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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and cytotoxic evaluation of 7-chloro-4-phenoxyquinolines with formyl, oxime and thiosemicarbazone scaffolds

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Abstract New 7-chloro-4-phenoxyquinoline derivatives bearing formyl, oxime and thiosemicarbazone functional groups were easily prepared using 4,7-dichloroquinoline and functionalized phenols as inexpensive and commercially available starting materials. Their chemical structures were confirmed by use of infrared and ^{1}H, ^{13}C nuclear magnetic resonance experiments. All the synthesized compounds were evaluated for their cytotoxicity against the cell lines MCF-7, SKBR-3, PC3, HeLa and human dermis fibroblast as non-tumor cells, in vitro using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) for assay. The quinoline derivatives **3a** and **3d** resulted as promising models for antitumor drugs, displaying good cytotoxic activity against four human cancer cell lines ($9.18\ \mu M < IC_{50} < 50.75\ \mu M$). The phenoxyquinoline **3d** stands out by its low unspecific cytotoxicity and high selectivity on tumor lines SKBR-3, HeLa and PC3 cells.

Keywords 7-Chloro-4-phenoxyquinoline · Lipinski's rule · OSIRIS software · In vitro antitumor and cytotoxic analysis

Introduction

New leads with anticancer potential are needed urgently since anticancer drugs used in clinics are commonly highly toxic and non-selective molecules. In addition, the resistance incidence for some chemotherapeutic agents has become remarkable in recent decades. In this sense, the design of more selective and safer anticancer agents stands out as an actual and vital task. Quinolines and their derivatives have shown to display a wide spectrum of biological activities. Quinoline nucleus is generally present in a large number of synthetic and natural molecules with relevant parasites growth inhibition properties. Moreover, different examples have revealed their potent anticancer activity (Afzal et al., 2015; Arafa et al., 2013; Zhao et al., 2005). Currently, quinoline derivatives are available as antimalarial (chloroquine, mefloquine, amodiaquinine, primaquine, etc.), antibacterial (ciprofloxacin, sparfoxacin, gatifloxacin, etc.) or anticancer drugs (camptothecin, irinotecan, topotecan, etc.). Hydroxyquinoline scaffolds also play an important role in anticancer drug development, as their derivatives have shown excellent results through different mechanism of action such as growth inhibitors by cell cycle arrest, apoptosis and inhibition of angiogenesis or cell migration disruption. Lenvatinib (**A**) and cabozantinib (**B**) are anticancer drugs based on the C-4 substituted aryl oxyquinoline skeleton while experimental anticancer drug

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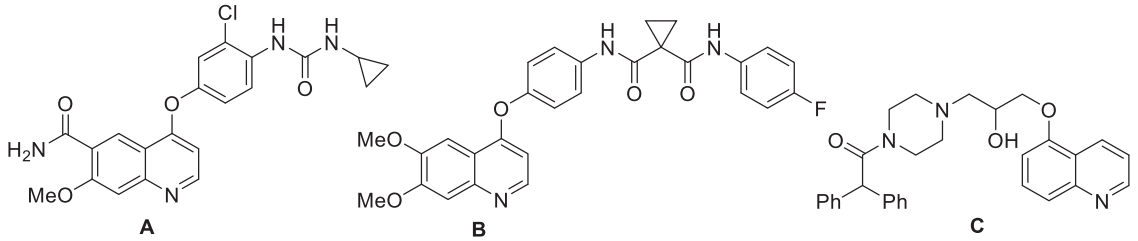


Fig. 1 Anticancer drugs with the aryl oxyquinoline moiety

dofequidar (MS-209, **C**; Katayama et al., 2009) is a 5-alkoxyquinoline derivative (Fig.1).

On the other hand, it is important to recall the fact that the pharmacological properties of synthetic drugs depend markedly on the structures of the pharmacophores incorporated into them. Thiosemicarbazones and oximes are structural moieties present in a wide variety of compounds with numerous biological activities including, antiviral (Banerjee et al., 2011), antitumor (Berényi et al., 2013; Arora et al., 2014), antifungal (Al-Amiery et al., 2012), among others. Hence, the synthesis of new series of bioactive compounds containing thiosemicarbazone and hydroxyquinoline fragments results promising. In fact, heterocyclic oximes and thiosemicarbazones, including quinoline derivatives, are polyfunctional substrates, widely used in the development of methods for the synthesis of biologically active compounds. These kinds of molecules could be prominent medicinal agents (Waghamale and Piste, 2013; Saad et al., 2011; Kaur et al., 2007; Chen et al., 2011). Based on these facts, increased attention is now given to the chemistry of quinoline derivatives, specially to the quinoline-2(8)-carboxaldehydethiosemicarbazones and 4-phenoxy-6,7-disubstituted quinoline (thio)semicarbazones, which have shown in vitro topoisomerase II action (Bisceglie et al., 2015) and c-Met kinase inhibition on a single-digital nanomolar level (Qi et al., 2013), respectively.

Taking into account the above stated, in the present study we have synthesized new 7-chloro-4-phenoxyquinolines possessing formyl, oximes and thiosemicarbazones scaffolds. Incorporation of these pharmacophores into 4-phenoxyquinoline nucleus would enhance anticancer properties of these molecules. Their potential human tumor cell growth inhibitory effect on MCF-7 (breast carcinoma, no overexpresses the HER2/c-erb-2 gene), SKBR-3 (breast carcinoma, overexpresses the HER2/c-erb-2 gene), PC3 (prostate carcinoma), HeLa (cervical epithelial carcinoma) cancer cell lines and for non-tumor cells (primary culture of human dermis fibroblast—control cells) was tested. All the prepared molecules have been subjected to absorption, distribution, metabolism and excretion (ADME) molecular properties prediction by Molinspiration online calculation software and MolSoft program, to determine their bioavailability following the Lipinski's "rule of five" (Lipinski et al., 1997). Additionally, their potential adverse effects against the organism based on the topological descriptors were explored for to potential risk assessment, employing the Osiris software (Osiris).

