



Trade Science Inc.

# Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 8(11), 2012 [437-446]

## Microwave assisted synthesis of some new thiazolopyrimidine derivatives with potential biological activity

Mohamed Mohamed Youssef<sup>1#</sup>, Mahmoud Ahmed Amin<sup>2##</sup>\*<sup>#</sup>Chemistry Department, Faculty of Science, Taif University, (SAUDIARABIA)<sup>1</sup>Chemistry Department, Faculty of Science, Cairo University, (EGYPT)<sup>2</sup>Chemistry Department, Faculty of Science, Suez Canal University, (EGYPT)

E-mail: aminmahmoud2000@yahoo.com

Received: 14<sup>th</sup> March, 2012 ; Accepted: 14<sup>th</sup> April, 2012

### ABSTRACT

Biginelli reaction of ethyl acetoacetate, thiourea and the proper aromatic aldehydes was used to produce ethyl 4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (**1a-d**). The latter compounds reacted with bromomalononitrile (**2**) to give ethyl 3-amino-5-aryl-2-cyano-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3a-d**) rather than the isomeric structures (**4a-d**). Thiazolopyrimidine derivatives (**3a-d**) reacted with carbon disulphide to yield ethyl 9-aryl-7-methyl-2,4-dithioxo-2,3,4,9-tetrahydro-1H-thiazolo[3,2-a:4,5-d']dipyrimidine-8-carboxylates (**5a-d**). The aforementioned reactions were carried out using both traditional chemical methods and with the assistance of the modern microwave technique. Comparison between both methods showed that microwave assisted method is preferred because of time and energy reduction as well as being environmentally friendly. Structures of the newly synthesized compounds were proved by using spectroscopic methods such as IR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and MS. The new compounds were tested for their biological activity as antioxidants, antibacterial or antifungal agents. Some of the new compounds were found to have moderate to good antioxidant and antimicrobial activities. © 2012 Trade Science Inc. - INDIA

### KEYWORDS

Biginelli reaction;  
2-Thioxopyrimidines;  
Thiazolopyrimidines;  
Thiazolodipyrimidines;  
Antioxidant activity;  
Antimicrobial activity.

### INTRODUCTION

Thiazolopyrimidines have been of interest due to their ability to inhibit 2-methylerythritol 2,4-cyclodiphosphate synthase<sup>[1]</sup>. They have been also used as analgesic and antiparkinsonian agents<sup>[2,3]</sup>, modulators of TRPV1 (Transient Receptor Potential Vanilloid-receptor 1)<sup>[4]</sup>, anticancer<sup>[5-7]</sup>, pesticides<sup>[8]</sup>, phosphate inhibitors<sup>[9]</sup>, for treating circulatory system diseases<sup>[10]</sup>, antimicrobial<sup>[11-13]</sup>, antiinflammatory<sup>[14]</sup> and insecti-

cides<sup>[15]</sup>.

The microwave technique has several advantages over traditional methods of synthesis. Reduced reaction times<sup>[16-19]</sup>, less effects on the environment and better reaction yields are some of the common advantages of using microwaves. In the present research, we used both the microwave technique as well as conventional methods to prepare some thiazolopyrimidine and thiazolodipyrimidine derivatives with expected biological activity.

## Full Paper

### EXPERIMENTAL

Melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and were uncorrected. I.R. (KBr discs) spectra were recorded on a Shimadzu FTIR-8201PC Spectrophotometer.  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra were recorded on a Varian Mercury 300 MHz and a Varian Gemini 200 MHz spectrometers using TMS as an internal standard and  $\text{DMSO-d}_6$ , and as a solvent. Chemical shifts were expressed as  $\delta$  (ppm) units. Mass spectra were recorded on Shimadzu GCMS-QP1000EX using an inlet type at 70 eV. The Micro analytical Center of Cairo University performed the microanalyses. Microwave reactions were performed with a Millstone Organic Synthesis Unit (MicroSYNTH with touch control terminal) with a continuous focused microwave power delivery system in a pressure glass vessel (10 mL) sealed with a septum under magnetic stirring. The temperature of the reaction mixture was monitored using a calibrated infrared temperature control under the reaction vessel, and control of the pressure was performed with a pressure sensor connected to the septum of the vessel.

#### Ethyl 4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (1a-d)

##### Method A

A solution of thiourea (0.76 g, 0.01 mole), ethyl acetoacetate (1.30 g, 0.01 mole) and the appropriate aromatic aldehyde (0.01 mole) in ethanol (50 mL) in the presence of conc. HCl (5 mL) was heated under reflux for 3 h. The reaction mixture was then allowed to stand at room temperature overnight whereby the solid precipitate so-formed was collected by filtration, washed with ethanol and crystallized from ethanol.

##### Method B

The same reactants of *Method A* were heated in microwave oven at 500 W and 140 °C for 15 min. The reaction mixture was treated in a similar manner to *Method A* to obtain compounds (1a-d).

**Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1a):** was obtained as pale green crystals in 55% yield (Method A) and 82% yield (Method B), m.p. 201 °C.  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  (ppm) 1.10 (t, 3H,

$\text{CH}_3$ ), 2.26 (s, 3H,  $\text{CH}_3$ ), 2.87 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 3.97 (q, 2H,  $\text{CH}_2$ ), 5.02 (s, 1H, pyrimidine H-4), 6.65 (d, 2H, Ar-H), 7.00 (d, 2H, Ar-H), 9.55 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable) and 10.23 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  (ppm) 14.1 ( $\text{CH}_3$ ), 17.2 ( $\text{CH}_3$ ), 53.5 (pyrimidine C-4), 59.5 ( $\text{N}(\text{CH}_3)_2$ ), 67.3 ( $\text{CH}_2$ ), 101.2, 112.2, 127.1, 131.2, 144.4, 150.0 (aromatic carbons + pyrimidine C-5 and C-6), 165.3 (C=S) and 173.8 (C=O). IR (KBr)  $\nu$ : 3268, 3188  $\text{cm}^{-1}$  (NH), 1718 (C=O), 1605, 1500 (Aromatic C=C). MS (70 eV): The molecular ion peak at  $m/z$  319 (11.2%).

Anal. Calcd. for  $\text{C}_{16}\text{H}_{20}\text{N}_3\text{O}_2\text{S}$  (319.42): C(60.16%), H(6.63%), N(13.16%), S(10.04); Found: C(60.3%), H(6.8%), N(13.4%), S(10.0%).

#### Ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1b):

was obtained as yellow crystals in 58% yield (Method A) and 87% yield (Method B), m.p. 144 °C.  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  (ppm) 1.22 (t, 3H,  $\text{CH}_3$ ), 2.26 (s, 3H,  $\text{CH}_3$ ), 3.25 (s, 3H,  $\text{OCH}_3$ ), 3.95 (q, 2H,  $\text{CH}_2$ ), 5.12 (s, 1H, pyrimidine H-4), 6.81 (d, 2H, Ar-H), 7.11 (d, 2H, Ar-H), 9.50 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable) and 10.18 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  (ppm) 14.0 ( $\text{CH}_3$ ), 17.4 ( $\text{CH}_3$ ), 53.5 (pyrimidine C-4), 63.9 ( $\text{OCH}_3$ ), 68.8 ( $\text{CH}_2$ ), 103.4, 113.1, 129.7, 134.2, 145.9 153.2 (aromatic carbons + pyrimidine C-5 and C-6), 165.6 (C=S) and 174.0 (C=O). IR (KBr)  $\nu$ : 3272, 3185  $\text{cm}^{-1}$  (NH), 1718 (C=O), 1603, 1506 (Aromatic C=C). MS (70 eV): The molecular ion peak at  $m/z$  306 (8.5%).

Anal. Calcd. for  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$  (319.42): C(58.80%), H(5.92%), N(9.14%), S(10.47); Found: C(59.0%), H(5.9%), N(9.3%), S(10.7%).

#### Ethyl 4-(2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1c):

was obtained as beige crystals in 42% yield (Method A) and 70% yield (Method B), m.p. 235 °C.  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  (ppm) 1.18 (t, 3H,  $\text{CH}_3$ ), 2.19 (s, 3H,  $\text{CH}_3$ ), 3.95 (q, 2H,  $\text{CH}_2$ ), 5.10 (s, 1H, pyrimidine H-4), 6.73-7.07 (m, 4H, Ar-H), 8.40 (s, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 9.55 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable) and 10.12 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  (ppm) 13.5 ( $\text{CH}_3$ ), 16.8 ( $\text{CH}_3$ ), 53.5 (pyrimidine C-4), 67.6 ( $\text{CH}_2$ ), 102.7, 112.6,

115.3, 122.0 127.7, 131.9, 144.6 150.9 (aromatic carbons + pyrimidine C-5 and C-6), 165.2 (C=S) and 172.6 (C=O). IR (KBr)  $\nu$ : 3280-3080  $\text{cm}^{-1}$  (broad, OH + NH), 1722(C=O), 1600, 1501 (Aromatic C=C). MS (70 eV): The molecular ion peak at  $m/z$  292 (14.1%).

Anal. Calcd. for  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$  (292.09): C(57.52%), H(5.52%), N(9.58%), S(10.97); Found: C(57.7%), H(5.8%), N(9.5%), S(11.1%).

**Ethyl 4-(furan-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1d)**: was obtained as brown crystals in 35% yield (Method A) and 62% yield (Method B), m.p. 176°C.  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  (ppm) 1.25 (t, 3H,  $\text{CH}_3$ ), 2.22 (s, 3H,  $\text{CH}_3$ ), 4.20 (q, 2H,  $\text{CH}_2$ ), 5.23 (s, 1H, pyrimidine H-4), 6.44 (d, 1H, furan-H), 6.56 (m, 1H, furan-H), 7.41 (d, 1H, furan-H), 9.34 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable) and 10.20 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  (ppm) 14.3 ( $\text{CH}_3$ ), 17.5 ( $\text{CH}_3$ ), 57.5 (pyrimidine C-4), 67.2 ( $\text{CH}_2$ ), 106.2, 110.9, 143.1, 145.3, 151.0 152.9 (furan carbons + pyrimidine C-5 and C-6), 165.8 (C=S) and 173.0 (C=O). IR (KBr)  $\nu$ : 3275, 3183  $\text{cm}^{-1}$  (NH), 1720 (C=O), 1607, 1500 (Aromatic C=C). MS (70 eV): The molecular ion peak at  $m/z$  266 (6.3%).

Anal. Calcd. for  $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$  (266.32): C(54.12%), H(5.30%), N(10.52%), S(12.04); Found: C(54.1%), H(5.4%), N(10.4%), S(12.0%).

**Ethyl 3-amino-5-aryl-2-cyano-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (3a-d)**

#### Method A

To a warm ethanolic potassium hydroxide solution [prepared by dissolving KOH (0.56 g, 0.01 mole) in ethanol (50 mL)] of each of (**1a-d**) (0.01 mole), bromomalononitrile (**2**) (1.45 g, 0.01 mole) was added portion-wise with stirring. The reaction mixture was then left overnight at room temperature, whereby the solid product that separated upon dilution with water was filtered off and crystallized from the proper solvent.

#### Method B

The same reactants of method A were heated at 140°C in microwave oven for 10 min. The reaction mixture was treated in a similar manner to method A to obtain compounds (**3a-d**).

**Ethyl 3-amino-2-cyano-5-(4-(dimethylamino)phenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (3a)**: was crystallized from dil. dioxane as yellowish green crystals in 56% yield (Method A) and 81% yield (Method B), m.p. 218°C.  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  (ppm) 1.35 (t, 3H,  $\text{CH}_3$ ), 2.34 (s, 3H,  $\text{CH}_3$ ), 2.95 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 4.15 (q, 2H,  $\text{CH}_2$ ), 6.22 (s, 1H, pyrimidine H-5), 6.60 (d, 2H, Ar-H), 6.97 (d, 2H, Ar-H) and 8.78 (s, 2H,  $\text{NH}_2$ ,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  (ppm) 14.5 ( $\text{CH}_3$ ), 17.3 ( $\text{CH}_3$ ), 58.8 (pyrimidine C-5), 59.7 ( $\text{N}(\text{CH}_3)_2$ ), 68.4 ( $\text{CH}_2$ ), 107.3 (CN), 112.2, 117.3, 127.1, 132.2, 149.4, 154.6, 157.3, 158.1, 158.9 (aromatic carbons + pyrimidine C-6 and C-7, C-8a + thiazole C-2, C-3), and 171.6 (C=O). IR (KBr)  $\nu$ : 3310, 3244  $\text{cm}^{-1}$  ( $\text{NH}_2$ ), 2217 (CN), 1724 (C=O), 1605, 1500 (Aromatic C=C). MS (70 eV): The molecular ion peak at  $m/z$  383 (7.3%).

