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RESEARCH ARTICLE

Synthesis and Characterization of Some New Derivatives of Thiourea and Study of Their Biological Activity

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Abstract

Some new derivatives of Suberyl Chloride synthesized by reacting with ammonium thiocyanate then the product is reacting with some amino acids to prepare thioureio-amino acid, as well as react with two amino hetrocyclic compounds are 2-aminobenzo[d]thiozole-6-carboxylic acid and thiophen-2-amine to prepare thiourea derivatives. This reaction was checked by thin-layer chromatography (TLC) method. All new compounds were characterized by melting points, elemental analysis, FT-IR and 1H&13C-NMR. The antibacterial action of these derivatives was also determined as well as study three of these derivatives as anti-breast cancer.

Keywords: *Suberyl Chloride, thioureio-amino acid, antibacterial, thiourea derivatives, anti-breast cancer.*

Introduction

Thiourea is an organic compound that consists of carbon, nitrogen, sulfur, and hydrogen atoms obtained from ammonium thiocyanate. The main reactive group is –CONHCSNH–. All the biological activities of this class of compounds are because of thiourea functionality [1]. Thiourea, having a considerably wide range of applications .The properties of urea and thiourea differ significantly because of the difference in electronegativity between sulfur and oxygen. Thus, thiourea is a versatile reagent in organic synthesis. The main application of thiourea is in textile processing. In addition, thiourea is commonly employed as a source of sulfide, e.g. for converting alkyl halides to thiols [2]. Thioureas are also used as building blocks for pyrimidine derivatives. Thus, thioureas condense with β-dicarbonyl compounds. The amino group on the thiourea initially condenses with a carbonyl, followed by cyclization and tautomerization. Thioureamoiety has become intensely synthesized due to its ability to undergo structural modifications [3]. The existing of two units of reactive primary amine groups has made thiourea a suitable precursor for a synthesis of many new compounds [4]. Thiourea derivatives are well known to display a broad spectrum of applications in pharmaceutical industry due to their biological properties such as antiparasitic [5], anticancer [6], antioxidant [7], antibacterial [8], antifungal [9], and anti-HIV [10].

Experimental

All materials were of hìghest purìty and supplìed by Merck, Sìgma Aldrìch and Fluka-Company. Meltìng poìnts were measured on a Bauchìmeltìng point device B-545(BauchìLabortechnìk AG, Swìtzerland, and Franc. Microanalytically data were obtained with a Vario, Elementary device (Shimadzu, Japan). The IR spectra were recorded on Schimadzu Fourier Transform Infra-red spectrophotometer (Model 270), used crystal KBr. NMR spectra were recorded on 400 MHz (^{1}H) and at 100 MHz and (^{13}C) spectrometers (Tahran, Iran) with TMS as the internal standard and on δ scale in ppm. (TLC) was performed on silica gel for (TLC) and spots were visualized by Iodine vapors. The reagents used were of analytical grade while the solvents were purified before use.

General Procedure of Preparation Derivatives (1-11)

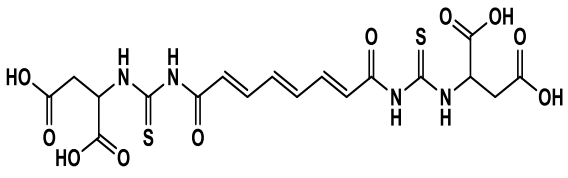
A solution of suberic chloride (0.72 g, 3.0 mmol) and NH4SCN (0.46 g, 6.0 mmol) in acetone (20 mL) was heated under reflux for 1 h. After cooling and filtration, a solution of the desired free amino acid or amino heterocyclic derivatives (6.0 mmol) in dry acetone (15 mL) was added and the mixture was heated under reflux for 6 h. After cooling, an excess of crushed ice was pouted on the mixture with vigrous stirring. The resulting result was collected, washed with acetone and recrystallized from EtOH or DMF-ether [11-15].

7-thiocyanatoheptanoyl isothiocyanate

1

Yield (72%) as yellowish white solid. ***m.p*** = 105 °C. ***Rf*** =0.66 , **FT-IR** (KBr, cm^{-1}): C-$H_{ali.}$(2951), S-C=O (1688), C-S-C (1174). **FT-IR** (KBr, cm^{-1}): N-H_{amide} (3410) N-H (3200), C-$H_{ali.}$(2987), C=O (1701), C=Oamide (1690). **^{1}H NMR:** □ = 0.82-1.84 (s, 8H, (-$CH_{2)4}$), 2.34-3.57 (s, 2H, -CO-CH_2-.). **^{13}C NMR:** □=11.55-23.96 (-CH_2-) $_6$, 167.35 (-CO-S), 90.31 (S-C-N).**Anal. Calc.** for $C_9H_{12}N_2OS_2$ (228.33): C 46.284, H 4.127, N 10.247, S 24.080

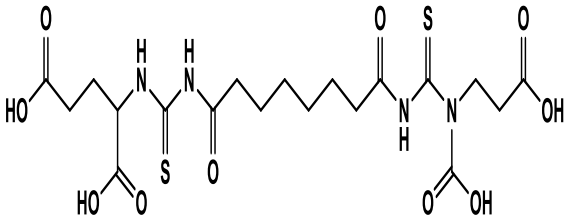
(7E, 9E, 11E)-6,13-dioxo-4,15-dithioxo-3,5,14,16-tetraazaoctadeca-7,9,11-triene-1,2,17,18-tetracarboxylic acid



