



## Synthesis and Biological Evolution of Derivatives of Thiosemicarbazide

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### Abstract:

We have in the present study, the pharmacological properties of derivatives of thiosemicarbazide, synthesis of substituted 1-(1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl) ethylidene) thiosemicarbazide are carried out by refluxing 5-acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one and thiosemicarbazide in equimolar ratio in the presence of alcohol, acetic acid. The chemical structures of the synthesized compounds were confirmed by means of IR, 1H-NMR, Mass spectral and Elemental analysis. These compounds were screened for anti-bacterial, anti-fungal and antioxidant activities. Antimicrobial activities of the compounds were also determined at different levels of concentration. Most of the synthesized compounds exhibited mild to moderate anti-bacterial, anti-fungal and antioxidant activities.

**Keywords:** Synthesis, Thiosemicarbazide, Antioxidant, Anti-Bacterial And Anti-Fungal Activities.

### Introduction:

Heterocyclic thiones and thiosemicarbazide, which contain chemically active N(H)C(S) or =NN(H)C(S) group, are useful model compounds for sulfur-containing analogues of purine and pyrimidine bases. In view of the pharmacological properties of thiosemicarbazide, pyrimidine derivatives and heterocyclic annulated pyrimidines continue to attract great interest due to the wide variety of interesting biological activities observed for these compounds, such as anticancer [1], antiviral [2], antitumor [3], anti-inflammatory [4], antimicrobial [5], antifungal [6], antihistaminic [7] and analgesic [8] activities. Thiosemicarbazide and their derivatives form an important class of organic compounds due to their structural chemistry and biological activities, such as antibacterial, antivirus

activities and cerebral infarction (Free radical scavenger) [9]. Thiosemicarbazide derivatives are reported to show biological activity, including antifungal, anti-HIV, analgesic, anti-inflammatory and anti-tumor effects [10-16]. It is also reported for dielectric studies [17]. Looking to the usefulness and importance of thiosemicarbazide and pyrimidine, it was considered worthwhile to the synthesis hybrid scaffolds.

### Material and Methods:

All solvents were distilled prior to use. TLC was performed on silica gel G. Melting points were determined by open capillary method and are uncorrected. 1H NMR spectra were recorded in CDCl<sub>3</sub>/DMSO-d<sub>6</sub> solution on a Bruker Avance II 400 NMR Spectrometer. Chemical shifts are reported in ppm using TMS as an

internal standard. IR spectra were obtained on a Shimadzu FT-IR spectrophotometer using KBr discs. Mass spectra were recorded by using Shimadzu gas chromatograph.

**Synthesis of substituted 1-(1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene)thiosemicarbazide (2a-i):**

A mixture of substituted 5-acetyl-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one (0.01 mol), thiosemicarbazide (0.01

mol), 30 mL of ethanol and 5mL acetic acid was added. The mixture was refluxed on water bath at 80-90°C for 5-6 hr. The progress of reaction was monitored by TLC. The excess of ethanol was distilled off and reaction mixture was poured in ice-cold water to isolate solid product. Further crystallized from methanol-acetic acid. Physical characterization data depicted in (Table 1).

**Table 1: Physical characterization data of synthesized new compound (2a-i)**

Entry	R1	R2	X	Molecular formula	MW	M.P. (°C)	Yield <sup>A</sup> (%)
2a	H	H	O	C <sub>14</sub> H <sub>17</sub> N <sub>5</sub> O <sub>2</sub> S	303	180	87
2b	OCH <sub>3</sub>	H	O	C <sub>15</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub> S	333	124	79
2c	OH	H	O	C <sub>14</sub> H <sub>17</sub> N <sub>5</sub> O <sub>2</sub> S	319	119	75
2d	Cl	H	O	C <sub>14</sub> H <sub>16</sub> ClN <sub>5</sub> O <sub>2</sub> S	337	125	91
2e	H	Cl	O	C <sub>14</sub> H <sub>16</sub> ClN <sub>5</sub> O <sub>2</sub> S	337	182	90
2f	H	H	S	C <sub>14</sub> H <sub>17</sub> N <sub>5</sub> S <sub>2</sub>	319	201	89
2g	OCH <sub>3</sub>	H	S	C <sub>15</sub> H <sub>19</sub> N <sub>5</sub> O <sub>2</sub> S <sub>2</sub>	349	146	76
2h	OH	H	S	C <sub>14</sub> H <sub>17</sub> N <sub>5</sub> O <sub>2</sub> S <sub>2</sub>	335	209	78
2i	H	Cl	S	C <sub>14</sub> H <sub>16</sub> ClN <sub>5</sub> S <sub>2</sub>	353	213	85

