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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of novel building blocks of 1*H*-pyrrolo[3,4-*b*] quinolin-3(2*H*)-one and evaluation of their antitumor activity

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Abstract A series of new building blocks consisting of 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one with potential as selective antitumor agents is described. Compounds were synthesized by using Heck reaction of *N*-allyl-1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one with *p*-bromophenyl acetic acid followed by formation of amide (**1a–h**, **2a–d**) by reaction with several secondary amines in good yields. The cytotoxicity of these compounds was evaluated against human cancer cell lines in vitro (SK–N–NH, A549). Studies suggest that most of these compounds were effective in inhibiting neuroblastoma cell growth, compound **1d** was the most potent one (% IC_{50} = 8.62 μM).

Keywords 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one · Synthesis · Antitumor activity · Neuroblastoma (SK–N–SH) cell line · Lung carcinoma A549 cell line

Introduction

The drug discovery has played an important role in the development novel and safer anticancer agents that have a broader spectrum of cytotoxicity to tumor cells. Therefore, new therapeutic targets have been reported that the antitumor efficacy of chemotherapeutic agents correlated with their growth-inhibiting, differentiation-inducing or apoptosis-inducing abilities (Viale *et al.*, 2004). In recent years, interest in the development of new anticancer drugs increased mainly from emerging resistance against drugs. Several anticancer targets have been investigated for the development of structurally new drugs, which were found to have limitations related to their side effects and development of acquired drug resistance. However, the knowledge of tumor biology has exploded during the past decades and this may pave the way for more active, targeted anticancer drugs, some of which are in clinical trials and in the market (Bradury, 2007). The developments of potential drugs have efficiently improved therapeutic index and tumor growth inhibition. The aim of most cancer chemotherapeutic drugs currently in clinical use is to kill malignant tumor cells by inhibiting some of the mechanisms implied in cellular division. Early approaches to selectively inhibit tumor growth were generally disappointing in clinical studies. The investigation of tumor growth inhibitors is a major obstacle in the medical field (Wu *et al.*, 2006).

The pyrroloquinoline, quinazolinone nucleus containing natural products represent the medicinally and pharmaceutically important class of compounds (Bonola *et al.*, 1968; Okumura *et al.*, 1968) because of inotropic, lusitropic properties (Freyne and Raeymaekers, 1997) and their diverse range of biological activities such as anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive agents (Chan *et al.*, 1997; Dempcy and Skibo, 1991). In past decades, 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one embedded numerous natural products have been identified (Michael, 2000–2005), such as cytotoxic alkaloids Luotonin A, Camptothecin (CPT), Aromathecin, Rosettacin, 22-Hydroxyacuminatine, Rutaecarpine etc.,

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and whose derivatives are clinically proven anticancer agents (Ma *et al.*, 1997; Wall *et al.*, 1966; Takimoto *et al.*, 1998; O'Leary and Muggia, 1998; Saltz *et al.*, 2000; Ozols, 2000; Rustum *et al.*, 2001; Ulukan and Swaan, 2002; Garcia-Carbenero and Supko, 2002). In addition, some therapeutic agents have been in the market and some are in clinical trials for the treatment of cancer.

A literature survey revealed that modification on pyrroloquinoline pharmacophore may result increase in its biological potencies (Bonola *et al.*, 1968; Okumura *et al.*, 1968; Freyne and Raeymaekers, 1997; Chan *et al.*, 1997; Dempcy and Skibo, 1991). We have introduced prop-1-enyl phenyl acetamides on 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one, which might be a potential tumor growth inhibitor. We have identified several classes of molecules as novel tumor growth inhibitors (Nagarapu *et al.*, 2008a, b, 2010, 2011a, b). In, an on-going program to discover and develop potential new anticancer agents, we discovered a series of novel 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one derivatives (Fig. 1) with combined antitumor efficacy/cytotoxicity against different cancer cell lines in vitro.

Materials and methods

Chemistry

General

All commercial reagents and solvents were used as received without further purification unless specified and reaction solvents were distilled before use. The reactions were monitored and Rf value were determined using analytical thin layer chromatography (TLC) with Merck Silica gel 60 and F_{254} precoated plates (0.25 mm thickness). Spot on the TLC plates were visualized using ultraviolet light (254 nm). Flash column chromatography was performed with Merck silica gel 60 (100–200 mesh). Melting points were determined in capillaries and are uncorrected. ^{1}H NMR spectra were recorded on Bruker DRX-300, Varian 400, and Varian-500 NMR spectrometers. ^{13}C NMR spectra's were recorded on Bruker DRX-300. Proton chemical shifts are reported in ppm(δ) relative to internal tetramethylsilane (TMS), δ 0.00 or with the solvent reference relative to TMS employed as the internal standard ($CDCl_3$, δ 7.26 ppm; DMSO-d_6 δ 2.54) and multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR 400 spectrometer; data is reported in wave numbers (cm^{-1}). Mass spectra were recorded on Agilent Technologies 1100 Series (Agilent Chemistation Software). High-resolution mass spectra (HRMS) were obtained by using ESI-QTOF mass spectrometry.

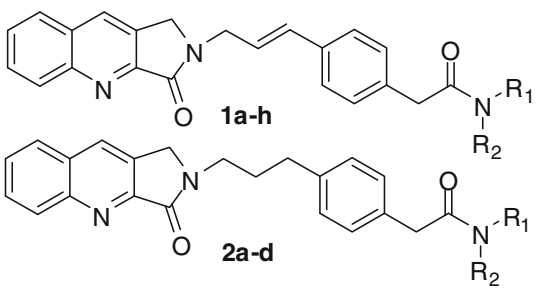


Fig. 1 Novel building blocks of 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one

*Synthesis of 1-(dimethoxymethyl)-2-nitrobenzene (**4**)*

To a solution of *o*-nitrobenzaldehyde (**3**, 10 g, 0.066 mol), methanesulfonic acid (0.2 g, 0.002 mol) in methanol: chloroform (2:1, 150 ml) was added at room temperature. The resulting mixture was refluxed in a Soxhlet apparatus containing 3 Å MS (15 g) for 24 h. After cooling to room temperature, Et_3N (1 ml) was added and the solvents was evaporated under vacuum and the residue obtained was purified by column chromatography over silica gel to afford yellow solid of compound **9.** Yield 98 %, mp 87–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.37 (s, 6H, 2 × CH_3), 5.90 (s, 1H, CH), 7.46 (t, $J = 7.55$ Hz, 1H, Ar–H), 7.57 (t, $J = 7.55$, 1H, Ar–H), 7.77 (t, $J = 6.79$, 7.17 Hz, 2H, Ar–H); EI–MS: $m/z = 197$ [M^+].

