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Discovery of 4-Anilinofuro[2,3-*b*]quinoline Derivatives as Selective and Orally Active Compounds against Non-Small-Cell Lung Cancers

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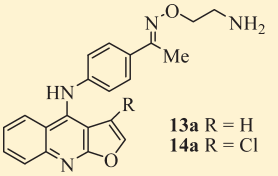
ABSTRACT: We have reported the preparation and anticancer evaluation of certain 4-anilinofuro-[2,3-*b*]quinolines. However, drawbacks such as lack of selective cytotoxicity, poor oral bioavailability, and poor water solubility exhibited by these compounds prompted us to search for newer derivatives. Among them, (*E*)-1-(4-(furo[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-aminoethyloxime (**13a**) is selectively active against the growth of NCI-H460 and is highly water-soluble (63 μg/mL). Its hydrochloride salt, **13a**·HCl exhibited not only excellent water solubility (1049 μg/mL) but also a high oral bioavailability (57.1%). Compound **13a** may cause cancer cell apoptosis through inducing mitotic arrest and mitotic catastrophe mechanism. Xenographic studies indicated the tumor size with **13a**·HCl treated nude mice was significantly lower than control. Further evaluation in an orthotopic lung cancer model indicated that **13a**·HCl can be absorbed readily through oral administration, distributed to lung tissue, and exhibited significant efficacy in inhibiting the growth of lung cancers.



INTRODUCTION

Acridine derivatives, especially 9-anilinoacridines, have been extensively studied as potential chemotherapeutic agents because of their capability of intercalating DNA, leading to the inhibition of mammalian topoisomerase II.[1−10] Among such derivatives, amsacrine (*m*-AMSA) has been clinically used for the treatment of leukemia and lymphoma.[1] Further structural modification has led to the discovery of improved broad spectrum anticancer agents that were capable of inhibiting the growth of certain solid tumors such as mammary adenocarcinoma, melanoma, and Lewis lung carcinoma.[9,10] These results prompted us to synthesize and evaluate 4-anilinofuro[2,3-*b*]quinoline derivatives that can be structurally related to 9-anilinoacridines by isosteric substitution of a benzene moiety for a furan ring.[11−15] Among these 4-anilinofuro[2,3-*b*]quinoline derivatives, 1-[4-(furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**1**, Chart 1) with a mean graph midpoint (GI_{50}) of 0.025 μM, was more active than *m*-AMSA (GI_{50} = 0.44 μM) in the NCI's full panel of 60 human cancer cells.[11] The antiproliferative potency of its hydroxyimino and methoxyimino derivatives, **2** and **3**, respectively, was also proved to be comparable to that of *m*-AMSA. Compound **1** had been selected as a lead compound and was evaluated by flow cytometric analysis for its effects on cell cycle distributions. Results indicated that **1** inhibited cell proliferation by the alteration of cell division and accumulation of cells in the G2/M phase followed by the cell apoptosis which is similar to microtubule-targeting agents such as paclitaxel but distinct from that of *m*-AMSA. This is interesting because 4-anilinofuro[2,3-*b*]quinoline derivatives, if proved to be active, could be developed as a new structural type of potential antimicrotubule drug candidates. However, some drawbacks such as lack of selective cytotoxicity, poor oral bioavailability, and poor water solubility exhibited by compound **1** and its hydroxyimino and methoxyimino derivatives **2** and **3**, respectively, prompted us to search for newer derivatives with better pharmacokinetic profiles and higher water solubility. In fact, low water solubility and low bioavailability are frequent problems in drug development, particularly in the area of anticancer drugs.[16−23]

Low water solubility is an intrinsic property of many natural and synthetic drug candidates and is usually associated with poor absorption and bioavailability.[16,17] Camptothecin (**4**, Chart 1), for example, is an antitumor alkaloid isolated from *Camptotheca acuminata*.[18,19] Its clinical use has been hampered until the recent structural optimization leading to the discovery of water-soluble derivatives such as topotecan and irinotecan. The introduction of aminoalkyl functionalities conferring water solubility to the quinoline nucleus is therefore one of the most successful strategies for the structural optimization of anticancer drugs.[20−24] Combretastatin A-4 is another example of a natural product that possesses poor water solubility.[24−29] In order to improve its water solubility and in vivo efficacy, the water-soluble combretastatin A-4 phosphate has been prepared as a prodrug.[30]

Recently, we have also synthesized certain indenoquinoline derivatives that bear aminoalkyl side chain as potential anticancer agents.[31−33] Our results indicated that introduction of the aminoalkyl side chain on the tetracyclic pharmacophore improved not only water solubility but also anticancer potency. For example, 9-methoxy-6-(piperazin-1-yl)-11*H*-indeno[1,2-*c*]quinolin-11-one *O*-3-(dimethylamino)propyloxime (**5**)[31] and

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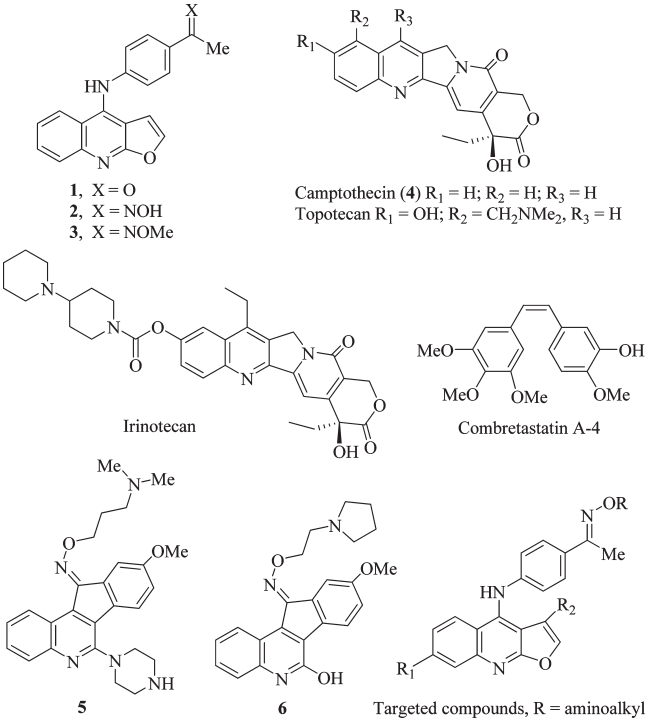
Chart 1. Structures of 1-[4-(Furo[2,3-*b*]quinolin-4-ylamino) phenyl]ethanone (1), Its Oxime 2 and Methyloxime 3, Camptothecin (4), Topotecan, Irinotecan, Combretastatin A-4, Aminoalkyl Substituted Indenoquinolines 5 and 6, and Targeted Compounds

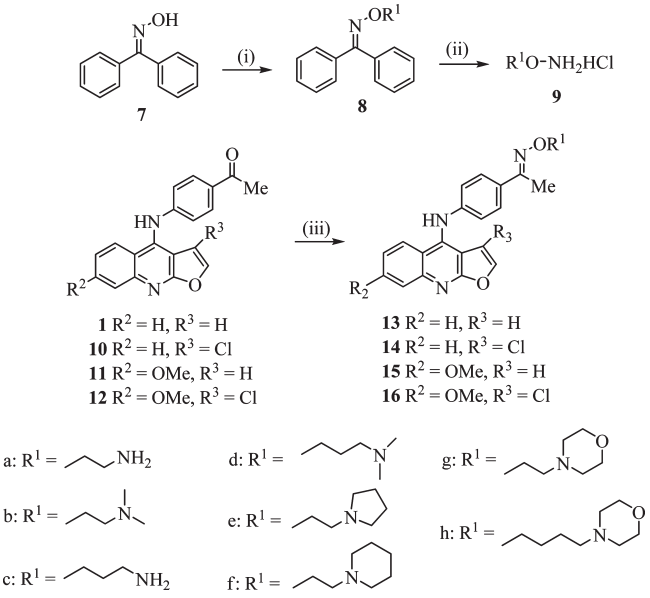


(*E*)-6-hydroxy-9-methoxy-11*H*-indeno[1,2-*c*]quinolin-11-one *O*-2-(pyrrolidin-1-yl)ethyloxime (**6**)[33] were found to be more active than **4** against the growth of A549 with IC_{50} values of 0.38 and 0.89 μM, respectively. The present report describes the synthesis and anticancer evaluation of 4-anilinofuro[2,3-*b*]quinoline derivatives which bear various aminoalkyl side chains with an aim to improve water solubility, selective cytotoxicity, and bioavailability of the lead compound **1**. Analogues of **1** have also been synthesized and evaluated.

RESULTS AND DISCUSSION

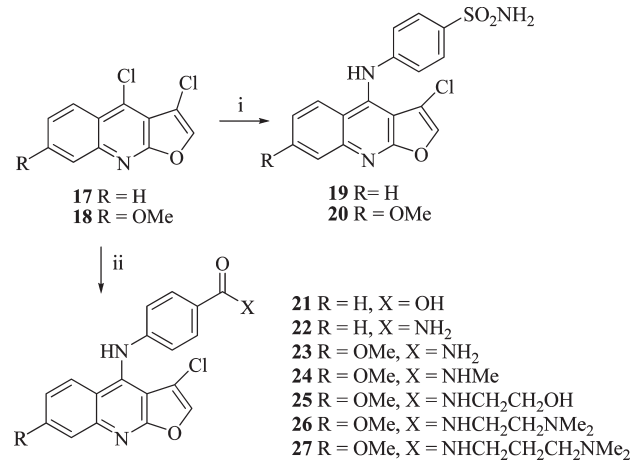
Synthesis of 4-Anilinofuro[2,3-*b*]quinoline Derivatives. The preparation of aminoalkyl substituted 4-anilinofuro[2,3-*b*]quinoline derivatives is outlined in Scheme 1. The known benzophenone oxime (**7**) was alkylated with aminoalkyl chlorides to give benzophenone aminoalkyloximes (**8a**−**h**) which were hydrolyzed with 3 N HCl to afford their respective aminoalkoxyamines (**9a**−**h**).[34] Reaction of 4-acetylanilinofuro[2,3-*b*]quinolines (**1**)[11] with the respective aminoalkoxyamines (**9a**−**h**) gave exclusively (*E*)-1-[4-(furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone aminoalkyloximes (**13a**−**h**) in a good overall yield. The configuration of the aminoalkyloxime moiety was determined by the ^{13}C NMR spectra. The carbon of CH_3 which is *anti* to the aminoalkyloxime moiety (*Z*-form) shifted upfield from δ 30.6 ppm (carbonyl precursor) to δ 18.8 ppm, while that of the *syn* isomer (*E*-form) further shifted from 30.6 to 11.5 ppm.[35] The CH_3 carbon peak appeared at δ 12.63 ppm for compound **13a**, indicating that the methyl group is *syn* to the aminoalkyloxime moiety and the sole product of (*E*)-form isomer was obtained. The stereospecific oximination to give

Scheme 1[a]



[a] Reagents and conditions: (i) R^1Cl, NaH, DMF; (ii) 3 N HCl, reflux; (iii) $R^1ONH_2 \cdot HCl$, K_2CO_3, EtOH, reflux.

Scheme 2[a]



[a] Reagents and conditions: (i) 4-aminobenzenesulfonamide, EtOH/H_2O, conc HCl; (ii) 4-substituted aniline, EtOH/H_2O, conc HCl.

E-form product rather than the *Z*-isomer can be realized in which the aminoalkoxy side chain proximate the methyl group is less sterically hindered.[36] Accordingly, the (*E*)-form configuration was assigned for compounds **13b** (CH_3 carbon peak appeared at δ 12.74), **13c** (δ 12.54), **13d** (δ 12.52), **13e** (δ 12.87), **13f** (δ 12.65), **13g** (δ 12.70), and **13h** (δ 12.54). Compounds **14a**−**h**, **15a**−**h**, and **16a**−**h** were obtained from their respective carbonyl precursors **10**, **11**, and **12**[14] under the same reaction conditions.

Certain analogues of compound **1** have been synthesized as depicted in Scheme 2. Treatment of 3,4-dichlorofuro[2,3-*b*]quinoline (**17**)[37] and 3,4-dichloro-7-methoxyfuro[2,3-*b*]quinoline (**18**)[14] with 4-aminosufonamide afforded 4-(3-chlorofuro[2,3-*b*]quinolin-4-ylamino)benzenesulfonamide (**19**) and 4-(3-chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)benzenesulfonamide

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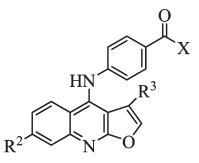
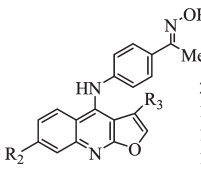
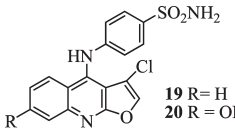
Table 1. Inhibition of in Vitro Cancer Cells by 4-Anilinofuro[2,3-*b*]quinoline Derivatives[a]



1 $R^2 = R^3 = H$, X = Me
21 $R^2 = H$, $R^3 = Cl$, X = OH
22 $R^2 = H$, $R^3 = Cl$, $X = NH_2$
23 $R^2 = OMe$, $R^3 = Cl$, $X = NH_2$
24 $R^2 = OMe$, $R^3 = Cl$, X = NHMe
25 $R^2 = OMe$, $R^3 = Cl$, $X = NHCH_2CH_2OH$
26 $R^2 = OMe$, $R^3 = Cl$, $X = NHCH_2CH_2NMe_2$
27 $R^2 = OMe$, $R^3 = Cl$, $X = NHCH_2CH_2CH_2NMe_2$



2, 3, 13 $R^2 = R^3 = H$
14 $R^2 = H$, $R^3 = Cl$
15 $R^2 = OMe$, $R^3 = H$
16 $R^2 = OMe$, $R^3 = Cl$



19 R= H
20 R = OMe

Compound		% growth of cancer cells					
		MCF- 7		NCI-H460		SF-268	
	R^1	20 μg/mL	4 μg/mL	20 μg/mL	4 μg/mL	20 μg/mL	4 μg/mL
1	-	61	69	30	33	39	40
2	H	58	64	21	27	43	50
3	Me	37	63	23	51	42	68
13a		-1	66	-1	33	-2	45
13b		0	59	0	94	-5	81
13c		-3	52	-2	22	-4	42
13d		22	84	7	52	0	62
13e		6	64	1	54	-3	66
13f		3	114	-1	99	-3	96
13g		56	120	23	108	32	121
13h		-2	76	-1	118	2	125
14a		-1	59	-1	32	-2	45
14b		-3	70	-1	68	2	71
14c		0	46	0	28	-4	41
14d		1	61	1	52	1	66
14e		-2	86	-1	69	-3	86
14f		26	121	3	101	31	120
14g		54	112	16	107	32	121
14h		-3	75	3	91	3	115
15a		8	71	11	14	27	46
15b		-1	67	-1	75	1	91
15c		18	100	16	105	56	103

Compound		% growth of cancer cells					
		MCF- 7		NCI-H460		SF-268	
	R^1	20 μg/mL	4 μg/mL	20 μg/mL	4 μg/mL	20 μg/mL	4 μg/mL
15d		2	59	5	82	3	90
15e		3	63	5	69	6	104
15f		2	77	9	84	44	106
15g		25	76	44	96	92	110
15h		75	83	21	89	44	110
16a		-1	66	3	13	16	43
16b		-2	51	-1	74	-1	102
16c		3	101	8	91	48	109
16d		1	66	4	66	1	103
16e		1	55	5	53	5	102
16f		-1	56	3	67	48	112
16g		37	85	68	97	108	104
16h		5	96	20	87	99	110
19	-	90	91	79	86	96	98
20	-	33	90	17	97	ND	ND
21	-	61	62	81	89	73	80
22	-	92	93	97	97	97	97
23	-	66	90	77	96	ND	ND
24	-	47	72	27	58	35	52
25	-	74	96	82	98	100	103
26	-	44	97	60	112	68	119
27	-	72	91	36	92	71	94

[a] In this protocol, each cell line was inoculated and preincubated on a microtiter plate. Each of the tested compounds was then added at concentrations of 20.0 and 4.0 μg/mL and the culture incubated for 48 h. End-point determinations were made with sulforhodamine B, a protein-binding dye. Results for each test agent are reported as the percent of growth of the treated cells against that of the untreated control cells.

