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Der Pharma Chemica, 2014, 6(6):203-210  
(<http://derpharmachemica.com/archive.html>)



ISSN 0975-413X  
CODEN (USA): PCHHAX

## Synthesis and evaluation of new pyrazoline and thiazolidinone derivatives as anticancer activity

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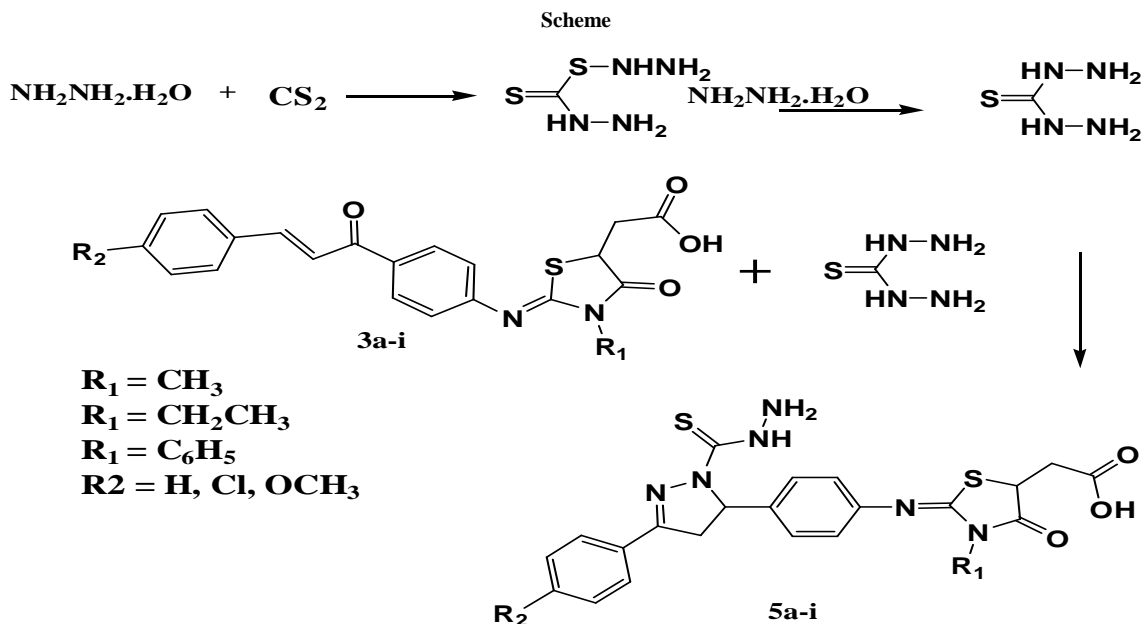
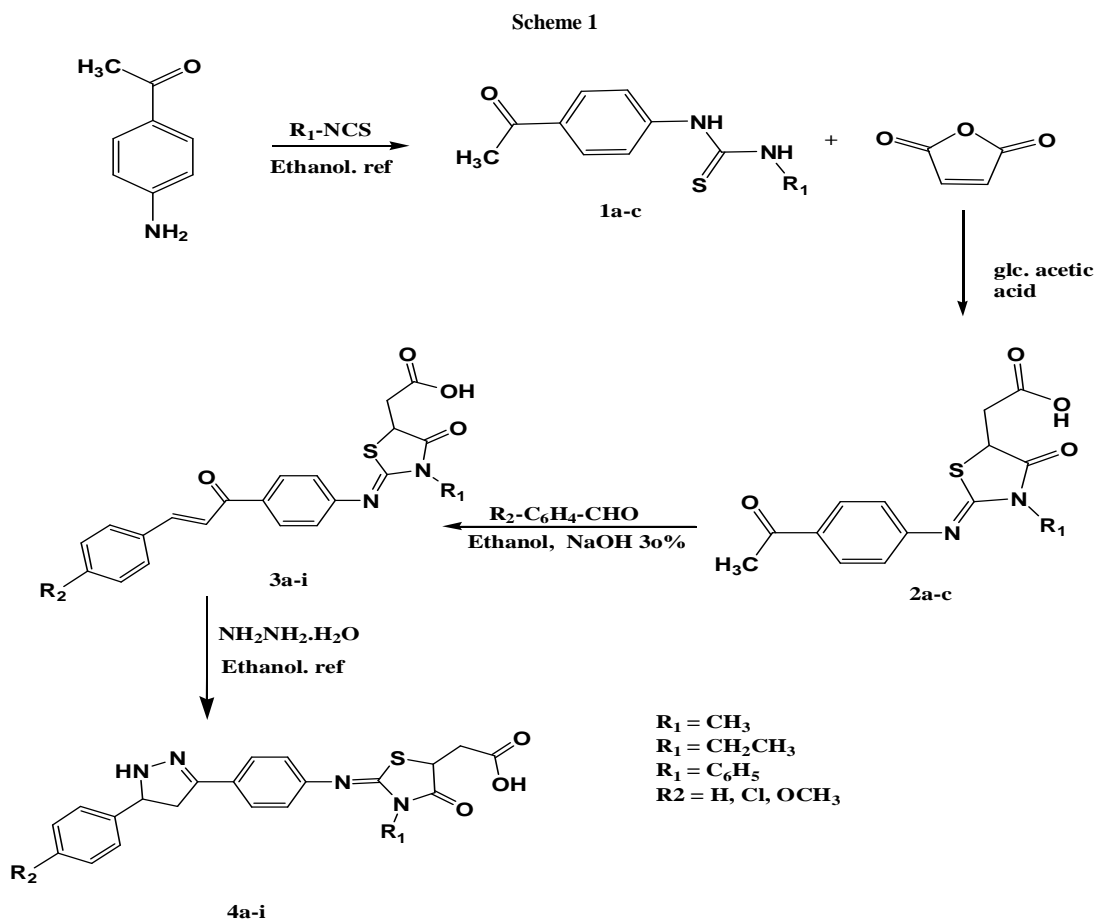
### ABSTRACT

