

# THE INTERNATIONAL JOURNAL OF SCIENCE & TECHNOLEDGE

## Utility of 2, 4-Dihydroxybenzylidene Thiosemicarbazones in the Synthesis of Some Bioactive and Anti-Corrosive Heterocyclic Compounds

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### Abstract:

The important organic compound 3-((2,4-dihydroxybenzylidene) amino)-2-thioxoimidazolidin-4-one (3) has been prepared by the reaction of 2,4-dihydroxybenzaldehyde with thiosemicarbazide to give 2,4-dihydroxybenzylidene thiosemicarbazone (1), followed by cyclization of compound 1 with ethyl chloroacetate in the presence of fused sodium acetate. The synthesized compound 3 was considered as the started material for synthesis some novel thiohydantoin derivatives (4-13). Also, 2,4-dihydroxybenzylidene thiosemicarbazone (1) was used for the preparation of 2 and 5. All the synthesized compounds have been characterized on the bases of IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, mass spectrometer and elemental analyses. Some of 2-thiohydantoin derivatives (5,6,11) were tested for in-vitro antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*), Gram-negative bacteria (*Salmonella typhimurium*, *Escherichia coli*) and fungi (*Candida albicans* and *Aspergillus fumigatus*). This paper also interested with flame retardants and anticorrosive additives based on some previously prepared thiohydantoin derivatives 4-((2-(5-(4-methoxyphenyl) thiazol-2-yl) hydrazono)methyl) benzene-1, 3-diol (5), 5-(2-chlorobenzylidene-3-(2, 4-dihydroxybenzylidene) amino)-2-thioxoimidazolidin-4-one (6), and 4-(2-chlorophenyl)-1-(2,4-dihydroxybenzylidene)-6-oxo-2-thioxo-2,3,5,6-tetrahydro-1H-imidazo [4,5c]pyridine -7-carbonitrile (11), which were physically added to epoxy organic coating. The flame retardants technique was observed via a limited oxygen index (LOI) method, and anti-corrosive was evaluated with salt spray (or salt fog) test. The coating evaluation showed that, the incorporation of thiohydantoin derivatives into varnish improved the flame residency, corrosion resistance, and some physical properties of mild steel perversely coated with modified epoxy varnish

**Keywords:** 2, 4-dihydroxybenzylidene thiosemicarbazone, Multi-component reactions, Anti-microbial and anti-corrosion Activity

### 1. Introduction

Thiohydantoin is a sulfur analog of hydantoin with one or both carbonyl groups replaced by thiocarbonyl groups (1). Among the known thiohydantoin, 2-thiohydantoin is most notably known due to their wide applications as hypolipidemic (2), anticarcinogenic (3), antimutagenic (4), antithyroidal (5) antiviral (e.g., against herpes simplex virus, HSV) (6), human immunodeficiency virus (HIV) (7) and tuberculosis (8), antimicrobial (antifungal and antibacterial) (9), anti-ulcer and anti-inflammatory agents (10), as well as pesticides (11). In addition, 2-thiohydantoin is useful intermediates in the synthesis of natural products (12,13). Also, 2-thiohydantoin has been used as reference standards for the development of C-terminal protein sequencing (14), as reagents for the development of dyes (15) and in textile printing, metal cation complexation and polymerization catalysis (16).

It has been found that some hydantoin derivatives have anti-corrosion inhibitors and flame retardant properties, whereas 2-thiohydantoin (17), 1-(2-ethylamino)-2-methylimidazoline (imidazoline), N-[3(2-amino-ethylamino-ethyl)]-acetamide (amide) and 1-(2-ethylamino)-2-methylimidazolidine (imidazolidine) were used as corrosion inhibitors for steel in a 0.5 M HCl solution (18).

The inhibition of corrosion of iron in 2M nitric acid and 2M sulfuric acid solutions by substituted phenyl hydantoin as 1-phenylhydantoin (1), 3-hydroxymethyl-1-phenylhydantoin (2), 3-carboxy-1-phenylhydantoin (3), 5-benzylidenehydantoin (4), 5-methyl-2-thiohydantoin (5), 1,3-dimethyl-5-phenylazo-2-thiohydantoin (6), and 5,5-dimethyl-2,4-dithiohydantoin (7), compounds was measured using weight loss, thermometric, and polarization methods. The three methods gave consistent results. The efficiency of hydantoin derivatives inhibitors under investigation increases, according to 3 > 2 > 4 > 1 > 6 > 5 > 7. The corrosion inhibition may be due to the adsorption of the hydantoin molecules (with a high negative charge density at the hetero atom) on the metal surface<sup>(19)</sup>.

Corrosion and fire have much serious economic, environmental, human health, technological and cultural safety consequences for different societies, so fighting and resisting of corrosion and fire have recently captured the high attention of scientists and scientific researches.

In our daily life some conventional materials such as metals, wood, glass, and ceramic have been progressively replaced with synthetic polymers, due to their versatility, good mechanical and physical properties, low density, and easy molding. Although these advantages of polymeric materials, there are serious drawbacks, such as poor fire resistance, but there are attempts to overcome this problem by inserting a fire retardant into the polymer backbone<sup>(20-22)</sup>.

The flame retardants, which added to the polymer are one of the two types, reactive additives and normal additives: Reactive additives are those added to the polymer during polymerization or a post-processing step that chemically bond to the polymer chain. Either they copolymerize as a new polymer monomer or they graft onto the polymer via a post-polymerization reaction.

Normal additives are those which do not chemically bond to the polymer and are mixed into the polymer either during polymer formulation or during melt compounding of the thermoplastic polymer. Normal additives are part of polymer formulations and tend to be the most common type of flame-retardant additive.

All types of flame-retardant chemistries fall into one (or more) of three mechanisms of flame-retardant action<sup>(23)</sup>.

### 1.1. Gas Phase Flame Retardants (Ex. Halogen, Phosphorus)

These materials reduce the heat released in the gas phase from combustion by scavenging reactive free radicals.

### 1.2. Endothermic Flame Retardants (Ex. Metal Hydroxides, Carbonates)

These materials function in the gas phase and condensed phase by releasing non-flammable gases (H<sub>2</sub>O, CO<sub>2</sub>), which dilute the fuel and cool the polymer through endothermic decomposition of the flame-retardant additive. The lower polymer temperature slows the pyrolysis rate. These materials also leave behind a ceramic-like residue, which protects the underlying polymer.

### 1.3. Char-Forming Flame Retardants (Intumescent)

Exposure to heat initiates a series of chemical and physical processes, leading to a tumescent condition. This state is characterized by fire-resistant insulating foam. The foam serves to isolate heat and oxygen from the fuel source, extinguishing the fire.

Unfortunately, epoxy resins tend to burn easily with high smoke and gas release. Therefore, this paper is concerned with enhancing the fire resistance of epoxy resins by adding some thiohydantoin derivatives, which acting as normal flame retardants containing nitrogen, as well as corrosion inhibition.

