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Synthesis and Antineoplastic Activity of Quinoline Derivatives

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Designed as a new series of molecules that contain the quinoline substructure, several 11*H*-indolo[3.2-*c*]quinoline derivatives were synthesized and subjected to biological evaluation. Several compounds were found to exhibit cytotoxic activity against the growth of colon (HTC-8), liver (BEL-7402), gastric (BCG-823), pulmonary gland (A549), and ovary (A2780) cancer cell lines. The structure–activity relationship of these compounds is discussed.

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Introduction

In recent years there has been intense interest in the design and analysis of inhibitors of epidermal growth factor receptor (EGFR) with anti-tumour activities.[1] For example, compound PD-153035 was reported to have a specific inhibitory activity toward EGFR tyrosine kinase.[2] Compound ZD1839 was found to be effective for non-small-cell lung cancer and was recently approved for clinical use in Japan.[3] Both compounds contain the quinoline substructure. In 2003, He et al. designed and synthesized a series of 11*H*-indolo[3.2-*c*]quinoline derivatives (**A**) that exhibited high cytotoxic activity on HL-60 and small-cell lung cancer[4] (Fig. 1). To further explore the structure–activity relationship of compounds that contain the quinoline substructure in detail, we synthesized a series of new compounds that share the quinoline unit while having different substituted groups. Based on results from assays using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] method,[5,6] several compounds were found to possess cytotoxic activity against the growth of colon (HTC-8), liver (BEL-7402), gastric (BCG-823), pulmonary gland (A549), and ovary (A2780) cancer cell lines.

The synthetic procedures for the preparation of 11*H*-indole[3,2-*c*]quinoline derivatives are shown in Scheme 1. Compound **1a** was synthesized using the conventional Kubo method.[7] Various side chains were introduced onto position 6 of **1a** (Scheme 1), which yielded the corresponding quinoline derivatives **1b**–**d**.[8] The 4-substituted compounds **2**, **4**, **6**, and **8** were formed from the condensation of compounds **1a**–**d** and the corresponding aniline derivatives based on known procedures.[9] The cyclized 11*H*-indolo[3,2-*c*]quinoline derivatives **3**, **5**, **7**, and **9** were then obtained in acetic acid in the presence of palladium(II) acetate under reflux.[4]

Results and Discussion

Table 1 shows the cytotoxic activities of the synthesized compounds **2a**–**4d** derived from 11*H*-indole[3,2-*c*]quinoline by varying the substituents at the 4- and 6-positions.

Among the assayed compounds, the 6-methoxy derivatives **2** and 6-(3-morpholinopropoxy) derivatives **8** showed the highest cytotoxic activities, followed by the 6-(2-methoxyethoxy) derivatives **6**. 6-Hydroxy derivatives **4** exhibited no obvious inhibitory activity. These results indicated that compounds bearing methoxy and (3-morpholinopropoxy) groups at the 6-position had good activities.

The compounds bearing a 3-chloro-4-fluorophenyl amino group at the 4-position (**2a**, **4a**, **6a**, **8a**) exhibited higher

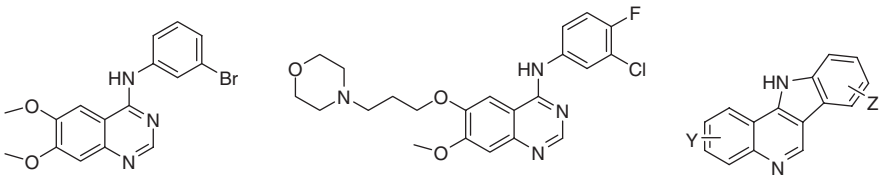

Fig. 1. Structures of quinoline derivatives.

