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Synthesis and biological activities of some new spiro 1,2,4-triazole derivatives having sulfonamide moiety

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Abstract: A new series of spiro 1,2,4-triazoles **5-9a-j** were prepared by the reaction of appropriate amidrazones **4** with cyclic ketones in catalytic amount of *p*-toluene sulfonic acid. The structures of the titled compounds have been elucidated by the elemental analysis and spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and MS). The biological activities of the prepared compounds were investigated using well-established methods from the literature.

Keywords: Amidrazone; nitrilimines; spiro 1,2,4-triazole; sulfonamide; cyclic ketone.

1. Introduction

Amidrazones represent a class of substances with interesting biological properties. The interest in amidrazones and their derivatives stems not only from their biological relevance but also from their applications as precursors and intermediates for the synthesis of many heterocyclic compounds[1-3] and as ligands in coordination chemistry. It has been established that they can exhibit antibacterial, antifungal[4-6], antitumor[7] and antituberculosis activities[8]. They were also found as effective herbicides[9], pesticides[10], and insecticides[11]. Amidrazones synthesized from different hydrazonoyl halides were reported to react with α-haloesters in the presence of triethylamine as a base under reflux to afford 1,3,5-substituted *4,5*-dihydro-1,2,4-triazin-6-ones[12]. Several studies, reported the formation and investigation of biological activities of some spiroheterocyclic compounds having triazole, tetrazine thiadiazole, thiadiazines, thiazolidinone and triazine moieties[13-17]. Recently, unknown dispiroheterocycles containing triazole and tetrazine moieties have been disclosed[14-17].

Sulfonamide derivatives are known to exhibit various pharmacological properties such as anti-angiogenic, anti-tumor, anti-inflammatory and anti-analgesic, anti-tubercular, anti-glaucoma, anti-HIV, cytotoxic, anti-microbial, anti-malarial agents[18]. Considering the previous reports on the biological activities and syntheses of sulfonamides we report here synthesis and antimicrobial activity of new spiro-heterocycles having 1,2,4-triazole and piperidone derivatives via cyclization of amidrazones containing sulfonamide moiety with cyclic ketones.

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2. Experimental

2.1. Reagents and Instrumentation

Melting points were determined on an A. Krüss Melting Point Meter equipped with a thermometer and are uncorrected. The IR spectra were measured as potassium bromide pellets using a Satellite 3000 Mid infrared spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at room temperature in DMSO-d_6 solution using tetramethylsilane (TMS) as internal reference. Chemical shifts were recorded as δ values in parts per millions (ppm) downfield from internal TMS. Electron impact (EI) mass spectra were run on a Shimadzu GCMS-QP1000 EX spectrometer at 70 eV. All compounds were analyzed satisfactorily for C, H and N. The amidrazones **4** were prepared according to the literature procedures[19-22]. Sodium azide, triphenylphosphine and tetrabutylammonium iodide were obtained from Fluka Chemie Company, Switzerland. Sulfathiazole, sulfadiazine, dioxane, tetrahydrofuran (THF) and triethylamine were purchased from Avocado Research Chemicals, England, and used without further purification.

*2.2. Synthesis of Spiro 4,5-dihyro-1,2,4-triazole derivatives (**5-9a-j**).*

To a stirred solution of the appropriate amidrazone **4** (10 mmol) and the respective cycloalkanone (20 mmol) in dioxane (50 mL), the catalytic amount of *p*-toluenesulfonic acid (0.1 g) was added. The reaction mixture was refluxed to the completion (monitoring the reaction progress by TLC). The excess of the solvent was evaporated and the residue was triturated with methanol or ethanol. The resulting crude solid product was collected and recrystallized from ethanol. The following compounds were prepared using this method:

*3-Acetyl-1-[4-(thiazol-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.4]non-2-ene (**5a**):* Yield: 65%; m.p.: 197-199 ^{o}C; IR (KBr) ν_{max}: cm^{-1} 3382, 3355 (NH's), 1695 (CH_3-C=O), 1622 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 11.70 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 4H, Ar-H), 8.71 (d, 1H, thiazole), 6.62 (d, 1H, thiazole), 5.65 (s, 1H, NH triazole ring), 2.45 (*s*, 3H, $COCH_3$), 2.37-1.60 (m, 8H, cyclopentane); ^{13}C NMR (DMSO-d_6): *δ* 192.3 (C=O), 169.1, 142.2, 139.6, 135.4, 129.6, 127.4, 119.1, 116.5 (Ar-C, C=N and thiazole-C), 92.8 (spiro-C), 34.9, 24.9 (cyclopentane-C), 26.5 (CH_3); MS: *m/z* 405 [M^+]; Anal. Calcd. for $C_{17}H_{19}N_5O_3S_2$ (405.50): C, 50.35; H, 4.72; N, 17.27; Found: C, 50.57; H, 4.60; N, 17.15.