## 2. Experimental

### 2.1. Instruments

All melting points were measured with a Gallenkamp melting point apparatus. IR spectra (KBr) were acquired with a Perkin-Elmer model 157 infrared spectrophotometer. <sup>1</sup>H-NMR spectra were recorded on a Bruker spectrophotometer at 400 MHz using tetramethylsilane (TMS) as internal standard. <sup>13</sup>C-NMR spectra were recorded on the same spectrometer at 100 MHz in DMSO-*d*<sub>6</sub> as solvent. Electron Ionization (EI)-MS were measured at a Shimadzu GC-MS-QP-1000 EX mass spectrometer instrument operating at 70 eV.

### 2.2. Synthesis

#### 2.2.1. Synthesis of 2,4-dihydroxybenzylidene thiosemicarbazones (1)

A mixture of 2,4-dihydroxybenzaldehyde (0.01 mol) and thiosemicarbazide (0.01 mol) in ethanol (30 mL) was heated under reflux for 4 h, then cooled. The solid formed was filtered off, dried and purified by recrystallization from ethanol to give compound **1** as pale yellow crystals, m. p. 200-202 °C, yield 78%, FT-IR (KBr cm<sup>-1</sup>),  $\nu_{\max}$ : 3374(OH), 3270-3125(NH<sub>2</sub>), 3233(NH), 1631 (C=C), 1353 (C=S). <sup>1</sup>H NMR ( $\delta$ ppm) (DMSO-*d*<sub>6</sub>):  $\delta$  = 11.06-9.74 (s, 2H, 2×OH), 9.75 (s, 1H, NH), 8.3 (s, 1H, CH=N), 7.71 (s, 2H, NH<sub>2</sub>) and 6.24-7.66 (m, 3H, Ar-H) ppm.; Anal Calcd for C<sub>8</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>S (M. wt. = 211): C, 45.49; H, 4.26; N, 19.90; S, 15.16; Found: C, 45.46; H, 4.23; N, 19.87; S, 15.13.

#### 2.2.2. Synthesis of N,N,1-triacetoxy-2-(2,4-dihydroxybenzylidene)hydrazinecarbothioamide (2)

A mixture of **1** (0.01 mol) and acetic anhydride (15 mL) was heated under reflux for 3 h, then cooled and poured into ice-diluted hydrochloric acid. The solid obtained was filtered off, washed with water, dried and purified by recrystallization with ethanol to give compound **2** as pale brown crystals, m.p. 127-129 °C, yield 50%, FT-IR (KBr cm<sup>-1</sup>),

$\nu_{\max}$  : 3343(OH),1699(C=N), 1608 (C=O),1426(C=S).  $^1\text{H NMR}$  ( $\delta_{\text{ppm}}$ ) (DMSO-*d*6): $\delta$  10.88-11.61 (s, 2H, 2 $\times$ OH), 8.30(s, 1H, CH=N), 6.21-7.53(m, 3H, H-Aromatic ring), 2.18-2.48(s, 9H, 3 $\times$ COCH<sub>3</sub>), ppm.; Anal Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>8</sub>S (M. wt = 385): C, 43.64; H, 3.89; N, 10.90; S, 8.32; Found: C, 43.61; H, 3.86 N, 10.88; . S, 8.30.

### 2.2.3. Synthesis of 3-((2, 4-dihydroxybenzylidene) amino)-2-thioxoimidazolidin-4-one (3)

A mixture of **1** (0.01 mol) and ethyl chloroacetate (0.01 mol) in the presence of fused sodium acetate in ethanol (30 mL) was heated under reflux for 6 h, and then cooled. The solid formed was filtered off, dried and purified by recrystallization from ethanol to give compound **3** as pale yellow crystals, m.p. 260-262°C, yield 70%; FT-IR (KBr cm<sup>-1</sup>),  $\nu_{\max}$ : 3360(OH), 3244(NH),1697(C=O),1627.9(C=N),1381(C=S).  $^1\text{H NMR}$  ( $\delta_{\text{ppm}}$ ) (DMSO-*d*6): $\delta$  10.04-11.89 (s, 2H, OH),11.00 (s, 1H, NH),8.47 (s, 1H, CH=N), 6.31-7.34 (m,3H, Ar-ring) and 3.99(s, 2H, NCH<sub>2</sub>CO) ppm.; Anal Calcd for C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>S (M. wt. 251); C, 47.80; H, 3.58;N, 16.73 ;S, 12.75; Found: C, 47.77; H, 3.55;N, 16.70 ;S, 12.72.

### 2.2.4. Synthesis of 4-(3- acetyl-5-oxo-2-thioxoimidazolidin-1-yl) imino) methyl)-1, 3-phenylene diacetate (4)

A mixture of **3** (0.01 mol) and acetic anhydride (15 mL) was heated under reflux for 3 h, then cooled and poured into ice-diluted hydrochloric acid. The solid obtained was filtered off, washed with water, dried and purified by recrystallization with ethanol to give **4**. C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>6</sub>S (M. wt. 377), pale brown powder, m.p. 178-180°C, yield 50%; FT-IR (KBr cm<sup>-1</sup>),  $\nu_{\max}$ : 1723(C=O),1649 (C=N), 1367(C=S); MS (m/z, %): 377(M<sup>+</sup>, 22) and 251.9, 35); Anal Calcd: C, 50.93; H, 3.98;N, 11.14 ;S, 8.49; Found: C, 50.90; H, 3.95;N, 11. 11;S, 8.46.

### 2.2.5. Synthesis of 4-((2-(5-(4-methoxyphenyl) thiazol-2- yl) hydrazono) methyl) benzene-1, 3-diol (5)

A mixture of **1** (0.01 mol) and 9-bromomethyl aryl ketones such as (4-methoxy phenacyl bromide) (0.01 mol) in the presence of fused sodium acetate (0.03 mol) in ethanol was heated under reflux for 6 h, then cooled and poured into water. The solid formed was filtered off, dried and purified by recrystallization with ethanol to give **5**. C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>S (M.wt. 341), brown color, m.p. 190-192°C, yield 50%; FT-IR (KBr cm<sup>-1</sup>),  $\nu_{\max}$ :3444-3476(OH), 3298 (NH), 1623 (C=N), 1501 (C=C).  $^1\text{H NMR}$  ( $\delta_{\text{ppm}}$ ) (DMSO-*d*6):  $\delta$ 10.02-11.10 (s,2H, OH),9.67 (s,1H,1NH), 8.22(s,1H, CH=N),6.23-7.97(m,8H, Ar-H and proton thiazole),3.9(OCH<sub>3</sub>) ppm.  $^{13}\text{C-NMR}$  spectrum (100 MHz, DMSO-*d*6,  $\delta$ , ppm)177 (C=S), 160.88 (C-OH), 158.42(C=O), 141.15(CH=N), 133.35, 131.37,130.38, 128.7, 111, 112.7, 108.17,102.7, (phenyl ring), 57.19(OCH<sub>3</sub>); MS:m/z 342.2 (14.%) of C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>S and m/z at 235(12%) ; Anal Calcd: C, 59.82; H, 4.40; N, 12.31; S, 9.38; Found: C, 59.80; H, 4.37; N, 12.28;S, 9.35.

