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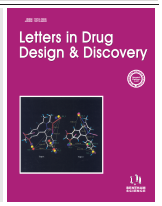

Synthesis and Anti-Oxidant Evaluation of Some Novel Sulfa Drugs

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Abstract: ***Background*:** Curcumins were reported to possess anti-inflammatory and antiangiogenic. Furthermore, Curcumin is a very potent free radical scavenger than vitamin E. Moreover, cyanoacetamides were reported to possess, antimicrobial antifungal, insulin releasing, anti-inflammatory and antitumor. Thus the present study focuses on the synthesis of some novel structure hybrids incorporating either curcumin or cyanoacetamide with sulphonamide, aiming to reach a more potent antioxidant agent.

***Methods*:** 4-arylazoenol derivatives **12-16** *and E*-hydrazo derivatives **19-23** were prepared and their structure was confirmed by variable spectra analysis. The newly synthesized compounds were screened for their antioxidant activity using ABTS and Bleomycin-dependent DNA damage methods.

***Results*:** Coupling of the diazonium salts **7-11** of different sulpha drugs with curcumin **1** or with cyanoacetamide **18** afforded the corresponding 4-arylazoenol derivatives **12-16** *and E*-hydrazo derivatives **19-23.** Among all the synthesized compounds, **12-16, 18**, **20** and **22** were the most potent antioxidant compounds.

***Conclusion*:** The objective of the present study was to synthesize and evaluate the antioxidant activity of some novel sulfonamides structure hybrids incorporating either curcumin or *N*-[4-(aminosulfonyl) phenyl]-2-cyanoacetamide moiety with the hope of discovering new structure serving as antioxidant agent. The data showed clearly that most of compounds displayed good *in vitro* antioxidant activities.

Keywords: *N*-[4-(aminosulfonyl)phenyl]-2-cyanoacetamide, sulphonamides, diazonium salt, anti-oxidant, curcumin, antifungal.

1. INTRODUCTION

Curcumin was reported to possess many biological properties such as anti-inflammatory and antiangiogenic activities [1-3]. Furthermore, different types of antioxidants (vitamins C and E, glutathione, lipoic acid, *etc*.) have chain oxidation processes, causing thus a high scientific interest [4, 5]. Curcumin is a more potent free radical scavenger when compared with vitamin E [6]. Studies have shown that Curcumin is a powerful scavenger of the superoxide anion, the hydroxyl radical, nitrogen dioxide and protects DNA against singlet-oxygen-induced strand [7, 8].

Moreover, cyanoacetamides were used as a key intermediate to design different heterocyclic moiety with different ring sizes [9]. In addition, many cyanoacetamide derivatives have been reported to possess, antimicrobial [10], antifungal [11], insulin releasing [12], anti-inflammatory [13], and antitumor properties [14]. Furtheremore, some sulfonamides are reported as antibacterial [15], antifungal [16] and anticancer agent [17]. They also have valuable application in medicine for the treatment of Alzheimer's disease [18].

In view of the above-mentioned facts and in continuation of our interest in the synthesis of biologically active heterocycles [19-23], the present study focuses on the synthesis of some novel structure hybrids incorporating either curcumin or cyanoacetamide with sulphonamide. This combination was suggested to investigate the influence of such hybridization and structure variation on the anticipated biological activities, aiming to reach a more potent antioxidant agent.

2. MATERIALS AND METHODS

2.1. General

Melting points were obtained on capillary melting point apparatus and were uncorrected. Infrared (IR) spectra υ (cm^{-1}) were performed on a nicolet i55 FTIR Spectrophotometer in Faculty of Science and Arts, Ulla, Taibah University,

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KSA. The ^{1}H-NMR and ^{13}C-NMR spectra were determined on a Bruker Spectrophotometer at 600 and 150 MHz respectively, using TMS as an internal reference and DMSO-d6 as solvent and were carried out in the king Abdulaziz University, KSA. Mass spectra (MS) were measured on 70 eV with a Varian MAT 311 A Spectrometer. Elemental analyses (C, H and N) were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. Biological activities were carried out in Pharmacognosy Department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt.

2.2. Experimental

2.2.1. General Procedure for the Synthesis of 4-arylazo Curcumin 12-16

A solution of $NaNO_2$ (0.4 g, 5.8 mole in 5 mL H_2O) was added drop wise to a well cooled stirred solution of 4-aminobenzenesulfonic acid **2** (0.87 g, 0.005 mol), *p*-aminobenzenesulphonamide **3** (0.86 g, 0.00 5 mol), *N*-(4-aminophenylsulfonyl) acetamide **4** (1.07 g, 0.005mol), 1-(4-aminophenylsulfonyl) guanidine **5** (1.07 g,0 .005 mol) and 4-amino-*N*-(4,6-dimethylpyrimidin-2-yl) benzenesulfonamide **6** (1.4 g, 0.005 mol) in a mixture of concentrated HCl (3 mL) and H_2O (3 mL). The above cooled diazonium solution was added slowly to a well stirred solution of curcumin **1** (1.84 g, 0.005 mol) in pyridine (25 mL). The reaction was stirred for 2 h. The formed precipitate was filtered off, dried and crystallized from EtOH /benzene to give the sulpha derivatives **12**, **13**, **14**, **15** and **16**, respectively.

2.2.1.1. 4-((E)-((1E, 3E, 6E)-3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(3-hydroxy-4-methoxyphenyl)-5-oxohepta-1, 3, 6-trien-4-yl) diazenyl) benzenesulfonic acid 12

Yield: 65%, reddish brown powder. m.p.: above 315 ^{o}C; IR (νmax, cm^{-1}): 1097, 1177 (SO_2), 1511 (N=N), 1592 (C=C), 1692 (C=O), 3373, 3424, 3504 (4OH); ^{1}H NMR (600MHz, $CDCl_3$/DMSO-d6) (δ/ppm): 3.12 (br, 2H, 2 OH phenolic), 3.77 (s, 3H, OCH_3), 3.93(s, 3H, OCH_3), 6.48-7.89 (m, 14H, Ar–H, 2CH=CH), 8.68 (br, 1H, OH acid) 12.50 (br, 1H, OH enolic); ^{13}C-NMR (150 MHz, $CDCl_3$/DMSO-d6) (δ/ppm): 184.2 (C_5), 183.6 (C_3), 147.9 (C_1), 147.8 ($C_{5''}$), 147.7($C_{5'}$), 143.7 ($C_{4'}$), 143.4($C_{4''}$), 138.9 ($C_{4'''}$),130.5 ($C_{1'''}$), 139.2 (C_7), 126.8 ($C_{2'''}$,$C_{6'''}$), 125.1 ($C_{1'}$), 124.6 ($C_{1''}$), 122.9 ($C_{2''}$, $_{6'''}$), 121.2(C_2), 119.8 ($C_{2''}$), 118.3($C_{2'}$), 116.1 (C_6), 115.9 ($C_{3'''}$,$_{5'''}$), 115.8 ($C_{3'}$),115.7 ($C_{3''}$), 111.4($C_{6''}$), 111.0 ($C_{6'}$), 110.3 (C_4) , 55.87 (2C, OCH_3); MS *m/z* (rel. int.%): 552 (14.6, M^+), 344 (14.6), 272 (12.2), 228 (17.1), 195 (22.0), 150 (46.3), 98 (58.5), 77 (56.1), 55 (100), 52 (58.8); Anal. Calc. for $C_{27}H_{24}N_2O_9S$: C, 58.69; H, 4.38; N, 5.07; Found: C, 58.62; H, 4.33; N, 5.01.