*3-Acetyl-1-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.4]non-2-ene (**5b**):* Yield: 71%; m.p.: 216-218 ^{o}C; IR (KBr) ν_{max}: cm^{-1} 3374, 3350 (NH's), 1693 (CH_3-C=O), 1626 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 11.74 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 4H, Ar-H), 8.41 (d, 2H, pyrimidine), 6.83 (t, 1H, pyrimidine), 5.63 (s, 1H, NH triazole ring), 2.55 (*s*, 3H, $COCH_3$), 2.37-1.60 (m, 8H, cyclopentane); ^{13}C NMR (DMSO-d_6): *δ* 192.1 (C=O), 168.1, 156.4, 142.2, 139.7, 129.8, 127.3, 119.2, 110.6 (Ar-C, C=N and pyrimidine-C), 92.6 (spiro-C), 34.8, 24.6 (cyclopentane-C), 26.6 (CH_3); MS: *m/z* 400 [M^+]; Anal. Calcd. for $C_{18}H_{20}N_6O_3S$ (400.46): C, 53.99; H, 5.03; N, 20.99; Found: C, 54.23; H, 4.92; N, 21.10.

*3-Acetyl-1-[4-(thiazol-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.5]dec-2-ene (**5c**):* Yield: 66%; m.p.: 204-206 ^{o}C; IR (KBr) ν_{max}: cm^{-1} 3369, 3357 (NH's), 1695 (CH_3-C=O), 1624 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 11.76 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 4H, Ar-H), 8.71 (d, 1H, thiazole), 6.65 (d, 1H, thiazole), 5.65 (s, 1H, NH triazole ring), 2.54 (*s*, 3H, $COCH_3$), 2.07-1.16 (m, 10H, cyclohexane); ^{13}C NMR (DMSO-d_6): *δ* 192.4 (C=O), 168.4, 142.2, 139.3, 135.5, 129.7, 127.3, 119.2, 116.2 (Ar-C, C=N and thiazole-C), 92.1 (spiro-C), 35.9, 24.8, 23.2 (cyclohexane-C), 26.5 (CH_3); MS: *m/z* 419 [M^+]; Anal. Calcd. for $C_{18}H_{21}N_5O_3S_2$ (419.53): C, 61.53; H, 5.05; N, 16.69; Found: C, 61.70; H, 4.96; N, 16.55.

*3-Acetyl-1-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.5]dec-2-ene (**5d**):* Yield: 65%; m.p.: 192-194 ^{o}C; IR (KBr) ν_{max}: cm^{-1} 3377, 3357 (NH's), 1693 (CH_3-C=O), 1628 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 11.71 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 4H, Ar-H), 8.40 (d, 2H, pyrimidine), 6.82 (t, 1H, pyrimidine), 5.61 (s, 1H, NH triazole ring), 2.55 (*s*, 3H, $COCH_3$), 1.98-1.16 (m, 10H, cyclohexane); ^{13}C NMR (DMSO-d_6): *δ* 191.9 (C=O), 168.2, 156.5, 142.3, 139.4, 135.5, 129.6, 127.5, 119.3, 110.4 (Ar-C, C=N and pyrimidine-C), 91.8 (spiro-C), 35.8, 24.6, 23.1 (cyclohexane-C), 26.4 (CH_3); MS: *m/z* 414

[M^+]; Anal. Calcd. for $C_{19}H_{22}N_6O_2S$ (414.49): C, 55.06; H, 5.35; N, 20.28; Found: C, 54.78; H, 5.50; N, 20.39.

