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Short communication

2,3-Disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines: A novel class of antitumor agents

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Abstract

A series of 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines were synthesized and evaluated for their cytotoxic activity *in vitro* against five human cancer cell lines (human lung carcinoma cell line: A549, human leukemia cell lines: K562 and Molt-4, human prostate cancer cell line: PC-3, human breast carcinoma cell line: MDA-MB-231). Most of these compounds show potent activity against these tumor cell lines, especially against the A549 cell line. The cell cycle analysis was also studied by flow cytometry measurement on A549 cell line.

Keywords: Imidazoquinazoline derivatives; Antitumor activity

1. Introduction

Quinazoline compounds have been well-recognized for their pharmacological properties, such as anticonvulsant [1,2], sedative, antihypertensive [3,4], vasodilator [5], antiinflammatory [6], antibiosis [7], phosphodiesterase inhibitors [8], and fibrinogen receptor antagonists [9]. Among them, 4-anilinoquinazolines are verified as the most promising small molecule EGFR tyrosine kinase inhibitors [10–14]. For example, PD153035 (6,7-dimethoxy-4-(3-bromophenyl)amino-quinazoline) was discovered as the potent inhibitor of EGFR tyrosine kinase (IC_{50} 0.025 nM) [14]. IRESSA™ (gefitinib, ZD1839), the novel drugs granted by FDA, was used for treatment of non-small-cell lung cancer (Fig. 1).

Most of the SAR researches of 4-anilinoquinazolines focused on the variation of substitutions at its 6- and 7-positions as well as the substitutions at the 4-anilino portion. However, the activity of the 4-anilinoquinazoline family could be modulated by changing the quinazoline core structure through incorporating the imidazo moiety on its 6- and 7-positions [15–23]. In this present work, we would like to report the 2,3-disubstituted-8-arylamino-3*H*-imidazo[4,5-*g*]quinazoline's cytotoxic activity *in vitro* against human lung cell lines (Fig. 2). Several of these compounds showed promising antiproliferative effect against tumor cell lines.

2. Results and discussion

2.1. Chemistry

2.1.1. Synthesis of derivatives

The synthesis of a series of 2,3-disubstituted-8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines (Scheme 1) was accomplished according to our procedure reported previously [24]. The methodology of parallel solid-phase synthesis was employed using arylamines as the first building blocks, alkylamines as the second building blocks, alkylaldehydes as the third building blocks and 4-chloro-7-fluoro-6-nitroquinazoline as the scaffold. The reaction sequence is illustrated in Scheme 1. Starting from 4-(4-formyl-3-methoxyphenoxy)butyryl AM resin **1**, in the presence of $NaBH_3CN$ in DMF, an arylamine was attached to the resin by reductive amination. The resin-bound

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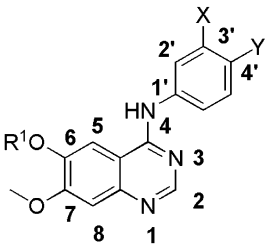


PD 153035 X = Br, Y = H, R = CH_3
IRESSA (ZD1839) X = Cl, Y = F
R = 3-morpholinopropan-1-yl

Fig. 1. The structure of 4-anilinoquinazolines, PD153035 and IRESSA.

arylamine **3** was then reacted with 4-chloro-7-fluoro-6-nitroquinazoline scaffold **8** to yield the corresponding chemoselective resin-bound quinazoline **4**, which was then treated with an alkylamine to give resin-bound compound **5**. The imidazo ring of resin-bound compound **6** was formed through the reduction of nitro group of resin-bound compound **5** with tin chloride and intramolecular cyclization with an alkylaldehyde in one step at 50 °C. Then the desired 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazoline **7** was obtained in good yield and purity after the cleavage of resin-bound compound **6** by using TFA/DCM (1:1). The products were characterized by electrospray LC–MS and ^{1}H NMR.

2.2. Biological activities

All compounds were evaluated for their cytotoxic activity *in vitro* against five human cancer cell lines (human lung carcinoma cell line: A549, human leukemia cell lines: K562 and Molt-4, human prostate cancer cell line: PC-3, human breast carcinoma cell line: MDA-MB-231) using IRESSA as the reference drug. The results are summarized in Table 1.

