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Synthesis, cytotoxicity, and anti-inflammatory evaluation of 2-(furan-2-yl)-4-(phenoxy)quinoline derivatives. Part 4

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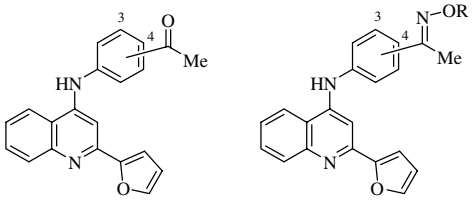
Abstract—A number of 2-(furan-2-yl)-4-phenoxyquinoline derivatives have been synthesized and evaluated for anti-inflammatory evaluation. 4-[(2-Furan-2-yl)quinolin-4-yloxy]benzaldehyde (**8**), with an IC_{50} value of 5.0 μM against β-glucuronidase release, was more potent than its tricyclic furo[2,3-*b*]quinoline isomer **3a** (>30 μM), its 4′-COMe counterpart **7** (7.5 μM), and its oxime derivative **13a** (11.4 μM) and methyloxime derivative **13b** (>30 μM). For the inhibition of lysozyme release, however, oxime derivative **12a** (8.9 μM) and methyloxime derivative **12b** (10.4 μM) are more potent than their ketone precursor **7** and their respective tricyclic furo[2,3-*b*]quinoline counterparts **4a** and **4b**. Among them, 4-{4-[(2-furan-2-yl)-quinolin-4-yloxy]phenyl}but-3-en-2-one (**10**) is the most active against lysozyme release with an IC_{50} value of 4.6 μM, while **8** is the most active against β-glucuronidase release with an IC_{50} value of 5.0 μM. (*E*)-1-{3-[(2-Furan-2-yl)quinolin-4-yloxy]phenyl}ethanone oxime (**11a**) is capable of inhibiting both lysozyme and β-glucuronidase release with IC_{50} values of 7.1 and 9.5 μM, respectively. For the inhibition of TNF-α formation, 1-{3-[(2-furan-2-yl)quinolin-4-yloxy]phenyl}ethanone (**6**) is the most potent with an IC_{50} value of 2.3 μM which is more potent than genistein (9.1 μM). For the inhibitory activity of fMLP-induced superoxide anion generation, **11a** (2.7 μM), **11b** (2.8 μM), and **13b** (2.2 μM) are three of the most active. None of above compounds exhibited significant cytotoxicity.

1. Introduction

Quinolin-4(1*H*)-one moiety is a characteristic component of a large number of antibacterial and/or anticancer agents.[1–5] The biological activity of these quinolone derivatives depends not only on the bicyclic heteroaromatic pharmacophore but also on the nature of the peripheral substituents and their spatial relationship. With a phenyl group appended on C-2 position of quinolin-4(1*H*)-one, a number of 2-phenylquinolone derivatives have been discovered to possess antimitotic activity.[6–8] Recently, we have synthesized certain 4-anilino-2-phenylquinoline derivatives and their isomeric 4-anilino-2-(furan-2-yl)quinolines for anticancer evaluation.[9–11] Among them, 1-(3-{2-[(furan-2-yl)quinolin-4-yl]amino}phenyl)-ethanone **1a**, its oxime **2a** and methyloxime **2b** (Chart 1) exhibited cytotoxic activity with mean GI_{50} values of 10.5, 6.85, and 20.6 μM, respectively, while the mean GI_{50} values for their 4-substituted counterparts **1b**, **2c**, and **2d** are 4.36, 5.54, and 5.99 μM, respectively.[11] We have also synthesized certain 9-anilinoacridine, 9-phenoxyacridine, 4-anilinofuro[2,3-*b*]quinoline, and 4-phenoxyfuro[2,3-*b*]quinoline derivatives for anti-inflammatory evaluation.[12–15] Some



1a 3-substituted
1b 4-substituted

2a 3-substituted, R = H
2b 3-substituted, R = Me
2c 4-substituted, R = H
2d 4-substituted, R = Me

Chart 1. Structures of 4-anilino-2-(furan-2-yl)quinoline derivatives.

Keywords: Quinoline; 2-(Furan-2-yl)-4-phenoxyquinoline; Anti-inflammatory activity.
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of them were found to be more potent than the calmodulin inhibitor trifluoperazine, which inhibits the degranulation and superoxide anion generation in neutrophils. To explore more potent anti-inflammatory agents and to establish structure–activity relationships, we described herein the synthesis and anti-inflammatory evaluation of 2-(furan-2-yl)-4-phenoxyquinoline derivatives whose structures belong to isomers of 4-phenoxyfuro[2,3-*b*]quinolines (Chart 2). Although 2-(furan-2-yl)quinoline skeleton is not a system with three fused aromatic rings, its third furan ring is appended at C(2), which can accommodate itself in a virtually coplanar fashion to the tricyclic furo[2,3-*b*]quinoline.[16]

Due to structural similarity between 2-(furan-2-yl)-4-phenoxyquinolines and their isomeric 4-anilino-2-(furan-2-yl)quinoline (Chart 1), newly synthesized compounds were also evaluated for their cytotoxicity against three representative cancer cell lines (MCF7, NCI-H460, and SF-268) because highly cytotoxic agents will hardly be developed as anti-inflammatory drug candidates.