### 2.2.6. Synthesis of 5-(2-chlorobenzylidene-3-(2, 4-dihydroxybenzylidene) amino)-2-thioxoimidazolidin-4-one (6)

A mixture of **3** (0.01mol) and o-chlorobenzaldehyde (0.01 mol)) in ethanolic solution of NaOH (0.5 gm in 30 mL ethanol) was heated under reflux for 8 h, cooled to room-temp, poured onto ice cold water and drops of 10% HCl. The solid obtained was filtered off, washed well with hot water, dried and recrystallized from ethanol to give **6**. C<sub>17</sub>H<sub>12</sub>ClN<sub>3</sub>O<sub>3</sub>S (M.wt. 373.5), reddish brown color, m.p. 160-162°C, yield 80%; FT-IR (KBr cm<sup>-1</sup>),  $\nu_{\max}$  : 3444-3347(brOH), 3260(NH), 1705-1695(C=O), 1633 (C=N), 1511 (C=C), 1381(C=S).  $^1\text{H NMR}$  ( $\delta_{\text{ppm}}$ ) (DMSO*d*6): $\delta$  10.01-10.66(s, 2H, OH ),10.40(s, 1H, 1NH), 8.58(s, 1H, CH=N),6.33-7.54(m, 8H, Ar-H and olefinic proton) ppm.  $^{13}\text{C-NMR}$  spectrum (100 MHz, DMSO-*d*6,  $\delta$ , ppm)177 (C=S), 160 (C-OH), 157.82(C=O), 143.3(CH=N), 133.8, 129.9, 126.7, 112.5,102-107 (phenyl ring); Anal Calcd: C, 54.62; H, 3.21; Cl, 9.50; N, 11.24 ;S, 8.57; Found: C, 54.60; H, 3.18; Cl, 9.47; N, 11.21;S, 8.54.

### 2.2.7. Synthesis of 4-(3-acetyl-4-(2-chlorobenzylidene) -5- oxo-2-thioxoimidazolidin-1-yl) imino) methyl)-3-hydroxyphenyl acetate (7)

A mixture of **6** (0.01 mol) and acetic anhydride (15 mL) was heated under reflux for 3 h, then cooled and poured into ice-diluted hydrochloric acid. The solid obtained was filtered off, washed with water, dried and purified by recrystallization with ethanol to give **7**. C<sub>21</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>5</sub>S (M.wt. 457.5), pale brown color, m.p. 140-142°C, yield 50%; FT-IR (KBr cm<sup>-1</sup>),  $\nu_{\max}$  : 3353 (OH), 1717(C=O), 1651 (C=N), 1368(C=S);MS: m/z 457 (12%) of C<sub>21</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>5</sub>S and m/z at m/z 408.9(8%); Anal Calcd: C, 55.08; H, 3.50;Cl, 7.76; N, 9.18;S, 6.99; Found: C, 55.05; H, 3.49; Cl, 7.71; N, 9.15;S, 6.96.

### 2.2.8. Synthesis of 3-(2- chlorophenyl)-6- ((2, 4 -dihydroxybenzylidene) amino) 2, 3a, 4, 6-tetrahydroimidazo[4,5c] pyrazole-5-(3H) thione (8)

A mixture of **6** (0.01mol), and hydrazine hydrate (0.01mol) were added in ethanol (30 mL) was heated under reflux for 8 h, then cooled. The solvent was evaporated to dryness and the residue was recrystallized from ethanol to give **8**. C<sub>17</sub>H<sub>14</sub>ClN<sub>5</sub>O<sub>2</sub>S (M.wt. 387.5), reddish brown color, m.p. 110-112 °C and yield 60%; FT-IR (KBr cm<sup>-1</sup>),  $\nu_{\max}$  : 3380-3310 (OH),3270(NH),1625 (C=N), 1357(C=S). ; Anal Calcd: C, 52.65; H, 3.61; Cl, 9.16; N, 18.06;S, 8.26; Found: C, 52.62; H, 3.58; Cl, 9.13; N, 18.03;S, 8.23.

### 2.2.9. Synthesis of 10-(2-chlorophenyl)-3-((2,4-dihydroxybenzylidene) amino)-3,9,10,10a-tetrahydrobenzo[b]imidazo[4,5-e] [1,4] diazepine-2-(1H)-thione (9)

A mixture of **6** (0.01mol) with 1,2-diaminobenzene (0.01 mol) in sodium ethoxide (0.5 gm in 30 mL ethanol). The reaction mixture was refluxed for 8 h, then cooled and poured into ice cold water, drop 10% HCl. The solid obtained was filtered off, washed with hot water, dried and purified by recrystallization with ethanol to give **9**. C<sub>23</sub>H<sub>18</sub>ClN<sub>5</sub>O<sub>2</sub>S (M.wt. 463.5), brown color, m.p. 138-140°C, yield 75%; FT-IR (KBr cm<sup>-1</sup>),  $\nu_{\max}$ :3447 (OH), 3210(NH), 1627 (C=N), 1316(C=S).  $^1\text{H NMR}$  ( $\delta_{\text{ppm}}$ ) (DMSO*d*6):  $\delta$  12.85-12.95(s,2H, 2 $\times$ OH),9.68(s,1H, NH),8.3(s,1H, CH=N),7.36-7.61(m,7H, Ar-H) and 6.92(s,1H,

NH-diazoepine) ppm.  $^{13}\text{C}$ - NMR spectrum (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm) 181(C=S), 143.3(CH=N), 134, 143.5, 103-108, 121.9, 128, 114.8, 126.5, 134, 143.5, 128, 126, 128.1, 128.6, 132(two benzene ring), 58.1, 52.6(diazoepine) ; Anal Calcd: C, 59.55; H, 3.88; Cl, 7.66; N, 15.10; S, 6.90; Found: C, 59.52; H, 3.85; Cl, 7.63; N, 15.07; S, 6.87.

#### 2.2.10. 4-(((1,9-diacetyl-10-(2-chlorophenyl)-2-thio-1,9,10,10a-tetrahydrobenzo[b]imidazo[4,5-e] [1,4] diazepin-3(2H)-yl) imino) methyl)-3-hydroxyphenyl acetate (10)

A mixture of **9** (0.01 mol) and acetic anhydride (25 mL) was heated under reflux for 3 h, then cooled and poured into ice-diluted hydrochloric acid. The solid obtained was filtered off, washed with water, dried and purified by recrystallization with ethanol to give **10**.  $\text{C}_{29}\text{H}_{24}\text{ClN}_5\text{O}_5\text{S}$  (M.wt.589.5), dark brown color, m.p.108- 110 °C, yield 60%; FT-IR (KBr  $\text{cm}^{-1}$ ),  $\nu_{\text{max}}$ : 3437(OH), 1623 (C=N), 1312 (C=S).  $^1\text{H}$ NMR ( $\delta$ ppm) (DMSO $d_6$ ):  $\delta$  12.86(s,1H, OH),8.3(s,1H, CH=N),7.36-7.61(m,7H,Ar-H), 2.20-2.50 (s, 9H,3 $\times$ COCH $_3$ ) ppm;MS: m/z 592 (M+2, Cl,10.94%) of  $\text{C}_{29}\text{H}_{24}\text{ClN}_5\text{O}_5\text{S}$  and m/z 465 (9.04) ; Anal Calcd: C, 59.03; H, 4.07; Cl, 6.02; N, 11.87;S, 5.43; Found: C, 59.00; H, 4.04; Cl, 6.00; N, 11.84;S, 5.40.