*Synthesis of 2-(dimethoxymethyl)aniline (**5**)*

To a solution of compound **4** (10 g, 0.05 mol) in ethanol (100 ml), $Na_2S{\cdot}3H_2O$ (10 g, 0.12 mol) was added and refluxed for 25 min. After cooling to room temperature, Et_3N (1 ml) was added, then solvent was concentrated under *vacuo.* The residue obtained was dissolved in a mixture of Et_2O (100 ml), Et_3N (5 ml) and water (100 ml). The aqueous phase was extracted with ethyl acetate (3 × 100 ml) and the organic phase was washed with water. The combined organic phases was dried over sodium sulfate and evaporated under vacuum to afford yellow oil. Yield 78 %. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.31 (s, 6H, 2 × CH_3), 4.09–4.23 (br, 2H, NH_2), 5.30 (s, 1H, CH), 6.57 (d, $J = 7.63$ Hz, 1H, Ar–H), 6.67 (t, $J = 7.63$ Hz, 1H, Ar–H), 7.06 (t, $J = 7.63$ Hz, 1H, Ar–H), 7.26 (t, $J = 7.63$ Hz, 1H, Ar–H); EI–MS: $m/z = 167$ [M^+].

*Synthesis of N-allyl-1H-pyrrolo[3,4-b]quinolin-3(2H)-one (**7**)*

To a stirred solution of compound **5** (9.5 g, 0.068 mol) and compound **6** (9.5 g, 0.068 mol) in toluene (25 ml),

p-toluenesulfonic acid (0.58 mg, 0.0034 mol) was added at room temperature. The reaction mixture was refluxed using Dean–Stark apparatus until no more water was collected and then solvent from the reaction mixture was evaporated under vacuum. The residue obtained was triturated with diethyl ether and precipitate of compound **11** was filtered out and purified by column chromatography over silica gel to afford brownish solid. Yield 73 %, mp 153–155 °C. IR (KBr, v cm^{-1}): 3028, 2919, 1698, 1572, 1500, 1414, 1239, 1133, 1001, 925, 785, 628. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.30 (d, $J = 6.23$ Hz, 2H, CH_2), 4.44 (s, 2H, CH_2), 5.24–34 (m, 2H, =CH_2), 5.80–5.96 (m, 1H, =CH), 7.52–7.60 (m, 1H, Ar–H), 7.69–7.70 (m, 2H, Ar–H), 8.07 (s, 1H, Ar–H), 8.31 (d, $J = 8.30$ Hz, 1H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.24, 46.52, 118.39, 127.36, 127.44, 127.91, 129.45(2), 129.94, 130.14, 131.78(2), 148.22, 150.64; ESI–MS: $m/z = 225$ $[M + H]^+$.

*Synthesis of (E)-N-(prop-1-enyl)-1H-pyrrolo[3,4-b] quinolin-3(2H)-one (**8**)*

To mixture a compound **7** (700 mg, 3.15 mmol), triphenylphosphine (165 mg, 0.63 mmol), and $PdCl_2$ (26 mg, 0.15 mmol) in 10 ml of DMF/H_2O, 8/2(v/v) was refluxed for 4 h. The reaction mixture was filtered out and pale-gray solid obtained after filtration. The filtrate was diluted with 30 ml of water and extracted with dichloromethane (3 × 30 ml). The combined organic phases were dried over sodium sulfate, evaporated under vacuum. The residue obtained was purified by column chromatography over silica gel to afford brown solid. Yield 91 %, mp 166–168 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.82 (d, $J = 7.93$ Hz, 3H, CH_3), 4.80 (s, 2H, CH_2), 5.41–5.55 (m, 1H, =CH), 7.14 (d, $J = 15.67$ Hz, 1H, =CH), 7.74 (t, $J = 7.17$ Hz, 1H, Ar–H), 7.87 (t, $J = 8.30$ Hz, 1H, Ar–H), 8.14 (d, $J = 7.74$ Hz, 1H, Ar–H), 8.20 (d, $J = 8.30$ Hz, 1H, Ar–H), 8.61 (s, 1H, Ar–H); ESI–MS: $m/z = 225$ $[M + H]^+$.

*Synthesis of 1H-pyrrolo[3,4-b]quinolin-3(2H)-one (**9**)*

A compound **8** (500 mg, 0.72 mmol) was refluxed in 6 N HCl (15 ml) for 2 h. The reaction mixture was then neutralized with K_2CO_3 and extracted with ethyl acetate (3 × 30 ml). The organic phases were washed with water, dried over sodium sulfate and evaporated under vacuum. The residue obtained was purified by flash chromatography over silica gel to afford white solid. Yield 86 %, mp > 270 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.56 (s, 2H, CH_2), 7.65 (t, $J = 7.17$ Hz, 1H, Ar–H), 7.79 (t, $J = 8.05$ Hz, 1H, Ar–H), 7.98 (t, $J = .93$ Hz, 1H, Ar–H), 8.24 (d, $J = 8.49$ Hz, 1H, Ar–H), 8.42 (s, 1H, Ar–H), 9.15 (s, 1H, NH); EI–MS: $m/z = 184$ $[M^+]$.

*Synthesis of Luotonin A (**10**)*

Condensation of compound **9** (200 mg, 0.22 mmol) with isatoic anhydride (36 mg, 0.22 mmol) was subjected to microwave irradiation at 450 watts for 10 min under solvent free condition. The residue obtained was purified by flash chromatography over silica gel to afford white solid **10**. Yield 62 %; mp 249–250 °C. IR (KBr, ν cm^{-1}): 3042, 2945, 2817, 1676, 1610, 1593, 1423, 1106, 1007, 757, 689; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.33 (s, 2H, CH_2), 7.57 (t, $J = 7.45$ Hz, 1H, Ar–H), 7.67 (t, $J = 7.55$ Hz, 1H, Ar–H), 7.84 (t, $J = 7.74$ Hz, 2H, Ar–H), 7.92 (d, $J = 7.93$ Hz, 1H, Ar–H), 8.10 (d, $J = 7.93$ Hz, 1H, Ar–H), 8.38–8.44 (m, 2H, Ar–H), 8.47 (d, $J = 8.68$ Hz, 1H, Ar–H); ESI–MS: $m/z = 286$ $[M + H]^+$.

