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Bioorganic & Medicinal Chemistry 14 (2006) 6847–6858
Bioorganic & Medicinal Chemistry

Synthesis and biological evaluation of 4-morpholino-2-phenylquinazolines and related derivatives as novel PI3 kinase p110α inhibitors

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Received 23 May 2006; revised 19 June 2006; accepted 19 June 2006
Available online 11 July 2006

Abstract—A series of 4-morpholino-2-phenylquinazolines and related derivatives were prepared and evaluated as inhibitors of PI3 kinase p110α. In this series, the thieno[3,2-*d*]pyrimidine derivative **15e** showed the strongest inhibitory activity against p110α, with an IC_{50} value of 2.0 nM, and inhibited proliferation of A375 melanoma cells with an IC_{50} value of 0.58 μM. Moreover, **15e** was found to be selective for p110α over other PI3K isoforms and protein kinases, making it the first example of a selective PI3K p110α inhibitor.

1. Introduction

Phosphoinositide 3-kinase (PI3K) is an enzyme that catalyzes phosphorylation of the 3-hydroxyl position of phosphatidylinositides (PIs) and is known to regulate various cellular functions, including cell proliferation and survival.[1–3] The 3-phosphorylated phospholipids generated by PI3K activity bind to the pleckstrin homology (PH) domain of protein kinase B (PKB), causing translocation of PKB to the cell membrane and subsequent phosphorylation of PKB. Phosphorylated PKB inhibits apoptosis-inducing proteins such as FKHR, Bad, and caspases, and is thought to play an important role in cancer progression.[4] Negative regulation of PI3K signaling is mediated by the lipid phosphatase PTEN, which dephosphorylates products of PI3K. Loss of expression or function of PTEN occurs in many human cancers[5,6] and mutation of PTEN is one of the most common mutations in human cancers,[7] making PI3Ks potential therapeutic targets for proliferative disorders such as cancer.

The PI3Ks known to date[8–10] are divided into classes I–III, and class I is further subclassified into classes Ia and Ib. Among these isoforms, class Ia enzymes are thought to play the most important role in cell proliferation in response to growth factor-tyrosine kinase pathway activation.[11] The *PIK3CA* gene, which encodes PI3K p110α, is amplified and overexpressed in ovarian and other cancers,[12,13] and is also mutated in a spectrum of cancers.[14–17] Thus, class Ia PI3Ks, and particularly p110α, are potential targets in treatment of cancer, and their inhibitors are potential cancer therapeutic agents. To date, reported PI3K inhibitors include the fungal metabolite wortmannin and the flavonoid-related compound LY294002 (Fig. 1). Although wortmannin is a potent PI3K inhibitor with a low nanomolar IC_{50} value, it has low in vivo anti-tumor activity.[18] Moreover, wortmannin is unstable in solution, probably due to the

Keywords: PI3 kinase; p110α; Inhibitor; Cancer treatment.
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doi:10.1016/j.bmc.2006.06.046

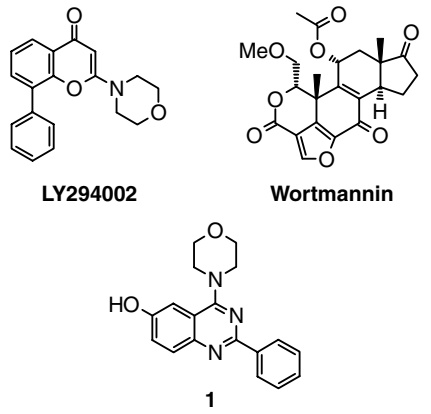


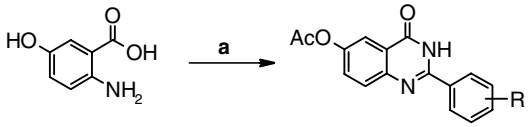
Figure 1. Structure of PI3K inhibitors.

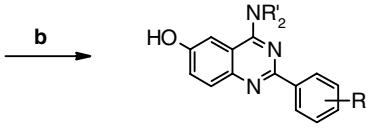
presence of a reactive furan ring.[19] LY294002 is more stable, but is a relatively weak PI3K inhibitor with an IC_{50} value of 0.63 μM.[20] Furthermore, neither wortmannin nor LY294002 exhibits selectivity among PI3K isoforms, and the lack of isoform-specific PI3K inhibitors has made it difficult to understand the biological roles of individual PI3K isoforms.[21,22] We have carried out high-throughput screening to obtain novel PI3K p110α inhibitors, and 4-morpholino-2-phenylquinazolin-6-ol **1** was discovered as a p110α inhibitor with an IC_{50} value of 1.3 μM. We now report the synthesis and evaluation of a new class of compounds derived from **1**, 4-morpholino-2-phenylquinazolines and related compounds, which are novel, potent, and highly selective PI3K p110α inhibitors.

2. Chemistry

As shown in Scheme 1, the 6-hydroxy-2-phenylquinazolines **5a–d** were prepared from 5-hydroxyanthranilic acid **2**. Condensation of **2** with phenylimidate in refluxing methanol followed by treatment with acetic anhydride afforded the known 6-acetoxyquinazolinone **3**.[23] Chlorination of **3** with phosphorus oxychloride followed by treatment with appropriate amines in refluxing THF then gave **5a–d**. The 6-hydroxy-4-(morpholino)quinazoline derivatives with a substituent on the benzene at C2, **6a–g**, were also prepared from 5-hydroxyanthranilic acid **2**. Condensation of **2** with the corresponding imidates and subsequent acetylation gave the 6-acetoxyquinazolinones **4a–g**. When the imidates were not commercially available, they were prepared by treatment of the corresponding nitriles with hydrochloric acid and ethanol. Chlorination of **4a–g** and subsequent reaction with morpholine gave **6a–g**. The ester groups of **6d** and **6e** were reduced with lithium aluminum hydride to provide **6h** and **6i**, and hydrogenation of **6f** and **6g** gave **6j** and **6k**, respectively.

For the synthesis of **10a** and **10c**, the corresponding 2-substituted phenylimidates were difficult to prepare from nitriles using the method described above; **10a** and **10c** were therefore synthesized from the known anthranilamide **7b**,[24] as shown in Scheme 2. Reaction of **7b** with acyl chlorides and cyclization under basic conditions gave the quinazolinones **8a** and **8c**, which were converted to **9a** and **9c** via demethylation with hydrobromic acid and subsequent acetylation with acetic anhydride. Chlorination of **9a** and **9c** followed

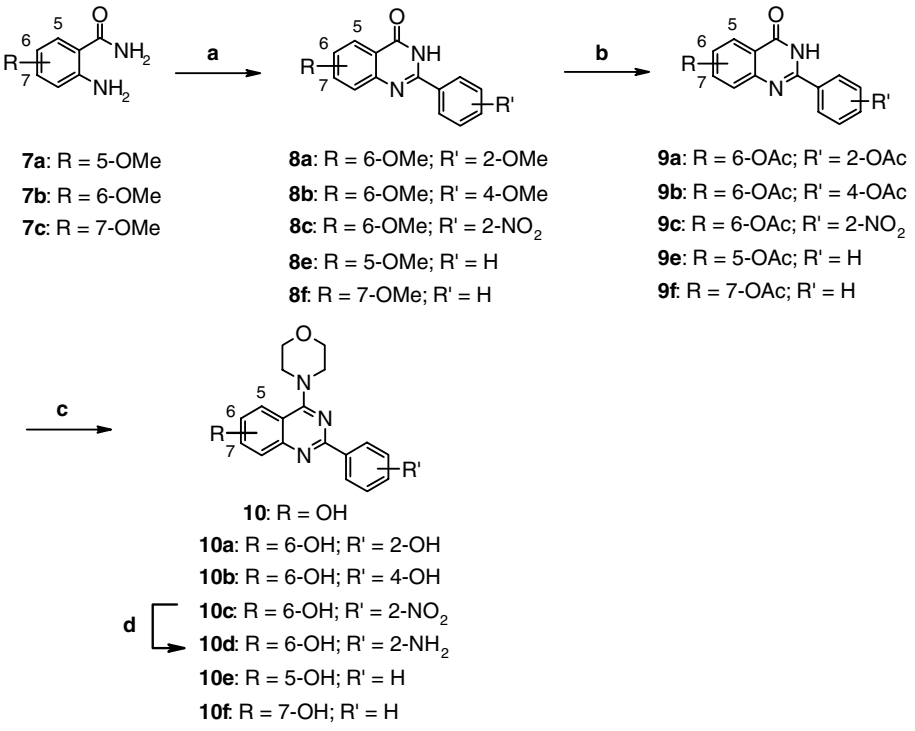




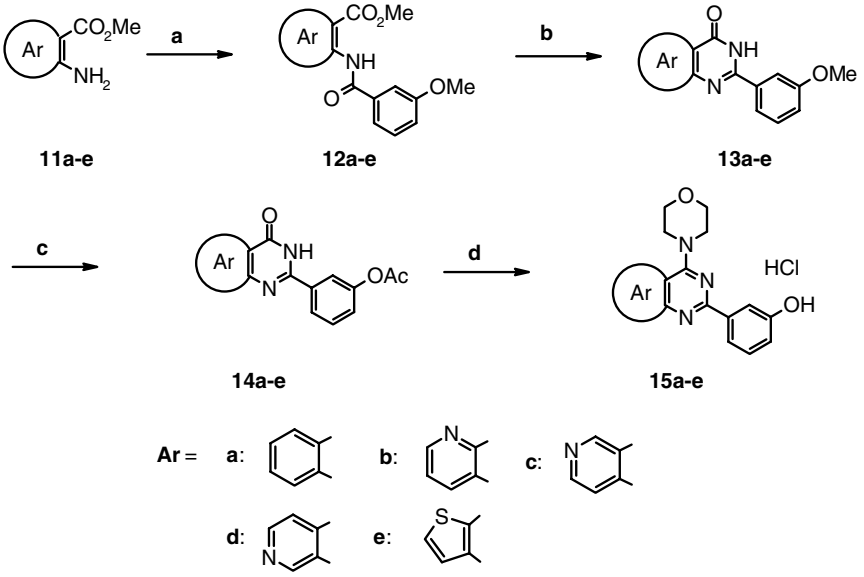
5a: NR'_2 = piperidino
5b: NR'_2 = 4-hydroxypiperidino
5c: NR'_2 = 4-oxopiperidino
5d: NR'_2 = 2-methoxyethylamino

