International Journal of Advanced Research in Chemical Science (IJARCS)
Volume 3, Issue 9, September 2016, PP 29-36
ISSN 2349-039X (Print) & ISSN 2349-0403 (Online)
http://dx.doi.org/10.20431/2349-0403.0309004
www.arcjournals.org

Synthesis and Biological Activities Evaluation of New Spiro Heterocycles Containing 1,2,4-Triazole, Piperidine and Sulfonamide Moieties

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Abstract: *A newseries of novel substituted 1,2,4,8-tetraazaspiro[4.5]dec-2-enes have been synthesized from the reaction of 4-piperidone oximes having 1-methyl, 1-benzyl, and 1-isopropyl groups with appropriate nitrilimines. The microanalysis and spectroscopical data (IR, ^1H NMR, ^{13}C NMR and MS) of the synthesized compounds are in full agreement with their molecular structure. The microbial features of the synthesized compounds were studied by a known method.Some of titled compounds exhibited significant antimicrobial activity on several strains of microbes.*

Keywords: *Antimicrobial activity, nitrilimines, piperidine, sulfonamide, 1,2,4-triazole.*

1. Introduction

The interest in the chemistry of hydrazonoyl halides is a consequence of the fact that they undergo a wide variety of reactions which provide routes to many of heterocyclic and spiro heterocyclic compounds [1-4]. Spiro heterocyclic compounds possess various pharma-cological properties and hence their synthesis is of interest to organic chemists. Such compounds display pronounced antimicrobial [5], analgesic [6], anti-inflammatory [6], antimycobacterial [7], antifungal [8], antitumor [9,10] and antiviral [9,10] activities. Among these heterocycles, spiro azoles have been identified as privileged structures in medicinal chemistry and have attracted increasing interest in the recent years [11-14].

A survey of the literature has shown that compounds having azole derivatives to possess diverse biological activity and are widely used in a medicinal chemistry [15-18]. The 1,2,4-triazole derivatives has received a considerable attention in view of their diverse pharmacological activities [19-22] such as antimicrobial [23,24] sedative, anticonvulsant [25], anti-inflammatory properties [26]and anticancer agents. They are also use as intermediates in obtaining colour photosensitive materials as well as toners, inks and other photographic materials such as magenta coupler in a photosensitive emulsion layer [27-30]. The most developed procedure for construction of spirocompounds depends mainly on 1,3-dipolar cycloadditions to exocyclic double bonds [31]. Recently, we described a versatile and efficient one-pot synthesis of hexa and octaazadispiroheterocyclic compounds utilizing 1,4-cyclohexanedione oxime or methyl hydrazones and nitrilimines, generated in situ from the corresponding hydrazonoyl halides by the action of a suitable base [32,33].

In continuation of our research studies dealing with the utility of hydrazonoyl halides for the synthesis of various heterocyclic ring and spiroheterocyclic systems via 1,3-dipolar cycloaddition methodology [34-40],it was of interest to study a facile synthesis of 1,2,4,8-tetraazaspiro[4.5]dec-2-enes from the reaction of 1-substituted-4-piperidone oximes with hydrazonoyl chlorides having sulfonamide moiety. Our objective after such synthesis was to investigate their biological activities as antimicrobial agents.

2. Material and Methods

2.1. Apparatus and Chemicals

Melting points were determined using an electro thermal melting temperature apparatus and are uncorrected. The IR spectra were measured as KBr pellets using a Satellite 3000 Mid infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at r. t. in DMSO-d_6 solution u sing tetramethylsilane (TMS) as internal reference. Chemical shifts are expressed in δ (ppm) downfield from TMS and coupling constants are in Hertz (Hz). Electron impact (EI) mass spectra were run on a Shimadzu GCMS-QP1000 EX spectrometer at 70 eV. Elemental analysis were carried out at micro analytical laboratory, Cairo University, Cairo, Egypt. 1-Methyl, 1-benzyl and 1-isopropyl-4-piperidone was purchased from Avocado Research Chemicals, England, and used without further purification.

Hydrazonoyl chlorides **1** employed in this study, were prepared via direct coupling of the appropriate sulfa drug diazonium chloride with 3-chloroacetylacetone or phenacyl chloride or α-chloroacetoacetanilide or α-bromo-2-acetylfuran or α-bromo-2-acetylthiophene or ω-bromoacetonaphthone in sodium acetate/ethanol solution following standard procedures [41]. 1-substituted-4-piperidone oximes **3** were obtained by reacting the appropriate 1-substituted-4-piperidone with hydroxylamine hydrochloride in excess following reported procedures [37,42].

2.2. Synthesis of 1,2,4,8-tetraazspiro[4.5]dec-2-enes (General procedure)

To a stirred solution of hydrazonoyl halides **1** (5 mmol) and 1-substituted-4-piperidone oximes **3** (10 mmol) in 1,4-dioxane (50-70 ml), triethylamine (5 mmol) in 1,4-dioxane (10 ml) dropwise added at room temperature. Stirring was continued to reaction completion for 12-24 hours (monitoring the reaction progress by TLC). The solvent was then removed under vacuum, and the residual solid was washed with water (100 ml) to get rid of the triethylamine salt. In some cases the residue was extracted with chloroform (3x30 ml) and the combined extracts were washed with water (50 ml), dried over anhydrous sodium sulfate. The solvent ($CHC1_3$) was evaporated in vacuum, and the crude product was triturated with ethanol (10-20 ml). The crude solid products were collected and recrystallized from appropriate solvents to afford the desired compounds **4a-u**.The following compounds were prepared using this method:

