# Synthesis and Preliminary Antimicrobial Screening of New Benzimidazole Heterocycles

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A series of 2-methylbenzimidazole incorporated to different heterocycles through ethyl or carbamoylethyl groups at position **1** of benzimidazole were synthesized. Also 3-(2-methylbenzimidazol-1-yl)propanoic acid hydrazide incorporated with semicarbazides and thiosemicarbazides were prepared. Moreover, the triazole **5e** underwent Michael addition and alkylation reaction. Some of the newly synthesized compounds showed considerable antimicrobial activity against gram positive, negative bacteria and yeast.

**Key words:** Semicarbazides, Thiosemicarbazides, Thiadiazole, Thiazoline, Thiazolidinone, Triazole, Michael addition, Alkylation reaction

## INTRODUCTION

It has been obvious that the benzimidazole moiety possessing heterocyclic systems exhibit a wide spectrum of biological activities such as antibacterial (Fahmy *et al.*, 1996; Wolley, 1944; Ozaki *et al.*, 1978; Sengupta *et al.*, 1978) and fungicidal (Shukla *et al.*, 1988; Omar *et al.*, 1996) activities, also many hydrazine derivatives have a broad spectrum of biological activities (Rastogi *et al.*, 1970; Meenakshi *et al.*, 1991).

On the other hand, broad spectrum of biological activities was associated with benzimidazole, various semicarbazide and thiosemicarbazide (Dewani *et al.*, 1973) and their cyclized products such as oxazoles, oxadiazoles, triazoles (Ferandes *et al.*, 1986) and thiadiazoles (Singh *et al.*, 1981) have been reported to possess antibacterial and antifungal activities. Based on these findings, syntheses of some new benzimidazole heterocycles were carried out for the purpose of evaluation as antimicrobial agents.

## MATERIALS AND METHODS

All melting points were uncorrected and were taken in open capillaries on a Gallenkamp apparatus. Infrared spectra were determined in KBr on a Perkin Elmer Model-137 infracord. The $^1$HNMR spectra were measured in DMSO-$d_6$ or $CDCl_3$ using Jeol EX-270MHz spectrometer. The mass spectra were recorded on GCMS-QP 1000 EX Sehimadzu gas chromatography US apparatus.

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### Synthesis of compounds

**Butyl-3-(2-methylbenzimidazol-1-yl) propanoate (1)**

To a mixture of 2-methylbenzimidazole (Vogel, 1989) (1.32 g, 0.01 mole) and butyl acrylate (1.28 g, 0.01 mole), a few drops of dry pyridine was added, the reaction mixture was heated in a sand bath at 120°C for 4 h. The oily product was washed with water (40 ml) several times then dried under vacuum to give the compound **1**. b.p 220°C at normal atmospheric pressure, Table I, II

**3-(2-Methylbenzimidazol-1-yl)propanoic acid hydrazide (2)**

A mixture of obtained oily product **1** (2.6 g, 0.01 mole) and hydrazine hydrate (99%, 3.3 g, 0.11 mole) in 20 ml of absolute ethanol was refluxed for 5 h. The reaction mixture was concentrated under reduced pressure, cooled and the precipitated solid was filtered off, and recrystallized from ethanol to give compound **2**, Table I, II.

**4-Aryl-1-[(2-methylbenzimidazol-1-yl) carboethyl] semicarbazides ($3_{a-c}$), 4-Aryl and/ or alkyl-1-[(2-methylbenzimidazol-1-yl) carboethyl] thiosemicarbazides ($3_{d-f}$)**

General method:

A mixture of compound **2** (2.2 g, 0.01 mole) and the suitable aryl isocyanate and alkyl or arylisothiocyanate (0.01 mole) in 50 ml dry benzene was refluxed for 5 h. The solid formed after cooling was filtered off to give compounds $\mathbf{3}_{a-f}$, Table I, II.

**1-[(2-Arylamino-1,3,4-oxadiazol-5-yl)ethyl]-2-methylbenzimidazoles (4a,b) and 1-[(2-arylamino-1,3,4-thiadiazol-5-yl)ethyl]2-methylbenzimidazoles (4c-e)**

General method :

Compound $\mathbf{3}_{b\text{-}f}$ (0.01 mole) was dissolved in cold concentrated sulphuric acid (10 ml) and the resulting solution was left overnight at room temperature, then poured into crushed ice with stirring. The solid product was filtered, washed with water several times to give the desired compounds $\mathbf{4}_{a\text{-}e}$, Table I, II.

**1-[(1-Aryl-2-hydroxy-1,3,4-triazol-5-yl)ethyl]-2-methylbenzimidazoles ($5_{a\text{-}c}$) and 1-[(1-cyclohexyl or phenyl-2-mercapto-1,3,4-triazol-5-yl)ethyl]-2-methylbenzimidazoles ($5_{d,e}$)**

General method :

To a solution of sodium hydroxide (50 ml, 8%) was added (0.01 mole) of compound $\mathbf{3}_{a\text{-}c,e,f}$. The reaction mixture was refluxed with stirring for 4 h. It was cooled to 5-8° C and filtered off. The filtrate was neutralized with cold hydrochloric acid solution (40 ml, 3 N) to pH 7 and the solid formed was filtered, washed with water (60 ml) to give compounds $\mathbf{5}_{a\text{-}e}$, Table I, II.

