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SYNTHESIS AND PHARMACOLOGICAL PROFILE OF 1-ARYL-3-SUBSTITUTED PYRROLO[3,2-*c*]QUINOLINES

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ABSTRACT: A series of 1-aryl-3-substituted pyrrolo[3,2-*c*]quinolines were synthesized and evaluated for their anti-ulcer activity. While 3-substituents of pyrrolo[3,2-*c*]quinolines mostly affected the *in vitro* H^+/K^+ ATPase activity, 1-aryl substituents of pyrrolo[3,2-*c*]quinolines affected the *in vivo* gastric acid secretion. In addition, the compounds with good *in vivo* activity protected from ethanol-induced ulcer.

Keyword: Enzyme inhibitor, Gastrointestinal activity

Recently, there have been considerable interests in the gastric H^+/K^+ ATPase. This enzyme is responsible for the gastric acid secretion[1], and has thus been viewed as an important target for peptic ulcer therapy.[2,3] The substituted benzimidazole derivatives such as omeprazole, pantoprazole, and lansoprazole have been marketed as irreversible inhibitors of the gastric H^+/K^+ ATPase, and were shown to be effective in the treatment of peptic ulcer.[4] However, the substituted benzimidazole derivatives may cause hypergastrinemia and bacterial overgrowth due to the long duration of action.[5] Many groups thus began to search the freely reversible, non-covalent inhibitors of the enzyme.[6,7,8,9] Recently, Leach *et al.* reported that 1-aryl pyrrolo[3,2-*c*]quinolines act as reversible gastric H^+/K^+ ATPase inhibitors.[10,11] In the course of our search on the gastric H^+/K^+ ATPase inhibitors to develop effective anti-ulcer drugs, a convenient synthetic method for 1,2,3-trisubstituted pyrrolo[3,2-*c*]quinolines was developed.[12] The synthetic methods *via* Root A and B was used to prepare various 1-aryl-3-substituted pyrrolo[3,2-*c*]quinolines in the present study. We report here the synthesis and the pharmacological profile of a series of 1-aryl-3-substituted pyrrolo[3,2-*c*]quinolines as anti-ulcer agents.

Synthesis of 1-aryl-3-substituted pyrrolo[3,2-*c*]quinolines.

A literature survey indicated that there are limited synthetic methods generally applicable to the synthesis of various 1-aryl-3-substituted pyrrolo[3,2-*c*]quinoline derivatives.[13,14] We examined palladium-catalyzed Heck reaction on 4-arylamino-3-iodoquinolines which were prepared according to the literature procedures .[15,16]

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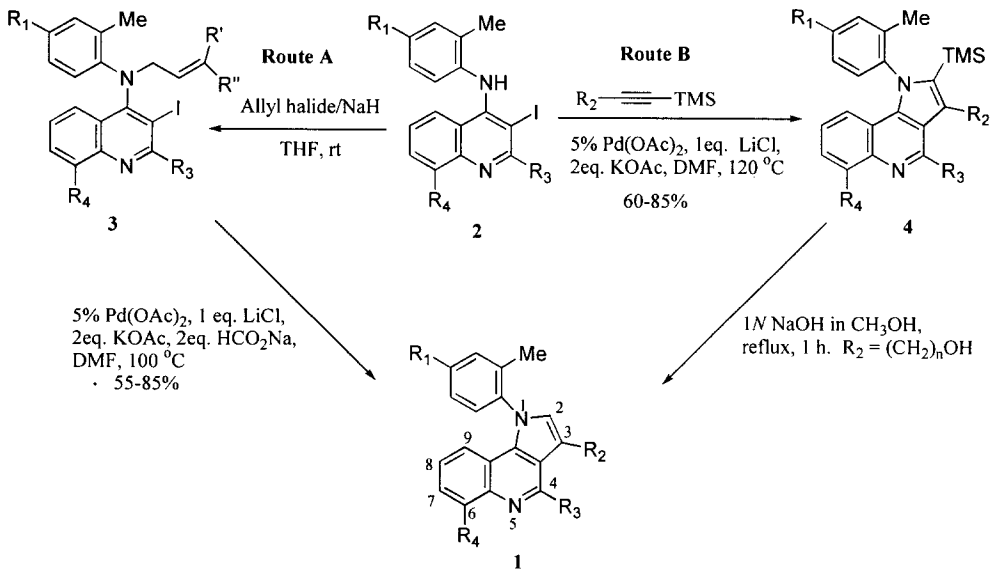
We first examined intramolecular palladium-catalyzed Heck reaction of 4-(*N*-allyl-*N*-aryl)amino-3-iodoquinolines (**3**) to obtain 3-alkyl-1-aryl pyrrolo[3,2-*c*]quinolines (**1b**, **1c**, **1f**, **1g**, **1j**, **1k**, **1l**, **1m**, **1n**, **1o**) *via* route A in Scheme 1.[16,17] The yields of intramolecular palladium-catalyzed cyclization were 55%-85% under 100 °C. However, the intramolecular reaction provided only carbon alkyl chains. To introduce various functionalities to R_2 of pyrrolo[3,2-*c*]quinolines, we then examined our recently reported intermolecular palladium-catalyzed heteroannulation with 1-trimethylsilyl alkynes,[12] and sequential desilylation of 1-aryl-2-trimethylsilyl-3-substituted pyrrolo[3,2-*c*]quinolines (**4**) *via* route B in Scheme 1. The yields of intermolecular palladium-catalyzed cyclization were 60%-85% under 120 °C. While trifluoroacetic acid was suitable for desilylation of 3-alkyl-1-aryl-2-trimethylsilyl pyrrolo[3,2-*c*]quinolines to afford **1a**, **1b**, **1f**, **1k**, **1l**, and **1m**, 1-aryl-3-hydroxyalkyl pyrrolo[3,2-*c*]quinolines required 1*N* NaOH in methanol under reflux to provide **1d**, **1e**, **1h**, and **1i**.



