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Design and Synthesis of New Compounds Derived from Phenyl Hydrazine and Different Aldehydes as Anticancer Agents

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Abstract

In this work we synthesized new derivatives from Phenyl Hydrazine and series of different Aldehydes (derivatives of benzylidenes). The synthesized compounds contain different aromatic Aldehydes which attached by Benzene ring via Hydrazine moiety in glacial acetic acid. These derivatives were characterized by TLC, melting points, Infrared Red, Proton Nuclear Magnetic Resonance, Carbon Thirteen Nuclear Magnetic Resonance and Mass Spectroscopy. Finally, these synthesized derivatives were tested for antiproliferative activity against multiple normal and cancerous cell lines, HepG2 (Liver cancer) and MCF-7 (Breast cancer) cell lines were used for cytotoxic assay.

Keywords

Phenyl Hydrazine, Aromatic Aldehydes, Benzylidene Synthesis, Cytotoxic Assay, Anticancer, HepG2 and MCF-7

1. Introduction

Cancer is a public health menace. The disease is of a great concern to both developed and developing countries due to its high morbidity and mortality. In many countries, it has become second largest killer after cardiovascular disease [1]. In 2012, there were 14 million new cases and 8.2 million deaths [1]. Among men, lung cancer was the most predominant, while among women, it was breast cancer. It was reported that there were 24 million cancer cases annually and 14.6 million annual deaths by the end of 2015 [2]. These troubling figures compel policy makers and the researchers to combat this disease. Cancer is a collection of different life-threatening

diseases characterized by uncontrolled growth of cells leading to invasion of surrounding tissue and often spreading to other parts of the body [3] [4]. Searching for new anticancer agents having heterocyclic nucleus continues worldwide at various laboratories [5] [6] [7]. It was reported that some aromatic compounds have demonstrated anticancer activities, but their mechanism of action is not established. For example, the anticancer activity of these compounds may be due to their intercalating properties or covalent binding abilities to DNA [8]. In addition, cell membrane interaction of these compounds is also proposed as their mechanism of actions [9]. In this work, organic compounds using Phenyl hydrazine and series of aromatic aldehydes are synthesized and tested as anticancer drugs, which have benzene ring attached to five or six membered rings (Benzimidazole) or (Phthalazine, Quinazoline, Quinoxalines). We aimed the synthesis of compounds formed of benzene ring attached by Hydrazine moiety which is two nitrogen atoms but not fused in the ring as Phthalazines, Quinazolines, Quinoxalines or Benzimidazoles [10]-[34]. These new compounds have two nitrogen atoms in side chain as a bridge between benzene ring and aromatic aldehydes.

2. Materials

2.1. Reagents

All solvents and reagents were obtained from commercial sources and were used without further purification except Glacial Acetic acid and Petroleum ether (PE). Phenyl Hydrazine was purchased from Sigma Aldrich (Cairo, Egypt). Series of Aromatic Aldehydes were acquired from Sigma Aldrich (Cairo, Egypt). Absolute Ethanol, Ehanol 95%, Glacial Acetic Acid, Ethyl Acetate, Petroleum Ether and Chloroform were purchased from Piochem (Cairo, Egypt). Distilled water was used for the experiments.

2.2. Instruments

Progress of chemical reactions was observed using TLC (Merck, silica gel plates 60 F254) and visualized using a UV-Vis spectrometer at 254 nm. Melting points were determined by Mel-Temp apparatus. NMR spectra were performed in Chloroform (7.26 ppm), with trimethyl silane as an internal standard, using Bruker Avance 500 spectrometer at ambient temperature, at drug discovery unit, Faculty of Pharmacy, Ain Shams University (ASU, Cairo, Egypt). All chemical shifts were expressed in parts per million (δ), and coupling constants (J) in Hz. FTIR spectra were recorded using KBr pellets on a model 883 double beam infrared spectrophotometer Bruker in 200 - 4000 cm^{-1}, at drug discovery unit, Faculty of Pharmacy, Ain Shams University (ASU, Cairo, Egypt). MS spectra were recorded using a Bruker Esquire 2000 by APC or ES ionization, at drug discovery unit, Faculty of Pharmacy, Ain Shams University (ASU, Cairo, Egypt).

2.3. Cell Culture: HepG2, MCF-7

Cell line was obtained from Nawah Scientific Inc. (Mokatam, Cairo, Egypt).

Cells were maintained in DMEM media supplemented with 100 mg/mL of streptomycin, 100 units/mL of penicillin and 10% of heat-inactivated fetal bovine serum in humidified, 5% (v/v) CO_2 atmosphere at 37˚C [35] [36].

