Furo[3,2-*h*]quinoline Derivatives as a Gastric H^+/K^+-ATPase Inhibitors

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Furo[3,2-*h*]quinoline derivatives were synthesized as a gastric H^+/K^+-ATPase inhibitors. The oxycyclization of 7 and 8-positions in quinoline potentiated the inhibitory activity, while no significant changes in biological activity were observed by the variation of substituents in furan ring. The several furo[3,2-*h*]quinoline derivatives were worthy of in vivo investigation for their anti-secretory and anti-ulcer activity.

Keywords : Furo[3,2-*h*]quinoline, Gastric H^+/K^+-ATPase inhibitors, Anti-secretory.

Introduction

The presence of acid is a fundamental factor in the pathogenesis of gastric and duodenal ulcers, reflux esogastritis, and nonsteroidal antiinflammatory drug-induced lesions.[1] Therefore, it is mandatory to control acid secretion for treatment of these diseases. While acid secretion by parietal cells is regulated through several stimulatory receptors such as histamine H_2-receptor, muscarine receptor and gastrin receptor, the final step of acid secretion is mediated by the gastric H^+/K^+-ATPase, so-called proton pump.[2] Proton pump inhibitors have been expected to have potential clinical advantage over histamine H_2 receptor antagonists, because acid secretion is inhibited irrespective of the stimulus.[3] The substituted benzimidazole derivatives irreversibly suppress gastric H^+/K^+-ATPase, resulting in a long-lasting and potent antisecretory effect.[4,5] Although these derivatives exert superior healing of acid-related disorders compared to histamine H_2 receptor antagonists, long-term treatment with omeprazole causes bacterial overgrowth in the upper gut due to profound long-standing acid suppression.[6] Sustained acid inhibition due to a long-term treatment with acid inhibitors also induces hypergastrinemia, resulting in the development of gastric enterochromaffin-like (ECL) cell carcinoids in rat[7] and a slight hyperplasia of ECL cells in humans.[8] Recently, many research groups have been interested in the development of reversible gastric H^+/K^+-ATPase inhibitors to overcome the potential side effects of irreversible proton pump inhibitors.[9-18] In quinoline compounds, formation of hydrogen-bonding between the 3-substituted carbonyl oxygen and the 4-arylamine was important factor in maintaining good biological activity.[10] In contrast to restricted 3,4-substituents in quinoline compounds, the 8-position of the quinoline ring tolerated variety of substitutents in maintaining biological activities. In this report, we were particularly interested in biological activity of furo[3,2-*h*]quinoline derivatives in attempt to find new development candidates.

Experimental Section

The ^{1}H NMR spectra were obtained on a Varian Gemini 200 MHz NMR Spectrometer. The GC-MS spectra were obtained on a Shimazu QP 1000 GC/MS. Melting points were determined on MUL-TEM apparatus and were uncorrected. All chemicals were used directly as obtained from commercial sources unless otherwise noted. The H^+/K^+-ATPase-inhibitory and gastric antisecretory activity were tested by the reported methods.[22]

2-Allyl-6-nitrophenol (2a). 2-Allyl-6-nitrophenyl ether (24 g, 0.13 mol) was heated at 200 °C for 3 h with passing nitrogen. The reaction mixture was cooled and poured into 200 mL of cold water. The product was extracted with two 250-mL portions of diethyl ether. The ethereal layer was dried over anhydrous $MgSO_4$ and concentrated. The 2-allyl-6-nitrophenol was obtained in 70% isolated yield after silica gel column chromatography (hexane:ethyl acetate = 9 : 1) as yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.47 (d, 2H, J = 6.4 Hz, CH_2), 5.05-5.14 (m, 2H, vinyl), 5.95 (m, 1H, vinyl), 6.90 (dd, 1H, J = 8.4, 1.4 Hz, ArH), 7.44 (dd, 1H, J = 7.4, 1.4 Hz, ArH), 8.91 (dd, 1H, J = 8.4, 1.4 Hz, ArH), 10.93 (s, 1H, OH); Mass m/e (%) 78 (17), 104 (19), 132 (83), 162 (100), 179 (5.3, M^+).

