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Short communication

Synthesis and anticancer evaluation of certain 4-anilinofuro[2,3-*b*]quinoline and 4-anilinofuro[3,2-*c*]quinoline derivatives

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Abstract

Certain linear 4-anilinofuro[2,3-*b*]quinoline and angular 4-anilinofuro[3,2-*c*]quinoline derivatives were synthesized and evaluated in vitro against the full panel of NCI's 60 cancer cell lines. For the linear 4-anilinofuro[2,3-*b*]quinoline derivatives, 1-[4-(furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**5a**) is the most cytotoxic with a mean GI_{50} value of 0.025 μM. Substitution at either furo[2,3-*b*]quinoline ring (**2a**, **2b**, and **5b**) or 4-anilino moiety (**3**–**7**) led to a decrease of cytotoxicity. For the angular 4-anilinofuro[3,2-*c*]quinoline derivatives, (*E*)-1-[3-(furo[3,2-*c*]quinolin-4-ylamino)phenyl]ethanone oxime (**14a**) exhibited potent inhibitory activities on UO-31, UACC-257, and UACC-62, with GI_{50} values of 0.03, < 0.01, and < 0.01 μM respectively. The same cytotoxicity profile was observed for its methyl counterpart, **14b**, in which the GI_{50} values against UO-31, UACC-257, and UACC-62 was < 0.01, 0.04 and < 0.01 μM respectively. These results deserve full attention especially because **14a** and **14b** are relatively non-cytotoxic with the mean GI_{50} value of 7.73 and 8.91 μM respectively.

Keywords: 4-Anilinofuro[2,3-*b*]quinoline; 4-Anilinofuro[3,2-*c*]quinoline; Cytotoxicity

1. Introduction

9-Anilinoacridine derivatives have been extensively studied as potential chemotherapeutic agents due to their capability of intercalating DNA leading to the inhibition of mammalian topoisomerase II [1–3]. Among such derivatives, 4′-(9-acridinylamino)methanesulfonyl-*m*-anisidine (amsacrine, *m*-AMSA) has been clinically used for the treatment of leukemia and lymphoma [1]. Further structural modification lead to the discovery of an improved broad spectrum antitumor agent, 3-(9-acridinylamino)-5-(hydroxymethyl)aniline (AHMA), which is capable of inhibiting the growth of certain solid tumors such as mammary adenocarcinoma, melanoma, and Lewis lung carcinoma in mice [3]. These results prompted us to synthesize and evaluate 4-anilinofuro[2,3-*b*]quinoline derivatives, which can be structurally related to 9-anilinoacridines by isosteric substitution of a benzene moiety for a furan ring [4,5]. Among them, 1-[4-(furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**5a**) exhibited an excellent cytotoxicity against the growth of 60 cancer cells with a mean GI_{50} value of 0.025 μM [4]. Similar approaches to this kind of compounds were also reported where benzene moiety was isosterically replaced with thiazole ring [6,7]. The present report describes the influence of substituents with respect to the anticancer activity of 4-anilinofuro[2,3-*b*]quinoline derivatives. To further explore the structure–activity relationships, the linear furo[2,3-*b*]quinoline was replaced with the angular furo[3,2-*c*]quinoline, which constitutes an important group of natural products [8]. Recently, we have synthesized certain α-methylidene-γ-butyrolactone bearing quinolones and evaluated their cytotoxicities on the ground that through the intercalation of quinolone, the α-methylidene-γ-butyrolactone can specifically alkylate DNA molecule [9]. This versatile α-methylidene-γ-butyrolactone moiety has also been appended on the 9-anilino group in an attempt to prepare a bifunctional agents in which the furo[3,2-*c*]quinoline ring functions as an intercalator while the lactone ring plays the role of an alkylating unit.

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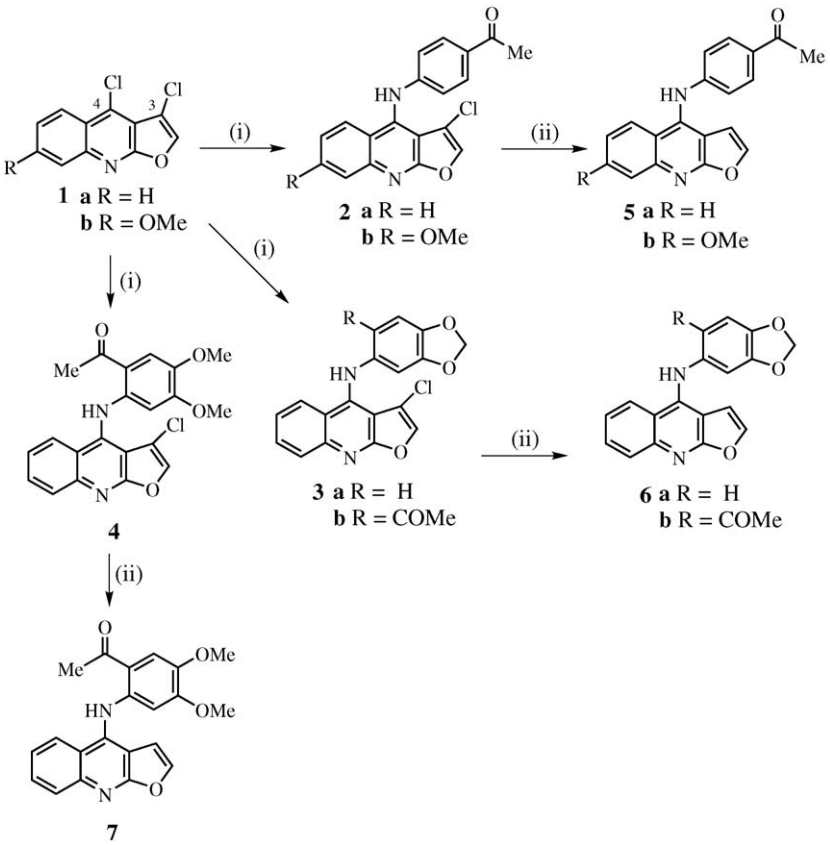
2. Chemistry

