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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and anticancer activity of novel tetrahydroquinoline and tetrahydropyrimidoquinoline derivatives

Ehab M. Gedawy[1] · **Asmaa E. Kassab**[1] · **Afaf A. El-Malah**[1]

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Abstract A series of new tetrahydroquinolines with different substituents at C-2 and C-4 positions in addition to several tetrahydropyrimidoquinolin-4-amines and tetrahydropyrimidoquinoline-2,4-diamines were synthesized. The in vitro anticancer activity of all newly synthesized compounds was tested against human colon carcinoma (HCT116) and human breast adenocarcinoma (MCF7) cell lines. Seven compounds **1a**, **5a**, **5b**, **6a**, **6b**, **7a** and **7b** showed potent anticancer activity against both HCT116 and MCF7 cell lines with IC_{50} between 16.33 and 34.28 μM. All these compounds were more potent than imatinib ($IC_{50} = 34.40$ μM) and tamoxifen ($IC_{50} = 34.30$ μM). Compound **7b** was the most active against HCT116 cell line with 2.1-fold more potent antitumor activity than imatinib. Also, compounds **1a**, **5b** and **6a** exhibited the highest anticancer activity against MCF7 cell line, having two- to 1.79-fold more potent anticancer activity than tamoxifen.

Keywords Tetrahydroquinolines · Tetrahydropyrimidoquinolin-4-amines · Tetrahydropyrimidoquinoline-2,4-diamines · Synthesis · Anticancer activity

✉ Ehab M. Gedawy
ehab_gedawy@yahoo.com

[1] Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Cairo University, 33 Kasr El-Aini Street, Cairo 11562, Egypt

Introduction

The discovery of new leads with anticancer potential is still a great interest of medicinal chemists, hoping that they may design more selective and safer anticancer agents. The quinoline core is naturally occurring in many alkaloids with potent antitumor activity, for example, camptothecin (Fig. 1) (Wall *et al*., 1966). It was reported also that a large number of quinolines and their derivatives possessed potent anticancer activity (Chen *et al*., 2005a, b, 2006; Zhao *et al*., 2005; Li *et al*., 2006; Tseng *et al*., 2008, 2012; Al-Said *et al*., 2011; Luniewski *et al*. 2012; Karthikeyan *et al*., 2015). Several studies supported that the pyrimidine nucleus is an important pharmacophore in various antitumor agents (Ghorab *et al*., 1996, 2006a, b; Ghorab, 2000; Abou El Ella *et al*., 2008; Liu *et al*., 2014; Shao *et al*., 2014; Kandeel *et al*., 2015; Ma *et al*., 2015). Moreover, it is present in potent marketed anticancer drugs, for example, gefitinib (Iressa™) (Wakeling *et al*., 2002) and erlotinib (Tarceva™) (Moyer *et al*., 1997), and thus, it is considered as attractive target for the design of new anticancer agents. Recently, several tetrahydroquinolines and their pyrimidine derivatives were synthesized and evaluated for their anticancer activity, and it was found that the tetrahydropyrimidoquinolines **I** and **II** exhibited potent anticancer activity (Faidallah and Rostomb, 2013; Alqasoumi *et al*., 2010) (Fig. 2).

Taking into consideration the above findings, and in an effort to identify novel potent anticancer leads through the combination of the two active anticancer moieties, we decided to prepare several tetrahydroquinolines with different groups at C-2 and C-4 positions, several tetrahydropyrimidoquinolin-4-amines and tetrahydropyrimidoquinoline-2,4-diamines with different aryl groups at position number 5 to substantiate the possible effects of these substitutions on the

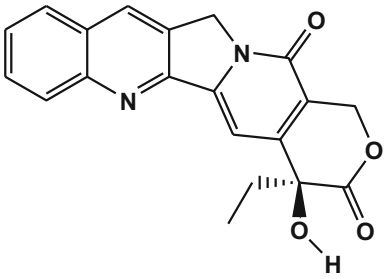


Fig. 1 Structure of camptothecin

anticancer activity against both human colon carcinoma (HCT116) and human breast adenocarcinoma (MCF7) cell lines.

Materials and methods

Chemistry

Melting points were obtained on a Griffin apparatus and were uncorrected. Microanalyses for C, H and N were carried out at the microanalytical center, Al-Azhar University. IR spectra were recorded on a Shimadzu 435 spectrometer, using KBr disks. ^{1}H NMR and ^{13}C NMR spectra were performed on JOEL NMR FXQ-300 MHz and JOEL NMR FXQ-400 MHz using TMS, as the internal standard. Mass spectra were recorded on a GCMP-QP1000 EX Mass spectrometer. Progress of the reactions was monitored by TLC, using precoated aluminum sheet silica gel MERCK 60F 254, and was visualized by UV lamp. The substituted benzylidenmalononitriles **4a** and **b** were synthesized from the condensation of the appropriate benzaldehyde with malononitrile in ethanol, in the presence of catalytic amount of potassium hydroxide according to the reported procedure (Patai and Israeli, 1960).

General procedure for the preparation of compounds (1a–c)

A mixture of cyclohexanone (4.9 g, 0.05 mol), the appropriate pyridine carboxaldehyde (0.05 mol), ethyl cyanoacetate (5.65 g, 0.05 mol) and ammonium acetate (30.8 g, 0.4 mol) in n-butanol (150 mL) was heated under reflux for 8 h. After cooling, the separated solid was filtered, washed with ethanol, dried and crystallized from ethanol.

2-Oxo-4-(pyridin-2-yl)-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (***1a***) Brown solid (ethanol); this compound was prepared from heating under reflux a mixture of cyclohexanone (4.9 g, 0.05 mol), 2-pyridine carboxaldehyde (5.35 g, 0.05 mol), ethyl cyanoacetate (5.65 g, 0.05 mol) and ammonium acetate (30.8 g, 0.4 mol) in n-butanol (150 mL) for 8 h. After cooling, the separated solid was filtered and washed with ethanol. It was obtained 7.53 g of **1a** (yield 60 %), brown solid; mp > 300 °C; IR (KBr) ν_{max}: 3143, 2222, 1647 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz,): δ = 12.40 (1H, s, NH, D_2O exchangeable), 8.71–8.60 (1H, m, J = 6.0 Hz, H-6′), 7.98–7.87 (1H, m, J = 6.0 Hz, H-4′), 7.54–7.48 (1H, m, J = 6.0 Hz, H-3′), 7.46–7.42 (1H, m, J = 6.0 Hz, H-5′), 2.64–2.59 (2H, m, H-8), 2.11–2.03 (2H, m, H-5), 1.69–1.66 (2H, m, H-7), 1.59–1.54 (2H, m, H-6); ^{13}C NMR (DMSO-d$_6$, 300 MHz,): δ = 159.58 (C, C-4), 158.32 (C, C=O), 150.73 (C, C-2′), 150.08 (CH, C-6′), 147.68 (CH, C-4′), 135.54 (C, C-8a), 131.46 (CH, C-5′), 123.46 (C, C-3), 115.90 (C, C≡N), 112.43 (CH, C-3′), 100.72 (C, C-4a), 27.21 (CH_2, C-8), 24.77 (CH_2, C-5), 21.67 (CH_2, C-7), 20.44 (CH_2, C-6); EIMS m/z 251 $[M]^+$ (41.51), 78 (100); Anal. Calcd. for