Material and methods

Chemistry

The melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. The infrared (IR) spectra were recorded using a Infralum FT-02 spectrophotometer in KBr. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AM-400 or AC-300 spectrometers. Chemical shifts are reported in ppm (δ) relative to the solvent peak ($CDCl_3$, 7.24 ppm for ^{1}H and 77.23 ppm for ^{13}C; or dimethyl sulfoxide (DMSO)-d6, 2.5 ppm for ^{1}H and 39.51 ppm for ^{13}C). Signals are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; m, multiplet. A Hewlett Packard 5890a series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector with an Hewlett Packard (HP) Mass Spectrometry (MS) Chemstation Data system was used for MS identification at 70 eV using a 60 m capillary column coated with HP-5 (5 %-phenyl-poly(dimethyl-siloxane)). Elemental analyses were performed on a Perkin Elmer 2400 Series II analyzer and were within ±0.4 of theoretical values. The reaction progress was monitored using thin layer chromatography (TLC) on a silufol UV254 TLC aluminum sheet.

Synthesis of polyfunctionalized quinolines **3a–d** of the series **I** tested in this work were easily carried out using diverse aldehydes **2a–d** and 4,7-dichloroquinoline **1** as starting materials following our published procedure (Bueno et al., 2012). Briefly, 0.50 g (2.5 mmol) of 4,7-dichloroquinoline **1**, 0.37 g (3.01 mmol) of benzaldehydes **2a–d** and 1.0 g (7.60 mmol) of K_2CO_3 were dissolved in 3 mL of Dimethylformamide (DMF). The resulting mixture was subjected to reflux under vigorous stirring for 8 h, according to TLC monitoring. The reaction mass was diluted with water and extracted with dichloromethane (2 × 30 mL). Finally, the organic phases were dehydrated using Na_2SO_4, and concentrated under vacuum. Compounds **3a–d**

were purified by columm chromatography using petroleum ether and ethyl acetate combinations as eluting solvents.

*4-((7-Chloroquinolin-4-yl)oxy)benzaldehyde (**3a**)*

White solid, 80 %, mp 130–135 °C; IR (KBr) ν_{max} 1698, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 10.03$ (1H, s, –CHO), 8.76 (1H, d, $J = 5.1$ Hz, 2-H), 8.22 (1H, d, $J = 8.9$ Hz, 5-H) 8.12 (1H, d, $J = 1.9$ Hz, 8-H), 7.98–8.02 (2H, dd, $J = 8.6$, 1.9 Hz, 3′-H, 5′-H), 7.52–7.55 (1H, dd, $J = 8.9$, 2.0 Hz, 6-H), 7.30–7.34 (2H, dd, $J = 8.5$, 2.2 Hz, 2′-H, 6′-H), 6.71 (1H, d, $J = 5.1$ Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 187.9$ (–CHO), 161.5 (C-4′), 156.2 (C-4), 152.2 (C-2), 150.3 (C-8a), 136.5 (C-7), 136.2 (C-1′), 131.9 (C-2′, C-5′), 129.6 (C-8), 128.3 (C-6), 128.3 (C-4a), 127.7 (C-3), 126.4 (C-5), 119.5 (C-3′, C-5′); Gas Chromatography-Mass Spectrometry (GC-MS): $t_R = 24.0$ min.; MS (Electron Impact (EI)), *m/z* (%):285 [(M+2), 30], 283 ($M^{+\bullet}$, 99), 219 (33), 121(100), 99 (49); Anal. Calcd for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; N, 4.94. Found: C, 67.41; H, 3.31; N, 4.85.

*2-((7-Chloroquinolin-4-yl)oxy)benzaldehyde (**3b**)*

White solid, 65 %, mp 80–83 °C; IR (KBr) ν_{max} 1698, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 10.02$ (1H, s, –CHO), 8.62 (1H, d, $J = 6.7$ Hz, 2-H), 8.07 (1H, d, $J = 8.5$ Hz, 5-H), 8.03–7.96 (1H, ddd, $J = 8.7$, 7.4, 1.9 Hz, 4′-H), 8.01 (1H, d, $J = 1.6$, Hz, 8-H), 7.50–7.48 (1H, dd, $J = 8.5$, 1.9 Hz, 6-H), 7.46–7.41 (1H, ddd, $J = 7.8$, 1.9 Hz, 6′-H), 7.34–7.32 (1H, dd, $J = 8.7$, 7.8,1.9 Hz, 5′-H), 7.20–7.07 (1H, dd, $J = 8.7$, 1.9 Hz, 3′-H), 6.57 (1H, d, $J = 6.7$ Hz, 3-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 188.8$ (–CHO), 164.2 (C-4), 160.0 (C-2′) 151.4 (C-2), 150.2 (C-8a), 132.8 (C-7), 131.3 (C-4′), 129.1 (C-6′), 127.4 (C-1′), 127.2 (C-8), 126.7 (C-5), 126.4 (C-6), 122.0 (C-5′), 119.1 (C-3′), 118.9 (4a), 101.9 (C-3); GC-MS: $t_R = 26.0$ min.; MS (EI), *m/z* (%):285 [(M+2), 33], 283 ($M^{+\bullet}$, 99), 219 (45), 121(99), 99 (35); Anal. Calcd for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; N, 4.94. Found: C, 67.40; H, 3.32; N, 4.90.

*4-((7-Chloroquinolin-4-yl)oxy)-3-methoxybenzaldehyde (**3c**)*

White solid, 65 %, mp 140–143 °C; IR (KBr) ν_{max} 1690, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 10.02$ (1H, s, –CHO), 8.70 (1H, d, $J = 5.2$ Hz, 2-H), 8.32 (1H, d, $J = 8.9$ Hz, 5-H), 8.10 (1H, d, $J = 1.9$ Hz, 8-H), 7.61 (1H, d, $J =$ 1.6 Hz, 2′-H), 7.58–7.53 (2H, t, $J = 9.1$ Hz, 2.0 Hz, 5′-H, 6′-H), 7.35 (1H, d, $J = 8.0$ Hz, 6-H), 6.45 (1H, d, $J = 5.2$ Hz, 3-H), 3.85 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7 (–CHO), 160.8 (C-4), 152.3 (C-2), 152.2 (C-3′), 150.3 (C-4′), 147.6 (C-8a), 136.2 (C-7), 135.1(C-1′), 128.1 (C-5), 127.2 (C-8), 125.2 (C-6′), 123.4 (C-6), 122.8 (C-5′), 119.4 (C-4a), 111.6 (C-2′), 104.1 (C-3), 56.1 (OCH_3); GC-MS: $t_R = 25.8$ min.; MS (EI), *m/z* (%):315 [(M+2), 32], 313 ($M^{+\bullet}$ 98), 282 (32), 176 (100), 162 (35), 151 (34), 135 (48); Anal. Calcd for $C_{17}H_{12}ClNO_3$: C, 65.08; H, 3.86; N, 4.46. Found: C, 65.28; H, 3.67; N, 4.64.

