Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2012, 4(6):2202-2207
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Syntheses and antimicrobial activity of some new thiohydantoin and thiazole derivatives

Heba A. El Hady[*1]

**Chemistry Department, Faculty of Science(For Girls), Al –Azhar University Nasr City, Egypt.*
[1]Umm- al qura University Faculty of applied Science (For Girls) Chemistry Department .

ABSTRACT

*5-(p-Tolyl)-2-[(p-tolylethylidene)hydrazino] thiazole **(3)** and 3-[(p-tolylethylidene)amino]-2-thiohydantoin **(6)** have been prepared via cyclization of p-methyl acetophenone thiosemicarbazone **(2)** with p-methylphenacyl bromide and ethyl chloroacetate in presence of fused sodium acetate . Acetylation of 2,3 and 6 with acetic anhydride afforded the corresponding diacetyl derivative**(5)** and mono acetyl derivatives **(4** and **7)**. Reaction of 2-thiohydantoin **(6)** with thiophene-2-carboxaldhyde and chloroacetic acid gives 5-(thiophen-2-ylidene)-3-[(p-tolylethylidene)amino] -2-thiohydantoin **(8)** and 3-[(p- tolylethylidene)amino] -2-thiohydantoin-5-yl acetic acid **(10)** . The mass spectral fragmentation patterns of some prepared thiazole and 2-thiohydantoin derivatives have been investigated in order to elucidate the structure of the synthesized compounds. The prepared compounds also exhibited antimicrobial activity.*

Keywords: Thiosemicarbazide , thiohydantoin , thiazole , antimicrobial activity , minimum inhibition concentration

.

INTRODUCTION

The chemistry and properties of thiohydantoins and their derivatives have been investigated for more than 145 years. The hydantoin moiety represents an important pharmacophore, which is present in various biologically active compounds. The 1-aminohydantoin [1,2] is an antimicrobial drug for the treatment of urinary tract infections, while its analog dantrolene [1,2] represents a well known skeletal muscle relaxant. Another 1-aminohydantoin, azmilide, is a promising drug candidate for the treatment of cardiac arrhythmia. Phenylhydantoin, [3] 5,5-diphenylhydantoin is an anticonvulsant used for the treatment of epilepsy. This paper now reports the synthesis of thiazole and 2-thiohydantoin derivatives by using p-methyl acetophenone thiosemicarbazone **(2)** as a key starting material. The electron impact (EI) ionization mass spectral fragmentation patterns of some synthesized compounds are described.

MATERIALS AND METHODS

Melting points were taken in open capillaries with a Thomas uni-melt apparatus un corrected. NMR spectra were recorded on a general electric QE 300 instrument and chemical shifts are given with respect to TMS. IR spectra were recorded on a perkine-Elmer 1420 spectrometer and a Biorad FTS7 (KBR). Mass spectra were obtained on a Jeol JMS D-300 spectrometer operating at 70 ev. Microanalysis were conducted using an elemental analyzer 1106.

4-Methyl acetophenone thiosemicarbazone (2) .
A mixture of 4 methyl acetophenone **(1)** (0.01 mol) and thiosemicarbazide (0.01 mol) in ethanol (50 ml) was heated under reflux for 4 hr. the solid formed after cooling saw filtered of ,washed with water, dried and purified by crystallization with benzene to give **1** as colorless crystals yield 75% m.p. **155ºC**. IR(KBr): 3350, 3130(NH2), 3220 (NH), 1625 (C=N), 1350 (C=S) cm^{-1}.^{1}H-NMR (DMSO-d6): δ 2.32 (s, 3H, CH3), 2.15(s,3H, CH3), 7.02 (s, 2H,

NH2), 7.24-7.78 (m, 4H, H-phenyl ring), 10.12 (s, 1H, NH) ppm. MS(m/z, %) ;194(3.9),193 (23.3), 148 (2.3), 147 (3.9), 116 (9.3), 106 (5.4), 104 (10.9), 92 (8.5), 91 (21.7) 90 (6.3), 88 (13.2), 77 (11.6), 75 (9.3), 65 (13.2), 62 (20.9), 61 (17.8), 60 (100), 59 (11.6), 58 (8.5), 51 (34.4), 50 (6.2). Cald.:C,57.97;H, 6.28;N, 20.28; S, 15.45.Found :C,58.02; H, 6.12; N,19.97; S, 15.27.

