Synthesis of 4-Phenylamino-3-vinylquinoline Derivatives as Gastric H^+/K^+-ATPase Inhibitors

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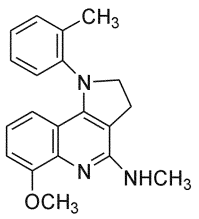
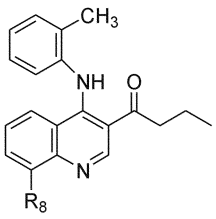
There has been continuing interest in the development of reversible gastric H^+/K^+-ATPase inhibitors as anti-ulcer agent to overcome the potential side effects of irreversible inhibitors.[1] Several quinoline analogs have been developed as reversible inhibitors (Scheme 1),[2-6] and some of them were clinically evaluated.[7-9] In our laboratories, various substituent modifications of quinoline have been carried out for the purpose of finding novel agents with biological activities.[10-13]

The previous reports indicated that the orientation of 4-(phenylamino) substituent in quinolines was a very important factor in gastric H^+/K^+-ATPase inhibitory activity.[5] Literature survey indicated that a variety of 3-substituents, which would be an important factor in controlling the orientation of 4-phenylamino substituent could be tolerated.[8,9] Although a wide spectrum of 3-substituents were tested, there were no precedent of using vinyl group as a 3-substituent.

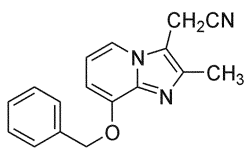
In this study, various substituted-vinyl groups were introduced at the 3-position of 4-phenylaminoquinoline derivatives to obtain novel gastric H^+/K^+-ATPase inhibitors. The 4-(phenylamino)-3-vinylquinoline derivatives were prepared using the palladium-catalyzed Heck reaction as a key reaction,[14,15] and their activities were tested against gastric H^+/K^+-ATPase *in vitro*.



SK& F 96356



SK&F 96067 R_8 =OCH_3
SK&F 97574 R_8 = OCH_2CH_2OH



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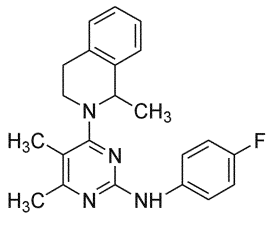