<sup>A</sup> Isolated Yield

**Anti-Microbial Activity:**

All the title compounds were screened for their anti-bacterial and anti-fungal activities. The antibacterial activity of the synthesized compounds was tested against one-gram positive bacteria (*Staphylococcus aureus*) and two-gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) using Muller-Hinton agar medium. The anti-fungal activities of the compounds were tested against one fungus namely *Candida albicans* using Muller-Hinton agar medium. For preliminary screening, the anti-microbial tests were carried out by the cup-plate method. Antimicrobial activities of the compounds were also determined at different levels of concentration.

**Antibacterial Study:**

The antibacterial activity of compounds (2a-i) was assayed at different level of concentration (25, 50, 100 µg/mL) in solvent DMSO against strains of gram +ve and gram -ve pathogenic bacteria (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*). Initially, susceptibility testing was carried out by measuring the inhibitory zone diameter on Muller-Hinton agar, with conventional cup-plate method. The plates were incubated at 37.5°C for 24 hr and the inhibitory zone diameters were measured in millimeter (mm). The inhibitory effects of compounds (2a-i) against these organisms are depicted in Table 2. The results were compared with Doxycycline and Ampicillin.

**Antifungal Study:**

The antifungal activities of compounds (**2a-i**) were assayed in vitro at different level of concentration (25, 50, 100 µg/mL) in solvent DMSO against *C. albicans*. Fluconazole was used as standard

fungicide for the antifungal test. Muller-Hinton agar was used as basal medium for test fungi, Screening was carried out by conventional cup-plate method. The plates were then incubated at 37.5°C for 48 hours. The zone of inhibition was measured in mm. (**Table 2**)

**Table 2: Antimicrobial–screening results of synthesized new compound (2a-i)**

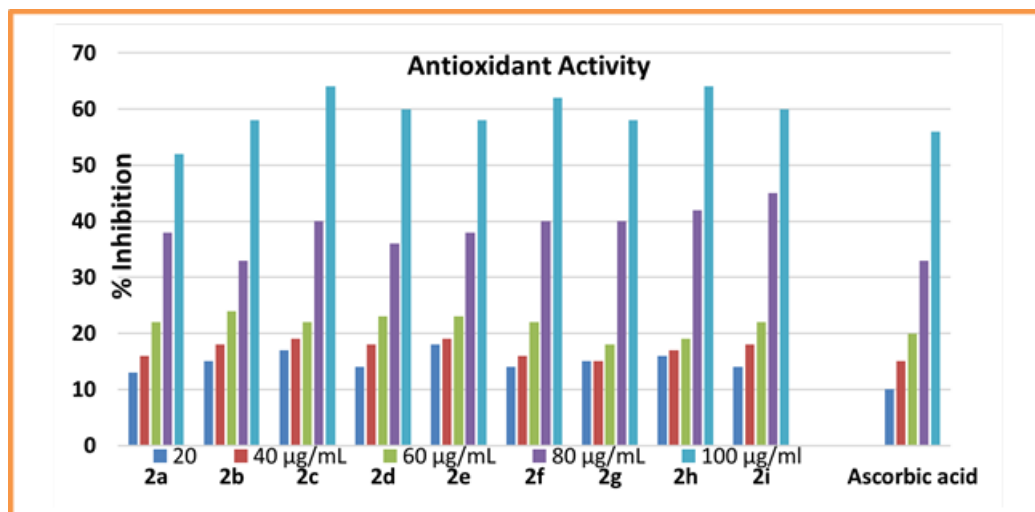
Entry	Bacterial Strain									Fungal Strain		
	<i>E. Coli</i>			<i>P. Aeruginonasa</i>			<i>S. Aureus</i>			<i>C. Albican</i>		
	100 µg	50 µg	25 µg	100 µg	50 µg	25 µg	100 µg	50 µg	25 µg	100 µg	50 µg	25 µg
<b>2a</b>	13	11	9	10	8	-	13	10	-	14	11	9
<b>2b</b>	12	10	8	9	7	-	13	10	-	13	10	8
<b>2c</b>	12	10	8	9	7	-	12	10	-	13	10	8
<b>2d</b>	11	10	8	8	6	-	10	9	-	12	10	8
<b>2e</b>	13	11	9	10	8	-	11	9	-	14	11	9
<b>2f</b>	11	9	8	9	7	-	12	9	-	12	10	8
<b>2g</b>	12	10	8	9	7	-	12	10	-	13	11	8
<b>2h</b>	13	10	8	10	8	-	13	10	-	12	10	8
<b>2i</b>	13	11	9	10	8	-	12	9	-	14	11	9
Ampiciline	18	15	12	15	12	9	32	29	24	-	-	-
Doxicycline	35	30	20	14	12	10	36	32	25	-	-	-
Fluconazole	-	-	-	-	-	-	-	-	-	33	30	11