*Synthesis of (E)-N-{4-[3-(3-oxo-1H-pyrrolo[3,4-b] quinolin-2(3H)-yl)prop-1-enyl]phenyl}acetic acid (**12**)*

To a suspension of compound **7** (5 g, 0.022 mol), 4-bromophenyl acetic acid (**11**, 7.2 g, 0.033 mol), CS_2CO_3 (21 g, 0.066 mol), PPh_3 (864 mg, 3.3 mmol) and $Pd(OAc)_2$ (246 mg, 1.1 mmol) in DMF:H_2O (2:1, 200 ml) was refluxed for 16 h at 120 °C. Then, the solvent was evaporated under vacuum. The residue obtained was extracted with diethyl ether and water. The aqueous solution was acidified with 2 N HCl to adjust the *p*H 2 and then extracted with ethyl acetate (3 × 200 ml). The combined organic phases was washed with water, dried over sodium sulfate and evaporated under vacuum. The residue obtained was purified over column chromatography over silica gel to afford compound **15**. Yield 83 %, mp 192–194 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.55 (s, 2H, CH_2), 4.44 (d, $J = 6.04$ Hz, 2H, CH_2), 4.68 (s, 2H, CH_2), 6.32–6.45 (m, 1H, =CH), 6.66 (d, $J = 16.05$ Hz, 1H, =CH), 7.21 (d, $J = 8.12$ Hz, 2H, Ar–H), 7.42 (d, $J = 8.12$ Hz, 2H, Ar–H), 7.73 (t, $J = 7.45$ Hz, 1H, Ar–H), 7.87 (t, $J = 7.55$ Hz, 1H, Ar–H), 8.12 (d, $J = 8.12$ Hz, 1H, Ar–H), 8.21 (d, $J = 8.49$ Hz, 1H, Ar–H), 8.59 (s, 1H, Ar–H); ESI–MS: $m/z = 358$ $[M + H]^+$.

*Synthesis of N-{4-[3-(3-oxo-1H-pyrrolo[3,4-b] quinolin-2(3H)-yl)propyl] phenyl} acetic acid (**13**)*

To a solution of compound **12** (5 g, 0.014 mol), Pd/C (500 mg, 10 % on wt) in methanol (200 ml) was stirred under H_2 atmosphere at room temperature for 12 h. The reaction was monitored by TLC. The reaction mixture was filtered through Celite bed and the resulting methanol was evaporated under vacuum to afford off white solid compound **13.** Yield 90 %, mp 184–186 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.04 (m, 2H, CH_2), 2.69 (t, $J = 7.55$ Hz, 2H, CH_2), 3.45 (s, 2H, CH_2), 3.75 (t, $J = 7.08$ Hz, 2H, CH_2),

4.61 (s, 2H, CH_2), 7.16 (s, 4H, Ar–H), 7.65 (t, $J = 7.45$ Hz, 1H, Ar–H), 7.79 (t, $J = 7.55$ Hz, 1H, Ar–H), 7.97 (d, $J = 7.93$ Hz, 1H, Ar–H), 8.27 (d, $J = 8.49$ Hz, 1H, Ar–H), 8.36 (s, 1H, Ar–H); ESI–MS: $m/z = 360$ $[M + H]^+$.

*General procedure for the synthesis of 1H-pyrrolo [3,4-b]quinolin-3(2H)-one derivatives (**1a–h, 2a–d**)*

To a solution of compound (**12**, 100 mg, 0.28 mmol), EDC·HCl (53 mg, 0.28 mmol), HOBt (38 mg, 0.28 mmol), DIPEA (72 mg, 0.56 mmol) and phenyl piperazine (45 mg, 0.28 mmol) in CH_2Cl_2 (5 ml) was stirred for overnight and solvents were evaporated under vacuum. The residue obtained was dissolved in water and extracted with ethyl acetate (3 × 25 ml). The organic phases were washed with sat. sodium bicarbonate solution, dried over sodium sulfate and evaporated under vacuum. The residue obtained was purified by column chromatography over silica gel to afford off white solid compound **1a**.

*Synthesis of (E)-N-{3-[4-(2-oxo-2-(4-phenylpiperidin-1-yl) ethyl)phenyl]allyl}-1H-pyrrolo[3,4-b] quinolin-3(2H)-one (**1a**)*

The general synthetic method described above afforded **1a** as off white solid. Yield 81 %, mp 171–173 °C. IR (KBr, ν cm^{-1}): 2954, 2819, 1689, 1639, 1479, 1378, 1236, 1139, 1051, 977, 758; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.97–3.12 (m, 4H, 2 × CH_2), 3.56–3.67 (m, 4H, 2 × CH_2), 3.72 (s, 2H, CH_2), 4.44 (d, $J = 6.04$ Hz, 2H, CH_2), 4.65 (s, 2H, CH_2), 6.26–6.39 (m, 1H, =CH), 6.65 (d, $J = 16.05$ Hz, 1H, =CH), 6.77 (t, $J = 7.23$ Hz, 1H, Ar–H), 6.86 (d, $J = 7.93$ Hz, 2H, Ar–H), 7.12–7.23 (m, 4H, Ar–H), 7.37 (d, $J = 8.30$ Hz, 2H, Ar–H), 7.68 (t, $J = 7.46$ Hz, 1H, Ar–H), 7.82 (t, $J = 7.28$ Hz, 1H, Ar–H), 8.06 (d, $J = 8.12$ Hz, 1H, Ar–H), 8.20 (d, $J = 9.40$ Hz, 1H, Ar–H), 8.51 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 525.2266; found: 525.2252.

*Synthesis of (E)-N-{3-[4-(2-(4-(4-methoxyphenyl) piperidin-1-yl)-2-oxoethyl) phenyl]allyl}-1H-pyrrolo[3,4-b] quinolin-3(2H)-one (**1b**)*

The general synthetic method described above afforded **1b** as off white solid. Yield 72 %, mp 206–209 °C. IR (KBr, ν cm^{-1}): 2964, 2847, 1682, 1637, 1502, 1382, 1288, 1153, 1053, 906, 743; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.84–2.98 (m, 4H, 2 × CH_2), 3.55–3.61 (m, 4H, 2 × CH_2), 3.68 (s, 2H, CH_2), 3.71 (s, 3H, OCH_3), 4.48 (d, $J = 6.43$ Hz, 2H, CH_2), 4.64 (s, 2H, CH_2), 6.25–6.34 (m, 1H, =CH), 6.64 (d, $J = 15.84$ Hz, 1H, =CH), 6.74 (d, $J = 8.97$ Hz, 2H, Ar–H), 6.80 (d, $J = 8.41$ Hz, 2H, Ar–H), 7.19 (d, $J = 7.92$ Hz, 2H, Ar–H), 7.39 (d, $J = 7.92$ Hz, 2H, Ar–H), 7.66 (t, $J = 7.67$ Hz, 1H, Ar–H), 7.79 (t, $J = 7.42$ Hz, 1H, Ar–H), 7.98 (d, $J = 8.41$ Hz, 1H, Ar–H), 8.26 (d, $J = 8.41$ Hz, 1H, Ar–H), 8.39 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 555.2372; found: 555.2357.