2-(2-Methylallyl)-6-nitrophenol (2b). The compound was obtained as a solid in 72% isolated yield through the above procedure: mp 51-52 °C; ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3H, CH_3), 3.41 (s, 2H, CH_2), 4.66 (d, 1H, J = 1.2 Hz), 4.84 (d, 1H, J = 1.2 Hz), 6.91 (dd, 1H, J = 8.6, 1.2 Hz), 7.45 (dd, 1H, J = 7.4, 1.2 Hz), 7.99 (dd, 1H, J = 8.6, 1.2 Hz), 10.93 (s, 1H, OH); Mass m/e (%) 51 (100), 77 (67), 91 (48), 103 (39), 115 (54), 131(81), 146 (66), 176 (73), 193 (51, M^+).

2-Methyl-7-nitro-2,3-dihydrobenzo[*b*]furan (4a). 2-Allyl-6-nitrophenol (5.87 g, 32.8 mmol) was dissolved in 100 mL of dichloromethane and anhydrous $AlCl_3$ (4.36 g, 32.8 mmol) was slowly added with stirring. The reaction mixture was allowed to react for 0.5 h at room temperature. Precooled 100 mL of 10% sodium hydroxide solution was slowly added to the reaction mixture with ice cooling. The resulting product was extracted with two 250-mL portions of diethyl ether. The ethereal layer was dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated. The benzo[*b*]furan was obtained in 97% isolated yield after silica gel column chromatography (hexane:ethyl acetate = 9 : 1):

mp 65-66 °C; ^{1}H NMR ($CDCl_3$) δ 1.53 (d, 3H, J = 6.3 Hz), 2.87 (dd, 1H, J = 15.9, 7.2 Hz), 3.40 (dd, 1H, J = 15.9, 8.4 Hz), 5.22 (m, 1H), 6.87 (dd, 1H, J = 8.4, 7.2 Hz), 7.38 (dd, 1H, J = 7.2, 1.2 Hz), 7.85 (dd, 1H, J = 8.4, 1.2 Hz); Mass m/e (%) 77 (88), 103 (31), 117 (23), 132 (100), 162 (21), 179 (53, M^+).

2,2-Dimethyl-7-nitro-2,3-dihydrobenzo[*b*]furan (4b). The compound was obtained as a yellow oil in 90% isolated yield through the above procedure: mp 62-63 °C; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 6H), 3.07 (s, 2H), 6.85 (dd, 1H, J = 8.4, 7.2 Hz), 7.63 (dd, 1H, J = 7.2, 1.2 Hz), 7.86 (dd, 1H, J = 8.4, 1.2 Hz); Mass m/e (%) 51 (82), 63 (30), 77 (58), 91 (32), 103 (29), 115 (43), 131 (100), 146 (72), 176 (69), 193 (48, M^-).

2-Methyl-7-nitrobenzo[*b*]furan (4c). 1-Nitro-2-(2-propinyloxy)benzene (24 g, 0.14 mol) was dissolved in 60 mL of PEG-200. The resulting solution was refluxed for 3 h at 220 °C with passing nitrogen. The reaction mixture was cooled and poured into 200 mL of cold water. The product was extracted with two 250-mL portions of diethyl ether. The ethereal layer was dried over anhydrous $MgSO_4$ and concentrated. The 2-methyl-7-nitrobenzo[*b*]furan was obtained in 63% isolated yield after silica gel column chromatography as yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 6.52 (s, 1H), 7.26 (dd, 1H, J = 8.4, 1.2 Hz), 7.75 (d, 1H, J = 8.4 Hz), 8.03 (d, 1H, J = 8.4 Hz); Mass m/e (%) 77 (71), 103 (77), 177 (M^-).

7-Amino-2-methyl-2,3-dihydrobenzofuran (5). 2-Methyl-7-nitro-2,3-dihydrobenzofuran (3.01 g, 16.8 mmol) was dissolved in 100 mL of absolute methanol. After addition of 5% Pd/C (2.0 g) and $HCONH_4$ (5.0 g) to the reaction mixture, the resulting mixture was stirred for 20 h at room temperature. The solution was filtered and concentrated. The residue was dissolved in 50 mL of diethyl ether and washed with H_2O (50 mL). The ethereal layer was dried over $MgSO_4$, filtered off, and concentrated. The 7-amino-2-methyl-2,3-dihydrobenzo[*b*]furan was obtained in 80% yield after silica gel column chromatography: ^{1}H NMR ($CDCl_3$) δ 1.52 (d, 3H, J = 6.2 Hz), 2.85 (dd, 1H, J = 15.3, 7.9 Hz), 3.32 (dd, 1H, J = 15.3, 8.7 Hz, CH_2), 3.65 (brs, 2H), 4.90-5.05 (m, 1H), 6.67-6.78 (m, 3H); Mass m/e (%) 77 (100), 106 (30.5), 131 (20.5), 149 (5.0, M^+).