#### 2.2.11. Synthesis of 4 -(2-chlorophenyl)-1- (2,4- dihydroxybenzylidene)-6- oxo-2-thio-2,3,5,6- tetrahydro-1H-imidazo [4,5c] pyridine -7-carbonitrile (11)

A mixture of chalcone of thiohydantoin**6**(0.01mol; 2.18gm), (0.02 mol; 2.66gm) ethylcyanoacetate and ammonium acetate (0.01mol; 0.77gm) in ethanol (30mL) was heated under reflux for 12 h. Cooled and poured into ice cold water, drop 10% HCl. The solid obtained was filtered off, washed with hot water, dried and purified by recrystallization with ethanol to give **11**.  $\text{C}_{20}\text{H}_{12}\text{ClN}_5\text{O}_3\text{S}$  (M.wt. 437.5), brown color, m .p. 188 -190°C and yield 65%; FT-IR (KBr  $\text{cm}^{-1}$ ) ,  $\nu_{\text{max}}$  : 3363 (OH), 3317(NH), 2260( $\nu\text{C}\equiv\text{N}$ ), 1630(C=O), 1625 (C=N), 1357(C=S).  $^1\text{H}$  NMR ( $\delta$ ppm) (DMSO $d_6$ ):  $\delta$ 11.36-10.10(s,2H, 2 $\times$ OH),11.19-11.10(s,2H,1NH),8.46(s,1H, CH=N),6.31-7.37 (m,3H, Ar-H) ppm. Anal Calcd: C, 54.86; H, 2.74; Cl, 8.11; N, 16.00; S, 7.31; Found: C, 54.83; H, 2.70; Cl, 8.08; N, 15.97;S, 7.28.

#### 2.2.12. Synthesis of 3 -(chlorophenyl)-1- (2,4- dihydroxybenzylidene)-2,6- dithio-2,3,5,6- tetrahydro-1H-imidazo [4,5c] pyridine -7-carbonitrile (12)

A mixture of **11** (0.01mol), and phosphorus pentasulphide (0.01 mol) in the presence of catalytic drop off (pyridine) were heated under reflux for 6 h. Cooled and poured into ice cold water, drop 10% HCl. The solid obtained was filtered off, washed with hot water, dried and purified by recrystallization with toluene to give **12**.  $\text{C}_{20}\text{H}_{12}\text{ClN}_5\text{O}_2\text{S}_2$  (M W453.5), brown color, m.p. 300 -302°C and yield 60%; FT-IR (KBr  $\text{cm}^{-1}$ ),  $\nu_{\text{max}}$  : 3433(OH),3270(NH),1625(C=N), 1304(C=S). Anal Calcd: C, 52.97; H, 2.65; Cl, 7.83; N, 15.43; S, 14.11; Found: C, 52.94; H, 2.63; Cl, 7.80; N, 15.40; S, 14.08.

#### 2.2.13. Synthesis of 4- (2- chlorophenyl)-1-(2,4-dihydroxy benzylidene) amino)-3,6-dihydroimidazo[4,5-d] pyrazolo[3,4-b] pyridine -2H- thione (13)

A mixture of **12** (0.01mol), and hydrazine hydrate (0.01mol) was added in ethanol (30 mL) was heated under reflux for 8 h, and then cooled. The solvent was evaporated to dryness and the residue was recrystallized from ethanol to give **13**.  $\text{C}_{20}\text{H}_{14}\text{ClN}_7\text{O}_2\text{S}$  (M 451.5), pale brown color, m.p. 310-312°C and yield 60%; FT-IR (KBr  $\text{cm}^{-1}$ ),  $\nu_{\text{max}}$ : 3464 (OH), 3336-3237(NH $_2$ ),3181(NH),1282 (pyrazole ring). $^1\text{H}$  NMR ( $\delta$ ppm) (DMSO $d_6$ ):  $\delta$ 11.80-10.6(s,2H, 2 $\times$ OH),10.80-9.5(s,2H, NH),8.3(s,1H, CH=N),7.08-7.34(m,3H, Ar-H) and 4.5(s,2H, NH $_2$ ) ppm. Anal Calcd: C, 53.16; H, 3.10; Cl, 7.86; N, 21.70; S, 7.08; Found: C, 53.13; H, 3.07; Cl, 7.83; N, 21.67; S, 7.05.

### *2.3. Coating Composition and Film Preparation*

The coating compositions were prepared by means of incorporating thiohydantoin derivatives (**5**, **6**, and **11**), in the ratio of 1.0, 2.0 and 3 %, into epoxy varnish. The coating compositions were applied to steel and wood panels by means of a brush or by sweeping. All efforts were made to maintain a uniform film thickness of 50 +/- 5 $\mu\text{m}$  for evaluating the properties of modified films.

#### 2.3.1. Drying Time

To determine Set-To-Touch Time-lightly touch the test film at a point not less than 15 mm from the film edges with the tip of a clean finger and immediately places the fingertip against a piece of clean glass. Observe if any of the coating transferred to the glass. The film considered to set to-touch when it still shows a tacky condition, but none of it adheres to the finger (Surface dry).

#### 2.3.2. Hard Dry Time

With the end of the thumb resting on the test film and the forefinger supporting the test panel, exert a maximum downward pressure (without twisting) of the thumb on the film. Lightly polish the contacted area with a soft cloth. The film considered dry-hard when any mark left by the thumb completely removed by the polishing operation<sup>(24)</sup>.

### *2.4. Anti-Corrosion Testing*

The test pieces were 20 x 20 x 3 mm. The paint formulations were evaluated on coated mild steel panels. To ensure that the steel panels were free of all surface contamination before the coating application, mechanically pre-treatment, involving polishing with wire brushing and sand paper for cleaning of the surface to obtain a smooth surface, followed by degreasing with acetone and then rinsed with distilled water, dried between two filter papers. A salt fog chamber was utilized for each of the resin formulations; with a set of three coated panels being placed in the salt spray chamber

according to ASTM<sup>(25)</sup>. The corrosion resistance was evaluated in terms of blistering, scribe failure and a degree of rusting, in relation to ASTM standards<sup>(26-28)</sup>.

### 2.5. Flame Retardant Testing Method

The performance of epoxy varnish, with incorporated thiohydantoin derivatives(**5,6**and**11**) additives, was evaluated in a limited oxygen index (LOI) chamber. LOI values were determined by standardized test methods<sup>(29)</sup>. The test panels were prepared using a combustible material (wood specimen). It was important that the panels were free of any surface contamination, or imperfections, prior to the coating application. Hand tool cleaning (sand paper) was carefully used to treat the faces and edges of the panels. Final dry film thickness (DFT) was 50 +/- 5µm. In all cases, the film application was applied by means of brushing. Following 10 days of air drying, the panels under study were heated at 50-60°C for 2 h. to eliminate any remaining solvent.