Three new series of (2-{4-[3-(4-substituted-phenyl)-acryloyl]-phenylimino}-4-oxo-3-substituted-thiazolidin-5-yl)-acetic acid (**2a-c**), (2-{4-[5-(4-substituted-phenyl)-1H-pyrazol-3-yl]-phenylimino}-4-oxo-3-substituted-thiazolidin-5-yl)-acetic acid. (**4a-i**), and (2-{4-[5-(4-substituted-phenyl)-1-hydrazinothiocarbonyl-4,5-dihydro-1H-pyrazol-3yl]-phenylimino}-4-oxo-3-substituted-thiazolidin-5-yl)-acetic acid (**5a-i**) were synthesized. Reaction of compound (1) with maleic anhydride afforded (2), The latter was condensed with aromatic aldehydes to afford compounds (3). Treatment of compound (3) with hydrazine hydrate or thiocarbohydrazide resulted in the formation of (4), and (5) respectively. The purity of all new compounds was checked by TLC and elucidation of their structures was confirmed by IR, <sup>1</sup>HNMR, the target compounds were evaluated for their anticancer activities in comparison with, doxorubicin as reference drug.

**Key words:** maleic anhydride, thiocarbohydrazide, anticancer, doxorubicin.

### INTRODUCTION

Different possibilities of heterocyclic modifications with a wide spectrum of pharmacological properties are the most important grounds for investigation of this class of compounds. So, Design of new substances based on privileged scaffolds is one of the successful directions in drug discovery. There have been many reports in literature depicting that the presence of heterocyclic moieties proves to be more potent and efficacious than a simple aryl group [1-5]. There has been considerable interest in the chemistry of thiazolidinone ring systems, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities. Thiazolidinone derivatives are known to exhibit diverse bioactivities such as anticonvulsant [6], antimicrobial [7], antifungal [8], anti-inflammatory [9] and anticancer [10] activities. On the other hand, Many pyrazoline derivatives are acknowledged to possess a wide range of bioactivities. The pyrazoline motif makes up the core structure of numerous biologically active compounds. Thus, some representatives of this heterocycle exhibit antiviral/antitumor [11-13] antibacterial [14,15, 20, 21], anti-inflammatory [16], analgesic [17], fungistatic [18], and antihyperglycemic activities [19]. Pyrazolines play an essential role in biological activities. Combination of these two mentioned scaffolds in one molecule according seems to be a promising 'hybrid pharmacophore' approach to new anticancer agents. Dictated by the previous research results of thiazolidinone derivatives, the aim of the presented work was to synthesize new substituted thiazolidinones with an Pyrazoline fragment and to investigate their anticancer activity.



## MATERIALS AND METHODS

Melting points °C were determined by open capillary tube method using Electro thermal 9100 melting point apparatus and were uncorrected. The IR spectra were recorded as potassium bromide discs on Shimadzu-435 IR spectrophotometer and Bruker FT-IR spectrophotometer. The <sup>1</sup>H NMR spectra, in <sup>\*</sup>CDCl<sub>3</sub> or DMSO-d<sub>6</sub> as a solvent, were recorded on Varian Gemini 400 spectrophotometer at 400 MHz, Varian Chemical shifts are reported as δ (ppm) relative to tetramethylsilane (TMS) as internal standard.

**synthesis of 1-(4-Acetyl-phenyl)-3-substituted thiourea. 1a-c**

A mixture of 4-aminoacetophenone (1.35 gm, 10 mmol), the appropriate isothiocyanate (10 mmol) in 1,4-dioxan (15 ml) and 5 drops triethylamine was refluxed for 6 hours. The separated solid was filtered, washed with water, dried and recrystallized from DMF/water to give compounds (1a-C).