General Procedure for the preparation of 2-acyl-3-alkoxyacrylates (6) and 2-acyl-3-arylaminoacrylate esters (7). A mixture of the β-keto ester (1 equiv), trimethyl orthoformate (2 equiv), and acetic anhydride (1 equiv) was heated at reflux for the appropriate time, and then the volatile components were removed *in vacuo* (typically 90 °C/0.3 mmHg). The residual liquid consisted largely of the 2-acyl-3-alkoxyacrylates **6** as a mixture of E/Z isomers. The compound **6** was mixed with the appropriate aniline (1 equiv), warmed on a steam bath for 10 min, and then poured into petroleum ether with vigorous stirring. The product was filtered off and washed with ether to give compound **7**, usually as a mixture of E/Z isomers. In some cases, a substantial second crop could be recovered from the mother liquors after acid wash to remove unreacted aniline.

7-Butyryl-2-methyl-3,9-dihydro-2*H*-furo[3,2-*h*]quinoline-6-one (8). 2-Butyryl-3-arylaminoacrylate was slowly added into boiling diphenyl ether solution. Heating was continued at reflux for 4 h. After cooling, the solution was poured into petroleum ether with vigorous stirring. The resulting solid was filtered off and washed with ether. The product was obtained in 80% yield: mp 201-202 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H, J = 7.4 Hz), 1.45 (t, 3H), 1.75 (m, 2H), 3.27 (t, 2H), 3.50 (dd, 1H), 5.05-5.25 (m, 1H), 7.18 (d, 1H, J = 8.1 Hz), 7.93 (d, 1H, J = 8.1 Hz), 8.64 (s, 1H), 10.59 (brs, 1H); Mass m/e 271 (M^-).

7-Butyryl-2-methyl-3,9-dihydro-2*H*-furo[3,2-*h*]quinoline-6-yl methanesulfonate (9a). The compound **8** (3 g, 11.4 mmol) and Et_3N (1.35 g, 13.3 mmol) was dissolved in 30 mL of methylene chloride. The methanesulfonyl chloride (1.53 g, 13.3 mmol) was slowly added to the reaction mixture at 0 °C. The resulting solution was stirred for 30 min and washed with aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered off, and evaporated to remove the solvent. The product was obtained by column chromatography and subsequent recrystallization in 90% isolated yield: mp 130-133 °C; ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3H J = 7.4 Hz), 1.60 (d, 3H, J = 6.2 Hz), 1.66-1.85 (m, 2H), 3.00 (t, 2H), 3.05 (dd, 1H), 3.41 (s, 3H), 3.55 (dd, 1H, J = 16.1, 9.1 Hz), 5.19-5.31 (m, 1H), 7.50 (d, 1H, J = 8.4 Hz), 7.80 (d, 1H, J = 8.4 Hz), 9.04 (brs, 1H); Mass m/e 349 (M^-).

1-[2-Methyl-6-(2-methylphenylamino)-2,3-dihydrofuro-[3,2-*h*]quinoline-7-yl]butane-1-one (10a). 7-Butyryl-2-methyl-3,9-dihydro-2*H*-furo[3,2-*h*]quinoline-6-yl methanesulfonate (0.2 g, 0.57 mmol) and 2-methylaniline (0.12 g, 1.1 mmol) was dissolved in 10 mL of acetonitrile and the resulting solution was refluxed for 1 h. The resulting mixture was concentrated and the residue was dissolved in 10 mL of ethyl acetate. The organic solution was washed with aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered off and then evaporated. The product was obtained by column chromatography and subsequent recrystallization in 98% yield: mp 186-187 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H J = 7.4 Hz), 1.57 (d, 3H, J = 6.2 Hz), 1.70-1.91 (m, 2H), 2.31 (s, 3H), 2.91 (dd, 1H, J = 15.7, 8.1 Hz), 3.06 (t, 2H, J = 7.2 Hz), 3.40 (dd, 1H, J = 16.0, 9.1 Hz), 5.08-5.20 (m, 1H), 6.83-7.27 (m, 6H), 9.09 (s, 1H), 11.95 (brs, 1H); Mass m/e 360 (M^-).