**1-[*N*-(2-Arylimino-4-oxo-oxazolidin-3-yl)carbamoylethyl]-2-methylbenzimidazoles ($6_{a,b}$) and 1-[*N*-(2-alkyl or aryl-imino-4-oxo-thiazolidin-3-yl) carbamoylethyl]-2-methyl benzimidazoles ($6_{c,d}$)**

General method:

A mixture of compound $\mathbf{3}_{a,b,e,f}$ (0.001 mole), chloroacetic acid (0.0123 g , 0.0013 mole) and anhydrous sodium acetate (0.22 g, 0.0013 mole) was refluxed for 6 h in absolute ethanol, the reaction mixture was concentrated under reduced pressure to give compounds $\mathbf{6}_{a\text{-}d}$ ,Table I, II.

**1-[*N*-(2-Arylimino4-methyloxazolin-3-yl)carbamoylethyl]-2-methylbenzimidazoles ($7_{a,b}$) and 1-[*N*-(2-alkyl or aryl-imino-4-methylthiazolin-3-yl) carbamoyl ethyl]-2-methyl-benzimidazoles ($7_{c,d}$)**

General method :

A mixture of compound $\mathbf{3}_{a,b,e,f}$ (0.002 mole) and chloroacetone (0.3 ml, 0.0025 mole) was refluxed for 4 h in isopropanol (20 ml). The reaction mixture was concentrated under reduced pressure, cooled to 5-8°C to give compounds $\mathbf{7}_{a\text{-}d}$ , Table I, II.

**1-{[1-Phenyl-2(3H)-thioxo-3-(2-carbamoylethyl)-1,3,4-triazol-5-yl]ethyl}-2-methylbenzimidazole (8)**

To a mixture of compound **5e** (0.5 g, 0.0015 mole) and acrylamide (0.12 g, 0.0017 mole), a few drops of triethylamine was added. The reaction mixture fused in a sand bath at 120°C for 4 h. On cooling, the solid material was suspended in water, filtered off, dried to give the compound **8,** Table I, II.

**1-{[1-Phenyl-2(3H)-thioxo-3-(2-cyanoethyl)-1,3,4-triazol-5-yl]ethyl}-2-methyl benzimidazole (9)**

To a solution of compound $\mathbf{5}_{e}$ (0.8 g, 0.0025 mole) in 3 ml of triethylamine, was added acrylonitrile (0.15 g, 0.0028 mole). The reaction mixture was refluxed on a water bath for 6 h. The excess triethylamine was removed under reduced pressure and the residue was washed with petroleum ether (40-60°C) to give compound **9**, Table I, II.

**1-[(1-Phenyl-2-alkylthio-1,3,4-triazol-5-yl)ethyl]-2-methyl-benzimidazoles ($10_{a,b}$)**

*General method*:

To a suspension of compound $\mathbf{5}_{e}$ (0.5 g , 0.0015 mole) in ethanol (30 ml), sodium hydroxide solution (2 ml, 15 %) was added followed by addition of the appropriate alkyl halide (0.003 mole), namely, methyl iodide and ethyl iodide. The reaction mixture was refluxed on a water bath for 1 h, left at room temperature 25°C for 12 h, cooled to 5-8°C and neutralized with aqueous hydrochloric acid solution (5 ml, 1.76 N) to pH 7. The precipitate solid was filtered, washed with water (60 ml), dried to give the compounds $\mathbf{10}_{a,b}$, Table I, II.

**1-[(1-Phenyl-2-benzylthio-1,3,4-triazol-5-yl)ethyl]-2-methyl-benzimidazole (11)**

To a suspension of compound $\mathbf{5}_{e}$ (0.5 g, 0.0015 mole) in 10 ml ethanol, a solution of potassium hydroxide (0.5 g, 0.01 mole) in 10 ml ethanol was added with stirring until complete dissolving of the starting material, followed by addition of benzylchloride (0.4 g, 0.0032 mole). The reaction mixture was heated to reflux for 2 h. On cooling, and neutralization with hydrochloric acid (10 ml, 1 N), a precipitate formed was collected by filtration, washed with water and recrystallized from ethanol/water to give the compound **11**, Table I, II.

**1-[(1-Phenyl-2-carboethoxymethylthio-1,3,4-triazol-5-yl) ethyl]-2-methyl benzimidazole (12)**

To a mixture of compound $\mathbf{5}_{e}$ (1.6 g, 0.0015 mole) in 30 ml dry acetone, was added ethylchloroacetate (0.74 g, 0.006 mole) and anhydrous potassium carbonate (2 g, 0.02 mole). The reaction mixture was refluxed on a water bath for 3 h. It was cooled to 25°C, filtered to remove inorganic salts then the filtrate was concentrated under reduced pressure, colourless crystals were precipitated, collected by filtration, washed with water (80 ml) to give the compound **12**, Table I, II.

**1-[(1-Phenyl-2-carboxymethylthio-1,3,4-triazol-5-yl)ethyl]-2-methyl benzimidazole (13)**

The foregoing method was carried out the same as synthesis of compound **12** except that chloroacetic acid was used instead of ethylchloroacetate to give the desired compound **13**, Tables I, II.

## Antimicrobial activity

### Material and method

The antimicrobial screening of some newly prepared compounds was performed according to the disk diffusion method (Fahmy, 1997).

