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Synthesis and Anti Proliferative Activity of Thiosemicarbazone and 4-Thiazolidinones

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Research Article

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Abstract

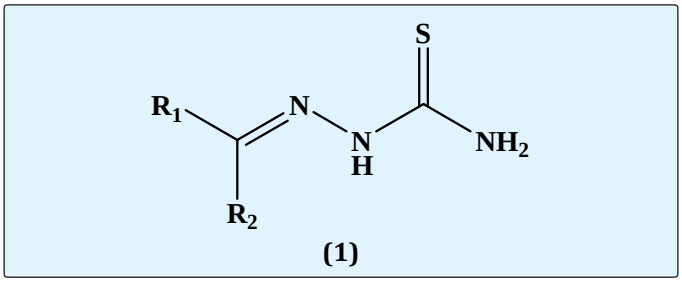
Thiosemicarbazone and 4-Thiazolidinones are heterocyclic compounds with a broad spectrum of biological activities such as anti-inflammatory, anti-viral, anti-bacterial, anti-fungal and anticancer. A series of ten derivatives of thiosemicarbazone and 4-thiazolidinones derivatives was synthesised and evaluated for their antiproliferative activity against human breast cancer cells (MCF-7). The structure of compounds was established by IR and ^{1}HNMR spectral studies. The synthesized compounds possessed good to moderate anticancer activity using Adriamycin as a standard. Out of ten synthesized compounds eight have GI_{50} value of <10 µg/ml demonstrating their potential activity. TGI for compound **6d** was found to be comparable to Adriamycin (<10 µg/ml).

Keywords: Thiosemicarbazone; 4-Thiazolidinones; Human Breast Cancer Cells

Introduction

Cancer is the second leading cause of death globally and is a multi-step disease. Deaths from cancer worldwide are projected to continue to rise to over 13.1 million in 2030 [1]. Cancer is a group of diseases and there is no specific treatment for some kinds of tumours. Emergence of resistance to anticancer drugs possesses a major clinical challenge in successful treatment of cancer since some tumour cells develop a particular phenotype, called multi drug resistance [MDR] [2]. Genotoxicity and cytotoxicity of anti-cancer drugs to the normal tissues is major problems in cancer therapy and produces the risk of inducing secondary malignancy as well as leads to many side effects [3]. Heterocyclic compounds have crucial role in our biological system and constitute a considerable quantum of the modern research that is being currently pursued throughout the world [4].

Thiosemicarbazone is formed from aldehyde/ketone when reacts with a thiosemicarbazide through a condensation reaction and it is a derivative of imine. Chemically, thiosemicarbazones have the following general structure while $R^1$and R^2 may be aromatic or heterocyclic systems [5].



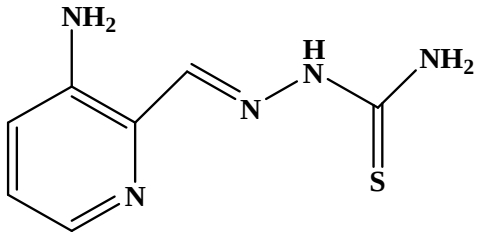
(1)

Thiosemicarbazones were found to inhibit Topoisomerase IIa (Figure 1) and Ribonucleotide

reductase (catalyses the synthesis of deoxyribonucleotide required for DNA synthesis) [6,7].

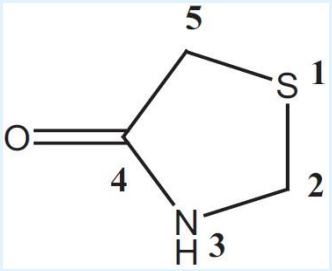
Thiosemicarbazones could stabilize cleavable complexes formed by Topo II and DNA, leading to apoptosis. The stabilization occurs as a result of alkylation of thiol residues on the topo IIa-DNA complex [6].

The 3-aminopyridine-2-carboxaldehyde thiosemicarbazone commonly known as Triapine **(2)** is the most promising thiosemicarbazone molecule undergoing clinical phase II studies for Cervical Cancer. It has been reported to inhibit ribonuclease diphosphate reductase, responsible for replication of tumor cells [8].



(2)

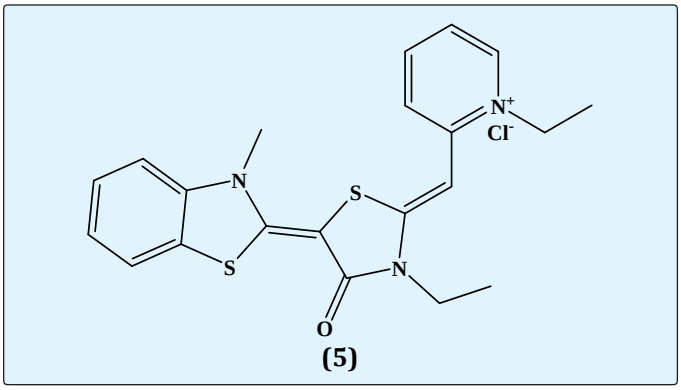
Thiazolidinones are a saturated form of thiazole, called thiazolidine, with a carbonyl group [9]. 1, 3-Thiazolidin-4-ones **(4)** are heterocycles that have an atom of sulphur at position 1, a nitrogen at position 3 and a carbonyl group at position 4 [10].