As shown in Table 1, most of compounds exhibited inhibitions on the growth of selected tumor cell lines, especially on A549 cell line and K562 cell line. Preliminary structure–activity relationship of this series of compounds' cytotoxicity against A549 cell line was investigated. The data of compound **7a–f** in Table 1 summarize the effect of different R^2 group on their activity, with identical substitutions on R^1 and R^3 positions of these compounds. In general, short chain or little steric hindrance of R^2 substitutions were beneficial for 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazoline's cytotoxicity on A549 cell line, such as compounds **7a** ($IC_{50} = 4.59$ μM, R^2 = isopropyl), **7b** ($IC_{50} = 2.81$ μM, R^2 = isobutyl) and **7c** ($IC_{50} = 6.05$ μM, R^2 = ethyl). However, long alkyl chain or butyl group on the R^2 position is detrimental to the compound's cytotoxicity, such as compounds **7e** ($IC_{50} = 22.05$ μM, R^2 = benzyl) and **7f** ($IC_{50} = 38.98$ μM, R^2 = *n*-hexyl). Compared with the data of **7a**, **7g–j**, which have the identical substitutions on R^1 and R^2 positions, the effect of R^3 group on the compound's cytotoxic activity is not apparent. All these compounds display the good cytotoxic activity with different substitutions on R^3 position, except a little loss of activity of compound **7j** (R^3 = γ-methoxypropyl, $IC_{50} = 15.76$ μM). With identical substitutions on R^2 and R^3 positions, 4′-F (compound **7k**, $IC_{50} = 4.25$ μM), and 3′,4′-di(OCH_3) (compound **7l**, $IC_{50} = 5.58$ μM) were found as promising substitutions on the R^1 position after the comparison of the data **7k–m**. In addition, compound **7k** was discovered as a promising and potent inhibitor against most of the selected cell lines (with $IC_{50} = 4.25$ μM against A549 cell line, $IC_{50} = 5.55$ μM against K562 cell line, $IC_{50} = 9.74$ μM against PC-3 cell line, $IC_{50} = 11.43$ μM against Molt-4 cell line).

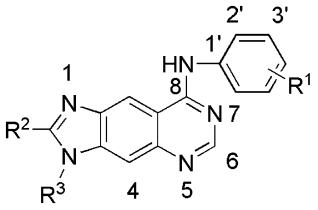


Fig. 2. The structure and positional designation of 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines.

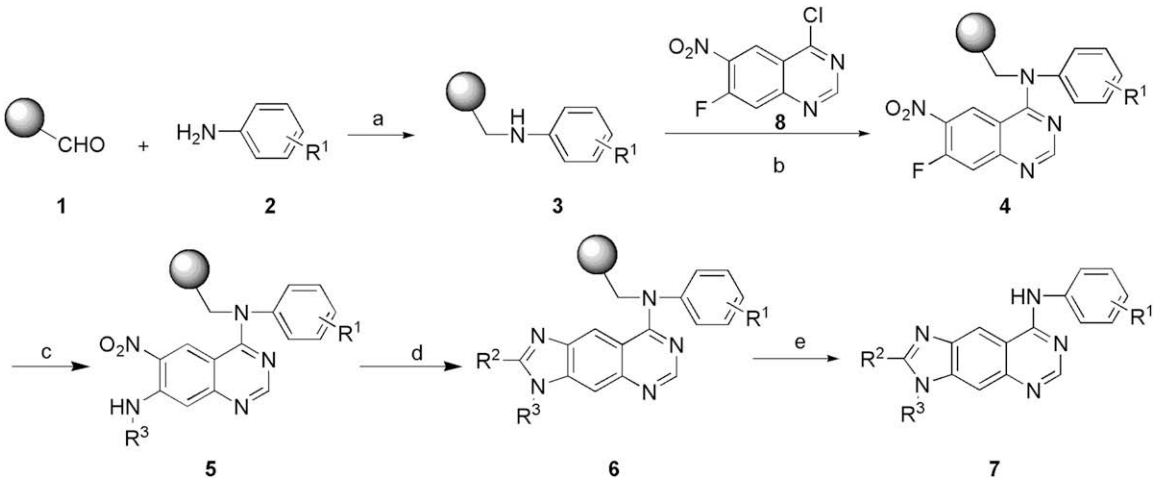
Next, flow cytometry was used to evaluate the effects of the most active compounds (**7a**, **7b** and **7k**) on the growth and division of A549 cells, by measuring the DNA content of eukaryotic cells. The results show the proportion of cells emitting a given level of fluorescent proportional to the DNA content. Unlike antimitotic agents which accumulate their DNA content in the G2/M phase of the cell cycle, the results in Table 2 show that compounds (**7a**, **7b** and **7k**) cause significant arrest of the cell cycle at the G0/G1 phase. As shown in Table 2, compounds **7a**, **7b** and **7k** caused significant arrest of the cell cycle at the G0/G1 phase, with a corresponding decrease in the proportion of cells in S phase in comparison with control cultures. This result is consistent with the behavior of an EGFR tyrosine kinase inhibitor, IRESSA (ZD1839).

