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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Halogenated 2-amino-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitriles as antitumor agents and structure–activity relationships of the 4-, 6-, and 9-positions

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Abstract A series of halogenated 2-amino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives were prepared via interaction of 8-hydroxyquinoline, 5-chloro-8-hydroxyquinoline, and 8-hydroxy-2-methylquinoline with various α-cyanocinnamonitriles. The assignments of the structure of all synthesized compounds were based on spectral data. The cytotoxic activities of the synthesized compounds against four human tumor cell lines MCF-7, HCT-116, HepG-2, and A549 in comparison with the reference drugs Vinblastine and Colchicine were determined by microculture tetrazolium assay. Several compounds showed significant cytotoxic activity. The structure–activity relationship studies reported that the substitution at 4-, 6-, and 9-positions in several 2-amino-4*H*-pyrano[3,2-*h*]quinoline nucleus with the specific halogen atom and lipophilicity increases the ability of the molecule against the different cell lines.

Keywords 8-Hydroxyquinoline derivatives · 4*H*-Pyrano[3,2-*h*]quinoline · Antitumor · Lipophilicity · SAR

Introduction

The chemistry of quinoline derivatives has attracted many researchers due to their applications as biological activities and pharmacological agents. Quinoline moiety is present in many classes of biologically active compounds (El-Agrody et al. 2013; Thomas et al. 2010; Chang et al. 2010; Larghi et al. 2009; Liu et al. 2009; Ramesh et al. 2009; Righi et al. 2008; Ganesh et al. 2008; Musiol et al. 2007). Many compounds that synthesized from 8-hydroxyquinoline and its derivatives have been also shown to have diverse therapeutic activities such as antiprotozoic drugs as well as antineoplastics (Jampilek et al. 2009) and antiproliferative (Musiol et al. 2008; Badawey and Kappe 1997) activities. In addition styrylquinoline derivatives have been explored as perspective HIV integrase inhibitors (Mrozek-Wilczkiewicz et al. 2010; Leonard and Roy 2008; Zouhiri et al. 2005) and biologically active compounds (Chang et al. 2010; Larghi et al. 2009, Ma et al. 2004; Jiang et al. 1990). They also exhibit antimalarial (Kaur et al. 2009), antitumor (Behforouz et al. 2007), antioxidant (Mallesha et al. 2013), antileishmanial (Rocha et al. 2005), and antiplatelet activities (Kuo et al. 2001). In addition several 4*H*-pyrano[3,2-*h*]quinoline derivatives has antitumor activity (El-Agrody et al. 2012; Al-Ghamdi et al. 2012) against different human tumor cell lines. Furthermore, they function as pharmacologically active synthetic compounds (Watson et al. 2001) such as DNA binding capabilities (Atwell et al. 1989) and DNA-intercalating carrier (Chen et al. 2000). In view of the above-mentioned findings, I report herein the synthesis of a series of halogenated 2-amino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives and their evaluation as antitumor, hoping to add some synergistic biological significance to the target molecules. The structural–activity relationship (SAR) of 4-, 6-, and 9-positions for the prepared compounds and lipophilicity was also discussed.

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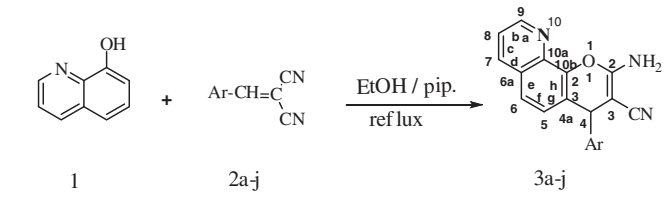
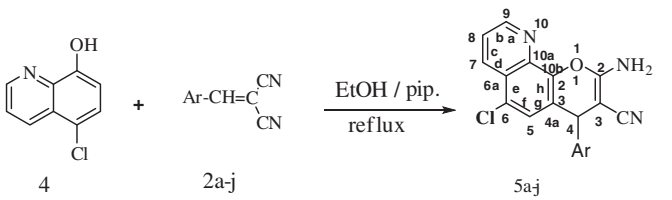
Scheme 1 Synthesis of 2-amino-4-aryl-4*H*-pyrano[3,2-*h*] quinoline-3-carbonitrile derivatives (3**a–j**)



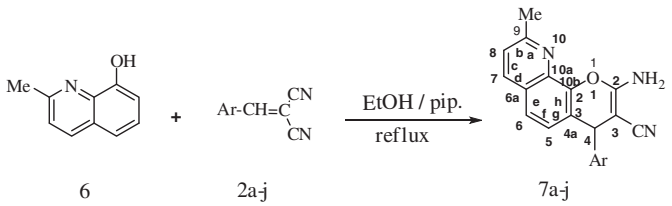
a; Ar = 2-ClC_6H_4
b; Ar = 3-ClC_6H_4
c; Ar = 4-ClC_6H_4
d; Ar = 2,3-$Cl_2C_6H_3$
e; Ar = 2,4-$Cl_2C_6H_3$
f; Ar = 2,5-$Cl_2C_6H_3$
g; Ar = 2,6-$Cl_2C_6H_3$
h; Ar = 3,4-$Cl_2C_6H_3$
i; Ar = 4-BrC_6H_4
j; Ar = 2,3,5-$MeOBr_2C_6H_2$

Scheme 2 Synthesis of 2-amino-4-aryl-6-chloro-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives (**5a–j**)



a; Ar = 2-ClC_6H_4
b; Ar = 3-ClC_6H_4
c; Ar = 4-ClC_6H_4
d; Ar = 2,3-$Cl_2C_6H_3$
e; Ar = 2,4-$Cl_2C_6H_3$
f; Ar = 2,5-$Cl_2C_6H_3$
g; Ar = 2,6-$Cl_2C_6H_3$
h; Ar = 3,4-$Cl_2C_6H_3$
i; Ar = 4-BrC_6H_4
j; Ar = 2,3,5-$MeOBr_2C_6H_2$

Scheme 3 Synthesis of 2-amino-4-aryl-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives (**7a–j**)



a; Ar = 2-ClC_6H_4
b; Ar = 3-ClC_6H_4
c; Ar = 4-ClC_6H_4
d; Ar = 2,3-$Cl_2C_6H_3$
e; Ar = 2,4-$Cl_2C_6H_3$
f; Ar = 2,5-$Cl_2C_6H_3$
g; Ar = 2,6-$Cl_2C_6H_3$
h; Ar = 3,4-$Cl_2C_6H_3$
i; Ar = 4-BrC_6H_4
j; Ar = 2,3,5-$MeOBr_2C_6H_2$

Results and discussion

Chemistry

Interaction of 8-hydroxyquinoline (**1**) with α-cyanomono, di or trisubstituted cinnamonitriles (**2a–j**) in ethanolic piperidine under reflux for 1 h afforded the corresponding 2-amino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives (**3a–j**) as depicted in Scheme 1. The 4-position of compounds **3a–j** is a chiral center and all the reaction progress was observed by TLC.

The assignment of structure **3** was established on the basis of spectral data. The infrared (IR) spectra of **3** showed the appearance of a NH_2 stretch at υ 3478–3407, 3371–3322, 3210–3188 cm^{-1} and a CN stretch at υ 2198–2186 cm^{-1}. The ^1H and ^{13}C NMR spectra of **3** revealed the presence of 4*H* signals at δ 5.56–4.89 (s, 1H, H-4) and 40.80–38.12 ppm (C-4), respectively. The ^{13}C NMR-attached proton test (APT) spectra of compound **3** provided additional evidence in support of the proposed structure. In addition, the mass spectra of compound **3** gave also additional evidences for the proposed structures.

In a similar manner, reaction of 5-chloro-8-hydroxyquinoline (**4**) with α-cyanomono, di or trisubstituted cinnamonitriles **2a–j** in ethanolic piperidine under reflux for 1 h gave 2-amino-4-aryl-6-chloro-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives (**5a–j**) as shown in Scheme 2. The 4-position of compounds **5a–j** is a chiral center and all the reaction progress was observed by TLC.

The assignment of structure **5** was established on the basis of spectral data. The IR spectra of **5** showed the appearance of a NH_2 stretch at υ 3479–3432, 3349–3321, 3205–3182 cm^{-1} and a CN stretch at υ 2201–2192 cm^{-1}. The ^1H and ^{13}C NMR spectra of **5** revealed the presence of 4*H* signals at δ 6.03–5.00 (s, 1H, H-4) and 40.50–36.78 ppm (C-4), respectively. The ^{13}C NMR-APT spectra of compound **5** provided additional evidence in support of the proposed structure. In addition, the mass spectra of compound **5** gave also additional evidences for the proposed structures.