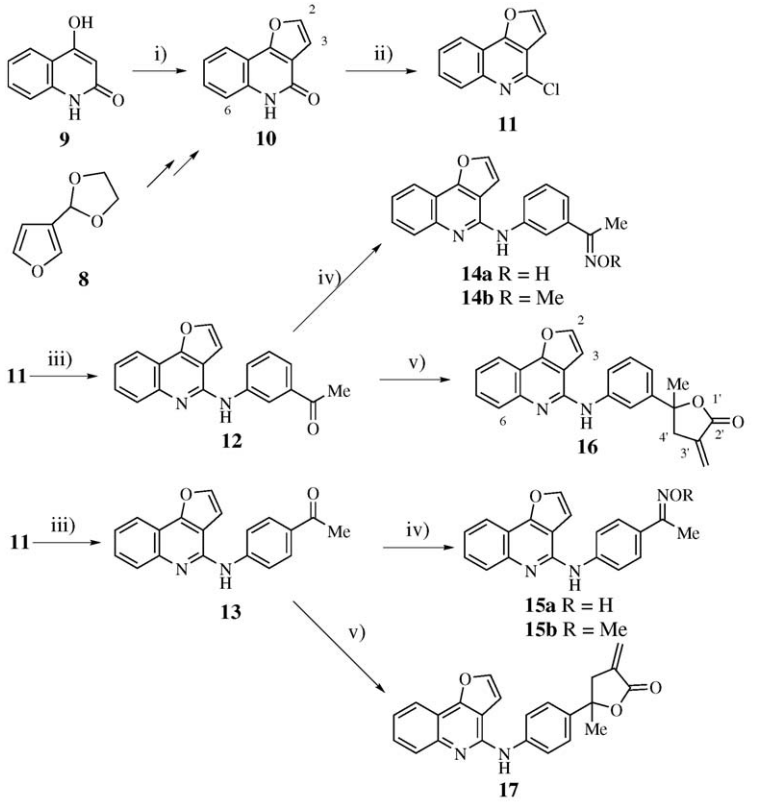
Preparation of the desired the linear 4-anilinofuro[2,3-*b*]quinoline derivatives is outlined in Scheme 1. Reaction of 3,4-dichloro-7-methoxyfuro[2,3-*b*]quinoline (**1b**) with 4-aminoacetophenone gave 1-[4-(3-chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**2b**) which was hydrogenated to give 1-[4-(7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**5b**) in 46% overall yield. Preparation of **5a** from the known 3,4-dichlorofuro[2,3-*b*]quinoline (**1a**) [10] has been previously described [4,5]. Treatment of **1a** with substituted anilines afforded 3-chloro-4-(substituted-phenylamino)furo[2,3-*b*]quinolines **3a**,**b** which was hydrogenated to afford 4-(substituted-phenylamino)-furo[2,3-*b*]quinolines **6a**,**b** in a good overall yield. Accordingly, compound **7** was prepared from its 3-chloro precursor **4** which was obtained by the treatment of **1a** with 2-amino-4,5-dimethoxyacetophenone.

The angular 4-anilinofuro[3,2-*c*]quinoline derivatives were synthesized from a sequence of reactions as depicted in Scheme 2. The known 4-hydroxyfuro[3,2-*c*]-quinoline (**10**) [11] was selected as the starting material, however, its preparation required five synthetic steps from 2-furan-3-yl-[1,3]dioxolane (**8**) and therefore is too tedious to be followed. According to the literature, Kraus and Ridgeway [12] have synthesized furan derivatives from substituted 1,3-diketones and chloroacetaldehyde in a single step. Thus, the commercially available 2,4-dihydroxyquinoline was treated with chloroacetaldehyde to give **10** in 82% yield. Chlorination of **10** with $POCl_3$ gave 4-chlorofuro[3,2-*c*]quinoline (**11**) [13] which was then treated with 3-aminoacetophenone in a solution of EtOH/H_2O (2:1) to afford the desired 1-[3-(furo[3,2-*c*]quinolin-4-ylamino)phenyl]ethanone (**12**) in an 85% overall yield. Treatment of **12** with NH_2OH gave exclusively (*E*)-1-[3-(furo[3,2-*c*]quinolin-4-ylamino)phenyl]-ethanone oxime (**14a**). The configuration of the oxime moiety was determined by through-space nuclear Overhauser effect spectroscopy (NOESY) which revealed coupling connectivity to CH_3 protons. Accordingly, (*E*)-1-[3-(furo[3,2-*c*]quinolin-4-ylamino)phenyl]ethanone *O*-methyloxime (**14b**) was obtained from the reaction of **12** and NH_2OMe. Reaction of **11** with 4-aminoacetophenone gave 1-[4-(furo[3,2-*c*]quinolin-4-ylamino)phenyl]ethanone (**13**) which was then treated with either NH_2OH or NH_2OMe to afford (*E*)-1-[4-(furo[3,2-*c*]quinolin-4-ylamino)phenyl]ethanone oxime (**15a**) and its methyl congener **15b** respectively. *Reformatsky*-type condensation of **12** and **13** with 2-(bromomethyl)acrylate and Zinc powder in THF afforded 5-[3-(furo[3,2-*c*]quinolin-4-ylamino)phenyl]-5-methyl-3-methylidenedihydrofuran-2-one (**16**) and the positional isomer **17** respectively.



Reagents and conditions: i) Substituted-anilines, EtOH-H_2O (2:1 v/v), HCl, reflux; ii) H_2, Pd/C, MeOH/CH_2Cl_2 (1:1 v/v).

Scheme 1.



Reagents and conditions: i) $ClCH_2CHO$; ii) $POCl_3$, Et_3N; iii) 3- or 4-aminoacetophenone, EtOH-H_2O (2:1); iv) NH_2OH HCl or NH_2OMe HCl, EtOH; v) ethyl 2-(bromomethyl)acrylate, Zn, THF.

