

## SYNTHESIS OF PYRAZOLYL-1-4- BENZOTHIAZINE DERIVATIVES.

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### **Abstract:**

A series of 2*H*,4*H* – 2-[3-methyl-4-(substituted) phenyl azo pyrazolon-5-one-1-yl]-carbonyl methyl -3-oxo-1,4-benzothiazine derivatives have been synthesized by the reaction of 2*H*, 4*H* –2 –hydrazino carbonyl methyl-3-oxo-1,4-benzothiazine with substituted acetoacetic ester derivatives using ultrasound and microwave irradiation in lesser time with higher yields. All the synthesized compounds were investigated for their antibacterial activities. The result indicated that the compounds shows convincing activities against Gram – positive bacteria (*Bacillus Subtilis* and *Streptococcus lactis*) when compared with standard drug (ampicillin trihydrate). These compounds were also synthesized by conventional method and their structures have been elucidated on the basis of spectral analyses and chemical analysis.

**Keywords:** 2-aminothiophenol, 1,4-benzothiazine, Ultrasound, MWI.

### **Introduction**

Enhancing the efficiency and maneuverability of organic synthesis constitutes one of the most exciting challenges to synthetic chemists. Within the last decade, green chemistry has attained the status of a major scientific discipline.<sup>1</sup> The investigation and application of green chemistry principles<sup>2</sup> has led to the development of cleaner and more benign chemical processes, with many of new technologies being developed each year. In today's world, synthetic chemists in both academia and industry are constantly challenged to consider more environmentally benign and sustainable methods for the generation of desired target molecules. Among twelve principles of green chemistry "design for energy efficiency" is one of the key principles of relevance to synthetic chemists.<sup>3</sup> Now-a-days, application of ultrasound (sonochemistry) has become an exciting field of research. The chemical effects of ultrasound are diverse and include substantial improvements in both stoichiometric and catalytic chemical reactions. Ultrasonic irradiation accelerates the reactivity million fold and many synthetically useful reactions were successfully accomplished.<sup>4-5</sup> As compared to conventional conditions, viz. strong base and long reaction time, the ultrasonic irradiation procedure is milder and more conventional leading to higher yields in shorter reaction time.<sup>6-7</sup>

Much attention has been given to the microwave dielectric heating in organic synthesis since first reported<sup>8</sup> acceleration of a chemical reaction under the influence of microwaves. It is significantly more energy efficient than the conventional heating<sup>9</sup> with the enhanced reaction

rates, simplified manipulation and work-up, and higher purity of final products.<sup>10-12</sup> It is notable that 1,4-benzothiazine is the pharmacophore of phenothiazines, which are well established anti-psychotic drugs,<sup>13</sup> and is also known as basic unit for their utility as dyestuffs,<sup>14</sup> photographic developers,<sup>15</sup> ultraviolet light absorbers and antioxidants.<sup>16</sup> Owing to the wide application of benzothiazines and their derivatives, rapid, safe, ecofriendly as well as economical method for the synthesis of 1,4-benzothiazines, is now reported (**Scheme 1**).

## Result and discussion

2-aminothiophenol (**1**) with an equimolar amount of maleic anhydride (**2**) in presence of ethanol and conc. H<sub>2</sub>SO<sub>4</sub> undergoes cyclization to form 3,4-dihydro-2-methoxycarbonylmethyl-3-oxo-2H-1,4-benzothiazine (**3**). The formation of (**3**) was explained on the basis of an IR band at 1740 & 1690cm<sup>-1</sup> due to ester and cyclic >C=O respectively. This was also confirmed from <sup>1</sup>HNMR signal at 3.6 ppm due to -CH<sub>3</sub>. The compound (**3**) was subsequently reacted with hydrazine hydrate in dry methanol to form (**4**). The formation of the compound **4** which was ascertained on the basis of IR bands at 3350, 3310 and 1630 due to NH-NH<sub>2</sub>. In <sup>1</sup>HNMR spectra disappearance of signal at 3.6 ppm due to -CH<sub>3</sub> & appearance of signal at 4.2 ppm and at 9.08 ppm due to NH<sub>2</sub> and -NH respectively confirms the formation of compound (**4**). The diazonium salt of primary amine when coupled with an acetoacetic ester at 0-5°C in presence of sodium acetate afforded (**5**). Furthermore the compound (**4**) undergoes cyclization with the compound (**5**) furnished 2H,4H - 2-[3-methyl-4-(substituted) phenyl azo pyrazolon-5-one-1-yl] carbonyl methyl -3-oxo-1,4-benzothiazine (**6**). The disappearance of signal at 4.2 ppm and appearance of signal at 2.2 ppm due to -CH<sub>3</sub> are main indications that cyclization took place. Also the molecular ion peak in mass spectra supports the structure.

