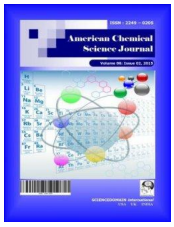

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Synthesis, Spectral Properties and Anti-tumor Evaluations of Some Novel 2-substituted-1,3-Thiazole Derivatives

Asmaa S. Salman[1*]

[1]*Department of Chemistry, Faculty of Science, Al-Azhar University, Girls' Branch, Nasr City, Cairo, Egypt.*

Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Reaction of N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine 1 with ammonium thiocyanate, phenyl isothiocyanate, acetic anhydride, phenacyl bromide, 2-chloro -*N*- (4-chlorophenyl) acetamide and acetic anhydride / cyanoacetic acid afforded the corresponding *N*-[4-(4-chlorophenyl)amino-1,3-thiazol-2-yl]thiourea 2, *N*-[4-(4-chlorophenyl)amino-1,3-thiazol-2-yl]-*N'*-phenylthiourea 3, *N*-acetyl-*N*-[4-(4-chlorophenyl)amino-1,3-thiazol-2-yl]acetamide 7,2-(1,3-thiazol-2-ylamino)-1 phenylethanone derivative 8, 2-(1,3-thiazol-2-ylamino)- *N*-(4-chlorophenyl)acetamide derivative 9 and *N*-(1,3-thiazol -2-yl)-2-cyanoacetamide derivative 11. Reaction 1 with phenyl isothiocyanate in basic DMF yielded the intermediate potassium salt 14, then treatment of intermediate 14 with *α*-halocarbonyl compounds such as ethyl chloroacetate and/ or 2-chloro-*N*-(4-chlorophenyl) acetamide afforded ethyl {*N'*-(1,3-thiazol-2-yl)-*N*-phenyl-carbamimidoyl)thio}acetate15 and 2-[(4-chlorophenyl)amino]-2-oxoethyl *N'*-(1,3-thiazol-2-yl)-*N*-phenyl-imidothiocarbamate16 respectively. Reaction 1 with 1*H*-pyrazole-4-carboxaldehyde 17 or 1*H*-indole-3-carboxaldehyde 18 afforded N^2-[(1*H*-pyrazol-4-yl) methylene]-1,3-thiazole-2,4-diamine19 and N^2-[(1H-indol-3-yl)methylene]-1,3-

**Corresponding author: E-mail: salman_2007_ok@yahoo.com;*

thiazol-2,4-diamine 20 respectively. Structures of the newly synthesized compounds have been confirmed by elemental analysis and spectra data. Some of the newly synthesized compounds were screened *in vitro* for their anti-tumor activities against human cancer cell line MCF-7.

Keywords: 1,3-thiazole-2,4-diamine; thiourea; carbamimidothioate; pyrazole; anti-tumor activities.

1. INTRODUCTION

The main objectives of medicinal chemistry are the design and synthesis, compounds having value as human therapeutic agents. In recent years, cancer is the biggest health issue in the world. Cancer disease which the control of cell growth and nuclear proliferation lost in one or more cells and end leading either to the tumor such as breast, prostate cancer, and therapeutic options include surgery, chemotherapy, and radiotherapy. The major goal of cancer treatment is to attain maximum therapeutic damage of tumor cells in a collection with the minimum concentration of the drug. This can be carried out by selective antitumor preparation, the cytostatic effects of which would be restricted within tumor tissue [1]. The find of new chemical structures that can act as more effective anticancer agents is still the main challenge hard to medicinal chemists. The important advances achieved over recent decades in the research and development of multiple anticancer drugs, existing anticancer drugs still have main limitations such as drug resistance, lack of selectivity and unwanted side effects. Thus, there is a strong request for the find and development of effective new cancer treatment devoid side effects [2-4].

In recent years development antitumor chemical drugs which including the heterocyclic ring which has interesting biological activities [5,6].Thiazole is five-membered heterocyclic ring have many biologically active Also, 2-amino-thiazoles offer a wide range of biological potencies including antimicrobial [7], antiviral [8], anti-inflammatory activities [9], anti-Alzheimer [10], anti-tubercular activity [11], anti-convulsant activity [12], anti-HIV-1 [13]. Antitumor activity of thiazole was easily based via being incorporated into a variety of therapeutically active agents like bleomycin [14], epothilones [15] and dasatinib [16,17].From literature survey, it was found that aminothiazole proved to have a broad spectrum of activity against most of the tested tumor cell lines [18-21].

On the way of continuing our work on the synthesis of new heterocyclic compounds with expected biological activities, we report herein the synthesis of some new 1,3-thiazole-2,4-diamine derivatives and their characterization by IR, NMR and Mass spectrometry techniques. Some synthesized compounds were also screened for their anti-tumor evaluation against the breast cancer cell line (MCF-7).

2. MATERIALS AND METHODS

2.1 General Conditions

Melting points were measured on a Gallenkamp apparatus and are uncorrected. IR spectra were measured using KBr discs on Pye Unicam SP-1000 spectrophotometer. The ^{1}H-NMR and ^{13}C NMR spectra were determined in DMSO-d_6 at 400 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 Ev. Elemental analyses were carried out at the Microanalytical center of Cairo University and the main chemical warfare laboratories. N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine **1** was prepared according to previously reported procedure [22].

2.2 Synthesis

2.2.1 *N*-[4-(4-Chlorophenyl)amino-1,3-thiazol-2-yl]thiourea 2

To N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine 1 (0.0 1 mol), concentrated hydrochloric acid (0.01mol) was added and the solution was warmed. A saturated solution of ammonium thiocyanate in water (5 gm in 3 mL) was added slowly in above solution. The mixture was reflux for 45 min. The reaction mixture was poured in cold water. The solid obtained was filtered off and recrystallized from ethanol to give 2 as yellow powder. Yield: 70 %. m.p.: 140-142˚C. IR (KBr): u/cm^{-1}: 3340, 3269, 3250, 3200 (NH_2,2 NH), 3066, 2931 (CH),1240 (C=S),1608 (C=N). ^{1}H-NMR (DMSO-d_6) δ ppm: 4.27 (s, 2H, NH_2 exchanged by D_2O),7.03 (s,1H , C_5-H thiazole) , 7.30-7.57 (m, 4H, Ar-H), 10.12 (s,1H, NH exchanged by D_2O) ,10.50 (s,1H, NH exchanged by D_2O) . MS m/z (%): 285 (M^+, 21.3), 269 (4.6), 113 (10.5), 111(28), 60 (6.1), 57 (100). Anal. Calcd. for $C_{10}H_9ClN_4S_2$ (284.79) : C, 42.17 ;H , 3.19 ; Cl, 12.45 ; N ,19.67 ; S , 22.52.Found: C, 42.07; H , 3.09 ; Cl , 12.25 ; N , 19.47 ; S, 22.32.

