

SYNTHESES OF 2-[(3,5-DIMETHYL-4-METHOXYPYRIDYL)ALKYL]-BENZOTHIAZOLIDINE DERIVATIVES AS A POTENTIAL GASTRIC H⁺/K⁺-ATPASE INHIBITOR¹

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Abstract: A series of 2-[(3,5-dimethyl-4-methoxypyridyl)alkyl]benzothiazolidine derivatives were synthesized and tested their inhibitory effects on gastric H⁺/K⁺-ATPase. Compound 4d exhibited potent *in vitro* inhibitory activity. © 1998 Elsevier Science Ltd. All rights reserved.

Since the inhibitory effect of omeprazole (1) on gastric H⁺/K⁺-ATPase results from the formation of S-S bond between the highly thiophilic intermediates and the thiol groups in gastric H⁺/K⁺-ATPase,² there have been efforts to develop a new class of gastric H⁺/K⁺-ATPase inhibitors by fine-tuning the nuclephilic/electrophilic properties of thiophile which could afford an enzyme-inhibitor complex with good stability in neutral condition.³

During an investigation of a new class of gastric H⁺/K⁺-ATPase inhibitors which is more stable under neutral and weakly acidic conditions, we recently observed that disulfide bond was formed from the reaction of benzothiazolidine analogue with 2-mercaptoethanol under the acidic condition.^{1,4} Based on this observation, we assumed that the benzothiazolidine analogue could inhibit H⁺/K⁺-ATPase, because the opening of a thiazolidine ring in the acidic media generates an iminium intermediate, which can react with a thiol group to form the disulfide bond.⁵ In modifying the structure of omeprazole, we replaced the benzimidazole moiety with a structurally similar benzothiazolidine ring and maintained the pharmacological effect of the pyridine ring moiety. Here, we report the syntheses and biological activities of benzothiazolidine derivatives (2 - 5) in which the benzothiazolidine ring moiety is connected with the pyridine moiety of omeprazole having different chain lengths.

Chemistry. The desired benzothiazolidine derivatives 2 - 5 were prepared by condensation of oxo compounds (8, 11, 12, 13, 15) either with the corresponding substituted 2-aminothiophenols or with *L*-cysteine ethyl ester hydrochloride (Scheme 1, 2). Oxo compounds were prepared as follows: 3,5-Dimethyl-4-methoxy-2-formylpyridine (8) was readily prepared from 6⁶ via substitution of the chloro group by treatment of aqueous NaOH solution, followed by partial oxidation with selenium oxide (Scheme 1). For the synthesis of 11, reaction of 6 with sodium cyanide, followed by acid catalyzed esterification with methanol, gave 9, which was then reduced with LAH to give 10. Partial oxidation of 10 with activated MnO₂ afforded 11 (Scheme 1). For the synthesis of 13, the vinylpyridine 12 was first prepared by reduction of 10 with LAH followed by dehydration of the resulting hydroxyethylpyridine intermediate with selenium oxide. It was then reacted with sodium ethyl acetoacetate and refluxed with 20 % HCl solution to give 13. For the syntheses of 14 and 15, the formylpyridine 8 was reacted with triphenylphosphonoranylidene-2-propanone to give 14, which was then hydrogenated over 10% Pd-C to give 15 (Scheme 2). The corresponding substituted 2-aminothiophenols were prepared by the following classical procedures that were well described in heterocyclic chemistry literature. Legisteine ethyl ester hydrochloride was purchased from Aldrich Chemical Company.

Reagents: a) NaOH, H₂O-THF (1;1), 40°C, 5 hr, (68 %); b) SeO₂, pyridine, reflux, 2.5 hr, (91 %) c) 2-Aminothiophenol, benzene, p-TsOH, reflux, 6 hr, (30 - 66 %); d) NaCN, MeOH-H₂O (3:1), 30°C, 20 hr, (50 %); e) EtOH, c-HCl, reflux, 6 hr, (63 %); f) LiAlH₄ (1.2 eq.), THF, -15°C, 1 hr, (71 %); g) MnO₂, CH₂Cl₂, rt, 24 hr, (10 %); h) SeO₂, pyridine, 100°C, 2 hr, (64 %); i) ethyl acetoacetate, Na, 110°C, 6 hr, (47 %); j) 20 % HCl, reflux, 6 hr, (66 %).