## Experimental

All chemicals were supplied by E. Merck (Germany) and S. D. Fine Chemicals (India). Melting points of all synthesized compounds were determined in open capillary tubes using Veego VMP-1 melting point apparatus and are expressed in °C and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminium plates (Merck) as adsorbent and uv light as visualizing agent. IR spectra in KBr pellets were recorded on Perkin-Elmer spectrophotometer in the range of 4000-400 cm<sup>-1</sup>. <sup>1</sup>H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using CDCl<sub>3</sub>/DMSO-d<sub>6</sub> as solvent and TMS as an internal standard (chemical shifts in δ ppm). The mass spectra were taken on a Jeol SX-102/PA-6000 (EI) spectrometer. C, H, N estimations were done on Carlo Erba 1108 (C H N) Elemental Analyser. The experiment under ultrasound irradiation was carried out in probe ultrasound manufactured by Dakshin pvt Ltd, Mumbai (Electrical Supply 230V A.C., 50 Hz). Microwave irradiations were carried out in an unaltered domestic microwave oven (Inalsa, Model No. IMW 17 M, 2450 MHz).

### *3,4-dihydro-2-methoxycarbonylmethyl-3-oxo-2H-1,4-benzothiazine (3):*

#### *Method A (Ultrasound Method):*

2-Aminothiophenol (**1**) (1.25 gm, 0.01 mole), maleic anhydride (**2**) (0.98 gm, 0.01 mole), Methanol (25 mL) and Conc. H<sub>2</sub>SO<sub>4</sub> (2 mL) were taken in 100 ml round bottom flask and subjected to sonication for 10 mins. After completion of the reaction (monitored by TLC) cooled, solid thus obtained was washed with 5% sodium bicarbonate solution and extracted in dichloromethane to afford **3**. (Yield 82 %).

*Method B (Microwave Method):*

2-Aminothiophenol (**1**) (1.25 gm, 0.01 mole), maleic anhydride (**2**) (0.98 gm, 0.01 mole), Methanol (20 mL) and Conc. H<sub>2</sub>SO<sub>4</sub> (2 ml) were irradiated in microwave oven in an Erlenmeyer flask for 2 min. On work-up as described above in method A, **3** was obtained. (Yield 85 %).

*Method C (Conventional):*

An equimolar mixture of compound **1** (0.01 mole), **2** (0.01 mole) and methanol (50 mL) were refluxed in presence of Conc. H<sub>2</sub>SO<sub>4</sub> (2 mL) for about 6-7 hrs. The product was isolated in a similar manner as in method A. (Yield 65 %).

IR (KBr, cm<sup>-1</sup>): 1740, 1690, 1480, 1394 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>, δ ppm): 2.88-2.94 (d, 2H, CH<sub>2</sub>), 3.61 (s, 3H, CH<sub>3</sub>), 3.85 (t, 1H, CH), 6.99 – 7.32 (m, 4H, ArH), 10.70 (s, 1H, ring NH).

*2-Hydrazinocarbonylmethyl-3, 4-dihydro-3-oxo-2H-1, 4-benzothiazine (4):*

*Method A (Ultrasound Method):*

Compound (**3**) (2.37 gm, 0.01 mole), hydrazine hydrate (2 gm, 0.02 mole) and dry methanol (20 mL) were taken in 100 ml round bottom flask and subjected to sonication for 8mins. After completion of the reaction (monitored by TLC) cooled, poured on crushed ice, solid thus obtained was washed with water and recrystallised from methanol to get **4**. (Yield 78 %, m.p. 190-192°C).