YH1885

Scheme 1

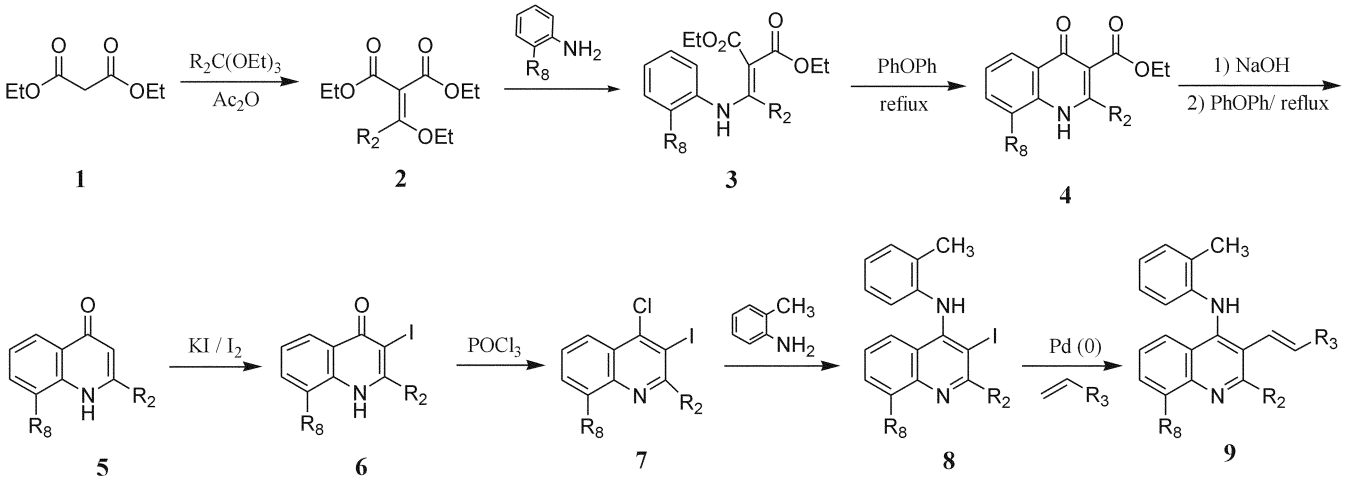
Synthesis

The general synthetic pathway for 4-(2-methylphenylamino)-3-vinylquinoline derivatives is outlined in Scheme 2. The reaction of diethyl malonate (**1**) with triethyl orthoformate (for R_2 = H) or triethyl orthoacetate (R_2 = CH_3) gave appropriately substituted compound **2**. Further reaction of **2** with appropriate anilines (R_8 = OCH_3, OCH_2CF_3, $OCH_2CH_2OCH_3$) gave the acyclic precursor **3** for the synthesis of quinolone **4**. Thermal cyclization of **3** in diphenyl ether gave the quinolone **4**, which could be hydrolyzed and decarboxylated by heating in diphenyl ether to provide quinolone **5**. The 3-iodoquinolone **6** was obtained by treatment of quinolone **5** with KI/I_2.[16] The 3-iodoquinolones **6** were aromitized by heating with phosphrous oxychloride to give 4-chloro-3-iodoquinolines **7**. Treatment of 4-chloro-3-iodoquinolines **7** with *o*-toluidine gave 4-(2-methylphenylamino)-3-iodoquinolines **8**. As we have been interested in applying palladium chemistry to pyridine[17] and quinoline moiety,[18] palladium-catalyzed Heck reaction with terminal alkenes was performed to afford 3-vinylquinolines **9** (Method A). For introduction of allylamine moiety, the amino group was protected with Boc group to prevent formation of p-allyl palladium complex with allylic amine substrates. The Boc group of the Heck coupling products was deprotected by trifluoroacetic acid (Method B). This reaction has proven to be quite general. The (*E*)-stereochemistry of the products was assigned by mechanistic assumption.[15]

Biological Activity

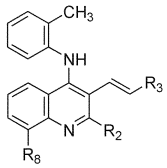
The *in vitro* inhibitory activity of the 3-vinylquinoline derivatives on gastric H^+/K^+-ATPase were examined. The IC_{50} values were determined by average of triplicate experiments and the results are presented in Table 1. SK&F 96067, a reversible gastric H^+/K^+-ATPase inhibitor, were included as a reference compound. Several compounds exhibited potent inhibitory activity on gastric H^+/K^+-ATPase.

While the substitution of 3-butyryl group in SK&F 96067 to vinyl groups substituted with ethoxy, ethoxycarbonyl, or phenyl group (entries **9a-9c**) diminished the inhibitory



Scheme 2

Table 1. *in vitro* H^+/K^+-ATPase activity of compounds



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	R_2	R_3	R_8	% Inhibition at 100 μM	IC_{50} (μM)	Synthetic method
9a	H	OEt	OCH_3	45%		A
9b	H	CO_2Et	OCH_3	24%		A
9c	H	Ph	OCH_3		88.6	A
9d	H	CH_2NHPh	OCH_3		22.1	B
9e	H	CH_2NHPh	OH	15%		C
9f	H	CH_2NHPh	OCH_2CF_3	9%		B
9g	CH_3	CH_2NHPh	OCH_3		1.1	B
9h	CH_3	CH_2NHPh	OCH_2CH_2OH	51%		C
9i	H	CH_2NHPh-2-CH_3	OCH_3		16.7	B
9j	CH_3	CH_2NHPh-2-CH_3	OCH_3	52%		B
9k	H	CH_2NHPh-2-OCH_3	OCH_3		5.3	B
9l	CH_3	CH_2NHPh-2-OCH_3	OCH_3		14.3	B
9m	H	CH_2NH-2-pyridyl	OCH_3		34.5	B
9n	CH_3	CH_2NH-2-pyridyl	OCH_3		4.9	B
9o	CH_3	CH_2NH-2-pyridyl	OCH_2CH_2OH		33.8	C
9p	H	CH_2NHCH_2Ph	OCH_3	NA		B
9q	H	CH_2OPh	OCH_3		47.3	A
9r	CH_3	CH_2OPh	OCH_3		88.6	A
9s	H	CH_2OPh-4-OCH_3	OCH_3		38.4	A
9t	CH_3	CH_2OPh-4-OCH_3	OCH_3		32.5	A
9u	H	SOPh	OCH_3	43%		A
9v	CH_3	SOPh	OCH_3		112.2	A
SK&F 96067					5.9	

