield. Deprotection of **9** with one molar equivalent of trimethylsilyl iodide in methylene chloride at room temperature for 30 min afforded the primary amine **10** in 100% yield. Treatment of **10** with dimethyl squarate in methanol gave the methyl ether **11** in 86% yield. Treatment of **11** with excess NH_3 in methanol afforded the amine **12a** in 92% yield as a powder.

The compound **12a** showed potent H_2 antagonistic activity[8] (IC_{50}=0.16μg/ml) together with weak inhibitory activity[9] (MIC=100μg/ml) against *Helicobacter pylori*.(Table 1) This prompted us to modify the compound **12a**, in particular, the primary amine part of the cyclobutenedione moiety and the piperidine part. The synthesis of the compounds **12b-j** with substituted amino group (R_2) was accomplished according to a method similar to that described for the synthesis of **12a** by using the corresponding amines in place of

ammonia in the final step of the synthesis. The compound **12k** was synthesized by following a similar sequence of reactions to that described for the synthesis of **12a** by using dimethylamine in place of piperidine in the amidation reaction of **7**.

The H_2 antagonistic and inhibitory activity against *Helicobacter pylori* are summarized in table 1. The compound **12a** showed potent H_2 antagonistic activity, 7 times more potent than ranitidine. The compounds **12b**, **12c**, **12d**, **12e**, **12f** with small alkyl group as amino substituent (R_2) (entry 2-6) showed potent H_2 antagonistic activity compared with ranitidine, but less potency than the amino compound **12a**. The compound **12g** and **12h** with methoxyethyl or dimethylaminoethyl group (entry 7, 8) showed a comparable activity to the compound **12b** with methylamino group. However, the compounds **12i** and **12j** with a large, quite lipophilic polyfluoroalkyl group (entry 9, 10) showed very weak H_2 antagonistic activity compared with ranitidine. Modification of piperidino part to dimethylamino group (**12k**) restored the potent H_2 antagonistic activity and the compound **12k** was as potent as **12a**.

Table 1 H_2 antagonistic activity and inhibitory activity against *Helicobacter pylori* of **12**



entry No	compound	R_1	R_2	H_2 antagonist activity IC_{50} (μg/ml)	Minimum inhibitory activity against *Helicobacter pylori* No. 9470 MIC (μg/ml)
1	**12a**#	pip	H	0.16	100
2	**12b**	pip	Me	0.69	12.5
3	**12c**	pip	*i*-Pr	0.78	12.5
4	**12d**	pip	allyl	0.51	>100
5	**12e**	pip	2-FEt	0.43	1.56
6	**12f**	pip	2-CNEt	0.31	25
7	**12g**	pip	2-MeOEt	0.48	>100
8	**12h**	pip	2-Me_2NEt	0.35	>100
9	**12i**	pip	F_7PrCH_2	39%*	6.25
10	**12j**	pip	F_5EtCH_2	43%*	25
11	**12k**	Me_2N	H	0.22	100
12	**cimetidine**			3.7	>100
13	**ranitidine**			1.05	>100
14	**roxatidine acetate**			1.43	>100

#**12a** was evaluated as monohydrochloride. *39% or 43% means %inhibition at 10μg/ml.

Next, the inhibitory activities of compound **12** against *Helicobacter pylori* were tested. The compounds **12b**, **12c**, **12e**, **12f**, **12i** and **12j** with hydrophobic alkyl group (entry 2, 3, 5, 6, 9, 10) showed quite potent inhibitory activity compared with the parent compound **12a**. The compounds **12d**, **12g** and **12h** with allyl group, methoxyethyl group and basic dimethylaminoethyl group (entry 4, 7, 8) showed weak inhibitory activity. Among them the compound **12e** with 2-fluoroehtyl substituent showed the most potent inhibitory activity at 1.56μg/ml (MIC). The compound **12k** with dimethylaminomethyl group in place of piperidinomethyl group showed a weak inhibitory activity, similar to that of **12a**. In contrast, H_2 antagonists such as cimetidine, ranitidine and roxatidine did not show any inhibitory activity against *Helicobacter pylori* (MIC= >100μg/ml)

In conclusion we obtained piperidinomethythiophene derivatives **12** which showed potent H_2 antagonistic activity and moderate inhibitory activity against *Helicobacter pylori*. Among these, the compound **12e** showed the most potent inhibitory activity against *Helicobacter pylori* and H_2 antagonistic activity even more potent than that of ranitidine.

References and notes

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8) H_2-antagonistic activity was determined according to the briefly modified method reported by Reinhardt et al in *Agents and Actions*, *4*, 217-221 (1974). A subsequent response (Guinea-pig, right atrium) to histamine following preincubation with compounds for 3 min was measured. Results were expressed as a percentage of the maximal response established in the absence of the compound for each preparation.

9) Determination of MICs were performed according to the method: Koga, K.; Kawada, H.; Utsui, Y.; Domon, H.; Yasuda, H. *J. Antimicrob. Chemother.*, **1996**, *37*, 919-929. Stock cultures of bacteria were grown on brain heart infusion agar (Diffco Laboratories, Detroit, USA) supplemented with 7% horse blood, at 37°C for 3 days. The MICs were determined by the two-fold dilution method. The inoculum size of bacteria was approximately 10^4 cfu. MICs were determined against a strain No. 9470

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