DOI: 10.1002/cmdc.200800057

Synthesis, Antiproliferative Activity, and Structure–Activity Relationships of 3-Aryl-1*H*-quinolin-4-ones

Zhu-Ping Xiao, Huan-Qiu Li, Lei Shi, Peng-Cheng Lv, Zhong-Cheng Song, and Hai-Liang Zhu*[a]

*The antiproliferative activities of 36 3-aryl-1*H*-quinolin-4-ones were determined against two cancer cell lines (Hep G2 and KB) in vitro. The results indicate that most of these compounds show good cytotoxic activity against human cancer cell lines, but no cytotoxicity against a human normal cell line (L02). The positive control compounds genistein and 5-fluorouracil show no selectivity at inhibiting the growth of the above three cell lines. Generally, compounds that bear a halogen atom at the 8 position and a methoxy group at the 3′ position exhibited remarkable cytotoxicity toward human cancer cell lines. Electron-withdrawing substituents at the 6 position decrease the antiproliferative activity significantly. We also put forward a pharmacophore model for 3-aryl-4-quinolinones binding with epidermal growth factor receptor protein tyrosine kinases (EGFR PTK). Out of the 36 synthetic compounds, 34 are reported for the first time.*

Introduction

Protein tyrosine kinases (PTK) have been intensively investigated because of their role in the transduction of proliferative signals in mammalian cells. Many transmembrane growth factor receptors possess intracellular PTK activity; after the external binding of a growth factor, the first step in the cellular signal transduction pathway that controls mitogenesis and cell proliferation is initiated.[1–3] The overexpression or inappropriate expression of normal or mutant PTK activity in these receptors can thus result in the loss of growth control and the unregulated cell proliferation that is associated with malignancy.[4] Therefore, selective interruption of signal transduction in tumor cells by specific inhibitors of PTK activity has recently emerged as a major approach for the design of tumor-specific drugs.[5–8] In the past decades, several classes of small molecules have been reported to be potent inhibitors of the PTK activity of a number of transmembrane growth factor receptors and cellular oncogene products, particularly epidermal growth factor receptor (EGFR).[9,10] Such compounds include the phenolic natural products erbstatin[11] and piceatannol[12] together with a number of synthetic compounds such as 4-(phenylamino)quinazolines,[13] which are competitive inhibitors at the peptide (tyrosine) binding site.

Isoflavones, a diverse group of plant natural products, are known to possess a variety of biological effects such as anti-osteoporosis, antiplatelet, antibacterial, and antitumor activity.[14–17] 3-Aryl-1*H*-quinolin-4-one is structurally derived from the isoflavone nucleus by isosteric substitution of the pyran oxygen atom with a nitrogen atom. The high similarity in chemical structure easily leads to the idea that a 3-aryl-1*H*-quinolin-4-one might possess similar biological properties as an isoflavone does. In fact, Tsai et al. found that an isoflavone, isobavachalcone, exhibited strong inhibitory effects on platelet aggregation in 1996.[15] Two years later, Huang and co-workers reported derivatives of 3-aryl-1*H*-quinolin-4-one that showed extremely high antiplatelet potency.[18] On the other hand, genistein, another isoflavone, was shown to possess EGFR PTK inhibitory activity.[19] In parallel, Traxler et al. reported derivatives of 3-aryl-1*H*-quinolin-4-one as inhibitors that compete with the ATP binding site of EGFR PTK. Moreover, in comparison with isoflavone derivatives, 3-aryl-1*H*-quinolin-4-ones show higher antiproliferative activity, and a more specific mechanism of action, which consists of the inhibition of EGFR PTK by interaction with the ATP binding site.[20] These positive results inspired us to systematically design and synthesize 3-aryl-1*H*-quinolin-4-ones for antiproliferative evaluation and structure–activity relationship analysis. Herein we describe the synthesis and cytotoxic activities of a series of 3-aryl-1*H*-quinolin-4-ones and their structure–activity relationships in vitro.

Results and Discussion

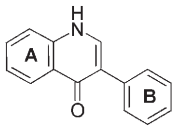
Chemistry

Owing to the substantial inhibitory potency of 3-aryl-1*H*-quinolin-4-one of the EGFR PTK,[20] we did not try to change the skeleton of 3-aryl-1*H*-quinolin-4-one, but rather, we chose to modify the structure of the A-ring and B-ring of the matrix. Early cytotoxic effects of 3-aryl-1*H*-quinolin-4-ones suggested

[a] *Dr. Z.-P. Xiao, Dr. H.-Q. Li, Dr. L. Shi, Dr. P.-C. Lv, Dr. Z.-C. Song, Prof. H.-L. Zhu*
State Key Laboratory of Pharmaceutical Biotechnology
Nanjing University, Nanjing 210093 (P.R. China)
Fax: (+86) 25-8359-2672
E-mail: zhuhl@nju.edu.cn

Supporting information for this article is available on the WWW under http://www.chemmedchem.org or from the author: ^{1}H NMR and MS data (compounds **3**–**38** except **15** and **27**); EIMS data (compounds **3**–**38** except **15** and **27**).