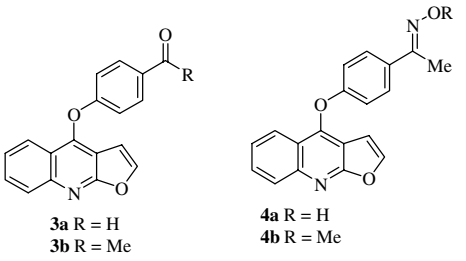
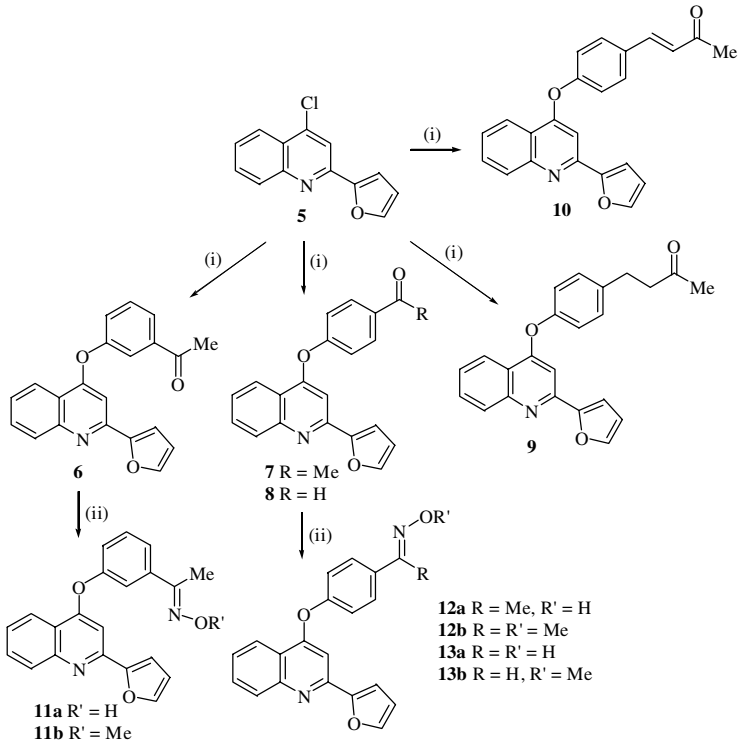


Chart 2. Structures of 4-phenoxyfuro[2,3-*b*]quinoline derivatives.

2. Chemistry

Preparation of 2-(furan-2-yl)-4-phenoxyquinoline derivatives is outlined in the Scheme 1. The known 4-chloro-2-(furan-2-yl)quinoline (**5**)[11] was treated with 3-hydroxyacetophenone to afford 1-{3-[(2-furan-2-yl)quinolin-4-yloxy]phenyl}ethanone (**6**), which was then reacted with hydroxylamine or methylhydroxylamine to give exclusively (*E*)-1-{3-[(2-furan-2-yl)-quinolin-4-yloxy]phenyl}ethanone oxime (**11a**) or its methyl derivative **11b**, respectively. Accordingly, compounds **7–10**, respectively, were obtained from **5** by the treatment with substituted phenols. Reaction of **7** and **8**, respectively, with NH_2OH or NH_2OMe provided their respective (*E*)-oximes **12a**, **13a** and (*E*)-methyloximes **12b**, **13b** in a good overall yield. The configuration of the oxime moiety was determined by through-space nuclear Overhauser effect spectroscopy (NOESY) which revealed coupling connectivity to CH_3 protons. We have also confirmed the configuration of the oxime and methyloxime moieties by the ^{13}C NMR spectra. The carbon of CH_3 which is *syn* to the OR′ moiety (*E*-form) shifted upfield (δ 11.86 ppm for (*E*)-**11a**, 12.49 for (*E*)-**11b**, 12.40 for (*E*)-**12a**, and 12.65 for (*E*)-**12b**), while that of the *anti* isomer (*Z*-form) shifted downfield (δ value of CH_3 is 11.50 ppm for the *syn* isomer and 18.75 ppm for the *anti* isomer of butan-2-one oxime).[17]



Scheme 1. Reagents and conditions: (i) 3- or 4-substituted phenol, K_2CO_3, acetone or THF in scaled bomb, 150 °C for 24 h (51–68%); (ii) NH_2OR, K_2CO_3, EtOH, reflux for 0.5 h (61–70%).