*3-((7-Chloroquinolin-4-yl)oxy)-4-methoxybenzaldehyde (**3d**)*

White solid, 73 %, mp 70–73 °C; IR (KBr) ν_{max} 1696, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.92$ (1H, s, –CHO), 8.64 (1H, d, $J = 5.2$ Hz, 2-H), 8.34 (1H, d, $J = 8.9$ Hz, 5-H), 8.09 (1H, d, $J = 2.0$ Hz, 8-H), 7.88–7.85 (1H, dd, $J = 8.4$, 2.0 Hz, 4′-H), 7.76 (1H, d, $J = 2.0$, 6′-H), 7.56–7.53 (1H, dd, $J = 8.9$, 2.0 Hz, 3′-H), 7.20 (1H, d, $J = 8.5$ Hz, 6-H), 6.39 (1H, d, $J = 5.2$, 3-H), 3.86 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 189.7$ (–CHO), 161.2 (C-4), 156.7 (C-2), 152.1 (C-3′), 150.2 (C-4′), 142.8 (C-8a), 136.2 (C-7), 130.5 (C-1′), 130.2 (C-5), 128.1 (C-8), 127.2 (C-6′), 123.4 (C-6), 123.2 (C-5′), 119.4 (C-4a), 112.8 (C-2′), 103.4 (C-3), 56.2 (OCH_3); GC-MS: $t_R = 26.4$ min.; MS (EI), *m/z* (%):315 [(M+2), 30], 313 ($M^{+\bullet}$, 100), 282 (35), 176 (98), 162 (36), 151 (34), 135 (50); Anal. Calcd for $C_{17}H_{12}ClNO_3$: C, 65.08; H, 3.86; N, 4.46. Found: 65.24; H, 3.63; N, 4.61

*Synthesis of (7-chloroquinolin-4-yl)oxy)benzaldehyde oximes (**4a–d**); General experimental procedure*

A mixture of benzaldehydes **3a**–**d** (14.13 mmol), hydroxylamine hydrochloride (17 mmol) and sodium carbonate (17 mmol) was homogenized in a mortar and added to a flask (25 mL). The mixture was irradiated in a domestic microwave oven set at medium-low power for a period of 5 min monitored by TLC. Then, 15 mL of distilled water was added to the reaction mixture, precipitating and filtering the formed oximes **4a**–**d**. The crude products were washed with water (2 × 10 mL) and dried under vacuum. Finally, the pure product was obtained by column chromatography using mixtures of petroleum ether-ethyl acetate as mobile phase.

*4-((7-Chloroquinolin-4-yl)oxy)benzaldehydeoxime (**4a**)*

White solid, 99 %, mp 170–173 °C; IR (KBr) ν_{max} 3217, 1583 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): $\delta = 10.02$ (1H, s, HC=N), 8.74 (1H, d, $J = 5.2$ Hz, 2-H), 8.32 (1H, d, $J = 8.9$ Hz, 5-H), 8.22 (1H, s, N–OH), 8.10 (1H, d, $J = 1.9$ Hz, 8-H), 7.75 (2H, d, $J = 8.6$ Hz, 2′-H, 6′-H), 7.69 (1H, dd, $J = 8.8$, 2.0 Hz, 6-H), 7.35 (2H, d, $J = 8.6$ Hz, 3′-H,5′-H), 6.71 (1H, d, $J = 5.1$ Hz, 3-H); ^{13}C NMR (100 MHz, DMSO-d6): $\delta = 187.9$ (–C=N–OH), 161.5 (C-4′), 156.2 (C-4), 152.2 (C-2), 150.3 (C-8a), (C-7), 136.2 (C-1′), 131.9 (C-2′, C-5′), 129.6 (C-8), 128.3 (C-6), 128.3 (C-4a), 127.7 (C-3),

126.4 (C-5), 119.5 (C-3′, C-5′); gas chromatography mass spectrometry (GC-MS): $t_R = 27.5$ min.; MS (EI), *m/z* (%): 298 ($M^{+\bullet}$, nd), 282 (30), 280 [($M^{+\bullet}$-H_2O), 100], 245 (60), 162 (50), 99 (45); Anal. Calcd for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.13; H, 3.90; N, 9.19.

*2-((7-Chloroquinolin-4-yl)oxy)benzaldehydeoxime (**4b**)*

White solid, 99 %, mp 158–160 °C; IR (KBr) ν_{max} 3248, 1588 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): $\delta = 10.02$ (1H, s, HC=N), 8.74 (1H, d, $J = 5.2$ Hz, 2-H), 8.32 (1H, d, $J = 8.9$ Hz, 5-H), 8.22 (1H, s, N–OH), 8.10 (1H, d, $J = 1.9$ Hz, 8-H), 7.75 (2H, d, $J = 8.6$ Hz, 2′,6′-H), 7.69 (1H, dd, $J = 8.8$, 2.0 Hz, 6-H), 7.35 (2H, d, $J = 8.6$ Hz, 3′,5′-H), 6.71 (1H, d, $J = 5.1$ Hz, 3-H); ^{13}C NMR (100 MHz, DMSO-d6): $\delta = 188.8$ (–C=N–OH), 164.2 (C-4), 160.0 (C-2′) 151.4 (C-2), 150.2 (C-8a), 132.8 (C-7), 131.3 (C-4′), 129.1 (C-6′), 127.4 (C-1′), 127.2 (C-8), 126.7 (5 C), 126.4 (C-6), 122.0 (C-5′), 119.1 (C-3′), 118.9 (4a), 101.9 (C-3); GC-MS: $t_R =$ 27.5 min.; MS (EI), *m/z* (%): 298 ($M^{+\bullet}$, nd), 282 (30), 280 [($M^{+\bullet}$-H_2O), 100], 245 (50), 162 (60), 99 (45); Anal. Calcd for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.53; H, 3.51; N, 9.20.