3-Acetyl-8-methyl-l-[4-(thiazol-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene4a: Yield 75%, m.p. 188-190 °C (ethanol). Anal. Calcd for $C_{18}H_{22}N_6O_3S_2$ (434.54): C 49.75%, H 5.10%, N 19.34%. Found: C 49.56%, H 4.98%, N 19.47%; MS: ($M^{+\cdot}$ = 343); IR, v/cm^{-1}: 3380, 3347 (NH's), 1689 (C=O), 1620 (C=N), 1347, 1156 (SO_2); ^{1}H NMR, δ/ppm: 11.61 (s, 1H, SO_2NH), 8.76 (d, 1H thiazole ring), 7.38-7.21 (m, 4H, Ar-H), 6.62 (d, 1H thiazole ring), 5.65 (s, 1H, NH), 2.82-1.80 (m, 8H, $4CH_2$) 2.56 (s, 3H, CH_3CO), 2.41 (s, 3H, NCH_3);^{13}C NMR (DMSO-d_6): δ/ppm 189.60 (C=O), 147.34 (C=N), 166.7-115.20 (Ar-C and thiazole-C),90.12 (spiro carbon), 52.89 ($2CH_2$),46.60 (NCH_3), 32.20 ($2CH_2$), 26.25 (CH_3)

3-Acetyl-8-isopropyl-l-[4-(thiazol-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene4b: Yield 72%, m.p. 193-195 °C (ethanol). Anal. Calcd. for $C_{20}H_{26}N_6O_3S_2$ (462.60): C 51.93%, H 5.67%, N 18.17%. Found: C 52.18%, H 5.80%, N 18.05%; MS: ($M^{+\cdot}$ = 462); IR, v/crn^{-1}: 3377, 3345 (NH's), 1687 (C=O), 1621 (C=N), 1346, 1154 (SO_2); ^{1}H NMR, δ/ppm: 11.64 (s, 1H, SO_2NH), 8.72 (d, 1H thiazole ring), 7.36-7.20 (m, 4H, Ar-H), 6.64 (d, 1H thiazole ring), 5.62 (s, 1H, NH), 2.86-1.82 (m, 8H, $4CH_2$) 2.56 (s, 3H, CH_3CO), 2.43 (1H, m, CH), 1.25 (6H, d, $2CH_3$). ^{13}C NMR (DMSO-d_6): δ/ppm 189.60 (C=O), 147.34 (C=N), 166.7-115.20 (Ar-C and thiazole-C),90.05 (spiro carbon), 52.87 ($2CH_2$),47.60 (NCH), 32.20 ($2CH_2$), 27.80 ($2CH_3$), 26.24 (CH_3).

3-Acetyl-8-benzyl-l-[4-(thiazol-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene 4c: Yield 75%, m.p. 176-178 °C (ethanol). Anal. Calcd for $C_{24}H_{26}N_6O_3S_2$ (510.64): C 56.45%, H 5.13%, N 16.46%. Found:C 56.20%, H 5.02%, N 16.33%; MS: ($M^{+\cdot}$ = 510); IR, v/cm^{-1}: 3375, 3344 (NH's), 1689 (C=O), 1622 (C=N), 1347, 1153 (SO_2); ^{1}H NMR, δ/ppm: 11.61 (s, 1H, SO_2NH), 8.76 (d, 1H thiazole ring), 7.38-7.21 (m, 4H, Ar-H), 6.62 (d, 1H thiazole ring), 5.65 (s, 1H, NH), 3.26 (2H, s, CH_2Ph), 2.82-1.83 (m, 8H, $4CH_2$) 2.56 (s, 3H, CH_3CO). ^{13}C NMR (DMSO-d_6): δ/ppm 189.60 (C=O), 147.34 (C=N), 166.97-115.24 (Ar-C and thiazole-C),90.10 (spiro carbon), 52.80 ($2CH_2$), 50.10 (CH_2Ph), 32.22 ($2CH_2$), 26.16 (CH_3)

3-Acetyl-8-methyl-l-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene4d: Yield 70%, m.p. 182-184 °C (ethanol). Anal. Calcd for $C_{19}H_{23}N_7O_3S$ (429.50): C 53.13%, H 5.40%, N 22.83%. Found:C 52.90%, H 5.53%, N 22.96%; MS: ($M^{+\cdot}$ = 429); IR, v/cm^{-1}: 3380, 3346 (NH's), 1690 (C=O), 1624 (C=N), 1344, 1152 (SO_2); ^{1}H NMR, δ/ppm: 11.65 (s, 1H, SO_2NH), 8.86 (d, 2H pyrimidine ring), 7.37-7.18 (m, 4H, Ar-H), 6.89 (t, 1H pyrimidine ring), 5.67 (s, 1H, NH), 2.81-1.80 (m, 8H, $4CH_2$) 2.55 (s, 3H, CH_3CO). 2.40 (s, 3H, NCH_3) ppm. ^{13}C NMR (DMSO-d_6): δ = 189.82 (C=O), 147.62 (C=N), 167.90-110.32 (Ar-C and pyrimidine-C), 90.14 (spiro carbon), 53.10 ($2CH_2$),46.62 (NCH3), 32.21 ($2CH_2$), 26.24 (CH_3).