2.4. Cytotoxicity Assay: HepG2, MCF-7

Cell viability was assessed by SRB assay. Aliquots of 100 µL cell suspension (5×10^3 cells) were in 96-well plates and incubated in complete media for 24 h. Cells were treated with another aliquot of 100 µL media containing drugs at various concentrations. After 72 h of drug exposure, cells were fixed by replacing media with 150 µL of 10% TCA and incubated at 4˚C for 1 h. The TCA solution was removed, and the cells were washed 5 times with distilled water. Aliquots of 70 µL SRB solution (0.4% w/v) were added and incubated in a dark place at room temperature for 10 min. Plates were washed 3 times with 1% acetic acid and allowed to air-dry overnight. Then, 150 µL of TRIS (10 mM) was added to dissolve protein-bound SRB stain; the absorbance was measured at 540 nm using a BMG LABTECH®-FLUOstar Omega microplate reader (Ortenberg, Germany) [35] [36].

3. Chemistry and Scheme

3.1. Scheme

3.2. Procedure and Synthesis of Compounds 3-13

Equimolar mixture of Phenyl hydrazine and series of Aromatic Aldehydes were stirred together in refluxing glacial acetic acid (Figure 1). TLC was made by 2:1 Petroleum Ether: Ethyl Acetate system. Precipitate was obtained from organic layer then water was added and more precipitate was retrieved. Product was purified by crystallization in Absolute Ethanol.

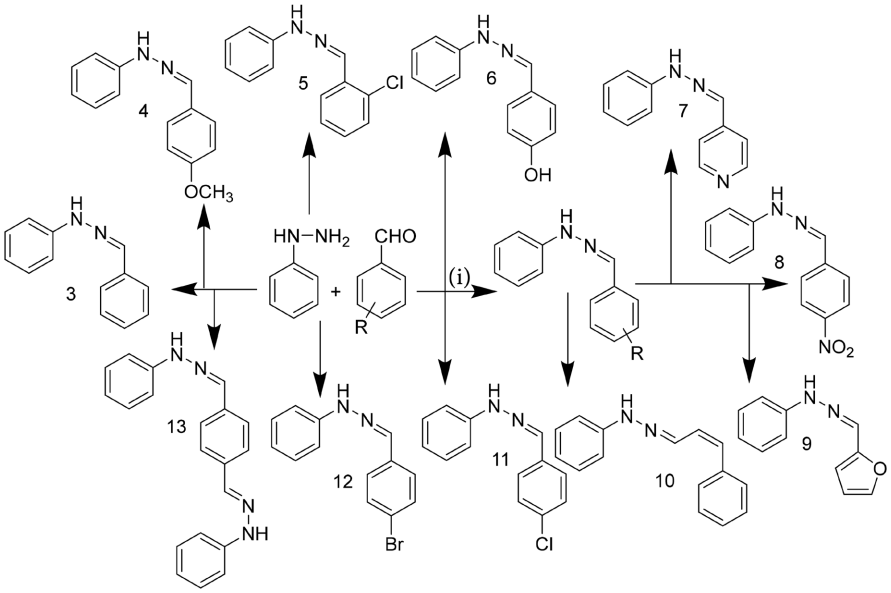


Figure 1. General scheme for compounds (3-13): (i) Series of Aromatic Aldehydes, Refluxing Glacial Acetic Acid, 135˚C, 1 - 16 Hrs.

3.2.1. Compound 3: (E)-1-benzylidene-2-phenylhydrazine

Yield 70%. m.p = 154˚C - 156˚C. IR: 688.75, 747.51 cm^{-1} (aromatic, bending), 880.40 cm^{-1} (N-H, overtone), 1064.45 cm^{-1} (C-N), 1518 cm^{-1} (N-H, bending), 1590 cm^{-1} (C=C, aromatic), 2450 cm^{-1} (aromatic, overtone), 3090 cm^{-1} (C-H, aromatic) and 3300 cm^{-1} (N-H, stretching). ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.90 - 7.50 ppm (m, aromatic protons), 7.65 ppm (s, -CH-) and 10.3 ppm (s, -NH-). ^{13}CNMR (100 MHz, $CDCl_3$): δ C1 (144.5 ppm), C2 (117 ppm), C3 (114 ppm), C4 (137 ppm), C5 (114 ppm), C6 (117 ppm), C7 (146 ppm), C1 (147.5 ppm), C2 (115 ppm), C3 (130 ppm), C4 (125 ppm), C5 (130 ppm) and C6 (115 ppm).