*4-((7-Chloroquinolin-4-yl)oxy)-3-methoxybenzaldehyde oxime (**4c**)*

White solid, 99 %, mp 180–183 °C; IR (KBr) ν_{max} 3250, 1580 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): $\delta = 10.02$ (1H, s, HC=N), 8.68 (1H, d, $J = 5.2$ Hz, 2-H), 8.35 (1H, d, $J = 8.9$ Hz, 5-H), 8.21 (1H, s, N–OH), 8.09 (1H, d, $J = 2.0$ Hz, 8-H), 7.69 (1H, dd, $J = 8.9$, 2.1 Hz, 6-H), 7.49 (1H, d, $J = 1.6$ Hz, 2′-H), 7.36 (1H, d, $J = 8.1$ Hz, 5′-H), 7.31 (1H, dd, $J = 8.2$, 1.6 Hz, 6′-H), 6.51 (1H, d, $J = 5.2$ Hz, 3-H), 3.74 (3H, s, OCH_3); ^{13}C NMR (100 MHz, DMSO-d6): $\delta =$ 189.7 (-C=N–OH), 161.2 (C-4), 156.7 (C-2), 152.1 (C-3′), 150.2 (C-4′), 142.8 (C-8a), 136.2 (C-7), 130.5 (C-1′), 130.2 (C-5), 128.1 (C-8), 127.2 (C-6′), 123.4 (C-6), 123.2 (C-5′), 119.4 (C-4a), 112.8 (C-2′), 103.4 (C-3), 56.2 (OCH_3); GC-MS: $t_R = 29.3$ min.; MS (EI), *m/z* (%):328 ($M^{+\bullet}$, nd), 312 (30), 310 [($M^{+\bullet}$-H_2O), 100], 279 (40), 176 (80), 99 (35); Anal. Calcd for $C_{17}H_{13}ClN_2O_3$: C, 62.11; H, 3.99; N, 8.52. Found: C, 62.31; H, 3.79; N, 8.71.

*3-((7-Chloroquinolin-4-yl)oxy)-4-methoxybenzaldehyde oxime (**4d**)*

White solid, 99 %, mp 190–192 °C; IR (KBr) ν_{max} 3216, 1581 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): $\delta = 10.02$ (1H, s, HC=N), 8.69 (1H, d, $J = 5.2$ Hz, 2-H), 8.36 (1H, d, $J = 8.9$ Hz, 5-H), 8.13 (1H, s, N–OH), 8.09 (1H, d, $J = 1.9$ Hz, 8-H), 7.69 (1H, dd, $J = 8.9$, 2.0 Hz, 6-H), 7.59 (1H, dd, $J = 8.7$, 1.7 Hz, 6′-H), 7.53 (1H, d, $J = 1.7$ Hz, 2′-H), 7.32 (1H, d, $J = 8.7$ Hz, 5′-H), 6.51 (1H, d, $J = 5.2$ Hz, 3-H), 3.75 (3H, s, OCH_3); ^{13}C NMR (100 MHz, DMSO-d6): $\delta =$ 190.7 (–C=N–OH), 160.8 (C-4), 152.3(C-2), 152.2(C-3′), 150.3(C-4′), 147.6(C-8a), 136.2(C-7), 135.1(C-8), 128.1(C-1′), 127.2 (C-5), 125.2 (C-6′), 123.4 (C-6), 122.8 (C-5′), 119.4 (C-4a), 111.6 (C-2′), 104.1 (C-3), 56.1 (OCH_3); GC-MS: $t_R = 30.0$ min.; MS (EI), *m/z* (%): 328 ($M^{+\bullet}$, nd), 312 (30), 310 [($M^{+\bullet}$-H_2O), 100], 279 (40), 176 (90), 99 (45); Anal. Calcd for $C_{17}H_{13}ClN_2O_3$: C, 62.11; H, 3.99; N, 8.52. Found: C, 62.31; H, 3.79; N, 8.73.

*Synthesis of (7-Chloroquinolin-4-yl)oxy)benzylidene) hydrazine-1-carbothioamides (**5a–d**); General experimental procedure*

A mixture of 0.2 g of benzaldehydes **3a–d** (14.13 mmol) and thiosemicarbazide 0.08 g (17 mmol) in 5 mL of ethanol was subjected to heating (60 °C) in a 25 mL flask until complete dissolution. Subsequently, some drops of the glacial acetic acid were added to the resulting solution. The precipitate formed was kept under stirring and heating for 1 h (TLC). Finally, the reaction mixture was cooled to room temperature and the formed solid was filtered and washed with cold ethanol to yield the products **5a–d**.

*2-(4-((7-Chloroquinolin-4-yl)oxy)benzylidene)hydrazine-1-carbothioamide (**5a**)*

White solid, 90 %, mp 190–193 °C; IR (KBr) ν_{max} 3176, 3070–3065, 1573, 1265 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): $\delta = 11.51$ (1H, s, HC=N), 8.73 (1H, d, $J = 4.6$ Hz, 2-H), 8.26–8.22 (2H, m, N–H, 5-H), 8.13–8.06 (3H, m, 8-H, NH_2), 7.97 (2H, d, $J = 7.9$ Hz, 3′-H, 5′-H), 7.66 (1H, d, $J =$ 8.2 Hz, 6-H), 7.32 (2H, d, $J = 7.9$ Hz, 2′-H, 6′-H), 6.69 (1H, d, $J = 4.6$ Hz, 3-H); ^{13}C NMR (100 MHz, DMSO-d6): $\delta =$ 178.5 (–C=N), 109.8 (–C=S), 159.0 (C-4′), 157.5 (C-4), 153.5 (C-2), 148.4 (C-8a), 146.8 (C-7), 135.7 (C-1′), 130.2 (C-2′,C-5′), 129.6 (C-8), 128.9 (C-6), 128.7 (C-4a), 123.2 (C-3), 121.4 (C-3′,C-5′), 115.9 (C-5); Anal. Calcd for $C_{17}H_{13}ClN_4OS$: C, 57.22; H, 3.67; N, 15.70. Found: C, 57.42; H, 3.82; N, 15.51.

*2-(2-((7-Chloroquinolin-4-yl)oxy)benzylidene)hydrazine-1-carbothioamide (**5b**)*

White solid, 80 %, mp 180–183 °C; IR (KBr) ν_{max} 3175, 3071–3065, 1573, 1264 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): $\delta = 11.53$ (1H, s, HC=N), 8.74 (1H, d, $J = 4.6$ Hz, 2-H), 8.26–8.22 (2H, m, N–H, 5-H), 8.14–8.08 (3H, m, 8-H, NH_2), 7.99 (2H, d, $J = 7.9$ Hz, 3′-H,5′-H), 7.70 (1H, d, J = 8.2 Hz, 6-H), 7.29 (2H, d, $J = 7.9$ Hz, 2′-H,6′-H), 7.06 (1H, d, $J = 4.6$ Hz, 3-H); ^{13}C NMR (100 MHz, DMSO-d6): $\delta = 178.5$ (–C=N), 109.8 (–C=S), 158.9 (C-4), 159.0

(C-2′), 153.5 (C-2), 148.4 (C-8a), 146.0 (C-7), 135.7 (C-4′), 135.1 (C-6′), 131.7 (C-1′), 128.7 (C-8), 128.9 (C-5), 124.7 (C-6), 123.9 (C-5′), 123.2 (C-3′), 115.9 (C-4a). Anal. Calcd for $C_{17}H_{13}ClN_4OS$: C, 57.22; H, 3.67; N, 15.70. Found: C, 57.42; H, 3.80; N, 15.54.