Similarly, reaction of 2-methyl-8-hydroxyquinoline (**6**) with α-cyanomono, di- or trisubstituted cinnamonitriles **2a–j** in ethanolic piperidine under reflux for 1 h gave 2-amino-4-aryl-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives (**7a–j**) as shown in Scheme 3. The 4-position of compounds **7a–j** is chiral center and all the reaction progress was observed by TLC.

The assignment of structure **7** was established on the basis of spectral data. The IR spectra of **7** showed the appearance of a NH_2 stretch at υ 3471–3431, 3366–3323, 3205–3182 cm^{-1} and a CN stretch at υ 2195–2188 cm^{-1}. The ^{1}H and ^{13}C NMR spectra of **7** revealed the presence of 4*H* signals at δ 6.01–4.97 (s, 1H, H-4) and 40.54–36.68 ppm (C-4), respectively. The ^{13}C NMR-APT spectra of compound **7** provided additional evidence in support of the proposed structure. In addition, the mass spectra of compound **7** gave also additional evidences for the proposed structures.

Antitumor activity

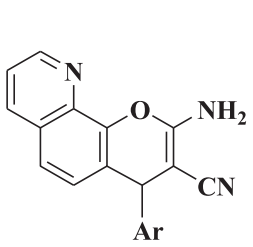
All the synthesized compounds **3a–j**, **5a–j**, and **7a–j** were screened for their in vitro antitumor activity against four human cancer cell lines: breast adenocarcinoma (MCF-7), human colon carcinoma (HCT-116), hepatocellular carcinoma (HepG-2), and lung carcinoma (A549) at various concentrations ranging from 0 to 50 µg/ml and the cell viability was measured by the microculture tetrazolium (MTT) assay as described in the literature (Rahman et al. 2001). In vitro cytotoxic evaluation using cell viability assay was performed at the Regional Center for Mycology & Biotechnology (RCMP), Al-Azhar University, Cairo, Egypt using Vinblastine and Colchicine as reference drugs. The inhibitory concentration (IC_{50}, in µg/ml) of target compounds **3a–j**, **5a–j**, and **7a–j** against the four human cancer cell lines MCF-7, HCT-116, HepG-2, and A549 were given in Table 1.

SAR studies

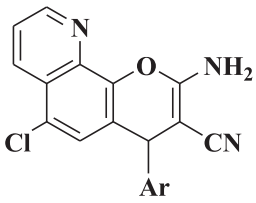
The partition coefficient (Log *P*), which is well known as an index of lipophilicity, is an important physicochemical parameter was measured by ACD/Labs Log *P* calculated, ver.14.02 and was cited in Table 1. The SAR studies at the 4-, 6-, and 9-positions and the relationship between lipophilicity and antitumor activity were explored. The SAR studies of compounds **3a–j** revealed that compounds **3d**, **b**, **h**, **a** has the highest potent antitumor activity (IC_{50} = 1.17–5.33 µg/ml) against breast adenocarcinoma (MCF-7) as compared to the other compounds **3j**, **f**, **e**, **c**, **i**, **g** (IC_{50} = 10.8–38.2 µg/ml) and the reference drug Vinblastine (IC_{50} = 6.1 µg/ml), while compounds **3d**, **b**, **h**, **a**, **j**, **f** has the higher potent antitumor activity (IC_{50} = 1.17–11 µg/ml) against MCF-7 as compared to the compounds **3e**, **c**, **i**, **g** (IC_{50} = 23.8–38.2 µg/ml), and the reference drug Colchicine (IC_{50} = 17.7 µg/ml). The comparison of IC_{50} values of the halosubstituted compounds **3a–j** at the phenyl ring at 4-position demonstrated that the dichloro atoms at 2,3-position or 3,4-position and the monochloro atom at 3-position or 2-position increased the antitumor activity profile against MCF-7 as compared to Vinblastine and Colchicine, suggesting that the dichloro atoms at 2,3-position or 3,4-position and the monochloro atom at 3-position or 2-position at the phenyl ring (hydrophobic group) at 4-position of the 4*H*-pyrano[3,2-*h*]quinoline moiety is preferred over the other substituted groups with decreasing of partition coefficient as shown in Table 1. Replacement of the 6-H for compound **3** with 6-Cl improved of the antitumor activities of compound **5**. Compounds **5b**, **i**, **e**, **d** (IC_{50} = 0.9–2.47 µg/ml) have the higher potent antitumor activities against the MCF-7 as compared to Vinblastine (IC_{50} = 6.1 µg/ml) and the other compounds **5f**, **h**, **j**, **a**, **c**, **g** (IC_{50} = 7.76–10.2 and >50 µg/ml), while compounds **5b**, **i**, **e**, **d**, **f**, **h**, **j**, **a**, **c** displayed good activity (IC_{50} = 0.9–10.2 µg/ml) against the MCF-7 as compared to Colchicine (IC_{50} = 17.7 µg/ml) and compound **5g** inactive (IC_{50} = >50 µg/ml). This potency could be attributed to the presence of the monochloro/bromo atom at 3-position or 4-position, the dichloro atoms at 2,4-position or 2,3-position of the phenyl ring (hydrophobic group) at 4-position of the 4*H*-pyrano[3,2-*h*]quinoline moiety with chloro atom at 6-position, suggesting that this positions at the phenyl ring at 4-position was superior in inhibiting the growth of MCF-7 than the other positions with increasing of partition coefficient as shown in Table 1. In addition, replacement of the 9-H for compound **3** with 9-Me improved of the antitumor activities of compound **7**. Compounds **7h**, **d**, **a**, **j**, **b**, **f** (IC_{50} = 1.24–5.92 µg/ml) exhibited very good activities against the MCF-7 as compared to Vinblastine (IC_{50} = 6.1 µg/ml) and Colchicine (IC_{50} = 17.7 µg/ml) and the other compounds **7c**, **e**, **i**, **g** (IC_{50} = 27.9–38.9 and >50 µg/ml). These data indicate that the activity of compounds **7h**, **d**, **a**, **j**, **b**, **f** was considerably attributed to the presence of the dichloro atoms at 3,4-position, 2,3-position, 2,5-position, monochloroatom at 2-position, 3-position and trisubstituted of the phenyl ring (hydrophobic group) at 4-position of the 4*H*-pyrano[3,2-*h*] quinoline moiety, suggesting that these positions were superior in inhibiting the growth of MCF-7 with 9-Me and with decreasing of partition coefficient as shown in Table 1.

In the case of human colon carcinoma (HCT-116), investigation of SAR revealed that the 2,3-dichlorosubstituted and the 3-chlorosubstituted phenyl **3d**, **b** exhibited good activity (IC_{50} = 1.3 and 1.35 µg/ml) as compared to Vinblastine (IC_{50} = 2.6 µg/ml) and the other compounds **3h**, **a**, **j**, **f**, **c**, **e**, **g**, **i** (IC_{50} = 3.9–43.7 µg/ml), while compounds **3d**, **b**, **h**, **a**, **j**, **f**, **c**, **e**, **g** has the higher potent antitumor activity (IC_{50} = 1.3–31.2 µg/ml) against HCT-116 as compared to Colchicine (IC_{50} = 42.8 µg/ml) and the compound **3i** (IC_{50} = 43.7 µg/ml). This indicated that the dichloro atoms at 2,3-position and the monochloro atom at 3-position have a variable influence on the cytotoxic activity against HCT-116 with decreasing of partition coefficient as shown in Table 1. Replacement of the 6-H for compound **3**

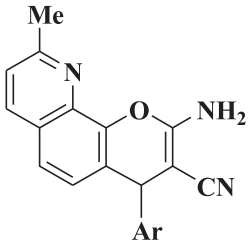
Table 1 SAR of the 4-aryl group and the IC (IC_{50}, in μg/ml) of target compounds against the four human cancer cell lines in comparison with Vinblastine and Colchicine as measured with the MTT method



(3a-j)



(5a-j)



(7a-j)