1-[6-(2-Methoxyphenylamino)-2-methyl-2,3-dihydrofuro[3,2-*h*]quinoline-7-yl]propane-1-one (10b). 7-Propionyl-2,3-dihydrofuro[3,2-*h*]quinoline-6-yl methanesulfonate (0.34 g, 10 mmol) and 2-methoxyaniline (0.25 g, 20 mmol) was dissolved in 15 mL of acetonitrile and the solution was refluxed for 1 h. The resulting solution was concentrated, and dissolved into 10 mL of ethyl acetate. The organic solution was washed with aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered off, and evaporated. The product was obtained by column chromatography and subsequent recrystallization in 85% yield: mp 147-149 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.4 Hz), 1.62 (d, 3H, J = 6.2 Hz), 1.70-1.91 (m, 2H), 3.01 (dd, 1H), 3.16 (q, 2H, J = 7.2 Hz), 3.43 (dd, 1H, J = 16.0, 9.1 Hz), 5.08-5.20 (m, 1H),

6.83-7.27 (m, 6H), 9.12 (s, 1H), 11.65 (brs, 1H); Mass m/e 362 (M^-).

6-Chloro-2-methylfuro[3,2-*h*]quinoline-7-carboxylic acid ethyl ester (9m). 2-Methyl-6-oxo-6,9-dihydrofuro[3,2-*h*]quinoline-7-carboxylic acid ethyl ester (1.54 g, 5.6 mmol) in 10 mL of phosphoryl chloride was heated at reflux for 1 h. Excess phosphoryl chloride was removed *in vacuo*, and the residue was poured into ice water. The resulting mixture was extracted with methylene chloride, dried over $MgSO_4$, and concentrated under reduced pressure to afford 6-chloro-2-methylfuro[3,2-*h*]quinoline-7-carboxylic acid ethyl ester in 73% yield: mp 175-176 °C; Mass m/e 289 (M^+).

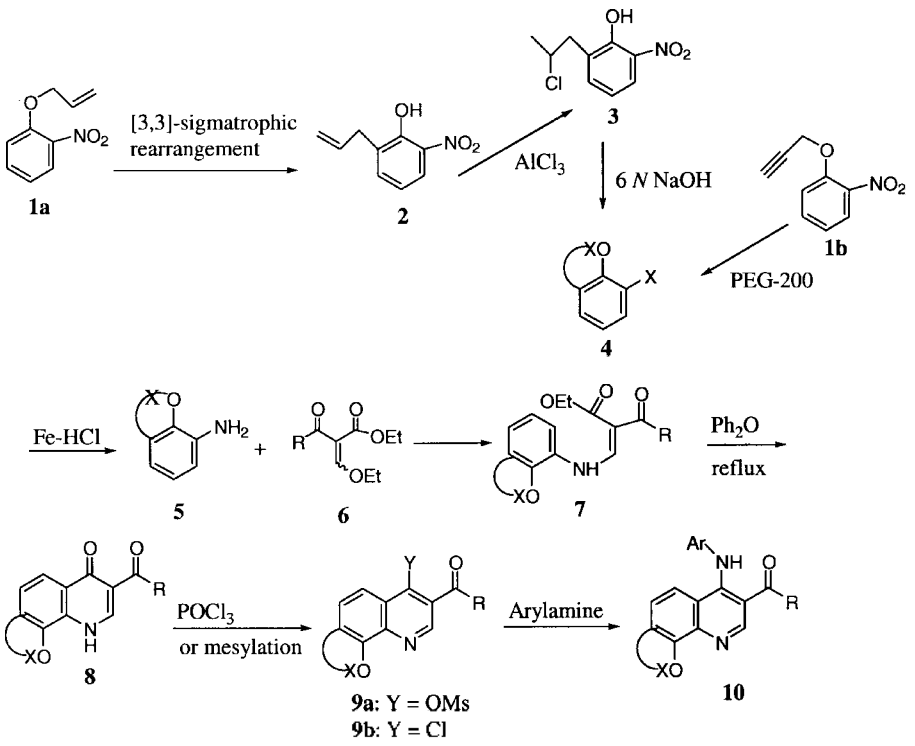
6-(2-Methylphenylamino)-2-methylfuro[3,2-*h*]quinoline-7-carboxylic acid ethyl ester (10m). A mixture of 6-(2-methoxyphenylamino)-2-methyl[3,2-*h*]quinoline-7-carboxylic acid ethyl ester (280 mg, 0.86 mmol) and 2-methoxyaniline (200 mg, 1.62 mmol) were dissolved in 10 mL of 1,4-dioxane. The reaction mixture was refluxed for 1 h at 110 °C and concentrated under reduced pressure. The residue was dissolved in 10 mL of ethyl acetate and washed with aqueous $NaHCO_3$. The resulting solution was concentrated and dissolved into 10 mL of ethyl acetate. The organic solution was washed with aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered off, and evaporated. The product was obtained in 78% yield by column chromatography and subsequent recrystallization: mp 176-177 °C; ^1H NMR ($CDCl_3$) δ 1.44 (t, 3H J = 7.1 Hz), 2.59 (s, 3H), 3.87 (s, 3H), 4.43 (q, 2H, J = 7.1 Hz), 6.47 (s, 3H), 6.71-7.52 (m, 6H), 9.30 (s, 1H), 10.25 (brs, 1H); Mass m/e 376 (M^-).