### 2.6. Screening Antimicrobial Activity

Preliminary screening for the antimicrobial activity of synthesized compounds using standardized disc-agar diffusion method<sup>(30)</sup> against *Staphylococcus aureus*, *Bacillus subtilis* (Gram positive bacteria), and *Salmonella*, *Escherichia coli* (gram-negative bacteria), and *Candida albicans*(yeast) *Aspergillus fumigatus*(fungi) compared with standard antimicrobial agents. The diameters of zone of inhibition were measured and compared with that of the standard, and the values were tabulated. Chloramphenicol was used as standard for the reference in the case of Gram – negative bacteria, Cephalothin was used as a standard reference in the case of Gram – positive bacteria and cycloheximide was used as the standard reference in the case of yeasts and fungi) and the observed zone of inhibition is presented in Table 1.

An antibiotic is a growing problem, some of this is due to the overuse of antibiotics in human, but some of it is probably due to the use of antibiotics as growth promoters in food of animals<sup>(31)</sup>. So, there is growing demand for new antibiotics. Thiohydantoin derivatives were reported to exhibit interesting antimicrobial activity<sup>(32)</sup>.

## 3. Results and Discussion

### 3.1. Chemistry

The synthetic pathways of preparation of novel heterocyclic compounds containing hetero nitrogen and sulfur atoms are shown in(scheme 1).In the present work ,the starting 2,4-dihydroxybenzylidene thiosemicarbazones (**1**) was prepared from 2,4-dihydroxy benzaldehyde and thiosemicarbazide in ethanol afforded(**1**). The structure **1** was confirmed by elemental analysis and spectral data.

Treatment of 2,4-dihydroxybenzylidene thiosemicarbazones (**1**)with acetic anhydride under reflux to yielded the corresponding *N,N*,1-triacetoxy-2-((2,4- dihydroxybenzylidene)hydrazine carbothioamide (**2**).The structure of the compound was confirmed on the basis of their elemental analysis and spectral data such as IR and NMR spectra .The IR and NMR of the compound showed disappearance of NH and NH<sub>2</sub> groups and revealed absorption bands characteristic for C=O and CH<sub>3</sub> groups in IR spectrum and nine protons of 3×COCH<sub>3</sub> at δ= 2.48 ppm in<sup>1</sup>HNMR spectrum.

The reaction of 2,4-dihydroxybenzylidene thiosemicarbazones (**1**)with ethyl chloroacetate in ethylchloroacetate in ethanol<sup>(33)</sup>containing fused sodium acetate to afford the corresponding 3-((2,4-dihydroxybenzylidene)amino)-2-thioxoimidazolidin-4-one (**3**).The structure(**3**)was elucidated by spectral data and elemental analysis (cf.Exp).The IR spectrum which showed absorption bands at 3360,3244 cm<sup>-1</sup>, attributable to νOH, νNH, and the two protons attributable NH, CH=N revealed signals in <sup>1</sup>HNMR spectrum (c.f.Exp)Acetylation of compound 3 with acetic anhydride under reflux to give 4-(((3- acetyl-5-oxo-2-thioxoimidazolidin-1-yl) imino )methyl)-1,3-phenylene diacetate (**4**).The infrared, which showed absence absorption bands of NH and 2×OH,whil in <sup>1</sup>HNMR which showed absence absorption bands of NH and two OH groups.

On the other hand 2, 4-dihydroxybenzylidene thiosemicarbazones (**1**) was allowed to react with 9-bromomethylaryl ketone such as (4-methoxy phenylbromide) in ethanol containing fused sodium acetate afforded the corresponding 4-((2-(5-(4-methoxy phenyl)thiazol-2-yl)hydrazono)methyl)benzene-1,3-diol (**5**).The confirmed structure of compound 5 by element analysis and spectral data. The infrared spectra which showed absorption bands at 3476, 3298cm<sup>-1</sup>, attributable to νOH, νNH.The<sup>1</sup>HNMR and <sup>13</sup>C NMR spectra of compound 5 revealed signals at δ=9.67,3.80ppm (NH and OCH<sub>3</sub>) and δ=141.15,57.19 for(CH=N and OCH<sub>3</sub>).

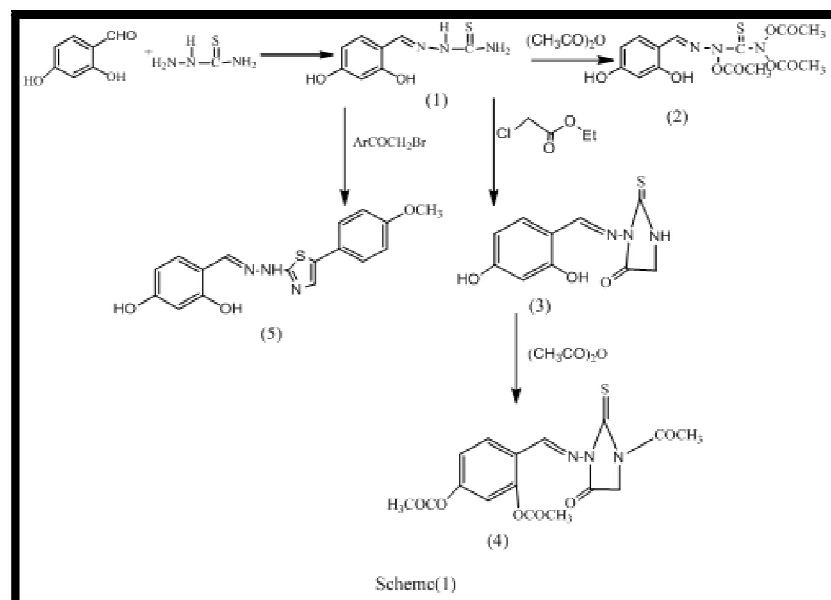


Figure 1

On the other hand In (scheme2) condensation of 3-((2,4-dihydroxybenzylidene)amino)-2-thioxoimidazolidin-4-one (**3**)<sup>(34)</sup> with aromatic aldehydes such as (2-chlorobenzaldehyde) ethanolic sodium hydroxide solution to formation 5-(2-chlorobenzylidene-3-(2,4-dihydroxybenzylidene) amino)-2-thioxoimidazolidin-4-one (**6**). The structure of **6** was confirmed by analytical and spectral data. The IR spectrum showed absorption bands at 3444, 3260 attributable to ( $\nu$ OH) and ( $\nu$ NH). <sup>1</sup>HNMR spectrum of **6** showed signals at  $\delta$ =6.70, 8.58 ppm due to presence of one proton of (C=CH, olefinic) and one proton of (CH=N). The <sup>13</sup>C-NMR spectrum of compound **6** revealed the signals characteristic for (C=CH, olefinic) at  $\delta$  = 120.2, whereas, the (CH=N) at  $\delta$  = 143.3 ppm.

The structure of **6** was established chemically via reaction with acetic anhydride under reflux to produce 4-(((3-acetyl-4-(2-chlorobenzylidene)-5-oxo-2-thioxoimidazolidin-1-yl)imino)methyl)-3-hydroxyphenyl acetate (**7**). The IR spectra of compound **7** which showed absence absorption bands of NH and one OH group. Also, MS of compound **7** gave fragments showing the isotopic pattern due to the presence of chlorine atom and appear molecular ion peak like molecular weight (CF. Exp).