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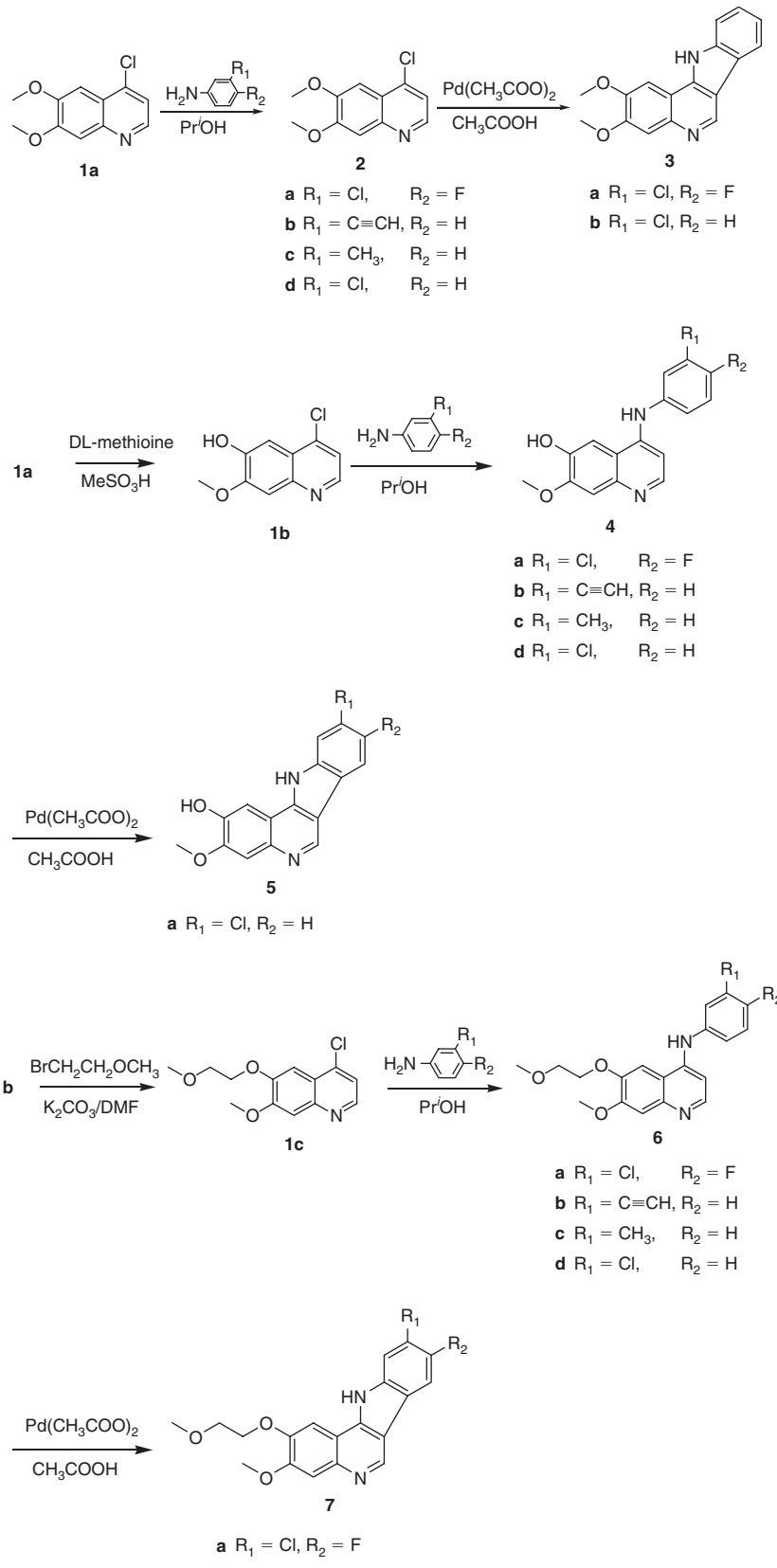
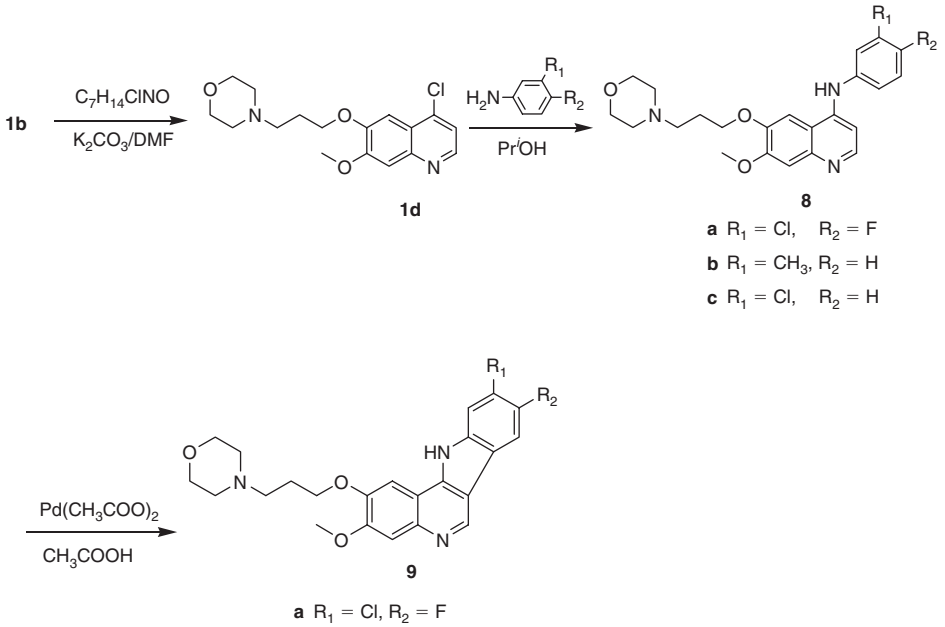

Cl
O
O
N
1a
H2N
R1
R2
PriOH
2
a R1 = Cl, R2 = F
b R1 = C≡CH, R2 = H
c R1 = CH3, R2 = H
d R1 = Cl, R2 = H
Pd(CH3COO)2
CH3COOH
HN
3
a R1 = Cl, R2 = F
b R1 = Cl, R2 = H
DL-methioine
MeSO3H
HO
1b
4
a R1 = Cl, R2 = F
b R1 = C≡CH, R2 = H
c R1 = CH3, R2 = H
d R1 = Cl, R2 = H
5
a R1 = Cl, R2 = H
BrCH2CH2OCH3
K2CO3/DMF
1c
6
a R1 = Cl, R2 = F
b R1 = C≡CH, R2 = H
c R1 = CH3, R2 = H
d R1 = Cl, R2 = H
7
a R1 = Cl, R2 = F

Scheme 1.



Scheme 1. (*Continued*)