6a: R = 3-OH
6b: R = 3-OMe
6c: R = 3-F
6d: R = 3-CO_2Me —c→ **6h**: R = 3-CH_2OH
6e: R = 4-CO_2Me —c→ **6i**: R = 4-CH_2OH
6f: R = 3-NO_2 —d→ **6j**: R = 3-NH_2
6g: R = 4-NO_2 —d→ **6k**: R = 4-NH_2

Scheme 1. Reagents and conditions: (a) (i) ethyl arylimidate hydrochloride, MeONa, MeOH, reflux; (ii) Ac_2O, AcONa, reflux; (b) (i) $POCl_3$, reflux; (ii) R_2NH, THF, reflux; (c) $LiAlH_4$, THF; (d) H_2, 10% Pd–C.



Scheme 2. Reagents and conditions: (a) (i) ArCOCl, Et_3N, THF; (ii) 2 N NaOH, MeOH, reflux; (b) (i) 48% HBr, AcOH; (ii) Ac_2O, AcONa, reflux; (c) (i) $POCl_3$, reflux; (ii) morpholine, reflux; (d) H_2, 10% Pd–C.



Scheme 3. Reagents and conditions: (a) ArCOCl, Et_3N, THF; (b) (i) 28% aq NH_3, MeOH; (ii) 2 N NaOH, MeOH, reflux; (c) (i) 48% HBr, AcOH, reflux; (ii) Ac_2O, AcONa, reflux; (d) (i) $POCl_3$, reflux; (ii) morpholine, reflux; (iii) 4 N HCl/AcOEt.

by reaction with morpholine gave **10a** and**10c**, respectively. Compounds **10b**, **10e**, and **10f** were also prepared from the appropriate methoxyanthranilamides **7a**–**c**, and **10c** was hydrogenated to provide **10d**.

The quinazoline derivative **15a**, the pyridopyrimidine derivatives **15b**–**d**, and the thienopyrimidine derivative **15e** were prepared as shown in Scheme 3. Acylation of the amino groups of **11a**–**e** with 3-methoxybenzoyl chloride provided **12a**–**e**, respectively. Treatment of **12a**–**e** with aqueous ammonium hydroxide followed by cyclization with aqueous sodium hydroxide provided **13a**–**e**, and demethylation of **13a**–**e**, acetylation, chlorination, and subsequent substitution with morpholine afforded the desired compounds **15a**–**e**, respectively.

3. Results and discussion

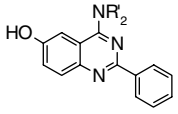
The lead compound **1** had an IC_{50} value of 1.3 μM for inhibition of p110α in an enzymatic scintillation proximity assay (SPA), which was performed using purified

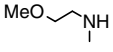
bovine p110α. In the SPA method, LY294002 inhibited p110α with an IC_{50} value of 0.63 μM, which is consistent with the IC_{50} value reported using the conventional TLC method.[20]

As shown in Table 1, the morpholino group at C4 of **1** is essential for p110α inhibitory activity; a substantial decrease in activity was observed with compound **5a**, the analogue of **1** with piperidine at C4. The importance of the morpholino group is further shown by the decreased activities of the 4-hydroxypiperidine and 4-piperidone derivatives, **5b** and **5c**, and compound **5d**, which has a 2-methoxyethylamino group at C4, showed approximately 10-fold lower activity than **1**. Interestingly, similar SARs for the morpholino group of LY294002 have been reported;[20] replacement of the morpholine of LY294002 with cyclic amines including piperidine and 4-hydroxypiperidine causes a dramatic decrease in the efficacy of these compounds against PI3K. This result suggests that the morpholine groups of **1** and LY294002 occupy the same region when bound to PI3K enzymes.

The effects on p110α inhibitory activity of introducing substituents onto the phenyl ring at C2 of **1** are shown in Table 2. While the 2- and 4-hydroxy derivatives, **10a** and **10b**, were about 2-fold less active than **1**, the 3-hydroxy derivative **6a** (IC_{50} value of 0.075 μM) was about 15-fold more potent than **1**. Replacement of the 3-hydroxy group of **6a** with a 3-methoxy group or a 3-fluoro group resulted in a decrease in activity (IC_{50} values of 0.60 and 1.8 μM for **6b** and **6c**, respectively). The 4-hydroxymethyl derivative **6i** had decreased activity in comparison with **1** (IC_{50} value of 3.7 μM), while the 3-hydroxymethyl derivative **6h** had an increased activity

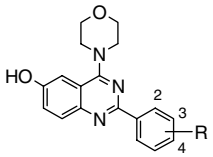
Table 1. Inhibition of p110α activity by 4-amino-substituted 6-hydroxy-2-phenylquinazolines



Compound	NR'_2	IC_{50}[a] (μM)
1		1.3
5a		>60
5b		12
5c		21
5d		15
LY294002		0.63

[a] IC_{50} values are means of at least two separate determinations with typical variations of less than ±20%.

Table 2. Inhibition of p110α activity by 4-morpholin-4-yl-2-phenyl-quinazolin-6-ols



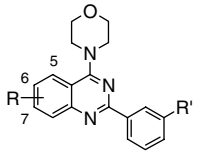
Compound	R	IC_{50}[a] (μM)
1	H	1.3
10a	2-OH	2.9
6a	3-OH	0.075
10b	4-OH	2.8
6b	3-OMe	0.60
6c	3-F	1.8
6h	3-CH_2OH	0.10
6i	4-CH_2OH	3.7
10d	2-NH_2	3.9
6j	3-NH_2	0.44
6k	4-NH_2	0.93

[a] IC_{50} values are means of at least two separate determinations with typical variations of less than ±20%.

(IC_{50} value of 0.10 μM). With respect to the amino derivatives, the positional trend was similar to those seen for the hydroxy and hydroxymethyl derivatives; that is, the 3-amino derivative **6j** was more active than the 2- and 4-amino substituted derivatives, **10d** and **6k**.

The effect of varying the position of the hydroxy group on the quinazoline ring of **1** was also investigated, as shown in Table 3. The 7-hydroxy derivative **10f** was about 8-fold less active than **1**, and a further decrease in activity was observed with the 5-hydroxy derivative **10e**. The 6-methoxy analogue **10g** was only slightly less potent than **1**, and surprisingly removal of the 6-hydroxy group of **1** resulted in only a 10-fold decrease in activity (**10h**: IC_{50} value of 14 μM), while removal of the 6-hydroxy group of **6a** retained activity (**15a**: IC_{50} value of 0.056 μM). These data suggest that the 6-hydroxy group is not essential for p110α inhibitory activity in analogues with a 3-hydroxyphenyl group at C2 of quinazoline ring.

Table 3. Inhibition of p110α activity by 4-morpholin-4-yl-2-phenyl-quinazolines



Compound	R	R′	IC_{50}[a] (μM)
1	6-OH	H	1.3
6a	6-OH	3-OH	0.075
10e	5-OH	H	>30
10f	7-OH	H	9.8
10g	6-OMe	H	2.1
10h	H	H	14
15a	H	3-OH	0.056

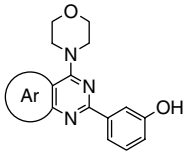
[a] IC_{50} values are means of at least two separate determinations with typical variations of less than ±20%.

Finally, the effects of exchanging the quinazoline ring of **15a** with other heterocycles are listed in Table 4. The activities of these derivatives against A375 tumor cell proliferation were also evaluated. Regarding the pyridopyrimidine derivatives, the pyrido[3,2-*d*]pyrimidine **15b**, the pyrido[4,3-*d*]pyrimidine **15c**, and the pyrido[3,4-*d*]-pyrimidine **15d** all suppressed both p110α activity and cell proliferation from 2- to 4-fold more than **15a**; these results suggest that the position of the nitrogen atom on the pyridine ring is not a crucial determinant of p110α inhibitory activity. Replacement of the quinazoline ring with thieno[3,2-*d*]pyrimidine afforded **15e**, which showed the highest activity in this series in both the enzyme (IC_{50} value of 0.0020 μM) and cellular (IC_{50} value of 0.58 μM) assays.

To determine whether **15e** inhibits intracellular PI3K in A375 cells, the effect of **15e** on fetal bovine serum-induced PKB phosphorylation was evaluated. As shown in Figure 2, serum-induced PKB phosphorylation was suppressed by **15e** with an IC_{50} value of 0.3–3 μM, which is consistent with the IC_{50} value in the cell proliferation assay. This result indicates that **15e** suppresses A375 cell proliferation by inhibition of intracellular PI3K.

