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In-vitro cytotoxic and radiosensitizing evaluation of novel 2-pyridone, isoquinoline, chromene and chromenopyridone derivatives

Mansour Sulaiman Al-Said[a], Marwa Galal El-Gazzar[b] and Mostafa Mohammed Ghorab[a,*]

[a] *Medicinal, Aromatic and Poisonous Plants Research Center, College of Pharmacy, King Saud University, Riyadh, 11451, Saudi Arabia*
[b] *Department of Drug Radiation Research, National Center for Radiation Research and Technology, Nasr City, Cairo, 11371, Egypt*

**Corresponding author at: Medicinal, Aromatic and Poisonous Plants Research Center, College of Pharmacy, King Saud University, Riyadh, 11451, Saudi Arabia. Tel.: +966.05.34292860; fax: +966.01.4670560. E-mail address: mmsghorab@yahoo.com (M.M. Ghorab).*

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ABSTRACT

On the account of the reported anticancer activity of 2-pyridone, a new series of ethyl-1,6-dihydropyridine-3-carboxylate (**4a-j**), 1-oxo-1,2-dihydroisoquinoline-7-carbonitrile (**6a-h**), 2*H*-chromene (**7**,**8**) and 3*H*-chromeno[3,4-*c*]pyridone derivatives (**9**,**10**) were synthesized and tested for *in-vitro* anticancer activity against *Ehrlich Ascites Carcinoma* (EAC) cell line and human liver cell line (HEPG2). The structures of the synthesized compounds were confirmed by analytical and spectral data. Furthermore, radiosensitization study was performed for the most potent compounds (**4a**, **4d**, **6a**, **6c**, **6e** and **10**).

1. Introduction

Compounds containing 2-pyridone moiety **I-IV** as a precursor have proven to possess several biologically properties (Scheme 1) [1-6]. In addition, different series of isoquinoline containing compounds **V** were reported to possess substantial cytotoxicity [7]. Furthermore, novel classes of chromenes bearing dithiazole **VI** or phenylthioamide **VII** moieties showed potent cytotoxicity [8], while chromene-carboxamides **VIII** and carboxylates proved potent anticancer activity on different cell lines and as inhibitors of tumor markers [9,10]. Based on the above information and as a continuation of a previous work on anticancer agents [11-16], we report the synthesis of novel 2-pyridone, isoquinoline, chromene and chromenopyridone as cytotoxic and radiosensitizing agents.

2. Experimental

2.1. Instrumentation

Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products. Melting points are uncorrected and were determined on a Stuart melting point apparatus (Stuart Scientific, Redhill, UK). Elemental analysis (C, H and N) were performed on Perkin-Elmer 2400 analyser (Perkin-Elmer, Norwalk, CT, USA) at The Microanalytical Laboratories of the Faculty of Science, Cairo University. All compounds were within ±0.4% of the theoretical values. The IR spectra (KBr) were measured on Shimadzu IR 110 spectrophotometer (Shimadzu, Koyoto, Japan). ^{1}H NMR spectra were obtained on a Bruker proton NMR-Avance 300 (300 MHz) (Bruker, Munich, Germany), in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as internal standard. Mass spectra were run on HP Model MS-5988 (Hewlett Packard, Palo, Alto, California, USA). All reactions were monitored by thin layer chromatograph (TLC) using precoated aluminium sheets Silica gel Merck 60F_{254} and were visualized by UV lamp (Merck, Darmstadt, Germany).

2.2. Synthesis

2.2.1. 2- Cyano-N-(3-ethylphenyl)acetamide (3)

A mixture of 3-ethylaniline, **1**, (1.21 g, 0.01 mol) and ethyl cyanoacetate (1.13 g, 0.01 mol) was refluxed for 3 h. The reaction mixture was concentrated and cooled. The obtained product was crystallized from ethanol to give compound **3** (Scheme 2). Yield: 88%. M.p.: 86-88 °C. IR (KBr, ν, cm^{-1}): 3317 (NH), 3100 (CH. Arom.), 2960, 2870 (CH aliph.), 2260 (C≡N), 1670 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, J = 0.66 Hz), 2.6 (q, 2H, CH_2, J = 0.66 Hz), 3.6 (s, 2H, CH_2), 4.2 (s, 1H, NH, exchangeable with D_2O), 7.0-7.7 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.6, 26.1, 32.9, 117.4, 119.2, 122.0, 125.6, 129.7, 140.8, 142.5, 169.6. Anal. calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.38, 14.88. Found: C, 70.50; H, 6.10; N, 14.60%.

2.2.2. Ethyl 4-substituted-2-amino-5-cyano-1-(3-ethyl phenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (4a-j)

General procedure: A mixture of compound **3** (1.88 g, 0.01 mol), appropriate aldehyde (0.01 mol) and ethyl cyanoacetate (0.113 g, 0.01 mol) in ethanol (50 mL) containing a catalytic amount of piperidine was refluxed for 4 h. The obtained solid was recrystallized from dioxane to give **4a-j** (Scheme 2), respectively.

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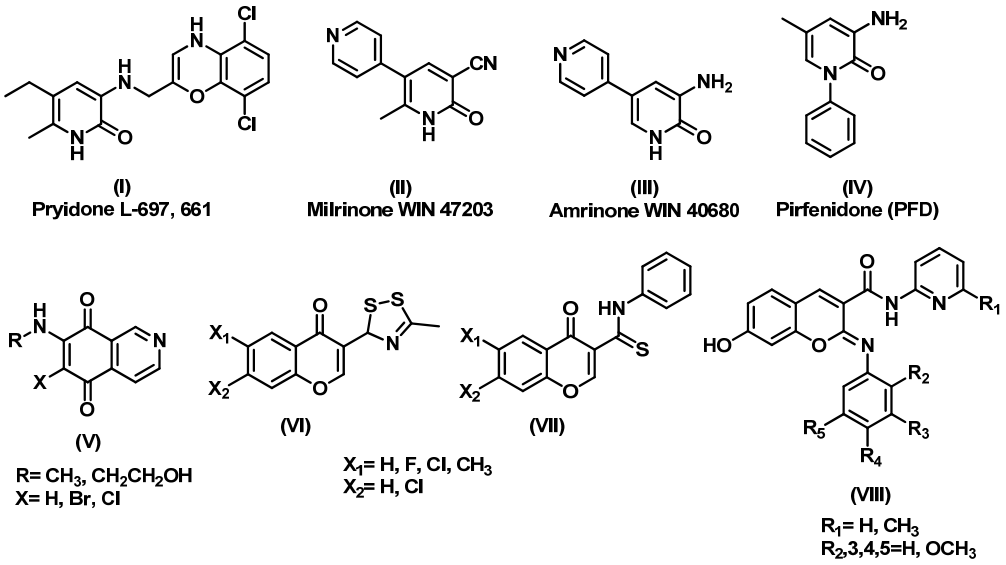