Anal. Calcd. for  $\text{C}_{19}\text{H}_{21}\text{N}_5\text{O}_2\text{S}$  (383.14): C(59.51%), H(5.52%), N(18.26%), S(8.36); Found: C(59.6%), H(5.8%), N(18.3%), S(8.3%).

**Ethyl 3-amino-2-cyano-5-(4-methoxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (3b)**: was crystallized from ethanol as yellow crystals in 48% yield (Method A) and 85% yield (Method B), m.p. 220°C.  $^1\text{H-NMR}$  (DMSO- $d_6$ ):  $\delta$  (ppm) 1.30 (t, 3H,  $\text{CH}_3$ ), 2.30 (s, 3H,  $\text{CH}_3$ ), 3.85 (s, 3H,  $\text{OCH}_3$ ), 4.18 (q, 2H,  $\text{CH}_2$ ), 6.31 (s, 1H, pyrimidine H-5), 6.80 (d, 2H, Ar-H), 7.15 (d, 2H, Ar-H), and 8.40 (s, 2H,  $\text{NH}_2$ ,  $\text{D}_2\text{O}$  exchangeable).  $^{13}\text{C-NMR}$  (DMSO- $d_6$ ):  $\delta$  (ppm) 14.8 ( $\text{CH}_3$ ), 17.4 ( $\text{CH}_3$ ), 59.6 (pyrimidine C-5), 62.1 ( $\text{OCH}_3$ ), 67.4 ( $\text{CH}_2$ ), 108.1 (CN), 113.1, 118.8, 129.0, 134.1, 151.4, 155.1, 157.8, 158.7, 159.3 (aromatic carbons + pyrimidine C-6 and C-7, C-8a + thiazole C-2, C-3), and 171.0 (C=O). IR (KBr)  $\nu$ : 3300, 3230  $\text{cm}^{-1}$  ( $\text{NH}_2$ ), 2210 (CN), 1720 (C=O), 1605, 1500 (Aromatic C=C). MS (70 eV): The molecular ion peak at  $m/z$  370 (8.1%).

Anal. Calcd. for  $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$  (370.43): C(58.36%), H(4.90%), N(15.12%), S(8.66); Found: C(58.5%), H(4.8%), N(15.3%), S(8.5%).

**Ethyl 3-amino-2-cyano-5-(2-hydroxyphenyl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (3c)**: was crystallized from ethanol as yellow crystals in 53% yield (Method A) and 85% yield

## Full Paper

(Method B), m.p. 277°C. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ (ppm) 1.32 (t, 3H, CH<sub>3</sub>), 2.34 (s, 3H, CH<sub>3</sub>), 4.05 (q, 2H, CH<sub>2</sub>), 6.24 (s, 1H, pyrimidine H-5), 6.80-7.18 (m, 4H, Ar-H), 8.15 (s, 1H, OH, D<sub>2</sub>O exchangeable) and 8.53 (s, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ (ppm) 14.3 (CH<sub>3</sub>), 17.1 (CH<sub>3</sub>), 58.8 (pyrimidine C-5), 67.1 (CH<sub>2</sub>), 107.3 (CN), 112.3, 116.1, 122.1, 126.3, 131.3, 137.1, 152.1, 157.1, 157.9, 158.8, 159.5 (aromatic carbons + pyrimidine C-6 and C-7, C-8a + thiazole C-2, C-3), and 173.0 (C=O). IR (KBr) v: 3320- 3118 cm<sup>-1</sup> (broad, OH + NH<sub>2</sub>), 2210 (CN), 1716 (C=O), 1600, 1500 (Aromatic C=C). MS (70 eV): The molecular ion peak at m/z 356 (12.5%).

Anal. Calcd. for C<sub>17</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>S (356.40): C(57.29%), H(4.52%), N(15.72%), S(9.00); Found: C(57.5%), H(4.6%), N(15.6%), S(9.1%).

**Ethyl 3-amino-2-cyano-5-(furan-2-yl)-7-methyl-5H-thiazolo[3,2-a]pyrimidine-6-carboxylate (3d):** was crystallized from dioxane as brown crystals in 40% yield (Method A) and 68% yield (Method B), m.p. 345°C. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ (ppm) 1.27 (t, 3H, CH<sub>3</sub>), 2.21 (s, 3H, CH<sub>3</sub>), 4.25 (q, 2H, CH<sub>2</sub>), 6.11 (s, 1H, pyrimidine H-5), 6.45 (d, 1H, furan-H), 6.61 (m, 1H, furan-H), 7.43 (d, 1H, furan-H) and 8.87 (s, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ (ppm) 14.7 (CH<sub>3</sub>), 17.5 (CH<sub>3</sub>), 62.3 (pyrimidine C-5), 67.4 (CH<sub>2</sub>), 107.1 (CN), 112.6, 114.1, 127.3, 135.1, 139.6, 143.1, 145.3, 151.0 152.9 (furan carbons + pyrimidine C-6 and C-7, C-8a + thiazole C-2, C-3) and 173.3 (C=O). IR (KBr) v: 3310, 3244 cm<sup>-1</sup> (NH<sub>2</sub>), 2210 (CN), 1722 (C=O), 1605, 1510 (Aromatic C=C). MS (70 eV): The molecular ion peak at m/z 330 (4.8%).

Anal. Calcd. for C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O<sub>3</sub>S (330.36): C(54.53%), H(4.27%), N(16.96%), S(9.71); Found: C(54.4%), H(4.4%), N(16.7%), S(9.8%).

**Ethyl 9-aryl-7-methyl-2,4-dithioxo-2,3,4,9-tetrahydro-1H-thiazolo[3,2-a:4,5-d']dipyrimidine-8-carboxylates (5a-d)**

### Method A

Each of compounds (3a-d) (0.01 mole) was heated under reflux with an excess of carbon disulphide (10 mL) for 8 h. The reaction mixture was then cooled, and

the solid that precipitated was filtered at the pump and crystallized from the proper solvent.

### Method B

The same reactants of method A were heated at 140°C in microwave oven for 15 minutes. The reaction mixture was treated in a similar manner to method A to obtain compounds (5a-d).

