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Synthesis and Evaluation of New Series of 1,3-Dioxolane Conjugated with Coumarin-Pyrazoline Derivatives as Anticancer Agents

Moath Kahtan Bashir[1,*], Nohad Abdul-Wahhab Al-Omari[2], Adnan Othman Omar[3]

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Iraq
[2]Department of Pharmacy, Al-Kitab University College, Kirkuk, Iraq
[3]Department of Chemistry, College of Science, University of Mosul, Iraq

ABSTRACT

Two novel series of 3-methyl-4-oxo-benzopyranyl[4,3-c][1-*H]* pyrazoline derivatives and its 7,8-dioxolanoderivatives were synthesized. The first series compounds were obtained according to knoevenagel reaction by condensing of salicylaldehyde with ethyl acetoacetate to produce 3-acetylcoumarin which reacts with hydrazine hydrate and its four derivatives to produce the first series final products, while the second series compounds were obtained by the same reaction but by condensing 2,4,5-trihydroxy benzaldehyde with ethyl acetoacetate to produce 3-acetyl-6,7-dihydroxycoumarin; the catechol moiety were methylated by dichloromethane using anhydrous potassium fluoride as a catalyst, and the 3-acetyl-6,7-dioxolanocoumarin was reacted with hydrazine hydrate and its four derivatives to produce the second series final products. The chemical structures of the synthesized compounds were established by analyzing their FTIR, ^{1}H-NMR and ^{13}C-NMR spectra. The two series compounds were bio-assayed to examine theircytotoxic effect against two cancer cell lines, which are MCF-7 and SKG. The IC_{50} of 1,3-dioxolane containing compounds were less than that of absent 1,3-dioxolane ring compounds especially for compounds Va and Vb in MCF-7 cell line and compounds Va, Vc, Ve in SKG cell line; such results may indicate the importance of 1,3-dioxolane ring in cytotoxic activity.

Keywords: 1,3-dioxolane, cancer, coumarin, pyrazoline, targeting.

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1. INTRODUCTION

Heterocyclic compounds with pyrazoline moiety are widely distributed in nature as in alkaloids, vitamins, pigments, and also found in plant and animal cells [1]. It have been got a huge interest from researchers due to its various pharmacological activities like analgesic, anti-inflammatory, antipyretic, antidiabetic, antidepressant, antimicrobial, uricosuric, and anticancer effects[2].

Coumarin containing compounds either naturally or synthetically were highly investigated for their pharmacological activities leading to the discovery of important activities against variety of disorders as the anti-inflammatory activity like esculitin, anticoagulant activity like warfarin, antibacterial activity like anthogenol, and anticancer activity [3][4].Hence in many studies, a diversity of coumarin-pyrazoline hybrid compounds have been synthesized and showed high anti-proliferative activities against wide range of tumor cell lines for examplea series of 6-pyrazolinyl coumarin have been synthesized and examined against 60 cell lines which showed high cytotoxic activity with a mean GI_{50} of 1.88 µM especially toward leukemia cell lines CCRF-CEM and MOLT-4 [5].

On the other Hand 1,3-dioxolane ring and 1,3-benzodioxole have been found to possess a great attention as it is present in many naturally occurring medicines, for example the naturally occurring antimitotic drugs which inhibit tubulin polymerization podophyllotoxin, cornigerine, steganacin, and combretastatin [6].Hence, the synthesized oxygen-bearing

heterocyclic compounds like 1,3-benzodioxolane have beenincluded in many cytotoxicity studies, for example, many synthesized compounds bearing 1,3-benzodioxolane were found to be effective in vivo against P388 lymphocytic leukemia [7], and against human colon carcinoma [8].