2.2.2 *N*-[4-(4- Chlorophenyl)amino-1,3-thiazol - 2-yl] -*N'*-phenylthiourea 3

A mixture of N^4-(4- chlorophenyl)-1,3-thiazole-2,4 -diamine **1** (0.01 mol) and phenyl isothiocyanate (0.01 mol) in 1,4-dioxane (40 mL) was refluxed in the presence of few drops of triethylamine (TEA) for 8h.The solid product separated from the hot mixture was filtered off, washed with water and recrystallized from pot. ether to give 3 as yellow powder .Yield : 55%. m.p.: 60 - 62°C. IR (KBr): υ/cm^{-1}: 3217, 3186, 3116 (3 NH), 3005, 2995 , 2935 (CH), 1250 (C= S) , 1597 (C=N). ^{1}H-NMR (DMSO - d_6) δ ppm : 7.11 (s,1H, C_5-H thiazole), 7.29 - 7.61 (m, 9H, Ar-H),10.02 (s ,1H, NH exchanged by D_2O), 11.03 (s,1H, NH exchanged by D_2O),11.54 (s,1H NH exchanged by D_2O) . MS *m/z* (%): 361 (M^+,1.1), 325 (3.8), 264 (9.3) , 230 (26.5) , 224 (7.2), 113 (26.4) , 55 (100) . Anal. Calcd. for $C_{16}H_{13}ClN_4S_2$ (360.88): C, 53.25 ; H, 3.63 ; Cl, 9.82 ; N, 15.52 ; S , 17.77. Found : C , 53.05 ; H , 3.43 ; Cl, 9.62 ; N, 15.32 ; S ,17.57.

2.2.3 3-[4-(4- Chlorophenyl)amino-1,3-thiazol -2-yl]-6-(4-methoxyphenyl)-4-oxo-1-phenyl-2-thioxo-1,2,3,4-tetrahydro- pyrimidine-5-carbonitrile 4

A mixture of thiourea derivative 3 (0.01 mol), ethyl cyanoacetate (0.01 mol) and anisaldehyde (0.01 mol) in ethanol 30 mL was added few drops of TEA. The reaction mixture was refluxed for 6h. The solid product separated from the hot mixture was filtered off, washed with water and recrystallized from ethanol to give 4 as a yellow plate. Yield: 80%. m.p.: 309 - 310°. IR (KBr): υ / cm^{-1}: 3275 (NH), 3027.2904, 2839 (CH), 2214 (CN), 1670 (C=O), 1246 (C=S).^{1}H-NMR (DMSO-d_6) δ ppm: 3.25 (s, 3H, OCH_3), 7.04 (s, 1H , C_5-H thiazole), 7.14 – 8.04 (m, 13H, Ar-H),8.27 (s, 1H, NH exchanged by D_2O).^{13}C NMR (DMSO-d_6) δ ppm:62.52 (OCH_3),115.26,115.43,116.63 (CN), 124,41, 129.84, 132.13, 133.97, 154.91 (C-N), 162.81 (C-O), 164 (C = O),180 (C-S), 186 (C=S). Anal. Calcd. for $C_{27}H_{18}ClN_5O_2S_2$ (544.04): C, 59.61 ; H , 3.33 ; Cl , 6.52 ; N, 12.87; S ,11.79. Found: C, 59.41; H, 3.13; Cl, 6.32; N, 12.67; S, 11.69.

2.2.4 6-(4-Aminophenyl)-1-[4-(4-chlorophenyl) amino-1,3-thiazol-2-yl]-4-(4-chloro-phenyl)-3-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione 6

A mixture of 1-(4-aminophenyl)-3-(4-chloro-phenyl) prop-2-en-1-one **5** (0.01 mol) and thiourea derivative **3** (0.01 mol) in ethanol (50 mL) and sodium hydroxide (0.01 mol) dissolved in minimum quantity of water was refluxed 6h. The reaction mixture was allowed to cooled and then acidified with dilute hydrochloric acid. The solid obtained was collected by filtration, washed with water, and recrystallized from ethanol to give 6 as a yellow granule. Yield: 75%. m.p.: 260-261°C. IR (KBr): υ/cm^{-1}: 3217, 3166, 3116 (NH_2, NH), 3035, 2985, 2936 (CH), 1254 (C=S). ^{1}H-NMR (DMSO-d_6) δ ppm 4.48 (d, 1H, C_4-H pyrimidine), 6.60 (d,1H,C_5-H pyrimidine), 5.02 (s, 2H, NH_2, exchanged by D_2O-), 7.11–7.81 (m, 18 H, Ar-H and C_5-H thiazole), 8.91 (s, 1H, NH, exchanged by D_2O). Anal. Calcd. for C31 H23 Cl2 N5 S2 (600.58) : C ,61.99 ; H , 3.86 ; Cl ,11.81 ; N, 11.66; S, 10.68. Found: C, 61.69; H, 3.66; Cl, 11.61; N, 11.46; S, 10.48.

2.2.5 *N*-Acetyl-*N*-[4-(4-chlorophenyl)amino-1,3 - thiazol-2-yl] acetamide 7

A mixture of N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine **1** (0.01 mol) and acetic anhydride (5 mL) was heated under reflux for 5h.Then, the reaction mixture was cooled and poured into ice. The solid product was filtered off, washed with water, dried and recrystallized from ethanol / DMF (2 :1) to give compound **7** as a brown powder. Yield: 70%. m.p.: 162-164°C. IR (KBr): υ/ cm^{-1}: 3136 (NH), 3055, 2981, 2877 (CH), 1670 (C=O) .^{1}H-NMR (DMSO- d6) δ ppm: 2.70. (s, 3H, CH_3), 2.86 (s , 3H , CH_3) , 6.83 (s, 1H , C_5- H thiazole), 7.48-7.61 (m, 4H, Ar-H), 8.91 (s, 1H, NH exchanged by D_2O).^{13}CNMR (DMSO-d_6) δ ppm: 21.09, 24.09 ($2CH_3$), 130.34 , 131.49 , 134.24, 138.83, 149.21,157.82 (C-N) ,168.42, 170.44 (2 C=O), 179 (C-S). Anal. Calcd. for $C_{13}H_{12}ClN_3O_2S$ (309.77): C, 50.40; H , 3.90 ; Cl ,11.44 ; N, 13.56; S, 10.35. Found: C, 50.20; H, 3.60; Cl, 11.24; N, 13.36; S, 10.25.

2.2.6 2-[4-(4-Chlorophenyl)amino-1,3-thiazol-2-ylamino]-1-phenylethanone 8

To a mixture of N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine **1** (0.01 mol) and phenacyl bromide (0.01 mol) in ethanol (30 mL) was added few drops of TEA. The reaction mixture was refluxed for 6h.The solid product separated after cool was filtered off, washed with water and recrystallized from ethanol to give 8 as brown plates. Yield: 70%. m.p.: 100-102°C. IR (KBr): υ/cm^{-1}:3186, 3147 (2 NH), 3059, 2924, 2850 (CH), 1685 (C = O). ^{1}H-NMR (DMSO-d_6) δ ppm: 4.21 (s, 2H, CH_2), 6.84 (s, 1H, C_5- H thiazole), 7.15-7.99 (m,9H,Ar-H),8.07(s,1H, NH exchanged by D_2O),

11.08 (s, 1H, NH exchanged by D_2O) . MS *m/z* (%): 344 (M^+, 15), 316 (12.5), 270 (28.9), 232 (3.8), 113 (4.3), 105 (100), 77(41.6). Anal. Calcd. for $C_{17}H_{14}ClN_3OS$ (343.83): C, 59.38; H, 4.10; Cl, 10.31; N, 12.22; S, 9.33.Found : C, 59.18; H, 4.00 ; Cl, 10.11; N, 12.02; S, 9.23.