**Antioxidant Activity:**

Free radical scavenging activity of the test compounds (**2a-i**) were determined by the 1, 1- diphenyl picryl hydroxyl (DPPH) assay method [18]. Drug stock solution (1 mg mL<sup>-1</sup>) was diluted to final concentrations of 2, 4, 6, 8 and 10 mg mL<sup>-1</sup> in methanol. DPPH methanol solution (1 mL, 0.3 mmol) was added to 2.5 mL of drug solutions of different concentrations and allowed to react at room temperature. After 30 min the absorbance values were measured at 518 nm and converted into the percentage antioxidant activity. Methanol was used as the solvent and ascorbic acid as the standard. Results are presented in **Table 3**. The standard drug used was ascorbic acid.

**Table 3 : Antioxidant activity of the compounds 2a-i**

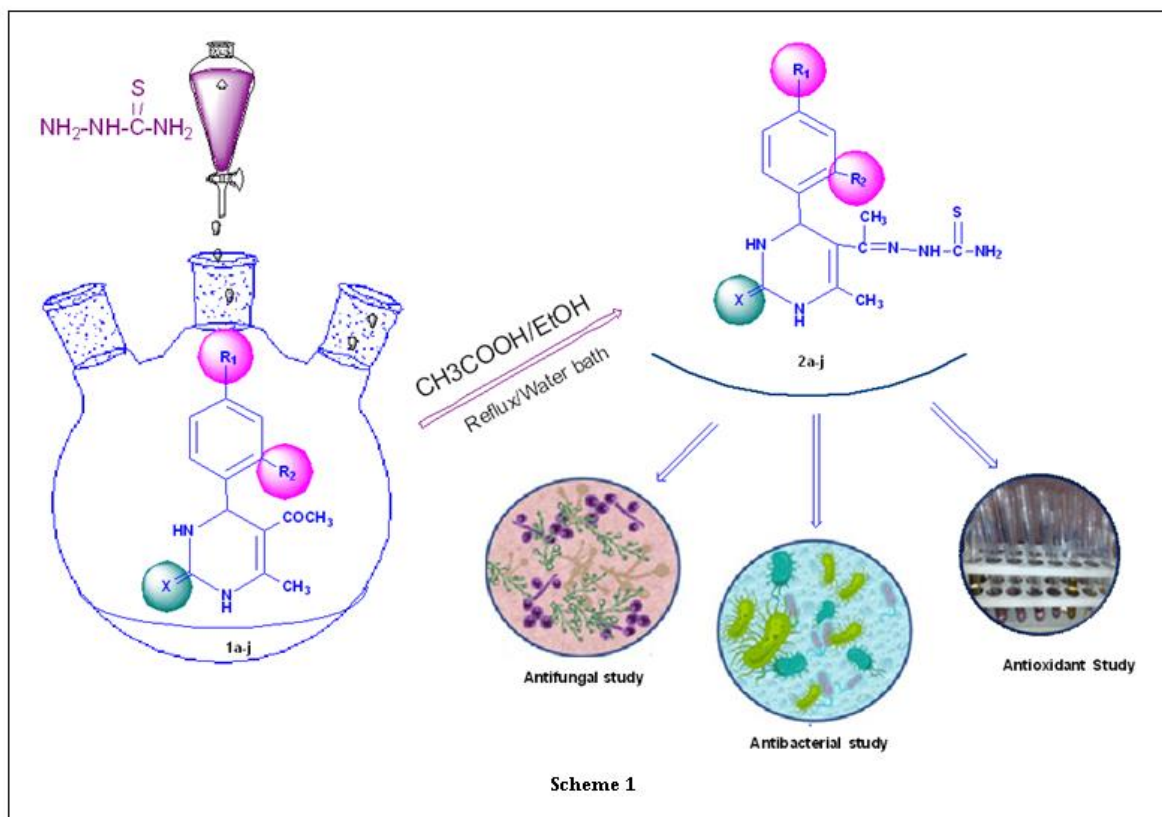
% Inhibition					
No. Compd.	20 µg/mL	40 µg/mL	60 µg/mL	80 µg/mL	100 µg/mL
2a	13	16	22	38	52
2b	15	18	24	33	58
2c	17	19	22	40	64
2d	14	18	23	36	60
2e	18	19	23	38	58
2f	14	16	22	40	62
2g	15	15	18	40	58
2h	16	17	19	42	64
2i	14	18	22	45	60
	2 µg/mL	4 µg/mL	6 µg/mL	8 µg/mL	10 µg/mL
Ascorbic acid	10	15	20	33	56