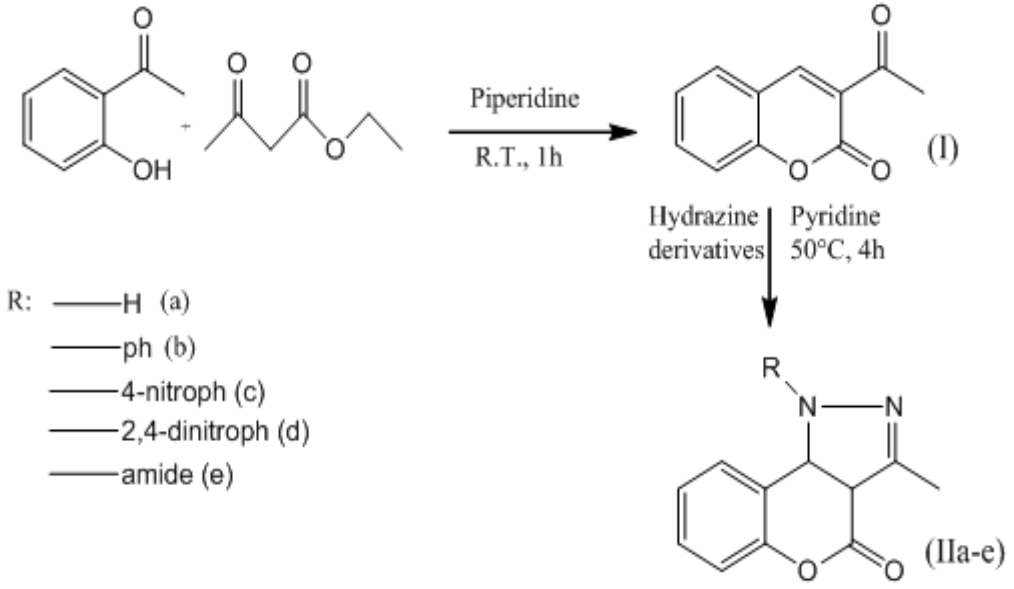
From the previously mentioned facts, this study aimed to synthesize a novel series of 3-methyl-4-oxo-benzopyranyl[4,3-c][1-*H*] pyrazoline with related four derivatives, then conjugate 1,3-dioxolane ring with these compounds to examine its influence in the cytotoxic activity in MCF-7 breast cancer & and SKG esophageal cancer cell lines.

2. MATERIAL AND METHODS

All the starting materials for the synthesis of the two series compounds were purchased from Sigma Aldrich and used without purification.IR spectra of the synthesized products were detected on Bruker Alpha FTIR-ATR Spectrophotometer (Germany) while their NMR spectra were scanned on Bruker (400MHz) spectrophotometer (Germany) in DMSO-d_6 using tetramethylsilane as an internal standard. Melting points were determined on an electrochemical CIA 9300 melting point apparatus (UK) using open capillary method. Elemental microanalysis was performed on Perkin-Elmer 2400 CHN analyzer (USA) and results were within ± 0.5% of theoretical values. The purity of compounds were checked on TLC plates performed on Merck Silica gel 60 F254 aluminum sheets using iodine vapor as visualizing agent.

Regarding tothe cytotoxicity study, the two cell lines MCF-7 and SKG were obtained from the Iraqi Center for Cancer and Medical Genetic Research (ICCMGR) Cell Bank Unit. Cell lines were maintainedin Roswell Park Memorial Institute(RPMI)-1640 medium (Sigma/USA) supplemented with 5% calf bovine serum (Capricorn/USA), 100 units/mL penicillin, and 100 µg/mL streptomycin. Cells were passaged using Trypsin-EDTA(Capricorn/USA), reseeded at 50% confluence twice a week, and incubated at 37 °C. MTT stain was supplied from Bioworld/USA.

