

Synthesis and Cytotoxicity Of Some Novel Substituted Hydronaphthalene Derivatives

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ABSTRACT

A new series of hydronaphthalene derivatives incorporated into or fused to different five or six membered nitrogen, oxygen, sulphur heterocyclic, S- glycosidic or N-glycosidic moieties and other related products had been described. The hydrazine derivative **2** was coupled with bromo-sugar to achieve N-glycosides in presence of acidic medium while, the products **4** and **15** were coupled with different bromo sugar achieving S-glycosides in presence of a basic medium. Moreover, other derivatives carrying different biologically active side chains and hetero cyclic substituents were synthesized starting with 6-methoxy-1-tetralone (**1**). Also, the X-ray data of compound **13C** was studied.

The cytotoxicity of some of the newly synthesized compounds was studied to evaluate their *in-vitro* inhibitory effects against cellular proliferation in human cultured breast carcinoma cell lines. It has been found that, the chalcone derivatives **13a-c** and their cyclized thiopyrimidine analogues **14a, b** appeared to be potent breast carcinoma growth inhibitors comparing to Doxorubicin .

Keywords:

Tetra and di-hydronaphthalene derivatives, imidazole, hydrazide, thiosemicarbazide, quinazoline-thiones, thiazolidinone, glycosides, cytotoxic, x- ray.

261. Introduction

1, 2, 3, 4-Tetrahydronaphthyl-heterocycles bearing compounds constitute a class of continued interest to the pharmaceutical, chemical and agrochemical communities. Many of these compounds have useful applications such as anticancer(1-5), antibacterial(6,7) , Antiviral(8), molluscidal(9,10)and analgesic activities(11,12). Literature survey indicated that this type of compounds could be enzymatically oxidized within the living cells to give products related to naphthaquinones which are known to possess various potent biological activities (6, 9, 10). In mammalian systems, molecular oxygen is directly incorporated in naphthalene metabolism(13), thus 1,2,3,4-tetrahydronaphthalene nucleus may undergo biological oxidation to furnish a quinonoid structure which may also take a part in the reduction of living cell anaerobic glycolysis rate(14). Recently, it has been reported that several tetrahydronaphthylheterocycles possess potent anticancer activity against liver and breast cancer(15) and good precursors for the synthesis of various antidepressants(16), natural alkaloids(17), cyclic amino acids(18) and novel antagonists(19) of human TRPV1. Also, we cannot overlook the importance of chalcones and their cyclized analogues which were reported to have various chemotherapeutic activities. Literature survey indicated that many quinazoline derivatives were reported as analgesic(20), sedative(21)), antimicrobial(22), or as anti-inflammatory agents(23).The present work deals with synthesis of some novel 1, 2, 3, 4-tetrahydro or 2, 3-dihydronaphthalene derivatives using 6-methoxy-1-tetralone (**1**) as a key starting material and investigating the anticancer activity of some of them.

2. MATERIALS AND METHODS

2.1 General Conditions

Melting points (θC_x uncorrected) were determined in open glass capillaries using a Barnstead 9001 Electrothermal melting point apparatus. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR Spectrum BX Spectrometer at cm^{-1} scale using KBr discs. ^1H -NMR and ^{13}C -NMR were recorded on a JEOL 300 MHz Spectrometer, chemical shifts are expressed in δ (PPm) with reference to TMS. The mass spectra were run at 70 e.v with Packard 5890. The Welt G C/MS Spectrometer, using the electron Ionization (EI) technique. Elemental analysis (C, H, N) were carried out at the Micro analytical Data Center, Faculty of Science, Cairo, Egypt, and were in full agreement with the proposed structures within $\pm 0.3\%$ of the theoretical values. Thin layer Chromatography was performed on precoated (0.75 mm) silica gel GF254 plates (E. Merck, Germany). Visualization was performed by illumination with UV light source (254 nm). X-ray crystal structures were determined using a single crystal X-ray Crystallography-Rigaku Rapid II system and the X-ray samples were prepared by recrystallization from hot ethanol.

2.2 Synthesis

2.2.1. Synthesis of 1-(6-methoxy-3, 4-dihydronaphthalen-1(2H)-ylidene) hydrazine (2)

A mixture of **1** (0.01 mol) and excess of hydrazine hydrate (5 mL) was heated under reflux for about 2 h. Then, the mixture was cooled to room temperature and poured onto ice cold water, the solid so formed was collected by filtration, washed with water and crystallized. (Table 1).

IR (ν cm^{-1}): 3216 (NH₂), 1630 (C=N), 1610 (C=C); ^1H -NMR (DMSO- d_6): δ 1.86 (m, 2H, H-3), 2.3 (t, 2H, H-2), 2.67 (t, 2H, H-4), 3.78 (s, 3H, OCH₃), 5.2 (s, 2H, NH₂), 6.59 (s, 1H, Ar, H-5), 6.75 (d, 1H, J=9HZ, Ar, H-7), 7.88 (d, 1H, J=9HZ, Ar, H-8), ^{13}C -NMR (DMSO- d_6) δ , 21.43 (C-3), 22.92 (C-2), 29.47 (C-4), 54.34 (OCH₃), 111.71, 111.92, 124.6, 125.6, 139.2, 146.6, 158.49 (Ar-C, C=N); MS: m/z (%): 190.0 (M⁺, 100).

2.2.2. Synthesis of 1-(6-methoxy-3, 4-dihydronaphthalen-1(2H)-ylidene) 2-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)hydrazine (3)

To a solution of **2** (0.01 mol) in acetone (10 mL), 2, 3, 4, 6-Tetra-O-acetyl- α -D-glucopyranosyl bromide (0.01 mol) in acetone (30 mL) was added followed by addition of few drops of acetic acid. The reaction mixture was heated with stirring on a water bath at 50-60 θC_x for 8 h, until the reaction was completed. The solvent was concentrated under reduced pressure after cooling and the product was poured onto ice cold water. The solid so formed was filtered off, washed with water, and then crystallized. (Table 1)

IR (ν cm^{-1}): 3300 (NH), 1742 (C=O), 1672 (C=N), 1593 (C=C); ^1H -NMR (DMSO- d_6): δ , 1.8 (m, 2H, H-3), 2.01-1.97 (m, 12H, 4xOAc), 2.71 (t, 2H, H-2), 2.95 (t, 2H, H-4), 3.76 (s, 3H, OCH₃), 3.91 (s, 2H, H-6'), 5.34-4.09 (m, 5H, H-5', 4', 3', 2', 1'), 6.9 (m, 2H, Ar, H-7, 5), 7.8 (d, 1H, J=9HZ, Ar, H-8), 8.08 (s, 1H, 1NH), ^{13}C -NMR (DMSO- d_6): δ , 20.91 (C-3), 21.85 (4xOAc), 22.91 (C-2), 29.47 (C-4), 54.34 (OCH₃), 60.91 (C-6'), 61.93, 62.32, 64.34, 68.94, 71.63, (C-5', 4', 3', 2', 1'), 111.72, 111.92, 123.76, 125.64, 139.25, 146.6, 158.65 (Ar-C, C=N), 168.72 (4xC=O); MS: m/z (%): 521.0 (M⁺, 14.6).