*Synthesis of (E)-N-{3-[4-(2-(4-(4-nitrophenyl)piperidin-1-yl)-2-oxoethyl phenyl]allyl}-1H-pyrrolo[3,4-b]quinolin-3(2H)-one (**1c**)*

The general synthetic method described above afforded **1c** as yellow solid. Yield 78 %, mp 157–159 °C. IR (KBr, ν cm^{-1}): 2926, 2851, 1689, 1635, 1522, 1372, 1239, 1026, 946, 787; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.39–3.52 (m, 4H, 2 × CH_2), 3.58–3.69 (m, 4H, 2 × CH_2), 3.77 (s, 2H, CH_2), 4.43 (d, $J = 6.23$ Hz, 2H, CH_2), 4.67 (s, 2H, CH_2), 6.31–6.44 (m, 1H, =CH), 6.65 (d, $J = 15.67$ Hz, 1H, =CH), 6.99 (d, $J = 9.44$ Hz, 2H, Ar–H), 7.21 (d, $J = 8.12$ Hz, 2H, Ar–H), 7.43 (d, $J = 8.12$ Hz, 2H, Ar–H), 7.73 (t, $J = 7.27$ Hz, 1H, Ar–H), 7.87 (t, $J = 7.75$ Hz, 1H, Ar–H), 8.06 (d, $J = 9.44$ Hz, 2H, Ar–H) 8.12 (d, $J = 8.30$ Hz, 1H, Ar–H), 8.21 (d, $J = 8.49$ Hz, 1H, Ar–H); 8.60 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 570.2117; found: 570.2089.

*Synthesis of (E)-N-{3-[4-(2-morpholino-2-oxoethyl) phenyl]allyl}-1H-pyrrolo [3,4-b]quinolin-3(2H)-one (**1d**)*

The general synthetic method described above afforded **1d** as off white solid. Yield 71 %, mp 166–168 °C. IR (KBr, ν cm^{-1}): 2943, 2831, 1693, 1651, 1464, 1254, 1166, 1053, 963, 758; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.41–3.47 (m, 4H, 2 × CH_2), 3.50–3.59 (m, 4H, 2 × CH_2), 3.67 (s, 2H, CH_2), 4.48 (d, $J = 6.42$ Hz, 2H, CH_2), 4.63 (s, 2H, CH_2), 6.21–6.35 (m, 1H, =CH), 6.65 (d, $J = 15.86$ Hz, 1H, =CH), 7.16 (d, $J = 8.30$ Hz, 2H, Ar–H), 7.34 (d, $J = 7.93$ Hz, 2H, Ar–H), 7.65 (t, $J = 7.17$ Hz, 1H, Ar–H), 7.80 (t, $J = 7.25$ Hz, 1H, Ar–H), 7.98 (d, $J = 7.93$ Hz, 1H, Ar–H), 8.27 (d, $J = 8.30$ Hz, 1H, Ar–H), 8.37 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 450.1794; found: 450.1780.

*Synthesis of (E)-N-{3-[4-(2-oxo-2-(pyrrolidin-1-yl) ethyl)phenyl]allyl}-1H-pyrrolo [3,4-b]quinolin-3(2H)-one (**1e**)*

The general synthetic method described above afforded **1e** as brown solid. Yield 68 %, mp 128–130 °C. IR (KBr, ν cm^{-1}): 2953, 2937, 1691, 1630, 1439, 1373, 1278, 1157, 1057, 995, 783; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77–1.86 (m, 2H, CH_2), 1.88–1.97 (m, 2H, CH_2), 3.31–3.38 (m, 2H, CH_2), 3.43–3.50 (m, 2H, CH_2), 3.61 (s, 2H, CH_2), 4.48 (d, $J = 5.86$ Hz, 2H, CH_2), 4.69 (s, 2H, CH_2), 6.32–6.40 (m, 1H, =CH), 6.68 (d, $J = 16.58$ Hz, 1H, =CH), 7.21(d, $J = 7.80$ Hz, 2H, Ar–H), 7.40 (d, $J = 7.80$ Hz, 2H, Ar–H), 7.72 (t, $J = 7.30$ Hz, 1H,

Ar–H), 7.86 (t, $J = 7.80$ Hz, 1H, Ar–H), 8.10 (d, $J = 7.80$ Hz, 1H, Ar–H), 8.24 (d, $J = 7.80$ Hz, 1H, Ar–H), 8.55 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 434.1844; found: 434.1821.

*(E)-N-{3-[4-(2-oxo-2-(piperidin-1-yl)ethyl)phenyl]allyl}-1H-pyrrolo[3,4-b] quinolin-3(2H)-one (**1f**)*

The general synthetic method described above afforded **1f** as off white solid. Yield 70 %, mp 144–147 °C. IR (KBr, ν cm^{-1}): 2931, 2853, 1687, 1628, 1383, 1166, 1129, 1021, 970, 768; ^1H NMR (400 MHz, DMSO-d_6): δ 1.23–1.44 (m, 4H, 2 × CH_2), 1.45–1.69 (m, 4H, 2 × CH_2), 2.97–3.08 (m, 2H, CH_2), 3.66 (s, 2H, CH_2), 4.43 (d, $J = 5.85$ Hz, 2H, CH_2), 4.68 (s, 2H, CH_2), 6.32–6.44 (m, 1H, =CH), 6.65 (d, $J = 15.29$ Hz, 1H, =CH), 7.18 (d, $J = 8.12$ Hz, 2H, Ar–H), 7.41 (d, $J = 8.12$ Hz, 2H, Ar–H), 7.73 (t, $J = 7.38$ Hz, 1H, Ar–H), 7.86 (t, $J = 7.65$ Hz, 1H, Ar–H), 8.12 (d, $J = 8.30$ Hz, 1H, Ar–H), 8.21 (d, $J = 8.49$ Hz, 1H, Ar–H), 8.49 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 448.2001; found: 448.1981.