3.2.2. Compound 4: (E)-1-(4-Methoxybenzylidene)-2-Phenylhydrazine

Yield 82.5%. m.p = 128˚C - 130˚C. ^{1}HNMR (400 MHz, $CDCl_3$): δ 3.86 ppm (s,-CH3-), 6.85 - 7.35 ppm (m, aromatic protons), 7.65 ppm (s,-CH-) and 9.9 ppm (s,-NH-). ^{13}CNMR (100 MHz, $CDCl_3$): δ C1 (54.3 ppm), C2 (158.9 ppm), C3 (113.6 ppm), C4 (129.8 ppm), C5 (124.8 ppm), C6 (129.8), C7 (113.6 ppm), C8 (143.8 ppm), C1 (145.2 ppm), C2 (112.2 ppm), C3 (129.5 ppm), C4 (128.8 ppm), C5 (129.5 ppm) and C6 (112.2 ppm).

3.2.3. Compound 5: (E)-1-(2-Chlorobenzylidene)-2-Phenylhydrazine

Yield 73%. m.p = 129˚C - 131˚C. ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.75 - 7.75 ppm (m, aromatic protons), 7.85 ppm (s, -CH-) and 10.5 ppm (s, -NH-). MS: m/z: 230.06 (100.0%), (M + 1) 231.05 (87.9%), (M + 2) 229.05 (12.1%).

3.2.4. Compound 6: 4-((2-Phenylhydrazono)methyl)phenol

Yield 86%. m.p = 178˚C - 181˚C. IR: 690.59, 743.83 cm^{-1} (aromatic, bending), 884.73 cm^{-1} (N-H, overtone), 1098.33 cm^{-1} (C-N), 1504 cm^{-1} (N-H, bending), 1596.49 cm^{-1} (C=C, aromatic), 1700 cm^{-1} (C=N), 3045 cm^{-1} (C-H, aromatic), 3290 cm^{-1} (N-H, stretching) and 2900 - 3625 cm^{-1} (OH). ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.85 - 7.55 ppm (m, aromatic protons), 7.7 ppm (s, -CH-), 7.85 ppm (s, -OH) and 9.88 ppm (s, -NH-). ^{13}CNMR (100 MHz, $CDCl_3$): δ C1 (158.82 ppm), C2 (117.56 ppm), C3 (130.8 ppm), C4 (125.4 ppm), C5 (130.8 ppm), C6 (117.56), C7 (140.7 ppm), C1 (146.22 ppm), C2 (113.9 ppm), C3 (129.5 ppm), C4 (122.8 ppm), C5 (129.5 ppm) and C6 (113.9 ppm).

3.2.5. Compound 7: 4-((2-Phenylhydrazono)methyl) pyridine

Yield 73%. m.p = 179˚C - 181˚C. ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.90-8.55 ppm (m, aromatic protons), 7.60 ppm (s, -CH-) and 8.15 (s, -NH-). ^{13}CNMR (100 MHz, $CDCl_3$): δ C2 (149.98 ppm), C3 (120.13 ppm), C4 (143.47 ppm), C5 (120.13 ppm), C6 (149.98 ppm), C7 (142.84 ppm), C1 (133.55 ppm), C2 (113.09 ppm), C3 (129.42 ppm), C4 (121.13 ppm), C5 (129.42 ppm) and C6 (113.09 ppm).

3.2.6. Compound 8: (E)-1-(4-Nitrobenzylidene)-2-Phenylhydrazine

Yield 32.2%. m.p = 110˚C - 112˚C. ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.80 - 7.40 ppm (m, aromatic protons), 7.55 ppm (s, -CH-) and 9.88 ppm (s, -NH-). ^{13}CNMR (100 MHz, $CDCl_3$): δ C1 (147.18 ppm), C2 (119.06 ppm), C3 (119.84 ppm), C4 (144.93 ppm), C5 (119.84 ppm), C6 (119.06 ppm), C7 (137.29 ppm), C1 (145.85 ppm), C2 (111.66

ppm), C3 (129.28 ppm), C4 (112.71 ppm), C5 (129.28 ppm) and C6 (111.66 ppm).