(4)

Thiazolidinones are represented by microtubule binding drugs that inhibit the function of the mitotic spindle, in order to halt the cell cycle in mitosis, and to induce apoptosis in tumor cells [11]. Antitumor mechanism of 4-thiazolidinones can be associated with their affinity to JNK-stimulating phosphatase-1 (JSP-1), tumor nacrosis factor TNF α, anti-aptotic biocomplex Bcl-X_L-BH3, integrin $\alpha_V\beta_3$ receptor, non-membrane protein tyrosine phosphatase (SHP-2), PPARγ-dependent/independent mechanisms etc [12-15].

The **MKT-077 (5),** 1-ethyl-2-[[3-ethyl-5-(methylbenzothiazolin-2-ylidene)-4-oxothiazolidin-2-ylidene] methyl] pyridinium chloride) I (formerly known as FJ-776) known for antiproliferative activity against cancer cell lines through its ability to inhibit members of the heat shock protein 70 (Hsp70) family of molecular chaperones. However, MKT-077 is rapidly metabolized, which limits its use as either a chemical probe or potential therapeutic [3].



(5)

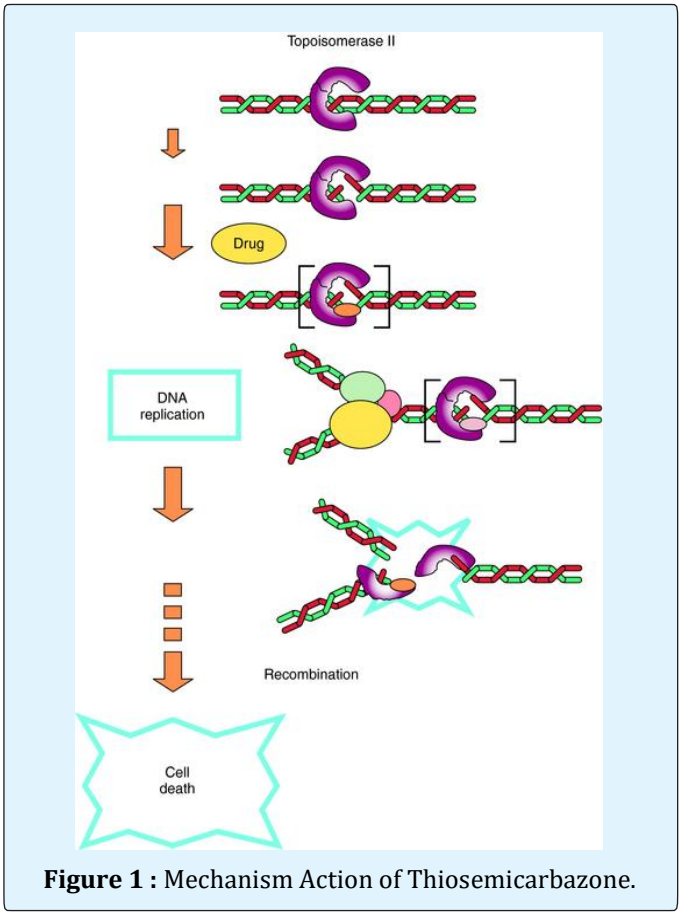


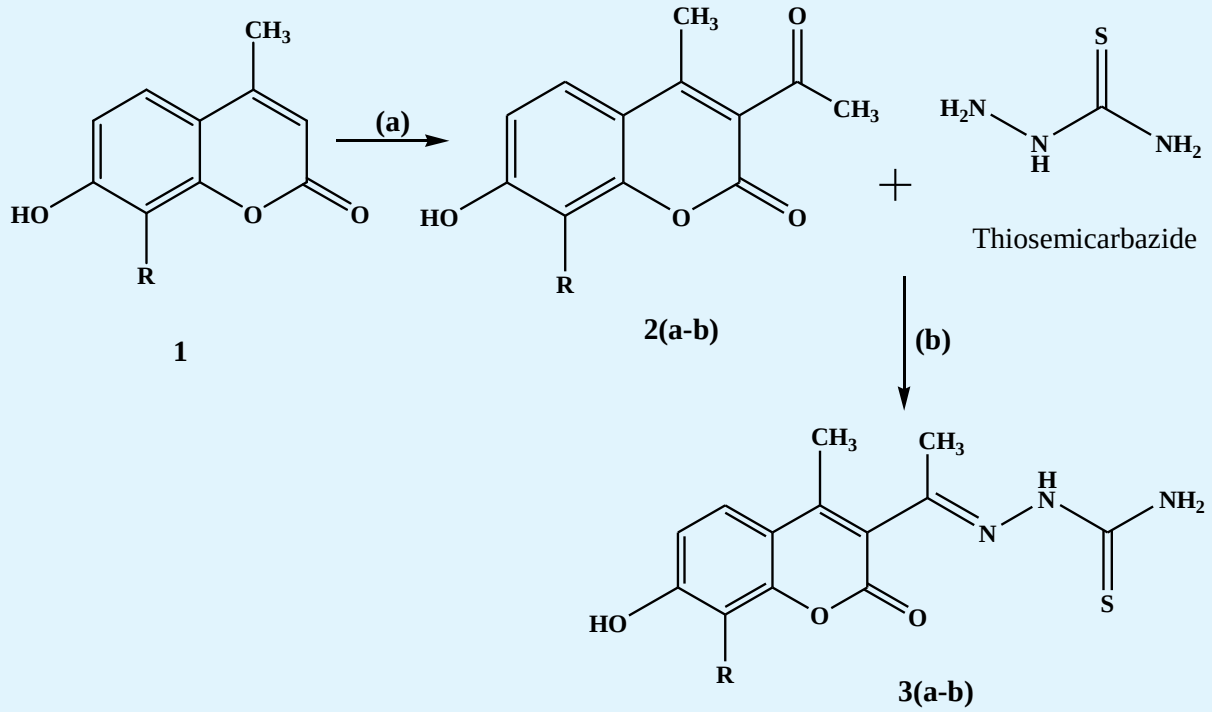