Scheme 2.

3. Biological results and discussion

All compounds 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 is inoculated and preincubated on a microtiter plate. Test agents are then added at a single concentration (100 μM) and the culture incubated for 48 h. End-point determinations are made with alamar blue [14]. Results for each test agent are reported as the percent of growth of the treated cells when compared to the untreated control cells. Compounds which reduced the growth of any one of the cell lines to 32% or less are passed on for evaluation in the full panel of 60 cell lines over a 5-log dose range. The results indicated all of them, with exception of **2a**, **4** and **7**, are active and were evaluated in vitro against the full panel of NCI's 60 cancer cell lines derived from nine cancer cell types including leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer [15]. For the linear 4-anilinofuro[2,3-*b*]quinoline derivatives, **5a** is the most cytotoxic with a mean GI_{50} value of 0.025 μM (Table 1). Substitution at either furo[2,3-*b*]quinoline ring (**2a**, **2b**, and **5b**) or 4-anilino moiety (**3**–**7**) led to a decrease of cytotoxicity. 7-Methoxy derivative **5b** (a mean GI_{50} value of 0.49 μM) was 20-fold less cytotoxic than **5a** while 3-chloro derivative **2a** became non-cytotoxic. Comparison of **2a** and **2b**, which bear an electron-withdrawing 3-Cl substituent, an electron-donating methoxy group improved cytotoxicity. In contrary, methoxy group for relatively electron-rich reduced furo[2,3-*b*]quinoline ring is unfavorable (**5a** vs. **5b**) indicated an optimum electronic environment is crucial. Each of the GI_{50} values for three representative cell lines, NCI-H460, MCF7, and SF-268 is comparable to the mean GI_{50} value for all 60 cancer cells. For example, **2b** possesses a mean GI_{50} value of 0.27 μM and the GI_{50} values of 0.22, 0.25, and 0.44 μM for NCI-H460, MCF7, and SF-268 respectively. However, UACC-62 was especially susceptible to **2b** (GI_{50} = 0.01 μM), **5a** (<0.01 μM), and **5b** (0.09 μM) while UACC-257 was resistant to **2b** (11.8 μM) and **5a** (15.8 μM). Compound **3a** (mean GI_{50} = 1.57 μM) and **6a** (14.7 μM) are less cytotoxic than their respective acetylated derivative **3b** (0.18 μM) and **6b** (0.22 μM) implied the importance of acetyl group to form H-bonding with DNA molecule. Replacement of the 1,3-methylenedioxyl substituent with an *ortho*-dimethoxy group led to the devoid of cytotoxicity (**3b** vs. **4**; **6b** vs. **7**). Again, UACC-62 was especially susceptible to **3a** (GI_{50} = 0.14 μM) and **6b** (0.07 μM) while UACC-257 was resistant to **3a** (9.15 μM) and **3b** (> 100 μM).

For the angular 4-anilinofuro[3,2-*c*]quinoline derivatives, 1-[3-(furo[3,2-*c*]quinolin-4-ylamino)phenyl]ethanone (**12**) (mean GI_{50} = 25.5 μM) was less cytotoxic than its 4-acetylanilino counterpart **13** (8.99 μM) and both hydroxyimino and methoxyimino derivatives (**14a**: 7.73 μM; **14b**: 8.91 μM). Cytotoxicity was increased by converting the car-

Table 1
In vitro cytotoxicity of 4-anilinofuro[2,3-*b*]quinoline and 4-anilinofuro[3,2-*c*]quinoline derivatives [GI_{50} (μM)][a]

Compound	NCI-H460 (Lung)	MCF7 (Breast)	SF-268 (CNS)	UO-31 (Renal)	UACC-257 (Melanoma)	UACC-62 (Melanoma)	Mean[b]
2b	0.22	0.25	0.44	0.30	11.8	0.01	0.27
3a	3.22	4.38	6.28	7.09	9.15	0.14	1.57
3b	0.22	0.05	0.51	3.10	100	0.20	0.18
5a	0.01	< 0.01	0.01	0.03	15.8	< 0.01	0.025
5b	0.20	0.20	0.18	0.25	0.16	0.09	0.49
6a	16.5	12.6	15.6	23.6	nd	13.9	14.7
6b	0.32	0.28	0.85	0.22	0.22	0.07	0.22
12	20.5	25.1	22.2	nd[c]	100	nd	25.5
13	4.71	8.22	14.0	20.4	13.2	10.7	8.99
14a	4.34	15.0	11.9	0.03	< 0.01	< 0.01	7.73
14b	11.8	18.1	15.4	< 0.01	0.04	< 0.01	8.91
15a	1.82	3.42	6.31	15.9	5.11	14.7	6.31
15b	15.6	13.8	16.4	18.9	17.2	12.2	15.1
16	15.6	3.71	10.5	1.89	0.02	0.65	4.38
17	14.8	3.31	2.95	nd	0.02	nd	3.16
m-AMSA	0.03	0.03	0.40	0.63	3.16	0.32	0.42

[a] Data obtained from NCI's in vitro disease-oriented tumor cell screen. GI_{50}: drug molar concentration causing 50% cell growth inhibition.
[b] Mean values over all cell lines tested. Theses cell lines are: leukemia (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, PRMI-8226, and SR); non-small cell lung cancer (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, and NCI-H522); colon cancer (COLC 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, and SW-620); CNS cancer (SF-268, SF-295, SF-539, SNB-19, SNB-75, and U251); melanoma (LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, and UACC-257); ovarian cancer (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3); renal cancer (786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, and UO-31); prostate cancer (PC-3 and DU-145); and breast cancer (MCF7, MCF7/ADR-RES, MDA-MB-231/ATCC, HS 578T, MDA-MB-435, MDA-N and T-47D).
[c] Not determined.

bonyl group to the respective hydroxyimino (**12** vs. **14a**; **13** vs. **15a**). A substituent of hydroxyiminoethyl was more cytotoxic than the methoxyiminoethyl counterparts (**14a** vs. **14b**; **15a** vs. **15b**). Both α-methylidene-γ-butyrolactone derivatives **16** (4.38 μM) and **17** (3.16 μM) exhibited strong inhibitory activity against the growth of all cancer cell lines tested indicating the important role played by the alkylating unit.