3.2.7. Compound 9: (E)-1-(furan-2-Ylmethylene)-2-Phenylhydrazine

Yield 65%. m.p = 113 – 115˚C. IR: 692.95, 743.06 cm^{-1} (aromatic, bending), 818.48 cm^{-1} (N-H, overtone), 1153.57 cm^{-1} (C-N), 1342.30 cm^{-1} (C-O), 1602.35 cm^{-1} (C=C, aromatic), 1604 cm^{-1} (N-H, bending), 1655 cm^{-1} (C=N), 2025 cm^{-1} (C-H, aromatic overtone), 3090 cm^{-1} (C-H, aromatic) and 3317.56 cm^{-1} (N-H, stretching). ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.85 - 7.55 ppm (m, aromatic protons), 7.60 ppm (s, -CH-) and 9.75 ppm (s, -NH-). ^{13}CNMR (100 MHz, $CDCl_3$): δ C2 (144.36 ppm), C3 (112.89 ppm), C4 (120.46 ppm), C5 (150.55 ppm), C6 (142.72 ppm), C1 (143 ppm), C2 (112.96 ppm), C3 (129.31 ppm), C4 (127.83 ppm), C5 (129.31 ppm) and C6 (112.96 ppm).

3.2.8. Compound 10: (E)-1-Phenyl-2-((E)-3-Phenylallylidene) Hydrazine

Yield 80.5%. m.p = 150˚C - 152˚C. ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.75 ppm (t,-CH-), 7.05 ppm (d,-CH-), 6.85 - 7.50 ppm (m, aromatic protons), 7.55 ppm (s,-CH-) and 9.75 ppm (s, -NH-). ^{13}CNMR (100 MHz, $CDCl_3$): δ C1 (132.5 ppm), C2 (130 ppm), C3 (127 ppm), C4 (125 ppm), C5 (127 ppm), C6 (130 ppm), C7 (134 ppm), C8 (123 ppm), C9 (140 ppm), C1 (145 ppm), C2 (118 ppm), C3 (129 ppm), C4 (122 ppm), C5 (129 ppm) and C6 (118 ppm).

3.2.9. Compound 11: (E)-1-(4-Chlorobenzylidene)-2-Phenylhydrazine

Yield 80.1%. m.p = 119˚C - 121˚C. IR: 691.09, 746.28 cm^{-1} (mono-sub.), 819.32 cm^{-1} (para-di-sub.) (aromatic, bending), 882.19 cm^{-1} (N-H, overtone), 1133.08 cm^{-1} (C-N), 1518.02 cm^{-1} (N-H, bending), 1598.38 cm^{-1} (C=C, aromatic), 1620.02 cm^{-1} (C=N), 2000 cm^{-1} (C=C, aromatic), 3000 cm^{-1} (C-H, aromatic) and 3310.61 cm^{-1} (N-H, stretching). ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.95-7.50 ppm (m, aromatic protons), 7.90 ppm (s,-CH-) and 10.10 ppm (s, -NH-). ^{13}CNMR (100 MHz, $CDCl_3$): δC1 (134.5 ppm), C2 (130.2 ppm), C3 (132.3 ppm), C4 (136.9 ppm), C5 (132.3 ppm), C6 (130.2 ppm), C7 (140.5 ppm), C1 (144.8 ppm), C2 (112 ppm), C3 (129.7 ppm), C4 (122.9 ppm), C5 (129 ppm) and C6 (112 ppm). MS: m/z: 230.06 (100.0%), (M + 1) 231.10 (63.7%), (M + 2) 229.05 (36.3%).

3.2.10. Compound 12: (E)-1-(4-Bromobenzylidene)-2-Phenylhydrazine

Yield 71%. m.p = 115˚C - 117˚C. ^{1}HNMR (400 MHz, $CDCl_3$): δ 7.0-7.60 ppm (m, aromatic protons), 7.98 ppm (s,-CH-) and 9.85 ppm (s, -NH-). ^{13}CNMR (100 MHz, $CDCl_3$): δ C1 (129.3 ppm), C2 (133.3 ppm), C3 (131.5 ppm), C4 (136.7 ppm), C5 (131.5 ppm), C6 (133.3 ppm), C7 (142.8 ppm), C1 (145.6 ppm), C2 (113.8 ppm), C3 (128 ppm), C4 (121.4 ppm), C5 (128 ppm) and C6 (113.8 ppm). MS: m/z: 276 (100.0%), (M + 1) 278.95 (70%), (M + 2) 280.95 (30%).