Table 1. Inhibitory action of quinoline derivatives

Samples	IC_{50} [M]				
	HCT-8	BEL-7402	BCG-823	A549	A2780
2a	2.07×10^{-6}	1.78×10^{-6}	0.64×10^{-6}	3.27×10^{-6}	0.42×10^{-6}
2b	4.27×10^{-6}	3.51×10^{-6}	2.21×10^{-6}	2.49×10^{-6}	1.58×10^{-6}
2c	5.69×10^{-6}	5.22×10^{-6}	3.35×10^{-6}	$>10 \times 10^{-6}$	1.51×10^{-6}
2d	4.14×10^{-6}	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	6.38×10^{-6}
3a	1.70×10^{-6}	1.78×10^{-6}	1.48×10^{-6}	1.18×10^{-6}	$<0.1 \times 10^{-6}$
3b	2.47×10^{-6}	2.37×10^{-6}	$>10 \times 10^{-6}$	3.12×10^{-6}	2.52×10^{-6}
4a	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	1.59×10^{-6}	$>10 \times 10^{-6}$	0.32×10^{-6}
4b	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
4c	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
4d	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
5a	3.00×10^{-6}	5.37×10^{-6}	$>10 \times 10^{-6}$	5.32×10^{-6}	4.01×10^{-6}
6a	4.43×10^{-6}	3.53×10^{-6}	3.08×10^{-6}	2.02×10^{-6}	4.64×10^{-6}
6b	$>10 \times 10^{-6}$	6.81×10^{-6}	$>10 \times 10^{-6}$	6.74×10^{-6}	$>10 \times 10^{-6}$
6c	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$	$>10 \times 10^{-6}$
6d	4.70×10^{-6}	$>10 \times 10^{-6}$	3.14×10^{-6}	$>10 \times 10^{-6}$	7.55×10^{-6}
7a	2.09×10^{-6}	3.21×10^{-6}	2.96×10^{-6}	5.44×10^{-6}	2.95×10^{-6}
8a	1.70×10^{-6}	1.78×10^{-6}	1.03×10^{-6}	1.24×10^{-6}	0.28×10^{-6}
8b	2.87×10^{-6}	5.33×10^{-6}	2.45×10^{-6}	4.11×10^{-6}	2.87×10^{-6}
8c	1.99×10^{-6}	$>10 \times 10^{-6}$	2.53×10^{-6}	4.39×10^{-6}	3.40×10^{-6}
9a	4.27×10^{-6}	4.61×10^{-6}	2.49×10^{-6}	3.56×10^{-6}	2.85×10^{-6}

anti-tumour activity ($IC_{50} < 10^{-6}$ M) than those with a 4-(3-chloroaniline) group (**2d**, **4d**, **6d**, **8c**), which demonstrated that the 3-chloro-4-fluorophenylamino group was a more effective substituent that led to higher activities than the 3-chloroaniline group.

Compounds **3a**, **3b**, **5a**, **7a**, and **9a**, which share the indole substructure, showed high inhibitory activity. Among them, compound **3a** (9-chloro-8-fluoro-2,3-dimethoxy-11*H*-indole[3,2-*c*]quinoline) had a prominent effect on the ovary cell line (A2780) ($IC_{50} < 0.1 \times 10^{-6}$ M). These results demonstrate that indole[3,2-*c*]quinoline derivatives have great potential for developing new anti-tumour agents.

Most of the examined compounds exhibited higher activities on human ovarian cancer cell lines (A2780) than on the other four cancer cell lines, which indicated that human ovarian cancer cells were most sensitive to these compounds.

Conclusions

In summary, the type of substituents derived from aniline and other groups at the 6-position of the assayed compounds had obvious, and, in some cases, dramatic effects on their biological activities. The revealed structure–activity relationship provides

new insights on factors that determine the anti-tumour activities of the corresponding compounds.

Experimental

All melting points were taken on an X-4 melting point apparatus. ^{1}H NMR spectra were carried out in $CDCl_3$, CD_3COCD_3, or (D_6)DMSO on an Avance Bruker (500 MHz) spectrometer (Bruker Biospin, Fällanden, Switzerland) using tetramethylsilane (TMS) as an internal standard. Mass spectra, infrared absorption spectra, and elemental analysis were determined, respectively, by Agilent HPLC MSD (Agilent, Santa Clara, CA, USA), AVATAR-360FT-IR (Thermo Nicolet, Madison, USA), and Perkin–Elmer 240-c (Perkin–Elmer, Massachusetts, USA) machines.

4-Chloro-7-methoxy-6-(2-methoxyethoxy)quinoline ***1h***

A stirred mixture of 4-chloro-7-methoxyquinolin-6-ol (0.5 g, 2.38 mmol), 1-bromo-2-methoxyethane (1.66 g, 11.9 mmol), dimethylformamide (DMF, 31 mL), and K_2CO_3 (2.3 g, 16.7 mmol) was heated at 90°C for 4.5 h. The reaction mixture was cooled and extracted with ethyl acetate, the organic layer was dried (Na_2SO_4), and the solvent concentrated under vacuum. The product was purified through a silica gel column using petroleum spirits/acetone (4:1) as eluent to give a white solid (0.467 g, 73.2%), mp 89–91°C. δ_H ($CDCl_3$, 500 MHz) 8.61 (d, *J* 4.8, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.38 (d, *J* 4.8, 1H), 4.38 (t, *J* 4.6, 2H), 4.05 (s, 3H), 3.93 (t, *J* 4.7, 2H), 3.52 (s, 3H).

4-Chloro-7-methoxy-6-(3-morpholinopropoxy)quinoline ***1i***

This compound was obtained in a similar manner as for the preparation of **1h**. Yield of the white product was 57.1 mg, mp 119–120°C. δ_H ($CDCl_3$, 500 MHz) 8.60 (d, *J* 4.8, 1H), 7.44 (s, 2H), 7.37 (d, *J* 4.8, 1H), 4.30 (t, *J* 6.5, 2H), 4.05 (s, 3H), 3.78 (m, 4H), 2.64 (m, 2H), 2.55 (m, 4H), 2.18 (t, *J* 6.6, 2H).

General Procedure for the Preparation of N-*Phenylquinolin-4-amine Derivatives (Method A)*

To a stirred mixture of the 6,7-substituted quinolines (**1f** or **1g**) in Pr^iOH was added the appropriate aniline dissolved in Pr^iOH that contained two drops of conc. HCl. The mixture was refluxed, and then cooled after completion of the reaction. Saturated $NaHCO_3$ was added and the resulting white solid was collected by filtration. Compounds **2a**–**d**, **4a**–**d**, **6a**–**d**, and **8a**–**c** were prepared by this method.

General Procedure for the Preparation of 11H-*Indolo[3,2-c]quinoline (Method B)*

A stirred mixture of the appropriate *N*-phenylquinolin-4-amine and palladium(II) acetate in acetic acid was heated under reflux in the presence of nitrogen until the reaction was complete. The resulting solid was collected by filtration and purified by column chromatography. Compounds **3a**,**b**, **5a**, **7a**, and **9a** were prepared by this method.