2.2.3. Synthesis of 1-(6-methoxy-3, 4-dihydronaphthalen-1(2H)-ylidene) hydrazinecarbodithioic acid (4)

To a mixture of **2** (0.01 mol) and excess of carbon disulphide (3 mL), DMF (1 mL) was added. Then the reaction mixture was heated under reflux on a water bath for 6 h. After the reaction was completed, the solvent was concentrated and poured onto ice cold water and left to settle for 1 h. Then the solid formed was filtered off, washed with water and crystallized. (Table 1)

IR (ν cm^{-1}): 3200 (NH), 1620 (C=N), 1590 (C=C), 1274 (C=S); ^1H -NMR (DMSO- d_6): δ , 1.91 (m, 3H, 2H-3 and SH), 2.6 (t, 2H, H-2), 2.7 (t, 2H, H-4), 3.75 (s, 3H, OCH₃), 6.5 (s, 1H, Ar, H-5), 6.6 (d, 1H, J=9HZ, Ar, H-7), 7.9 (d, 1H, J=9HZ, Ar, H-8), 8.5 (s, 1H, NH), ^{13}C -NMR (DMSO- d_6) δ , 20.84 (C-3), 23.82 (C-2), 29.7 (C-4), 54.45

(OCH_3), 111.73, 111.97, 124.68, 125.65, 139.31, 146.7, 158.54 (Ar-C, C=N), 198.98 (C=S); MS: m/z (%): 266 (M⁺, 93.9).

2.2.4. Synthesis of 1-(6-methoxy-3, 4-dihydronaphthalen-1(2H)-ylidene) 2-(2', 3', 4', 6'.-tetera-O-acetyl- β -D-glucopyranosyl) hydrazine carbonodithioate 5 a, b

A solution of compound 4 (0.01 mol) in acetone (10 mL) containing potassium hydroxide (0.01 mol) dissolved in dist. water (6ml) was added to a solution of 2, 3, 4, 6-Tetra-O-acetyl- α -D-glucopyranosyl bromide (0.01 mol) in acetone (10 mL). The reaction mixture was stirred at room temperature for 20 h until the reaction completion. Then the solution was concentrated under reduced pressure, poured onto ice cold water and left at 50°C for 24 h. The residue was washed with water, then filtered off, dried and crystallized. (Table 1)

Synthesis of 1-(6-methoxy-3, 4-dihydronaphthalen-1(2H)-ylidene)2-(2',3',4',6'.-tetera-O-acetyl- β -D-glucopyranosyl) hydrazine carbonodithioate 5-a

IR ($\nu_{\text{cm}^{-1}}$): 3446 (NH), 1751(C=O), 1630 (C=N), 1592 (C=C), 1275 (C=S); $^1\text{H-NMR}$ (DMSO-d₆): δ , 1.80 (m, 2H, H-3), 2.07-1.91 (m, 12H, 4xOAc), 2.75 (t, 2H, H-2), 2.94 (t, 2H, H-4), 3.77 (s, 3H, OCH_3), 3.91 (s, 2H, H-6'), 5.31-4.09 (m, 5H, H-5', 4', 3', 2', 1'), 7.04-6.86 (m, 2H, Ar, H-7, 5) 7.74 (d, 1H, J=9HZ, Ar, H-8), 8.1 (s, 1H, NH), $^{13}\text{C-NMR}$ (DMSO-d₆): δ , 20.84 (C-3), 21.91 (4xOAc), 23.82 (C-2), 29.70 (C-4), 54.44 (OCH_3), 60.91 (CH_2 , C-6'), 61.93, 62.31, 64.34, 68.93, 71.61(C-5', 4', 3', 2', 1'), 111.72, 111.96, 124.7, 125.5, 139.3, 146.7, 158.5 (Ar-C, C=N), 168.70 (4xC=O), 198.96 (C=S); MS: m/z (%): 596 (M⁺, 28).

Synthesis of 1-(6-methoxy-3, 4-dihydronaphthalen-1(2H)-ylidene) 2-(2',3',4',6'.-tetera-O-acetyl- β -D-galactopyranosyl) hydrazine carbonodithioate 5-b

IR ($\nu_{\text{cm}^{-1}}$): 3416 (s, 1H, NH), 1751.5 (C=O), 1630 (C=N), 1571 (C=C), 1274 (C=S); $^1\text{H-NMR}$ (DMSO-d₆): δ , 1.80 (m, 2H, H-3), 2.1-1.9 (m, 12H, 4xOAc), 2.73 (t, 2H, H-2), 2.95 (t, 2H, H-4), 3.77 (s, 3H, OCH_3), 3.91 (s, 2H, H-6'), 5.34-4.09 (m, 5H, H-5', 4', 3', 2', 1'), 7.1-6.7 (m, 2H, Ar, H-7, 5), 7.74 (d, 1H, J=8.8HZ, Ar, H-8), 8.11 (s, 1H, NH), $^{13}\text{C-NMR}$ (DMSO-d₆): δ , 20.84 (C-3), 21.92 (4xOAc), 23.82 (C-2), 29.70 (C-4), 54.44 (OCH_3), 60.9 (CH_2 , C-6'), 61.91, 62.31, 64.33, 68.9, 71.6 (C-5', 4', 3', 2', 1'), 111.94, 111.99, 124.69, 125.5, 139.9, 146.7, 158.54 (Ar-C, C=N), 168.7 (4xC=O), 197.02 (C=S); MS: m/z (%): 596 (M⁺, 15).

2.2.5. Synthesis of 1- (6-methoxy-3, 4-dihydronaphthalen-1(2H)-ylidene) formic acid hydrazine. (6a)

A mixture of 2 (0.01 mol) and formic acid (0.01mol) was heated at 60-80 °C for 30 minutes until the reaction was completed. The excess formic acid was concentrated. After cooling, the product was poured onto ice cold water, the solid product was washed with cold water, collected by filtration, dried and crystallized (table 1).