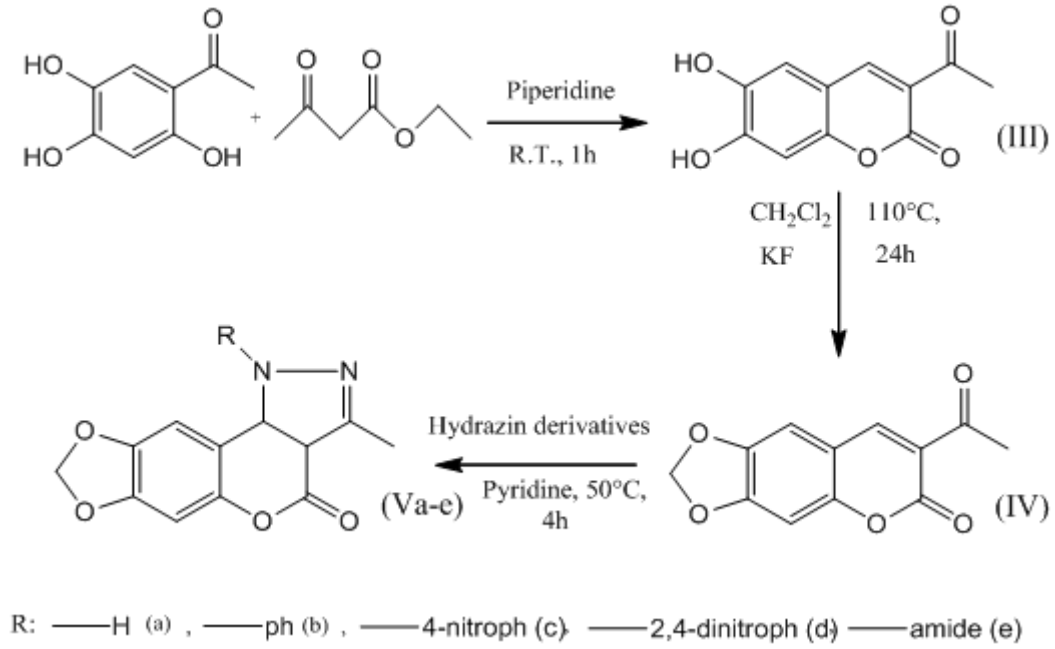
2.1 Synthesis



Scheme I: The synthesis of 3-methyl-4-oxo-benzopyranyl[4,3-c][1-*H*] pyrazoline derivatives (series I)

Synthesis of 3-acetylcoumarin (I)
To a mixture of salicylaldehyde(0.05 mole, 5.3 ml)and ethyl acetoacetate (0.5 mole, 6.3 ml), a few drops of piperidine were added. The reaction mixture was stirred for one hour at room temperature until 3-acetylcoumarin solidify; the content of the reaction was transferred to a filter paper and washed with absolute ethanol until it appear as white color, then recrystallized from methanol [9].

General procedure for the synthesis of 3-methylbenzopyranyl [4,3-c] [1-H] pyrazoline derivatives(II a-e)
These compounds were prepared from equivalent mole (0.01 mole) of 3-acetyl-coumarin (I) with equimole of hydrazine hydrate and its derivatives which are (hydrazine hydrate, phenyl hydrazine, 4-nitrophenyl hydrazine, 2,4-dinitrophenyl hydrazine, and semicarbazide) in minimum amount of pyridine. The reaction mixture was stirred for around 15 minutes, and for 4 hours at 50°C, then left around 1 hour to cool at room temperature; the reaction mixture was poured on to crushed ice. The precipitate was filtered and the product was re-crystallized from absolute ethanol [10][11].



Scheme II Synthesis of 3-methyl-4-oxo-7,8-dioxolano-benzopyranyl[4,3-c][1-H] pyrazoline derivatives.

General procedure for the synthesis of 3-acetyl-6,7-dihydroxycoumarin (III)
To a mixture of 2,4,5-trihydroxybenzaldehyde(0.002 mole, 0.308 g)and ethyl acetoacetate (0.002 mole, 0.25 ml), a few drops of piperidine were added. The reaction mixture was stirred for one hour at room temperature until 3-acetyl-6,7-dihydroxycoumarin solidify; the content of the reaction was transferred to a filter paper and washed with absolute ethanol until it appears as white color, then recrystallized from methanol [9].

General procedure for the synthesis of 3-acetyl-6,7-dioxolo-coumarin (IV)
Two molar concentrations of anhydrous potassium fluoride (0.004 mole, 0.23 g) werestirred with one molar concentration of 3-acetyl-6,7-dihydroxycoumarin (0.002 mole, 0.46 g) in anhydrous dimethylformamide (DMF) for one hour, then one molar concentration of CH_2Cl_2 (0.002 mole, 0.13 ml) was added to the mixture and the mixture was refluxed for 7 hours at 110-120°C; it was left to cool and washed with distilled water, absolute ethanol, dried over with magnesium sulfate, filtered and left to dry [12].

General procedure for the synthesis of 3-methyl-4-oxo-7,8-dioxolo-Benzopyranyl[4,3-c][1H]pyrazoline and its derivatives (Va-e)
These compounds were prepared from equivalent mole (0.001 mole) of 3-acetyl-6,7-dioxalonocoumarin (I) with equimole of hydrazine hydrate and its derivatives which are (hydrazine hydrate, phenyl hydrazine, 4-nitrophenyl hydrazine, 2,4-dinitrophenyl hydrazine, and semicarbazide) in minimum amount of pyridine. The reaction mixture was stirred for around 15 minutes, and for 4 hours at 50°C, then left around 1 hour to cool at room temperature; the reaction mixture was poured on to crushed ice. The precipitate was filtered and the product was re-crystallized from absolute ethanol [10][11].