3. Pharmacological results and discussion

3.1. Neutrophil degranulation

Activation of neutrophils with 1 μM formyl-methionyl-leucyl-phenylalanine (fMLP) in the presence of cytochalasin B (5 μg/mL) evoked the release of 21.2% and 19.8% of lysozyme and β-glucuronidase, respectively, of the initial cellular content. 4-[(2-Furan-2-yl)quinolin-4-yloxy]benzaldehyde (**8**), with an IC_{50} value of 5.0 μM against β-glucuronidase release, was more potent than its tricyclic furo[2,3-*b*]quinoline isomer **3a** (>30 μM), its 4′-COMe counterpart **7** (7.5 μM), and its oxime derivative **13a** (11.4 μM) and methyloxime derivative **13b** (>30 μM), and the calmodulin inhibitor, trifluoperazine (17.0 μM) which inhibits the degranulation and superoxide anion generation in neutrophils.[18,19] The same SAR was observed in which **7** is more active against β-glucuronidase release than its tricyclic furo[2,3-*b*]quinoline isomer **3b** (>30 μM), its *meta*-isomer **6** (>30 μM), and its oxime derivative **12a** (>30 μM) and methyloxime derivative **12b** (>30 μM), and the double bond inserted derivative **10** (17.0 μM). For the inhibition of lysozyme release, oxime derivative **12a** (with an IC_{50} value of 8.9 μM) and methyloxime derivative **12b** (10.4 μM) are more potent than their ketone precursor **7** (>30 μM) and their respective tricyclic furo[2,3-*b*]quinoline counterparts **4a** (>30 μM) and **4b** (>30 μM). The same SAR was observed in which oxime derivative **11a** (7.1 μM) was more potent than its ketone precursor **6** (>30 μM) and the positive trifluoperazine (8.3 μM). Insertion of a double bond between phenyl group and the carbonyl moiety led to more potent activity against lysozyme release but less potent against β-glucuronidase release (**10** vs **7**). Saturation of the double bond led to the decrease of both activities (**10** vs **9**). Among them, 4-{4-[(2-furan-2-yl)quinolin-4-yloxy]- phenyl}but-3-en-2-one (**10**) is the most active against lysozyme release with an IC_{50} value of 4.6 μM, while **8** is the most active against β-glucuronidase release with an IC_{50} value of 5.0 μM. (*E*)-1-{3-[(2-Furan-2-yl)quinolin-4-yloxy]phenyl}ethanone oxime (**11a**) is capable of inhibiting both lysozyme and β-glucuronidase release with IC_{50} values of 7.1 and 9.5 μM, respectively (see Table 1).

Table 1. IC_{50}[a,b] (μM) values of 2-(furan-2-yl)-4-phenoxyquinoline derivatives against neutrophil degranulation

Compound	Neutrophil degranulation[c]	
	Lysozyme	β-Glucuronidase
6	>30 (47.5 ± 6.2)**	>30 (38.5 ± 4.6)**
7	>30 (38.0 ± 9.4)**	7.5 ± 2.9
8	>30 (34.3 ± 4.5)**	5.0 ± 0.9
9	10.1 ± 3.0	>30 (49.5 ± 11.0)**
10	4.6 ± 0.7	17.0 ± 2.3
11a	7.1 ± 0.3	9.5 ± 3.9
11b	>30 (47.1 ± 10.5)**	>30 (42.4 ± 4.6)**
12a	8.9 ± 2.3	>30 (36.8 ± 4.4)**
12b	10.4 ± 0.6	>30 (41.8 ± 8.9)**
13a	24.5 ± 2.7	11.4 ± 2.6
13b	>30 (24.1 ± 11.8)*	>30 (19.5 ± 5.7)*
Trifluoperazine	8.3 ± 1.4	17.0 ± 2.3

[a] Values are means ± SE of at least three independent experiments.
[b] When 50% inhibition could not be reached at the highest concentration, the percentage of inhibition is given in parentheses.
[c] Induced by fMLP (1 μM)/cytochalasin B (5 μg/mL).
* $P < 0.05$.
** $P < 0.01$.

Table 2. IC_{50} values of 2-(furan-2-yl)-4-phenoxyquinoline derivative on TNF-α formation and nitric oxide production in RAW 264.7 cells

Compound	IC_{50}[a] (μM)	
	TNF-α formation[b]	Nitric oxide production[b]
6	2.3 ± 0.3	>30
7	>30	>30
8	>30	>30
9	>30	>30
10	>30	>30
11a	>30	>30
11b	>30	>30
12a	>30	>30
12b	>30	>30
13a	>30	>30
13b	>30	>30
Genistein	9.1 ± 0.6	nd[d]
1400W[c]	nd	7.2 ± 2.5

[a] Values are means ± SE of at least three independent experiments.
[b] Induced by LPS (1 μg/mL).
[c] *N*-(3-Aminomethyl)benzylacetamidine 2HCl.
[d] Not determined.

3.2. TNF-α release

TNF-α, an early cytokine produced by activated macrophages, plays an essential role in pathological inflammatory reactions. 1-{3-[(2-Furan-2-yl)quinolin-4-yloxy]-phenyl}ethanone (**6**), with an IC_{50} value of 2.3 μM against TNF-α formation in macrophage-like cell line RAW 264.7, was more potent than positive genistein (9.1 μM) and its congeners **7** – **13** which were inactive (>30 μM) (Table 2).