5-(p-Tolyl)-2- [(p-tolylethylidene)hydrazino] thiazole(3).
3-[(p-tolylethylidene)amino]-2-thiohydantoin (6).
A mixture of **2** (0.01 mol), ω-bromo methyl aryl ketone,(such as 4-methyl phenacyl bromide)(0.01 mol) ,and ethyl chloro acetate in ethanol (50 ml) in presence of fused sodium acetate (0.03 mol) was heated under reflux for 6 hr, then cooled and poured into water. The solid formed was filtered off, washed with water, dried and purified by suitable solvent to give **3** and **6** respectively .

5-(p-Tolyl)-2- [(p-tolylethylidene)hydrazino] thiazole (3), yield 65%, (EtOH), m.p.**120ºC**. IR (KBr): 3225(NH), 1625(C=N), 1609,1592(C=C) cm^{-1}.^{1}H-NMR (DMSO-d6): δ 2.21 (s,3H,CH3), 2.29(s,3H,CH3), 2.25(s,3H,CH3) ,6.99-7.82 (m, 9H ,Ar-H, H-phenyl and thiazole ring), 10.71(s,1H,NH) ppm**.** MS (m/z, %); 324 (.37) , 309 (0.1) , 308 (0.25), 306 (2.11) 293 (0.93), 288 (1.13), 279 (0.15),278 (0.25),230 (1.80),229 (0.11),203 (5.35),190 (2.06),188 (15.08),173 (9.98),161 (6.39),158 (9.54),149 (2.86),147 (65.6),142 (4.45),134 (10.01),131 (41.00),120 (2.80), 119 (3.41), 116 (6.39),105 (5.00) , 102 (10.93), 90 (100),83 (0.18), 78 (1.31), 76 (10.59), 72 (0.18) , 69 (1.06) , 64 (34.3), 62 (12.6) , 57 (1.85) , 52 (2.85) ,50 (10.43),. Calcd.: C, 71.02 ;H, 5.91; N, 13.08; S, 9.96.Found:C, 71.15; H, 5.80; N,13.15; S, 9.84.

3-[(p-tolylethylidene)amino]-2-thiohydantoin (6), yield, 80% (benzene); m.p.**184ºC.** IR (KBr): 3250(NH), 1625(C=N), 1357(C=S)cm^{-1}.^{1}H-NMR (DMSO-d6): δ 2.26 (s,3H,CH3), 2.14(s,3H,CH3), 3.65(s,2H,NCH2CO), 7.15-7.71(m,4H,H-phenyl ring), 10.98 (s,1H,NH) ppm. MS (m/z, %), 248 [(M+1) 18.2] , 246 [(M-1) 42.7], 245 (25.5), 233 (3.6), 232 (18.2), 204 (13.5), 202 (2.1) , 201 (6.8) , 200 (6.8), 173 (4.2), 159 (17.2), 158 (5.7), 157 (2.6), 148 (1.6), 147 (9.4), 133 (18.8), 132 (14.6), 131 (12.5), 130 (17.2), 119 (13.0), 118 (100), 117 (38.5) , 115 (30.2) , 114 (6.8)92 (15.1), 91 (39.6), 90 (07.3), 89 (17.2) , 88 (15.6) , 87 (32.8) , 77 (7.8) , 65 (41.1), 64 (13.5) , 63 (26.00), 62 (8.9) , 60 (18.20), 59 (6.3), 51 (10.9), 50 (15.1) .Calcd. ; C, 58.29; H, 5.26; N, 17.00; S,15.45.Found :C, 57.99; H, 5.46; N, 17.09; S, 15.25.