activity, the substitution with allylic amine moiety retained some activity (**9d**). Further modification of side chain phenyl group, either substitution at 2-position (**9i**, **9k**) or to change to pyridine (**9m**), did not improve the activity. It was noted that 2-methoxy (**9k**) group which can make H-bond to allylic amino proton helped to regain the activity. Changing the aniline group to benzylamino, phenoxy or sulfoxide did not provide improved activities (**9p**, **9q**, **9s**, **9u**).

Although substitution at 2-position was expected to be detrimental,[9] the introduction of 2-methyl group to **9d** to obtain **9g** gave a 20-fold increase in inhibitory activity. It was suspected that the loss of activity in earlier study arose

as a consequence of the perturbation of the conformation of the 4-arylamino group through a steric interaction with the 3-acyl group. In this study, the introduction of 2-methyl group was successful for **9g** and **9n**, and somewhat helpful for **9t** and **9v**, but not for **9j**, **9l**, and **9r**. This remarkable difference may come from the different spatial arrangement between acyl moiety and vinyl moiety.

The 8-position of the quinoline ring was known to tolerate a very wide variety of substituents with rather minimal steric constraints.[5] Thus modifications at this position was expected to have little effect on *in vitro* potency, and the main emphasis would be to manipulate the physicochemical properties of the molecule to further optimize in vivo activity. Unfortunately, modification of 8-methoxy group to hydroxyl, trifluoroethoxy, or hydroxyethoxy group (**9e**, **9f**, **9h**, **9o**) was all detrimental to the activity.

In conclusion, the diverse 4-(2-methylphenylamino)-3-vinylquinoline derivatives were synthesized by intermolecular Heck reaction with terminal alkene substrates. While the compounds substituted by allylamine group at 3-position of quinoline moiety showed improved activities, the compounds substituted with hydroxyethoxy group at 8-position gave lower activities compared to the methoxy substituted compounds. The 8-methoxy-2-methyl-4-(2-methylphenylamino)-3-(3-phenylamino-1-propenyl)quinoline (**9g**) showed 5-fold increase in *in vitro* gastric H^+/K^+-ATPase inhibitory activity over SK&F 96067.

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.[17] Compounds **2-7** were prepared according to the literature procedures.[8] Where R_2 is not hydrogen or R_8 is not methoxy, the procedure was slightly modified by using the appropriate reagents. For R_8 = OCH_2CH_2OH, they were prepared by obtaining **9** (R_8 = $OCH_2CH_2OCH_3$) followed by demethylation with BBr_3.

4-Chloro-3-iodo-8-methoxyquinoline (7). A mixture of 3-iodo-8-methoxy-1*H*-quinoline-4-one (**6**, 30.1 g, 0.1 mol) in 80 mL of phosphorus oxychloride was heated under reflux for 1 h, and slowly added to ice-water after cooling. The mixture was neutralized with dilute NaOH solution. The precipitate thus obtained was filtered and dried to afford 30.3 g (95%) of the product: ^{1}H NMR ($CDCl_3$) δ 4.09 (s, 3H), 7.12 (d, 1H, J = 7.5 Hz), 7.54 (dd, 1H, J = 7.5, 8.7 Hz), 7.81 (d, 1H, J = 8.7 Hz).

3-Iodo-4-(2-methylphenylamino)-8-methoxyquinoline (8). A mixture of 4-chloro-3-iodo-8-methoxyquinoline (41.5 g, 0.13 mol), 2-methylaniline (41 g, 0.4 mol) and 200 mL of diethyleneglycol in 500 mL round bottom flask was heated at 125 °C for 4 h. After cooling, the resulting solution was poured into 600 mL of methylene chloride and washed with saturated $NaHCO_3$ solution. The organic layer was dried with anhydrous $MgSO_4$, filtered off, and evaporated the solvent. The product was obtained by column chromatography in 83% isolated yield: mp; 155-156 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 4.07 (s, 3H), 6.08 (brs, 1H), 6.51 (m, 1H), 6.96-7.30 (m, 6H), 9.07 (s, 1H); *m/e* 390 (M^+).