3-Acetyl-1-[4-(thiazol-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.6]undec-2-ene ***(5e)****:* Yield: 67%; m.p.: 178-180 °C; IR (KBr) ν_{max}: cm^{-1} 3375, 3358 (NH's), 1695 (CH_3-C=O), 1625 (C=N), 1346, 1175 (SO_2); ^1H NMR (DMSO-d_6): δ 11.76, (s, 1H, NH), 8.27-7.06 (*m*, 4H, Ar-H), 8.70 (d, 1H, thiazole), 6.64 (d, 1H, thiazole), 5.63 (s, 1H, NH triazole ring), 2.54 (*s*, 3H, $COCH_3$), 2.35-1.42 (m, 12H, cycloheptane); ^{13}C NMR (DMSO-d_6): *δ* 192.4 (C=O), 168.2, 142.3, 139.4, 135.3, 129.7, 127.4, 119.3, 116.5 (Ar-C, C=N and thiazole-C), 91.6 (spiro-C), 39.4, 28.1, 22.3 (cycloheptane-C), 26.5 (CH_3); MS: *m/z* 433[M^+]; Anal. Calcd. for $C_{19}H_{23}N_5O_3S_2$ (433.55): C, 52.64; H, 5.35; N, 16.15; Found: C, 52.45; H, 5.24; N, 16.03.

3-Acetyl-1-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.6]undec-2-ene ***(5f)****:* Yield: 64%; m.p.: 188-190 °C; IR (KBr) ν_{max}: cm^{-1} 3373, 3365 (NH's), 1695 (CH_3-C=O), 1620 (C=N), 1346, 1175 (SO_2); ^1H NMR (DMSO-d_6): δ 11.69 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 4H, Ar-H), 8.36 (d, 2H, pyrimidine), 6.81 (t, 1H, pyrimidine), 5.62 (s, 1H, NH triazole ring), 2.56 (*s*, 3H, $COCH_3$), 2.34-1.40 (m, 12H, cycloheptane); ^{13}C NMR (DMSO-d_6): *δ* 191.8 (C=O), 168.3, 156.7, 142.5, 139.6, 135.1, 129.3, 127.4, 119.2, 110.4 (Ar-C, C=N and pyrimidine-C), 39.1, 28.3, 22.5 (cycloheptane-C), 91.8 (spiro-C), 26.4 (CH_3); MS: *m/z* 428 [M^+]; Anal. Calcd. for $C_{20}H_{24}N_6O_3S$ (428.52): C, 56.06; H, 5.65; N, 19.61; Found: C, 55.86; H, 5.53; N, 19.47.

3-Acetyl-1-[4-(thiazol-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.7]dodec-2-ene ***(5g)****:* Yield: 70%; m.p.: 166-168 °C; IR (KBr) ν_{max}: cm^{-1} 3373, 3361 (NH), 1696 (CH_3-C=O), 1627 (C=N), 1346, 1175 (SO_2); ^1H NMR (DMSO-d_6): δ 11.71 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 4H, Ar-H), 8.72 (d, 1H, thiazole), 6.61 (d, 1H, thiazole), 5.65 (s, 1H, NH triazole ring), 2.55 (*s*, 3H, $COCH_3$), 2.42-1.24 (m, 14H, cyclooctane); ^{13}C NMR (DMSO-d_6): *δ* 192.3 (C=O), 168.5, 142.3, 139.7, 135.5, 129.4, 127.6, 119.4, 116.5 (Ar-C, C=N and thiazole-C), 90.9 (spiro-C), 41.9, 36.5, 27.2, 21.8 (cyclooctane-C), 26.5 (CH_3); MS: *m/z* 447 [M^+]; Anal. Calcd. for $C_{20}H_{25}N_5O_3S_2$ (447.58): C, 53.67; H, 5.63; N, 15.65; Found: C, 53.45; H, 5.75; N, 15.55.

3-Acetyl-1-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.7]dodec-2-ene ***(5h)****:* Yield: 65%; m.p.: 169-171 °C; IR (KBr) ν_{max}: cm^{-1} 3366, 3360 (NH's), 1692 (CH_3-C=O), 1626 (C=N), 1346, 1175 (SO_2); ^1H NMR (DMSO-d_6): δ 11.76 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 4H, Ar-H), 8.40 (d, 2H, pyrimidine), 6.81 (t, 1H, pyrimidine), 5.66 (s, 1H, NH triazole ring), 2.55 (*s*, 3H, $COCH_3$), 2.42-1.24 (m, 14H, cyclooctane); ^{13}C NMR (DMSO-d_6): *δ* 192.2 (C=O), 168.1, 156.3, 142.0, 139.4, 135.2, 129.4, 127.2, 119.0, 110.2 (Ar-C, C=N and pyrimidine-C), 91.8 (spiro-C), 41.8, 36.3, 27.1, 21.6 (cyclooctane-C), 26.6 (CH_3); MS: *m/z* 442 [M^+]; Anal. Calcd. for $C_{21}H_{26}N_6O_3S$ (442.54): C, 57.00; H, 5.92; N, 18.99; Found: C, 56.85; H, 6.05; N, 18.87.