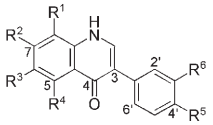
 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



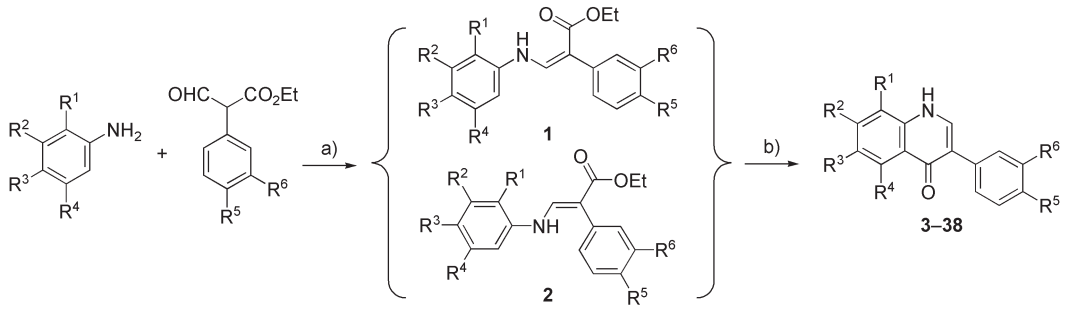
that the activity increased by the replacement of a chlorine atom by a methoxy group at the 4 position of the B-ring. Therefore, we focused our synthetic efforts on exploring the position effects of substituents on B-ring. As for the A-ring, both the electronic and position effects of substituents on the cytotoxicity were investigated. Six substituents (NO_2, F, Cl, Br, CH_3 and OMe) were used at the available positions, and these substituents were selected primarily for their wide range of electronic properties (from $\sigma = +0.78$ to -0.36). On the basis of this concept, 36 compounds were designed and synthesized for screening the antiproliferative activity in vitro. Out of the synthetic compounds, 34 were first reported (except compounds **15** and **27**).

Scheme 1 describes the straightforward synthesis of 3-aryl-1*H*-quinolin-4-ones **3**–**38**, which was accomplished by following a previously reported method with appropriate modifications.[21] In brief, enamines (**1** and **2**) were prepared by a dehydration reaction of ethyl 2-formyl-2-phenylacetate with different arylamines in ethanol.[16] The crude product consisted of *Z* and *E* isomers (**1** and **2**), but both of them could cyclize to form the final compound (3-arylquinol-4-one) so that further purification was not necessary. Cyclization of enamines in the presence of polyphosphoric acid (PPA) gave compounds **3**–**38** in good to high yields. In the literature, the reaction was performed over 120 °C in PPA. In our hands however, we found that the yields decreased extremely when the temperature was over 100 °C; the best temperature was between 70 and 80 °C, and high-purity products were obtained after ice was added. All of the compounds were fully characterized by spectroscopic methods, and the purity was confirmed by analytical methods. The structures and chemical features of the newly synthesized compounds are summarized in Table 1.

Table 1. Structures and physical properties of 3-arylquinol-4-ones.



Compd	R^1	R^2	R^3	R^4	R^5	R^6	Formula	mp [°C]	Yield [%]
3	H	H	Br	H	Cl	H	$C_{15}H_9BrClNO$	>300	82
4	H	F	H	F	Cl	H	$C_{15}H_8ClF_2NO$	>300	85
5	H	Cl	H	Cl	Cl	H	$C_{15}H_8Cl_3NO$	>300	85
6	Cl	H	H	H	Cl	H	$C_{15}H_9Cl_2NO$	>300	89
7	H	H	Cl	H	Cl	H	$C_{15}H_9Cl_2NO$	>300	86
8	H	H	CH_3	H	Cl	H	$C_{16}H_{12}ClNO$	>300	95
9	H	OCH_3	H	OH	Cl	H	$C_{17}H_{14}ClNO_3$	167–168	87
10	H	H	F	H	Cl	H	$C_{15}H_9ClFNO$	>300	88
11	F	H	H	H	Cl	H	$C_{15}H_9ClFNO$	>300	84
12	Cl	H	Cl	H	Cl	H	$C_{15}H_8Cl_3NO$	>300	90
13	F	H	F	H	Cl	H	$C_{15}H_8ClF_2NO$	>300	99
14	Br	H	Br	H	Cl	H	$C_{15}H_8Br_2ClNO$	>300	89
15	H	OCH_3	H	OCH_3	OCH_3	H	$C_{18}H_{17}NO_4$	240–241	79
16	H	Cl	H	Cl	OCH_3	H	$C_{16}H_{11}Cl_2NO_2$	281–283	83
17	H	F	H	F	OCH_3	H	$C_{16}H_{11}F_2NO_2$	>300	92
18	H	H	Br	H	OCH_3	H	$C_{16}H_{12}BrNO_2$	>300	89
19	H	H	Cl	H	OCH_3	H	$C_{16}H_{12}ClNO_2$	>300	87
20	Cl	H	H	H	OCH_3	H	$C_{16}H_{12}ClNO_2$	264–266	81
21	H	H	CH_3	H	OCH_3	H	$C_{17}H_{15}NO_2$	>300	78
22	H	H	F	H	OCH_3	H	$C_{16}H_{12}FNO_2$	>300	79
23	F	H	H	H	OCH_3	H	$C_{16}H_{12}FNO_2$	260–261	87
24	F	H	F	H	OCH_3	H	$C_{16}H_{11}F_2NO_2$	>300	95
25	Cl	H	Cl	H	OCH_3	H	$C_{16}H_{11}Cl_2NO_2$	242–244	94
26	Br	H	Br	H	OCH_3	H	$C_{16}H_{11}Br_2NO_2$	245–247	95
27	H	H	H	H	OCH_3	H	$C_{16}H_{13}NO_2$	>300	99
28	H	H	NO_2	H	OCH_3	H	$C_{16}H_{12}N_2O_4$	>300	98
29	H	Cl	H	Cl	H	OCH_3	$C_{16}H_{11}Cl_2NO_2$	244–246	76
30	H	H	Cl	H	H	OCH_3	$C_{16}H_{12}ClO_2$	298–299	96
31	H	H	Br	H	H	OCH_3	$C_{16}H_{12}BrO_2$	>300	92
32	Cl	H	H	H	H	OCH_3	$C_{16}H_{12}ClO_2$	196–198	99
33	Cl	H	Cl	H	H	OCH_3	$C_{16}H_{11}Cl_2NO_2$	164–165	87
34	F	H	F	H	H	OCH_3	$C_{16}H_{11}F_2NO_2$	244–245	99
35	H	H	CH_3	H	H	OCH_3	$C_{17}H_{15}NO_2$	265–266	86
36	H	H	F	H	H	OCH_3	$C_{16}H_{12}FNO_2$	268–269	91
37	F	H	H	H	H	OCH_3	$C_{16}H_{12}FNO_2$	200–201	71
38	Br	H	Br	H	H	OCH_3	$C_{16}H_{11}Br_2NO_2$	184–185	92



Scheme 1. Reagents and conditions: a) EtOH, 60–80 °C; b) PPA, 70–80 °C.