**Ethyl 9-(4-(dimethylamino)phenyl)-7-methyl-2,4-dithioxo-2,3,4,9-tetrahydro-1H-thiazolo[3,2-a:4,5-d']dipyrimidine-8-carboxylate (5a):** was crystallized from dilute ethanol as grey crystals in 50% yield (Method A) and 82% yield (Method B), m.p. 248°C. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ (ppm) 1.10 (t, 3H, CH<sub>3</sub>), 2.26 (s, 3H, CH<sub>3</sub>), 2.84 (s, 6H, N(CH<sub>3</sub>)<sub>2</sub>), 3.95 (q, 2H, CH<sub>2</sub>), 5.88 (s, 1H, pyrimidine H-9), 6.60 (d, 2H, Ar-H), 6.95 (d, 2H, Ar-H), 11.35 (s, 1H, NH, D<sub>2</sub>O exchangeable) and 12.12 (s, 1H, NH, D<sub>2</sub>O exchangeable). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ (ppm) 14.2 (CH<sub>3</sub>), 17.8 (CH<sub>3</sub>), 53.5 (pyrimidine C-9), 59.6 (N(CH<sub>3</sub>)<sub>2</sub>), 67.3 (CH<sub>2</sub>), 109.2, 111.3, 127.1, 132.2, 148.2, 154.3, 156.2 157.1, 161.9 (aromatic carbons + pyrimidine C-5a, C-7, C-8 + thiazole C-4a, C-10a), 171.3 (C=S), 175.1 (C=O) and 181.4 (C=S). IR (KBr) v: 3305, 3200 cm<sup>-1</sup> (NH), 1712 (C=O), 1605, 1500 (Aromatic C=C). MS (70 eV): The molecular ion peak at m/z 459 (3.2%).

Anal. Calcd. for C<sub>20</sub>H<sub>21</sub>N<sub>5</sub>O<sub>2</sub>S<sub>3</sub> (459.61): C(52.26%), H(4.61%), N(15.24%), S(20.93); Found: C(52.3%), H(4.7%), N(15.5%), S(20.8%).

**Ethyl 9-(4-methoxyphenyl)-7-methyl-2,4-dithioxo-2,3,4,9-tetrahydro-1H-thiazolo[3,2-a:4,5-d']dipyrimidine-8-carboxylate (5b):** was crystallized from ethanol as beige crystals in 53% yield (Method A) and 80% yield (Method B), m.p. 243°C. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ (ppm) 1.13 (t, 3H, CH<sub>3</sub>), 2.32 (s, 3H, CH<sub>3</sub>), 3.22 (s, 3H, OCH<sub>3</sub>), 4.10 (q, 2H, CH<sub>2</sub>), 5.95 (s, 1H, pyrimidine H-9), 6.80 (d, 2H, Ar-H), 7.12 (d, 2H, Ar-H), 11.30 (s, 1H, NH, D<sub>2</sub>O exchangeable) and 12.10 (s, 1H, NH, D<sub>2</sub>O exchangeable). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>): δ (ppm) 14.1 (CH<sub>3</sub>), 18.6 (CH<sub>3</sub>), 61.0 (pyrimidine C-9), 63.2 (OCH<sub>3</sub>), 67.3 (CH<sub>2</sub>), 110.4, 114.6, 130.0, 133.8 149.8, 155.2, 156.4, 157.9, 162.2 (aromatic carbons + pyrimidine C-5a, C-7, C-8 + thiazole C-4a, C-10a), 171.1 (C=S), 175.0 (C=O) and 181.5 (C=S). IR (KBr) v: 3310, 3200 cm<sup>-1</sup> (NH),



1718 (C=O), 1605, 1500 (Aromatic C=C). MS (70 eV): The molecular ion peak at  $m/z$  446 (4.0%).

Anal. Calcd. for  $C_{19}H_{18}N_4O_3S_3$  (446.57): C(52.10%), H(4.06%), N(12.55%), S(21.54); Found: C(52.0%), H(4.2%), N(12.5%), S(21.8%).

**Ethyl 9-(2-hydroxyphenyl)-7-methyl-2,4-dithioxo-2,3,4,9-tetrahydro-1H-thiazolo[3,2-a:4,5-d']-dipyrimidine-8-carboxylate (5c)**: was crystallized from dioxane as pale green crystals in 44% yield (Method A) and 79% yield (Method B), m.p. 295°C.  $^1H$ -NMR (DMSO- $d_6$ ):  $\delta$  (ppm) 1.28 (t, 3H,  $CH_3$ ), 2.25 (s, 3H,  $CH_3$ ), 4.16 (q, 2H,  $CH_2$ ), 6.11 (s, 1H, pyrimidine H-9), 6.80-7.20 (m, 4H, Ar-H), 8.22 (s, 1H, OH,  $D_2O$  exchangeable), 11.40 (s, 1H, NH,  $D_2O$  exchangeable) and 12.25 (s, 1H, NH,  $D_2O$  exchangeable).  $^{13}C$ -NMR (DMSO- $d_6$ ):  $\delta$  (ppm) 14.3 ( $CH_3$ ), 17.1 ( $CH_3$ ), 58.8 (pyrimidine C-5), 67.1 ( $CH_2$ ), 107.3 (CN), 107.9, 112.4, 120.1, 127.4, 133.3, 138.1, 154.0, 158.1, 158.9, 159.4, 161.0 (aromatic carbons + pyrimidine C-5a, C-7, C-8 + thiazole C-4a, C-10a), 171.4 (C=S), 174.8 (C=O) and 180.7 (C=S). IR (KBr)  $\nu$ : 3300, 3230  $cm^{-1}$  (NH), 1710 (C=O), 1600, 1500 (Aromatic C=C). MS (70 eV): The molecular ion peak at  $m/z$  432 (5.0 %).

Anal. Calcd. for  $C_{18}H_{16}N_4O_3S_3$  (432.54): C(49.98%), H(3.73%), N(12.95%), S(22.24); Found: C(49.8%), H(3.8%), N(13.1%), (22.1%).

**Ethyl 9-(furan-2-yl)-7-methyl-2,4-dithioxo-2,3,4,9-tetrahydro-1H-thiazolo[3,2-a:4,5-d']dipyr-imidine-8-carboxylate (5d)**: was crystallized from dioxane as dark green crystals in 37% yield (Method A) and 69% yield (Method B), m.p. 255°C.  $^1H$ -NMR (DMSO- $d_6$ ):  $\delta$  (ppm) 1.25 (t, 3H,  $CH_3$ ), 2.15 (s, 3H,  $CH_3$ ), 4.00 (q, 2H,  $CH_2$ ), 6.11 (s, 1H, pyrimidine H-9), 6.51 (d, 1H, furan-H), 6.78 (m, 1H, furan-H), 7.55 (d, 1H, furan-H), 11.40 (s, 1H, NH,  $D_2O$  exchangeable) and 12.25 (s, 1H, NH,  $D_2O$  exchangeable).  $^{13}C$ -NMR (DMSO- $d_6$ ):  $\delta$  (ppm) 14.5 ( $CH_3$ ), 17.1 ( $CH_3$ ), 62.1 (pyrimidine C-9), 66.8 ( $CH_2$ ), 106.6, 110.0, 123.3, 134.8, 138.7, 142.7, 144.9, 151.4 157.9 (furan carbons + pyrimidine C-5a, C-7, C-8 + thiazole C-4a, C-10a) 171.8 (C=S), 173.9(C=O) and 181.2 (C=S). IR (KBr)  $\nu$ : 3310, 3244  $cm^{-1}$  ( $NH_2$ ), 2210 (CN), 1722 (C=O), 1605, 1510 (Aromatic C=C). MS (70 eV): The molecular ion peak at  $m/z$  406 (4.3 %).