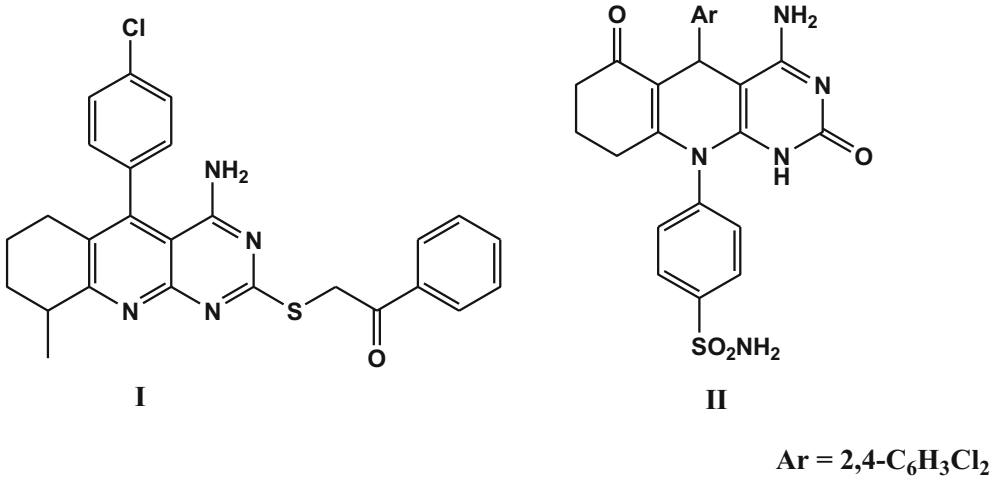


Fig. 2 Structure of potent anticancer tetrahydropyrimidoquinolines

$C_{15}H_{13}N_3O$ (251.28): C, 71.70; H, 5.21; N, 16.72. Found: C, 71.79; H, 5.24; N, 16.89.

2-Oxo-4-(pyridin-3-yl)-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile ***(1b)*** Yellow crystals (ethanol); this compound was prepared from heating under reflux a mixture of cyclohexanone (4.9 g, 0.05 mol), 3-pyridine carboxaldehyde (5.35 g, 0.05 mol), ethyl cyanoacetate (5.65 g, 0.05 mol) and ammonium acetate (30.8 g, 0.4 mol) in n-butanol (150 mL) for 8 h. After cooling, the separated solid was filtered and washed with ethanol. It was obtained 7.9 g of **1b** (yield 63 %), yellow crystals; mp 248–250 °C; IR (KBr) ν_{max}: 3147, 2218, 1658 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,): $\delta = 12.48$ (1H, s, NH, D_2O exchangeable), 8.69 (1H, d, $J = 4.8$ Hz, H-2′), 8.55 (1H, s, H-6′), 7.84 (1H, d, $J = 4.8$ Hz, H-4′), 7.58–7.53 (1H, m, $J = 4.8$ Hz, H-5′), 2.66–2.62 (2H, t, $J = 6.3$ Hz, H-8), 2.06–2.02 (2H, t, $J = 6.3$ Hz, H-5), 1.71–1.67 (2H, m, H-7), 1.60–1.55 (2H, m, H-6); ^{13}C NMR (DMSO-d_6, 400 MHz,): $\delta = 160.07$ (C, C-4), 158.91 (C, C=O), 151.22 (CH, C-2′), 150.67 (CH, C-6′), 148.23 (C, C-8a), 136.05 (CH, C-4′), 131.99 (C, C-3′), 124.02 (CH, C-5′), 116.46 (C, C-3), 112.89 (C, C-4a), 101.29 (C, C≡N), 27.71 (CH_2, C-8), 25.29 (CH_2, C-5), 22.22 (CH_2, C-7), 20.98 (CH_2, C-6); EIMS m/z 251 $[M]^+$ (100); Anal. Calcd. for $C_{15}H_{13}N_3O$ (251.28): C, 71.70; H, 5.21; N, 16.72. Found: C, 71.81; H, 5.25; N, 16.85.

2-Oxo-4-(pyridin-4-yl)-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile ***(1c)*** Orange solid (ethanol); this compound was prepared from heating under reflux a mixture of cyclohexanone (4.9 g, 0.05 mol), 4-pyridine carboxaldehyde (5.35 g, 0.05 mol), ethyl cyanoacetate (5.65 g, 0.05 mol) and ammonium acetate (30.8 g, 0.4 mol) in n-butanol (150 mL) for 8 h. After cooling, the separated solid was filtered and washed with ethanol. It was obtained 8.8 g of **1c** (yield 70 %), orange solid; mp > 300 °C; IR (KBr) ν_{max}: 3115, 2216, 1674 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,): $\delta = 12.51$ (1H, s, NH, D_2O exchangeable), 7.46 (2H, d, $J = 4.5$ Hz, H-2′, H-6′), 7.38 (2H, d, $J = 4.5$ Hz, H-3′, H-5′), 2.66–2.62 (2H, t, $J = 6.0$ Hz, H-8), 2.03–1.99 (2H, t, $J = 6.0$ Hz, H-5), 1.70–1.65 (2H, m, H-7), 1.60–1.55 (2H, m, H-6),; ^{13}C NMR (DMSO-d_6, 300 MHz,): $\delta = 159.98$ (C, C-4), 158.50 (C, C=O), 151.38 (C, C-4′), 151.23 (CH, C-2′, C-6′), 149.08 (C, C-8a), 148.76 (C, C-3), 143.43 (CH, C-3′, C-5′), 123.31 (C, C-4a), 115.86 (C, C≡N), 27.48 (CH_2, C-8), 24.57 (CH_2, C-5), 21.65 (CH_2, C-7), 20.51 (CH_2, C-6); EIMS m/z 251 $[M]^+$ (100); Anal. Calcd. for $C_{15}H_{13}N_3O$ (251.28): C, 71.70; H, 5.21; N, 16.72. Found: C, 71.83; H, 5.24; N, 16.87.

General procedure for the preparation of compounds (2a–c)

A mixture of the corresponding quinolones **1a–c** (0.0075 mol), N,N-dimethylaniline (10 mL) and phosphorous oxychloride (10 mL) was heated under reflux for 10 h. The reaction mixture was cooled and poured into crushed ice. The formed solid was filtered off, dried and crystallized from ethanol.

2-Chloro-4-(pyridin-2-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile ***(2a)*** Brown solid (ethanol); this compound was prepared from heating under reflux a mixture of compound **1a** (1.88 g, 0.0075 mol), N,N-dimethylaniline (10 mL) and phosphorous oxychloride (10 mL) for 10 h. The reaction mixture was cooled and poured into crushed ice. The formed solid was filtered off and dried. It was obtained 1.3 g of **2a** (yield 65 %), brown solid; mp 141–143 °C; IR (KBr) ν_{max}: 2280, 1600 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,): $\delta = 8.86$–8.82 (1H, m, H-6′), 7.49–7.12 (1H, m, H-4′), 6.87–6.54 (2H, m, H-5′, H-3′), 3.00–2.95 (2H, m, H-8), 1.95–1.51 (4H, m, H-7, H-5), 1.33–1.22 (2H, m, H-6); EIMS m/z 271 $[M+2]^+$ (20.26), 269 $[M]^+$ (59.10), 268 (100); Anal. Calcd. for $C_{15}H_{12}ClN_3$ (269.73): C, 66.79; H, 4.48; N, 15.58. Found: C, 66.83; H, 4.51; N, 15.46.