Scheme 1

Ethyl 2-amino-5-cyano-1-(3-ethylphenyl)-6-oxo-4-p-tolyl-1,6-dihydro-pyridine-3-carboxylate (**4a**): Yield: 71%. M.p.: 248-250 °C. IR (KBr, ν, cm^{-1}): 3309, 3207 (NH_2), 3059 (CH arom.), 2966, 2875 (CH aliph.), 2214 (C≡N), 1676, 1687 (2C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.1 (t, 3H, CH_3, J = 0.1 Hz), 1.3 (t, 3H, CH_3, J = 0.66 Hz), 1.9 (s, 3H, CH_3), 2.6 (q, 2H, CH_2, J = 0.1 Hz), 4.3 (q, 2H, CH_2, J = 0.66 Hz), 7.03-7.7 (m, 8H, Ar-H), 8.2 (s, 2H, NH_2, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.4, 15.2, 25.1, 31.9, 62.9, 86.1, 114.3, 115.0, 117.3, 119.8, 122.1, 125.8, 127.4, 130.6, 131.0, 133.2, 136.7, 140.9, 162.7, 163.2, 164.8, 168.7. MS (m/z, %): 401 (M^+, 5.1), 90 (100). Anal. calcd. for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.77; N, 10.47. Found: C, 71.40; H, 5.30; N, 10.70%.

Ethyl 2-amino-5-cyano-1-(3-ethylphenyl)-6-oxo-4-(4-methoxyphenyl)-1,6-dihydro-pyridine-3-carboxylate (**4b**): Yield: 89%. M.p.: >300 °C. IR (KBr, ν, cm^{-1}): 3309, 3207 (NH_2), 3088 ($CH_{arom.}$), 2966, 2839 (CH aliph.), 2214 (C≡N), 1676, 1680 (2C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.1 (t, 3H, CH_3, J = 0.1 Hz), 1.3 (t, 3H, CH_3, J = 0.66 Hz), 2.6 (q, 2H, CH_2, J = 0.1 Hz), 3.5 (s, 3H, OCH_3), 4.3 (q, 2H, CH_2, J = 0.66 Hz), 7.0-7.7 (m, 8H, Ar-H), 8.1 (s, 2H, NH_2, exchangeable with D_2O). MS (m/z, %): 417 (M^+, 7.4), 167 (100). Anal. calcd. for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.07. Found: C, 69.43; H, 5.45; N, 10.34%.

Ethyl 2-amino-5-cyano-1-(3-ethylphenyl)-6-oxo-4-(3-nitro phenyl)-1,6-dihydro-pyridine-3-carboxylate (**4c**): Yield: 80%. M.p.: 145-147 °C. IR (KBr, ν, cm^{-1}): 3227, 3209 (NH_2), 3082 (CH arom.), 2964, 2931, 2872 (CH aliph.), 2194 (C≡N), 1680, 1688 (2C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.05 (t, 3H, CH_3, J = 0.2 Hz), 1.3 (t, 3H, CH_3, J = 0.66 Hz), 2,6 (q, 2H, CH_2, J = 0.2 Hz), 4.3 (q, 2H, CH_2, J = 0.66 Hz), 7.2-7.7 (m, 9H, Ar-H), 8.3 (s, 2H, NH_2, exchangeable with D_2O). MS (m/z, %): 432 (M^+, 5.7), 74 (100). Anal. calcd. for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; N, 12.96. Found: C, 63.32; H, 4.21; N, 13.12%.

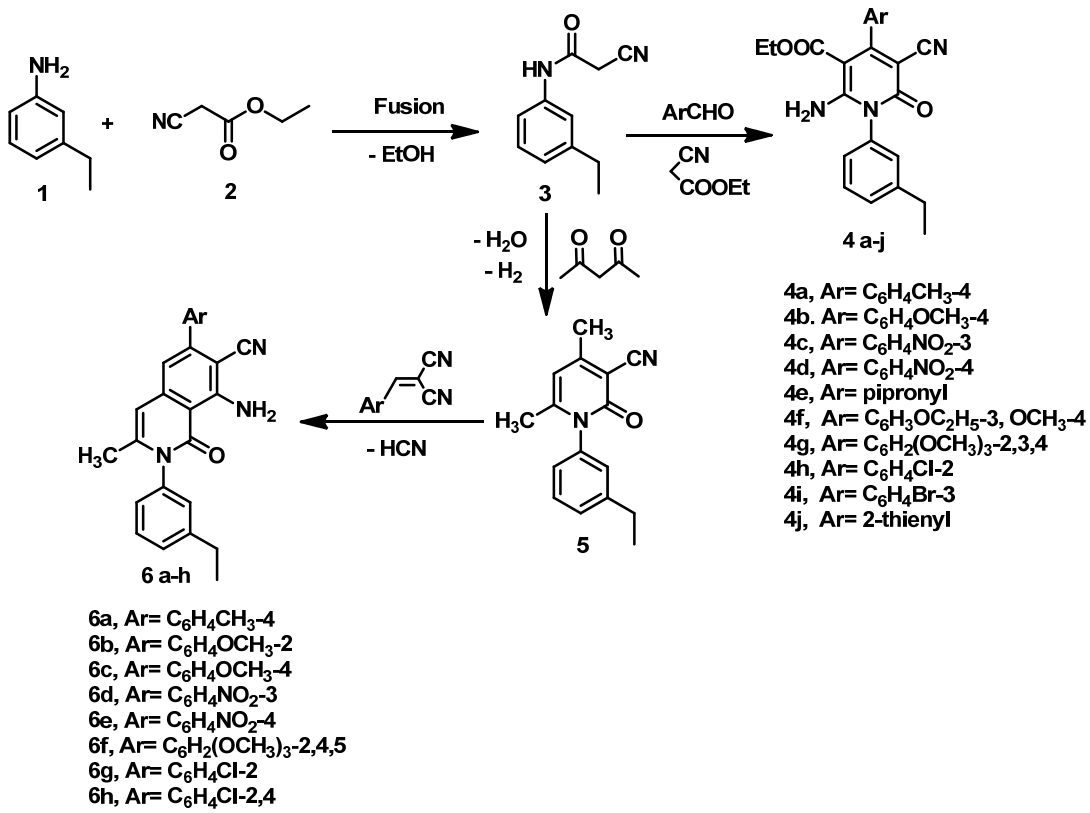
Ethyl 2-amino-5-cyano-1-(3-ethylphenyl)-6-oxo-4-(4-nitro phenyl)-1,6-dihydro-pyridine-3-carboxylate (**4d**): Yield: 78%. M.p.: 140-142 °C. IR (KBr, ν, cm^{-1}): 3227, 3209 (NH_2), 3082 (CH arom.), 2964, 2872 (CH aliph.), 2194 (C≡N), 1680, 1690 (2C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.05 (t, 3H, CH_3, J = 0.2 Hz), 1.3 (t, 3H, CH_3, J = 0.66 Hz), 2.6 (q, 2H, CH_2, J = 0.2 Hz), 4.3 (q, 2H, CH_2, J = 0.66 Hz), 7.2-7.7 (m, 8H, Ar-H), 8.3 (s, 2H, NH_2, exchangeable with D_2O). MS (m/z, %): 432 (M^+, 6.9), 90 (100). Anal. calcd. for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; N, 12.96. Found: C, 63.50; H, 4.90; N, 13.12%.