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Biological activity

The in vitro cytotoxic activity of the synthesized 3-aryl-1*H*-quinolin-4-ones **3**–**38** was studied on a panel of one human normal cell line (L02) and two human tumor cell lines (KB and Hep G2) by applying the MTT colorimetric assay. Compounds were tested over a range of concentrations from 0.01 to 100 μg mL^{-1}, and the calculated IC_{50} values, that is, the concentration (μg mL^{-1}) of a compound that was able to cause 50% cell death with respect to the control culture, are reported in Table 2. Genistein and 5-fluorouracil were used as reference compounds. The results show that 3-aryl-1*H*-quinolin-4-ones inhibited the growth of human cancer cell lines well, but scarcely inhibited normal cell lines. To the contrary, genistein and 5-fluorouracil showed no inhibitory selectivity toward all four cell lines. Against Hep G2 and KB, compound **37** was showed the most potent activity (with $IC_{50} = 0.01$ and 0.03 μg mL^{-1}, respectively) among the new compounds tested.

Table 2. Cell growth inhibitory activity of the 3-arylquinol-4-one series.

Compd	IC_{50} [μg mL^{-1}][a] Hep G2	L02	KB
3	66 ± 16	NA	74 ± 28
4	30 ± 7	NA	31 ± 7
5	76 ± 21	NA	NA
6	46 ± 16	NA	7.5 ± 2.2
7	NA	NA	59 ± 11
8	4.3 ± 1.9	66 ± 23	4.1 ± 1.4
9	4.3 ± 1.3	28 ± 18	0.82 ± 0.19
10	37 ± 16	NA	66 ± 23
11	1.1 ± 0.6	NA	4.4 ± 1.5
12	NA	NA	48 ± 11
13	0.20 ± 0.09	NA	4.8 ± 1.3
14	30 ± 9	22 ± 15	7.6 ± 2.1
15	1.1 ± 0.6	NA	0.32 ± 0.21
16	30 ± 5	NA	49 ± 8
17	5.1 ± 1.2	NA	4.3 ± 1.2
18	5.9 ± 1.7	NA	7.6 ± 1.5
19	2.0 ± 0.8	NA	1.1 ± 0.8
20	0.46 ± 0.09	9.3 ± 2.7	0.34 ± 0.13
21	0.33 ± 0.12	11.9 ± 3.5	0.28 ± 0.11
22	30 ± 6	65 ± 14	1.05 ± 0.9
23	0.43 ± 0.16	NA	0.29 ± 0.06
24	1.0 ± 0.4	NA	0.84 ± 0.18
25	1.2 ± 0.5	NA	0.91 ± 0.12
26	1.7 ± 0.8	NA	1.1 ± 0.7
27	1.1 ± 0.4	52 ± 24	0.31 ± 0.09
28	34 ± 11	NA	45 ± 9
29	1.2 ± 0.6	NA	0.12 ± 0.06
30	1.3 ± 0.8	28 ± 11	0.27 ± 0.09
31	0.45 ± 0.15	29 ± 14	0.31 ± 0.05
32	0.12 ± 0.04	NA	0.10 ± 0.07
33	0.22 ± 0.09	9.1 ± 2.7	0.14 ± 0.08
34	0.05 ± 0.02	97 ± 21	0.06 ± 0.04
35	0.27 ± 0.13	25 ± 8	0.15 ± 0.09
36	0.31 ± 0.17	35 ± 13	0.16 ± 0.11
37	0.01 ± 0.009	NA	0.03 ± 0.02
38	1.6 ± 0.6	NA	0.14 ± 0.08
5-fluorouracil	0.25 ± 0.07	6.8 ± 2.1	0.27 ± 0.14
genistein	1.1 ± 0.7	3.1 ± 1.3	0.56 ± 0.17

[a] NA = not active: $IC_{50} > 100$ μg mL^{-1}, the maximum concentration tested.

Against human cancer cell lines, compounds **5** and **6** were less active than **16** and **20**, respectively. This result indicates that replacement of the chlorine atom by a methoxy group at the 4′ position decreases the cytotoxic activity of 3-aryl-1*H*-quinolin-4-ones, but compounds **13** and **24** are exceptions to this. Other evidence is presented in Table 2, such as compounds **3** and **18**. Comparison of the cytotoxicities of **16** and **24** with **29** and **34** shows clearly that moving the methoxy group from the 4′ to the 3′ position significantly increases the activity.

As for the compounds with one substituent on the A-ring, we found a straightforward correlation between the electronic property and cytotoxicity; the more electron-donating group at the 6 position increases the cytotoxic. This was supported by compounds **21**, **22**, **27**, and **28**. Compounds that bore a halogen atom at the 8 position showed more activity than those with halogens at the 6 position, such as **6**, **7**, **23** and **22**. On the other hand, moving the substituents from the 5,7 positions to the 6,8 positions of the A-ring led to an increase or maintenance of activity, as exemplified by compounds **29**, **33**, **17** and **24**.