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Table 2. Antiproliferative Activity [IC_{50} (μM)][a] and Water Solubility of Selected 4-Anilinofuro[2,3-*b*]quinoline Derivatives

compd	NCI-H460 (SI)[b]	MCF7 (SI)	SF-268 (SI)	MRC-5	water solubility (μg/mL)
1					6
2					10
3					8
4	0.03 ± 0.003 (29.67)	11.12 ± 0.61 (0.08)	0.19 ± 0.006 (4.68)	0.89 ± 0.90	
13a	0.63 ± 0.03 (68.02)	9.34 ± 0.92 (4.59)	6.26 ± 1.02 (6.84)	42.85 ± 1.05	63
13a·HCl					1049
13c	7.08 ± 0.67 (6.07)	11.52 ± 0.02 (3.73)	7.53 ± 0.41 (5.71)	42.98 ± 0.86	58
14a	0.71 ± 0.02 (66.25)	31.01 ± 0.03 (1.52)	9.14 ± 0.72 (5.15)	47.04 ± 1.21	25
14c	16.21 ± 0.36 (2.90)	9.46 ± 0.23 (4.98)	32.53 ± 1.25 (1.46)	47.09 ± 2.27	36
15a	3.96 ± 0.14 (11.39)	36.23 ± 0.05 (1.24)	8.15 ± 0.44 (5.53)	45.11 ± 0.31	16
16a	3.86 ± 0.13 (12.30)	36.93 ± 0.31 (1.28)	7.48 ± 0.36 (6.34)	47.46 ± 0.38	17
DAR[c]	0.38 ± 0.04 (2.32)	5.03 ± 0.05 (0.17)	0.60 ± 0.02 (1.47)	0.88 ± 0.11	

[a] Values are the average of three separate determinations. [b] SI: selectivity index = (IC_{50} of MRC-5)/(IC_{50} of cancer cell line). [c] DAR, daunorubicin.

(**20**), respectively, in a fairly good yield. Under similar reaction conditions, compound **17** was reacted with 4-aminobenzoic acid and 4-aminobenzamide to give 4-(3-chlorofuro[2,3-*b*]quinolin-4-ylamino)benzoic acid (**21**) and 4-(3-chlorofuro[2,3-*b*]quinolin-4-ylamino)benzamide (**22**), respectively. 4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)benzamide (**23**) and its derivatives **24**−**27** were synthesized by treating **18** with 4-aminobenzamide and its derivatives, respectively, under the same reaction conditions.

Antiproliferative Activities and Water Solubilities. The newly synthesized 4-anilinofuro[2,3-*b*]quinoline derivatives were evaluated in vitro against a three-cell line panel consisting of MCF7 (breast), NCI-H460 (lung), and SF-268 (CNS). In this protocol, each cell line was inoculated and preincubated on a microtiter plate. Test agents were then added at 20.0 and 4.0 μg/mL, respectively, and the culture was incubated for 48 h. End-point determinations were made with sulforhodamine B, a protein-binding dye. Results for each test agent are reported as the percent of growth of the treated cells against the untreated control cells as shown in Table 1. The growth inhibitory activities of compounds **1**−**3** are comparable and are approximately equally potent to that of (*E*)-1-(4-(furo[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-aminoethyloxime (**13a**) against these three cancer cell lines at 4 μg/mL. However, compounds **1**−**3** are much less active than **13a** at 20 μg/mL, suggesting that these three lead compounds could be poorly water-soluble. Comparable antiproliferative activities of compounds **1**−**3** at 4 and 20 μg/mL have also implied the limitation of their water solubility. In the antiproliferative assay, compounds were dissolved completely in DMSO and then sequentially diluted with culture medium to various concentrations. Compounds with poor water solubility will gradually precipitate during the incubation which made concentrations not reported correctly. The improved water solubility of aminoalkyl substituted 4-anilinofuro[2,3-*b*]quinoline derivatives **13a**−**h**, **14a**−**h**, **15a**−**h**, and **16a**−**h** can be realized in which a positive correlation was observed for antiproliferative potency and the concentration of tested compounds. For example, **13a** inhibited only 34% of MCF7 cell growth at 4 μg/mL while the growth of MCF7 was completely inhibited at 20 μg/mL. The antiproliferative activity of **13a**, which bears an aminoethyl side chain, was comparable to that of its homologous aminopropyl counterpart **13c**. Compounds **13a** and **13c** exhibited more potent inhibitory activities than **13b** and **13d**, respectively, against the growth of both NCI-H460 and SF-268 at 4 μg/mL, indicating the terminal primary amine conferred greater activity. Compounds **13e**−**h** being inactive against all the cell lines tested at 4 μg/mL implied that the bulky cyclic five- or six-membered ring at the terminal aminoalkyl side chain is unfavorable. The same SARs were observed for **14a**−**h** in which the primary amine derivatives, **14a** and **14c**, are more active than their respective tertiary amine counterparts, **14b** and **14d**, while the cyclic five or six-membered ring derivatives, **14e**−**h**, were inactive at 4 μg/mL. Comparable cytotoxicities exhibited by **13a**−**h** and their respective 3-chloro counterpart **14a**−**h** indicated that a chloro group substituted at C-3 position of tricyclic furo[2,3-*b*]quinoline ring did not affect antiproliferative activities. Compounds **13c** and **14c** are more active than their respective C-7 methoxy counterparts **15c** and **16c**, indicating a methoxy substituent at C-7 position is unfavorable. Analogues of compound **1** and their derivatives, **19**−**27**, were found to be inactive against the growth of all cell lines tested.

The IC_{50} values and water solubilities of selected compounds **13a**, **13c**, **14a**, **14c**, **15a**, and **16a** are summarized in Table 2. For comparison, water solubilities of lead compounds **1**−**3** were also determined with a UV/vis spectrophotometer at a wavelength that varied between 315 and 420 nm.[38] Results indicated that the water solubility decreased in the order **13a** (63 μg/mL) > **13c** (58 μg/mL) > **14c** (36 μg/mL) > **14a** (25 μg/mL) > **16a** (17 μg/mL), **15a** (16 μg/mL) > **2** (10 μg/mL), **3** (8 μg/mL), **1** (6 μg/mL). Oximination improved water solubility by approximately 1.7-fold (**1**, 6 μg/mL vs **2**, 10 μg/mL). Introduction of a methyl group on the oxime moiety slightly decreased water solubility (**2**, 10 μg/mL vs **3**, 8 μg/mL). However, introduction of an aminoethyl group on the oxime moiety enhanced water solubility by more than 6-fold (**2**, 10 μg/mL vs **13a**, 63 μg/mL). The water solubility of **13a** can be further enhanced by the reaction with HCl to give its hydrochloride salt, **13a**·HCl (1049 μg/mL) which is approximately 17-fold more soluble than the free base. Substitution of the lipophilic chloro atom or a methoxy group on the tricyclic furoquinoline pharmacophore decreased water solubility so that **15a** and **16a** were less water-soluble than **13a**.

Compound **1** was nonselective and exhibited a GI_{50} of 0.025 μM in the NCI's full panel of 60 human cancer cells.[11] In contrast to compound **1**, compounds **13a**−**16a** are selectively active against the growth of NCI-H460 and the potency decreased in the order of **13a** (IC_{50} = 0.63 μM) > **14a** (0.71 μM) > **16a**

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Table 3. Pharmacokinetic Parameters of the Tested Compounds (1, 13a·HCl, and 14a) in fasted Male CD-1 (Crl) Mice

	PK Parameters	1	13a·HCl	14a
iv[a]	C_{max} (ng/mL)[c]	3064	1488.4	3601
	$AUC_{(0-inf)}$ (ng·h/mL)	211	362.6	409.8
	MRT (h)	0.1	2.5	6.1
	CL (mL/(min·kg))	158	91.9	81.3
	V_{ss} (L/kg)	1.2	13.5	30.0
	V_z (L/kg)	4.1	38.8	103.8
	$t_{1/2}$ (h)	0.3[d]	4.9[f]	14.7[f]
po[b]	C_{max} (ng/mL)	21	1905.0	114.3
	$AUC_{(0-inf)}$ (ng·h/mL)	45	2071.6	242.6
	T_{max} (h)	0.3	0.5	1.0
	MRT (h)	2.7	3.0	2.8
	$t_{1/2}$ (h)	2.0[e]	3.4[g]	1.7[h]
	bioavailability (%)	2.1	57.1	5.9

[a] iv: single intravenous dosing at 2.0 mg/kg. [b] po: single oral dosing at 20 mg/kg. [c] C_{max} was determined from the extrapolated plasma concentration at time 0. [d] $t_{1/2}$ was determined from 0.5 to 1.5 h time points. [e] $t_{1/2}$ was determined from 2 to 6 h time points. [f] $t_{1/2}$ was determined from 9 to 27 h time points. [g] $t_{1/2}$ was determined from 2 to 24 h time points. [h] $t_{1/2}$ was determined from 2 to 9 h time points.

(3.86 μM) > **15a** (3.96 μM) as shown in Table 2. With the exception of MCF7, a side chain of 2-aminoethyl group is more active than a 3-aminopropyl moiety as evidenced by the fact that **13a** is more active than **13c** while **14a** is more active than **14c**. Compounds **13a** and **14a** are selectively active against the growth of NCI-H460 with IC_{50} of 0.63 and 0.71 μM, respectively, and are inactive against the growth of human lung fibroblast cell line MRC-5, with IC_{50} of 42.85 and 47.04 μM, respectively. Although compounds **13a** and **14a** are less active than **4** and daunorubicin (DAR) against NCI-H460, the selectivity indexes (SI, (IC_{50} of MRC-5)/(IC_{50} of NCI-H460)) for **13a** and **14a** are 68.02 and 66.25, respectively, which are more favorable than for **4** (29.67) and DAR (2.32). Therefore, both compounds **13a** and **14a** were selected as new leads for further investigations.

Pharmacokinetic Evaluation. Pharmacokinetic properties of the lead compound **1** and two of the newly synthesized 4-anilinofuro[2,3-*b*]quinoline derivatives **13a**·HCl and **14a** were evaluated for their pharmacokinetic properties, and results are summarized in Table 3. Compound **1** exhibited low oral bioavailability (2.1% only) and short plasma half-life (2.0 h) following an oral dosing of 20 mg/kg. On the other hand, **13a**·HCl exhibited a high oral bioavailability (57.1%) and a moderate plasma half-life (3.4 h). Following an oral dosing of 20 mg/kg, **13a**·HCl showed rapid oral absorption in mice, with a short T_{max} of 0.5 h, while a significant second absorption peak appeared at 1.5 h after dosing. Interestingly, the third absorption peak was observed at 9 h postdose as shown in Figure 1. These results indicate the multiple absorption sites of **13a**·HCl in mouse after oral administration, likely also including enterohepatic recirculation. The mean C_{max} and AUC of **13a**·HCl were 1905 ng/mL and 2072 ng·h/mL, respectively. The multiple absorption of **13a**·HCl is unique and interesting because it usually occurs only in the sustain-released drugs with special formulation. Although compounds **13a** and **14a** exhibited comparable antiproliferative potency and selectivity, we decided not to further explore **14a** because of its low oral bioavailability (5.9%) and short plasma half-life (1.7 h) following an oral dosing of 20 mg/kg.

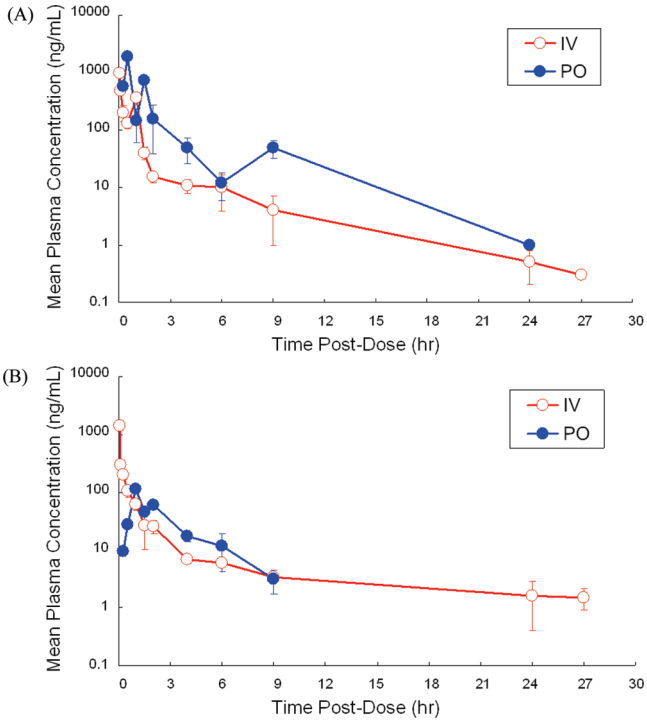

Figure 1. Mean plasma concentration−time profiles of **13a**·HCl (A) and **14a** (B) in male CD-1 (Crl) mice following single intravenous (iv, 2 mg/kg) and oral (po, 20 mg/kg) administration.

Preferential Inhibitory Activity of 13a to Lung Cancer Cell Lines. In order to examine whether compound **13a** has preferential inhibitory activity to lung cancer cell lines, five lung cancer cell lines including NCI-H460, A549, H1299, H661, and CL1−5; eight non-lung-cancer cell lines including 786-O, AGS, PC3, BT483, HeLa, SAS, SKHep, and CE81T; and two normal fibroblast cell lines including MRC-5 and Hs68 were employed for determing their IC_{50} values. Results in Table 4 showed that lung cancer cell lines are the most susceptible with an IC_{50} of 6.58 μM or less in each case while renal cell carcinoma (RCC 786-O) is the most resistant with an IC_{50} of 24.0 μM. Among these lung carcinomas, a specific cell type of non-small-cell lung carcinomas, NCI-H460, H661, and H1229 are the most susceptible with IC_{50} values of 0.63, 0.98, and 3.08 μM, respectively. The selectivity index (SI, (IC_{50} of MRC-5)/(IC_{50} of cancer cell)) for NCI-H460, H661, and H1229 is 68.02, 43.72, and 13.91, respectively.

Compound 13a Inhibits the Microtubule Formation, Causes Mitotic Arrest and Mitotic Catastrophe, and Induces Apoptosis. The observation of a numerous rounded-up H460 (Figure 2A) after 1 μM **13a** treatment for 24 h indicated that compound **13a** may influence the cell cycle. To determine the association between **13a**-induced growth inhibition and cell cycle deregulation, flow cytometry with PI staining was used to examine the ploidy levels of **13a** treated cells. The results in Figure 2B showed that **13a** induced H460 cell accumulation in 4N ploidy in a dose dependent manner after drug treatment for 24 h. These results suggested that **13a** may cause H460 cell arrest in the G2/M phase. In addition, the increase of the sub-G1 cell population after the 3 μM **13a** treatment for 24 h indicated that

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Table 4. Antiproliferative Activities [IC_{50} (μM)][a] of 13a against the Growth of Certain Different Types of Cancer Cells and the Human Lung Fibroblast Cell Lines

cell	type	IC_{50} (SI)[b]
H460	large cell lung carcinoma	0.63 ± 0.03 (68.02)
A549	human lung adenocarcinoma	6.58 ± 2.99 (6.51)
H1299	non-small-cell lung carcinoma	3.08 ± 1.12 (13.91)
H661	large cell lung carcinoma	0.98 ± 0.27 (43.72)
CL1−5	metastatic lung adenocarcinoma	5.18 (8.27)
RCC 786-O	renal cell carcinoma	24.0 ± 2.0 (1.77)
AGS	human stomach adenocarcinoma	13.77 ± 0.04 (3.09)
PC-3	human prostate cancer	11.85 ± 0.49 (3.62)
BT483	human breast carcinomas	10.16 ± 0.90 (4.22)
HeLa	human cervical epithelioid carcinoma	8.31 ± 0.60 (5.16)
SAS	human oral squamous carcinoma	15.50 ± 2.60 (2.76)
SKHep	hepatocellular carcinoma	13.13 ± 3.75 (3.26)
CE81T	human esophageal carcinoma	16.95 ± 1.88 (2.53)
MRC-5	human lung fibroblast	42.85 ± 1.05
Hs68	foreskin, fibroblast	28.90 ± 2.48

[a] Values are the average of three separate determinations. [b] SI: selectivity index = (IC_{50} of MRC-5)/(IC_{50} of cancer ell line).