2.2.7 2-(4-(4-Chlorophenyl)amino-1,3-thiazol-2-ylamino)-*N*-(4-chlorophenyl)acetamide 9

To a mixture of N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine 1 (0.01 mol) and 2-chloro-*N*-(4-chlorophenyl) acetamide (0.01 mol) in ethanol (30 mL) was added few drops of TEA. The reaction mixture was refluxed for 6h.The solid product separated after cool was filtered off, washed with water and recrystallized from ethanol to give 9 as a white plat .Yield: 80 %. m.p.:145-147℃. IR (KBr): υ/cm^{-1}: 3271 , 3197 , 3128 (3 NH) , 3082 , 2974 , 2931, 2893 (CH), 1678 (C=O) .^{1}H-NMR (DMSO-d_6) δ ppm: 4.22 (s, 2H , CH_2) , 6.85 (s, 1H, C_5 -H thiazole), 7.30 - 7.64 (m, 8 H, Ar-H), 8.27 (s, 1H, NH exchanged by D_2O) ,10.36 (s, 1H, NH exchanged by D_2O) , 10.93 (s, 1H, NH, exchanged by D_2O).^{13}C NMR (DMSO-d_6) δ ppm: 33.18 (CH_2) ,121.08, 123.21, 127.50, 128.87, 129.20 ,130.24, 134.45, 137.97, 138.01, 140.72, 147,02, 156.28 (C-N), 164.36 (C=O), 184.01 (C-S). Anal. Calcd. For $C_{17}H_{14}Cl_2N_4OS$(393.29) : C, 51.92; H, 3.59; Cl ,18.03; N,14.25; S, 8.15. Found: C, 51.62; H, 3.39; Cl, 18.00; N, 14.05; S, 8.00.

2.2.8 4-(4-Chlorophenyl)amino-1-[4-(4-chlorophenyl)amino-1,3-thiazol-2-yl]-1*H*-imidazole-2(3*H*)-thione 10

A mixture of acetamide derivative 9 (0.01mol) and ammonium thiocyanate (0.015 mol) in glacial acetic acid (20 mL) was refluxed for 6h. After cooling, the separated solid was filtered off and recrystallized from ethanol to give **10** as brown plates. Yield: 60 %.m.p.:170-172°C. IR (KBr): υ/ cm^{-1}: 3302, 3263, 3190 (3 NH), 3066, 2927(CH), 1261(C=S).^{1}H-NMR (DMSO-d_6) δ ppm: 7.29 (s , 1H, C_5- H thiazole), 7.35 (s,1H , C_4-H imidazole), 7.40 -7.71 (m, 8 H, Ar-H), 8.61 (s, 1H, NH exchanged by D_2O),10.02(s,1H, NH , exchanged by D_2O),11.21(s ,1H , NH exchanged by D_2O). ^{13}C NMR (DMSO-d_6) δ ppm: 120.12, 120.89, 126.90, 127.14, 127.56, 129.09, 129.19, 129.22, 137.59, 138.71 , 155.12 (C-N) , 170.70 (C-S),186 (C=S).Anal. Calcd. for $C_{18}H_{13}Cl_2N_5S_2$ (434.36): C , 49.77 ; H, 3.02 ; Cl, 16.32 ; N ,16.12 ; S, 14.76. Found: C, 49.57; H, 3.00; Cl, 16.12; N, 16.02; S, 14.46.

2.2.9 *N*-[4-(4-Chlorophenyl)amino-1,3-thiazol-2-yl]-2-cyanoacetamide 11

A solution of cyanoacetic acid (0.05 mo l) in acetic anhydride (15 mL) was heated under reflux over water bath for 5 minutes , then compounds **1** (0.05 mol) was added and the reaction mixture was heated for further 1h. at 60-70°C. The reaction mixture was cooled, and the precipitate was filtered off and recrystallized from ethanol to give **11** as a brown powder. Yield: 60%. m.p.: 141-143°C. IR (KBr): υ/cm^{-1}: 3136, 3100 (2 NH) , 3006, 2931 (CH), 2200 (CN), 1670 (C=O).^{1}H-NMR (DMSO-d_6) δ ppm: 4.02 (s, 2H, CH_2) , 6.83 (s,1H , C_5- H thiazole), 7.48 -7.61(m, 4 H, Ar-H), 10.22 (s, 1H , NH exchanged by D_2O),11.01(s ,1H , NH exchanged by D_2O).293 (M^+, 90.7),294 (M^+ +1, 19.8), 258 (4.9), 232 (4.9), 218 (11.5) , 190 (7.5),181 (16.5), 153 (100), 113 (43.4),77(27.2). Anal. Calcd. for $C_{12}H_9ClN_4OS$ (292.74): C,49.23 ; H , 3.10; Cl , 12.11 ; N, 19.14; S ,10.95. Found: C,49.03 ; H 3.00; Cl , 12.01 ; N, 19.04 ; S,10.65.

2.2.10 General procedure for the Synthesis of 12 and 13

Equimolecular mixture of *N*-[4-(4-chlorophenyl)-amino -1,3- thiazol – 2 -yl] -2- cyanoacetamide**11** (0.01 mol) and the selected aldehydes such as benzaldehyde and salicylaldehyde (0.01 mol) in 1,4-dioxane (20 mL) containing piperidine (0.5 mL) was heated under reflux for 6h. The reaction mixture was left to cool then poured onto ice / water containing few drops of hydrochloric acid and the formed solid product was collected by filtration and recrystallized from the appropriate solvent.

2.2.10.1 N-[4-(4-Chlorophenyl)amino-1,3-thiazol-2-yl]-2-cyano-3-phenylacrylamide 12

Yield: 60%. m.p.:170 - 172°C. IR (KBr): υ/cm^{-1}: 3170, 3124 (2 NH), 3047 , 2924 , 2877 (CH) , 2222(CN), 1693 (C=O).^{1}H-NMR (DMSO-d_6) δ ppm : 6.94 (s ,1H ,C_5-H thiazole), 7.29 – 7.71 (m, 10 H, Ar-H and C=CH), 11.24 (s, 1H, NH, exchanged by D_2O),11.78 (s,1H, NH exchanged by D_2O).Anal.Calcd. for $C_{19}H_{13}ClN_4OS$(380.85): C, 59.92 ; H , 3.44 ; Cl, 9.31; N, 14.71; S, 8.42. Found: C, 59.62; H , 3.24; Cl, 9.01; N ,14.51; S, 8.22.

2.2.10.2 N-[4-(4-Chlorophenyl)amino-1,3-thiazol-2-yl]-2-imino-2H-chromene-3-carboxamide 13

Yield: 75 %. m.p.: 308 - 310°C. IR (KBr): υ/cm^{-1}: 3209, 3190, 3170 (3NH) , 3051,2962 (CH) ,1689

(C=O).^{1}H-NMR (DMSO-d_6) δ ppm: 6.83 (s,1H, C_5-H thiazole),7.02 -7.59 (m, 9 H, Ar-H and C_4-H, coumarin),10.05 (s ,1H, NH exchanged by D_2O), 11.01(s,1H, NH exchanged by D_2O), 12.27 (s, 1H, NH exchanged by D_2O).^{13}C NMR (DMSO-d_6) δ ppm: 116.61 , 120.06 ,120.69 , 120.52, 123.61, 125.35 ,128.41,129.28 ,129.53 , 129.83, 132.11 , 157.34 (C-N) , 157.57 (C-O), 162.74 (C=O),180 (C-S). Anal. Calcd. for $C_{19}H_{13}ClN_4O_2S$ (396.85): C , 57.50 ; H , 3.30 ; Cl , 8.93; N , 14.12; S, 8.08. Found : C , 57.30 ; H , 3.20 ; Cl , 8.63 ; N, 14.02 ; S , 8.00 .