IR ($\nu_{\text{cm}^{-1}}$): 3438 (NH), 1682 (C=O), 1620(C=N), 1592(C=C). $^1\text{H-NMR}$ (CDCl_3): δ , 2.037 (m, 2H, H-3), 2.5 (t, 2H, H-2), 2.89 (t, 2H, H-4), 3.76 (s, 3H, OCH_3), 6.89-6.81 (m, 2H, Ar, H-7, 5), 7.8 (d, 1H, J=9HZ, Ar, H-8), 8.7 (s, 1H, NH), 10.6 (s, 1H, -CHO); $^{13}\text{C-NMR}$ (CDCl_3): δ , 20.7 (C-3), 22.4(C-2), 29.47 (C-4), 54.93 (OCH_3), 111.7, 112.04, 112.75, 125.2, 128.14, 146.2, 154.5 (Ar-C, C=N), 194.2 (C=O); MS: m/z (%): 218 (M⁺, 18.9).

2.2.6. Synthesis of 1- (6-methoxy-3, 4-dihydronaphthalen-1(2H)-ylidene) acetic acid hydrazine. (6b)

A mixture of compound 2 (0.01 mol) and acetyl chloride (5mL) was refluxed for 3 h. Then the excess acid was concentrated and the solid product was washed with cold water, collected by filtration and crystallized (table 1).

IR ($\nu_{\text{cm}^{-1}}$): 3321 (NH), 1673 (C=O), 1592 (C=C). $^1\text{H-NMR}$ (DMSO-d₆): δ , 1.8 (m, 2H, H-3), 2.01 (m, 2H, H-2) 2.2 (s, 3H, CH_3), 2.9 (t, 2H, H-4), 3.79 (s, 3H, OCH_3), 7.6-6.6 (m, 3H, Ar, H-8,7, 5), 8.2 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO-d₆): δ , 21.2(C-3), 25.4 (CH_3), 26.3 (C-2), 28.8 (C-4), 54.82 (OCH_3), 112.02, 112.7, 125.16, 128.1, 146.6, 149.5, 154.5 (Ar-C, C=N), 195.5(C=O); MS: m/z (%): 232 (M⁺, 0.17).

2.2.7. Synthesis of 7-methoxy- 4, 5-dihydro-3aH-naphtho [1, 2-d] imidazole (7)

A mixture of **2** (0.01mol) and formic acid (0.01 mol) was refluxed for 3 h. After the reaction was completed, the mixture solution was concentrated and poured onto ice cold water. The obtained product was collected by filtration washed with water then dried and crystallized. Another method was used to get the same product **7** by heating the compound **6a** above its melting point for 10 minutes. Then after cooling, the product was triturated with ethanol, the solid obtained was collected by filtration and crystallized. (Table 1)

IR (ν cm^{-1}): 1637 (C=N), 1593 (C=C); $^1\text{H-NMR}$ (DMSO- d_6): δ , 2.01-1.79 (m, 3H, 1H-3a, 2H-4), 2.7 (t, 2H, H-5), 3.8 (s, 3H, OCH_3), 6.89-6.80 (m, 2H, Ar, H-6, 8), 7.8 (d, 1H, J=9HZ, Ar, H-9), 8.1 (s, 1H, imidzol), $^{13}\text{C-NMR}$ (DMSO- d_6): δ , 27.6 (C-4), 29.6(C-5), 54.93 (OCH_3), 63.2 (C-3a), 111.6, 112.04, 112.81, 125.2, 128.2, 147.89, 148.01, 163.2 (Ar-C, C=N); MS: m/z (%): 199 (M+1, 9).

2.2.8. Synthesis of 1-[N-(6-methoxy-2, 3-dihydro-2H-naphthalen-1-ylidene)-hydrazinyl]ethylacetate (8)

A mixture of **2** (0.01 mol) and ethyl chloroacetate (0.01 mol) in presence of pyridine (10 ml), the reaction mixture was refluxed for 8 h, cooled, poured onto ice-water, the solid formed was washed with water, collected by filtration, dried and crystallized. (Table 1)

IR (ν cm^{-1}): 3200 (NH), 1715 (C=O) 1608 (C=C); $^1\text{H-NMR}$ (CDCl_3): δ , 1.2 (t, 3H, CH_3), 1.8 (m, 2H, H-3), 2.79-2.69 (m, 4H, 2CH_2 , H-4), 2), 3.49 (s, 2H, N- CH_2), 3.78 (s, 3H, OCH_3), 4.3 (q, 2H, OCH_2), 7.61-6.85 (m, 3H, Ar-H), 8.11 (s, 1H, NH); $^{13}\text{C-NMR}$ (CDCl_3): δ , 15.2 (CH_3), 21.1 (C-3), 25.9 (C-2), 29.1 (C-4), 32.8 (N- CH_2), 54.1 (OCH_3), 61.2 (OCH_2), 111.5, 111.7, 124.9, 126.07, 141.16, 146.3, 156.4 (Ar-C, C=N), 159.38 (C=O); MS: m/z (%): 276 (M+, 7.6).

2.2.9. Synthesis of 1-(6-Methoxy-3, 4-dihydronaphthalen-1(2H)ylidene)-acetohydrazide (9).

A mixture of **2** (0.01mol) and hydrazine hydrate (0.11 mol) in absolute ethanol (20 mL) was refluxed for 4 h. The reaction solution was concentrated and the solid product was washed with water, collected by filtration and crystallized. (Table 1)

IR (ν cm^{-1}): 3200 (NH), 3217 (NH_2), 1647 (C=O), 1608 (C=C); $^1\text{H-NMR}$ (CDCl_3): δ , 1.4 (s, 1H, NH_2), 1.8 (m, 2H, H-3), 2.77-2.60 (m, 4H, 2CH_2 , H-4, 2), 3.3 (s, 2H, N- CH_2), 3.7 (s, 3H, OCH_3), 7.6-6.6 (m, 3H, Ar-H), 8.1 (s, 1H, NH), 10.01 (s, 1H, NH); $^{13}\text{C-NMR}$ (CDCl_3): δ , 21.1 (C-3), 25.9 (C-2), 29.1 (C-4), 32.8 (N- CH_2), 54.3 (OCH_3), 111.5, 111.7, 124.9, 126.07, 141.16, 146.3, 156.4 (Ar-C, C=N), 169.9 (C=O); MS: m/z (%): 263 (M+, 14.7).

