SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW *N*-ETHYL-*N*-METHYL BENZENE SULFONAMIDE DERIVATIVES.

Ahmed M. El-Morsy

Organic Chemistry Department, faculty of Pharmacy (Boy's) Al-Azhar University, Nasr City, Cairo, Egypt.

ABSTRACT:

This article describes the synthesis of some novel sulfonamide having the biologically active hydrazones 1,3,4-thiadiazoles and 4-oxothiazolidines moieties 2-4, 7 and 10-13 respectively. Starting with 4-acetyl-*N*-ethyl-*N*-methyl benzene sulfonamide (1). The structure of the newly synthesized compounds was confirmed by elemental analysis, IR, ^{1}H-NMR and mass spectral data.

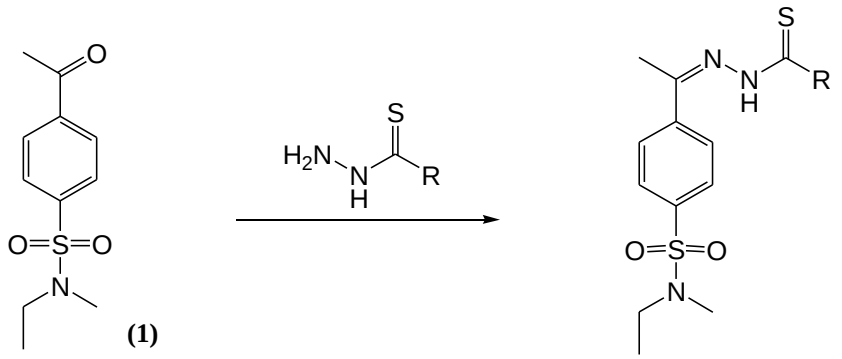
Keywords: *Sulfonamide, hydrazone, 1,3,4-thiazdiazine and oxothiazolidine.*

INTRODUCTION:-

Since resistance of pathogenic bacteria towards available antibiotics is rapidly becoming a major world wide problem, the design of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. In addition, primary and opportunistic fungal infections continue to increase rapidly because of increased number of immouno-compromised patients. As known, not only biochemical similarity of human cell and fungi forms a handicap for selective activity but also the easily gained resistance is the main problem encountered in developing safe and efficient antifungal. Sulfonamides have been demonstrated to possess antibacterial **(El-Gaby, 2000; Owen, *et al.*, 2007)**, antifungal **(El-Gaby *et al.*, 2002)**, insulin releasing **(Havale & Pal, 2009)**, carbonic anhydrase inhibitory **(Supuran, *et al.*, 2000),** hypoglycemic **(Wang, *et al.*, 2010),** anaesthetic **(Jouyban *et al.* 2004),** anti-tumor (**Basappa, *et al.*, 2010)**, anti-cancer and anti-inflammatory **(Reddy, *et al.*, 2004)**, activities.

RESULTS AND DISCUSSION:-

Condensation of compound (1) with hydrazine derivatives (**Klaymon & Bartosevi, 1979)** afforded hydrazone derivatives 2-4 respectively (Scheme 1). The structure of hydrazone were conformed on the basis of elemental analysis and spectral data.

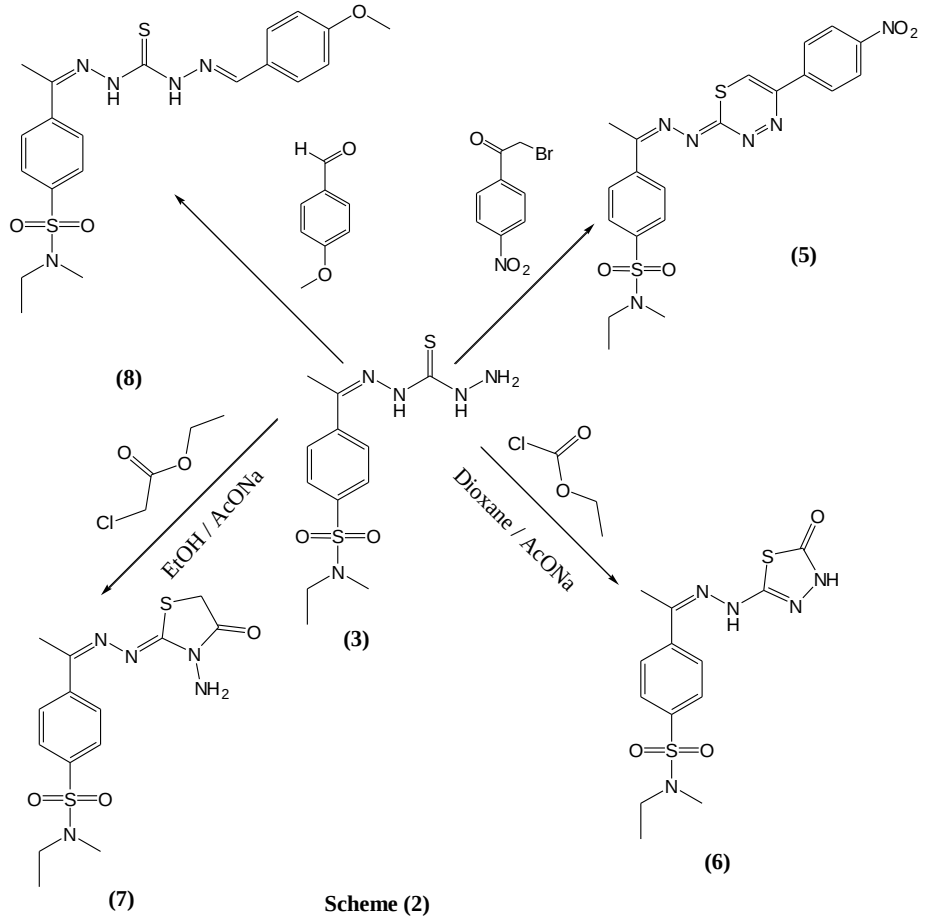


(1) **(2-4)**

2; R = SCH_3
3; R = $NHNH_2$
4; R = NH_2

(Scheme 1)

Interaction of compound 3 with 2-bromo-1-(4-nitrophenyl)ethanone yielded a compound 5. Also compound 3 reacted with ethylchloroformate and ethylchloroacetate to afford the corresponding derivatives 6 and 7, respectively. Condensation of 3 with 4-methoxybenzaldehyde gave hydrazone derivative 8. (scheme 2)



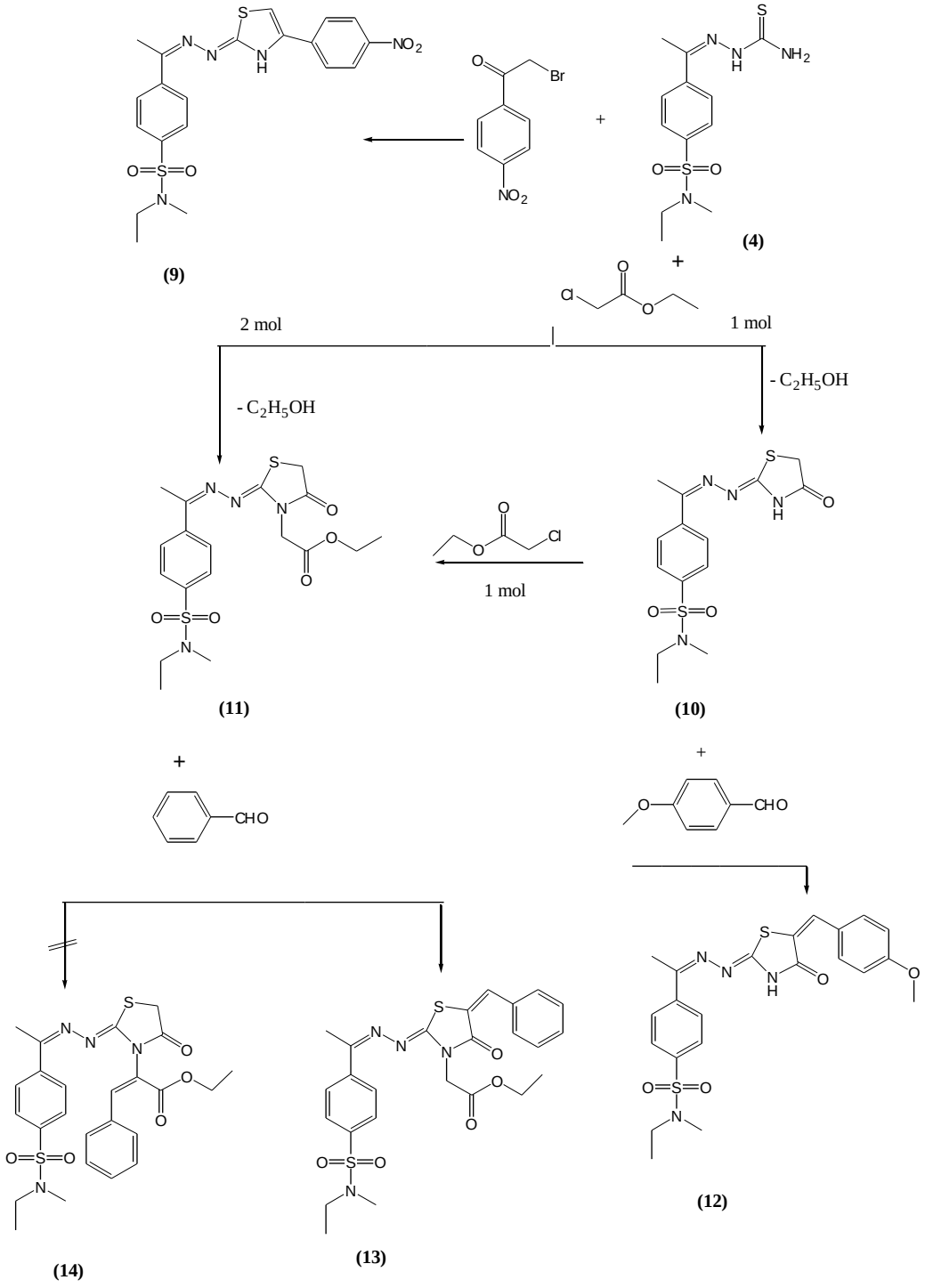
(8) **(5)** **(3)** **(7)** **(6)**

Scheme (2)

The behavior of the thiocarbamoyl function group in compound 4 towards some halocarbonyl reagents was investigated. Thus, interaction of compound 4 with 2- bromo-1-(4-nitrophenyl)ethanone afforded the corresponding derivative 9 (Scheme 3).

Cyclocondensation of compound 4 with an equiomolar ratio of ethylchloroaceate afforded the corresponding derivative 10, but when compound 4 was treated with two moles of ethyl chloroacetate under the same conditions gave derivative 11. The formation of 10, 11 were assumed to proceed via elimination of ethanol from intermediates derivatives, respectively. (Scheme 3).

Condensation of compound 10 with 4-methoxybenzldehyde gave arylidene derivative 12. Also condensation of derivative 11 with benzaldehyde (1 mol) in ethanol afforded compound 13 instead of compound 14 (scheme 3).



(Scheme 3)

EXPERIMENTAL

Melting points (^oC, uncorrected) were determined in open capillaries on a Gallen Kemp melting point apparatus (sanyoGallenKemp, Southborough UK). IR spectra (KBr) were recorded on 2- FT-IR 5300 spectrometer (υ, cm^{-1}). ^1H-NMR spectra were recorded at 250 MHz on a varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analysis were performed on Carlo Erba 1108 elemental analyzer (Herzeus, Hanau, Germany).

4-Acetyl-*N*-ethyl-*N*-mehylbenzenesulfonamide(1)

Was prepared according to the procedures reported in the literature (**EL-Kashef, *et al.*, 1986)**. Yield 74%; m.p. 70-71^oC.

N-Ethyl-4-(1-hydrazonoethyl)-*N*-methyl benzene sulfonamide derivatives (2-4).

To a solution of hydrazine derivatives namely methylhydrazine carbodithioate, thiocarbohydrazide and hydrazinecarbothioamide (0.01mol) in ethanol 50 ml, 4-acetyl-*N*-ethyl-*N*-methylbenzene sulfonamide (1) (2.4 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2hr. then left to cool. The solid product was collected by filtration and recrystallized from ethanol to give compounds 2-4, respectively.

Methyl-2[[1-[4-(*N*-ethyl-*N*-methylsulfamoyl)phenyl]ethylidine]hydrazine carbodithioate(2)

Yield, 65%; m.p. 138-140^oC; IR(KBr, cm^{-1}): 3172(NH), 1333, 1162 (SO_2). ^1H-NMR ($CDCl_3$): 1.15 (t,3H,CH_3ethyl), 2.34(s,3H,SCH_3), 2.66(s,3H,CH_3-C=N), 2.77(s,3H,CH_3-N), 3.15(q,2H,CH_2ethyl), 7.81,7.99(dd,4H, aromatic protons), 10.01 (s,1H, NH).Anal. Calcd. For $C_{13}H_{19}N_3O_2S_3$: C, 45.19; H. 5.54; N, 12.16; S, 27.84 Found : C, 45.06; H, 5.23; N, 12.04; S, 27.68

N-Ethyl-4-[1-(2-hydrazinocarbonothioyl)hydrazono)ethyl]-*N*-methyl benzene sulfonamide(3).

Yield, 77%; m.p. 131-133^oC; IR(KBr, cm^{-1}): 3356 (NH_2), 3269-3200(2NH), 1332, 1157 (SO_2). Ms m/z (%),329.44[M^+] (1.18)Anal. Calcd. For $C_{12}H_{19}N_5O_2S_2$: C, 43.75; H. 5.81; N, 21.26; O, 9.71; S, 19.47 Found : C, 43.46; H, 5.72; N, 21. 15; O, 9.54; S, 19.33

2-[1-[4-(*N*-ethyl-*N*-methylsulfamoyl)phenyl]ethylidene]hydrazine carbothioamide(4)

Yield, 79%; m.p. 175-176^oC; IR(KBr, cm^{-1}): 3400 (NH_2), 3158(NH), 1316, 1152 (SO_2). Ms m/z (%), 314.43[M^+] (11.21)Anal. Calcd. For $C_{12}H_{18}N_4O_2S_2$: C, 45.84; H. 5.77; N, 17.82; S, 20.40 Found: C, 45.75; H, 5.42; N, 17.61; S, 20.13.Found C, 45.69; H, 5.81; N, 17.33; S, 20.13

N-Ethyl-*N*-methyl-4[1-(4-(4-nitrophenyl)-2H-1,3,4-thiadiazin-2-ylidene)]- hydazono)-ethyl]benzene sulfonamide(5)

A mixture of 3 (3.3 g ,0.01mol),and 2-bromo-1-(4-nitrophenyl) ethanone (2.4g, 0.01 mol) was refluxed in ethanol (50ml) for 3 hr, the obtained product was collected by filtration and recrystallized from ethanol to give (5) yield 58% , m .p.140-142^oC IR(KBr, cm^{-1}): 1362, 1167 (SO_2). ^1H-NMR (DMSO-d_6): 1.15 (t,3H,CH_3ethyl), 2.03(s,1H,CH_3-N=N), 2.43(s,3H,CH_3-N-SO_2), 3.14(q,2H,CH_2 ethyl), 7.33,8.45(m, 8H, Ar-H)), 7.44 (s,1H, CH thiadiazine), MS m/z (%): 472 [M^+] (85.7), 393(100). Calcd. For $C_{20}H_{20}N_6O_4S_2$: C, 50.83; H, 4.27; N, 17.78; S, 13.57. Found : C, 50.65; H, 4.02; N, 17.54; S, 13.44

_N_-Ethyl-_N_-methyl-4[1-(1-(3H)-4-oxo-1,3,4-thiadiazol-2-yl)hydrazono] ethyl] benzene sulfonamide(6)

A mixture of 3 (3.3 g ,0.01mol) and ethylchloroformat (1.3g,0.01 mol)and fused sodium acetate (1.6g,0.02mol) in dioxan (50ml) was refluxed for 4 hr during the reflux a crystalline solid was separated. the separated product was collected by filtration and recrystallized from ethanol to give (6) yield 64% , m .p.142-143^{o}C IR(KBr, cm^{-1}): 3184(NH),1686(C=O),1386, 1162 (SO_2). ^{1}H-NMR (DMSO-d_6): 1.17(t,3H,CH_3 ethyl), 2.35(s,3H, CH_3-C=N), 2.79(s,3H,CH_3-N), 3.16(q, 2H, CH_2 ethyl), 7.86, 8.06(dd,4H, Ar-H AB-system), 9.18,9.03(2br, 2H,2NH). Calcd for $C_{13}H_{17}N_5O_3S_2$, C, 43.93; H, 4.82; N, 19.70; S, 18.04. Found C, 43.76; H, 4.74; N, 19.57; S, 17.90

_N_-Ethyl-_N_-methyl-4-[1-(3-amino-4,5-dihydro-4-oxo-thiazol-2-yl) hydazono)-ethyl]benzene sulfonamide(7)

A mixture of 3 (3.3 g ,0.01mol),and ethylchloroacetate (1.2 g,0.01 mol) and fused sodium acetate (1.6g,0.02mol) in ethanol 50ml was refluxed for 5 hr during the reflux a crystalline solid was separated. the separated product was collected by filtration and recrystallized from DMF to give (7). Yield 65%, m .p.148-150^{o}C IR(KBr, cm^{-1}): 3422(NH_2),1706(C=O) 1392, 1172 (SO_2). ^{1}H-NMR ($CDCl_3$,D_2O): 1.02 (t,3H,CH_3 of ethyl), 2.01(broad s,2H,NH_2 that disappeared on addition of D_2O), 2.23(s,3H,CH_3-C=N), 2.59(q,2H,CH_2 ethyl), 2.69(s, 3H, CH_3-N-S), 3.78 (s,2H, of thiazole), 6.90-7.30(dd,4H, of phenyl). Calcd. for $C_{14}H_{19}N_5O_3S_2$ C, 45.51; H, 5.18; N, 18.69; S, 17.36. Found ,C, 45.35; H, 5.01; N, 18.84; S, 17.14.

_N_-Ethyl-_N_-methyl-4-[5-(4-methoxybenzylidene)-hydrazinecarbonothioyl) hydrazonoethyl] benzene sulfonamide (8)

A mixture of (3) (0.01 mol) in ethanol and 4-methoxybenzaldehyde (0.01mol) was refluxed until a crystalline solid was separated. the separated product was collected by filtration and recrystallized from ethanol to give (8). Yield 60% ,m .p.179-181^{o}C. IR(KBr, cm^{-1}): 3179,3212(2NH), 1375, 1164 (SO_2). ^{1}H-NMR (DMSO-d_6): 1.15(t,3H,CH_3 ethyl), 2.38(s,3H,CH_3-C=N), 2.75(s,3H,CH_3-N), 3.16(q,2H,CH_2 ethyl), 3.87(s,3H,OCH_3), 6.98-7.80(m,8H,Ar-H), 8.62(s,1H,CH arylideine), 10.22, 10.85(2s,2H,2NH). Calcd. For $C_{20}H_{25}N_5O_3S_2$ C, 53.67; H, 5.63; N, 15.65; S, 14.33 found C, 53.46; H, 5.42; N, 15.45; S, 14.12.

_N_-Ethyl-_N_-methyl-4-[1-(4-(4-nitrophenyl)thiazol-2(3H)-ylidene)hydrazono)-ethyl]benzene sulfonamide(9)

A mixture of hydrazinecarbothioamide derivative 4 (3.1g, 0.01 mol), 2-bomo-1-(4-nirophenyl)ethanone (2.4 g., 0.01 mol.) in ethanol 50 ml was refluxed for 3hr. the obtained product was collected by filtration and recrystallized from ethanol to give 9. Yield, 58%; m.p. 247-249^{o}C; IR(KBr, cm^{-1}): 3264(NH), 1338, 1150 (SO_2). ^{1}H-NMR (DMSO-d_6): 1.15 (t,3H,CH_3ethyl), 2.43(s,3H,CH_3-C=N), 2.76(s,3H,CH_3-N), 3.14(q,2H,CH_2 ethyl), 7.33,8.45(m, 8H, Ar-H)), 9.44 (s,1H, CH thiazole), 13.62(s,1H, NH).Anal. Calcd. for $C_{20}H_{21}N_5O_4S_2$: C, 52.27; H. 4.61; N, 15.24; S, 13.96 Found : C, 52.01; H, 4.42; N, 15.01 ; S, 13.65.

_N_-Ethyl-_N_-methyl-4-[1-(4-oxothiazolidin-2-ylidene)hydrazono)-ethyl] benzene sulfonamide(10)

A mixture of hydrazine carbothioamide derivative 4 (3.1 g, 0.01 mol), ethyl chloroacetate (1.3g, 0.01 mol) and fused sodium acetate (1.6g, 0.02 mol) in ethanol 50 ml was heated under reflux for 4hr. during the reflux period, crystalline solid was separated.

The separated solid was filtered off, washed with ethanol and recrystallized from ethanol to give (10). Yield, 56%; m.p. 241-243^{o}C; IR(KBr, cm^{-1}): 3184(NH), 1686(CO); 1339,1162 (SO_2). Ms m/z (%): 354[M^+](19.2),[239](100). Anal. Calcd. for $C_{14}H_{18}N_4O_3S_2$: C, 47.44; H. 5.12; N, 15.81; S, 18.09 Found : C, 47.93; H, 4.87; N, 15.64 ; S, 17.76.

Ethyl-2-[2-(1-(4-(*N*-ethyl-*N*-methylsulfomoyl)phenyl)ethylidene)hydrazono)-4-oxothiazolidin-3-yl] acetate (11).

Method (A)

A mixture of hydrazine carbothioamide derivative 4 (3.1g, 0.01 mol), ethylchloroacetate (2.6g, 0.01 mol) and fused sodium acetate (1.6, 0.02 mol) in ethanol (50 ml) was heated under reflux for 8 hr. during the reflux period, crystalline solid was separated. The separated solid was filtered off, washed with ethanol and recrystallized from dioxane to give (11)

Method (B)

A mixture of compound (10) (3.5g, 0.01 mol), ethylchloroacetate (1.3g, 0.01 mol) and fused sodium acetate (1.6 g, 0.02 mol) in ethanol (50 ml) was heated under reflux for 6hr. during the reflux period, crystalline solid was separated. The separated solid was filtered off, washed with ethanol and recrystallized from ethanol to give(11). Yield, 77%; m.p. 263-265^{o}C; IR(KBr, cm^{-1}): 1715,1687(2C=O); 1334,1160 (SO_2).^{1}H-NMR (DMSO-d_6): 1.04 (2 t,6H,CH_3ethyl + CH_3 ethoxy), 2.39(s,3H,CH_3-C=N), 2.68(s,3H,CH_3-C=N), 3.03(2q,4H,CH_2 ethyl + CH_2 ethoxy), 3.90(s,2H, CH_2 of 4-oxothiazolidine), 3.97 (s,2H, NCH_2CO), 7.80, 8.05 (dd, 4H, Ar-H).Anal. Calcd. for $C_{18}H_{24}N_4O_5S_2$: C, 49.07; H. 5.49; N, 12.72; S, 14.56 Found : C, 48.87; H, 5.27; N, 12.50 ; S, 14.34.

***N*-ethyl-4-[1-((5-(4-methoxybenzylidene)-4-oxothiazolidin-2-ylidene)-hydrazono) ethyl]-N-methylbenzenesulfonamide (12).**

A mixture of compound (10) (3.5g, 0.01 mol) and 4-methoxybenzaldehyde (1.4g, 0.01 mol) in ethanol 50 ml., refluxed for 4 hr. during the reflux a crystalline solid was separated ,that filtered off, washed with ethanol and recrystallized from ethanol to give (12).

Yield, 70%; m.p. 178-180^{o}C; IR(KBr, cm^{-1}): 3176(NH), 1662(CO),1332,1157 (SO_2). ^{1}H-NMR (DMSO-d_6): 1.16 (t,3H,CH_3ethyl), 2.39(s,3H,CH_3-C=N), 2.76(s,3H,CH_3-N), 3.14(q,2H,CH_2 ethyl), 4.30(s,3H, OCH_3), 7.26-8.04(m,8H,Ar-H), 8.73(s,1H,CH benzylidene), 9.50(s,1H, NH). Anal. Calcd. for $C_{22}H_{24}N_4O_4S_2$: C, 55.91; H. 5.12; N, 11.86; S, 13.57 Found : C, 55.72; H, 5.00; N, 11.51 ; S, 13.32.

Ethyl-2-[5-benzylidene-2-(1-(4-(*N*-ethyl-N-methylsulfamoyl)phenyl) ethylidene) hydrazono]4-oxothiazolidin-3-yl]acetate (13).

A mixture of compound (11) (4.4g, 0.01 mol) and benzaldehyde (1.1 g, 0.01 mol) in ethanol 50 ml, was heated under reflux for 7 hr. during the reflux period, crystalline solid was separated. The separated solid was filtered off and recrystallized from ethanol to give (13).Yield, 54%; m.p. 264-265^{o}C; IR(KBr, cm^{-1}): 1686,1710(2CO), 1332, 1158 (SO_2). ^{1}H-NMR (DMSO-d_6): 1.13 (2t,6H,CH_3 of ethyl+CH_3 of ethoxy), 2.60(s,3H,CH_3-C=N), 2.76(s,3H,CH_3-N), 3.14(2q, 4H,CH_2 of ethyl + CH_2 of ethoxy), 4.67(s,2H, NCH_2CO), 7.48-8.05(m,10 H,Ar-H and CH benzylidene), Anal. Calcd. for $C_{25}H_{28}N_4O_5S_2$: C, 56.80; H. 5.34; N, 10.60; S, 12.13 Found : C, 56.61; H, 5.11; N, 10.40 ; S, 12.01.

Antimicrobial and antifungal screening (in-vitro study) (Gnayer & harbone, 1976; Muanza, *et al.*, 1994; Irab, *et al.*, 1996) 12-14

Antimicrobial and antifungal activities of nine newly synthesized compounds tested by measuring the inhibitory effects of such compounds tested by measuring the inhibitory effects of such compounds against gram-positive, gram –negative bacteria and unicellular, filamentous fungi using agar diffusion technique.

MATERIALS AND METHODS

Bacillus subtilis (NCTC-1040), staphylococcus Aureus (NCTC-7447), Escherichia Coli, Candida Albicans (IMRu-3669) and Asperigillus Niger, were used against test compounds and obtained from the microbiology department, faculty of Pharmacy, Al-Azhar University. Chloramphenicol and terbinafine were used as a reference drugs and also obtained from the same source.

Agar diffusion test

Tall of nutrient agar were melted and poured each in an empty sterile petridishes and left for 24h. A specific culture of each organism was spread with a dry sterile swab on the surface of previously prepared plates. Sterile discs 6-9 mm diameter were impregnated with solutions of tested compounds, left to dry and were then placed on the surface of inoculated plate. Discs of antimicrobial standard were put in the culture of plate agar and inoculated at 37^{o}C for 24h. After inoculation the plates were examined visually and zone of inhibition were measured.

The microbiological testing of the newly synthesized compounds were performing in the department of microbiology, Faculty of Pharmacy, Al-Azhar University, Nasr City, Cairo, Egypt.

Table : Antibacterial and antifungal activities

Comp. No.	Gram-positive		Gram-negative	Unicellular fungi	Filamentous fungi
	B.Subitis	S.Auras	E.Coli	C.Albicans	A. Niger
2	++++	++	++	+	+
3	++	+	+	+	++
4	++	+	+	++	+
5	++++	+++	+++	++	++
6	-	+	+	+	+
7	++	+	+	+	+
8	-	+	-	-	-
9	+++	+++	+++	+++	+++
10	+	+	+	+	-
11	+	++	++	+	+
12	++++	+++	+++	+++	+++
13	+	-	-	-	-
Chloramphenicol	++++	++++	++++	-	-
Terbinafine	-	-	-	++++	++++

- No inhibition zone, + inhibition zone (5-10mm), ++ inhibition zone (10-15 mm), +++ inhibition zone (15-20mm), ++++ inhibition zone (>20mm)

- **Antibacterial and Antifungal Activities:**

The results of antimicrobial testing (Table 1) show that compounds 5, 9 and 12 which contains electron with drowning groups, showed significant activity against gram-positive and gram-negative in addition to its activity against unicellular fungi (C. Albicans), and filamentous fungi (A-Niger), while the compounds 2,3,4,6,7,10 and 11 showed the moderate activity and the remaining compounds 8 and 13 showed weak activity which containing electron releasing groups.

REFERENCES

Basappa A., Murugan S., C.V. Kavitha, A. Purushothaman, K.G. Nevin, K. Sugahara, K.S. (2010): Ranga pp, Cancer let., 297, 231.

El-Gaby M.S.A., (2000): Phosphorus, sulfur and Silican, 156, 157 (2000)

El-Gaby M.S.A., Gaber A.M., Atalla A.A., Abd Al-Wahab K.A., (2002): IL Farmaco, 57, 613.

EL-Kashef H.S., Bayoumy B.E., Aly T.I.., (1986): Egypt, J., Pharma.Sci. 27,72.

Gnayer J., harbone J. B., (1976): Phytochemistry , 37, 19.

Havale S. H., Pal M., (2009): Bioorg-Med. Chem., 17, 1783.

Irab. O. N., Moo-Yong M., Anderson, w. A. (1996): International. J. Pharmacog., 34, 87

Jouyban A., M. Majidi, H. Jalilzadeh, K. (2004): Asad pour, IL Farmaco, 59, 505.

Klaymon D.L.,, Bartosevi J.F. (1979): Chem., T.S. Griffin, C.I. Mason, J.P. Scovilli, J. Med. Chem; 22,855

Muanza N., Kim B.W., Euler K. L., Williams L., (1994): International J. Pharmacog., 32, 337.

Owen D. J., Davis C.B.,. Hartnell R.O, Madge P.D., Thomson R.J., Chang A. K. I., Coppel R.L., Itzstein M., (2007): Bioorg. Med. Chem. Lett., 17 2274.

Reddy N. S., Mallireddigari M.R., Casenza S., Gummireddy K., Bell S., Reddy E. P., Reddy M. V., (2004): Bioorg. Med. Chem. Let., 14, 4093.

Supuran C.T., Briganti F., Menabuoni L., Mincione G.,, Mincine F., Scozzafava A., (2000): Eur. J. Med. Chem.., 35, 309.

Wang X., Wan K., Zhou C., (2010): Eur. J. Med. Chem., 45, 4631.

تحضير مشتقات جديدة من ـ ن ـ إيثيل و ـ ن ـ ميثيل بنزين سلفوناميد كمضادات للميكروبات

احمد محمد المرسى

قسم الكيمياء العضوية كلية الصيدلة- بنين) ـ جامعة الأزهر بالقاهرة

التفاعل بين 4- استيل- ن- ايثيل- ن- ميثيل بنزين سلفوناميد ومشتقات الهيدرازين يعطى مركبات جديدة من الهيدرازون والتى بتفاعلها مع بعض المركبات الأولية تم الحصول على مشتقات جديدة للسلفوناميد كما تم أيضا اختبار هذه المركبات ميكروبيولوجيا وجد ان بعضها اظهر فاعلية واضحة كمضادات للبكتريا والفطريات . وقد تم إثبات المركبات المحضرة عن طريق تحاليل العناصر والأشعة تحت الحمراء والرنيين النووى المغناطيسى وكذلك تحليل الكتلة.