### Result and Discussion:

In this paper, we would like to report the reactivity of substituted 5-acetyl-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one (1a-i) with thiosemicarbazide. The reaction of compounds 1a-i with thiosemicarbazide in the presence of ethanol,

acetic acid afforded the respective substituted 1-(1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene)thiosemicarbazide (2a-i) as only separated product in high yields in a one-step procedure (**Scheme 1**).



**1-(1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene)**

**thiosemicarbazide 2a.**

m.p.: 180<sup>0</sup>C. IR (KBr):  $\nu_{\text{maxcm}^{-1}}$  3350-3450 (NH<sub>2</sub> & NH), 3017 (Ar- CH), 2915 (CH in CH<sub>3</sub>), 1720 (C=O), 1518 (C=N), 1462 (C=C), 653 (C- S). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) :  $\delta$  1.03 (s, 3H, CH<sub>3</sub>), 2.30 (s, 3H, Ar-CH<sub>3</sub>), 4.16 (s, 2H, NH<sub>2</sub>), 5.56 (s, 1H, CH), 7.05-7.10 (m, 3H, Ar-CH), 7.12-7.26 (m, 2H, Ar-CH), 7.00 (s, 1H, NH). MS (m/z): 303M<sup>+</sup>. Elemental analysis: Calculated for (C<sub>14</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S) C: 55.42; H: 5.65; N: 23.08. found C:52.56; H:5.69; N:23.24.

**1-(1-(4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene)**

**thiosemicarbazide 2b.**

m.p.: 124<sup>0</sup>C. IR (KBr):  $\nu_{\text{cm}^{-1}}$  3345-3460 (NH & NH), 3041 (Ar-CH), 2920 (CH in CH<sub>3</sub>), 1725 (C=O), 1514 (C=N), 1457 (C=C). <sup>1</sup>H-NMR :  $\delta$  1.13 (s, 3H, CH<sub>3</sub>), 2.2 (s, 3H, Ar-CH<sub>3</sub>), 3.73 (s, 3H, OCH<sub>3</sub>) 4.18 (s, 2H, NH<sub>2</sub>), 5.60 (s, 1H, CH), 7.00-7.12 (dd, 2H, Ar-CH), 7.24-7.30 (dd, 2H, Ar-CH), 7.00 (s, 1H, NH). MS (m/z): 333M<sup>+</sup>. Elemental analysis: Calculated for (C<sub>15</sub>H<sub>19</sub>N<sub>5</sub>O<sub>2</sub>S) C: 54.04; H: 5.74; N: 21.01. found C:54.20; H:5.75; N:21.10.

