Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(1):117-123
(http://derpharmachemica.com/archive.html)

Synthesis and cytotoxic activity of acridine derivatives substituted with benzimidazole, benzoxazole and benzothiazole

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ABSTRACT

*Two novel series of 2-(Benzo[d]imidazole/oxazole/thiazole-2-yl))acridine-9(10H)-one**IVa-c**and10-(2-((4-(Benzo[d]imidazole/oxazole/thiazole-2-yl)phenyl)amino)-2-oxoethyl)-9-oxo-9,10-dihydroacridine-4-carboxylic acid**VIIa-c**were synthesized.The antitumor activity of the prepared compounds was evaluated against human breast cancer (MCF-7), hepatocellular carcinoma (HepG-2) and colon cancer (HCT-116) cell lines using Sulphorhodamine-B (SRB) assay method.Doxorubicin was used as a reference standard. Most of the tested compounds showed potent antitumor activity against HCT-116 cell line with IC_{50} range equal 4-31µM/mland the compound**VIIc**was the best active one (IC_{50} = 4.75 µM/ml). **VIIa**showed the same activity compared to the effect of the reference drug doxorubicin on Hep-2 cell line(IC_{50} = 3.75 µM/ml). Allof the tested compoundsshowed weak activity against MCF-7 cell line(IC_{50} = 5.01 µM/ml).*

Keywords: Acridine, Benzimidazole**,** Benzoxazole , Benzothiazole, HCT-116, MCF-7, HepG-2.

INTRODUCTION

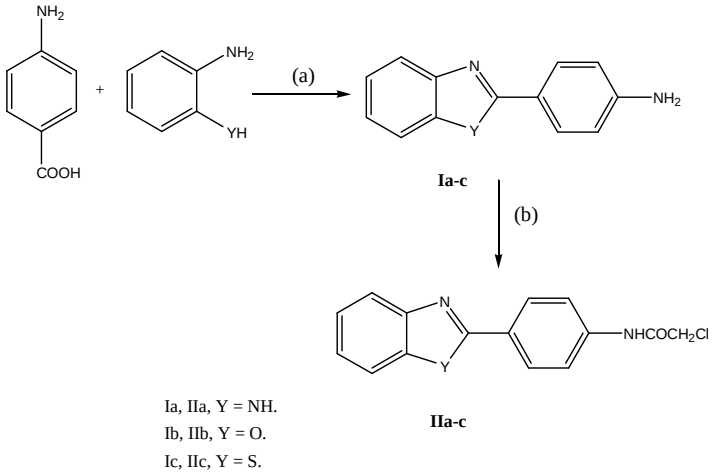
Cancer which is mostly caused by a mutation of normal cell has become the disease mostly urgent to be solved because of its high mortality[1]. Novel effective anticancer drugs with fewer side effects are currently needed to be developed. As a large percentage of chemotherapeutic drugs currently used in cancer therapeutics are DNA-binding and/or DNA-modifying agents, such as cisplatin, topotecan, adriamycin, etc.[2]. DNA has been regarded as one ofthe most significant targets in cancer treatment[3]. In addition, once drugs bind to DNA, the DNA structure will be changed, which will influence the activity of DNA-related enzymes, such as DNA topoisomerases. DNA topoisomerases regulate the winding of DNA and play critical roles in DNA replication, transcription, recombination, etc [4]. As cancer cells express high level of topoisomerase activity and show remarkable sensitivity to DNA-targeted drugs, a large number of anticancer drugs targeted DNA and topoisomerases have been currently designed and synthesized in these years [5]. In spite of the side effects caused by DNA-targeted compounds and topoisomerase inhibitors, it is still recognized as the main choice to prolong the patents' life. Therefore, the search for novel DNA binding agents and topoisomerase inhibitors remains a major role in the fight against cancer.

Acridine derivatives were primarily used as stains for dye manufacturing e.g., acridine orange [6].A number of marketed preparations based on the acridine nucleus were available[7] which represented various pharmacological activities such as antimicrobial[8-10], anti-diabetic (glyco-acridines) [11], anti-malarial[12,13], acetylcholinesterase inhibitory (for Alzheimer's disease AD)[14] , anti-herpes[15] ,and anti-cancer[16]. Acridines and their analogues represent an important class for treatment of cancer via different mechanisms. They inhibit cancer cells by inhibition of different enzymes such as topoisomerases (topo I and topo II),[17-19]telomerase[20,21]or kinase [22,23]. The acridine derivatives known as DNA-intercalators such as amsacrine[24-26]which was the first synthetic DNA intercalator drug in clinical trials that was used as antileukemic agent. It was acted by inhibition of topo II enzyme[27] but the significant clinical use of several of these compounds was limited by problems such as side effects, drug resistance and poor bioavailability [24].Now many *m*-AMSA derivatives have been developed to improve the activity and reduce the side effects, such as AHMA and its analogues[28]. Other acridine derivatives exhibit cytotoxic activity such as nitracrine[24], Acronycine[29] , DACA[30], C-1311[31]and BRACO-19[21](Fig. 1).