3-Acetyl-8-methyl-1-[4-(thiazol-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.5]dec-2-ene ***(5i)****:* Yield: 71%; m.p.: 186-188 °C; IR (KBr) ν_{max}: cm^{-1} 3374, 3355 (NH's), 1693 (CH_3-C=O), 1622 (C=N), 1346, 1175 (SO_2); ^1H NMR (DMSO-d_6): δ 11.70 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 4H, Ar-H), 8.71 (d, 1H, thiazole), 6.65 (d, 1H, thiazole), 5.64 (s, 1H, NH triazole ring), 2.54 (*s*, 3H, $COCH_3$), 2.07-1.14 (m, 8H, cyclohexane), 0.98 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6): *δ* 189.9 (C=O), 168.2, 142.2, 139.6, 135.4, 129.6, 127.4, 119.2, 116.5 (Ar-C, C=N and thiazole-C), 34.9, 27.8, 22.4 (cyclohexane-C), 90.9 (spiro-C), 31.4 (CH_3 at cyclohexane ring) 26.5 (CH_3); MS: *m/z* 433 [M^+]; Anal. Calcd. for $C_{19}H_{23}N_5O_3S_2$ (433.55): C, 52.64; H, 5.35; N, 16.15; Found: C, 52.85; H, 5.20; N, 16.28.

3-Acetyl-8-tert-butyl-1-[4-(thiazol-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro-[4.5]dec-2-ene ***(5j)****:* Yield: 69%; m.p.: 199-201 °C; IR (KBr) ν_{max}: cm^{-1} 3370, 3353, (NH's), 1695 (CH_3-C=O) 1622 (C=N), 1346, 1175 (SO_2); ^1H NMR (DMSO-d_6): δ 11.69 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 4H, Ar-H), 8.68 (d, 1H, thiazole), 6.63 (d, 1H, thiazole), 5.57 (s, 1H, NH triazole ring), 2.57 (*s*, 3H, $COCH_3$), 2.05-1.13 (m, 8H, cyclohexane), 0.92 (9H, s, $(CH_3)_3C$); ^{13}C NMR (DMSO-d_6): *δ* 189.9 (C=O), 168.2, 142.2, 139.6, 135.4, 129.6, 127.4, 119.1, 116.5 (Ar-C, C=N and thiazole-C), 90.8 (spiro-C), 35.2, 27.9, 22.6 (cyclohexane-C), 46.9, 35.7, 32.4, 24.0 (*tert*-butyl carbons), 26.4 (CH_3); MS: *m/z* 470 [M^+]; Anal. Calcd. for $C_{23}H_{30}N_6O_3S$ (470.60): C, 58.70; H, 6.43; N, 17.86; Found: C, 58.55; H, 6.31; N, 17.95.

*3-Benzoyl-1-[4-(thiazol-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.4]non-2-ene (**6a**):* Yield: 66%; m.p.: 219-221 °C; IR (KBr) ν_{max}: cm^{-1} 3368, 3345 (NH's), 1675 (Ph-C=O), 1596 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 11.56 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 9H, Ar-H), 8.74 (d, 1H, thiazole), 6.60 (d, 1H, thiazole), 5.63 (s, 1H, NH triazole ring), 89.8 (spiro-C), 2.37-1.60 (m, 8H, cyclopentane); ^{13}C NMR (DMSO-d_6): *δ* 185.2 (C=O), 167.9, 145.7, 142.4, 140.9, 139.1, 135.4, 130.4, 129.6, 126.3, 125.3, 119.3, 116.2 (Ar-C, C=N and thiazole-C), 34.6, 24.7 (cyclopentane-C); MS: *m/z* 467 [M^+]; Anal. Calcd. for $C_{22}H_{21}N_5O_3S_2$ (467.57): C, 56.51; H, 4.53; N, 14.98; Found: C, 56.25; H, 4.40; N, 15.10.