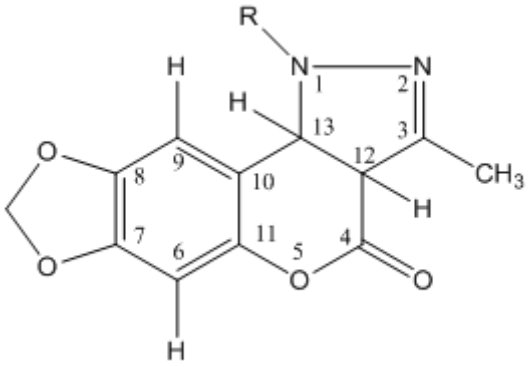
Methodology of in vitro MTT assay of compounds II (a-e) and V (a-e) in MCF-7 and SKG cell lines
This study was conducted at the Iraqi center for cancer and medical genetic research. SKG esophageal cancer cell line and MCF-7 breast cancer cell line, were obtained from the IRAQ Biotech Cell Bank Unit and maintained in RPMI-1640 supplemented with 10% Fetal bovine, 100 units/mL penicillin, and 100 µg/mL streptomycin. Cells were passaged using Trypsin-EDTA reseeded at 50% confluence twice a week, and incubated at 37 °C. The prepared compounds with the positive control (5-fluorouracil) were dissolved in dimethyl sulfoxide(DMSO) at six serial concentrations (500µg/ml, 250µg/ml, 125µg/ml, 62.5µg/ml, 31.25µg/ml, and 15.6µg/ml), the negative control was the cell culture media.To determine the cytotoxic effect, the MTT cell viability assay was conducted on 96-well plates.

Cell lines were seeded at 1×10^4cells/well. After 24h of confluent monolayer was achieved, cells were treated with tested compound. Cell viability was measured after 72 hrs. of treatment by removing the medium, adding 28 µL of 2 mg/mL solution of MTT (and incubating the cells for 1.5 h at 37 °C. After removing the MTT solution, the crystals remaining in the wells were solubilized by the addition of 130 µL of DMSO (Dimethyl Sulphoxide) followed by 37 °C incubation for 15 min with shaking. The absorbency was determined on a microplate reader at 492 nm (test wavelength); the assay was performed in triplicate. The inhibition rate of cell growth (the percentage of cytotoxicity) was calculated according to the following equation:

(A _ B)/A _ 100, where A is themean optical density of untreated wells, and B is the optical density of treated wells and the IC50(s) (compound concentration that inhibit 50% of cancer cells) were calculated for all synthesized compounds and compared with the standard cytotoxic drug 5-flourouracil (5-FU).Graph pad prism software was used to analyze data through non-linear regression; significant difference with respect to control: * $P<0.05$ [13].

3. RESULTS

The spectral data of the prepared compounds are according to the following structure numbering:



3.1 3-acetylcoumarin (I)
Yield, 95%, m.p. 119-120°C.IR (ν_{max}): 3036.40 (Ar C-H), 1728.80 (C=O of cyclic ester), 1671.59 (C=O of ketone), 1600.51 (Ar C=C)[14].

3.2 3-methyl-4-oxo-benzopyranyl [4,3-c] [1-H] pyrazoline (II a)
Yield, 49.5%, m.p. 217-219°C.IR (ν_{max}): 3422.59 (N-H), 3032.75 (Ar C-H), 1718.65 (C=O of cyclic ester), 1612.76 (C=N), 1565.33 (Ar C=C); ^{1}H-NMR (DMSO-*d6* 400MHz, δ ppm): δ 1.8 (s, 3H, CH_3), 3.3 (d, 1H attached to C12), δ 4.8 (dd, 1H attached to C13), δ 6.8 (s, 1H of NH group), δ 6.9-7.8 (m, 4H, Ar-H); ^{13}C-NMR (DMSO-*d6* 400MHz, δ ppm): 17, CH3; 47, C12; 53, C13; 116-158, Ar-carbons; 163, C=O; Anal. Cal. C, 65.34; Found C, 65.37; Cal. H, 4.98; Found H, 4.95; Cal. N, 13.85; Found N, 13.83.