Ethyl 2-amino-5-cyano-1-(3-ethylphenyl)-6-oxo-4-(4-pipronyl)-1,6-dihydro-pyridine-3-carboxylate (**4e**): Yield: 81%. M.p.: 160-162 °C. IR (KBr, ν, cm^{-1}): 3238, 3209 (NH_2), 3055 (CH arom.), 2924, 2872 (CH aliph.), 2234 (C≡N), 1678, 1689 (2C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.05 (t, 3H, CH_3, J = 0.2 Hz), 1.3 (t, 3H, CH_3, J = 0.66 Hz), 2.6 (q, 2H, CH_2, J = 0.2 Hz), 4.3 (q, 2H, CH_2, J = 0.66 Hz), 5.9 (s, 2H, CH_2-piperonyl), 7.2-7.7 (m, 7H, Ar-H), 8.3 (s, 2H, NH_2, exchangeable with D_2O). Anal. calcd. for $C_{24}H_{21}N_3O_5$: C, 66.81; H, 4.91; N, 9.74. Found: C, 66.50; H, 4.90; N, 9.51%.

Ethyl 2-amino-5-cyano-1-(3-ethylphenyl)-6-oxo-4-(3-ethoxy-4-methoxy)-1,6-dihydro-pyridine-3-carboxylate (**4f**): Yield: 76%. M.p.: 167-169 °C. IR (KBr, ν, cm^{-1}): 3223, 3209 (NH_2), 3055 (CH arom.), 2924, 2872 (CH aliph.), 2264 (C≡N), 1679, 1690 (2C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.05 (t, 3H, CH_3, J = 0.2 Hz), 1.3 (t, 6H, $2CH_3$, J = 0.66 Hz), 2.6 (q, 2H, CH_2, J = 0.2 Hz), 3.5 (s, 3H, OCH_3), 4.5 (q, 4H, $2CH_2$, J = 0.66 Hz), 7.2-7.7 (m, 7H, Ar-H), 8.3 (s, 2H, NH_2, exchangeable with D_2O). MS (m/z, %): 461 (M^+, 10.5), 167 (100). Anal. calcd. for $C_{26}H_{27}N_3O_5$: C, 67.66; H, 5.90; N, 9.10. Found: C, 67.32; H, 5.71; N, 9.42%.

Ethyl 2-amino-5-cyano-1-(3-ethylphenyl)-6-oxo-4-(2,3,4-trimethoxyphenyl)-1,6-dihydro-pyridine-3-carboxylate (**4g**): Yield: 87%. M.p.: 189-190 °C. IR (KBr, ν, cm^{-1}): 3223, 3209 (NH_2), 3055 (CH arom.), 2924, 2872 (CH aliph.), 2264 (C≡N), 1679, 1687 (2C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.05 (t, 3H, CH_3, J = 0.2 Hz), 1.3 (t, 3H, CH_3, J = 0.66 Hz), 2.6 (q, 2H, CH_2, J = 0.2 Hz), 3.8 (s, 9H, $3OCH_3$), 4.5 (q, 4H, $2CH_2$, J = 0.66 Hz), 7.2-7.7 (m, 6H, Ar-H), 8.3 (s, 2H, NH_2, exchangeable with D_2O). MS (m/z, %): 573 (M^+, 21), 90 (100). Anal. calcd. for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.32; H, 5.50; N, 8.65%.

Ethyl 2-amino-5-cyano-1-(3-ethylphenyl)-6-oxo-4-(2-chloro phenyl)-1,6-dihydro-pyridine-3-carboxylate (**4h**): Yield: 90%. M.p.: 200-201 °C. IR (KBr, ν, cm^{-1}): 3293, 3212 (NH_2), 3085 (CH arom.), 2935, 2872 (CH aliph.), 2234 (C≡N), 1660, 1678 (2C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.05 (t, 3H, CH_3, J = 0.2 Hz), 1.3 (t, 3H, CH_3, J = 0.66 Hz), 2.6 (q, 2H, CH_2, J = 0.2 Hz), 4.5 (q, 2H, $2CH_2$, J = 0.66 Hz), 7.2-7.7 (m, 8H, Ar-H), 8.3 (s, 2H, NH_2, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.8, 15.5, 31.2, 63.4, 86.1, 116.9, 117.3, 118.1, 119.8, 125.6, 128.0, 128.2, 129.0, 129.6, 130.7, 133.8, 135.3, 136.1, 142.6, 160.2, 162.3, 166.9, 172.3. Anal. calcd. for $C_{23}H_{20}ClN_3O_3$: C, 65.48; H, 4.78; N, 9.96. Found: C, 65.32; H, 4.71; N, 9.65%.



Scheme 2

Ethyl 2-amino-5-cyano-1-(3-ethylphenyl)-6-oxo-4-(3-bromo phenyl)-1,6-dihydro-pyridine-3-carboxylate (**4i**): Yield: 62%. M.p.: 96-98 °C. IR (KBr, ν, cm^{-1}): 3334, 3246 (NH_2), 3086 (CH arom.), 2981, 2829 (CH aliph.), 2212 (C≡N), 1649, 1966 (2C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 1.9 (t, 3H, CH_3, *J* = 0.66 Hz), 2.6 (q, 2H, CH_2, *J* = 6.66 Hz), 4.5 (q, 2H, CH_2, *J* = 0.66 Hz), 7.1-7.9 (m, 8H, Ar-H), 8.6 (s, 2H, NH_2, exchangeable with D_2O). MS (m/z, %): 466 (M^+, 15.8), 90 (100). Anal. calcd. for $C_{23}H_{20}BrN_3O_3$: C, 59.24; H, 4.32; N, 9.01. Found: C, 59.50; H, 4.20; N, 9.20%.