2.2.1.2. 4-((E)-((1E, 3E, 6E)-3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(3-hydroxy-4-methoxyphenyl)-5-oxohepta-1, 3, 6-trien-4-yl) diazenyl)benzenesulfonamide 13

Yield: 70 % ; reddish brown powder; m.p.: 177 ^{o}C; IR (νmax, cm^{-1}): 1090, 1180, (SO_2), 1508 (N=N) 1629 (C=C), 1634 (br, 2C=O), 3240, 3259, (NH_2, OH), 3443 (br, 2OH); ^{1}H-NMR (600 MHz, $CDCl_3$/DMSO-d6 (δ/ppm): 3.40 (br, 2H, 2 OH phenolic), 3.89 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.43-7.870 (m, 14H, Ar-H, 2CH=CH), 9.51 (br, 2H, NH_2), 13.55 (br, 1H, OH enolic); ^{13}C-NMR (150 MHz, $CDCl_3$/DMSO-d6) (δ/ppm): 184.1(C_5), 183.7 (C_3), 149.5 (C_1), 148.3 ($C_{5''}$),147.9 ($C_{5'}$), 146.7 ($C_{4'}$), 146.4 ($C_{4''}$), 143.5 ($C_{4'''}$), 139.7 ($C_{1'''}$), 136.2 (C_7), 127.3 ($C_{2'''}$,$C_{6'''}$), 126.3 ($C_{1'}$), 125.6 ($C_{1''}$), 122.8 ($C_{2'''}$, $C_{6'''}$), 120.9 (C_2), 119.9 ($C_{2''}$), 117.7 ($C_{2'}$), 116.8 (C_6), 115.8 ($C_{3'''}$, $_{5'''}$), 115.7($C_{3'}$), 115.6 ($C_{3''}$), 111.5 ($C_{6''}$), 110.7 ($C_{6'}$), 109.5 (C_4), 55.7 (OCH_3), 55.68 (OCH_3); MS *m/z* (rel. int.%) = 549 (M^+-2, 13.3) 548 (33.3), 403 (40.0), 313(40.0), 253 (33.3), 66 (60.6),150 (13.3), 117 (100) 82 (66.7), 80(60.0), 58(46.7); Anal. Calc. For $C_{27}H_{25}N_3O_8S$: C, 58.79; H, 4.57; N, 7.62. Found: C, 58.75; H, 4.50; N, 7.55.

2.2.1.3. 4-((E)-((1E, 3E, 6E)-3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(3-hydroxy-4-methoxyph-enyl)-5-oxohepta-1, 3, 6-trien-4-yl) diazenyl) N-acetyl-benzenesulfonamide 14

Yield: 73 %; reddish brown powder; m.p.: 247 ^{o}C; IR (νmax, cm^{-1}): 1160, 1085 (SO_2), 1508 (N=N), 1629 (C=C), 1634 (br, 2C=O), 3110, 3239 (NH, OH), 3422 (br, 2OH); ^{1}H-NMR (600 MHz, $CDCl_3$/DMSO-d6) (δ/ppm): 2.00 (s, 3H, CH_3) 2.97 (br, 2H, 2OH phenolic), 3.94 (s, 3H, OCH_3) , 3.87(s, 3H, OCH_3), 6.78-8.18 (m, 14H, Ar–H, 2CH=CH), 9.25 (br, 1H, NH) , 13.64 (br, 1H, OH enolic); ^{13}C- NMR (150 MHz, $CDCl_3$/DMSO-d6) (δ/ppm): 184.1 (C_5), 183.7 (C_3), 169.3 ($C_{7'''}$), 149.6 (C_1), 149.5($C_{5''}$), 148.4($C_{5'}$), 147.8 ($C_{4'}$), 146.8 ($C_{4''}$), 144.2 ($C_{4'''}$), 130.4 ($C_{1'''}$), 129.8 (C_7), 129.3 ($C_{2'''}$,$C_{6'''}$), 129.0 ($C_{1'}$), 128.9 ($C_{1''}$) 126.9 ($C_{2'''}$, $C_{6'''}$), 122.5 (C_2) 121.0 ($C_{2'''}$), 119.6 ($C_{2'}$),118.0 (C_6), 116.7($C_{3'''}$,$_{5'''}$), 116.0 ($C_{3'}$), 115.6 ($C_{3''}$), 111.4 ($C_{6''}$), 111.0 ($C_{6'}$), 108.9 (C_4), 55.9 (OCH_3), 55.8 (OCH_3), 23.4 (CH_3). MS *m/z* (rel. int.%): 611 (M^++H_2O, 13.3), 150 (29.7), 135(62.2), 106 (46.0), 69 (54.0), 52 (100); Anal. Calcd. For $C_{30}H_{31}N_3O_9S$: C, 59.10; H, 5.13; N, 6.89. Found: C, 59.16; H, 5.08; N, 6.82.