Anal. Calcd. for  $C_{16}H_{14}N_4O_3S_3$  (406.50): C(47.27%), H(3.47%), N(13.78%), S(23.66); Found: C(47.0%), H(3.4%), N(13.8%), S(23.8%).

### Anti-oxidant screening

#### Assay for erythrocyte hemolysis

Blood was obtained from rats by cardiac puncture and collected in heparinized tubes. Erythrocytes were separated from plasma and the buffy coat and washed three times with 10 volumes of 0.15 M NaCl. During the last washing, the erythrocytes were centrifuged at 2500 rpm for 10 min to obtain a constantly packed cell preparation. Erythrocyte hemolysis was mediated by peroxy radicals in this assay system<sup>[20]</sup>. A 10% suspension of erythrocytes in pH 7.4 phosphate-buffered saline (PBS) was added to the same volume of 200 mM 2,2'-azobis (2-amidinopropane)dihydrochloride (AAPH) solution (in PBS) containing samples to be tested at different concentrations. The reaction mixture was shaken gently while being incubated at 37°C for 24 hours. The reaction mixture was then removed, diluted with eight volumes of PBS and centrifuged at 2500 rpm for 10 min. The absorbance A of the supernatant was read at 540 nm. Similarly, the reaction mixture was treated with eight volumes of distilled water to achieve complete hemolysis, and the absorbance B of the supernatant obtained after centrifugation was measured at 540 nm. The percentage hemolysis was calculated by equation  $(1 - A/B) \times 100\%$ . The data were expressed as mean standard deviation. L-Ascorbic was used as a positive control.

#### Anti-oxidant activity screening assay - ABTS method

For each of the investigated compounds 2 mL of ABTS [2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid)] solution (60 mM) was added to 3 M  $MnO_2$  solution (25 mg/mL) all prepared in phosphate buffer (pH 7, 0.1 M). The mixture was shaken, centrifuged, filtered, and the absorbance ( $A_{control}$ ) of the resulting green-blue solution (ABTS radical solution) was adjusted at ca. 0.5 at  $\lambda$  734 nm. Then, 50  $\mu$ L of (2 mM) solution of the test compound in spectroscopic grade MeOH/ phosphate buffer (1:1) was added. The absorbance ( $A_{test}$ ) was measured and the reduction in color intensity was expressed as % inhibition. The %

## Full Paper

inhibition for each compound is calculated from the following equation<sup>[21]</sup>:

$$\% \text{ Inhibition} = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100$$

Ascorbic acid (vitamin C) was used as standard antioxidant (positive control). Blank sample was run without ABTS and using MeOH/phosphate buffer (1:1) instead of sample. Negative control sample was run with MeOH/phosphate buffer (1:1) instead of tested compound.

### Bleomycin-dependent DNA damage

The assay was done according to Aeschlach et al.<sup>[22]</sup> with minor modifications. The reaction mixture (0.5 mL) contained DNA (0.5 mg/mL), bleomycin sulfate (0.05 mg/mL), MgCl<sub>2</sub> (5 mM), FeCl<sub>3</sub> (50 μM) and samples to be tested at different concentrations. L-Ascorbic acid was used as a positive control. The mixture was incubated at 37° C for 1 hour. The reaction was terminated by addition of 0.05 mL EDTA (0.1 M). The color was developed by adding 0.5 mL thiobarbituric acid (TBA) (1%, w/v) and 0.5 mL HCl (25%, v/v) followed by heating at 80°C for 10 min. After centrifugation, the extent of DNA damage was measured by increase in absorbance at 532 nm.

### Antimicrobial screening

The newly synthesized heterocyclic compounds were tested for their antimicrobial activity against the following microorganisms: (a) Gram-negative: *Escherichia coli* and *Pseudomonas putide*; (b) Gram-positive: *Bacillus subtilis* and *Streptococcus lactis*; (c) Fungi: *Aspergillus niger* and *Penicillium sp.*; (d) Yeast: *Candida albicans*

### Media

Three types of specific media were used in this study:

#### Medium (1)

For bacteria (Nutrient Medium), consisting of (g/l distilled water): peptone, 5 and meat extract, 3. pH was adjusted to 7.0.

#### Medium 2

For fungi (Potato Dextrose Medium), consisting of (g/l distilled water): Infusion from potatoes, 4 and D(+)glucose, 20. pH was adjusted to 5.5.

#### Medium 3

For yeast (Universal Medium), consisting of (g/l distilled water): yeast extract, 3; malt extract, 3; peptone, 5 and glucose, 10. pH was adjusted to 5.5.

For solid media, 2% agar was added. All media were sterilized at 121°C for 20 minutes.

### Procedure (Filter paper diffusion method)<sup>[23]</sup>

Proper concentrations of microbial suspensions were prepared from 1 (for bacteria to 3 (for yeast and fungi)-day-old liquid stock cultures incubated on a rotary shaker (100 rpm). In the case of fungi, 5 sterile glass beads were added to each culture flask. The mycelia were then subdivided by mechanical stirring at speed No. 1 for 30 minutes. Turbidity of microorganisms was adjusted with a spectrophotometer at 350 nm to give an optical density of 1.0. Appropriate agar plates were aseptically surface inoculated uniformly by a standard volume (ca. 1 ml) of the microbial broth culture of the tested microorganism, namely *E. coli*, *P. putide*, *B. subtilis*, *S. Lactis*, *A. Niger*, *Penicillium sp.* And *C. albicans*.