2-Chloro-4-(pyridin-3-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile ***(2b)*** Blue solid (ethanol); this compound was prepared from heating under reflux a mixture of compound **1b** (1.88 g, 0.0075 mol), N,N-dimethylaniline (10 mL) and phosphorous oxychloride (10 mL) for 10 h. The reaction mixture was cooled and poured into crushed ice. The formed solid was filtered off and dried. It was obtained 1.37 g of **2b** (yield 68 %), blue solid; mp 232–234 °C; IR (KBr) ν_{max}: 2229, 1600 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,): $\delta = 8.73$ (1H, d, $J = 4.2$ Hz, H-2′), 8.64 (1H, s, H-6′), 7.92 (1H, d, $J = 7.8$ Hz, H-4′), 7.62–7.58 (1H, t, $J = 7.8$ Hz, H-5′), 2.98–2.94 (2H, t, $J = 6.3$ Hz, H-8), 2.43–2.39 (2H, t, $J = 6.3$ Hz, H-5), 1.85–1.80 (2H, m, H-7), 1.71–1.65 (2H, m, H-6); ^{13}C NMR (DMSO-d_6, 400 MHz,): $\delta = 163.53$ (C, C-8a), 153.33 (C, C-2), 150.72 (CH, C-2′), 148.37 (C, C-4), 142.93 (CH, C-6′), 130.56 (C, C-4a), 130.33 (CH, C-4′), 129.43 (C, C-3′), 123.36 (CH, C-5′), 114.89 (C, C-3), 113.13 (C, C≡N), 33.18 (CH_2, C-8), 26.71 (CH_2, C-5), 21.86 (CH_2, C-7), 21.78 (CH_2, C-6); EIMS m/z 271 $[M+2]^+$ (20.58), 269 $[M]^+$ (65.38), 268 (100); Anal. Calcd. for $C_{15}H_{12}ClN_3$ (269.73): C, 66.79; H, 4.48; N, 15.58. Found: C, 66.86; H, 4.51; N, 15.67.

2-Chloro-4-(pyridin-4-yl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile ***(2c)*** Gray solid (ethanol); this compound was prepared from heating under reflux a mixture of compound **1c** (1.88 g, 0.0075 mol), N,N-dimethylaniline

(10 mL) and phosphorous oxychloride (10 mL) for 10 h. The reaction mixture was cooled and poured into crushed ice. The formed solid was filtered off and dried. It was obtained 1.47 g of **2c** (yield 73 %), gray solid; mp 190–192 °C; IR (KBr) ν_{max}: 2233, 1597 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,): $\delta = 8.78$ (2H, d, $J = 5.7$ Hz, H-2′, H-6′), 7.48 (2H, d, $J = 5.7$ Hz, H-3′, H-5′), 2.97–2.93 (2H, t, $J = 6.0$ Hz, H-8), 2.40–2.36 (2H, t, $J = 6.0$ Hz, H-5), 1.83–1.77 (2H, m, H-7), 1.70–1.64 (2H, m, H-6),; ^{13}C NMR (DMSO-d_6, 400 MHz,): $\delta = 167.99$ (C, C-8a), 159.81 (C, C-2), 158.84 (C, C-4), 151.00 (CH, C-2′, C-6′), 148.84 (C, C-4′), 132.20 (C, C-3′, C-5′), 130.42 (C, C-4a), 111.54 (C, C-3), 111.42 (C, C≡N), 27.28 (CH_2, C-8), 27.21 (CH_2, C-5), 22.84 (CH_2, C-7), 22.17 (CH_2, C-6); EIMS m/z 271 $[M+2]^+$ (36.93), 269 $[M]^+$ (90.31), 268 (100); Anal. Calcd. for $C_{15}H_{12}ClN_3$ (269.73): C, 66.79; H, 4.48; N, 15.58. Found: C, 66.87; H, 4.52; N, 15.65.

General procedure for the preparation of compounds (3a–c)

To a cold solution of sodium (0.506 g, 0.022 mol) in absolute ethanol (50 mL), guanidine hydrochloride (1.84 g, 0.022 mol) was added. The formed sodium chloride was filtered and washed with ethanol, and the filtrate was evaporated under reduced pressure. The formed oily mass was diluted with pyridine (5 mL), and finally, the corresponding 2-chloroquinoline-3-carbonitrile **2a–c** (0.0033 mol) was added. The reaction mixture was heated under reflux for 5 h, cooled and finally poured on water (25 mL). The formed precipitate was filtered and crystallized from ethanol.

*5-(Pyridin-2-yl)-6,7,8,9-tetrahydropyrimido[4,5-b]quinoline-2,4-diamine **(3a)*** Brown solid (ethanol); to a cold solution of sodium (0.506 g, 0.022 mol) in absolute ethanol (50 mL), guanidine hydrochloride (1.84 g, 0.022 mol) was added. The formed sodium chloride was filtered and washed with ethanol, and the filtrate was evaporated under reduced pressure. The formed oily mass was diluted with pyridine (5 mL), and finally, the corresponding 2-chloroquinoline-3-carbonitrile **2a** (0.89 g, 0.0033 mol) was added. The reaction mixture was heated under reflux for 5 h, cooled and finally poured on water (25 mL). The formed precipitate was filtered and washed with ethanol. It was obtained 0.78 g of **3a** (yield 81 %), brown solid; mp > 300 °C; IR (KBr) ν_{max}: 3417–3240, 1604 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,); $\delta = 8.00–6.40$ (8H, m, H-3′, H-4′, H-5′, H-6′ and $2NH_2$), 2.85–2.80 (2H, m, H-8), 1.90–1.75 (2H, m, H-5), 1.30–1.15 (4H, m, H-6, H-7); EIMS m/z 292 $[M]^+$ (2.42), 63 (100); Anal. Calcd. for $C_{16}H_{16}N_6$ (292.34): C, 65.74; H, 5.52; N, 28.75. Found: C, 65.83; H, 5.55; N, 28.88.

*5-(Pyridin-3-yl)-6,7,8,9-tetrahydropyrimido[4,5-b]quinoline-2,4-diamine **(3b)*** Orange crystals (ethanol); to a cold solution of sodium (0.506 g, 0.022 mol) in absolute ethanol (50 mL), guanidine hydrochloride (1.84 g, 0.022 mol) was added. The formed sodium chloride was filtered and washed with ethanol, and the filtrate was evaporated under reduced pressure. The formed oily mass was diluted with pyridine (5 mL), and finally, the corresponding 2-chloroquinoline-3-carbonitrile **2b** (0.89 g, 0.0033 mol) was added. The reaction mixture was heated under reflux for 5 h, cooled and finally poured on water (25 mL). The formed precipitate was filtered and washed with ethanol. It was obtained 0.82 g of **3b** (yield 86 %), orange crystals; mp 174–176 °C; IR (KBr) ν_{max}: 3367–3167, 1597 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,): $\delta = 8.75$ (1H, s, H-2′), 8.55 (1H, d, H-6′), 8.45–8.40 (1H, m, H-4′), 7.85–7.80 (1H, m, H-5′),7.38 (2H, s, C-4 NH_2, D_2O exchangeable), 6.58 (2H, s, C-2 NH_2, D_2O exchangeable), 2.60–2.55 (2H, m, H-8), 2.20–2.14 (2H, m, H-5),1.80–1.75 (2H, m, H-7), 1.70–1.60 (2H, m, H-6); EIMS m/z 293 $[M+1]^+$ (0.02), 78 (100); Anal. Calcd. for $C_{16}H_{16}N_6$ (292.34): C, 65.74; H, 5.52; N, 28.75. Found: C, 65.88; H, 5.50; N, 28.92.