*Method B (Microwave Method):*

Compound (**3**) (1.19 gm, 0.005 mole), hydrazine hydrate (1gm, 0.01 mole) and dry methanol (10 mL) were irradiated in microwave oven in an Erlenmeyer flask for 2 min. the product that separated out was filter, washed with water and recrystallised from methanol to obtain **4**. (Yield 82 %).

*Method C (Conventional):*

In a round bottom flask (100 mL) fitted with a reflux condenser, a mixture of **3** (0.01 mole) and hydrazine hydrate (0.02 mole) in dry methanol (70 mL) were heated on a steam bath for 6 hr. The reaction mixture was then concentrated, cooled & recrystallized to get the product. (Yield 58 %).

IR (KBr, cm<sup>-1</sup>): 3350, 3310, 1630 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>, δ ppm): 2.64-2.69 (d, 2H, CH<sub>2</sub>), 3.82 (t, 1H, CH), 4.22 (s, 2H, NH<sub>2</sub>), 6.98 – 7.30 (m, 4H, ArH), 9.09 (s, 1H, NH), 10.65 (s, 1H, ring NH).

*Ethyl-2-(4-methoxyphenylazo)-3-oxobutanolate (5a):*

To an ice cold solution of p-anisidine (0.02 mole) in a mixture of concentrated HCl (8 mL) and water (11 mL), a cold aqueous solution of sodium nitrite (1.40 gm) was added in portions under ice cold condition. The diazonium salt so formed was then filtered into an already cooled (0°C) solution containing sodium acetate (16 gm) and ethylacetoacetate (0.02 mole) in ethanol (50 mL), then the solution was stirred vigorously. The separated solid was washed with water and recrystallised from ethanol. (Yield 80%, m.p. 42-44°C). Similarly 5b-5e were prepared. (5b m.p. 45-47°C; 5c m.p. 50-52°C; 5d m.p. 75-77°C; 5e m.p. 65-67°C).

*General Procedure:*

*Method A (Ultrasound Method):*

**4** (1.18 gm, 0.005 mole), **5a-e** (0.005 mole) and glacial acetic acid (20 mL) were taken in 100 mL round bottom flask and subjected to sonication. Upon completion of the reaction (monitored by TLC) the reaction mixture was then cooled, poured in to crushed ice. The precipitate was filtered and the solid was then recrystallized from ethanol to give titled compounds **6a-6e**. The physical data of the compounds are given **Table 1**.

*Method B (Microwave Method):*

Equal mole of **4**, **5a-e** and glacial acetic acid (8 mL) were irradiated in microwave oven in an Erlenmeyer flask for 4 min. The product was isolated in a similar manner as described above.

*Method C (Conventional):*

An equimolar mixture of **4** and **5a-e** (0.005 mole) together with glacial acetic acid (50 mL) were refluxed in a round bottom flask for 9 hrs. After conclusion of the reaction (TLC), the reaction mixture poured onto crushed ice; the solid mass that separated out was filtered, washed with water and crystallized with ethanol to give the desired compounds **6a-e**.

*2H, 4H – 2-[3-methyl-4-(methoxy)-phenylazo-pyrazolon-5-one-1-yl]-carbonyl- methyl -3-oxo-1, 4-benzothiazine (6a):*

IR (KBr,  $\text{cm}^{-1}$ ) : 3296, 3210, 1680, 1580  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ ,  $\delta$  ppm): 2.12 (s, 3H,  $\text{CH}_3$ ), 3.76 (s, 3H,  $\text{OCH}_3$ ), 2.61-2.65 (d, 2H,  $\text{CH}_2$ ), 4.10 (t, 1H, CH), 5.42 (s, 1H, OH), 6.99 – 7.47 (m, 8H, ArH), 10.14 (s, 1H, NH), 10.68 (s, 1H, ring NH).