2.2.11 General procedure for the synthesis of compounds 15 and 16

To a cold suspension of powdered potassium hydroxide (0.01 mol) in DMF (20 mL) was added compound **1**(0.01 mol) and phenyl isothiocyanate (0.01 mol). The reaction mixture was stirred at room temperature for 6h, and then treated with ethyl chloroacetate and /or 2-chloro -*N*-(4-chloro-phenyl)acetamide (0.01 mol) and the stirring was continued at room temperature for further 10h. The reaction mixture was poured into 50 mL of cold water. The result solid products were collected by filtration and recrystallized from a mixture of ethanol / DMF (1:1) to give compounds **15** and **16**.

2.2.11.1 *Ethyl {N'- [4-(4-chlorophenyl)amino-1,3-thiazol-2-yl]-N-phenyl-carbamimidoyl) thio} acetate 15*

Yield: 60%. m.p.:166-168℃.IR(KBr): υ/cm^{-1}: 3283, 3201 (2 NH), 1670 (C=O).^{1}H-NMR (DMSO-d_6) δ ppm: 1.02 (t , 3 H, $CH_2\underline{CH_3}$) ,4.06 (q , 2H, $\underline{CH_2}$ CH_3),4.25 (s, 2H, CH_2),6.81(s, 1H, C_5-H thiazole) , 6.98 - 7.70 (m , 9H, Ar-H), 11.23 (s, 1H, NH exchanged by D_2O) ,11.74 (s, 1H, NH exchanged by D_2O).^{13}C NMR (DMSO-d_6) δ ppm: 19 (CH_3) , 33.29(CH_2),110, 120.67 ,121.09 ,122.20 ,123.51,124.07 ,124.63, 125.10 ,128.91 , 129.43, 129.69 ,135.73 ,148.61,156.35 (C-N) ,172.08 (C= O), 182 (C - S) . Anal. Calcd. for $C_{20}H_{19}ClN_4O_2S_2$ (446.97): C, 53.74 ; H, 4.28 ; Cl, 7.93 ; N, 12.53 ; S, 14.35. Found: C, 53.54; H, 4.08; Cl, 7.63; N, 12.33; S, 14.15.

2.2.11.2 *2-[(4-Chlorophenyl)amino]-2-oxoethyl N'-(4-(4-chlorophenyl)amino- 1,3-thiazol -2-yl)-N-phenyl–imidothiocarbamate 16*

Yield: 60%. m.p.: 125-126°C. IR (KBr): υ/cm^{-1}: 3275 , 3190 , 3116 (3 N H) , 3055 , 2978 , 2923 , 2839 (CH), 1670 (C=O) .^{1}H-NMR (DMSO-d_6) δ ppm:4.52 (s,2H, CH_2), 6.84 (s,1H, C_5- H thiazole) ,6.59-7.64 (m,13H, Ar-H) ,10.24 (s, 1H, NH exchanged by D_2O),10.36(s ,1H , NH exchanged by D_2O),10.39 (s ,1H , NH exchanged by D_2O). ^{13}C NMR (DMSO-d_6) δ ppm:33.18 (CH_2),121.14, 123.22,124.02, 127.38 , 127.50, 128.70 ,128.87, 128.91, 129.08, 129.48, 129.75, 130.24, 130.81, 137.97, 138.01, 138.33, 138.88, 140.72, 147.02, 156.27(C - N) , 164.83 (C=O), 184 , 187 (2 C-S). Anal.Calcd. for $C_{24}H_{19}Cl_2N_5OS_2$ (528.47) : C , 54.54 ; H , 3.62 ; Cl ,13.42 ; N, 13.25 ; S ,12.13. Found: C, 54.24; H, 3.42; Cl, 13.22; N, 13.05; S, 12.03.

2.2.12 General Procedure for the Synthesis of 19 and 20

A mixture of compound **1** (0.01 mol) and 1,3-diphenyl-1*H*- pyrazole-4-carboxaldehyde **17** or 2-(4-bromophenyl)-1*H*-indole-3-carboxaldehyde **18** (0.01 mol) was refluxed in ethanol (30 mL) for 15h.The reaction mixture was cooled and poured into crushed ice and filtered. The product obtained was recrystallization from ethanol/ DMF (1:3) to obtain schiff bases **19** and **20**.

2.2.12.1 *N^4-(4-Chlorophenyl)-N^2-(1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-1,3-thiazole -2,4-diamine 19*

Yield: 75 %. m.p.: 302 - 304 ℃. IR (KBr): υ/cm^{-1}: 3124 (NH) , 3005 , 2993 , 2812 (CH).^{1}H- NMR (DMSO- d_6) δ ppm: 7.04 (s , 1H , C_5- H thiazole), 7.36 -7.98 (m , 15 H, Ar-H and C_5- H pyrazole), 8.85 (s, 1H, N = CH), 12.15 (s, 1H, NH exchanged by D_2O).^{13}C NMR (DMSO-d_6) δ ppm : 119.70, 119.93 ,122.59 , 128.19 ,129.01 ,129.14 ,129.38, 129.64, 129.89, 130, 130.17,135.27, 152.01 (C-N), 185.09 (C-S). Anal. Calcd. for $C_{25}H_{18}ClN_5S$ (455.96) : C, 65.85 ; H, 3.98 ; Cl, 7.78 ; N, 15.36; S, 7.03. Found: C, 65.65; H, 3.68; Cl, 7.58; N, 15.16; S, 7.00.

2.2.12.2 *N^2-(2-(4-Bromophenyl)-1H-indol-3-yl) methylene)-N^4-(4-chlorophenyl)-1,3-thiazole - 2,4-diamine 20*

Yield: 75%. m.p.: 280-282°C. IR (KBr): υ/cm^{-1}: 3208 , 3167 (2 NH) , 3020 , 2974, 2904 , 2866 (CH).^{1}H-NMR (DMSO - d_6) δ ppm : 7.11 - 7.30 (m, 9 H , Ar-H and C_5- H thiazole) , 7.50 (d, 1H, indole), 7.70 - 7.80 (m , 2H, indole), 8.18 (d ,1H, indole), 9.94 (s,1H ,N= CH) ,11.01 (s, 1H, NH, exchanged by D_2O), 12.42 (s, 1H, NH exchanged by D_2O).^{13}C NMR (DMSO-d_6) δ ppm : 112.52 ,114.09 ,121.51 ,122.51, 122.99, 123.95; 124.33, 126.20 ,129.43, 132.24, 132.38, 136.37, 147.90 (C-N), 185.48 (C-S). Anal. Calcd. for $C_{24}H_{16}BrClN_4S$ (507.83) : C, 56.76 ; H, 3.18 ; Br,

15.73 ; Cl, 6.98 ; N, 11.03; S, 6.31.Found : C, 56.56 ; H ,3.08 ; Br ,15.63 ; Cl , 6.68 ; N , 11.00 ; S , 6.01.

2.3 *In vitro* Antitumor Screening

In vitro anti-tumor activity of newly synthesized compounds **3, 4, 6, 7, 9, 10, 11, 13, 15, 16** and **19** were evaluated against human breast cancer cell line (MCF-7. Breast cancer cell line (MCF-7) was obtained from the American type Cultures Collection (ATCC, Rockyille, MD) were kindly provided by Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt. Cell viability was determined by the crystal violet assay [23].