Enzyme preparation. H^+/K^--ATPase was prepared from the fundic mucosae of New Zealand white rabbits (2-3 Kg, male) as described previously.[22] The mucosal layer of the gastric fundus was scraped, and homogenized in 40 mM Tris/HCl, pH 7.4 containing 0.25 M sucrose, 2 mM HEPEs, 2 mM $MgCl_2$, 2 mM EDTA. The homogenate was centrifuged at 10,000 × g for 30 min at 4 °C. The resulting supernatant was recentrifuged at 100,000 × g for 60 min at 4 °C. The pellets were resuspended in 40 mM Tris/HCl buffer (pH 7.4), and stored at -70 °C. The protein concentration of the preparation was determined by the method of Bradford.[23]

***In vitro* screening of furo[3,2-*h*]quinoline derivatives**. Prepared enzyme (25 μg) was incubated at 37 °C in 250 μL of a medium consisting of 4 mM Tris/HCl, pH 7.4, 4 mM $MgCl_2$, 5 μg/mL nigercin in methanol, 6.7 mM NH_4Cl. Specific H^-/K^+-ATPase activity was determined after subtracting the basal enzyme activity which was measured without KCl and NH_4Cl. After incubation for 30 min, the reaction was terminated by the addition of 30% cold TCA, and centrifuged. The inorganic phosphate released in the supernatant was determined by the method of Yoda and Hokin.[24] Assay medium for the H^-/K^+-ATPase activity contained 2% methanol, which did not affect the enzyme activity.

Chemistry

Although synthetic methods of 2,3-dihydrobenzofurans were reported by acid-mediated cyclization such as strong acids, $AlCl_3$ and $TiCl_4$.[19] the reaction with electron-withdrawing substitutents provided low yields of desired benzo[*b*]furans under acid-mediated cyclization. The requisite nitro substituted benzofurans were synthesized as shown in



Scheme 1

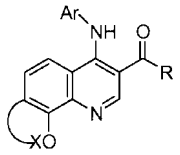
Scheme 1.

The thermal [3,3]-sigmatrophic rearrangement of compound **1a** gave 2-allyl-6-nitrophenol **2** in 70% yield. Addition of 1.0 equivalent of $AlCl_3$ to compound **2** at room temperature provided a mixture of compound **3** and **4** in a ratio of 9:1. The treatment of mixture of compound **3** and **4** with aqueous sodium hydroxide gave 7-nitro-2.3-dihydrobenzo[*b*]furan in 90-97% yield.[20] Although the formation of 5 or 6-membered ring in Claisen rearrangements of phenyl propargyl ethers was quiet dependent upon the nature of substituents on phenyl ring.[21] only aromatized 7-nitrobenzo[*b*]furan (**4**) has been achieved by the thermal Claisen rearrangement of compound **1b** and sequential cyclization in PEG-200 as a solvent at 220 °C in 63% yield. The nitro group of compound **4** was easily reduced to amino compound **5** under hot Fe/HCl conditions in quantitative yield. Reaction of the appropriately substituted *β*-keto ester with a trialkyl orthoformate gave compound **6** as a mixture of *E* and *Z* isomers. Further reaction of compound **6** with aminobenzofuran gave the acyclic precursor **7**. The high temperature cyclization of compound **7** in diphenyl ether gave the quinoline **8**. which could be chlorinated with phosphorous oxychloride or mesylated with methanesulfonyl chloride to give compound **9**. Subsequent displacement reaction of compound **9** with arylamines gave compound **10** in high yields.