*Synthesis of (E)-N,N-diisopropyl-N-{4-[3-(3-oxo-1H-pyrrolo[3,4-b]quinolin-2(3H)-yl)prop-1-enyl] phenyl}acetamide (**1g**)*

The general synthetic method described above afforded **1g** as off white solid. Yield 75 %, mp 194–196 °C. IR (KBr, ν cm^{-1}): 2964, 2928, 1689, 1640, 1465, 1330, 1241, 1126, 1043, 990, 753; ^1H NMR (300 MHz, DMSO-d_6): δ 0.95 (d, $J = 6.61$ Hz, 3H, CH_3), 1.20 (d, $J = 6.42$ Hz, 3H, CH_3), 1.28 (d, $J = 6.61$ Hz, 6H, 2 × CH_3), 3.62 (s, 2H, CH_2), 3.91–4.05 (m, 2H, 2 × CH), 4.43 (d, $J = 5.85$ Hz, 2H, CH_2), 4.68 (s, 2H, CH_2), 6.32–6.45 (m, 1H, CH), 6.64 (d, $J = 15.67$ Hz, 1H, =CH), 7.17 (d, $J = 8.12$ Hz, 2H, Ar–H), 7.42 (d, $J = 8.12$ Hz, 2H, Ar–H); 7.73 (t, $J = 7.08$ Hz, 1H, Ar–H); 7.86 (t, $J = 7.08$ Hz, 1H, Ar–H), 8.13 (d, $J = 8.30$ Hz, 1H, Ar–H), 8.26 (d, $J = 8.49$ Hz, 1H, Ar–H), 8.60 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 464.2314; found: 464.2292.

*Synthesis of (E)-N-(2-hydroxyethyl)-N-{4-[3-(3-oxo-1H-pyrrolo[3,4-b]quinolin-2(3H)-yl)prop-1-enyl]phenyl}acetamide (**1h**)*

The general synthetic method described above afforded **1h** as yellowish solid. Yield 79 %, mp 172–174 °C. IR (KBr, ν cm^{-1}): 2944, 2833, 1532, 1405, 1238, 1127, 1056, 963, 765; ^1H NMR (500 MHz, DMSO-d_6): δ 3.38–3.48 (m, 4H, 2 × CH_2), 4.47 (d, $J = 5.84$ Hz, 2H, CH_2), 4.66 (t, $J = 5.24$ Hz, 2H, CH_2), 4.70 (s, 2H, CH_2), 6.36–6.44 (m, 1H, =CH), 6.68 (d, $J = 15.74$ Hz, 1H, =CH), 7.25 (d, $J = 7.34$ Hz, 2H, Ar–H), 7.43 (d, $J = 7.34$ Hz, 2H, Ar–H), 7.76 (t, $J = 7.34$ Hz, 1H, Ar–H), 7.90 (t, $J = 7.34$ Hz, 1H, Ar–H), 8.01 (s, 1H, NH), 8.15 (d, $J = 7.34$ Hz, 1H, Ar–H), 8.25 (d, $J = 8.39$ Hz, 1H, Ar–H), 8.62 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 424.1637; found: 424.1609.

*Synthesis of N-{3-[4-(2-oxo-2-(4-phenylpiperidin-1-yl)ethyl)phenyl]propyl}-1H-pyrrolo[3,4-b]quinolin-3(2H)-one (**2a**)*

The general synthetic method described above afforded **2a** as brownish solid. Yield 76 %, mp 162–164 °C. IR (KBr, ν cm^{-1}): 3052, 2934, 2810, 1695, 1643, 1464, 1382, 1234, 1153, 1035, 968. 754; ^1H NMR (300 MHz, DMSO-d_6): δ 2.00 (m, 2H, CH_2), 2.65 (t, $J = 7.56$ Hz, 2H, CH_2), 2.95–3.12 (m, 4H, 2 × CH_2), 3.54–3.73 (m, 8H, 4 × CH_2), 4.62 (s, 2H, CH_2), 6.76 (t, $J = 7.26$ Hz, 1H, Ar–H), 6.87 (d, $J = 7.93$ Hz, 2H, Ar–H), 7.09–7.23 (m, 6H, Ar–H), 7.68 (t, $J = 7.65$ Hz, 1H, Ar–H), 7.82 (t, $J = 7.55$ Hz, 1H, Ar–H), 8.07 (d, $J = 7.93$ Hz, 1H, Ar–H), 8.19 (d, $J = 9.06$ Hz, 1H, Ar–H), 8.51 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 527.2423; found: 527.2400.

*Synthesis of N-{3-[4-(2-(4-(4-methoxyphenyl)piperidin-1-yl)-2-oxoethyl) phenyl] propyl}-1H-pyrrolo[3,4-b] quinolin-3(2H)-one (**2b**)*

The general synthetic method described above afforded **2b** as white solid. Yield 80 %, mp 178–180 °C. IR (KBr, ν cm^{-1}): 2924, 2821, 1689, 1632, 1512, 1383, 1249, 1157, 1036, 973, 909, 784; ^1H NMR (300 MHz, DMSO-d_6): δ 1.98 (m, 2H, CH_2), 2.62 (t, $J = 7.36$ Hz, 2H, CH_2), 2.82–2.98 (m, 4H, 2 × CH_2), 3.53–3.73 (m, 9H, 3 × CH_3, OCH_3), 4.64 (s, 2H, CH_2), 6.80 (d, $J = 8.87$ Hz, 2H, Ar–H), 6.88 (d, $J = 8.87$ Hz, 2H, Ar–H), 7.15 (d, $J = 8.12$ Hz, 2H, Ar–H), 7.20 (d, $J = 7.93$ Hz, 2H, Ar–H), 7.72 (t, $J = 7.82$ Hz, 1H, Ar–H), 7.86 (t, $J = 7.55$ Hz, 1H, Ar–H), 8.12 (d, $J = 7.93$ Hz, 1H, Ar–H), 8.20 (d, $J = 7.93$ Hz, 1H, Ar–H), 8.58 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 557.2529; found: 557.2506.

*Synthesis of N-{3-[4-(2-(4-(4-nitrophenyl)piperidin-1-yl)-2-oxoethyl)phenyl] propyl}-1H-pyrrolo[3,4-b]quinolin-3(2H)-one (**2c**)*

The general synthetic method described above afforded **2c** as yellow solid. Yield 69 %, mp 182–184 °C. IR (KBr, ν cm^{-1}): 2944, 2841, 1687, 1635, 1460, 1371, 1210, 1131, 1017, 987, 768; ^1H NMR (500 MHz, DMSO-d_6): δ 1.97 (m, 2H, CH_2), 2.62 (t, $J = 7.34$ Hz, 2H, CH_2), 3.39–3.50 (m, 4H, 2 × CH_2), 3.57–3.73 (m, 6H, 3 × CH_2), 4.65 (s, 2H, CH_2), 6.90 (d, $J = 9.75$ Hz, 2H, Ar–H), 7.14 (d, $J = 7.80$ Hz, 2H, Ar–H), 7.20 (d, $J = 7.80$ Hz, 2H,

Ar–H), 7.72 (t, $J = 7.35$ Hz, 1H, Ar–H), 7.85 (t, $J = 7.35$ Hz, 1H, Ar–H), 8.05 (d, $J = 9.75$ Hz, 2H, Ar–H), 8.11 (d, $J = 7.80$ Hz, 1H, Ar–H), 8.19 (d, $J = 8.78$ Hz, 1H, Ar–H), 8.57 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 572.2274; found: 572.2281.