*2-(4-((7-Chloroquinolin-4-yl)oxy)-3-methoxybenzylidene) hydrazine-1-carbothioamide (**5c**)*

Gray solid, 77 %, mp 155–158 °C; IR (KBr) ν_{max} 3177, 3071–3065, 1573, 1264 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): $\delta = 11.40$ (1H, s, HC=N), 8.70 (1H, d, $J = 5.0$ Hz, 2-H), 8.38 (1H, d, $J = 9.0$ Hz, 5-H), 8.13–8.08 (2H, m, 8-H, N–H), 8.08–8.02 (3H, m, 6′-H, NH_2), 7.71 (1H, dd, $J =$ 9.0, 1.4 Hz, 6-H), 7.63 (1H, dd, $J = 9.0$, 1.5 Hz, 2′-H), 7.29 (1H, d, $J = 9.0$ Hz, 3′-H), 6.50 (1H, d, $J = 5.0$ Hz, 3-H), 3.74 (3H, s, OCH_3); ^{13}C NMR (100 MHz, DMSO-d6): $\delta =$ 178.5 (–C=N), 157.1 (–C=S), 153.5 (C-4), 151.7 (C-2), 148.4 (C-3′), 146.8 (C-4′), 146.5 (C-8a), 135.7 (C-7), 134.2 (C-1′), 130.8 (C-5), 128.7 (C-8), 126.1 (C-6′), 123.2 (C-6), 121.3 (C-5′), 115.9 (C-4a), 111.9 (C-2′), 109.8 (C-3), 56.1 (OCH_3); Anal. Calcd for $C_{18}H_{15}ClN_4O_2S$: C, 55.89; H, 3.91; N, 14.48. Found: C, 55.67; H, 3.13; N, 14.29.

*2-(3-((7-Chloroquinolin-4-yl)oxy)-4-methoxybenzylidene) hydrazine-1-carbothioamide (**5d**)*

Yellow solid, 76 %, mp 145–148 °C; IR (KBr) ν_{max} 3178, 3070–3065, 1573, 1265 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): $\delta = 11.54$ (1H, s, HC=N), 8.68 (1H, d, $J = 5.2$ Hz, 2-H), 8.34 (1H, d, $J = 9.0$ Hz, 5-H), 8.32 (1H, s, N–H), 8.20 (2H, s, NH_2), 8.09 (1H, d, $J = 4.5$ Hz, 8-H), 7.78 (1H, s, 2′-H), 7.68 (1H, d, $J = 9.0$ Hz, 6-H), 7.40 (1H, d, $J = 8.1$ Hz, 6′-H), 7.34 (1H, d, $J = 8.1$ Hz, 5′-H), 6.50 (1H, d, $J = 5.2$ Hz, 3-H), 3.78 (3H, s, OCH_3); ^{13}C NMR (100 MHz, DMSO-d6): $\delta = 178.5$ (–C=N), 159.0 (–C=S), 153.5 (C-4), 151.7 (C-2), 148.4 (C-3′), 146.8 (C-4′), 146.5(C-8a), 135.7(C-7), 134.2 (C-1′), 128.9 (C-5), 128.7 (C-8), 128.6(C-6′), 123.2 (C-6), 122.5 (C-5′), 115.9 (C-4a), 111.7 (C-2′), 109.8(C-3), 56.1 (OCH_3); Anal. Calcd for $C_{18}H_{15}ClN_4O_2S$: C, 55.89; H, 3.91; N, 14.48. Found: C, 55.01; H, 3.73; N, 14.28.

Biological activity

Reagents and compounds

Human tumor cell lines and culture media: The cells were kindly donated by Dr Marie France Poupon, Curie Institute, Paris- France. PC3 (prostate carcinoma), HeLa (cervical epithelial carcinoma) were grown in RPMI 1640 medium (Invitrogen) supplemented with 10 % heat inactivated fetal bovine serum, 1 % of L-glutamine, 1 % streptomicyn, 100 units/mL penicillin (all obtained from Sigma Aldrich USA). MCF-7 (breast carcinoma, no overexpresses the HER2/c-erb-2 gene), SKBR-3 (breast carcinoma, overexpresses the HER2/c-erb-2 gene) and primary culture of normal human dermis fibroblast used as control cells were grown in Dulbecco's Modified Eagle Medium (Invitrogen). Cells were grown in a humidified incubator with 5 % CO_2 and 95 % air at 37 °C until they reach the exponential growth phase. For treatments exponentially growing cells were collected, counted, re-suspended in fresh culture medium and incubated in 96-sterile-well plates.

Cytotoxic activity

Cell viability was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) for assay, which is based on the ability of viable cells to metabolically reduce a yellow tetrazolium salt (MTT; Sigma) to a purple formazan product. This reaction takes place when mitochondrial reductases are active (Mosmann, 1983). Cells were grown in 96-well plates (5×10^3 cells/well) for 24 h. Cultures were carried out at 37 °C in a humidified atmosphere with 5 % CO_2. cells were incubated with the synthetics products or chemotherapeutic drugs in 100 µL of complete culture medium containing 0, 1, 5, 10, 25, 100 µg/mL concentrations of each compounds for 72 h. After incubation, the medium was removed and the cells were treated with 100 µL 0.4 mg/mL MTT for 3 h at 37 °C. Subsequently, 100 µL DMSO was added to the mixture. The solubilized formazan product was quantified with the help of a microtiter plate reader TECAN-sunrise at 570 nm. Adriamycin was used as a positive control in the assay. In all cases, the compounds were dissolved in DMSO, at the final concentration in the culture medium was lower than 1 %, a concentration that had neither cytotoxic effect nor caused any interference with the colorimetric detection method.