3.2.11. Compound 13: 1,4-bis((2-Phenylhydrazono)methyl)benzene

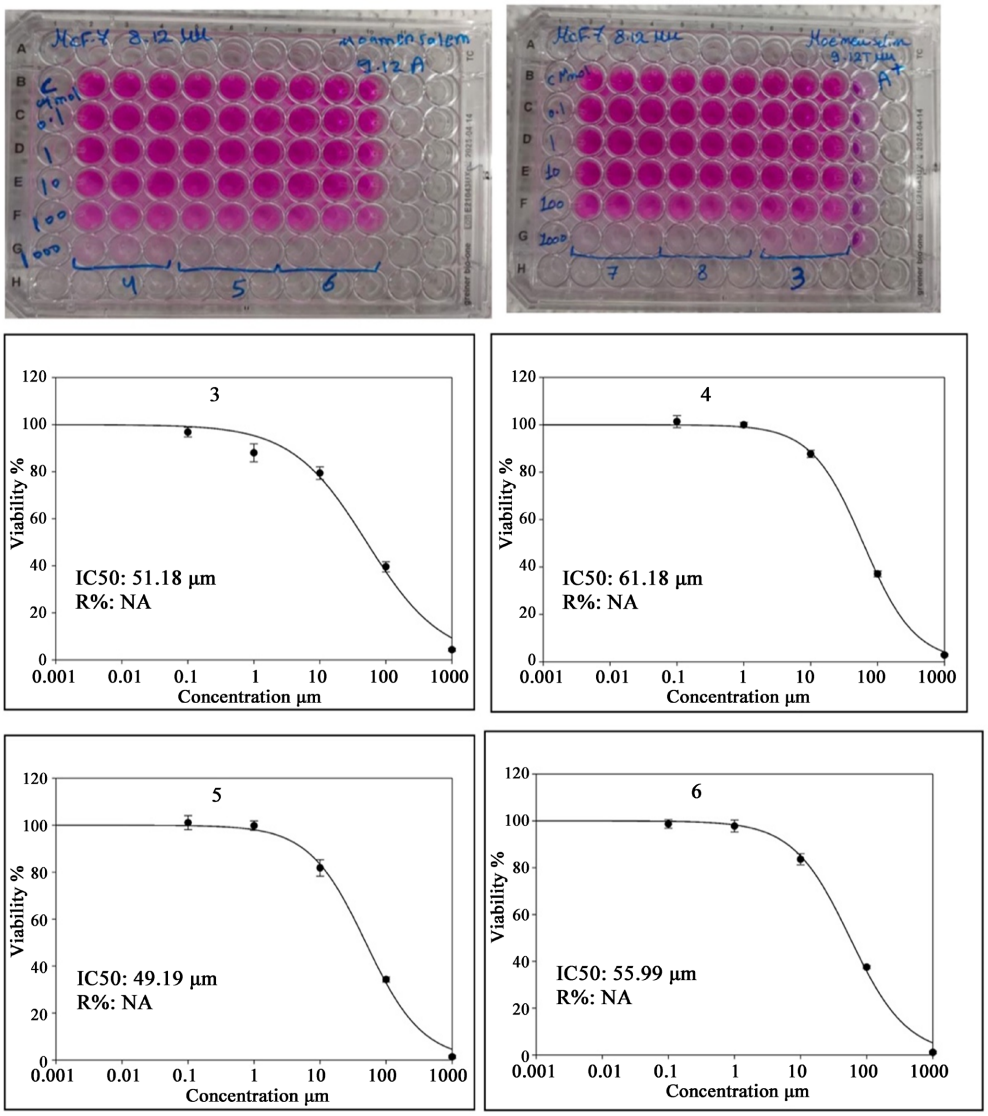
Yield 62%. m.p = 220˚C - 222˚C. IR: 690.53, 743.71 cm^{-1} (aromatic, bending), 885.30 cm^{-1} (N-H, overtone), 1130.68 cm^{-1} (C-N), 1522.08 cm^{-1} (N-H, bending), 1588.48 cm^{-1} (C=C, aromatic), 1600.36 cm^{-1} (C=N), 1925.25 cm^{-1} (C-H, aromatic overtone), 3075.25 cm^{-1} (C-H, aromatic) and 3299.42 cm^{-1} (N-H, stretching).

^{1}HNMR (400 MHz, $CDCl_3$): δ 6.95 - 7.90 ppm (m, aromatic protons), 7.75 ppm (s, -CH-), 10.03 ppm (s,-NH-). ^{13}CNMR (100 MHz, $CDCl_3$): δ C1 (145 ppm), C2 (115 ppm), C3 (130 ppm), C4 (122 ppm), C5 (130 ppm), C6 (115 ppm), C7 (140 ppm), C8 (136 ppm), C9 (129 ppm), C10 (129 ppm), C11 (136 ppm), C12 (129 ppm), C11 (136 ppm), C12 (129 ppm), C13 (129 ppm), C14 (140 ppm), C15 (145 ppm), C16 (115 ppm), C17 (130 ppm), C18 (122 ppm), C19 (130 ppm) and C20 (115 ppm).