**1-(4-Acetyl-phenyl)-3-phenyl-thiourea (1a)** : m.p.=220°C and IR(KBr): 3189.3160 (NH), 1720(C=O) <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3.63 (s,3H, CH<sub>3</sub>C=O), 6.62-7.56 (m, 9H, aromatic CH), 8.4 (s, 2H,NH (D<sub>2</sub>O exchange)).

**1-(4-Acetyl-phenyl)-3-methyl-thiourea (1b)** : m.p.=159°C and IR(KBr): 3250.3182 (NH), 1725(C=O), <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3.50 (s,3H, CH<sub>3</sub>C=O), 2.5 (s,3H, CH<sub>3</sub>), 6.83-7.56 (m, 4H, aromatic CH), 9.1 (s, 2H,NH (D<sub>2</sub>O exchange)).

**1-(4-Acetyl-phenyl)-3-ethyl-thiourea (1c)** : m.p.=180°C and IR(KBr): 3231.3175 (NH), 1710(C=O), <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3.43 (s,3H, CH<sub>3</sub>C=O), 1.14 (t, 3H, CH<sub>3</sub>), 3.12(q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 6.83-7.56 (m, 4H, aromatic CH), 8.7 (s, 2H,NH (D<sub>2</sub>O exchange)).

**Synthesis of [2-(4-Acetyl-phenylimino)-4-oxo-3-substituted-thiazolidin-5-yl]-acetic acid (2a-c).**

In a 100 ml round bottom flask fitted with reflux condenser and a CaCl<sub>2</sub> guard tube. substituted thiourea derivatives (0.01 mol) and maleic anhydride (0.01mol) in glacial acetic acid (25 ml) were refluxed for 20 hrs. Excess of the solvent was removed under vacuum. The solid was dried and recrystallized from ethanol.

**[2-(4-Acetyl-phenylimino)-4-oxo-3-phenyl-thiazolidin-5-yl]-acetic acid (2a)** : m.p.=45°C and IR(KBr): 2800-3100 (broad, -OH), 1720,1715, 1613(C=O). <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 2.8 (s, 3H, CH<sub>3</sub>C=O), 3.2 (d, 3H, CH<sub>2</sub>C=O), 3.9 (t, 1H, -CH-), 7.23-8.56 (m, 9H, aromatic CH), 11.2 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**[2-(4-Acetyl-phenylimino)-4-oxo-3-methyl-thiazolidin-5-yl]-acetic acid (2b)**: m.p. = 55°C and IR(KBr): 2800-3100 (broad, -OH), 1720, 1715, 1613(C=O). <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3 (s, 3H, CH<sub>3</sub>C=O), 3.3 (d,3H, CH<sub>2</sub>C=O), 3.9 (t, 1H, -CH-), 2.5 (s,3H, CH<sub>3</sub>), 7.13-8.56 (m, 4H, aromatic CH), 11.2 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**[2-(4-Acetyl-phenylimino)-4-oxo-3-ethyl-thiazolidin-5-yl]-acetic acid (2c)** : m.p. = 48°C and IR(KBr): 2800-3100 (broad, -OH), , 1720, 1715, 1613(C=O). <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) : δ = 3.1 (s, 3H, CH<sub>3</sub>C=O), 3.4 (d,3H, CH<sub>2</sub>C=O), 3.9 (t, 1H, -CH-) 1.12 (t, 3H, CH<sub>3</sub>), 3.5(q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 7.23-8.56 (m, 4H, aromatic CH), 11.2 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**Synthesis of (2-{4-[3-(4-substituted-phenyl)-acryloyl]-phenylimino}-4-oxo-3-substituted-thiazolidin-5-yl)-acetic acid (3a-i)**

To a solution of substituted acetophenone (0.01 mol) in ethanol (20 ml) contain 10 ml of 30% NaOH taken in a conical flask (100 ml) substituted benzaldehyde (0.02 mol) was added and stirring over night. Then neutralized, the orange ppt was filtered, wash, and dried.