$^{13}\text{C}$  NMR (500 MHz, DMSO- $\text{d}_6$ , ppm): 11.5 ( $\text{CH}_3$ ), 32.8 ( $\text{CH}_2$ ), 55.8 ( $\text{OCH}_3$ ), 78.4 (CH), 123-146 (ArH), 146.1 (C=N), 152.5 (C=N), 160.4 (C=O), 165.2 (C=O).

MS (m/z): 438 ( $\text{M}^+$ )

*2H, 4H – 2-[3-methyl-4-(methyl)-phenylazo-pyrazolon-5-one-1-yl]-carbonyl- methyl -3-oxo-1, 4-benzothiazine (6b)*

IR (KBr,  $\text{cm}^{-1}$ ) : 3310, 3215, 1690, 1570  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ ,  $\delta$  ppm): 2.23 (s, 3H,  $\text{CH}_3$ ), 2.32 (s, 3H,  $\text{CH}_3$ ), 2.8-2.85 (d, 2H,  $\text{CH}_2$ ), 3.99 (t, 1H, CH), 5.32 (s, 1H, OH), 7.02 – 7.54 (m, 8H, ArH), 10.10 (s, 1H, NH), 10.77 (s, 1H, ring NH).

$^{13}\text{C}$  NMR (500 MHz, DMSO- $\text{d}_6$ , ppm): 11.8 ( $\text{CH}_3$ ), 20.58 ( $\text{CH}_3$ ), 30.69 ( $\text{CH}_2$ ), 79.8 (CH), 123-140 (ArH), 151.1 (C=N), 154.3 (C=N), 165.7 (C=O), 168.2 (C=O).

MS (m/z): 422 ( $\text{M}^+$ )

*2H, 4H – 2-[3-methyl-4-(chloro)-phenylazo-pyrazolon-5-one-1-yl]-carbonyl- methyl -3-oxo-1, 4-benzothiazine (6c):*

IR (KBr,  $\text{cm}^{-1}$ ) : 3324, 3221, 1685, 1550  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ ,  $\delta$  ppm): 2.20 (s, 3H,  $\text{CH}_3$ ), 2.84-2.94 (d, 2H,  $\text{CH}_2$ ), 4.13 (t, 1H, CH), 5.22 (s, 1H, OH), 6.87 – 7.68 (m, 8H, ArH), 10.20 (s, 1H, NH), 10.70 (s, 1H, ring NH).

$^{13}\text{C}$  NMR (500 MHz, DMSO- $\text{d}_6$ , ppm): 11.8 ( $\text{CH}_3$ ), 31.24 ( $\text{CH}_2$ ), 78.8 (CH), 123-140 (ArH), 150.4 (C=N), 155.7 (C=N), 164.8 (C=O), 169.5 (C=O).

*2H, 4H – 2-[3-methyl-4-(nitro)-phenylazo-pyrazolon-5-one-1-yl]-carbonyl- methyl -3-oxo-1, 4-benzothiazine (6d):*

IR (KBr,  $\text{cm}^{-1}$ ) : 3330, 3215, 1681, 1535  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ ,  $\delta$  ppm): 2.28 (s, 3H,  $\text{CH}_3$ ), 2.83-2.89 (d, 2H,  $\text{CH}_2$ ), 4.12 (t, 1H, CH), 5.25 (s, 1H, OH), 6.93 – 7.54 (m, 8H, ArH), 10.19 (s, 1H, NH), 10.72 (s, 1H, ring NH).

$^{13}\text{C}$  NMR (500 MHz, DMSO- $\text{d}_6$ , ppm): 12.1 ( $\text{CH}_3$ ), 30.21 ( $\text{CH}_2$ ), 80.4 (CH), 124-142 (ArH), 148.2 (C=N), 152.5 (C=N), 167.3 (C=O), 170.4 (C=O).