DNA fragmentation and apoptosis may be followed by G2/M arrest caused by compound **13a**. This hypothesis was supported by the results from Figure 2C showing that **13a** can induce the cleavage of both caspase 3 and PARP, two apoptotic signaling molecules involoved in DNA fragmentation, in a dose dependent manner. Together, these results indicated that compound **13a** may cause mitotic cell death through the activation of the metaphase checkpoint and an apoptosis program (Figure 2A−C).

To ensure that the cells are ready to complete cell division, the mitotic spindle checkpoint plays a crucial role in regulating mitosis. Mitotic catastrophe was defined as centrosome overduplication, multipolar spindle formation, and unbalanced division which seemed to occurr in the **13a** treated H460 cells. In order to clarify whether **13a** induced mitotic catastrophe, immunofluorescence analysis using antibodies against α-tubulin was performed to examine the effect of **13a** at a low concentration of 3 μM on the microtubule organization. Normal microtubule distribution in interphase and metaphase of control H460 cells is shown in Figure 2D (right panel). The microtubule distribution of **13a** treated H460 cells was less extended and showed many aster-like structures (Figure 2D, right panel) when compared to the control with two centrosomes in metaphase (Figure 2D, left panel). Three to four representatives of the **13a**-treated H460 cells (12 h) coimmunostained by α-tubulin and DAPI are shown in Figure 2D in a higher magnification (1000×). These cells showed abnormal centrosome number 9 ± 2 (50 cells were counted) and revealed that the increased centrosomes were localized at each pole of the multiple spindles, and the cells not deriving from equal division appeared. In addition, the immunoblotting analysis results (Figure 2E) showed the increase of two mitotic specific immunoreactivities, MPM2 and cyclin B, in a dose dependent manner upon compound **13a** treatment for 16 h. Together with the immunofluorescence data in Figure 2D, these data clearly demonstrated that compound **13a** treatment induced mitotic arrest but not G2 arrest of H460 cells (G2/M arrest in Figure 2B). Moreover, these data strongly

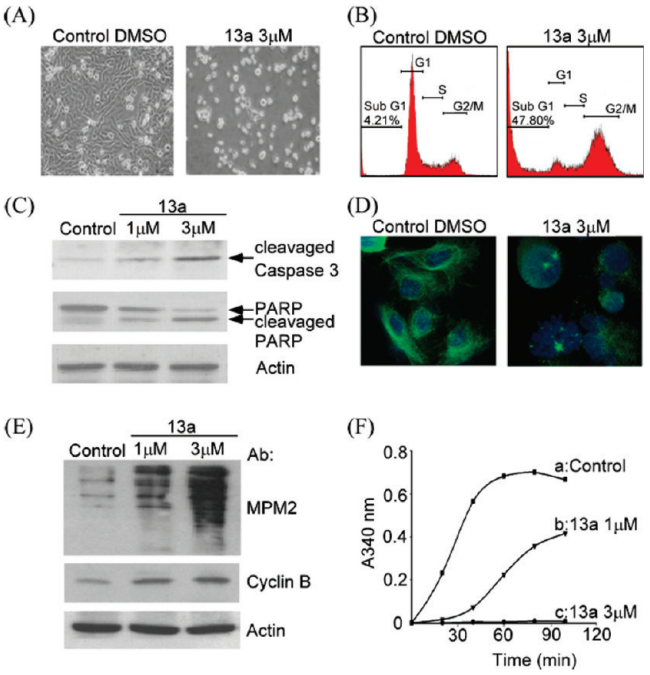

Figure 2. Compound **13a** caused mitotic arrest at G2/M, induced apoptosis and mitotic catastrophe of NCI-H460. (A) H460 cells treated with compound **13a** showed round-up phenotype. (B) Accumulation at G2/M phase accompanied by significant increase of Sub-G1 phase cell population after treatment with compound **13a**. Compound **13a** at 3 μM can induce sub-G1 phase accumulation after 24 h of treatment. (C) Compound **13a** can induce caspase cleavage and activation. (D) Compound **13a** can cause mitotic catastrophe. Compound **13** treated H460 cells were subjected to immunofluorescence analysis using tubulin antibody and DAPI staining. Green color indicated the α-tubulin. (E) Immunoblotting analysis showed the increase of two mitotic specific immunoreactivities, MPM2 and cyclin B, after compound **13a** treatment. (F) Compound **13a** can inhibit the tubulin polymerization in vitro.

suggested that compound **13a** may cause cancer cell apoptosis through inducing mitotic arrest and mitotic catastrophe mechanism.

To investigate the underlying mechanism of how compound **13a** may cause mitotic arrest and mitotic catastrophe, we investigated the inhibitory effects of compound **13a** on microtubule-spindle formation using H460 cells. Turbidity (OD 340 nM) increase indicated the microbutule formation in the in vitro light-scattering assay. Figure 2Fa showed that 5 μg of bovine tubulin can trigger the spontaneous microtubule formation that can be inhibited by preincubation with compound **13a**. Compound **13a** at 1 μM can inhibit about 50% of the microtubule formation (Figure 2Fb) whereas 3 μM can completely inhibit the microtubule formation (Figure 2Fc). These data indicated that the direct binding and inhibition of the microtubule formation may at least play a part in the mechanism of mitotic arrest and mitotic catastrophe induced by compound **13a**.

Molecular Modeling Studies. A possible binding site of **13a**, which was obtained by docking simulation using Autodock 3.0,[39] is proposed herein. A comparison of binding modes of **13a**, paclitaxel, colchicine, and vinblastine is shown in Figure 3A. The binding site of vinblastine is located in the $\alpha_2-\beta_1$ interface, encompassed by T7, H10, and S9 in the α_2 subunit and by H6, T5, and H6−H7 in the β_1 subunit,[40] while that of colchicine is encompassed by S8, S9, T7, H7, and H8 within β subunits, a

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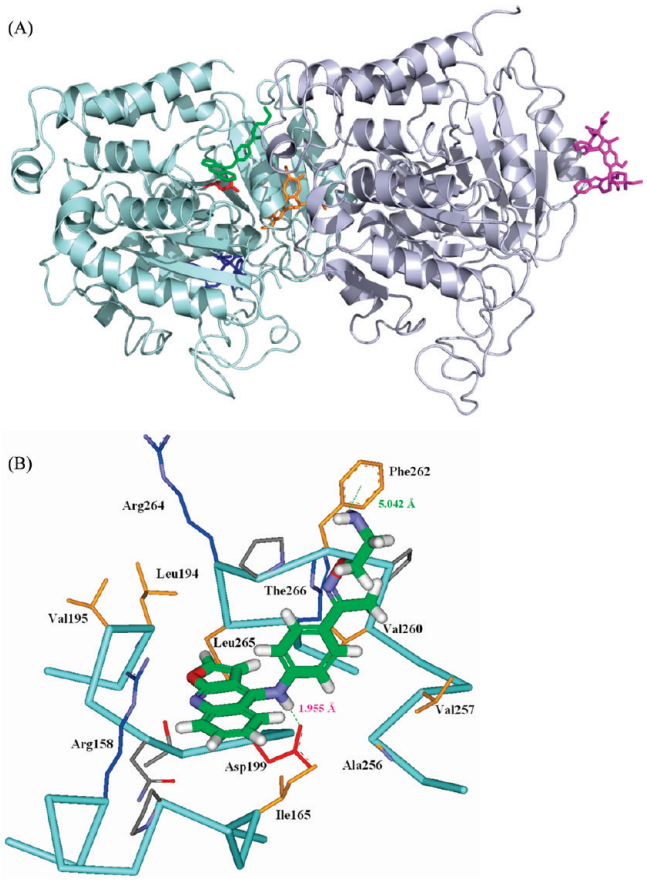

Figure 3. (A) An overview of binding sites of **13a** (in green), paclitaxel (in blue), vinblastine (in pink), and colchicine (in gold) in α-tubuline (in gray) and β-tubuline (in light blue) whose Asp199 side chain is specified in red because it contributes the major interaction with the studied compound. (B) Detailed interaction between β-tubulin (whose backbone is in light blue) and **13a** (in green).

region near the α−β interface within a dimer.[41] Both vinblastine and colchicine can prevent microtubual formation and destabilize polymerization of microtubules.[42] Paclitaxel is bound in the β subunit, and the interaction with M-loop, a connection between S7 and H9, is believed to enhance the polymerization of microtubules.[42] As indicated in Figure 3A, **13a** is bound in a site boxed by H5, H6, H7, H8, S5, and S7 within the β subunit and detailed interaction is illustrated in Figure 3B. The carbonyl of the COOH group of Asp199 is located 1.955 Å from the hydrogen of the 4-NH group of **13a**, whereas the center of mass of the Phe262 benzene ring is located 5.042 Å from the hydrogen of the terminal NH_2 group inducing the formation of the benzene−amine complex.[43] On the other hand, Ile165, Leu194, and Val195 form a hydrophobic cleft to accommodate the furo[2,3-*b*]quinoline moiety of **13a**, whereas Ala256, Val257, and Val260 provide hydrophobic interaction to the para-substituted 4-aniline moiety.

Topoisomerases Assay. The topoisomerases inhibitory activities of compounds **13a**·HCl, **13c**, **14a**, **14c**, **15a**, and **16a** were investigated in vitro. The supercoiled plasmid DNA relaxation experiments were performed according to the protocol described previously.[33] Results indicated no significant topoisomerases I and II inhibitory activities can be detected in all compounds examined, even at 30 μM.

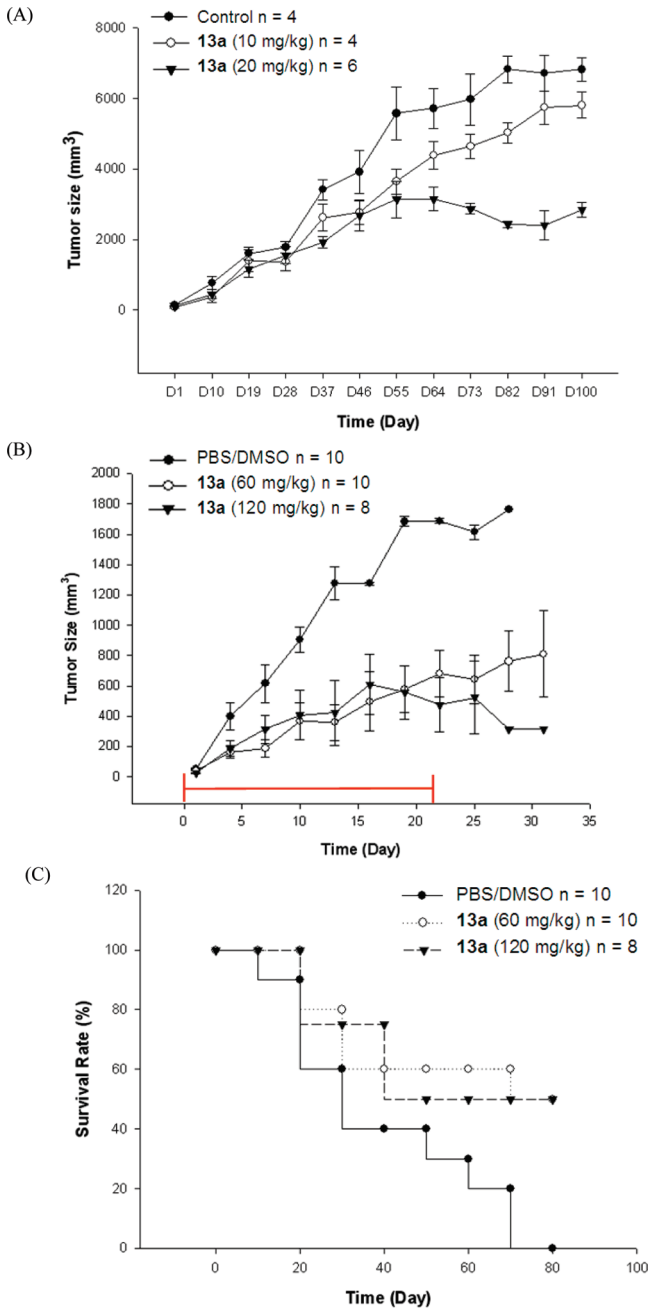

Figure 4. Effects of compound **13a**·HCl against human large cell carcinoma cell line NCI-H460 growth in the xenograft nude mice model: (A) intraperitoneal administration (ip); (B) oral administration (OR); (C) Kaplan−Meier survival analysis.

Xenographic Studies of Lung Cancer Model. Compound **13a**·HCl was evaluated against tumor growth in vivo in a nude mouse xenograft model. In this approach, we first injected 1×10^6 NCI-H460 cells into mice subcutaneously. Until tumorigensis (tumor size reached to 5 mm^3), administration of **13a**·HCl in the peritumoral region lasted for 6 days. Compound **13a**·HCl was dissolved in vehicle, DMSO/Tween 80/PBS (1:1:8). The final administration doses were 10 and 20 mg/kg, respectively for ip injection, while the doses were 60 and 120 mg/kg, respectively, for oral administration. A total of 14 nude mice have been tested (4 for control, 4 for 10 mg/kg concentrations, and 6 for 20 mg/kg

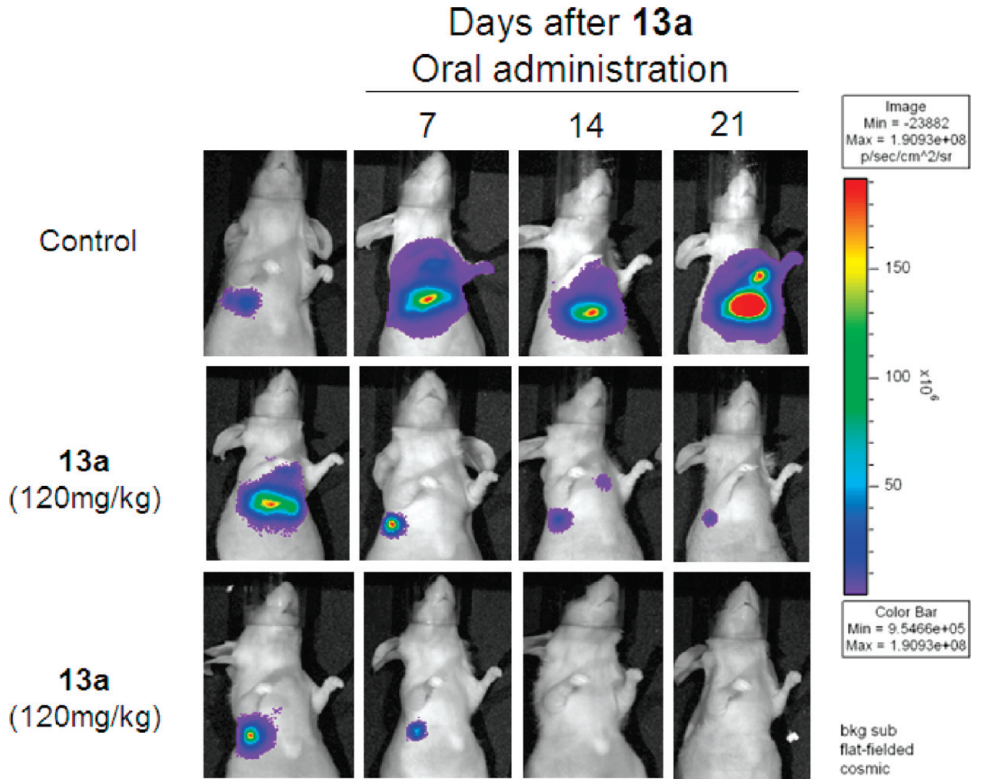

Figure 5. Effects of compound **13a**·HCl against human lung adenocarcinoma H1299 growth in orthotopic murine model.

concentrations). As shown in Figure 4A (ip) and Figure 4B (oral), the tumor size of **13a**·HCl treated nude mice were significantly lower than that of the control. In terms of tumor growth curve, there is a significant difference between treatment of 10 and 20 mg/kg at later period. Although the sample size is only 14, the preliminary results showed the excellent tumor regression and long-term survival of **13a**·HCl-treated mice in the xenograft model. The survival rate has been improved for **13a**·HCl treated nude mice as shown in Figure 4C. Therefore, compound **13a** is a potential anticancer drug candidate that is effective both in vitro and in vivo.