2.2.10. Synthesis of (E) 1-(6-methoxy-3,4-dihydronaphthalene-1(2H)ylidene)-2-(arylidene hydrazine(10a, b)

To a solution of **2** (0.01mol) in glacial acetic acid (10mL), the appropriate aldehydes (0.01mol), namely, furaldehyde and 2, 6 - diflorobenzaldehyde was added. The reaction mixture was refluxed for 3-4 h. After cooling, the separated solid was collected by filtration, washed with water, dried and crystallized. (Table 1)

Synthesis of (E) 1-(6-methoxy-3, 4-dihydronaphthalene-1(2H)ylidene)-2-(2,6-diflourobenzylidene hydrazine(10a)

IR (ν cm^{-1}): 1656, 1627 (C=N), 1578 (C=C); $^1\text{H-NMR}$ (CDCl_3): δ , 1.8 (t, 2H, H-3), 2.89 (m, 4H, 2CH_2 , H-4, 2), 3.7 (s, 3H, OCH_3), 7.9-6.6 (m, 6H, Ar-H), 8.4 (s, 1H, N=CH), $^{13}\text{C-NMR}$ (CDCl_3): δ , 22.4 (C-3), 25.2(C-2), 29.4 (C-4), 53.7 OCH_3 , 106.2, 111.29, 111.7, 112.8, 121.4, 124.7, 125.9, 139.4, 141.15, 146.2, 154.01, 158.4 (Ar-C, C=N); MS: m/z (%): 314 (M+, 100).

Synthesis of (E) 1-(6-methoxy-3,4-dihydronaphthalene-1(2H)ylidene)-2-(furan-2-ylmethyleden hydrazine(10b)

IR (ν cm^{-1}): 1656, (C=N), 1582 (C=C); $^1\text{H-NMR}$ (CDCl_3): δ , 2.02-1.99 (m, 2H, H-3), 2.3-2.2 (m, 2H, H-2), 2.5 (m, 2H, H-4), 3.78 (s, 3H, OCH_3), 6.6-6.4 (m, 5H, Ar-H), 7.9 (d, 1H, J=9HZ, Ar, H-8), 8.8 (s, 1H, N=CH); $^{13}\text{C-NMR}$ (CDCl_3): δ , 22.4 (C-3), 25.5 (C-2), 29.1 (C-4), 53.7 (OCH_3), 106.09, 106.29, 107.09, 108.2, 111.6, 121.4, 124.7, 125.5, 135.4, 146.15, 154.01, 156.2 (2C), 158.4 (Ar-C, C=N); MS: m/z (%): 266 (M+, 100).

2.2.11. Synthesis of 1-(6-methoxy-3, 4-dihydronaphthalen-1(2H) -ylidene)-4-phenyl thiosemicarbazide (11).

A mixture of **2** (0.002 mol) and phenyl isothiocyanate (0.002 mol) in dry benzene (30 mL) was refluxed for 45 minutes. After cooling, the solid so formed was filtered off and crystallized. (Table 1).

IR ($\nu_{\text{cm}^{-1}}$): 3285, 3224 (2NH), 1611 (C=N), 1593 (C=C), 1237 (C=S); $^1\text{H-NMR}$ (CDCl_3): δ , 2.03-1.9 (m, 2H, H-3), 2.6 (t, 2H, H-2), 2.77 (t, 2H, H-4), 3.82 (s, 3H, OCH₃), 6.6 (s, 1H, Ar, H-5), 6.80, 6.83 (d, d, 1H, J=8.8 Hz, Ar, H-4'), 7.2 (m, 1H, Ar, H-7), 7.4 (t, 2H, Ar, H-3', 5'), 7.7 (d, 2H, J=8.8 Hz, Ar, H-2', 6'), 7.9 (d, 1H, J=8.8 Hz, Ar, H-8), 8.7 (s, 1H, NH), 9.4 (s, 1H, NH). $^{13}\text{C-NMR}$ (CDCl_3): δ , 20.2 (C-3), 24.12 (C-2), 28.35 (C-4), 54.04 (OCH₃), 111.49, 112.16, 122.80, 124.61, 124.97, 127.46, 136.70, 141.02, 145.8, 150.9, 159.66 (Ar-C, C=N), 174.55 (C=S). MS: m/z (%): 325 (M⁺, 17).

2.2.12. Synthesis of 2-[(6-methoxy-3, 4-dihydro-2H-naphthalin-1-ylidene)-hydrazino]-3-phenyl-thiazolidin-4-one (12).

To a solution mixture of 44 (0.001 mol), in ethanol (20 mL), chloroacetic acid (0.001 mol) and sodium acetate (0.001 mol) was added and refluxed for 3 h. After cooling, the solid product was filtered off, washed with water, dried and crystallized. (Table 1)

IR ($\nu_{\text{cm}^{-1}}$): 1728 (C=O), 1620 (C=N), 1579 (C=C) $^1\text{H-NMR}$ (CDCl_3): δ , 1.8-1.7 (m, 2H, H-3), 2.6 (t, 2H, H-2), 2.7 (t, 2H, H-4), 3.8 (s, 3H, OCH₃), 3.9 (s, 2H, -CH₂ thiazolidinone), 6.7 (s, 1H, Ar, H-5), 6.8, 6.7 (d, d, 1H, J=8.8, Ar, H-4'), 7.5-7.3 (m, 5H, Ar, H-2', 3', 5', 6', 7), 8.2 (d, 1H, J=8.8 Hz, Ar, H-8). $^{13}\text{C-NMR}$ (CDCl_3): δ , 20.9 (C-3), 25.99 (C-2), 29.02 (C-4), 31.27 (CH₂ thiazolidinone), 53.98 (OCH₃), 111.3, 111.7, 124.04, 126.05, 126.35, 127.37, 127.8, 133.46, 140.07, 141.49, 150.9, 159.13, 159.5, 161.59 (Ar-C, 2C=N), 170.5 (C=O). MS: m/z (%): 365 (M⁺, 33.9).

2.2.13. Synthesis of 2-(arylidene)-6-methoxy-3, 4-dihydronaphthalene-1(2H)-one. (13a-c)

To a solution of 4 (0.005 mol) and the appropriate aldehydes (0.005 mol) namely trimethoxybenzaldehyde, furfuraldehyde, and 2, 6-difluorobenzaldehyde in ethanol (30 mL), a solution of 10% sodium hydroxide (15 mL) was added drop wisely over 10 minutes while stirring at room temperature. After the complete addition, the reaction mixture was continued stirred for further 1 h. The precipitate so formed was collected by filtration, washed with water and crystallized. (Table 1)

Synthesis of (E) 6-methoxy-2-(3, 4, 5-trimethoxybenzylidene)-3, 4-dihydronaphthalen-1(2H)-one (13a).