**(2-{4-[3-(4-phenyl)-acryloyl]-phenylimino}-4-oxo-3-phenyl-thiazolidin-5-yl)-acetic acid. (3a).** IR(KBr): 2800-3100 (broad, -OH), , 1720, 1715, 1613(C=O). <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3.4 (d,3H, CH<sub>2</sub>C=O), 3.9 (t, 1H, -CH-), 7.20-8.56 (m, 15H, aromatic CH), 11.5 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[3-(4-chloro-phenyl)-acryloyl]-phenylimino}-4-oxo-3-phenyl-thiazolidin-5-yl)-acetic acid. (3b).** IR(KBr): 2800-3100 (broad, -OH), , 1720, 1715, 1613(C=O). <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3.4 (d,3H, CH<sub>2</sub>C=O), 3.9 (t, 1H, -CH-), 7.11-8.56 (m, 15H, aromatic CH), 11.2 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[3-(4-methoxy-phenyl)-acryloyl]-phenylimino}-4-oxo-3-phenyl-thiazolidin-5-yl)-acetic acid. (3c).** IR(KBr): 2800-3100 (broad, -OH), , 1720, 1715, 1613(C=O). <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3.3 (d,2H, CH<sub>2</sub>C=O), 3.6 (s,3H, CH<sub>3</sub>O), 3.9 (t, 1H, -CH-), 7.33-8.56 (m, 15H, aromatic CH, CH=CH), 11.4 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[3-(4-phenyl)-acryloyl]-phenylimino}-4-oxo-3-methyl-thiazolidin-5-yl)-acetic acid. (3d).** IR(KBr): 2800-3100 (broad, -OH), , 1720, 1715, 1613(C=O). <sup>1</sup>H NMR (DMSO- d<sub>6</sub>)δ = 3.2 (d,2H, CH<sub>2</sub>C=O), 3.9 (t, 1H, -CH-), 7.23-8.56 (m, 10H, aromatic CH, CH=CH), 11.0 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[3-(4-chloro-phenyl)-acryloyl]-phenylimino}-4-oxo-3-methyl-thiazolidin-5-yl)-acetic acid. (3e).** IR(KBr): 2800-3100 (broad, -OH), , 1720, 1715, 1613(C=O). <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3.5 (d,2H, CH<sub>2</sub>C=O), 4.0 (t, 1H, -CH-), 7.53-8.56 (m, 10H, aromatic CH, CH=CH), 11.3 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[3-(4-methoxy-phenyl)-acryloyl]-phenylimino}-4-oxo-3-methyl-thiazolidin-5-yl)-acetic acid. (3f).** IR(KBr): 2800-3100 (broad, -OH), 1720, 1715, 1613(C=O); <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3.4 (d,2H, CH<sub>2</sub>C=O), 3.7 (s,3H, CH<sub>3</sub>O), 4.2 (t, 1H, -CH-), 7.43-8.56 (m, 10H, aromatic CH, CH=CH), 11.6 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[3-(4-phenyl)-acryloyl]-phenylimino}-4-oxo-3-ethyl-thiazolidin-5-yl)-acetic acid. (3g).** IR(KBr): 2800-3100 (broad, -OH), 1720, 1715, 1613(C=O). <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3.5 (d,2H, CH<sub>2</sub>C=O), 3.8 (t, 1H, -CH-), 7.73-8.56 (m, 10H, aromatic CH, CH=CH), 11.8 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[3-(4-chloro-phenyl)-acryloyl]-phenylimino}-4-oxo-3-ethyl-thiazolidin-5-yl)-acetic acid. (3h).** IR(KBr): 2800-3100 (broad, -OH), 1720, 1715, 1613(C=O); <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3.1 (d,2H, CH<sub>2</sub>C=O), 3.9 (t, 1H, -CH-), 7.66-8.56 (m, 10H, aromatic CH, CH=CH), 11.2 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[3-(4-methoxy-phenyl)-acryloyl]-phenylimino}-4-oxo-3-ethyl-thiazolidin-5-yl)-acetic acid. (3i).** IR(KBr): 2800-3100 (broad, -OH), 1720, 1715, 1613(C=O). <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 3.4 (d,2H, CH<sub>2</sub>C=O), 3.7 (s,3H, CH<sub>3</sub>O), 4.0 (t, 1H, -CH-), 7.76-8.56 (m, 10H, aromatic CH, CH=CH), 12.2 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**Synthesis of (2-{4-[5-(4-substituted-phenyl)-1H-pyrazol-3-yl]-phenylimino}-4-oxo-3-substituted-thiazolidin-5-yl)-acetic acid. (4a- i)**

A mixture of compound **3a** (2.50 g, 0.006 mol) in absolute ethanol (20 mL) and hydrazine hydrate (0.29 g, 0.006 mol) was refluxed for 5 h. After completion of reaction, the reaction mixture was cooled, poured into crushed ice and then neutralized with HCl. The precipitate was filtered, washed with water, dried and recrystallized from methanol. The physical and spectral data of the title compounds (**IV a-i**) are given in Table 1