3.3. Superoxide formation

In the superoxide anion generation experiments, neutrophils were stimulated with fMLP (0.3 μM)/cytochalasin B (5 μg/mL) or phorbol 12-myristate 13-acetate (PMA; 3 nM) for 10 min in the presence of cytochrome *c*, and the superoxide anion generation was measured in terms of superoxide dismutase-inhibitable cytochrome *c* reduction.[20,21] As shown in Table 3, compounds **11a** and **11b** had potent inhibitory effects on fMLP-induced superoxide anion generation with IC_{50} values of 2.7 and 2.8 μM, respectively, while their *para*-substituted counterparts **12a** and **12b** were inactive. The same SAR was observed in which *meta*-COMe-substituted derivative **6** (6.7 μM) is more potent than its *para*-substituted counterpart **7** (12.3 μM). The inhibitory activity of fMLP-induced superoxide anion generation decreased in the order of **13b** (2.2 μM) > **8** (5.9 μM) > **7** (12.3 μM) indicates a methyloxime is more favorable than an aldehyde which in turn is more favorable than a ketone substituent at *para*-position of the phenoxy moiety. The same SAR was observed in which *meta*-methyloxime-substituted derivative **11b** (2.8 μM) is more potent than its ketone-substituted counterpart **6** (6.7 μM). Insertion of a double bond between phenyl

Table 3. IC_{50}[a] (μM) values of 2-(furan-2-yl)-4-phenoxyquinoline derivatives against neutrophil superoxide formation

Compound	Superoxide formation (nmol)	
	fMLP[b]	PMA[c]
6	6.7 ± 0.6	>30
7	12.3 ± 0.1	>30
8	5.9 ± 0.9	>30
9	5.9 ± 1.1	>30
10	11.3 ± 1.6	>30
11a	2.7 ± 0.7	>30
11b	2.8 ± 0.8	7.1 ± 1.2
12a	>30	>30
12b	>30	>30
13a	17.5 ± 1.1	>30
13b	2.2 ± 0.4	7.2 ± 2.2
DPI[d]	1.3 ± 0.2	1.4 ± 0.7

[a] Values are means ± SE of at least three independent experiments.
[b] Induced by fMLP (0.3 μM)/cytochalasin B (5 μg/ml).
[c] Induced by PMA (3 nM).
[d] Diphenylene iodonium chloride.

group and the carbonyl moiety does not enhance the inhibitory effect (**10** vs **7**). Saturation of the double bond led to the increase of inhibitory activity (**9** > **10**). Among them, only **11b** and **13b** are active on the inhibitory effect of PMA-induced superoxide anion generation in rat neutrophils. Because fMLP and PMA activate NADPH oxidase to produce superoxide anion through different cellular signaling mechanisms.[22] No appreciable effect of **6**–**10**, **11a**, and **13a** on PMA-induced response suggests the involvement of PMA-independent signaling pathway.

3.4. Preliminary cytotoxic evaluation

All the synthesized (2-furan-2-yl)quinoline derivatives were evaluated in vitro against a 3-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.[23] Results for each test agent were 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 considered to be cytotoxic. According to these criteria, 4-phenoxy derivative **6**, its oxime **11a** and methyloxime **11b** are considered as non-cytotoxic (Table 4). However, strong cytotoxicity demonstrated by their respective 4-anilino counterparts **1a**, **2a**, and **2b** indicated that the bridged atom between quinoline and phenyl group is crucial in which the nitrogen is more favorable than the oxygen. The same SAR was observed in which oxygen-bridged compounds **7**, **12a**, and **12b** are non-cytotoxic, while their respective nitrogen-bridged counterparts **1b**, **2c**, and **2d** are cytotoxic agents.

4. Conclusion

(2-Furan-2-yl)-4-phenoxyquinoline derivatives **7** and **8** exhibited potent inhibitory activities against β-glucuronidase release in neutrophils with IC_{50} values of 5.0 and 7.5 μM, respectively, while their respective tricyclic 4-phenoxyfuro[2,3-*b*]quinoline isomers **3a** and **3b** were inactive (>30 μM) indicating that the 2-(furan-2-yl)quinoline skeleton is more favorable than the tricyclic furo[2,3-*b*]quinoline heterocycle to be developed as anti-inflammatory agents. The same SAR was observed for the inhibition of lysozyme release in which 2-(furan-2-yl)quinoline**s** **12a** and **12b** are potent inhibitors, while their respective furo[2,3-*b*]quinoline counterparts **4a** and **4b** are inactive. These results are interesting because none of the synthesized (2-furan-2-yl)-4-phenoxyquinoline derivatives exhibited significant cytotoxicity.

Table 4. Cytotoxicity of 2-(furan-2-yl)-4-phenoxyquinoline derivatives

Compound	Growth percentage[a]			
	MCF7 (breast cancer)	NCI-H460 (lung cancer)	SF-268 (CNS cancer)	Mean GI_{50} (μM)[b,c]
1a	11	1	17	10.5
1b	2	1	19	4.36
2a	25	0	26	6.85
2b	50	17	98	20.6
2c	88	1	81	5.54
2d	83	17	111	5.99
6	66	38	46	nd[d]
7	78	49	66	nd
8	73	78	91	nd
9	55	28	85	nd
11a	56	37	39	nd
11b	61	40	41	nd
12a	97	90	114	nd
12b	80	44	62	nd
13a	93	55	94	nd
13b	87	80	114	nd

[a] 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.[23] 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.
[b] Data obtained from NCI's in vitro disease-oriented tumor cell screen.[24] GI_{50}: drug molar concentration causing 50% cell growth inhibition.
[c] Mean values over all 60 cell lines tested.
[d] Not determined.