2

Yield (76%) as light yellow solid. ***m.p*** = 158 °C. ***Rf*** =0.70 , **IR** : C-S (1213), $NH_{amide.}$ (3211), C-$H_{ali.}$(2951), C=$O_{carboxyl}$ (1718), CO-N (1683), O-$H_{carboxyl}$ (2682-3003). **^{1}H NMR**: □ = 0.37-1.73 (s, 8H, (-$CH_{2)4}$), 2.06-2.95 (s, 2H, -CO-CH_2-.),9.97 (s,1H,NH-CS),9.23 (s,1H,NH-CO),3.05-3.5 (-CH-CH_2-), 12.68 ,12.7 (s, 2H,2COOH) .**^{13}C NMR:** □=21.22-30.00 (-CH_{2}-)$_6$, 163.46 (-CO-N), 165 (C=S), 55.94,65.3 (CH_2-CH-NH), 182.37,177.6 (COOH).Anal. Calc. for $C_{18}H_{20}N_4O_{10}S_2$ (516.50): C 41.379, H 4.09, N 10.197, S 11.871

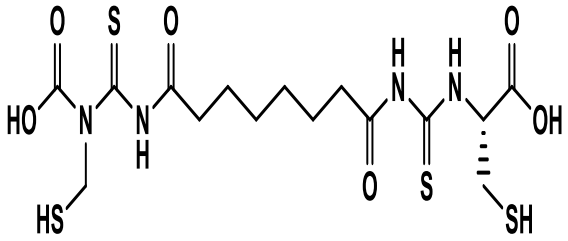
3-carboxy-6, 13-dioxo-4, 15-dithioxo-3, 5, 14, 16-tetraazanonadecane-1, 17, 19-tricarboxylic acid



3

Yield (70%) as light yellow solid. ***m.p*** = 189-166 °C. ***Rf*** =0.64 **FT-IR**: $NH_{amide.}$ (3382), C-$H_{ali.}$(2900), C=$O_{carboxyl}$ (1701), CO-N (1661), O-$H_{carboxyl}$ (2700-3170). □ = 0.82-1.84 (s, 8H, (-$CH_{2)4}$), 2.34-3.57 (s, 2H, -CO-CH_2-.). **^{1}H NMR**: □ = 0.53-1.20 (s, 8H, (-$CH_{2)4}$), 2.10-2.29(s, 2H, -CO-CH_2-.),9.98 (s,1H,NH-CS),9.30(s,1H,NH-CO), 3.23-3.6 (-CH-CH_2-), 12.23 ,12.6 (s, 2H,2COOH).**^{13}C NMR:**□=14.08-20.00 (-CH_{2}-)$_6$, 162.22 (-CO-N), 168 (C=S), 55.9-77.3(CH_2)$_2$-CH-NH, 188.14,184.51 (COOH.Anal. Calc. for $C_{19}H_{28}N_4O_{10}S_2$ (536.57): C 43.311, H 5.002, N 9.742, S 11.145.

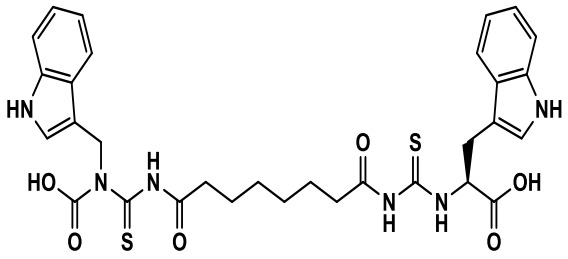
((8-(3-carboxy-3-(mercaptomethyl)thioureido)-8-oxooctanoyl)carbamothioyl) cysteine



4

Yield (72%) as a yellow color solid. ***m.p*** = 170 °C. ***Rf*** = 0.62 FT-**IR**: $NH_{amide.}$ (3211), C-$H_{ali.}$(2881), C=$O_{carboxyl}$ (1716), CO-N (1688), O-$H_{carboxyl}$ (2692-3003),SH (2350). **^{1}H NMR**: □ = 0.33-1.88 (s, 8H, (-CH_2)$_4$), 2.03-3.36 (s, 2H, -CO-CH_2-.),9.96 (s,1H,NH-CS), 9.44 (s,1H,NH-CO),3.69-3.79 (-CH-CH_2-), 12.79 (s, 1H,COOH) 11.67 (s,1H,SH). **^{13}C NMR:** □=10.39-24.60 (-CH_2-)$_6$, 160.37 (-CO-N), 169.89 (C=S), 55.94,76.3 (CH-CH_2-SH), 176.6 (COOH) .**Anal. Calc**. for $C_{15}H_{24}N_4O_6S_4$ (484.62): C 37.751, H 4.862, N 11.100, S 18.641.