To check selectivity for p110α, the most active compound **15e** and LY294002 were evaluated against other PI3K isoforms (Table 5). LY294002 exhibited no selectivity for p110α over p110β, a class Ia PI3K, and only showed 3- to 4-fold selectivities over p110γ (class Ib) and PI3K C2β (class II). On the other hand, **15e** showed about 10-fold selectivity for p110α over p110β and was >100-fold more selective for p110α versus p110γ and PI3K C2β, showing that **15e** is a p110α inhibitor with greater isoform selectivity than LY294002. Next, we investigated the selectivity of **15e** for p110α over other protein kinases, including PKA, KDR, PKCα, and cyclin E/CDK2. The inhibitory activities against these protein kinases were 91, 3.4, 466, and 28 μM, respectively, indicating a greater than 1000-fold selectivity of **15e** for p110α over these kinases.

Table 4. Inhibition of p110α activity and A375 cell proliferation by 3-(4-morpholin 4-ylquinazolin-2-yl)phenol and related heterocycles



Compound	Ar	IC_{50}[a] (μM)	
		p110α	A375
15a		0.056	5.7
15b		0.027	3.1
15c		0.013	3.5
15d		0.019	2.8
15e		0.0020	0.58

[a] IC_{50} values are means of at least two separate determinations with typical variations of less than ±20% for both the p110α enzyme assay and the A375 cell proliferation assay.

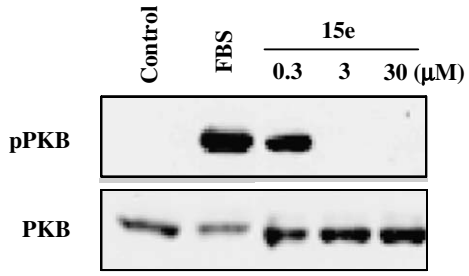


Figure 2. Effect of **15e** on fetal bovine serum-mediated PKB phosphorylation in A375 cells. Cells were grown to confluence in 12-well plates and growth-arrested in serum-free medium overnight. The cells were then exposed to the indicated concentrations of **15e** for 1 h and subsequently stimulated with fetal bovine serum (FBS) for 15 min. The cell lysate was subjected to SDS–PAGE and Western blot analysis.

Table 5. Inhibition of PI3K isoforms by LY294002 and **15e**

Compound	IC_{50}[a] (μM)			
	p110α	p110β	p110γ	PI3K C2β
LY294002	0.63	0.34	1.6	2.1
15e	0.0020	0.016	0.66	0.22

[a] IC_{50} values are means of at least two separate determinations with typical variations of less than ±20%.

4. Conclusion

We have reported the SARs for p110α inhibition by a series of 4-morpholino-2-phenylquinazolines and related analogues. The lead compound **1**, which was discovered in our chemical library, is a novel p110α inhibitor with an IC_{50} value of 1.3 μM. The morpholino group of **1** is essential for p110α inhibitory activity. Introduction of a 3-hydroxy group on the phenyl group of **1** resulted in significantly greater p110α inhibitory activity. Replacement of the quinazoline ring with a thieno[3,2-*d*]pyrimidine ring resulted in **15e**, which inhibited p110α with an IC_{50} value of 2.0 nM and suppressed A375 tumor cell proliferation with a submicromolar IC_{50}. Furthermore, **15e** is a highly selective inhibitor for p110α among other kinases, making it the first example of a p110α-selective PI3K inhibitor. Other types of selective p110α inhibitors will be reported in future publications.

5. Experimental

5.1. Chemistry

^{1}H NMR spectra were measured with a JEOL EX400 or GX500 spectrometer; chemical shifts are expressed in δ units using tetramethylsilane as the standard (in NMR description, s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet, and br, broad peak). Mass spectra were recorded with a Hitachi M-80 or JEOL JMS-DX300 spectrometer. Silica gel column chromatography was performed by Wakogel C-200 or Merck Silica gel 60.

5.1.1. 3-[6-(Acetyloxy)-4-oxo-3,4-dihydroquinazolin-2-yl]phenyl acetate (4a). HCl gas was bubbled through a solution of 3-hydroxybenzonitrile (3.6 g, 30 mmol) in a mixture of $CHCl_3$ (50 mL), EtOH (3 mL), and dioxane (10 mL) with cooling below 10 °C for 15 min. After standing at 5 °C for 18 h, the resulting solid was collected and washed with Et_2O to give ethyl 3-hydroxybenzenecarboximidoate hydrochloride as a light pink solid (5.3 g, 87%); ^{1}H NMR (DMSO-d_6) δ 1.47 (3H, t, J = 6.9 Hz), 4.63 (2H, q, J = 6.9 Hz), 7.20–7.28 (1H, m), 7.39–7.47 (2H, m), 7.54–7.60 (1H, m), 10.35 (1H, br s), 11.71 (1H, br s); FAB-MS *m*/*e* $(MH)^+$ 166.

A mixture of ethyl 3-hydroxybenzenecarboximidoate hydrochloride (5.3 g, 26 mmol), **2** (3.1 g, 20 mmol), and NaOMe (1.1 g, 20 mmol) in MeOH (100 mL) was refluxed for 0.5 h. After cooling to room temperature, the reaction mixture was poured into water, and the resulting solid was collected by filtration, and washed with $CHCl_3$ to afford crude 6-hydroxy-2-(3-hydroxyphenyl)quinazolin-4(3*H*)-one. To the obtained gray solid, NaOAc (120 mg) and Ac_2O (36 mL) were added and the reaction mixture was heated at reflux for 0.5 h. After cooling to room temperature, the resulting precipitate was collected by filtration and washed with MeOH to give **4a** (1.2 g, 18%) as a colorless solid; ^{1}H NMR (DMSO-d_6) δ 2.33 (6H, s), 7.33–7.41 (1H, m), 7.55–7.66 (2H, m), 7.76–7.90 (2H, m), 7.94–8.00 (1H, m), 8.04–8.12 (1H, m), 12.65 (1H, br s); FAB-MS *m*/*e* $(MH)^+$ 339.

5.1.2. 2-(3-Methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-6-yl acetate (4b). Compound **4c** was prepared from ethyl 3-methoxybenzenecarboximidoate hydrochloride[25] and **2** according to the same procedure as that for **4a**. Compound **4b** was obtained as a colorless solid (29% yield); ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 3.87 (3H, s), 7.12–7.20 (1H, m), 7.47 (1H, t, J = 7.8 Hz), 7.58–7.65 (1H, m), 7.72–7.89 (4H, m), 12.61 (1H, br s); FAB-MS *m*/*e* $(MH)^+$ 311.

5.1.3. 2-(3-Fluorophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl acetate (4c). Compound **4c** was prepared from ethyl 3-fluorobenzenecarboximidoate hydrochloride[25] and **2** according to the same procedure as that for **4a**. Compound **4c** was obtained as a colorless solid (13% yield); ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 7.40–7.50 (1H, m), 7.55–7.67 (2H, m), 7.78–7.90 (2H, m), 7.96–8.09 (2H, m), 12.68 (1H, br s); FAB-MS *m*/*e* $(MH)^+$ 299.

5.1.4. Methyl 3-[6-(acetyloxy)-4-oxo-3,4-dihydroquinazolin-2-yl]benzoate (4d). HCl gas was bubbled through a solution of methyl 3-cyanobenzoate[26] (4.9 g, 30 mmol) in $CHCl_3$ (50 mL) and EtOH (3mL) for 15 min with cooling below 10 °C. After standing at 5 °C for 17h, the reaction mixture was concentrated and the resulting solid was washed with Et_2O to give methyl 3-[ethoxy(imino)methyl]benzoate hydrochloride as a colorless solid (3.2 g, 43%); ^{1}H NMR (DMSO-d_6) δ 1.50 (3H, t, J = 6.9 Hz), 3.92 (3H, s), 4.65 (2H, q, J = 6.9 Hz), 7.76–7.85 (1H, m), 7.29–8.42 (2H, m), 8.55–8.60 (1H, m); FAB-MS *m*/*e* $(MH)^+$ 208.

Compound **4d** was prepared from methyl 3-[ethoxy(imino)methyl]benzoate hydrochloride and **2** according to the same procedure as that for **4a**. Compound **4d** was obtained as a colorless solid (32% yield); ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 3.92 (3H, s), 7.60–7.76 (2H, m), 7.81–7.90 (2H, m), 8.11–8.20 (1H, m), 8.38–8.45 (1H, m), 8.75–8.79 (1H, m), 12.82 (1H, br s); FAB-MS *m*/*e* $(MH)^+$ 339.

5.1.5. Methyl 4-[6-(acetyloxy)-4-oxo-3,4-dihydroquinazolin-2-yl]benzoate (4e). To a solution of methyl 4-cyanobenzoate (4.8 g, 30 mmol) in EtOH (12 mL) was added 4 N HCl/AcOEt. After standing at room temperature for 23 h, Et_2O was added to the reaction mixture and the resulting solid was collected to give methyl 4-[ethoxy(imino)methyl]benzoate hydrochloride as a colorless solid (4.8 g, 66%); ^{1}H NMR (DMSO-d_6) δ 1.49 (3H, t, J = 6.9 Hz), 3.91 (3H, s), 4.63 (2H, q, J = 6.9 Hz), 8.13–8.25 (4H, m); FAB-MS *m*/*e* $(MH)^+$ 208.