3. Conclusion

The antiproliferative activity of 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines against a variety of cancer cell lines was evaluated. Most of them displayed potent cytotoxic activity in the micromolar range, especially against the A549 cell line and K562 cell line. The preliminary SAR of this series of compounds' cytotoxic activity against A549 cell line was investigated. The cell cycle analysis on A549 cell line indicated that these compounds cause significant arrest of the cell cycle at the G0/G1 phase.

4. Experimental protocols

^{1}H NMR and spectra were recorded on a Bruker AM 400 instrument at 400 and 500 MHz (chemical shifts are expressed as δ values relative to TMS as internal standard). LC–MS (ESI) spectra were recorded a Finnigan Mat LCQ mass



Scheme 1. Solid-phase synthesis of 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines **7**. Reagents and conditions: (a) $NaBH_3CN$ (10 equiv, 0.1 M) in DMF/AcOH (99:1), rt, 24 h, (b) 4-chloro-7-fluoro-6-nitroquinazoline **8** in THF (10 equiv, 0.1 M), Et_3N (10 equiv, 0.1 M), 24 h, repeat, (c) R^3NH_2 (20 equiv, 0.2 M) in DCM, 24 h, (d) R^2CHO (10 equiv, 0.1 M), $SnCl_2 \cdot 2H_2O$ (2 M) in DMF, 50 °C, 1 h and (e) TFA/DCM = 1:1, 1 h.

Spectrophotometer 214 nm using a Betasil C18 (3 μm, 100 Å, 3 × 50 mm) column.

4.1. Synthesis

4.1.1. Synthesis of derivatives [24]

To the 4-(4-formyl-3-methoxyphenoxy)butyryl AM resin **1** (220 mg, 0.2 mmol sealed within a polypropylene mesh packet) was added an arylamine (10 equiv, 0.1 M), $NaBH_3CN$ (10 equiv, 0.1 M) in anhydrous DMF/HOAC (99:1). The mixture was shaken for 24 h at room temperature. The resin was then washed with DMF (three times), DCM (three times), and MeOH (three times). The resulting resin-bound compound **3** was coupled with 4-chloro-7-fluoro-6-nitroquinazoline **8** (10 equiv, 0.1 M) using triethylamine (10 equiv, 0.1 M) in anhydrous THF at room temperature for 24 h. The resin was washed with DMF (three times), DCM (three times), and MeOH (three times). This procedure was repeated. Resin-bound compound **4** was reacted with an alkylamine (20 equiv, 0.2 M) in DCM for 24 h at room temperature. The resin was washed with DMF (three times), DCM (three times), and MeOH (three times) to afford resin-bound compound **5**. Reduction and cyclization reaction of resin-bound compound **5** were carried out using an alkylaldehyde (10 equiv, 0.1 M) and $SnCl_2 \cdot 2H_2O$ (2 M) in DMF to afford resin-bound compound **6**. After being washed with DMF (three times), DCM (three times), and MeOH (three times), the resin-bound tricycle quinazoline **6** was treated with TFA/DCM = 1:1 at room temperature for 1 h and the solvent was removed under the reduced pressure. The pure product **7** was obtained after a flash column purification with eluant EtOAc/EtOH = 97:3.