Figure 1 : Mechanism Action of Thiosemicarbazone.

Experimental Section

Materials and Methods

The synthesis was carried out using chemicals of LR grade and obtained from Spectrochem, Loba Chem. All the solvents used for the reaction were of LR grade and purified before use in different reactions. The identification and characterization of the compound were carried out by determining by following melting point on VEEGO and were uncorrected. TLC development was conducted on 0.25 mm silica gel plates (Merck silica gel 60 F_{254} on aluminium). All the IR spectra of the synthesized compounds were recorded on Bruker Alpha-E FTIR-ATR. ^{1}HNMR spectra were recorded on Bruker Advance II (400MHz) spectrometer using DMSO d_6 as solvent at SAIF, Panjab University, and Chandigarh. TMS (Tetramethylsilane) was taken as standard and chemical shift data were reported in parts per million (*ppm*) where s, d, t and m are designated as singlet, doublet, triplet and multiplet respectively.

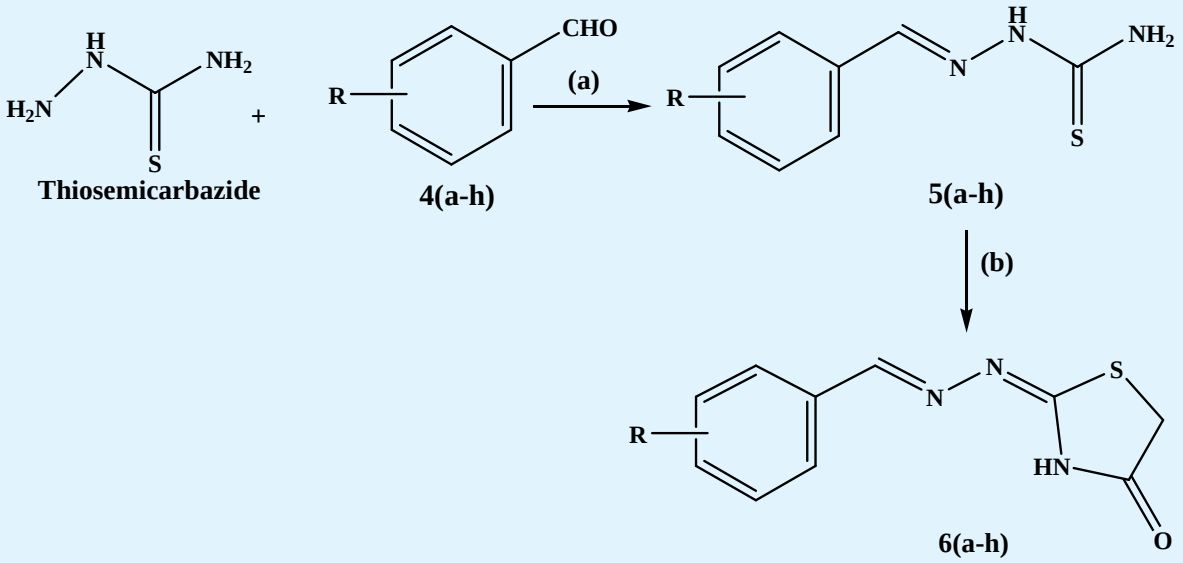
The derivatives are synthesized by proposed reaction scheme (Figures 2 and 3).