Whatman No. 1 filter paper disks of 5 mm diameter were sterilized by autoclaving for 15 min. at 121°C. The sterile disks were impregnated with prepared compounds (600 µg/disk). Agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 5°C for 1

**Table I.** Physical and analytical data of the prepared compounds

| Compd.No. | M.P. °C (Solvent for recrystallization) | Yield % | Formulae (M.wt.) | Analysis %, Calculated/Found | | | |
|---|---|---|---|---|---|---|---|
| | | | | C | H | N | S |
| **1** | - | 90 | $C_{18}H_{20}N_2O_2$ (260.33) | 69.20<br>69.22 | 7.76<br>7.85 | 10.76<br>10.79 | - |
| **2** | 160<br>Ethanol | 91 | $C_{11}H_{14}N_4O$ (218.25) | 60.53<br>60.49 | 6.47<br>6.45 | 25.67<br>25.63 | - |
| **3a** | 230<br>(AcOH/Water) | 83 | $C_{18}H_{18}ClN_5O_2$ (371.86) | 58.14<br>58.10 | 4.88<br>4.83 | 18.84<br>18.80 | - |
| **3b** | 208<br>(AcOH/Water) | 86 | $C_{19}H_{21}N_5O_3$ (367.40) | 62.11<br>62.08 | 5.76<br>5.72 | 19.06<br>19.02 | - |
| **3c** | 210<br>(AcOH/Water) | 85 | $C_{18}H_{19}N_5O_2$ (337.42) | 64.07<br>64.15 | 5.68<br>5.72 | 20.76<br>20.81 | - |
| **3d** | 280<br>(AcOH/Water) | 75 | $C_{13}H_{17}N_5OS$ (291.41) | 53.58<br>53.62 | 5.89<br>5.91 | 24.04<br>24.09 | - |
| **3e** | 220<br>(AcOH/Water) | 84 | $C_{18}H_{25}N_5OS$ (359.55) | 60.13<br>60.09 | 7.02<br>7.08 | 19.48<br>19.52 | - |
| **3f** | 254<br>(AcOH/Water) | 87 | $C_{18}H_{19}N_5OS$ (353.48) | 61.16<br>61.11 | 5.43<br>5.40 | 19.82<br>19.79 | - |
| **4a** | 250<br>(DMF/Water) | 87 | $C_{19}H_{19}N_5O_2$ (349.43) | 65.30<br>65.32 | 5.49<br>5.51 | 20.04<br>20.08 | - |
| **4b** | 210<br>(DMF/Water) | 70 | $C_{18}H_{17}N_5O$ (319.40) | 67.68<br>67.67 | 5.37<br>5.39 | 21.93<br>21.91 | - |
| **4c** | 260<br>(DMF/Water) | 72 | $C_{13}H_{15}N_5S$ (273.39) | 57.12<br>57.15 | 5.54<br>5.59 | 25.62<br>25.66 | - |
| **4d** | 190<br>(DMF/Water) | 71 | $C_{18}H_{23}N_5S$ (341.52) | 63.29<br>63.35 | 6.73<br>6.62 | 20.51<br>20.56 | - |
| **4e** | 224<br>(DMF/Water) | 70 | $C_{18}H_{17}N_5S$ (335.46) | 64.44<br>64.42 | 5.12<br>5.08 | 20.88<br>20.84 | - |
| **5a** | 315<br>(DMF/Water) | 79 | $C_{18}H_{16}Cl\ N_5O$ (353.84) | 61.09<br>61.12 | 4.56<br>4.57 | 19.79<br>19.83 | - |
| **5b** | 295<br>(DMF/Water) | 81 | $C_{19}H_{19}N_5O_2$ (349.43) | 65.30<br>65.33 | 5.49<br>5.50 | 20.04<br>20.09 | - |
| **5c** | 310<br>(DMF/Water) | 83 | $C_{18}H_{17}N_5O$ (319.40) | 67.68<br>67.64 | 5.37<br>5.38 | 21.93<br>21.87 | - |
| **5d** | 240<br>(DMF/Water) | 82 | $C_{18}H_{23}N_5S$ (341.52) | 63.29<br>63.31 | 6.73<br>6.67 | 20.51<br>20.53 | - |
| **5e** | 303<br>(DMF/Water) | 90 | $C_{18}H_{17}N_5S$ (335.46) | 64.53<br>64.47 | 5.12<br>5.09 | 20.88<br>20.82 | - |
| **6a** | 175<br>($CHCl_3$/Pet.ether) | 65 | $C_{20}H_{18}ClN_5O_3$ (411.88) | 58.32<br>58.28 | 4.41<br>4.37 | 17.00<br>16.95 | - |
| **6b** | 180<br>($CHCl_3$/Pet.ether) | 70 | $C_{21}H_{21}N_5O_4$ (407.47) | 61.89<br>61.91 | 5.21<br>5.18 | 17.19<br>17.22 | - |
| **6c** | 206<br>($CHCl_3$/Pet.ether) | 71 | $C_{20}H_{25}N_5O_2S$ (399.57) | 60.11<br>60.15 | 6.32<br>6.36 | 17.53<br>17.55 | - |
| **6d** | 235<br>($CHCl_3$/Pet.ether) | 78 | $C_{20}H_{19}N_5O_2S$ (393.51) | 61.04<br>61.06 | 4.88<br>4.92 | 17.80<br>17.83 | - |
| **7a** | 204<br>($CHCl_3$/Pet.ether) | 53 | $C_{21}H_{20}ClN_5O_2$ (409.91) | 61.53<br>61.56 | 4.93<br>4.98 | 17.09<br>17.12 | - |