*Synthesis of N-{3-[4-(2-morpholino-2-oxoethyl) phenyl]propyl}-1H-pyrrolo[3,4-b]quinolin-3(2H)-one (**2d**)*

The general synthetic method described above afforded **2d** as off white solid. Yield 72 %, mp 150–152 °C. IR (KBr, ν cm^{-1}): 2941, 2863, 1685, 1643, 1390, 1260, 1123, 1038, 968, 754; ^1H NMR (300 MHz, DMSO-d_6): δ 2.04 (m, 2H, CH2), 2.68 (t, $J = 7.55$ Hz, 2H, CH_2), 3.39–3.52 (m, 4H, 2 × CH_2), 3.53–3.64 (m, 4H, 2 × CH_2), 3.72 (t, $J = 7.17$ Hz, 2H, CH_2), 4.61 (s, 2H, CH_2), 7.10 (d, $J = 8.12$ Hz, 2H, Ar–H), 7.17 (d, $J = 7.74$ Hz, 2H, Ar–H), 7.66 (t, $J = 7.26$ Hz, 1H, Ar–H), 7.79 (t, $J = 7.47$ Hz, 1H, Ar–H), 8.00 (d, $J = 7.74$ Hz, 1H, Ar–H), 8.22 (d, $J = 8.30$ Hz, 1H, Ar–H), 8.43 (s, 1H, Ar–H); HRMS (ESI^+) calcd for $C_{32}H_{30}N_4O_2$ $[M + Na]^+$: 452.1950; found: 452.1941.

In vitro antitumor activity evaluation by MTT proliferation assay

The cancer cell lines (SK–N–SH, A549) were obtained from ATCC. The cytotoxic activity in vitro was measured using the MTT assay. The cells were plated in 24-well plates at a density 2.0×10^4 in 500 µl of medium per well of 24-well plate and treated with drugs in triplicates. The cells were incubated for 48 h at 37 °C under a 5 % CO_2 atmosphere. The MTT [3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide] solution 100 µg/ml was added in RPMI-1640 media, after cells were treated with the drug for 48 h and cells were incubated for further 2–3 h at 37 °C. The purple formazan crystals were dissolved in 100 µl DMSO. After 10 min the optical density was measured at 540 nm on ELISA plate reader. The % cell viability calculated by comparing the absorbance of treated cell versus untreated cells.

Results and discussion

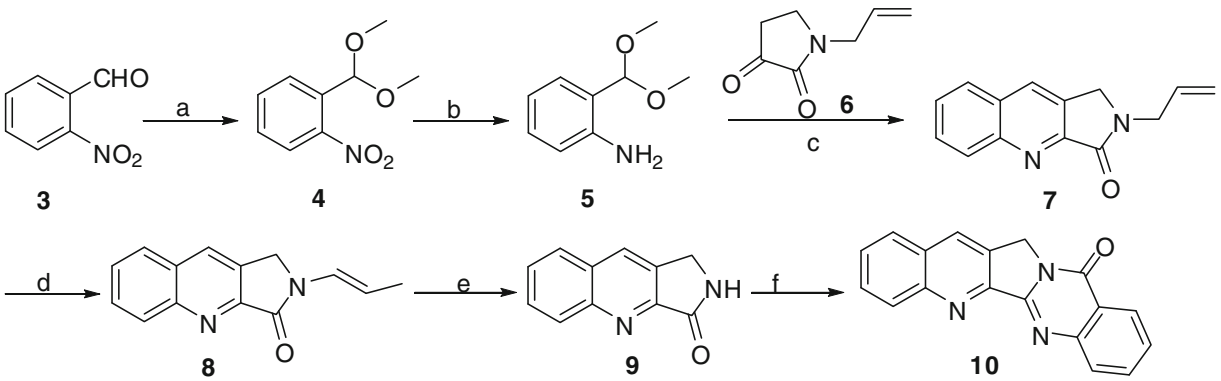
Chemistry

Synthesis of N-allyl-1H-pyrrolo[3,4-b]quinolin-3(2H)-one

Friedländer condensation of *N*-allylpyrrolidine-2,3-dione (**6**) with dimethylacetal of *o*-amino benzaldehyde (**5**) in the presence of cat. *p*-TSA provided *N*-allylpyrroloquinolinone (**7**) in yield 73 % (Scheme 1). The use of dimethylacetal of *o*-amino benzaldehyde in Friedländer condensation reaction is a convenient method for synthesis of **7** in high yield. The *N*-allylpyrrolidine-2,3-dione (**6**) in turn was obtained by modification of the original Sundberg method (Sundberg *et al.*, 1986). The reaction of ethyl acrylate with allylamine gave the Michael addition product which underwent cyclization with diethyl oxalate in sodium methoxide solution to give ethyl *N*-allyl-4,5-dioxopyrrolidine-3-carboxylate. Then, refluxed with 10 % aqu. HCl smoothly gives **6** due to hydrolysis and decarboxylation of the ester (Nagarapu *et al.*, 2011a, b).