N-*(3-Chloro-4-fluorophenyl)-6,7-dimethoxyquinolin-4-amine* ***2a***

This compound was obtained in 95.3% yield by the general procedure described in Method A, mp 191–192°C. ν_{max} (KBr)/cm^{-1} 3439, 3282, 2925, 1630, 1587, 1506, 1256, 1220, 999, 842, 801, 544. δ_H ($CDCl_3$, 500 MHz) 8.46 (s, 1H), 7.42 (s, 1H), 7.36 (s, 1H), 7.20 (m, 2H), 7.1 (s, 1H), 6.84 (d, *J* 4.8, 1H), 6.37 (s, 1H), 4.05 (s, 6H). δ_C ($CDCl_3$, 125 MHz) 154.7, 152.2, 148.8, 148.6, 146.3, 146.2, 138.7, 123.9, 122.6, 120.3, 117.9, 114.4, 108.5, 101.7, 101.2, 56.3, 56.0. *m*/*z* 332.0 (M^+, 63%), 334.1 ($M^+ + 2$, 33), 108.7 (60), 75.0 (80), 63.0 (100). (Found: C 61.6, H 4.2, N 8.3. Calc. for $C_{17}H_{14}ClFN_2O_2$: C 61.4, H 4.2, N 8.4%.)

N-*(3-Ethynylphenyl)-6,7-dimethoxyquinolin-4-amine* ***2b***

This compound was obtained in 89.7% yield by the general procedure described in Method A, mp 221–223°C. ν_{max} (KBr)/cm^{-1} 3249, 1659, 1582, 1508, 1438, 1274, 1255. δ_H ((D_6)DMSO, 500 MHz) 8.33 (d, *J* 5.3, 1H), 7.63 (s, 1H), 7.41 (m, 3H), 7.27 (s, 1H), 7.22 (d, *J* 6.7, 1H), 6.90 (d, *J* 5.4, 1H), 4.21 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H). δ_C ((D_6)DMSO, 125 MHz) 152.5, 148.9, 148.0, 146.7, 145.4, 141.5, 130.3, 127.0, 125.0, 123.2, 122.7, 114.5, 107.8, 101.9, 101.4, 83.7, 81.3, 56.4, 56.0. *m*/*z* 304.1 (M^+, 60%), 83.8 (97), 65.9 (100). (Found: C 74.5, H 5.2, N 9.3. Calc. for $C_{19}H_{16}N_2O_2$: C 75.0, H 5.3, N 9.2%.)

*6,7-Dimethoxy-*N-m-*tolylquinolin-4-amine* ***2c***

This compound was obtained in 51.2% yield by the general procedure described in Method A, mp 225–226°C. ν_{max} (KBr)/cm^{-1} 3266, 1631, 1592, 1515, 1489, 1275, 1255. δ_H ($CDCl_3$, 500 MHz) 8.44 (d, *J* 5.3, 1H), 7.39 (s, 1H), 7.30 (m, 1H), 7.17 (s, 1H), 7.11 (m, 2H), 6.97 (m, 2H), 6.66 (s, 1H), 4.0 (s, 3H), 3.99 (s, 3H), 2.39 (s, 3H). δ_C ($CDCl_3$, 125 MHz) 152.3, 149.1, 148.5, 146.6, 146.0, 140.5, 139.6, 129.4, 124.9, 122.7, 119.1, 114.6, 108.8, 102.8, 98.9, 56.1, 55.9, 21.4. *m*/*z* 294.2 (M^+, 75%), 85.9 (100), 83.9 (95), 48.9 (86). (Found: C 73.0, H 5.7, N 9.3. Calc. for $C_{18}H_{18}N_2O_2$: C 73.5, H 6.2, N 9.5%.)

N-*(3-Chlorophenyl)-6,7-dimethoxyquinolin-4-amine* ***2d***

This compound was obtained in 91.5% yield by the general procedure described in Method A, mp 209–210°C. ν_{max} (KBr)/cm^{-1} 3601, 1625, 1576, 1510, 1360, 1258, 1213. δ_H ((D_6)DMSO, 500 MHz) 8.34 (d, *J* 4.8, 1H), 7.6 (s, 1H), 7.41 (t, *J* 7.9, 1H), 7.33 (m, 2H), 7.28 (s, 1H), 7.13 (d, *J* 7.8, 1H), 6.97 (d, *J* 4.9, 1H), 3.93 (s, 3H), 3.91 (s, 3H). δ_C ((D_6)DMSO, 125 MHz) 152.3, 148.9, 148.6, 146.2, 145.8, 143.2, 134.1, 131.4, 122.9, 121.0, 119.8, 114.9, 108.5, 102.6, 101.3, 56.3, 56.0. *m*/*z* 314.2 (M^+, 10%), 316.2 ($M^+ + 2$, 5), 84.0 (63), 66.0 (87), 47.9 (100). (Found: C 65.2, H 4.5, N 8.6. Calc. for $C_{17}H_{15}ClN_2O_2$: C 64.9, H 4.8, N 8.9%.)

*9-Chloro-8-fluoro-2,3-dimethoxy-11*H-*indolo[3,2-c]quinoline* ***3a***

This compound was obtained in 30.3% yield by the general procedure described in Method B, mp 287–289°C. ν_{max} (KBr)/cm^{-1} 3418, 1628, 1514, 1467, 1287. δ_H ((D_6)DMSO, 500 MHz) 9.46 (s, 1H), 8.34 (d, *J* 9.6, 1H), 7.93 (s, 1H), 7.88 (d, *J* 6.1, 1H), 7.54 (s, 1H), 4.0 (s, 3H), 3.97 (s, 3H). δ_C ((D_6)DMSO, 125 MHz) 154.0, 152.2, 152.1, 149.7, 142.3, 140.9, 139.6, 135.7, 121.7, 118.0, 113.4, 111.0, 107.8, 107.1, 101.7, 56.4, 56.2. *m*/*z* 330.0 (M^+, 65%), 332.0 ($M^+ + 2$, 25), 84.0 (73), 66.0 (100). (Found: C 61.9, H 3.7, N 8.4. Calc. for $C_{17}H_{12}ClFN_2O_2$: C 61.7, H 3.7, N 8.5%.)