Orthotopic Murine Model of Lung Cancers (H-1229). Compound **13a**·HCl was further investigated in orthotopic lung cancer model in nude mice using H-1229 cells. Results reported in Figure 5 indicated that **13a**·HCl can be absorbed readily through oral administration, distributed to lung tissue, and exhibited significant efficacy in inhibiting the growth of lung cancers.

CONCLUSION

We have synthesized certain aminoalkyl side chain bearing 4-anilinofuro[2,3-*b*]quinoline derivatives for anticancer evaluation. Results indicated that the introduction of an aminoalkyl side chain on the 4-anilinofuro[2,3-*b*]quinoline pharmacophore improved not only water solubility but also selective cytotoxicity. Among them, (*E*)-1-(4-(furo[2,3-*b*]quinolin-4-ylamino)phenyl) ethanone *O*-2-aminoethyloxime (**13a**) is selectively active against the growth of non-small-cell lung carcinoma such as NCI-H460 and NCI-H661. Xenographic studies indicated that the tumor size of the **13a**·HCl treated nude mice was significantly lower than that of the control. Orthotopic lung cancer model in nude mice using H1229 cells further indicated that **13a**·HCl can be absorbed readily through oral administration and distributed to lung tissue and exhibited significant efficacy in inhibiting the growth of lung cancers. These results indicated that **13a** is a potential anticancer drug candidate selectively active against the growth of non-small-cell lung cancers.

EXPERIMENTAL SECTION

General. Melting points were determined on a Electrothermal IA9100 melting point apparatus and are uncorrected. UV spectra (λ_{max} in nm) were recorded in spectroscopic grade MeOH on a Shimadzu UV-160A UV−vis spectrophptometer. Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a Varian-Unity-400 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard. NMR data are given as multiplicity (s = singlet; d = doublet; dd = double doublet; t = triplet; and m = multiplet), numbers of protons, coupling constants (J), and types of protons (Pyr = pyrrolidinyl; Pip = piperidinyl; Mor = morphorlinyl). Thin-layer chromatography was performed on silica gel 60 F-254 plates purchased from E. Merck and Co. High-resolution mass spectroscopic (HRMS) data were provided by the Joint Center for High Valued Instruments at National Sun Yat-sen University using Bruker APEX II (ESI) mass spectrometer. The elemental analyses were performed in the Instrument Center of National Science Council at National Cheng-Kung University and National Chung-Hsing University using a Heraeus CHN-O Rapid EA instrument. Purity of tested compounds was greater than 95%.

(*E*)-1-(4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-Aminoethyloxime (13a). A mixture of 1-[4-(furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone[11] (**1**, 0.30 g, 1 mmol), 2-aminoethoxyamine·HCl[34] (0.28 g, 2.5 mmol), and K_2CO_3 (0.69 g, 5.0 mmol) in EtOH (10 mL) was refluxed for 4 h (TLC monitoring). The mixture was evaporated under reduced pressure to give a residue which was

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dissolved in CH_2Cl_2 (50 mL). The CH_2Cl_2 layer was washed with H_2O, brine, dried (Na_2SO_4), and evaporated. Purification of residue with flash column chromatography (FC, silica gel, MeOH/CH_2Cl_2 = 1/50) and then crystallization from EtOH gave **13a** (0.45 g, 96%). Mp: 112−113 °C. IR (KBr): 3216, 1578, 1517. UV (MeOH): 372 (4.22), 260 (4.52), 208 (4.53). ^{1}H NMR (400 MHz, DMSO-d_6): 2.29 (s, 3H, CH_3), 3.17 (m, 2H, $OCH_2\underline{CH_2}N$), 4.35 (t, 2H, J = 5.0 Hz, $O\underline{CH_2}CH_2N$), 5.94 (d, 1H, J = 2.8 Hz, 3-H), 7.33−7.35 (m, 2H, ArH), 7.57−7.61 (m, 1H, 6-H), 7.78−7.88 (m, 4H, 2-, 7-H, ArH), 8.00 (d, 1H, J = 8 0.0 Hz, 5-H), 8.23 (br s, 2H, NH_2), 8.60 (d, 1H, J = 8.4 Hz, 8-H), 10.37 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 12.63, 38.27, 69.78, 103.86, 106.07, 117.21, 122.75 (2C), 123.76, 123.95, 125.02, 127.01 (2C), 130.81, 131.82, 141.60, 141.98, 143.07, 144.76, 155.14, 160.44. Anal. Calcd for $C_{21}H_{20}N_4O_2 \cdot 0.6H_2O \cdot 0.5HCl$: C, 64.77; H, 5.62; N, 14.39. Found: C, 64.88; H, 5.97; N, 14.17. HRMS (ESI) calcd for $C_{21}H_{21}N_4O_2$ $[M + H]^+$ 361.1664, found 361.1663.

A mixture of **13a** (0.38 g) and 6 N HCl (2 mL) in EtOH (20 mL) was stirred for 2 h at room temperature. The precipitate was collected and crystallized from EtOH to give **13a**·HCl. Anal. Calcd for $C_{21}H_{20}N_4O_2 \cdot 0.6H_2O \cdot 1.8HCl$: C, 57.74; H, 5.31; N, 12.83. Found: C, 58.07; H, 5.71; N, 12.43.

(*E*)-1-(4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-(Dimethylamino)ethyloxime (13b). **13b** was obtained from **1** and 2-dimethylaminoethoxyamine·HCl as described for **13a**: 90% yield as a deep brown liquid. IR (KBr): 3221, 1578, 1519. UV (MeOH): 372 (4.18), 260 (4.48), 208 (4.50). ^{1}H NMR (400 MHz, $CDCl_3$): 2.27 (s, 3H, CH_3), 2.37 (s, 6H, $N(CH_3)_2$), 2.74 (t, 2H, J = 5.8 Hz, $OCH_2\underline{CH_2}N$), 4.35 (t, 2H, J = 5.8 Hz, $O\underline{CH_2}CH_2N$), 6.19 (d, 1H, J = 2.8 Hz, 3-H), 6.90 (br s, 1H, NH), 7.15−7.17 (m, 2H, ArH), 7.47−7.52 (m, 2H, 2-H, 6-H), 7.67−7.74 (m, 3H, 7-H, ArH), 8.04 (dd, 1H, J = 8.8, 1.2 Hz, 5-H), 8.09 (dd, 1H, J = 8.8, 2.4 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.74, 45.91 (2C), 58.20, 72.29, 105.73, 106.09, 118.31, 120.61, 120.92 (2C), 123.86, 127.10 (2C), 129.21, 129.23, 132.12, 140.27, 141.68, 142.84, 145.99, 154.00, 163.28. Anal. Calcd for $C_{23}H_{24}N_4O_2 \cdot 2.0H_2O \cdot 1.1HCl$: C, 59.46; H, 6.31; N, 12.06. Found: C, 59.68; H, 6.40; N, 11.77. HRMS (ESI) calcd for $C_{23}H_{25}N_4O_2$ $[M + H]^+$ 389.1977, found 389.1979.

(*E*)-1-(4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-3-Aminopropyloxime (13c). **13c** was obtained from **1** and 3-aminopropoxyamine·HCl as described for **13a**: 96% yield. Mp: 83−85 °C. IR (KBr): 3237, 1578, 1517. UV (MeOH): 366 (4.20), 258 (4.48), 210 (4.50). ^{1}H NMR (400 MHz, $CDCl_3$): 1.90 (quin, 2H, J = 6.4 Hz, $OCH_2\underline{CH_2}CH_2N$), 2.25 (s, 3H, CH_3), 2.88 (t, 2H, J = 6.8 Hz, $OCH_2CH_2\underline{CH_2}N$), 4.30 (t, 2H, J = 6.0 Hz, $O\underline{CH_2}CH_2CH_2N$), 6.17 (d, 1H, J = 2.8 Hz, 3-H), 7.03 (br s, 1H, NH), 7.14−7.17 (m, 2H, ArH), 7.46−7.50 (m, 2H, 2-H, 6-H), 7.66−7.73 (m, 3H, 7-H, ArH), 8.04−8.10 (m, 2H, 5-H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.54, 33.25, 39.34, 72.01, 105.74, 106.01, 118.31, 120.69, 120.98 (2C), 123.79, 127.01 (2C), 129.16, 129.18, 132.14, 140.39, 141.67, 142.76, 145.97, 153.72, 163.27. Anal. Calcd for $C_{22}H_{22}N_4O_2 \cdot 0.9H_2O$: C, 67.64; H, 6.14; N, 14.34. Found: C, 67.97; H, 6.32; N, 14.02. HRMS (ESI) calcd for $C_{22}H_{23}N_4O_2$ $[M + H]^+$ 375.1821, found 375.1823.

(*E*)-1-(4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-3-(Dimethylamino)propyloxime (13d). **13d** was obtained from **1** and 3-dimethylaminopropoxyamine·HCl as described for **13a**: 75% yield. Mp: 83−85 °C. IR (KBr): 3219, 1578, 1519. UV (MeOH): 368 (4.26), 258 (4.53), 210 (4.53). ^{1}H NMR (400 MHz, $CDCl_3$): 1.99−2.06 (m, 2H, $OCH_2\underline{CH_2}CH_2N$), 2.25 (s, 3H, CH_3), 2.39 (s, 6H, $N(\underline{CH_3})_2$), 2.59 (t, 2H, J = 7.6 Hz, $OCH_2CH_2\underline{CH_2}N$), 4.26 (t, 2H, J = 6.2 Hz, $O\underline{CH_2}CH_2CH_2N$), 6.19 (d, 1H, J = 2.8 Hz, 3-H), 6.93 (br s, 1H, NH), 7.14−7.17 (m, 2H, ArH), 7.47−7.52 (m, 2H, 2-H, 6-H), 7.67−7.74 (m, 3H, 7-H, ArH), 8.04−8.10 (m, 2H, 8-H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.52, 26.93, 44.93 (2C), 56.34, 71.99, 105.74, 106.07, 118.34, 120.75, 120.96 (2C), 123.81, 127.03 (2C), 129.14, 129.19, 132.07, 140.40, 141.75, 142.77, 145.97, 153.92, 163.27. Anal. Calcd for $C_{24}H_{26}N_4O_2 \cdot 0.5H_2O$: C, 67.43; H, 6.39; N, 13.11. Found: C, 67.35; H, 6.69; N, 12.94. HRMS (ESI) calcd for $C_{24}H_{27}N_4O_2$ $[M + H]^+$ 403.2134, found 403.2136.

(*E*)-1-(4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-(Pyrrolidin-1-yl)ethyloxime (13e). **13e** was obtained from **1** and 2-pyrrolidin-1-ylethoxyamine·HCl as described for **13a**: 61% yield as a brown liquid. IR (KBr): 3217, 1577, 1519. UV (MeOH): 372 (4.22), 260 (4.56), 208 (4.51). ^{1}H NMR (400 MHz, $CDCl_3$): 2.06−2.10 (m, 4H, Pyr-H), 2.26 (s, 3H, CH_3), 3.24 (br s, 4H, Pyr-H), 3.35 (t, 2H, J = 4.8 Hz, $OCH_2\underline{CH_2}N$), 4.60−4.63 (m, 2H, $O\underline{CH_2}CH_2N$), 6.23 (d, 1H, J = 2.8 Hz, 3-H), 7.15−7.18 (m, 2H, ArH), 7.29 (br s, 1H, NH), 7.46−7.51 (m, 2H, 2-H, 6-H), 7.63−7.66 (m, 2H, ArH), 7.69−7.73 (m, 1H, 7-H), 8.07−8.14 (m, 2H, 8-H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.87, 23.27 (2C), 53.80, 54.27 (2C), 69.56, 105.71, 106.51, 118.65, 120.44 (2C), 121.11, 123.86, 127.10 (2C), 129.10, 129.24, 130.76, 140.15, 142.48, 142.92, 146.00, 155.58, 163.22. Anal. Calcd for $C_{25}H_{26}N_4O_2 \cdot 1.0H_2O \cdot 1.0HCl$: C, 64.03; H, 6.23; N, 11.95. Found: C, 64.19; H, 6.44; N, 11.87. HRMS (ESI) calcd for $C_{25}H_{27}N_4O_2$ $[M + H]^+$ 415.2134, found 415.2135.

(*E*)-1-(4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-(Piperidin-1-yl)ethyloxime (13f). **13f** was obtained from **1** and 2-piperidin-1-ylethoxyamine·HCl as described for **13a**: 85% yield as a brown liquid. IR (KBr): 3221, 1579, 1519. UV (MeOH): 368 (4.15), 260 (4.51), 206 (4.51). ^{1}H NMR (400 MHz, $CDCl_3$): 1.44−1.48 (m, 2H, Pip-H), 1.57−1.65 (m, 4H, Pip-H), 2.25 (s, 3H, CH_3), 2.53−2.78 (m, 4H, Pip-H), 3.81 (t, 2H, J = 5.6 Hz, $OCH_2\underline{CH_2}N$), 4.37 (t, 2H, J = 6.0 Hz, $O\underline{CH_2}CH_2N$), 6.18 (d, 1H, J = 2.4 Hz, 3-H), 7.02 (br s, 1H, NH), 7.14−7.17 (m, 2H, ArH), 7.46−7.50 (m, 2H, 2-H, 6-H), 7.66−7.73 (m, 3H, 7-H, ArH), 8.05−8.10 (m, 2H, 8-H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.65, 24.13, 25.79, 25.87, 54.89, 54.93, 57.85, 72.18, 105.72, 106.06, 118.34, 120.72, 120.94 (2C), 123.78, 127.04 (2C), 129.17 (2C), 132.11, 140.38, 141.71, 142.77, 145.99, 153.83, 163.28. HRMS (ESI) calcd for $C_{26}H_{29}N_4O_2$ $[M + H]^+$ 429.2290, found 429.2292.