Ethyl 2-amino-5-cyano-1-(3-ethylphenyl)-6-oxo-4-(thiophen-2-yl)-1,6-dihydro-pyridine-3-carboxylate (**4j**): Yield: 71%. M.p.: 105-107 °C. IR (KBr, ν, cm^{-1}): 3325, 3209 (NH_2), 3100 (CH arom.), 2931, 2872 (CH aliph.), 2210 (C≡N), 1658 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 1.7 (t, 3H, CH_3, *J* = 0.66 Hz), 2.6 (q, 2H, CH_2, *J* = 6.66 Hz), 4.7 (q, 2H, CH_2, *J* = 0.66 Hz), 7.2-7.7 (m, 4H, Ar-H), 7.5-8.4 (m, 3H, 3CH thiophene), 8.7 (s, 2H, NH_2, exchangeable with D_2O). Anal. calcd. for $C_{21}H_{19}N_3O_3S$: C, 64.10; H, 4.87; N, 10.68. Found: C, 64.50; H, 4.70; N, 10.40%.

2.2.3. 1-(3-Ethylphenyl)-4,6-dimethyl-2-oxo-1,2-dihydro pyridine-3-carbonitrile (5)

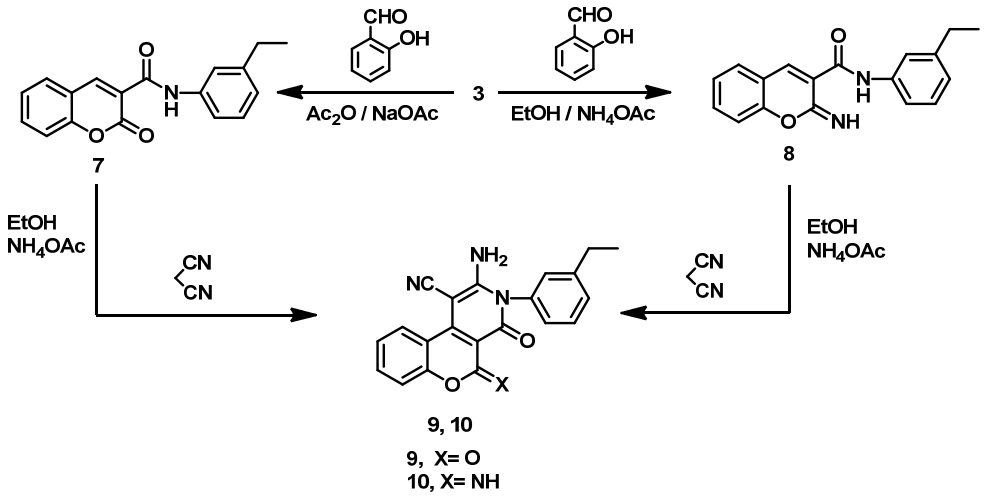
Equimolar amounts of compound **3** (1.88 g, 0.01 mol) and acetylacetone (1.00 g, 0.01 mol) were refluxed in ethanol (50 mL) containing piperidine (0.5 mL) for 5 h. The reaction mixture was triturated with ethanol and the solid obtained was recrystallized from dioxane to give compound **5** (Scheme 2). Yield: 86%. M.p.: 198-200 °C. IR (KBr, ν, cm^{-1}): 3100 (CH arom.), 2931, 2872 (CH aliph.), 2210 (C≡N), 1660 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 1.5 (2s, 6H, $2CH_3$), 2.6 (q, 2H, CH_2, *J* = 0.66 Hz), 5.6 (s, 1H, CH-pyridine), 7.2-7.7 (m, 4H, Ar-H). Anal. calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.50; H, 6.70; N, 11.40%.

2.2.4. 6-Substituted- 8-amino-2-(3-ethylphenyl)-3-methyl-1-oxo- 1,2-dihydro- isoquinoline-7-carbonitrile (6a-h)

General procedure: A mixture of compound **5** (1.5 g, 0.01 mol), benzylidine-malononitrile (0.01 mol) in ethanol (50 mL) containing (0.5 mL) piperidine was refluxed for 6 h. The reaction mixture was cooled and poured onto ice water acidified with dil. HCl. The solid obtained was recrystallized from dioxane to give compounds **6a-h** (Scheme 2).

8-Amino-2-(3-ethylphenyl)-3-methyl-1-oxo-6-p-tolyl-1,2-dihydro- isoquinoline-7-carbonitrile (**6a**): Yield: 90%. M.p.: 108-109 °C. IR (KBr, ν, cm^{-1}): 3325, 3209 (NH_2), 3080 (CH arom.), 2931, 2872 (CH aliph.), 2210 (C≡N), 1658 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 1.7 (s, 3H, CH_3), 2.6 (q, 2H, CH_2, *J* = 0.66 Hz), 5.7 (s, 1H, CH-pyridine), 6.9-7.5 (m, 8H, Ar-H), 8.7 (s, 2H, NH_2, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 12.9, 21.3, 26.4, 33.8, 96.0, 100.3, 116.8, 118.2, 118.9, 119.8, 121.7, 124.5, 126.8, 127.6, 130.9, 133.4, 134.8, 139.0, 140.9, 142.4, 144.6, 147.8, 151.3, 158.4. Anal. calcd. for $C_{26}H_{23}N_3O$: C, 79.36; H, 5.89; N, 10.68. Found: C, 79.50; H, 5.70; N, 10.40%.

Amino-2-(3-ethylphenyl)-3-methyl-1-oxo-6-(2-methoxy phenyl)-1,2-dihydro- isoquinoline-7-carbonitrile (**6b**): Yield: 92%. M.p.: 114-116 °C. IR (KBr, ν, cm^{-1}): 3325, 3209 (NH_2), 3080 (CH arom.), 2931, 2872 (CH aliph.), 2212 (C≡N), 1658 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 2.6 (q, 2H, CH_2, *J* = 0.66 Hz), 3.8 (s, 3H, OCH_3), 5.7 (s, 1H, CH-pyridine), 6.9-7.9 (m, 8H, Ar-H), 8.7 (s, 2H, NH_2, exchangeable with D_2O). MS (*m/z*, %): 409 (M^+, 5.12), 105 (100). Anal. calcd. for $C_{26}H_{23}N_3O_2$: C, 76.26; H, 5.66; N, 10.26. Found: C, 76.50; H, 5.70; N, 10.50%.