Treatment of **6** with hydrazine hydrate in ethanol to give 3-(2-chlorophenyl)-6-((2,4-dihydroxybenzylidene) amino)2,3a,4,6-tetrahydroimidazo[4,5c] pyrazole-5-(3H) thione (**8**). The IR spectrum which lack absorption band of C=O group.

Also 10-(2-chlorophenyl)-3-((2,4-dihydroxybenzylidene)amino)-3,9,10,10a-tetrahydrobenzo[b]imidazo[4,5-e][1,4]diazepine-2-(1H)-thione (**9**)<sup>(35)</sup> were prepared from the condensation of chalcone derivative **6** with O-phenylenediamine in sodium ethoxide (NaOH/ETOH).

The structure of **9** was confirmed by analytical and spectral data. IR spectrum showed disappearance of C=O of chalcone and appearance of NH bands of diazepine. <sup>1</sup>HNMR spectra showed signal at 6.92 ppm attributable to one singlet proton for NH of diazepine. The <sup>13</sup>C-NMR spectra revealed the signals

The structure of compound **9** was established chemically via the reaction with acetic anhydride under boiling to give 4-(((1,9-diacetyl-10-(2-chlorophenyl)-2-thioxo-1,9,10,10a-tetrahydrobenzo[b]imidazo[4,5-e][1,4]diazepin-3(2H)-yl)imino)methyl)-3-hydroxyphenyl acetate (**10**). IR spectrum which of absorption bands of only one OH and disappeared of two NH and other OH groups. Its <sup>1</sup>HNMR spectrum showed lack signals of three protons corresponding to (two NH and one OH). The mass spectrum showed m/z 592 (22%) promoting its molecular formula. (cf. exp)

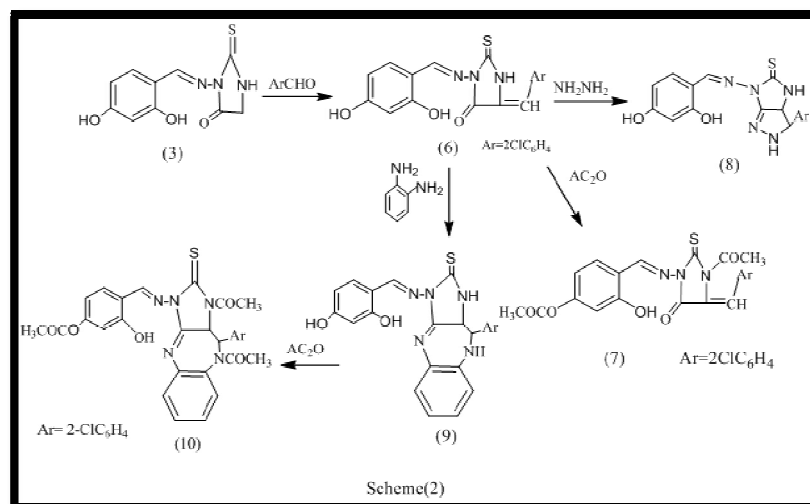


Figure 2

On other hand the reaction of 3-[(2,4- dihydroxybenzylidene )amine ]-4-oxo-imidazolidin -2-thiones (6)with ethyl cyanoacetate in the presence of ammonium acetate in ethanol under reflux afforded the corresponding 4 -(2-chlorophenyl)-1- (2,4- dihydroxybenzylidene )-6- oxo-2-thioxo-2,3,5,6- tetrahydro-1H-imidazo [4,5c]pyridine -7-carbonitrile(11) in (scheme 3).

The structure 11 was elucidated on the basis of spectral data and element analysis. The IR spectrum show appearance of absorption band at 2260cm<sup>-1</sup>attributable to  $\nu$ C $\equiv$ N.<sup>1</sup>HNMR spectrum, which lack of signal of C=CH group and revealed signal at  $\delta$ =11.19-11.10 ppm attributable of NH of thepyridine ring.

Reaction of compound 11with phosphorous pentasulfide in dry pyridine (36)to afford 3-(chlorophenyl)-1-(2,4-dihydroxybenzylidene)-2,6-dithioxo-2,3,5,6- tetrahydro-1H-imidazo [4,5c] pyridine -7-carbonitrile (12).The structure of12was confirmed by element analysis and spectral data .In the IR spectrum, which disappearance of C=O which replaced by C=S group at 1304cm<sup>-1</sup>.The synthesis of 4-(2-chlorophenyl)-1-(2,4-dihydroxybenzylidene) amino )-3,6-dihydroimidazo [4,5-d] pyrazolo[3,4-b]pyridine-2H- hione(13) via the reaction of a compound 12 with hydrazine hydrate in ethanol (scheme3).

The compound 13 was established by spectral data. The infrared spectrum of 13 was identified by absence of  $\nu$ C $\equiv$ N of two groups and which revealed an absorption band in 1282cm<sup>-1</sup> of pyrazole ring and absorption band 3336-3237 cm<sup>-1</sup>(NH<sub>2</sub>).The <sup>1</sup>HNMR spectrum, which showed of the signal of two protons for NH<sub>2</sub> $\delta$ =4.5 ppm signal of one proton for NH-pyrazole ring  $\delta$ =10.8 ppm.

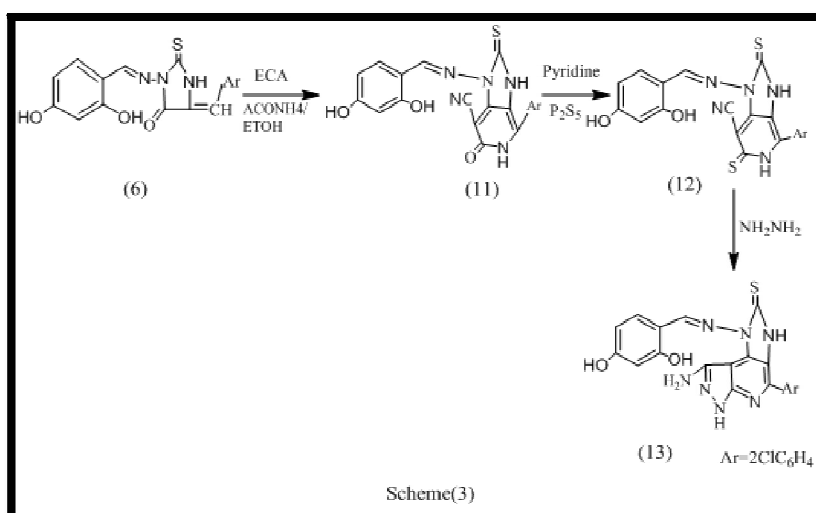


Figure 3

### 3.2. Screening Antimicrobial Activity

The results of this study showed that the compound (5, 6 and 11) was the high potent thiohydantoin derivative against Staphylococcus aureus, Bacillus subtilis (Gram positive bacteria), more than Salmonella, Escherichia coli (gram – negative bacteria). (5, 6 and 11) compounds synthesized have high potentials against Candida albicans (yeast) both (6 and 11) not have any effect at Aspergillusfumigatus(fungi), but compound (5) has low effective at Aspergillusfumigatus(fungi).