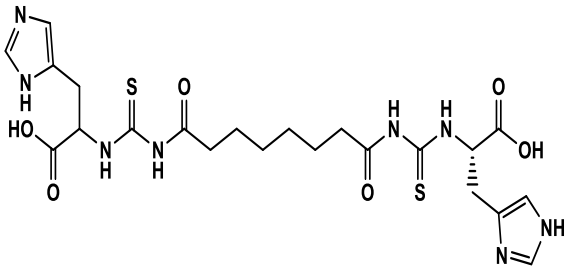
((8-(3-((1H-indol-3-yl) methyl)-3-carboxy thioureido)-8-oxooctanoyl) carbamothioyl) tryptophan



5

Yield (70%) as a yellow color solid. ***m.p*** = 188 °C. ***Rf*** = 0.72 **FT-IR** : $NH_{amide.}$ (3385), C-$H_{ali.}$(2935), C=$O_{carboxyl}$ (1703), CO-N (1645), O-$H_{carboxyl}$ (2550-3251),N—H $_{Iadol}$ (3337). **^{1}H NMR**: □ = 0.56-1.18 (s, 8H, (-CH_2)$_4$), 1.90-3.05 (s, 2H, -CO-CH_2-.),9.56 (s,1H,NH-CS),9.13 (s,1H,NH-CO),8.36 (s,1H,NH $_{Indol}$),3.5-3.9 (-CH-CH_2-),7.16-7.54 (m,8H, aromatic protone) 12.57 (s, H,COOH). **^{13}C NMR:** □=21.22-29.16 (-CH_2-)$_6$, 162.3 (-CO-N), 168.6 (C=S), 56.9, 67.2 (CH-CH_2-N-), 173.4 (COOH),105.3-129.5 (Aromatic-C). $C_{31}H_{34}N_6O_6S_2$ (650.77): C 57.216, H 5.100, N 11.923, S 9,274

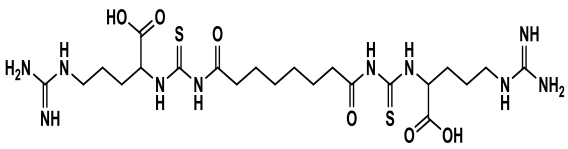
((8-(3-((S)-1-carboxy-2-(1H-imidazol-4-yl)ethyl)thioureido)-8-oxooctanoyl) carbamothioyl) histidine



6

Yield (66%) as the color is brown. ***m.p*** = 160 °C. ***Rf*** = 0.6 **FT-IR** : N-$H_{amide.}$ (3400), C-$H_{ali.}$(2978), C=$O_{carboxyl}$ (1701), CO-N (1680), O-$H_{carboxyl}$ (2492-2911), N-H $_{histidine}$ (3200). **^{1}H NMR**: □ = 0.69-1.02 (s, 8H, (-CH_2)$_4$), 1.03-2.71 (s, 2H, -CO-CH_2-.), 9.59 (s, 1H, NH-CS), 9.45 (s, 1H, NH-CO), 3.0-3.31 (-CH-CH_2-), 12.63 (s, 1H, COOH) .**^{13}C NMR:** □=12.4-23.9 (-CH_2-)$_6$, 157 (-CO-N), 167 (C=S), 64.8,79.3 (CH-CH_2-), 180.3 (COOH). $C_{22}H_{30}N_8O_6S_2$ (566.65): C 45.817, H 5.331, N 19.006, S 10,190

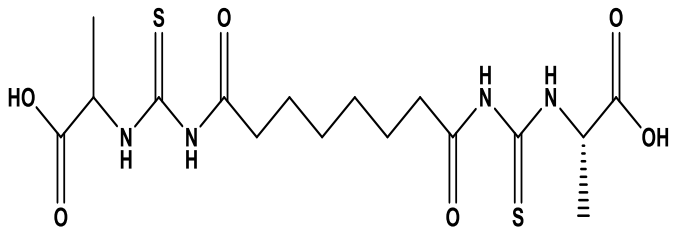
((8-(3-(1-carboxy-4-guanidinobutyl) thioureido)-8-oxooctanoyl) carbamothioyl) arginine



7

Yield (76%) as a Yellow color solid. ***m.p*** = 162 °C. ***Rf*** = 0.66 **FT-IR** : $NH_{amide.}$ (3100), C-$H_{ali.}$(2953), C=$O_{carboxyl}$ (1717), CO-N (1670), O-$H_{carboxyl}$ (2524-3043),NH_2 (3150,3209), =NH_2 (3444,3400). **^{1}H NMR**: □ = 0.81-1.80 (s, 8H, (-CH_2)$_4$), 1.88-2.34 (s, 2H, -CO-CH_2-), 9.97 (s,1H,NH-CS), 9.2 (s,1H,NH-CO), 8.0 (s,1H,NH), 8.23 (s,2H,NH_2), 2.61-3.57 (-CH-CH_2-CH_2-), 12.23 ,12.7 (s, H,COOH) **^{13}C NMR:** □=16.7-29.9 (-CH_2-)$_6$, 144.6 (-C=NH), 160.3 (C=S), 181.6 (COOH), 60.6-68.4 N-(CH_2)$_3$-CH-. $C_{22}H_{40}N_{10}O_6S_2$ (604.75): C 43.097, H 6.165, N 12.553, S 10.190.