**Table I.** Continued

| Compd.No. | M.P. °C (Solvent for recrystallization) | Yield % | Formulae (M.wt.) | Analysis %, Calculated/Found | | | |
|---|---|---|---|---|---|---|---|
| | | | | C | H | N | S |
| **7b** | 190<br>($CHCl_3$/Pet.ether) | 50 | $C_{22}H_{23}N_5O_3$<br>(405.50) | 65.16<br>65.14 | 5.73<br>5.69 | 17.27<br>17.21 | - |
| **7c** | 131<br>($CHCl_3$/Pet.ether) | 58 | $C_{21}H_{27}N_5OS$<br>(397.59) | 63.44<br>63.41 | 6.86<br>6.81 | 17.62<br>17.60 | - |
| **7d** | 212<br>($CHCl_3$/Pet.ether) | 60 | $C_{21}H_{21}N_5OS$<br>(391.53) | 64.42<br>64.45 | 5.42<br>5.48 | 17.89<br>17.92 | - |
| **8** | 225<br>(Ethanol/Water) | 76 | $C_{21}H_{22}N_6OS$<br>(406.56) | 62.04<br>62.12 | 5.46<br>5.41 | 20.67<br>20.51 | 7.88<br>7.84 |
| **9** | 108<br>(Ethanol) | 78 | $C_{21}H_{20}N_6S$<br>( 388.49 ) | 64.92<br>64.95 | 5.19<br>5.25 | 21.63<br>21.69 | 8.25<br>8.29 |
| **10a** | 134<br>(Ethanol/Water) | 85.45 | $C_{19}H_{19}N_5S$<br>(349.45) | 65.30<br>65.27 | 5.49<br>5.47 | 20.04<br>19.98 | 9.17<br>9.13 |
| **10b** | 110<br>(Ethanol/Water) | 86.2 | $C_{20}H_{21}N_5S$<br>(363.48) | 66.08<br>66.06 | 5.83<br>5.81 | 19.27<br>19.23 | 8.82<br>8.78 |
| **11** | 130<br>(Ethanol/Water) | 75.8 | $C_{25}H_{23}N_5S$<br>(425.54 ) | 70.55<br>70.59 | 5.45<br>5.49 | 16.46<br>16.49 | 7.53<br>7.58 |
| **12** | 94<br>(Ethanol/Water) | 79.3 | $C_{22}H_{23}N_5O_2S$<br>(421.57 ) | 62.68<br>62.71 | 5.51<br>5.51 | 16.61<br>16.65 | 7.60<br>7.57 |
| **13** | 210<br>(Ethanol/Water) | 48 | $C_{20}H_{19}N_5O_2S$<br>(393.46) | 61.05<br>61.09 | 4.87<br>4.50 | 17.80<br>17.84 | 8.15<br>8.20 |

**Table II.** Spectral data for prepared compounds.

| Compd. No. | IR (KBr $cm^{-1}$), $^1$H-NMR (DMSO-$d_6$ or $CDCl_3$ 270 MHz, δ ppm), MS *m/z* (%) |
|---|---|
| **1** | IR: 2960 (CH), 1732 (C=O) and 1186 (C-O).<br>$^1$H-NMR ($CDCl_3$): 0.80 (3H , t, *J*=7 Hz, $CH_2\underline{CH_3}$) , 1.25 (2H , m, $\underline{CH_2}CH_3$), 1.45 (2H, m, $OCH_2\underline{CH_2}$ $CH_2$ ), 2.55 (3H, s, $CH_3$ at $C_2$ of benzimidazole), 2.70 (2H, t, *J*=7 Hz, $NCH_2\underline{CH_2}$), 3.95 (2H, t, *J*=6 Hz, $OCH_2$), 4.30 (2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$ ) and at 7.10-7.60 (4H, m, aromatic protons). |
| **2** | IR: 3440, 3274, 3145 ($NH_2$ and NH)and 1645 (C=O).<br>$^1$H-NMR ($CDCl_3$): 2.45(3H, s, $CH_3$ at $C_2$ of benzimidazole), 2.65(2H, t, *J*=7 Hz, $NCH_2\underline{CH_2}$), 4.45(2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$), 7.50(2H, s, $NH_2$ ) and at 7.20-7.65 (5H, m, 4 aromatic protons and NH).<br>MS: ($M^+$. ,$C_{11}H_{14}N_4O$) at *m/z* 218 (83.12 %) and the base peak at *m/z* 145(100 % ). |
| **3a** | IR: 3290 (NH), 3031 (CH) and 1735, 1656 (two C=O).<br>MS: ($M^+$.,$C_{18}H_{18}ClN_5O_2$) at *m/z* 371, 373 (3.6%, 1.21 %) and base peak at *m/z* 145 (100 %). |
| **3b** | IR: 3227 (NH), 3001 (CH) and 1724, 1682 (two C=O).<br>$^1$H-NMR (DMSO-$d_6$): 2.55 (3H, s, $CH_3$ at $C_2$ of benzimidazole), 2.75(2H, t, *J*=7Hz, $NCH_2\underline{CH_2}$), 3.70(3H, s, $OCH_3$), 4.45(2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$ ), 6.50-7.55 (8H, m, aromatic protons) and 8.05, 8.65, 9.75 (3H, 3 s, 3 NH). |
| **3c** | IR: 3371, 3221(NH), 3008 (CH) and 1720, 1674 (two C=O). |
| **3d** | IR: 3190 (NH), 2929 (CH), 1689 (C=O) and 1194 (C=S). |
| **3e** | IR: 3198 (NH), 3004 (CH), 1685 (C=O), 1189 (C=S).<br>$^1$H-NMR (DMSO-$d_6$): 1.10-1.75 (10H, m, $5CH_2$ of cyclohexyl), 2.55 (3H,s, $CH_3$ at $C_2$ of benzimidazole), 2.75 (2H, t, *J*=7 Hz, $NCH_2\underline{CH_2}$), 4.05 (1H, br, CH of cyclohexyl), 4.45 (2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$) and 7.10-7.55 (4H, m , aromatic protons), 8.05, 9.15, 9.75 (3H, 3 s, 3 NH).<br>MS: ($M^+$.,$C_{18}H_{25}N_5OS$) at *m/z* 359.1 (6.46 %) and base peak at *m/z* 145.1 (100 %). |
| **4a** | IR: 3395 (NH), 3000 (CH), 1651 (C=N) and 1103 (C-O).<br>MS: ($M^+$.,$C_{19}H_{19}N_5O_2$) at *m/z* 349.40 (0.81 %) and the base peak at *m/z* 122.90 (100%). |
| **4b** | IR: 3400 (NH), 3052, 2950 (CH), 1640 (C=N) and 1106 (C-O).<br>MS: fragments at *m/z* 227 (8.1%), m/z 145 (65.46%), *m/z* 131(64.77%), *m/z* 93(89.9%) and base peak at 132 (100%). |
| **4c** | IR: 3386 (NH), 2993 (CH) and 1652 (C=N).<br>$^1$H-NMR (DMSO-$d_6$): 2.50 (3H, s, $CH_3$ at $C_2$ of benzimidazole), 3.15 (2H, t, *J*=7 Hz, $NCH_2\underline{CH_2}$), 3.30 (3H, s, NH-$\underline{CH_3}$), 4.50 (2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$), 7.15-7.50 (4H, m, aromatic protons ) and 13.50 (1H, s, NH). |
| **4d** | IR: 3381(NH), 3010, 2960 (CH) and 1659 (C=N). |
| **4e** | IR: 3390 (NH), 3008 (CH) and 1660 (C=N).<br>MS: (M+.,$C_{18}H_{17}N_5S$) at *m/z* 335.40 (0.57%) and the base peak at *m/z* 132 (100%). |