Compounds	Ar	MCF-7	HCT-116	HepG-2	A549	Log *P*
3a	2-ClC_6H_4	5.33 ± 0.2	4.64 ± 0.1	5.57 ± 0.1	4.07 ± 0.3	3.35 ± 0.50
3b	3-ClC_6H_4	1.42 ± 0.3	1.35 ± 0.2	1.87 ± 0.2	1.23 ± 0.1	3.35 ± 0.50
3c	4-ClC_6H_4	24.9 ± 0.05[a]	24 ± 0.05[a]	w[a]	21.1 ± 0.05	3.35 ± 0.50
3d	2,3-$Cl_2C_6H_3$	1.17 ± 0.11	1.3 ± 0.12	1.41 ± 0.18	38 ± 0.03	3.82 ± 0.50
3e	2,4-$Cl_2C_6H_3$	23.8 ± 0.3	24.3 ± 0.11	12.1 ± 0.1	19.5 ± 0.2	3.96 ± 0.50
3f	2,5-$Cl_2C_6H_3$	11 ± 0.22	12.8 ± 0.2	11.5 ± 0.12	7.95 ± 0.02	3.87 ± 0.50
3g	2,6-$Cl_2C_6H_3$	38.2 ± 0.04	31.2 ± 0.04	36.3 ± 0.06	33.6 ± 0.03	3.96 ± 0.50
3h	3,4-$Cl_2C_6H_3$	3.08 ± 0.13	3.9 ± 0.15	2.44 ± 0.11	2.05 ± 0.12	3.82 ± 0.50
3i	4-BrC_6H_4	34.8 ± 0.15	43.7 ± 0.13	NA[a]	w	3.53 ± 0.53
3j	2,3,5-$MeOBr_2C_6H_2$	10.8 ± 0.11	6.71 ± 0.11	10.4 ± 0.05	5.73 ± 0.07	4.23 ± 0.66
5a	2-ClC_6H_4	8.8 ± 0.16	7.94 ± 0.3	4.62 ± 0.11	5.66 ± 0.16	4.10 ± 0.70
5b	3-ClC_6H_4	0.9 ± 0.07	3.04 ± 0.2	0.7 ± 0.06	2.67 ± 0.07	4.10 ± 0.70
5c	4-ClC_6H_4	10.2 ± 0.04	12.1 ± 0.11	11.9 ± 0.07	22.1 ± 0.04	4.10 ± 0.70
5d	2,3-$Cl_2C_6H_3$	2.47 ± 0.13	7.94 ± 0.05	1.48 ± 0.11	15.6 ± 0.13	4.57 ± 0.70
5e	2,4-$Cl_2C_6H_3$	1.18 ± 0.14	3.01 ± 0.22	0.87 ± 0.12	1.79 ± 0.14	4.71 ± 0.70
5f	2,5-$Cl_2C_6H_3$	7.76 ± 0.12	12.2 ± 0.02	11.5 ± 0.14	8.23 ± 0.12	4.62 ± 0.70
5g	2,6-$Cl_2C_6H_3$	w	34.3 ± 0.04	44.5 ± 0.12	24.3 ± 0.12	4.71 ± 0.70
5h	3,4-$Cl_2C_6H_3$	7.96 ± 0.15	18.6 ± 0.13	3.98 ± 0.13	14.4 ± 0.15	4.57 ± 0.70
5i	4-BrC_6H_4	0.99 ± 0.01	5.81 ± 0.11	1.23 ± 0.03	3.1 ± 0.01	4.28 ± 0.74
5j	2,3,5-$MeOBr_2C_6H_2$	8.09 ± 0.2	3.72 ± 0.15	8.97 ± 0.12	2.28 ± 0.12	4.98 ± 0.84
7a	2-ClC_6H_4	2.56 ± 0.22	33.9 ± 0.2	14.5 ± .21	27.8 ± 0.22	3.81 ± 0.50
7b	3-ClC_6H_4	5.79 ± 0.01	21.4 ± 0.1	3.01 ± .11	24 ± 0.01	3.81 ± 0.50
7c	4-ClC_6H_4	27.9 ± 0.12[a]	15.8 ± 0.2[a]	1.8 ± .15	w	3.81 ± 0.50
7d	2,3-$Cl_2C_6H_3$	1.52 ± 0.1	39.5 ± 0.4	5.39 ± .1	31.8 ± 0.1	4.28 ± 0.50
7e	2,4-$Cl_2C_6H_3$	36 ± 0.13	45.5 ± 0.2	23.9 ± 0.14	36.6 ± 0.13	4.42 ± 0.50
7f	2,5-$Cl_2C_6H_3$	5.92 ± 0.2	35.8 ± 0.12	10.5 ± 0.3	22.4 ± 0.2	4.33 ± 0.50
7g	2,6-$Cl_2C_6H_3$	w	w	w	w	4.42 ± 0.50
7h	3,4-$Cl_2C_6H_3$	1.24 ± 0.3	23.7 ± 0.04	1.83 ± 0.2	13.7 ± 0.3	4.28 ± 0.50
7i	4-BrC_6H_4	38.9 ± 0.14[a]	22.8 ± 0.13[a]	5.5 ± 0.13	36.7 ± 0.14	3.99 ± 0.53
7j	2,3,5-$MeOBr_2C_6H_2$	4.95 ± 0.15	42.2 ± 0.2	9.38 ± 0.14	22.2 ± 0.15	4.69 ± 0.66
V	–	6.1 ± 0.01	2.6 ± 0.04	4.6 ± 0.11	3.78 ± 0.01	–
C	–	17.7 ± 0.03	42.8 ± 0.08	10.6 ± 0.13	21.3 ± 0.03	–

IC_{50} values expressed in μg/ml as the mean values of triplicate wells from at least three experiments and are reported as the mean ± standard error

[a] [**1a**]

w weak activity (IC_{50} > 50 μg/ml), *NA* not active, *V* Vinblastine, *C* Colchicine

with 6-Cl resulted in reduction of potency for the compound **5**. Compounds **5e**, **b**, **j** exhibited near activities (IC_{50} = 3.01–3.72 μg/ml) and the other compounds **5i**, **a**, **d**, **c**, **f**, **h**, **g** exhibited moderate to lower activities (IC_{50} = 5.81–34.3 μg/ml) against HCT-116 as compared to Vinblastine (IC_{50} = 2.6 μg/ml), while compounds **5e**, **b**, **j**, **i**, **a**, **d**, **c**, **f**, **h**, **g** exhibited good activity (IC_{50} = 3.01–34.3 μg/ml) against HCT-116 as compared to Colchicine (IC_{50} = 42.8 μg/ml) with decreasing of partition coefficient as shown in Table 1, suggesting that the dichloro atoms at 2,4-position and the monochloro atom at 3-position have the more variable influence on the cytotoxic activity against HCT-116 than the another groups. In addition, replacement of the 9-H for compound **3** with 9-Me resulted in more reduction of antitumor activities of compound **7**. Compounds **7c**, **b**, **i**, **h**, **j**, **a**, **f**, **d**, **e**, **g** exhibited near or moderate to lower activities (IC_{50} = 15.8–45.5 and >50 μg/ml) against HCT-116 as compared to Vinblastine (IC_{50} = 2.6 μg/ml), while compounds **7c**, **b**, **i**, **h**, **j**, **a**, **f**, **d** exhibited good activity (IC_{50} = 15.8–39.5 μg/ml) against HCT-116 as compared to Colchicine (IC_{50} = 42.8 μg/ml) with increasing of partition coefficient as shown in Table 1, suggesting that monochloro atom at 4-position or 3-position and the monobromo atom at 4-position is preferred over another groups.

Furthermore, compounds **3d**, **b**, **h** (IC_{50} = 1.41–2.44 μmol/l) showed good antitumor activities against hepatocellular carcinoma (HepG-2) as compared to Vinblastine (IC_{50} = 4.6 μg/ml) and the other compounds **3a**, **j**, **f**, **e**, **g**, **c** (IC_{50} = 5.57–36.3 and >150 μg/ml) and compound **3i** was inactive, while compounds **3d**, **b**, **h**, **a**, **j** (IC_{50} = 1.41–5.57 μg/ml) exhibited good antitumor activities against HepG-2 as compared to Colchicine (IC_{50} = 10.6 μg/ml) and the other compounds **3f**, **e**, **g**, **c** (IC_{50} = 11.5–36.3 and >150 μg/ml) and compound **3i** was inactive with decreasing of partition coefficient as shown in Table 1, suggesting that the dichloro atoms at 2,3-position, 3,4-position and the monochloro atom at 3-position have the more variable influence on the cytotoxic activity against HepG-2 than the another groups. Replacement of the 6-H for compound **3** with 6-Cl resulted in improvement of potency for the compound **5**. Compounds **5b**, **e**, **i**, **d**, **h**, **a** exhibited good activities (IC_{50} = 0.7–4.62 μg/ml) and the other compounds **5j**, **f**, **c**, **g** exhibited moderate to lower activities (IC_{50} = 8.97–44.5 μg/ml) against HepG-2 as compared to Vinblastine (IC_{50} = 4.6 μg/ml), while compounds **5b**, **e**, **i**, **d**, **h**, **a**, **j** exhibited good activity (IC_{50} = 0.7–8.97 μg/ml) against HepG-2 as compared to Colchicine (IC_{50} = 10.6 μg/ml) with increasing of partition coefficient as shown in Table 1, suggesting that the monochloro/bromo atom at 3-position or 4-position, the dichloro atoms at 2,4-position, 2,3-position have the more variable influence on the cytotoxic activity against HepG-2 than the another groups. In addition, replacement of the 9-H for compound **3** with 9-Me resulted in improvement of antitumor activities of compound **7**. Compounds **7c**, **h**, **b** exhibited good activities (IC_{50} = 1.5–3.01 μg/ml) against HepG-2 as compared to Vinblastine (IC_{50} = 4.6 μg/ml), while compounds **7d**, **i**, **j**, **f**, **a**, **e** exhibited near or moderate to lower activities (IC_{50} = 5.39–23.9 and >50 μg/ml) and compounds **7c**, **h**, **b**, **d**, **i**, **j**, **f** (IC_{50} = 1.5-10.5 μg/ml) showed good activities against HepG-2 as compared to Colchicine (IC_{50} = 10.6 μg/ml) and the other compounds **7a**, **e**, **g** with increasing of partition coefficient as shown in Table 1, suggesting that the monochloro atom at 4-position or 3-position and the dichloro atoms at 3,4-position have the more variable influence on the cytotoxic activity against HepG-2 than the another groups.