Taking cognizance of potential anticancer activity of benzimidazole[32-34], benzoxazole[35-36] or benzothiazole[37,38]nucleus, which was linked with acridine ring by an appropriate linker this combination may increase the DNA binding affinity and the cytotoxic activity so, it was decided to synthesize acridine derivatives with benzimidazole, benzoxazole and benzothiazole substituent at C2 position of acridine ring **IVa-c**(Scheme 2) or at NH group with *N*-phenyl-acetamide as a linker with acridine skeleton **VIIa-c** (Scheme 2) and evaluate their cytotoxic activity against liver cancer (HepG-2), colon cancer (HCT-116) and breast cancer (MCF-7) cell lines.

The postulated schemes for the synthesis of the new compounds as follow

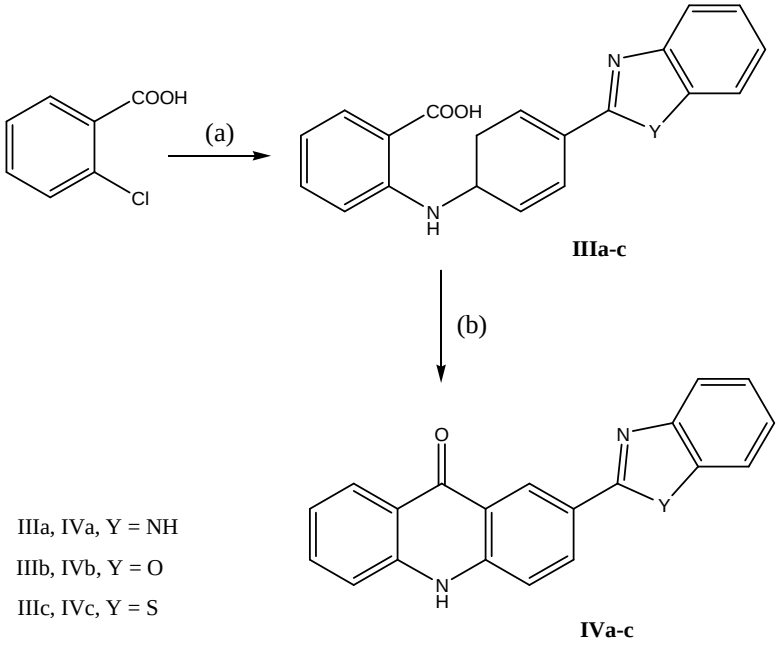
Scheme 1 for starting materials :-



Ia, IIa, Y = NH.
Ib, IIb, Y = O.
Ic, IIc, Y = S.

Reagents and coditions : (a) PPA, 220 ^{0}C/4 h; (b), ClCH2COCl, DMF, TEA, R.T/10 h.

Scheme 2:-



Reagents and coditions : (a) Ia-c, anhyd. K_2CO_3, CuO, DMF, reflux/24 h; (b) PPA, 150 ^oC/4 h.

MATERIALS AND METHODS

2.1. General experimental section

Melting points were uncorrected; they were detected using Electrothermal Stuart 5MP3 digital melting point apparatus. Thin layer chromatography (TLC) was performed using Kiesel gel 0.25 mm, 60 G F 254, Merck Silica gel plates and the running solvent system was chloroform/methanol (9.5:0.5), ultraviolet light was used to detect the spots. Elemental microanalyses were performed at the micro analytical center, Faculty of Science, Cairo University, Mass spectra were detected on Fennigan MAT, SSQ 7000, Mass spectrometer, (70 eV (EI)) at the micro analytical Center, Faculty of Science, Cairo University. The ^{1}H-NMR spectra were recorded in DMSO-d6 on a Varian Mercury spectrometer (400 MHz) at the magnetic resonance unit at Beni Suef University. Chemical shifts are expressed in values (ppm) and tetramethylsilane (TMS) is the internal standard, addition of D_2O was used to confirm the exchangeable protons.