The X-ray crystal structure of quercetin in complex with Hck tyrosine kinase has been determined.[22] The keto function accepts a hydrogen bond from the backbone NH of Met769, whereas the 3-hydroxy substituent donates a hydrogen bond to the backbone carbonyl of Gln767. On the other hand, the 2-phenyl substituent of the chromenone moiety occupied the region between Thr766 and Asp831. As for 3-aryl-1*H*-quinolin-4-ones with the substituent matrix of genistein, Traxler reported another binding model:[20] the chlorophenyl ring fits in the "sugar pocket" to make a sulfur–aromatic interaction with Cys773. By mimicking ATP the 5-hydroxy substituent serves as a hydrogen bond acceptor (Met769 as donor); however, in this case, the donor is the 7-hydroxy substituent (Gln767 as acceptor). The structure–activity relationship of our 3-aryl-1*H*-quinolin-4-ones indicates that compounds that bear a halogen atom, especially fluorine, at the 8 position show more activity than those that bear a halogen at the 6 position. From this result, we suspected that the binding model of our 3-aryl-1*H*-quinolin-4-ones in the ATP binding site of EGFR PTK is consistent with that of quercetin. The fluorine (chlorine) atom at the 8 position of a 3-aryl-1*H*-quinolin-4-one mimics the keto function of the quercetin, which results in the NH–fluorine (chlorine) intermolecular hydrogen bond; meanwhile, a NH at the 1 position of a 3-aryl-1*H*-quinolin-4-one mimics the 3-hydroxy group of the quercetin and serves as a hydrogen donor.

Conclusions

For all the compounds, cytotoxic activity against one human normal cell line (L02) and two cancer cell lines (Hep G2 and KB) was determined. The chemical modification of 3-aryl-1*H*-quinolin-4-one generated some potent compounds, with IC_{50} values up to >20-fold lower than those of the reference compound, 5-fluorouracil. The series of 3-aryl-1*H*-quinolin-4-ones show good cytotoxic activity against human cancer cell lines and no cytotoxic activity against a normal cell line (L02). Compounds that bear a halogen atom at the 8 position and a me-

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

thoxy group at the 3′ position exhibited remarkable cytotoxicity toward human cancer cell lines. Compounds with a substituent at the 4′ position had, in general, decreased activity. A clear correlation between the cytotoxicity and electronic properties of a substituent, that is, electron-donating substituent enhances the antiproliferative activity, was found. The potent compounds **34** and **37**, which show low cytotoxicity toward a human normal cell line, are now undergoing further lead optimization in our laboratory for development as an anticancer agents.

Experimental Section

Cell and cytotoxicity assay: The cytotoxic activity of 3-aryl-1*H*-quinolin-4-ones **3**–**38** was determined by using a standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)-based colorimetric assay (Sigma), by using 5-fluorouracil and genistein as reference drugs. Briefly, cell lines were seeded at a density of 7× 103 cells per well in 96-well microtiter plates (Costar). After 24 h, exponentially growing cells were exposed to the indicated compounds at final concentrations that ranged from 0.1 to 100 μg mL^{-1}. After 48 h, cell survival was determined by the addition of a 5 mg mL^{-1} solution of MTT in phosphate-buffered saline(PBS, 10 μL). After 4 h, 10% SDS in 0.01 N HCl (100 μL) was added, and the plates were incubated at 37 °C for a further 18 h; optical absorbance was measured at 570 nm on an LX300 Epson Diagnostic microplate reader. Survival ratios were expressed in percentages with respect to untreated cells. IC_{50} values were determined from replicates of six wells from at least two independent experiments.

Chemistry: All chemicals (reagent grade) were purchased from Aldrich and Sinopharm Chemical Reagent Co., Ltd. (China). Melting points (uncorrected) were determined on a Taike XT4 MP apparatus (Beijing, China). EI mass spectra were obtained on a Waters GCT mass spectrometer, and ^{1}H NMR spectra were recorded on a Bruker DPX-300, AV-300 or AV-500 spectrometer at 25 °C; tetramethylsilane and the residual solvent signals were used as internal standards. Chemical shifts are reported in ppm (δ). Elemental analyses were performed on a CHN-O-Rapid instrument and were within ±0.4% of the theoretical values.

General Procedure for the Preparation of 3-aryl-1*H*-quinolin-4-ones: The synthesis of starting enamines have been previously published.[18] A mixture of enamine (10.0 mmol) and PPA (20 g) was stirred for 2–5 h (monitored with TLC) at 70–80 °C. The residue was cooled, poured into ice-water (30 g). The precipitate was filtered, washed with H_2O to give a white to light-yellow solid with high purity in good to high yield.

6-Bromo-3-(4-chlorophenyl)-1*H*-quinolin-4-one (3): Light yellow powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 7.46 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.6 Hz, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.83 (d×d, J = 8.8 Hz, J = 2.2 Hz, 1H), 8.27 (s, 2H), 8.30 ppm (d, J = 2.0 Hz, 1H); EIMS *m/z*: 335 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_9BrClNO$: C 53.84, H 2.71, N 4.19, found: C 53.87, H 2.70, N 4.18.

3-(4-Chlorophenyl)-5,7-difluoro-1*H*-quinolin-4-one (4): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 7.07 (t, J = 10.1 Hz, 1H), 7.16 (d, J = 9.9 Hz, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H), 8.11 ppm (s, 1H); EIMS *m/z*: 291 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_8ClF_2NO$: C 61.77, H 2.76, N 4.80, found: C 61.86, H 2.77, N 4.79.

5,7-Dichloro-3-(4-chlorophenyl)-1*H*-quinolin-4-one (5): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 7.39 (s, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.57 (s, 1H), 7.67 (d, J = 8.2 Hz, 2H), 8.13 ppm (s, 1H); EIMS *m/z*: 323 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_8Cl_3NO$: C 55.50, H 2.48, N 4.32, found: C 55.61, H 2.47, N 4.33.