4. Results

4.1. Cytotoxicity Results of MCF-7

MCF-7 cell line was used to assay the antiproliferative activity of compounds (3-8), compound 8 was the most potent in this group with IC_{50} value of 45.39 µm and compound 7 was the lowest in potency with IC_{50} value of 100.09 µm (Figure 2). Microscopical examination of the tested compounds in the cell lines at concentration of 100 µm used to confirm the calculation of the IC_{50} (Figure 3).



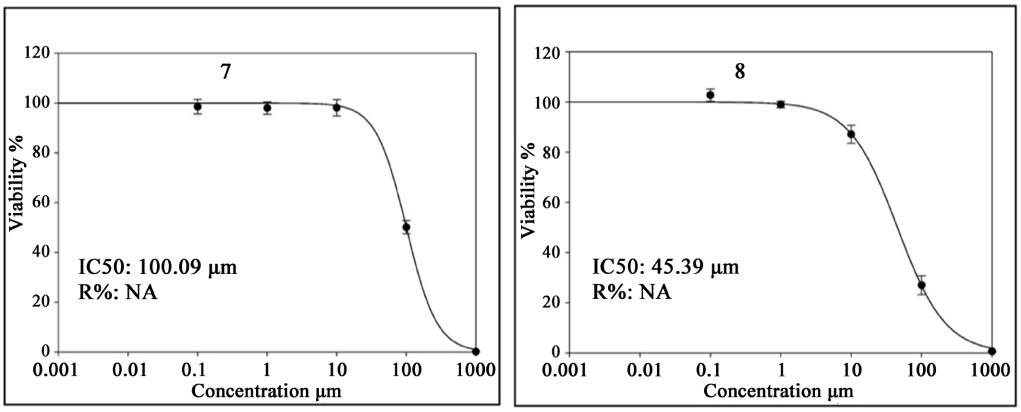


Figure 2. IC_{50} Values of compounds 3-8 against MCF-7 Cell line [35] [36].

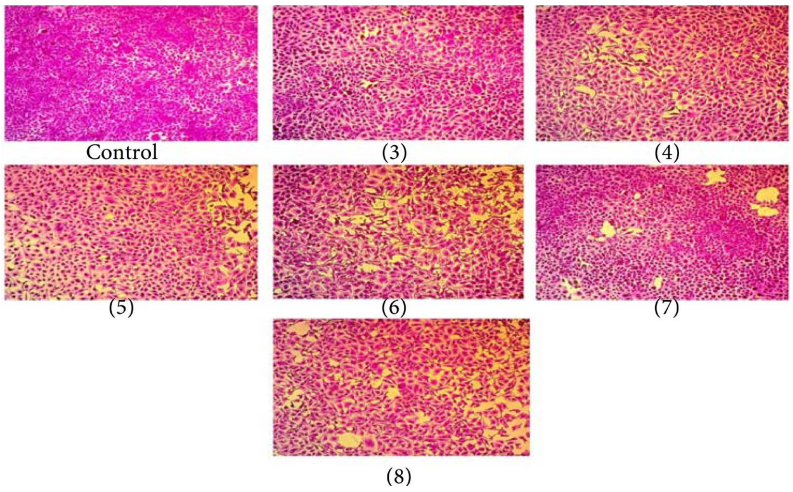
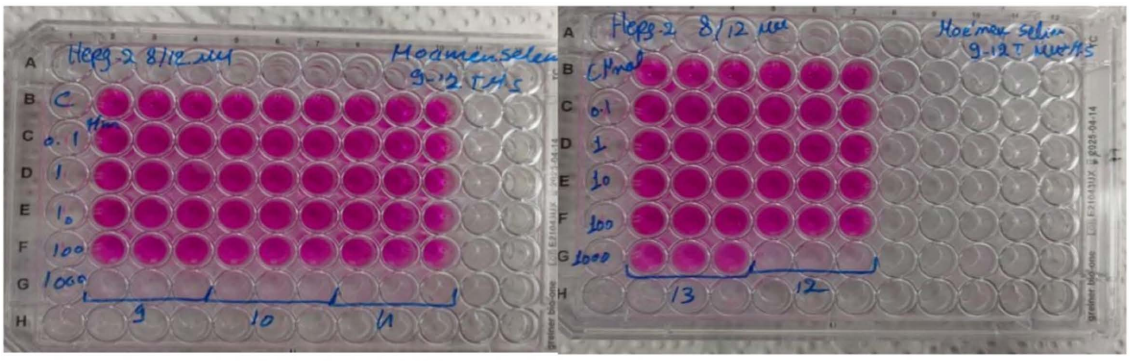


Figure 3. MCF-7 cell lines under microscopic examination of control and compounds (3 - 8) at 100 µm concentration [35] [36].