(*E*)-1-(4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-Morpholinoethyloxime (13g). **13g** was obtained from **1** and 2-morpholinoethoxyamine·HCl as described for **13a**: 73% yield. Mp 92−93 °C. IR (KBr): 3269, 1578, 1518. UV (MeOH): 372 (4.33), 260 (4.67), 208 (4.62). ^{1}H NMR (400 MHz, $CDCl_3$): 2.25 (s, 3H, CH_3), 2.58−2.60 (m, 4H, Mor-H), 2.78 (t, 2H, J = 5.6 Hz, $OCH_2\underline{CH_2}N$), 3.73−3.76 (m, 4H, Mor-H), 4.37 (t, 2H, J = 5.6 Hz, $O\underline{CH_2}CH_2N$), 6.18 (d, 1H, J = 2.8 Hz, 3-H), 6.97 (br s, 1H, NH), 7.14−7.17 (m, 2H, ArH), 7.46−7.50 (m, 2H, 2-H, 6-H), 7.66−7.73 (m, 3H, 7-H, ArH), 8.04−8.10 (m, 2H, 8-H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.70, 54.05 (2C), 57.61, 60.95 (2C), 72.03, 105.70, 106.13, 118.36, 120.66, 120.88 (2C), 123.84, 127.06 (2C), 129.19 (2C), 131.97, 140.28, 141.78, 142.83, 145.98, 154.02, 163.26. Anal. Calcd for $C_{25}H_{26}N_4O_3 \cdot 0.5H_2O$: C, 68.32; H, 6.19; N, 12.75. Found: C, 68.20; H, 6.21; N, 12.78. HRMS (ESI) calcd for $C_{25}H_{27}N_4O_3$ $[M + H]^+$ 431.2083, found 431.2080.

(*E*)-1-(4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-4-Morpholinobutyloxime (13h). **13h** was obtained from **1** and 4-morpholinobutoxyamine·HCl as described for **13a**: 73% yield. Mp: 87−88 °C. IR (KBr): 3263, 1579, 1518. UV (MeOH): 368 (4.23), 260 (4.60), 208 (4.57). ^{1}H NMR (400 MHz, $CDCl_3$): 1.62−1.79 (m, 4H, $OCH_2(\underline{CH_2})_2CH_2N$), 2.25 (s, 3H, CH_3), 2.38−2.46 (m, 6H, OCH_2-$(CH_2)_2\underline{CH_2}N$, Mor-H), 3.72−3.74 (m, 4H, Mor-H), 4.23 (t, 2H, J = 5.6 Hz, $O\underline{CH_2}(CH_2)_2CH_2N$), 6.16 (d, 1H, J = 2.8 Hz, 3-H), 7.06 (br s, 1H, NH), 7.14−7.16 (m, 2H, ArH), 7.45−7.46 (m, 2H, 2-H, 6-H), 7.66−7.70 (m, 3H, 7-H, ArH), 8.04−8.09 (m, 2H, 8-H, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.54, 23.07, 27.18, 53.68 (2C), 58.82, 66.93 (2C), 73.94, 105.72, 105.99, 118.30, 120.69, 121.00 (2C), 123.78, 126.99 (2C), 129.14, 129.18, 132.23, 140.42, 141.64, 142.74, 145.96, 153.60, 163.27. Anal. Calcd for $C_{27}H_{30}N_4O_3 \cdot 0.8H_2O$: C, 68.56; H,

6.73; N, 11.84. Found: C, 68.47; H, 6.94; N, 11.81. HRMS (ESI) calcd for $C_{27}H_{31}N_4O_3$ 459.2396, found $[M + H^+]$ 459.2399.

(*E*)-1-(4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)phenyl)-ethanone *O*-2-Aminoethyloxime (14a). **14a** was obtained from 1-[4-(3-chlorofuro[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**10**)[14] and 2-aminoethoxyamine·HCl as described for **13a**: 95% yield. Mp: 169−172 °C. IR (KBr): 3146, 1580, 1514. UV (MeOH): 382 (4.09), 264 (4.32), 236 (4.53), 208 (4.52). ^{1}H NMR (400 MHz, $CDCl_3$): 2.22 (s, 3H, CH_3), 3.04 (t, 2H, J = 5.2 Hz, $OCH_2\underline{CH_2}N$), 4.22 (t. 2H, J = 5.2 Hz, $O\underline{CH_2}CH_2N$), 6.86−6.89 (m, 2H, ArH), 7.18 (br s, 1H, NH), 7.29−7.34 (m, 1H, 6-H), 7.53−7.56 (m, 2H, ArH), 7.66−7.70 (m, 2H, 2-H, 7-H), 7.81 (dd, 1H, J = 8.8, 0.8 Hz, 5-H), 8.06 (d, J = 8.8 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.56, 41.55, 75.66, 107.99, 110.11, 118.09 (2C), 120.05, 123.99, 124.41, 127.11 (2C), 129.09, 129.89, 130.68, 140.65, 141.53, 144.62, 146.77, 154.44, 160.73. Anal. Calcd for $C_{21}H_{19}ClN_4O_2 \cdot 0.4H_2O$: C, 62.74; H, 4.96; N, 13.94. Found: C, 62.40; H, 5.17; N, 13.76. HRMS (ESI) calcd for $C_{21}H_{20}ClN_4O_2$ $[M + H]^+$ 395.1275, found 395.1274.

(*E*)-1-(4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)phenyl)-ethanone *O*-2-(Dimethylamino)ethyloxime (14b). **14b** was obtained from **10** and 2-dimethylaminoethoxyamine·HCl as described for **13a**: 97% yield. Mp: 118−122 °C. IR (KBr): 3398, 1578, 1520. UV (MeOH): 382 (4.12), 264 (4.33), 234 (4.50), 210 (4.48). ^{1}H NMR (400 MHz, $CDCl_3$): 2.22 (s, 3H, CH_3), 2.51 (s, 6H, $N(CH_3)_2$), 2.94 (t, 2H, J = 5.4 Hz, $OCH_2\underline{CH_2}N$), 4.42 (t, 2H, J = 5.4 Hz, $O\underline{CH_2}CH_2N$), 6.86−6.90 (m, 2H, ArH), 7.19 (br s, 1H, NH), 7.32−7.36 (m, 1H, 6-H), 7.53−7.56 (m, 2H, ArH), 7.67−7.71 (m, 2H, 2-H, 7-H), 7.83−7.86 (m, 1H, 5-H), 8.07−8.09 (m, 1H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.78, 45.10 (2C), 57.48, 70.87, 110.10, 117.10, 118.01 (2C), 120.09, 124.02, 124.39, 127.14 (2C), 129.10, 129.91, 130.38, 140.70, 141.44, 144.75, 146.75, 154.77, 160.72. Anal. Calcd for $C_{23}H_{23}ClN_4O_2 \cdot 1.5H_2O$: C, 61.40; H, 5.83; N, 12.45. Found: C, 61.17; H, 5.98; N, 12.09. HRMS (ESI) calcd for $C_{23}H_{24}ClN_4O_2$ $[M + H]^+$ 423.1588, found 423.1587.

(*E*)-1-(4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)phenyl)-ethanone *O*-3-Aminopropyloxime (14c). **14c** was obtained from **10** and 3-aminopropoxyamine·HCl as described for **13a**: 98% yield. Mp: 114−116 °C. IR (KBr): 3143, 1579, 1512. UV (MeOH): 382 (4.11), 264 (4.32), 234 (4.50), 210 (4.49). ^{1}H NMR (400 MHz, $CDCl_3$): 1.92 (quin, 2H, J = 6.4 Hz, $OCH_2\underline{CH_2}CH_2N$), 2.19 (s, 3H, CH_3), 2.90 (t, 2H, J = 6.8 Hz, $OCH_2CH_2\underline{CH_2}N$), 4.26 (t, 2H, J = 6.0 Hz, $O\underline{CH_2}CH_2CH_2N$), 6.87−6.90 (m, 2H, ArH), 7.19 (br s, 1H, NH), 7.30−7.34 (m, 1H, 6-H), 7.53−7.56 (m, 2H, ArH), 7.66−7.70 (m, 2H, 2-H, 7-H), 7.82 (dd, 1H, J = 8.4, 1.0 Hz, 5-H), 8.06 (d, 1H, J = 8.4 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.55, 32.43, 39.09, 71.75, 107.94, 110.13, 118.16 (2C), 120.04, 123.98, 124.43, 127.09 (2C), 129.08, 129.90, 130.83, 140.63, 141.61, 144.56, 146.78, 154.02, 160.75. HRMS (ESI) calcd for $C_{22}H_{22}ClN_4O_2$ $[M + H]^+$ 409.1431, found 409.1430.

(*E*)-1-(4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)phenyl)-ethanone *O*-3-(Dimethylamino)propyloxime (14d). **14d** was obtained from **10** and 3-dimethylaminopropoxyamine·HCl as described for **13a**: 96% yield. Mp: 104−106 °C. IR (KBr): 3147, 1578, 1520. UV (MeOH): 382 (4.17), 266 (4.45), 236 (4.62), 208 (4.59). ^{1}H NMR (400 MHz, $CDCl_3$): 1.87−1.94 (m, 2H, $OCH_2\underline{CH_2}CH_2N$), 2.20 (s, 3H, CH_3), 2.26 (s, 6H, $N(CH_3)_2$), 2.39−2.42 (m, 2H, $OCH_2CH_2\underline{CH_2}N$), 4.21 (t, 2H, J = 6.4 Hz, $O\underline{CH_2}CH_2CH_2N$), 6.87−6.90 (m, 2H, ArH), 7.18 (br s, 1H, NH), 7.30−7.34 (m, 1H, 6-H), 7.54−7.57 (m, 2H, ArH), 7.66−7.70 (m, 2H, 2-H, 7-H), 7.82 (dd, 1H, J = 8.6, 1.0 Hz, 5-H), 8.06 (d, 1H, J = 8.4 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.49, 27.52, 45.44 (2C), 56.52, 72.29, 107.86, 110.11, 118.18 (2C), 119.99, 123.94, 124.46, 127.06 (2C), 129.08, 129.87, 131.04, 140.58, 141.65, 144.43, 146.80, 153.75, 160.74. Anal. Calcd for $C_{24}H_{25}ClN_4O_2 \cdot 0.5H_2O$: C, 64.64; H, 5.88; N, 12.56. Found: C, 64.41; H, 6.03; N, 12.77. HRMS (ESI) calcd for $C_{24}H_{26}ClN_4O_2$ $[M + H]^+$ 437.1744, found 437.1747.

(*E*)-1-(4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)phenyl)-ethanone *O*-2-(Pyrrolidin-1-yl)ethyloxime (14e). **14e** was obtained from **10** and 2-pyrrolidin-1-ylethoxyamine·HCl as described for **13a**: 92% yield. Mp: 208−210 °C. IR (KBr): 3241, 1578, 1513. UV (MeOH): 382 (4.15), 286 (4.31), 264 (4.37), 236 (4.58). ^{1}H NMR (400 MHz, $CDCl_3$): 2.12 (br s, 4H, Pyr-H), 2.22 (s, 3H, CH_3), 3.32−3.40 (m, 6H, Pyr-H, $OCH_2\underline{CH_2}N$), 4.62−4.65 (m, 2H, $O\underline{CH_2}CH_2N$), 6.87−6.90 (m, 2H, ArH), 7.19 (br s, 1H, NH), 7.33−7.37 (m, 1H, 6-H), 7.53−7.56 (m, 2H, ArH), 7.68−7.73 (m, 2H, 2-H, 7-H), 7.84−7.87 (m, 1H, 5-H), 8.08−8.10 (m, 1H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.86, 23.26 (2C), 53.66, 54.20 (2C), 69.26, 108.36, 110.10, 117.80 (2C), 120.27, 124.12, 124.28, 127.20 (2C), 129.16, 129.68, 129.94, 140.85, 141.21, 145.15, 146.75, 155.76, 160.72. Anal. Calcd for $C_{25}H_{25}ClN_4O_2 \cdot 0.2H_2O \cdot 1.0H_2O$: C, 61.40; H, 5.44; N, 11.46. Found: C, 61.61; H, 5.64; N, 11.16. HRMS (ESI) calcd for $C_{25}H_{26}ClN_4O_2$ $[M + H]^+$ 449.1744, found 449.1746.

(*E*)-1-(4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)phenyl)-ethanone *O*-2-(Piperidin-1-yl)ethyloxime (14f). **14f** was obtained from **10** and 2-piperidin-1-ylethoxyamine·HCl as described for **13a**: 69% yield. Mp: 136−138 °C. IR (KBr): 3386, 1578, 1516. UV (MeOH): 382 (4.17), 266 (4.49), 236 (4.62), 206 (4.66). ^{1}H NMR (400 MHz, $CDCl_3$): 1.41−1.65 (m, 6H, Pip-H), 2.20 (s, 3H, CH_3), 2.52 (br s, 4H, Pip-H), 2.75 (t, 2H, J = 6.0 Hz, $OCH_2\underline{CH_2}N$), 4.23 (t, 2H, J = 6.2 Hz, $O\underline{CH_2}CH_2N$), 6.86−6.90 (m, 2H, ArH), 7.18 (br s, 1H, NH), 7.30−7.35 (m, 1H, 6-H), 7.54−7.57 (m, 2H, Ar−H), 7.67−7.57 (m, 2H, 2-H, 7-H), 7.82−7.86 (m, 1H, 5-H), 8.06−8.09 (m, 1H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.65, 24.08, 25.80 (2C), 54.88 (2C), 57.78, 72.01, 107.91, 110.10, 118.13 (2C), 120.00, 123.95, 124.44, 127.08 (2C), 129.08, 129.87, 130.86, 140.61, 141.59, 144.49, 146.77, 153.96, 160.73. Anal. Calcd for $C_{26}H_{27}ClN_4O_2 \cdot 1.1H_2O \cdot 1.0$ HCl: C, 60.14; H, 5.86; N, 10.79. Found: C, 59.92; H, 6.12; N, 10.47. HRMS (ESI) calcd for $C_{26}H_{28}ClN_4O_2$ $[M + H]^+$ 463.1901, found 463.1904.

(*E*)-1-(4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)phenyl)-ethanone *O*-2-Morpholinoethyloxime (14g). **14g** was obtained from **10** and 2-morpholinoethoxyamine·HCl as described for **13a**: 96% yield. Mp: 121−122 °C. IR (KBr): 3391, 1579, 1514. UV (MeOH): 382 (4.11), 264 (4.34), 234 (4.50), 210 (4.49). ^{1}H NMR (400 MHz, $CDCl_3$): 2.19 (s, 3H, CH_3), 2.54−2.57 (m, 4H, Mor-H), 2.75 (t, 2H, J = 5.6 Hz, $OCH_2\underline{CH_2}N$), 3.72−3.74 (m, 4H, Mor-H), 4.33 (t, 2H, J = 5.6 Hz, $O\underline{CH_2}CH_2N$), 6.86−6.89 (m, 2H, ArH), 7.18 (br s, 1H, NH), 7.28−7.33 (m, 1H, 6-H), 7.52−7.56 (m, 2H, ArH), 7.67−7.70 (m, 2H, 2-H, 7-H), 7.81 (dd, 1H, J = 8.8, 0.8 Hz, 5-H), 8.06 (dd, 1H, J = 8.6, 0.6 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.63, 53.98 (2C), 57.54, 66.90 (2C), 71.87, 107.97, 110.06, 117.97 (2C), 120.03, 123.91, 124.33, 127.03 (2C), 129.00, 129.82, 130.60, 140.60, 141.44, 144.56, 146.67, 154.03, 160.66. Anal. Calcd for $C_{25}H_{25}ClN_4O_3 \cdot 1.0H_2O \cdot 0.5$HCl: C, 59.91; H, 5.53; N, 11.18. Found: C, 60.05; H, 5.68; N, 10.88. HRMS (ESI) calcd for $C_{25}H_{26}ClN_4O_3$ $[M + H]^+$ 465.1693, found 465.1695.