**Table II.** Continued

| Compd. No. | IR (KBr $cm^{-1}$), $^1$H-NMR (DMSO-$d_6$ or $CDCl_3$ 270 MHz, δ ppm), MS *m/z* (%) |
|---|---|
| **5a** | IR: 3440 (OH), 3400 (NH), 3020, 3000 (CH), 1705 (C=O) and 760 (C-Cl).<br>The presence of OH and C=O indicates keto-enol tautomer.<br>MS: ($M^+$.,$C_{18}H_{16}ClN_5O$) at *m/z* 354 , 356 (16.76%, 5.25%) and the base peak at *m/z* 145 (100%). |
| **5b** | IR: 3442 (OH), 3402(NH), 3006 (CH) and 1701 (C=O). |
| **5c** | IR: 3440 (OH), 3405 (NH), 3010 (CH) and 1700 (C=O) |
| **5d** | IR: 3492 (NH), 2991, 3000 (CH) and 2595 (SH).<br>$^1$H-NMR (DMSO-$d_6$): 1.10-1.75 (10H, m, $5CH_2$ of cyclohexyl), 2.50 (3H, s, $CH_3$ at $C_2$ of benzimidazole), 3.25 (2H, t, *J*=7 Hz, $NCH_2\underline{CH_2}$), 4.35 (1H, br, CH of cyclohexyl), 4.60 (2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$), 7.15-7.50 (4H, m, aromatic protons) and 13.55 (1H, s, NH). |
| **5e** | IR: 3439 (NH), 2990 (CH) and 2600 (SH).<br>$^1$H-NMR (DMSO-$d_6$): 2.50 (3H, s, $CH_3$ at $C_2$ of benzimidazole), 2.95 (2H, t, *J*=7 Hz, $NCH_2\underline{CH_2}$), 4.40 (2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$), 7.10-7.55 (9H, m, aromatic protons) and NH is out of scale.<br>MS: ($M^+$.,$C_{18}H_{17}N_5S$) which is the base peak at *m/z* 335.10 (100%). |
| **6a** | IR: 3420 (NH), 2996 (CH), 1704 (C=O) and 1671 (CONH).<br>$^1$H-NMR (DMSO-$d_6$): 2.45 (3H, s, $CH_3$ at $C_2$ of benzimidazole), 3.05 (2H, t, *J*=7 Hz, $NCH_2\underline{CH_2}$), 3.90 (2H, s, $CH_2$ of oxazolidine), 4.45 (2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$), 6.50-7.55 (9H, m, 8 aromatic protons and NH proton).<br>MS: fragments at *m/z* 375.5 (1.12%), *m/z* 281, 283 (3.04%, 1.13%), *m/z* 153, 155 (71.81%, 23.64%), *m/z* 131 (20.4%) and base peak at *m/z* 145 (100%). |
| **6b** | IR: 3400 (NH), 3000 (CH), 1700 (C=O) and 1660 (CONH).<br>MS: fragments at *m/z* 276.5 (11.31%), *m/z* 248.50 (2.10%), *m/z* 159 (8.40%), *m/z* 132 (20.60%), *m/z* 131 (16.30 %) and base peak at *m/z* 145 (100%). |
| **6c** | IR: 3401 (NH), 3002, 2990 (CH), 1702 (C=O) and 1664 (CONH). |
| **6d** | IR: 3405 (NH), 3001 (CH), 1705 (C=O) and 1669 (CONH).<br>1H-NMR (DMSO-$d_6$): 2.40 (3H, s, $CH_3$ at $C_2$ of benzimidazole), 3.05 (2H, t, *J* = 7 Hz, $NCH_2\underline{CH_2}$), 3.95 (2H, s, $CH_2$ of thiazolidinone), 4.45 (2H, t, *J* = 6 Hz, $N\underline{CH_2}CH_2$), 7.10-7.50 (10H, m, 9 aromatic protons and NH proton).<br>MS: ($M^+$.,$C_{20}H_{19}N_5O_2S$) at *m/z* 394.10 (4.99%) and the base peak at *m/z* 132 (100%). |
| **7a** | IR: 3400 (NH), 3000 (CH), 1679 (C=O), 1143 (C-O) and 748 (C-Cl).<br>$^1$H-NMR (DMSO-$d_6$): 2.35 (3H, s , $CH_3$ at $C_4$ of oxazoline) , 2.80 (3H, s, $CH_3$ at $C_2$ of benzimidazole), 3.35 (2H, t, *J*=7 Hz, $NCH_2\underline{CH_2}$), 4.75 (2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$), 5.65 (1H, s, CH at $C_5$ of oxazoline), 7.25-8.20 (8H, m, aromatic protons) and 9.85 (1H, s, NH).<br>MS: ($M^+$.,$C_{21}H_{20}ClN_5O_2$) at *m/z*, 409.9,411.9 (0.5%,0.15%) and the base peak at *m/z* 132 (100%). |
| **7b** | IR: 3402 (NH), 2998 (CH), 1681 (C=O) and 1126 (C-O).<br>$^1$H-NMR (DMSO-$d_6$): 2.35 (3H, s, $CH_3$ at $C_4$ of oxazoline), 2.85 (3H, s, $CH_3$ at $C_2$ of benzimidazole), 3.35 (2H, t, *J*=7 Hz, $NCH_2\underline{CH_2}$), 3.70 (3H, s, $OCH_3$), 4.70 (2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$), 5.65 (1H, s, CH at $C_5$ of oxazoline) |