5. Experimental

5.1. General

TLC: precoated (0.2 mm) silica gel 60 F_{254} plates from EM Laboratories, Inc.; detection by UV light (254 nm). All chromatographic separations were performed using silica gel (Merck 60 230–400 mesh). Mp: Electrothermal IA9100 melting point apparatus; uncorrected. ^1H and ^{13}C NMR spectra: Varian-Unity-400 spectrometer at 400 and 100 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-{3-[(2-Furan-2-yl)quinolin-4-yloxy]phenyl}ethanone (6). A mixture of 4-chloro-2-(furan-2-yl)quinoline[11] (**5**, 0.46 g, 2 mmol), 4-hydroxyacetophenone (0.27 g, 2 mmol), K_2CO_3 (0.41 g, 3 mmol), and acetone (60 mL) was heated in a sealed steel bomb at 150 °C for 24 h (TLC monitoring). The resulting mixture was evaporated under reduced pressure and then H_2O (100 mL) was added. The precipitate was collected, washed with H_2O, and purified by flash column chromatography (FC, silica gel; MeOH/CH_2Cl_2 = 1/20) to give **6** (0.44 g, 67%). Mp 109–111 °C. ^{1}H NMR ($CDCl_3$): 2.63 (3H, s, $COCH_3$), 6.51 (1H, dd, J = 3.6, 1.8 Hz, 4′-H), 6.98 (1H, s, 3-H), 7.13 (1H, dd, J = 3.6, 0.8 Hz, Ar-H), 7.39–7.63 (4H, m, Ar-H), 7.71–7.93 (3H, m, Ar-H), 8.12 (1H, m, 5-H), 8.28 (1H, m, 8-H). ^{13}C NMR ($CDCl_3$): 26.70, 100.85, 110.18, 112.20, 120.53, 121.55, 122.15, 125.34, 125.48, 125.93, 129.00, 130.55, 130.65, 139.39, 143.90, 149.74, 149.91, 153.34, 154.92, 161.71, 196.92. Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.57; H, 4.60; N, 4.25. Found: C, 76.47; H, 4.83; N, 4.10.

5.1.2. 1-{4-[(2-Furan-2-yl)quinolin-4-yloxy]phenyl}ethanone (7). Obtained from **5** and 4-hydroxyacetophenone as described for **6** in 65% yield. Mp 156–157 °C. ^{1}H NMR ($CDCl_3$): 2.65 (3H, s, $COCH_3$), 6.54 (1H, dd, J = 3.2, 1.6 Hz, 4′-H), 7.13 (1H, s, 3-H), 7.27 (3H, m, 3′-H, Ar-H), 7.54 (2H, m, 5′-, 6-H), 7.77 (1H, m, 7-H), 8.08 (2H, m, Ar-H), 8.21 (2H, m, 5-, 8-H). ^{13}C NMR ($CDCl_3$): 26.55, 102.08, 110.93, 112.40, 115.77, 120.08 (2C), 120.60, 121.59, 126.20, 128.73, 130.52, 130.89 (2C), 130.95, 134.16, 144.23, 149.69, 158.80, 196.65. Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.57; H, 4.60; N, 4.25. Found: C, 76.41; H, 4.64; N, 4.27.

5.1.3. 4-[(2-Furan-2-yl)quinolin-4-yloxy]benzaldehyde (8). Obtained from **5** and 4-hydroxybenzaldehyde in THF as described for **6** in 51% yield. Mp 107–109 °C. ^{1}H NMR ($CDCl_3$): 6.54 (1H, dd, J = 3.2, 1.6 Hz, 4′-H), 7.18 (2H, m, 3-, 3′-H), 7.33 (2H, m, Ar-H), 7.54 (2H, m, 5′-, 6-H), 7.77 (1H, m, 7-H), 8.00 (2H, m, Ar-H), 8.17 (2H, m, 5-, 8-H), 10.04 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): 102.32, 112.34, 112.78 (2C), 116.42, 120.56, 121.68, 122.41, 126.64, 127.46, 129.83, 131.52, 132.02, 132.28 (2C), 133.60, 144.48, 144.73, 159.81, 190.64. Anal. Calcd for $C_{20}H_{13}NO_3$: C, 76.17; H, 4.16; N, 4.44. Found: C, 76.03; H, 4.34; N, 4.33.