C.No.	R
3a	H
3b	NO_2

Reagents and Conditions: (a) Phosphorus oxychloride, Acetic acid, reflux, 30 minutes. (b) Acetic acid, Ethanol, stirring, 2 hours, rt.

Figure 2 : Proposed Reaction Scheme I.



C.No.	R
6a	H
6b	4-Br
6c	4-Cl
6d	4-F
6e	4-CH_3
6f	4-OCH_3
6g	4-CN
6h	4-NO_2

Reagents and Conditions: (a) Acetic acid, Ethanol, stirring, 2 hours, rt. (b) Ethyl-2- Chloroacetate ($ClCH_2COOEt$), Sodium acetate, Ethanol, reflux, 16-24 hours.

Figure 3 : Proposed Reaction Scheme II.

General Procedure for the synthesis of 2a-2b

To a solution of 6g of 7-hydroxy-4-methyl-8-substituted-*2H*-chromen-2-one **(1)** in acetic acid (32 mL), phosphorous oxychloride (11.2 mL) was added. The mixture was heated at reflux for 30 minutes. After cooling, the precipitate was collected and recrystallized from ethanol, to give 3-acetyl-7-hydroxy-4-methyl-8-substituted-*2H*-chromen-2-one **2(a-b).**

General Procedure for Synthesis of 3a-3b

Thiosemicarbazide (0.01 mol) and 3-5 drops of acetic acid were added to a solution of 3-Acetyl-7-hydroxy-4-methyl-8-substituted-2*H*-chromen-2-one **2(a-b)** (0.01 mol) in ethanol. The reaction was processed under magnetic stirring for 2 hours at room temperature. The precipitate was filtered off, washed with ethanol then dried. Additional amount of desired compound could be recovered from the filtrate after cooling. After drying, the product **3(a-b)** was recrystallized from ethanol [14].

1-(1-(7-Hydroxy-4-methyl-2-oxo-2*H*-chromen-3-yl) ethylidene) thiosemicarbazide (3a): Colour : Off-White; **Nature** : Crystalline**; Yield:** 37.61%; **Melting Point** : 161.8 °C; $\mathbf{R_f}$: 0.56 (Chloroform: Methanol 9.6: 0.4); **IR (cm^{-1}):** 3408.15 cm^{-1} (O-H stretch), 3352.88 cm^{-1} (N-H stretch), 3166.75 cm^{-1} (Ar-C-H stretch), 2924.11 cm^{-1} (Alkane C-H stretch), 1705.77 cm^{-1} (C=O stretch), 1608.47 cm^{-1} (C=N stretch), 1522.90 cm^{-1} (Ar-C=C stretch), 1312.64 cm^{-1} (C-N stretch), 1202.13 cm^{-1} (C-O), 994.76 cm^{-1} (C=S stretch); **^{1}HNMR (DMSO-d_6, 400MHz, *ppm*) :** δ 2.16 (s, 3H, H_3C-C=C); δ 2.44 (s, 1H, C-OH; δ 2.50 (s, 3H, H_3C-C=N); δ 6.70-6.79 (d, 1H, Ph); δ 7.81-7.83 (d, 2H, Ph); δ 8.63 (**s,** 2H, NH_2); δ 8.93(s, 1H, N-H).

1-(1-(7-Hydroxy-4-methyl-8-nitro-2-oxo-2*H*-chromen-3-yl) ethylidene) thiosemicarbazide (3b): Colour:

Yellow; **Nature** : Crystalline**; Yield:** 40.65%; **Melting Point** : 146.6 °C; **R_f** : 0.48 (Chloroform: Methanol 9.6: 0.4); **IR (cm^{-1}):** 3509.55 cm^{-1} (N-H stretch), 3415.13 cm^{-1} (O-H stretch), 3150.78cm^{-1} (Ar-C-H stretch), 2915.66 cm^{-1} (Alkane C-H stretch), 1734.56 cm^{-1} (C=O stretch), 1623.95 cm^{-1} (C=N stretch), 1528.97 cm^{-1} (Ar-C=C stretch), 1483.78 cm^{-1} and 1369.95 cm^{-1} (N=O stretch), 1290.42 cm^{-1} (C-O stretch), 1161.77 cm^{-1} (C-N), 909.51 cm^{-1} (C=S stretch); **^{1}HNMR (DMSO-d_6, 400MHz, *ppm*):** δ 1.85 (s, 3H, H_3C-C=C); δ 2.33 (s, 3H, H_3C-C=N**);** δ 2.50 (s, 1H, C-OH); δ 7.41-7.43 (d, 1H, Ph); δ 7.86-7.98 (d, 2H, Ph); δ 8.14 (s, 2H**,** NH_2**);** δ 8.24 (s, 1H**,** NH**.**

General Procedure for the synthesis of 6(a-h): A solution of 0.01 mol of thiosemicarbazones **6(a-h)**, 0.011 mol of ethyl-2-chloroacetate, and 0.04 mol of sodium acetate (anhydrous) in ethanol was stirred and refluxed to the completion of the reaction (16-24 hours). After, this the solution was cooled to 0ºC, the precipitate was collected with filter under vacuum and washed with hot methanol and water [14].