*9-Chloro-2,3-dimethoxy-11*H-*indolo[3,2-c]quinoline* ***3b***

This compound was obtained in 38.0% yield by the general procedure described in Method B, mp 260–261°C. ν_{max} (KBr)/cm^{-1} 1571, 1512, 1286, 1230. δ_H ((D_6)DMSO, 500 MHz) 9.38 (s, 1H), 8.25 (d, *J* 8.3, 1H), 7.87 (s, 1H), 7.70 (s, 1H), 7.51 (s, 1H), 7.33 (d,

J 8.3, 1H), 3.99 (s, 3H), 3.94 (s, 3H). δ_C ((D$_6$)DMSO, 125 MHz) 151.5, 149.4, 142.2, 141.9, 140.8, 139.7, 130.2, 121.8, 121.4, 121.1, 113.5, 111.8, 111.3, 109.0, 101.6, 56.3, 56.1. *m/z* 312.2 (M^+, 50%), 314.4 ($M^+ + 2$, 18), 149.2 (100), 83.9 (87), 65.9 (78). (Found: C 65.0, H 4.1, N 9.0. Calc. for $C_{17}H_{13}ClN_2O_2$: C 65.3, H 4.2, N 9.0%.)

4-(3-Chloro-4-fluoro-phenylamino)-7-methoxyquinolin-6-ol ***4a***

This compound was obtained in 35.5% yield by the general procedure described in Method A, mp 241–242°C. ν_{max} (KBr)/cm^{-1} 3041, 1728, 1587, 1503, 1279, 1223. δ_H ((D$_6$)DMSO, 500 MHz) 8.34 (d, *J* 6.7, 1H), 7.81 (s, 1H), 7.69 (m, 1H), 7.57 (t, *J* 8.9, 1H), 7.46 (m, 1H), 7.35 (s, 1H), 6.75 (d, *J* 6.7, 1H), 3.9 (s, 3H). δ_C ((D$_6$)DMSO, 125 MHz) 155.2, 152.8, 148.1, 146.9, 145.7, 142.4, 138.1, 124.4, 123.2, 120.4, 118.0, 114.7, 106.0, 105.0, 101.4, 56.3. *m/z* 319.1 ($M^+ + 1$, 54%), 108.7 (70), 76.0 (91), 53.0 (100). (Found: C 60.6, H 4.1, N 8.6. Calc. for $C_{16}H_{12}ClFN_2O_2$: C 60.3, H 3.8, N 8.8%.)

4-(3-Ethynylphenylamino)-7-methoxyquinolin-6-ol ***4b***

This compound was obtained in 85.0% yield by the general procedure described in Method A, mp 251–252°C. ν_{max} (KBr)/cm^{-1} 3282, 3212, 2924, 2853, 1594, 1576, 1522, 1482. δ_H ((D$_6$)DMSO, 500 MHz) 8.33 (d, *J* 6.2, 1H), 7.75 (s, 1H), 7.46 (m, 3H), 7.34 (m, 2H), 6.83 (d, *J* 6.2, 1H), 4.24 (s, 1H), 3.99 (s, 3H). δ_C ((D$_6$)DMSO, 125 MHz) 153.7, 149.9, 147.4, 143.5, 140.0, 130.5, 128.6, 126.4, 124.2, 123.4, 114.1, 104.9, 103.9, 100.9, 83.4, 81.8, 56.5. *m/z* 290.5 (M^+, 25%), 100.1 (65), 84.2 (96), 66.0 (100), 46.2 (86). Found: C 74.4, H 4.9, N 9.6. Calc. for $C_{18}H_{14}N_2O_2$: C 74.5, H 4.9, N 9.7%.)

*7-Methoxy-4-*m*-tolylaminoquinolin-6-ol* ***4c***

This compound was obtained in 30.7% yield by the general procedure described in Method A, mp 228–229°C. ν_{max} (KBr)/cm^{-1} 3227, 1604, 1589, 1525, 1506, 1286, 1261, 1219. δ_H ((D$_6$)DMSO, 500 MHz) 8.25 (d, *J* 5.4, 1H), 7.61 (s, 1H), 7.26 (m, 2H), 7.12 (m, 2H), 6.92 (d, *J* 7.5, 1H), 6.82 (d, *J* 5.5, 1H), 3.94 (s, 3H), 2.31 (s, 3H). δ_C ((D$_6$)DMSO, 125 MHz) 152.0, 147.2, 147.1, 146.4, 144.5, 141.2, 139.1, 129.6, 124.5, 122.7, 119.3, 115.2, 107.5, 105.0, 101.5, 56.1, 21.5. *m/z* 282.3 ($M^+ + 2$, 100%), 91.1 (40), 77.1 (55), 65.1 (60), 51.1 (32). (Found: C 72.4, H 6.1, N 9.5. Calc. for $C_{17}H_{16}N_2O_2$: C 72.8, H 5.8, N 10.0%.)