Selectivity index (SI) and statistical analysis

The SI was calculated as the IC_{50} (control cells)/IC_{50} (tumoral cell line) ratio. A SI > 1 indicates that the cytotoxicity on tumoral cells surpassed that on healthy non-tumoral cells (Nugroho et al., 2013). All experiments were performed at least three times. The results are expressed as mean ± SD. Anova test were performed. Only post hoc Dunnet test $P < 0.01$ was considered to be statistically significant. The dose–response curves were plotted with the OriginPro ver.8.0 programs, and 50 % growth inhibitory concentrations (IC_{50}) of synthetics products or chemotherapeutic drugs were determined by a non-linear regression of individual experiments calculated through computation with GraphPad prism v.5.02 software program (Intuitive Software for Science, San Diego, CA, USA).

Results and discussion

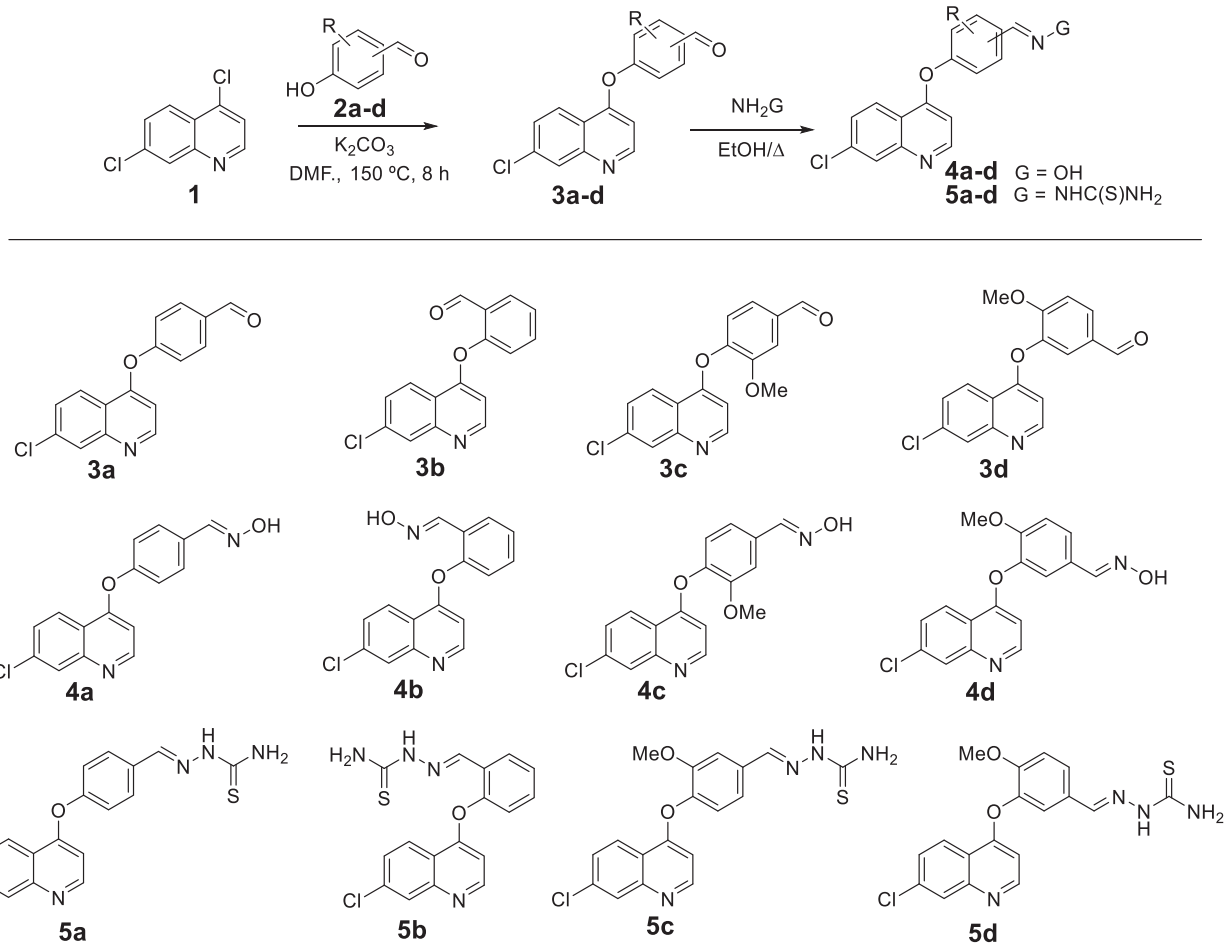
Chemistry

The 4-((7-chloroquinolin-4-yl)oxy)benzaldehyde molecules **3a–d** were easily obtained from inexpensive and commercially available 4,7-dichloroquinoline **1** and functionalized phenols **2** (*p*-hydroxybenzaldehyde **2a**, *o*-hydroxybenzaldehyde **2b**, vanillin **2c** and iso-vanillin 2**d**) through a nucleophilic reaction in the presence of K_2CO_3 in DMF (Scheme1).

Then, prepared quinolin-4-oxybenzaldehydes **3** were subjected to addition-elimination reactions with hydroxyamine and thiosemicarbazine to generate a small series of 7-chloro-4-phenoxyquinolines possessing oxime and thiosemicarbazone scaffolds **4** and **5**, respectively. All compounds were prepared in good to excellent yields, and obtained as stable crystalline substances with well-defined melting points. Their structures were easily assigned by IR and MS (Table 1), and confirmed by ^{1}H and ^{13}C NMR experiments.

Computational analysis: study of bioavailability parameters

It is well known that a considerable number of new synthetic compounds with significant activity failed during human clinical trials due to ADME and toxicity problems (Hou et al., 2006). One of the preliminary steps in high-throughput screening process for drug research is to use in silico drug-likeness evaluation of desired molecules to be prepared, giving information about its bioavailability. Taking into consideration these facts, the Molinspiration Cheminformatics software (Lipinski et al., 1997) was used in this study. Therefore, all synthesized molecules were subjected to the Lipinski's Rule of Five analysis, associated to drug-like physicochemical parameters (molecular weight, lipophilicity (Log P), hydrogen bond acceptor and donor properties, polar surface area and rotatable bonds), which can predict oral bioavailability and membrane permeability of the synthetic molecules. Thus, according to these criteria, all the quinoline derivatives studied in the current research displayed good bioavailability properties as no violation to



Scheme 1 Synthesis of tested 7-chloro-4-phenoxyquinoline derivatives

Table 1 Physicochemical properties of prepared 4-phenoxyquinoline derivatives **3–5**