8-Chloro-3-(4-chlorophenyl)-1*H*-quinolin-4-one (6): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 7.38 (t, J = 7.9 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 7.7 Hz, 1H), 8.04 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 11.72 ppm (d, J = 8.2 Hz, 1H); EIMS *m/z*: 289 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_9Cl_2NO$: C 62.09, H 3.13, N 4.83, found: C 61.97, H 3.14, N 4.83.

6-Chloro-3-(4-chlorophenyl)-1*H*-quinolin-4-one (7): White powder, ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.37 (d, J = 8.3 Hz, 2H), 7.54 (s, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.88 (s, 1H), 8.34 (s, 1H), 11.96 ppm (s, 1H); EIMS *m/z*: 289 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_9Cl_2NO$: C 62.09, H 3.13, N 4.83, found: C 61.98, H 3.14, N 4.84.

3-(4-Chlorophenyl)-6-methy-1*H*-quinolin-4-one (8): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 2.43 (s, 3H), 7.43 (d, J = 8.6 Hz, 2H), 7.52 (s, 2H), 7.78 (d, J = 8.6 Hz, 2H), 8.01 (s, 1H), 8.16 ppm (s, 1H); EIMS *m/z*: 269 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}ClNO$: C 71.25, H 4.48, N 5.19, found: C 71.14, H 4.49, N 5.20.

3-(4-Chlorophenyl)-5-hydroxy-7-methoxy-1*H*-quinolin-4-one (9): Yellow crystal, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.82 (s, 3H), 7.41 (d, J = 8.6 Hz, 2H), 7.66 (d, J = 8.6 Hz, 2H), 7.96 (s, 1H), 12.49 ppm (s, 1H); EIMS *m/z*: 301 $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{14}ClNO_3$: C 64.67, H 4.47, N 4.44, found: C 64.71, H 4.47, N 4.43.

6-Fluoro-3-(4-chlorophenyl)-1*H*-quinolin-4-one (10): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 7.45 (d, J = 8.6 Hz, 2H), 7.58–7.62 (m, 1H), 7.70 (d×d, J = 9.2 Hz, J = 4.6 Hz, 1H), 7.79 (d, J = 8.6 Hz, 2H), 7.79 (d×d, J = 9.5 Hz, J = 3.1 Hz, 1H), 8.26 ppm (s, 1H); EIMS *m/z*: 273 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_9ClFNO$: C 65.83, H 3.31, N 5.12, found: C 65.77, H 3.31, N 5.13.

8-Fluoro-3-(4-chlorophenyl)-1*H*-quinolin-4-one (11): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 7.36 (d×d, J = 13.1 Hz, J = 8.0 Hz, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.61–7.63 (m, 1H), 7.76 (d, J = 8.6 Hz, 2H), 8.03 (d, J = 8.0 Hz, 1H), 8.08 ppm (s, 1H); EIMS *m/z*: 273 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_9ClFNO$: C 65.83, H 3.31, N 5.12, found: C 65.89, H 3.32, N 5.13.

6,8-Dichloro-3-(4-chlorophenyl)-1*H*-quinolin-4-one (12):White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 7.43 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 7.99 (d, J = 2.5 Hz, 1H), 8.03 (s, 1H), 8.08 ppm (d, J = 2.4 Hz, 1H); EIMS *m/z*: 323 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_8Cl_3NO$: C 55.50, H 2.48, N 4.32, found: C 55.61, H 2.48, N 4.33.

3-(4-Chlorophenyl)-6,8-difluoro-1*H*-quinolin-4-one (13): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 7.42 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 9.2 Hz, 1H), 7.71 (d, J = 8.6 Hz, 2H), 7.72 (m, 1H), 8.07 ppm (s, 1H); EIMS *m/z*: 291 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_8ClF_2NO$: C 61.77, H 2.76, N 4.80, found: C 61.69, H 2.76, N 4.80.

6,8-Dibromo-3-(4-chlorophenyl)-1*H*-quinolin-4-one (14): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 7.43 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H), 8.03 (s, 1H), 8.20 (s, 1H), 8.27 ppm (s, 1H); EIMS *m/z*: 413 $[M]^+$; elemental analysis calcd (%) for $C_{15}H_8Br_2ClNO$: C 43.57, H 1.95, N 3.39, found: C 43.65, H 1.94, N 3.39.

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

5,7-Dimethoxy-3-(4-methoxyphenyl)-1*H*-quinolin-4-one (15):[23,24] Yellow crystal, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 2.90 (s, 3H), 3.82 (s, 3H), 3.89 (s, 3H), 6.17 (d, J = 1.7 Hz, 1H), 6.26 (d, J = 1.7 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.96 ppm (s, 1H); EIMS *m/z*: 311 $[M]^+$; elemental analysis calcd (%) for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50, found: C 69.53, H 5.49, N 4.50.

5,7-Dichloro-3-(4-methoxyphenyl)-1*H*-quinolin-4-one (16): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.76 (s, 3H), 6.92 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 2.0 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.59 (s, 1H), 8.03 ppm (s, 1H); EIMS *m/z*: 319 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{11}Cl_2NO_2$: C 60.02, H 3.46, N 4.37, found: C 60.11, H 3.47, N 4.34.

5,7-Difluoro-3-(4-methoxyphenyl)-1*H*-quinolin-4-one (17): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.75 (s, 3H), 6.91 (d, J = 8.8 Hz, 2H), 7.04–7.13 (m, 2H), 7.52 (d, J = 8.7 Hz, 2H), 8.01 ppm (s, 1H); EIMS *m/z*: 287 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{11}F_2NO_2$: C 66.90, H 3.86, N 4.88, found: C 66.96, H 3.85, N 4.84.