5.1.4. 4-{4-[(2-Furan-2-yl)quinolin-4-yloxy]phenyl}butan-2-one (9). Obtained from **5** and 4-hydroxybenzylacetone as described for **6** in 52% yield. Mp 137–138 °C. ^{1}H NMR ($CDCl_3$): 2.18 (3H, s, $COCH_3$), 2.82, 2.94 (4H, two m, CH_2CH_2CO), 6.51 (1H, dd, J = 3.4, 2.0 Hz, 4′-H), 6.98 (1H, s, 3-H), 7.14 (3H, m, 3′-, ArH), 7.28 (2H, m, ArH), 7.51 (2H, m, 5′-, 6- H), 7.73 (1H, m, 7-H), 8.011 (1H, d, J = 8.6 Hz, 5-H), 8.29 (1H, m, 8-H). ^{13}C NMR ($CDCl_3$): 29.13, 30.04, 44.98, 100.55, 110.06, 112.10, 120.68, 120.88 (2C), 121.69, 125.68, 128.93, 130.05 (2C), 130.41, 138.30, 143.77, 149.66, 149.93, 152.76, 153.58, 162.23, 208.62. Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.28; H, 5.37; N, 3.92. Found: C, 77.00; H, 5.43; N, 3.85.

5.1.5. 4-{4-[(2-Furan-2-yl)quinolin-4-yloxy]phenyl}but-3-en-2-one (10). Obtained from **5** and 4-hydroxybenzylideneacetone as described for **6** in 57% yield. Mp 126–128 °C. ^{1}H NMR ($CDCl_3$): 2.35 (3H, s, $COCH_3$), 6.51 (1H, dd, J = 3.4, 2.0 Hz, 4′-H), 6.63 (1H, d, J = 16.0 Hz, CH=C*H*(C=O)CH_3), 6.95 (1H, s, 3-H), 7.06–7.13 (3H, m, 5′-, ArH), 7.29 (2H, m, ArH), 7.43–7.54 (3H, m, 3′-, 6-H, and C*H*=CH(C=O)CH_3), 7.72 (1H, m, 7-H), 8.03 (1H, d, J = 8.6 Hz, 5-H), 8.31 (1H, m, 8-H). ^{13}C NMR ($CDCl_3$): 27.86, 100.42, 108.51, 110.19, 112.22, 120.71, 120.91 (2C), 121.65, 125.84, 128.38, 130.19 (2C), 130.44, 138.38, 143.77, 144.09, 149.58, 150.14, 152.24, 153.79, 162.33, 198.68. Anal. Calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94. Found: C, 77.59; H, 4.79; N, 3.64.

5.1.6. (*E*)-1-{3-[(2-Furan-2-yl)quinolin-4-yloxy]phenyl}ethanone oxime (11a). To a suspension of **6** (0.17 g, 0.5 mmol) in EtOH (10 mL) were added $NH_2OH{\cdot}HCl$ (0.18 g, 2.5 mmol) and potassium carbonate (0.16 g, 1.3 mmol). The reaction mixture was refluxed for 2 h (TLC monitoring). After cooling, the solvent was removed in vacuo and the residue was suspended in ice water (20 mL). The precipitate obtained was collected and crystallized from MeOH to give **11a** (0.12 g, 70 %). Mp 186–187 °C. ^{1}H NMR ($CDCl_3$): 2.28 (3H, s, N=CCH_3), 6.52 (1H, dd, J = 3.8, 1.8 Hz, 4′-H), 7.01 (1H, s, 3-H), 7.20 (2H, m, 3′-, Ar-H), 7.45–7.62 (5H, m, 5′-, 6-, Ar-H), 7.76 (1H, m, 7-H), 8.11 (1H, d, J = 8.0 Hz, 5-H), 8.31 (1H, dd, J = 8.4, 1.4 Hz, 8-H), 10.44 (1H, br s, NOH).^{13}C NMR ($CDCl_3$): 11.86, 100.62, 110.25, 112.10, 118.40, 120.45, 121.10, 121.55, 123.12, 125.76, 128.06, 130.05, 130.63, 139.45, 143.83, 149.25, 149.90, 152.32, 152.85, 154.33, 162.14. Anal. Calcd for $C_{21}H_{16}N_2O_3{\cdot}0.3H_2O$: C, 72.10; H, 4.79; N, 8.01. Found: C, 72.24; H, 4.90; N, 7.93.

5.1.7. (*E*)-1-{3-[(2-Furan-2-yl)quinolin-4-yloxy]phenyl}ethanone *O*-methyloxime (11b). Obtained from **6** and $NH_2OMe{\cdot}HCl$ as described for **11a**: 66% yield. Mp 63–64 °C. ^{1}H NMR ($CDCl_3$): 2.24 (3H, s, N=CCH_3), 3.99 (3H, s, $NOCH_3$), 6.51 (1H, dd, J = 3.6, 1.6 Hz, 4′-H), 6.99 (1H, s, 3-H), 7.09 (1H, d, J = 3.6 Hz, 3′-H), 7.21 (1H, ddd, J = 7.6, 2.6, 1.2 Hz, Ar-H), 7.44–7.64 (5H, m, 5′-, 6-, Ar-H), 7.74 (1H, m, 7-H), 8.11 (1H, d, J = 8.4 Hz, 5-H), 8.30 (1H, dd, J = 8.4, 1.0 Hz, 8-H).^{13}C NMR ($CDCl_3$): 12.49, 62.08, 100.76, 110.01, 112.10, 118.60, 120.65, 121.36, 121.67, 123.12, 125.74, 129.04, 130.14, 130.44, 139.19, 143.78, 149.80, 150.01, 153.43, 153.61, 154.65, 162.00. Anal. Calcd for $C_{22}H_{18}N_2O_3{\cdot}0.3H_2O$: C, 72.62; H, 5.16; N, 7.70. Found: C, 72.73; H, 5.06; N, 7.82.