(*E*)-1-(4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)phenyl)-ethanone *O*-4-Morpholinobutyloxime (14h). **14h** was obtained from **10** and 4-morpholinobutoxyamine·HCl as described for **13a**: 86% yield. Mp: 112−113 °C. IR (KBr): 3138, 1614, 1580, 1512. UV (MeOH): 382 (4.14), 266 (4.45), 236 (4.58), 206 (4.56). ^{1}H NMR (400 MHz, $CDCl_3$): 1.60−1.77 (m, 4H, $OCH_2(\underline{CH_2})_2CH_2N$), 2.20 (s, 3H, CH_3), 2.40 (t, 2H, J = 7.6 Hz, $OCH_2(CH_2)_2\underline{CH_2}N$), 2.46 (br s, 4H, Mor-H), 3.72−3.74 (m, 4H, Mor-H), 4.19 (t, 2H, J = 6.4 Hz, $O\underline{CH_2}(CH_2)_2CH_2N$), 6.86−6.90 (m, 2H, ArH), 7.17 (br s, 1H, NH), 7.30−7.34 (m, 1H, 6-H), 7.53−7.57 (m, 2H, ArH), 7.66−7.71 (m, 2H, 2-H), 7.82 (dd, 1H, J = 8.4, 1.2 Hz, 5-H), 8.06 (dd, 1H, J = 8.4, 0.4 Hz, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.53, 23.04, 27.17 (2C), 53.67 (2C), 58.82, 66.90, 73.84, 107.90, 110.12, 118.19 (2C), 120.01, 123.95,

124.45, 127.06 (2C), 129.11, 129.87, 131.04, 140.61, 141.63, 144.46, 146.81, 153.70, 160.75. Anal. Calcd for $C_{27}H_{29}ClN_4O_3 \cdot 0.3H_2O$: C, 65.06; H, 5.99; N, 11.24. Found: C, 64.96; H, 6.25; N, 11.07. HRMS (ESI) calcd for $C_{27}H_{30}ClN_4O_3$ $[M + H]^+$ 493.2006, found 493.2004.

(*E*)-1-(4-(7-Methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-Aminoethyloxime (15a). **15a** was obtained from 1-[4-(7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**11**)[14] and 2-aminoethoxyamine·HCl as described for **13a**: 66% yield. Mp: 91−93 °C. IR (KBr): 3219, 1581, 1517. UV (MeOH): 358 (4.22), 248 (4.44), 212 (4.48). ^{1}H NMR (400 MHz, DMSO-d_6): 2.22 (s, 3H, CH_3), 2.88 (t, 2H, J = 5.8 Hz, $OCH_2\underline{CH_2}N$), 3.92 (s, 3H, OCH_3), 4.12 (t, 2H, J = 5.8 Hz, $O\underline{CH_2}CH_2N$), 6.08 (d, 1H, J = 2.4 Hz, 3-H), 7.13−7.19 (m, 3H, 6-H, ArH), 7.29 (d, 1H, J = 2.4 Hz, 2-H), 7.66−7.69 (m, 2H, ArH), 7.74 (d, 1H, J = 2.8 Hz, 8-H), 8.27 (d, 1H, J = 9.6 Hz, 5-H), 9.48 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 12.20, 40.72, 55.35, 75.17, 103.70, 105.72, 106.75, 113.14, 115.49, 120.69 (2C), 124.39, 126.59 (2C), 130.28, 141.47, 142.06, 142.73, 147.70, 153.70, 160.09, 163.44. HRMS (ESI) calcd for $C_{22}H_{23}N_4O_3$ $[M + H]^+$ 391.1770, found 391.1769.

(*E*)-1-(4-(7-Methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-(Dimethylamino)ethyloxime (15b). **15b** was obtained from **11** and 2-dimethylaminoethoxyamine·HCl as described for **13a**: 88% yield. Mp: 150−152 °C. IR (KBr): 3256, 1580, 1518. UV (MeOH): 360 (4.26), 250 (4.47), 210 (4.50). ^{1}H NMR (400 MHz, $CDCl_3$): 2.26 (s, 3H, CH_3), 2.36 (s, 6H, $N(CH_3)_2$), 2.75 (t, 2H, J = 5.8 Hz, $OCH_2\underline{CH_2}N$), 3.95 (s, 3H, OCH_3), 4.34 (t, 2H, J = 5.8 Hz, $O\underline{CH_2}CH_2N$), 6.16 (d, 1H, J = 2.4 Hz, 3-H), 6.95 (br s, 1H, NH), 7.10−7.15 (m, 3H, 6-H, ArH), 7.39 (d, 1H, J = 2.4 Hz, 2-H), 7.40 (d, 1H, J = 2.8 Hz, 8-H), 7.65−7.68 (m, 2H, ArH), 7.92 (d, 1H, J = 9.2 Hz, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.70, 45.85 (2C), 55.48, 58.17, 72.21, 104.80, 105.74, 107.20, 113.24, 116.74, 120.72 (2C), 122.04, 127.04 (2C), 131.86, 140.47, 141.80, 141.87, 148.04, 154.04, 160.57, 163.85. Anal. Calcd for $C_{24}H_{26}N_4O_3 \cdot 0.5H_2O$: C, 67.43; H, 6.37; N, 13.11. Found: C, 67.43; H, 6.58; N, 12.83. HRMS (ESI) calcd for $C_{24}H_{27}N_4O_3$ $[M + H]^+$ 419.2083, found 419.2086.

(*E*)-1-(4-(7-Methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-3-Aminopropyloxime (15c). **15c** was obtained from **11** and 3-aminopropoxyamine·HCl as described for **13a**: 68% yield as a light yellow liquid. IR (KBr): 3220, 1582, 1518. UV (MeOH): 362 (4.12), 260 (4.35), 210 (4.40). ^{1}H NMR (400 MHz, DMSO-d_6): 1.82 (quin, 2H, J = 6.6 Hz, $OCH_2\underline{CH_2}CH_2N$), 2.20 (s, 3H, CH_3), 2.73 (t, 2H, J = 6.8 Hz, $OCH_2CH_2\underline{CH_2}N$), 3.92 (s, 1H, OCH_3), 4.19 (t, 2H, J = 6.4 Hz, $O\underline{CH_2}CH_2CH_2N$), 6.08 (d, 1H, J = 2.4 Hz, 3-H), 7.12−7.18 (m, 3H, 6-H, ArH), 7.28 (d, 1H, J = 2.4 Hz, 2-H), 7.66−7.69 (m, 2H, ArH), 7.74 (d, 1H, J = 2.8 Hz, 8-H), 8.28 (d, 1H, J = 9.6 Hz, 5-H), 9.50 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 12.11, 31.28, 37.87, 55.34, 71.14, 103.68, 105.72, 106.74, 113.14, 115.46, 120.68 (2C), 124.40, 126.54 (2C), 130.29, 141.47, 142.05, 142.71, 147.70, 153.36, 160.08, 163.43. HRMS (ESI) calcd for $C_{23}H_{25}N_4O_3$ $[M + H]^+$ 405.1927, found 405.1926.

(*E*)-1-(4-(7-Methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-3-(Dimethylamino)propyloxime (15d). **15d** was obtained from **11** and 3-dimethylaminopropoxyamine·HCl as described for **13a**: 79% yield. Mp: 95−97 °C. IR (KBr): 3327, 1580, 1516. UV (MeOH): 364 (4.32), 264 (4.60), 206 (4.61). ^{1}H NMR (400 MHz, DMSO-d_6): 1.82 (quin, 2H, J = 6.6 Hz, $OCH_2\underline{CH_2}CH_2N$), 2.18 (s, 6H, $N(\underline{CH_3})_2$), 2.19 (s, 3H, CH_3), 2.37 (t, 2H, J = 7.2 Hz, $OCH_2CH_2\underline{CH_2}N$), 3.92 (s, 1H, OCH_3), 4.15 (t, 2H, J = 6.4 Hz, $O\underline{CH_2}CH_2CH_2N$), 6.08 (d, 1H, J = 2.8 Hz, 3-H), 7.13−7.19 (m, 3H, 6-H, ArH), 7.29 (d, 1H, J = 2.4 Hz, 2-H), 7.66−7.68 (m, 2H, ArH), 7.74 (d, 1H, J = 2.8 Hz, 8-H), 8.27 (d, 1H, J = 9.2 Hz, 5-H), 9.47 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 12.11, 26.81, 44.97 (2C), 55.34, 55.67, 71.60, 103.68, 105.72, 106.75, 113.13, 115.46, 120.69 (2C), 124.38, 126.54 (2C), 130.33, 141.47, 142.05, 142.68, 147.70, 153.31, 160.08, 163.43. Anal. Calcd for $C_{25}H_{28}N_4O_3 \cdot 1.2H_2O$: C, 66.12; H, 6.75; N, 12.34. Found: C, 66.28; H, 6.82; N, 12.08. HRMS (ESI) calcd for $C_{25}H_{29}N_4O_3$ $[M + H]^+$ 433.2240, found 433.2243.

(*E*)-1-(4-(7-Methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-(Pyrrolidin-1-yl)ethyloxime (15e). **15e** was obtained from **11** and 2-pyrrolidin-1-ylethoxyamine·HCl as described for **13a**: 81% yield. Mp: 123−124 °C. IR (KBr): 3244, 1585, 1525. UV (MeOH): 362 (4.28), 260 (4.50), 210 (4.54). ^{1}H NMR (400 MHz, DMSO-d_6): 1.69−1.72 (m, 4H, Pyr-H), 2.20 (s, 3H, CH_3), 2.60 (br s, 4H, Pyr-H), 2.83 (t, 2H, J = 5.6 Hz, $OCH_2\underline{CH_2}N$), 3.91 (s, 3H, OCH_3), 4.24 (t, 2H, J = 6.0 Hz, $O\underline{CH_2}CH_2N$), 6.08 (d, 1H, J = 2.8 Hz, 3-H), 7.13−7.18 (m, 3H, 6-H, ArH), 7.28 (d, 1H, J = 2.8 Hz, 2-H), 7.66−7.68 (m, 2H, ArH), 7.74 (d, 1H, J = 2.4 Hz, 5-H), 8.25 (d, 1H, J = 9.2 Hz, 8-H), 9.47(br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 12.33, 23.11 (2C), 54.13 (2C), 54.28, 55.40, 72.39, 103.73, 105.77, 106.75, 113.147, 115.56, 120.69 (2C), 124.42, 126.65 (2C), 130.21, 141.47, 142.13, 142.78, 147.73, 153.64, 160.12, 163.46. Anal. Calcd for $C_{26}H_{28}N_4O_3 \cdot 1.2H_2O$: C, 66.99; H, 6.57; N, 12.02. Found: C, 67.12; H, 6.73; N, 11.73. HRMS (ESI) calcd for $C_{26}H_{29}N_4O_3$ $[M + H]^+$ 445.2240, found 445.2241.

(*E*)-1-(4-(7-Methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-(Piperidin-1-yl)ethyloxime (15f). **15f** was obtained from **11** and 2-piperidin-1-ylethoxyamine·HCl as described for **13a**: 72% yield. Mp: 116−119 °C. IR (KBr): 3221, 1618, 1585, 1526. UV (MeOH): 362 (4.35), 260 (4.57), 210 (4.59). ^{1}H NMR (400 MHz, DMSO-d_6): 1.35−1.50 (m, 6H, Pip-H), 2.18 (s, 3H, CH_3), 2.42 (m, 4H, Pip-H), 2.62 (t, 2H, J = 5.8 Hz, $OCH_2\underline{CH_2}N$), 3.92 (s, 3H, OCH_3), 4.22 (t, 2H, J = 6.0 Hz, $O\underline{CH_2}CH_2N$), 6.07 (d, 1H, J = 2.8 Hz, 3-H), 7.12−7.17 (m, 3H, 6-H, ArH), 7.29 (d, 1H, J = 2.8 Hz, 2-H), 7.65−7.68 (m, 2H, ArH), 7.74 (d, 1H, J = 2.8 Hz, 5-H), 8.25 (d, 1H, J = 9.2 Hz, 8-H), 9.46 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 12.26, 23.86, 25.54 (2C), 54.40 (2C), 55.36, 57.34, 71.57, 103.70, 105.73, 106.75, 113.14, 115.49, 120.68 (2C), 124.37, 126.59 (2C), 130.24, 141.45, 142.07, 142.72, 147.70, 153.48, 160.09, 163.44. HRMS (ESI) calcd for $C_{27}H_{31}N_4O_3$ $[M + H]^+$ 459.2396, found 459.2395.

(*E*)-1-(4-(7-Methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-Morpholinoethyloxime (15g). **15g** was obtained from **11** and 2-morpholinoethoxyamine·HCl as described for **13a**: 80% yield. Mp: 148−149 °C. IR (KBr): 3208, 1617, 1578, 1524. UV (MeOH): 362 (4.32), 262 (4.56), 246 (4.53), 206 (4.61). ^{1}H NMR (400 MHz, DMSO-d_6): 2.18 (s, 3H, CH_3), 2.43−2.46 (m, 4H, Mor-H), 2.64 (t, 2H, J = 6.0 Hz, $OCH_2\underline{CH_2}N$), 3.57 (m, 4H, Mor-H), 3.91 (s, 3H, OCH_3), 4.24 (t, 2H, J = 6.0 Hz, $O\underline{CH_2}CH_2N$), 6.07 (d, 1H, J = 2.8 Hz, 3-H), 7.137.18 (m, 3H, 6-H, ArH), 7.28 (d, 1H, J = 2.4 Hz, 2-H), 7.65−7.68 (m, 2H, ArH), 7.74 (d, 1H, J = 2.8 Hz, 5-H), 8.25 (d, 1H, J = 9.6 Hz, 8-H), 9.46 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 12.33, 53.72 (2C), 55.40, 57.10, 66.24 (2C), 71.43, 103.72, 105.77, 106.75, 113.16, 115.56, 120.70 (2C), 124.41, 126.63 (2C), 130.24, 141.47, 142.12, 142.75, 147.73, 153.60, 160.12, 163.46. Anal. Calcd for $C_{26}H_{28}N_4O_4$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.98; H, 6.27; N, 11.71. HRMS (ESI) calcd for $C_{26}H_{29}N_4O_4$ $[M + H]^+$ 461.2189, found 461.2187.

(*E*)-1-(4-(7-Methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-4-Morpholinobutyloxime (15h). **15h** was obtained from **11** and 4-morpholinobutoxyamine·HCl as described for **13a**: 71% yield. Mp: 100−102 °C. IR (KBr): 3211, 1578, 1519. UV (MeOH): 362 (4.35), 260 (4.56), 210 (4.57). ^{1}H NMR (400 MHz, $CDCl_3$): 1.60−1.86 (m, 2H, $OCH_2(\underline{CH_2})_2CH_2N$), 2.25 (s, 3H, CH_3), 2.39−2.46 (m, 6H, Mor-H, $OCH_2(CH_2)_2\underline{CH_2}N$), 3.72−3.74 (m, 4H, Mor-H), 3.95 (s, 3H, OCH_3), 4.22 (t, 2H, J = 6.4 Hz, $O\underline{CH_2}$-$(CH_2)_2CH_2N$), 6.15 (d, 1H, J = 2.8 Hz, 3-H), 6.90 (br s, 1H, NH), 7.10 (d, 1H, J = 2.4 Hz, 6-H), 7.12−7.15 (m, 2H, ArH), 7.39 (d, 1H, J = 2.8 Hz, 2-H), 7.40 (d, 1H, J = 2.4 Hz, 5-H), 7.65−7.68 (m, 2H, ArH), 7.91 (d, 1H, J = 9.6 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.55,

23.06, 27.18, 53.68 (2C), 55.48, 58.82, 66.91 (2C), 73.92, 104.70, 105.74, 107.18, 113.17, 116.73, 120.79 (2C), 121.98, 126.98 (2C), 132.05, 140.48, 141.74, 141.77, 148.02, 153.63, 160.56, 163.85. Anal. Calcd for $C_{28}H_{32}N_4O_4$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.94; H, 6.81; N, 11.04. HRMS (ESI) calcd for $C_{28}H_{33}N_4O_4$ $[M + H]^+$ 489.2502, found 489.2503.