They grow as monolayer and routinely maintained in RPMI-1640 medium supplemented with 10 % inactivated fetal calf serum (FBS) and 50 µg/mL gentamycin at 37°C in a humidified atmosphere containing 5%CO_2.Three hours after seeding, vehicle or cannabinoids at different concentrations were added to the medium and then daily with each change of medium for 4 days. After the treatment, cells were fixed by 4 % paraformaldehyde solution in FBS. Then crystal violet solution (0.5 % crystal violet in 20 % methanol / water) was added .The excess crystal violet solution was washed away with distilled water and the remaining crystals were dissolved in Sorenson's buffer (0.1 M sodium citrate in 50% ethanol/water pH 4.2). Viability was determined by absorbance at 540 nm wavelength using Spectra Max M5 microplate reader.

Number of viable cells was determined using ELISA reader as previously mentioned before and the percentage of viability was calculates as:

$$[1-(OD_t / OD_c)] \times 100\ \%$$

Where OD_t is mean optical density of well treated with the test sample, OD_c is mean optical density of untread cell. IC_{50} values the concentration required to cause toxic effects in 50% if intact cells was estimated from graphic plots. Experiments were carried out in triplicate, and results are reported in Table 1.

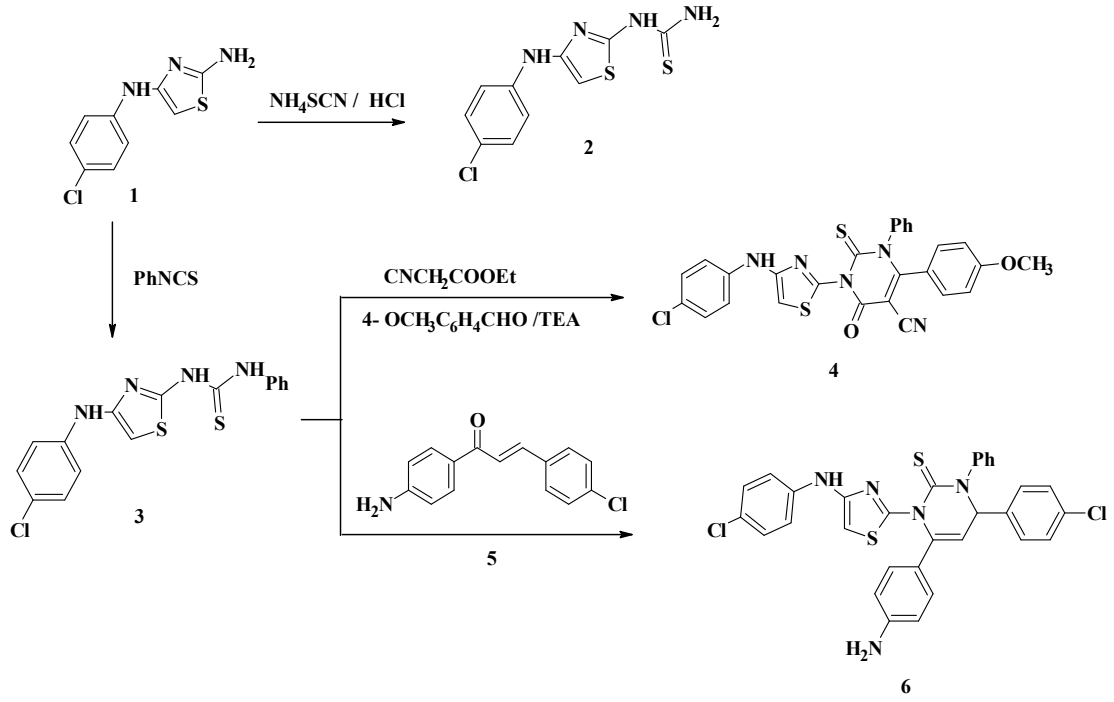
3. RESULTS AND DISCUSSION

3.1 Chemistry

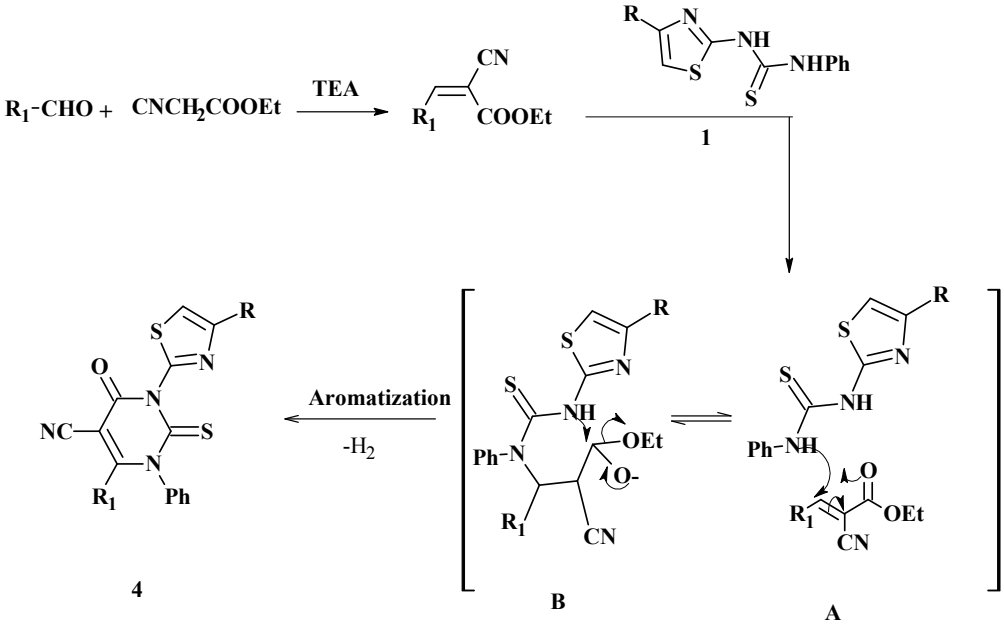
The synthesis of the new compounds is outlined in Schemes 1- 4. The key starting compound N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine **1** was prepared by heating a mixture of equimolar amounts of the 2- chloro –*N* -(4 - chlorophenyl)-acetamide and thiourea according to the reported method [22]. Reaction N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine 1 with ammonium thiocyanate in the presence of HCl [24] afforded *N*-[1,3-thiazol-2-yl]thiourea derivative e **2** (Scheme 1). The structure of **2** was supported on the basis of elemental analyses and spectral data. The ^{1}H-NMR spectrum (DMSO-d_6) of compound **2** showed a D_2O- exchangeable single signals at *δ* 4.27 ppm, *δ* 10.12 ppm and *δ* 10.50 ppm assigned to NH_2 and two NH protons respectively. Its mass spectrum showed a molecular ion peak at m/z 485 corresponding to a molecular formula $C_{10}H_9ClN_4S_2$..