IR ($\nu_{\text{cm}^{-1}}$): 1670 (C=O), 1645 (C=C, vinyl), $^1\text{H-NMR}$ (DMSO-d₆): δ , 1.99-1.97 (m, 2H, H-3), 2.8 (m, 2H, H-4), 3.8-3.09 (4s, 12H, 4x OCH₃), 6.9-6.8 (m, 4H, Ar-H), 7.62 (s, 1H, vinyl), 7.8 (d, 1H, J=9 Hz, Ar, H-8); $^{13}\text{C-NMR}$ (DMSO-d₆): δ , 26.1 (C-3), 28.6 (C-4), 54.8 (OCH₃), 55.3 (2C, OCH₃), 59.4 (OCH₃), 106.8 (2C-2', 6'), 111.6, 112.5, 112.9, 125.6, 128.01, 129.2, 130.2, 134.6, 137.3, 145.2, 152.1, 162.5 (C-Ar, vinyl), 184.6 (C=O); MS: m/z (%): 354 (M⁺, 75).

Synthesis of 2-(furan-2-ylmethylene)-6-methoxy-3, 4-dihydronaphthalen-1(2H)-one (13b).

IR ($\nu_{\text{cm}^{-1}}$): 1659 (C=O), 1600 (C=C, vinyl), 1585 (C=C) $^1\text{H-NMR}$ (DMSO-d₆): δ , 2.96 (t, 2H, H-3), 3.22 (t, 2H, H-4), 3.84 (s, 3H, OCH₃), 6.9-6.6 (m, 4H, Ar-H), 7.41 (s, 1H, vinyl), 7.9-7.8 (m, 2H, Ar, H-7,8); $^{13}\text{C-NMR}$ (DMSO-d₆): δ , 25.81 (C-3), 27.30 (C-4), 55.05 (OCH₃), 111.8, 112.2, 113.2, 116.37, 120.88, 126.86, 129.43, 131.2, 144.85, 145.66, 151.15, 162.6 (C-Ar, vinyl), 184.5 (C=O); MS: m/z (%): 254 (M⁺, 100).

Synthesis of 2-(2, 6-difluorobenzylidene)-6-methoxy-3, 4-dihydronaphthalen-1(2H)-one (13c).

IR ($\nu_{\text{cm}^{-1}}$): 1666 (C=O), 1624 (vinyl), 1597 (C=C); $^1\text{H-NMR}$ (DMSO-d₆): δ , 2.1 (t, 2H, H-3), 2.5 (t, 2H, H-4), 3.7 (s, 3H, OCH₃), 6.8-6.2 (m, 5H, Ar-H), 7.06 (s, 1H, vinyl), 7.68 (d, 1H, J=9 Hz, Ar, H-8); $^{13}\text{C-NMR}$ (DMSO-d₆): δ , 23.16 (C-3), 23.95 (C-4), 50.2 (OCH₃), 106.09, 106.29, 107.09, 108.26, 116.8, 121.4, 124.7, 125.5, 135.4, 141.1, 151.01, 154.05, 156.04, 158.4 (C-Ar, vinyl), 180.4 (C=O); MS: m/z (%): 300 (M⁺, 100).

2.2.14. Synthesis of 4-aryl-8-methoxy-4,4a,5,6-tetrahydrobenzo[h]quinazoline-2(3H)-thione (14a-c)

To a mixture of 13a-c (0.01 mol), and thiourea (0.01 mol), a solution of potassium hydroxide (1.12 g) in ethanol (30 mL) was added. The reaction mixture was then refluxed for 1-2 h. After cooling, the solid so formed was filtered off, washed with water, and crystallized. (Table 1)

Synthesis of 8-methoxy 4-(-3,4,5-trimethoxy phenyl) 4,4a,5,6-tetrahydrobenzo[h]quinazoline-2(3H)-thione (14a).

IR ($\nu_{\text{cm}^{-1}}$): 3193 (NH), 1670 (C=N), 1592 (C=C), 1241 (C=S); $^1\text{H-NMR}$ (DMSO- d_6): δ , 1.89 (m, 2H, H-5), 2.15 (m, 1H, H-4a), 2.63 (m, 2H, H-6), 3.91-3.7 (s, br. 12H, 4xOCH₃), 4.86 (s, 1H, H-4), 7.5-6.6 (m, 5H, Ar-H), 8.9 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6): δ , 23.24 (C-5), 27.48 (C-6), 54.7 (OCH₃), 55.5 (3xOCH₃), 58.11 (C-4a), 59.6 (C-4), 103.8, 107.9, 110.4, 113.6, 122.7, 126.4, 136.6, 137.2, 138.1, 152.6 (C-3', 4', 5'), 158.5 (Ar-C, C=N), 173.8 (C=S); MS: m/z (%): 412 (M⁺, 60).

Synthesis of 8-methoxy 4-(furan-2-yl) 4, 4a, 5, 6-tetrahydrobenzo[h]quinazoline-2(3H)-thione (14b).

IR ($\nu_{\text{cm}^{-1}}$): 3189 (NH), 1678 (C=N), 1606 (C=C), 1249 (C=S); $^1\text{H-NMR}$ (DMSO- d_6): δ , 1.98-1.93 (m, 2H, H-5), 2.1 (m, 1H, H-4a), 2.7-2.6 (m, 2H, H-6), 3.74 (s, 3H, OCH₃), 5.02 (s, 1H, H-4), 6.28-7.62 (m, 6H, Ar-H), 9.03 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6): δ , 22.74 (C-5), 27.05 (C-6), 44.01, 51.05 (2C, 4, 4a), 54.4 (OCH₃), 105.2, 106.4, 109.8, 113.2, 119.8, 122.4, 126.7, 136.9, 142.3, 153.4, 158.2 (Ar-C, C=N), 174.03 (C=S); MS: m/z (%): 312 (M⁺, 100).

Synthesis of 8-methoxy 4-(2,6-difurophenyl) 4,4a,5,6-tetrahydrobenzo[h]quinazoline-2(3H)-thione (14c).

IR ($\nu_{\text{cm}^{-1}}$): 3425 (NH), 1684 (C=N), 1610 (C=C), 1250 (C=S); $^1\text{H-NMR}$ (DMSO- d_6): δ , 1.7-1.6 (m, 2H, H-5), 2.1-2.01 (m, 1H, H-4a), 2.6-2.4 (m, 2H, H-6), 3.74 (s, 3H, OCH₃), 5.4 (s, 1H, H-4), 7.42-6.7 (m, 5H, Ar-H), 7.64 (d, 1H, J=9HZ, Ar, H-10), 8.8 (s, 1H, NH); $^{13}\text{C-NMR}$ (DMSO- d_6): δ , 23.29 (C-5), 27.90 (C-6), 39.6, 47.9 (2C, 4, 4a), 54.5 (OCH₃), 104.06, 110.1, 111.15, 111.47, 113.2, 116.7, 119.7, 122.4, 126.2, 129.7, 136.7, 158.26 (Ar-C, C=N), 173.9 (C=S); MS: m/z (%): 358 (M⁺, 41).