3-Acetyl-8-isopropyl-l-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene4e: Yield 77%, m.p. 202-204 °C (methanol). Anal. Calcd for $C_{21}H_{27}N_7O_3S$ (457.56): C 55.13%, H 5.95%, N 21.43%. Found: C 54.90%, H 6.05, N 21.30%; MS: ($M^{+\cdot}$ = 457); IR, v/cm^{-1}: 3370, 3342 (NH's), 1688 (C=O), 1621 (C=N), 1340, 1151 (SO_2); ^{1}H NMR, δ/ppm: 11.65 (s, 1H, SO_2NH), 8.86 (d, 2H pyrimidine ring), 7.37-7.18 (m, 4H, Ar-H), 6.89 (t, 1H pyrimidine ring), 5.67 (s, 1H, NH),2.86-1.83 (m, 8H, $4CH_2$) 2.56 (s, 3H, CH_3CO) 2.35 (m, 1H, CH), 1.26 (s, 6H, $2CH_3$);^{13}C NMR (DMSO-d_6): δ = 189.76 (C=O), 147.66 (C=N), 167.87-110.23 (Ar-C and pyrimidine-C),90.10 (spiro carbon), 53.12 ($2CH_2$), 47.60 (CH), 32.20 ($2CH_2$), 27.45 ($2CH_3$).

3-Acetyl-8-benzyl-l-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene 4f: Yield 75%, m.p. 216-218 °C (methanol). Anal. Calcd. for $C_{25}H_{27}N_7O_3S$ (505.60): C 59.39%, H 5.38%, N 19.39%. Found: C 59.60%, H 5.26%, N 19.27%; MS: ($M^{+\cdot}$= 505); IR, v/cm^{-1}: 3378, 3344 (NH's), 1689 (C=O), 1620 (C=N), 1345, 1150 (SO_2); ^{1}H NMR, δ/ppm: 11.65 (s, 1H, SO_2NH), 8.86 (d, 2H pyrimidine ring), 7.37-7.18 (m, 4H, Ar-H), 6.89 (t, 1H pyrimidine ring), 5.67 (s, 1H, NH), 3.25 (s, 2H, $PhCH_2$), 2.86-1.83 (m, 8H, $4CH_2$) 2.56 (s, 3H, CH_3CO). ^{13}C NMR (DMSO-d_6): δ = 189.62 (C=O), 147.64 (C=N), 167.90-110.32 (Ar-C and pyrimidine-C), 90.12 (spiro carbon),53.16 ($2CH_2$),50.05 ($PhCH_2$), 32.24 ($2CH_2$), 26.21 (CH_3).

3-Benzoyl-8-methyl-l-[4-(thiazol-2-yl-sulfonyl) phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene4g: Yield 72%, m.p. 234-236 °C (methanol). Anal. Calcd for $C_{23}H_{24}N_6O_3S_2$ (496.61): C 55.63%, H 4.87%, N 16.92%. Found: C 55.40%, H 4.76%, N 17.06%; MS: ($M^{+\cdot}$ = 496); IR, v/cm^{-1}: 3367, 3342 (NH's), 1655 (C=O), 1615 (C=N), 1346, 1152 (SO_2); ^{1}H NMR, δ/ppm: 11.61 (s, 1H, SO_2NH), 8.76 (d, 1H thiazole ring), 7.38-7.21 (m, 4H, Ar-H), 6.62 (d, 1H thiazole ring), 5.65 (s, 1H, NH), 2.82-1.83 (m, 8H, $4CH_2$) 2.36 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6): δ/ppm 184.64 (C=O), 147.78 (C=N), 167.27-115.21 (Ar-C and thiazole-C),90.00 (spiro carbon), 53.102 ($2CH_2$),46.65 (NCH_3), 32.10 ($2CH_2$).

3-Benzoyl-8-isopropyl-l-[4-(thiazol-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene4h: Yield 68%, m.p. 225-227 °C (ethanol). Anal. Calcd for $C_{25}H_{28}N_6O_3S_2$ (524.67): C 57.23%, H 5.38%, N 16.02%. Found: C 57.50%, H 5.50%, N 15.90%; MS: ($M^{+\cdot}$ = 524); IR, v/cm^{-1}: 3365, 3341 (NH's), 1656 (C=O), 1612 (C=N), 1345, 1152 (SO_2); ^{1}H NMR, δ/ppm: 11.61 (s, 1H, SO_2NH), 8.76 (d, 1H thiazole ring), 7.38-7.21 (m, 4H, Ar-H), 6.62 (d, 1H thiazole ring), 5.65 (s, 1H, NH), 2.90-1.68 (m, 8H, $4CH_2$) 2.42 (s, 3H, CH), 1.3 (s, 6H, $3CH_3$);^{13}C NMR (DMSO-d_6): δ/ppm 184.60 (C=O), 147.84 (C=N), 167.17-115.14 (Ar-C and thiazole-C),89.90 (spiro carbon), 53.20 ($2CH_2$),47.60 (CH), 31.80 ($2CH_2$), 27.46 ($2CH_3$).