The reaction of N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine **1** with phenyl isothiocyanate in 1,4-dioxane in the present of TEA [25] to give the *N*-[1,3-thiazol-2-yl]-*N'*-phenylthiourea derivative **3** (Scheme1). The IR spectrum displayed absorption bands at 3217 cm^{-1} , 3186 cm^{-1}, 3116 cm^{-1} and 1250 cm^{-1} due to 3 NH and C=S groups respectively. The ^{1}H-NMR spectrum (DMSO–d_6) showed a D_2O-exchangeable three signals at δ 10.02 ppm, *δ* 11.03 ppm and *δ* 11.54 ppm assigned to three NH protons. The mass spectrum showed a molecular ion peak at *m/z* 361 corresponding to a molecular formula $C_{16}H_{13}ClN_4S_2$.Further structure elucidation of compound **3** was obtained through the study of its reactivity towards chemical reagents. Thus, the reaction of **3** with ethyl cyanoacetate and anisaldehyde in the present of TEA as catalysis [26] to give 4-oxo-2-thioxo-1,2,3,4-tetra-hydropyrimidine-5-carbonitrile **4**. A plausible mechanism for the formation **4** which the intermediate **A** and **B** are obtained first, then intrarmolecular cyclization to give **4** (Scheme 2). The IR spectrum of **4** displayed absorptions band at 3275 cm^{-1} (NH) , 2214 cm^{-1} (CN) ,1670 cm^{-1} (C=O) and 1246 cm^{-1} (C=S). The ^{1}H-NMR spectrum (DMSO-d_6) showed a D_2O- exchange-able signal at δ 8.27 ppm assigned to NH proton and signal at *δ* 3.25 ppm for OCH_3 proton.^{13}C NMR spectrum showed signal at *δ* 62.52 ppm (OCH_3), *δ* 116.63 ppm (CN), *δ* 162.81 ppm (C = O) and *δ* 186 ppm (C = S). The reaction of thiourea derivatives **3** with 1-(4-aminophenyl)-3-(4-chlorophenyl)prop-2-en-1-one **5** in the presence of sodium hydroxide to give pyrimidine-2(1*H*)-thione derivative **6**. The IR spectrum displayed absorptions band at 3217 cm^{-1}, 3166 cm^{-1}, 3116 cm^{-1}, 1254 cm^{-1} to NH_2 , NH and C=S groups respectively. The ^{1}H-NMR spectrum

(DMSO–d_6) showed a D_2O-exchangeable signals at δ 5.02 ppm , δ 8.91 ppm assigned to NH_2 and NH protons and the signal at *δ* 4.48 ppm, *δ* 6.60 ppm assigned to C_4-H and C_5-H pyrimidine.

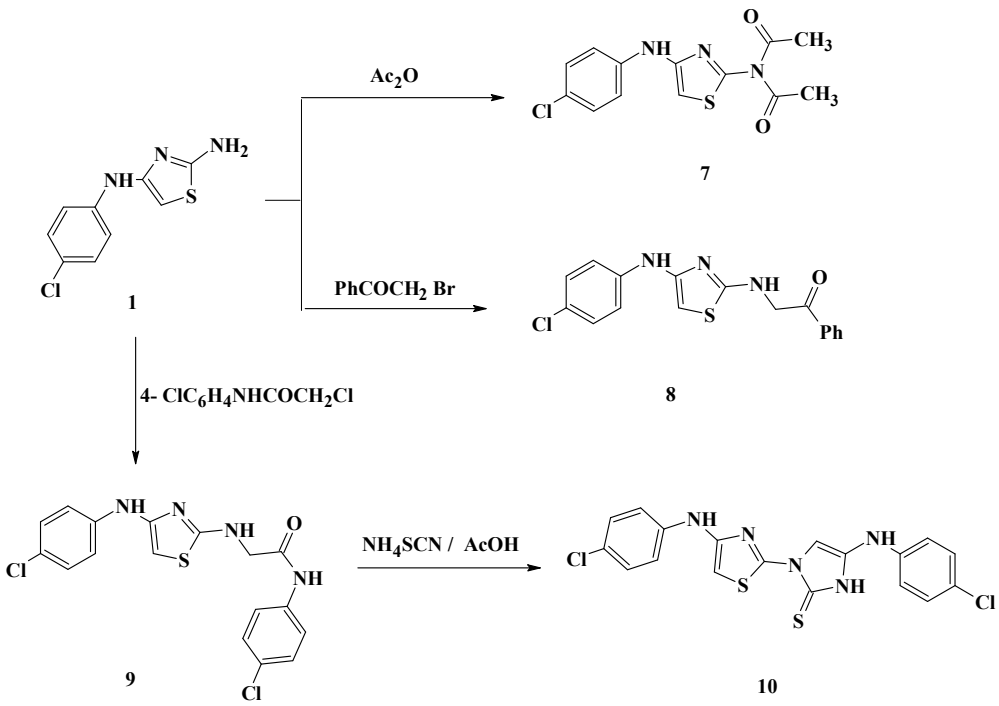


Scheme 1. Synthesis of compounds 1-6



R= 4- Cl C_6H_4NH ,R_1= 4- $OCH_3C_6H_4$

Scheme 2. Proposed mechanism of formation of compound 4



Scheme 3. Synthesis of compounds 7-10

Diacylation of thiazole derivative **1** using acetic anhydride under reflux condition [27] gave *N*-acetyl-*N*-1,3-thiazol-2-yl] acetamide derivative **7** (Scheme 3). The structure of compound 7 was established based on both elemental analysis and spectral data. The ^{1}H-NMR showed singlet signals at *δ* 2.70 ppm , *δ* 2.86 ppm for acetyl protons.^{13}C NMR spectrum showed the signal at δ 168.42 ppm , δ 170.44 ppm to (2 C=O).

Condensation of thiazole derivative **1** with phenacyl bromide and /or 2-chloro-*N*-(4-chlorophenyl)acetamide in the presence of catalytic amount of TEA in ethanol [28] afforded 2-(1,3-thiazol-2-ylamino)-1-phenyl- ethanone derivative **8** and /or 2-(1,3-thiazol-2-ylamino)-*N*-(4-chlorophenyl)acetamide **9**. The structure of the compound **8** and **9** were based on their elemental analysis and spectral data. ^{1}H NMR spectrum of **8** exhibited a singlet signal at δ 4.21 ppm due to CH_2.The mass spectrum of **8** displayed the molecular ion peak at m/z 344 corresponding to the molecular formula $C_{17}H_{14}Cl N_3OS$. Cyclocondensation of 2-(1,3-thiazol-2-yl-amino)-*N*-(4-chlorophenyl)acetamide **9** with ammonium thiocyanate in glacial acetic acid [29] afforded 1- (1,3-thiazol-2-yl) -1*H*-imidazole-2(3*H*) - thione derivative **10** (Scheme 3).The ^{1}H NMR spectrum (DMSO–d_6) of **10** showed a D_2O-exchangeable signal at *δ* 8.61 ppm, δ 10.02 ppm and *δ* 11.21 ppm assigned to the 3 NH protons. In addition ^{13}C NMR spectrum showed the signal at δ 186 to C=S.

Reaction, of N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine **1** with mixture of acetic anhydride and cyanoacetic acid [30] to yield the corresponding *N*-[1,3-thiazol-2-yl]-2-cyanoacetamide derivative **11** (Scheme 4).The structure of **11** has been assigned as a reaction product on the basis of analytical and spectral data. The IR spectrum displayed absorption bands at 3136 cm^{-1}, 3100 cm^{-1} and 2200 cm^{-1} due to 2 NH and CN groups respectively .The mass spectrum showed a molecular ion peak at *m/z* 293 corresponding to a molecular formula $C_{12} H_9 Cl N_4OS$.