2-[(p-tolylethylidene)acetyl hydrazino]-thiazole(4).
A solution of **3** (0.01 mol) in acetic anhydride (30 ml) was heated under reflux for 2hr, then cooled and poured onto ice-water .The solid formed dried and purified by crystallization from petroleum ether (60-80) to give **4** as orange crystals ,yield 60% ,) , m.p.**140ºC**. IR (KBr): 1710(C=O),1630 (C=N), 1610,1593(C=C) cm^{-1}.^{1}H-NMR (DMSO-d_6): δ 2.25 (s,3H,CH_3) , 2.25 (s,3H,CH_3) , 2.11 (s,3H,CH_3) , 2.3 (s,3H,$COCH_3$) , 6.89 -7.85 (m, 9H ,Ar-H, H-phenyl and thiazole ring), ppm.

MS(m/z, %);364 [(M+1) 5.5] ,362[(M-1) 11], 347 (3.7) , 346 (3.7), 323 (21.1), 322 (26.6),321 (100), 320 (74.3), 319 (32.1),307 (10), 306 (21.1), 293 (8.3),292 (10.1), 289 (8.3), 288 (11.9),275 (7.8), 263 (8.8), 248 (11.9) ,247 (22.0), 233 (8.3), 231(7.3),230 (7.3), 217(5.5), 216 (10.1), 205 (27.5), 204 (27.5), 203 (32.1),202 (16.5), 190 (18.3), 188 (15.6), 187 (11.0), 176(22.0), 175 (62.4), 174 (27.5), 171 (11,0), 163 (7.3), 162 (7.3), 161 (10.1), 158 (8.30), 148 (41.2), 147 (17.3), 146 (20.6),144 (6.4),143 (15.6), 140 (7.3) , 134(11.9), 133 (28.4), 132 (61.5), 131 (27.5), 118 (33.9), 117(64.2), 115 (22), 91(77.1), 90 (30.3), 88 (24.8), 77 (22.9), 63 (20.2), 60 (20.2), 59 (15.6), 51 (20.2) . Calcd. :C,69.42; H, 5.78; N,11.57; S,8.81.Found: C,68.99; H, 5.86; N,11.25; S, 8.97.

4-methylacetophenone – 2,4-diacetyl thiosemicarbazone (5).
A solution of **2** (0.01 mol) in acetic anhydride (25 ml) was heated under reflux for 2 hr, then cooled and poured onto ice water .The resulting solid was filtered off ,washed with water, dried and purified by recrystallization from benzene to give **5** as white crystals ,yield 70% , m.p.**202ºC**. IR(KBr): 3220 (NH), 1710 , 1695(C=O),1620(C=N), 1354 (C=S) cm^{-1}.^{1}H-NMR (DMSO-d_6): δ 2.15(s,3H,CH_3), 2.08(s,3H,CH_3), 2.22(s,3H,$COCH_3$), 2.08(s,3H,$COCH_3$), 7.21-7.80(m, 4H, H-phenyl ring) ppm. MS (m/z, %); 292 [(M+1) 24.1], 290 [(M-1) 27.6] , 234 (100) ,193 (17.2), 192 (48.3), 190 (72.4), 176 (27.6) , 175 (17.2) , 174 (3.4),158 (7.8), 157 (27.6), 150 (24.1), 149 (41.4), 148 (58.6), 147 (82.8), 136 (20.7),135 (31.0), 133 (51.7), 132 (75.9), 119 (41.4) ,118 (96.6),117 (79.3), 116 (44.8), 115 (27.6), 114 (34.5), 112 (24.1), 106 (27.6), 105 (17.2), 103 (34.5), 96 (17.2), 92 (48.3), 91 (51.7), 90 (58.6), 89 (34.5), 82 (31.0), 82 (31.0), 79 (10.3) , 78 (41.4) , 75 (24.1) , 69 (17.2), 68 (31.0), 65 (65.5) ,64 (17.2), 61 (17.2) , 60 (31.0) ,59 (72.4), 57 (41.4) , 56 (27.4), 55 (89.7), 54 (31.0) , 52 (31.0) ,52 (34.0),50 (51.0). Calc.: C,57.73; H, 5.84; N, 14.43; S, 10.99. Found: C,57.60; H, 5.84; N, 14.43; S, 10.88.