(*E*)-1-(4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-Aminoethyloxime (16a). **16a** was obtained from 1-[4-(3-chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**12**)[14] and 2-aminoethoxyamine·HCl as described for **13a**: 98% yield. Mp: 108−110 °C. IR (KBr): 3133, 1580, 1520. UV (MeOH): 374 (4.15), 246 (4.49), 210 (4.47). ^{1}H NMR (400 MHz, DMSO-d_6): 2.14 (s, 3H, CH_3), 2.81 (t, 2H, J = 6.4 Hz, $OCH_2\underline{CH_2}N$), 3.94 (s, 3H, OCH_3), 4.05 (t, 2H, J = 5.8 Hz, $O\underline{CH_2}CH_2N$), 6.85−6.87 (m, 2H, ArH), 7.20 (dd, 1H, J = 9.2, 2.4 Hz, 6-H), 7.37 (d, 1H, J = 2.4 Hz, 8-H), 7.49−7.52 (m, 2H, ArH), 8.11 (d, 1H, J = 9.2 Hz, 5-H), 8.24 (s, 1H, 2-H), 9.12 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 12.12, 41.00, 55.57, 75.65, 106.72, 107.53, 109.95, 115.74 (2C), 116.64, 117.26, 124.84, 126.80 (2C), 127.76, 140.67, 141.13, 147.02, 148.04, 153.59, 160.81, 161.35. HRMS (ESI) calcd for $C_{22}H_{22}ClN_4O_3$ $[M + H]^+$ 425.1380, found 425.1382.

(*E*)-1-(4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-(Dimethylamino)ethyloxime (16b). **16b** was obtained from **12** and 2-dimethylaminoethoxyamine·HCl as described for **13a**: 88% yield. Mp: 102−104 °C. IR (KBr): 3130, 1581, 1518. UV (MeOH): 374 (4.19), 248 (4.55), 210 (4.55). ^{1}H NMR (400 MHz, $CDCl_3$): 2.21 (s, 3H, CH_3), 2.33 (s, 6H, $N(CH_3)_2$), 2.70 (t, 2H, J = 6.0 Hz, $OCH_2\underline{CH_2}N$), 3.95 (s, 3H, OCH_3), 4.30 (t, 2H, J = 6.0 Hz, $O\underline{CH_2}CH_2N$), 6.87−6.89 (m, 2H, ArH), 6.96 (dd, 1H, J = 9.4, 2.6 Hz, 6-H), 7.12 (br s, 1H, NH), 7.36 (d, 1H, J = 2.6 Hz, 8-H), 7.54−7.56 (m, 2H, ArH), 7.61 (s, 1H, 2-H),7.68 (d, 1H, J = 9.4 Hz, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.71, 45.94 (2C), 55.51, 58.22, 72.26, 106.14, 106.86, 110.11 (2C), 114.80, 117.19, 118.11, 125.66, 127.11 (2C), 130.83, 139.40, 141.64, 144.48, 149.04, 154.05, 161.00, 161.38. Anal. Calcd for $C_{24}H_{25}ClN_4O_3\cdot 0.2H_2O$: C, 63.12; H, 5.62; N, 12.27. Found: C, 62.94; H, 5.64; N, 12.07. HRMS (ESI) calcd for $C_{24}H_{26}ClN_4O_3$ $[M + H]^+$ 453.1693, found 453.1691.

(*E*)-1-(4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-3-Aminopropyloxime (16c). **16c** was obtained from **12** and 3-aminopropoxyamine·HCl as described for **13a**: 43% yield. Mp: 115−116 °C. IR (KBr): 3386, 1584, 1513. UV (MeOH): 374 (4.02), 344 (4.02), 246 (4.42), 206 (4.46). ^{1}H NMR (400 MHz, $CDCl_3$): 1.90 (quin, 2H, J = 6.8 Hz, $OCH_2\underline{CH_2}CH_2N$), 2.14 (s, 3H, CH_3), 2.83 (t, 2H, J = 7.2 Hz, $OCH_2CH_2\underline{CH_2}N$), 3.94 (s, 3H, OCH_3), 4.16 (t, 2H, J = 6.4 Hz, $O\underline{CH_2}CH_2CH_2N$), 6.84−6.77 (m, 2H, ArH), 7.21 (dd, 1H, J = 9.6, 2.4 Hz, 6-H), 7.37 (d, 1H, J = 2.4 Hz, 8-H), 7.47−7.52 (m, 2H, ArH), 8.14 (d, 1H, J = 9.6 Hz, 5-H), 8.24 (s, 1H, 2-H), 9.18 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 12.10, 28.68, 36.91, 55.56, 70.39, 106.71, 107.56, 109.92, 115.69 (2C), 116.68, 117.55, 124.85, 126.43, 126.83 (2C), 140.63, 141.14, 147.13, 148.03, 153.81, 160.82, 161.34. HRMS (ESI) calcd for $C_{23}H_{24}ClN_4O_3$ $[M + H]^+$ 439.1537, found 439.1535.

(*E*)-1-(4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-3-(Dimethylamino)propyloxime (16d). **16d** was obtained from **12** and 3-dimethylaminopropoxyamine·HCl as described for **13a**: 79% yield. Mp: 96−98 °C. IR (KBr): 3247, 1615, 1583, 1523. UV (MeOH): 374(4.20), 346 (4.17), 248 (4.55), 210 (4.56). ^{1}H NMR (400 MHz, $CDCl_3$): 1.85−1.96 (m, 2H, $OCH_2\underline{CH_2}CH_2N$), 2.20 (s, 3H, CH_3), 2.28 (s, 6H, $N(\underline{CH_3})_2$), 2.44 (t, 2H, J = 7.6 Hz, $OCH_2CH_2\underline{CH_2}N$), 3.95 (d, 3H, OCH_3), 4.22 (t, 2H, J = 6.4 Hz, $O\underline{CH_2}CH_2CH_2N$), 6.86−6.90 (m, 2H, ArH), 6.96 (dd, 1H, J = 9.6, 2.6 Hz, 6-H), 7.12 (br s, 1H, NH), 7.36 (d, 1H, J = 2.6 Hz, 8-H), 7.54−7.56 (m, 2H, ArH), 7.61 (s, 1H, 2-H), 7.69 (d, 1H, J = 9.6 Hz, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.48, 27.40, 45.33 (2C), 55.50, 56.49, 72.20, 106.11, 106.89, 110.13, 114.80, 117.18, 118.15 (2C), 125.66, 127.08 (2C), 130.95, 139.38, 141.68, 144.43, 149.06, 153.80, 161.01, 161.39. Anal. Calcd for $C_{24}H_{25}ClN_4O_3\cdot 1.0H_2O$: C, 61.91; H, 6.03; N, 11.55. Found: C, 61.61; H, 6.34; N, 11.57. HRMS (ESI) calcd for $C_{25}H_{28}ClN_4O_3$ $[M + H]^+$ 467.1850, found 467.1851.

(*E*)-1-(4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-(Pyrrolidin-1-yl)ethyloxime (16e). **16e** was obtained from **12** and 2-pyrrolidin-1-ylethoxyamine·HCl as described for **13a**: 98% yield. Mp: 116−117 °C. IR (KBr): 3137, 1617, 1580, 1520. UV (MeOH): 374 (4.14), 344 (4.13), 246 (4.52), 206 (4.58). ^{1}H NMR (400 MHz, $CDCl_3$): 1.67−1.70 (m, 4H, Pyr-H), 2.13 (s, 3H, CH_3), 2.50−2.55 (m, 4H, Pyr-H), 2.76−2.79 (m, 2H, $OCH_2\underline{CH_2}N$), 4.19 (t, 2H, J = 6.0 Hz, $O\underline{CH_2}CH_2N$), 6.84−6.88 (m, 2H, ArH), 7.20 (dd, 1H, J = 9.4, 2.6 Hz, 6-H), 7.37 (d, 1H, J = 2.6 Hz, 8-H), 7.48−7.52 (m, 2H, ArH), 8.12 (d, 1H, J = 9.6 Hz, 5-H), 8.24 (s, 1H, 2-H), 9.13 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 12.22, 23.09 (2C), 54.07 (2C), 54.31, 55.57, 72.33, 106.72, 107.57, 109.94, 115.70 (2C), 116.66, 117.28, 124.84, 126.84 (2C), 127.62, 140.65, 141.16, 147.08, 148.04, 153.59, 160.82, 161.34. Anal. Calcd for $C_{26}H_{27}ClN_4O_3\cdot 0.1HCl$: C, 64.70; H, 5.66; N, 11.61. Found: C, 64.75; H, 6.28; N, 11.29. HRMS (ESI) calcd for $C_{26}H_{28}ClN_4O_3$ $[M + H]^+$ 479.1850, found 479.1852.

(*E*)-1-(4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-(Piperidin-1-yl)ethyloxime (16f). **16f** was obtained from **12** and 2-piperidin-1-ylethoxyamine·HCl as described for **13a**: 98% yield. Mp: 126−127 °C. IR (KBr): 3135, 1617, 1580, 1521. UV (MeOH): 374 (4.13), 346 (4.12), 246 (4.47), 210 (4.47). ^{1}H NMR (400 MHz, $CDCl_3$): 1.34−1.38 (m, 2H, Pip-H), 1.44−1.51 (m, 4H, Pip-H), 2.11 (s, 3H, CH_3), 2.37−2.46 (br s, 4H, Pip-H), 3.60 (t, 2H, J = 5.6 Hz, $OCH_2\underline{CH_2}N$), 3.93 (s, 3H, OCH_3), 4.17 (t, 2H, J = 2.6 Hz, $O\underline{CH_2}CH_2N$), 6.83−6.87 (m, 2H, ArH), 7.20 (dd, 1H, J = 9.4, 2.6 Hz, 6-H), 7.36 (d, 1H, J = 2.6 Hz, 8-H), 7.48−7.51 (m, 2H, ArH), 8.11 (d, 1H, J = 9.4 Hz, 5-H), 8.24 (s, 1H, 2-H), 9.12 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 12.24, 23.86, 25.52 (2C), 54.40 (2C), 55.60, 57.39, 71.39, 106.73, 107.58, 109.96, 115.72 (2C), 116.67, 117.31, 124.86, 126.86 (2C), 127.67, 140.67, 141.18, 147.08, 148.06, 153.59, 160.84, 161.36. Anal. Calcd for $C_{27}H_{29}ClN_4O_3\cdot 0.4H_2O$: C, 64.83; H, 6.00; N, 11.20. Found: C, 64.78; H, 6.31; N, 11.08. HRMS (ESI) calcd for $C_{27}H_{30}ClN_4O_3$ $[M + H]^+$ 493.2006, found 493.2005.

(*E*)-1-(4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-2-Morpholinoethyloxime (16g). **16g** was obtained from **12** and 2-morpholinoethoxyamine·HCl as described for **13a**: 99% yield. Mp: 99−101 °C. IR (KBr): 3149, 1613, 1582, 1522. UV (MeOH): 374 (4.12), 344 (4.11), 248 (4.55), 206 (4.63). ^{1}H NMR (400 MHz, $CDCl_3$): 2.13 (s, 3H, CH_3), 2.52−2.63 (br s, 4H, Mor-H), 2.72 (br s, 2H, $OCH_2\underline{CH_2}N$), 3.54−3.68 (m, 4H, Mor-H), 4.24 (m, 2H, $O\underline{CH_2}CH_2N$), 6.85−6.87 (m, 2H, ArH), 7.21 (dd, 1H, J = 9.4, 2.6 Hz, 6-H), 7.37 (d, 1H, J = 2.6 Hz, 8-H), 7.50−7.52 (m, 2H, ArH), 8.12 (d, 1H, J = 9.4 Hz, 5-H), 8.24 (s, 1H, 2-H), 9.15 (br s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 12.26, 53.42 (2C), 55.58, 56.78, 65.84 (2C), 71.26, 106.73, 107.60, 109.94, 115.70 (2C), 116.68, 117.27, 124.85, 126.88 (2C), 127.55, 140.65, 141.16, 147.13, 148.04, 153.89, 160.83, 161.34. Anal. Calcd for $C_{26}H_{27}ClN_4O_4\cdot 2.0H_2O$: C, 58.81; H, 5.88; N, 10.55. Found: C, 58.55; H, 6.15; N, 10.36. HRMS (ESI) calcd for $C_{26}H_{28}ClN_4O_4$ $[M + H]^+$ 495.1799, found 495.1801.

(*E*)-1-(4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl)ethanone *O*-4-Morpholinobutyloxime (16h). **16h** was obtained from **12** and 4-morpholinobutoxyamine·HCl as described for **13a**: 98% yield. Mp: 124−126 °C. IR (KBr): 3142, 1614, 1585, 1515. UV (MeOH): 374 (4.06), 344 (4.06), 246 (4.48), 206 (4.51). ^{1}H NMR (400 MHz, $CDCl_3$): 1.54−1.78 (m, 4H, $OCH_2(\underline{CH_2})_2CH_2N$), 2.20 (s, 3H, CH_3), 2.33−2.46 (m, 6H, $OCH_2(CH_2)_2\underline{CH_2}N$, Mor-H), 3.72−3.74 (m, 4H, Mor-H), 3.95 (s, 3H, OCH_3), 4.19 (t, 2H, J = 6.4 Hz,

$OCH_2(CH_2)_2CH_2N$), 6.86−6.89 (m, 2H, ArH), 6.96 (dd, 1H, J = 9.4, 2.6 Hz, 6-H), 7.12 (br s, 1H, NH), 7.36 (d, 1H, J = 2.6 Hz, 8-H), 7.54−7.56 (m, 2H, ArH), 7.61 (s, 1H, 2-H), 7.70 (d, 1H, J = 9.4 Hz, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): 12.54, 23.02, 27.16, 53.65 (2C), 55.51, 58.81, 66.88 (2C), 73.82, 106.11, 106.86, 110.11, 114.78, 117.18, 118.16 (2C), 125.65, 127.06 (2C), 130.95, 139.39, 141.66, 144.43, 149.04, 153.72, 161.00, 161.38. Anal. Calcd for $C_{28}H_{31}ClN_4O_4 \cdot 0.7 H_2O$: C, 62.78; H, 6.10; N, 10.46. Found: C, 62.66; H, 6.40; N, 10.51. HRMS (ESI) calcd for $C_{28}H_{31}ClN_4O_4$ $[M + H]^+$ 523.2112, found 523.2115.

4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)benzenesulfonamide (19). To a solution of 3,4-dichlorofuro[2,3-*b*]quinoline[37] (**17**, 0.48 g, 2 mmol) and 4-aminobenzenesulfonamide (0.52 g, 3 mmol) in EtOH/H_2O 2:1 (15 mL) was added concentrated HCl until pH 6 resulted. The mixture was heated to reflux for 24 h (TLC monitoring), and then the solvent was evaporated in vacuo to give a residual solid. After addition of ice−water (40 mL), the mixture was was neutralized with 1 N NaOH solution. The resulting precipitate was collected and purified by flash column chromatography (FC, silica gel CH_2Cl_2) to give **19** (0.40 g, 54%). Mp: 210−212 °C. IR (KBr): 3448. UV (MeOH): 371 (3.44), 236 (3.95), 209 (3.98). ^{1}H NMR (400 MHz, DMSO-d_6): 6.89−6.93 (m, 2H, ArH), 7.12 (br s, 2H, NH_2), 7.58−7.63 (m, 3H, 6-H, ArH), 7.81−7.85 (m, 1 H, 7-H), 8.04−8.06 (m, 1H, 5-H), 8.19−8.22 (m, 1H, 8-H), 8.42 (s, 1H, 2-H), 9.41 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 109.83, 110.98, 114.60 (2C), 122.43, 123.43, 125.02, 127.39 (2C), 128.47, 130.33, 134.62, 139.72, 143.20, 145.82, 149.41, 160.65. HRMS (ESI) calcd for $C_{17}H_{13}ClN_3O_3S$ $[M + H]^+$ 374.0366, found 374.0364.