Scheme 3

8-Amino-2-(3-ethylphenyl)-3-methyl-1-oxo-6-(4-methoxy phenyl)-1,2-dihydro-isoquinoline-7-carbonitrile (**6c**): Yield: 97%. M.p.: 122-124 °C. IR (KBr, ν, cm^{-1}): 3325, 3209 (NH_2), 3080 (CH arom.), 2931, 2860 (CH aliph.), 2200 (C≡N), 1658 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 2.6 (q, 2H, CH_2, *J* = 0.66 Hz), 3.7 (s, 3H, OCH_3), 5.7 (s, 1H, CH-pyridine), 6.9-7.8 (m, 8H, Ar-H), 8.7 (s, 2H, NH_2, exchangeable with D_2O). MS (*m/z*, %): 409 (M^+, 12.1), 90 (100). Anal. calcd. for $C_{26}H_{23}N_3O_2$: C, 76.26; H, 5.66; N, 10.26. Found: C, 76.60; H, 5.70; N, 10.10%.

8-Amino-2-(3-ethylphenyl)-3-methyl-1-oxo-6-(3-nitro phenyl)-1,2-dihydro-isoquinoline-7-carbonitrile (**6d**): Yield: 89%. M.p.: 98-100 °C. IR (KBr, ν, cm^{-1}): 3325, 3220 (NH_2), 3080 (CH arom.), 2931, 2850(CH aliph.), 2208 (C≡N), 1658 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 2.6 (q, 2H, CH_2, *J* = 0.66 Hz), 5.7 (s, 1H, CH-pyridine), 6.9-7.5 (m, 8H, Ar-H), 8.7 (s, 2H, NH_2, exchangeable with D_2O). MS (*m/z*, %): 424 (M^+, 18.2), 90 (100). Anal. calcd. for $C_{25}H_{20}N_4O_3$: C, 70.74; H, 4.75; N, 13.20. Found: C, 70.50; H, 4.70; N, 13.40.

8-Amino-2-(3-ethylphenyl)-3-methyl-1-oxo-6-(4-nitro phenyl)-1,2-dihydro-isoquinoline-7-carbonitrile (**6e**): Yield: 85%. M.p.: 106-108 °C. IR (KBr, ν, cm^{-1}): 3340, 3218 (NH_2), 3080 (CH arom.), 2940, 2872 (CH aliph.), 2218 (C≡N), 1658 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 2.6 (q, 2H, CH_2, *J* = 0.66 Hz), 5.7 (s, 1H, CH-pyridine), 6.9-7.5 (m, 8H, Ar-H), 8.7 (s, 2H, NH_2, exchangeable with D_2O). MS (*m/z*, %): 424 (M^+, 20.3), 141 (100). Anal. calcd. for $C_{25}H_{20}N_4O_3$: C, 70.74; H, 4.75; N, 13.20. Found: C, 70.50; H, 4.50; N, 13.60%.

8-Amino-2-(3-ethylphenyl)-3-methyl-1-oxo-6-(2, 4, 5-trimet-hoxyphenyl)-1,2-dihydro- isoquinoline-7-carbonitrile (**6f**): Yield: 79%. M.p.: 117-119 °C. IR (KBr, ν, cm^{-1}): 3364, 3209 (NH_2), 3080 (CH arom.), 2931, 2836 (CH aliph.), 2213 (C≡N), 1658 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 2.6 (q, 2H, CH_2, *J* = 0.66 Hz), 3.7 (3S, 9H, $3OCH_3$), 5.7 (s, 1H, CH-pyridine), 6.9-7.6 (m, 6H, Ar-H), 8.7 (s, 2H, NH_2, exchangeable with D_2O). MS (*m/z*, %): 469 (M^+, 24.1), 90 (100). Anal. calcd. for $C_{28}H_{27}N_3O_4$: C, 71.62; H, 5.80; N, 8.95. Found: C, 71.30; H, 5.40; N, 9.10%.

8-Amino-2-(3-ethylphenyl)-3-methyl-1-oxo-6-(2-chlorophenyl)-1,2-dihydro- isoquinoline-7-carbonitrile (**6g**): Yield: 80%. M.p.: 107-110 °C. IR (KBr, ν, cm^{-1}): 3370, 3230 (NH_2), 3080 (CH arom.), 2920, 2860 (CH aliph.), 2209 (C≡N), 1658 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 2.6 (q, 2H, CH_2, *J* = 0.66 Hz), 5.7 (s, 1H, CH-pyridine), 7.1-7.7 (m, 8H, Ar-H), 8.7 (s, 2H, NH_2, exchangeable with D_2O). MS (*m/z*, %): 413 (M^+, 35), 105 (100). Anal. calcd. for $C_{25}H_{20}ClN_3O$: C, 72.55; H, 4.87; N, 10.15. Found: C, 72.70; H, 4.70; N, 10.50%.

8-Amino-2-(3-ethylphenyl)-3-methyl-1-oxo-6-(2,4-dichloro phenyl)-1,2-dihydro- isoquinoline-7-carbonitrile (**6h**): Yield: 87%. M.p.: 97-99 °C. IR (KBr, ν, cm^{-1}): 3325, 3209 (NH_2), 3080 (CH arom.), 2930, 2856(CH aliph.), 2198 (C≡N), 1658 (C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 2.6 (q, 2H, CH_2, *J* = 0.66 Hz), 5.7 (s, 1H, CH-pyridine), 6.9-7.9 (m, 7H, Ar-H), 8.7 (s, 2H, NH_2, exchangeable with D_2O). MS (*m/z*, %): 448 (M^+, 5.9), 141 (100). Anal. calcd. for $C_{25}H_{20}Cl_2N_3O$: C, 66.97; H, 4.27; N, 9.37. Found: C, 66.60; H, 4.60; N, 9.60%.

2.2.5. N-(3-ethylphenyl)-2-oxo-2H-chromene-3-carboxamide (7)

To a solution of compound **3** (1.88 g, 0.01 mol) in acetic anhydride (20 mL), salicyladehyde (1.22 g, 0.01 mol) and fused sodium acetate (0.8 g, 0.01 mo) was added. The reaction mixture was refluxed for 2 h, cooled and the solid obtained was crystallized from ethanol to give compound **7** (Scheme 3). Yield: 69%. M.p.: 117-119 °C. IR (KBr, ν, cm^{-1}): 3417(NH), 1766 (2C=O). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.3 (t, 3H, CH_3, *J* = 0.2 Hz) 2.6 (q, 2H, CH_2, *J* = 0.2 Hz), 7.3-8.0 (m, 8H, Ar-H), 8.35 (s, 1H, CH), 8.42 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 14.1, 30.2, 113.6, 117.5, 119.8, 122.7, 124.2, 125.6, 127.0, 127.9, 129.6, 130.2, 133.5, 136.1, 140.2, 153.6, 161.2, 164.3. Anal. calcd. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.60; H, 5.70; N, 4.50%.