*5-(Pyridin-4-yl)-6,7,8,9-tetrahydropyrimido[4,5-b]quinoline-2,4-diamine **(3c)*** Brown solid (ethanol); to a cold solution of sodium (0.506 g, 0.022 mol) in absolute ethanol (50 mL), guanidine hydrochloride (1.84 g, 0.022 mol) was added. The formed sodium chloride was filtered and washed with ethanol, and the filtrate was evaporated under reduced pressure. The formed oily mass was diluted with pyridine (5 mL), and finally, the corresponding 2-chloroquinoline-3-carbonitrile **2c** (0.89 g, 0.0033 mol) was added. The reaction mixture was heated under reflux for 5 h, cooled and finally poured on water (25 mL). The formed precipitate was filtered and washed with ethanol. It was obtained 0.74 g of **3c** (yield 77 %), brown solid; mp > 300 °C; IR (KBr) ν_{max}: 3369–3134, 1597 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,): $\delta = 8.70$ (2H, d, H-2′, H-6′), 7.62 (2H, d, H-3′, H-5′), 7.39 (2H, s, C-4 NH_2, D_2O exchangeable), 6.50 (2H, s, C-2 NH_2, D_2O exchangeable), 2.65–2.60 (2H, m, H-8), 2.15–2.10 (2H, m, H-5), 1.80–1.75 (2H, m, H-7), 1.65–1.60 (2H, m, H-6); EIMS m/z 291$[M-1]^+$ (3.58), 269 (100); Anal. Calcd. for $C_{16}H_{16}N_6$ (292.34): C, 65.74; H, 5.52; N, 28.75. Found: C, 65.84; H, 5.55; N, 28.90.

*General procedure for the preparation of compounds (**5a and b**)*

To a solution of menthone (1.54 g, 0.01 mol) in absolute ethanol (30 mL), the appropriate arylidenemalononitrile **4a** and **b** (0.01 mol) and ammonium acetate (6.08 g,

0.08 mol) were added. The mixture was heated under reflux for 5 h. The separated solid was collected by filtration, dried and crystallized from ethanol.

*2-Amino-4-(4-chlorophenyl)-8-isopropyl-5-methyl-5,6,7,8-tetrahydro-quinoline-3-carbonitrile **(5a)*** Buff solid (ethanol); to a solution of menthone (1.54 g, 0.01 mol) in absolute ethanol (30 mL), arylidenemalononitrile **4a** (1.88 g, 0.01 mol) and ammonium acetate (6.08 g, 0.08 mol) were added. The mixture was heated under reflux for 5 h. The separated solid was collected by filtration, dried and washed with ethanol. It was obtained 2.75 g of **5a** (yield 81 %), buff solid; mp 162–164 °C; IR (KBr) ν_{max}: 3421,3344, 2210, 1616 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,): $\delta = 7.60–7.52$ (2H, dd, $J = 6.0$ Hz, H-2′, H-6′), 7.44–7.29 (2H, dd, $J = 6.0$ Hz, H-3′, H-5′), 6.53 (2H, s, NH_2, D_2O exchangeable), 2.95–2.90 (1H, m, H-8), 2.66–2.58 (2H, m, $CH(CH_3)_2$ isopropyl, H-5), 1.66–1.57 (4H, m, H-6, H-7), 0.99 (3H, d, $J = 6.6$ Hz, C-5 CH_3), 0.71 (3H, d, $J = 7.5$ Hz, –$CHCH_3$ isopropyl), 0.65 (3H, d, $J = 7.2$ Hz, –$CHCH_3$ isopropyl); ^{13}C NMR (DMSO-d_6, 400 MHz,): $\delta = 164.32$ (C, C-2), 156.85 (C, C-8a), 152.84 (C, C-4), 134.90 (C–Cl, C-4′), 130.18 (C, C-1′), 129.45 (CH, C-3′, C-5′), 128.96 (CH, C-2′, C-6′), 128.86 (C, C-4a), 127.14 (C, C-3), 116.48 (C, C≡N), 46.91 (CH, C-8), 32.22 (CH, –$CHCH_3$ isopropyl), 29.83 (CH, C-5), 28.30 (CH_2, C-6), 21.56 (CH_2, C-7), 20.62 (CH_3, C-5 CH_3), 16.55 (CH_3, –$CHCH_3$ isopropyl), 16.35 (CH_3, –$CHCH_3$ isopropyl); EIMS m/z 341 $[M+2]^+$ (4.28), 339 $[M]^+$ (12.58), 297 (100); Anal. Calcd. for $C_{20}H_{22}ClN_3$ (339.86): C, 70.68; H, 6.52; N, 12.36. Found: C, 70.84; H, 6.58; N, 12.45.

*2-Amino-4-(4-fluorophenyl)-8-isopropyl-5-methyl-5,6,7,8-tetrahydro-quinoline-3-carbonitrile **(5b)*** Yellow crystals (ethanol); to a solution of menthone (1.54 g, 0.01 mol) in absolute ethanol (30 mL), arylidenemalononitrile **4b** (1.72 g, 0.01 mol) and ammonium acetate (6.08 g, 0.08 mol) were added. The mixture was heated under reflux for 5 h. The separated solid was collected by filtration, dried and washed with ethanol. It was obtained 2.16 g of **5b** (yield 67 %), yellow crystals; mp 122–124 °C; IR (KBr) ν_{max}: 3491,3352, 2210, 1612 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,): $\delta = 7.41$ (2H, d, $J = 7.8$ Hz, H-2′, H-6′), 7.36 (2H, d, $J = 7.8$ Hz, H-3′, H-5′), 6.52 (2H, s, NH_2, D_2O exchangeable), 2.92–2.91 (1H, m, H-8), 2.70–2.63 (2H, m, –$CHCH_3$ isopropyl, H-5), 1.66–1.57 (4H, m, H-6, H-7), 0.99 (3H, d, $J = 6.9$ Hz, C-5 CH_3), 0.72 (3H, d, $J = 7.2$ Hz, –$CHCH_3$ isopropyl), 0.63 (3H, d, $J = 7.2$ Hz, –$CHCH_3$ isopropyl); ^{13}C NMR (DMSO-d_6, 300 MHz,): $\delta = 163.44$ (C, C-2), 160.30 (C, C-8a), 157.55 (C–F, C-4′), 152.81 (C, C-4), 132.76 (CH, C-3′), 131.43 (CH, C-5′), 130.87 (CH, C-2′), 130.08 (CH, C-6′), 124.87 (C, C-1′), 115.50 (C, C-4a), 115.43 (C, C-3), 113.90 (C, C≡N), 46.16 (CH, C-8), 33.78(CH, –$CHCH_3$ isopropyl), 28.97 (CH, C-5), 28.22 (CH_2, C-6), 21.26 (CH_2, C-7), 20.21 (CH_3, C-5 CH_3), 16.33 (CH_3, –$CHCH_3$ isopropyl), 15.88 (CH_3, –$CHCH_3$ isopropyl); EIMS m/z 323 $[M]^+$ (1.27), 43 (100); Anal. Calcd. for $C_{20}H_{22}FN_3$ (323.41): C, 74.28; H, 6.86; N, 12.99. Found: C, 74.35; H, 6.90; N, 13.01.