3.2. Synthesis and characterization

Compounds **Ia-c**[39, 40], **IIa-c**[40, 41], **V**[42] **VI**[43]were prepared according to the previously reported procedures.

3.2.1. General procedure for intermediates IIIa-c

A mixture of compounds **Ia-c** (0.01 mol), 2- chlorobenzoic acid (2.34 g, 0.015 mol), anhydrous potassium carbonate (1.51 g, 0.011 mol) and copper oxide (0.02 g) was heated under reflux in dry N,N- dimethylformamide (25 mL) for 24 h. The reaction mixture was cooled, poured onto ice-cold water and acidified with dil HCl. The separated solid was filtered, washed with water, dried and recrystallized from aqueous ethanol to give intermediates **IIIa-c**.

3.2.1.1.2-((4-(Benzo[*d*]imidazole -2-yl)phenyl)amino) benzoic acid (IIIa). Yield 87 %; mp > 300 ^oC. IR υ_{max} / cm^{-1} 3600-2646 br.(OH), 3375, 3297 (2NH), 3040 (CH arom.), 1688 (C=O). ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.48 (s, 1H, NH, D_2O exchangeable); 6.77 (d, J_{value} = 8.4 Hz, 2H, ArH); 7.46-7.54 (m, 4H, ArH + 1H, NH, D_2O exchangeable); 7.71-7.73 (m, 4H, ArH); 8.01 (d, J_{value} = 8.4 Hz, 2H, ArH); 14.80 (s, 1H, OH, D_2O exchangable).

MS (EI): m/z (%): 235 (100), 329 (19). Anal.Calcd. For $C_{20}H_{15}N_3O_2$ (329.35): C,72.94; H, 4.59; N, 12.76. Found: C, 73.08; H, 4.65; N, 12.94

3.2.1.2.2-((4-(Benzo[*d*]oxazole -2-yl)phenyl)amino) benzoic acid (IIIb). Yield 90 %; mp 210-212 ^oC.IR υ_{max} / cm^{-1} 3500-2600 br.(OH), 3367 (NH), 3040 (CH arom.), 1680 (C=O). ^1H NMR (400 MHz, d_6-DMSO) δ 4.20 (s, 1H, NH D_2O exchangeable), 6.76 (d, J_{value} = 8.8 Hz, 2H, ArH); 7.26-7.32 (m, 4H, ArH); 7.51-7.72 (m, 4H, ArH); 8.06(d, J_{value} = 8.8 Hz, 2H, ArH). MS (EI): m/z (%): 331 (100), 330 (50). Anal.Calcd. For $C_{20}H_{14}N_2O_3$(330.34): C,76.91; H, 3.87; N, 8.97. Found: C, 77.12; H, 3.91; N, 9.08.

3.2.1.3. 2-((4-(Benzo[*d*]thiazole-2-yl)phenyl)amino) benzoic acid (IIIc). Yield 82 %; mp 105-107 ^oC.IR υ_{max} / cm^{-1} 3500 : 2600 br.(OH), 3445 (NH), 3057 (CH arom.), 1663 (C=O). ^1H NMR (400 MHz, d_6-DMSO) δ 3.63 (s, 1H, NH D_2O exchangeable), 6.79 (d, J_{value} = 8.4 Hz, 2H, ArH); 7.36-7.49 (m, 4H, ArH); 7.83-7.93 (m, 4H, ArH); 8.04(d, J_{value} = 8.4 Hz, 2H, ArH). MS (EI): m/z (%): 221 (100), 346 (1). Anal.Calcd. For $C_{20}H_{14}N_2O_2S$(346.40): C,69.35; H, 4.07; N, 8.09. Found: C, 69.59; H, 4.13; N, 8.21.

3.2.2. General procedure for compounds IVa-c

A mixture of compounds **IIIa-c** (0.01 mol) and polyphosphoric acid (25 g) was heated at 150°C for 4 h. The reaction mixture was cooled then poured onto ice-cold 10% aqueous sodium carbonate solution (200 mL). The formed solid was filtered, washed with water, dried and recrystallized from methanol.