Biological Activity

In the previous report, small variation of ortho substitution of the arylamino group showed a significant change in the biological activity. It was assumed that the twisting aryl ring further out of the plane of the quinoline potentiated the biological activity. Our study was focused on the variation of substituent in the arylamino group. Although 2-methoxy-3-pyridyl instead of 2-methylphenyl group gave similar activity to 2-methylphenyl group (**10e**), *o*-methoxy substituents showed low gastric inhibition activity (**10b**). Addition of hydroxy group or elimination of methyl group from 2-methylphenyl was also unfavorable (**10c**. **d**). We also examined the size of 3-substituent for achieving high potency. 1-propanone group also retained good IC_{50} value with various aryl substituents (**10f-h**). On the other hand. aromatized benzofuran derivatives were examined with three different 3-acyl substituents (**10i-10q**). The different acyl substituents showed similar gastric inhibition effect with various 4-aryl substituents. Finally. dimethylhydrofuran fused quinoline derivatives which

Table 1. Biological activities of furo-fused quinoline derivatives



10

Entry	OX-	R	Ar	IC_{50} (μM) or % inhibition at 100 μM
10a	$OCH(CH_3)CH_2$-	$CH_2CH_2CH_3$	2-CH_3Ph	8.9
10b	"	"	2-CH_3OPh	57%
10c	"	"	4-OH-2-CH_3Ph	34%
10d	"	"	Ph	61%
10e	"	"	2-CH_3O-3-Pyridyl	24
10f	"	CH_2CH_3	2-CH_3Ph	12
10g	"	"	2-CH_3OPh	5
10h	"	"	2-CH_3O-3-Pyridyl	32
10i	$OC(CH_3)$=CH-	$CH_2CH_2CH_3$	2-CH_3Ph	59%
10j	"	"	2-CH_3OPh	22
10k	"	"	2-CH_3O-3-Pyridyl	14%
10l	"	"	2-CH_3OPh	59%
10m	"	OCH_2CH_3	2-CH_3Ph	12
10n	"	"	2-CH_3O-3-Pyridyl	23%
10o	"	CH_2CH_3	2-CH_3OPh	13
10p	"	"	2-CH_3Ph	60
10q	"	"	2-CH_3O-3-Pyridyl	28
10r	$OC(CH_3)_2CH_2$-	$CH_2CH_2CH_3$	2-CH_3Ph	21
10s	"	"	2-CF_3Ph	26
10t	"	"	2-CH_3-3-Pyridyl	38
SKF96067				15
Omeprazole				15

[a] ^{1}H NMR and MS spectra were consistent with assigned structures.

were substituted with 2-substituted phenyl or pyridine (**10r-10t**) were examined. The compound containing trifluoromethylphenyl instead of methylphenyl exhibited similar IC_{50} value. The effect of quinoline 3-acyl substituents indicates that neither electron-withdrawing ability nor hydrogen-bonding potential alone is sufficient for imparting high activity. Although there may be some direct effect of this group on binding ability to the enzyme, it is also likely that this reflects the critical nature of the precise geometry achieved in the *syn*-5 form. Modifications of substituents of furan in 7,8-position of the quinoline tolerated good *in vitro* biological potency.

Conclusions

The present results show that introduction of furan ring to quinoline potentiated the inhibitory activity of the compounds, while no significant biological activity changes were observed by variations of substituents of furan moiety. We observed that modifications of substituent of aryl group also retained *in vitro* potency. Furo[3,2-*h*]quinoline derivatives act as a gastric H^+/K^--ATPase inhibitors. Several furo[3,2-*h*]quinoline derivatives are worthy of *in vivo* investigation for their anti-secretory and anti-ulcer activity.

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