2.2.15. Synthesis of 3, 4-dihydro-6-methoxynaphthalene-1(2H)-thione (15)

To a solution of **4** (0.01 mol) in dry xylene (10 mL), phosphorus pentasulphide (0.02 mol) was added. The mixture was heated under reflux for 6 hrs, the solvent was concentrated, and after cooling the precipitate so formed was washed with water, filtered off, and crystallized. (Table 1)

IR ($\nu_{\text{cm}^{-1}}$): 1610 (C=C), 1205 (C=S); $^1\text{H-NMR}$ (DMSO- d_6): δ , 2.1 (s, 1H, SH), 2.65 (t, 2H, H-3), 2.89 (t, 2H, H-4), 3.7 (s, br, 3H, OCH₃), 3.96 (m, 1H, H-2), 7.9-6.7 (m, 3H, Ar-H); $^{13}\text{C-NMR}$ (DMSO- d_6): δ , 21.1 (C-3), 27.8 (C-4), 54.5 (OCH₃), 111.3, 111.4, 120.9, 122.6, 127.3, 131.4, 133.9, 157 (Ar-C); MS: m/z (%): 192 (M⁺, 1.5).

2.2.16. synthesis of cyclohexyl (1,2-dihydro-7-methoxynaphthalen-4-yl)sulfane (16)

A mixture of **15** (0.01 mol) in ethanol (10 mL) and a solution of aqueous potassium hydroxide (0.01 mol) dissolved in distilled water (6 mL) was added to a solution of 2, 3, 4, 6-tetra-O-acetyl- α -D-glucopyranosyl bromide (0.01 mol) in acetone (30 mL). The reaction mixture was stirred at room temperature for 20 hrs, then, the solvent was concentrated under reduced pressure. The mixture was poured onto ice cold water. The solid so formed was filtered off, washed with water and crystallized. (Table 1)

IR ($\nu_{\text{cm}^{-1}}$): 1750 (C=O), 1604 (C=C); $^1\text{H-NMR}$ (DMSO- d_6): δ , 2.3-1.94 (m, 12H, 4xOAc), 2.68 (t, 2H, H-3), 2.89 (t, 2H, H-4), 3.7 (s, 3H, OCH₃), 3.96-3.85 (m, 4H, H-2, 6'), 5.3-4.2 (m, 5H, H-5', 4', 3', 2', 1'), 6.9-6.8 (m, 2H, Ar, H-7, 5), 7.2 (d, 1H, J=9HZ, Ar, H-8); $^{13}\text{C-NMR}$ (DMSO- d_6): δ , 21.02 (C-3), 27.9 (C-4), 54.52 (OCH₃), 60.8 (CH₂, C-6'), 61.9, 62.3, 64.2, 68.9, 71.6, 94.9 (C-5', 4', 3', 2', 1', 2), 111.4, 113.01, 120.9, 122.6, 131.4, 133.9, 157.4 (Ar-C, C-2), 168.6 (4xC=O); MS: m/z (%): 522 (M⁺, 8).

3. RESULT AND DISCUSSION

3.1. chemistry

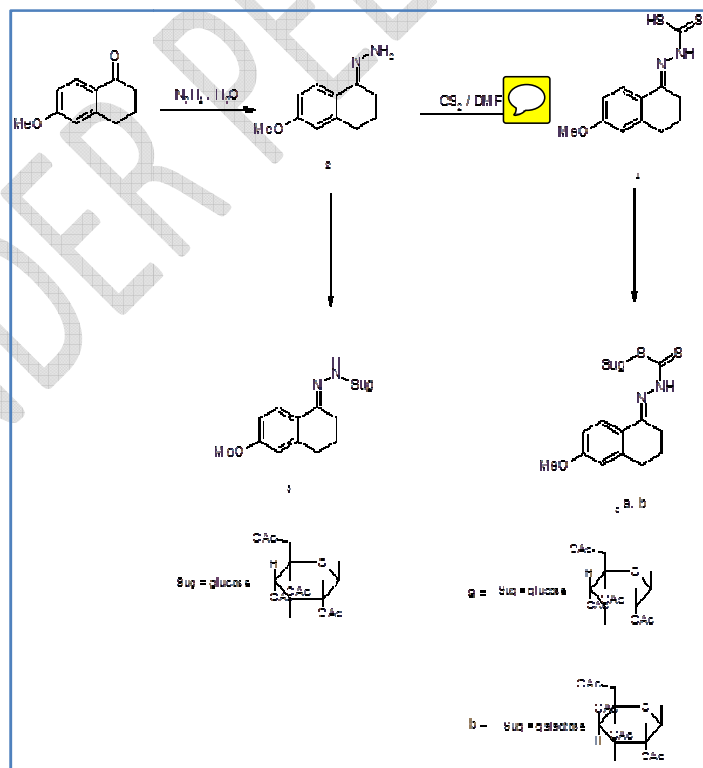
In this study, synthesis of the desired compounds was achieved by allowing the starting 6-methoxy-1-tetralone (**1**) to react with hydrazine hydrate to give 6-methoxy-3,4-dihydronaphthalene-1(2H)-ylidene hydrazine (**2**), which was allowed to react with 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide to afford 1-(6-methoxy-3,4-dihydronaphthalene-1(2H)-ylidene)-2-(2',3',4',6'-tetra-O-acetyl- β -D-glucopyranosyl)hydrazine (**3**). Also, upon the reaction of the hydrazine derivative **2** with carbon disulphide afforded the corresponding 1-(6-methoxy-3,4-dihydronaphthalene-1(2H)-ylidene)hydrazinecarbodithioic acid (**4**) which was treated with 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide in acetone containing potassium hydroxide as a basic medium to give the products **5a,b** (Scheme 1, table 1). On the other, the compound **6a** was obtained by reacting the compound **2** with formic acid at a temperature 60-80°C, while the acetyl hydrazine derivative **6b** was obtained upon refluxing the compound **2**

with acetyl chloride. Furthermore, condensation of **2** with formic acid for 3 h gave the naphtho [1,2-d] imidazole derivative **7**. Also, compound **7** was obtained by heating the compound **6a** above its melting point. Furthermore, the reaction of compound **2** with ethyl chloroacetate gave the ester derivative **8** which was refluxed with hydrazine hydrate to give the acetic acid hydrazide product **9**. Also, condensation of the hydrazine derivative **2** with different aldehydes namely, furaldehyde and 2, 6 – diflorobenzaldehyde gave the corresponding Schiff's bases **10a, b**. On the other hand, the product **11** was achieved by reacting the hydrazine derivative **2** with phenyl isothiocyanate. The product **11** was also allowed to react with chloroacetic acid in presence of sodium acetate giving rise the thiazolidin-4-one derivative **12** (Scheme 2, table 1)