3.3 1-phenyl-3-methyl-4-oxo-benzopyranyl [4,3-c] pyrazoline (II b)
Yield 76 %, m.p. 195-197°C.IR (ν_{max}): 3032.64 (Ar C-H), 1692.17 (C=O of cyclic ester), 1589.95 (C=N), 1564.49 (Ar C=C); ^{1}H-NMR (DMSO-*d6* 400MHz, δ ppm): δ 2.2 (s, 3H, CH_3), δ 3.1 (d, 1H attached to C12), δ 4.6 (d, 1H attached to C13), δ 6.7-7.9 (m, 9H, Ar-H);^{13}C-NMR (DMSO-*d6* 400MHz, δ ppm): 13, CH3; 51, C12; 54, C13; 111-153, Ar-carbons; 161, C=O; Anal. Cal. C, 73.37; Found C, 73.38; Cal. H, 5.07; Found H, 5.05; Cal. N, 10.07; Found N, 10.06.

3.4 1-[p-Nitrophenyl]-3-methyl-4-oxo-benzopyranyl [4,3-c] pyrazoline (II c)
Yield 50.1 %, m.p. 240-241°C.IR (ν_{max}): 3209.05 (Ar C-H), 1699.02 (C=O of cyclic ester), 1597.16 (C=N), 1511.12 (Ar C=C), 1503.73 (Asym. NO), 1328.98 (Sym. NO); ^{1}H-NMR (DMSO-*d6* 400MHz, δ ppm): δ 2.2 (s, 3H, CH_3), δ 2.9 (d, 1H attached to C12), δ 4.2 (d, 1H attached to C13), δ 7.1-8.4 (m, 8H, Ar-H);^{13}C-NMR (DMSO-*d6* 400MHz, δ ppm): 16, CH3; 49, C12; 53, C13; 112-153, Ar-carbons; 163, C=O; Anal. Cal. C, 63.16; Found C, 63.21; Cal. H, 4.05; Found H, 3.99; Cal. N, 13.00; Found N, 12.97.

3.51-[2,4-dinitrophenyl]-3-methyl-4-oxo-benzopyranyl[4,3-c] pyrazoline (II d)

Yield 54.8 %, m.p. 210-212°C.IR (ν_{max}): 3311.10 (Ar C-H), 1719.47 (C=O of cyclic ester), 1603.52 (C=N), 1539.14 (Ar C=C), 1503.77 (Asym. NO), 1318.54 (Sym. NO); ^{1}H-NMR (DMSO-*d6* 400MHz, δ ppm): δ 2.1 (s, 3H, CH_3), δ 3.1 (d, 1H attached to C12), δ 4.7 (d, 1H attached to C13), δ 7.4-8.9 (m, 7H, Ar-H);^{13}C-NMR (DMSO-*d6* 400MHz, δ ppm): 16, CH3; 49, C12; 57, C13; 116-149, Ar-carbons; 165, C=O; Anal. Cal. C, 55.44; Found C, 55.47; Cal. H, 3.28; Found H, 3.20; Cal. N, 15.21; Found N, 15.19.

3.6 1-Acetamide-3-methyl-4-oxo-benzopyranyl [4,3-c] pyrazoline (II e)

Yield 81 %, m.p. 230-231°C. IR (ν_{max}): 3475.16 (N-H), 3143.45 (Ar C-H), 1728.01 (C=O of cyclic ester), 1638.68 (Amide C=O), 1610.48 (C=N), 1530.17 (Ar C=C); ^{1}H-NMR (DMSO-*d6* 400MHz, δ ppm): δ 1.9 (s, 3H, CH_3), δ 3.4 (d, 1H attached to C12), δ 5.1 (d, 1H attached to C13), δ 6.5 (s, 2H, NH_2 group), δ 7.4-7.9 (m, 4H, Ar-H);^{13}C-NMR (DMSO-*d6* 400MHz, δ ppm): 15, CH3; 48, C12; 50, C13; 119-157, Ar-carbons; 159, Amide C=O;165, cyclic ester C=O; Anal. Cal. C, 58.77; Found C, 58.79; Cal. H, 4.52; Found H, 4.49; Cal. N, 17.13; Found N, 17.11.