*4.1.1.1. 2-Isopropyl-3-(3-ethoxypropyl)-8-(4-methoxyphenylamino)-3H-imidazo[4,5-g]quinazoline (**7a**).* Yield: 85% LC–MS (ESI) *m/z* 420.6 ($M + H^+$). ^1H NMR (400 MHz, d_6-DMSO) δ 9.61 (1H, br s), 8.84 (1H, s), 8.47 (1H, s), 7.85 (1H, s), 7.78–7.80 (2H, m), 6.98–7.00 (2H, m), 4.37–4.41 (2H, t, *J* = 6.4 Hz), 3.79 (3H, s), 3.37–3.42 (5H, m), 2.02–2.05 (2H, m), 1.40–1.41 (6H, d, *J* = 6.8 Hz), 1.13–1.17 (3H, t, *J* = 7.0 Hz).

*4.1.1.2. 2-Ethyl-3-(3-ethoxypropyl)-8-(4-methoxyphenylamino)-3H-imidazo[4,5-g]quinazoline (**7c**).* Yield: 88% LC–MS (ESI) *m/z* 406.6 ($M + H^+$). ^1H NMR (400 MHz, d_6-DMSO) δ 9.61 (1H, br s), 8.83 (1H, s), 8.46 (1H, s), 7.82 (1H, s), 7.77–7.79 (2H, m), 6.97–6.99 (2H, m), 4.33–4.36 (2H, t, *J* = 6.8 Hz), 3.78 (3H, s), 3.32–3.40 (4H, m), 2.96–3.01 (2H, q, *J* = 7.4 Hz), 2.00–2.03 (2H, m), 1.40–1.43 (3H, t, *J* = 7.4 Hz), 1.12–1.15 (3H, t, *J* = 6.8 Hz).

*4.1.1.3. 2-Propyl-3-(3-ethoxypropyl)-8-(4-methoxyphenylamino)-3H-imidazo[4,5-g]quinazoline (**7d**).* Yield: 82% LC–MS (ESI) *m/z* 420.6 ($M + H^+$). ^1H NMR (400 MHz, d_6-DMSO) δ 9.62 (1H, br s), 8.83 (1H, s), 8.47 (1H, s), 7.83 (1H, s), 7.78–7.80 (2H, m), 6.97–6.99 (2H, m), 4.34–4.38 (2H, t, *J* = 7.0 Hz), 3.82 (3H, s), 3.33–3.42 (4H, m), 2.93–2.97 (2H, t, *J* = 7.4 Hz), 2.00–2.04 (2H, m), 1.89–1.95 (2H, m), 1.13–1.17 (3H, t, *J* = 7.0 Hz), 1.05–1.09 (3H, t, *J* = 7.4 Hz).

*4.1.1.4. 2-Benzyl-3-(3-ethoxypropyl)-8-(4-methoxyphenylamino)-3H-imidazo[4,5-g]quinazoline (**7e**).* Yield: 82% LC–MS (ESI) *m/z* 468.6 ($M + H^+$). ^1H NMR (400 MHz, d_6-DMSO) δ 9.63 (1H, br s), 8.85 (1H, s), 8.45 (1H, s), 7.82 (1H, s), 7.77–7.79 (2H, m), 7.27–7.29 (2H, m), 7.24–7.26 (1H, m), 7.21–7.23 (2H, m), 6.96–6.98 (2H, m), 4.31–4.34 (2H, t, *J* = 6.8 Hz), 3.77 (3H, s), 3.78 (2H, s), 3.28–3.39 (4H, m), 1.84–1.91 (2H, m), 1.12–1.15 (3H, t, *J* = 7.0 Hz).

*4.1.1.5. 2-Hexyl-3-(3-ethoxypropyl)-8-(4-methoxyphenylamino)-3H-imidazo[4,5-g]quinazoline (**7f**).* Yield: 87% LC–MS (ESI) *m/z* 462.7 ($M + H^+$). ^1H NMR (400 MHz, d_6-DMSO) δ 9.60 (1H, br s), 8.81 (1H, s), 8.45 (1H, s), 7.81 (1H, s), 7.77–7.79 (2H, m), 6.96–6.98 (2H, m), 4.32–4.36 (2H, t, *J* = 6.6 Hz), 3.77 (3H, s), 3.31–3.40 (4H, m), 2.92–

Table 1
Cytotoxicity of the target compounds against five human cancer lines *in vitro*