**(2-{4-[5-phenyl]-1H-pyrazol-3-yl]-phenylimino}-4-oxo-3-phenyl-thiazolidin-5-yl)-acetic acid. (4a)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.96 (d,2H, CH<sub>2</sub>), 3.42 (d,3H, CH<sub>2</sub>C=O), 3.93 (t, 1H, -CH-), 7.00-8.41 (m, 14H, aromatic CH, NH), 11.7 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-Chloro-phenyl)-1H-pyrazol-3-yl]-phenylimino}-4-oxo-3-phenyl-thiazolidin-5-yl)-acetic acid. (4b)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.97 (d,2H, CH<sub>2</sub>), 3.45 (d,3H, CH<sub>2</sub>C=O), 3.92 (t, 1H, -CH-), 7.10-8.68 (m, 14H, aromatic CH, NH), 12.2 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-methoxyphenyl)-1H-pyrazol-3-yl]-phenylimino}-4-oxo-3-phenyl-thiazolidin-5-yl)-acetic acid. (4c)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.88 (d,2H, CH<sub>2</sub>), 3.39 (d,2H, CH<sub>2</sub>C=O), 3.87 (s,3H, CH<sub>3</sub>O), 3.9 (t, 1H, -CH-), 7.09-8.23 (m, 14H, aromatic CH, NH), 11.55 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-phenyl]-1H-pyrazol-3-yl]-phenylimino}-4-oxo-3-methyl-thiazolidin-5-yl)-acetic acid. (4d).** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.89 (d,2H, CH<sub>2</sub>), 3.28 (d,2H, CH<sub>2</sub>C=O), 3.79 (t, 1H, -CH-), 7.23-8.49 (m, 9H, aromatic CH, NH), 11.29 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-sChloro-phenyl)-1H-pyrazol-3-yl]-phenylimino}-4-oxo-3-methyl-thiazolidin-5-yl)-acetic acid. (4e)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1,89 (d,2H, CH<sub>2</sub>), 3.58 (d,2H, CH<sub>2</sub>C=O), 4.01 (t, 1H, -CH-), 7.53-8.41 (m, 9H, aromatic CH, NH), 11.73 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-methoxyphenyl)-1H-pyrazol-3-yl]-phenylimino}-4-oxo-3-substituted-thiazolidin-5-yl)-acetic acid. (4f).** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.83 (d,2H, CH<sub>2</sub>), 3.44 (d,2H, CH<sub>2</sub>C=O), 3.97 (s,3H, CH<sub>3</sub>O), 4.2 (t, 1H, -CH-), 7.43-8.33 (m, 9H, aromatic CH, NH), 11.56 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5phenyl]-1H-pyrazol-3-yl]-phenylimino}-4-oxo-3-ethyl-thiazolidin-5-yl)-acetic acid. (4g)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.90 (d,2H, CH<sub>2</sub>), 3.35 (d,2H, CH<sub>2</sub>C=O), 3.85 (t, 1H, -CH-), 7.73-8.43 (m, 9H, aromatic CH, NH), 11.27 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-chloro-phenyl)-1H-pyrazol-3-yl]-phenylimino}-4-oxo-3-ethyl-thiazolidin-5-yl)-acetic acid. (4h).** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1,82 (d,2H, CH<sub>2</sub>), 3.41 (d,2H, CH<sub>2</sub>C=O), 3.92 (t, 1H, -CH-), 7.66-8.64 (m, 9H, aromatic CH, NH), 11.62 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-methoxyphenyl)-1H-pyrazol-3-yl]-phenylimino}-4-oxo-3-ethyl-thiazolidin-5-yl)-acetic acid. (4i).** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.99 (d,2H, CH<sub>2</sub>), 3.42 (d,2H, CH<sub>2</sub>C=O), 3.87 (s,3H, CH<sub>3</sub>O), 4.0 (t, 1H, -CH-), 7.76-8.52 (m, 9H, aromatic CH, NH), 12.9 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**Synthesis of thiocarbohydrazide**

The hydrazine hydrate (0.75 mol) was placed in flask, temperature was lowered to 10°C and the stirring rate was controlled at 800 rpm. The Carbon disulfide (0.25 mol) was added dropwise over about one hour, while maintaining the temperature below 15°C. After addition the reaction mixture continued to be agitated for 30 min at room temperature. The resultant mixture was then heated to 80°C and refluxed for 5h. The reaction mixture cooled and the solid precipitate separated by filtration, washed and dried, recrystallized with water. Yield (80%) melting point 172-174 °C. ( m.p 170–172 °C reported in the literature.