Whatman No. 3 filter paper discs of 10 mm diameter were sterilized by autoclaving for 15 minutes at 121°C. Test compounds were dissolved in 80% ethyl alcohol to give final concentration of 5 μg/ml. The sterile discs were impregnated with the test compounds (5 μg/disc). After the impregnated discs have been air dried, they were placed on the agar surface previously seeded with the organism to be tested. Discs were gently pressed with forceps to insure thorough contact with the media. Three discs were arranged per dish, suitably spaced apart, i.e. the discs should be separated by a distance that is equal to or slightly greater than the sum of the diameters of inhibition produced by each disc alone. Each test compound was conducted in triplicate. Plates were kept in the refrigerator at 5°C for 1 hour to permit good diffusion before transferring them to an incubator at 37°C for 24 hours for bacteria and at 30°C for 72 hours for yeast and fungi.

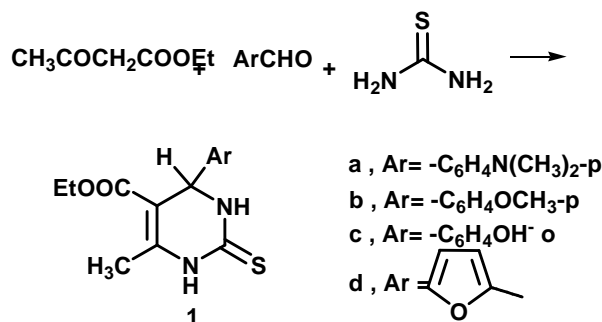
## RESULTS AND DISCUSSION

Prompted by the aforesaid biological and medicinal activities, samples of differently substituted thiazolopyrimidines and thiazolodiprimidines are syn-

thesized by using both traditional chemical methods and modern microwave technique. The reaction of the precursor ethyl 4-aryl-6-substituted-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates (**1a-b**) with some bifunctional reagents seems to be a facile convenient route for the synthesis of such samples. The newly synthesized compounds are tested for their antioxidant and antimicrobial activities.

The precursor pyrimidine derivatives (**1a-b**) were prepared by the acid catalyzed condensation of ternary mixture of aromatic aldehyde, ethyl acetoacetate and thiourea in ethanol containing a catalytic amount of hydrochloric acid, commonly known as Biginelli reaction<sup>[24,25]</sup>.

Compounds (**1a-d**), prepared by Biginelli's method, showed correct values of elemental analyses, as well as compatible spectroscopic data. The IR ( $\bar{\nu}$ ,  $\text{cm}^{-1}$ ) spectra of (**1a-d**) displayed absorption bands near 3270, 3180 (2NH), 3050, 2980 (CH), 1720 (C=O).

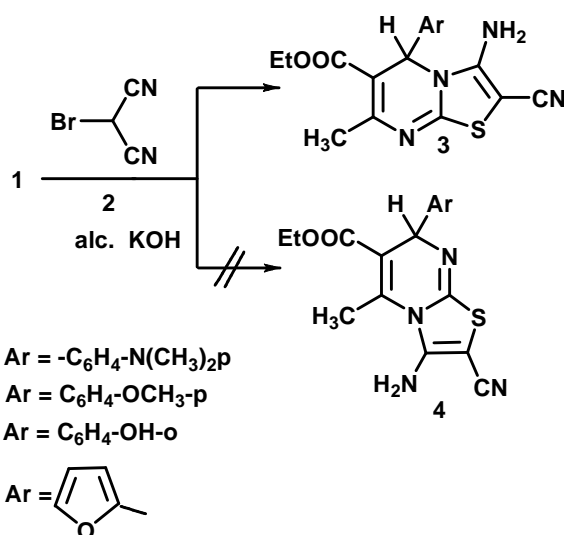


$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ) of (**1a**), as an example, showed signals ( $\delta$  ppm) 1.10 (t, 3H,  $\text{CH}_3$ ), 2.26 (s, 3H,  $\text{CH}_3$ ), 2.87 (s, 6H,  $\text{N}(\text{CH}_3)_2$ ), 3.97 (q, 2H,  $\text{CH}_2$ ), 5.02 (s, 1H, pyrimidine H-4), 6.65 (d, 2H, aromatic protons), 7.00 (d, 2H, aromatic protons), 9.55 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable) and 10.23 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable). Its  $^{13}\text{C-NMR}$  ( $\text{DMSO-d}_6$ ), as an example, showed signals ( $\delta$  ppm) at 14.1 ( $\text{CH}_3$ ), 17.2 ( $\text{CH}_3$ ), 53.5 (pyrimidine C-4), 59.5 ( $\text{N}(\text{CH}_3)_2$ ), 64.3 ( $\text{CH}_2$ ), 101.2, 112.2, 127.1, 131.2, 144.4, 150.0 (aromatic carbons + pyrimidine C-5 and C-6), 165.3 (C=S) and 173.8 (C=O). Mass spectrum of (**1b**), as an example, showed the molecular ion Peak at  $m/z$  306 (8.5%) corresponding to the molecular formula  $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ .

Synthesis of compounds (**1a-b**) was repeated by using microwave-assisted reaction conditions. The obtained products were identical in all aspects (m.p., mixed

m.p., IR spectra) to products (**1a-d**) prepared by Biginelli's method. Using microwave irradiation as a source of energy has several advantages over the traditional methods. Better reaction yields, reduced reaction times and less effect on the environment are some of the advantages of using microwave-assisted reaction conditions (experimental).

Treating a solution of each of (**1a-d**) in ethanol containing potassium hydroxide with bromomalononitrile (**2**) yielded in each case a single product which could be formulated to be 5H-thiazolo[3,2-a]pyrimidine structure **3** or the isomeric 7H-thiazolo-[3,2-a]pyrimidine structure **4**.