Compound **4e** was prepared from methyl 4-[ethoxy(imino)methyl]benzoate hydrochloride and **2** according to the same procedure as that for **4a**. Compound **4e** was obtained as a colorless solid (46% yield); ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 3.91 (3H, s), 7.60–7.68 (1H, m), 7.79–7.91 (2H, m), 8.07–8.14 (2H, m), 8.27–8.35 (2H, m), 12.76 (1H, br s); FAB-MS *m*/*e* $(MH)^+$ 339.

5.1.6. 2-(3-Nitrophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl acetate (4f). Compound **4f** was prepared from ethyl 3-nitrobenzenecarboximidoate hydrochloride[27,28] and **2** according to the same procedure as that for **4a**. Compound **4a** was obtained as a colorless solid (43% yield); ^{1}H NMR (DMSO-d_6) δ 2.34 (3H, s), 7.61–7.69 (1H, m), 7.81–7.91 (2H, m), 8.39–8.47 (1H, m), 8.57–8.65 (1H, m), 8.99–9.04 (1H, m), 12.94 (1H, br s); FAB-MS *m*/*e* $(MH)^+$ 326.

5.1.7. 2-(4-Nitrophenyl)-4-oxo-3,4-dihydroquinazolin-6-yl acetate (4g). Compound **4g** was prepared from ethyl 4-nitrobenzenecarboximidoate hydrochloride[28] and **2** according to the same procedure as that for **4a**. Compound **4g** was obtained as a pale yellow solid (44% yield); ^{1}H NMR (DMSO-d_6) δ 2.34 (3H, s), 7.62–7.70 (1H, m), 7.81–7.92 (2H, m), 8.40 (4H, s), 12.90 (1H, br s); FAB-MS *m*/*e* $(MH)^+$ 326.

5.1.8. 2-Phenyl-4-piperidin-1-ylquinazolin-6-ol (5a). A mixture of piperidine (3 mL) and 4-chloro-2-phenylqui-

nazolin-6-yl acetate[23] (600 mg, 2.0 mmol) in THF (10 mL) was refluxed for 3 h. After concentration in vacuo, the resulting residue was dissolved in $CHCl_3$, washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was chromatographed on silica gel eluting with hexane/AcOEt (3:1) and crystallized from AcOEt to give **5a** (565 mg, 89%) as a colorless solid: mp 260–262 °C; ^{1}H NMR (DMSO-d_6) δ 1.65–1.85 (6H, m), 3.60–3.75 (4H, m), 7.23 (1H, d, J = 2.4 Hz), 7.36 (1H, dd, J = 2.4, 9.3 Hz), 7.41–7.53 (3H, m), 7.77 (1H, d, J = 9.3 Hz), 8.40–8.50 (2H, m), 10.08 (1H, s); FAB-MS *m/e* $(MH)^+$ 306; Anal. Calcd for $C_{19}H_{19}N_3O{\cdot}0.6H_2O$: C, 72.18; H, 6.44; N, 13.29. Found: C, 72.23; H, 6.21; N, 13.00.

5.1.9. 4-(4-Hydroxypiperidin-1-yl)-2-phenylquinazolin-6-ol (5b). Compound **5b** was prepared from 4-chloro-2-phenylquinazolin-6-yl acetate and 4-hydroxypiperidine according to the same procedure as that for **5a**. Compound **5b** was obtained as a colorless solid (59% yield): mp 249–250 °C (AcOEt/hexane); ^{1}H NMR (DMSO-d_6) δ 1.55–1.75 (2H, m), 1.90–2.05 (2H, m), 3.20–3.40 (2H, m), 3.75–3.90 (1H, m), 3.95–4.15 (2H, m), 4.81 (1H, d, J = 4.4 Hz), 7.24 (1H, d, J = 2.4 Hz), 7.36 (1H, dd, J = 2.4, 9.6 Hz), 7.42–7.53 (3H, m), 7.77 (1H, d, J = 9.6 Hz), 8.40–8.50 (2H, m), 10.08 (1H, s); FAB-MS *m/e* $(MH)^+$ 322; Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.07. Found: C, 71.03; H, 5.97; N, 13.03.

5.1.10. 1-(6-Hydroxy-2-phenylquinazolin-4-yl)piperidin-4-one (5c). To a solution of piperidin-4-one hydrochloride (600 mg, 4.4 mmol) and 4-chloro-2-phenylquinazolin-6-yl acetate (650 mg, 2.2 mmol) in DMF (10 mL) was added $NaHCO_3$ (600 mg, 7.1 mmol) and the reaction mixture was heated at 55 °C for 8 h. After the reaction mixture was concentrated in vacuo, the residue was diluted with AcOEt and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated. The resulting solid was recrystallized from AcOEt/hexane to give **5c** (340 mg, 48%) as a colorless solid: mp 258–262 °C (dec); ^{1}H NMR (DMSO-d_6) δ 2.62–2.70 (4H, m), 4.02–4.10 (4H, m), 7.31–7.55 (5H, m), 7.82 (1H, d, J = 8.8 Hz), 8.42–8.50 (2H, m), 10.14 (1H, s); FAB-MS *m/e* $(MH)^+$ 318; Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.24; H, 5.45; N, 12.89.

5.1.11. 4-[(2-Methoxyethyl)amino]-2-phenylquinazolin-6-ol (5d). Compound **5d** was prepared from 4-chloro-2-phenylquinazolin-6-yl acetate and (2-methoxyethyl)amine according to the same procedure as that for **5a**. Compound **5d** was obtained as a colorless solid (400 mg, 62%): mp 212–215 °C (AcOEt/hexane); ^{1}H NMR (DMSO-d_6) δ 3.31 (3H, s), 3.67 (2H, t, J = 5.8 Hz), 3.78–3.86 (2H, m), 7.30–7.51 (5H, m), 7.65 (1H, d, J = 8.8 Hz), 8.04 (1H, br), 8.40–8.50 (2H, m), 9.88 (1H, s); FAB-MS *m/e* $(MH)^+$ 296; Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.20; H, 5.89; N, 14.28.

5.1.12. 2-(3-Hydroxyphenyl)-4-morpholin-4-ylquinazolin-6-ol (6a). Compound **4a** (1.2 g, 3.6 mmol) in phosphorus oxychloride (15 mL) was refluxed for 1 h. The reaction mixture was evaporated and dried in vacuo. The residue was dissolved in $CHCl_3$, washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Morpholine (20 mL) was added to the resulting residue in toluene (40 mL) and the reaction mixture was refluxed for 14 h. After evaporation, the residue was chromatographed on silica gel eluting with $CHCl_3$/MeOH (15:1) and recrystallized from $CHCl_3$/MeOH/hexane to give **6a** (601 mg, 51%) as a pale yellow solid: mp 280–284 °C; ^{1}H NMR (DMSO-d_6) δ 3.64–3.72 (4H, m), 3.82–3.91 (4H, m), 6.83–6.89 (1H, m), 7.25–7.31 (2H, m), 7.37 (1H, dd, J = 2.4, 8.7 Hz), 7.79 (1H, d, J = 9.3 Hz), 7.87–7.93 (2H, m), 9.49 (1H, s), 10.12 (1H, s); FAB-MS *m/e* $(MH)^+$ 324; Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.50; H, 5.25; N, 12.97.

5.1.13. 2-(3-Methoxyphenyl)-4-morpholin-4-ylquinazolin-6-ol (6b). Compound **6b** was prepared from **4b** according to the same procedure as that for **6a**. Compound **6b** was obtained as a colorless solid (59% yield): mp 226–228 °C ($CHCl_3$/MeOH/hexane); ^{1}H NMR (DMSO-d_6) δ 3.66–3.71 (4H, m), 3.83–3.88 (7H, m), 7.02–7.08 (1H, m), 7.26 (1H, d, J = 2.4 Hz), 7.35–7.45 (2H, m), 7.81 (1H, d, J = 9.3 Hz), 7.98–8.01 (1H, m), 8.02–8.07 (1H, m), 10.13 (1H, s); FAB-MS *m/e* $(MH)^+$ 338; Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.33; H, 5.65; N, 12.39.

5.1.14. 2-(3-Fluorophenyl)-4-morpholin-4-ylquinazolin-6-ol (6c). Compound **6c** was prepared from **4c** according to the same procedure as that for **6a**. Compound **6c** was obtained as a colorless solid (51% yield): mp 270–274 °C ($CHCl_3$/MeOH/hexane); ^{1}H NMR (DMSO-d_6) δ 3.67–3.75 (4H, m), 3.82–3.90 (4H, m), 7.26–7.35 (2H, m), 7.41 (1H, dd, J = 2.4, 8.8 Hz), 7.51–7.59 (1H, m), 7.83 (1H, d, J = 8.8 Hz), 8.12–8.18 (1H, m), 8.26–8.33 (1H, m), 10.20 (1H, s); FAB-MS *m/e* $(MH)^+$ 326; Anal. Calcd for $C_{18}H_{16}N_3O_2F$: C, 66.45; H, 4.96; N, 12.92; F, 5.84. Found: C, 66.39; H, 4.96; N, 12.87; F, 5.95.

5.1.15. Methyl 3-(6-hydroxy-4-morpholin-4-ylquinazolin-2-yl)benzoate (6d). Compound **6d** was prepared from **4d** according to the same procedure as that for **6a**. Compound **6d** was obtained as a pale brown solid (35% yield): mp 184–186 °C ($CHCl_3$/MeOH/Et_2O/hexane); ^{1}H NMR (DMSO-d_6) δ 3.67–3.75 (4H, m), 3.83–3.95 (7H, m), 7.28 (1H, d, J = 2.4 Hz), 7.41 (1H, dd, J = 1.5, 8.3), 7.66 (1H, t, J = 7.8 Hz), 7.86 (1H, d, J = 9.3 Hz), 8.05 (1H, d, J = 7.9 Hz), 8.70 (1H, d, J = 7.8 Hz), 9.00–9.06 (1H, m), 10.19 (1H, s); FAB-MS *m/e* $(MH)^+$ 366; Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.56; H, 5.31; N, 11.62.