3.7 3-methyl-4-oxo-7,8-dioxolano-benzopyranyl[4,3-c][1-H] pyrazoline (V a)
Yield 52.3 %, m.p. 207-208°C.IR (ν_{max}): 3139.11 (N-H), 2923.19 (Ar C-H), 1702.12 (C=O of cyclic ester), 1622.00 (C=N), 1585.20 (Ar C=C), 1159.80 (Asym. C-O-C);^{1}H-NMR (DMSO-*d6* 400MHz, δ ppm): δ 2.0 (s, 3H, CH_3), δ 3.3 (d, 1H attached to C12), δ 5.1 (d, 1H attached to C13), δ 6.3 (s, 2H, CH_2 of 1,3-dioxolane ring), δ 6.8(s, 1H, Ar-H), δ 7.6 (s, 1H, Ar-H), δ 8.9 (s, 1H, NH); ^{13}C-NMR (DMSO-*d6* 400MHz, δ ppm): 18, CH3; 42, C12; 51, C13; 105, CH_2 of dioxolane ring; 106-159, Ar-carbons; 164, C=O; Anal. Cal. C, 58.54; Found C, 58.53; Cal. H, 4.09; Found H, 4.01; Cal. N, 11.38; Found N, 11.32.

3.8 1-phenyl-3-methyl-4-oxo-7,8-dioxolano-benzopyranyl[4,3-c] pyrazoline (V b)
Yield 48.8 %, m.p. 227-228°C.IR (ν_{max}): 2903.26 (Ar C-H), 1707.64 (C=O of cyclic ester), 1618.61 (C=N), 1592.02 (Ar C=C), 1148.68 (Asym. C-O-C);^{1}H-NMR (DMSO-*d6* 400MHz, δ ppm): δ 1.6 (s, 3H, CH_3), δ 3.5 (d, 1H attached to C12), δ 4.6 (d, 1H attached to C13), δ 6.1 (s, 2H, CH_2 of 1,3-dioxolane ring), δ 6.6-7.6 (m, 7H, Ar-H); ^{13}C-NMR (DMSO-*d6* 400MHz, δ ppm): 15, CH3; 46, C12; 54, C13; 103, CH_2 of dioxolane ring; 104-157, Ar-carbons; 162, C=O; Anal. Cal. C, 67.07; Found C, 67.09; Cal. H, 4.38; Found H, 4.30; Cal. N, 8.69; Found N, 8.58.

3.9 1-[p-Nitrophenyl-3-methyl-4-oxo-7,8-dioxolano-benzopyranyl[4,3-c] pyrazoline (V c)
Yield 59.6 %, m.p. 225-226°C.IR (ν_{max}): 2942.59 (Ar C-H), 1712.51 (C=O of cyclic ester), 1609.32 (C=N), 1539.44 (Ar C=C), 1509.37 (Asym. NO_2), 1335.25 (Sym. NO_2), 1158.97 (Asym. C-O-C);^{1}H-NMR (DMSO-*d6* 400MHz, δ ppm): δ 1.4 (s, 3H, CH_3), δ 3.4 (d, 1H attached to C12), δ 5.2 (d, 1H attached to C13), δ 6.5 (s, 2H, CH_2 of 1,3-dioxolane ring), δ 6.7-8.4 (m, 6H, Ar-H); ^{13}C-NMR (DMSO-*d6* 400MHz, δ ppm): 17, CH3; 44, C12; 53, C13; 98, CH_2 of dioxolane ring; 106-159, Ar-carbons; 163, C=O; Anal. Cal. C, 58.86; Found C, 58.88; Cal. H, 3.57; Found H, 3.56; Cal. N, 11.44; Found N, 11.39.

3.10 1-[2,4-dinitrophenyl-3-methyl-4-oxo-7,8-dioxolano-benzopyranyl[4,3-c] pyrazoline (V d)
Yield 57.2 %, m.p. 223-225°C.IR (ν_{max}): 2933.37 (Ar C-H), 1705.08 (C=O of cyclic ester), 1629.61 (C=N), 1582.97 (Ar C=C), 1504.46 (Asym. NO_2), 1321.76 (Sym. NO_2), 1164.22 (Asym. C-O-C);^{1}H-NMR (DMSO-*d6* 400MHz, δ ppm): δ 1.7 (s, 3H, CH_3), δ 3.6 (d, 1H attached to C12), δ 4.7 (d, 1H attached to C13), δ 5.8 (s, 2H, CH_2 of 1,3-dioxolane ring), δ 6.4-9.0 (m, 5H, Ar-H);^{13}C-NMR (DMSO-*d6* 400MHz, δ ppm): 16, CH3; 47, C12; 54, C13; 99, CH_2 of dioxolane ring; 103-154, Ar-carbons; 165, C=O; Anal. Cal. C, 52.43; Found C, 52.41; Cal. H, 2.93; Found H, 2.84; Cal. N, 13.59; Found N, 13.53.