The present results also demonstrated compound **14a** to possess potent inhibitory activities on UO-31, UACC-257, and UACC-62, with GI_{50} values of 0.03, < 0.01, and < 0.01 μM respectively. The same cytotoxicity profile was observed for its methyl counterpart, **14b**, in which the GI_{50} values against UO-31, UACC-257, and UACC-62 was < 0.01, 0.04 and < 0.01 μM respectively. However, compounds **15a** and **15b**, the positional isomers of **14a** and **14b**, respectively, did not exhibit selective cytotoxicity.

4. Conclusion

A number of linear 4-anilinofuro[2,3-*b*]quinoline and angular anilinofuro[3,2-*c*]-quinoline derivatives were synthesized and evaluated for anticancer activities. For the linear 4-anilinofuro[2,3-*b*]quinolines, compounds **2b**, **3b**, **5a**, **5b**, and **6b** exhibited potent cytotoxicities with mean GI_{50} values of 0.27, 0.18, 0.025, 0.49, and 0.22 μM respectively. Although compounds **14a** and **14b** demonstrated only marginal cytotoxicity against all 60 cancer cells, they are capable of selectively inhibiting one of the renal cancer cells, UO-31, and two of the melanoma cancer cells, UACC-257 and UACC-62, with GI_{50} value of less than 0.04 μM in each case. Compounds **15a** and **15b**, the positional isomers of **14a** and **14b**, respectively, did not exhibit selective cytotoxicity suggested the spatial arrangement of anilinofuro[3,2-*c*]quinoline derivatives is crucial for cytotoxicity profile. These results deserve full attention especially because **14a** and **14b** are relatively non-cytotoxic with the mean GI_{50} value of 7.73 and 8.91 μM respectively.

5. Experimental protocols

5.1. Chemistry

TLC: precoated (0.2 mm) silica gel 60 F_{254} plates from EM Laboratories, Inc.; detection by UV light (254 nm). Melting-point (m.p.): Electrothermal IA9100 digital m.p. apparatus; uncorrected. ^{1}H and ^{13}C-NMR spectra: Varian-Unity-400 spectrometer at 400 and 100 MHz or Varian-Gemini-200 spectrometer at 200 and 50 MHz, chemical shifts δ in ppm with $SiMe_4$ as an internal standard (= 0 ppm), coupling constants *J* in Hz. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer, and results were within ± 0.4% of calculated values.

*5.1.1. 1-[4-(3-Chloro-7-methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**2b**)*

To a solution of 3,4-dichloro-7-methoxyfuro[2,3-*b*]quinoline (**1b**, 268 mg, 1 mmol) and 4-aminoacetophenone (270 mg, 2 mmol) in EtOH/H_2O 2:1 (15 ml) was added concentrated HCl until pH 6 resulted. The mixture was refluxed for 24 h. (TLC monitoring) and then the solvent evaporated

in vacuo to give a residual solid, to which was added ice-water (40 ml), and 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 **2b** (220 mg, 60%). M.p.: 235–236 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.54 (*s*, 3H, Me); 3.97 (*s*, 3H, OMe); 6.84 (*m*, 2H, ArH); 7.05 (*dd*, 1H, *J* = 9.4, 2.4, H-C(6)); 7.12 (*br s*, 1H, NH); 7.41 (*d*, 1H, *J* = 2.4, H-C(8)); 7.65 (*s*, 1H, H-C(2)); 7.74 (*d*, 1H, *J* = 9.4, H-C(5)); 7.86 (*m*, 2H, ArH). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 26.23; 55.59; 106.98; 107.88; 110.18; 115.97; 116.19 (2C); 118.11; 125.10; 130.32 (2C); 130.82; 139.99; 140.23; 148.45; 148.82; 161.30; 196.46. Anal. Calcd. for $C_{18}H_{11}ClN_2O_3$: C 63.82, H 3.27, N 8.27; found: C 63.76, H 3.28, N 7.90. Anal. Calcd. for $C_{20}H_{15}ClN_2O_3$: C 65.49, H 4.12, N 7.64; found: C 65.64, H 4.19, N 7.68.

*5.1.2. Benzo [1,3]dioxol-5-yl-(3-chlorofuro[2,3-*b*]quinolin-4-yl)amine (**3a**)*

From **1a** and 3,4-(methylenedioxy)aniline as described for **2b**: 83% yield, m.p.: 154–156 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.97 (*s*, 2H, CH_2); 6.51 (*dd*, 1H, *J* = 8.0, 1.6, ArH); 6.56 (*d*, 1H, *J* = 1.6, ArH); 6.72 (*d*, 1H, *J* = 8.0, ArH); 7.26 (*m*, 2H); 7.63 (*s*, 1H); 7.64 (*ddd*, 1H, *J* = 8.4, 6.8, 1.2, H-C(7)); 7.78 (*d*, 1H, *J* = 8.4, H-C(8)); 8.04 (*d*, 1H, *J* = 8.4, H-C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 101.43; 103.23; 105.63; 108.48; 110.11; 114.07; 118.60; 123.47; 124.63; 128.59; 129.86; 137.83; 139.75; 143.88; 144.37; 146.54; 148.37; 160.45. Anal. Calcd. for $C_{18}H_{11}ClN_2O_3$: C 63.82, H 3.27, N 8.27; found: C 63.76, H 3.28, N 7.90.