Compounds **20**−**27** were prepared from **17** and **18** by the same procedures as described for **19**.

4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)benzenesulfonamide (20). This compound was obtained as a white solid in 53% yield. Mp: 199−200 °C. IR (KBr): 3345, 1619, 1586, 1504. UV (MeOH): 346 (4.19), 256 (4.58), 211 (4.45). ^{1}H NMR (400 MHz, DMSO-d_6): 3.95 (s, 3H, OCH_3), 6.87−6.90 (m, 2H, ArH), 7.12 (br s, 2H, NH_2), 7.24 (dd, 1H, J = 9.4, 2.4 Hz, 6-H), 7.41 (d, 1H, J = 2.4 Hz, 8-H), 7.59−7.63 (m, 2H, ArH), 8.06 (d, 1H, J = 9.6 Hz, 5-H), 8.31 (s, 1H, 2-H), 9.34 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 55.65, 106.80, 109.04, 109.80, 114.48 (2C), 117.36, 117.83, 124.73, 127.37 (2C), 134.49, 139.68, 141.82, 148.04, 149.37, 160.94, 161.22. HRMS (ESI) calcd for $C_{18}H_{15}ClN_3O_4S$ $[M + H]^+$ 404.0472, found 404.0470.

4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)benzoic Acid (21). This compound was obtained as a white solid in 53% yield. Mp: 265−267 °C. IR (KBr): 3285, 1580. UV (MeOH): 377 (4.13), 261 (4.33), 236 (4.50), 211 (4.43). ^{1}H NMR (400 MHz, DMSO-d_6): 6.84−6.88 (m, 2H, ArH), 7.57−7.61 (m, 1H, 6-H), 7.74−7.77 (m, 2H, ArH), 7.80−7.84 (m, 1H, 7-H), 8.03 (d, 1H, J = 8.4 Hz, 5-H), 8.21 (dd, 1H, J = 8.4, 0.8 Hz, 8-H), 8.40 (s, 1H, 2-H), 9.45 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 109.86, 110.80, 114.58 (2C), 121.44, 122.36, 123.46, 124.95, 128.41, 130.30, 131.06 (2C), 139.73, 143.12, 145.79, 150.47, 160.63, 167.19. HRMS (ESI) calcd for $C_{18}H_{12}ClN_2O_3$ $[M + H]^+$ 339.0536, found 339.0533.

4-(3-Chlorofuro[2,3-*b*]quinolin-4-ylamino)benzamide (22). This compound was obtained as a light yellow solid in 62% yield. Mp: 198−200 °C. IR (KBr): 3444, 3363, 1638, 1603, 1583, 1524. UV (MeOH): 377 (3.98), 261 (4.20), 236 (4.35), 210 (4.30). ^{1}H NMR (400 MHz, DMSO-d_6): 6.86−6.89 (m, 2H, ArH), 7.11 (br s, 1H, NH), 7.57−7.61 (m, 1H, 6-H), 7.73−7.84 (m, 4H, ArH, 7-H, and NH), 8.03 (dd, 1H, J = 8.4, 0.8 Hz, 5-H), 8.24 (dd, 1H, J = 8.4, 0.8 Hz, 8-H), 8.38 (s, 1H, 2-H), 9.32 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 109.91, 110.09, 114.76 (2C), 122.06, 123.50, 124.70, 125.50, 128.37, 129.00 (2C), 130.20, 140.23, 142.76, 145.79, 148.92, 160.71, 167.61. HRMS (ESI) calcd for $C_{18}H_{13}ClN_3O_2$ $[M + H]^+$ 338.0696, found 338.0694.

4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)benzamide (23). This compound was obtained as a light yellow solid in 59% yield. Mp: 284−286 °C. IR (KBr): 3396, 2362, 1616. UV (MeOH): 347 (4.19), 251 (4.53), 212 (4.50). ^{1}H NMR (400 MHz, DMSO-d_6): 3.95 (s, 3H, OCH_3), 6.83−6.85 (m, 2H, ArH), 7.09 (br s, 1H, NH), 7.22 (dd, 2H, J = 9.2, 2.6 Hz, 6-H), 7.40 (d, 1H, J = 2.8 Hz, 8-H), 7.72−7.74 (m, 3H, ArH and NH), 8.10 (d, 1H, J = 9.2 Hz, 5-H), 8.27 (s, 1H, 2-H), 9.24 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 55.62, 106.76, 108.27, 109.92, 114.68 (2C), 117.01, 117.52, 124.85, 125.38, 129.02 (2C), 140.04, 141.46, 148.04, 148.94, 160.89, 161.31, 167.64. HRMS (ESI) calcd for $C_{19}H_{15}ClN_3O_3$ $[M + H]^+$ 368.0802, found 368.0801.

4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)-*N*-methylbenzamide (24). This compound was obtained as a pale yellow solid in 60% yield. Mp: 162−163 °C. IR (KBr): 3395, 2375, 1613, 1507. UV (MeOH): 348 (3.97), 250 (4.15), 208 (4.15). ^{1}H NMR (400 MHz, $CDCl_3$): 2.998 (d, 3H, J = 2.8 Hz, CH_3), 3.96 (s, 3H, OCH_3), 6.10 (br s, 1H, NH), 6.85−6.88 (m, 2H, ArH), 7.00 (dd, 1H, J = 9.2, 2.4 Hz, 6-H), 7.11 (br s, 1H, NH), 7.38 (d, 1H, J = 2.8 Hz, 8-H), 7.63 (s, 1H, 2-H), 7.65−7.68 (m, 2H, ArH), 7.69 (d, 1H, J = 9.6 Hz, 5-H). ^{13}C NMR (100 MHz, $CDCl_3$): 26.80, 55.56, 106.89, 110.41, 115.37, 117.08 (2C), 117.68, 125.31, 127.89, 128.33 (2C), 128.52, 139.86, 140.70, 146.76, 148.90, 161.15, 161.31, 167.55. Anal. Calcd for $C_{20}H_{16}ClN_3O_3 \cdot 1.2 H_2O$: C, 59.54; H, 4.60; N, 10.42. Found: C, 59.81; H, 4.67; N, 10.20.

4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)-*N*-(2-hydroxyethyl)benzamide (25). This compound was obtained as a pale yellow solid in 56% yield. Mp: 145−147 °C. IR (KBr): 3337, 2928, 2361, 1717. UV (MeOH): 348 (4.02), 210 (4.25). ^{1}H NMR (400 MHz, DMSO): 3.27−3.32 (m, 2H, $NHCH_2CH_2O$), 3.50 (t, 2H, J = 6.0 Hz, $NHCH_2CH_2O$), 3.94 (s, 3H, OCH_3), 6.84−3.86 (m, 2H, ArH), 7.22 (dd, 2H, J = 9.2, 2.4 Hz, 6-H), 7.38 (d, 1H, J = 2.4 Hz, 8-H), 7.70−7.72 (m, 2H, ArH), 8.11 (d, 1H, J = 8.8 Hz, 5-H), 8.19 (t, 1H, J = 5.6 Hz, NH), 8.26 (s, 1H, 2-H), 9.24 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO): 42.08, 55.65, 59.96, 106.78, 108.17, 109.96, 114.84 (2C), 116.97, 117.54, 124.88, 125.72, 128.67 (2C), 140.32, 141.45, 148.08, 148.81, 160.93, 161.36, 166.05. Anal. Calcd for $C_{21}H_{18}ClN_3O_4 \cdot 0.8H_2O$: C, 59.17; H, 4.63; N, 9.86. Found: C, 59.21; H, 4.70; N, 9.80.

4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)-*N*-(2-(dimethylamino)ethyl)benzamide (26). This compound was obtained as a yellow solid in 60% yield. Mp: 128−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.30 (s, 6H, $N(CH_3)_2$), 2.57 (t, 2H, J = 5.6 Hz, $NCH_2CH_2N(CH_3)_2$), 3.53 (m, 2H, $NCH_2CH_2N(CH_3)_2$), 3.95 (s, 3H, OCH_3), 6.84−6.87 (m, 2H, ArH), 6.96−7.02 (m, 2H, NH, 6-H), 7.16 (br s, 1H, NH), 7.37 (d, 1H, J = 2.4 Hz, 8-H), 8.62 (s, 1H, 2-H), 7.70−7.74 (m, 3H, 5-H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): 36.91, 45.01 (2C), 55.53, 57.87, 106.85, 107.08, 110.14, 115.43, 116.91 (2C), 117.62, 125.32, 127.66, 128.55 (2C), 139.80, 140.72, 146.82, 148.87, 161.10, 161.30, 166.84. Anal. Calcd for $C_{23}H_{23}ClN_4O_3 \cdot 0.2H_2O \cdot 1.0HCl$: C, 57.67; H, 5.13; N, 11.70. Found: C, 57.55; H, 5.16; N, 11.54.

4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)-*N*-(3-(dimethylamino)propyl)benzamide (27). This compound was obtained as a yellow solid in 65% yield. Mp: 119−120 °C. IR (KBr): 3428, 1503, 1262. UV (MeOH): 348 (3.98), 250 (4.13), 208 (4.21). ^{1}H NMR (400 MHz, DMSO): 1.79−1.86 (m, 2H, $NCH_2CH_2CH_2N$), 2.55 (s, 6H, $N(CH_3)_2$), 2.86−2.90 (m, 2H, $NCH_2CH_2CH_2N(CH_3)_2$), 3.26−3.31 (m, 2H, $NCH_2CH_2CH_2N(CH_3)_2$), 3.94 (s, 3H, OCH_3), 6.85−6.87 (m, 2H, ArH), 7.22 (dd, 1H, J = 9.2, 2.8 Hz, 6-H), 7.39 (d, 1H, J = 2.4 Hz, 8-H), 7.70−7.73 (d, 2H, ArH), 8.12 (d, 2H, J = 9.2 Hz, 5-H), 8.27 (s, 1H, 2-H), 8.43 (t, 1H, J = 5.6 Hz, NH), 9.30 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO): 25.11, 36.51, 42.76 (2C), 55.14, 55.61, 106.73, 108.23, 109.89, 114.71 (2C), 116.99, 117.50, 124.85, 125.38, 128.64 (2C), 140.20, 141.45, 148.03, 148.92, 160.87, 161.29, 166.04. Anal. Calcd for

$C_{24}H_{25}ClN_4O_3 \cdot 0.6H_2O \cdot 1.0HCl$: C, 57.63; H, 5.48; N, 11.20. Found: C, 57.64; H, 5.54; N, 11.02.

Cell Lines and Culture Conditions. Cell lines were purchased from Bioresource Collection and Research Center (Hsinchu, Taiwan). Cancer cell lines were the following: lung cancer cell lines, NCI-H460, A549, H1299, H661, and CL1−5; non-lung-cancer cell lines, 786-O, AGS, PC3, BT483, HeLa, SAS, SKHep, and CE81T; normal fibroblast cell lines, Hs68 and MRC-5, which were employed for determining their IC_{50} values. Each cell line was maintained in standard medium and grown as a monolayer in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum, 2 mM glutamine, 100 units/mL penicillin, and 100 g/mL streptomycin. Cultures were maintained at 37 °C with 5% CO_2 in a humidified atmosphere.

Cell Proliferation and Cell Viability MTT Assay. The experimental procedures were similar as described previously.[33]

Solubility Measurements.[38]. Equilibrium solubilities were determined by adding an excess amount of solid to the medium (water, doubly distilled), followed by 5 min of sonification and overnight equilibration by stirring at ambient temperature (25 ± 0.1 °C). The samples were centrifuged, and aliquots were removed. Standard solutions were prepared for each compound in order to quantify the aforementioned saturated solutions, and reference curves were plotted for each compound. The absorbance of each saturated and standard solution was measured with a UV/vis spectrophotometer at a wavelength that varied between 315 and 420 nm.

Single Dose Pharmacokinetic Studies. The tested compounds (**1**, **13a**, and **14a**) were evaluated by Rosetta Pharmamate Co., Ltd., Taiwan (R.O.C.), and the experimental procedures were similar as described previously.[33]

Human Lung Cancer Xenograph Experiment (In Vivo Tumoregenesis Assay). Compound **13a** has been selected as a new drug candidate because of its selective cytotoxicity, higher oral bioavailability (57.1%), and moderate plasma half-life (3.4 h). Human lung cancer cells NCI-H460 were grown in RPMI1640 with 10% NBS until near confluence and then harvested by trypsinization. Cells (5×10^6) were then mixed with Matrigel (BD Biosciences) to achieve 40% Matrigel in the final solution. The cell preparation was then injected subcutaneously into the flanks of 6−8-week-old Balb/c nude mice. For treatment, compound **13a** was prepared in DMSO, 1.4% Tween 80, and 1% sodium carboxymethylcellulose (Sigma) normal saline solution; the vehicle control was with the same mixture lacking **13a**. On the basis of the dose for acute toxicity, compound **13a** was dosed at two different concentrations (10 and 20 mg per day for ip administration; 60 and 120 mg per day for oral administration), together with the control group. Subcutaneous tumors were measured with the standard clipper ruler method. Final tumor weight at the end of the study was documented after animal sacrifice and dissection of tumor tissue.

Orthotropic Lung Cancer Model in Nude Mice. The efficacy of **13a** was investigated in orthotropic lung cancer model in nude mice using H-1299 or Tumor fragments. These experiments were completed and show that the lead compound has great efficacy in inhibiting tumor growth in vivo. Tumor fragments (H-1299) for orthotopic implantation were prepared by removing orthotopic donor tumors (0.5−1.0 g), placing them into a sterile Petri dish and cutting viable portions of tumor tissue into 1 mm diameter pieces using the "crossed scalpels" technique. The pieces were mixed thoroughly, then weighed and divided into approximately 50 mg portions. Each portion was loaded into the proximal end of a 16-gauge, 2 in. long Teflon catheter (Becton Dickinson, Sandy, UT) and forced through the catheter once using the air pressure from a 1 mL syringe. This ensured that the tissue would not obstruct the cannula when the endobronchial implantations were performed. Each aliquot of tissue was then loaded into the proximal end of a cannula for implantation. Then three drops of medium were added to keep it moist and a 1 mL cannula containing 200 μL of air was attached. On the morning of implantation, mice were irradiated with 500 rads from a γ source. After preparation of the tumor syringes, the animals were anesthetized with ketamine/xylazine (160/12 mg/kg, im; C.D.M.V. Inc., Guelph, Ontario, Canada) and placed in the supine recumbent position with head elevated slightly for implantation. The spine was straightened by exerting traction on both head and tail. After a small tracheostomy incision was made, the cannula was passed into the right caudal lobe by inserting it into the trachea and advancing it gently in a caudal direction at an angle of 10−20° to the axis of the trachea. When resistance was encountered the cannula was withdrawn 1−2 mm. The tumor tissue was then expelled and the cannula withdrawn. The wound was closed with sterile wound clips and the animals returned to their cages, dorsal side up, with upper body elevated on rolled-up sterile drapes. Mice with lung cancer were then treated **13a** orally for 2 weeks. Nude mice were examined daily for signs of morbidity. Animal and primary tumor weights were recorded and mean values calculated for 10 weeks.

Statistical Analysis. Analyses were performed on a Macintosh computer using a Statview statistical program (Abacus Concepts, Berkeley, metastatic, orthotropic lung cancer model 159 CA). Primary tumor sizes were compared by the Kruskal−Wallis test. Metastatic incidences were compared using Fisher's exact test. In all cases, $P < 0.05$ was considered to be significant.

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ABBREVIATIONS USED

MDR, multidrug resistance; MTT, microculture tetrazolium; IC_{50}, concentration of 50% growth inhibition; SI, selectivity index; SAR, structure−activity relationship; DAR, daunorubicin; *m*-AMSA, amsacrine

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