*3-Benzoyl-1-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.4]non-2-ene (**6b**):* Yield: 67%; m.p.: 236-238 °C; IR (KBr) ν_{max}: cm^{-1} 3371, 3347 (NH's), 1676 (Ph-C=O), 1597 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 11.58 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 9H, Ar-H), 8.44 (d, 2H, pyrimidine), 6.81 (t, 1H, pyrimidine), 5.58 (s, 1H, NH triazole ring), 2.37-1.60 (m, 8H, cyclopentane); ^{13}C NMR (DMSO-d_6): *δ* 185.5 (C=O), 168.1, 156.6, 145.6, 142.4, 140.8, 139.3, 130.3, 129.6, 126.3, 125.3, 119.3, 110.2 (Ar-C, C=N and pyrimidine-C), 89.9 (spiro-C), 34.8, 24.7 (cyclopentane-C); MS: *m/z* 462 [M^+]; Anal. Calcd. for $C_{23}H_{22}N_6O_3S$ (462.53): C, 59.73; H, 4.79; N, 18.17; Found: C, 59.55; H, 4.95; N, 18.05.

*3-(2-Furoyl)-1-[4-(thiazol-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.4]non-2-ene (**7a**):* Yield: 70%; m.p.: 197-199 °C; IR (KBr) ν_{max}: cm^{-1} 3375, 3355 (NH's), 1665 (Ar-C=O), 1616 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 11.63 (*s*, 1H, SO_2NH), 78.27-7.06 (*m*, 7H, Ar-H), 8.66 (d, 1H, thiazole), 6.58 (d, 1H, thiazole), 5.65 (s, 1H, NH triazole ring), 2.37-1.60 (m, 8H, cyclopentane); ^{13}C NMR (DMSO-d_6): *δ* 173.6 (C=O), 168.2, 142.2, 139.6, 135.6, 138.8, 129.8, 129.5, 128.2, 127.4, 125.6,119.3, 116.4 (Ar-C, C=N and thiazole-C), 90.6 (spiro-C), 34.7, 24.6 (cyclopentane-C); MS: *m/z* 457[M^+]; Anal. Calcd. for $C_{20}H_{19}N_5O_4S_2$ (457.53): C, 52.50; H, 4.19; N, 15.31; Found: C, 52.67; H, 4.06; N, 15.43.

*3-(2-Furoyl)-1-[4-(thiazol-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.5]dec-2-ene (**7c**):* Yield: 71%; m.p.: 226-228 °C; IR (KBr) ν_{max}: cm^{-1} 3377, 3352 (NH's), 1666 (Ar-C=O), 1615 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 11.64 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 7H, Ar-H), 8.67 (d, 1H, thiazole), 6.56 (d, 1H, thiazole), 5.60 (s, 1H, NH triazole ring), 2.05-1.12 (m, 10H, cyclohexane); ^{13}C NMR (DMSO-d_6): *δ* 173.5 (C=O), 168.2, 142.3, 139.7, 135.7, 138.8, 129.8, 129.2, 128.2, 127.3, 125.6, 119.4, 116.5 (Ar-C, C=N and thiazole-C), 90.4 (spiro-C), 36.2, 25.1, 23.2 (cyclohexane-C); MS: *m/z* 471 [M^+]; Anal. Calcd. for $C_{21}H_{21}N_5O_4S_2$ (471.56): C, 53.49; H, 4.49; N, 14.85; Found: C, 53.35; H, 4.55; N, 14.73.

*3-(2-Thenoyl)-1-[4-(thiazol-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.4]non-2-ene (**8a**):* Yield: 72%; m.p.: 218-220 °C; IR (KBr) ν_{max}: cm^{-1} 3365, 3345 (NH's), 1665 (Ar- C=O), 1612 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 11.66, (s, 1H, SO_2NH), 8.27-7.06 (*m*, 7H, Ar-H), 8.70 (d, 1H, thiazole), 6.63 (d, 1H, thiazole), 5.63 (s, 1H, NH triazole ring), 2.35-1.58 (m, 8H, cyclopentane); ^{13}C NMR (DMSO-d_6): *δ* 174.6 (C=O), 168.1, 145.4, 142.2, 141.8, 135.6, 134.8, 129.4, 128.0, 127.8, 125.7, 120.8, 116.2 (Ar-C, C=N and thiazole-C), 88.8 (spiro-C), 34.8, 24.9 (cyclopentane-C); MS: *m/z* 473[M^+]; Anal. Calcd. for $C_{20}H_{19}N_5O_3S_2$ (473.60): C, 50.72; H, 4.04; N, 14.79; Found: C, 50.90; H, 3.90; N, 14.65.