2.2.1.4. 4-((E)-((1E, 3E, 6E)-3-hydroxy-1-(4-hydroxy-3-methoxyphenyl) -7-(3-hydroxy-4-methoxyphenyl) -5-oxohepta-1, 3, 6-trien-4-yl) diazenyl)1-(phenylsulfonyl) guanidine 15

Yield: 68 %; reddish brown powder; m.p.: 190 ^{o}C; IR (νmax, cm^{-1}): 1090, 1210 (SO_2), 1510 (N=N), 1634 (br, 2C=O), 3226, 3347 (NH_2, NH, OH), 3442 (br, 2OH); ^{1}H-NMR (600 MHz, $CDCl_3$/DMSO-d6) (δ/ppm): 3.37(br, 2H, 2OH, phenolic), 3.73 (s, 3H, OCH_3), 3.84(s, 3H, OCH_3), 6.44-7.99 (m, 14H, Ar–H, 2CH=CH), 8.65(br, 2H, NH_2), 9.50 (br, 1H, $NHSO_2$), 9.85 (br, 1H, =NH), 13.54 (br, 1H, OH enolic); ^{13}C-NMR ($CDCl_3$/DMSOd6) (δ/ppm): 183.8 (C_5), 183.0 (C_3), 158.3 ($C_{7'''}$), 149.5(C_1), 149.2 ($C_{5''}$),147.9 ($C_{5'}$), 146.7 ($C_{4'}$), 140.5 ($C_{4''}$), 138.2, ($C_{4'''}$), 135.9 ($C_{1'''}$), 129.9 (C_7), 127.1($C_{2'''}$, $C_{6'''}$), 126.4 ($C_{1'}$), 125.7 ($C_{1''}$), 124.9 ($C_{2'''}$,$C_{6'''}$), 122.9 (C2) 121.0 ($C_{2'''}$), 119.8 ($C_{2'}$), 116.8 (C_6), 115.8 ($C_{3'''}$,$_{5'''}$), 115.7 ($C_{3'}$), 111.5 ($C_{3''}$), 110.7($C_{6''}$), 111.0 ($C_{6'}$), 109.5 (C_4), 55.7 (OCH_3), 55.6 (OCH_3). Anal. Calc. for $C_{29}H_{31}N_5O_8S$: C, 57.13; H, 5.13; N, 11.49. Found: C, 57.13; H, 5.13; N, 11.49. MS *m/z* (rel. int.%): 609.19 (31.6, M-CH_4), 520 (31.6), 356 (100), 313(31.6), 284(100), 166 (94.7), 149 (57.9), 128 (94.7)111 (52.6), 91 (63.2), 57 (63.2).

2.2.1.5. 4-((E)-((1E, 3E, 6E)-3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(3-hydroxy-4-methoxyphe-nyl)-5-oxohepta-1,3,6-trien-4-yl)diazenyl)-N-(4,6-dimethylpyrimidin-2-yl) benzene sulfonamide 16

Yield: 81 %; reddish brown powder; m.p.: above 320 ^{o}C; IR (νmax, cm^{-1}): 1096, 1154, (SO_2), 1508 (N=N), 1629 (C=C), 1634 (br, 2C=O), 3240, 3259 (NH_2, OH), 3443 (br,

2OH); ^{1}H- NMR (600 MHz, $CDCl_3$/DMSO-d6) (δ/ppm): 2.26 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3. 16 (br, 2H, 2 OH phenolic), 3.78 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.46-8.10 (m, 14H, Ar–H, 2CH=CH), 9.25 (br, 1H, NH), 12.29 (br, 1H, OH enolic); ^{13}C-NMR ($CDCl_3$/DMSO-d6) (δ/ppm): 183.9 (C_5), 183.0 (C_3) 167.3 ($C_{7'''}$), 156.3 ($C_{8''',10'''}$) , 149.6 (C_1), 148.4 ($C_{5''}$), 147.9 ($C_{5'}$), 147.0 ($C_{4'}$), 146.8 ($C_{4''}$), 143.8, ($C_{4'''}$), 140.5 ($C_{1'''}$), 136.4 (C_7), 130.2 ($C_{2'''}$, $C_{6'''}$), 129.9 ($C_{1'}$), 126.5 ($C_{1''}$), 125.3 ($C_{2'''}$, $_{6'''}$), 122.8 (C_2), 119.7 ($C_{2''}$), 117.9 ($C_{2'}$), 116.3 (C_6), 116.1($C_{3'''}$,$_{5'''}$), 115.9 ($C_{3'}$), 115.8 ($C_{3''}$), 113.4 ($C_{6''}$),111.3 ($C_{6'}$), 111.2 ($C_{9'''}$), 109.0 (C_4), 55.8 (2C, OCH_3), 23.2 (2C, CH_3). MS (m/z) (rel. int.%): 657 (13.0, M^+), 498 (21.7), 214 (13.0), 145(8.7), 122.6 (34.8),105 (39.1), 77 (34.8), 80 (60), 64 (100), 55(65); Anal. Calc. for $C_{33}H_{31}N_5O_8S$: C, 60.26; H, 4.75; N, 10.65. Found: C, 60.20; H, 4.71; N, 10.98.

2.2.2. General procedure for the synthesis of 4((Z)-2-(2-(4-arylhydrazono)-(2-cyanoacetamido) benzenesulfonamide 19-23

A well stirred solution of 4-aminobenzenesulfonic acid 2 (0.87 g, 0.005 mol), *p*-aminobenzenesulphonamide **3** (0.86 g, 0.005 mol), *N*-(4-aminophenylsulfonyl) acetamide **4** (1.07 g, 0.005 mol), 1-(4-aminophenylsulfonyl) guanidine **5** (1.07 g, 0.005 mol) and 4-amino-*N*-(4,6-dimethylpyrimidin-2-yl) benzene sulfonamide **6** (1.4 g, 0.005 mol) in a mixture of concentrated HCl (3 mL) and H_2O (3 mL) was cooled in an ice bath and then a solution of $NaNO_2$ (0.4 g, 0.0058 mol in 5 mL H_2O) was added drop wise. The above cooled diazonium solution was added slowly to a well stirred solution of 4-(2-cyanoacetamido) benzene sulfonamide **18** (1.2 g, 0.005 mol) in pyridine (25 mL). The reaction mixture was stirred for 2 h. The crude product was filtered off, dried well and crystallized from EtOH/benzene to give compounds respectively **19-23**.

2.2.2.1. (E)-4-(2-(2-N-(4-aminosulfonylphenyl)-amino-1-cyano-2-oxoethylidene) hydra zinyl) benzene sulfonic acid 19

Yield, 67%; Yellow sheet; mp: 304-305 °C; IR (KBr): ν_{max}, cm^{-1}: 1155, 1329 (SO_2), 1532 (N=N), 1674 (C=O), 2222 (CN), 3181, 3233, 3325, 3397 (OH, NH_2, 2NH); ^{1}H-NMR (DMSO-d6) (δ/ppm): 6.50-8.53 (m, 8H, Ar–H), 9.76 (br, 2H, NH_2), 11.92 (br, 1H, NH=N), 12.72 (br, 1H, NHCO), 13.85 (br, 1H, HO); ^{13}C-NMR (DMSO-d6) (δ/ppm): 158.1(CO), 148.3($C_{1'}$), 143.8($C_{4'}$), 140.8(C_4), 128.5(2C, $C_{3'}$), 127.3(2C, C_2), 123.8 (2C, C_3)119.9(2C, $C_{2'}$), 115.7(CN), 109.1(NH-N=C) ; MS *m/z* (rel. int.%): 342 (M^+-SO_3H, 0.1), 223 (1.2), 197 (0.5), 97 (0.7), 79 (100), 71 (2.5), 51 (22.6), 50 (18.9. Anal. Calcd. for $C_{15}H_{13}N_5O_6S_2$: C, 42.55; H, 3.09; N, 16.54. Found: C, 42.50; H, 3.01; N, 16.64.