3.11 1-Acetamido-3-methyl-4-oxo-7,8-dioxolo-benzopyranyl[4,3-c] pyrazoline (V e)
Yield 60.1 %, m.p. 235-236°C.IR (ν_{max}): 3334.20 (N-H), 2923.11 (Ar C-H), 1696.68 (C=O of cyclic ester), 1631.74 (Amide C=O), 1592.94 (C=N), 1553.51 (Ar C=C), 1150.93(Asym. C-O-C);^{1}H-NMR (DMSO-*d6* 400MHz, δ ppm): δ 2.2 (s, 3H, CH_3), δ 3.7 (d, 1H attached to C12), δ 5.0 (d, 1H attached to C13), δ 5.8 (s, 2H, CH_2 of 1,3-dioxolane ring), δ 6.7 (s, 2H, NH_2), δ 6.9 (s, 1H, Ar-H), δ 7.1 (s, 1H, Ar-H); ^{13}C-NMR (DMSO-*d6* 400MHz, δ ppm): 14, CH3; 48, C12; 51, C13; 99, CH_2 of dioxolane ring; 103-159, Ar-carbons; 163, C=O; Anal. Cal. C, 53.98; Found C, 54.00; Cal. H, 3.83; Found H, 3.79; Cal. N, 14.53; Found N, 14.47.

The IC_{50}(concentration that inhibit 50% of cancer cells) of the prepared compounds are summarized in Table I.

Table I: The $IC_{50}$of prepared compounds in MCF-7 and SKG cell lines

MCF-7 Breast cancer		SKG Esophageal cancer	
Compound	**IC_{50} µg/ml**	**Compound**	**IC_{50}µg/ml**
Control	35.58	Control	5.61
IIa	51.32	IIa	752.00
IIb	8.93	IIb	67.15
IIc	111.40	IIc	489.80
IId	331.30	IId	75.78
IIe	320.00	IIe	297.90
Va	8.97	Va	37.00
Vb	11.15	Vb	135.40
Vc	562.90	Vc	104.60
Vd	230.40	Vd	241.20
Ve	223.10	Ve	22.89

4. DISCUSSION

The hybridization of cytotoxic active heterocyclic molecules like coumarin and pyrazoline is a new approach to make compounds with a significant cytotoxic activity like the study made by Kumar et al.[15] who hybridized coumarin with

pyrazoline in a new series which showed a good cytotoxic effect against three cell lines which are breast, renal, and non-small cell lung cancers; the study rationalized the difference in cytotoxic activity between synthesized hybrid compounds to the difference in resisting hydrolysis of its lactone ring in the circulation, where effective compounds resist hydrolysis until reaching its target site.

Conjugation of 1,3-dioxolane ring with other cytotoxic molecules were highly investigated to improve activity and reduce side effects like the study made by Lue et al.[16] who prepared a novel series bearing 1,3-benzodioxole moiety and found an excellent effect on telomerase enzyme inhibition with an IC_{50} of 0.9 µM which is even better than 5-Fluorouracil.

In this study, the synthesis of 3-acetylcoumarin which is the row compound for series I was in a very good yield, then its hybridization with hydrazine derivatives to produce series I compounds were also in a good percentage of yield according to literature reviews [14].For series II compounds, the synthesis and methylation of catechol moiety of the compound 3-acetyl-6,7-dihydroxycoumarin through using anhydrous KF as Lewis acid and anhydrous CH_2Cl_2 as methyl group donor produced a good yield according to Clark et al method [12]. The physical properties and spectrometric analysis data confirmed the identity of synthesized compounds.

InMCF-7 breast cancer cell line, the IC_{50} results showed that 1,3-dioxolane ring conjugated compounds Va, Vd, and Ve have less IC_{50} values (better effect) than non-conjugated compounds (Figure I). In SKG esophageal cancer cell line, the IC_{50} results showed that 1,3-dioxolane ring conjugated compounds Va, Vc, and Ve have less IC_{50} values (better effect) than non-conjugated compounds (Figure II). Such results may be attributed to the presence of 1,3-dioxolane ring which showed a high cytotoxic activity through many mechanisms like inhibition of tubulin polymerization[6] and telomerase enzyme inhibitory activity[15]. The difference in cytotoxic activity between derivatives in the same series may be due to the differences in interaction with the target site.