**Synthesis of (2-{4-[5-(4-substituted-phenyl)-1-hydrazinothiocarbonyl-4,5-dihydro-1H-pyrazol-3yl]-phenylimino}-4-oxo-3-substituted-thiazolidin-5-yl)-acetic acid (5a-i)**

A mixture of compound III (0.01mol) and thiocarbohydrazide (0.01mol) in ethanol, a few drops of glacial acetic acid were added to initiate the reaction. The progress of the reaction was monitored by TLC. The residue was cooled, kept overnight and the precipitate was collected by filtration and recrystallization with ethanol. The physical and spectral data of the title compounds (5a-i) are given in Table 2

**(2-{4-[5-(phenyl)-1-hydrazinothiocarbonyl-4,5-dihydro-1H-pyrazol-3yl]-phenylimino}-4-oxo-3-phenyl-thiazolidin-5-yl)-acetic acid (5a)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.90 (d,2H, CH<sub>2</sub>), 3.24 (d,3H, CH<sub>2</sub>C=O), 3.90 (t, 1H, -CH-), 7.22-9.54 (m, 17H, aromatic CH, NH, NH<sub>2</sub>), 11.7 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-chloro-phenyl)-1-hydrazinothiocarbonyl-4,5-dihydro-1H-pyrazol-3yl]-phenylimino}-4-oxo-3-phenyl-thiazolidin-5-yl)-acetic acid (5b)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.95 (d,2H, CH<sub>2</sub>), 3.23 (d,3H, CH<sub>2</sub>C=O), 3.97 (t, 1H, -CH-), 7.29-8.98 (m, 17H, aromatic CH, NH, NH<sub>2</sub>), 12.2 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-methoxy-phenyl)-1-hydrazinothiocarbonyl-4,5-dihydro-1H-pyrazol-3yl]-phenylimino}-4-oxo-3-phenyl-thiazolidin-5-yl)-acetic acid (5c)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.91 (d,2H, CH<sub>2</sub>), 3.29 (d,2H, CH<sub>2</sub>C=O), 3.87 (s,3H, CH<sub>3</sub>O), 3.9 (t, 1H, -CH-), 7.19-9.08 (m, 17H, aromatic CH, NH, NH<sub>2</sub>), 12.55 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-phenyl)-1-hydrazinothiocarbonyl-4,5-dihydro-1H-pyrazol-3yl]-phenylimino}-4-oxo-3-methyl-thiazolidin-5-yl)-acetic acid (5d)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.99 (d,2H, CH<sub>2</sub>), 3.27 (d,2H, CH<sub>2</sub>C=O), 3.96 (t, 1H, -CH-), 7.18 -9.24 (m, 12H, aromatic CH, NH, NH<sub>2</sub>), 12.46 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-chloro-phenyl)-1-hydrazinothiocarbonyl-4,5-dihydro-1H-pyrazol-3yl]-phenylimino}-4-oxo-3-methyl-thiazolidin-5-yl)-acetic acid (5e)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.98 (d,2H, CH<sub>2</sub>), 3.38 (d,2H, CH<sub>2</sub>C=O), 3.99 (t, 1H, -CH-), 7.50-9.33 (m, 12H, aromatic CH, NH, NH<sub>2</sub>), 12.11 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-methoxy-phenyl)-1-hydrazinothiocarbonyl-4,5-dihydro-1H-pyrazol-3yl]-phenylimino}-4-oxo-3-methyl-thiazolidin-5-yl)-acetic acid (5f)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.94 (d,2H, CH<sub>2</sub>), 3.29 (d,2H, CH<sub>2</sub>C=O), 3.86 (s,3H, CH<sub>3</sub>O), 4.2 (t, 1H, -CH-), 7.53-9.10 (m, 12H, aromatic CH, NH, NH<sub>2</sub>), 12.06 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-phenyl)-1-hydrazinothiocarbonyl-4,5-dihydro-1H-pyrazol-3yl]-phenylimino}-4-oxo-3-ethyl-thiazolidin-5-yl)-acetic acid (5g)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.91 (d,2H, CH<sub>2</sub>), 3.45 (d,2H, CH<sub>2</sub>C=O), 3.87 (t, 1H, -CH-), 7.63-8.99 (m, 12H, aromatic CH, NH, NH<sub>2</sub>), 12.77 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-chloro-phenyl)-1-hydrazinothiocarbonyl-4,5-dihydro-1H-pyrazol-3yl]-phenylimino}-4-oxo-3-ethyl-thiazolidin-5-yl)-acetic acid (5h)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.97 (d,2H, CH<sub>2</sub>), 3.37 (d,2H, CH<sub>2</sub>C=O), 3.94 (t, 1H, -CH-), 7.36-9.11 (m, 12H, aromatic CH, NH, NH<sub>2</sub>), 12.32 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).

**(2-{4-[5-(4-methoxy-phenyl)-1-hydrazinothiocarbonyl-4,5-dihydro-1H-pyrazol-3yl]-phenylimino}-4-oxo-3-ethyl-thiazolidin-5-yl)-acetic acid (5i)** <sup>1</sup>H NMR (DMSO- d<sub>6</sub>) δ = 1.89 (d,2H, CH<sub>2</sub>), 3.33 (d,2H, CH<sub>2</sub>C=O), 3.97 (s,3H, CH<sub>3</sub>O), 4.0 (t, 1H, -CH-), 7.66-8.95 (m, 12H, aromatic CH, NH, NH<sub>2</sub>), 12.8 (br-s, 1H, -OH) (D<sub>2</sub>O exchange).