Compd	R^1	R^2	R^3	Cytotoxicity (IC_{50}, μM)[a]				
				A549	K562	PC-3	Molt-4	MDA-MB-231
IRESSA	–	–	–[b]	13.59 ± 2.05	9.36 ± 1.13	15.10 ± 3.78	15.02 ± 0.32	36.61 ± 6.08
7a	4′-CH_3O	$(CH_3)_2CH$	$C_2H_5O(CH_2)_2CH_2$	4.59 ± 1.44	5.18 ± 1.22	>100	>100	>100
7b	4′-CH_3O	$(CH_3)_2CHCH_2$	$C_2H_5O(CH_2)_2CH_2$	2.81 ± 2.46	14.40 ± 0.15	>100	>100	>100
7c	4′-CH_3O	CH_3CH_2	$C_2H_5O(CH_2)_2CH_2$	6.05 ± 0.49	>100	>100	>100	>100
7d	4′-CH_3O	$CH_3CH_2CH_2$	$C_2H_5O(CH_2)_2CH_2$	18.33 ± 5.45	>100	>100	>100	>100
7e	4′-CH_3O	$C_6H_5CH_2$	$C_2H_5O(CH_2)_2CH_2$	22.05 ± 5.17	12.88 ± 0.73	>100	>100	15.49 ± 2.61
7f	4′-CH_3O	$CH_3(CH_2)_4CH_2$	$C_2H_5O(CH_2)_2CH_2$	38.98 ± 3.99	40.88 ± 6.61	>100	>100	>100
7g	4′-CH_3O	$(CH_3)_2CH$	Cyclo-C_6H_{11}	7.31 ± 3.63	19.31 ± 0.76	22.97 ± 4.74	7.69 ± 1.39	21.08 ± 3.37
7h	4′-CH_3O	$(CH_3)_2CH$	$(CH_3)_2CH$	6.26 ± 3.25	>100	>100	>100	35.73 ± 5.93
7i	4′-CH_3O	$(CH_3)_2CH$	$CH_3(CH_2)_2CH_2$	8.29 ± 0.97	>100	18.89 ± 5.05	11.46 ± 2.55	>100
7j	4′-CH_3O	$(CH_3)_2CH$	$CH_3O(CH_2)_2CH_2$	15.76 ± 1.69	>100	>100	>100	>100
7k	4′-F	$(CH_3)_2CH$	$CH_3(CH_2)_2CH_2$	4.25 ± 1.59	5.55 ± 0.34	9.74 ± 2.09	11.43 ± 3.39	20.00 ± 6.32
7l	3′,4′-Di(CH_3O)	$(CH_3)_2CH$	$CH_3(CH_2)_2CH_2$	5.58 ± 0.76	18.51 ± 0.10	>100	6.63 ± 2.60	19.97 ± 3.28
7m	4′-CH_3	$(CH_3)_2CH$	$CH_3(CH_2)_2CH_2$	12.14 ± 6.06	>100	24.82 ± 5.65	>100	10.65 ± 1.62
7n	3′,4′-Di(CH_3O)	$CH_3CH_2CH_2$	$CH_3O(CH_2)_2CH_2$	11.46 ± 4.36	14.33 ± 0.32	24.59 ± 1.28	10.93 ± 4.53	20.63 ± 3.64
7o	H	$(CH_3)_2CH$	Cyclo-C_6H_{11}	22.05 ± 4.34	17.35 ± 0.16	24.73 ± 3.07	2.83 ± 1.45	>100

[a] Each experiment was independently performed three times and expressed as means ± SD.
[b] The structure of IRESSA was listed in Fig. 1.

2.96 (2H, t, $J = 7.6$ Hz), 1.99–2.02 (2H, m), 1.83–1.88 (2H, m), 1.42–1.47 (2H, m), 1.29–1.36 (4H, m), 1.12–1.15 (3H, t, $J = 7.0$ Hz), 0.87–0.90 (3H, t, $J = 6.8$ Hz).

*4.1.1.6. 2-Isopropyl-3-isopropyl-8-(4-methoxyphenylamino)-3H-imidazo[4,5-g]quinazoline (**7h**).* Yield: 90% LC–MS (ESI) *m/z* 376.6 ($M + H^+$). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.62 (1H, br s), 8.81 (1H, s), 8.43 (1H, s), 7.82 (1H, s), 7.76–7.78 (2H, m), 6.96–6.98 (2H, m), 4.81–4.84 (1H, q, $J = 6.9$ Hz), 3.26–3.30 (1H, q, $J = 6.7$ Hz), 1.74–1.75 (6H, d, $J = 6.9$ Hz), 1.51–1.52 (6H, d, $J = 6.7$ Hz).