*5.1.3. 1-[6-(3-Chlorofuro[2,3-*b*]quinolin-4-yl)amino)benzo [1,3]dioxol-5-yl]ethanone (**3b**)*

From **1a** and 6′-amino-3′,4′-(methylenedioxy)acetophenone as described for **2b**: 60% yield, m.p.: 226–228 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.67 (*s*, 3H, Me); 5.91 (*s*, 2H, CH_2); 6.00 (*s*, 1H, ArH); 7.28 (*s*, 1H, ArH); 7.48 (*ddd*, 1H, *J* = 8.4, 6.8, 1.2, H-C(6)); 7.74 (*s*, 1H, H-C(2)); 7.75 (*ddd*, 1H, *J* = 8.4, 6.8, 1.2, H-C(7)); 8.03 (*d*, 1H, *J* = 8.4, H-C(8)); 8.12 (*d*, 1H, *J* = 8.4, H-C(5)); 11.62 (*s*, 1H, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.16; 95.66; 101.67; 109.44; 110.88; 112.14; 122.90; 123.66; 125.14; 128.98; 130.09; 139.13; 140.04; 141.88; 146.35; 147.11; 153.14; 160.75; 199.14. Anal. Calcd. for $C_{20}H_{13}ClN_2O_4$: C 63.08, H 3.44, N 7.36; found: C 63.14, H 3.56, N 7.28.

*5.1.4. 1-[2-(3-Chlorofuro[2,3-*b*]quinolin-4-yl)-4,5-dimethoxyphenyl]ethanone (**4**)*

From **1a** and 2-amino-4,5-dimethoxyacetophenone as described for **2b**: 70% yield, m.p.: 234–235 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.71 (*s*, 3H, Me); 3.45 (*s*, 3H, OMe); 3.91 (*s*, 3H, OMe); 6.10 (*s*, 1H, ArH); 7.30 (*s*, 1H, ArH); 7.46 (*ddd*, 1H, *J* = 8.4, 6.8, 1.2, H-C(6)); 7.74 (*ddd*, 1H, *J* = 8.4, 6.8, 1.2, H-C(7)); 7.74 (*s*, 1H, H-C(2)); 8.01 (*dd*, 1H, *J* = 8.4, 0.8, H-C(8)); 8.12 (*d*, 1H, *J* = 8.4, H-C(5)); 11.53 (*s*, 1H, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.02; 55.67; 56.59; 98.36; 110.96; 111.14; 112.02; 113.92; 122.02; 124.07; 124.63; 128.92; 130.10; 139.53; 141.50; 141.60; 144.32; 146.26; 154.90; 160.80; 199.47. Anal. Calcd. for $C_{21}H_{17}ClN_2O_4$: C 63.56, H 4.32, N 7.06; found: C 63.44, H 4.35, N 7.03.

*5.1.5. 1-[4-(7-Methoxyfuro[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**5b**)*

A solution of **2b** (366 mg, 1 mmol) in MeOH/CH_2Cl_2 (1:1, 100 ml) was hydrogenated for 3 h (TLC monitoring) under H_2 with Pd/C (20 mg). The reaction mixture was filtered and the filtrate concentrated in vacuo to give a residual solid, which was purified by FC (silica gel; CH_2Cl_2) to give **5b** (252 mg, 76%). M.p.: 137–139 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.58 (*s*, 3H, Me); 3.92 (*s*, 3H, OMe); 6.33 (*d*, 1H, *J* = 2.6, H-C(3)); 7.05–7.14 (*m*, 3H, H-C(6) and Ar-H); 7.25 (*br s*, 1H, NH); 7.39 (*d*, 1H, *J* = 2.6, H-C(2)); 7.51 (*d*, 1H, *J* = 2.8, H-C(8)); 7.91–7.98 (*m*, 3H, H-C(5) and Ar-H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 26.29; 55.48; 105.50; 107.09; 107.33; 114.60; 117.41; 117.80 (2C); 122.52; 130.18 (2C); 131.18; 138.76; 142.87; 146.34; 148.01; 160.76; 163.50; 196.61. Anal. Calcd. for $C_{20}H_{16}N_2O_3{\cdot}H_2O$: C 68.56, H 5.18, N 7.99; found: C 68.81, H 5.57, N 7.69.

Compounds **6a**, **6b**, and **7** were prepared from **3a**, **3b**, and **4**, respectively, by the same procedures as described for **5b**.

*5.1.6. Benzo [1,3]dioxol-5-yl-furo[2,3-*b*]quinolin-4-ylamine (**6a**)*

Yield 77%; m.p.: 196–197 °C; ^{1}H-NMR (200 MHz, DMSO): δ 5.87 (*d*, 1H, *J* = 2.8, H-C(3)); 6.05 (*s*, 2H, CH_2); 6.81 (*m*, 3H, Ar-H); 7.01 (*s*, 1H, NH); 7.36 (*d*, 1H, *J* = 2.8, H-C(2)); 7.44 (*ddd*, 1H, *J* = 8.4, 6.8, 1.2, H-C(6)); 7.67 (*ddd*, 1H, *J* = 8.4, 6.8, 1.2, H-C(7)); 8.02 (*dd*, 1H, *J* = 8.4, 1.2, H-C(8)); 8.04 (*dd*, 1H, *J* = 8.4, 1.2, H-C(5)). ^{13}C-NMR (50 MHz, DMSO): δ 101.64; 103.36; 105.48; 106.65; 108.50; 116.63; 118.26; 120.23; 123.36; 128.89; 129.11; 134.43; 141.91; 143.02; 145.63; 145.80; 148.33; 163.35. Anal. Calcd. for $C_{18}H_{12}N_2O_3$: C 71.05, H 3.97, N 9.21; found: C 70.82, H 4.04, N 9.12.