Table I: Physical and spectral data of compounds

Compounds IVa-i	Molecular Formula	M.p. °C	Yield %	IR
4 a	C <sub>26</sub> H <sub>22</sub> N <sub>4</sub> O <sub>3</sub> S	170-173	61%	3203 (NH), 2800-3100 (broad, -OH), 1715, 1613(C=O),
4 b	C <sub>26</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>3</sub> S	127-129	44%	3193 (NH), 2700-3250 (broad, -OH), 1701, 1619(C=O),
4 c	C <sub>27</sub> H <sub>24</sub> N <sub>4</sub> O <sub>4</sub> S	198-200	71%	3234 (NH), 2600-3120 (broad, -OH), 1705, 1618(C=O),
4 d	C <sub>21</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub> S	167-169	74	3253 (NH), 2650-3140 (broad, -OH), 1710, 1623(C=O),
4 e	C <sub>21</sub> H <sub>19</sub> ClN <sub>4</sub> O <sub>3</sub> S	184-186	68	3221 (NH), 2670-3130 (broad, -OH), 1712, 1611(C=O),
4 f	C <sub>22</sub> H <sub>22</sub> N <sub>4</sub> O <sub>4</sub> S	153-155	62	3243 (NH), 2600-3160 (broad, -OH), 1708, 1616(C=O),
4 g	C <sub>22</sub> H <sub>22</sub> N <sub>4</sub> O <sub>3</sub> S	202-204	57	3183 (NH), 2750-3200 (broad, -OH), 1702, 1608(C=O),
4 h	C <sub>22</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>3</sub> S	216-218	48	3212 (NH), 2800-3210 (broad, -OH), 1709, 1621(C=O),
4 i	C <sub>23</sub> H <sub>24</sub> N <sub>4</sub> O <sub>4</sub> S	227-229	72	3270 (NH), 2850-3220 (broad, -OH), 1715, 1624(C=O),

Table 2 : Physical and spectral data of compounds

Compound Va-i	Molecular Formula	M.p. °C	Yield %	IR
5 a	C <sub>27</sub> H <sub>24</sub> N <sub>6</sub> O <sub>3</sub> S <sub>2</sub>	145-147	47%	3253, 3222, 3179 (NH, NH <sub>2</sub> ), 2800-3100 (broad, -OH), 1715,1613(C=O),
5 b	C <sub>27</sub> H <sub>23</sub> ClN <sub>6</sub> O <sub>3</sub> S <sub>2</sub>	163-165	59%	3218, 3190,3193 (NH, NH <sub>2</sub> ), 2700-3250 (broad, -OH), 1701,1619(C=O),
5 c	C <sub>28</sub> H <sub>26</sub> N <sub>6</sub> O <sub>4</sub> S <sub>2</sub>	137-139	48%	3170,3198,3234 (NH, NH <sub>2</sub> ), 2600-3120 (broad, -OH), 1705,1618(C=O),
5 d	C <sub>22</sub> H <sub>22</sub> N <sub>6</sub> O <sub>3</sub> S <sub>2</sub>	187-188	38%	3345, 3267, 3178 (NH, NH <sub>2</sub> ), 2650-3140 (broad, -OH), 1710,1623(C=O),
5 e	C <sub>21</sub> H <sub>21</sub> ClN <sub>6</sub> O <sub>3</sub> S <sub>2</sub>	141-143	61%	3277, 3200,3163 (NH, NH <sub>2</sub> ), 2670-3130 (broad, -OH), 1712,1611(C=O),
5 f	C <sub>22</sub> H <sub>24</sub> N <sub>6</sub> O <sub>4</sub> S <sub>2</sub>	152-153	57%	3328, 3290,3143 (NH, NH <sub>2</sub> ), 2600-3160 (broad, -OH), 1708,1616(C=O),
5 g	C <sub>22</sub> H <sub>24</sub> N <sub>4</sub> O <sub>3</sub> S <sub>2</sub>	173-174	51%	3228, 3200,3190 (NH, NH <sub>2</sub> ), 2750-3200 (broad, -OH), 1702,1608(C=O),
5 h	C <sub>22</sub> H <sub>23</sub> ClN <sub>6</sub> O <sub>3</sub> S <sub>2</sub>	155-157	34%	3306, 3230,3123 (NH, NH <sub>2</sub> ), 2800-3210 (broad, -OH), 1709,1621(C=O),
5 i	C <sub>23</sub> H <sub>26</sub> N <sub>6</sub> O <sub>4</sub> S <sub>2</sub>	143-144	49%	3212, 3187,3160 (NH, NH <sub>2</sub> ), 2850-3220 (broad, -OH), 1715,1624(C=O),