4-(3-Chlorophenylamino)-7-methoxyquinolin-6-ol ***4d***

This compound was obtained in 65.6% yield by the general procedure described in Method A, mp 255–256°C. ν_{max} (KBr)/cm^{-1} 3054, 1587, 1523, 1479, 1294, 1241. δ_H ((D$_6$)DMSO, 500 MHz) 8.34 (d, *J* 5.6, 1H), 7.6 (s, 1H), 7.41 (t, *J* 8.0, 1H), 7.36 (s, 1H), 7.30 (m, 2H), 7.14 (d, *J* 7.9, 1H), 6.93 (d, *J* 5.6, 1H), 3.96 (s, 3H). δ_C ((D$_6$)DMSO, 125 MHz) 152.7, 147.1, 146.9, 146.1, 143.2, 142.9, 134.1, 131.4, 123.3, 121.2, 120.1, 115.3, 106.5, 105.0, 102.5, 56.3. *m/z* 301.2 ($M^+ + 1$, 8%), 63.1 (60), 53.1 (35), 41.1 (100). (Found: C 64.2, H 4.7, N 9.0. Calc. for $C_{16}H_{13}ClN_2O_2$: C 63.9, H 4.4, N 9.3%.)

*9-Chloro-3-methoxy-11*H*-indolo[3,2-c]quinolin-2-ol* ***5a***

This compound was obtained in 65.3% yield by the general procedure described in Method B, mp 280–281°C. ν_{max} (KBr)/cm^{-1} 3082, 1701, 1608, 1529, 1458, 1296. δ_H ((D$_6$)DMSO, 500 MHz) 9.39 (s, 1H), 8.27 (d, *J* 8.4, 1H), 7.72 (s, 1H), 7.67 (d, *J* 1.6, 1H), 7.53 (s, 1H), 7.33 (dd, *J* 8.4, 1.7, 1H), 3.98 (s, 1H). δ_C ((D$_6$)DMSO, 125 MHz) 151.4, 147.3, 141.2, 140.7, 139.9, 130.2, 121.8, 121.4, 121.2, 113.2, 111.8, 108.6, 104.7, 56.2. *m/z* 298.9 (M^+, 100%), 283.9 (35), 256.3 (40), 191.7 (30), 73.6 (15). (Found: C 64.3, H 3.5, N 9.6. Calc. for $C_{16}H_{11}ClN_2O_2$: C 64.3, H 3.7, N 9.4%.)

N-*(3-Chloro-4-fluorophenyl)-7-methoxy-6-(2-methoxyethoxy)quinolin-4-amine* ***6a***

This compound was obtained in 79.7% yield by the general procedure described in Method A, mp 90–91°C. ν_{max} (KBr)/cm^{-1} 1633, 1594, 1515, 1503, 1471, 1250, 1229. δ_H ($CDCl_3$, 500 MHz) 8.46 (d, *J* 5.3, 1H), 7.38 (s, 1H), 7.34 (m, 1H), 7.21 (s, 1H), 7.19 (s, 1H), 7.16 (m, 1H), 6.83 (d, *J* 5.3, 1H), 6.59 (s, 1H), 4.27 (t, *J* 4.7, 2H), 4.0 (s, 3H), 3.86 (d, *J* 4.7, 2H), 3.48 (s, 3H). δ_C ($CDCl_3$, 125 MHz) 155.8, 153.9, 152.7, 148.8, 148.4, 146.4, 146.2, 137.4, 124.3, 122.0, 117.4, 114.3, 109.0, 102.5, 100.8, 70.9, 68.6, 59.3, 56.0. *m/z* 376.2 (M^+, 45%), 318.2 (49), 128.9 (40), 75.1 (38), 63.1 (42), 58.8 (100). (Found: C 60.8, H 4.8, N 7.2. Calc. for $C_{19}H_{18}ClFN_2O_3$: C 60.6, H 4.8, N 7.4%.)

N-*(3-Ethynylphenyl)-7-methoxy-6-(2-methoxyethoxy)quinolin-4-amine* ***6b***

This compound was obtained in 49.2% yield by the general procedure described in Method A, mp 88–89°C. ν_{max} (KBr)/cm^{-1} 3479, 3246, 2930, 1626, 1574, 1506, 1451, 1357, 1254, 1216, 1132, 927, 856. δ_H ($CDCl_3$, 500 MHz) 8.38 (d, *J* 5.4, 1H), 7.44 (s, 1H), 7.35 (m, 2H), 7.32–7.27 (m, 3H), 6.94 (d, *J* 5.3, 1H), 4.29 (t, *J* 4.6, 2H), 3.97 (s, 3H), 3.85 (t, *J* 3.8, 2H), 3.47 (s, 3H), 3.13 (s, 1H). δ_C ($CDCl_3$, 125 MHz) 152.9, 148.5, 148.0, 146.3, 145.6, 140.6, 129.7, 127.6, 124.9, 123.5, 122.1, 114.5, 108.3, 102.9, 101.0, 83.0, 77.8, 70.9, 68.7, 59.3, 56.0. *m/z* 348.3 (M^+, 30%), 254.2 (65), 229.2 (85), 75.2 (77), 63.2 (70), 59.2 (95), 45.2 (100). (Found: C 72.8, H 5.8, N 8.2. Calc. for $C_{21}H_{20}N_2O_3$: C 72.4, H 5.8, N 8.0%.)

*7-Methoxy-6-(2-methoxyethoxy)-*N*-*m*-tolylquinolin-4-amine* ***6c***

This compound was obtained in 52.0% yield by the general procedure described in Method A, mp 200–201°C. ν_{max} (KBr)/cm^{-1} 3419, 2917, 2658, 1633, 1589, 1509, 1471, 1417, 1276, 1228, 1069, 863, 792. δ_H ($CDCl_3$, 500 MHz) 8.42 (d, *J* 5.3, 1H), 7.39 (s, 1H), 7.31 (m, 1H), 7.26 (s, 1H), 7.13 (m, 2H), 6.9 (d, *J* 7.4, 1H), 6.95 (d, *J* 5.4, 1H), 4.32 (t, *J* 4.6, 2H), 4.0 (s, 3H), 3.88 (t, *J* 4.8, 2H), 3.50 (s, 3H), 2.4 (s, 3H). δ_C ($CDCl_3$, 125 MHz) 152.8, 148.3, 148.0, 146.9, 140.2, 139.6, 129.4, 125.0, 122.7, 119.1, 114.2, 108.4, 102.3, 101.2, 70.9, 68.8, 59.3, 56.0, 21.5. *m/z* 338.4 (M^+, 15%), 219.3 (17), 91.2 (25), 77.2 (27), 65.2 (34), 59.2 (91), 45.2 (100). (Found: C 71.4, H 6.2, N 8.5. Calc. for $C_{20}H_{22}N_2O_3$: C 71.0, H 6.6, N 8.3%.)