**1-(1-(4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene)**

**thiosemicarbazide 2c**

m.p.: 119<sup>0</sup>C. IR (KBr):  $\nu_{\text{maxcm}^{-1}}$  3500 (OH), 3367-3489 (NH<sub>2</sub> & NH), 3032 (Ar-CH), 2926 (CH in CH<sub>3</sub>), 1764 (C=O), 1522 (C=N), 1453 (C=C). <sup>1</sup>H-NMR :  $\delta$  1.12 (s, 3H, CH<sub>3</sub>), 2.01 (s, 3H, Ar-CH<sub>3</sub>), 4.30 (s, 2H, NH<sub>2</sub>), 5.60 (s, 1H, CH), 6.61-6.72 (dd, 2H, Ar-CH), 6.75-6.82 (dd, 2H, Ar-CH), 7.01 (s, 1H, NH), 9.86 (s, 1H, OH). MS (m/z): 319M<sup>+</sup>. Elemental analysis: Calculated for (C<sub>14</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S) C: 52.65; H: 5.37; N: 21.93; found C:52.42; H:5.39; N:22.02.

**1-(1-(4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene)**

**thiosemicarbazide 2d.**

m.p.: 125<sup>0</sup>C. IR (KBr):  $\nu_{\text{maxcm}^{-1}}$  3389-3450 (NH<sub>2</sub> & NH), 3040 (Ar- CH), 2935 (CH in CH<sub>3</sub>), 1722 (C=O), 1519 (C=N), 1448 (C=C). <sup>1</sup>H- NMR :  $\delta$  1.12 (s, 3H, CH ), 2.2 (s, 3H, Ar-CH ), 4.18 (s, 2H, NH ), 5.78 (s, 1H, CH), 7.01 (s, 1H, NH), 7.02-7.10 (dd, <sup>3</sup>2H, Ar-CH), <sup>3</sup>7.31-7.45 (dd, 2H, Ar-CH). MS (m/z): 337M<sup>+</sup>. Elemental analysis: Calculated for (C<sub>14</sub>H<sub>16</sub>ClN<sub>5</sub>O<sub>2</sub>S) C: 49.77; H: 4.76; N: 20.72; found C:49.56; H:4.89; N:20.87.

**1-(1-(4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene)**

**thiosemicarbazide 2e.**

m.p.: 182<sup>0</sup>C. IR (KBr):  $\nu_{\text{maxcm}^{-1}}$  3320-3428 (NH<sub>2</sub> & NH), 3018 (Ar- CH), 2912 (CH in CH<sub>3</sub>), 1724 (C=O), 1532 (C=N), 1463 (C=C). <sup>1</sup>H- NMR :  $\delta$  1.3 (s, 3H, CH<sub>3</sub>), 2.2 (s, 3H, Ar-CH<sub>3</sub>), 4.02 (s, 2H, NH<sub>2</sub>), 5.84 (s, 1H, CH), 7.01 (s, 1H, NH), 7.12-7.30 (m, 3H, Ar-CH), 7.20-7.28 (m, 1H, Ar-CH). MS (m/z): 337M<sup>+</sup>.  
Elemental analysis: Calculated for (C<sub>14</sub>H<sub>16</sub>ClN<sub>5</sub>O<sub>2</sub>S) C: 49.77; H: 4.76; N: 20.72. found C:49.68; H:4.80; N:20.80

**1-(1-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene)**

**thiosemicarbazide 2f.**

m.p.: 201<sup>0</sup>C. IR (KBr):  $\nu_{\text{maxcm}^{-1}}$  3364-3412 (NH<sub>2</sub> & NH), 3048 (Ar- CH), 2932 (CH in CH<sub>3</sub>),

1726 (C=O), 1513 (C=N), 1446 (C=C). <sup>1</sup>H-NMR : δ 1.23 (s, 3H, CH<sub>3</sub>), 2.29 (s, 3H, Ar-CH<sub>3</sub>), 4.23 (s, 2H, NH<sub>2</sub>), 5.19 (s, 1H, CH), 6.89 (s, 1H, NH), 7.33-7.45 (m, 3H, Ar-CH), 7.24-7.31 (m, 2H, Ar-CH). MS (m/z): 319M<sup>+</sup>. Elemental analysis: Calculated for (C<sub>14</sub>H<sub>17</sub>N<sub>5</sub>S<sub>2</sub>) C: 52.64; H: 5.35; N: 21.93; found C:52.50; H:5.40; N:22.06.