5.1.16. Methyl 4-(6-hydroxy-4-morpholin-4-ylquinazolin-2-yl)benzoate (6e). Compound **6e** was prepared from **4e** according to the same procedure as that for **6a**. Compound **6e** was obtained as a colorless solid (34% yield): mp 239–241 °C ($CHCl_3$/MeOH/Et_2O); ^{1}H NMR (DMSO-d_6) δ 3.68–3.74 (4H, m), 3.84–3.92 (7H, m), 7.28 (1H, d, J = 2.9 Hz), 7.41 (1H, dd, J = 2.4, 9.3), 7.84 (1H, d, J = 9.2 Hz), 8.05–8.11 (2H, m), 8.53–8.59 (2H, d, J = 7.8 Hz), 10.23 (1H, s); FAB-MS *m/e*

$(MH)^+$ 366; Anal. Calcd for $C_{20}H_{19}N_3O_4$: C, 65.74; H, 5.24; N, 11.50. Found: C, 65.63; H, 5.18; N, 11.67.

5.1.17. 4-Morpholin-4-yl-2-(3-nitrophenyl)quinazolin-6-ol (6f). Compound **6f** was prepared from **4f** according to the same procedure as that for **6a**. Compound **6f** was obtained as a yellow solid (52% yield): mp 226–227 °C ($CHCl_3$/toluene); ^1H NMR (DMSO-d_6) δ 3.69–3.78 (4H, m), 3.83–3.92 (4H, m), 7.29 (1H, d. J = 3.0 Hz), 7.42 (1H, dd, J = 2.4, 8.8 Hz), 7.80 (1H, t, J = 7.8 Hz), 7.87 (1H, d, J = 8.8 Hz), 8.29–8.35 (1H, m), 8.81–8.87 (1H, m), 9.14–9.18 (1H, m), 10.25 (1H, br s); FAB-MS m/e $(MH)^+$ 353; Anal. Calcd for $C_{18}H_{16}N_4O_4{\cdot}0.2H_2O$: C, 60.74; H, 4.64; N, 15.74. Found: C, 60.62; H, 4.46; N, 15.60.

5.1.18. 4-Morpholin-4-yl-2-(4-nitrophenyl)quinazolin-6-ol (6g). Compound **6g** was prepared from **4g** according to the same procedure as that for **6a**. Compound **6g** was obtained as a yellow solid (76% yield): mp 266–269 °C ($CHCl_3$); ^1H NMR (DMSO-d_6) δ 3.70–3.78 (4H, m), 3.82–3.90 (4H, m), 7.29 (1H, d. J = 2.4 Hz), 7.43 (1H, dd, J = 2.4, 8.8 Hz), 7.87 (1H, t, J = 8.8 Hz), 8.32–8.38 (2H, m), 8.63–8.70 (2H, m), 10.29 (1H, br s); FAB-MS m/e $(MH)^+$ 353; Anal. Calcd for $C_{18}H_{16}N_4O_40.2H_2O$: C, 60.74; H, 4.64; N, 15.74. Found: C, 60.76; H, 4.54; N, 15.86.

5.1.19. 2-[(3-Hydroxymethyl)phenyl]-4-morpholin-4-ylquinazolin-6-ol (6h). To a solution of **6d** (325 mg, 0.89 mmol) in THF (40 mL) was added $LiAlH_4$ (67 mg, 1.8 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched by the addition of water (0.1 mL), 1 N NaOH (0.1 mL), and water (0.3 mL). The reaction mixture was dried over anhydrous Na_2SO_4, filtered through a pad of silica gel, and concentrated in vacuo. The resulting solid was recrystallized from THF/hexane to give **6h** (158 mg, 52%) as a colorless solid: mp 204–206 °C; ^1H NMR (DMSO-d_6) δ 3.65–3.75 (4H, m), 3.82–3.94 (4H, m), 4.60 (2H, d, J = 5.8 Hz), 5.28 (1H, t, J = 5.8 Hz), 7.27 (1H, d, J = 2.5 Hz), 7.35–7.48 (3H, m), 7.82 (1H, d, J = 9.3 Hz), 8.29–8.36 (1H, m), 8.40–8.45 (1H, m), 10.13 (1H, s); FAB-MS m/e $(MH)^+$ 338; Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.60; H, 5.77; N, 12.29.

5.1.20. 2-[(4-Hydroxymethyl)phenyl]-4-morpholin-4-ylquinazolin-6-ol (6i). Compound **6i** was prepared from **6e** according to the same procedure as that for **6h**. Compound **6i** was obtained as a colorless solid (50% yield): mp 260–263 °C; ^1H NMR (DMSO-d_6) δ 3.64–3.74 (4H, m), 3.80–3.91 (4H, m), 4.58 (2H, d, J = 5.4 Hz), 5.26 (1H, t, J = 5.8 Hz), 7.26 (1H, d, J = 2.9 Hz), 7.38 (1H, dd, J = 2.4, 8.8 Hz), 7.44 (2H, d, J = 8.3 Hz), 7.80 (1H, d, J = 9.3 Hz), 8.37–8.45 (2H, m), 10.11 (1H, s); FAB-MS m/e $(MH)^+$ 338; Anal. Calcd for $C_{19}H_{19}N_3O_3{\cdot}0.3H_2O$: C, 66.58; H, 5.76; N, 12.26. Found: C, 66.36; H, 5.59; N, 12.10.

5.1.21. 2-(3-Aminophenyl)-4-morpholin-4-ylquinazolin-6-ol (6j). To a solution of **6f** (860 mg, 2.4 mmol) in a mixture of methanol (30 mL), ethanol (30 mL), and THF (30 mL) was added 10% Pd–C (130 mg). After stirring in a hydrogen atmosphere at room temperature for 2 h, the reaction mixture was filtered through a pad of Celite and the filtrate was evaporated. The residue was recrystallized from MeOH/EtOH to give **6j** (571 mg, 73%) as a colorless solid: mp 274–277 °C; ^1H NMR (DMSO-d_6) δ 3.60–3.70 (4H, m), 3.80–3.90 (4H, m), 5.17 (2H, br s), 6.61–6.70 (1H, m), 7.12 (1H, t, J = 7.8 Hz), 7.25 (1H, d, J = 2.5 Hz), 7.37 (1H, dd, J = 2.4, 8.8 Hz), 7.60–7.65 (1H, m), 7.69–7.73 (1H, m), 7.76 (1H, d, J = 9.2 Hz), 10.08 (1H, s); FAB-MS m/e $(MH)^+$ 323; Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38. Found: C, 66.94; H, 5.74; N, 17.32.

5.1.22. 2-(4-Aminophenyl)-4-morpholin-4-ylquinazolin-6-ol (6k). Compound **6k** was prepared from **6g** according to the same procedure as that for **6j**. Compound **6k** was obtained as a pale yellow solid (26% yield): mp 285 °C (MeOH/$CHCl_3$/hexane); ^1H NMR (DMSO-d_6) δ 3.57–3.67 (4H, m), 3.80–3.90 (4H, m), 5.51 (2H, br s), 6.59–6.66 (2H, m), 7.21 (1H, d, J = 3.0 Hz), 7.31 (1H, dd, J = 2.4, 8.8 Hz), 7.69 (1H, d, J = 8.8 Hz), 8.11–8.18 (2H, m), 9.95 (1H, s); FAB-MS m/e $(MH)^+$ 323; Anal. Calcd for $C_{18}H_{18}N_4O_2{\cdot}0.1CHCl_3$: C, 65.03; H, 5.46; N, 16.76. Found: C, 64.93; H, 5.40; N, 16.85.

5.1.23. 6-Methoxy-2-(2-methoxyphenyl)quinazolin-4(3*H*)-one (8a). To an ice-cooled solution of 2-amino-5-methoxybenzamide (**7b**)[24] (570 mg, 3.4 mmol) and Et_3N (720 mg, 7.1 mmol) in THF (10 mL) was added 2-methoxybenzoyl chloride (710 mg, 4.2 mmol). After stirring for 3h at room temperature, the reaction mixture was concentrated in vacuo and then MeOH (30 mL) and 2 N NaOH (20 mL) were added to the resulting residue. The reaction mixture was refluxed for 14 h and acidified with concentrated HCl. The resulting precipitate was collected by filtration to give **8a** (710 mg, 73%) as a colorless solid; ^1H NMR (DMSO-d_6) δ 3.88 (3H, s), 3.92 (3H, s), 7.13 (1H, t, J = 7.8 Hz), 7.24 (1H, d, J = 8.3 Hz), 7.49–7.63 (3H, m), 7.72 (1H, dd, J = 1.5, 7.8 Hz), 7.80 (1H, d, J = 8.8 Hz); FAB-MS m/e $(MH)^+$ 283.