Compounds	Formula	Yield (%)	*M*p (°C)	MW (g/mol)	MS ($M^{+\bullet}$, *m/z*)
3a	$C_{16}H_{10}NClO_2$	85	130–133	283.5	283
3b	$C_{16}H_{10}NClO_2$	65	80–83	283.5	283
3c	$C_{17}H_{12}NClO_3$	65	140–143	313.5	313
3d	$C_{17}H_{12}NClO_3$	73	70–73	313.5	313
4a	$C_{16}H_{11}ClN_2O_2$	99	170–173	298.7	280[a]
4b	$C_{16}H_{11}ClN_2O_2$	99	158–160	298.7	280[a]
4c	$C_{17}H_{13}ClN_2O_3$	99	180–183	328.8	310[a]
4d	$C_{17}H_{13}ClN_2O_3$	99	190–192	328.8	310[a]
5a	$C_{17}H_{13}ClN_4OS$	90	190–193	356.8	nd
5b	$C_{17}H_{13}ClN_4OS$	80	180–183	356.8	nd
5c	$C_{18}H_{15}ClN_4O_2S$	77	155–158	386.9	nd
5d	$C_{18}H_{15}ClN_4O_2S$	76	145–148	386.9	nd

nd not detected

[a] ion corresponds to H_2O elimination

Table 2 Molecular properties related to bioavailability of new 4-aryloxyquinoline derivatives **3–5**

Compounds	Type	MW (g/mol)	% Absorption	Log *P*	TPSA	H_A	H_D	ROTB	Lipinski's rule violation	Drug-score
3a	**I**	283.7	95.48	4.37	39.18	3	0	3	0	0.10
3b	**I**	283.7	95.48	4.37	39.18	3	0	3	0	0.14
3c	**I**	313.7	92.29	4.16	48.43	4	0	4	0	0.10
3d	**I**	313.7	92.29	4.16	48.43	4	0	4	0	0.12
4a	**II**	298.7	89.09	4.98	57.72	4	1	3	0	0.45
4b	**II**	298.7	89.09	4.98	57.72	4	1	3	0	0.46
4c	**II**	328.8	86.94	4.79	63.95	5	1	4	0	0.44
4d	**II**	328.8	86.94	4.79	63.95	5	1	4	0	0.43
5a	**III**	356.8	83.97	4.50	72.54	5	3	5	0	0.46
5b	**III**	356.8	83.97	4.50	72.54	5	3	5	0	0.47
5c	**III**	386.9	80.79	4.31	81.77	6	3	6	0	0.47
5d	**III**	386.9	80.79	4.31	81.77	6	3	6	0	0.47
Adr.	–	543.5	37.90	0.48	206.1	12	7	5	1	7.19

Percentage of absorption is calculated by % Absorption = 109−(0.345 × TPSA)

Drug-score was calculated by OSIRIS program

TPSA, topological polar surface area, *Log P* logarithm of partition coefficient of the molecule in an octanol/water system calculated by Molinspiration online tool, H_A hydrogen bond acceptors, H_D hydrogen bond donors, *ROTB* number of rotatable bonds, Adr.adriamycin

this rules was observed (Table 2). However, it should be noted that the values of calculated partition coefficient (Log P) are above the lipophilicity optimum interval ($0 < \text{Log } P < 3$). This means that all synthetized quinoline molecules have a low water solubility character (Log $P > 4.31$-4.98) that could compromise the absorption properties of these compounds (Kerns and Di, 2008).

Bearing this in mind, we addressed to study different molecular descriptors as the topological polar surface area (TPSA = 39.18–81.77; ROTB ≤ 10) and the absorption percentage (% Abs).This study confirmed the potential intestinal absorption, bioavailability and hematoencephalic barrier permeation of our compounds according to Veber's rules (TPSA < 140 A^2; Veber et al., 2002). The same way a good plasmatic membrane permeability as their % Abs ranged between 80.78 and 95.48 %, even higher than the adriamycin, could be expected (Zhao et al., 2002). In summary, this in silico study pointed the quinoline derivatives synthesized in our work as potential models for new antitumor agents development.

Cytotoxic activity

In this study, 12 substituted phenoxyquinolines **3–5** of the series **I–III** were tested in four cancer cell lines, as well as a normal cell line. MCF-7, SKBR-3, PC3, HeLa were used to study their potential human tumor cell growth inhibitory effect. As control cells, primary culture of human dermis fibroblast (non-tumor cells) was employed to discern an unspecific cytotoxicity of prepared phenoxyquinolines. Reference anticancer drug was adriamycin and the cytotoxic activity was evaluated using MTT assay. Biological results are shown in Table 3. The analysis of the quinoline derivatives of each series (**I**, **II** and **III**) and the cytotoxic activities revealed some structure–activity relationships. First, some quinoline derivatives **3** with formyl function (series **I**) and quinolines **5** possessing thiosemicarbazone scaffold (series **III**) were active against all four cancer cell lines (comp. **3a**, **3d**, **5d**), while quinoline molecules **4** bearing oxime function (series **II**) resulted practically inactive against all cancer cell lines studied (comp. **4a, 4b, 4c** and **4d**). Within the series **I**, phenoxyquinoline **3a** has more pronounced cytotoxic effect on breast carcinoma cells with IC_{50} 18.47 μM, whereas phenoxyquinoline **3d** displayed considerable cytotoxic activity against cervical epithelial carcinoma cells (IC_{50} 9.18 μM) close to adriamycin toxic effect (IC_{50} 3.62 μM). Despite the cytotoxic activity of our compounds are lower than the adriamycin drug, we found a new potential lead in cervix cancer research, **3d**, $IC_{50} < 10$ μM. On the other hand, the **3a** and **3d** compounds presented also midcytotoxic activity against PC3 cells, 22.14 and 21.29 μM, respectively. Phenoxyquinolines **5c** and **5d** (series **III**) exhibited also significant cytotoxic activity against PC3 and HeLa tumor cells (Table 3).Among this series, the compound **5d** showed the best inhibitory action with a IC_{50} equal to 11.58 μM.

According with the structure–activity relationship analysis, the inclusion of an oxime functional group (series **II**) decreases the potential inhibitory action against these carcinoma lines. Nevertheless, although the best result was acquired with the carbonyl group original from vainillin, the thiosemicarbazone functional group insertion allows to reach good results in more cell's variability. In consequence, compound **5d** has been active against more cancer cells lines.

Regarding the cytotoxicity on human dermis fibroblast, in general the phenoxyquinolines are not toxic for normal human cells, however a low activity was detected for thephenoxyquinoline **3d** (IC_{50} 328.34 μM). The phenoxyquinoline **5d** was the most toxic compound showing IC_{50} 61.28 μM.