Synthesis of Luotonin A

The synthesis of Luotonin A (**10**), the target molecule was achieved by modified procedure utilizing readily available materials (Dallavalle and Merlini, 2002). The precursor **8** was synthesized from the isomerisation of allyl group with $PdCl_2$–PPh_3, followed by deprotection of allyl with 10 % HCl in 86 % yield. The condensation of an equimolar



Scheme 1 Synthesis of Luotonin A. [a]Regents and conditions: (a) MeOH, methanesulfonic acid, Reflux, 16 h, 98 %; (b) Na_2S, Ethanol, 80 °C, 2 h, 78 %; (c) *p*-TSA, toluene, reflux, 12 h, 73 %; (d) $PdCl_2$, PPh_3, DMF/H_2O 8/2, reflux, 4 h, 91 %; (e) 6 N HCl, reflux, 2 h, 86 %; (f) Isatoic anhydride, mircrowave irradiation, 10 min, 62 %

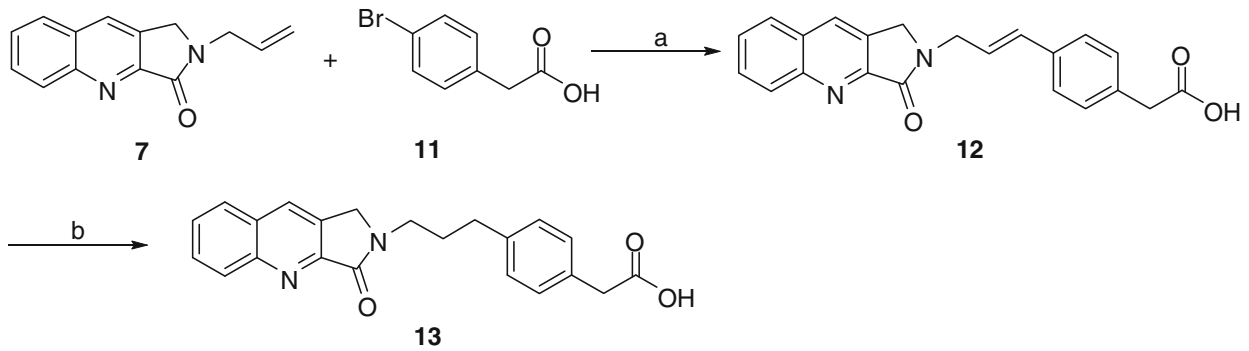
mixture of lactum (**9**) with isatoic anhydride was achieved by microwave irradiation at 450 watts for 10 min under solvent free condition to give Luotonin A (**10**) in 62 % yield (Scheme 1).

Synthesis of novel building blocks of 1H-pyrrolo [3,4-b]quinolin-3(2H)-one

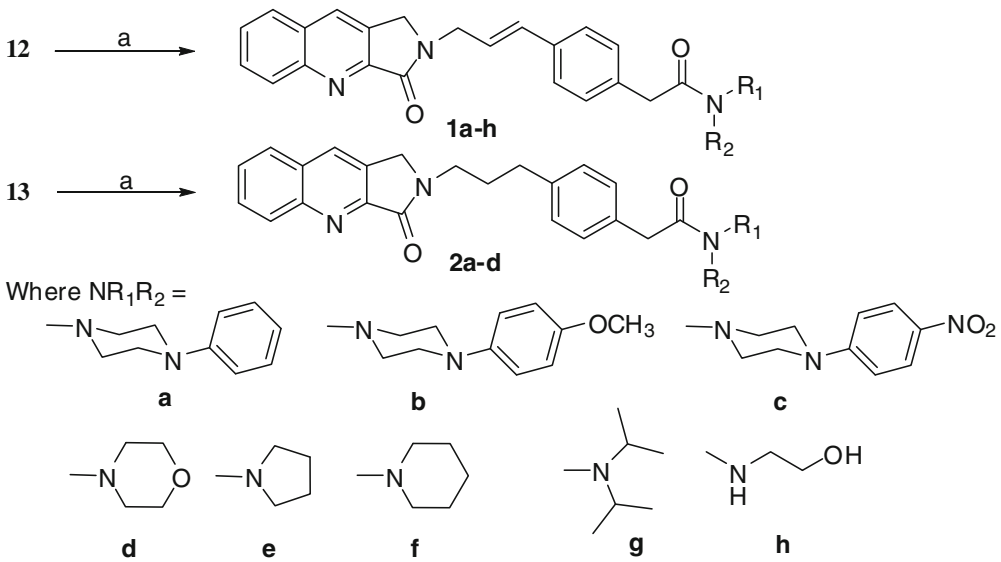
N-Allyl-1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one (**7**) has also been utilized for generating a few analogues by Mizoroki–Heck reaction (Mizoroki *et al.*, 1971; Heck and Nolley, 1972). The analogues **1a–h** have been prepared by the reaction of **7** with 4-bromophenyl acetic acid, $Pd(OAc)_2$, triphenylphosphine, Cs_2CO_3 in DMF:H_2O (4:1) to give **13** (Scheme 2). Acidic functionality in compound **13** was exploited to prepare variety of amides by reaction with various secondary amines by utilizing peptide coupling reagents EDC·HCl and HOBt (Scheme 3). In a view to check the activity potencies, the unsaturation in compound **14** was reduced with Pd/C/H_2 in methanol; once again acid was converted to amide by reaction with various secondary amines (Schemes 2, 3).

Micro analytical and spectral studies

All the compounds have been characterized by micro analytical and spectral data. HRMS (ESI^+) of a model compound **1a** showed molecular weight 525.2252 $[M + Na]^+$, its molecular formula was established as $C_{32}H_{30}N_4O_2$. ^1H NMR spectrum (300 MHz, DMSO-d_6) of **1a** exhibited signals arising due to typical prop-1-enyl phenyl acetamide. The spectrum showed two multiplets at δ 2.97–3.12 for four protons and δ 3.56–3.67 for four protons, two singlets appeared at δ 3.72, δ 4.65 for each two protons and doublet appeared at δ 4.44 for two protons with $J = 6.04$ Hz. The spectrum also revealed the presence



Scheme 2 Synthesis of compound **12, 13**. [a]Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, CS_2CO_3, DMF:H_2O(8:2), 120 °C, 4 h, 83 %; (b) H_2, Pd/C, methanol, 12 h, 90 %



Scheme 3 Synthesis of 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one derivatives. [a]Reagents and conditions: (a) EDC·HCl, HOBt, DIEA, CH_2Cl_2, rt, 12 h, 68–81 %

of a multiplet at δ 6.26–6.39 for one olefinic proton and a doublet at δ 6.65 for one olefinic proton with $J = 16.05$ Hz. The aromatic protons appeared at δ 6.77–8.51 (14H), respectively.

Pharmacology

Cytotoxicity of all the compounds were evaluated against SK–N–SH (human neuroblastoma cell line) and A549 (human lung carcinoma cell line) cells by the standard MTT Assay method (Mosmann, 1983). The various human tumor cell growth inhibitor potential was determined. The inhibitory activities were presented as micromolar concentrations of the compound that cause 50 % inhibition per unit of enzyme (IC_{50}) under the assay conditions, Luotonin A and Doxorubicin (DOX) were used as a reference drug.