		Mean* of zone diameter, nearest whole mm.											
organism		Gram - positive bacteria				Gram - negative bacteria				Yeasts and Fungi**			
		<i>Staphylococcus aureus</i> (ATCC 25923)		<i>Bacillus subtilis</i> (ATCC 6635)		<i>Salmonella typhimurium</i> (ATCC 14028)		<i>Escherichia coli</i> (ATCC 25922)		<i>Candida albicans</i> (ATCC 10231)		<i>Aspergillus fumigatus</i>	
conc.	sample	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml	1 mg/ml	0.5 mg/ml
	5	19I	16I	15I	13I	7L	6L	15I	14I	29H	25H	9L	8L
	6	13I	10I	18I	16I	9L	8L	13I	12I	27H	25H	7L	6L
	11	14I	11I	18I	14I	11L	6L	14L	10L	28H	25H	11L	8L
	control	35	26	35	25	36	28	38	27	35	28	37	26

Table 1: Anti-Microbial Activity of Thiohydantoin Derivatives

The antimicrobial screening data show that the compounds exhibit antimicrobial properties. The increased activity of the novel thiohydantoin can be explained by the hydroxyl group, which acts as more powerful and potent bactericidal agents

The structural feature may increase the activity of the tested compound since possess free Cl and hydroxyl groups.  $\pi$ -electron delocalization over the thiohydantoin increases the lipophilic character and favors its permeation through the lipid layer of the bacterial membranes. It was concluded that thiohydantoin acting as electrophilic agents have a positive effect and inhibited bacterial growth<sup>(37)</sup>.

### 3.3. Coating Evaluation

After the successful preparation of the Thiohydantoin compounds, some of these compounds ( 5 , 6 and 11 ) were selected, and physically inserted into a coating formulation as modifiers, after that, the influence of these modifications on some properties of epoxy coating such as the drying time of film formation, as well as the possibility of using these derivatives as anti-corrosive and as flame retardants, were studied.

These results are tabulated in table (2) and represented in the figure (1) for drying time, table (3) and figures (2-5) for anti-corrosion, and table (4) and figure (7) for flame retardant.

### 3.4. Drying Time

From the previous table 2 and Figure 7 it is clear that insert thiohydantoin modifiers leads to shortening in both surface and hardener drying times.

As the increasing percentage of modifier, the drying times decrease.

Sample No.	Modifier %	Surface dry (minute)	Hardener dry (minute)
Blank	0.00	235	410
Epoxy modified with 5	1.00	150	390
	2.00	140	345
	3.00	115	310
Epoxy modified with 6	1.00	160	400
	2.00	145	365
	3.00	120	310
Epoxy modified with 11	1.00	160	370
	2.00	130	300
	3.00	110	270

Table 2: Surface Dry and Hardener Dry of Epoxy Modifier with Thiohydantoin Derivatives at 25°C



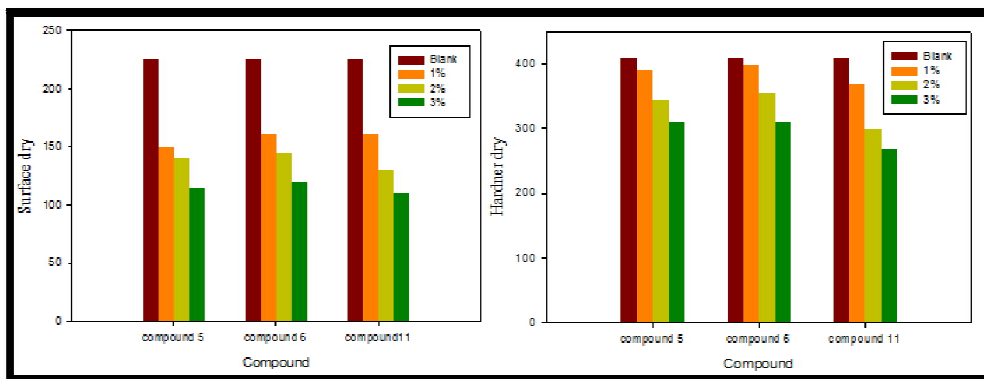


Figure 4: Plot of Effect Modification and Concentration on Surface Dry & Hard Dry- of Modified Epoxy.

3.5. Corrosion Resistance

The modified epoxy paint compositions were prepared by means of incorporating thiohydantoin derivatives (5, 6, and 11) by the ratio of 1.0, 2.0 and 3.0% by weight into epoxy paint and adjusted film thickness about  $50 \pm 5\mu\text{m}$  were evaluated as the anti-corrosive. After preparing the coated test panels according to experimental section, they were exposed to salt spray tests (salt fog) according to ASTM for 500 h. The blistering size is graded from 10 to 0, where 10 representative of no blistering and 0 representative of the largest blister. Blistering frequency is denoted by F, M, MD and D (few, medium, medium dense and dense). Painted, or coated, specimens subjected to a corrosive environment are also evaluated by recording the average maximum and minimum creep age from the scribe mark. Scribe failure is also rated on a scale from 10 to 0, with 10 being (zero mm) from the scribe mark and 0 is (16 mm) from the scribe mark. Finally, the comparison of the surface appearance, to determine the percentage of the area that has been rusted, is also used. The rust grade is rated on ascale from 10 to 0, where 10 is non-rusting and 0 is severe rusting.

The corrosion resistance of the painted films of modified sample is given in Table (3) and Fig (2,3,4, ad5); explains the photo of the painted films after salt test spray (5% of NaCl).

Sample	Modifier %	Blistering		Scribe Failure (mm)	Rust Grade
		Size	Frequency		
Blank	0	2	M	13	2
Epoxy modified with 5	1.00	3	M	6	4
	2.00	4	M	3	6
	3.00	7	MD	2	6
Epoxy modified with 6	1.00	5	MD	10	3
	2.00	6	Few	6	7
	3.00	8	M	4	8
Epoxy modified with 11	1.00	4	Few	10	6
	2.00	6	M	7	8
	3.00	6	MD	6	8

Table 3: Evaluation the Corrosion Resistance of the Painted Films

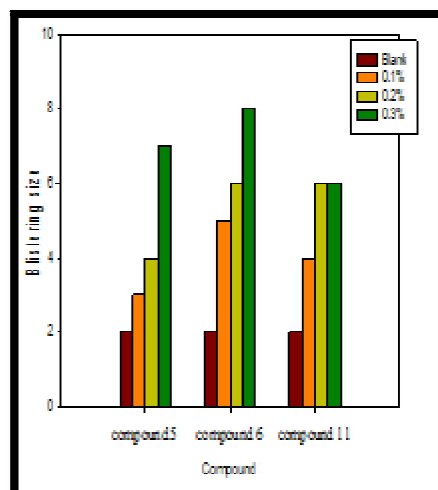


Figure 5: Plot of Effect Modification and Concentration on Blistering of Modified Epoxy

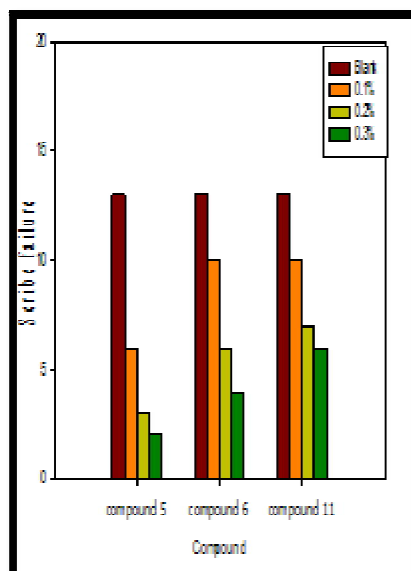


Figure 6: Plot of Effect Modification and Concentration on Scribe Failure of Modified Epoxy