*General procedure for the preparation of compounds (**6a** and **b**)*

A mixture of the appropriate 2-aminoquinoline-3-carbonitriles **5a** and **b** (0.01 mol) and excess formamide (15 mL) was refluxed on an oil bath for 15 h at 210 °C. The mixture was cooled. The separated solid was filtered, dried and crystallized from ethanol.

*5-(4-Chlorophenyl)-9-isopropyl-6-methyl-6,7,8,9-tetrahydropyrimido-[4,5-b]quinolin-4-amine **(6a)*** Brown solid (ethanol); A mixture of 2-aminoquinoline-3-carbonitrile **5a** (3.4 g, 0.01 mol) and excess formamide (15 mL) was refluxed on an oil bath for 15 h at 210 °C. The mixture was cooled. The separated solid was filtered and dried. It was obtained 2.5 g of **6a** (yield 68 %), brown solid; mp 155–157 °C IR (KBr) ν_{max}: 3468,3305, 1600 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,): $\delta = 7.81$ (1H, s, H-2), 7.40 (2H, d, $J = 9.0$ Hz, H-2′, H-6′), 7.24 (2H, d, $J = 9.0$ Hz, H-3′, H-5′), 6.19 (2H, s, NH_2, D_2O exchangeable), 2.41–2.34 (1H, m, H-9), 2.24–2.22 (2H, m, –$CHCH_3$ isopropyl, H-6), 1.48–1.34 (4H, m, H-7, H-8), 0.94 (3H, d, C-6 CH_3), 0.77 (3H, d, –$CHCH_3$ isopropyl), 0.52 (3H, d, –$CHCH_3$ isopropyl); ^{13}C NMR (DMSO-d_6, 300 MHz,): $\delta = 162.87$ (CH, C-9a), 160.57 (C, C-4), 155.79 (C, C-10a), 155.54 (CH, C-2), 145.18 (C, C-5), 131.56 (C–Cl, C-4′), 130.76 (CH, C-3′), 129.89 (CH, C-5′), 129.19 (C, C-1′), 127.84 (C, C-5a), 120.77 (CH, C-2′), 120.74 (CH, C-6′), 112.81 (C, C-4a), 47.23 (CH, C-9), 34.77 (CH, –$CHCH_3$ isopropyl), 28.77 (CH, C-6), 27.16 (CH_2, C-7), 20.33 (CH_2, C-8), 20.11 (CH_3, C-6 CH_3), 17.63 (CH_3, –$CHCH_3$ isopropyl), 16.50 (CH_3, –$CHCH_3$ isopropyl); EIMS m/z 368 $[M+2]^+$ (15.59), 366 $[M]^+$ (0.35), 257 (100); Anal. Calcd. for $C_{21}H_{23}ClN_4$ (366.89): C, 68.75; H, 6.32; N, 15.27. Found: C, 68.87; H, 6.29; N, 15.41.

*5-(4-Fluorophenyl)-9-isopropyl-6-methyl-6,7,8,9-tetrahydropyrimido-[4,5-b]quinolin-4-amine **(6b)*** Orange solid (ethanol); A mixture of 2-aminoquinoline-3-carbonitrile **5b** (3.23 g, 0.01 mol) and excess formamide (15 mL) was refluxed on an oil bath for 15 h at 210 °C. The mixture was cooled. The separated solid was filtered and dried. It was obtained 2.94 g of **6b** (yield 84 %), orange solid; mp 260–262 °C; IR (KBr) ν_{max}: 3500, 3321, 1595 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz,): $\delta = 8.43$ (1H, s, H-2), 7.65–7.55 (4H, m, H-2′, H-6′ and NH_2), 7.48 (2H, d, $J = 7.5$ Hz, H-3′, H-5′), 3.15–3.13 (1H, m, H-9), 2.93–2.91 (1H, m, H-6), 2.74–2.72 (1H, m, –$CHCH_3$ isopropyl), 1.77–1.70 (4H, m, H-7, H-8), 1.06 (3H, d, $J = 6.6$ Hz, C-6

CH_3), 0.85 (3H, d, $J = 6.9$ Hz, –$CHCH_3$ isopropyl), 0.70 (3H, d, $J = 6.6$ Hz, –$CHCH_3$ isopropyl); ^{13}C NMR (DMSO-d_6, 400 MHz,): $\delta = 166.85$ (CH, C-9a), 163.96 (C, C-4), 162.69 (C, C-10a), 157.49 (CH, C-2), 157.49 (C–F, C-4′), 145.47 (C, C-5), 135.55 (C, C-1′), 133.54 (CH, C-3′), 132.54 (CH, C-5′), 131.98 (C, C-5a), 131.09 (CH, C-2′), 131.01 (CH, C-6′), 117.17 (C, C-4a), 47.43 (CH, C-9), 29.97 (CH, –$CHCH_3$ isopropyl), 29.37 (CH, C-6), 28.69 (CH_2, C-7), 21.56 (CH_2, C-8), 20.89 (CH_3, C-6 CH_3), 17.07 (CH_3, –$CHCH_3$ isopropyl), 16.24 (CH_3, –$CHCH_3$ isopropyl); EIMS m/z 350 $[M]^+$ (8.72), 43 (100); Anal. Calcd. for $C_{21}H_{23}FN_4$ (350.43): C, 71.98; H, 6.62; N, 15.99. Found: C, 72.06; H, 6.59; N, 16.07.

*General procedure for the preparation of compounds (**7a** and **b**)*

Guanidine hydrochloride (2.1 g, 0.025 mol) was added to a solution of sodium (2.6 g, 0.113 mol) in methanol (95 mL), and the precipitated sodium chloride was filtered off. The *o*-amino cyano derivative **5a** or **5b** (0.015 mol) was added to the filtrate. The reaction mixture was heated under reflux for 6 h. The mixture was cooled, and the separated solid was filtered, washed well with ethanol and crystallized from ethanol.