3.2.2.1. 2-(Benzo[*d*]imidazole -2-yl)) acridin-9(10H)-one(IVa).Yield 84 %; mp 240-242 ^oC.IR υ_{max} / cm^{-1} 3374, 3235 (2NH), 3040 (CH arom.), 1628 (C=O).^1H NMR (400 MHz, d_6-DMSO) δ 3.36 (s, 1H, NH, D_2O exchangeable); 5.51 (s, 1H, NH, D_2O exchangeable); 6.66-7.85(m, 11H, ArH). MS (EI): m/z (%): 235 (100), 329 (18). Anal.Calcd. For $C_{20}H_{13}N_3O$ (311.34): C,77.16; H, 4.21; N, 13.50. Found: C, 77.83; H, 4.27; N, 13.74.

3.2.2.2.2-(Benzo[*d*]oxazole-2-yl)) acridine-9(10H)-one (IVb).Yield 82 %; mp 171-173 ^oC.IR υ_{max} / cm^{-1} 3470 (NH), 3060 (CH arom.), 1629 (C=O). ^1H NMR (400 MHz, d6-DMSO) δ 5.95 (s, 1H, NH, D_2O exchangeable); 6.69-7.88 (m, 11H, ArH). MS (EI): m/z (%): 83 (100), 312 (3). Anal.Calcd. For $C_{20}H_{12}N_2O_2$(312.32): C,76.91; H, 3.87; N, 8.97. Found: C, 77.12; H, 3.91; N, 9.08.

3.2.2.3. 2-(Benzo[*d*]thiazole-2-yl)) acridin-9(10H)-one(IVc).Yield 75 %; mp 150-152 ^oC.IR υ_{max} / cm^{-1} 3447 (NH), 3058 (CH arom.), 1627 (C=O). ^1H NMR (400 MHz, d_6-DMSO) δ 5.59 (s, 1H, NH, D_2O exchangeable); 6.66-7.85 (m, 11H, ArH). MS (EI): m/z (%): 138 (100), 328 (9). Anal.Calcd. For $C_{20}H_{12}N_2OS$ (328.93): C,73.15; H, 3.68; N, 8.53. Found: C, 73.31; H, 3.74; N, 8.67.

3.2.3. General procedure for compounds VIIa-c

A mixture of compounds **IIa-c** (0.04 mol), acridine-4-carboxylic acid **VI** (2.39 g, 0.01 mol), and anhydrous potassium carbonate (1.5 g, 0.011 mol) was heated under reflux in dry N, N-dimethylformamide (25 mL) for 24 h. The reaction mixture was cooled, poured onto ice-cold water, filtered, dried and recrystallized from methanol to give compounds **VIIa-c.**

3.2.3.1.10-(2-((4-(Benzo[*d*]imidazole -2-yl)phenyl)amino)-2-oxoethyl)-9-oxo-9,10-dihydroacridine-4-carboxylic acid (VIIa). Yield 73 %; mp 288-290 ^oC.IR υ_{max} / cm^{-1} 3600 : 2600 br.(OH), 3370, 3252 (2NH) , 3057 (CH arom.), 2924 (CH aliph.), 1679 (br.band of 2 C=O), 1605 (C=O of acridine). ^1H NMR (400 MHz, d_6-DMSO) δ 3.58 (s, 1H, NH, D_2O exchangable); 5.03 (s, 2H, CH_2); 7.47-8.25 (m, 15H, ArH + 1H, NH, D_2O exchangable); 10.86 (s, 1H, OH, D_2O exchangable). MS (EI): m/z (%): 63 (100), 488 (22). Anal.Calcd. For $C_{29}H_{20}N_4O_4$(488.49): C,71.30; H, 4.13; N, 11.47. Found: C, 71.49; H, 4.19; N, 11.72.

3.2.3.2. 10-(2-((4-(Benzo[*d*] oxazole -2-yl)phenyl)amino)-2-oxoethyl)-9-oxo-9,10-dihydroacridine-4-carboxylic acid (VIIb). Yield 82 %; mp 145-147 ^oC. IR υ_{max} / cm^{-1} 3466 : 2673 br.(OH), 3297 (NH) , 3053 (CH arom.), 2900 (CH aliph.), 1675 (br.band of 2 C=O), 1609 (C=O of acridine). ^1H NMR (400 MHz, d_6-DMSO) δ 4.06 (s, 2H, CH_2); 5.74 (s, 1H, NH, D_2O exchangable); 7.36-8.19 (m, 15H, ArH + 1H, NH, D_2O)10.42 (s, 1H, OH, D_2O exchangable). MS (EI): m/z (%): 106 (100), 489 (75). Anal.Calcd. For $C_{29}H_{19}N_3O_5$ (489.48): C,71.16; H, 3.91; N, 8.58. Found: C, 71.42; H, 3.95; N, 8.75.