*5.1.7. 1-[6-(Furo[2,3-*b*]quinolin-4-yl)amino)benzo [1,3]dioxol-5-yl]ethanone (**6b**)*

Yield 74%; m.p.: 254–256 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.66 (*s*, 3H, Me); 5.99 (*s*, 2H, CH_2); 6.49 (*s*, 1H, ArH); 6.57 (*d*, 1H, *J* = 2.6, H-C_3); 7.31 (*s*, 1H, ArH); 7.53 (*ddd*, 1H, *J* = 8.4, 6.8, 1.4, H-C(6)); 7.66 (*d*, 1H, *J* = 2.6, H-C(2)); 7.74 (*ddd*, 1H, *J* = 8.4, 6.8, 1.4, H-C(7)); 8.12 (*dd*, 1H, *J* = 8.6, 0.8, H-C(8)); 8.21 (*dd*, 1H, *J* = 8.6, 0.8, H-C(5)); 11.87 (*s*, 1H, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.25; 96.86; 101.88; 105.72; 109.62; 110.53; 113.58; 121.14; 122.32; 124.69; 128.83; 129.44; 138.36; 140.62; 144.22; 144.36; 146.01; 153.02; 162.79; 199.65. Anal. Calcd. for $C_{20}H_{14}N_2O_4$: C 69.36, H 4.07, N 8.09; found: C 69.11, H 4.15, N 8.02.

*5.1.8. 1-[2-(Furo[2,3-*b*]quinolin-4-yl)-4,5-dimethoxyphenyl]ethanone (**7**)*

Yield 74%; m.p.: 195–197 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.70 (*s*, 3H, Me); 3.69 (*s*, 3H, OMe); 3.95 (*s*, 3H,

OMe); 6.55 (*d*, 1H, *J* = 2.4, H-C(3)); 6.59 (*s*, 1H, ArH); 7.32 (*s*, 1H, ArH); 7.55 (*ddd*, 1H, *J* = 8.4, 6.8, 1.2, H-C(6)); 7.65 (*d*, 1H, *J* = 2.4, H-C(2)); 7.75 (*ddd*, 1H, *J* = 8.4, 6.8, 1.2, H-C(7)); 8.13 (*dd*, 1H, *J* = 8.4, 1.2, H-C(8)); 8.25 (*dd*, 1H, *J* = 8.4, 1.2, H-C(5)); 11.38 (*s*, 1H, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.07; 55.88; 56.61; 99.71; 106.06; 109.41; 113.48; 113.88; 120.73; 122.26; 124.64; 128.66; 129.59; 138.83; 141.71; 142.15; 143.65; 145.87; 154.74; 162.79; 199.93. Anal. Calcd. for $C_{21}H_{18}N_2O_4 \cdot 0.4H_2O$: C 68.25, H 5.13, N 7.58; found: C 68.10, H 5.11, N 7.54.

*5.1.9. 4-Chlorofuro[3,2-*c*]quinoline (**11**)*

A mixture of 2,4-dihydroxyquinoline (**9**, 2.42 g, 15 mmol), KI (0.50 g) and 40% chloroacetaldehyde (5.20 ml, 6.28 g, 32 mmol) in 1.0 N KOH (20 ml) was heated at reflux for 4 h (TLC monitoring). After cooling, the resulting precipitate was collected, washed with H_2O, purified by FC (CH_2Cl_2/EtOAc 3:1) and recrystallized from EtOH to give **10** (3.05 g, 82%). M.p.: 245–246 °C; ^{1}H-NMR (400 MHz, DMSO): δ 7.07 (*d*, 1H, *J* = 2.4, H-C(3)); 7.29 (*ddd*, 1H, *J* = 8.0, 6.8, 1.2, H-C(8)); 7.47 (*dd*, 1H, *J* = 8.4, 1.2, H-C(7)); 7.53 (*ddd*, 1H, *J* = 8.4, 6.8, 1.2, H-C(9)); 7.92 (*dd*, 1H, *J* = 8.0, 1.2, H-C(6)); 8.09 (*d*, 1H, *J* = 2.4, H-C(2)); 11.74 (*br s*, 1H, NH). ^{13}C-NMR (100 MHz, DMSO): δ 107.60; 111.15; 115.45; 115.90; 120.04; 122.18; 129.38; 136.90; 145.37; 155.27; 158.75.

A mixture of **10** (0.22 g, 1.19 mmol), $POCl_3$ (4 ml) and Et_3N (1 ml) was heated at 110 °C for 8 h. To the cold reaction mixture was added ice-water (20 ml), and neutralized with 10 N NaOH. The brown precipitate was collected, washed with cold H_2O and purified by FC (CH_2Cl_2) to give **11** (0.21 g, 86%). M.p.: 111–112 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.03 (*d*, 1H, *J* = 2.2, H-C(3)); 7.64 (*m*, 1H, H-C(8)); 7.73 (*m*, 1H, H-C(7)); 7.82 (*d*, 1H, *J* = 2.2, H-C(2)); 8.14 (*dd*, 1H, *J* = 8.0, 2.0, H-C(9)); 8.25 (*dd*, 1H, *J* = 7.4, 2.0, H-C(6)). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 106.33, 116.65, 119.80, 120.11, 127.19, 128.81, 129.21, 144.29, 145.03, 145.22, 156.38.

*5.1.10. 1-[3-(Furo[3,2-*c*]quinolin-4-ylamino)phenyl]ethanone (**12**)*

To a solution of **11** (408 mg, 2 mmol) and 3-aminoacetophenone (406 mg, 3 mmol) in EtOH/H_2O (2:1, 20 ml) was added concentrated HCl until pH 6 resulted. The mixture was refluxed for 40 min and then the solvent evaporated in vacuo to give a residual solid, which was suspended in ice-water (40 ml) and neutralized with 2 N NaOH. The resulting precipitate was collected and purified by FC (*n*-hexane/EtOAc 2:1) to give **12** (602 mg, 99%). M.p.: 233–234 °C; ^{1}H-NMR (200 MHz, DMSO): δ 2.65 (*s*, 3H, Me); 7.66 (*m*, 4H, H-C(8) and Ar-H); 7.78 (*d*, 1H, *J* = 2.2, H-C(3)); 8.00 (*m*, 3H, 2H-C(7, 9) and Ar-H); 8.19 (*dd*, 1H, *J* = 8.0, 1.2, H-C(6)), 8.35 (*d*, 1H, *J* = 2.2, H-C(2)); 8.38 (*br s*, 1H, NH), 11.60 (*br s*, 1H, HCl); ^{13}C-NMR (50 MHz, DMSO): δ 26.87, 107.23, 110.97, 113.15, 120.19, 121.11, 123.35, 125.34, 125.78, 128.19, 130.06, 130.45, 137.29, 137.70, 138.05, 146.71, 148.61, 156.09, 197.52. Anal. Calcd. for $C_{19}H_{14}N_2O_2$•HCl: C 67.36, H 4.46, N 8.27; found: C 67.02, H 4.49, N 8.19.