*5-(4-Chlorophenyl)-9-isopropyl-6-methyl-6,7,8,9-tetrahydropyrimido-[4,5-b]quinoline-2,4-diamine **(7a)*** White solid (ethanol); guanidine hydrochloride (2.1 g, 0.025 mol) was added to a solution of sodium (2.6 g, 0.113 mol) in methanol (95 mL), and the precipitated sodium chloride was filtered off. The *o*-amino cyano derivative **5a** (5.09 g, 0.015 mol) was added to the filtrate. The reaction mixture was heated under reflux for 6 h. The mixture was cooled, and the separated solid was filtered, washed well with ethanol. It was obtained 4.29 g of **7a** (yield 75 %), white solid; mp 284–286 °C; IR (KBr) ν_{max}: 3360–3197, 1658 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz,): $\delta = 7.43$ (2H, d, $J = 6.9$ Hz, H-2′, H-6′), 7.24 (2H, d, $J = 6.9$ Hz, H-3′, H-5′), 7.08 (2H, s, C-4 NH_2, D_2O exchangeable), 5.36 (2H, s, C-2 NH_2, D_2O exchangeable), 2.90–2.85 (1H, m, H-9), 2.62–2.57 (2H, m, –$CHCH_3$ isopropyl, H-6), 1.65–1.61 (4H, m, H-7, H-8), 0.99 (3H, d, $J = 6.9$ Hz, C-6 CH_3), 0.71 (3H, d, $J = 6.9$ Hz, –$CHCH_3$ isopropyl), 0.65 (3H, d, $J = 6.6$ Hz, –$CHCH_3$ isopropyl); ^{13}C NMR (DMSO-d_6, 300 MHz,): $\delta = 168.93$ (C, C-2), 163.14 (C, C-9a), 157.54 (C, C-4), 152.84 (C, C-10a), 145.56 (C, C-5), 135.31 (C, C-1′), 131.94 (C, C-4′), 129.57 (C, C-5a), 128.65 (CH, C-3′), 127.42 (CH, C-5′), 126.45 (C, C-4a), 116.46 (CH, C-2′), 115.40 (CH, C-6′), 46.40 (CH, C-9), 29.59 (CH, –**C**HCH**3** isopropyl), 28.58 (CH, C-6), 28.14 (CH_2, C-7), 22.11 (CH_2, C-8), 20.50 (CH_3, C-6 **C**H_3), 17.35 (CH_3, –CH**C**H_3 isopropyl), 15.87 (CH_3, –CH**C**H_3 isopropyl); EIMS m/z 383 $[M+2]^+$ (0.12), 381 $[M]^+$ (0.08), 315 (100); Anal. Calcd. for $C_{21}H_{24}ClN_5$ (381.9): C, 66.04; H, 6.33; N, 18.34. Found: C, 66.13; H, 6.37; N, 18.47.

*5-(4-Fluorophenyl)-9-isopropyl-6-methyl-6,7,8,9-tetrahydropyrimido-[4,5-b]quinoline-2,4-diamine **(7b)*** Buff solid (ethanol); guanidine hydrochloride (2.1 g, 0.025 mol) was added to a solution of sodium (2.6 g, 0.113 mol) in methanol (95 mL), and the precipitated sodium chloride was filtered off. The *o*-amino cyano derivative **5b** (4.84 g, 0.015 mol) was added to the filtrate. The reaction mixture was heated under reflux for 6 h. The mixture was cooled, and the separated solid was filtered, washed well with ethanol. It was obtained 4.21 g of **7b** (yield 77 %), buff solid; mp 272–274 °C; IR (KBr) ν_{max}: 3363–3194, 1662 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz,): $\delta = 7.41$ (2H, d, $J = 12.0$ Hz, H-2′, H-6′), 7.33 (2H, d, $J = 12.0$ Hz, H-3′, H-5′), 7.03 (2H, s, C-4 NH_2, D_2O exchangeable), 6.52 (2H, s, C-2 NH_2, D_2O exchangeable), 2.94–2.89 (1H, m, H-9), 2.67–2.63 (2H, m, –$CHCH_3$ isopropyl, H-6), 1.66–1.58 (4H, m, H-7, H-8), 1.00 (3H, d, $J = 6.9$ Hz, C-6 CH_3), 0.72 (3H, d, $J = 6.9$ Hz, –$CHCH_3$ isopropyl), 0.65 (3H, d, $J = 6.9$ Hz, –$CHCH_3$ isopropyl); ^{13}C NMR (DMSO-d_6, 400 MHz,): $\delta = 133.29$ (C, C-2), 131.80 (C, C-9a), 131.58 (C, C-4), 130.66 (C, C-4′), 130.58 (C, C-10a), 125.34 (C, C-5), 116.94 (C, C-1′), 116.03 (CH, C-3′, C-5′), 115.95 (C, C-5a), 115.81 (CH, C-2′, C-6′), 115.74 (C, C-4a), 46.64 (CH, C-9), 29.29 (CH, –$CHCH_3$ isopropyl), 28.69 (CH, C-6), 28.23 (CH_2, C-7), 21.45 (CH_2, C-8), 20.93 (CH_3, C-6 CH_3), 16.90 (CH_3, –$CHCH_3$ isopropyl), 16.36 (CH_3, –$CHCH_3$ isopropyl); EIMS m/z 365 $[M]^+$ (18.26), 144 (100); Anal. Calcd. for $C_{21}H_{24}FN_5$ (365.45): C, 69.02; H, 6.62; N, 19.16. Found: C, 69.09; H, 6.67; N, 19.24.

Biological testing

Materials and methods

The human colon carcinoma (HCT116) and human breast adenocarcinoma (MCF7) cell lines were obtained as a gift from NCI, MD, USA.

All chemicals and solvents were purchased from Sigma-Aldrich.

Measurement of anticancer activity

Anticancer screening of the newly synthesized compounds was measured in vitro, on HCT116 and MCF7 cell lines, using Sulforhodamine-B stain (SRB) assay, applying the method of Skehan *et al*., (1990) as follows:

Cells were plated in 96-multi-well plates (104 cells/well), for 24 h, before treatment with the compound to

Table 1 Concentrations required for 50 % inhibition of cell viability (IC_{50})

Compound no.	IC_{50} in μM[a]	
	HCT116	MCF7
1a	50.59	17.13
1b	69.72	>100
1c	66.53	>100
2a	75.09	>100
2b	61.71	>100
2c	69.51	55.39
3a	66.43	37.67
3b	60.27	83.90
3c	76.71	54.79
5a	29.96	30.43
5b	34.28	18.65
6a	30.68	19.12
6b	32.40	24.09
7a	26.41	27.55
7b	16.33	27.26
Imatinib	34.40	–
Tamoxifen	–	34.30

[a] The values given are means of three experiments

allow attachment to the wall of the plate. Different concentrations of the compounds (0, 1, 2.5, 5 and 10 μg/mL) were added to the cell monolayer in triplicate, and wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37 °C, in atmosphere of 5 % CO_2. After 48 h, cells were fixed, washed and stained with Sulforhodamine-B stain. Excess stain was washed with acetic acid, and attached stain was recovered with Tris EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and compound concentration was plotted to get the survival curve for each tumor cell line. For each experimental agent, IC_{50} (concentration which caused 50 % inhibition of cell viability) was calculated and results are given in Table 1.

Results

In vitro anticancer screening

The in vitro anticancer activity of all newly synthesized compounds was evaluated, using HCT116 and MCF7 cell lines. Imatinib and tamoxifen, potent anticancer drugs, were used, in this study, as reference standards.

The relationship between surviving fraction and sample concentration was plotted to obtain the survival curve. The calculated response parameter was IC_{50} (concentration of the compound which causes 50 % inhibition of cell viability).

The synthesized compounds $IC_{50,}$ compared to Imatinib and tamoxifen, are shown in Table 1, and the results are represented graphically in Fig. 3.