| **7b** | 7.25-8.25 (8H, m, aromatic protons) and 9.85 (1H, s, NH).<br>MS: ($M^+$.,$C_{22}H_{23}N_5O_3$) at *m/z* 405.1 (0.92%) and the base peak at *m/z* 145 (100%). |
| **7c** | IR: 3407 (NH), 2990 (CH) and 1676 (C=O).<br>MS: ($M^+$.,$C_{21}H_{27}N_5OS$) at *m/z* 398.2 (2.75%) and the base peak at *m/z* 145 (100%). |
| **7d** | IR: 3396 (NH), 2995 (CH) and 1671 (C=O).<br>$^1$H-NMR ($CDCl_3$): 1.50 (3H, s, $CH_3$ at $C_4$ of thiazoline), 2.50 (3H, s, $CH_3$ at $C_2$ of benzimidazole), 2.75 (2H, t, *J*=7 Hz, $NCH_2\underline{CH_2}$), 4.45 (2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$), 5.50 (1H, s, CH at $C_5$ of thiazoline), 6.95-7.60 (10H, m, 9 aromatic protons and NH proton).<br>MS: ($M^+$.,$C_{21}H_{21}N_5OS$) which is the base peak at *m/z* 391.1 (100%). |
| **8** | IR: 3388, 3200 ($NH_2$), 1660 (C=O) and 1160 (C=S).<br>MS: ($M^+$.,$C_{21}H_{22}N_6OS$) at *m/z* 406.1(24.63%) and the base peak at *m/z* 334.9 (100%). |
| **9** | IR: 2220 (C=N) and 1080 (C=S).<br>MS: ($M^+$.,$C_{21}H_{20}N_6S$) at *m/z* 388.1 (69.66%) and the base peak at *m/z* 145 (100%). |
| **10a** | IR: 2995 (CH), 1600 (C=C), 1667 (C=N) and 1325 (S-$CH_3$). |
| **10b** | IR: 3000 (CH), 1602 (C=C) and 1664 (C=N).<br>$^1$H-NMR ($CDCl_3$): 1.35 (3H, t, *J*=7 Hz, $SCH_2\underline{CH_3}$), 2.35 (3H, s, $CH_3$ at $C_2$ of benz- imidazole), 3.05 (2H, t, *J*= 7 Hz, $NCH_2\underline{CH_2}$), 3.15 (2H, q, *J*=7 Hz, $S\underline{CH_2}CH_3$), 4.45 (2H, t, *J*=6 Hz, N $\underline{CH_2}CH_2$) and 6.65-7.65 (9H, m, aromatic protons). |
| **11** | IR: 3004 (CH), 1607 (C=C) and 1662 (C=N).<br>MS: ($M^+$.,$C_{25}H_{23}N_5S$) at m/z 424.91 (9.4 %) and the base peak at m/z 90.98 (100%). |
| **12** | IR: 3003 (CH) and 1735 (C=O).<br>$^1$H-NMR ($CDCl_3$): 1.25 (3H, t, *J*=7 Hz, $OCH_2\underline{CH_3}$), 2.35 (3H, s, $CH_3$ at $C_2$ of benzimida- zole), 3.05 (2H, t, *J*=7 Hz, $NCH_2\underline{CH_2}$), 3.95 (2H, s, $SCH_2$), 4.15 (2H, q, *J*=7 Hz, $O\underline{CH_2}CH_3$), 4.45 (2H, t, *J*=6 Hz, $N\underline{CH_2}CH_2$), 6.65-7.65 (9H, m, aromatic protons). |
| **13** | IR: 3380-2450 (OH), 1690 (C=O), 1598 (C=C) and 1265 (C-O). |

**Table III.** Antimicrobial activity of the tested compounds

| Compound No. | *B. cereus.* | *E. coli.* | *S. cerevisae.* | *A. niger.* |
|---|---|---|---|---|
| Gentamycin | +++ | +++ | - | - |
| Ampicillin | +++ | +++ | - | - |
| Amoxacillin | ++++ | + | - | - |
| Erythromycin | ++ | ++ | - | - |
| **1** | + | ++ | +++ | ++ |
| **2** | - | - | - | - |
| **3d** | - | - | - | - |
| **4a** | - | - | - | - |
| **5e** | + | + | | |
| **6a** | - | - | - | - |
| **7b** | +++ | +++ | +++ | ++ |
| **8** | - | - | - | - |
| **10a** | + | - | - | - |
| **12** | + | - | - | - |
| **13** | - | - | - | - |

Highly active = +++ (inhibition zone>12 mm )
Moderately active = ++ (inhibition zone 9-12 mm )
Slightly active = + ( inhibition zone 6-9 mm )
Inactive = - ( inhibition zone<6 mm )

h. to permit good diffusion and then transferred to an incubator at 37°C for 24 h. for bacteria, at 28°C for 72 h. for yeast and fungi. Then examined for the inhibition zones caused by the prepared compounds on the micro-organisms. The results of the preliminary screening test are listed in Table III.