4.2. Cytotoxicity Results of HepG2

HepG2 cell line was used to assay the antiproliferative activity of compounds (9-13), compound 10 was the most potent in this group with IC_{50} value of 127.69 µm and compound 13 was the lowest in potency with IC_{50} value of 558.66 µm (**Figure 4**). Microscopical examination of the tested compounds in the cell lines at concentration of 100 µm used to confirm the calculation of the IC_{50} (**Figure 5**).



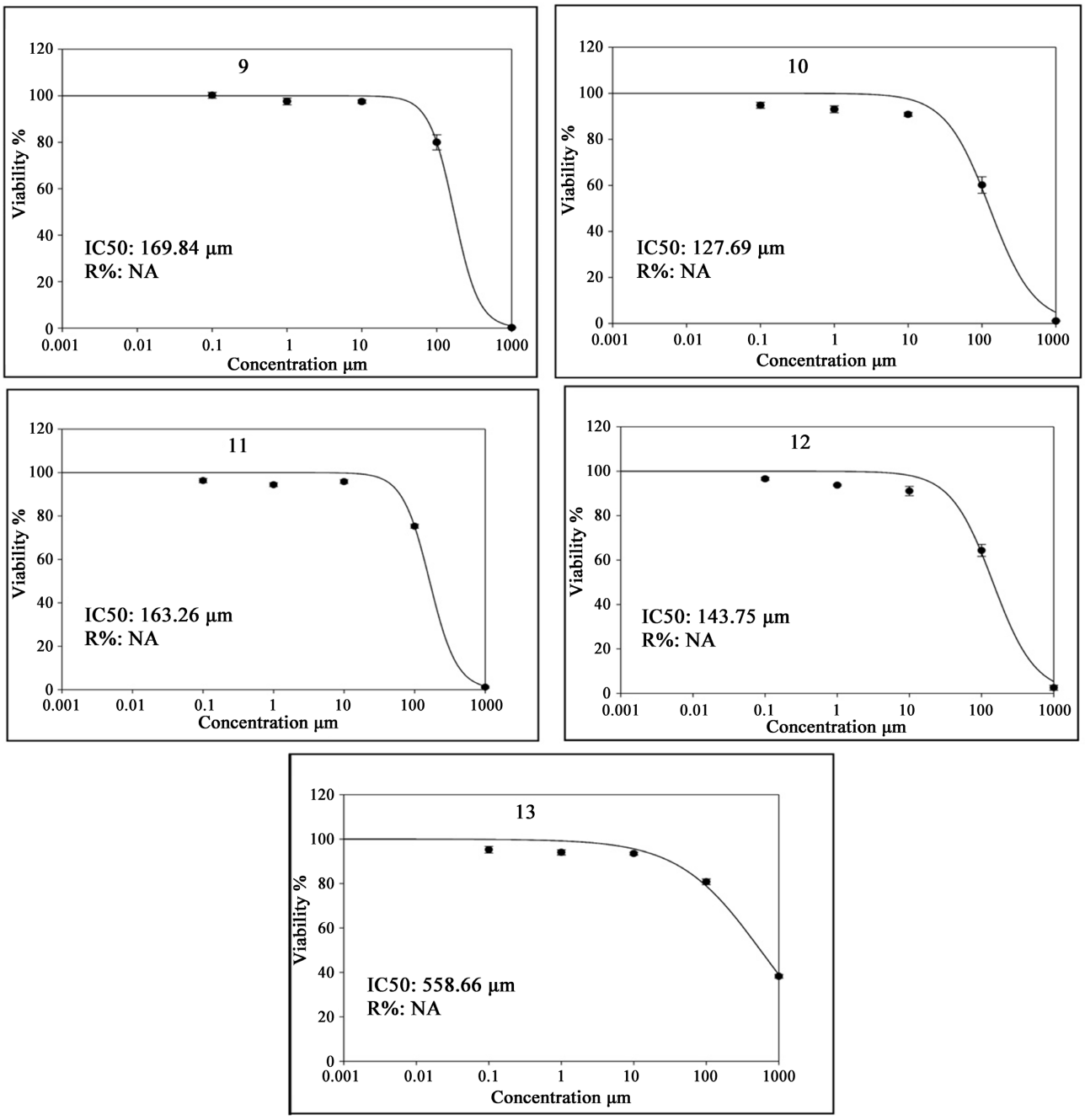
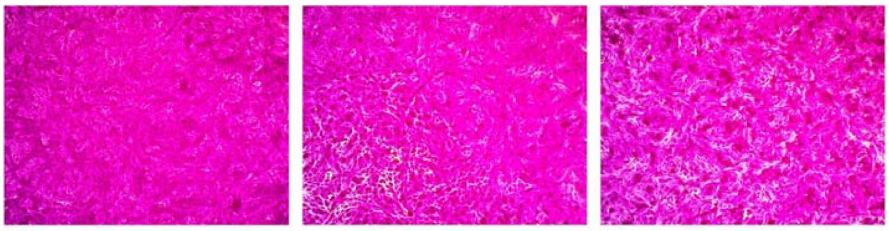
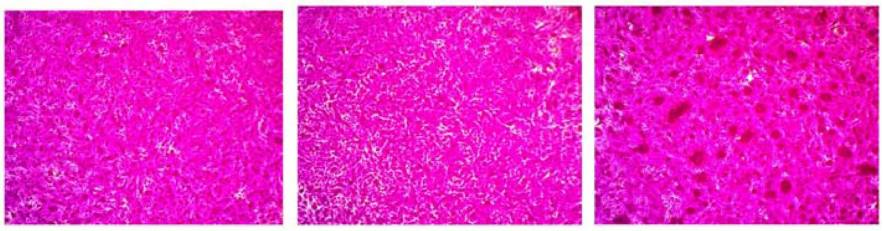