2.2.6. N-(3-ethylphenyl)-2-imino-2H-chromene-3-carboxamide (8)

A mixture of compound **3** (1.88 g, 0.01 mol), salicyladehyde (1.22 g, 0.01 mol) and anhydrous ammonium acetate (1.15 g, 0.15 mol) in ethanol (20 mL) was refluxed for 2 h. The solid obtained was recrystallized from ethanol to give compound **8** (Scheme 3). Yield: 59%. M.p.: >300 °C. IR (KBr, ν, cm^{-1}): 3344, 3166 (2NH), 1720 (C=O), 1570 (C=N). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.1 (t, 3H, CH_3, *J* = 0.2 Hz) 2.7 (q, 2H, CH_2, *J* = 0.2 Hz), 6.9-8.3 (m, 8H, Ar-H), 8.7 (s, 1H, CH-4), 9.5 (s, 1H, NH imino, exchangeable with D_2O), 12.5 (s, 1H, NHCO, exchangeable with D_2O). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 13.4, 31.2, 114.6, 115.8, 117.1, 119.8, 122.6, 123.3, 124.7, 126.2, 127.5, 128.7, 130.6, 133.8, 137.1, 152.9, 162.7, 171.3. Anal. calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52, N, 9.58. Found: C, 73.60; H, 5.20; N, 9.30%.

2.2.7. 2-Amino-3-(3-ethylphenyl)-4,5-dioxo-4,5-dihydro-3H-chromeno(3,4-c)pyridine-1-carbonitrile (9) and 2-amino-3-(3-ethylphenyl)-5-imino-4-oxo-4,5-dihydro-3H-chromeno (3,4-c)pyridine-1-carbonitrile (10)

Equimolar amounts of compounds **7** or **8**, malononitrile (0.66 g, 0.01mol) anhydrous ammonium acetate (1.115 g, 0.01 mol) in ethanol were refluxed for 4 h. The solid obtained by filtration was recrystallized from dioxane to give compound **9** and **10**, (Scheme 3) respectively.

2-Amino-3-(3-ethylphenyl)-4,5-dioxo-4,5-dihydro-3H-chromeno(3,4-c)pyridine-1-carbonitrile (**9**): Yield: 61%. M.p.: >300 °C. IR (KBr, ν, cm^{-1}): 3090 (CH arom.), 2976, 2865 (CH aliph.), 1684, 1654 (2C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3, *J* = 0.66 Hz), 2.6 (q, 2H, CH_2, *J* = 0.66 Hz), 6.9-7.5 (m, 8H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 15.8, 34.3, 73.9, 116.5, 117.9, 118.0, 119.2, 122.6, 125.3, 126.1, 127.0, 127.8, 128.9, 129.3, 135.6, 141.2, 153.6, 156.4, 158.8, 161.4, 167.5. MS *(m/z*, %): 357 (M^+, 17.8), 76 (100). Anal. calcd. for $C_{21}H_{15}N_3O_3$: C, 70.8; H, 4.23; N, 11.76. Found: C, 75.40; H, 4.60; N, 4.10.

2-Amino-3-(3-ethylphenyl)-5-imino-4-oxo-4,5-dihydro-3H-chromeno[3,4-c]pyridine-1-carbonitrile (**10**): Yield: 58%. M.p.: >300 °C. IR (KBr, ν, cm^{-1}): 3312, 3256, 3216 (NH, NH_2), 3070(CH arom.), 2925, 2853 (CH aliph.), 1690(C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2[t, 3H, CH_3, *J* = 0.66 Hz), 2.6 (q, 2H, CH_2, *J* = 0.66 Hz), 6.9-7.8 (m, 8H, Ar-H), 8.7 (s, 1H, NH, exchangeable with D_2O), 10.1 (s, 2H, NH_2, exchangeable with D_2O). MS *(m/z*, %): 356 (M^+, 18.1), 76 (100). Anal. calcd. for $C_{21}H_{16}N_4O_2$: C, 70.77; H, 4.53; N, 15.72. Found: C, 75.50; H, 5.43; N, 8.40.

2.3. In-vitro anticancer screening

2.3.1. Animals, chemicals and facilities

Ehrlich Ascites Carcinoma cells (EAC) were maintained in female Swiss albino mice weighing 25-30 g (the holding company for biological products and vaccines, VACSERA, Cairo, Egypt) were housed at a constant temperature (24 °C) with alternating 12 h light and dark cycles and fed standard laboratory food (Milad CO., Cairo, Egypt) and water ad libitum. All chemicals and reagents were of the highest grade commercially available. Facilities including animal house, biochemical equipments have been made available by the National Center for Radiation Research and Technology (NCRRT), Atomic Energy Authority (AEA), Cairo, Egypt. Animal care and handling was done according to the guidelines set by the world health organization, Geneva, Switzerland and approved from the committee for animals care at NCRRT.

2.3.4. In-vitro anticancer activity using Ehrlich Ascites Carcinoma (EAC) cells

Ehrlich Ascites Carcinoma cells (EAC) were obtained by needle aspiration of aseptic fluid from preinoculated mice; under aseptic conditions. Tumor cells suspension (2.5x10^6 per mL) was prepared in RPMI-1640 media. Tested compounds were prepared with various dilutions by dissolving: 100, 50, 25 and 10 mg of the tested compounds in DMSO (1 mL). In a set of sterile test tubes 0.8 mL RPMI-1640 media containing (glutamine, fetal calf serum as nutrient, streptomycin and penicillin), 0.1 mL of each of the tested compounds (corresponding to 100, 50, 25 and 10 mg) were mixed then 0.1 mL of tumor cell suspension (2x10^6) was added. The test tubes were incubated at 37 °C for 2 h. Trypan blue exclusion test was carried out to calculate the percentage of non-viable cells after 2 h of incubation [17]. The total number of cells/mL will be determined using the following calculations:

Cells/mL = average cells count per 5 squares x dilution factor x 10^4 (1)

Total cells = cells/mL x the original volume of fluid from which the cell sample was removed (2)

% cell non-viability = total non-viable cells (stained) / total cells x 100 (3)

The results of in-vitro anticancer activity experiments are presented in (Table 1).

Table 1. In-vitro anticancer screening of the newly synthesized compounds against *Ehrlich Ascites Carcinoma* Tumor Cells (EAC).