3-Benzoyl-8-benzyl-l-[4-(thiazol-2-yl-sulfonyl) phenyl]-l,2,4,8-tetraazaspiro[4.5] dec-2-ene4i: Yield 66%, m.p. 213-215 °C (ethanol). Anal. Calcd for $C_{29}H_{28}N_6O_3S_2$ (572.71): C 60.82%, H 4.93%, N 14.67%. Found: C 61.06%, H 5.05%, N 14.55%; MS: ($M^{+\cdot}$= 572); IR, v/crn^{-1}: 3365, 3338 (NH's), 1654 (C=O), 1614 (C=N), 1344, 1153 (SO_2); ^{1}H NMR, δ/ppm: 11.61 (s, 1H, SO_2NH), 8.76 (d, 1H thiazole ring), 7.38-7.21 (m, 4H, Ar-H), 6.62 (d, 1H thiazole ring), 5.55 (s, 1H, NH), 3.36 (s, 2H, $PhCH_3$), 2.82-1.83 (m, 8H, $4CH_2$). ^{13}C NMR (DMSO-d_6): δ/ppm 184.52 (C=O), 147.81 (C=N), 167.12-115.18 (Ar-C and thiazole-C),89.82 (spiro carbon), 53.10 ($2CH_2$),50.05 ($PhCH_2$), 31.86 ($2CH_2$).

8-Methyl-3-phenylaminocarbonyl-l-[4-(thiazol-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraaza-spiro[4.5]dec-2-ene4j: Yield 72%, m.p. 238-240 °C (ethanol). Anal. Calcd for $C_{23}H_{25}N_7O_3S_2$ (511.63): C 54.00%, H 4.93%, N 19.19%. Found: C 53.77%, H 5.05%, N 19.30%; MS: ($M^{+\cdot}$ = 511); IR, v/cm^{-1}: 3368, 3340 (NH's), 1665 (C=O), 1605 (C=N), 1345, 1144 (SO_2); 'H NMR, δ/ppm: 11.72 (s, 1H, SO_2NH), 9.86 (1H, s, Ph-NH),8.76 (d, 1H thiazole ring), 7.38-7.21 (m, 4H, Ar-H), 6.62 (d, 1H thiazole ring), 5.70 (s, 1H, NH), 2.92-1.65 (m, 8H, $4CH_2$) 2.40 (s, 3H, NCH_3). ^{13}C NMR (DMSO-d_6): δ/ppm 159.80 (C=O), 147.37 (C=N), 166.70-115.22 (Ar-C and thiazole-C),90.12 (spiro carbon), 52.89 ($2CH_2$),46.60 (NCH_3), 31.94 ($2CH_2$).

8-Benzyl-3-phenylaminocarbonyl-l-[4-(thiazol-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraaza-spiro[4.5]dec-2-ene 4k: Yield 70%, m.p. 229-231 °C (ethanol). Anal. Calcd for $C_{29}H_{29}N_7O_3S_2$ (587.73): C 74.97%, H 6.29%, N 14.57%. Found: C 75.22%, H 6.17%, N 14.68%; MS: ($M^{+\cdot}$ = 587);

IR, ν/crn^{-1}: 3366, 3347 (NH's), 1660 (C=O), 1608 (C=N), 1342, 1150 (SO_2); ^1H NMR, δ/ppm: 11.61 (s, 1H, SO_2NH), 9.88 (1H, s, Ph-NH), 8.76 (d, 1H thiazole ring), 7.38-7.21 (m, 4H, Ar-H), 6.62 (d, 1H thiazole ring), 5.68 (s, 1H, NH), 3.40 (s, 2H $PhCH_2$), 2.86-1.84 (m, 8H, $4CH_2$);^{13}C NMR (DMSO-d_6): δ/ppm 159.56 (amide C=O), 147.34 (C=N), 166.67-115.23 (Ar-C and thiazole-C),88.95 (spiro carbon), 52.87 ($2CH_2$),49.78 ($PhCH_2$),31.90 ($2CH_2$).

8-Isopropyl-3-phenylaminocarbonyl-l-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-l,2,4,8-tetra-azaspiro[4.5]dec-2-ene 41: Yield 75%, m.p. 234-236 °C (methanol). Anal. Calcd for $C_{26}H_{30}N_8O_3S$ (534.64): C 58.41%, H 5.66%, N 20.96%. Found: C 58.65%, H 5.75%, N 21.10%; MS: ($M^{+\cdot}$ = 534); IR, ν/crn^{-1}: 3370, 3345 (NH's), 1665 (C=O), 1610 (C=N), 1348, 1153 (SO_2); ^1H NMR, δ/ppm: 11.60 (s, 1H, SO_2NH), 9.84 (s, 1H, PhNH), 8.86 (d, 2H pyrimidine ring), 7.37-7.18 (m, 9H, Ar-H), 6.89 (t, 1H pyrimidine ring), 2.41 (s, H, CH), 1.29 (s, 6H, $2CH_3$);^{13}C NMR (DMSO-d_6): δ/ppm: 159.65 (amide C=O), 143.6 (C=N), 167.9-110.3 (Ar-C and pyrimidine-C), 88.97 (spiro carbon), 52.90 ($2CH_2$), 47.50 (CH), 31.80 ($2CH_2$), 27.44 ($2CH_3$).