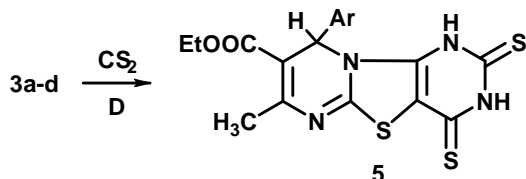
Preferring structure (**3**) over structure (**4**) was firstly based on comparison of  $^1\text{H-NMR}$  spectral data for compounds (**1**) and (**3**). Thus,  $^1\text{H-NMR}$  spectrum of (**3b**) showed, in addition to the ethyl ester, methoxy, aromatic and NH proton signals, a singlet signal (3H) at  $\delta$  2.30 ppm assigned for the  $\text{CH}_3$  protons and a singlet signal (1H) at  $\delta$  6.31 assigned for the pyrimidine H-5. The appearance of the  $\text{CH}_3$  protons signal at the same position as that for the  $\text{CH}_3$  protons signal in (**1b**), and also the downfield shift for the pyrimidine H-5 in (**3b**) compared with the pyrimidine H-4 in (**1b**), which appeared at  $\delta=5.12$  ppm, indicates that the moiety around H-5 in (**3b**) differs from that around H-4 in (**1b**). Also, the moiety around  $\text{CH}_3$  at C-7 in (**3b**) is almost similar to that around  $\text{CH}_3$  at C-6 in (**1b**). Consequently, structure **3** could be tentatively assigned for the reaction products. Structure **4** would show different  $\delta$  values for  $\text{CH}_3$  groups in (**4b**) and (**1b**), and similar  $\delta$  val-

## Full Paper

ues for H-7 in (4b) and H-4 in (1b). A more conclusive evidence for structure 3 is based on carrying out NOE experiment on compound 3b. Structure 4, having CH<sub>3</sub> group at C-5 and NH<sub>2</sub> at C-3 in close proximity, would show a change in CH<sub>3</sub> position signal due to NOE. Actually, upon performing NOE experiment, the position of the CH<sub>3</sub> group was not affected, which indicates that CH<sub>3</sub> and NH<sub>2</sub> are not close to each other, preferring structure 3 for the reaction product.

Compounds (3a-d) could be re-synthesized by using microwave-assisted reaction conditions. Comparing compounds produced by the traditional method with those prepared by the microwave-assisted conditions indicates that the reaction time is reduced to 10 minutes instead of overnight standing. Also, the reaction yields were improved from 40-53% to 68-85%.

Compounds (3), as typical enaminonitriles, could be used as precursors for the preparation of thiazolodipyrimidines. Thus, heating under reflux a mixture of each of (3a-d) with an excess of carbon disulphide yielded, in each case, 9-aryl-2,4-dithioxo-7-methylthiazolo[3,2-a:4,5-d]dipyrimidine-8-carboxylates (5a-d).



a, Ar = C<sub>6</sub>H<sub>4</sub>-N(CH<sub>3</sub>)<sub>2</sub>-p

b, Ar = C<sub>6</sub>H<sub>4</sub>-OCH<sub>3</sub>-p

c, Ar = C<sub>6</sub>H<sub>4</sub>-OH-o

d, Ar =

Besides correct values of elemental analyses, the IR spectra ( $\bar{\nu}$ , cm<sup>-1</sup>) of compounds (5a-d) displayed absorption bands near 3300, 3220 (2NH), 3050, 2975, 2865 (CH), 1715 (C=O). <sup>1</sup>H-NMR spectrum (DMSO-d<sub>6</sub>) of (5a), as an example, showed signals at ( $\delta$ , ppm) at 1.10 (t, 3H, CH<sub>3</sub>), 2.26 (s, 3H, CH<sub>3</sub>), 2.84 (s, 6H, N(CH<sub>3</sub>)<sub>2</sub>), 3.95 (q, 2H, CH<sub>2</sub>), 5.88 (s, 1H, pyrimidine H-9), 6.60 (d, 2H, aromatic Protons), 6.95 (d, 2H, aromatic protons), 11.35 (s, 1H, NH, D<sub>2</sub>O exchangeable) and 12.12 (s, 1H, NH, D<sub>2</sub>O exchangeable). <sup>13</sup>C-NMR spectrum (DMSO-d<sub>6</sub>) of (5b), as an example, showed signals  $\delta$  (ppm) 14.1 (CH<sub>3</sub>), 18.6

(CH<sub>3</sub>), 61.0 (pyrimidine C-9), 63.2 (OCH<sub>3</sub>), 67.3 (CH<sub>2</sub>), 110.4, 114.6, 130.0, 133.8, 149.8, 155.2, 156.4, 157.9, 162.2 (aromatic carbons + pyrimidine C-5a, C-7, C-8 + thiazole C-4a, C-10a), 171.1 (C=S), 175.0 (C=O) and 181.5 (C=S). Mass spectrum of (5a), as an example, showed the molecular ion peak at m/z 459 (8.2%) corresponding to the molecular formula C<sub>20</sub>H<sub>21</sub>N<sub>5</sub>O<sub>2</sub>S<sub>3</sub>.

Again, synthesis of compounds (5a-d) was carried out by using microwave-assisted reaction conditions and the products were found to be identical in all aspects (m.p., mixed m.p., IR spectra). Reaction time were reduced from 8 hours to 15 minutes, yields were improved from 37-53% to 69-82%.

## Biological evaluation

### Anti-oxidant screening:

The newly synthesized compounds were tested for anti-oxidant activity as reflected in the ability to inhibit lipid peroxidation in rat brain and kidney homogenates and rat erythrocyte hemolysis. The pro-oxidant activities of the aforementioned compounds were assessed by their effects on bleomycin-induced DNA damage. TABLE 1 shows the anti-oxidant assays by erythrocyte hemolysis, which reveals that compounds (3a) and (3b) showed interesting anti-oxidant activity in the lipid peroxidation assays and considerable inhibitory activ-

TABLE 1 : Anti-oxidant assays by erythrocyte hemolysis (A/B×100)

Compounds	Absorbance of Samples (A)	Hemolysis (%)
Complete hemolysis	0.660	-
With distilled water (B)		
Ascorbic acid	0.026	3.93
1a	0.082	10.33
1b	0.075	9.12
1c	0.090	13.01
1d	0.092	14.12
3a	0.035	5.22
3b	0.031	4.68
3c	0.045	6.92
3d	0.051	8.02
5a	0.115	21.60
5b	0.112	19.25
5c	0.132	24.07
5d	0.130	23.12



ity in the hemolysis assay. Compounds (3c) and (3d) showed moderate anti-oxidant and inhibitory activity.

TABLE 2 shows the anti-oxidant assay by ABTS method. Compounds (3a), (3b), (3c) and (3d) showed potent anti-oxidant activity.

TABLE 2. Anti-oxidant assays by ABTS method [Abs.(control)-Abs.(test)/Abs.(control)×100]

Compounds	Absorbance of sample	Inhibition (%)
ABTS control	0.54	0
Ascorbic acid	0.06	88
1a	0.20	63.0
1b	0.23	57.4
1c	0.29	46.3
1d	0.28	48.1
3a	0.10	81.5
3b	0.12	77.7
3c	0.15	72.2
3d	0.13	75.9
5a	0.45	16.6
5b	0.42	22.2
5c	0.48	11.1
5d	0.43	20.3

All compounds have been tested on bleomycin-dependent DNA damage. The results, shown in TABLE 3, indicate that compounds (3a-d) may have some protective activity towards DNA from the damage induced by bleomycin.