*3-(2-Thenoyl)-1-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.5]-dec-2-ene (**8d**):* Yield: 73%; m.p.: 198-200 °C; IR (KBr) ν_{max}: cm^{-1} 3365, 3346 (NH's), 1660 (Ar-C=O), 1610 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 11.59 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 7H, Ar-H), 8.38 (d, 2H, pyrimidine), 6.81 (t, 1H, pyrimidine), 5.61 (s, 1H, NH triazole ring), 2.04-1.13 (m, 10H, cyclohexane); ^{13}C NMR (DMSO-d_6): *δ* 174.8 (C=O), 168.4, 156.8, 145.6, 142.2, 141.9, 135.7, 129.5, 129.3, 128.5, 125.2, 116.2, 110.5 (Ar-C, C=N and pyrimidine-C), 88.9 (spiro-C), 36.1, 25.3, 23.1 (cyclohexane-C); MS: *m/z* 482 [M^+]; Anal. Calcd. for $C_{22}H_{22}N_6O_3S_2$ (482.59): C, 54.76; H, 4.60; N, 17.41; Found: C, 53.60; H, 4.05; N, 19.35.

*3-(2-Naphthoyl)-1-[4-(thiazol-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.4]non-2-ene (**9a**):* Yield: 61%; m.p.: 212-213 °C; IR (KBr) ν_{max}: cm^{-1} 3369, 3350 (NH), 1606 (Ar-C=O), 1608 (C=N), 1346, 1175 (SO_2); ^{1}H NMR (DMSO-d_6): δ 11.66 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 11H, Ar-H), 8.76 (d, 1H, thiazole), 6.66 (d, 1H, thiazole), 5.53 (s, 1H, NH triazole ring), 2.37-1.60 (m, 8H, cyclopentane); ^{13}C NMR (DMSO-d_6): *δ* 185.4 (C=O), 168.0, 145.6, 142.7, 141.6, 135.6, 135.7, 132.3, 133.0, 132.7, 130.0, 128.9, 128.5, 127.9, 127.7, 126.6, 125.6, 120.9, 116.2 (Ar-C, C=N and thiazole-C), 89.8 (spiro-C), 34.9, 24.9 (cyclopentane-

C); MS: *m/z* 517 [M^+]; Anal. Calcd. for $C_{26}H_{23}N_5O_3S_2$ (517.63): C, 60.33; H, 4.48; N, 13.53; Found: C, 60.15; H, 4.60; N, 13.65.

*3-(2-Naphthoyl)-1-[4-(pyrimidin-2-yl-sulfonyl)phenyl]-1,2,4-triazaspiro[4.4]-non-2-ene (**9b**):* Yield: 62%; m.p.: 165-167 °C; IR (KBr) ν_{max}: cm^{-1} 3367, 3355 (NH's), 1655 (Ar-C=O), 1605 (C=N), 1346, 1175 (SO_2); ^1H NMR (DMSO-d_6): δ 11.67 (*s*, 1H, SO_2NH), 8.27-7.06 (*m*, 11H, Ar-H), 8.46 (d, 2H, pyrimidine), 6.85 (t, 1H, pyrimidine), 5.55 (s, 1H, NH triazole ring), 2.34-1.51 (m, 8H, cyclopentane); ^{13}C NMR (DMSO-d_6): δ 185.6 (C=O), 168.2, 156.6, 145.6, 142.7, 141.6, 135.6, 132.3, 133.2, 132.7, 130.1, 128.9, 128.5, 127.9, 127.6, 126.8, 125.7, 120.9**,** 110.4 (Ar-C, C=N and pyrimidine-C), 89.7 (spiro-C), 34.8, 24.7 (cyclopentane-C); MS: *m/z* 512 [M^+]; Anal. Calcd. for $C_{27}H_{24}N_6O_3S$ (512.59): C, 63.27; H, 4.72; N, 16.40; Found: C, 63.40; H, 4.62; N, 16.28.

3. Results and Discussion

The precursors of amidrazones hydrazonoyl halides **1** employed, in this study, were prepared according to the reported literature procedures[19-22]. Treatment of the hydrazonoyl halides **1** with sodium azide in the presence of tetrabutylammonium iodide at room temperature gave azidohydrazones **2** (Figure 1). The obtained hydrazonoyl azides **2** were reacted with triphenylphosphine to afford phosphonimines **3** (Figure 1). It was found that the hydrolysis of compounds **3** with aqueous hydrochloric acid gave triphenylphosphine oxide and amidrazones **4** (Figure 1). A plausible mechanism for this acid hydrolysis could be an initial protonation of nitrogen followed by an attack from oxygen on the phosphorous atom[19].