*5.1.11. 1-[4-(Furo[3,2-*c*]quinolin-4-ylamino)phenyl]ethanone (**13**)*

Compound **13** was obtained from **11** and 4-aminoacetophenone as described for **12**, which was purified by FC (*n*-hexane/AcOEt 2:1) and recrystallized from EtOH in 93% yield. M.p.: 238–239 °C; ^{1}H-NMR (400 MHz, DMSO): δ 2.61 (*s*, 3H, Me); 7.52 (*ddd*, 1H, *J* = 8.0, 6.8, 0.8, H-C(7)); 7.62 (*d*, 1H, *J* = 2.0, H-C(3)); 7.70 (*ddd*, 1H, *J* = 8.4, 6.8, 1.6, H-C(8)); 7.94 (*dd*, 1H, *J* = 8.4, 0.8, H-C(9)); 8.05 (*m*, 2H, Ar-H); 8.16 (*dd*, 1H, *J* = 8.0, 1.6, H-C(6)); 8.24 (*d*, 1H, *J* = 2.0, H-C(2)); 8.34 (*m*, 2H, Ar-H); 9.80 (*br s*, 1H, NH), 11.98 (*br s*, 1H, HCl). ^{13}C-NMR (100 MHz, DMSO): δ 26.51; 105.82; 111.65; 114.60; 118.52; 119.58; 124.21; 127.12; 128.96; 129.67; 130.34; 144.51; 145.42; 145.66; 148.42; 155.68; 196.76. Anal. Calcd. for $C_{19}H_{14}N_2O_2$•HCl: C 67.36, H 4.46, N 8.27; found: C 67.76, H 4.55, N 8.28.

*5.1.12. (*E*)-1-[3-(Furo[3,2-*c*]quinolin-4-ylamino)phenyl]ethanone oxime (**14a**)*

To a suspension of **12** (151 mg, 0.50 mmol) in ethanol (5 ml) was added NH_2OH·HCl (70 mg, 1 mmol). The reaction mixture was refluxed for 30 min (TLC monitoring), then concentrated in vacuo to give a solid which was collected, washed by H_2O (20 ml), and crystallized from EtOH to give **14a** (144 mg, 90%). M.p.: 224–226 °C; ^{1}H-NMR (200 MHz, DMSO): δ 2.21 (*s*, 3H, Me); 7.50 (*m*, 3H, H-C(7) and Ar-H); 7.64 (*d*, 1H, *J* = 2.0, H-C(3)); 7.70 (*ddd*, 1H, *J* = 8.4, 7.2, 1.4, H-C(8)); 7.91 (*m*, 2H, H-C(9) and Ar-H); 8.14 (*m*, 2H, H-C(6) and Ar-H); 8.28 (*d*, 1H, *J* = 2.0, H-C(2)); 10.65 (*br s*, 1H, NH); 11.29 (*br s*, 1H, NOH). ^{13}C-NMR (50 MHz, DMSO): δ 11.54; 107.40; 110.85; 112.94; 120.28; 121.42; 121.69; 123.62; 123.88; 124.29; 125.44; 129.77; 130.65; 136.32; 138.51; 146.84; 148.61; 152.38; 156.18. Anal. Calcd. for $C_{19}H_{15}N_3O_2$•$0.2H_2O$: C 71.11, H 4.84, N 13.09; found: C 71.08, H 4.93, N 13.11.

*5.1.13. (*E*)-1-[3-Furo[3,2-*c*]quinolin-4-ylamino]phenyl]ethanone O-methyloxime (**14b**)*

To a suspension of **12** (151 mg, 0.5 mmol) in EtOH (5 ml) was added NH_2OMe·HCl (84 mg, 1 mmol). The reaction mixture was refluxed for 30 min (TLC monitoring), then concentrated in vacuo to give a solid which was collected, washed by H_2O (20 ml), and crystallized from MeOH to give **14b** (145 mg, 87%). M.p.: 222–223 °C; ^{1}H-NMR (400 MHz, DMSO): δ 2.23 (*s*, 3H, Me); 3.94 (*s*, 3H, NOMe); 7.54–7.74 (*m*, 5H, 3H-C(3, 7, 8) and Ar-H); 7.84 (*m*, 1H, Ar-H); 7.97 (*d*, 1H, *J* = 8.4, H-C(9)); 8.06 (*m*, 1H, Ar-H), 8.16 (*d*, 1H, *J* = 8.0, H-C(6)); 8.32 (*d*, 1H, *J* = 1.2, H-C(2)); 11.38 (*br s*, 1H, NH); 15.25 (*br s*, 1H, HCl). ^{13}C-NMR (100 MHz, DMSO): δ 12.36; 61.71; 107.47; 110.87; 112.98; 120.28; 121.23; 121.70; 123.28; 124.10; 124.84; 125.44; 129.87; 130.62; 136.56; 137.38; 146.80; 148.65; 153.63; 156.13. Anal. Calcd. for $C_{20}H_{17}N_3O_2$•HCl: C 65.31, H 4.93, N 11.42; found: C 64.99, H 5.02, N 11.21.