Compound No	Non-viable cells (%) Concentration (µg/mL)				IC_{50} [a] (µg/mL)	IC_{50} [a] (µM)
	100	50	25	10		
4a	100	50	25	10	25	62.34
4b	100	50	25	10	50	119.9
4c	100	60	40	10	46	106.48
4d	60	75	50	20	25	57.87
4e	100	90	70	10	45	104.4
4f	100	50	25	10	50	108.45
4g	95	55	40	5	48	83.76
4h	90	70	30	10	49	116.38
4i	95	60	30	10	49	105.15
4j	95	65	20	5	47	119.59
6a	95	80	60	10	23	58.52
6b	50	10	0	0	100	244.5
6c	100	100	60	30	15	36.67
6d	100	60	40	5	46	108.49
6e	100	90	50	20	25	58.96
6f	100	70	40	10	43	91.68
6g	100	50	25	10	50	121.06
6h	100	60	30	5	48	107.14
7	30	0	0	0	>100[b]	-
8	20	0	0	0	>100[b]	-
9	100	80	25	10	44	123.24
10	100	90	60	30	21	58.98
Doxorubicin	100	68	30	24	37	68.13

[a] IC_{50} value: corresponds to the compound concentration causing 50% mortality in net cells.
[b] Compounds with IC_{50} >100 lg/mL are considered to be inactive.

2.3.5. In-vitro anticancer activity using liver human tumor cell lines (HEPG2)

The human tumor cell line (HEPG2) was available at the National Cancer Institute, Cairo, Egypt. Irradiation was performed in the National Cancer Institute, Cairo, Egypt using Gamma cell-40 (^{60}Co) source. The anticancer activity of the newly synthesized compounds was mesured using the Sulfo-Rhodamine-B stain (SRB) assay by the method of Skehan *et al.* [18]. Cells were plated in 96-multiwell plate (10^4 cells/well) for 24 h before treatment with the compounds to allow attachment of cell to the wall of the plate. Tested compounds were dissolved in DMSO and diluted with saline to the appropriate volume. Different concentrations of the compounds under test (5.0, 12.5, 25.0 and 50.0 µM) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37 °C and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed and stained for 30 min. with 0.4% (wt/vol) with SRB dissolved in 1% acetic acid. Unbounded dye was removed by four washes with 1% 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 drug concentration was plotted to get the survival curve of each tumor cell line after the specified time. The concentration required for 50% inhibition of cell viability (IC_{50}) was calculated and compared with the reference drug doxorubicin and the results are given in Table 2.

Table 2. In-vitro anticancer evaluation of compounds **4a**, **4d**, **6a**, **6c**, **6e** and **10** against human liver cell line (HEPG2).

Compound No	Compound concentration (μM)				IC_{50} (μM)
	5.0	12.5	25.0	50.0	
	Surviving fraction (mean ± SE)[a]				
Doxorubicin	0.921 ± 0.020	0.846 ± 0.020	0.761 ± 0.010	0.494 ± 0.030	38.46
4a	0.845 ± 0.002	0.724 ± 0.009	0.576 ± 0.028	0.376 ± 0.047	31.2
4d	0.623 ± 0.018	0.523 ± 0.031	0.367 ± 0.022	0.271 ± 0.012	11.7
6a	0.723 ± 0.012	0.635 ± 0.041	0.523 ±0.047	0.244 ± 0.022	21.81
6c	0.922 ± 0.064	0.744 ± 0.014	0.630 ± 0.016	0.436 ± 0.012	38.9
6e	0.876 ± 0.064	0.744 ± 0.014	0.509 ± 0.016	0.312 ± 0.012	25.83
10	0.910 ± 0.064	0.789 ± 0.014	0.598 ± 0.016	0.309 ± 0.012	32.2

[a] Each value is the mean of three experiments ± standard error.

Table 3. In-vitro anticancer evaluation of compounds **4a**, **4d**, **6a**, **6c**, **6e** and **10** against human liver cell line (HEPG2) after subjection to radiation.

Compound No	Compound concentration (μM) + irradiation (8 Gy) Surviving fraction (mean ± SE) [a]				IC_{50} (μM)
	5.0	12.5	25.0	50.0	
4a	0.587 ± 0.01	0.376 ± 0.02	0.329 ± 0.05	0.198 ± 0.06	5.03
4d	0.487 ± 0.07	0.398 ± 0.01	0.198 ± 0.01	0.100 ± 0.08	6.37
6a	0.355 ± 0.01	0.276 ± 0.01	0.245 ± 0.01	0.187 ± 0.07	2.68
6c	0.535 ± 0.04	0.498 ± 0.01	0.287 ± 0.01	0.198 ± 0.06	8.38
6e	0.589 ± 0.04	0.234 ± 0.01	0.218 ± 0.01	0.156 ± 0.06	6.04
10	0.398 ± 0.04	0.212 ± 0.01	0.200 ± 0.01	0.189 ± 0.06	3.35

[a] Each value is the mean of three experiments ± standard error.

2.4. Radiosensitizing evaluation

The most potent compounds resulted from the *in vitro* anticancer screening; compounds **4a**, **4d**, **6a**, **6c**, **6e** and **10**, were selected to be evaluated again for their *in vitro* anticancer activity alone and in combination with γ-radiation. This study was conducted to evaluate the ability of these compounds to enhance the cell killing effect of γ-radiation. Cells were subjected to a single dose of γ-radiation at a dose level of 8 Gy with a dose rate of 2 Gy/min. Irradition was performed in the National Cancer Institute, Cairo University, using Gamma cell-40 (^{60}Co) source. The surviving fractions were expressed as means ± standard error. The results were given in Table 3.

3. Results and discussion

3.1. Chemistry

Schemes 1 and 2 outline the synthetic pathway used to obtain 1,6-dihydropyridines (**4a-j**), 1,2-dihydroisoquinolines (**6a-h**), 2*H*-chromenes (**7** and **8**) and 3*H*-chromeno[3,4-c]pyridines (**9** and **10**). The starting material, 3-cyano-*N*-(3-ethylphenyl) acetamide, **3**, was prepared via reaction of 3-ethylaniline **1** with ethyl cyanoacetate **2**. Compound **3** was confirmed by elemental analysis, IR, ^{1}H NMR and mass spectral data (Scheme 1). Upon treatment of compound **3** with required aldehyde and ethyl cyanoacetate in the presence of catalytic amount of piperidine furnished ethyl 4-substituted-2-amino-5-cyano-1-(3-ethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate, **4a-j**. The structure of compounds **4a-j** was deduced from elemental analyses and spectral data (Scheme 1). Cycloaddition occurred upon treatment of compound **3** with acetylacetone to furnish 2-pyridone derivative **5** which upon reaction with the corresponding arylidinemalononitriles yielded the correspondingisoquinoline derivatives **6a-h** (Scheme 2).