2.2.2.2. (E)-2-cyano-N-(4-aminosulfonylphenyl)-2-(2-(4-aminosulfonylphenyl) hydrazono)-acetamide 20

Yield, 82%; scarlet red dye; mp: above 315 °C; IR (KBr): ν_{max}, cm^{-1}: 1156, 1340 (SO_2), 1530 (N=N), 1672 (C=O), 2229 (CN), 3190, 3247, 3345, (2NH_2, 2NH); ^{1}H-NMR (DMSO-d6o(δ/ppm): 6.90-7.94 (m, 8H, Ar–H), 9.89 (br, 2H, NH_2), 11.99 (br, 1H, NH_2), 12.27 (br, 1H, NH=N), 12.67 (br, 1H, NHCO); ^{13}C-NMR (DMSO-d6) (δ/ppm): 159.1(CO), 144.2($C_{1'}$), 140.7(C_4), 139.0 (C_1), 138.8 ($C_{4'}$), 127.0 (2C, $C_{3'}$), 126.9 (2C, C_2), 126.4 (2C, C_3), 120.0 (2C, $C_{2'}$), 115.9 (CN),109.5 (NH-N=C); MS *m/z* (rel. int. %): 406 ([M^+-NH_2], 0.6), 234 (2.5), 2224 (86.0), 198 (13.0), 173 (18.2), 172 (100), 156 (62.6), 108 (53.1), 92 (88.6), 77 (23.2), 57 (18.9), 52 (21.4); Anal. Calc. for $C_{15}H_{13}N_5O_6S_2$: C, 42.65; H, 3.34; N, 19.89. Found: C, 42.60; H, 3.28; N, 19.82.

2.2.2.3. (E)-2-cyano-N-(4-aminosulfonylphenyl)-2-(2-(4-N-acetylaminosulfonylphenyl) hydrazono) acetamide 21

Yield, 82%; orange dye; mp: 305-307 °C; IR (KBr): ν_{max}, cm^{-1}: 1368, 1159 (SO_2), 1534 (N=N), 2235(CN), 1671, 1711 (2C=O), 3187, 3224, 3367 (NH_2, 3NH); ^{1}H-NMR (DMSO-d6) (δ/ppm): 1.92 (s, 3H, CH_3), 6.95-8.01 (m, 8H, Ar–H), 9.88 (br, 2H, NH_2), 11.77 (br,s, 1H, NHCO), 12.01 (br, 1H, NH=N), 12.67 (br, 1H , $NHSO_2$); ^{13}C-NMR (DMSO-d6): δ 168.5(CO_{acetyl}), 159.0 (CO), 145.7 ($C_{1'}$), 140.6 (C_4), 138.7 (C_1), 133.8 ($C_{4'}$), 129.0 (2C, $C_{3'}$), 126.4 (2C, C_2), 119.9 (2C, C_3), 115.8 (2C, $C_{2'}$), 110.3 (CN), 110.2 (NH-N=C), 23.0(CH_3). Anal. For $C_{17}H_{16}N_6O_6S_2$: C, 43.96; H, 3.47; N, 18.09. Found: C, 43.96; H, 3.47; N, 18.09.

2.2.2.4. (E)-2-cyano-N-(4-aminosulfonylphenyl)-2-(2-(4-guanidinosulfonylphenyl) hydrazono) acetamide 22

Yield, 82%; Scarlet red dye; mp: 273-275 °C; IR (KBr): ν_{max}, cm^{-1}: 1391, 1136 (SO_2), 1531 (N=N), 1630 (C=N), 1671 (C=O), 2222 (CN), 3189, 3231, 3336, 3381, 3425, (2NH_2, 4NH); ^{1}H-NMR (DMSO-d6) (δ/ppm): 3.72 (br, 1H, NH=C), 7.02 (br, 2H, C-NH_2), 7.61-8.34 (m, 8H, Ar–H), 8.80 (br, 1H, NH-SO_2), 8.81 (br, 2H, SO_2NH_2), 9.88 (br, 1H, NH=N) 11.83 (br, 1H , NHCO); ^{13}C-NMR (DMSO-d6) (δ/ppm): 159.6 (CO) , 143.5 (C=NH), 142.0 ($C_{1'}$), 140.9 (C_4), 138.6 (C_1), 126.7 ($C_{4'}$), 126.3 (2C, $C_{3'}$), 126.2 (2C, C_2), 119.9 (2C, C_3), 115.4 (2C, $C_{2'}$), 110.7. (CN), 108.0 (NH-N=C); MS: m/z (rel. int.%): 438 ([M^+-CN], 14.6), 373 (1.3), 272 (12.2), 320 (2.6), 268 (4.8), 249 (2.3), 223 (10.4), 172 (65.9), 156 (42.1), 108 (24.4), 92 (42.5), 85 (48.4), (58.5), 71 (51.5), 57 (100), 52 (3.2); Anal. for $C_{16}H_{16}N_8O_5S_2$: Calc. C, 41.37; H, 3.47; N, 24.12. Found: C, 41.30; H, 3.41; N, 24.20.