1-Acetyl-3-[(p-tolylethylidene) amino]-2-thiohydantoin (7).
A solution of **6** (0.01 mol) in acetic anhydride (25 ml) was heated under reflux for 2 hr, then cooled and poured onto ice water .The resulting solid was filtered off ,washed with water, dried and purified by recrystallization from benzene to give **7** as yellow crystals ,yield 68% , m.p.**158ºC**. IR(KBr):1703 -1672(C=O),1627(C=N), 1353(C=S) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.10 (s,3H,$COCH_3$), 2.25 (s,3H,CH_3), 2.19(s,3H,CH_3), 3.65 (s,2H,NCH_2CO), 7.11 - 7.75 (m,4H, H –phenyl ring) ppm.

MS (m/z, %); 288 [(M-1) 38.5] , 274 (11.0) , 273 (9.9), 248 (23.1) , 246 (44.0), 245 (28.6), 235 (6.6) , 234 (13.2) , 233 (12.1), 232 (100), 231 (50.5), 213 (9.9), 255 (16.5), 203 (45.10), 200 (13.20), 199 (7.7), 198 (5.50) , 190 (11.0), 186 (8.8) , 177 (15.4) , 176 (12.1), 175 (15.4), 174 (16.5), 160 (9.9), 156 (35.2) , 155 (28.8) ,149 (24.2), 148 (17.6), 146 (15,4), 144 (17.6) , 143 (15.4), 142 (7.7) ,136 (7.7) , 135 (5.50), 134 (6.60),132 (19.8), 131 (17.6), 130 (22.0),128 (22.2), 125 (5.50), 124 (7.70),116 (17.6), 115 (38.5), 110 (42.9),106 (7.7), 105 (22.01), 103 (12.1), 91 (52.7) , 90 (19.8) , 89 (20.9) , 76 (14.3), 73 (20.9), 69 (24.2), 52 (16.5), 51 (13.2), 50 (18.7) . Calcd.: C , 85.13; H , 5.19; N, 14.53; S, 11.07.Found : C, 57.99; H, 5.32; N, 14.21; S, 11.19.

5-Thiophen-2-ylidene-3-[(p-tolylethylidene)amino]-2-thiohydantoin (8).
A solution of **6** (0.01 mol), thiophen-2-carboxaldehyde (0.01 mol) and pipredine(1 ml) was fused on a hot plate at **100-110ºC** for 2hr. The reaction mixture was cooled and a acidified with dilute hydrochloric acid (2 N) .The crude product was filtered off, washed with water, dried and purified by crystallization from ethanol to give **8** as pale yellow crystals yield 80% , , m.p.**100ºC**. IR(KBr): 3262(NH), 1695(C=O),1630(C=N), 1351(C=S), 1605,1585(C=C) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.23(s,3H,CH_3), 2.29(s,3H,CH_3), 6.85-7.98(m,8H,H-phenyl ,H-thiophene ring and olefinic proton),10.53(s,1H,NH) ppm. MS (m/z, %): 342 [(M+1) 15.2] , 340 [(M-1)27.2] , 339 (15.9) ,328 (7.30), 326 (30.5), 325 (23.2),251 (8.5), 250 (9.80), 248 (12.80), 247 (37.8), 246 (39.6), 145 (22.6),234 (12.4), 233 (6.7), 232 (13.4), 231 (9.1), 230 (7.30, 225 (11.00),212 (505), 204 (11.00), 191 (4.3), 185 (6.1), 184 (4.30), 190 (6.70) , 182 (6.10),180 (7.90), 176 (11.0), 174 (16.5), 173 (12.8), 171 (4.30),170 (4.30), 169 (11.6), 168 (12.8), 165 (4.30), 164 (5.50), 162 (4.90),159 (9.10), 158 (4.90), 155 (6.10), 149 (15.9), 147 (12.8), 143 (14.0), 142 (14.0), 141 (13.4), 140 (56.7), 139 (40.9), 133 (26.8), 132 (32.3), 130 (12.8), 129 (12.2), 127 (18.9), 119 (23), 112 (13.40), 111 (37.4),110 (26.2), 109 (19.50), 98 (22.6),96 (26.80), 95 (18.90), 94 (12.80),92 (9.10), 91 (65.20), 90 (42.70) ,85(31.7), 84 (100.00), 83 (36.00), 79 (7.90), 78 (13.40), 77 (13.40) , 76 (11.00), 75 (13.40), 73 (12.80),69 (25.6), 66 (16.5) , 64 (2.07) ,65 (44.5) , 64 (2.7) , 63 (27.40), 60 (11.6), 59 (10.40) , 55 (13.4), 52 (14.6), 51 (33.5).Calc.: C, 59.82; H, 4.39; N, 12.31; S, 18.76.