Furthermore, Perkin reaction was carried when compound **3** was reacted with salicyaldehyde in the presence ofacetic anhydride containing sodium acetate to give the corresponding 2-oxochromene derivative **7**, while reaction of compound **3** with saliclyaldehyde in ammonium acetate furnished 2-iminochromene **8**. The structure of compound **7** and **8** was supported in the basis of elemental analyses, IR, ^{1}H NMR and mass spectral data. The chromene derivative **7** and **8** were further reacted with malononitrile in the presence of ammonium acetate to give the corresponding chromeno pyridine derivatives **9** and **10**, respectively (Scheme 3). The structure of compounds **9** and **10** was elucidated from elemental analyses and spectral data.

3.2. In-vitro anticancer screening

3.2.1. In-vitro anticancer activity using Ehrlich Ascites Carcinoma (EAC) cells

Doxorubicin, the reference drug used in this study is one of the most effective antitumor agents used to produce regressions in acute leukemia's, Hodgkin's disease, and other lymphomas. The relationship between survival ratio and drug concentration was plotted to obtain the survival curve of *Ehrlich Ascites Carcinoma* (EAC) cells and human liver cell line (HEPG2). The response parameter calculated was IC_{50} value (Tables 1 and 2), which corresponds to the compound concentration causing 50% mortality in net cells.

3.2.2. Structure Activity Relationship (SAR)

The cytotoxicity of twenty-two compounds was examined on *Ehrlich Ascites Carcinoma* (EAC) cells. It is clear from the results in (Table 1) that in the series of 1,6-dihydropyridine **4a-j**, the most potent in this series is the 4-methyl derivative **4a** (IC_{50} = 62.34 μM) which was found to be more potent than the reference drug (IC_{50} = 68.13 μM) and also more potent than the corresponding 4-methoxy derivative **4b** (IC_{50} = 119.9 μM) and the 3-ethoxy-4-methoxy derivative **4f** (IC_{50} = 108.45 μM) and is nearly as potent as the trimethoxy derivative **4g** (IC_{50} = 83.76 μM). On the other hand, the 4-nitro derivative **4d** (IC_{50} = 57.87 μM) was found to be more potent than the corresponding 3-nitro derivative **4c** (IC_{50} = 106.48 μM), finally, the least potent in this series was the halogenated derivatives **4h** and **4i** (IC_{50} = 116.38 and 105.15 μM). Concerning the series of 1,2-dihydroisoquinoline **6a-h**, the most potent in this series is the 4-methoxy derivative **6c** (IC_{50} = 36.67 μM) which was found to be more potent than the reference drug (IC_{50} = 68.13 μM) and the corresponding 4-methyl derivative **6a** (IC_{50} = 58.52 μM), the trimethoxy derivative **6f** (IC_{50} = 91.68 μM) and the 2-methoxy derivative **6b** (IC_{50} = 244.5 μM) which is the least potent in this series. On the other hand, the 4-nitro derivative **6e** (IC_{50} = 58.96 μM) was found to be more potent than the corresponding 3-nitro derivative **6d** (IC_{50} = 108.49 μM), while, the chloro derivatives **6g** and **6h** showed nearly equipotent activity (IC_{50} = 121.06 and 107.14 μM). Finally, the chromeno[3,4-*c*]pyridone derivatives **9** and **10** (IC_{50} = 123.24 and 58.98 μM) showed more potent activity than the corresponding chromene derivatives **7** and **8** which showed no IC_{50}.

3.2.3. In-vitro anticancer activity using liver human tumor cell lines (HEPG2)

This study was performed to evaluate the cytotoxic activity of the most potent six compounds resulted from EAC assay (compounds **4a**, **4d**, **6a**, **6c**, **6e** and **10**). We can conclude from the results obtained from (Table 2) that indeed these compounds showed potent activity on HEPG2 cell line. The most potent was the 4-nitro dihydropyridone derivative **4d** (IC_{50} = 11.7 µM) which is more potent than doxorubicin (IC_{50} = 38.46 µM), while, the increasing order of the rest of the compounds was as follows: 4-methyl isoquinoline derivative **6a** (IC_{50} = 21.81 µM), the 4-nitro isoquinoline derivative **6e** (IC_{50} = 25.83 µM), the 4-methyl dihydropyridone derivative **4a** (IC_{50} = 31.2 µM), the chromeno[3,4-*c*]pyridine **10** (IC_{50} = 32.2 µM) and the 4-methoxy isoquinoline **6c** (IC_{50} = 38.9 µM).

3.3. Radiosensitizing evaluation

The rationale for combining chemotherapy and radiotherapy is based mainly on two ideas, one being spatial cooperation, which is effective if chemotherapy is sufficient to eradicate subclinical metastases and if the primary local tumor is effectively treated by radiotherapy. In this regard, no interaction between radiotherapy and chemotherapy is required. The other idea is the enhancement of radiation effects. Cytotoxic agents can enhance radiation effects by direct enhancement of the initial radiation damage by incorporating drugs into DNA, inhibiting cellular repair, accumulating cells in a radiosensitive phase or eliminating radioresistant phase cells, eliminating hypoxic cells or inhibiting the accelerated repopulation of tumor cells [17]. Consequently, the ability of the most six active compounds **4a**, **4d**, **6a**, **6c**, **6e** and **10**, to enhance the cell killing effect of γ-irradiation was studied. From the results obtained in (Table 2), compound **4a** showed an *in vitro* cytotoxic activity with IC_{50} value of 31.2 µM, when the cells were subjected to different concentrations of the compound alone. While, when the cells were subjected to the same concentrations of compound **4a**, and irradiated with a single dose of γ-radiation at a dose level of 8 Gy, as shown in (Table 3), the IC_{50} value was synergistically decreased to 5.03 µM. Similarly, compounds **4d**, **6a**, **6c**, **6e** and **10** showed IC_{50} values of 11.7, 21.81, 38.9, 25.83 and 32.2 µM, respectively, when used alone, as shown in (Table 2). The IC_{50} value was decreased to 6.37, 2.68, 8.38, 6.04 and 3.35 µM, respectively, when the cells were treated with compounds **4d**, **6a**, **6c**, **6e**, and **10** in combination with γ-radiation. From these results, we can conclude that the combination of compounds **4a**, **4d**, **6a**, **6c**, **6e** and **10** and ionizing radiation synergistically enhanced growth inhibition on liver cancer cells, compared with each agent alone.

4. Conclusion

We report in this work the synthesis of new 2-pyridone, isoquinoline, chromene and chromenopyridone derivatives. It was clearly observed from the results of in-vitro cytotoxic screening that some of the synthesized compounds exhibited significant anticancer activity on *Ehrlich Ascites Carcinoma* (EAC) and human liver tumor cell line (HEPG2). While, combining these compounds with radiation at the same concentrations enhances their activity which demonstrates the importance of the combination therapy for the patients with cancer to decrease the side effects of both drugs and radiation.

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