Finally, compounds **3b**, **h** (IC_{50} = 1.23 and 2.05 μg/ml) showed a significant antitumor activities against lung carcinoma (A549) as compared to Vinblastine (IC_{50} = 3.79 μg/ml) and the other compounds **3a**, **j**, **f**, **e**, **c**, **g**, **d**, **i** (IC_{50} = 4.07–38 and >50 μg/ml), while compounds **3b**, **h**, **a**, **j**, **f**, **e**, **c** (IC_{50} = 1.23–21.1 μg/ml) exhibited good activities as compared to Colchicine (IC_{50} = 21.3 μg/ml) and the other compounds **3g**, **d**, **i** (IC_{50} = 33.6, 38 and >50 μg/ml) with increasing of partition coefficient as shown in Table 1. This is due to the presence of the monochloro atom at 3-position and the dichloro atoms at 3,4-position which have the more variable influence on the cytotoxic activity against A549 than the another groups. Replacement of the 6-H for compound **3** with 6-Cl resulted in improvement of potency for the compound **5**. Compounds **5e**, **j**, **b**, **i** exhibited good activities (IC_{50} = 1.79–3.1 μg/ml) and the other compounds **5a**, **f**, **h**, **d**, **c**, **g** exhibited moderate to lower activities (IC_{50} = 5.66–24.3 μg/ml) against A549 as compared to Vinblastine (IC_{50} = 3.79 μg/ml), while compounds **5e**, **j**, **b**, **i**, **a**, **f**, **h**, **d** (IC_{50} = 1.79–15.6 μg/ml) showed good activities against A549 as compared to Colchicine (IC_{50} = 21.3 μg/ml) and the other compounds **5c**, **g** (IC_{50} = 22.1 and 24.3 μg/ml) with increasing of partition coefficient as shown in Table 1, suggesting that the dichloro atoms at 2,4-position and the trisubstituted have the higher influence on the cytotoxic activity against A549 than the another groups. Furthermore, replacement of the 9-H for compound **3** with 9-Me resulted reduction of antitumor activities of compound **7**. All the compound **7** exhibited lower activities (IC_{50} = 13.7–36.7 and >50 μg/ml) against A549 as compared to Vinblastine (IC_{50} = 3.79 μg/ml), while compound **7h** showed good activity against A549 as compared to Colchicine (IC_{50} = 21.3 μg/ml) and the other compounds **7j**, **f**, **b**, **a**, **d**, **e**, **i**, **c**, **g** (IC_{50} = 22.2–36.7 and >50 μg/ml) with increasing of partition coefficient as shown in Table 1, suggesting that the dichloro atoms at 3,4-position is preferred over than the another groups.

Conclusions

In conclusion, halogenated 4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives **3a–j**, **5a–j**, and **7a–j** was synthesized. Structures of the synthesized compounds were elucidated on the basis of IR, ^{1}H NMR, ^{13}C NMR, and MS data. Among the newly synthesized compounds **3d**, **b**, **h**, **a**, **5b**, **i**, **e**, **d**, **7h**, **d**, **a**, **j**, **b**, **f** and **3d**, **b**, **h**, **a**, **j**, **f**, **5b**, **i**, **e**, **d**, **f**, **h**, **j**, **a**, **c**, **7h**, **d**, **a**, **j**, **b**, **f** showed highest inhibition against MCF-7 as compared to Vinblastine and Colchicine respectively, while compounds **3d**, **b**, **5e**, **b**, **j** and **3d**, **b**, **h**, **a**, **j**, **f**, **c**, **e**, **g**, **5e**, **b**, **j**, **i**, **a**, **d**, **c**, **f**, **h**, **g**, **7c**, **b**, **i**, **h**, **j**, **a**, **f**, **d** exhibited the best growth inhibitory activity against HCT-116 as compared to the standard drugs Vinblastine and Colchicine respectively, and compounds **3d**, **b**, **h**, **5b**, **e**, **i**, **d**, **h**, **a**, **7c**, **h**, **b** and **3d**, **b**, **h**, **a**, **j**, **5b**, **e**, **i**, **d**, **h**, **a**, **j**, **7c**, **h**, **b**, **d**, **i**, **j**, **f** exhibited the best growth inhibitory activity against HepG-2 as compared to Vinblastine and Colchicine, respectively, while compounds **3b**, **h**, **5e**, **j**, **b**, **i** and **3b**, **h**, **a**, **j**, **f**, **e**, **c**, **5e**, **j**, **b**, **i**, **a**, **f**, **h**, **d**, **7h** showed highest inhibition against A549 as compared to Vinblastine and Colchicine, respectively. On the basis of SAR, lipophilicity and the partition coefficient (Log *P*) are beneficial for antitumor activity. The highest inhibition activity of the halogenated 4*H*-pyrano[3,2-*h*]quinoline derivatives **3a–j**, **5a–j** and **7a–j** is in the following order:

6-Cl analogs **5a–j** > unsubstituted analogs **3a–j** >9-Me analogs **7a–j**

Further investigations are essential to gain deeper insight into structure–activity aspects and to predict the optimal structural parameters, which could be beneficial in development of antitumor therapeutics.

Experimental

All chemicals were purchased from Sigma-Aldrich Chemical Co. Melting points were determined with a Stuart Scientific Co. Ltd apparatus and are uncorrected. IR spectra were determined as KBr pellets on a Jasco FT/IR 460 plus spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a BRUKER AV 500/600 MHz spectrometer. ^{13}C NMR spectra were obtained using APT, with this technique, the signals of CH and CH_3 carbon atoms appears normal (up) and the signal of CH_2 and Cq environments appears negative (down). The MS were measured on a Shimadzu GC/MS-QP5 spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 microanalyser. Analytical thin layer chromatography (TLC) on silica gel-precoated F254 Merck plates to check the purity of the compounds.

General procedure for the synthesis of 2-amino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (**3a–j**), 2-amino-4-aryl-6-chloro-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (**5a–j**) and 2-amino-4-aryl-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile derivatives (**7a–j**).

A solution of 8-hydroxyquinoline 1, 5-chloro-8-hydroxyquinoline 4, or 8-hydroxy-2-methyl-quinoline 6 (0.01 mol) in EtOH (30 mL) was treated with α-cyanomono, di or trisubstituted cinnamonitriles **2a–j** (0.01 mol) and piperidine (0.5 mL). The reaction mixture was heated under reflux with stirring for 1 h. The solid product formed was collected by filtration and recrystallized from a suitable solvent to give **3a–j**, **5a–j**, and **7a–j**. The physical and spectral data of compounds **3a–j**, **5a–j**, and **7a–j** are as follows:

2-amino-4-(2-chlorophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (3a)

Yellow crystals from ethanol; yield 87 %; m.p. 289–290 °C; IR (KBr, υ_{max} cm^{-1}): 3478, 3323, 3195 (NH_2), 2196 (CN), 1658 (C=N) ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.96–7.06 (m, 9H, aromatic), 7.29 (bs, 2H, NH_2), 5.44 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.50 (C-2), 150.27 (C-9), 143.27 (C-10b), 137.35 (C-10a), 136.24 (C-7), 128.92 (C-5), 127.93 (C-6a), 124.34 (C-4a), 123.88 (C-8), 122.88 (C-6), 120.51 (CN), 54.63 (C-3), 38.48 (C-4), 142.05, 132.10, 129.83, 128.09, 127.83, 126.09 (aromatic), MS *m/z* (%): 335 (M^++2, 5.51), 333 (M^+,17.23) with a base peak at 222 (100); anal. calcd. for $C_{19}H_{12}ClN_3O$: C, 68.37; H, 3.62; N, 12.59. Found: C, 68.41; H, 3.64; N, 12.63 %.