2-(2-Benzylidenehydrazono) thiazolidin-4-one (6a): Colour : White; **Nature** : Amorphous**; Yield:** 72.4%; **Melting Point** : 109.8 °C; **R_f** : 0.52 (Chloroform: Methanol 9.6: 0.4); **IR (cm^{-1}):** 3397.08 cm^{-1} (N-H stretch), 2961.82 cm^{-1} (Ar-C-H stretch), 2848.16 cm^{-1} (alkane-C-H stretch), 1704.33 cm^{-1} (C=O stretch), 1634.12 cm^{-1} (C=N stretch), 1552.45cm^{-1} (Ar-C=C stretch), 1381.11 cm^{-1} (C-N stretch); **^{1}HNMR (DMSO-d_6, 400MHz, *ppm*):** δ 2.50 (s, 2H, H_2C-S); δ 4.05 (s, 1H, HC=N); δ 7.37-7.40 (t, 3H, Ph); δ 7.64-7-66 (d, $2H_{ortho}$, Ph); δ 8.19 (s, 1H, HN-C).

2-(2-(4-Bromobenzylidene)hydrazono)thiazolidin-4-one (6b): Colour : Off**-** White; **Nature** : Amorphous**; Yield:** 34.7%; **Melting Point** : 194.4 °C; **R_f** : 0.46 (Chloroform: Methanol 9.6: 0.4); **IR (cm^{-1}):** 3377.59 cm^{-1} (N-H stretch), 3028.37 cm^{-1} (Ar-C-H stretch), 2919.71 cm^{-1} (Alkane-C-H stretch), 1708.72 cm^{-1} (C=O stretch), 1636.87 cm^{-1} (C=N stretch), 1582.62 cm^{-1} (Ar-C=C stretch), 1322.05cm^{-1} (C-N stretch), 729.18cm^{-1} (C-Br stretch).

2-(2-(4-Chlorobenzylidene)hydrazono)thiazolidin-4-one (6c): Colour : Off**-** White; **Nature** : Amorphous**; Yield:** 64.2%; **Melting Point** : 191.2 °C; **R_f** : 0.54 (Chloroform: Methanol 9.6: 0.4); **IR (cm^{-1}):** 3399.45 cm^{-1} (N-H stretch), 3045.43 cm^{-1} (Ar-C-H stretch), 2918.98 cm^{-1} (Alkane-C-H stretch), 1709.67 cm^{-1} (C=O stretch), 1634.33 cm^{-1}(C=N stretch), 1485.09 cm^{-1} (Ar-C=C stretch), 1326.71cm^{-1} (C-N stretch), 823.12cm^{-1} (C-Cl stretch);**^{1}HNMR (DMSO-d_6, 400MHz, *ppm*):** δ 1.21 (s, 2H, H_2C-S); δ 4.19 (s, 1H, HC=N); δ 7.72-7.74 (d, $2H_{meta}$, Ph); δ 7.49-7.50 (d, $2H_{ortho}$, Ph); δ 8.30 (s, 1H, HN-C).

2-(2-(4-Fluorobenzylidene)hydrazono) thiazolidin-4-one (6d): Colour : Off**-** White; **Nature** : Amorphous**; Yield:** 39.4%; **Melting Point** : 212.4°C; **R_f** : 0.52 (Chloroform: Methanol 9.6: 0.4); **IR (cm^{-1}):** 3401.61 cm^{-1} (N-H stretch), 3165.78 cm^{-1} (Ar-C-H stretch), 2922.74 cm^{-1} (Alkane-C-H stretch), 1708.36 cm^{-1} (C=O stretch), 1639.62 cm^{-1} (C=N stretch), 1598.40 cm^{-1} (Ar-C=C stretch), 1329.21cm^{-1} (C-N stretch), 1015.19 cm^{-1} (C-F stretch); **^{1}HNMR (DMSO-d_6, 400MHz, *ppm*):** δ 3.45 (s, 2H, H_2C-S); δ 3.87 (s, 1H, HC=N); δ 7.23-7.26 (d, $2H_{meta}$, Ph); δ 7.71-7.75(d, $2H_{ortho}$, Ph); δ 8.21(s, 1H, HN-C).