2.2.2.5. (E)-2-cyano-N-(4-aminosulfonylphenyl)-2-(2-(4-N-(4,6-dimethylpyrimidin-2-yl) aminosulfonylphenyl)-hydrazono) acetamide 23

Yield, 82%; orange dye; mp: above 315 °C; IR (KBr): ν_{max}, cm^{-1}: 1157, 1337, (SO_2), 1523 (N=N), 1625 (C=N), 1677 (C=O), 2217(CN), 3185, 3237, 3364 (2NH_2, 4NH),). ^{1}H-NMR (DMSO-d6) (δ/ppm): 2.24 (br, s, 6H, 2CH_3), 6.55(s, 1H, $CH_{pyrimidine}$), 7.01-7.87 (m, 10H, Ar–H, NH_2), 8.87 (br, 1H, NH), 9.92 (br, 1H, NHCO), 12.00 (s,1H, NH-N=C); ^{13}C-NMR (DMSO-d6) (δ/ppm): 167.1($C_{2\ pyrimiidine}$), 159.2 (2C, $C_{4,6\ pyrimiidine}$), 156.1 (CO), 145.8 ($C_{1'}$), 141.3 (C_4), 138.7 (C_1), 129.4 ($C_{4'}$), 127.0 (2C, $C_{3'}$), 126.2 (2C, C_2), 120.0 (2C, C_3), 115.4 (2C, $C_{2'}$), 113.3 (CN), 110.4 ($C_{5\ pyrimiidine}$), 109.7 (NH-N=C), 22.9(2C, 2CH_3). MS: *m/z* (rel. int.%): 328 (0.1, M^+- 4-*N*-carbonylaminobenzenesulfon-amide), 260 (0.5), 221 (0.6), 199 (0.5, 4-N-carbonylaminobenzenesulfonamide), 191 (0.8), 172 (4.5), 126(19.8), 98 (11.6), 82(13.9), 77 (100), 71 (20.5), 52 (41.3); Anal. for $C_{21}H_{20}N_8O_5S_2$: C, 47.72; H, 3.81; N, 21.20. Found: C, 47.66; H, 3.75; N, 21.14.

2.3. Pharmacological Studies

More details about the ABTS Screening Assay [24] and the Bleomycin-dependent DNA damage assay [25, 26] are presented in literature [19-22].

3. RESULTS AND DISCUSSION

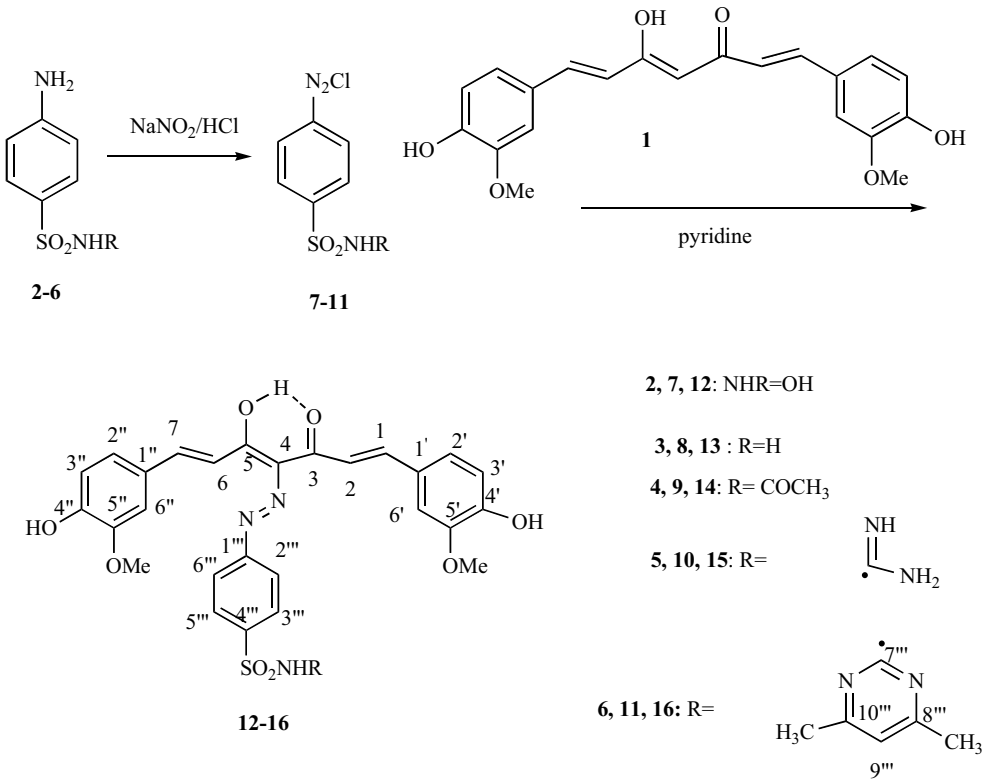
3.1. Chemistry

The synthetic strategies adopted to obtain the corresponding sulpha derivatives are depicted in Schemes **1** and **2**. Fadda *et al*. [23], synthesized a new azodisperse dyes *via* coupling of curcumin **1** different aromatic diazonium chlorides. These dyes are capable of dyeing different types of fibers, also they showed a wide spectrum of biological activity [23]. Consequently, the authors decided to couple the diazonium salts of different sulpha drugs with curcumin **1**, aiming to reach a more potent antioxidant agent. Thus, curcumin **1** coupled with the diazonium salts **7-11** to afford the corresponding 4-arylazo derivatives **12-16** (Scheme **1**).

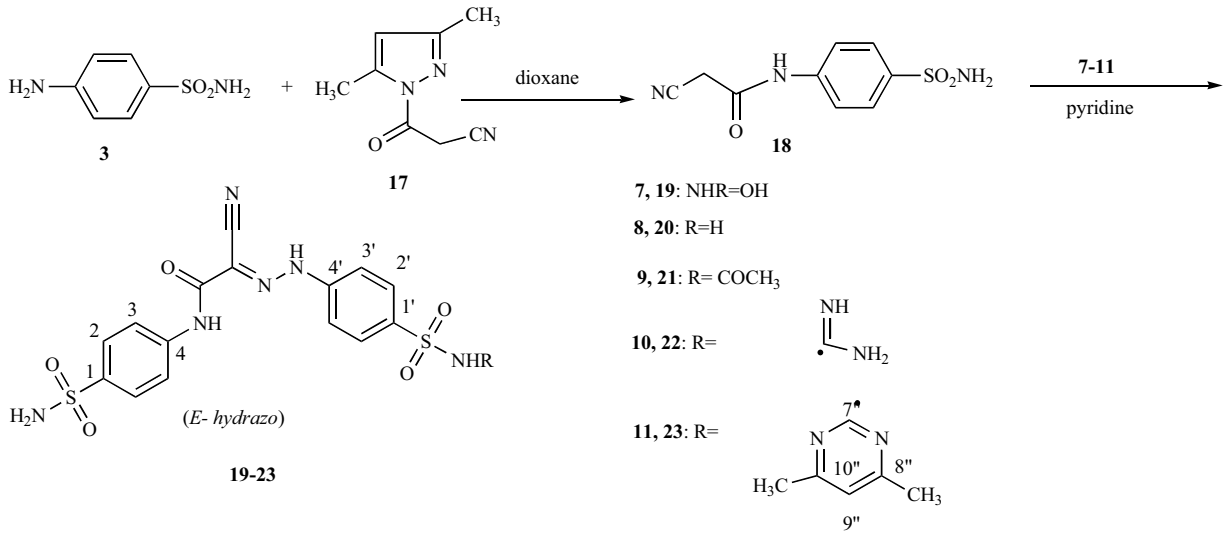
The structure of curcumin derivatives **12-16** was elucidated based on its analytical and spectral data. The analytical and spectral data of curcumin derivatives **12-16** showed clearly that compounds **12-16** were found in the enolazo-forms. IR spectrum of compound **16** taken as a typical example of series prepared, revealed absorption bands at (1096, 1154), 1508, 1629, 1634 (br) and (3240, 3259, 3443) cm^{-1} corresponding to SO_2, N=N, C=C and 2C=O, (3OH, NH) groups, respectively. Its ^{1}H-NMR spectrum displayed four singlet signals at δ= (2.26, 2.30) and (3.78, 3.92) ppm due to methyl and methoxy protons respectively, three broad signals at δ 3.16, 9.25, 12.29 ppm due to 2phenolic OH, NH and enolic OH protons respectively and the aromatic protons at δ = 6.46-8.10. Furthermore, ^{13}C-NMR spectrum showed three signals at δ 109.0, 55.8 and 23.2 ppm due to (C_4), (2C, OCH_3) and (2C, CH_3). Its mass spectrum displayed the molecular ion peak at m/z 657 corresponding to a molecular formula $C_{33}H_{31}N_5O_8S$.