5.1.24. 6-Methoxy-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one (8b). Compound **8b** was prepared from **7b** and 4-methoxybenzoyl chloride according to the same procedure as that for **8a**. Compound **8b** was obtained as a colorless solid (82% yield); ^1H NMR (DMSO-d_6) δ 3.85 (3H, s), 3.89 (3H, s), 7.08 (2H, d, J = 8.8 Hz), 7.43 (1H, dd, J = 2.9, 8.8 Hz), 7.53 (1H, d, J = 2.9 Hz), 7.68 (1H, d, J = 8.8 Hz), 8.16 (2H, d, J = 8.8 Hz), 12.38 (1H, br s); FAB-MS m/e $(MH)^+$ 283.

5.1.25. 6-Methoxy-2-(2-nitrophenyl)quinazolin-4(3*H*)-one (8c). Compound **8c** was prepared from **7b** and 2-nitrobenzoyl chloride according to the same procedure as that for **8a**. Compound **8c** was obtained as a pale yellow solid (85% yield); ^1H NMR (DMSO-d_6) δ 3.91 (3H, s), 7.39–8.00 (6H, m), 8.21 (1H, d, J = 7.8 Hz); FAB-MS m/e $(MH)^+$ 298.

5.1.26. 5-Methoxy-2-phenylquinazolin-4(3*H*)-one (8e). Compound **8e** was prepared from **7a**[29] and benzoyl

chloride according to the same procedure as that for **8a**. Compound **8e** was obtained as a colorless solid (93% yield): ^{1}H NMR (DMSO-d_6) δ 3.89 (3H, s), 7.02 (1H, d, J = 8.3 Hz), 7.26 (1H, d, J = 8.3 Hz), 7.50–7.62 (3H, m), 7.71 (1H, t, J = 8.3 Hz), 8.15–8.20 (2H, m), 12.20 (1H, br s); FAB-MS *m/e* (MH)$^+$ 253.

5.1.27. 7-Methoxy-2-phenylquinazolin-4(3*H*)-one (8f).[30] Compound **8f** was prepared from **7c**[31] and benzoyl chloride according to the same procedure described for **8a**. Compound **8f** was obtained as a colorless solid (75% yield): ^{1}H NMR (DMSO-d_6) δ 3.92 (3H, s), 7.10 (1H, dd, J = 2.5, 8.8 Hz), 7.19 (1H, d, J = 2.5 Hz), 7.52–7.62 (3H, m), 8.06 (1H, d, J = 8.8 Hz), 8.16–8.21 (2H, m), 12.41 (1H, br s); FAB-MS *m/e* (MH)$^+$ 253.

5.1.28. 2-[6-(Acetyloxy)-4-oxo-3,4-dihydroquinazolin-2-yl]phenyl acetate (9a). A mixture of **8a** (690 mg, 2.4 mmol), 48% HBr (50 mL), and AcOH (50 mL) was refluxed for 48 h. The reaction mixture was concentrated in vacuo. Acetic anhydride (30 mL) and NaOAc (100 mg) were added to the resulting residue and the reaction mixture was heated at reflux for 0.5 h. After concentration, the solid obtained was washed with methanol and Et_2O to give **9a** (525 mg, 67%) as a colorless solid; ^{1}H NMR (DMSO-d_6) δ 2.18 (3H, s), 2.33 (3H, s), 7.28–7.33 (1H, m), 7.40–7.46 (1H, m), 7.57–7.64 (2H, m), 7.72 (1H, d, J = 8.8 Hz), 7.80 (1H, dd, J = 1.5, 7.8 Hz), 7.85 (1H, d, J = 2.5 Hz), 12.57 (1H, br s); FAB-MS *m/e* (MH)$^+$ 339.

5.1.29. 4-[6-(Acetyloxy)-4-oxo-3,4-dihydroquinazolin-2-yl]phenyl acetate (9b). Compound **9b** was prepared from **8b** according to the same procedure as that for **9a**. Compound **9b** was obtained as a colorless solid (74% yield); ^{1}H NMR (DMSO-d_6) δ 2.32 (3H, s), 2.33 (3H, s), 7.30–7.36 (2H, m), 7.62 (1H, dd, J = 2.9, 8.8 Hz), 7.79 (1H, d, J = 8.8 Hz), 7.86 (1H, d, J = 2.9 Hz), 8.19–8.25 (2H, m), 12.65 (1H, br s); FAB-MS *m/e* (MH)$^+$ 339.

5.1.30. 2-(2-Nitropheyl)-4-oxo-3,4-dihydroquinazolin-6-yl acetate (9c). Compound **9c** was prepared from **8c** according to the same procedure as that for **9a**. Compound **9c** was obtained as a pale yellow solid (74% yield); ^{1}H NMR (DMSO-d_6) δ 2.34 (3H, s), 7.63 (1H, dd, J = 2.9, 8.8 Hz), 7.72 (1H, d, J = 8.7 Hz), 7.80–7.96 (4H, m), 8.21–8.25 (1H, m); FAB-MS *m/e* (MH)$^+$ 326.

5.1.31. 4-Oxo-2-phenyl-3,4-dihydroquinazolin-5-yl acetate (9e). Compound **9e** was prepared from **8e** according to the same procedure as that for **9a**. Compound **9e** was obtained as a colorless solid (92% yield); ^{1}H NMR (DMSO-d_6) δ 2.34 (3H, s), 7.15–7.20 (1H, m), 7.53–7.68 (4H, m), 7.83 (1H, t, J = 8.3 Hz), 8.13–8.18 (2H, m), 12.48 (1H, br s); FAB-MS *m/e* (MH)$^+$ 281.

5.1.32. 4-Oxo-2-phenyl-3,4-dihydroquinazolin-7-yl acetate (9f). Compound **9f** was prepared from **8f** according to the same procedure described as that for **9a**. Compound **9f** was obtained as a colorless solid (74% yield); ^{1}H NMR (DMSO-d_6) δ 2.34 (3H, s), 7.30 (1H, dd, J = 2.2, 8.8 Hz), 7.50 (1H, d, J = 1.9Hz), 7.53–7.64 (3H, m), 8.15–8.21 (3H, m), 12.60 (1H, br s); FAB-MS *m/e* (MH)$^+$ 281.

5.1.33. 2-(2-Hydroxyphenyl)-4-morpholin-4-ylquinazolin-6-ol (10a). Compound **10a** was prepared from **9a** according to the same procedure described as that for **6a**. Compound **9a** was obtained as a colorless solid (49% yield): mp 234–236 °C ($CHCl_3$/Et_2O/hexane); ^{1}H NMR (DMSO-d_6) δ 3.75–3.90 (8H, m), 6.90–6.97 (2H, m), 7.27–7.44 (3H, m), 7.80 (1H, d, J = 8.8 Hz), 8.41 (1H, dd, J = 1.5, 7.8 Hz), 10.23 (1H, s), 14.20 (1H, s); FAB-MS *m/e* (MH)$^+$ 324; Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.75; H, 5.43; N, 12.89.

5.1.34. 2-(4-Hydroxyphenyl)-4-morpholin-4-ylquinazolin-6-ol (10b). Compound **10b** was prepared from **9b** according to the same procedure as that for **6a**. Compound **10b** was obtained as a colorless solid (28% yield): mp 301–303 °C (EtOH/AcOEt); ^{1}H NMR (DMSO-d_6) δ 3.60–3.70 (4H, m), 3.80–3.90 (4H, m), 6.83–6.89 (2H, m), 7.23 (1H, d, J = 2.4 Hz), 7.34 (1H, dd, J = 2.4, 8.8 Hz), 7.73 (1H, d, J = 8.8 Hz), 8.26–8.32 (2H, m), 9.78 (1H, s), 10.06 (1H, s); FAB-MS *m/e* (MH)$^+$ 324; Anal. Calcd for $C_{18}H_{17}N_3O_30.2H_2O$: C, 66.13; H, 5.36; N, 12.85. Found: C, 66.23; H, 5.17; N, 12.67.

5.1.35. 4-Morpholin-4-yl-2-(2-nitrophenyl)quinazolin-6-ol (10c). Compound **10c** was prepared from **9c** according to the same procedure as that for **6a**. Compound **10c** was obtained as a colorless solid (31% yield): mp 228–231 °C (AcOEt); ^{1}H NMR (DMSO-d_6) δ 3.58–3.65 (4H, m), 3.75–3.82 (4H, m), 7.27 (1H, d. J = 2.4 Hz), 7.42 (1H, dd, J = 2.4, 8.8 Hz), 7.67 (1H, dt, J = 1.4, 7.8 Hz), 7.75–7.81 (2H, m), 7.86 (1H, dd, J = 1.0, 7.8 Hz), 8.21 (1H, dd, J = 1.5, 7.8 Hz), 10.26 (1H, s); FAB-MS *m/e* (M+H)$^+$ 353; Anal. Calcd for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.30; H, 4.54; N, 15.99.

5.1.36. 2-(2-Aminophenyl)-4-morpholin-4-ylquinazolin-6-ol (10d). Compound **10d** was prepared from **10e** according to the same procedure as that for **6j**. Compound **10d** was obtained as a colorless solid (19% yield): mp 245–246 °C (AcOEt); ^{1}H NMR (DMSO-d_6) δ 3.58–3.70 (4H, m), 3.82–3.90 (4H, m), 6.55–6.63 (1H, m), 6.76 (1H, dd, J = 1.0, 8.3 Hz), 7.08–7.14 (1H, m), 7.22–7.39 (4H, m), 7.78 (1H, d, J = 8.8 Hz), 8.38 (1H, dd, J = 1.4, 8.3 Hz), 10.08 (1H, s); FAB-MS *m/e* (MH)$^+$ 323; Anal. Calcd for $C_{18}H_{18}N_4O_2$·0.1AcOEt·0.1H_2O: C, 66.37; H, 5.75; N, 16.83. Found: C, 66.37; H, 5.50; N, 16.58.