Scheme 1

OCH₃

$$H_3C$$
 CH_3
 $A(R_1=H)$
 $A(R_1=H)$

Reagents: a) CH₃CHO (6.0 eq.), 10 % NaOH, 0°C, 2 min, (26 %); b) Triphenylphosphoranylidene-2-propanone, THF, 40°C, 5 hr (18 %); c) Substituted-2-aminothiophenol, benzene, p-TsOH, reflux, 6 hr, (30 - 66 %); d) H₂/Pd-C, MeOH, 14psi, rt, 1 hr, (90 %); e) L-Cysteine ethyl ester.HCl, benzene, reflux, 6 hr, (69 %).

Scheme 2

Results and Discussion

All compounds were tested for *in vitro* inhibitory activities of gastric H⁺/K⁺-ATPase by using a previously reported method, and the results are summarized in Table 1.

We initially examined the effects of the chain length connecting the benzothiazolidine ring and pyridine moiety on structure-activity relationships and found that the ethylene unit's compound (n = 2) exhibited a high inhibitory activity compared to other compounds (n = 0, 1, 3). Therefore, we prepared the extended set of 2-[(3,5-dimethyl-4-methoxypyridyl)ethyl]benzothiazolidine derivatives for further investigation. Either the replacement of benzothiazolidine ring with a cysteine ring (4j) or of 3,5-dimethyl-4-methoxypyridyl moiety with pyridyl one (4k) reduced the activity significantly, whereas the addition of a double bond in the ethylene unit (4i) resulted in a modest reduction of activity. In addition, the methylation of nitrogen in the benzothiazolidine ring (4h) also reduced the activity.

A variety of substitutions at the 5- or 6- position in the benzothiazolidine ring were made. The trifluoromethyl (4d) and fluoro (4c) derivatives which have the electron withdrawing group at the 5- position showed higher potency than parent compound (4a) with $IC_{50} = 24 \mu M$ and 33 μM , respectively, while the substitution at the 6- position rendered the compound (4g) inactive.

The trifluoromethyl derivative (4d) was further investigated for its *in vivo* inhibitory activity by measuring the gastric secretion and acidity in rats. The volume of gastric juice was decreased by 21% and the acid output was decreased by 38% at the dose of 30 mg/Kg of 4d (n = 8, po administration). This result indicated that a benzothiazolidine derivative could be used as a novel (H^+/K^+)-ATPase inhibitor.

Mechanistic and further in vivo studies are currently underway.

ro innium.
OCH₃
H₃C CH₃
R₁
R₂
R₂

Table 1: In vitro inhibition of (H+/K+)-ATPase activity.

Compd.	n	R_1	R ₂	R_3	R ₄	Inhibition(%)b	IC ₅₀ (μM)
2	0	Н	Н	Н	H	0	
3	1	H	H	H	Н	58.5	
4a	2	Н	H	H	H	24.6	
4b	2	CH_3	H	H	H	96.4	98
4c	2	CH ₃	F	Н	H	81.0	33
4d	2	CH ₃	CF ₃	Н	Н	84.4	24
4e	2	CH ₃	CH_3	H	Н	0	
4f	2	CH ₃	Cl	H	H	20.0	>100
4g	2	CH ₃	H	Cl	Н	0	
4h	2	CH ₃	Н	H	CH ₃	17.0	
4i	(CH=CH)	CH ₃	H	H	H	61.1	>100
4j	2	H	(L-Cysteine ethylester)			19.8	
			. N. ^				
4k		СН	,X _s _(O)			0	
5	3	CH ₃	Н	H	Н	0	
Omeprazole						95	3.8

a: performed at pH = 7.4 buffer solution. b: measured at the concentration of 400 μ M.

References and Notes

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