Furthermore, coupling reaction of **18**, which was prepared in a high yield and purity *via* cyanoacetylation of **3** with 3, 5-dimetyl-1-cyanoacetyl Pyrazole **17** [27] through the modification of the reported procedure [28] with of diazonium salts **7-11** to afford the corresponding *E*-hydrazo derivatives **19-23** (Scheme **2**).

The analytical and spectral data of Sulfonamide derivatives **19-23** showed clearly that compounds **19-23** were found in the *E*-hydrazo forms. Compound **25** was taken as a typical example of the series prepared, revealed absorption bands in the IR spectrum at (3425, 3381, 3336, 3231, 3189) 2222, 1671, 1630 1531 and (1391, 1136) cm^{-1} corresponding to ($2NH_2$, 4NH), (CN), (C=O), (C=N), (N=N) and (SO_2) functions, respectively. Its ^{1}H-NMR spectrum showed six broad singlet signals at δ 3.72, 7.02, 8.80, 8.81, 9.88 and 11.83 ppm due to NH=C, C-NH_2, NH=N, NH-SO_2, SO_2NH_2 and NHCO protons in addition to aromatic protons at δ 7.61-8.34 ppm. Furthermore, its ^{13}C-NMR signals at 110.7 at 108.0 due to (CN), (NH-N=C) carbons respectively. Moreover, its mass spectrum showed the molecular ion peak at m/z 438 (M^+-CN) which in agreement with the molecular formula $C_{16}H_{16}N_8O_5S_2$.



Scheme 1. Synthesis of curcumin derivatives **12-16**.



Scheme 2. Synthesis of sulfonamide derivatives **19-23**.

3.2. Pharmacology

3.2.1. ABTS Antioxidant Assay

The newly synthesized compounds were screened for their antioxidant activity using ABTS method which was reported by Lissi *et al*. [24].

The results, Table **1**, Showed that most of compounds anchored to curcumin moiety **12-16** displayed good antioxidant compared with ascorbic acid as shown in Table **1**.

On the other hand, curcumin **1** exhibited higher activity than the ascorbic acid. Furthermore, compounds **18**, **20** and **22** have good antioxidant activity. Whereas, compound **21**

Table 1. Assay for ABTS Antioxidant activity and Bleomycin-dependent DNA damage.

Compound No.	Absorbance	ABTS %Inhibition	Bleomycin-dependent DNA damage Absorbance
Control	0.500	0.00	-----
Ascorbic Acid	0.061	87.80	0.062
1	0.011	97.78	0.052
3	0.418	16.40	0.086
12	0.129	75.42	0.094
13	0.120	77.14	0.052
14	0.131	75.04	0.088
15	0.066	87.42	0.105
16	0.091	82.66	0.077
18	0.089	82.20	0.750
19	0.398	20.40	-------
20	0.058	88.40	0.055
21	0.162	67.60	------
22	0.079	84.20	0.083
23	0.320	36.00	-------

% Inhibition= [A (control) - A (test)/ A (control)] X 100 Eqn. (1)
A (control): Absorbance for ascorbic acid
A (test): Absorbance for the tested samples
Control: Ascorbic acid.