*2H, 4H – 2-[3-methyl-4-phenylazo-pyrazolon-5-one-1-yl]-carbonyl- methyl -3-oxo-1, 4-benzothiazine (6e):*

IR (KBr,  $\text{cm}^{-1}$ ) : 3318, 3225, 1695, 1520  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz, DMSO- $\text{d}_6$ ,  $\delta$  ppm): 2.32 (s, 3H,  $\text{CH}_3$ ), 2.8-2.9 (d, 2H,  $\text{CH}_2$ ), 4.10 (s, 1H, CH), 5.18 (s, 1H, OH), 6.9 – 7.52 (m, 8H, ArH), 10.14 (s, 1H, NH), 10.77 (s, 1H, ring NH). MS (m/z): 408 ( $\text{M}^+$ )

### Antimicrobial evaluation

The newly synthesized compounds, shown in **Table 1** were tested for their antimicrobial activity against the following microorganisms: (a) Gram-negative: *Escherichia coli*, *Pseudomonas putide*; (b) Gram-positive: *Bacillus subtilis*, *Streptococcus lactis*; (c) Fungi: *Aspergillus niger*, *Penicillium sp.*; (d) Yeast: *Candida albicans*. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion method.<sup>17</sup> The compounds were tested at a concentration of 100 µg/mL. The zone of inhibition was measured in mm and compared with reference standard ampicillin trihydrate (50µg/mL). The compounds tested displayed good activity towards Gram positive bacteria, but were less active against Gram-negative bacteria. The results of antibacterial screening studies are reported in **Table 2**.

### Acknowledgement:

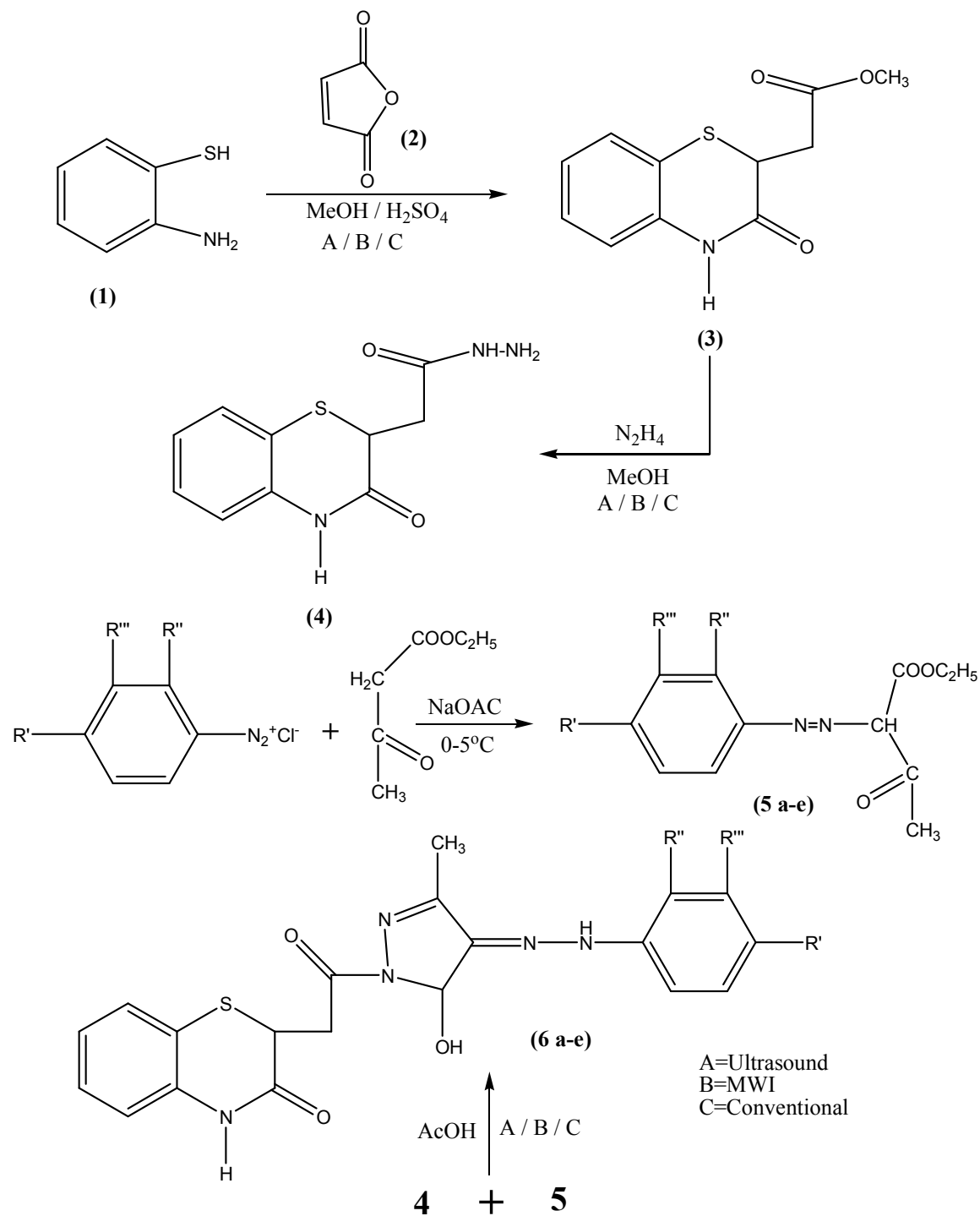
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**Scheme 1. Synthesis of pyrazolyl-1,4-benzothiazine**