Comparison of cytotoxicity and nonspecific cytotoxicity of the tested compounds is presented in Table 4. According to this results, quinoline compound **3d** presented a high selectivity for the four tumor cell lines MCF-7, SKBR-3, PC3 and HeLa evaluated for the cells control, while the compounds **3c** and **5b** were more specific for tumor lines PC3, displaying high selectivity ($SI > 7.7$). At that time, the quinoline derivative **3a** tested for all tumor lines showed a moderate selectivity ($SI \leq 7.7$), as well as derivatives **3c** in MCF-7 and HeLa, and **5d** for HeLa.

The remaining compounds have low SI values ($SI < 5.5$) with respect to control cells. Several studies have shown

Table 3 Biological activity of the 7-chloro-4-phenoxyquinolines **3–5**

Compounds	Type	Cytotoxicity IC_{50} (μM)				Unspecific cytotoxicity IC_{50} (μM)
		MCF-7	SKBR-3	PC3	HeLa	Human dermis fibroblast
3a	**I**	**18.47** ± 1.05	31.62 ± 1.02	22.14 ± 1.16	25.17 ± 1.00	123.05 ± 1.01
3b	**I**	NA	NA	NA	84.35 ± 1.02	275.50 ± 1.26
3c	**I**	54.89 ± 1.01	NA	21.29 ± 1.14	41.22 ± 3.12	318.78 ± 1.02
3d	**I**	50.75 ± 1.04	29.01 ± 1.04	23.11 ± 1.18	**9.18** ± 1.07	328.34 ± 1.39
4a	**II**	NA	NA	NA	NA	334.78 ± 1.01
4b	**II**	NT	NT	NT	NT	NT
4c	**II**	NA	NA	NA	NA	NA
4d	**II**	NA	NA	NA	NA	NA
5a	**III**	NA	NA	50.76 ± 1.04	89.85 ± 1.02	280.27 ± 1.02
5b	**III**	NA	NA	31.89 ± 1.00	94.09 ± 1.02	280.27 ± 1.01
5c	**III**	NA	NA	**15.17** ± 1.13	**16.39** ± 1.04	258.46 ± 1.03
5d	**III**	52.16 ± 1.01	**17.70** ± 1.00	**18.01** ± 1.06	**11.58** ± 1.80	61.28 ± 1.00
Adr.	0.74 ± 0.05	1.66 ± 0.08	2.36 ± 0.4	3.62 ± 0.12	2.45 ± 0.37	

Marked in bold parameters indicated a pronounced anticancer activity

Adr. adriamycin, *NA* not active ($IC_{50} > 100$ μM), *NT* not tested

Table 4 Selectivity index of the prepared 7-chloro-4-phenoxyquinolines **3–5**

Compounds	Type	Selective index, SI[a]				In silico toxic effects			
		MCF-7	SKBR-3	PC3	HeLa	Mutagenic (M)	Tumorigenic (T)	Irritant (I)	Reproductive (R)
3a	**I**	6.7	3.9	5.6	4.9	high-risk	non-risk associated	high-risk	non-risk associated
3b	**I**	—	—	2.0	3.3	high-risk	non-risk associated	high-risk	non-risk associated
3c	**I**	5.8	—	15.0	7.7	high-risk	non-risk associated	high-risk	non-risk associated
3d	**I**	**6.5**	**11.3**	**14.2**	**35.7**	high-risk	non-risk associated	high-risk	non-risk associated
4a	**II**	—	—	—	—	non-risk associated	non-risk associated	non-risk associated	non-risk associated
4c	**II**	—	—	—	—	non-risk associated	non-risk associated	non-risk associated	non-risk associated
4d	**II**	—	—	—	—	non-risk associated	non-risk associated	non-risk associated	non-risk associated
5a	**III**	—	—	5.5	3.1	non-risk associated	non-risk associated	non-risk associated	non-risk associated
5b	**III**	—	—	**8.8**	3.0	non-risk associated	non-risk associated	non-risk associated	non-risk associated
5c	**III**	—	—	**17.0**	**15.8**	non-risk associated	non-risk associated	non-risk associated	non-risk associated
5d	**III**	1.2	3.5	3.4	5.3	non-risk associated	non-risk associated	non-risk associated	non-risk associated
Adr.		3.3	1.5	1.0	0.7	non-risk associated	non-risk associated	non-risk associated	non-risk associated

[a] Marked in bold parameters indicated a pronounced selectivity

that adriamicyn have harmful effects on health and can lead to the development of primary and secondary drug resistance in tumor cells, thereby limiting the clinical success of cancer chemotherapy (Sánchez et al., 2009). Our results showed that the majority of the phenoxyquinolines obtained have a significant selectivity for tumor cells.

On the other hand, the information acquired from the topological analysis of the tested compounds, allowed us to afford substantial information about their potential toxic effects such as mutagenic (M), tumorigenic (T), irritant (I) and reproductive (R; Table 3). Only phenoxyquinolines with formyl function (**3a–d**, series **I**) showed a high-risk profile as tumorigenic and irritant agents.

In an attempt to corelate the bioassay results and the bioavailability expressed through the calculated partition coefficient (CLog *P*), we can concluded that: (1) all molecules have log *P* values lower than five according to Lipinsky's rule, but these values do not entry in the optimal interval; (2) reference drug (adriamycin) has much more marked lipophilic character than the tested aryloxyquinolines and (3)within the group of active molecules there are not much differences between their lipophilicity.

Conclusion

We have easily prepared, by a common and efficient pathway, a new series of 7-chloro-4-phenoxyquinoline derivatives possessing formyl, oxime and thiosemicarbazone scaffolds. The cytotoxicity displayed by these compounds showed to be related to the chemical nature of the function and their position on the aryl moiety linked to the 4-oxyquinoline ring and not to be related to the lipophilicity of the compounds. The 7-chloro-7-phenoxyquinoline derivatives **3a** and **3d** stand out as interesting models for antitumor drugs, displaying good cytotoxic activity against four human cancer cells lines. Compounds **3c**, **3d** have been more selective than other prepared phenoxyquinolines, while **5d** have low selective indexes for all tumor cells. The phenoxyquinoline **3d** stands out by their low unspecific cytotoxicity and highly exceptional selectivity for HeLa cells. These results are important data for the design and synthesis of new 7-chloro-7-phenoxyquinoline-based molecules, which could be a good lead for the development of new anticancer agents.

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Compliance with ethical standards

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

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