2-amino-4-(3-chlorophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (3b)

Yellow crystals from ethanol; yield 88 %; m.p. 240-241 °C; IR (KBr, υ_{max} cm^{-1}): 3407, 3322, 3205 (NH_2), 2196 (CN), 1656 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.20–7.08 (m, 9H, aromatic), 7.22 (bs, 2H, NH_2), 4.89 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.41 (C-2), 150.28 (C-9), 143.04 (C-10b), 136.44 (C-10a), 136.00 (C-7), 128.26 (C-5), 127.80 (C-6a), 124.28 (C-4a), 123.75 (C-8), 122.23 (C-6), 120.25 (CN), 55.41 (C-3), 40.80 (C-4), 148.02, 134.82, 130.84, 130.17, 127.06, 126.71 (aromatic), MS *m/z* (%): 335 (M^++2, 2.95), 333 (M^+,8.32) with a base peak at 222 (100); anal. calcd. for $C_{19}H_{12}ClN_3O$: C, 68.37; H, 3.62; N, 12.59. Found: C, 68.40; H, 3.64; N, 12.61 %.

2-amino-4-(4-chlorophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (3c)

Prepared as previously described (El-Agrody and Al-Ghamdi 2011).

2-amino-4-(2,3-dichlorophenyl)-4*H*-pyrano[3,2-*h*] quinoline-3-carbonitrile (3d)

Yellow crystals from benzene; yield 87 %; m.p. 281–283 °C; IR (KBr, υ_{max} cm^{-1}): 3466, 3349, 3188 (NH_2), 2186 (CN), 1646 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.97–7.08 (m, 8H, aromatic), 7.32 (bs, 2H, NH_2), 5.56 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.54 (C-2), 150.35 (C-9), 143.36 (C-10b), 137.33 (C-10a), 136.29 (C-7), 129.17 (C-5), 128.75 (C-6a), 124.42 (C-4a), 123.87 (C-8), 122.90 (C-6), 119.99 (CN), 54.27 (C-3), 39.99 (C-4), 150.09, 133.95, 130.20, 129.51, 127.96, 125.99 (aromatic), MS *m/z* (%): 371 (M^++4, 2.15), 369 (M^++2, 12.05), 366 (M^+,18.29) with a base peak at 222 (100); anal. calcd. for $C_{19}H_{11}Cl_2N_3O$: C, 61.98; H, 3.01; N, 11.41. Found: C, 61.94; H, 2.98; N, 11.38 %.

2-amino-4-(2,4-dichlorophenyl)-4*H*-pyrano[3,2-*h*] quinoline-3-carbonitrile (3e)

Yellow crystals from ethanol; yield 86 %; m.p. 238–240 °C; IR (KBr, υ_{max} cm^{-1}): 3472, 3322, 3210 (NH_2), 2192 (CN), 1657 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.94–7.02 (m, 8H, aromatic), 7.32 (bs, 2H, NH_2), 5.42 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.50 (C-2), 150.13 (C-9), 143.32 (C-10b), 137.32 (C-10a), 136.05 (C-7), 128.52 (C-5), 128.11 (C-6a), 125.93 (C-4a), 123.79 (C-8), 122.83 (C-6), 119.93 (CN), 54.23 (C-3), 38.12 (C-4), 149.99, 135.95, 132.97, 131.82, 130.65, 127.75 (aromatic). In ^{13}CNMR-APT spectrum CH, CH_3 [positive (up)], CH_2, Cq [negative (down)], revealed the following signals at δ: 160.50 (C-2 ↓), 150.13 (C-9 ↑), 149.99 (aromatic ↓), 143.32 (C-10b ↓), 137.32 (C-10a ↓), 136.05 (C-7 ↑), 135.95 (aromatic ↓), 132.97 (aromatic ↑), 131.82 (aromatic ↑), 130.65 (aromatic ↑), 128.52 (C-5 ↑), 128.11 (C-6a ↓), 127.75 (aromatic ↓), 125.93 (C-4a ↓), 123.79 (C-8 ↑), 122.83 (C-6 ↑), 119.93 (CN ↓), 54.23 (C-3 ↓), 38.12 (C-4 ↑); MS *m/z* (%): 371 (M^++4, 1.28), 369 (M^++2, 7.59), 367 (M^+,11.82) with a base peak at 222 (100); anal. calcd. for $C_{19}H_{11}Cl_2N_3O$: C, 61.98; H, 3.01; N, 11.41. Found: C, 62.00; H, 3.05; N, 11.45 %.

2-amino-4-(2,5-dichlorophenyl)-4*H*-pyrano[3,2-*h*] quinoline-3-carbonitrile (3f)

Yellow crystals from benzene/ethanol; yield 84 %; m.p. 293–294 °C; IR (KBr, υ_{max} cm^{-1}): 3475, 3330, 3188 (NH_2), 2198 (CN), 1656 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.92–7.05 (m, 8H, aromatic), 7.13 (bs, 2H, NH_2), 5.41 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.53 (C-2), 151.15 (C-9), 143.38 (C-10b), 137.39 (C-10a), 136.15 (C-7), 128.72 (C-5), 128.18 (C-6a), 126.03 (C-4a), 123.99 (C-8), 122.91 (C-6), 119.99 (CN), 54.65 (C-3), 38.45 (C-4), 149.78, 131.55, 130.67, 130.12, 129.65, 127.87 (aromatic); MS *m/z* (%): 371 (M^++4, 2.76), 369 (M^++2, 14.64), 367 (M^+,23.66) with a base peak at 222 (100); anal. calcd. for $C_{19}H_{11}Cl_2N_3O$: C, 61.98; H, 3.01; N, 11.41. Found: C, 61.95; H, 3.06; N, 11.46 %.

2-amino-4-(2,6-dichlorophenyl)-4*H*-pyrano[3,2-*h*] quinoline-3-carbonitrile (3g)

Yellow crystals from benzene; yield 84 %; m.p. 295–296 °C; IR (KBr, υ_{max} cm^{-1}): 3471, 3361, 3188 (NH_2), 2196 (CN), 1660 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.96–6.96 (m, 8H, aromatic), 7.26 (bs, 2H, NH_2), 6.03 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.88 (C-2), 150.34 (C-9), 143.95 (C-10b), 137.03 (C-10a), 136.04 (C-7), 128.69 (C-5), 128.00 (C-6a), 123.68 (C-4a), 122.26 (C-8), 119.75 (C-6), 118.21 (CN), 51.87 (C-3), 37.20 (C-4), 137.14, 135.63, 134.87, 130.83, 130.65, 130.08, 125.24 (aromatic); MS *m/z* (%): 371 (M^++4, 4.32), 369 (M^++2, 23.64), 367 (M^+, 34.64) with a base peak at 222 (100); anal. calcd. for $C_{19}H_{11}Cl_2N_3O$: C, 61.98; H, 3.01; N, 11.41. Found: C, 61.92; H, 3.10; N, 11.50 %.

2-amino-4-(3,4-dichlorophenyl)-4*H*-pyrano[3,2-*h*] quinoline-3-carbonitrile (3h)

Yellow crystals from benzene/ethanol; yield 84 %; m.p. 289–290 °C; IR (KBr, υ_{max} cm^{-1}): 3430, 3371, 3196 (NH_2), 2187 (CN), 1666 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.97–7.09 (m, 8H, aromatic), 7.32 (bs, 2H, NH_2), 5.46 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.57 (C-2), 150.36 (C-9), 143.76 (C-10b), 137.29 (C-10a), 136.03 (C-7), 129.02 (C-5), 127.99 (C-6a), 125.98 (C-4a), 123.85 (C-8), 122.35 (C-6), 119.91 (CN), 53.83 (C-3), 38.88 (C-4), 143.40, 132.29, 131.81, 131.09, 130.80, 130.08 (aromatic); MS *m/z* (%): 371 (M^++4, 2.18), 369 (M^++2, 11.75), 367 (M^+, 18.14) with a base peak at 255 (100); anal. calcd. for $C_{19}H_{11}Cl_2N_3O$: C, 61.98; H, 3.01; N, 11.41. Found: C, 62.07; H, 3.09; N, 11.48 %.

2-amino-4-(4-bromophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (3i)

Prepared as previously described (El-Agrody and Al-Ghamdi 2011).