Method A

3-(2-Ethoxycarbonyl-1-ethenyl)-8-methoxy-4-(2-methylphenylamino)quinoline (**9b**). Palladium acetate (24 mg, 0.1 mmol), (n-Bu)$_4$NCl (480 mg, 2 mmol), KOAc (400 mg, 4 mmol), ethyl vinylacetate (400 mg, 4.0 mmol), 3-iodo-4-(2-methylphenylamino)-8-methoxyquinoline (780 mg, 4 mmol), and DMF (40 mL) were added to a pressure tube equipped with a stirring bar. After heating the reaction mixture for 2 h at 100 °C, the resulting solution was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography to provide **9b** in 30% yield as oil: ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3H, J = 7.2 Hz), 2.38 (s, 3H), 4.05 (s, 3H), 4.05 (s, 3H), 4.20 (q, 2H, J = 7.2 Hz), 6.01 (brs, 1H), 6.45 (d, 1H, J = 16.0 Hz), 6.60-7.35 (m, 7H), 7.75 (d, 1H, J = 16.4 Hz); *m/e* 362 (M^+).

Method B

8-Methoxy-4-(2-methylphenylamino)-3-(3-phenylamino-1-propenyl)quinoline (9d). Palladium acetate (18 mg, 0.75 mmol), (n-Bu)$_4$NCl (360 mg, 1.5 mmol), KOAc (300 mg, 3 mmol), *t*-butyl *N* -allyl-*N*-phenylcarbamate (700 mg, 3.0 mmol), 3-iodo-4-(2-methylphenylamino)-8-methoxyquinoline (585 mg, 3 mmol), and DMF (30 mL) were added to a pressure tube equipped with a stirring bar. After heating the reaction mixture for 2 h at 100 °C, the resulting solution was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The 8-methoxy-4-(2-methylphenylamino)-3-(3-*N*-Bocphenylamino-1-propenyl)-quinoline was obtained as intermediate. The intermediate was dissolved in CH_2Cl_2 (30 mL) and trifluroacetic acid (2 mL) was slowly added to the solution at room temperature for about 30 min. The result solution was neutralized with saturated $NaHCO_3$. The organic layer was dried with anhydrous $MgSO_4$, filtered off, and evaporated the solvent. The product was purified by column chromatography to provide **9d** in 39% isolated yield: mp 108-110 °C; ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H), 3.84 (d, 2H), 4.06 (s, 3H), 5.70 (brs, 1H), 6.27-7.32 (m, 13H), 8.91 (s, 1H); *m/e* 395 (M^+).

Method C

8-Hydroxy-4-(2-methlphenylamino)-3-(3-phenylamino-1-propenyl)quinoline (**9g**). To a mixture of 8-methoxy-4-(2-methylphenylamino)-3-(3-phenylamino-1-propenyl)quinoline (0.25 g, 0.63 mmol) in methylene chlororide (10 mL) was added boron tribromide. The mixture was stirred for 2 h at ambient temperature, washed with aqueous sodium carbonate, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford 0.15 g (63%) of **9g**:

mp 161-162 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.84 (d, 2H, J = 5.4 Hz), 5.84 (brs, 1H), 6.25-7.35 (m, 12H), 8.74 (s, 1H); *m/e* 381 (M^+).

***In vitro* screening of 4-(phenylamino)-3-vinylquinoline derivatives.** H^+/K^+-ATPase was prepared from the fundic mucosae of New Zealand white rabbits (2-3 Kg, male) as described previously.[13] 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.[19]

Prepared enzyme (25 mg) was incubated at 37 °C in 250 mL of a medium consisting of 4 mM Tris/HCl, pH 7.4, 4 mM $MgCl_2$, 5 mg/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.[20] Assay medium for the H^+/K^+-ATPase activity contained 2% methanol, which did not affect the enzyme activity.

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