6-Bromo-3-(4-methoxyphenyl)-1*H*-quinolin-4-one (18): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 3.78 (s, 3H), 6.95 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 9.0 Hz, 1H), 7.65 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 2.0 Hz, 1H), 8.14 (d, J = 6.0 Hz, 1H), 8.27 (d, J = 2.0 Hz, 1H), 12.13 ppm (s, 1H); EIMS *m/z*: 329 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}BrNO_2$: C 58.20, H 3.66, N 4.24, found: C 58.26, H 3.65, N 4.21.

6-Dichloro-3-(4-methoxyphenyl)-1*H*-quinolin-4-one (19): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 3.76 (s, 3H), 6.95 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 9.0 Hz, 1H), 7.64 (d, J = 1.8 Hz, 2H), 7.67 (d, J = 9.0 Hz, 1H), 8.13 (d, J = 6.0 Hz, 1H), 8.21 (s, 1H), 12.14 ppm (s, 1H); EIMS *m/z*: 285 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}ClNO_2$: C 67.26, H 4.23, N 4.90, found: C 67.31, H 4.22, N 4.84.

8-Chloro-3-(4-methoxyphenyl)-1*H*-quinolin-4-one (20): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 3.76 (s, 3H), 6.93 (d, J = 8.7 Hz, 2H), 7.32 (t, J = 7.8 Hz, 1H), 7.58 (d, J = 9 Hz, 2H), 7.81 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 6.3 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 11.58 ppm (s, 1H); EIMS *m/z*: 285 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}ClNO_2$: C 67.26, H 4.23, N 4.90, found: C 67.29, H 4.22, N 4.87.

3-(4-Methoxyphenyl)-6-methyl-1*H*-quinolin-4-one (21): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 2.42 (s, 3H), 3.78 (s, 3H), 6.93 (d, J = 8.7 Hz, 2H), 7.48 (s, 2H), 7.64 (d, J = 8.7 Hz, 2H), 7.99 (s, 1H), 8.04 (d, J = 6 Hz, 1H), 11.89 ppm (s, 1H); EIMS *m/z*: 265 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{15}NO_2$: C 76.96, H 5.70, N 5.28, found: C 76.98, H 5.71, N 5.31.

6-Fluoro-3-(4-methoxyphenyl)-1*H*-quinolin-4-one (22): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 3.78 (s, 3H), 6.95 (d, J = 8.7 Hz, 2H), 7.54–7.60 (m, 1H), 7.65 (d, J = 4.5 Hz, 2H), 7.69 (s, 1H), 7.78 (d, J = 2.1 Hz, 1H), 7.85 (d, J = 6 Hz, 1H), 8.14 (d, J = 6.0 Hz, 1H), 12.14 ppm (s, 1H); EIMS *m/z* 269 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}FNO_2$: C 71.37, H 4.49, N 5.20, found: C 71.41, H 4.48, N 5.24.

8-Fluoro-3-(4-methoxyphenyl)-1*H*-quinolin-4-one (23): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 3.78 (s, 3H), 6.95 (d, J = 9.0 Hz, 2H), 7.28 (d, J = 8.7 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 2.1 Hz, 2H), 7.97 (d, J = 6 Hz, 2H), 12.09 ppm (s, 1H); EIMS *m/z*: 269 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}FNO_2$: C 71.37, H 4.49, N 5.20, found: C 71.42, H 4.48, N 5.21.

6,8-Difluoro-3-(4-methoxyphenyl)-1*H*-quinolin-4-one (24): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 3.75 (s, 3H), 6.92 (d, J = 9.0 Hz, 2H), 7.60–7.74 (m, 4H), 7.96 (s, 1H), 12.24 ppm (s, 1H); EIMS *m/z*: 287 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{11}F_2NO_2$: C 66.90, H 3.86, N 4.88, found: C 66.92, H 3.87, N 4.85.

6,8-Dichloro-3-(4-methoxyphenyl)-1*H*-quinolin-4-one (25): White powder, ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ = 3.75 (s, 3H), 6.92 (d, J = 9.0 Hz, 2H), 7.60–7.74 (m, 4H), 7.96 (s, 1H), 12.24 ppm (s, 1H); EIMS *m/z*: 319 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{11}Cl_2NO_2$: C 60.02, H 3.46, N 4.37, found: C 60.06, H 3.45, N 4.34.

6,8-Dibromo-3-(4-methoxyphenyl)-1*H*-quinolin-4-one (26): Light yellow powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.79 (s, 3H), 6.99 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 7.97 (s, 1H), 8.23 (d, J = 2.2 Hz, 1H), 8.30 (d, J = 2.2 Hz, 1H), 11.52 ppm (s, 1H); EIMS *m/z*: 409 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{11}Br_2NO_2$: C 46.98, H 2.71, N 3.42, found: C 46.91, H 2.72, N 3.42.

3-(4-Methoxyphenyl)-1*H*-quinolin-4-one (27):[25] White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.78 (s, 3H), 6.96 (d, J = 8.6 Hz, 2H), 7.33 (t, J = 7.4 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 8.6 Hz, 2H), 8.09 (d, J = 5.8 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 11.97 ppm (d, J = 6.6 Hz, 1H); EIMS *m/z*: 251 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{13}NO_2$: C 76.48, H 5.21, N 5.57, found: C 76.40, H 5.21, N 5.58.

3-(4-Methoxyphenyl)-6-nitro-1*H*-quinolin-4-one (28): Yellow powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.78 (s, 3H), 6.98 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.6 Hz, 1H), 8.39–8.42 (m, 2H), 8.96 (s, 1H), 12.48 ppm (s, 1H); EIMS *m/z*: 296 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}N_2O_4$: C 64.86, H 4.08, N 9.46, found: C 64.95, H 4.07, N 9.45.