2-amino-4-(3,5-dibromo-2-methoxyphenyl)-4*H*-pyrano [3,2-*h*]quinoline-3-carbonitrile (3j)

Pale yellow crystals from ethanol; yield 81 %; m.p. 224–226 °C; IR (KBr, υ_{max} cm^{-1}): 3435, 3337, 3200 (NH_2), 2190 (CN), 1657 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.97–7.27 (m, 7H, aromatic), 7.35 (bs, 2H, NH_2), 5.13 (s, 1H,

H-4), 3.59 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.23 (C-2), 151.01 (C-9), 142.21 (C-10b), 137.99 (C-10a), 133.91 (C-7), 132.06 (C-5), 127.93 (C-6), 125.13 (C-6a), 124.70 (C-4a), 123.34 (C-8), 117.28 (CN), 61.35 (CH_3), 54.35 (C-3), 36.88 (C-4), 153.32, 140.99, 132.45, 125.35, 120.11,118.56 (aromatic); MS *m/z* (%): 489 (M^++4, 2.33), 487 (M^++2, 4.63), 485 (M^+, 2.37) with a base peak at 222 (100); anal. calcd. for $C_{20}H_{13}Br_2N_3O_2$: C, 49.31; H, 2.69; N, 8.63. Found: C, 49.40; H, 2.71; N, 8.70 %.

2-amino-6-chloro-4-(2-chlorophenyl)-4*H*-pyrano[3,2-*h*] quinoline-3-carbonitrile (5a)

Yellow needles from benzene; yield 84 %; m.p. 298–300 °C; IR (KBr, υ_{max} cm^{-1}): 3479, 3326, 3205 (NH_2), 2198 (CN), 1659 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.06–7.19 (m, 9H, aromatic), 7.30 (bs, 2H, NH_2), 5.44 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.25 (C-2), 151.17 (C-9), 142.88 (C-10b), 138.01 (C-10a), 132.45 (C-7), 130.08 (C-5), 125.22 (C-6), 124.85 (C-6a), 123.41 (C-8), 120.90 (C-4a), 119.75 (CN), 54.45 (C-3), 38.53 (C-4), 141.30, 132.12, 131.40, 129.25, 128.03, 125.66 (aromatic), MS *m/z* (%): 369 (M^++2, 5.1), 367 (M^+,15.01) with a base peak at 256 (100); anal. calcd. for $C_{19}H_{11}Cl_2N_3O$: C, 61.98; H, 3.01; N, 11.41. Found: C, 61.92; H, 3.06; N, 11.49 %.

2-amino-6-chloro-4-(3-chlorophenyl)-4*H*-pyrano[3,2-*h*] quinoline-3-carbonitrile (5b)

Yellow crystals from benzene; yield 85 %; m.p. 273–275 °C; IR (KBr, υ_{max} cm^{-1}): 3441, 3321, 3205 (NH_2), 2201 (CN), 1659 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.06-7.12 (m, 9H, aromatic), 7.34 (bs, 2H, NH_2), 5.03 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.20 (C-2), 151.18 (C-9), 142.52 (C-10b), 138.14 (C-10a), 132.54 (C-7), 127.33 (C-5), 125.22 (C-6), 124.97 (C-6a), 123.44 (C-8), 121.74 (C-4a), 119.97 (CN), 55.23 (C-3), 40.32 (C-4), 147.47, 133.39, 130.90, 127.44, 126.53, 126.34 (aromatic), MS *m/z* (%): 369 (M^++2, 15.3), 367 (M^+, 45.03) with a base peak at 256 (100); anal. calcd. for $C_{19}H_{11}Cl_2N_3O$: C, 61.98; H, 3.01; N, 11.41. Found: C, 62.07; H, 3.23; N, 11.61 %.

2-amino-6-chloro-4-(4-chlorophenyl)-4*H*-pyrano[3,2-*h*] quinoline-3-carbonitrile (5c)

Yellow crystals from benzene; yield 81 %; m.p. 276–278 °C; IR (KBr, υ_{max} cm^{-1}): 3444, 3349, 3188 (NH_2), 2199 (CN), 1657 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.01–7.02 (m, 9H, aromatic), 7.12 (bs, 2H, NH_2), 5.01 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.26 (C-2), 151.23 (C-9), 142.55 (C-10b), 138.66 (C-10a), 132.23(C-7), 127.33 (C-5), 125.89 (C-6), 125.05 (C-6a), 123.49 (C-8), 121.84 (C-4a), 120.07 (CN), 55.28 (C-3), 40.11 (C-4), 140.47, 132.32, 130.50, 129.64, 127.93, 127.31 (aromatic), MS *m/z* (%): 369 (M^++2, 6.87), 367 (M^+, 20.11) with a base peak at 256 (100); anal. calcd. for $C_{19}H_{11}Cl_2N_3O$: C, 61.98; H, 3.01; N, 11.41. Found: C, 61.87; H, 2.94; N, 11.25 %.

2-amino-6-chloro-4-(2,3-dichlorophenyl)-4*H*-pyrano [3,2-*h*]quinoline-3-carbonitrile (5d)

Pale yellow crystals from benzene; yield 81 %; m.p. 298–300 °C; IR (KBr, υ_{max} cm^{-1}): 3479, 3324, 3182 (NH_2), 2195 (CN), 1656 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.55–7.11 (m, 8H, aromatic), 7.38 (bs, 2H, NH_2), 5.56 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.30 (C-2), 151.26 (C-9), 143.79 (C-10b), 137.99 (C-10a), 130.34 (C-7), 128.84 (C-5), 125.37 (C-6), 124.99 (C-6a), 123.54 (C-8), 120.39 (C-4a), 119.65 (CN), 54.08 (C-3), 39.98 (C-4), 143.02, 132.53, 130.20, 129.82, 125.64 (aromatic), MS *m/z* (%): 405 (M^++4, 1.55), 403 (M^++2, 9.12), 401 (M^+, 14.02) with a base peak at 256 (100); anal. calcd. for $C_{19}H_{10}Cl_3N_3O$: C, 56.67; H, 2.50; N, 10.44. Found: C, 56.79; H, 2.70; N, 10.60 %.

2-amino-6-chloro-4-(2,4-dichlorophenyl)-4*H*-pyrano [3,2-*h*]quinoline-3-carbonitrile (5e)

Pale yellow crystals from benzene; yield 80 %; m.p. 277–279 °C; IR (KBr, υ_{max} cm^{-1}): 3471, 3327, 3196 (NH_2), 2193 (CN), 1660 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.06–7.20 (m, 8H, aromatic), 7.36 (bs, 2H, NH_2), 5.44 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.23 (C-2), 151.21 (C-9), 142.95 (C-10b), 137.97 (C-10a), 132.82 (C-7), 128.21 (C-5), 125.62 (C-6), 124.96 (C-6a), 123.48 (C-8), 120.32 (C-4a), 119.64 (CN), 53.99 (C-3), 38.15 (C-4), 140.34, 133.14, 132.90, 132.47, 129.46, 125.31 (aromatic). In ^{13}CNMR-APT spectrum CH, CH_3 [positive (up)], CH_2, Cq [negative (down)], revealed the following signals at δ: 160.23 (C-2 ↓), 151.21 (C-9 ↑), 142.95 (C-10b ↓), 140.34 (aromatic ↓), 137.97 (C-10a ↓), 133.14 (aromatic ↓), 132.90 (aromatic ↓), 132.82 (C-7 ↑), 132.47 (aromatic ↑), 129.46 (aromatic ↑), 128.21 (C-5 ↑), 125.62 (C-6 ↓), 125,31 (aromatic ↑), 124.96 (C-6a ↓), 123.48 (C-8 ↑), 120.32 (C-4a ↓), 119.64 (CN ↓), 53.99 (C-3 ↓), 38.15 (C-4 ↑). MS *m/z* (%): 405 (M^++4, 3.61), 403 (M^++2, 20.48), 401 (M^+, 31.19) with a base peak at 256 (100); anal. calcd. for $C_{19}H_{10}Cl_3N_3O$: C, 56.67; H, 2.50; N, 10.44. Found: C, 56.47; H, 2.33; N, 10.31 %.

2-amino-6-chloro-4-(2,5-dichlorophenyl)-4*H*-pyrano [3,2-*h*]quinoline-3-carbonitrile (5f)

Pale yellow crystals from benzene; yield 82 %; m.p. > 300 °C; IR (KBr, υ_{max} cm^{-1}): 3476, 3347, 3196 (NH_2), 2196 (CN), 1650 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6)

δ: 9.58–7.26 (m, 8H, aromatic), 7.38 (bs, 2H, NH_2), 5.46 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.32 (C-2), 151.22 (C-9), 143.02 (C-10b), 137.95 (C-10a), 132.48 (C-7), 129.31 (C-5), 125.37 (C-6), 124.95 (C-6a), 123.51 (C-8), 119.83 (C-4a), 119.65 (CN), 53.62 (C-3), 38.89 (C-4), 142.94, 132.34, 132.00, 131.19, 131.04, 125.57 (aromatic); MS *m/z* (%): 405 (M^++4, 2.22), 403 (M^++2, 12.26), 401 (M^+, 18.11) with a base peak at 256 (100); anal. calcd. for $C_{19}H_{10}Cl_3N_3O$: C, 56.67; H, 2.50; N, 10.44. Found: C, 56.70; H, 2.63; N, 10.54 %.