TABLE 3 : Assays for bleomycin-dependent DNA damage

Compound	Absorbance of samples
Ascorbic acid	0.020
3a	0.026
3b	0.029
3c	0.037
3d	0.033

### Antimicrobial evaluation

The newly synthesized heterocyclic compounds listed in TABLE 4 were tested for their antimicrobial activity against the following microorganisms: *Escherichia coli*, *Pseudomonas putida*, *Bacillus subtilis*, *Streptococcus lactis*, *Aspergillus niger*, *Penicillium sp.* and *candida albicans*. The preliminary screening of the investigated compounds was performed using the filter paper disc-diffusion

TABLE 4 : Antimicrobial activities of the newly synthesized compounds.

Cpm. No.	Inhibition zone (mm)						
	Gram-negative		Gram-positive		Fungi	Yeast	
	<i>E. coli</i>	<i>P. putida</i>	<i>B. subtilis</i>	<i>S. lactis</i>	<i>A. niger</i>	<i>P. sp.</i>	<i>C. albicans</i>
1a	12	8	6	8	5	5	0
1b	14	9	6	7	4	2	0
1c	6	3	0	0	2	2	0
1d	3	2	0	0	0	0	0
3a	15	11	9	6	7	5	0
3b	12	7	7	5	7	5	0
3c	0	0	0	0	0	0	0
3d	2	2	0	0	0	0	0
5a	10	7	8	6	4	3	0
5b	11	8	9	6	5	2	0
5c	4	2	0	0	0	0	0
5d	3	0	0	0	0	0	0
Chloram-Phinicol®	22	21	18	19	20	12	0
Ampicillin®	24	20	19	22	24	14	14

*E. coli* = *Escherichia coli* ~ *P. putida* = *Pseudomonas putida* ~ *B. subtilis* = *Bacillus subtilis* ~ *S. lactis* = *Streptococcus 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 : 1-10 mm ~ Not sensitive = Inhibition zone : 0 mm ~ \* each result represents the average of triplicate readings.

## Full Paper

method. The most active compounds were (1a), (1b), (3a), (3b), (5a), and (5b), which showed moderate to slight inhibitory action to the microorganisms. The rest of compounds showed slight to no sensitivity at all to the tested organisms, and the results are summarized in TABLE 4.

### ACKNOWLEDGEMENT

This research is financed by Al-Taif University, Al-Taif, Kingdom of Saudi Arabia. Project number 1-432-1282.

### REFERENCES

- [1] J.G.Geist, S.Lauw, V.Illarinova, M.Fischer, T.Gwawert, F.Rohdich, W.Eisenreich, J.Kaiser, M.Groll, C.Scheurer, S.Wittlin, J.L.Alonso-Gomez, W.B.Schweizer, A.Bacher, F.Diederich; *ChemMed Chem*, **5**(7), 1092 (2010).
- [2] A.-E.-G.Amr, S.S.Maigali, M.M.Abdulla; *Monatsh.Chem.*, **139**(11), 1409 (2008).
- [3] A.-E.-G.Amr, S.S.Maigali, M.M.Abdulla; *ChemInfo*, **40**(8), 155-168 (2009).
- [4] B.J.Branstetter, J.G.Breitenbucher, A.D.Leb sack, W.Xiao; U.S. Pat., WO 005303, (2008).
- [5] E.E.Flefel, M.A.Salama, M.El-Shahat, M.A.El-Hashash, A.F.El-Faragy; *Phosphorus and Sulphur*, **182**(8), 1739 (2007).
- [6] A.E.G.Hammam, M.A.Sharaf, N.A.Abdel-Hafez; *ChemInfo.*, **32**(26), 101 (2001).
- [7] M.Said, Kh.Abouzid, A.Mouneer, A.Ahmedy, A.-M.Osman; *Arch.Pharm.Res.*, **27**(5), 471-477 (2004).
- [8] W.Linder, W.Brandes; U.S. Pat 367820, (1991).
- [9] R.Duval, S.Kolb, E.Braud, D.Genest, C.Garbay; *J.Comb.Chem.*, **11**(6), 947 (2009).
- [10] H.Ohnishi, H.Kosuzume, Y.Suzuki, E.Mochida; J.P. 000046, WO 002945, (1983).
- [11] A.Jesus, C.Yves; Fr. Pat., 2,222,375, (1975).
- [12] A.E.Rashad, A.H.Shamroukh, R.E.Abdel-Megeid, W.A.El-Sayed; *Synth.Comm.*, **40**, 1149 (2010).
- [13] T.I.El-Emary, Sh.A.Abdel-Mohsen; *Phosphorus & Sulphur*, **181**, 2459 (2006).
- [14] M.R.Eugene, P.L.James, A.Z.Stephen; Ger. Pat. 2,701,853, (1977).
- [15] P.Jacques, P.Andre, T.Laurent; Fr. Pat., 2,197,513, (1974).
- [16] M.Sosnowski, L.Skulski; *Molecules*, **7**, 867 (2002).
- [17] B.Gregg, K.Golden, J.Quinn; *J.Org.Chem.*, **72**, 5890 (2007).
- [18] R.Lerebours, C.Wolf; *Org.Lett.*, **9**, 2737 (2007).
- [19] N.Marion, R.Gealageas, S.Nolan; *Org.Lett.*, **9**, 2653 (2007).
- [20] Y.Morimoto, K.Tanaka, Y.Iwakiri, S.Tokuhiro, S.Fukushima, Y.Takeuchi; *Biol.Pharm.Bull.*, **18**(10), 1417 (1995).
- [21] E.Lissi, B.Modak, R.Torres, J.Escobar, A.Urzua; *Free Radic.Res.*, **30**, 471 (1999).
- [22] R.Aeschlach, J.Loliger, B.C.Scott, A.Murciao, J.Butler, B.Halliwell, O.Aruoma; *Food Chem. Toxicol.*, **32**, 31 (1994).
- [23] D.L.Coffen, D.G.Korzan; *J.Org.Chem.*, **36**, 390-395 (1971).
- [24] P.Biginelli; *Gazz.Chem.Ital.*, **23**, 360 (1893).
- [25] D.J.Brown; 'The Chemistry of Heterocyclic Compounds', A.Weissberger, E.C.Taylor, (Eds); John Wiley and Sons, Inc., New York, NY, **16**, 440 (1962).