**1-(1-(4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene) thiosemicarbazide 2g.**

m.p.: 146<sup>0</sup>C. IR (KBr):  $\nu_{\max}$ cm<sup>-1</sup> 3345-3489 (NH<sub>2</sub> & NH), 3036 (Ar-CH), 2926 (CH in CH<sub>3</sub>), 1722 (C=O), 1520 (C=N), 1460 (C=C). <sup>1</sup>H-NMR : δ 0.95 (s, 3H, CH<sub>3</sub>), 2.1 (s, 3H, Ar-CH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 4.31 (s, 2H, NH<sub>2</sub>), 5.65 (s, 1H, CH), 6.98 (s, 1H, NH), 7.02-7.12 (dd, 2H, Ar-CH), 7.13-7.26 (dd, 2H, Ar-CH). MS (m/z): 349M<sup>+</sup>. Elemental analysis: Calculated for (C<sub>15</sub>H<sub>19</sub>N<sub>5</sub>O<sub>2</sub>S<sub>2</sub>): C: 51.54; H: 5.47; N: 20.06; found C:51.40; H:5.50; N:20.14.

**1-(1-(4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene) thiosemicarbazide 2h.**

m.p.: 209<sup>0</sup>C. IR (KBr):  $\nu_{\max}$ cm<sup>-1</sup> 3512 (OH), 3386-3488 (NH<sub>2</sub> & NH), 3024 (Ar-CH), 2939 (CH in CH<sub>3</sub>), 1720 (C=O), 1526 (C=N), 1452 (C=C). <sup>1</sup>H-NMR : δ 1.25 (s, 3H, CH<sub>3</sub>), 1.68 (s, 3H, CH<sub>3</sub>), 4.20 (s, 2H, NH<sub>2</sub>), 5.88 (s, 1H, CH), 6.60-6.72 (dd, 2H, Ar-CH), 6.82-6.96 (dd, 2H, Ar-CH), 7.00 (s, 1H, NH), 10.01 (s, 1H, OH). MS (m/z): 335M<sup>+</sup>. Elemental analysis: Calculated for (C<sub>14</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>S<sub>2</sub>) C: 50.12; H: 5.12; N: 20.89; found C:50.30; H:5.24; N:20.94.

**1-(1-(4-(2-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene) thiosemicarbazide 2i.**

m.p.: 213<sup>0</sup>C. IR (KBr):  $\nu_{\max}$ cm<sup>-1</sup> 3374-3450 (NH<sub>2</sub> & NH), 3019 (Ar-CH), 2917 (CH in CH<sub>3</sub>), 1726 (C=O), 1518 (C=N), 1454 (C=C). <sup>1</sup>H-NMR : δ 1.04 (s, 3H, CH<sub>3</sub>), 2.2 (s, 3H, Ar-CH<sub>3</sub>), 4.44 (s, 2H, NH<sub>2</sub>), 5.78 (s, 1H, CH), 7.13-7.23 (m, 3H, Ar-CH), 7.45-7.60 (m, 1H, Ar-CH), 7.70 (s, 1H, NH). MS (m/z): 353M<sup>+</sup>. Elemental analysis: Calculated for (C<sub>14</sub>H<sub>16</sub>ClN<sub>5</sub>S<sub>2</sub>) C: 47.53; H: 4.56; N: 19.78; found C:47.60; H:4.70; N:19.80.

**Biological Evaluation:**

Most of the synthesized compound exhibited mild to moderate antibacterial, anti-fungal and antioxidant activity against the tested microorganism when compared to standard drug (Doxycycline, Ampicillin for anti-bacterial, Fluconazole for anti-fungal and Ascorbic acid for antioxidant respectively) at different levels of concentration.

**Conclusions:**

An efficient synthesis of substituted 1-(1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene)thiosemicarbazide 2a-i. The biological evaluation of activities of

substituted 1-(1-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)ethylidene)thiosemicarbazide 2a-i exhibited mild to moderate anti-microbial and antioxidant activity at different levels of concentration against *Escherichia Coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albican*, Free radical scavenging activity of the test compounds (2a-i) were moderate by the 1, 1-diphenyl picryl hydrazyl (DPPH) assay method.

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