Figure 4. IC_{50} Values of compounds 9 - 13 against HepG2 Cell line [35] [36].





(11) (12) (13)

Figure 5. HepG2 cell lines under microscopic examination of control and compounds (9-13) at 100 µm concentration [35] [36].

4.3. Summary of the Cytotoxic assay Results of All Compounds

Compound	IC_{50}	Cell Line Type	Standard Drug	IC_{50}
3	51.18	MCF-7	Vincristine	0.82
4	61.18	MCF-7	Vincristine	0.82
5	49.19	MCF-7	Vincristine	0.82
6	55.99	MCF-7	Vincristine	0.82
7	100.09	MCF-7	Vincristine	0.82
8	45.39	MCF-7	Vincristine	0.82
9	169.84	HepG2	Doxorubicin	9.5
10	**127.69**	HepG2	Doxorubicin	9.5
11	163.26	HepG2	Doxorubicin	9.5
12	143.75	HepG2	Doxorubicin	9.5
13	555.66	HepG2	Doxorubicin	9.5

Figure 6. Summary of the cytotoxic assay results of all compounds against standard drugs [35] [36].

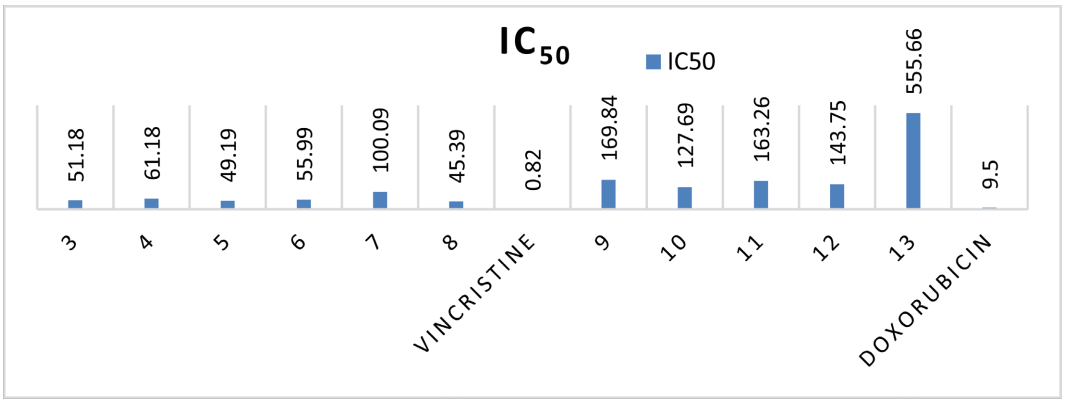


Figure 7. Summary of the cytotoxic assay results of all compounds against standard drugs [35] [36].

5. Conclusion

From the above findings, we concluded that all tested compounds have potential antiproliferative activity on both cell lines which were tested. For MCF-7 cell line, compound 8 was found to be the most potent compound in the group scoring 45.39 µm IC50, compound 7 was the lowest in potency scoring 100.09 µm IC50. For HepG2 cell line, compound 10 was found to be the most potent compound among the other compounds scoring 127.69 µm IC50 and compound

13 was the lowest in potency in this group (Figure 6, Figure 7).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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