### Results of antimicrobial activity

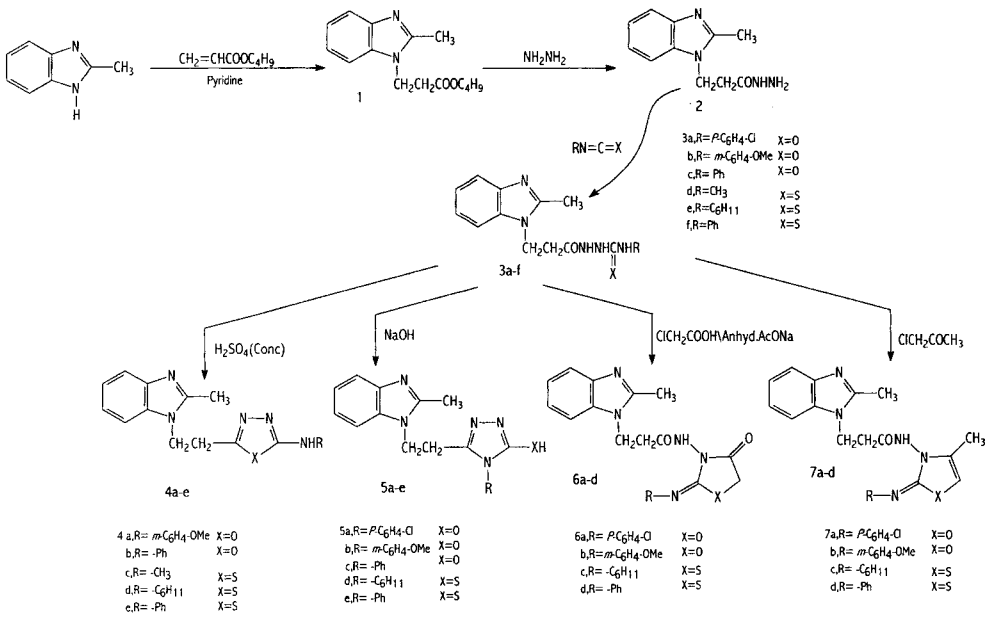
The from data obtained it was found that ester **1** was highly active against S. cerevisae and moderately active against E. coli and A. niger, while compound **7b** was found to be highly active against B. cereus, E. coli and S. cerevisae and moderately active against A. niger, due to the high activity of this compound, we tested different concentrations of it, we found the MIC was 300 µg.

Also, compounds **5e**, **10$_a$** and **12** were found to be slightly active against B. cereus. But all the tested compounds were found to be inactive against S. cerevisae and A. niger except compounds **1** and **7b**. So compound **7b** was found to be the most active compound.

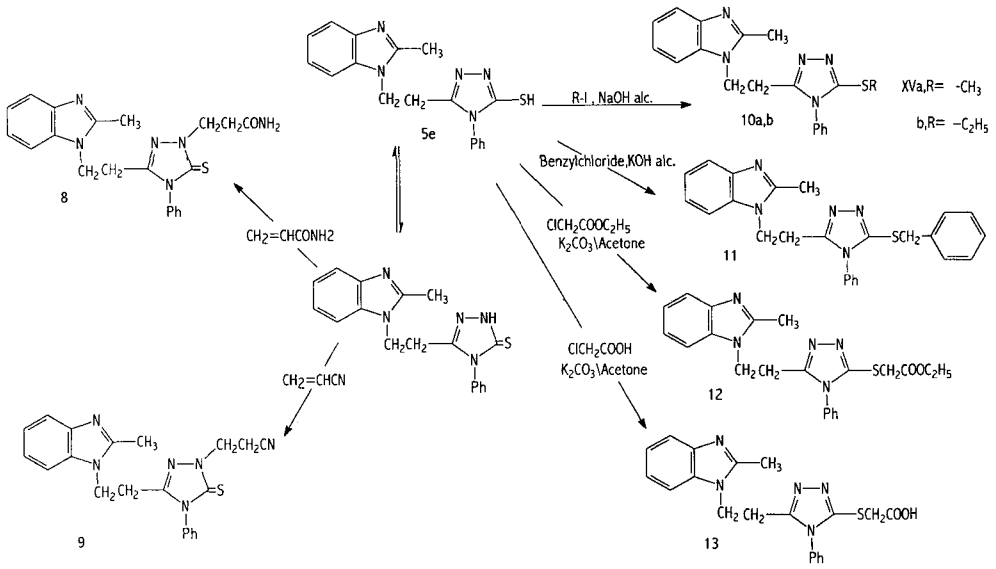
## RESULTS AND DISCUSSION

Fusion of 2-methylbenzimidazole with butylacrylate in the presence of a few drops of pyridine afforded the ester **1**. This compound was transformed to the hydrazide **2** by treatment with hydrazine hydrate (99%). The hydrazide **2** was considered as the key intermediate for the synthesis of several series of new compounds. Condensation of **2** with different substituted arylisocyanate and alkyl or aryl-isothiocyanate in dry benzene afforded the corresponding semicarbazide and thiosemicarbazide derivatives **3a-f** (Scheme 1). The latter **3b-f** was reacted with concentrated sulphuric acid (Girl *et al.*, 1994) and underwent cyclization to give 1,3,4-oxadiazol derivatives **4a, b** and 1,3,4-thiadiazol derivatives **4c-e** while cyclocon-densation of **3a, b, c, e, f** with 8% sodium hydroxide (Nofal *et al.*, 1997) gave 1,3,4-triazole derivatives **5a-e** (Scheme 1).