From the analysis of the in vitro observed data, it was found, interestingly, that compounds **5a**, **5b**, **6a**, **6b**, **7a** and **7b** showed potent anticancer activity against both HCT116 and MCF7 cell lines, with IC_{50} between 16.33 and 34.28 μM. In addition, compound **1a** (IC_{50} = 17.13 μM) was the most potent compound against MCF7 cell line. Thus, all these compounds are more potent than imatinib (IC_{50} = 34.40 μM) and tamoxifen (IC_{50} = 34.30 μM).

Compound **7b** was found to be the most active against HCT116 cell line (IC_{50} = 16.33 μM), with 2.1-fold more potent antitumor activity than imatinib. Compounds **1a**, **5b** and **6a** (IC_{50} : 17.13, 18.65 and 19.12 μM) exhibited, also, the highest anticancer activity against MCF7 cell line, having two- to 1.79-fold more potent anticancer activity than tamoxifen.

It was found that Compound **3a** (IC_{50} = 37.67 μM) showed antitumor activity against MCF7 cell line, in comparison with tamoxifen.

Moreover, compounds **1a–c**, **2a–c** and **3a–c** showed moderate anticancer activity against HCT116 cell line, while compounds **1b**, **1c**, **2a** and **2b** were inactive against MCF7 cell line.

It was observed that, among the quinoline derivatives **1a–c**, only compound **1a,** with 2-pyridyl moiety at C-4 position, showed potent anticancer activity. Replacement of the carbonyl group at C-2 position with a chloro group in compounds **2a–c** resulted in a marked decrease in the activity. Also the pyrimidoquinolines **3a–c** exhibited weak activity.

Introduction of branched cyclohexyl moiety in quinoline derivatives **5a** and **b** abolished the anticancer potency of these derivatives. Interestingly, in the same manner, this

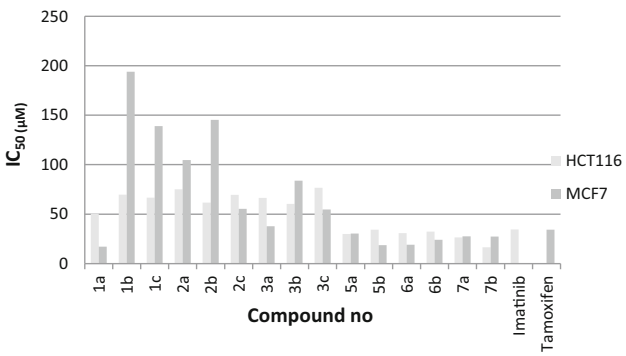
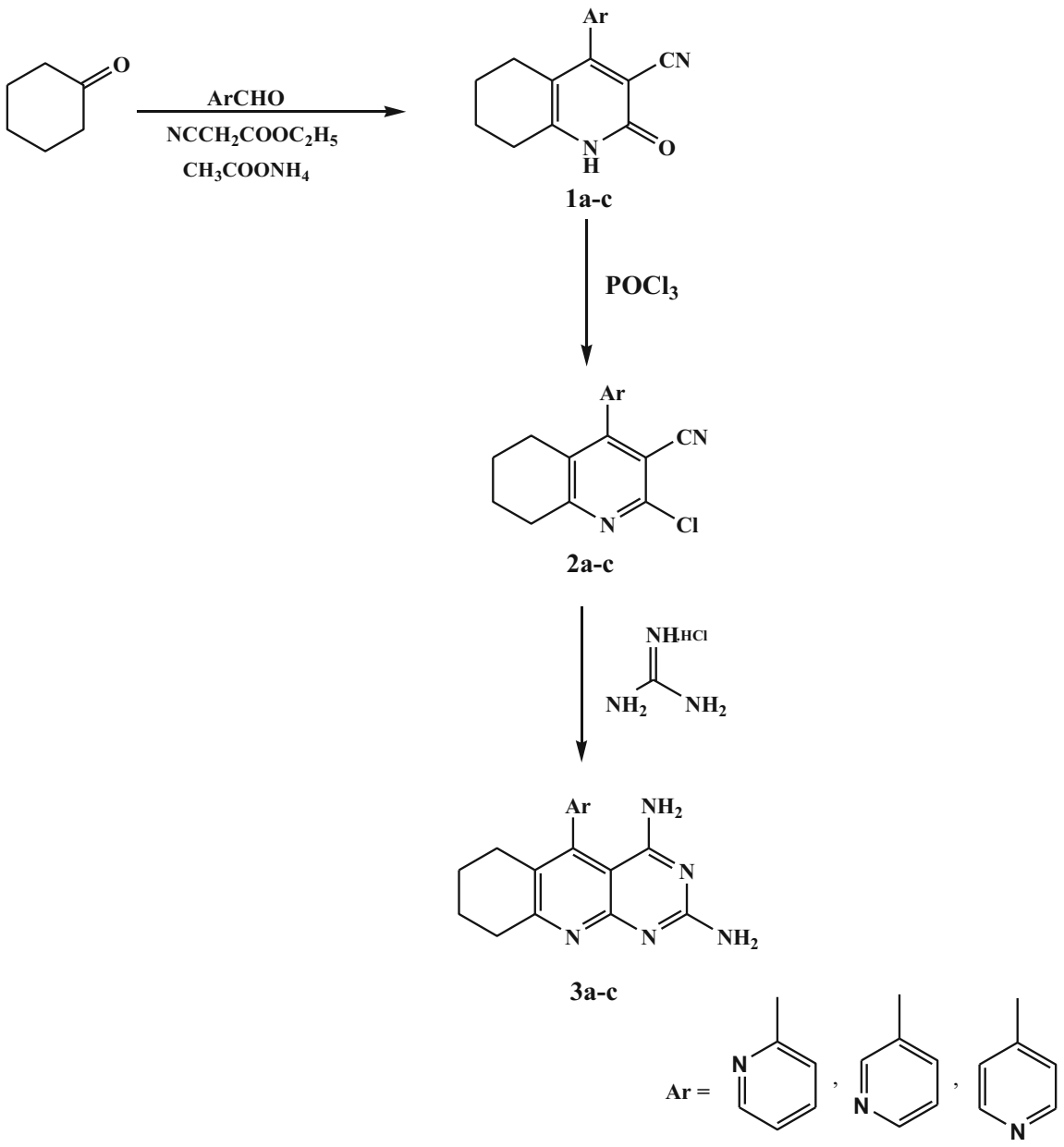


Fig. 3 Anticancer activity of the synthesized compounds against HCT116 and MCF7 cell lines compared to imatinib and tamoxifen