The condensation of amidrazones **4** with cyclic ketones in refluxing dioxane in the presence of catalytic amount of *p*-toluenesulfonic acid (PTSA) produced spiro 4,5-dihydro-1H-1,2,4-triazole derivatives containing sulfonamide moiety **5-9a-j** (Figure 1) in good yields. The reaction progress was monitored by TLC to follow the completion of the synthesis.

The structures of the newly synthesized amidrazones **4** were elucidated on the basis of their spectroscopic data and elemental analyses. Electron impact (EI) mass spectra of the compounds **4a-j** displayed the correct molecular ions ($M^{+\cdot}$) in accordance with the suggested structures. The IR spectra exhibited typical stretching absorption bands of C=O of conjugate ketone, anilide and ester groups at about 1725-1650 cm^{-1}, NHs were observed in the region of 3470-3220 cm^{-1} and 1150, 1060 cm^{-1} was attributed to SO_2 of sulfonamide group. The ^1H NMR spectra of these amidrazones in DMSO-d_6 showed three characteristic signals, i.e. singlet at 12.6-12.4 ppm (SO_2NH), singlet of the NNH group in the region of 6.3-6.0 ppm and singlet of NH_2 near 4.9-5.0 ppm. In addition, the characteristic singlet signal of the CONH group in compounds containing anilide group was observed at about 10.8-9.8 ppm and the expected proton signals of the aromatic rings were in the range of 8.4-6.9 ppm. The ^{13}C NMR spectra exhibited characteristic signals for the Ar-C=O carbon at about 192-159 ppm and for the C=N moiety at about 143-141 ppm.

The structural assignment of the prepared spiro 1,2,4-triazoles **5-9a-j** was based on elemental analysis, spectral data and literature values[20-22]. Physical properties, molecular ion peaks and microanalysis are presented in experimental section. The IR spectra of these compounds revealed the presence of NH band of dihydrotriazole ring resonating near 3370-3350 cm^{-1}. In addition to the bands of characteristic functional groups, the ^1H NMR spectra of products **5-9a-j** in DMSO-d_6 display a characteristic singlet in the region of 5.6-5.5 ppm due to NH proton of dihydrotriazole ring. Also, the spectra exhibited a characteristic singlet at 12.7-12.6 ppm due to SO_2NH proton. The ^{13}C NMR spectra displayed characteristic signals of the suggested structures. The signal at 90-95 ppm, which is attributed to C-5 (spiro carbon) of dihydrotriazole ring was of special significance, which is similar to the reported values of spiro carbons flanked by two nitrogens in five-membered heterocycles[23,25]. The spectral data of the obtained compounds **5-9a-j** are summarized in the experimental section.