Also, cyclization of compounds **3a, b, e, f** with chloro-acetic acid in the presence of anhydrous sodium acetate afforded the corresponding oxazolidinone derivatives **6a, b** and thiazolidinone derivatives **6c, d** respectively accord-




**Scheme 1.** Synthetic scheme for benzimidazole derivatives I



**Scheme 2.** Synthetic scheme for benzimidazole derivative II

ing to a reported method (Ebeid *et al.*, 1987).

On the other hand, cyclocondensation of **3a, b, e, f** with chloroacetone in presence of isopropyl alcohol afforded the corresponding oxazolin derivatives **7a, b** and thiazolin derivatives **7c, d** respectively, (Ebeid *et al.*, 1987). (Scheme 1).

Moreover, the trizole **5e** underwent Michael addition reaction (El-Tamany *et al.*, 1997) with some unsaturated compounds such as acrylamide and acrylonitrile to give the addition products **8, 9** respectively where the addition took place on the N3-atom of the triazole ring (Scheme 2). Where the alkylation of compound **5e** with different alkyl halide (El-Tamany et al., 1997) afforded compounds **10a, b** and **11** (Scheme 2). Also alkylation of **5e** with ethyl-chloroacetate and monochloroacetic acid gave the corresponding compounds **12, 13** (Scheme 2).

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## REFERENCES

Dewani, M. B., Pathak, V. S., and Amine, U. M., Synthesis of some 1-acyl-4-substituted thiosemicarbazides, *Indian J. Chem.*, 11, 1078-1079 (1973).

Ebeid, M. Y., Amin, K. M., and Hussein, M. M., Coumarinyl thiazolines and coumarinyl thiazolidin-4-ones as potential antimicrobial agents, *ibid.*, 28, 183-191 (1987).

Fahmy, H. H., Synthesis of some new quinoline derivatives of potential antimicrobial activity, *Egypt. J. Pharm. Sci.*, 38, 403-414 (1997).

Fahmy, H. H., Omar, M. T., and Mohamed, H. S., Synthesis of some new benzimidazole derivatives with evalution of their antimicrobial activity, *Egypt. J. Pharm. Sci.*, 37, 597-607 (1996), *Egypt. J. Chem.*, 40, 159-166 (1997).

Ferandes, P. S. and Sonar, T. M., Synthesis and biological activity of heterocyclic derivatives derived from ethyl-2-hydroxy-quinoxaline-3-carboxylate, *J. Indian Chem. Soc.*, LXIII, 427-429 (1986).

Girl, S. and Khan, M. H., Synthesis of some 1-[5`-aryl-1, 3`,4`-thiadiazole-2`-yl]-3-chloro-4-substituted-2-azetidinones as potential fungicides, *J. Indian Chem. Soc.*, 71, 201-202 (1994).

Meenakshi, S., Dixit, K. S., and Barthwal, J. P., Synthesis and biological evaluation of substituted indolyl-1,2,4-triazoles, *J. Indian Chem. Soc.*, 68, 466-469 (1991).

Nofal, Z. M., Kamel, M. M., El-Masry, A. H., Omar, M. T., and Sarhan, A. I., Synthesis of some coumarin derivatives of possible biological activity, *Egypt. J. Pharm. Sci.*, 38, 159-169 (1997).

Omar, M. T., Fahmy. H. H., Hamad, M. M., Shehab El-Dean, A., and Mohamed, H. S., Synthesis of some new benzimidazole derivatives as antimicrobial agents, *Egypt. J. Pharm. Sci.*, 37, 99-106 (1996).

Ozaki, Shoichiro, Ike Yoshimasa, Mori, Haruki (Mitsuitoatsu Chemicals, Inc.) Japan Kokai, 1-Carbamoyl uracils, *Chem. Abs.*, 88, 18660 (1978).

Rastogi, U. K., Arora, R. C., Sinhar, J. N., and Pamar, S. S., Interrelationship between monoamins oxidase inhibitor and central nervous system depressant activity of substituted quinazolone hydrazide, *J. Prakt. Chem.*, 312, 744-750 (1970).

Sengupta, A. K. and Goyal. M., Silicon (IV) complexes of tridentate or tetradentate bifunctional Shiff base derivative from 2,4-pentadione, *J. Indian Chem. Soc.*, 60, 764-769 (1978).

Shukla, J. S. and Fadogan, M., Synthesis of 2-substituted-thiobenzimidazoles as possible bio-active agents, ibid., LXV, 225-226 (1988).

Singh, S., Yadav, L. D. S., and Singh, H., Synthesis and anti-fungal activity of some 1,3,4-thiadiazolo[3,2-a]-S-triazine-7-thiones and *N*-acyl-*N*-(5-araylkyl/aryl)-1,3,4-thiadiazol-2-yl)thiourease, *Indian. J. Chem.*, 20B, 518-520 (1981).

Vogel, A. I., "Text book of practical organic chemistry" 15th edition, Longman Group UK Ltd, 1163 (1989).

Wolley, D. W., Microestimation of inorganic constituents of bone, *J. Biol. Chem.*, 152, 255-278 (1944).