8-Benzyl-3-phenylaminocarbonyl-l-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraaza-spiro[4.5]dec-2-ene 4m: Yield 74%, m.p. 242-244 °C (ethanol). Anal. Calcd for $C_{30}H_{30}N_8O_3S$ (582.69): C 61.84%, H 5.19%, N 19.23%. Found: C 62.10%, H 5.06%, N 19.34%; MS: ($M^{+\cdot}$ = 582); IR, ν/cm^{-1}: 3372, 3347 (NH's), 1665 (C=O), 1603 (C=N), 1345, 1155 (SO_2); ^1H NMR, δ/ppm: 11.60 (s, 1H, SO_2NH), 9.84 (s, 1H, PhNH), 8.86 (d, 2H pyrimidine ring), 7.37-7.18 (m, 9H, Ar-H), 6.89 (t, 1H pyrimidine ring), 3.41 (s, 2H, $PhCH_2$);^{13}C NMR (DMSO-d_6): δ/ppm: 159.68 (amide C=O), 146.89 (C=N), 167.92-110.34 (Ar-C and pyrimidine-C),88.96 (spiro carbon), 52.96 ($2CH_2$), 49.60 ($PhCH_2$), 31.78 ($2CH_2$).

3-(2-Furyl)-8-methyl-l-[4-(thiazol-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene 4n: Yield 63%), m.p. 193-195 °C (methanol). Anal. Calcd for $C_{21}H_{22}N_6O_4S_2$ (486.58): C 51.84%, H 4.56%, N 17.27%. Found: C 52.11%, H 4.70%, N 17.41%. MS: ($M^{+\cdot}$ = 486); IR, ν/cm^{-1}: 3375, 3337 (NH's), 1660 (C=O), 1600 (C=N), 1351, 1154 (SO_2); ^1H NMR, δ/ppm: 11.61 (s, 1H, SO_2NH), 8.76 (d, 1H thiazole ring), 8.23-7.22 (m, 7H, Ar-H), 6.62 (d, 1H thiazole ring), 5.62 (s, 1H, NH), 2.84-1.81 (m, 8H, $4CH_2$) 2.34 (s, 3H, NCH_3);^{13}C NMR (DMSO-d_6): δ/ppm 173.68 (C=O), 147.30 (C=N), 166.65-115.16(Ar-C and thiazole-C),90.12 (spiro carbon), 52.90 ($2CH_2$),46.68 (NCH_3), 31.78 ($2CH_2$).

3-(2-Furyl)-8-isopropyl-l-[4-(thiazol-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene 4o: Yield 65%, m.p. 210-212 °C (methanol). Anal. Calcd for $C_{23}H_{26}N_6O_4S_2$ (514.63): C 53.68%, H 5.09%, N 16.33%. Found: C 53.45%, H 4.97%, N 16.22%; MS: ($M^{+\cdot}$ = 514) ; IR, ν / c m^{-1} : 3370, 3335 (NH's), 1662 (C=O), 1598 (C=N), 1349, 1151 (SO_2); ^1H NMR, δ/ppm: 11.61 (s, 1H, SO_2NH), 8.76 (d, 1H thiazole ring), 8.23-7.24 (m, 7H, Ar-H), 6.62 (d, 1H thiazole ring), 5.65 (s, 1H, NH), 2.86-1.83 (m, 8H, $4CH_2$),2.38 (s, 1H, CH), 1.30 (s, 6H, $2CH_3$). ^{13}C NMR (DMSO-d_6): δ/ppm 173.54 (C=O), 147.34 (C=N), 166.74-115.20 (Ar-C and thiazole-C), 90.02 (spiro carbon), 52.91 ($2CH_2$), 47.24 (CH), 31.85 ($2CH_2$), 27.46 ($2CH_3$)

8-Bezyl-3-(2-furyl)-l-[4-(thiazol-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene 4p: Yield 62%, m.p. 204-206 °C (ethanol). Anal. Calcd for $C_{27}H_{26}N_6O_4S_2$ (562.67): C 57.64%, H 4.66%, N 14.94%. Found: C 57.85%, H 4.53%, N 15.05%; MS: ($M^{+\cdot}$ = 562); IR, ν/cm^{-1}: 3372, 3340 (NH's), 1665 (C=O), 1596 (C=N), 1345, 1147 (SO_2); ^1H NMR, δ/ppm: 11.61 (s, 1H, SO_2NH), 8.76 (d, 1H thiazole ring), 8.26-7.23 (m, 4H, Ar-H), 6.62 (d, 1H thiazole ring), 5.65 (s, 1H, NH), 3.36 (s, 2H, $PhCH_2$), 2.83-1.81 (m, 8H, $4CH_2$);^{13}C NMR (DMSO-d_6): δ/ppm 173.65 (C=O), 147.34 (C=N), 166.7-115.20 (Ar-C and thiazole-C),90.00 (spiro carbon), 52.89 ($2CH_2$),49.87 ($PhCH_2$), 32.20 ($2CH_2$).

8-Methyl-l-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-3-(2-thienyl)-l,2,4,8-tetraazaspiro[4.5]-dec-2-ene 4q: (1.33 g, 64%), m.p. 213-215 °C (ethanol). Anal. Calcd for $C_{22}H_{23}N_7O_3S_2$(497.60): C 53.10%, H 4.66%, N 19.70%. Found: C 52.87%, H 4.78%, N 19.57%; MS: ($M^{+\cdot}$ = 497); IR, ν/cm^{-1}: 3368, 3346 (NH's), 1660 (C=O), 1615 (C=N), 1346, 1153 (SO_2); ^1H NMR, δ/ppm: 11.60 (s, 1H, SO_2NH), 8.86 (d, 2H pyrimidine ring), 8.36-7.16 (m, 7H, Ar-H), 6.89 (t, 1H pyrimidine ring),2.86-1.83 (m, 8H, $4CH_2$),2.31 (s, 3H, NCH_3);^{13}C NMR (DMSO-d_6): δ = 174.54 (C=O), 147.63 (C=N), 167.9-110.37 (Ar-C and pyrimidine-C),89.95 (spiro carbon), 52.70 ($2CH_2$), 46.64 (CH_3), 31.90 ($2CH_2$).