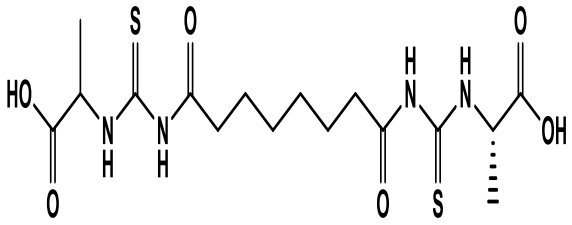
((8-(3-(1-carboxyethyl) thioureido)-8-oxooctanoyl) carbamothioyl) alanine



8

Yield (70%) as a yellow color solid. ***m.p*** = 148 °C. ***Rf*** = 0.56 **FT-IR** $NH_{amide.}$ (3403), C-$H_{ali.}$(2978), C=$O_{carboxyl}$ (1701), CO-N (1690), O-$H_{carboxyl}$ (2524-3043), N-H (3200).**^{1}H NMR**: □ = 0.90-1.18 (s, 8H, (-CH_2)$_4$), 1.90-3.0 (s, 2H, -CO-CH_2-), 9.56 (s, 1H, NH-CS), 9.13 (s, 1H, NH-CO), 3.01-3.99 (-CH-CH_3), 12.37 (s, H, COOH) **13CNMR:** □=14.49-19.98 (-CH_2-)$_6$, 157.5 (-CO-N), 163.9 (C=S), 189.25(COOH), 69.3 (–N-CH-CH_3). $C_{16}H_{26}N_4O_6S_2$ (434.53): C 43.645, H 5.423, N 12.421, S 14.106

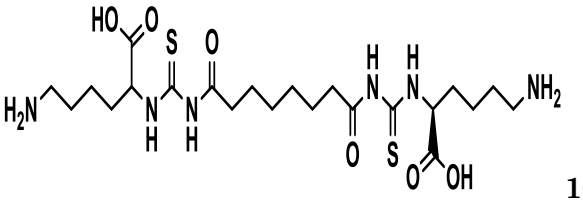
((8-(3-(5-amino-1-carboxypentyl) thioureido)-8-oxooctanoyl) carbamothioyl) .



9

Yield (72%) as a yellow color solid. ***m.p*** = 174 °C. ***Rf*** =0.7 **FT-IR** $NH_{amide.}$ (3403), C-$H_{ali.}$(2987), C=$O_{carboxyl}$ (1701), CO-N (1689), O-$H_{carboxyl}$ (2524-3083), NH_2 (3180,3240) **^{1}H NMR**: □ = 0.12-1.10 (s, 8H, (-CH_2)$_4$), 1.30-2.44 (s, 2H, -CO-CH_2-), 9.88 (s,1H,NH-CS), 9.67 (s,1H,NH-CO), 8.44 (s,2H,NH_2), 3.31-3.79 (-CH)$_4$-CH-), 12.98 (s, H,COOH) .**^{13}C NMR:** □= 21.51-29.66 (-CH_2-)$_6$, 149.6 (-CO-N), 153.4 (C=S), 181.9 (COOH), 56.3-79.3 N-(CH_2)$_4$-N-. $C_{22}H_{40}N_6O_6S_2$ (548.72): C 47.492, H 6.843, N 15.100, S 11.219

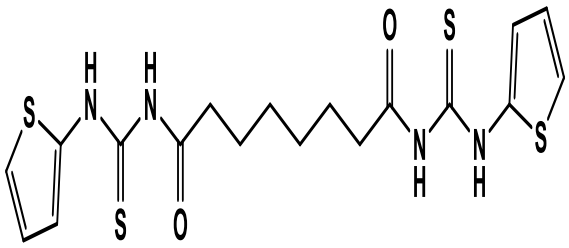
((8-(3-((S)-5-amino-1-carboxypentyl) thioureido)-8-oxooctanoyl) carbamothioyl)l ysine



10

Yield (70%) as a dark yellow color solid. ***m.p*** = 186°C. ***Rf*** =0.66 **FT-IR** $NH_{amide.}$ (3261), C-$H_{ali.}$(2965), C=$O_{carboxyl}$ (1720), CO-N (1685), O-$H_{carboxyl}$ (2632-3116), C=N $_{Indo\ cycle}$ (1627).,C-S $_{Indo}$ (684). **^{1}H NMR**: □ = 0.82-1.68 (m, 8H, (-CH_2)$_4$), 1.73-2.34 (m, 2H, -CO-CH_2-), 9.97 (s,1H,NH-CS), 9.23 (s,1H,NH-CO), 8.44 (s,2H,NH_2), 3.31-3.79 (-CH)$_4$-CH-), 12.93 (s, H,COOH) **^{13}C NMR:** □=18.2-22.0 (-CH_2-)$_6$, 149.4 (-CO-N), 163.4 (C=S), 171.5 (COOH), (115-129) phenyl carbone .$C_{26}H_{36}N_6O_6S_4$ (656.85): C 47.673, H 3.434, N 12.281, S 19.217