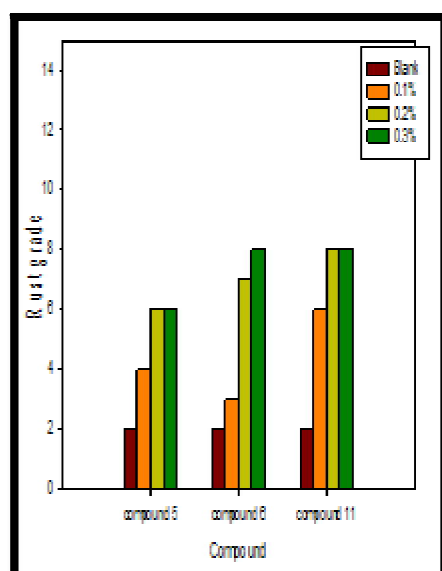


Figure 7: Plot of Effect Modification and Concentration Rust Grade of Modified Epoxy

Concerning with the blistering test the dates given in tables (3) show that all modifiers improve the blistering and as the concentration of modifier increase blistering resistance increase. Particularly modified varnish by modifier 5-(2-chlorobenzylidene-3-(2,4-dihydroxybenzylidene) amino)-2-thioxoimidazolidin-4-one (6). About the Scribe failure test from the data given in tables (3); it is clear that the adding of modifiers improves the scribe value. It is clear that the compounds 4-((2-(5-(4-methoxyphenyl) thiazol-2-yl) hydrazono )methyl) benzene-1,3-diol (5) give the best results which shifts from 13 mm within epoxy varnish along to (2 mm) within epoxy varnish modified 3%.The order of inhibition can be arranged as follows: 5>6>11.

Finally rust grade of epoxy modified films the adding of modifiers in all percentage improves the rust grade inhibition, especially the modifier 4 -(2-chlorophenyl)-1- (2,4- dihydroxybenzylidene )-6-oxo-2-thioxo-2,3,5,6- tetrahydro-1H-imidazo [4,5c]pyridine-7-carbonitrile (11).From the previous study it is clear that there are satisfactory differences between the blank and modified samples, the thiohydantoin derivatives (5, 6 and 11) are considered a corrosion inhibitor for mild steel when added to epoxy coating. The improvement of corrosion resistance may be attributed to the introducing of a compound that containing nitrogen, sulfur, and oxygen atoms and aromatic rings into its structure. Corrosion inhibition is caused by the adsorption of thiohydantoin molecules onto the surface of the mild steel as shown in Figure (6).



Figure 8: The Photo of the Painted Samples after Exposed to Salt Spray Test (5%NaCl)

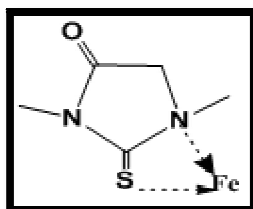


Figure 9: Adsorption of Thiohydantoin on Mild Steel Surface

### 3.5.1. Evaluation of Thiohydantoin Derivatives as a Flame Retardant

Flame retardancy are materials that are conducted to provide fire protection for flammable consumer goods, as well as to mitigate fire growth in a wide range of fires This paper is in the field of applied science that is concerned with the study of flame retardants.

The LOI is defined as the minimum concentration oxygen, expressed as a percentage that will support combustion of a polymer. It is measured by passing a mixture of oxygen and nitrogen over a burning specimen, and reducing the oxygen level until a critical level is reached. The LOI is expressed as:

$$LOI = 100 \frac{[O_2]}{[O_2] - [N_2]}$$

This method proved suitable as a semi-quantitative indicator of the effectiveness of the flame retardant during the research and development phase of the work. This was due to the fact that the equipment is relatively inexpensive and the size of the test sample that is required is reasonably small. It is clear that the incorporation of thiohydantoin derivatives into epoxy paint, in the ratio's mentioned in the experimental section, results in enhanced flame retardancy when compared with an epoxy control sample. The results obtained from the LOI test are shown in table (4) and figure (7), which proved that increasing the percentage of modifier of thiohydantoin derivative compound (5,6, and11) lead to increasing limiting oxygen index (LOI) (11>5>6)

The improvement of LOI value may be attributed to the introducing of a compound that containing nitrogen, sulfur, oxygen, and chlorine atoms and aromatic rings within their structure.

Sample	Modifier %	Limiting Oxygen Index (LOI)
Blank	0.00%	20
Epoxy modified with 5	1.00%	30
	2.00%	38
	3.00%	40
Epoxy modified with 6	1.00%	26
	2.00%	32
	3.00%	34
Epoxy modified with 11	1.00%	33
	2.00%	40
	3.00%	45

Table 4: Limiting Oxygen Index (LOI) of Modified Epoxy Thiohydantoin

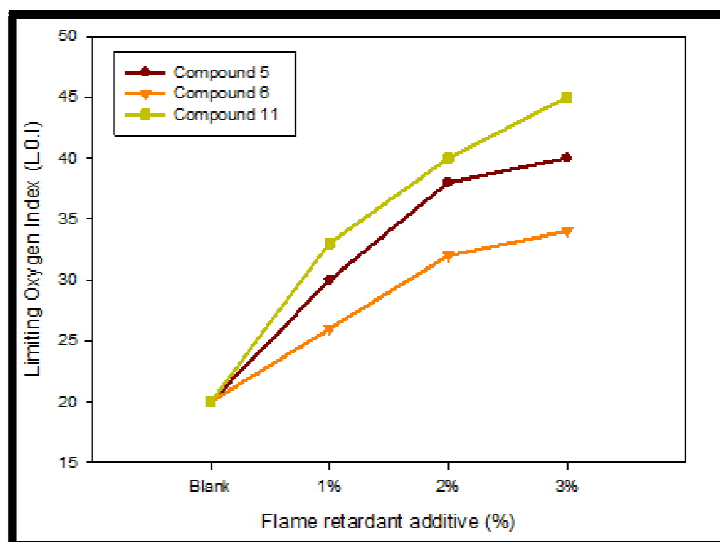


Figure 10: Limiting Oxygen Index (LOI) – Flame Retardant Additive Curve in Absence and Presence of Different Concentration of Modified Epoxy

#### 4. Conclusion

In the present work, a series of some new heterocyclic compounds (**1-13**) containing thiohydantoin moiety were synthesized, the structures of the new compounds were confirmed by suitable physical, chemical methods and were tested for their antimicrobial activities. Compounds (**5,6, and 11**) were the most potent thiohydantoin derivative against Gram-positive and Gram-negative bacteria. Also, they are exhibiting an impressive result as a new green corrosion inhibitor as well as flame retardant additives when physically incorporating into epoxy resin to form a new modified epoxy varnish. Corrosion inhibitor was carried out by using salt spray technique, and flame retardant was evaluated by measuring the limiting oxygen index (LOI) of the coated films.

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