8-Isopropyl-l-[4-(thiazol-2-yl-sulfonyl)phenyl]-3-(2-thienyl)-l,2,4,8-tetraazaspiro[4.5]dec-2-ene 4r: Yield 66%, m.p. 221-223 °C (ethanol). Anal. Calcd for $C_{23}H_{26}N_6O_3S_3$(530.69): C 52.06%, H 4.94%, N 15.84%. Found: C 51.83%, H 5.10%, N 15.72%; MS: ($M^{+\cdot}$ = 530);. IR, ν/cm^{-1}: 3374, 3347 (NH's), 1660 (C=O), 1610 (C=N), 1347, 1151 (SO_2); ^1H NMR, δ/ppm: 11.61 (s, 1H, SO_2NH), 8.76 (d, 1H thiazole ring), 8.38-7.16 (m, 7H, Ar-H), 6.62 (d, 1H thiazole ring), 5.65 (s, 1H, NH), 2.82-1.83 (m, 8H, $4CH_2$) 2.33 (s, 1H, CH), 1.26 (s, 6H, $2CH_3$); ^{13}C NMR (DMSO-d_6): δ/ppm 174.60 (C=O), 147.34 (C=N), 166.76-115.20 (Ar-C and thiazole-C),90.10 (spiro carbon), 52.80 ($2CH_2$),47.20 (CH),32.20 ($2CH_2$), 27.46 ($2CH_3$)

8-Benzyl-l-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-3-(2-thienyl)-l,2,4,8-tetraazaspiro[4.5]-dec-2-ene 4s: Yield 65%, m.p. 207-209 °C (ethanol). Anal. Calcd for $C_{28}H_{27}N_7O_3S_2$(573.70): C 58.62%, H 4.74%, N 17.09%. Found: C 58.40%, H 4.88%, N 16.95%; MS: ($M^{+\cdot}$ = 573);. IR, v/cm^{-1}: 3370, 3341 (NH's), 1660 (C=O), 1605 (C=N), 1342, 1147 (SO_2); ^{1}H NMR, δ/ppm: 11.60 (s, 1H, SO_2NH), 8.86 (d, 2H pyrimidine ring), 8.37-7.18 (m, 7H, Ar-H), 6.89 (t, 1H pyrimidine ring), 3.40 (s, 2H, PhCH_2),2.90-1.80 (8H, m, $4CH_2$);^{13}C NMR (DMSO-d_6): δ = 174.56 (C=O), 147.36 (C=N), 167.92-110.37 (Ar-C and pyrimidine-C), 90.05 (spiro carbon), 53.00 ($2CH_2$), 49.94 (PhCH_2), 31.87 ($2CH_2$).

8-Methyl-3-(2-naphthyl)-l-[4-(thiazol-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]dec-2-ene 4t: Yield 58%, m.p. 257-259 °C (ethanol). Anal. Calcd for $C_{27}H_{26}N_6O_3S_2$ (546.67): C 59.32%, H 4.79%, N 15.37%. Found: C 59.10%, H 4.92%, N 15.50%; MS: ($M^{+\cdot}$ = 546);. IR, v/cm^{-1}: 3368, 3342 (NH's), 1650 (C=O), 1597 (C=N), 1350, 1156 (SO_2); ^{1}H NMR, δ/ppm: 11.61 (s, 1H, SO_2NH), 8.76 (d, 1H thiazole ring), 8.83-7.25 (m, 11H, Ar-H), 6.62 (d, 1H thiazole ring), 5.71 (s, 1H, NH), 3.00-1.81(m, 8H, $4CH_2$), 2.36 (s, 3H, NCH_3);^{13}C NMR (DMSO-d_6): δ/ppm 182.60 (C=O), 147.34 (C=N), 166.7-115.20 (Ar-C and thiazole-C),90.12 (spiro carbon), 89.66 (spiro carbon), 52.87 ($2CH_2$),46.60 (NCH_3), 31.80 ($2CH_2$).