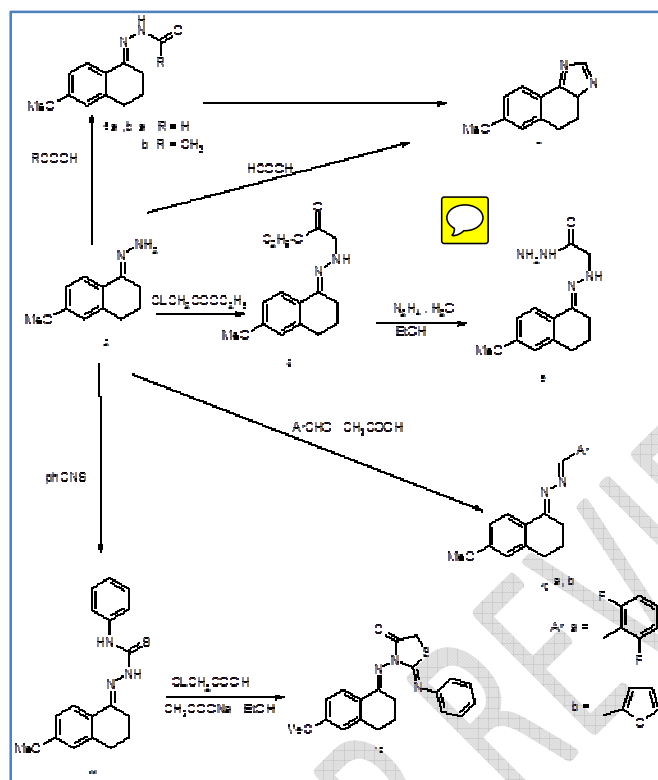
Moreover, according to the known chemotherapeutic activities of the chalcones and their cyclized quinazoline ring systems, it was of interest to allow the starting material 6-methoxy tetralone (**1**) to react with different aldehydes namely, trimethoxybenzaldehyde, furaldehyde, and 2, 6-diflorobenzaldehyde in ethanol containing 10% sodium hydroxide to give a novel series of chalcones **13a-c** which were reacted with thiourea to give the corresponding quinazoline derivatives **14a-c**. The condensation products (chalcones) has been confirmed through the x-ray crystallographic analysis of compound **13c** as in (figure1-table2) which clearly showed that the condensation product exists solely in the E-form, as this form satisfies both steric and stereoelectronic effects. In the bond lengths and bond angles for the Inspection of figure (1) α , β -unsaturated carbonyl moiety are typical for what is well established for such systems with minor deviations which may be due to the effect of the tetrahydronaph-thone ring system.

Also, treating of **1** with phosphorus pentasulphide gave 3,4-dihydro-6-methoxynaphthalene-1(2H)-thione (**15**) which was coupled with 2, 3, 4, 6-tetra-o-acetyl- α -D-gluco-pyranosylbromide in basic media to get the product **16** (Scheme 3, table 1)..

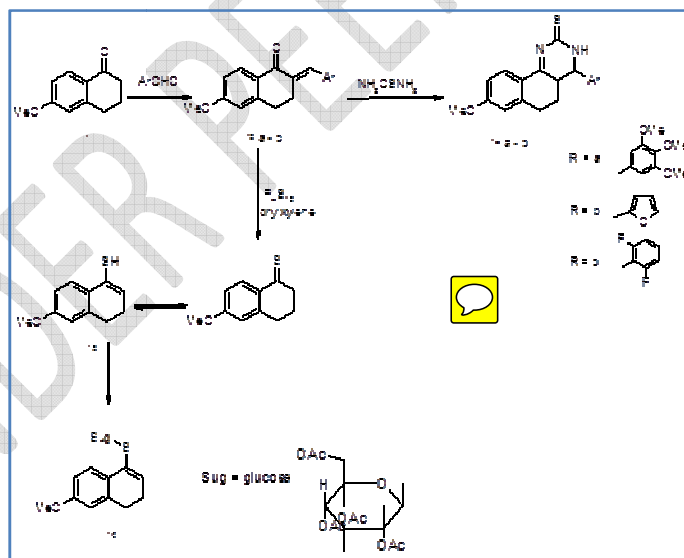
The structures of the newly synthesized compounds were established and confirmed on the basis of their micro-elemental analysis and spectral data. Some of the synthesized derivatives were selected as representative examples to evaluate their anticancer activity against breast carcinoma cell lines (MCF-7).



Scheme 1: Synthetic pathway of compounds 2-5a,b



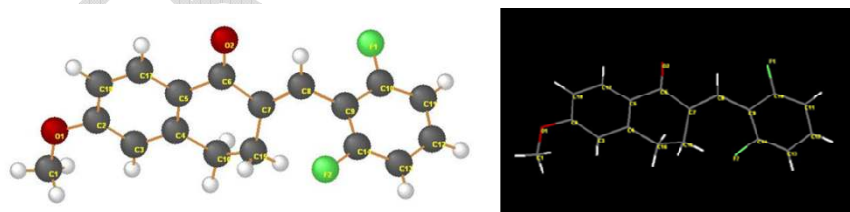
Scheme 2: Synthetic pathway of compounds 6-12



Scheme 3: Synthetic pathway of compounds 13-16

Table 1: Physicochemical Properties of the newly synthesized compounds (2-16)