N_1,N_8-bis(thiophen-2-ylcarbamothioyl) octane diamide



11

Yield (70%) as a dark yellow color solid. ***m.p*** = 186°C. ***Rf*** =0.66 **FT-IR** $NH_{amide.}$ (3172), C-$H_{ali.}$(2924), C=$O_{carboxyl}$ (1720), CO-N (1695), NH-C=O (3223), C-$S_{thiophene}$ (613). **1H NMR**: □ = 0.68-0.82 (s, 8H, (-CH_2)$_4$), 1.20-2.80 (s, 2H, -CO-CH_2-), 9.67 (s,1H,NH-CS), 9.35 (s,1H,NH-CO), 7.60-7.88 (m,6H,aromatic proton), 12.70 (s, H,COOH) **^{13}C NMR:** □=15.8-23.0 (-CH_2-)$_6$, 153.1 (-CO-N), 160.2 (C=S), 171.9 (COOH). $C_{18}H_{22}N_4O_2S_4$ (454.64): C 46.871, H 4.128, N 12.081, S 27. 629.

Antimicrobial Evolution

The newly synthesized compounds were selected for the ìrantìmìcrobìal activities against bacteria. The microorganisms used were *Staphylococcus aureus* (Gram positive), *Escherìchìacolì*, (Gram negative) by using the agar diffusion method to select the most potent compounds [16]. 5 mg of each compound was dissolved in dìmethyl sulfoxìde (DMSO, 1 mL) then complete up to 10 mL with distal water to give a concentration of 500 µg/mL. The bacteria were maintained on Muller hentone agar media, the dishes incubated at 37 °C for 24 hr. The efficiency of the tested compounds was compared to the DMSO, zone of inhibition measured by ruler [17].

2-Azetidinone Derivative as Anticancer

Materials and Methods

Methyl thiazolyl Tetrazolium (MTT) Solution

Methyl thiazolyl tetrazolium (0.2g) (Bio-world, USA) was dissolved in 100 ml of PBS in order to prepare a 2 mg/ml concentration of the dye. The solution was filtered through 0.2 µm syringe filter to remove any blue formazan product, and then stored in sterile, dark, screw-capped bottles at 4°C. The solution was used within no longer than 2 weeks of preparation.

Cytotoxicity Assay [18, 19]

MTT cell viability assay was conducted on 96-well plates (Santacruz Biotechnology, USA), MCF7 Human Breast cancer cells were seeded at 10000 cells/well, 200 µl of cells in growth medium were added to each well of a sterile 96-well micro titration plate. The plates were sealed with a self-adhesive film, lid placed on and incubated at 37°C. After 24hr or confluent monolayer is achieved, when the cells were in exponential growth, the medium was removed and serial dilutions of the extract were added to the wells at 2-fold serial dilutions (dilution the stock1/10ml). Triplicates were used for each. Control cells treated with Serum Free Media only. Afterwards, the plates were re-incubated at 37°C for 72 hrs. Cell viability was measured after 72 hrs of exposure by removing the medium, adding 28 µl of 2 mg/ml solution of MTT (Bio-World, USA) and incubating for 1.5h at 37°C. After removing the MTT solution, the crystals remaining in the wells was solubilised by the addition of 130 µl of DMSO (Dimethyl Sulphoxide) (Santacruz Biotechnology, USA) followed by 37°C incubation for 15 min with shaking. The absorbency was determined on a microplate reader (Biochrom, UK) at 584 nm (test wavelength); the assay was performed in 5 replicates.

Endpoint parameters that are calculated for each individual cell line included:

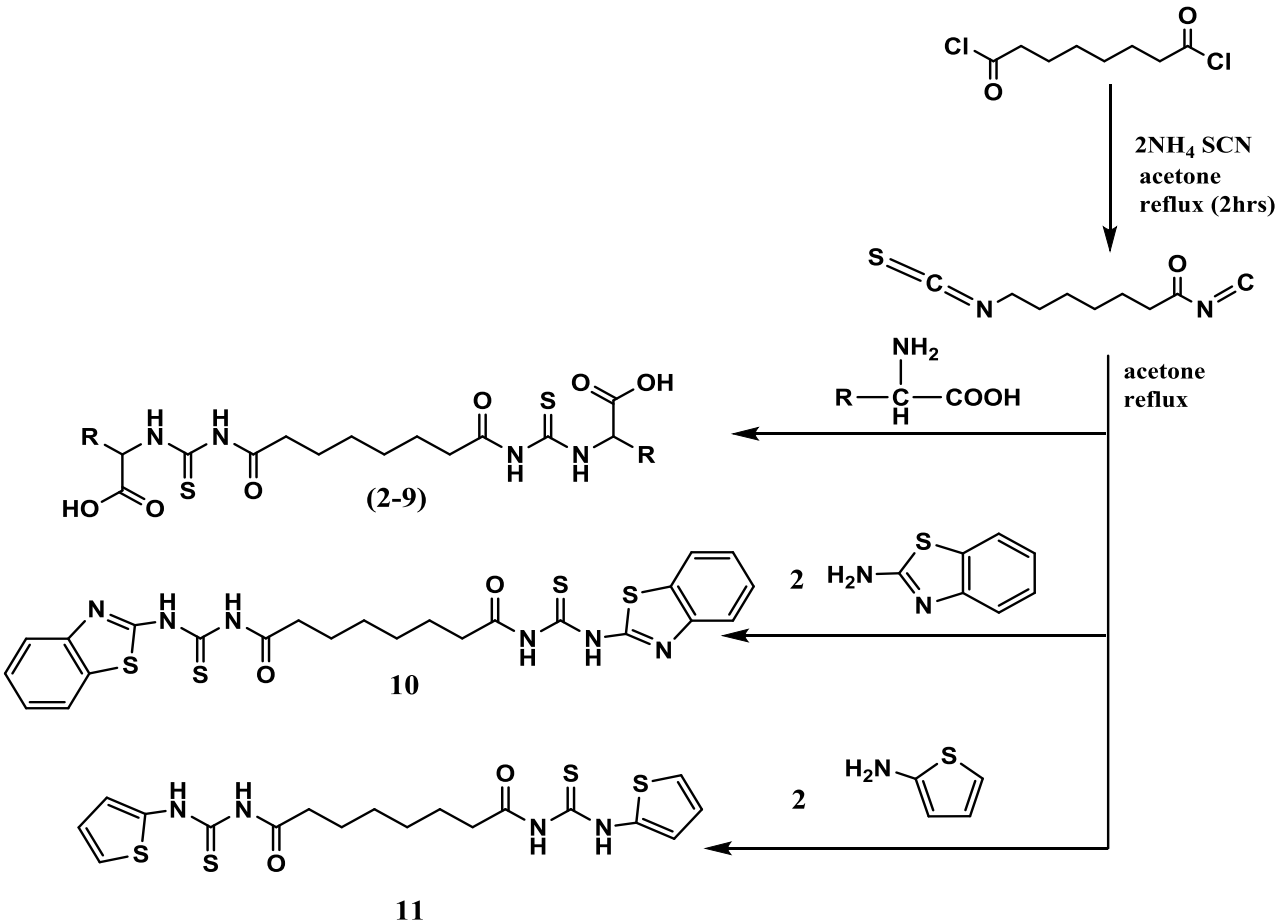
- Percentage of cell growth or percentage of cell proliferation (PR) = mean of treatment / mean of control.
- The lowest concentration that kills 50% of cells (LC50).

Cell Culture for Normal Embrynoic Cells

The rat embryo fibroblast (REF) cell line were cultured in a RPMI-1640 medium with 10% fetal bovine serum (FBS), 100 units/mL penicillin, and 100 µg/mL streptomycin and then incubated at 37 °C. All the cell lines were supplied by the Iraqi Biotechnology Company, Cell culture lab, Baghdad, Iraq. These cells are regularly assessed for standard growth characteristics, and they are regularly authenticated. The anticancer activity of the synthesized derivative *in vitro* was determined against a human breast MCF-7 cancer cell line using MTT cell viability assay.