### Antitumor screening

Ninths representative compounds and reference drug Doxorubicin was performed utilizing Sulfo-Rodamine B (SRB) standard method [20] have been tested for cytotoxic activity against human mammary carcinoma cell line (MCF7) in the National Cancer Institute, Cairo University. The screening involves calculation of the percentage growth or surviving fraction of the drug treated cell lines compared by untreated control using Sulforhodamine B (SRB) colorimetric assay. Sulforhodamine B is a bright pink aminoxanthene anionic dye with two sulfonic acid groups that bind electrostatically to protein basic amino acid residue of trichloroacetic acid (TCA) fixed cells under mild acidic condition. [21] Culture fixed with (TCA) were stained for 30 minutes with 0.4 % w/v Sulforhodamine B dissolved in 1 % acetic acid, and protein bound dye was extracted with 10mM tris base [tris(hydroxymethyl) aminomethane ] for determination of optical density in a computer-interfaced, 96-well microtiter plate reader. The optical density measured is linear with cell number of the survival fraction. Therefore, the assay is a sensitive measure of drug induced cytotoxicity with the best signal to noise ratio. The assay also, provides a colorimetric end point that is nondestructive, indefinite stable and visible to naked eye. [21]

### Procedure:

Cells were plated in 96-multiwell plate (10<sup>4</sup> cells/well) for 24 hours before treatment with the compound(s) to allow attachment of cell to the wall of the plate. Different concentrations of compound under test (0.0, 1.0, 2.5, 5.0 and 10.0 µg/ml) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compound(s) for 48 hours at 37°C and in atmosphere of 5 % CO<sub>2</sub>. After 48 hours, cells were fixed, washed and stained with Sul-forhodamine B stain. Excess stain was washed with acetic acid and attached stain was recovered with tri EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve of the tumor cell line after the specified compound.

Table18. Cytotoxic activity of the newly synthesized compounds

Figure.	Comp. No	IC50 µM
1	1 a	5.57
2	2 a	5.25
3	3 a	6.93
4	4 a	5.34
5	4 d	3.84
6	4 i	3.22
7	5 a	5.19
8	5 d	4.95
9	5 i	3.30
10	DOX	0.45

(IC<sub>50</sub> µM) (against MCF7 cell line)

**RESULTS AND DISCUSSION**

The present work involves the synthesis of the target thiazolidone and pyrazoline derivatives. Schemes 1-2 summarize the steps followed in the synthesis of the key intermediate and the final compounds. 1-(4-Acetyl-phenyl)-3-substituted thiourea compound (**1a-c**) was prepared through the reaction appropriate isothiocyanate derivatives with p-amino acetophenone in 1, 4-dioxan containing triethylamine according to the reported method [22]. It was then cyclized to thiazolidinone [2-(4-Acetyl-phenylimino)-4-oxo-3-substituted-thiazolidin-5-yl]-acetic acid (**2a-c**) through reaction with the maleic anhydride in ethanol [23, 24]. Chalcones (2-{4-[3-(4-substituted-phenyl)-acryloyl]-phenylimino}-4-oxo-3-substituted-thiazolidin-5-yl)-acetic acid (**3a-i**) as shown in scheme 1 were prepared by reaction (2) with the appropriate benzaldehyde derivatives in ethanol containing 30% sodium hydroxide [25]. The target derivatives (**4a-i**) were obtained by refluxing of (**3a-i**) with hydrazine hydrate in ethanol [26]. As shown in scheme 2 refluxing of thiocarbohydrazide with compound (**3a-i**) in ethanol containing few drops of glacial acetic acid yielded compound (**5a-i**) [27].

From the observed antitumor activity data of substituted thiourea, thiazolidinone-5-acetic acid and chalcon derivatives compound **3**, **2**, **1** showed moderate activity with IC<sub>50</sub> values 6.93-5.22 μM, respectively and compound pyrazoline and pyrazoline hydrazone **4a,4d**, **4i**, **5a**, **5d**, **5i** showed good activity only compound **4i**, **5i** exhibited promising anticancer activity with IC<sub>50</sub> values 3.22, 3.30 μM respectively. Active compounds **4i**, and **5i** gave improved activity compared with starting compound **1** (6.93 μM), **Table 3**.

**CONCLUSION**

The newly synthesized compounds of condensed heterocyclic substituted thiourea and substituted thiazolidinone-5-acetic acid, and a structure hybrid compounds comprised of thiazolidinone-5-acetic acid and pyrazoline or pyrazoline hydrazone were evaluated for the cytotoxic activity against human mammary carcinoma cell line (MCF7). The obtained results revealed compounds **4i**, **5i**, with lower IC<sub>50</sub> values than their precursor compound **1,2,3** (more active) but still higher than that of the reference drug Doxorubicin.

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