2-amino-6-chloro-4-(2,6-dichlorophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (5g)

Colorless needles from benzene; yield 82 %; m.p. > 300 °C; IR (KBr, υ_{max} cm^{-1}): 3475, 3325, 3188 (NH_2), 2199 (CN), 1661 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.07–7.05 (m, 8H, aromatic), 7.42 (bs, 2H, NH_2), 6.03 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.59 (C-2), 151.30 (C-9), 143.55 (C-10b), 137.71 (C-10a), 132.53 (C-7), 130.37 (C-5), 125.37 (C-6), 124.73 (C-6a), 123.49 (C-8), 119.38 (C-4a), 118.91 (CN), 51.95 (C-3), 37.04 (C-4), 136.56, 135.54, 134.96, 130.90, 128.85, 124.86 (aromatic); MS *m/z* (%): 405 (M^++4, 2.06), 403 (M^++2, 11.77), 401 (M^+, 18.14) with a base peak at 256 (100); anal. calcd. for $C_{19}H_{10}Cl_3N_3O$: C, 56.67; H, 2.50; N, 10.44. Found: C, 56.80; H, 2.63; N, 10.60 %.

2-amino-6-chloro-4-(3,4-dichlorophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (5h)

Pale yellow needles from benzene; yield 82 %; m.p. 257–259 °C; IR (KBr, υ_{max} cm^{-1}): 3470, 3321, 3199 (NH_2), 2199 (CN), 1658 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.04–7.27 (m, 8H, aromatic), 7.39 (bs, 2H, NH_2), 5.06 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.18 (C-2), 151.11 (C-9), 145.97 (C-10b), 138.13 (C-10a), 132.44 (C-7), 128.21 (C-5), 125.25 (C-6), 125.04 (C-6a), 123.40 (C-8), 121.22 (C-4a), 119.89 (CN), 54.94 (C-3), 38.97 (C-4), 142.56, 131.34, 131.18, 129.99, 129.65, 126.23 (aromatic); MS *m/z* (%): 405 (M^++4, 1.52), 403 (M^++2, 8.89), 401 (M^+, 13.37) with a base peak at 256 (100); anal. calcd. for $C_{19}H_{10}Cl_3N_3O$: C, 56.67; H, 2.50; N, 10.44. Found: C, 56.57; H, 2.38; N, 10.27 %.

2-amino-6-chloro-4-(4-bromophenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (5i)

Yellow crystals from ethanol; yield 86 %; m.p. 228-230 °C; IR (KBr, υ_{max} cm^{-1}): 3445, 3330, 3182 (NH_2), 2192 (CN), 1658 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.95–7.18 (m, 9H, aromatic), 7.25 (bs, 2H, NH_2), 5.00 (s, 1H, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.30 (C-2), 150.25 (C-9), 144.95 (C-10b), 137.47 (C-10a), 135.98 (C-7), 127.77 (C-5), 126.67 (C-6), 123.68 (C-6a), 122.20 (C-8), 121.30 (C-4a), 117.68 (CN), 55.59 (C-3), 40.50 (C-4), 143.03, 131.63, 129.94, 127.45, 121.78 (aromatic), MS *m/z* (%): 380 (M^+–Cl+4, 2.08), 378 (M^+–Cl+2, 5.02), 376 (M^+–Cl, 3.37) with a base peak at 222 (100); anal. calcd. for $C_{19}H_{11}BrClN_3O$: C, 55.30; H, 2.69; N, 10.18. Found: C, 55.37; H, 2.73; N, 10.23 %.

2-amino-6-chloro-4-(3,5-dibromo-2-methoxyphenyl)-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (5j)

Pale yellow Crystals from ethanol; yield 81 %; m.p. 223-225 °C; IR (KBr, υ_{max} cm^{-1}): 3432, 3337, 3182 (NH_2), 2192 (CN), 1657 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.07–7.29 (m, 7H, aromatic), 7.39 (bs, 2H, NH_2), 5.25 (s, 1H, H-4), 3.69 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.43 (C-2), 151.21 (C-9), 142.78 (C-10b), 138.06 (C-10a), 134.91 (C-7), 132.30 (C-5), 125.25 (C-6a), 124.90 (C-4a), 123.43 (C-8), 120.93 (C-6), 117.00 (CN), 61.32 (CH_3), 54.19 (C-3), 36.78 (C-4), 154.34, 141.49, 132.50, 125.86, 120.00, 118.29 (aromatic); MS *m/z* (%): 490 (M^+–Cl+6, 0.85), 488 (M^+–Cl+4, 3.53), 486 (M^+–Cl +2, 4.41), 484 (M^+–Cl, 2.19) with a base peak at 222 (100); anal. calcd. for $C_{20}H_{12}Br_2\ ClN_3O_2$: C, 46.05; H, 2.32; 6.80; N, 8.06. Found: C, 46.16; H, 2.41; N, 8.13 %.

2-amino-4-(2-chlorophenyl)-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (7a)

Yellow crystals from ethanol; yield 88 %; m.p. 238–239 °C; IR (KBr, υ_{max} cm^{-1}): 3470, 3366, 3196 (NH_2), 2195 (CN), 1659 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.46–6.82 (m, 8H, aromatic), 7.16 (bs, 2H, NH_2), 5.43 (s, 1H, H-4), 2.72 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.54 (C-2), 159.11 (C-9), 142.86 (C-10b), 136.91 (C-10a), 136.30 (C-7), 128.90 (C-5), 125.21 (C-6a), 123.84 (C-8), 122.93 (C-4a), 120.52 (C-6), 120.07 (CN), 54.73 (C-3), 38.56 (C-4), 24.84 (CH_3) 142.16, 136.08, 131.97, 130.42, 129.84, 126.20 (aromatic), MS *m/z* (%): 349 (M^++2, 1.56), 347 (M^+,4.63) with a base peak at 236 (100); anal. calcd. for $C_{20}H_{14}ClN_3O$: C, 69.07; H, 4.06; N, 12.08. Found: C, 69.11; H, 4.14; N, 12.13 %.

2-amino-4-(3-chlorophenyl)-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (7b)

Yellow crystals from ethanol; yield 87 %; m.p. 236–238 °C; IR (KBr, υ_{max} cm^{-1}): 3464, 3346, 3200 (NH_2), 2188 (CN), 1655 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.19–7.09 (m, 8H, aromatic), 7.17 (bs, 2H, NH_2), 4.97 (s, 1H, H-4), 2.69 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.41 (C-2), 159.12 (C-9), 149.51 (C-10b), 137.09

(C-10a), 135.18 (C-7), 128.92 (C-5), 125.79 (C-6a), 122.50 (C-4a), 123.54 (C-8), 121.45 (C-6), 120.38 (CN), 55.84 (C-3), 40.54 (C-4), 144.76, 136.05, 129.58, 131.78, 128.60, 126.17 (aromatic), MS *m/z* (%): 349 (M^++2, 4.35), 347 (M^+, 13.27) with a base peak at 236 (100); anal. calcd. for $C_{20}H_{14}ClN_3O$: C, 69.07; H, 4.06; N, 12.08. Found: C, 69.14; H, 4.16; N, 12.15 %.

2-amino-4-(4-chlorophenyl)-9-methyl-4*H*-pyrano[3,2-*h*] quinoline-3-carbonitrile (7c)

Prepared as previously described (El-Agrody and Al-Ghamdi, 2011).

2-amino-4-(2,3-dichlorophenyl)-9-methyl-4*H*-pyrano [3,2-*h*]quinoline-3-carbonitrile (7d)

Yellow crystals from benzene; yield 87 %; m.p. 240–241 °C; IR (KBr, υ_{max} cm^{-1}): 3458, 3323, 3196 (NH_2), 2193 (CN), 1656 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.22–7.00 (m, 7H, aromatic), 7.23 (bs, 2H, NH_2), 5.53 (s, 1H, H-4), 2.71 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.59 (C-2), 159.17 (C-9), 144.69 (C-10b), 136.89 (C-10a), 136.10 (C-7), 128.72 (C-5), 126.32 (C-6a), 123.66 (C-8), 123.01 (C-4a), 119.98 (C-6), 119.95 (CN), 54.38 (C-3), 40.08 (C-4), 24.97 (CH_3), 142.94, 136.31, 132.32, 130.16, 129.47, 124.96 (aromatic); MS *m/z* (%): 385 (M^++4, 1.21), 383 (M^++2, 8.81), 381 (M^+, 12.44) with a base peak at 236 (100); anal. calcd. for $C_{20}H_{13}Cl_2N_3O$: C, 62.84; H, 3.43; N, 10.99. Found: C, 62.75; H, 3.56; N, 11.06 %.