Scheme 1

Biological activity

A series of 1-aryl-3-substituted pyrrolo[3,2-*c*]quinolines were tested for their inhibitory effects on gastric H^+/K^+ ATPase, and their IC_{50} values are presented in Table 1. Omeprazole and SK&F 96067,[9] a reversible gastric H^+/K^+ ATPase inhibitor, were included as reference compounds. Compounds **1a**, **1b**, **1c**, **1f**, **1g**, **1j**, **1n**, and **1o** exhibited potent inhibitory activities. It appears that the R_2 substituents influence the *in vitro* activity. Carbon chains as R_2 substituents provided compounds with high *in vitro* activity which was comparable or more potent than that of either omeprazole or SK&F 96067. Introduction of a corresponding hydroxyalkyl group resulted in the less active compounds (**1d**, **1e**). On the other hand, either methoxy or hydroxy group as R_4 substituents was preferred for the *in vitro* activity. When a trifluoromethoxy group was introduced at R_4, the inhibitory activity was decreased (**1k**). Replacement of Hydrogen atom by methyl group at R_3 also resulted in the reduction of the *in vitro* activity (**1b** vs. **1l**). Substituents of R_1 had little effect on gastric H^+/K^+ ATPase activity.

The *in vivo* anti-secretory activity of the compounds was evaluated by using pylorus-ligated rats. A significant loss of the *in vivo* activity was observed when the methoxy group was replaced by hydroxy group at R_4 (**1a** vs **1b**). Similar to the *in vitro* activity, alkyl substituents at R_2 resulted in the good *in vivo* activity

Table 1. Effect of compounds on the *in vitro* H^+/K^+ATPase activity and *in vivo* anti-secretory activity

Compound	R_1	R_2	R_3	R_4	IC_{50} (μM)[a]	ED_{50} (mg/kg)[b]
1a	H	CH_3	H	OH	4.8 ± 0.8	58 ± 11.0
1b	H	CH_3	H	OCH_3	8.2 ± 0.3	13 ± 6.5
1c	H	$CH(CH_3)_2$	H	OCH_3	17.0 ± 3.0	90 ± 12.0
1d	H	CH_2OH	H	OCH_3	100.0 ± 12.0	ND[c]
1e	H	CH_2CH_2OH	H	OCH_3	80.0 ± 7.8	ND
1f	F	CH_3	H	OCH_3	14.0 ± 1.2	10 ± 2.6
1g	F	CH_2CH_3	H	OCH_3	5.7 ± 0.4	13 ± 3.1
1h	F	CH_2OH	H	OCH_3	>100	ND
1i	F	CH_2CH_2OH	H	OCH_3	>100	ND
1j	OAc	CH_3	H	OCH_3	3.4 ± 0.4	47 ± 6.1
1k	H	CH_3	H	OCF_3	>100	ND
1l	H	CH_3	CH_3	OCH_3	>>100	ND
1m	F	CH_3	CH_3	OCH_3	72.0 ± 2.7	ND
1n	OH	CH_2CH_3	H	OCH_3	4.8 ± 3.1	59 ± 5.8
1o	OH	$CH(CH_3)_2$	H	OCH_3	7.2 ± 2.4	49 ± 3.3
SK&F 96067					18.0 ± 3.6	20 ± 4.1
Omeprazole					22.4 ± 1.2	3.2 ± 1.1

[a]Microsomal fractions containing gastric H^+/K^+ ATPase activity were prepared from rabbit stomachs by differential centrifugations. Enzyme preparation was incubated at 37 °C in the presence of various concentrations of the indicated compounds, and the remaining activity was determined spectrophotometrically.[18] Values represent the mean ± SEM (n=3).

[b]Gastric anti-secretory activity was determined by Shay's method[19] with some modification. Acid concentration as well as gastric juice volume were measured 5 h after the pylorus ligation of the SD rats. Values represent the mean ± SEM (n=3).

[c]ND, not determined.

(**1b**, **1f**, and **1g**). The replacement of hydrogen atom to fluorine atom at R_1 retained high anti-secretory action (**1b** vs. **1f**). The anti-secretory effect of the compounds was further confirmed by using the ethanol-induced ulcer model. Oral administration of 95% ethanol produced severe band-like mucosal hemorrhage in the grandular stomach. Control rats treated with ethanol alone had gastric lesion of 63.6 ± 7.07 mm. Compounds with potent *in vivo* anti-secretory activity (**1b**, **1f**, and **1g**) protected from the ethanol-induced ulcer formation. The protective effect against ethanol-induced ulcer may be mainly mediated by the inhibition of gastric acid secretion via the inhibition of gastric H^+/K^+ ATPase activity.

Based on the present results, 1-aryl-3-substituted [3,2-*c*]quinolines may be effective for ulcer treatment, and among them, compounds with either hydrogen atom or fluorine atom at R_1 (**1b**, **1f**, and **1g**) exhibited the

potent anti-secretory action. The active compounds will be further evaluated for assessing their clinical utility in peptic ulcer therapy.

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