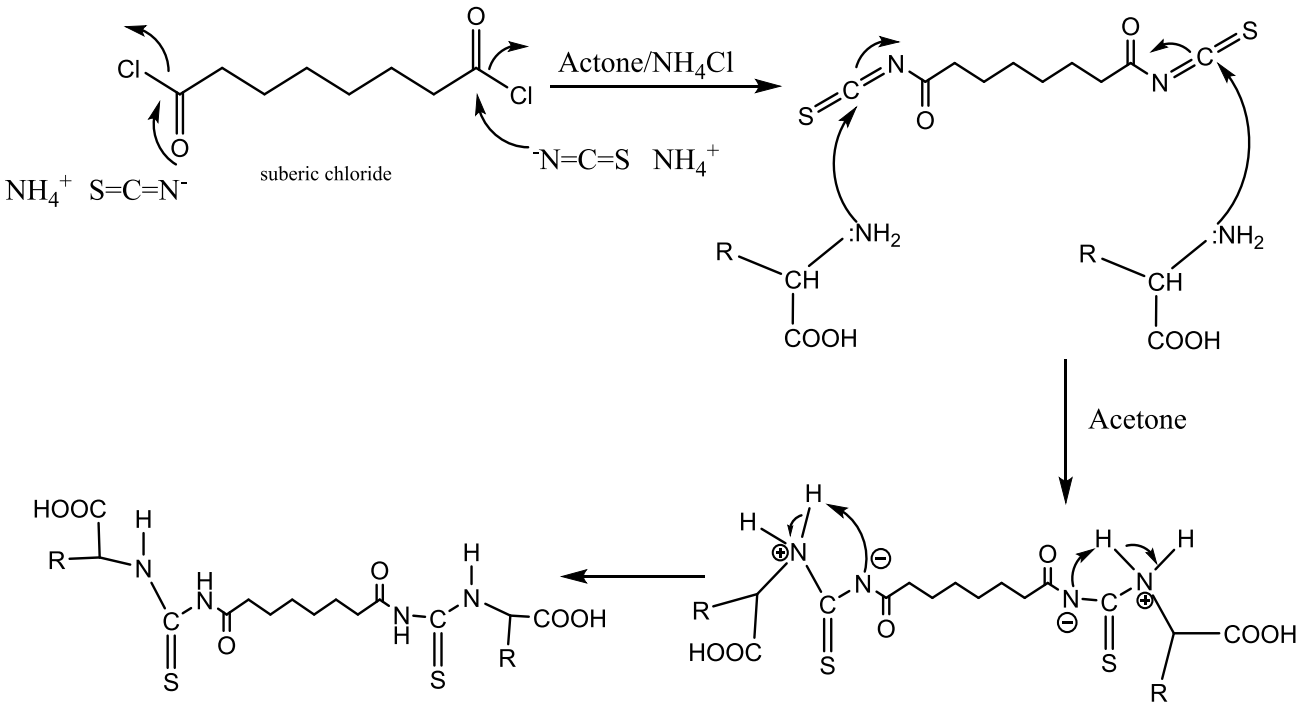
Result and Discussion

In our present work, suberyl chloride has been selected as a spacer building block for the synthesis of new derivatives of suberyl chloride treatment of 1 with NH4SCN in acetone, following react with some of amino acids to prepared the new derivatives of the suberic-thioureido-amino acid derivatives and thiourea derivatives in 66-76% yield. The synthetic reactions are summarized in Scheme 1.



no.	R	time (h)	no.	R	time (h)
2	-CH_2-COOH	6			
3	--CH_2-CH_2-COOH	6	7		7
4	-CH_2-SH	6			
5		8	8	-CH_3	6
6		8	9	--$(CH_2)_4$-NH_2	7

Scheme 1: Synthesis of suberyl chloride derivatives when react with amino acids and amino heterocyclic



Scheme 2: Mechanism of suberyl chloride derivatives when react with amino acids

The structures of 2-11 were determined by their 1H, and 13C NMR The suberic protons showed almost a similar pattern (-CH2-)4 protons appeared as multiplets in the region δ 0.33-1.88 ppm, while(-CH2-CO-) proton signals are oriented as multiplets in the region δ 1.03-3.57 ppm. (-NH-CO-) were appeared as singlet in the region δ 1.03-3.57 ppm of the amino acid moieties are oriented by depending on the functional group. The other protons of the amino acids were fully analyzed [20]. The ^{13}C NMR spectra of 2-11 contained almost similar (-CH2-CO-) resonance signals of the suberic C- and thioureido carbon atoms. The chemical shifts between δ 153.4 and 169.8 ppm were assigned to C=S carbon atom of the thioureido moiety , while the resonance in the range of δ 149.4-167.3 ppm were assigned to the carbonyl group of the CSNHCO residues[21].

Biological Activity

Control of microbial population is necessary to prevent show of disease, infection, decomposition, spoilage and contamination and caused by them. The newly synthesized compounds were screened for the antimicrobial activity in vìtro against bacteria (*Staphylococcus aureus* and *Escherichia coli*) .The antimicrobial activity results discovered– that most of the tested compounds have moderate to strong activity. The most effective compounds are tested against *aureus* in comparison with *E coli*; in other hand 10 are the most activity than other derivatives. These compounds were compared with the reference compounds (DMSO) we found that they have an antimicrobial activity higher or almost equal to them [22].

Compounds	E-Coli	Aureus
1		+
2	-	+
3	-	+
4	-	+
5	-	+
6	-	+
7	-	+
8	-	+
9	-	+
10	+	++
11	-	+

(++) Inhibition with diameter (10-12) mm
(+) Inhibition with diameter (9-6) mm
(-)There is no inhibition

In general the result of the synthesized compound showed better anticancer potential (IC50 = 400μM) after 72 hr [23].

In derivative 9 showed relatively less inhibitory activity than previous compounds against breast cancer cells with a half-lethal dose IC50 = 141.2 µg / ml and the gradient inhibiting rates of 400-6.2 µg / ml were shown in Figure 1.

In addition to the relative maintenance of the vitality of the living cells, it is derivative 10, which was a lethal half dose IC50 = 96.4 µg / ml at the concentration of the derivative 400 µg / ml and 36.3 ± 1.7% as in Figure 2.

While derivative 11 showed a weak inhibitory effect against breast cancer cells with a half-lethal dose IC50 = 135.8 µg / ml as Figure 3.