2-(2-(4-Methylbenzylidene)hydrazono)thiazolidin-4-one (6e):Colour: White; **Nature** : Amorphous**; Yield:** 39.4%; **Melting Point** : 230.1°C; **R_f**: 0.48 (Chloroform: Methanol 9.6: 0.4); **IR (cm^{-1}):** 3401.68cm^{-1} (N-H stretch), 3030.11 cm^{-1} (Ar-C-H stretch), 2919.77 cm^{-1} (Alkane-C-H stretch), 1710.46 cm^{-1} (C=O stretch), 1640.75 cm^{-1} (C=N stretch), 1441.81 cm^{-1} (Ar-C=C stretch), 1326.60 cm^{-1} (C-N stretch); **^{1}HNMR (DMSO-d_6, 400MHz, *ppm*):** δ 2.36 (s, 2H, H_3C-C), δ 3.85 (s, 2H, H_2C-S); δ 5.16 (s, 1H, HC=N); δ 7.26-7.28 (d, $2H_{meta}$, Ph); δ 7.63-7.64 (d, $2H_{ortho}$, Ph); δ 8.35 (s, 1H, HN-C).

2-(2-(4-Methoxybenzylidene)hydrazono)thiazolidin-4-one (6f): **Colour :** Cream; **Nature** : Crystalline**; Yield:** 50.4%; **Melting Point** : 65.7°C; **R_f** : 0.51 (Chloroform: Methanol 9.6: 0.4); **IR (cm^{-1}):** 3368.54 cm^{-1} (N-H stretch), 3128.21 cm^{-1} (Ar-C-H stretch), 2851.38 cm^{-1} (alkane-C-H stretch), 1694.17 cm^{-1} (C=O stretch), 1631.86cm^{-1} (C=N stretch), 1551.47cm^{-1} (Ar-C=C), 1246.34cm^{-1} (C-N stretch), 1014.03cm^{-1} (C-O stretch); **^{1}HNMR (DMSO-d_6, 400MHz, *ppm*):** δ 1.65 (s, 2H, H_2C-S); δ 1.99 (s, 3H, H_3C-O-); δ 4.89 (s, 1H, HC=N); δ 7.01-7.04 (d, $2H_{ortho}$, Ph); δ 7.57-7.59 (d, $2H_{meta}$, Ph); δ 8.11 (s, 1H, HN-C).

2-(2-(4-Cyanobenzylidene)hydrazono)thiazolidin-4-one (6g): Colour : Dark Green; **Nature** : Amorphous**; Yield:** 42.0%; **Melting Point** : 245.5°C; **R_f** : 0.54 (Chloroform: Methanol 9.6: 0.4); **IR (cm^{-1}):** 3418.10 cm^{-1} (N-H stretch), 3095.65 cm^{-1} (Ar-C-H stretch), 2917.84 cm^{-1} (Alkane-C-H stretch), 2228.59 cm^{-1} (C≡N stretch), 1708.72 cm^{-1} (C=O stretch), 1676.18cm^{-1} (C=N stretch), 1563.04 cm^{-1} (Ar-C=C stretch), 1243.09cm^{-1} (C-N stretch).

2-(2-(4-Nitrobenzylidene)hydrazono)thiazolidin-4-one (6h): Colour: Brown; **Nature**: Amorphous**; Yield:** 46.33%; **Melting Point** : 113.5°C; **R_f** : 0.6 (Chloroform: Methanol 9.6: 0.4); **IR (cm^{-1}):** 3378.57 cm^{-1} (N-H stretch),

3069.73 cm^{-1} (Ar-C-H stretch), 2917.84 cm^{-1} (Alkane-C-H stretch), 1708.80 cm^{-1} (C=O stretch), 1684.37 cm^{-1} (C=N stretch), 1629.54 cm^{-1} (Ar-C=C stretch), 1558.98 cm^{-1} and 1335.04cm^{-1} (N=O), 1016.08cm^{-1} (C-N stretch); **^{1}HNMR (DMSO-d_6, 400MHz, *ppm*):** δ1.76 (s, 2H, H_2C-S); δ 4.16 (s, 1H, HC=N); δ 7.87-7.88 (d, $2H_{ortho}$, Ph); δ 8.21-8.26 (d, $2H_{meta}$, Ph); δ 8.47 (s, 1H, HN-C).

In Vitro Anti Proliferative Screening

The anti-proliferative screening of all the synthesized compounds was conducted against breast cancer cells line (MCF-7) to determine the growth inhibitory effects of the compounds. Vehicle used for testing was Dimethylsulfoxide (DMSO). *In vitro* testing was done using SRB assay protocol; each derivative was tested at 4 dose levels (10 µg/ml, 20 µg/ml, 40 µg/ml, 80 µg/ml) [16-18].

Results and Discussion

The 2-(2-benzylidenehydrazono) thiazolidin-4-one was synthesized in good yield by reacting 1-(benzylidene)thiosemicarbazide and ethyl-2-chloroacetate in the presence of sodium acetate and ethanol. All the reactions were monitored by thin layer chromatography using suitable solvent system under UV light and analysed. After the completion of the reaction the products were purified by recrystallization with suitable solvents. All the derivatives were characterized by various physical properties like state, R_f value, melting point and spectral techniques like IR and HNMR.