The reaction of cyanoacetamide derivatives **11** with benzaldehyde [31] gave the benzalidine derivative **12** , while its reaction with salicyl-aldehyde [32] produced the coumarin derivative **13**. The plausible mechanism for the formation of compound **13** may be attributed to the initial, through the formation of the arylidine derivative **C** followed by intarmolecular cyclization to give **13**.The structure of compounds **12** and **13** were as signed on the basis of the elemental analysis and spectral data. The IR spectrum of compound **13** revealed the absence of CN absorption band and the presence of new absorption bands at

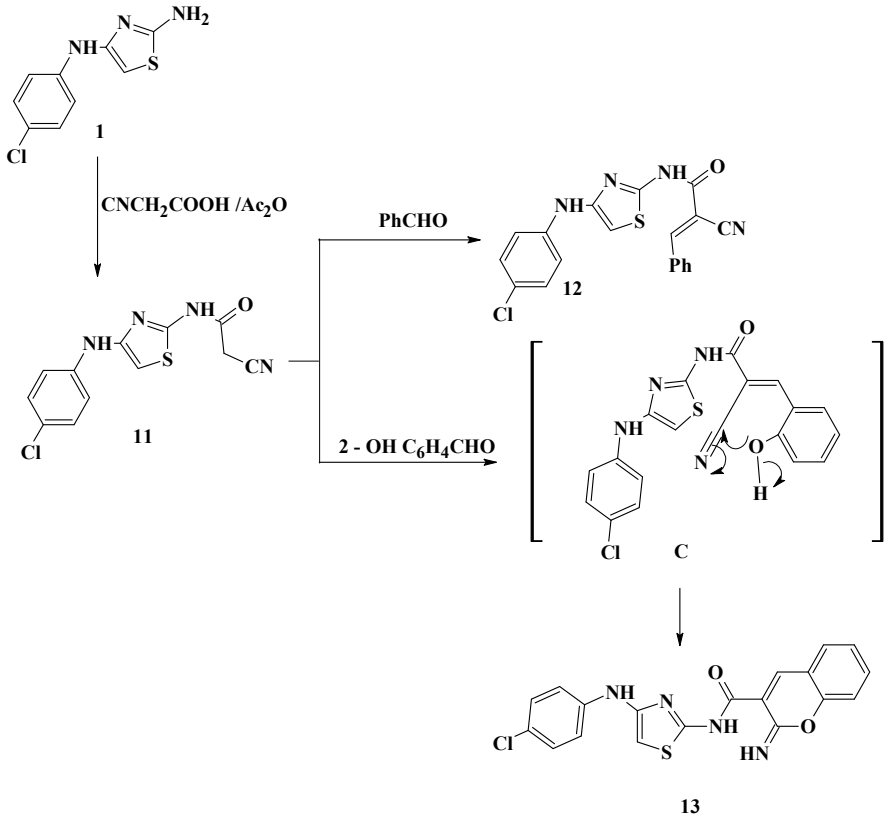
3209 cm^{-1}, 3190 cm^{-1}, 3170 cm^{-1} assignable to 3 NH groups and band at 1689 cm^{-1} due to C= O group. ^{13}C NMR data showed signals at δ162.74 ppm to C= O.

Reaction of N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine **1** with phenyl isothiocyanate in dry DMF at room temperature yielded the non-isolable intermediate **14** and then reaction with *α*-halo-carbonyl compounds [33] such as ethyl chloro-acetate and / or 2 – chloro - *N*- (4-chlorophenyl) acetamide afforded ethyl {*N*'- [1,3-thiazol- 2-yl]-*N*-phenyl-carbamimidoyl)thio} acetate **15** and 2-[(4-chlorophenyl) amino] -2 - oxoethyl *N*'-(1,3-thiazol-2-yl)-*N*-phenyl–imidothiocarbamate **16** (Scheme 5).The structures of compounds **15** and **16** were established and confirmed by their elemental analysis and spectral data. For example IR spectrum of **15** showed absorption bands at 3283 cm^{-1}, 3201cm^{-1} and 1670 cm^{-1} corresponding to 2 NH and C=O groups respectively. The ^1H-NMR spectrum of **15** showed a triplet at δ 1.02 ppm, a quartet at δ 4.06 ppm correspond to CH_2CH_3 group and singlet at δ 4.25 ppm correspond to CH_2 protons. In addition, ^{13}C NMR data showed signals at δ 19 ppm, δ 33.29 ppm, δ 172.08 ppm to CH_3 ,CH_2 and C= O respectively.

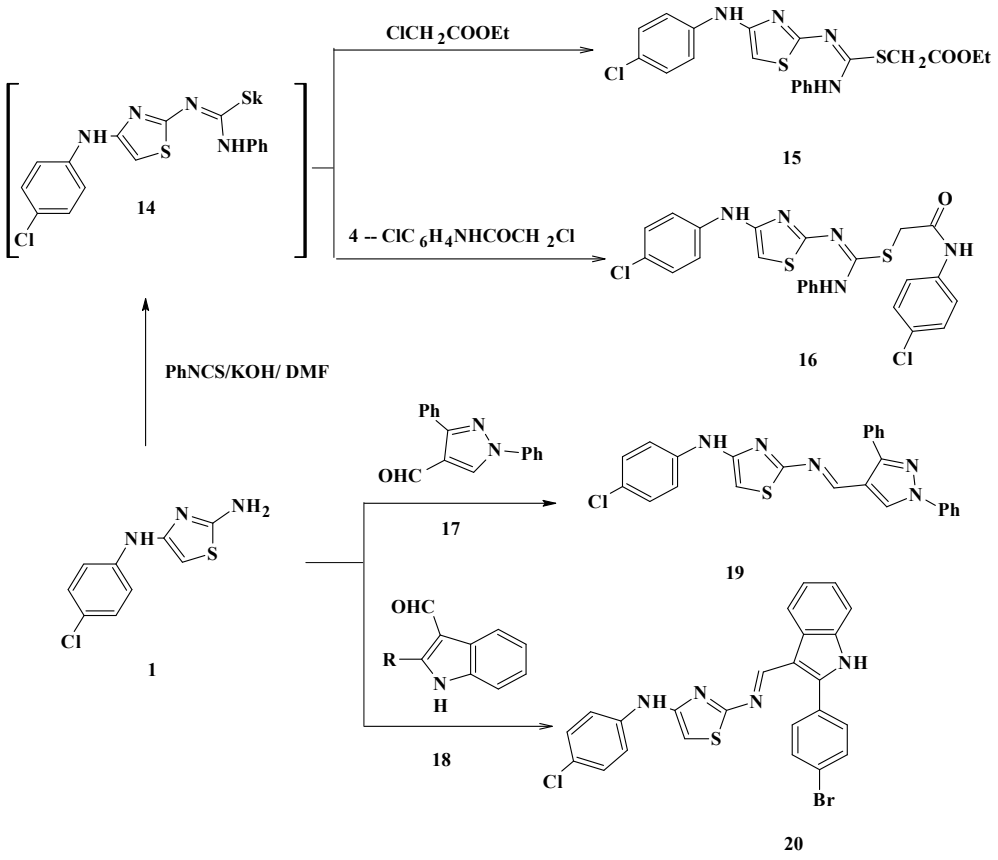
Moreover, the reaction of compounds **1** with 1,3-diphenyl–1*H*- pyrazole-4-carboxaldehyde **17** or 2-(4-bromophenyl)-1*H*-indole-3-carboxaldehyde **18** [34,35] afforded N^2 -(substituted methylene)-N^4-(4-chlorophenyl)-1,3-thiazol-2,4-diamine **19** and **20** respectively (Scheme 5).The structures of **19** and **20** were elucidated by microanalysis and spectral data. For example IR spectrum of **20** showed absorption bands at 3208 cm^{-1}, 3167cm^{-1} corresponding to 2 NH groups. The ^1H-NMR spectrum of **20** showed a single signal at δ 9.94 ppm corresponds to N=CH proton.