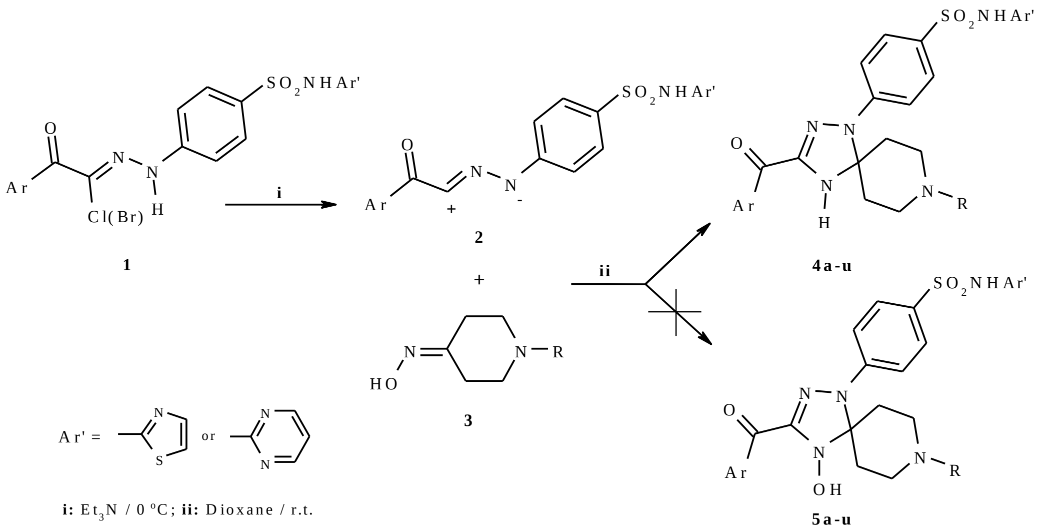
8-Methyl-3-(2-naphthyl)-l-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-l,2,4,8-tetraazaspiro[4.5]-dec-2-ene 4u: Yield 56%, m.p. 263-265 °C (ethanol). Anal. Calcd for $C_{28}H_{27}N_7O_3S$ (541.64): C 62.09%, H 5.02%, N 18.10%. Found: C 61.85%, H 5.18%, N 18.06%; MS: ($M^{+\cdot}$ = 541);. IR, v/cm^{-1}: 3372, 3343 (NH's), 1652 (C=O), 1598 (C=N), 1351, 1158 (SO_2); ^{1}H NMR, δ/ppm: 11.60 (s, 1H, SO_2NH), 8.82 (d, 2H pyrimidine ring), 8.87-7.28 (m, 11H, Ar-H), 6.89 (t, 1H pyrimidine ring), 5.70 (s, 1H, NH), 3.01-1.80 (m, 8H, $4CH_2$),2.38 (s, 2H, NCH_3) ppm. ^{13}C NMR (DMSO-d_6): δ/ppm 182.62 (ArC=O), 147.60 (C=N), 167.91-110.33 (Ar-C and pyrimidine-C), 89.68 (spiro carbon), 53.00 ($2CH_2$), 46.64 (CH_3), 32.10 ($2CH_2$),

2.3. Screening for Antimicrobial Activity

Antimicrobial activity screening of the synthesized compounds was determined by the agar dilution technique as recommended by the Clinical and Laboratory Standard Institute (CLSI).[32] The tested compounds were dissolved in dimethyl sulfoxide (DMSO). An inoculum of about 1.5 x 10^8 colony forming unit per spot was applied to the surfaces of Mueller–Hinton agar plates containing graded concentrations of the respective compound; plates were incubated at 37 ^{o}C for 18 h. The spot with the lowest concentration of compound showing no growth was defined as the minimum inhibitory concentration (MIC). All organisms used in this study were standard strains were obtained from the Microbiology laboratory (Al-Aqsa University) and included bacterial strain such as *Enterococci, Escherichia coli, Staphylococcus aureus, Klebsiellaspp, Proteus spp,* and fungi strain such as *Aspergillusniger, Candida albicans*. The MIC of Tetracycline and fluconazole was determined concurrently as reference for antibacterial and antifungal activities, respectively (Table 1). Control DMSO was carried out with each experiment.

3. Results and Discussion

The required nitrilimines **2** generated in situ by base-promoted dehydrohalogenation of the corresponding hydrazonoyl halides **1** (Scheme 1). Treatment of the resulting non-isolable nitrilimines **2**, 1,3-dipole, with appropriate l-substituted-4-piperidone oximes **3** in 1,4-dioxane or tetrahydrofuran in presence of triethylamine as a base, gave in each case a single product that proved to be the respective 1,3,8-trisubstituted spirotriazoles **4a-u** instead of the expected 4-hydroxyspirotriazole derivatives **5** (Scheme 1). The proposed mechanism involved an initial formation of the spiro intermediates **5** via 1,3-dipolar cycloaddition of nitrilimines **2** to the exocyclic double bond (N=C) of oxime**3**. which tautomerize to amine oxide-type intermediates that are deoxygenated by triethylamine [42].



Ar / Ar' / R	Ar / Ar' / R	Ar / Ar' / R
a, Me/2-thiazolyl/Me	**h**, Ph/2-thiazolyl/CHMe2	**o**, 2-Furyl/2-thiazolyl/Me
b, Me/2-thiazolyl/$CHMe_2$	**i**, Ph/2-thiazolyl/CHPh	**p**, 2-Furyl/2-thiazolyl/CH_2Ph
c, Me/2-thiazolyl/CH_2Ph	**j**, PhNH/2-thiazolyl/Me	**q**, 2-Thienyl/2-pyrimidinyl/Me
d, Me/2-pyrimidinyl/Me	**k**, PhNH/2-thiazolyl/CH_2Ph	**r**, 2-Thienyl/2-thiazolyl/$CHMe_2$
e, Me/2-pyrimidinyl/-$CHMe_2$	**l**, PhNH/2-pyrimidinyl/CHMe2	**s**, 2-Thienyl/2-pyrimidinyl/CH_2Ph
f, Me/2-pyrimidinyl/CH_2Ph	**m**, PhNH/2-pyrimidinyl/CH_2Ph	**t**, 2-Naphthyl/2-thiazolyl/Me
g, Ph/2-thiazolyl/Me	**n**, 2-Furyl/2-thiazolyl/Me	**u**, 2-Naphthyl/2-pyrimidinyl/Me

Scheme: *Synthetic pathway of 1,2,4,8-tetaazspiro[4.5]dec-2-enes **4a-u**.*

It is worth mentioning that, the nitrile oxides generated in *situ* from respective hydroxamoyl chlorides upon action of triethylamine as a base are found to react with substituted oximes to give the 4-hydroxy-4,5-dihydro-l ,2,4-oxadiazoles [45].The purity of obtained compounds was controlled by TLC and elemental analysis. Both the analytical and spectral data (IR, ^{1}H NMR, ^{13}C NMR and mass spectra) of the synthesized spirotriazoles were in full agreement with the proposed structures.