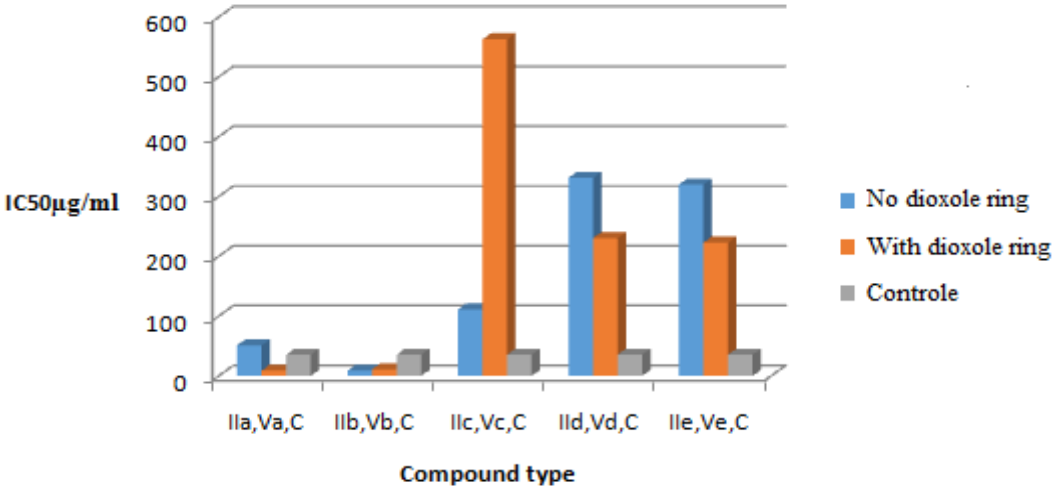


Figure I: Comparison of IC_{50}(s) between non-dioxole containing derivatives, dioxole containing derivatives, with controlin MCF-7 cell line

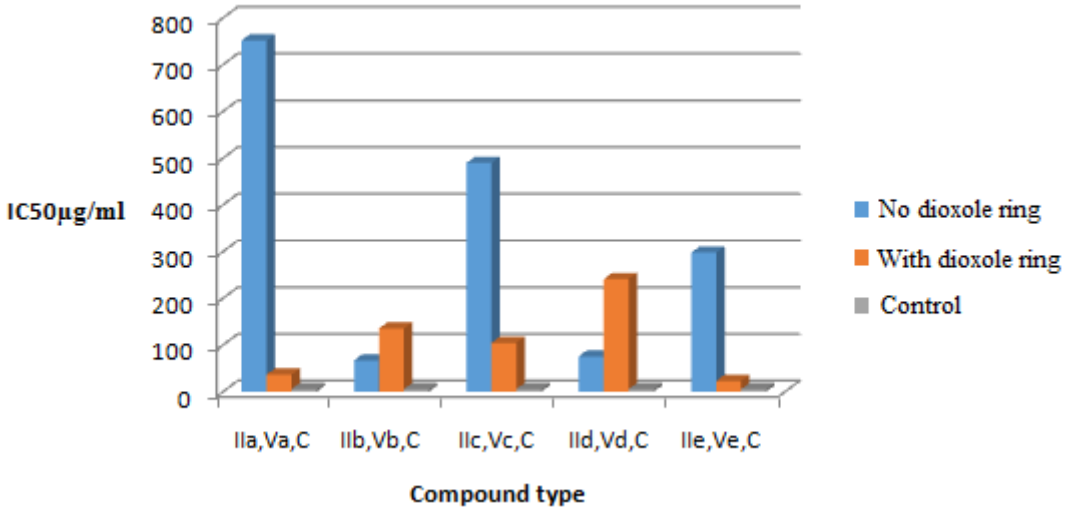


Figure II: Comparison of IC_{50}(s) between non-dioxole containing derivatives, dioxole containing derivatives, with controlin SKG cell line

CONCLUSION

Hybridization of coumarin with pyrazoline is a technique used in many studies to improve the cytotoxic activity of these two compounds, and in an effort to potentiate the activity of these conjugates, 1,3-dioxolane ring was coupled to such conjugate. IC_{50} results showed improvement in cytotoxic effect for compounds Va and Vb in MCF-7 cell line and compounds Va, Vc, and Ve in SKG cell line. Such effects may be due to better interaction with the target site, however a mechanistic and simulation docking studies may be needed to understand the cytotoxic effect of such compounds.

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