1-Acetyl-3- [(p-tolylethylidene)amino]-5-thiophen-2-ylidene-2-thiohydantoin (9).
A solution of **8** (0.01 mol) in acetic anhydride (25 ml) was heated under reflux for 2 hr, then cooled and poured onto ice water .The resulting solid was filtered off ,washed with water, dried and purified by recrystallization from benzene to give **9** as yellow crystals ,yield 80% , m.p.**80ºC**. IR(KBr): 1710-1703(br-C=O), 1629 (C=N), 1606, 1586 (C=C),1352(C=S)cm^{-1}, ^{1}H-NMR (DMSO-d_6): δ 2.01 (s,3H,$COCH_3$), 2.27 (s,3H,CH_3), 2.18 (s,3H,CH_3), 6.89- 7.97 (m,8H, H –phenyl,H-thiophen ring and olefinic protone) ppm. MS (m / z, %): 358[(M+2)6.3],384[(M+1) 15.2] , 382[(M-1),29], 36 (5.4), 343 (6.3), 342 (13.4), 341 (37.5), 340 (37.5),339 (22.3), 328 (22.3), 327 (30.4), 326 (100), 325 (61.6), 308 (13.5), 298 (11.60), 252 (5.40), 251 (9.9) , 250 (40.2), 235 (5.4), 232 (17.9), 231 (13.4), 215 (5.4), 205 (5.5), 204 (11.6), 182 (3.6), 181 (16.1), 176 (19.6), 175 (10.7), 173 (13.4), 168 (14.4), 160 (8.0), 156 (8.9),148 (0.99) , 146 (7.1), 145 (8.90), 144 (17.0), 142 (16.1) , 141 (19.6),140 (75.0), 139 (64.3), 138 (7.1), 135 (32.1), 134 (8.9), 133 (17.9), 132 (22.3), 131 (5.4), 127 (7.1), 123 (9.80), 118 (13.4), 117 (56.3) , 116 (25.9), 115 (25.9), 114(15.2),110 (12.5),106 (2.7), 102 (11.60),

101 (7.10), 99 (3.60) , 97 (16.10) , 96 (25.4), 95 (19.0), 92 (12.50), 91 (25.0), 90 (14.30), 88 (7.10), 84 (11.6), 83 (5.4), 82 (11.3) , 81 (11.6) 80 (11.6), 79 (13.4), 73 (6.50), 69 (8.90), 68 (12.50) ,64 (5.40, 63 (5.90), 60 (00.90), 56 (5.40), 55 (10.70),53 (3.60), 52 (8.0), 51 (6.3), 50 (6.3) . Calcd. :C, 59.53; H, 4.43; N, 10.96; S, 16.71.Found : C, 58.99; H4.65; N, 10.84; S,16.65.

3-[(p-tolylethylidene)amino]-2-thiohydantoin-5-yl acetic acid (10).
A mixture of **6** (0.01 mol), chloroacetic acid (0.01 mol) and sodium metal (0.5 gm) in xyline (50 ml) was heated under reflux for 4hr. Then filtered upon hot and the filtrate concentrated the solid formed was filtered off ,dried and purified by crystallization from ethanol to give **10** as yellow crystals, yield 65%, , m.p.**220ºC**. IR(KBr): 3230(NH), 1720,1703(C=O), 1625(C=N), 1355(C=S), 3308 – 2873 (br-OH) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 2.25(s,3H,CH_3), 2.16(s,3H,CH_3), 3.65(s,2H,NCH_2CO), 7.21-7.95(m,7H,H-pyenyl ring, oleifinic protons), 10.50(s,1H,NH), 11.52(s,1H,OH) ppm . MS (m/z, %) : 307 [(M+2) 0.33], 293 (0.16), 264 (0.81), 262 (0.15), 261 (0.15), 249 (3.19), 246 (2.09), 232 (1.24), 230 (3.49), 205 (2.85), 190 (3.45), 186 (2.14), 183(1.63), 177 (1.12), 176 (1.13)174 (5.66), 161 (5.03), 159 (2.38), 156 (2.86), 14 (31.74),135 (1.89), 134 (16.4), 118 (100), 115 (34.16), 106 (6.7), 104 (43.7),