3.2.3.3. 10-(2-((4-(Benzo[*d*] thiazole-2-yl)phenyl)amino)-2-oxoethyl)-9-oxo-9,10-dihydroacridine-4-carboxylic acid (VIIc). Yield 70 %; mp 95-97 ^{o}C.IR υ_{max} / cm^{-1} 3600 : 2363 br.(OH), 3200 (NH), 3054 (CH arom.), 2920 (CH aliph.), 1660 (br.band of 2 C=O), 1601 (C=O of acridine). ^{1}H NMR (400 MHz, d_6-DMSO) δ 4.06 (s, 2H, CH_2); 5.72 (s, 1H, NH, D_2O exchangable); 7.34-7.55 (m, 4H, ArH); 7.75-8.13 (m, 11H, ArH); 10.03 (s, 1H, OH, D_2O exchangable). MS (EI): m/z (%): 226 (100), 505(12). Anal.Calcd. For $C_{29}H_{19}N_3O_4S$(505.54): C,68.90; H, 3.79; N, 8.31. Found: C, 69.18; H, 3.76; N, 8.48.

3.3. ***Pharmacological studies***

3.3.1. In vitro cytotoxic activity evaluation by SRB assay

Cytotoxic activity of the newly synthesized compounds was evaluated againstMCF7, HEPG2, HCT116 cancer cell lines using Sulphorhodamine-B (SRB) assay method as previously reported by Skehan *et al [44]*. Antitumor activity evaluation was performed at the Center for Genetic Engineering, Al-Azhar University, Cairo, Egypt. Reagents and chemicals were purchased from Sigma Aldrich Chemical Company (St.Louis, Mo, U.S.A.).The tested cell lines were obtained from the American Type Culture Collection (ATCC, Minisota, U.S.A.) through the Tissue Culture Unit, The Egyptian Organization for Biological Products and Vaccines (Vacsera, Egypt).Cells were seeded for 24h in a 96 well microtiter plates at a concentration of 1000-2000 cells/well, (100 µl/well), then cells were incubated for 48 h with various concentrations (0, 6.25, 12.5, 25, 50, 100 µg/ml) of the tested compounds, 3 wells were used for each concentration, after incubation , the cells were fixed with 10%trichloroacetic acid (150 µl/well) for 1 h at 4^{O}C, washed by distilled water for 3 times. Wells were stained for 10-30 min at room temperature with 0.4% SRB(100/well), dissolved in 1% acetic acid (70µl/well). Washed with acetic acid 1% to remove unbound dye till colorless drainage obtained. The plates were subjected to air drying, 24 h not exposed to UV. The dye was solubilized with 150 µl/well of 10 m MT rise-EDTA (PH 7.4) for 5 min on a shaker at 1600 rpm. The optical density (OD) of each well was measured spectrophotometrically at545 nm with an ELISA microplate reader. Survival curve was obtained by plotting the percent of surviving cells against different concentrations of the tested compounds. The IC_{50} values were calculated using sigmoidal concentration– response curve fitting models (Sigmaplot software).

RESULTS AND DISCUSSION

Chemistry

Compounds Ia-c were synthesized according the reported procedure through dehydration using poly phosphoric acid. The synthesis of compounds **IVa-c &VIIa-c** was shown in Scheme 1&2. The Ullmann coupling of 2-chlorobenzoic acid with compounds **Ia-c[39,40]**in DMF produced compounds **IIIa-c**.

The structure of the synthesized compounds was confirmed using HNMR, IR and mass spectrum. which upon heated with PPA at 150 ^{o}C gave compounds **IVa-c**. In scheme 2, the Ullmann coupling of 2-chlorobenzoic acid with anthranilic acid in DMF produced compound **V[41]**which was cyclized by conc. H_2SO_4at100 ^{o}C to form acridone **VI[42]**that was heated under reflux with compounds **IIa-c[40,43]** in DMF to give compounds **VIIa-c**.