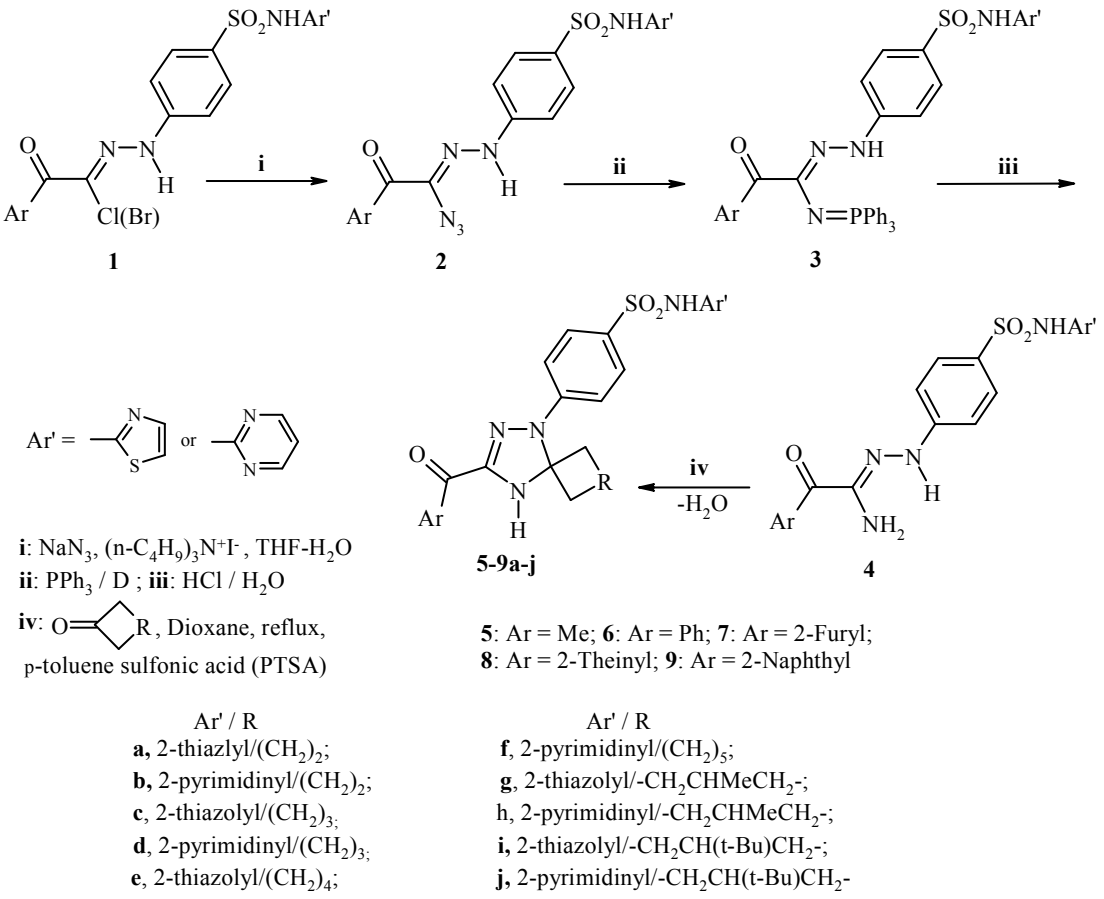

Figure 1. Synthetic pathway for the preparation of compounds **4** and **5-9a-j.**

Table 1. Antimicrobial screening results of the tested compounds

Cpd. No.	Diameter of the inhibition zone in mm*						
	Antibacterial activity					Antifungal activity	
	Euterococci	*E. coli*	*S. aureus*	*Klebsiella spp*	*Proteus spp*	*C. albicans*	*A. niger*
5a	16	17	17	13	16	15	14
5b	13	18	15	11	10	17	18
5c	19	15	11	14	16	18	16
5d	18	16	17	18	19	16	12
6b	16	19	16	19	11	19	11
7a	13	12	14	16	17	16	19
7b	19	15	11	14	16	18	16
8a	18	16	17	18	19	16	12
8b	16	19	16	19	11	19	11
9a	13	12	14	16	17	16	19
Tet.[a]	21	20	19	21	22	–	–
Flu.[b]	–	–	–	–	–	21	23
DMF	–	–	–	–	–	–	–

*Calculated as average of three values. [a]Tetracycline, [b]Fluconazole

A standard nutrient agar disc diffusion method[26,27] was followed to determine the activity of the synthesized compounds against the sensitive organisms *Euterococci*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella spp* and *Proteus spp*, as bacterial strains and two species of fungi, namely *Aspergillus niger* and *Candida albicans*. The compounds were tested at a concentration of 1 mg mL^{-1} in *N,N*-dimethyl formamide (DMF) solution, measuring the average diameter of the inhibition zone in mm. The results showed that all the tested compounds exhibited a marked degree of activity against bacteria and fungi compared with well-known antibacterial and antifungal substances such as tetracycline and fluconazole. According to NCCLS[27], inhibition zones for tetracycline and fluconazole < 14 mm is considered resistant, between 15 and 18 mm is considered weakly sensitive and > 19 mm is considered sensitive. Also, the results showed that the degree of inhibition varied with the tested compounds (Table 1). The thiazolyl and pyrimidinyl moieties generally led to a dramatic improvements in activity against both bacteria and fungi. The present study can lead medicinal chemists to design and synthesize similar compounds with enhanced biological potency in future.

4. Conclusion

New series of novel functionalized spiro1,2,4-triazols **5-9a-j** bearing sulfonamide moiety were synthesized upon treatment of amidrazones **4a-j** with cyclic ketones in refluxing dioxane, which were examined for their antimicrobial activities, and they were found to possess various antimicrobial activities towards all the microorganisms tested. Shortly, the biological activity is strongly dependent on the nature and size of the substituents on triazole ring.

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