5.1.37. 4-Morpholin-4-yl-2-phenylquinazolin-5-ol (10e). Compound **10e** was prepared from **9e** according to the same procedure as that for **6a**. Compound **10e** was obtained as a colorless solid (12% yield): mp 153–154 °C (AcOEt/hexane); ^{1}H NMR (DMSO-d_6) δ 3.60–3.70 (4H, m), 3.75–3.83 (4H, m), 6.88 (1H, dd, J = 1.0, 7.8 Hz), 7.29 (1H, dd, J = 1.0, 8.3 Hz), 7.46–7.54 (3H, m), 7.58 (1H, t, J = 7.8 Hz), 8.40–8.48 (2H, m), 10.73 (1H, s); FAB-MS *m/e* (M+H)$^+$ 308; Anal.

Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.32; H, 5.47; N, 13.66.

5.1.38. 4-Morpholin-4-yl-2-phenylquinazolin-7-ol (10f). Compound **10f** was prepared from **9f** according to the same procedure as that for **6a**. Compound **10f** was obtained as a colorless solid (19% yield): mp 245–246 °C (AcOEt/hexane); ^{1}H NMR (DMSO-d_6) δ 3.71–3.86 (8H, m), 7.03 (1H, dd, J = 2.4, 8.8 Hz), 7.12 (1H, d, J = 2.4 Hz), 7.47–7.53 (3H, m), 7.91 (1H, d, J = 8.8 Hz), 8.42–8.49 (2H, m), 10.49 (1H, s); FAB-MS *m/e* $(MH)^+$ 308; Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.44; H, 5.49; N, 13.64.

5.1.39. Methyl 3-[(3-methoxybenzoyl)amino]pyridine-2-carboxylate (12b). To a mixture of methyl 3-aminopyridine-2-carboxylate (**11b**)[32] (4.9 g, 32 mmol) and Et_3N (5.3 mL, 38 mmol) in $CHCl_3$ (40 mL) was added dropwise 3-methoxybenzoyl chloride at 5 °C. After stirring at room temperature for 2.5 h, the reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting solid was recrystallized from AcOEt to give **12b** (7.9 g, 86%) as a colorless solid; ^{1}H NMR ($CDCl_3$) δ 3.91 (3H, s), 4.08 (3H, s), 7.11–7.17 (1H, m), 7.41–7.50 (1H, m), 7.53–7.64 (3H, m), 8.44–8.50 (1H, m), 9.33 (1H, dd, J = 1.5, 8.6 Hz), 11.95 (1H, br s); FAB-MS *m/e* $(MH)^+$ 287.

5.1.40. Methyl 4-[(3-methoxybenzoyl)amino]nicotinate (12c). To a mixture of methyl 4-aminonicotinate (**11c**)[33] (5.0 g, 33 mmol) and Et_3N (5.5 mL, 39 mmol) in THF (70 mL) was added dropwise 3-methoxybenzoyl chloride at 0 °C. After stirring at room temperature for 10 min, the reaction mixture was diluted with AcOEt and water. The aqueous layer was extracted with AcOEt and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give **12c** as a brown solid (8.7 g, 92%); ^{1}H NMR ($CDCl_3$) δ 3.91 (3H, s), 4.02 (3H, s), 7.11–7.17 (1H, m), 7.41–7.49 (1H, m), 7.56–7.63 (2H, m), 8.67 (1H, d, J = 5.9 Hz), 8.81 (1H, d, J = 5.9 Hz), 9.21 (1H, s), 12.10 (1H, br s); FAB-MS *m/e* $(MH)^+$ 287.

5.1.41. Methyl 3-[(3-methoxybenzoyl)amino]isonicotinate (12d). Compound **12d** was prepared from **11d**[33] according to the same procedure as that for **12b**. Compound **12d** was obtained as a pale yellow solid (75% yield); ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s), 4.02 (3H, s), 7.09–7.15 (1H, m), 7.41–7.48 (1H, m), 7.55–7.60 (2H, m), 7.85 (1H, d, J = 5.4 Hz), 8.46 (1H, d, J = 4.8 Hz), 10.19 (1H, s), 11.61 (1H, br s); FAB-MS *m/e* $(MH)^+$ 287.

5.1.42. Methyl 3-[(3-methoxybenzoyl)amino]thiophene-2-carboxylate (12e). Compound **12e** was prepared from **11e** according to the same procedure as that for **12b**. Compound **12e** was obtained as a colorless solid (79% yield); ^{1}H NMR (DMSO-d_6) δ 3.85 (3H, s), 3.89 (3H, s), 7.22–7.29 (1H, m), 7.43–7.59 (3H, m), 8.00 (1H, d, J = 5.5 Hz), 8.10 (1H, d, J = 5.5 Hz), 10.97 (1H, s); FAB-MS *m/e* $(MH)^+$ 292.

5.1.43. 2-(3-Methoxyphenyl)pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (13b). To a solution of **12b** (7.9 g, 28 mmol) in MeOH (500 mL) was added 28% aqueous NH_3 (600 mL). After stirring at room temperature for 16 h, the reaction mixture was concentrated to one-half of its initial volume and the resulting solid was collected to give 3-[(3-methoxybenzoyl)amino]pyridine-2-carboxamide (6.2 g, 83%): ^{1}H NMR (DMSO-d_6) δ 3.32 (3H, s), 3.86 (3H, s), 7.20–7.28 (1H, m), 7.47–7.58 (3H, m), 7.68 (1H, dd, J = 4.4, 8.6 Hz), 8.13 (1H, br s), 8.38 (1H, dd, J = 1.5, 4.4 Hz), 8.64 (1H, br s), 9.15 (1H, dd, J = 1.5, 8.6 Hz), 13.35 (1H, br s); FAB-MS *m/e* $(MH)^+$ 272.

To a mixture of 3-[(3-methoxybenzoyl)amino]pyridine-2-carboxamide (6.2 g, 23 mmol) in 2-PrOH (220 mL) was added 2 N NaOH (80 mL). After stirring at reflux for 3 h, the reaction mixture was neutralized with concentrated HCl and the resulting precipitate was collected to give **13b** (4.47 g, 77%) as a colorless solid; ^{1}H NMR (DMSO-d_6) δ 3.87 (3H, s), 7.11–7.20 (1H, m), 7.46 (1H, t, J = 8.1), 7.75–7.85 (3H, m), 8.10–8.17 (1H, m), 8.73–8.79 (1H, m), 12.80 (1H, br s); FAB-MS *m/e* $(MH)^+$ 254.

5.1.44. 2-(3-Methoxyphenyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (13c). To a solution of **12c** (200 mg, 0.70 mmol) in MeOH (25 mL) was added 28% aqueous NH_3 (30 mL). After stirring at room temperature for 2 h, the reaction mixture was concentrated in vacuo to give a mixture of **13c** and uncyclized 4-[(3-methoxybenzoyl)amino]nicotinamide. To the obtained crude mixture, 2-PrOH (6.3 mL) and 2 N NaOH (2.3 mL) were added and the mixture was heated at reflux for 3 h, then neutralized with 2 N HCl. The resulting precipitate was collected and washed with water to give **13c** (88 mg, 50%) as a colorless solid; ^{1}H NMR (DMSO-d_6) δ 3.87 (3H, s), 7.15–7.26 (1H, m), 7.38–7.86 (4H, m), 8.84 (1H, d, J = 5.3 Hz), 9.30 (1H, s), 12.80 (1H, br s); FAB-MS *m/e* $(M+H)^+$ 254.

5.1.45. 2-(3-Methoxyphenyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (13d). Compound **13d** was prepared from **12d** according to the same procedure as that for **13c**. Compound **13d** was obtained as a colorless solid (67% yield); ^{1}H NMR (DMSO-d_6) δ 3.87 (3H, s), 7.01–7.13 (1H, m), 7.36–7.46 (1H, m), 7.80–7.98 (3H, m), 8.38–8.54 (1H, m), 8.93–9.04 (1H, m); FAB-MS *m/e* $(MH)^+$ 254.

5.1.46. 2-(3-Methoxyphenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (13e). Compound **13e** was prepared from **12e** according to the same procedure as that for **13b**. Compound **13e** was obtained as a colorless solid (91% yield); ^{1}H NMR (DMSO-d_6) δ 3.87 (3H, s), 7.10–7.17 (1H, m), 7.40–7.50 (2H, m), 7.68–7.78 (2H, m), 8.21 (1H, d, J = 5.3 Hz), 12.72 (1H, br s); FAB-MS *m/e* $(MH)^+$ 259.

5.1.47. 3-(4-Oxo-3,4-dihydroquinazolin-2-yl)phenyl acetate (14a). Compound **14a** was prepared from **13a**[23] according to the same procedure as that for **9a**. Compound **14a** was obtained as a colorless solid (quantita-

tive yield); ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 7.36–7.42 (1H, m), 7.52–7.65 (2H, m), 7.74–7.79 (1H, m), 7.83–7.91 (1H, m), 7.96–8.00 (1H, m), 8.06–8.12 (1H, m), 8.14–8.20 (1H, m); FAB-MS *m/e* $(MH)^+$ 281.