Effects of the compounds on the viability of human cancer cells

Results, expressed as % IC_{50} values, are presented in Table 1. All the compounds were tested and displayed antiproliferative activity in micromolar range (% IC_{50} range: 8.62–86.75 μM, Table 1). The data obtained from MTT assay showed that most of prepared compounds showed significant inhibitory effects on SK–N–SH and A549 cell lines, and the potencies of some compounds were comparative to the lead compound Luotonin A and Doxorubicin, some compounds showed moderate

Table 1 Antitumor activity of 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one derivatives

Compounds	% IC_{50} ± SEM [μM][a]	
	SK–N–SH[b]	A549[c]
12	56.63 ± 2.01	–
13	–	–
1a	51.91 ± 1.31	53.46 ± 7.30
1b	56.34 ± 3.20	–
1c	56.19 ± 1.87	43.81 ± 3.88
1d	08.62 ± 0.37	46.19 ± 2.98
1e	57.22 ± 1.63	–
1f	38.28 ± 0.53	67.79 ± 4.82
1 g	43.21 ± 4.20	70.12 ± 2.64
1 h	42.12 ± 1.77	–
2a	42.01 ± 1.50	65.42 ± 1.83
2b	48.90 ± 4.00	68.83 ± 3.60
2c	40.23 ± 1.50	–
2d	–	–
Luotonin A[d]	61.08 ± 1.07	61.25 ± 4.89
Dox[e]	19.90 ± 3.01	24.27 ± 5.33

[a] Experiments were performed in triplicates; values represented as means ± SEM from three independent determinations of a representative experiment at 50 μM concentration

[b] Antiproliferative effects in human SK–N–SH neuroblastoma cells

[c] Antiproliferative effects in human A549 lung carcinoma cells

[d] Luotonin A

[e] Doxorubicin is a reference drug

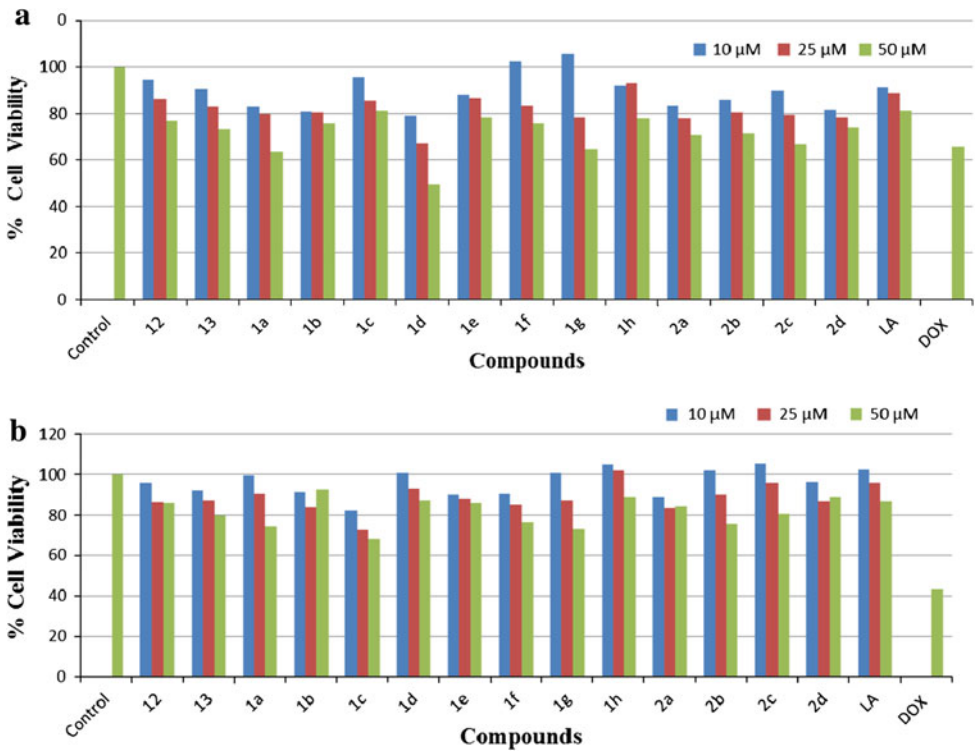


Fig. 2 SK–N–SH human neuroblastoma (**a**) and human A549 lung carcinoma (**b**) cells were treated with various concentrations (10, 25 and 50 μM) of compounds **12**, **13**, **1a–h**, **2a–d** for 48 h. A viability assay was carried out. Experiments were performed in triplicate; data are expressed as means of the triplicate determinations of a representative experiment in % cell viability of untreated cells (100 %). Luotonin A (LA) and Doxorubicin (DOX) is a reference drug

cytotoxicity against SK–N–SH and A549 cell lines (Fig. 2). For A549 cancer cell line most of the compounds showed moderate cell viability (Fig. 2b).

The cytotoxicity of the resulting pyrroloquinolinone derivatives appeared to be related to the nature of propyl phenyl acetic acid moiety with different secondary amines. For SK–N–SH tumor cell line, most of the prepared compounds showed potent growth inhibition potential. It has been observed from Fig. 2a that most of the compounds with prop-1-enyl phenyl acetamide moieties have higher cytotoxicity than those with propyl phenyl acetamide moiety. For all derivatives with several secondary amine moieties, the activities appeared to be related to the different secondary amines. Pyrrolidinyl (**1e**) and piperidinyl (**1f**) derivatives are less active than the morpholino (**1d**) derivative. The higher inhibition of the cell growth were exhibited by compound **1d** (% IC_{50} = 8.62 μM) containing morpholine moiety against SK–N–SH neuroblastoma cell line (Fig. 2a; Table 1). However, the introduction of prop-1-enyl phenyl acetamide with secondary amines (morpholine) has enhanced the enzyme binding affinity. The derivatives **1b**, **1c, 1g, 1h, 2a,** and **2c** exhibited moderate cell growth inhibition.

Conclusion

Finally, synthesis of Luotonin A leading to discovery of novel building blocks of 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one as antitumor agents has been achieved. Compounds **1a–h**, **2a–d** were synthesized by the reaction of *N*-allyl-1*H*-pyrrolo [3,4-*b*]quinolin-3(2*H*)-one with 4-bromophenyl acetic acid followed by amidation with several secondary amines. All the new molecules were screened in viability assays against human neuroblastoma (SK–N–SH) and lung carcinoma (A549) cells in vitro. In general, most of the prepared compounds showed significantly cytotoxic effect against human tumor cell lines. Compound **1d** was found to be potent tumor growth inhibitors against the neuroblastoma SK–N–SH cells. These finding suggested that further study of tumor cell metastasis, antiproliferative mechanism, angiogenesis of these compounds could lead to drug discovery.

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