5,7-Dichloro-3-(3-methoxyphenyl)-1*H*-quinolin-4-one (29): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.78 (s, 3H), 6.87 (d×d, J = 8.0 Hz, J = 2.4 Hz, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.24 (d, J = 2.3 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.38 (d, J = 1.8 Hz, 1H), 7.58 (d, J = 1.8 Hz, 1H), 8.11 (s, 1H), 12.08 ppm (s, 1H); EIMS *m/z*: 319 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{11}Cl_2NO_2$: C 60.02, H 3.46, N 4.37, found: C 60.11, H 3.46, N 4.36.

6-Chloro-3-(3-methoxyphenyl)-1*H*-quinolin-4-one (30): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.79 (s, 3H), 6.85–6.89 (m, 1H), 7.29–7.35 (m, 3H), 7.65 (d, J = 8.8 Hz, 1H), 7.70 (d×d, J = 8.8 Hz, J = 2.4 Hz, 1H), 8.14 (d, J = 2.3 Hz, 1H), 8.24 (d, J = 6.0 Hz, 1H), 12.23 ppm (d, J = 5.5 Hz, 1H); EIMS *m/z*: 285 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}ClO_2$: C 67.26, H 4.23, N 4.90, found: C 67.32, H 4.22, N 4.89.

6-Bromo-3-(3-methoxyphenyl)-1*H*-quinolin-4-one (31): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.79 (s, 3H), 6.85–6.89 (m, 1H), 7.27–7.35 (m, 3H), 7.58 (d, J = 8.8 Hz, 1H), 7.81 (d×d, J = 8.8 Hz, J = 2.2 Hz, 1H), 8.24 (d, J = 6.0 Hz, 1H), 8.29 (d, J = 2.2 Hz, 1H), 12.22 ppm (d, J = 5.6 Hz, 1H); EIMS *m/z*: 329 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}BrO_2$: C 58.20, H 3.66, N 4.24, found: C 58.31, H 3.66, N 4.23.

8-Chloro-3-(3-methoxyphenyl)-1*H*-quinolin-4-one (32): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.79 (s, 3H), 6.88–6.91 (m, 1H), 7.23 (d, J = 7.9 Hz, 1H), 7.30–7.40 (m, 3H), 7.85 (d×d, J = 7.7 Hz, J = 1.3 Hz, 1H), 8.01 (d, J = 5.9 Hz, 1H), 8.20 (d×d, J = 8.0 Hz, J = 1.2 Hz, 1H), 11.66 ppm (d, J = 5.6 Hz, 1H); EIMS *m/z*: 285 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}ClO_2$: C 67.26, H 4.23, N 4.90, found: C 67.37, H 4.22, N 4.90.

6,8-Dichloro-3-(3-methoxyphenyl)-1*H*-quinolin-4-one (33): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.79 (s, 3H), 6.89–6.92 (m, 1H), 7.23 (d, J = 7.7 Hz, 1H), 7.30–7.36 (m, 2H), 8.03 (s, 1H), 8.04 (d, J = 2.4 Hz, 1H), 8.13 (d, J = 2.4 Hz, 1H), 11.86 ppm (s, 1H);

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

EIMS *m/z*: 319 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{11}Cl_2NO_2$: C 60.02, H 3.46, N 4.37, found: C 60.02, H 3.46, N 4.37.

6,8-Difluoro-3-(3-methoxyphenyl)-1*H*-quinolin-4-one (34): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): $\delta = 3.79$ (s, 3H), 6.86–6.90 (m, 1H), 7.23–7.34 (m, 3H), 7.68–7.91 (m, 2H), 8.05 (d, $J = 3.3$ Hz, 1H), 12.34 ppm (s, 1H); EIMS *m/z*: 287 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{11}F_2NO_2$: C 66.90, H 3.86, N 4.88, found: C 66.81, H 3.86, N 4.89.

6-Methyl-3-(3-methoxyphenyl)-1*H*-quinolin-4-one (35): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): $\delta = 2.43$ (s, 3H), 3.79 (s, 3H), 6.83–6.86 (m, 1H), 7.28–7.30 (m, 2H), 7.35–7.36 (m, 1H), 7.50 (s, 2H), 8.00 (s, 1H), 8.13 (d, $J = 6.2$ Hz, 1H), 11.96 ppm (d, $J = 5.8$ Hz, 1H); EIMS *m/z*: 265 $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{15}NO_2$: C 76.96, H 5.70, N 5.28, found: C 76.87, H 5.71, N 5.28.

6-Fluoro-3-(3-methoxyphenyl)-1*H*-quinolin-4-one (36): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): $\delta = 3.79$ (s, 3H), 6.85–6.89 (m, 1H), 7.29–7.31 (m, 2H), 7.37–7.38 (m, 1H), 7.55–7.62 (m, 1H), 7.69 (d×d, $J = 9.3$ Hz, $J = 4.7$ Hz, 1H), 7.85 (d×d, $J = 9.5$ Hz, $J = 2.9$ Hz, 1H), 8.23 (d, $J = 6.2$ Hz, 1H), 12.20 ppm (d, $J = 6.2$ Hz, 1H); EIMS *m/z*: 269 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}FNO_2$: C 71.37, H 4.49, N 5.20, found: C 71.47, H 4.49, N 5.19.

8-Fluoro-3-(3-methoxyphenyl)-1*H*-quinolin-4-one (37): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): $\delta = 3.79$ (s, 3H), 6.86–6.90 (m, 1H), 7.23–7.37 (m, 4H), 7.56–7.63 (m, 1H), 8.00–8.03 (m, 2H), 7.69 (d×d, $J = 9.3$ Hz, $J = 4.7$ Hz, 1H), 7.85 (d×d, $J = 9.5$ Hz, $J = 2.9$ Hz, 1H), 12.17 ppm (d, $J = 5.7$ Hz, 1H); EIMS *m/z*: 269 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{12}FNO_2$: C 71.37, H 4.49, N 5.20, found: C 71.44, H 4.48, N 5.19.