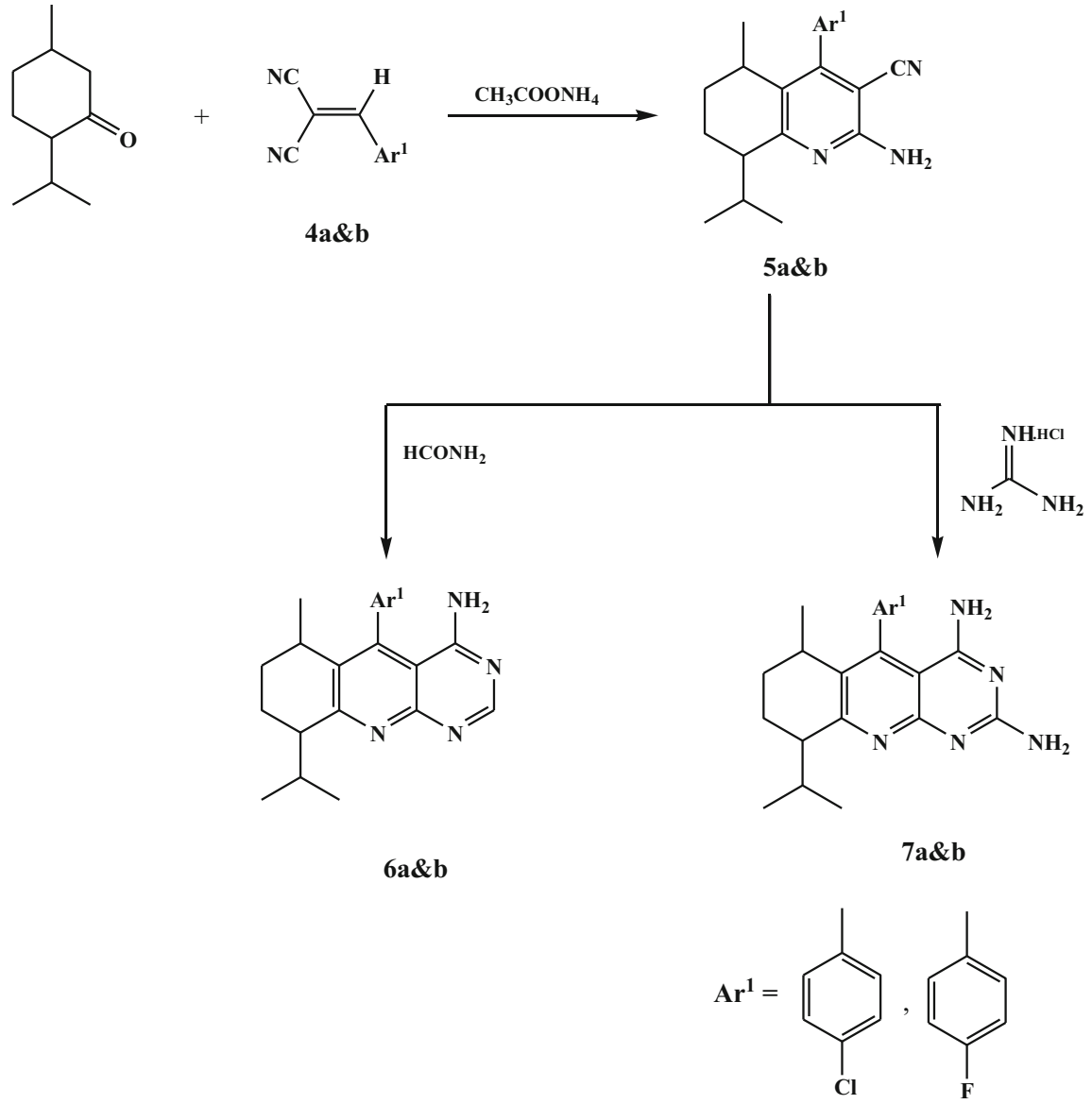


Scheme 1 The synthetic path and reagents for the preparation of target compounds 1–3

modification in the pyrimidoquinoline derivatives **6a** and **b** and **7a** and **b** resulted in a marked increase in the anticancer activity against both HCT116 and MCF7 cell lines.

In this study, we can conclude that:

1. The anticancer activity of the synthesized quinoline and pyrimidiquinoline compounds appeared to be related to the cycloalkyl moiety fused to the pyridine ring, since the best activity was obtained by compounds bearing the branched cyclohexyl moiety.
2. The aryl group at C-4 position in quinoline derivatives and at position number 5 in pyrimidoquinolines exhibited a considerable effect on the activity. Compounds with 2-pyridyl, 4-chlorophenyl or 4-fluorophenyl showed potent anticancer activity.
3. In quinoline derivatives, it was clear that the substituents at position 2 have a marked effect on the anticancer activity, since compounds with carbonyl or amino groups possessed potent anticancer activity, while those with chloro group at C-2 position were inactive.
4. The introduction of amino group at C-4 position or C-2 and C-4 positions in pyrimidoquinolines was tolerated, and resulted in potent anticancer activity.
5. Tetrahydroquinolines and their fused pyrimidine derivatives represent novel and promising class of



Scheme 2 The synthetic path and reagents for the preparation of target compounds 5–7

anticancer agents, so further studies are required to explore the mechanism of action and to optimize the anticancer activity of these derivatives.

Discussion

Chemistry

The synthesis of the target compounds is outlined in Schemes 1 and 2. In this work, the desired 3-cyanoquinolines **1a–c** were prepared via one pot reaction of cyclohexanone, the appropriate pyridine carboxyaldehyde, ethyl cyanoacetate and ammonium acetate. The IR spectra of **1a–c** revealed the presence of absorption bands at 3147–3115 cm^{-1} corresponding to NH group and absorption band at 2222–2216 cm^{-1} attributed to CN group, in addition to an absorption band at 1674–1647 cm^{-1} corresponding to C=O group. On the other hand, the ^1H NMR spectra of these compounds showed exchangeable singlet signals at δ 12.40–12.51 ppm, indicating the presence of NH proton. On refluxing **1a–c** with phosphorus oxychloride, the corresponding 2-chloro derivatives **2a–c** were obtained. The IR spectra of these compounds revealed the disappearance of the absorption bands corresponding to NH and C=O groups, whereas the ^1H NMR spectra disclosed the disappearance of NH signal, which indicated the success of chlorination. Reacting compounds **2a–c** with guanidine base—after liberation from its hydrochloric

salt—in pyridine afforded the pyrimidoquinoline-2,4-diamines **3a–c**. The IR spectra of **3a–c** showed the presence of an absorption band at 3417–3134 cm^{-1} attributed to NH_2 groups and indicated the disappearance of the absorption band corresponding to CN group. Besides, the ^1H NMR spectra of these compounds showed two exchangeable singlet signals at δ 6.50–6.58 and 7.38–7.39 ppm, corresponding to two NH_2 protons. The substituted benzylidenmalononitrile **4a** and **b** were synthesized from the condensation of the appropriate benzaldehyde with malononitrile in ethanol, in the presence of catalytic amount of potassium hydroxide [25]. The 2-amino-4-arylquinoline-3-carbonitriles **5a** and **b** were prepared via refluxing menthone with the appropriate benzylidenmalononitrile **4a** and **b,** in the presence of ammonium acetate in ethanol. The ^1H NMR spectra of **5a** and **5b** showed the presence of exchangeable singlet signals at δ 6.53 and 6.52 ppm, respectively, corresponding to NH_2 protons. The target 4-aminopyrimidoquinoline derivatives **6a** and **b** were obtained through heating **5a** and **b,** under reflux with excess formamide. The IR spectra of these compounds revealed the disappearance of the absorption band belonging to CN group. Moreover the ^1H NMR spectra of **6a** and **6b** showed the presence of singlet signal at δ 7.81 and 8.43 ppm, respectively, corresponding to C_2 proton. Reacting the 2-aminoquinoline-3-carbonitriles **5a** and **b** with guanidine base afforded the 2,4-diaminopyrimidoquinolines **7a** and **b**. The ^1H NMR spectra of **7a** and **7b** showed two NH_2 peaks as exchangeable singlet signals, at δ 5.36, 7.08 and δ 6.52, 7.03 ppm, respectively.

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