2-amino-4-(2,4-dichlorophenyl)-9-methyl-4*H*-pyrano [3,2-*h*]quinoline-3-carbonitrile (7e)

Yellow crystals from ethanol; yield 86 %; m.p. 249–250 °C; IR (KBr, υ_{max} cm^{-1}): 3475, 3328, 3196 (NH_2), 2193 (CN), 1660 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.44–7.02 (m, 7H, aromatic), 7.35 (bs, 2H, NH_2), 5.44 (s, 1H, H-4), 2.73 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.52 (C-2), 159.18 (C-9), 144.13 (C-10b), 137.55 (C-10a), 136.34 (C-7), 128.52 (C-5), 126.11 (C-6a), 123.79 (C-8), 123.93 (C-4a), 122.89 (C-6), 120.03 (CN), 54.29 (C-3), 38.19 (C-4), 23.73 (CH_3), 149.91, 134.75, 132.97, 131.66, 130.61, 127.45 (aromatic); MS *m/z* (%): 385 (M^++4, 1.27), 383 (M^++2, 7.74), 381 (M^+, 12.2) with a base peak at 236 (100); anal. calcd. for $C_{20}H_{13}Cl_2N_3O$: C, 62.84; H, 3.43; N, 10.99. Found: C, 62.88; H, 3.50; N, 11.05 %.

2-amino-4-(2,5-dichlorophenyl)-9-methyl-4*H*-pyrano [3,2-*h*]quinoline-3-carbonitrile (7f)

Yellow crystals from benzene/ethanol; yield 84 %; m.p. 266–268 °C; IR (KBr, υ_{max} cm^{-1}): 3471, 3356, 3179 (NH_2), 2194 (CN), 1656 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.23–7.01 (m, 7H, aromatic), 7.23 (bs, 2H, NH_2), 5.44 (s, 1H, H-4), 2.71 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.63 (C-2), 159.01 (C-9), 143.92 (C-10b), 136.85 (C-10a), 136.08 (C-7), 126.33 (C-5), 124.93 (C-6a), 123.64 (C-8), 123.01 (C-4a), 119.92 (C-6), 119.50 (CN), 55.85 (C-3), 40.14 (C-4), 24.95 (CH_3), 142.96, 132.27, 131.77, 131.01, 130.72, 128.95 (aromatic); MS *m/z* (%): 385 (M^++4, 3.61), 383 (M^++2, 20.48), 381 (M^+, 31.19) with a base peak at 236 (100); anal. calcd. for $C_{20}H_{13}Cl_2N_3O$: C, 62.84; H, 3.43; N, 10.99. Found: C, 62.79; H, 3.39; N, 10.71 %.

2-amino-4-(2,6-dichlorophenyl)-9-methyl-4*H*-pyrano [3,2-*h*]quinoline-3-carbonitrile (7g)

Yellow crystals from benzene; yield 85 %; m.p. 289–290 °C; IR (KBr, υ_{max} cm^{-1}): 3470, 3375, 3187 (NH_2), 2189(CN), 1660 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.22–6.87 (m, 7H, aromatic), 7.18 (bs, 2H, NH_2), 6.01 (s, 1H, H-4), 2.71 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.93 (C-2), 159.13 (C-9), 143.54 (C-10b), 136.59 (C-10a), 135.64 (C-7), 126.36 (C-6a), 124.21 (C-5), 123.46 (C-8), 122.95 (C-4a), 119.75 (C-6), 118.18 (CN), 52.02 (C-3), 37.24 (C-4), 24.97 (CH_3), 137.27, 136.10, 134.83, 130.81, 130.01, 128.65 (aromatic). In ^{13}CNMR-APT spectrum CH, CH_3 [positive (up)], CH_2, Cq [negative (down)], revealed the following signals at δ: 160.93 (C-2 ↓), 159.13 (C-9 ↓), 143.54 (C-10b ↓), 137.27 (aromatic ↓), 136.59 (C-10a ↓), 136.10 (aromatic ↓), 135.64 (C-7 ↑), 134.83 (aromatic ↓), 130.81 (aromatic ↑), 130.01(aromatic ↑), 128.65 (aromatic ↑), 126.36 (C-6a ↓), 124.21 (C-5 ↑), 123.46 (C-8 ↑), 122.95 (C-4a ↓), 119.75 (C-6 ↑), 118.18 (CN ↓), 52.02 (C-3 ↓), 37.24 (C-4 ↑), 24.97 (CH_3 ↑). MS *m/z* (%): 385 (M^++4, 2.06), 383 (M^++2, 11.77), 381 (M^+, 18.14) with a base peak at 236 (100); anal. calcd. for $C_{20}H_{13}Cl_2N_3O$: C, 62.84; H, 3.43; N, 10.99. Found: C, 62.88; H, 3.50; N, 11.05 %.

2-amino-4-(3,4-dichlorophenyl)-9-methyl-4*H*-pyrano [3,2-*h*]quinoline-3-carbonitrile (7h)

Yellow crystals from benzene/ethanol; yield 83 %; m.p. 268–270 °C; IR (KBr, υ_{max} cm^{-1}): 3479, 3336, 3196 (NH_2), 2190 (CN), 1664 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.96–7.06 (m, 7H, aromatic), 7.30 (bs, 2H, NH_2), 5.42 (s, 1H, H-4), 2.73 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.51 (C-2), 151.36 (C-9), 143.45 (C-10b), 137.56 (C-10a), 136.23 (C-7), 129.42 (C-5), 128.09 (C-6a), 126.08 (C-4a), 123.95 (C-8), 122.77 (C-6), 120.11 (CN), 53.88 (C-3), 38.92 (C-4), 24.71 (CH_3), 141.40, 132.39, 131.83, 131.19, 130.80, 129.03 (aromatic). MS *m/z* (%): 385 (M^++4, 0.88), 383 (M^++2, 4.93), 381 (M^+, 7.91) with a base

peak at 236 (100); anal. calcd. for $C_{20}H_{13}Cl_2N_3O$: C, 62.84; H, 3.43; N, 10.99. Found: C, 62.85; H, 3.47; N, 11.03 %.

2-amino-4-(4-bromophenyl)-9-methyl-4*H*-pyrano[3,2-*h*] quinoline-3-carbonitrile (7i)

Prepared as previously described (El-Agrody and Al-Ghamdi 2011).

2-amino-4-(3,5-dibromo-2-methoxyphenyl)-9-methyl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitrile (7j)

Pale yellow crystals from ethanol; yield 81 %; m.p. 224–226 °C; IR (KBr, υ_{max} cm^{-1}): 3431, 3333, 3201 (NH_2), 2191 (CN), 1659 (C=N); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.20–7.03 (m, 6H, aromatic), 7.23 (bs, 2H, NH_2), 5.25 (s, 1H, H-4), 3.70 (s, 3H, OCH_3), 2.70 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 160.69 (C-2), 159.16 (C-9), 142.75 (C-10b), 142.44 (C-10a), 136.96 (C-7), 132.18 (C-5), 126.22 (C-6a), 123.61 (C-8), 122.95 (C-4a), 120.49 (C-6), 120.27 (CN), 61.36 (Me), 54.59 (C-3), 36.68 (C-4), 24.96 (CH_3), 154.14, 136.09, 134.48, 118.26, 117.01 (aromatic); MS *m/z* (%): 503 (M^++4, 1.65), 501 (M^++2, 3.05), 499 (M^+, 1.65) with a base peak at 236 (100); anal. calcd. for $C_{21}H_{15}Br_2N_3O_2$: C, 50.33; H, 3.02; N, 8.38. Found: C, 50.40; H, 3.10; N, 8.50 %.

Antitumor screening

Cell culture and cytotoxicity evaluation using viability assay

Compounds **3a–j**, **5a–j**, and **7a–j** were initially evaluated for in vitro antitumor activity against three different human cell lines: MCF-7, HCT-116, HepG-2, and A549 in comparison with Vinblastine and Colchicine. The measurements of cell growth and the viabilities and in vitro cytotoxicity evaluation using viability assay were determined as described in the literature (Rahman et al. 2001) and the result was cited in Table 1.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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