The total 10 derivatives of thiosemicarbazone and 4-thiazolidinones were synthesized. The yield of the synthesized derivatives was found to be in the range of 34.7-72.4%. The colour of derivatives varied from White to Brown. The R_f value was observed in the range of 0.46-0.60 using solvent system Chloroform: Methanol (9.6: 0.4). The melting point of all compound ranged between 65.7-230.1°C and are uncorrected.

The IR spectra of thiosemicarbazones **3(a-b)** displayed stretching of C=N at 1623.95-1608.47 cm^{-1} and C=S at 994.76-909.51 cm^{-1}. HNMR spectra of thiosemicarbazones **3(a-b)** had singlet of three protons in region δ 2.33-2.50 *ppm* indicated the presence of H_3C-C=N, singlet at δ 8.14-8.63 *ppm* showed two proton of NH_2 group, singlet at δ 8.24-8.93 showed one proton of NH.

For the 4-thiazolidiones compounds **6(a-h)**, IR spectra showed bands C=O stretch at 1710.46-1694.17 $cm^{-1}$and C=N stretch at 1684.37-1631.86 cm^{-1}.
^{1}HNMR spectra had singlet of two protons in region of δ 1.21-3.85 *ppm* indicated the presence of S-CH_2-, singlet at δ 3.87-4.16 *ppm* showed one proton of HC=N group, singlet at δ 8.11-8.35 *ppm* showed one proton of C-NH.

Anti Proliferative Screening

All the synthesized compounds were screened against MCF-7 cell line to determine their growth inhibitory effect. *In vitro* testing was done using SRB assay protocol, each derivative was tested at 4 dose levels (10 µg/ml, 20 µg/ml, 40 µg/ml, 80 µg/ml). Adriamycin was employed as a positive control. The order for the % control growth inhibition of MCF-7 cell line at 40 µg/ml was found to be 11c> 8b>11f >11d > 11g>8a >11b >11e>11h>11a and have been presented in Table 1-5

% Control Growth				
	Drug Concentrations (µg/ml)			
C. No.	10	20	40	80
3a	-14.2	-23.7	-33.8	-18.4
3b	-24.7	-26.7	-33.4	-29.9
6a	17.7	20.8	25.5	19.8
6b	-7.2	-11.1	-15.7	-10.0
6c	-25.7	-33.2	-44.5	-26.9
6d	-32.8	-36.1	-42.2	-30.1
6e	-15.2	-13.6	-18.4	-13.3
6f	-29.3	-28.8	-32.1	-30.9
6g	-10.4	-19.7	-28.3	-6.4
6h	11.4	10.9	9.1	9.6
ADR	-35.2	-53.6	-61.4	-47.3

Table 1: *In vitro* percentage control growth of MCF-7 cell line at different concentrations of compounds (Experiment 1).

% Control Growth				
	Drug Concentrations (µg/ml)			
C. No.	10	20	40	80
3a	-10.8	-12.1	-15.7	-8.6
3b	-23.8	-28.4	-38.5	-19.8
6a	13.8	15.0	16.5	24.7
6b	-8.9	-14.1	-19.8	-15.9
6c	-26.8	-32.4	-42.3	-25.5
6d	-17.7	-18.3	-20.1	-17.7
6e	-18.1	-15.1	-20.4	-15.5
6f	-31.7	-28.6	-36.2	-29.0
6g	-11.5	-20.7	-27.4	-6.0
6h	11.2	10.3	9.4	9.2
ADR	-39.1	-58.1	-65.4	-54.5

Table 2: In vitro percentage control growth of MCF-7 cell line at different concentrations of compounds (Experiment 2).

% Control Growth				
	Drug Concentrations (µg/ml)			
C. No.	10	20	40	80
3a	-18.1	-25.1	-32.0	17.2
3b	-23.8	-30.6	-36.3	-25.2
6a	13.9	19.5	28.8	32.3
6b	-17.3	-27.6	-35.0	-18.6
6c	-29.8	-39.7	-26.7	-14.3
6d	-26.2	-28.6	-37.8	-30.0
6e	-19.7	-25.8	-14.1	-17.7
6f	-32.0	-30.0	-38.4	-32.2
6g	-12.2	-21.6	-29.7	-7.2
6h	12.7	10.5	8.4	7.7
ADR	-29.7	-42.8	-56.1	-46.7

Table 3: *In vitro* percentage control growth of MCF-7 cell line at different concentrations of compounds (Experiment 3).

% Control Growth				
	Drug Concentrations (µg/ml)			
C. No.	10	20	40	80
3a	-14.4	-20.3	-27.2	-3.3
3b	-24.1	-28.6	-36.1	-25.0
6a	15.1	18.4	23.6	25.6
6b	-11.1	-17.6	-23.5	-14.8
6c	-27.5	-35.1	-37.9	-22.3
6d	-25.5	-27.7	-33.4	-25.9
6e	-17.7	-18.2	-17.6	-15.5
6f	-31.0	-29.1	-35.5	-30.7
6g	-11.3	-20.7	-28.5	-6.5
6h	11.8	10.6	9.0	8.9
ADR	-34.7	-51.5	-61.0	-49.5

Table 4: Average values of percentage control growth of MCF-7 cell line at different drugs concentrations.