*4.1.1.7. 2-Isopropyl-3-(3-methoxypropyl)-8-(4-methoxyphenylamino)-3H-imidazo[4,5-g]quinazoline (**7j**).* Yield: 87% LC–MS (ESI) *m/z* 406.6 ($M + H^+$). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.94 (1H, br s), 8.68 (1H, s), 8.57 (1H, s), 7.81 (1H, s), 7.71–7.73 (2H, m), 6.95–6.96 (2H, m), 4.32–4.35 (2H, t, $J = 6.9$ Hz), 3.79 (3H, s), 3.31–3.36 (6H, m), 2.09–2.14 (2H, m), 1.48–1.49 (6H, d, $J = 6.6$ Hz).

*4.1.1.8. 2-Isopropyl-3-butyl-8-(4-methylphenylamino)-3H-imidazo[4,5-g]quinazoline (**7m**).* Yield: 91% LC–MS (ESI) *m/z* 374.6 ($M + H^+$). ^{1}H NMR (400 MHz, d_6-DMSO) 9.62 (1H, br s), 8.83 (1H, s), 8.50 (1H, s), 7.83 (1H, s), 7.79–7.81 (2H, m), 7.39–7.40 (2H, m), 4.32–4.35 (2H, t, $J = 7.0$ Hz), 3.25–3.28 (1H, m), 2.31 (3H, s), 1.86–1.89 (2H, m), 1.45–1.47 (6H, d, $J = 7.0$ Hz), 1.43–1.46 (2H, m), 0.98–1.01 (3H, t, $J = 7.4$ Hz).

*4.1.1.9. 2-Isopropyl-3-cyclohexyl-8-phenylamino-3H-imidazo[4,5-g]quinazoline (**7o**).* Yield: 88% LC–MS (ESI) *m/z* 386.6 ($M + H^+$) ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.72 (1H, s), 8.28 (1H, s), 8.07 (1H, s), 7.79–7.81 (2H, m), 7.66 (1H, br s), 7.41–7.45 (2H, m), 7.15–7.19 (1H, m), 4.29–4.31 (1H, m), 3.28–3.31 (1H, m), 1.93–2.04 (4H, m), 1.64–1.87 (4H, m), 1.49–1.50 (6H, d, $J = 6.8$ Hz), 1.34–1.46 (2H, m).

Physicochemical data for compounds **7b**, **7g**, **7i**, **7k**, **7l** and **7n** were reported in Ref. [24].

4.2. Biology

4.2.1. Cytotoxic assay

The tumor cell lines panel consisted of A549, K562, PC-3, Molt-4 and MDA-MB-231. Cultured cancer cells were grown in the presence of the putative anticancer agents in 96-well plates. After 96 h treatment, the cell growth rates were determined by MTT assay and the IC_{50} values were calculated with LOGIT method. Assays were performed in triplicate on three independent experiments.

4.2.2. Cell cycle analysis

Test substances were dissolved in DMSO and diluted to 10 μmol/l. A549 cells (5×10^4 cells/ml, 5 ml) were cultured in five flasks for 24 h with test compounds (for each test compound, one flask was used) or without any addition. The cells were harvested, washed with PBS and centrifuged. The fixation of cells was realized through the addition of 4 ml ethanol (70% ice-cold) and then keeping cells at −20 °C overnight until DNA staining. The fixed cells were treated with 100 μg/ml Rnase A in PBS for 1 h, followed by staining with 50 μg/ml propidium iodide in PBS in the dark. The DNA content of eukaryotic cells was then measured with flow cytometery.

Table 2
Cell cycle distribution by flow cytometry in A549 cells treated for 24 h

Compound	G0/G1 (%)	S (%)	G2/M (%)
Control	61.26 ± 7.63	29.52 ± 5.98	9.22 ± 1.79
IRESSA (ZD1839)	76.12 ± 2.47	19.24 ± 4.51	4.64 ± 4.02
7a	80.38 ± 6.63	16.22 ± 5.18	3.40 ± 2.07
7b	81.47 ± 5.67	15.41 ± 4.81	3.12 ± 2.75
7k	86.28 ± 1.90	10.73 ± 1.78	2.99 ± 2.68

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