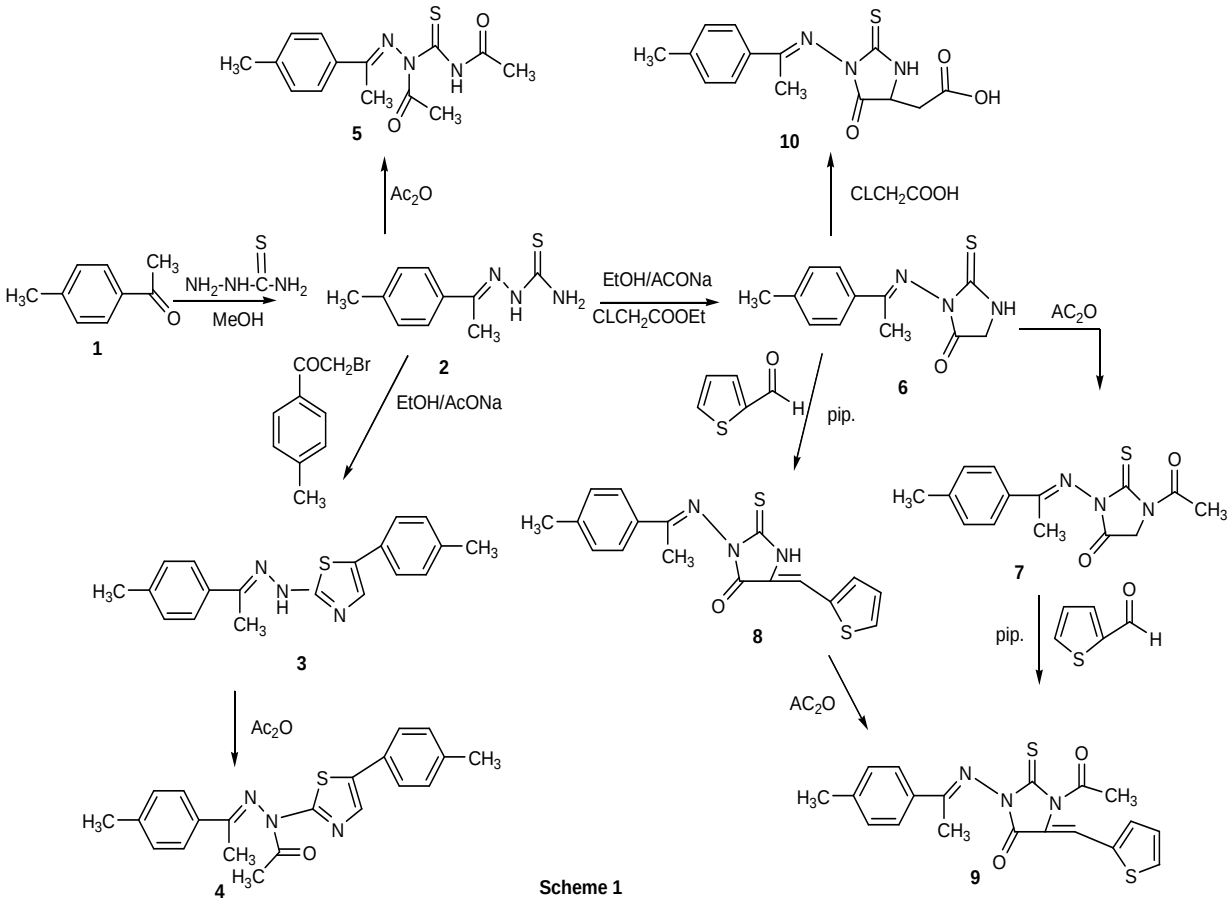
93 (7.37), 91 (48.80), 89 (11.76), 86 (5.14), 82 (1.63), 77 (16.79), 65 (15.83), 62 (11.75), 58(11.8),55 (5.86), 52 (5.86), 50 (14.99) . Calcd. :C, 55.08; H, 4.91; N, 13.77; S, 10.49.Found : C, 55.17; H, 4.85; N, 13.05; S 10.6

RESULTS AND DISCUSSION

The reaction of 4-methylacetophenone **(1)** with thiosemicarbazide in methanol under reflux gave the corresponding 4-methylacetophenone thiosemicarbazone**(2)**. Treatment [4,5] of compound **2** with 4-methylpheynacyl bromide and ethyl chloroacetate in presence of fused sodium acetate in ethanol under reflux yielded the corresponding 5-(p-tolyl)-2- [(p-tolylethylidene)hydrazino] thiazole **(3)** and 3-[(p-tolylethylidene)amino]-2-thiohydantoin **(6)**. Acetylation of thiosemicarbazone **(2)**, thiazole **(3)** and 2-thiohydantoin **(6)** with acetic anhydride under reflux led to the formation of 4-methylacetophenone – 2,4-diacetyl thiosemicarbazone **(5)**, 2-[(p-tolylethylidene)acetyl hydrazino]-thiazole **(4)** and 1-acetyl-3-[(p-tolylethylidene) amino]-2-thiohydantoin **(7)**, respectively.

Condensation [6] of 3-[(p-tolylethylidene)amino]-2-thiohydantoin **(6)** with thiophene-2- carboxaldehyde in presence of piperidine under reflux led to the formation of 5-thiophen-2-ylidene-3-[(p-tolylethylidene)amino]-2-thiohydantoin **(8,Scheme1).** Acylation of compound **8** with acetic anhydride afforded the corresponding 1-acetyl-3-[(p-tolylethylidene)amino]-5-thiophen-2-ylidene-2-thiohydantoin **(9)**. The structure of **9** was also established via reaction of compound **7** with thiophene-2-carboxaldehyde in presence of piperidine.

Heating [7] of 2-thiohydantoin**(6)** with chloroacetic acid in xyline in the presence of sodium metal under reflux gave the corresponding 3-[(p-tolylethylidene)amino]-2-thiohydantoin-5-yl acetic acid **(10,Scheme1)**.



Scheme 1

Anti-microbial activity

Using paper disk agar diffusion technique, [10,11] all the newly synthesized compounds were tested in vitro for antibacterial activity against the Staphylococcus aureus (RCMB 000108) and bacillus subtilis (RCMB 000109) (as gram positive bacteria) while Pesudomonas aeruginoca (RCMB 000103) and Escherichia coli(RCMB 000106) (as gram negative bacteria) . Also these compounds were tested in vitro against some fungi as Aspergillus fumigatus (RCMB 002006), Geotrichum candidum (RCMB 05008), candida albicans (RCMB 005003), and Syncephalastrum racemosum (RCMB 005004) to know their antifungal activity . The compounds were tested for bacteria at 5 mg/ml , but for fungi at 10 mg/ml concentration and the activity was determined by measuring the zone

of inhibition .The screening results given in table **1** indicate that all the compounds exhibited antimicrobial activities .

Table 1 Antimicrobial activity of some synthesized compounds

Microorganism		2	3	4	5	6	7	8	9	10
Gram positive bacteria	*Staphylococcus aureus*	+ +	+ +	-	+ +	+ + +	++	+ +	+ + +	+ + +
	Bacillus subtilis	+ + +	+ +	-	+ + +	+ + +	++	+ + +	+ + +	+ + +
Gram negative bacteria	*Pseudomonas aeruginoca*	-	+ +	++	++	+ + +	++	+ +	+ +	+ + +
	Escherichia coli	+ +	+ +	-	+ +	+ + +	++	+ +	+ + +	+ + +
Antifungal activity	*Aspergillus fumigatus*	+ +	+ +	+ +	+ +	+++	++	+ +	+ +	+ + +
	Geotrichum candidum	+ +	+ +	+ +	+ +	+ + +	+ +	+ +	+ +	+ + +
	Candida albicans	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
	Syncephalastrum racemousum	-	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ + +

Note (-) No antimicrobial activity, (+) Mild activity, (+ +) Moderate activity, (+ + +) Marked activity.

Minimum inhibition concentration

Using agar plate method ,[12] the minimum inhibition concentration (MIC) of compounds **3, 5, 9** and **10** were determined against antimicrobial activity such as gram positive bacteria , gram negative bacteria and fungi. The minimum inhibition concentration (MIC) results given in table **2** . The compound **10**gave the lowest concentration compared to the other compounds that been tested against several microorganisms as shown in table **2**. Compound **5** was the second drug giving lower(MIC) against the tested microorganisms except in case of Staphylococus aureus band Bacillus subtilis . However compound **3** demonstrated the higher concentration against the tested microorganisms.

Table :2 Antimicrobial Activity as MIC (µg / ml)of tested samples against tested microorganisms

Microorganism		3	5	9	10
Gram positive bacteria	*Staphylococcus aureus*	62.5	15.6	7.8	1.9
	Bacillus subtilis	13.2	7.8	3.9	0.95
Gramnegative bacteria	*Pseudomon asaeruginoca*	125	7.8	62.5	3.9
	Escherichia coli	62.5	3.9	15.6	0.95
Antifungal activity	*Aspergillusfumigatus*	62.5	15.6	31.2	1.9
	Geotrichum candidum	62.5	15.6	62.5	7.8
	Candida albicans	125	62.5	125	31.2
	Syncephalastrum racemousum	500	125	250	31.2

CONCLUSION

The researches study the successful synthesis and antimicrobial activity of some new thiohydantoin , thiazole derivatives .The investigation of antifungal and antibacterial activity data revealed that all the tested compounds showed moderate to good inhibition in DMSO. All the compounds exhibited antimicrobial activities . Compounds 6 and 10 showed higher activity against bacteria and fungi . Also, Compounds 3, 5, 7and 8 showed moderate activity against bacteria and fungi. Compound 9 showed higher activity against bacteria and moderate activity against fungi. The good activity is attributed to the presence of pharmacologically active COOH , COCH3 , CH3 , thiazole , thiophene and thiohydantoin ring.

It is worth mentioning that the attachment of carboxylic group to thiohydantoin ring produce strong antimicrobial activity. Also the presence of acetyl group with thiophene ring in compound **9** showed higher activity against bacteria . As we consider all results obtained from antifungal and antibacterial tests together we can say that entire compounds tested are more active towards fungi and some bacteria. These preliminary results of biological activity of the tested compounds could offer an encouraging framework in this field that may lead to the discovery of novel antimicrobial agent

REFERENCES

[1] Wilson, L.J. and Portlock, D.E.*; Tetrahedron Lett.*, **39,** 5135 **(1998).**
[2] Bêhai, I.; *Tetrahedron Lett.*, **44**, 7475 **(2003).**
[3] Brouilette, W.L.; Jestkov, V.P.; Brown, M.L.; Akhtar, M.S.; Deloney, T.M. and Brown, G.M.; *J. Med.chem.*, **37**, 3289 **(1994).**
[4] Mohamed, S.N.; Unis, N. and Abd El-Hady, H.; *Indian J.Chem.*, **45 (2006).**
[5] Mohamed, S.N.; Unis, N. and Abd El-Hady, H.; *Egypt. J.chem.*, **49** (2), 209 **(2006).**
[6] Kiec.Kononowicz, K. and Szyman´ska, E.; *I I Farmaco*, **57**, 909 **(2002).**

[7] Hasanen, J.A.; *Egypt. J. Chem*., **50** (2), 203 **(2007).**
[8] El-Deen, I.M. and Ibrahim, H.K.; *Chemical Paper*, **58**, 200 **(2004).**
[9] Shivakama, H.B.; Shivanada,M.K. and Akberali, P.M.; *J. Indian Chem.Soc*., **75**, 532 **(1998).**
[10] Rathore H.s.;Mittal S. and Kumar S.; *Pestic . Res .J*.12103**(2000).**
[11] Rahman A.;Choudhary , M.I. and Thomsen W. J.; Bioassay Techniques for Drug Development . Harwood Academic Publishers , the Netherlands pp.16. **(2001).**
[12] Damyanova,S.; Gomez L.M.; Banares, M.A. and Fierro**,**J.L.G.; *Chem. Mater*. **12** , 501 **(2000).** 777