Comp. No	M.P.(°C)	Cryst. Solvent	Yield (%)	Molecular Formula (M. Wt.)
2	65-67	EtOH	95	C ₁₁ H ₁₄ N ₂ O (190)
3	75-77	EtOH	84	C ₂₅ H ₃₃ N ₂ O ₁₀ (521)
4	130-132	EtOH	85	C ₁₂ H ₁₄ N ₂ OS ₂ (266)
5a	87-89	EtOH	78	C ₂₆ H ₃₃ N ₂ O ₁₀ S ₂ (596)
5b	99-101	EtOH	80	C ₂₆ H ₃₃ N ₂ O ₁₀ S ₂ (596)
6a	77-79	DilEtOH	75	C ₁₂ H ₁₄ N ₂ O ₂ (218)
6b	95-97	DilEtOH	70	C ₁₃ H ₁₆ N ₂ O ₂ (232)
7	170-172	DilEtOH	65	C ₁₂ H ₁₂ N ₂ O(200)
8	88-90	Chloroform	82	C ₁₅ H ₂₀ N ₂ O ₃ (276)
9	188-190	DilEtOH	85	C ₁₃ H ₁₈ N ₄ O ₂ (262)
10a	190-192	DilEtOH	88	C ₁₈ H ₁₆ F ₂ N ₂ O(314)
10b	298-300	DilEtOH	89	C ₁₆ H ₁₆ N ₂ O ₂ (268)
11	188-190	EtOH	95	C ₁₈ H ₁₉ N ₃ OS (325)
12	227-229	DilEtOH	92	C ₂₀ H ₁₉ N ₃ O ₂ S(365)
13a	98-100	DilEtOH	92	C ₂₁ H ₂₁ O ₅ (353)
13b	103-105	DilEtOH	95	C ₁₆ H ₁₄ O ₃ (254)
13c	119-121	DilEtOH	87	C ₁₈ H ₁₄ F ₂ O ₂ (300)
14a	145-147	DilEtOH	94	C ₂₂ H ₂₄ N ₂ O ₄ S(412)
14b	231-233	EtOH	89	C ₁₇ H ₁₆ N ₂ O ₂ S(312)
14c	250-252	EtOH	85	C ₁₉ H ₁₆ F ₂ N ₂ OS(358)
15	219-221	DMF/water	70	C ₁₁ H ₁₂ OS (195)
16	212-214	EtOH	65	C ₂₅ H ₃₁ O ₁₀ S (525)

**Figure (1)Crystal Structure of compound 13c**

291

Table 2: Some selected bond lengths and bond angles of compound 13c

Bond lengths (Å)	
C5-C17	1.398(2)
C7-C8	1.334(2)
C7-C15	1.501(2)
C6-C7	1.498(2)
Bond angles (°)	
O2-C6-C7	121.23(16)
C7-C8-C9	128.34(17)
C8-C7-C15	126.43(15)

292

293 3.2 In vitro cytotoxic screening (Anticancer Activity Screening)

294 Preliminary experiments were performed using the breast carcinoma cell line (MCF-7) to identify the potential toxicity of twelve
 295 selected compounds (4, 5a, 8, 9, 10a, 13a-c, 14a,b, 15, 16) in comparison to the known anticancer drug Doxorubicin by SRB
 296 method Skehan et al. (24), (1990) as follows: Cells were plated in 96-multiwell plate (104 cells/ well) for 24 h before treatment
 297 with compounds to allow attachment of cell to the wall of the plate. Different concentration of the compound under test (0.0, 1,
 298 2.5, 5 and 10 g/ml) were added to the cell monolayer triplicate wells which were prepared for each individual dose. Monolayer
 299 cells were incubated with the compounds for 48 h at 37°C and in atmosphere of 5% CO₂. After 48 h, cells were fixed, washed
 300 and stained with Sulfo-Rhodamine-B stain. Excess stain was washed with acetic acid and attached stain was recovered with Tris
 301 EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration
 302 is plotted to get the survival curve of each tumor cell line after the specified compound. The dose response curve of compounds
 303 was analyzed using Emax model. IC₅₀ was defined as the drug concentration required to reduce fluorescence to 50% of that of
 304 the control.

305 Twelve different derivatives (4, 5a, 8, 9, 10a, 13a-c, 14a,b, 15, 16) were selected as representative examples to evaluate their in-
 306 vitro inhibitory effects against cellular proliferation in human cultured breast cell lines using Doxorubicin as a reference drug.
 307 Depending upon the data of the table (3), most of the evaluated derivatives exhibited good cytotoxic activity. It has been found
 308 that, the chalcone derivatives and their cyclized thiopyrimidine analogues 13a-c, 14a,b appeared to be potent breast carcinoma
 309 growth inhibitors. The highest potency was gained by the trimethoxy phenyl chalcone 13a (IC₅₀; 3.4 μM) and the cyclized
 310 furanylthiopyrimidine analogue 14b (IC₅₀; 4.8 μM) comparing to Doxorubicin (IC₅₀; 0.13 μM).

311 On the other hand, moderate cytotoxicity was obtained by the thio-tetralone, thiosemicarbazide compounds 4, 8, 15 (IC₅₀; 8.5,
 312 19.1, 28.8 μM, respectively) and the nucleoside derivatives 5a, 16 (IC₅₀; 8.2, 17.3 μM). Unfortunately, the ester analogue 8
 313 appeared to be inactive as cytotoxic agents.

314 Further designing and optimization are required to synthesize new compounds of more anticancer potency.

315 Cytotoxicity assessment against MCF-7 breast adenocarcinoma cell line Data analysis

316 The dose response curve of compounds was analyzed using Emax model.

$$\% \text{ Cell viability} = (100 - R) \times \left(1 - \frac{[D]^m}{K_d^m + [D]^m} \right) + R$$

317

318 Where R is the residual unaffected fraction (the resistance fraction), [D] is the drug concentration used, K_d is the drug
 319 concentration that produces a 50% reduction of the maximum inhibition rate and m is a Hill-type coefficient. IC₅₀ was defined as
 320 the drug concentration required to reduce fluorescence to 50% of that of the control (i.e., K_d = IC₅₀ when R=0 and E_{max} =100-
 321 R) (25).

322

**Table (3): Cytotoxicity assessment of some selected compounds
Against MCF-7 breast adenocarcinoma cell line.**

Compound no.	IC ₅₀ (μM)	R fraction %
4	28.8	0.0
5a	8.2	1.4
8	8.5	0.0
9	182	---
10a	115.5	---
13a	3.5	33
13b	16.9	0.0
13c	5.4	15
14a	7.7	34.7
14b	4.8	12.1
15	19.1	0.0
16	17.3	0.0
Doxorubicin	0.13	0.0

^a IC₅₀, compound concentration required to inhibit tumor cell line proliferation by 50%

^b Values are means of three experiments

^c R fraction %, percentage of unaffected fraction

4. CONCLUSION

A novel series of some new substituted hydronaphthalene derivatives were synthesized and evaluated for their anticancer activity. The preliminary invitro cytotoxic evaluation revealed that the chalcone derivatives and their cyclized thiopyrimidine analogues (13a-c, 14a, b) appeared to be potent breast carcinoma growth inhibitors comparing to Doxorubicin. So, more studies and synthesis of these compounds with more modifications aiming to obtain new active derivatives of more potency towards other carcinoma cell lines must be in our future work.

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