5.1.8. (*E*)-1-{4-[(2-Furan-2-yl)quinolin-4-yloxy]phenyl}ethanone oxime (12a). Obtained from **7** and NH_2O-H·HCl as described for **11a**: 65% yield. Mp 249–250 °C. ^{1}H NMR ($CDCl_3$): 2.34 (3H, s, N=CCH_3), 6.56 (1H, dd, J = 3.6, 1.4 Hz, 4′-H), 7.06 (1H, s, 3-H), 7.19 (1H, d, J = 3.6 Hz, 3′-H), 7.25 (2H, m, Ar-H),

7.57 (2H, m, 5′-, 6-H), 7.75–7.84 (3H, m, 7-, Ar-H), 8.10 (1H, d, J = 8.8 Hz, 5-H), 8.33 (1H, dd, J = 8.4, 1.4 Hz, 8-H), 10.81 (1H, br s, NOH). ^{13}C NMR ($CDCl_3$): 12.40, 101.19, 111.44, 112.94, 121.05, 121.34 (2C), 122.36, 126.70, 127.95, 128.68 (2C), 131.73, 135.40, 144.96, 150.41, 152.42, 152.91, 155.10, 155.23, 163.18. Anal. Calcd for $C_{21}H_{16}N_2O_3 \cdot 0.3H_2O$: C, 72.10; H, 4.79; N, 8.01. Found: C, 72.05; H, 4.74; N, 8.01.

5.1.9. (*E*)-1-{4-[(2-Furan-2-yl)quinolin-4-yloxy]phenyl}ethanone *O*-methyloxime (12b). Obtained from **7** and $NH_2OMe \cdot HCl$ as described for **11a**: 68% yield. Mp 111–112 °C. ^{1}H NMR ($CDCl_3$): 2.28 (3H, s, N=CCH_3), 4.03 (3H, s, NOCH_3), 6.52 (1H, dd, J = 3.6, 1.6 Hz, 4′-H), 7.03 (1H, s, 3-H), 7.14 (1H, d, J = 3.6 Hz, 3′-H), 7.22 (2H, m, Ar-H), 7.52 (2H, m, 5′-, 6-H), 7.72–7.80 (3H, m, 7-, Ar-H), 8.12 (1H, d, J = 8.4 Hz, 5-H), 8.28 (1H, dd, J = 8.4, 1.4 Hz, 8-H). ^{13}C NMR ($CDCl_3$): 12.65, 62.04, 100.90, 110.27, 112.21, 120.62, 120.81 (2C), 121.70, 125.86, 128.07 (2C), 128.93, 130.62, 133.99, 143.96, 149.66, 149.95, 153.38, 153.80, 155.23, 161.92. Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.72; H, 5.07; N, 7.82. Found: C, 73.67; H, 5.20; N, 7.68.

5.1.10. (*E*)-4-[(2-Furan-2-yl)quinolin-4-yloxy]benzaldehyde oxime (13a). Obtained from **8** and $NH_2OH \cdot HCl$ as described for **11a**: 61% yield. Mp 201–202 °C. ^{1}H NMR ($CDCl_3$): 6.53 (1H, dd, J = 3.6, 2.0 Hz, 4′-H), 7.06 (1H, s, 3-H), 7.18 (1H, d, J = 3.6 Hz, 3′-H), 7.25 (2H, m, Ar-H), 7.55 (2H, m, 5′-, 6-H), 7.73 (2H, m, Ar-H), 7.78 (1H, m, 7-H), 8.10 (1H, d, J = 8.8 Hz, 5-H), 8.20 (1H, s, N=CH), 8.30 (1H, dd, J = 8.4, 1.2 Hz, 8-H), 10.80 (1H, br s, NOH). ^{13}C NMR ($CDCl_3$): 101.21, 110.72, 112.54, 120.76, 121.29 (2C), 121.91, 126.23, 128.27, 129.06 (2C), 130.38, 131.15, 144.33, 148.86, 149.57, 150.23, 153.01, 155.59, 162.25. Anal. Calcd for $C_{20}H_{14}N_2O_3 \cdot 0.3H_2O$: C, 71.54; H, 4.39; N, 8.34. Found: C, 71.48; H, 4.54; N, 7.96.