6,8-Dibromo-3-(3-methoxyphenyl)-1*H*-quinolin-4-one (38): White powder, ^{1}H NMR ([D$_6$]DMSO, 300 MHz): $\delta = 3.79$ (s, 3H), 6.89–6.93 (m, 1H), 7.20–7.23 (m, 1H), 7.29–7.34 (m, 2H), 8.02 (d, $J = 6.0$ Hz, 1H), 8.25 (d, $J = 2.4$ Hz, 1H), 8.31 (d, $J = 2.2$ Hz, 1H), 11.59 ppm (d, $J = 5.8$ Hz, 1H); EIMS *m/z*: 409 $[M]^+$; elemental analysis calcd (%) for $C_{16}H_{11}Br_2NO_2$: C 46.98, H 2.71, N 3.42, found: C 46.91, H 2.71, N 3.41.

Acknowledgements

This work was financed by a grant (Project 30772627) from the National Natural Science Foundation of China.

Keywords: 3-aryl-1*H*-quinolin-4-ones · cytotoxicity · natural products · protein tyrosine kinases · structure–activity relationships

[1] A. Ullrich, J. Schlessinger, *Cell* **1990**, *61*, 203–212.
[2] S. R. Hubbard, J. H. Till, *Annu. Rev. Biochem.* **2000**, *69*, 373–398.
[3] M. J. Hayman, P. J. Enrietto, *Cancer Cells* **1991**, *3*, 302–307.
[4] I. Dikic, S. Giordano, *Curr. Opin. Cell Biol.* **2003**, *15*, 128–135.
[5] F. M. Uckun, C. Mao, *Curr. Pharm. Des.* **2004**, *10*, 1083–1091.
[6] D. Fabbro, D. Parkinson, A. Matter, *Curr. Opin. Pharmacol.* **2002**, *2*, 374–381.
[7] F. A. Al-Obeidi, J. J. Wu, K. S. Lam, *Biopolymers* **1998**, *47*, 197–223.
[8] P. Traxler, P. Furet, *Pharmacol. Ther.* **1999**, *82*, 195–206.
[9] C. Conrad, I. Ischenko, G. Koehl, U. Wiegand, M. Guba, M. Yezhelyev, A. J. Ryan, A. Barge, E. K. Geissler, S. R. Wedge, K.-W. Jauch, C. J. Bruns, *Anti-Cancer Drugs* **2007**, *18*, 569–579.
[10] L. Smith II, E. L. Piatnitski, A. S. Kiselyov, X.-H. Ouyang, X.-L. Chen, S. Burdzovic-Wizemann, Y.-J. Xu, W.-T. Pan, X. Chen, Y. Wang, R. L. Rosler, S. N. Patel, H.-H. Chiang, D. L. Milligan, J. Columbus, W. C Wong, J. F. Doody, Y. R. Hadari, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1643–1646.
[11] K. Umezawa, T. Hori, H. Tajima, M. Imoto, K. Isshiki, T. Takeuchi, *FEBS Lett.* **1990**, *260*, 198–200.
[12] R. L. Geahlen, J. L. McLaughlin, *Biochem. Biophys. Res. Commun.* **1989**, *165*, 241–245.
[13] A. M. Thompson, A. J. Bridges, D. W. Fry, A. J. Kraker, W. A. Denny, *J. Med. Chem.* **1995**, *38*, 3780–3788.
[14] L. Li, L. V. Modolo, L. L. Escamilla-Trevino, L. Achnine, R. A. Dixon, X-Q. Wang, *J. Mol. Biol.* **2007**, *370*, 951–963.
[15] W.-J. Tsai, W.-C. Hsin, C.-C. Chen, *J. Nat. Prod.* **1996**, *59*, 671–672.
[16] Z.-P. Xiao, J.-Y. Xue, S.-H. Tan, H.-Q. Li, H.-L. Zhu, *Bioorg. Med. Chem.* **2007**, *15*, 4212–4219.
[17] F. H. Lo, N. K. Mak, K. N. Leung, *Biomed. Pharmacother.* **2007**, *61*, 591–595.
[18] L.-J. Huang, M.-C. Hsieh, C.-M. Teng, K.-H. Lee, S.-C. Kuo, *Bioorg. Med. Chem.* **1998**, *6*, 1657–1662.
[19] T. Akiyama, J. Ishida, S. Nakagawa, H. Ogawara, S. Watenabe, N. Itoh, M. Shibuya, Y. Fukami, *J. Biol. Chem.* **1987**, *262*, 5592–5595.
[20] P. Traxler, J. Green, H. Mett, U. Séquin, P. Furet, *J. Med. Chem.* **1999**, *42*, 1018–1026.
[21] M. Yamato, Y. Takeuchi, M. R. Chang, K. Hashigaki, T. Tsuruo, T. Tashiro, S. Tsukagoshi, *Chem. Pharm. Bull.* **1990**, *38*, 3048–3052.
[22] F. Sicheri, I. Moarefi, J. Kuriyan, *Nature* **1997**, *385*, 602–609.
[23] M. Croisy, C. Huel, E. Bisagni, *Heterocycles* **1997**, *45*, 683–690.
[24] B. Joseph, A. Behard, B. Lesur, G. Guillaumet, *Synlett* **2003**, 1542–1544.
[25] O. V. Singh, R. S. Kapil, *Synlett* **1992**, 751–752.

Received: February 26, 2008
Revised: March 21, 2008
Published online on April 24, 2008

 © 2008 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim