

HETEROAROMATIZATION WITH SULFONAMIDO PHENYL ETHANONE: PART (IV). SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NEW N-ETHYL-N-METHYLBENZENESULFONAMIDE, 1,3,4-THIADIAZOLE, 1,3,4-THIADIAZINE, 4-OXOTHIAZOLIDINE AND PYRAZOLO[5,1-c][1,2,4]TRIAZINE DERIVATIVES

MAHMOUD M. ABDELALL,^a MAHMOUD S. BASHANDY^a and AHMAD M. EL-MORSY^b

a; Chemistry Department, Faculty of Science (Boy's), Al-Azhar University, Nasr City, Cairo, Egypt.

b; Organic Chemistry Department, Faculty of pharmacy (Boy's), Al-Azhar University, Nasr City, Cairo, Egypt.

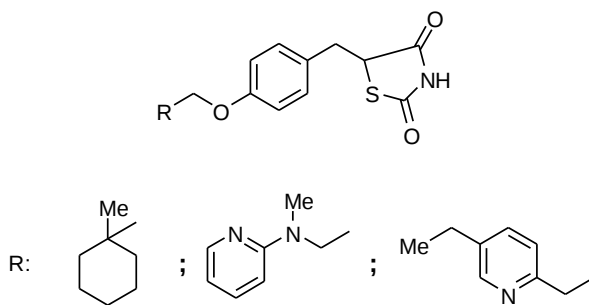
Abstract

This article describes the synthesis of some novel sulfonamide having the biologically active, hydrazones **7-11**, 1,3,4-thiadiazoles **15-18**, **20**, 1,3,4-thiadiazine **19**, 4-oxothiazolidines **21**, **26-29** and pyrazolo[5,1-c][1,2,4]triazine **32** moieties starting with 4-acetyl-N-ethyl-N-methylbenzenesulfonamide (**1**). The structure of the newly synthesized compounds was confirmed by elemental analysis, IR, ¹H NMR, and mass spectral data.

Keywords: sulfonamide, hydrazone, 1,3,4-thiadiazole, 1,3,4-thiadiazine, 4-oxothiazolidine, pyrazolo[5,1-c][1,2,4]triazine

Introduction

Sulfonamides have been demonstrated to possess antibacterial,¹⁻⁴ antifungal,⁵ insulin releasing,⁶⁻⁸ carbonic anhydrase inhibitory,⁹⁻¹² hypoglycemic,¹³ anesthetic,¹⁴ anti-tumor,^{15,16} anti-cancer and anti-inflammatory¹⁷⁻¹⁹ activities. Some active sulfonamides as anti-bacterial are also known for their immune modifying effects.²⁰ The 4-oxothiazolidine derivatives, known as the "Glitazones" (**Fig. 1**) are sometimes referred to as insulin enhancers.²¹

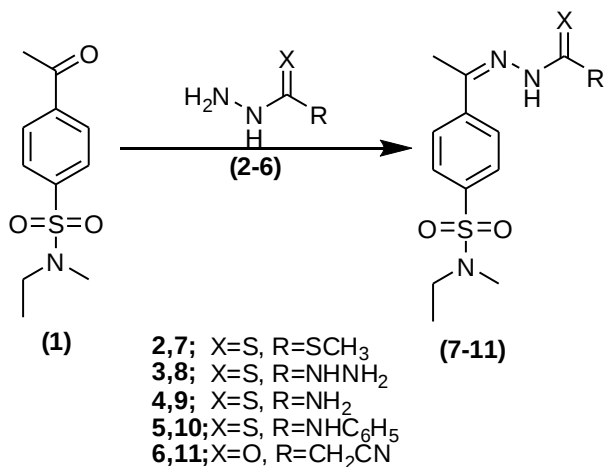


(Fig. 1)

In view of these reports and as a continuation of our previous work,²²⁻²⁶ directed towards the synthesis of substituted benzenesulfonamide conjugated with 1,3,4-thiadiazole, 1,3,4-thiadiazine, 4-oxothiazolidines and pyrazolo[5,1-c][1,2,4]triazine moieties. This article reports a new and convenient method for the synthesis of such ring systems that are required to medicinal chemistry utilizing 4-acetyl-N-ethyl-N-methylbenzenesulfonamide (**1**) as a reaction intermediate to form a variety of heterocyclic compounds having sulfonamide function.

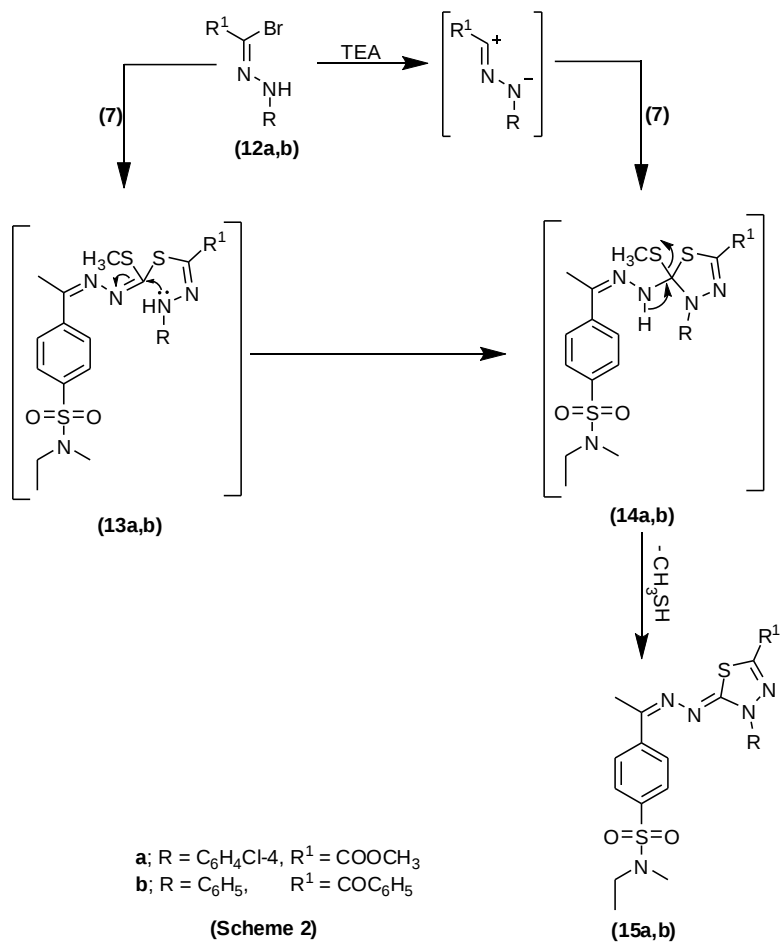
Results and Discussion

Condensation of 4-acetyl-N-ethyl-N-methylbenzenesulfonamide (**1**) with hydrazine derivatives named as methyl hydrazinecarbodithioate,²⁷ thiocarbohydrazide, hydrazinecarbothioamide, N-phenylhydrazinecarbothioamide and 2-cyanoacetohydrazide (**2-6**) in refluxing ethanol afforded hydrazone derivatives **7-11**, respectively (**Scheme 1**). The structure of hydrazones were confirmed on the basis of elemental analysis and spectral data. Thus, ¹H NMR spectrum of **7** showed singlet at δ 2.34 ppm for SCH₃, singlet at δ 2.66 ppm for CH₃-C=N and a singlet at δ 10.01 ppm for NH group, while ¹H NMR spectrum of **10** showed singlet at δ 2.38 ppm for CH₃-C=N and two singlet at δ 8.83, 9.34 ppm for 2NH groups. IR spectrum of **11** showed absorption bands at 3169 cm⁻¹ for NH group and 2262 cm⁻¹ for CN group, while ¹H NMR spectrum of **11** showed singlet at δ 2.29 ppm for CH₃-C=N, singlet at δ 4.26 ppm for CH₂CN and singlet at δ 11.18 ppm for NH group.



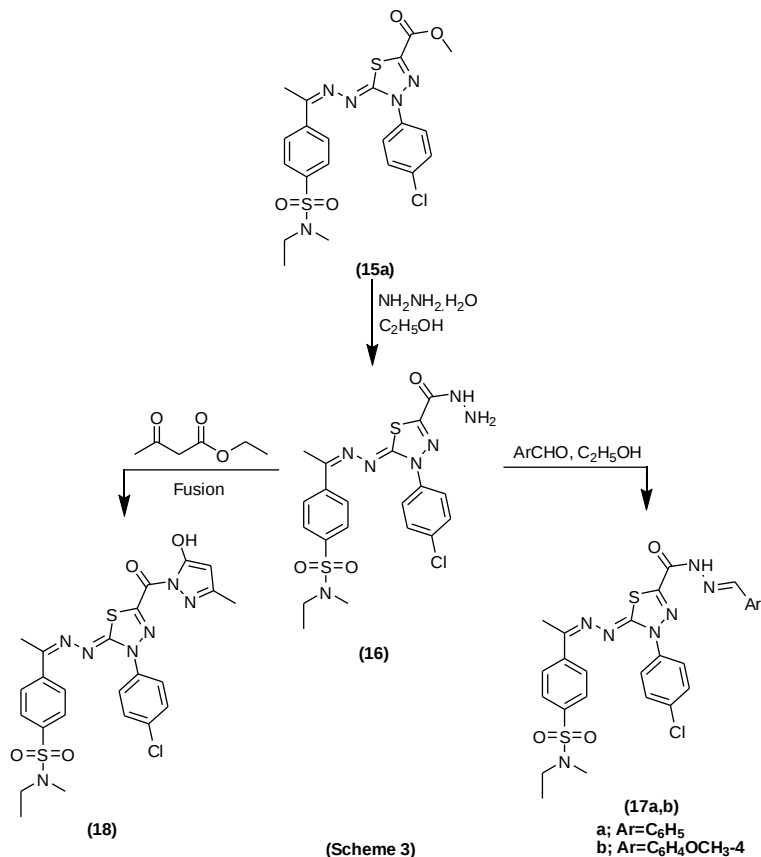
(Scheme 1)

Interaction of hydrazonecarbodithioate derivative **7** with hydrazonoyl bromides **12a,b**²⁸⁻³⁰ in ethanol containing triethylamine gave the corresponding 1,3,4-thiazole derivatives **15a,b**, respectively. The formation of **15a,b** can be rationalized via elimination of methylmercaptan from the corresponding cyclo adduct intermediates **14a,b**, which is assumed to be formed from 1,3-dipolar cyclo addition of nitrileimines to the thiocarbonyl double bond. Also, alternatively, the formation of **15a,b** can be explained by a stepwise involving substitution to give acyclic hydrazone intermediates **13a,b**, which was readily cyclized to afford the cyclic adduct intermediates **14a,b** (Scheme 2). The structures **15a,b** were established from elemental analysis and spectral data.

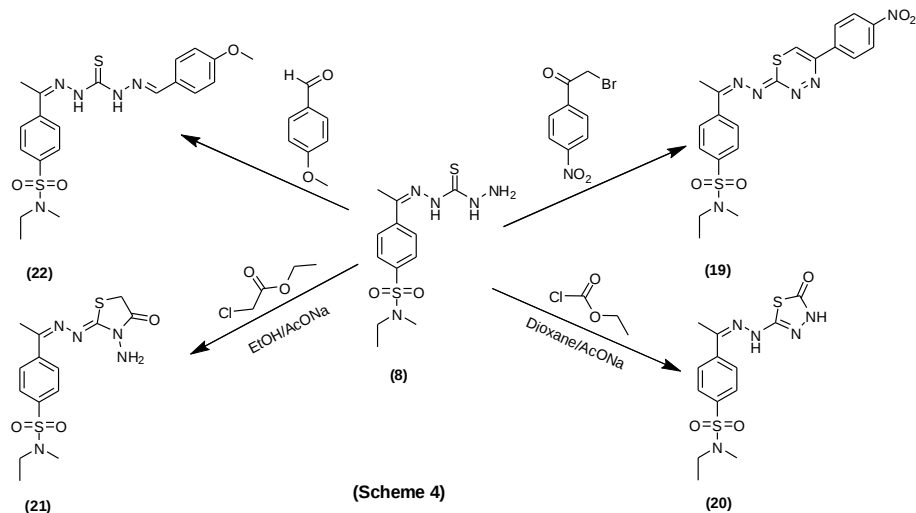


Hydrazonolysis of methyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate derivative **15a** in refluxing ethanol gave the corresponding hydrazide which identified as 4-(1-((3-(4-chlorophenyl)-5-(hydrazinecarbonyl)-1,3,4-thiadiazol-2(3H)-ylidene)-hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (**16**). The ¹H NMR of **16** exhibited triplet signals at δ 1.16 ppm for CH₃ of ethyl group, broad singlet at δ 1.65 ppm for NH₂ group, singlet at δ 2.48 ppm for CH₃-C=N, singlet at δ 2.78 ppm for CH₃-N, quartet at δ 3.16 ppm for CH₂ of ethyl group, multiplet at δ 7.45-8.11 ppm for the aromatic protons, and singlet at δ 9.18 ppm for NH group. Interaction of 3-(4-chlorophenyl)-5-(hydrazinecarbonyl)-1,3,4-thiadiazole derivative **16** with aromatic aldehydes namely benzaldehyde and 4-methoxybenzaldehyde in ethanol at

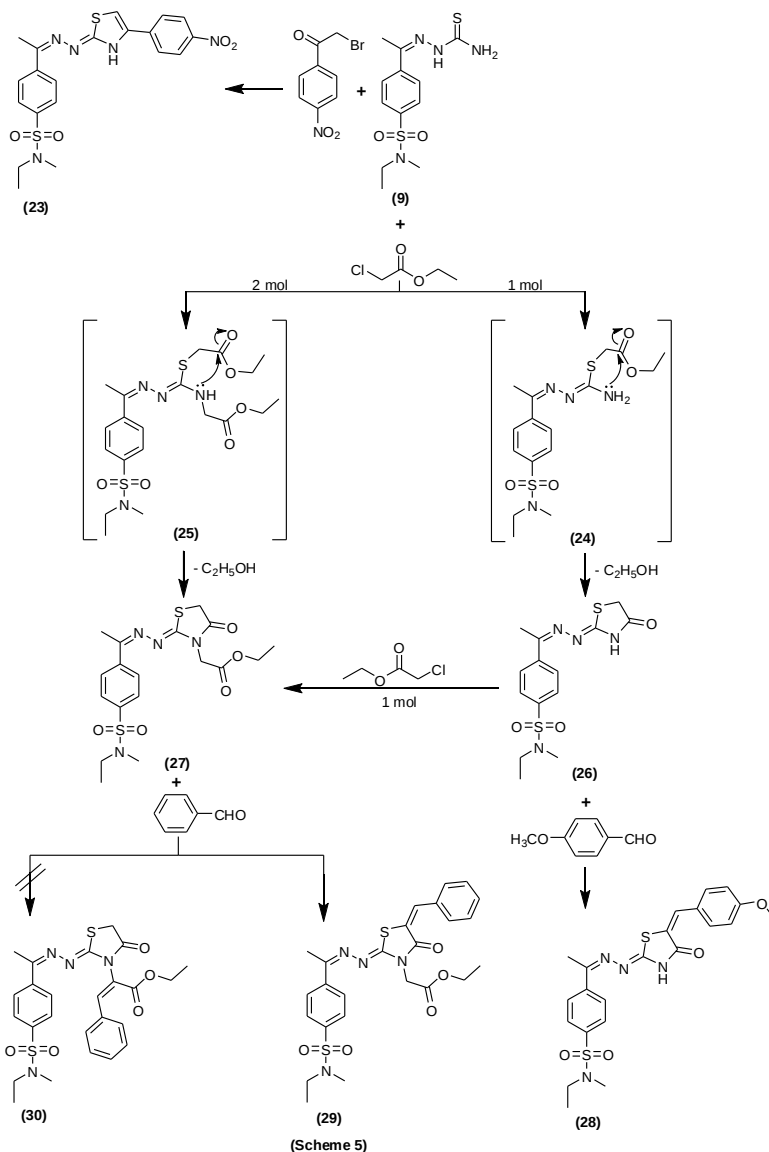
reflux temperature gave hydrazone derivatives **17a,b** respectively. Moreover, fusion of 3-(4-chlorophenyl)-5-(hydrazinecarbonyl)-1,3,4-thiadiazole derivative **16** with ethyl acetoacetate afforded **18**, (**Scheme 3**).



Interaction of 1-(2-(hydrazinecarbonothioyl)hydrazono)ethyl derivative **8** with 2-bromo-1-(4-nitrophenyl)ethanone in refluxing ethanol yielded 1,3,4-thiadiazine derivative **19**. Compound **8** was subjected to react with chloro esters namely ethyl chloroformate and ethyl chloroacetate to afford the corresponding 1,3,4-thiadiazole and 4-oxothiazolidine derivatives **20** and **21**, respectively (**Scheme 4**). Condensation of **8** with 4-methoxybenzaldehyde in refluxing ethanol afforded hydrazone derivative **22**. ^1H NMR spectrum of **22** showed the presence of two methyl groups at δ 2.38, 2.75 ppm and methoxy group at δ 3.87 ppm, (**Scheme 4**).

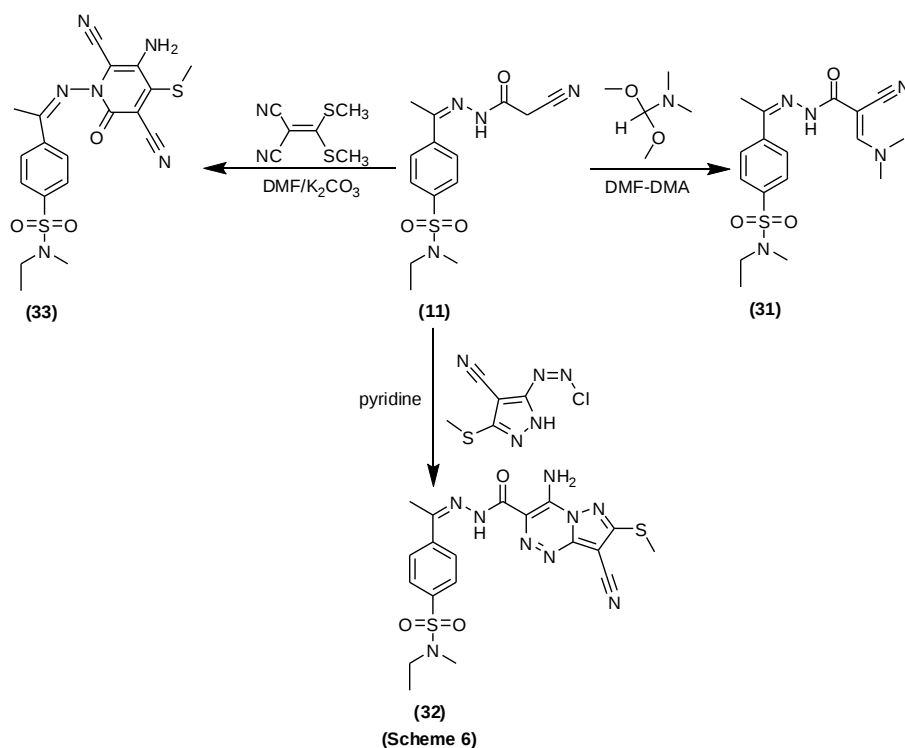


The behavior of the thiocarbamoyl functional group in **9** towards some halo carbonyl reagents was investigated. Thus, interaction of **9** with 2-bromo-1-(4-nitrophenyl)ethanone in ethanol afforded thiazole derivative **23** (Scheme 5). Cyclocondensation of hydrazinecarbothioamide derivative **9** with an equimolar ratio of ethyl chloroacetate in ethanol sodium acetate solution under reflux afforded the corresponding 1-((4-oxothiazolidin-2-ylidene)hydrazono)ethyl derivative **26**, but when compound **9** was treated with two moles of ethyl chloroacetate under the similar reaction conditions gave N-ethoxycarbonylmethyl-4-oxothiazolidine derivative **27**. The formation of **26,27** were assumed to proceed *via* elimination of ethanol from intermediates ethoxycarbonylmethyl and bis(ethoxycarbonylmethyl) derivatives **24,25** respectively. Structure **27** was further confirmed unequivocally by an independent synthesis from the reaction of **26** with ethyl chloroacetate in ethanol sodium acetate solution, (Scheme 5). ¹H NMR of **27** revealed two singlet signals at δ 2.39, 2.68 ppm for two methyl groups, and two singlet signals at δ 3.90, 3.97 ppm for two methylene groups. Condensation of 1-((4-oxothiazolidin-2-ylidene)hydrazono)ethyl derivative **26** with 4-methoxybenzaldehyde in ethanol/piperidine solution at reflux temperature, gave arylidene derivative **28**. Also, condensation of N-ethoxycarbonylmethyl-4-oxothiazolidine derivative **27** with benzaldehyde (1 mol) in ethanol/piperidine solution afforded **29** instead of **30** due to the most reactivity of methylene group of 4-oxothiazolidine ring in **27**, (Scheme 5).



The active methylene group of 1-(2-(2-cyanoacetyl)hydrazono)ethyl derivative **11** was allowed to react with dimethylformamide dimethylacetal (DMF-DMA) in boiling xylene to yield 4-(1-(2-(2-cyano-3-(dimethylamino)acryloyl)-hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (**31**). The ¹H NMR spectrum of **31** showed the presence of four methyl groups at δ 2.30, 2.73, 3.27 and 3.41 ppm of ethylidene, methylamino and N,N-dimethylamino, respectively

(Scheme 6). Coupling of **11** with the diazotized heterocyclic amine are excellent building blocks for the synthesis of poly condensed heterocyclic derivatives. Thus, coupling of **11** with 5-(chlorodiazenyl)-3-(methylthio)-1H-pyrazole-4-carbonitrile in pyridine solution at 0-5°C afforded high yields of the pyrazolo[5,1-c][1,2,4]triazine derivative **32**. Finally, treatment of **11** with 2-(bis(methylthio)methylene)malononitrile in dimethylformamide in the presence of anhydrous potassium carbonate gave 2-oxopyridine-3,6-dicarbonitrile derivative **33**, (Scheme 6).



Antimicrobial and Antifungal Activities³¹⁻³³

The results of antimicrobial screening (**Table 1**) shows that compounds **7**, **27** and **31** contains methyl hydrazinecarbodithioate, N-ethoxycarbonylmethyl-4-oxothiazolidine and 2-(2-cyano-3-(dimethylamino)acryloyl)hydrazone moieties, respectively are highly active compounds against antimicrobial activity, gram-positive (*B. Subtilis*, *S. Aureus*), gram-negative (*E. Coli*), and Antifungal Activity, Unicellular Fungi (*C. Albicans*), Filamentous Fungi (*A. Niger*), while the compounds **9**, **15a**, **19** and **28** contains hydrazinecarbothioamide, methyl-1,3,4-thiadiazole-2-carboxylate, 1,3,4-thiadiazine and 5-(*p*-methoxybenzylidene)-4-oxothiazolidine moieties, respectively showed the moderate active, and the remaining compounds **15b** and **16** contains 1,3,4-thiadiazole-2-benzoyl and 5-hydrazinecarbonyl-1,3,4-thiadiazole moieties, respectively showed weak active.

Experimental

Melting points (°C, uncorrected) were determined in open capillaries on a Gallen Kemp melting point apparatus (Sanyo GallenKemp, Southborough, UK). Pre-coated silica gel plates (silica gel 0.25 mm, 60 G F 254; Merck, Germany) were used for thin layer chromatography, dichloromethane/methanol (9.5:0.5 mL) mixture was used as a developing solvent system and the spots were recorded. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν , cm^{-1}). ¹H NMR spectra were recorded at 300 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 analyses were performed on Carlo Erba 1108 Elemental Analyzer (Heraeus, Hanau, Germany). All compounds were within ± 0.4 % of the theoretical values. 4-acetyl-N-ethyl-N-methylbenzenesulfonamide (**1**) was prepared according to the procedures reported in the literature.³⁴ Yield, 74%; m.p. 70-71°C; IR (KBr, cm^{-1}): 1686 (CO), 1341,1167 (SO₂). ¹H NMR (CDCl₃): 1.12 (t, 3H, CH₃ ethyl), 2.36 (s, 3H, CH₃CO), 2.76 (s, 3H, CH₃-N), 3.14 (q, 2H, CH₂ ethyl) 7.85,8.08 (dd, 4H, Ar-H AB-system). Anal. Calcd. for C₁₁H₁₅NO₃S: C, 54.75; H, 6.27; N, 5.80; O, 19.89; S, 13.29. Found: C, 54.63; H, 6.04; N, 5.65; O, 19.67; S, 13.04.

N-Ethyl-4-(1-hydrazonoethyl)-N-methylbenzenesulfonamide derivatives (7-11)

To a solution of hydrazine derivatives, namely methyl hydrazinecarbodithioate, thiocarbohydrazide, hydrazinecarbothioamide, N-phenylhydrazinecarbothioamide and 2-cyanoacetohydrazide **2-6** (0.01 mol), in ethanol 50 mL, 4-acetyl-N-ethyl-N-methylbenzenesulfonamide (**1**) (2.4g, 0.01 mol) was added. The reaction mixture

was heated under reflux for 2h. then left to cool. The solid product was collected by filtration and recrystallized from ethanol to give compounds 7-11, respectively.

Methyl 2-(1-(4-(N-ethyl-N-methylsulfamoyl)phenyl)ethylidene)hydrazinecarbodithioate (7)

Yield, 65%; m.p. 138-140°C; IR (KBr, cm^{-1}): 3172 (NH), 1333,1162 (SO_2). ^1H NMR (CDCl_3): 1.15 (t, 3H, CH_3 ethyl), 2.34 (s, 3H, SCH_3), 2.66 (s, 3H, $\text{CH}_3\text{-C=N}$), 2.77 (s, 3H, $\text{CH}_3\text{-N}$), 3.15 (q, 2H, CH_2 ethyl), 7.81, 7.99 (dd, 4H, Ar-H AB-system), 10.01 (s, 1H, NH). Anal. Calcd. for $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_2\text{S}_3$: C, 45.19; H, 5.54; N, 12.16; O, 9.26; S, 27.84. Found: C, 45.06; H, 5.23; N, 12.04; O, 9.05; S, 27.68.

N-Ethyl-4-(1-(2-(hydrazinecarbonothioyl)hydrazono)ethyl)-N-methylbenzenesulfonamide (8)

Yield, 77%; m.p. 131-133°C; IR (KBr, cm^{-1}) 3356,3279 (NH_2), 3169,3200 (2NH), 1332,1157 (SO_2). MS m/z (%): 326 [M^+] (1.18). Anal. Calcd. for $\text{C}_{12}\text{H}_{19}\text{N}_5\text{O}_2\text{S}_2$: 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)hydrazinecarbothioamide (9)

Yield, 79%; m.p. 175-176°C; IR (KBr, cm^{-1}): 3400,3237 (NH_2), 3158 (NH), 1316,1152 (SO_2). MS m/z (%): 314 [M^+] (11.21). Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}_2\text{S}_2$: C, 45.84; H, 5.77; N, 17.82; O, 10.18; S, 20.40. Found: C, 45.75; H, 5.42; N, 17.61; O, 9.95; S, 20.13.

2-(1-(4-(N-Ethyl-N-methylsulfamoyl)phenyl)ethylidene)-N-phenylhydrazinecarbothioamide (10)

Yield, 65%; m.p. 184-186°C; IR (KBr, cm^{-1}): 3308,3188 (2NH), 1337,1164 (SO_2). ^1H NMR (CDCl_3): 1.16 (t, 3H, CH_3 ethyl), 2.38 (s, 3H, $\text{CH}_3\text{-C=N}$), 2.78 (s, 3H, $\text{CH}_3\text{-N}$), 3.17 (q, 2H, CH_2 ethyl), 7.27-7.87 (m, 9H, Ar-H), 8.83,9.34 (2s, 2H, 2NH), Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_2\text{S}_2$: C, 55.36; H, 5.68; N, 14.35; O, 8.19; S, 16.42. Found: C, 55.12; H, 5.44; N, 14.14; O, 7.97; S, 16.11.

4-(1-(2-(2-Cyanoacetyl)hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (11)

Yield, 70%; m.p. 166-168 (KBr, cm^{-1}): 3169 (NH), 2262 (CN), 1688 (CO), 1330,1160 (SO_2). ^1H NMR (DMSO-d_6): 1.09 (t, 3H, CH_3 ethyl), 2.29 (s, 3H, $\text{CH}_3\text{-C=N}$), 2.67 (s, 3H, $\text{CH}_3\text{-N}$), 3.04 (q, 2H, CH_2 ethyl), 4.26 (s, 2H, CH_2CN), 7.78,7.98

(dd, 4H, Ar-H AB-system), 11.18 (s, 1H, NH). Anal. Calcd. for $C_{14}H_{18}N_4O_3S$: C, 52.16; H, 5.63; N, 17.38; O, 14.89; S, 9.95. Found: C, 51.98; H, 5.44; N, 17.15; O, 14.64; S, 9.71.

4-(1-((3,5-disubstituted-1,3,4-thiadiazol-2(3H)-ylidene)hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide derivatives (15a,b)

A mixture of methyl hydrazinecarbodithioate derivative **7** (3.5g, 0.01 mol) and the appropriate hydrazoneyl bromide namely, methyl 2-bromo-2-(2-(4-chlorophenyl)hydrazono)acetate and 2-oxo-N',2-diphenylacetohydrazoneyl bromide **12a,b** (0.01 mol) in ethanol 50 mL, contains triethylamine as a catalyst. The reaction mixture was refluxed for 3h. The resulting product was collected by filtration and recrystallized from ethanol to give **15a,b** respectively.

Methyl(4-(4-chlorophenyl)-5-((1-(4-(N-ethyl-N-methylsulfamoyl)phenyl)ethylidene)hydrazono)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (15a)

Yield, 71%; m.p. 196-197°C; IR (KBr, cm^{-1}): 1744 (CO), 1336,1156 (SO_2). 1H NMR ($CDCl_3$): 1.16 (t, 3H, CH_3 ethyl), 2.49 (s, 3H, $CH_3-C=N$), 2.78 (s, 3H, CH_3-N), 3.16 (q, 2H, CH_2 ethyl), 4.02 (s, 3H, CH_3 ester), 7.45-8.08 (m, 8H, Ar-H). Anal. Calcd. for $C_{21}H_{22}ClN_5O_4S_2$: C, 49.65; H, 4.36; N, 13.79; O, 12.60; S, 12.62. Found: C, 49.34; H, 4.01; N, 13.46; O, 12.34; S, 12.48.

4-(1-((5-Benzoyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (15b)

Yield, 78%; m.p. 204-205°C; IR (KBr, cm^{-1}): 1697 (CO), 1341,1158 (SO_2). 1H NMR ($CDCl_3$): 1.17 (t, 3H, CH_3 ethyl), 2.51 (s, 3H, $CH_3-C=N$), 2.79 (s, 3H, CH_3-N), 3.17 (q, 2H, CH_2 ethyl), 7.51-8.36 (m, 14H, Ar-H). Anal. Calcd. for $C_{26}H_{25}N_5O_3S_2$: C, 60.10; H, 4.85; N, 13.48; O, 9.24; S, 12.34. Found: C, 59.84; H, 4.68; N, 13.24; O, 9.02; S, 12.05.

4-(1-((3-(4-Chlorophenyl)-5-(hydrazinecarbonyl)-1,3,4-thiadiazol-2(3H)-ylidene)hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (16)

To a solution of methyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate derivative **15a** (5.1g, 0.01 mol) in ethanol 50 mL, hydrazine hydrate (0.5g, 0.01 mol) was added. The reaction mixture was heated under reflux for 2h. then left to cool. The solid product was collected by filtration and recrystallized from ethanol to give **16**. Yield, 73%; m.p. 188-190°C; IR (KBr, cm^{-1}): 3400,3325 (NH_2), 3189 (NH), 1672

(CO), 1336,1160 (SO₂). ¹H NMR (CDCl₃): 1.16 (t, 3H, CH₃ ethyl), 1.65 (br, 2H, NH₂), 2.48 (s, 3H, CH₃-C=N), 2.78 (s, 3H, CH₃-N), 3.16 (q, 2H, CH₂ ethyl), 7.45-8.11 (m, 8H, Ar-H), 9.18 (br, 1H, NH). Anal. Calcd. for C₂₀H₂₂ClN₇O₃S₂: C, 47.28; H, 4.36; N, 19.30; O, 9.45; S, 12.62. Found: C, 47.04; H, 4.12; N, 19.14; O, 9.25; S, 12.41.

4-(1-((5-(2-Arylidenehydrazinecarbonyl)-3-(4-chlorophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (17a,b)

To a solution of 3-(4-chlorophenyl)-5-(hydrazinecarbonyl)-1,3,4-thiadiazol derivative **16** (5.1g, 0.01 mol) in ethanol 50 mL, the appropriate aromatic aldehyde namely benzaldehyde and 4-methoxybenzaldehyde (0.01 mol) was added. The reaction mixture was heated under reflux for 1h. the solid product was collected by filtration and recrystallized from ethanol to give **17a,b** respectively.

4-(1-((5-(2-Benzylidenehydrazinecarbonyl)-3-(4-chlorophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (17a)

Yield, 71%; m.p. 151-152°C; IR (KBr, cm⁻¹): 3188 (NH), 1674 (CO), 1330,1156 (SO₂). MS m/z (%): 596 [M⁺] (5.7). Anal. Calcd. for C₂₇H₂₆ClN₇O₃S₂: C, 54.40; H, 4.40; N, 16.45; O, 8.05; S, 10.76. Found: C, 54.25; H, 4.24; N, 16.26; O, 7.88; S, 10.53.

4-(1-((3-(4-Chlorophenyl)-5-(2-(4-methoxybenzylidene)hydrazinecarbonyl)-1,3,4-thiadiazol-2(3H)-ylidene)hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (17b)

Yield, 68%; m.p. 162-164°C; IR (KBr, cm⁻¹): 3176 (NH), 1666 (CO), 1340,1160 (SO₂). ¹H NMR (CDCl₃): 1.16 (t, 3H, CH₃ ethyl), 2.51 (s, 3H, CH₃-C=N), 2.77 (s, 3H, CH₃-N), 3.16 (q, 2H, CH₂ ethyl), 3.85 (s, 3H, OCH₃), 6.94-8.01 (m, 12H, Ar-H) 9.60 (br, 1H, NH), 9.89 (s, 1H, CH arylidene). Anal. Calcd. for C₂₈H₂₈ClN₇O₄S₂: C, 53.71; H, 4.51; N, 15.66; O, 10.22; S, 10.24. Found: C, 53.54; H, 4.32; N, 15.45; O, 10.03; S, 10.02.

4-(1-((3-(4-chlorophenyl)-5-(5-hydroxy-3-methyl-1H-pyrazole-1-carbonyl)-1,3,4-thiadiazol-2(3H)-ylidene)hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (18)

To a solution of 3-(4-chlorophenyl)-5-(hydrazinecarbonyl)-1,3,4-thiadiazol derivative **16** (5.1g, 0.01 mol), ethyl acetoacetate (1.3g, 0.01 mol) was added. The reaction mixture was heated under reflux for 3h. The obtained product was collected

by filtration and recrystallized from ethanol to give **18**. Yield, 59%; m.p. 261-263°C; IR (KBr, cm^{-1}): 3422 (OH), 1673 (CO), 1334,1162 (SO_2). ^1H NMR (CDCl_3): 1.18 (t, 3H, CH_3 ethyl), 2.01 (s, 3H, CH_3 pyrazole), 2.37 (s, 3H, $\text{CH}_3\text{-C=N}$), 2.77 (s, 3H, $\text{CH}_3\text{-N}$), 3.18 (q, 2H, CH_2 ethyl), 7.43-8.05 (m, 8H, Ar-H), 8.40 (s, 1H, CH pyrazole), 13.15 (br, 1H, OH). Anal. Calcd. for $\text{C}_{24}\text{H}_{24}\text{ClN}_7\text{O}_4\text{S}_2$: C, 50.21; H, 4.21; N, 17.08; O, 11.15; S, 11.17. Found: C, 50.02; H, 4.10; N, 16.87; O, 11.01; S, 11.04.

N-Ethyl-N-methyl-4-((1E)-1-((5-(4-nitrophenyl)-2H-1,3,4-thiadiazin-2-ylidene)-hydrazono)ethyl)benzenesulfonamide (19)

A mixture of 1-(2-(hydrazinecarbonothioyl)hydrazono)ethyl derivative **8** (3.3g, 0.01 mol) and 2-bromo-1-(4-nitrophenyl)ethanone (2.4g, 0.01 mol) in ethanol 40 mL was refluxed for 2h. the solid product which formed was collected by filtration and recrystallized from ethanol to give **19**. Yield, 76%; m.p. 140-142°C; IR (KBr, cm^{-1}): 1341,1158 (SO_2). MS m/z (%): 472 [M^+] (85.7), 393 (100). Anal. Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_6\text{O}_4\text{S}_2$: C, 50.83; H, 4.27; N, 17.78; O, 13.54; S, 13.57. Found: C, 50.65; H, 4.02; N, 17.54; O, 13.41; S, 13.44.

N-Ethyl-N-methyl-4-(1-(2-(5-oxo-4,5-dihydro-1,3,4-thiadiazol-2-yl)hydrazono)-ethyl)benzenesulfonamide (20)

A mixture of 1-(2-(hydrazinecarbonothioyl)hydrazono)ethyl derivative **8** (3.3g, 0.01 mol), ethyl chloroformate (1.1g, 0.01 mol) and fused sodium acetate (1.6g, 0.02 mol) in dioxane 50 mL was refluxed for 1h, the obtained product was collected by filtration, washed with water and recrystallized from a mixture of DMF/EtOH to give **20**. Yield, 64%; m.p. 142-143°C; IR (KBr, cm^{-1}): 3176 (NH), 1741 (CO), 1336,1159 (SO_2). ^1H NMR (DMSO-d_6): 1.17 (t, 3H, CH_3 ethyl), 2.35 (s, 3H, $\text{CH}_3\text{-C=N}$), 2.79 (s, 3H, $\text{CH}_3\text{-N}$), 3.16 (q, 2H, CH_2 ethyl), 7.86,8.06 (dd, 4H, Ar-H AB-system), 9.18,9.03 (2br, 2H, 2NH). Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{N}_5\text{O}_3\text{S}_2$: C, 43.93; H, 4.82; N, 19.70; O, 13.50; S, 18.04. Found: C, 43.76; H, 4.74; N, 19.57; O, 13.36; S, 17.90.

4-(1-((3-Amino-4-oxothiazolidin-2-ylidene)hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (21)

A mixture of 1-(2-(hydrazinecarbonothioyl)hydrazono)ethyl derivative **8** (3.3g, 0.01 mol), ethyl chloroacetate (1.2g, 0.01 mol) and fused sodium acetate (1.6g, 0.02 mol) in ethanol 50 mL was refluxed for 2h, the obtained product was collected by

filtration, washed with water and recrystallized from DMF to give **21**. Yield, 65%; m.p. 148-150°C; IR (KBr, cm⁻¹): 3422,3244 (NH₂), 1689 (CO), 1332,1161 (SO₂). ¹H NMR (CDCl₃): 1.15 (t, 3H, CH₃ ethyl), 2.53 (s, 3H, CH₃-C=N), 2.76 (s, 3H, CH₃-N), 3.14 (q, 2H, CH₂ ethyl), 3.84 (s, 2H, CH₂ cyclo), 5.12 (s, 2H, NH₂), 7.76,8.05 (dd, 4H, Ar-H AB-system). Anal. Calcd. for C₁₄H₁₉N₅O₃S₂: C, 45.51; H, 5.18; N, 18.96; O, 12.99; S, 17.36. Found: C, 45.35; H, 5.01; N, 18.84; O, 12.78; S, 17.14.

N-Ethyl-4-(1-(2-(2-(4-methoxybenzylidene)hydrazinecarbonothioyl)-hydrazono)ethyl)-N-methylbenzenesulfonamide (22)

A mixture of 1-(2-(hydrazinecarbonothioyl)hydrazono)ethyl derivative **8** (3.3g, 0.01 mol), 4-methoxybenzaldehyde (1.4g, 0.01 mol) in ethanol 50 mL was refluxed for 3h. the obtained product was collected by filtration, and recrystallized from dioxane to give **22**. Yield, 60%; m.p. 179-181°C; IR (KBr, cm⁻¹): 3179,3212 (2NH), 1304,1166 (SO₂). ¹H NMR (DMSO-d₆): 1.15 (t, 3H, CH₃ ethyl), 2.38 (s, 3H, CH₃-C=N), 2.75 (s, 3H, CH₃-N), 3.16 (q, 2H, CH₂ ethyl), 3.87 (s, 3H, OCH₃), 6.98-7.80 (m, 8H, Ar-H), 8.62 (s, 1H, CH arylidene), 10.22,10.85 (2s, 2H, 2NH). Anal. Calcd. for C₂₀H₂₅N₅O₃S₂: C, 53.67; H, 5.63; N, 15.65; O, 10.72; S, 14.33. Found: C, 53.46; H, 5.42; N, 15.45; O, 10.54; S, 14.12.

N-Ethyl-N-methyl-4-(1-((4-(4-nitrophenyl)thiazol-2(3H)-ylidene)hydrazono)-ethyl)benzenesulfonamide (23)

A mixture of hydrazinecarbothioamide derivative **9** (3.1g, 0.01 mol), 2-bromo-1-(4-nitrophenyl)ethanone (2.4g, 0.01 mol) in ethanol 50 mL was refluxed for 3h. the obtained product was collected by filtration, and recrystallized from ethanol to give **23**. Yield, 58%; m.p. 247-249°C; IR (KBr, cm⁻¹): 3264 (NH), 1338,1155 (SO₂). ¹H NMR (DMSO-d₆): 1.15 (t, 3H, CH₃ ethyl), 2.43 (s, 3H, CH₃-C=N), 2.76 (s, 3H, CH₃-N), 3.14 (q, 2H, CH₂ ethyl), 7.33-8.45 (m, 8H, Ar-H), 9.44 (s, 1H, CH thiazole), 13.62 (s, 1H, NH). Anal. Calcd. for C₂₀H₂₁N₅O₄S₂: C, 52.27; H, 4.61; N, 15.24; O, 13.93; S, 13.96. Found: C, 52.01; H, 4.42; N, 15.01; O, 13.64; S, 13.65.

N-Ethyl-N-methyl-4-(1-((4-oxothiazolidin-2-ylidene)hydrazono)ethyl)-benzenesulfonamide (26)

A mixture of hydrazinecarbothioamide derivative **9** (3.1g, 0.01 mol), ethyl chloroacetate (1.3g, 0.01mol) and fused sodium acetate (1.6g, 0.02 mol) in ethanol 50 mL was heated under reflux for 4h. during the reflux period, crystalline solid was

separated. The separated solid was filtered off, washed with ethanol and recrystallized from ethanol to give **26**. Yield, 56%; m.p. 241-243°C; IR (KBr, cm^{-1}): 3184 (NH), 1686 (CO), 1339,1162 (SO_2). MS m/z (%): 354 [M^+] (19.2). Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_4\text{O}_3\text{S}_2$: C, 47.44; H, 5.12; N, 15.81; O, 13.54; S, 18.09. Found: C, 47.21; H, 4.87; N, 15.64; O, 13.31; S, 17.76.

Ethyl 2-(2-((1-(4-(N-ethyl-N-methylsulfamoyl)phenyl)ethylidene)hydrazono)-4-oxothiazolidin-3-yl)acetate (27)

Method (A): A mixture of hydrazinecarbothioamide derivative **9** (3.1g, 0.01 mol), ethyl chloroacetate (2.6g, 0.02 mol) and fused sodium acetate (1.6g, 0.02 mol) in ethanol 50 mL was heated under reflux for 8h. during the reflux period, crystalline solid was separated. The separated solid was filtered off, washed with ethanol and recrystallized from dioxane to give **27**.

Method (B): A mixture of 1-((4-oxothiazolidin-2-ylidene)hydrazono)ethyl derivative **26** (3.5g, 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 6h. during the reflux period, crystalline solid was separated. The separated solid was filtered off, washed with ethanol and recrystallized from ethanol to give **27** m.p., mixed m.p., and TLC determined with authentic sample gave no depression. Yield, 77%; m.p. 263-265°C; IR (KBr, cm^{-1}): 1715,1687 (2CO), 1334,1160 (SO_2). ^1H NMR (DMSO- d_6): 1.04 (2t, 6H, CH_3 ethyl + CH_3 ethoxy), 2.39 (s, 3H, $\text{CH}_3\text{-C=N}$), 2.68 (s, 3H, $\text{CH}_3\text{-N}$), 3.03 (2q, 4H, CH_2 ethyl + CH_2 ethoxy), 3.90 (s, 2H, CH_2 cyclo), 3.97 (s, 2H, NCH_2CO), 7.80,8.05 (dd, 4H, Ar-H AB-system). Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{N}_4\text{O}_5\text{S}_2$: C, 49.07; H, 5.49; N, 12.72; O, 18.16; S, 14.56. Found: C, 48.87; H, 5.27; N, 12.50; O, 17.94; S, 14.34.

N-Ethyl-4-(1-((-5-(4-methoxybenzylidene)-4-oxothiazolidin-2-ylidene)-hydrazono)ethyl)-N-methylbenzenesulfonamide (28)

A mixture of 1-((4-oxothiazolidin-2-ylidene)hydrazono)ethyl derivative **26** (3.5g, 0.01 mol) and 4-methoxybenzaldehyde (1.4g, 0.01 mol) in ethanol 50 mL, contains piperidine as a catalyst was heated under reflux for 4h. during the reflux period, crystalline solid was separated. The separated solid was filtered off, washed with ethanol and recrystallized from ethanol to give **28**. Yield, 70%; m.p. 178-180°C; IR (KBr, cm^{-1}): 3176 (NH), 1662 (CO), 1332,1157 (SO_2). ^1H NMR (DMSO- d_6): 1.16 (t, 3H, CH_3 ethyl), 2.39 (s, 3H, $\text{CH}_3\text{-C=N}$), 2.76 (s, 3H, $\text{CH}_3\text{-N}$), 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; O, 13.54; S, 13.57. Found: C, 55.72; H, 5.00; N, 11.51; O, 13.31; S, 13.32.

Ethyl 2-(5-benzylidene-2-((1-(4-(N-ethyl-N-methylsulfamoyl)phenyl)ethylidene)hydrazono)-4-oxothiazolidin-3-yl)acetate (29)

A mixture of N-ethoxycarbonylmethyl-4-oxothiazolidine derivative **27** (4.4g, 0.01 mol) and benzaldehyde (1.1g, 0.01 mol) in ethanol 50 mL, contains piperidine as a catalyst was heated under reflux for 4h. during the reflux period, crystalline solid was separated. The separated solid was filtered off and recrystallized from ethanol to give **29**. Yield, 54%; m.p. 264-265°C; IR (KBr, cm^{-1}): 1686, 1710 (2CO), 1332, 1158 (SO_2). 1H NMR (DMSO- d_6): 1.13 (2t, 6H, CH_3 ethyl + CH_3 ethoxy), 2.60 (s, 3H, $CH_3-C=N$), 2.76 (s, 3H, CH_3-N), 3.14 (2q, 4H, CH_2 ethyl + CH_2 ethoxy), 4.67 (s, 2H, NCH_2CO), 7.48-8.05 (m, 10H, Ar-H + CH benzylidene). Anal. Calcd. for $C_{25}H_{28}N_4O_5S_2$: C, 56.80; H, 5.34; N, 10.60; O, 15.13; S, 12.13. Found: C, 56.61; H, 5.11; N, 10.40; O, 15.05; S, 12.01.

4-(1-(2-(2-cyano-3-(dimethylamino)acryloyl)hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (31)

A mixture of 1-(2-(2-cyanoacetyl)hydrazono)ethyl derivative **11** (3.2g, 0.01 mol) and dimethylformamide-dimethylacetal, (DMF-DMA) (1.2g, 0.01 mol), in dry xylene 30 mL was refluxed for 3h. The obtained solid was recrystallized from ethanol to give **31**. Yield, 66%; m.p. 179-180°C; IR (KBr, cm^{-1}): 3358 (NH), 2184 (CN), 1678 (CO), 1328, 1148 (SO_2). 1H NMR (DMSO- d_6): 1.12 (t, 3H, CH_3 ethyl), 2.30 (s, 3H, $CH_3-C=N$), 2.73 (s, 3H, CH_3-N), 3.09 (q, 2H, CH_2 ethyl), 3.27, 3.41 (2s, 6H, $(CH_3)_2N$), 7.77, 7.93 (dd, 4H, Ar-H AB-system), 7.98 (s, 1H, CH), 8.96 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{23}N_5O_3S$: C, 54.09; H, 6.14; N, 18.55; O, 12.72; S, 8.49. Found: C, 53.92; H, 6.01; N, 18.36; O, 12.56; S, 8.27.

4-(1-(2-(4-Amino-8-cyano-7-(methylthio)pyrazolo[5,1-c][1,2,4]triazine-3-carbonyl)hydrazono)ethyl)-N-ethyl-N-methylbenzenesulfonamide (32)

To a stirred solution of 1-(2-(2-cyanoacetyl)hydrazono)ethyl derivative **11** (3.2g, 0.01 mol) in pyridine 50 mL, 5-(chloro diazenyl)-3-(methylthio)-1H-pyrazole-4-carbonitrile (2.0g, 0.01 mol) (prepared by diazotization of 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile (1.5g, 0.01 mol) in concentrated HCl 6 mL with sodium nitrite (0.7g, 0.01 mol) in 5 mL H_2O at 0-5°C) was added portion wise over 30 min.

with constant stirring, after complete addition, the reaction mixture was stirred for a further 1h. at 0-5°C, the solid product was filtered off washed with water, dried and recrystallized from dioxane to give **32**. Yield, 65%; m.p. 232-234°C; IR (KBr, cm⁻¹): 3411,3362 (NH₂), 3155 (NH), 2222 (CN), 1680 (CO), 1340,1156 (SO₂). MS m/z (%): 487 [M⁺] (1.01), 118 (100). Anal. Calcd. for C₁₉H₂₁N₉O₃S₂: C, 46.81; H, 4.34; N, 25.86; O, 9.84; S, 13.15. Found: C, 46.68; H, 4.12; N, 25.65; O, 9.60; S, 13.02.

4-(1-(5-Amino-3,6-dicyano-4-(methylthio)-2-oxopyridin-1(2H)-ylimino)ethyl)-N-ethyl-N-methylbenzenesulfonamide (33)

A mixture of 1-(2-(2-cyanoacetyl)hydrazono)ethyl derivative **11** (3.2g, 0.01 mol), anhydrous potassium carbonate (1.4g, 0.01 mol) and 2-(bis(methylthio)methylene)malononitrile (1.7g, 0.01 mol) in DMF 30 mL. The reaction mixture was heated at 50-60°C with stirring until odor of methanethiol is ceased, after cooling the reaction mixture poured into ice crush 100g then acidified with 1N HCl. The solid product which formed was collected and recrystallized from dioxane to give **33**. Yield, 67%; m.p. 213-215°C; IR (KBr, cm⁻¹): 3412,3355 (NH₂), 2208 (CN), 1665 (CO), 1328,1162 (SO₂). MS m/z (%): 444 [M⁺] (71.4), 104 (100). Anal. Calcd. for C₁₉H₂₀N₆O₃S₂: C, 51.34; H, 4.53; N, 18.91; O, 10.80; S, 14.43. Found: C, 51.15; H, 4.36; N, 18.78; O, 10.68; S, 14.22.

Antimicrobial and Antifungal screening (*in-vitro* study)

Antimicrobial and Antifungal activities of nine newly synthesized 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 Petri dishes and left for 24 h. 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°C for 24 h. After inoculation the plates were examined visually and the zone of inhibition were measured.

Table 1: Antibacterial and Antifungal Activities

Comp. No.	Gram-Positive		Gram-Negative	Unicellular Fungi	Filamentous Fungi
	B. Subtilis	S. Aureus	E. Coli	C. Albicans	A. Niger
7	+++	++++	+++	+++	+++
9	+	++	++	+	+
15a	++	++	+	++	++
15b	-	+	-	-	-
16	-	+	-	+	-
19	++	+	+	+	+
27	+++	+++	++++	+++	++
28	+	++	++	+	+
31	++	+++	+++	+++	+++
Chloramphenicol	++++	++++	++++	-	-
Terbinafine	-	-	-	++++	++++

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

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