N-*(3-Chlorophenyl)-7-methoxy-6-(2-methoxyethoxy)quinolin-4-amine* ***6d***

This compound was obtained in 43.7% yield by the general procedure described in Method A, mp 81–82°C. ν_{max} (KBr)/cm^{-1} 3288, 2930, 1625, 1579, 1505, 1479, 1356, 1256, 1208, 1095, 915, 857. δ_H ($CDCl_3$, 500 MHz) 8.47 (d, *J* 5.3, 1H), 7.39 (s, 1H), 7.33 (t, *J* 8.0, 1H), 7.29 (m, 1H), 7.24 (s, 1H), 7.18 (dd, *J* 6.7, 1.3, 1H), 7.12 (dd, *J* 6.9, 1.0, 1H), 7.0 (d, *J* 5.3, 1H), 4.29 (t, *J* 4.6, 2H), 3.99 (s, 3H), 3.86 (t, *J* 4.8, 2H), 3.49 (s, 3H). δ_C ($CDCl_3$, 125 MHz) 152.8, 148.7, 148.6, 146.4, 145.4, 142.2, 135.2, 130.6, 123.6, 121.0, 119.1, 114.8, 108.9, 103.6, 101.0, 70.9, 68.7, 59.3, 56.0. *m/z* 358.3 (M^+, 5%), 75.1 (35),

59.0 (99), 45.1 (100). (Found: C 63.4, H 5.2, N 8.0. Calc. for $C_{19}H_{19}ClN_2O_3$: C 63.6, H 5.3, N 7.8%.)

*9-Chloro-8-fluoro-3-methoxy-2-(2-methoxyethoxy)-11*H*-indolo[3,2-c]quinoline* ***7a***

This compound was obtained in 56.0% yield by the general procedure described in Method B, mp 107–108°C. ν_{max} (KBr)/cm^{-1} 3401, 1631, 1556, 1511, 1466, 1376, 1288. δ_H ((D$_6$)DMSO, 500 MHz) 9.36 (s, 1H), 8.29 (d, *J* 9.6, 1H), 7.85 (s, 1H), 7.81 (d, *J* 6.1, 1H), 7.50 (s, 1H), 4.28 (t, *J* 4.4, 2H), 3.95 (s, 3H), 3.81 (t, *J* 4.4, 2H), 3.38 (s, 3H). δ_C ((D$_6$)DMSO, 125 MHz) 153.8, 151.9, 151.8, 148.5, 142.5, 141.7, 135.5, 132.0, 129.1, 113.5, 113.1, 111.2, 109.1, 107.5, 102.6, 70.6, 68.3, 58.8, 56.1. *m/z* 374.2 (M$^+$, 47%), 376.4 (M$^+$ + 2, 15), 316.0 (65), 58.9 (100). (Found: C 60.5, H 4.1, N 7.9. Calc. for $C_{19}H_{16}ClFN_2O_3$: C 60.9, H 4.3, N 7.5%.)

N-*(3-Chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinolin-4-amine* ***8a***

This compound was obtained in 85.0% yield by the general procedure described in Method A, mp 183–184°C. ν_{max} (KBr)/cm^{-1} 3340, 1625, 1582, 1531, 1500, 1354, 1247. δ_H ($CDCl_3$, 500 MHz) 8.41 (d, *J* 5.3, 1H), 7.39 (s, 1H), 7.37 (s, 1H), 7.20 (m, 3H), 6.82 (d, *J* 5.3, 1H), 4.22 (t, *J* 6.6, 2H), 4.01 (s, 3H), 3.74 (t, *J* 4.3, 4H), 2.59 (t, *J* 7.0, 2H), 2.51 (m, 4H), 2.13 (m, 2H). δ_C ($CDCl_3$, 125 MHz) 156.0, 153.0, 148.7, 147.1, 147.0, 137.0, 130.9, 128.8, 124.6, 122.3, 117.4, 114.2, 107.7, 102.2, 100.6, 67.5, 66.9, 56.1, 55.4, 53.7, 26.1. *m/z* 445.2 (M$^+$, 64%), 447.4 (M$^+$ + 2, 20), 56.1 (52), 100.0 (79), 42.1 (80), 69.9 (90), 128.0 (100). (Found: C 61.9, H 5.7, N 9.7. Calc. for $C_{23}H_{25}ClFN_3O_3$: C 62.0, H 5.7, N 9.4%.)