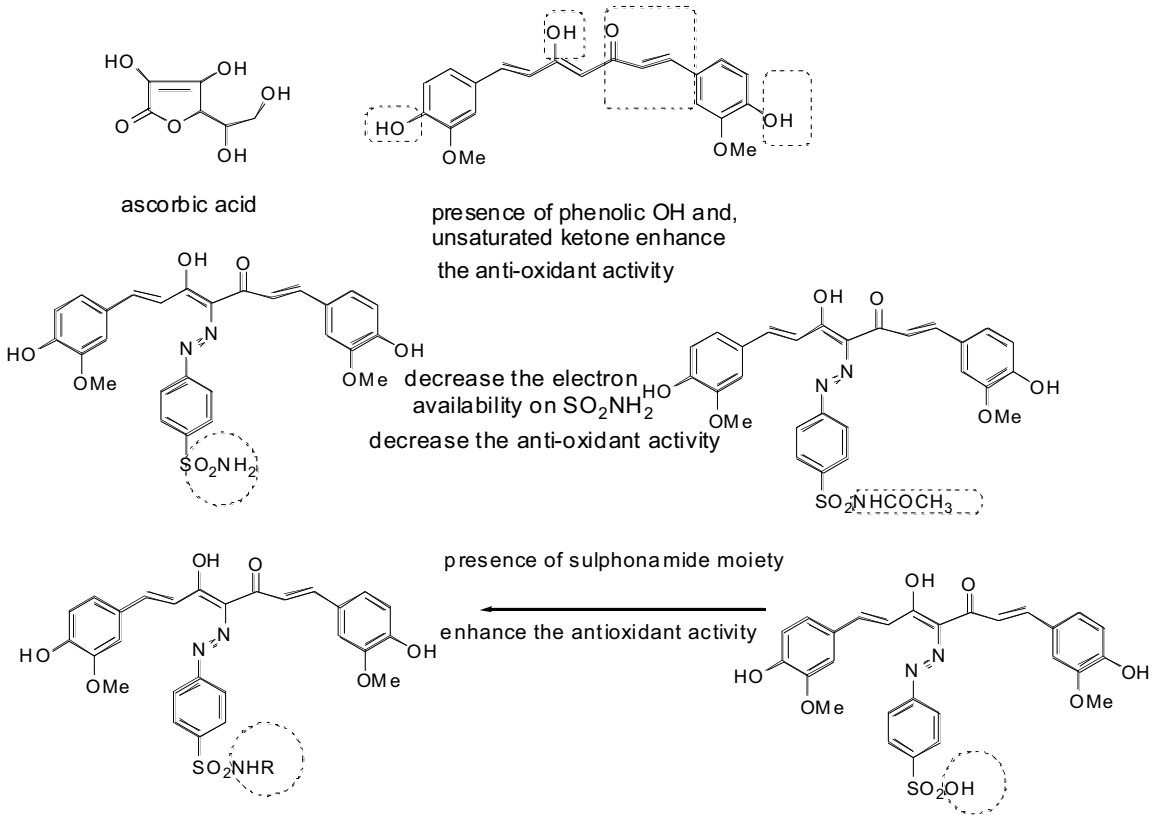


Fig. (1). Structure activity relationship of the more potent antioxidant compounds.

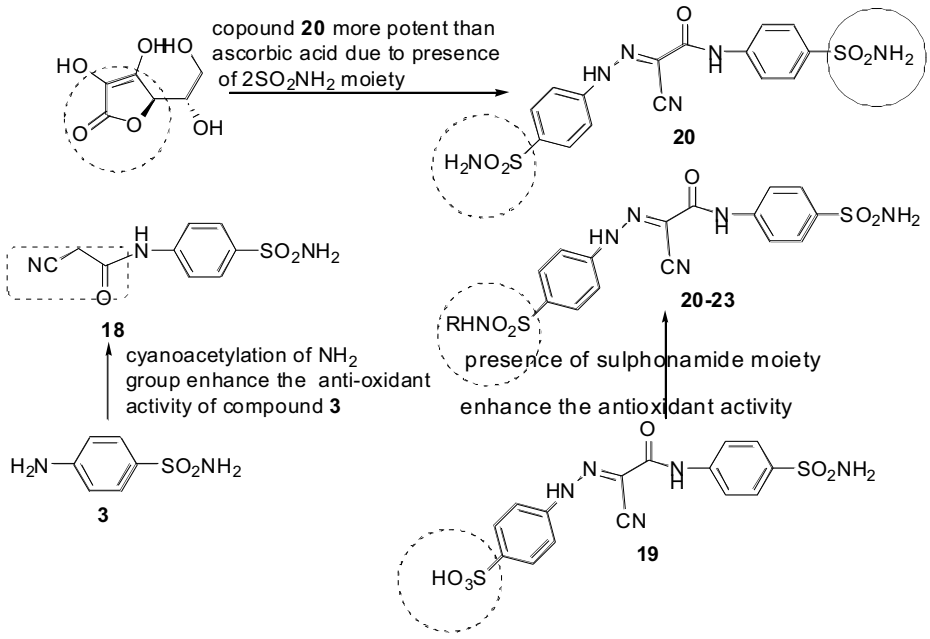


Fig. (2). Structure activity relationship of the more potent antioxidant compounds.

has moderate antioxidant activity and the rest of compounds have weak activities.

3.3. Bleomycin-dependent DNA Damage Assay

Furthermore, the protective activity against DNA damage induced by bleomycin iron complex was examined for the more potent anti-oxidant compounds **1, 12, 13, 14, 15, 16, 18, 20** and **22**. The results in Table **1** showed that compounds **1** (0.052) and **20** (0.055) exhibited high protection against DNA damage induced by the bleomycin iron complex than Ascorbic acid, thus, diminishing chromogen formation between the damaged DNA and TBA molecules [27, 28].

By comparing the results obtained for the antioxidant properties of the reported compounds with their structures, the following structure activity relationships (SAR's) were postulated (Figs. **1**, **2**): (i) Curcumin **1** (97.78%) and **20** (88.40%) are more potent than ascorbic acid which may be attributable to the presence of phenolic OH, α,β-unsaturated ketone or $2SO_2NH_2$ moieties (ii) Compounds **14** (75.04%) is less potent than compound **13** (77.14%), which may be due to the decrease in the electron availability of SO_2NH_2 moiety (iii) Compounds **13** (77.14%), **15** (87.42) and **16** (82.66%) are potent than compound **12** (75.42%), which may be due to the presence of sulphonamide moiety. (iv) Compound **16** (82.66%) exhibited good antioxidant activity than the azo derivatives which may be due to the presence of NH_2-C=NH moiety (Fig. **2**). (v) Cyanoacetamide **18** (82.20%) was more potent than compound **3** which may be attributed to the presence of cyanoacetamide moiety. (vi) Compounds **20-23** (88.40-36.00%) was more potent than compound **19** (20.40%), which may be attributed to the replacement of SO_3H by SO_2NHR moiety.

CONCLUSION

The objective of the present study was to synthesize and evaluate the antioxidant activity of some novel sulfonamides structure hybrids incorporating either curcumin or *N*-[4-(aminosulfonyl) phenyl]-2-cyanoacetamide moiety with the hope of discovering new structure serving as antioxidant agent. The data showed clearly that most of the compounds displayed good *in vitro* antioxidant activities.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Srivastava, R.; Srimal, R.C. Modification of certain inflammation-induced biochemical changes by curcumin. *Ind. J. Med. Res*., **1985**, *81*, 215-223.

[2] Ruby, A.J.; Kuttan, G.; Babu, K.D.; Rajasekharan, K.N.; Kuttan, R. Anti-tumour and antioxidant activity of natural curcuminoids. *Cancer Lett*., **1995**, *94*, 79-83.

[3] Li, C.J.; Zhang, L.J.; Dezube, B.J.; Crumpacker, C.S.; Pardee, A.B. Three inhibitors of type 1 human immunodeficiency virus long terminal repeat-directed gene expression and virus replication. *Proc. Natl. Accad Sci. USA*, **1993**, *90*, 1839-1842.

[4] Costa, D.; Gomes, A.; Lima, J.L.F.C.; Fernandes, E. Singlet oxygen scavenging activity of non-steroidal anti-inflammatory drugs. *Redox. Rep*., **2008**, *13*, 153-160.

[5] Costa, D.; Vieira, A.; Fernandes, E. Dipyrone and aminopyrine are effective scavengers of reactive nitrogen species. *Redox Rep*., **2006**, *11*(3), 136-142.