5.1.48. 3-(4-Oxo-3,4-dihydropyrido[3,2-*d*]pyrimidin-2-yl)phenyl acetate (14b). Compound **14b** was prepared from **13b** according to the same procedure as that for **9a**. Compound **14b** was obtained as a colorless solid (93% yield); ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 7.30–7.36 (1H, m), 7.57 (1H, t, J = 7.9 Hz), 7.76 (1H, dd, J = 4.2, 8.3 Hz), 7.98–8.17 (3H, m), 8.69–8.74 (1H, m); FAB-MS *m/e* $(MH)^+$ 282.

5.1.49. 3-(4-Oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-2-yl)phenyl acetate (14c). Compound **14c** was prepared from **13c** according to the same procedure as that for **9a**. Compound **22b** was obtained as a colorless solid (93% yield); ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 7.36–7.43 (1H, m), 7.51–7.65 (2H, m), 7.99–8.04 (1H, m), 8.10–8.16 (1H, m), 8.76–8.84 (1H, m), 9.27 (1H, s); FAB-MS *m/e* $(MH)^+$ 282.

5.1.50. 3-(4-Oxo-3,4-dihydropyrido[3,4-*d*]pyrimidin-2-yl)phenyl acetate (14d). Compound **14d** was prepared from **13d** according to the same procedure as that for **9a**. Compound **14d** was obtained as a colorless solid (98% yield); ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 7.26–7.33 (1H, m), 7.51–7.59 (1H, m), 7.86–7.91 (1H, m), 8.02–8.07 (1H, m), 8.15–8.22 (1H, m), 8.49–8.54 (1H, s), 9.00–9.03 (1H, m); FAB-MS *m/e* $(MH)^+$ 282.

5.1.51. 3-(4-Oxo-3,4-dihydrothieno[3,2-*d*]pyrimidin-2-yl)phenyl acetate (14e). Compound **14e** was prepared from **13e** according to the same procedure as that for **9a**. Compound **14e** was obtained as a colorless solid (89% yield); ^{1}H NMR (DMSO-d_6) δ 2.32 (3H, s), 7.34–7.39 (1H, m), 7.48 (1H, d, J = 5.3 Hz), 7.55–7.63 (1H, m), 7.91–7.95 (1H, m), 8.02–8.07 (1H, m), 8.24 (1H, d, J = 5.3 Hz); FAB-MS *m/e* $(MH)^+$ 287.

5.1.52. 3-(4-Morpholin-4-ylquinazolin-2-yl)phenol hydrochloride (15a). Compound **14a** (3.5 g, 13 mmol) in phosphorus oxychloride (31 mL) was refluxed for 3 h and concentrated in vacuo. The residue was dissolved in THF (25 mL) and morpholine (25 mL) was added to it. After stirring at reflux for 1.5 h, the reaction mixture was diluted with water and extracted with a mixture of AcOEt and THF. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. After chromatography on silica gel eluting with $CHCl_3$/MeOH (96:4), the residue was dissolved in a mixture of THF (18 mL) and methanol (18 mL). HCl/AcOEt (4 N, 0.63 mL) was added to the solution and the mixture was concentrated and recrystallized from MeOH to give **15a** (1.37 g, 31%) as a colorless solid: mp 214–220 °C; ^{1}H NMR (DMSO-d_6) δ 3.75–3.95 (4H, m), 4.15–4.35 (4H, m), 7.10–7.20 (1H, m), 7.40–7.50 (1H, m), 7.63–7.72 (1H, m), 7.82 (1H, s), 7.90 (1H, d, J = 7.8 Hz), 7.96–8.05 (1H, m), 8.16–8.30 (2H, m), 10.10 (1H, br s); FAB-MS *m/e* $(MH)^+$ 308; Anal. Calcd for $C_{18}H_{17}N_3O_2$·HCl: C, 62.88; H, 5.28; N, 12.22; Cl, 10.31. Found: C, 62.71; H, 5.16; N, 12.21; Cl, 10.12.

5.1.53. 3-(4-Morpholinopyrido[3,2-*d*]pyrimidin-2-yl)phenol hydrochloride (15b). Compound **15b** was prepared from **14b** according to the same procedure described for **15a**. Compound **15b** was obtained as a colorless solid (47% yield): mp 223–228 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.80–3.95 (4H, m), 4.73 (4H, br), 7.05–7.20 (1H, m), 7.43 (1H, t, J = 7.8 Hz), 7.80–7.85 (1H, m), 7.91 (1H, d, J = 7.8 Hz), 8.00 (1H, dd, J = 4.0, 8.3 Hz), 8.60 (1H, d, J = 7.8 Hz), 8.91 (1H, dd, J = 1.5, 4.4 Hz), 10.02 (1H, br s); FAB-MS *m/e* $(MH)^+$ 309; Anal. Calcd for $C_{17}H_{16}N_4O_2$·HCl·0.6H_2O: C, 57.42; H, 5.16; N, 15.76; Cl, 9.97. Found: C, 57.57; H, 4.99; N, 15.89; Cl, 9.87.

5.1.54. 3-(4-Morpholinopyrido[4,3-*d*]pyrimidin-2-yl)phenol hydrochloride (15c). Compound **15c** was prepared from **14c** according to the same procedure described for **15a**. Compound **15c** was obtained as a colorless solid (16% yield): mp 261–266 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.74–3.93 (4H, m), 4.17–4.32 (4H, m), 7.00–7.13 (1H, m), 7.40 (1H, t, J = 7.8 Hz), 7.85–8.10 (3H, m), 8.79 (1H, d, J = 6.4 Hz), 9.51 (1H, s), 9.90 (1H, br); FAB-MS *m/e* $(MH)^+$ 309; Anal. Calcd for $C_{17}H_{16}N_4O_2$·1.1HCl·0.3H_2O: C, 57.70; H, 5.04; N, 15.83; Cl, 11.02. Found: C, 57.74; H, 5.04; N, 15.83; Cl, 11.03.

5.1.55. 3-(4-Morpholinopyrido[3,4-*d*]pyrimidin-2-yl)phenol hydrochloride (15d). Compound **15d** was prepared from **14d** according to the same procedure described for **15a**. Compound **15d** was obtained as a colorless solid (26% yield): mp 269–274 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.74–3.92 (4H, m), 4.05–4.23 (4H, m), 7.05 (1H, dd, J = 1.9, 8.3 Hz), 7.39 (1H, t, J = 7.8 Hz), 7.85–7.97 (2H, m), 8.07 (1H, d, J = 5.9 Hz), 8.66 (1H, d, J = 5.9 Hz), 9.44 (1H, s), 9.83 (1H, br); FAB-MS *m/e* $(MH)^+$ 309; Anal. Calcd for $C_{17}H_{16}N_4O_2$HCl: C, 59.22; H, 4.97; N, 16.25; Cl, 10.28. Found: C, 59.17; H, 4.95; N, 16.48; Cl, 10.25.

5.1.56. 3-(4-Morpholinothieno[3,2-*d*]pyrimidin-2-yl)phenol hydrochloride (15e). Compound **15e** was prepared from **14e** according to the same procedure described for **15a**. Compound **15e** was obtained as a colorless solid (57% yield): mp 207–210 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.75–3.92 (4H, m), 4.05–4.28 (4H, m), 7.05 (1H, dd, J = 2.0, 7.9 Hz), 7.40 (1H, t, J = 7.8 Hz), 7.73 (1H, d, J = 5.8 Hz), 7.80 (1H, s), 7.86 (1H, d, J = 7.8 Hz), 8.51 (1H, d, J = 5.3 Hz), 9.90 (1H, br); FAB-MS *m/e* $(M+H)^+$ 314; Anal. Calcd for $C_{16}H_{15}N_3O_2S$·HCl: C, 54.93; H, 4.61; N, 12.01; S, 9.17; Cl, 10.13. Found: C, 54.78; H, 4.48; N, 12.02; S, 9.07; Cl, 10.04.

5.2. Scintillation proximity assay (SPA) for p110α

Bovine p110α was expressed in an Sf9/Baculovirus system and purified as a GST-fusion protein. The test compounds dissolved in DMSO (0.5 μL) and p110α enzyme were mixed in 25 μL of buffer solution (20 mM

Tris–HCl (pH 7.4), 160 mM NaCl, 2 mM dithiothreitol, 30 mM $MgCl_2$, 0.4 mM EDTA, and 0.4 mM EGTA). Then, 25 μL of 5 mM Tris–HCl supplemented with 1 μg PI (Sigma), 0.125 μCi [γ-^{33}P]ATP (Amersham Pharmacia), and 1 μM non-radiolabeled ATP (Sigma) were added to the mixture to initiate the reaction. After the reaction had proceeded at room temperature for 120 min, 0.2 mg of wheat germ agglutinin-coated SPA beads (Amersham) in 150 μL PBS was added. The mixture was left to stand for 5 min and then centrifuged at 300*g* for 2 min. The radioactivity was measured using TopCount (Packard). The reported IC_{50} values are means of at least two separate determinations with typical variations of less than ±20%.

5.3. Proliferation assays

A375 melanoma cells were cultured in DMEM with 10% fetal bovine serum and streptomycin/penicillin. Test compounds in volumes of 1 μL were spotted onto a 96-well culture plate, followed by addition of cells (1×10^4 in 100 μL). After 46 h incubation, 10 μL of Alamar Blue reagent was added to each well, and after a further 2 h the excitation/emission wavelengths at 544/590 nm were measured using a FLUOstar instrument. The reported IC_{50} values are means of at least two separate determinations with typical variations of less than ±20%.

Acknowledgments

We thank Drs. K. Matsuda and N. Taniguchi for preparation of the manuscript, and members of the Division of Analytical Research for performing instrumental analysis.

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