3.1. Spectral Data Analysis of Spiro Compounds 4a-u

The characterization data of synthesized spiro compounds **4a-u** are given in the experimental section. These compounds **4a-u** gave satisfactory analysis for the proposed structures which are confirmed on the bases of their spectroscopic data. The electron impact (EI) mass spectra displayed the correct molecular ions ($M^{+\cdot}$) in accordance with the suggested structures. The IR spectra showed the strong absorption band of NH of the triazole ring in the region 3380-3360 cm^{-1}, in addition to, characteristic band of SO_2NH in the region of 3340-3220 cm^{-1}, (Ar-C=O) at about 1690-1650 cm^{-1} and bands at 1340, 1150 cm^{-1} attributed to SO_2 of sulfonamide group. In the ^{1}H NMR spectra, a characteristic signal due to the NH proton of the triazole ring appeared at 5.7-5.5 ppm and this values are similar to reported in literature [43]. The signals at 8.70, 6.60 ppm and 8.40, 6.80 ppm are attributed to thiazole and pyrimidine protons, respectively. Also, the spectra exhibit a characteristic singlet at 11.7-11.6 ppm due to SO_2NH proton.

The structures of compounds **4a-u** were further confirmed by ^{13}C NMR spectra, which account for the different carbons of these spirotriazoles. The signal at 88-90 ppm was attributed to the C-5 (spiro carbon) of the triazole ring is of special significance. This assignment is in good agreement with literature data for spiro carbons [36,37]. The signal at about 147 ppm was attributed to the C-3 carbon of the triazoles, and this is similar to reported values of azomethine carbons of five-membered heterocycles [37].

3.2. Antimicrobial Activity

Most of the synthesized compounds were screened in vitro for their antimicrobial activity against a variety of bacterial strains such as E*nterococci*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiellaspp*, *Proteus spp*, and fungi such as *Aspergillusniger*, *Candida albicans*, employing the nutrient agar disc diffusion method[30] at 1-100 mg/ml concentration in dimethyl sulfoxide (DMSO) which used as solvent control, by measuring the average diameter of the inhibition zone in mm. The results are given in Table.All the experiments were carried out in triplicate. The results showed that all the tested compounds exhibited good degree of activity.

Table: *Antimicrobial screening results of the tested compounds**

Comp. No.	Antibacterial activity					Antifungal activity	
	Enter.	*E. coli*	*S. aureus*	*K.spp*	*P. spp*	*C. alb.*	*A. niger*
4a	16	18	16	16	15	19	18
4b	18	19	14	15	17	20	19
4c	17	14	15	17	14	18	18
4d	16	19	17	18	15	20	19
4e	17	17	17	19	13	19	19
4f	15	14	15	18	16	17	18
4g	19	16	14	15	19	16	15
4i	16	16	17	14	14	18	16
4j	14	14	16	15	16	16	17
4k	16	17	14	13	15	17	15
4m	19	17	18	19	18	19	18
4n	17	15	15	16	15	16	16
4p	19	19	14	16	19	17	17
4q	17	20	18	17	18	14	18
4r	16	18	16	15	18	15	19
4s	15	17	18	17	16	14	16
4t	20	19	17	16	18	17	19
DMSO	--	--	--	--	--	--	--

**Calculated as average of three values.*

Enter. = Enterococci, E. coli = Escherichia coli, S. aureus = Staphylococcus aureus, K. spp = Klebsiellaspp, P. spp = Proteus spp,C. alb. = Candida albicans, A. niger = Aspergillus niger.

against different strains of bacteria and fungi compared with well-known antibacterial and antifungal substances such as tetracycline and fluconazole respectively. According to National Committee for Clinical Laboratory Standards (NCCLS, 2004) methodology, zones of inhibition for tetracycline and fluconazole < 14 mm were considered resistant, between 15 and 18 mm were considered weakly sensitive and > 19 mm were considered sensitive. Presence of sulphonamide moieties showed a better spectrum of activity than the reference drug.

4. Conclusion

In conclusions, the reaction of nitrilimines 2 with 1-methyl, 1-isopropyl and l-benzyl-4-piperidone oximes 3 leads to formation of novel heterocyclic spirotriazoles 4a-u containing benzenesulfonamide moiety and evaluated for their in vitro antibacterial, and antifungal activities. From the screening results, it found to possess various antimicrobial activities towards all the microorganisms tested. The results confirm that, the antimicrobial activity is strongly dependent on the nature of the substituents on triazinone and thiadiazinone nucleus. The pyrimidinyl, thiazolyl derivatives generally led to dramatic improvements in activity against both bacteria and fungi. In short, the present study can lead medicinal chemists to design and synthesize similar compounds with enhanced biological potency in future.

Acknowledgments

The authors are great thankful to the Qatar Charity for the financial support of this research through Ibhath grant.

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