7-Methoxy-6-(3-morpholinopropoxy)-N-m-*tolylquinolin-4-amine* ***8b***

This compound was obtained in 35.1% yield by the general procedure described in Method A, mp 198–199°C. ν_{max} (KBr)/cm^{-1} 2948, 2851, 1623, 1578, 1507, 1487, 1356, 1274, 1210, 1116, 1066, 860. δ_H ($CDCl_3$, 500 MHz) 8.30 (d, *J* 5.0, 1H), 7.32∼7.28 (m, 3H), 7.16 (m, 2H), 7.01 (d, *J* 7.5, 1H), 6.9 (d, *J* 5.3, 1H), 4.22 (t, *J* 6.6, 2H), 3.97 (s, 3H), 3.74 (t, *J* 4, 4H), 2.57 (t, *J* 7.1, 2H), 2.49 (m, 4H), 2.40 (s, 3H), 2.12 (t, *J* 6.9, 2H). δ_C ($CDCl_3$, 125 MHz) 152.9, 148.5, 147.4, 146.8, 140.0, 139.7, 129.5, 125.3, 122.8, 119.2, 114.1, 107.4, 102.1, 100.7, 67.5, 67.0, 56.0, 55.4, 53.7, 26.2, 21.5. *m/z* 407.3 (M$^+$, 55%), 280.1 (28), 128.2 (100), 100.1 (72), 70.0 (43), 56.0 (35). (Found: C 71.0, H 7.3, N 10.6. Calc. for $C_{24}H_{29}N_3O_3$: C 70.7, H 7.2, N 10.3%.)

N-*(3-Chlorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinolin-4-amine* ***8c***

This compound was obtained in 82.6% yield by the general procedure described in Method A, mp 173–174°C. ν_{max} (KBr)/cm^{-1} 3391, 3035, 1607, 1590, 1511, 1465, 1275. δ_H ($CDCl_3$, 500 MHz) 8.44 (m, 1H), 7.35 (s, 1H), 7.29 (m, 3H), 7.20 (d, *J* 7.9, 1H), 7.11 (d, *J* 7.9, 1H), 7.0 (d, *J* 5.3, 1H), 4.1 (m, 2H), 3.94 (s, 3H), 3.7 (t, *J* 4.1, 4H), 2.5 (t, *J* 7.0, 2H), 2.4 (m, 4H), 2.05 (m, 2H). δ_C ((D$_6$)DMSO, 125 MHz) 155.3, 153.2, 148.9, 140.6, 139.4, 135.7, 134.4, 131.9, 127.3, 125.4, 124.2, 112.2, 104.2, 100.4, 100.0, 67.2, 63.8, 56.8, 54.1, 51.6, 23.3. *m/z* 427.1 (M$^+$, 30%), 429.4 (M$^+$ + 2, 12), 127.9 (80), 100.2 (93), 96.7 (75), 69.8 (69), 55.8 (64), 41.4 (100). (Found: C 64.4, H 6.3, N 9.7. Calc. for $C_{23}H_{26}ClN_3O_3$: C 64.6, H 6.1, N 9.8%.)

*9-Chloro-8-fluoro-3-methoxy-2-(3-morpholinopropoxy)-11*H*-indolo[3,2-c]quinoline* ***9a***

This compound was obtained in 22.6% yield by the general procedure described in Method B, mp 189–190°C. δ_H ((D$_6$)DMSO, 500 MHz) 9.38 (s, 1H), 8.33 (d, *J* 9.6, 1H), 7.90 (s, 1H), 7.84 (d, *J* 6.1, 1H), 7.53 (s, 1H), 4.22 (t, *J* 6.1, 2H), 3.9 (s, 3H), 3.61 (m, 4H), 2.56 (m, 2H), 2.47 (m, 4H), 2.06 (m, 2H). δ_C ((D$_6$)DMSO, 125 MHz) 153.8, 151.6, 148.6, 142.8, 142.4, 141.5, 135.4, 121.9, 117.3, 113.5, 113.0, 111.3, 109.6, 107.6, 102.5, 67.2, 66.5, 56.1, 55.3, 53.7, 26.1. *m/z* 444.4 (M$^+$ + 1, 45%), 301.3 (39), 128.3 (98), 97.3 (100). (Found: C 62.6, H 5.2, N 9.8. Calc. for $C_{23}H_{23}ClFN_3O_3$: C 62.2, H 5.2, N 9.5%.)

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References

[1] P. M. Harari, *Endocr. Relat. Cancer* **2004**, *11*, 689. doi:10.1677/ERC.1.00600

[2] A. J. Bridges, H. Zhou, D. R. Cody, G. W. Rewcastle, A. McMichael, H. D. H. Showalter, D. W. Fry, A. J. Kraker, W. A. Denny, *J. Med. Chem.* **1996**, *39*, 267. doi:10.1021/JM9503613

[3] F. Cappuzzo, A. Ardizzoni, H. Soto-Parra, C. Gridelli, P. Maione, M. Tiseo, C. Calandri, S. Bartolini, A. Santoro, L. Crinò, *Lung Cancer* **2003**, *41*, 227. doi:10.1016/S0169-5002(03)00189-2

[4] L. He, H.-X. Chang, T.-C. Chou, S. Niramol, C. C. Cheng, *Eur. J. Med. Chem.* **2003**, *38*, 101. doi:10.1016/S0223-5234(02)01420-4

[5] T. Mosmann, *J. Immunol. Methods* **1983**, *65*, 55. doi:10.1016/0022-1759(83)90303-4

[6] J. Carmichael, W. G. DeGraff, A. F. Gazdar, J. D. Minna, J. B. Mitchell, *Cancer Res.* **1987**, *47*, 936.

[7] K. Kubo, T. Shimizu, S.-I. Ohyama, H. Murooka, A. Iwai, K. Nakamura, K. Hasegawa, Y. Kobayashi, N. Takahashi, K. Takahashi, S. Kato, T. Izawa, T. Isoe, *J. Med. Chem.* **2005**, *48*, 1359. doi:10.1021/JM030427R

[8] C. S. Harris, L. F. Hennequin, J. G. Kettle, O. A. Willerval, *Tetrahedron Lett.* **2005**, *46*, 7715. doi:10.1016/J.TETLET.2005.09.038

[9] A. Wissner, F. M. Brawner, S. K. Rabindran, R. Nilakantan, L. M. Greenberger, R. Shen, Y.-F. Wang, H.-R. Tsou, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2893. doi:10.1016/S0960-894X(02)00598-X