5.1.14. (E)*-1-[4-(Furo[3,2-*c*]quinolin-4-ylamino)phenyl]ethanone oxime (**15a**)*

From **13** and NH_2OH·HCl as described for **14a**: 88% yield. M.p.: 267–268 °C; ^{1}H-NMR (400 MHz, DMSO): δ 2.21 (*s*, 3H, Me); 7.55 (*m*, 1H, H-C(7)); 7.69 (*m*, 2H, H-C(3, 8)); 7.78–7.86 (*m*, 4H, Ar-H); 7.95 (*d*, 1H, *J* = 8.4, H-C(9)); 8.15 (*d*, 1H, *J* = 8.4, H-C(6)); 8.31 (*d*, 1H, *J* = 2.0, H-C(2)); 10.74 (*br s*, 1H, NH); 11.22 (*br s*, 1H, NOH). ^{13}C-NMR (100 MHz, DMSO): δ 11.36; 106.74; 110.94; 113.29; 119.94 (2C); 120.92; 122.59; 124.82; 126.22; 126.51 (2C); 129.42; 129.97; 133.56; 137.42; 146.31; 148.43; 152.35; 155.85. Anal. Calcd. for $C_{19}H_{15}N_3O_2$•0.2H_2O: C 71.11, H 4.84, N 13.09; found: C 71.45, H 4.84, N 12.73.

5.1.15. (E)*-1-[4-Furo[3,2-*c*]quinolin-4-ylamino]phenyl]ethanone O-methyloxime (**15b**)*

From **13** and NH_2OMe·HCl as described for **14b**: 84% yield. M.p.: 231–232 °C; ^{1}H-NMR (400 MHz, DMSO): δ 2.24 (*s*, 3H, Me); 3.95 (*s*, 3H, NOMe); 7.60 (*m*, 1H, H-C(7)); 7.72–7.84 (*m*, 6H, H-C(3, 8) and Ar-H); 8.00 (*d*, 1H, *J* = 8.4, H-C(9)); 8.18 (*d*, 1H, *J* = 8.0, H-C(6)); 8.35 (*d*, 1H, *J* = 2.4, H-C(2)); 11.58 (*br s*, 1H, NH); 15.68 (*br s*, 1H, HCl). ^{13}C-NMR (100 MHz, DMSO): δ 12.21; 61.62; 107.29; 110.96; 113.10; 120.20 (2C); 120.92; 123.49; 125.38; 127.11 (2C); 129.42; 130.49; 133.57; 137.42; 146.72; 148.39; 153.48; 156.12. Anal. Calcd. for $C_{20}H_{17}N_3O_2$•1.2HCl: C 64.03, H 4.89, N 11.20; found: C 64.22, H 4.97, N 10.97.

*5.1.16. 5-[3-(Furo[3,2-*c*]quinolin-4-ylamino)phenyl]-5-methyl-3-methylenedihydro-furan-2-one (**16**)*

To a solution of **12** (151 mg, 0.5 mmol) in dry THF (30 ml), activated Zn powder (85 mg, 0.75 mmol), hydroquinone (3 mg), and ethyl 2-(bromomethyl)acrylate (260 mg, 0.75 mmol) were added. The mixture was refluxed under N_2 for 2 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl solution (150 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The combined CH_2Cl_2 extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to give a residual solid, which was purified by FC (*n*-hexane/AcOEt 3:1) and recrystallized from EtOH to give **16** (144 mg, 78%). M.p.: 85–87 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.79 (*s*, 3H, Me); 3.20 (*m*, 2H, H-C(4′)); 5.66 (*t*, 1H, *J* = 2.4, C(3′)=CH); 6.29 (*t*, 1H, *J* = 2.4, C(3′)=CH); 6.79 (*d*, 1H, *J* = 2.0, H-C(3)); 7.08 (*ddd*, 1H, *J* = 8.0, 1.6, 0.8 Hz, Ar-H); 7.42 (*m*, 2H, H-C(7) and Ar-H); 7.61 (*m*, 1H, H-C(8)); 7.75 (*d*, 1H, *J* = 2.0 Hz, H-C(2)); 7.89 (*m*, 4H, H-C(9), Ar-H and NH); 8.12 (*dd*, 1H, *J* = 8.0, 1.4, H-C(6)). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 29.95; 42.71; 83.98; 104.27; 110.72; 115.01; 115.89; 118.41; 119.17; 119.74; 122.69; 123.66; 127.12; 128.67; 129.39; 135.04; 140.41; 144.01; 145.10; 145.51; 148.48; 156.74; 169.77. HRMS (EI): Calcd. for $C_{23}H_{18}N_2O_3$: 370.1312; found: 370.1309.

*5.1.17. 5-[4-(Furo[3,2-*c*]quinolin-4-ylamino)phenyl]-5-methyl-3-methylenedihydro-furan-2-one (**17**)*

Compound **17** was obtained from **13** as described for **16**, which was purified by FC (*n*-hexane/AcOEt 3:1) and recrystallized from EtOAc in 88% yield. M.p.: 109–111 °C; ^{1}H-NMR (200 MHz, DMSO): δ 1.72 (*s*, 3H, Me); 3.23 (*m*, 2H, H-C(4′)); 5.77 (*t*, 1H, *J* = 2.4, C(3′)=CH); 6.10 (*t*, 1H, *J* = 2.4, C(3′)=CH); 7.41 (*m*, 3H, H-C(7) and Ar-H); 7.56 (*d*, 1H, *J* = 2.2, H-C(3)); 7.60 (*m*, 1H, H-C(8)); 7.81 (*dd*, 1H, *J* = 8.4, 1.2, H-C(9)); 8.07 (*d*, 1H, *J* = 8.0, 1.2, H-C(6)); 8.15 (*m*, 2H, Ar-H); 8.18 (*d*, 1H, *J* = 2.2, H-C(2)); 9.39 (*br s*, 1H, NH). ^{13}C-NMR (50 MHz, DMSO): δ 29.15; 41.92; 84.00; 105.68; 111.20; 114.29; 119.28 (2C); 122.15; 123.26; 124.65 (2C); 126.81; 128.50; 135.78; 137.42; 140.39; 144.83; 145.01; 145.33; 148.76; 155.27; 169.31. Anal. Calcd. for $C_{23}H_{18}N_2O_3$•0.4H_2O: C 73.16, H 5.02, N 7.42; found: C 73.47, H 5.11, N 7.07.

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