3.2 *In Vitro* Anti-Tumor Activity

The *in vitro* anticancer activity of the newly synthesized compounds **3, 4, 6, 7,9, 10, 11, 13**, **15, 16** and **19** are evaluated against human breast cancer cell line (MCF- 7) and cell viability was determined by the crystal violet assay. Cisplatin used as a reference drug. The results are presented in (Table 1; Figs. 1 and 2).



Scheme 4. Synthesis of compounds 11 – 13



Scheme 5. Synthesis of compounds 14-20

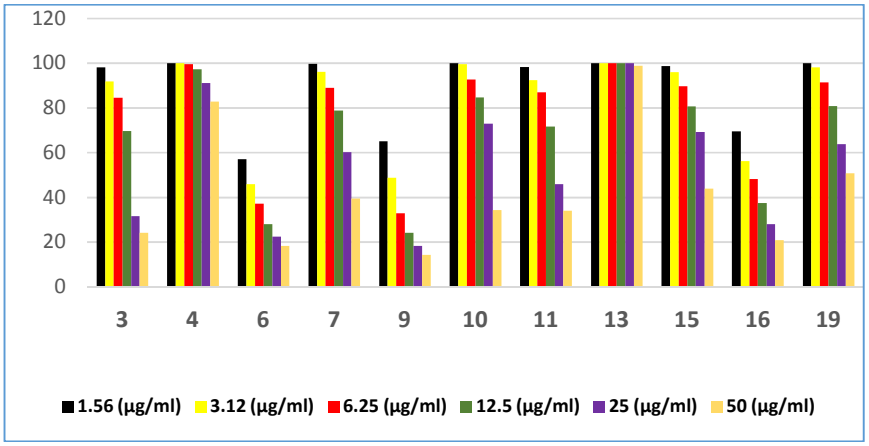


Fig. 1. Cell viability % of human breast cancer MCF- 7 with different concentrations of the tested compounds

The results indicated that compounds **6**, **9** and **16** showed the highest inhibitory effect against breast cancer cell line (MCF-7) than control drug cisplatin. Compounds **3, 7,10** and **11** showed moderated growth inhibitory effect and compounds **4, 13, 15** and **19** showed very low activity towards human breast cancer cell line (MCF- 7).

Comparing compound **6** with **9** and **16**, it is obvious that the presence of the pyrimidine ring at position **2** of thiazole ring, in compound **6**

Table 1. *In vitro* anticancer activities of synthesis compounds against human breast cancer MCF- 7 cell line

Compd No.	Compound concentration (µg/ml)						
	1.56 (µg/ml)	3.12 (µg/ml)	6.25 (µg/ml)	12.5 (µg/ml)	25 (µg/ml)	50 (µg/ml)	IC50 (µg/ml)
	Cell viability %						
3	98.12±0.19	91.75±0.12	84.52±0.34	69.78±1.44	31.63±0.33	24.17±021	19±0.43
4	100±0.12	100±0.14	99.63±0.02	97.28±0.12	91.13±0.08	82.85±014	170±3.8
6	57.09±1023	45.93±0.39	37.18±0.2	28.06±0.04	22.37±0.08	18.29±0.23	2.55±0.07
7	99.71±0.07	96.18±0.14	89.04±0.25	78.93±0.13	60.22±1.46	39.35±0.17	37.2±0.8
9	65.13±1.73	48.65±0.54	32.94±0.32	24.13±0.09	18.26±0.08	14.31±0.15	2.99±0.17
10	100	99.61±0.04	92.73±0.15	84.68±0.24	72.95±1.71	34.26±0.44	39.8±0.6
11	98.24±0.12	92.31±0.25	86.95±0.21	71.66±1.94	45.91±0.75	34.06±0.42	23±0.8
13	100	100	100	100	100	98.76±0.02	>400
15	98.72±0.08	96.04±0.21	89.72±0.44	80.63±0.39	69.18±1.24	43.84±0.98	43.9±1.3
16	69.41±0.31	56.29±0.39	48.12±0.32	37.54±0.75	28.04±0.42	20.87±0.26	5.53±0.25
19	100	98.12±0.08	91.45±0.23	80.75±0.16	63.82±0.24	50.67±1.25	52.5±1.3
Cisplatin	70.88±0.16	61.74±0.36	52.85±.98	46.71±1.37	34.62±0.89	23.79±0.41	5.71±0.21

IC_{50} value: corresponds to the concentration required required to cause toxic effects in 50% if intact

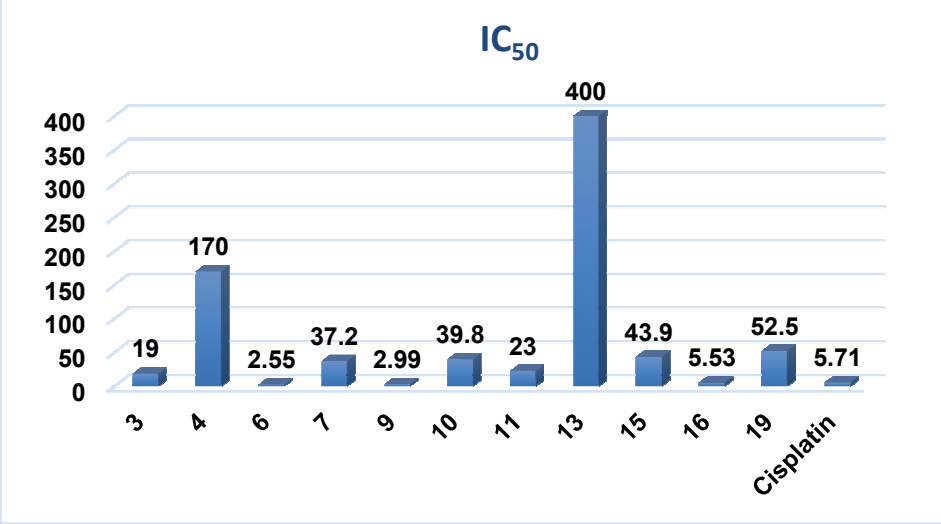


Fig. 2. Evaluation of IC_{50} of test compounds

resulted in a higher inhibitory effect than **9** which has a N- (4- chlorophenyl) acetamide group at position **2** of thiazole ring and **16** which has a 2-[(4-chlorophenyl) amino]-2-oxoethyl N-phenyl-imidothiocarbamate group at position 2 of thiazole ring. The antiproliferative activity of the test compounds against tumor cell to measure by IC_{50} μg / mL which is concentration require causing toxic effects in 50% if intact.

4. CONCLUSION

In this work, variety of heterocyclic systems have been synthesized from N^4-(4-chlorophenyl)-1,3-thiazole-2,4-diamine. The new synthesis compounds **3, 4, 6, 7,9, 10, 11, 13, 15, 16** and **19** have been evaluated for the in vitro anti-tumor activity against human breast cancer cell line (MCF-7) and cell viability was determined by the crystal violet assay ,cisplatin used as a reference drug. Compounds **6**, **9** and **16** showed best cytotoxic activity against cancer cell higher than that of cisplatin .Hence it can be suggested that **6, 9** and **16** could be used as leads in the design and development of new anticancer drugs.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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