5.1.11. (*E*)-4-[(2-Furan-2-yl)quinolin-4-yloxy]benzaldehyde *O*-methyloxime (13b). Obtained from **8** and NH_2O-Me·HCl as described for **11a**: 63% yield. Mp 122–123 °C. ^{1}H NMR ($CDCl_3$): 4.00 (3H, s, NOCH_3), 6.52 (1H, dd, J = 3.4, 1.8 Hz, 4′-H), 7.05 (1H, s, 3-H), 7.17 (1H, d, J = 3.4 Hz, 3′-H), 7.22 (2H, m, Ar-H), 7.52 (2H, m, 5′-, 6-H), 7.68–7.79 (3H, m, 7-, Ar-H), 8.11 (1H, s, N=CH), 8.14 (1H, d, J = 8.0 Hz, 5-H), 8.27 (1H, dd, J = 8.6, 1.2 Hz, 8-H). ^{13}C NMR ($CDCl_3$): 62.13, 101.08, 110.47, 112.26, 120.58, 121.08 (2C), 121.67, 125.97, 128.86, 129.00 (2C), 129.61, 130.73, 144.05, 147.48, 149.86, 150.14, 153.22, 155.77, 161.80. Anal. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.23; H, 4.69; N, 8.14. Found: C, 73.28; H, 4.74; N, 8.06.

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References and notes

1. Fang, K. C.; Chen, Y. L.; Sheu, J. Y.; Wang, T. C.; Tzeng, C. C. *J. Med. Chem.* **2000**, *43*, 3809.
2. Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem.* **2001**, *44*, 2374.
3. Tzeng, C. C.; Chen, Y. L. *Chin. Pharm. J.* **2002**, *54*, 229.
4. Sheu, J. Y.; Chen, Y. L.; Tzeng, C. C.; Hsu, S. L.; Fang, K. C.; Wang, T. C. *Helv. Chim. Acta* **2003**, *86*, 2481.
5. Zhao, Y. L.; Chen, Y. L.; Sheu, J. Y.; Chen, I. L.; Wang, T. C.; Tzeng, C. C. *Bioorg. Med. Chem.* **2005**, *13*, 3921.
6. Chen, K.; Kuo, S. C.; Hsieh, M. C.; Mauger, A.; Lin, C. M.; Hamel, E.; Lee, K. H. *J. Med. Chem.* **1997**, *40*, 3049.
7. Nakamura, S.; Kozuka, M.; Bastow, K. F.; Tokuda, H.; Nishino, H.; Suzuki, M.; Tatsuzaki, J.; Natschke, S. L. M.; Kuo, S. C.; Lee, K. H. *Bioorg. Med. Chem.* **2005**, *13*, 4396.
8. Lai, Y. Y.; Huang, L. J.; Lee, K. H.; Xiao, Z.; Bastow, K. F.; Yamori, T.; Kuo, S. C. *Bioorg. Med. Chem.* **2005**, *13*, 265.
9. Zhao, Y. L.; Chen, Y. L.; Chang, F. S.; Tzeng, C. C. *Eur. J. Med. Chem.* **2005**, *40*, 792.
10. Chen, Y. L.; Huang, C. J.; Huang, Z. Y.; Tseng, C. H.; Chang, F. S.; Yang, S. H.; Lin, S. R.; Tzeng, C. C. *Bioorg. Med. Chem.* **2006**, *14*, in press.
11. Zhao, Y. L.; Chen, Y. L.; Tzeng, C. C.; Chen, I. L.; Wang, T. C.; Han, C. H. *Chem. Biodiver.* **2005**, *2*, 205.
12. Chen, Y. L.; Lu, C. M.; Chen, I. L.; Tsao, L. T.; Wang, J. P. *J. Med. Chem.* **2002**, *45*, 4689.
13. Chen, Y. L.; Chen, I. L.; Lu, C. M.; Tzeng, C. C.; Tsao, L. T.; Wang, J. P. *Bioorg. Med. Chem.* **2003**, *11*, 3921.
14. Chen, Y. L.; Chen, I. L.; Lu, C. M.; Tzeng, C. C.; Tsao, L. T.; Wang, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 387.
15. Kuan, Y. H.; Lin, R. H.; Tsao, L. T.; Chen, Y. L.; Tzeng, C. C.; Wang, J. P. *Biochem. Pharmacol.* **2005**, *70*, 901.
16. Atwell, G. J.; Bos, C. D.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1988**, *31*, 1048.
17. Silverstein, R. M.; Webster, F. X. ^{13}C NMR Spectrometry. In *Spectrometric Identification of Organic Compounds*; Rose, N., Ed.; John Wiley: New York, 1998; pp 217–249.
18. Smith, R. J.; Bowman, B. J.; Iden, S. S. *Immunology* **1981**, *44*, 677.
19. Ochs, D. L.; Reed, P. W. *Biochem. Biophys. Res. Commun.* **1981**, *102*, 958.
20. Market, M.; Andrew, P. C.; Babior, B. M. *Methods Enzymol.* **1984**, *105*, 358.
21. Wang, J. P.; Tsao, L. T.; Raung, S. L.; Lin, P. L.; Lin, C. N. *Free Radic. Biol. Med.* **1999**, *26*, 580.
22. Segal, A. W.; Abo, A. *Trends Biochem. Sci.* **1993**, *18*, 43.
23. Gray, G. D.; Wickstrom, E. *Biotechniques* **1996**, *21*, 780.
24. Monks, A.; Scuderio, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langlay, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. *J. Natl. Cancer Inst.* **1991**, *83*, 757.