[6] Zhao, B.L.; Li, X.J.; He, R.G.; Cheng, S.J.; Xin, W.J. Scavenging effect of extracts of green tea and natural antioxidants on active oxygen radicals. *Cell Biophys*., **1989**, *14*, 175-185.

[7] Unnikrishnan, M.K.; Rao, M.N.A. Curcumin inhibits nitrogen dioxide induced oxidation of hemoglobin. *Mol. Cell. Biochem.,* **1995**, *146*, 35-37.

[8] Subramanian, M.; Sreejayan, N.; Rao, M.N.A.; Devasagayam, T.P.A.; Singh, B.B. Diminution of singlet oxygen-induced DNA damage by curcumin and related antioxidants. *Mutat. Res*., **1994**. *311*, 249-255.

[9] Fadda, A.A.; Bondock, S.; Rabie, R.; Etman, H.A. Cyanoacetamide derivatives as synthons in heterocyclic synthesis. *Turk. J. Chem*., **2008**, *32*, 259-260.

[10] El-Gaby, M.S.A.; Atalla, A.A.; Gaber, A.M.; Abd Al-Waha, K.A. Studies on aminopyrazoles: Antibacterial activity of some novel pyrazolo[1,5-a] pyrimidines containing sulfonamido moieties. *IL Farm*., **2000**, *55*, 596-602.

[11] El-Gaby, M.S.A.; Gaber, A.M.; Atalla, A.A.; Abd Al-Waha K.A. Novel synthesis and antifungal activity of pyrrole and pyrrolo[2,3-d]pyrimidine derivatives containing sulfonamido moieties. *IL Farm*., **2002**, *57*, 613-617.

[12] Maren, T.H. Relations between structure and biological activity of sulfonamides. *Annu. Rev. Phurmacol. Toxicol*., **1976**, *16*, 309-327.

[13] Roadman, C.M.; Aviv, G.L. Preparation of N-benzyl-3-aryl-2-cyanoacrylamides activity for treatment of neoplastic disorders. WO Patent 0055128, 2000.

[14] El-Bialya, S.A.A.; Gouda, M.A. Cyanoacetamide in heterocyclic chemistry: Synthesis, antitumor and antioxidant activities of some new benzothiophenes. *J. Heterocyclic. Chem.,* **2011**, *48*, 1280-1286.

[15] Green, O.M.; McKenzie, A.R.; Otterbein, L.R. Inhibitors of the acetyltransferase domain of N-acetylglucosamine-1-phosphate-uridylyltransferase/glucosamine-1-phosphate-acetyltransferase (GlmU). Part 2: Optimization of physical properties leading to antibacterial aryl sulfonamides. *Bioorg. Med. Chem. Lett*., **2012**, *22*, 7019-7023.

[16] Ezabadi, I.R.; Camoutsis, C.; Zoumpoulakis, P.; Geronikaki, A.; Soković, M.; Glamočilija, J.; Čirič, A. Sulfonamide-1,2,4-triazole derivatives as antifungal and antibacterial agents: Synthesis, biological evaluation, lipophilicity and conformational studies. *Bioorg. Med. Chem*., **2008**, *16*, 1150-1161.

[17] Ma, T.; Fuld, A.D.; Rigas, J.R.; Hagey, A.E.; Gordon, G.B.; Dmitrovsky, E.; Dragnev, K.H. A phase I trial and *in vitro* studies combining ABT-751 with carboplatin in previously treated non-small cell lung cancer patients. *Chemotherapy*, **2012**, *58*, 321-329.

[18] Roush, W. R.; Gwaltney, S.L.; Cheng, J.; Scheidt, K.A.; McKerrow, J.H.; Hansell, E. Vinyl sulfonate esters and vinyl sulfonamides: potent, irreversible inhibitors of cysteine proteases. *J. Am. Chem. Soc*., **1998**, *120*, 10994-10995.

[19] Gouda, M.A. Synthesis and antioxidant evaluation of some new pyrazolopyridine derivatives. *Arch. Pharm*., **2012**, *345*, 155-162.

[20] Gouda, M.A.; Berghot, M.A.; Baz, E.A.; Hamama, W.S. Synthesis, antitumor and antioxidant evaluation of some new thiazole and thiophene derivatives incorporated coumarin moiety. *Med. Chem. Res*., **2012**, *21*, 1062-1070.

[21] Gouda, M.A.; Abu-Hashem, A.A. Synthesis, characterization, antioxidant and antitumor evaluation of some new thiazolidine and thiazolidinone derivatives. *Arch. Pharm*., **2011**, *344*, 170-177.

[22] Hamama, W.S.; Berghot, M.A.; Baz, E.A.; Gouda, M.A. Synthesis and antioxidant evaluation of some new 3-substituted coumarins. *Arch. Der. Pharm*., **2011**, *344*, 710-718.

[23] Fadda, A.A.; Badria, F.A.; Elattar, K.M. Synthesis and evaluation of curcumin analogues as cytotoxic agents. *Med. Chem. Res*., **2010**, *19*, 413-430.

[24] Lissi, E.A.; Modak, B.; Torres, R.; Esocbar, J.; Urzua, A. Total antioxidant potential of resinous exudates from Heliotropium species, and a comparison of the ABTS and DPPH methods. *Free Radic. Res*., **1999**, *30*, 471-477.

[25] Gutteridge, J.M.C.; Rowley, D.A.; Halliwell, B. Superoxide-dependent formation of hydroxyl radicals in the presence of iron salts. Detection of 'free' iron in biological systems by using bleomycin-dependent degradation of DNA. *Biochem. J*., **1981**, *199*, 263-265.

[26] Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki,T.; Miyata, N. New series of antiprion compounds: pyra-

zolone derivatives have the potent activity of inhibiting protease-resistant prion protein accumulation. *J. Med. Chem*., **2007**, *50*, 5053-5056.

[27] Gorobets, Y.N.; Yousefi, B.H.; Belaj, F.; Kappe, C.O. Rapid microwave-assisted solution phase synthesis of substituted 2-pyridone libraries. *Tetrahedron*, **2004**, *60*, 8633-8644.

[28] Elham S.; Darwish, A.-.F.; Azza, M.; Attaby, F.A.; Al-Shayea, O.N. Synthesis and antimicrobial evaluation of some novel thiazole, pyridone, pyrazole, chromene, hydrazone derivatives bearing a biologically active sulfonamide moiety. *Int. J. Mol. Sci*., **2014**, *15*, 1237-1254.