The IR spectra of compounds **IIIa-c** characterized by the appearance of an absorption band at 3600-2500 cm^{-1} corresponding to OH & NH groups and at 1688-1663 cm^{-1} corresponding to C=O group. The ^{1}H NMR spectra of compound **IIIa** revealed the existence of two singlet signals exchangeable with D_2O corresponding to 2 NH groups at δ 6.48, 7.48 and one singlet signal exchangeable with D_2O corresponding to OH group at δ 14.80. Compounds **III b&c** showed a singlet signal of NH group exchangeable with D_2O at δ 4.20, 3.63. In addition, the mass spectrum of **IIIa** showed the molecular ion peak at *m/z* 329 ($M^{+\cdot}$) 18.95% and base ion peak at *m/z* 208. The IR spectra of compounds **IVa-c** showed the appearance of an absorption band at 3470-3235 cm^{-1} corresponding to NH group and an absorption band at 1629-1627 cm^{-1} corresponding to C=O group. The ^{1}HNMR spectra confirmed the structure of **IVa** by the appearance of two singlet signals exchangeable with D_2O for the 2 NH protons at δ 3.36, 5.51 ppm and the disappearance of the singlet signal for OH proton of compound **IIIa at** δ 14.80 ppm. In addition, ^{1}H NMR spectrum of **IVb&c** showed the appearance of one singlet signal exchangeable with D_2O of NH protonat δ 5.59, 5.95 ppm.

Furthermore, the mass spectrum of compound **IVc** showed a molecular ion peak at *m/z* 328 ($M^{+\cdot}$) 8.56% and base ion peak at *m/z* 138.

^{1}H NMR spectra of compounds **VIIa-c** showed the appearance of a singlet signal at 4.06-5.03 ppm corresponding to CH_2 protons. Compound **VIIa** revealed the existence of two singlet signals D_2O exchangeable corresponding to 2

NH groups at δ 3.58, 7.48 ppm and one singlet signal D_2O exchangeable corresponding to OH group at δ 10.68 ppm. Compounds **VIIb&c**showed a singlet signal D_2O exchangeable atδ 5.72-5.74 ppm corresponding to NH group and one singlet signal D_2O exchangeable corresponding to OH group at δ 10.03-10.42 ppm. In addition, the mass spectrum of **VIIc** showed the molecular ion peak at *m/z* 505 ($M^{+\cdot}$) 12.02% and base ion peak at *m/z* 226.

3. Pharmacological screening

In this work, cytotoxic activity of the newly synthesized compounds **IVa-c** &**VIIa-c** were evaluated against liver cancer (HepG-2), colon cancer (HCT-116) and breast cancer (MCF-7) cell lines, using sulphorhodamine-B (SRB) assay method. IC_{50} was calculated and represented in µM/ml (Table 1). Doxorubicin was used as a reference drug as anticancer agent. Most of the tested compounds **IVa-c & VIIa-c** exhibited very good cytotoxic activity against colon cancer cell line (HCT-116) with IC_{50} ranged from 4.75 to 5.25µM/ml. Compound **VIIc** was the best active one with IC_{50} = 4.75 µM/ml, the rest of the tested compounds are arranged in the following order **IVc**>**IVa**>**VIIb**>**VIIa**>**IVb** according to their IC_{50} values compared to doxorubicin (7.25uM/mL (Table 1).Activity against liver cancer cell line (HepG-2) revealed that; compounds **VIIa&VIIb** showed similar activity as reference drug doxorubicin with IC_{50} values of3.75 and 3.88 µM/ml respectively. All the tested compounds showed weak or no activity against breast cancer (MCF-7) cell line compared to to doxorubicin (table 1).

Table 1: IC50 values for the newly synthesized acridine derivatives (µM/ml)

	HepG2	HCT-116	MCF-7
Doxorubicin	3.75	7.25	4.63
Compound IVa	4.55	5.25	17.35
Compound IVb	6.95	30.94	288.40
Compound IVc	13.80	4.82	> 200
Compound VIIa	3.75	10.94	5.01
Compound VIIb	3.88	5.25	5.24
Compound VIIc	6.25	4.75	8.03

CONCLUSION

From the current results it can be concluded that the synthesized acridine derivatives **IVa-c**&**VIIa-c** showed cytotoxic activity against colon cancer cells HCT-116 (four compounds **IVa&c**&**VIIb&c** were more potent and efficacious than the reference drug, doxorubicin) greater than their cytoxicity against both liver cancer HepG-2 (two compounds are active **VIIa&b**) and breast cancer MCF-7 (all compounds were weak or inactive). Among all the compounds, compound **VIIc** displayed the highest cytotoxic activity against HCT-116 cells.

In addition the combination of benzazoles on C2 position of acridine ring played an important role on the cytotoxic activity against HCT-116 but had no effect on other cancer cell lines. Furthermore the combination of benzazoles at NH group of acridine ring resulted in compounds with strong cytotoxic activity against both HCT-116 and HepG-2.

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