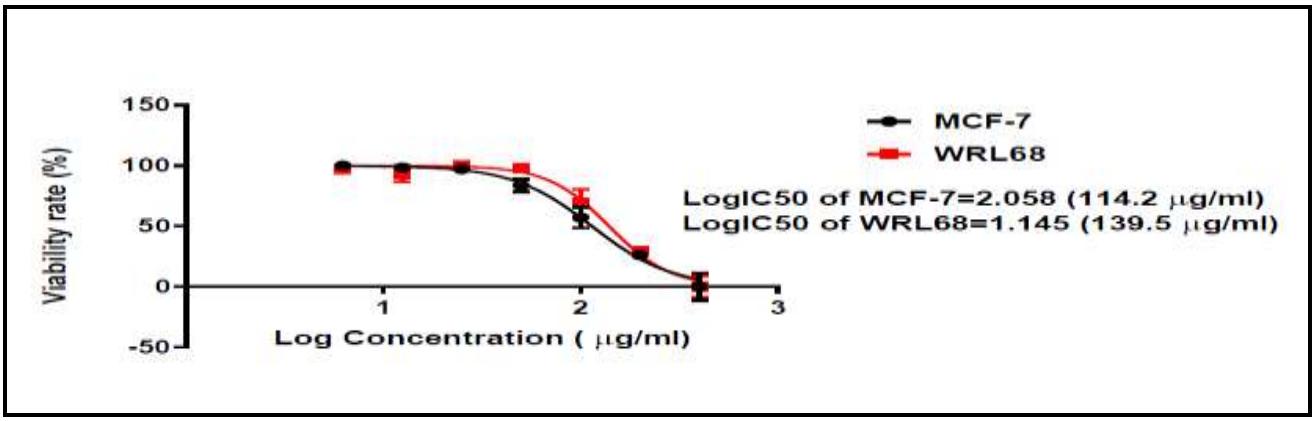


Figure 2: represents the inhibitory effect of the compound 9

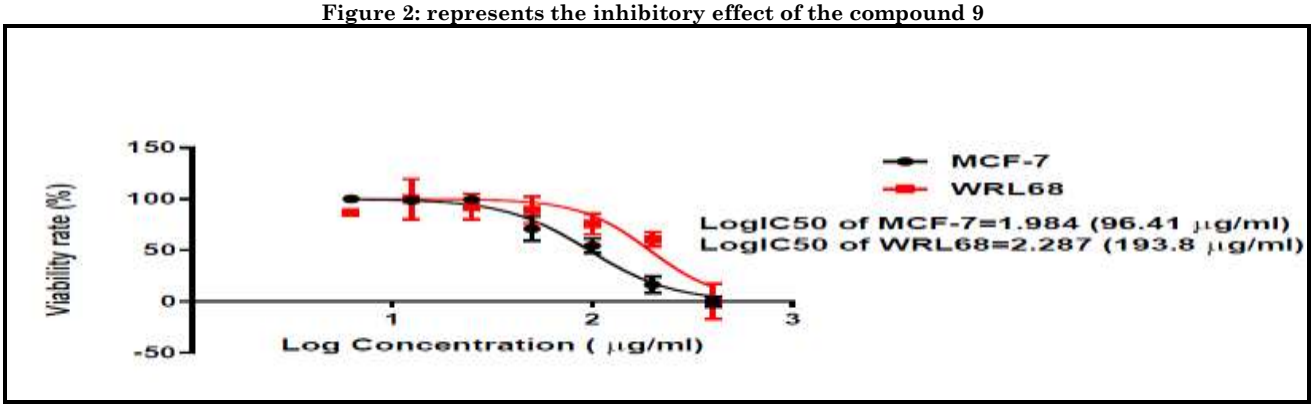


Figure 3: represents the inhibitory effect of the compound 10

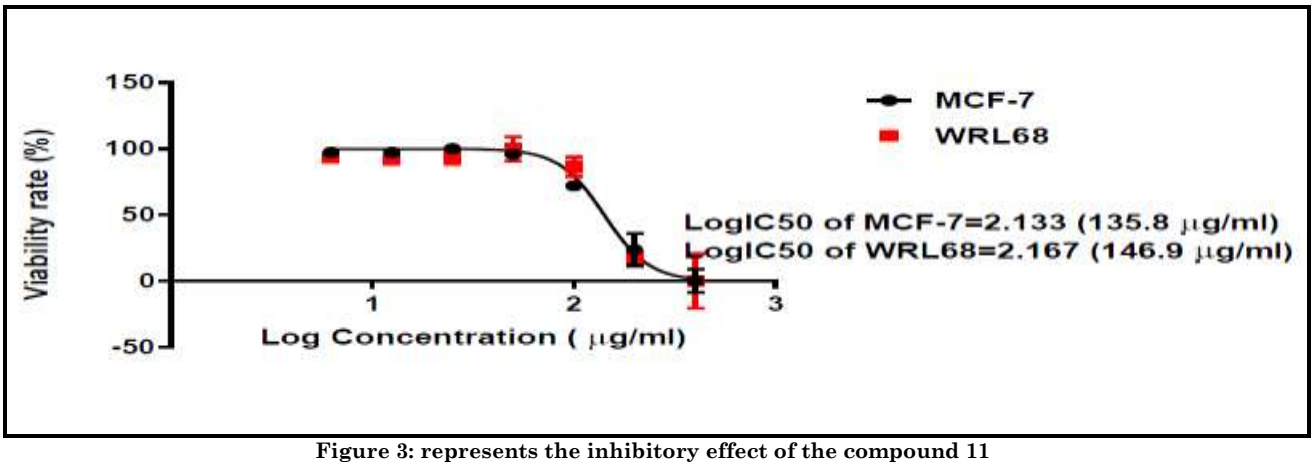


Figure 3: represents the inhibitory effect of the compound 11

Conclusion

In this study we are reported synthesis of many derivatives from suberic acid react with some deferent amino acids to prepare thiourea derivatives. These derivatives were found active against positive and not active to negative bacterial and not response to DMSO and three of derivatives [9, 10, 11] was study as anti-cancer and found the derivative 10 is good inhibitor to anti-cancer cells. These derivatives confirmed from spectral data analysis; FT-IR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis.

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