**Table 1. Characterization of the synthesized compounds.**

Compound	R'	R''	R'''	Molecular formula*	Melting point (°C)	Yield (%) / Time**		Conv.
						Ultrasound	MWI	
6a	OCH <sub>3</sub>	H	H	C <sub>21</sub> H <sub>19</sub> N <sub>5</sub> O <sub>4</sub> S	252-254	83/18	87/4	60/9
6b	CH <sub>3</sub>	H	H	C <sub>21</sub> H <sub>19</sub> N <sub>5</sub> O <sub>3</sub> S	266-268	84/20	88/4	57/8
6c	Cl	H	H	C <sub>20</sub> H <sub>16</sub> N <sub>5</sub> O <sub>3</sub> SCl	285-287	80/20	84/4	60/9
6d	NO <sub>2</sub>	H	H	C <sub>20</sub> H <sub>16</sub> N <sub>6</sub> O <sub>5</sub> S	278-289	79/18	82/3	60/8
6e	H	H	H	C <sub>20</sub> H <sub>17</sub> N <sub>5</sub> O <sub>3</sub> S	248-250	80/20	85/3	58/8

\*All the compounds gave satisfactory elemental analysis.

\*\*Time in mins for ultrasound and MWI and in hrs for Conv.

**Table 2. Antimicrobial activities of some newly synthesized compounds.**

Comound	Inhibition Zone (mm)						
	Gram-negative		Gram-positive		Fungi		Yeast
	<i>E.coli</i>	<i>P.Putide</i>	<i>B.Subtilis</i>	<i>S.lactis</i>	<i>A.niger</i>	<i>P.Sp.</i>	<i>C.Albicans</i>
6a	10	8	16	16	12	10	5
6b	8	8	14	14	10	10	5
6c	12	10	17	15	8	8	5
6d	7	5	12	11	8	8	5
6e	5	0	10	8	0	0	0
Ampicilin®	24	20	19	22	24	14	14

*E.coli.* = *Escherichia coli*; *P.Putide* = *Pseudomonas Putide*; *B. Subtilis* = *Bacillus Subtilis*; *S. lactis* = *Sterptococcus lactis*; *A. niger* = *Aspergillus niger*; *P. Sp.* = *Penicillium Sp*; *C. Albicans* = *candida Albicans*.

The sensitivity of microorganisms to the tested compounds is identified in the following manner\*;

Highly Sensitive = Inhibition zone: 15-20 mm

Moderately Sensitive = Inhibition zone: 10-15 mm

Slightly Sensitive = Inhibition zone: 5-10 mm

Not Sensitive = Inhibition zone: 0 mm

\* Each result represents the average of triplicate readings.