	Drug concentrations (µg/ml) calculated from graph#	
C.No.	TGI	GI_{50}*
3a	-	<10
3b	-	<10
6a	-	>80
6b	-	<10
6c	-	<10
6d	<10	<10
6e	-	<10
6f	64.3	<10
6g	-	<10
6h	-	>80
ADR	<10	<10

Table 5: Synthesized compounds concentrations (µg/ml) as TGI, LC_{50} and GI_{50} calculated for MCF-7 cell line.
#calculated from graph; GI_{50} = Concentration of drug causing 50% inhibition of cell growth; TGI = Concentration of drug causing total inhibition of cell growth; ADR = Adriamycin, Positive control compound.

Conclusion

In the present study, ten derivatives was synthesized and evaluated against human breast cancer (MCF -7). The % control growth inhibition data clearly indicated that all the synthesized compounds possessed good to moderate anticancer activity. Out of the ten synthesized derivatives, the compound **6c** at concentration 40 µg/ml possess best activity. However, in the thiosemicarbazone derivatives the compound (**3b)** was found to be the second most active compound. The aliphatic thiosemicarbazone possessed comparable activity to the cyclic thiazolidinone derivatives. The 8-substitutedthiosemicarbazone **(3b)** was found to be more potent than the its unsubstituted variant **(3a).**

The 4-thiazolidinone possessing substituents having positive field effect like $-OCH_3$ **(6f)** and –Cl **(6c)** had better activity than the substituents only possessing the electron withdrawing effect. However, the substituted thiazolidinones either with electron withdrawing (6c, 6b, 6d, 6g) or electron donating substituents **(6e)** were observed to have better activity than the unsubstituted compound (**6a)**.

The parameters like LC_{50}, GI_{50} and TGI_{50} were calculated using the graph (Figure 4 and 5) obtained by plotting drug concentration and % control inhibition. The LC_{50} which is the concentration of drug acting as lethal for 50% of cells could not be observed for all the compounds. The values of TGI observed for two compounds were <10 µg/ml and 64.3 µg/ml respectively. TGI for compound **6d** was comparable to Adriamycin (<10 µg/ml).

For 50% growth inhibition of cells, the parameter calculated is GI_{50}. For getting the idea of the activity of compounds the GI_{50} value of ≤ 10^{-6} molar (1 µmolar) or ≤ 10µg/ml has been considered to demonstrate activity in case of pure compounds. From the table 1-5 and figures 4and 5 it has been clearly implied that all the compounds except **6a** and **6h** have GI_{50} value of <10 µg/ml demonstrating their potential activity.

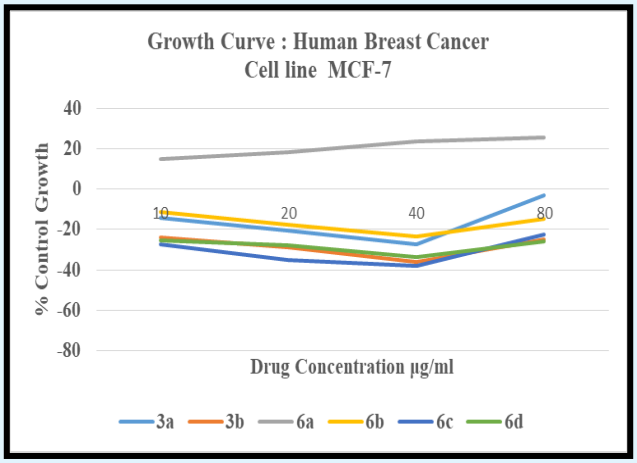


Figure 4: A graph of % control growth versus drug conc. of compounds.

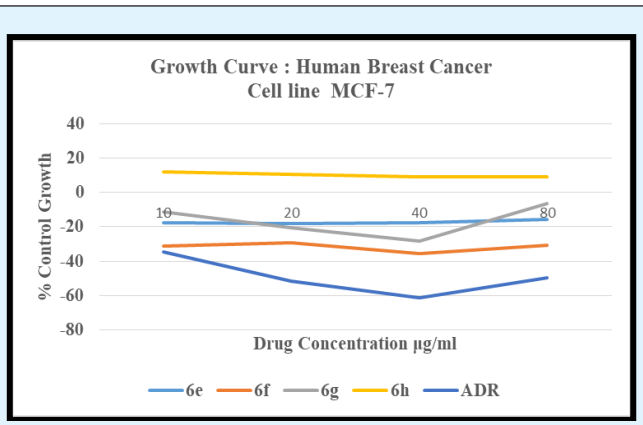


Figure 5: A graph of % control growth versus drug conc. of compounds.

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