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SYNTHESIS AND BIOLOGICAL ACTIVITIES EVALUATION OF SOME NEW SPIRO 1,2,4-TRIAZOLE DERIVATIVES HAVING SULFONAMIDE MOIETY

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ABSTRACT

A series of new spiro 1,2,4-triazoles **V-IXa-j** were synthesized by the reaction of appropriate amidrazones **IV** with cyclic ketones in the presence of *p*-toluene sulfonic acid as a catalyst. The structures of the synthesized compounds have been confirmed by the elemental analysis and spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR and MS). The microbial features of the synthesized compounds were studied using well-established methods from literature.

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

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GRAPHICAL ABSTRACT

Synthesis and Biological Activities Evaluation of Some New Spiro 1,2,4-Triazole Derivatives Containing Sulfonamide Moiety

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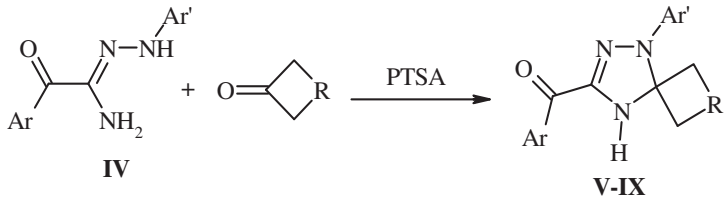

IV **V-IX**

V, Ar = Me; **VI**, Ar = Ph; **VII**, Ar = 2-Furyl;
VIII, Ar = 2-Tienyl; **IX**, Ar = 2-Naphthyl

1. Introduction

Amidrazones represent a class of substances with interesting biological properties. It has been established that they can exhibit antibacterial and antifungal [1-3], antitumor [4], or antituberculosis activities [5]. They were also found as effective herbicides [6], pesticides [7], and insecticides [8]. 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 [9-11] or as ligands in coordination chemistry. Amidrazones synthesized from different hydrazonoyl halides are reported to react with α-haloesters in the presence of triethylamine as a base under reflux afforded 1,3,5-substituted 4,5-dihydro-1,2,4-triazin-6-ones [12]. Several studies, involving 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 reported by Dalloul [14-17].

Sulfonamide derivatives exhibit a range of bioactivities, including anti-angiogenic, anti-tumor, anti-inflammatory and anti-analgesic, anti-tubercular, anti-glaucoma, anti-HIV, cytotoxic, anti-microbial and anti-malarial agents [18]. Taking into account all previous commentaries of the biological activities of sulfonamides and in continuation of our study on the synthesis of biologically active heterocycles [19-21], efforts have been made to synthesize a series of new spiro heterocycles containing 1,2,4-triazole and piperidone derivatives via cyclization of amidrazones having sulfonamide moiety with cyclic ketones in anticipation of expected interesting biological activities.

2. Results and Discussion

The precursors of amidrazones hydrazonoyl halides **I** employed in this study were prepared according to reported literature procedures [22-25]. Treatment of the hydrazonoyl halides **I** with sodium azide in presence of tetrabutylammonium iodide at room temperature gave azidohydrazones **II** (Figure). The obtained hydrazonoyl azides **II** reacted with triphenylphosphine afforded phosphonimines **III** (Figure). It was found that the hydrolysis of compounds **III** with aqueous hydrochloric acid gave the triphenylphosphine oxide and the amidrazones **IV,** respectively (Figure). The most plausible mechanism for this acid hydrolysis is the one that involves initial protonation of nitrogen followed by the attack of oxygen on the phosphorous atom [22].

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

2.2. Spectral data analysis of compounds IV and V-IXa-j.

The structure of the newly synthesized amidrazones **IV** was elucidated on the basis of their spectroscopic data and elemental analyses. The electron impact (EI) mass spectra of these compounds **4a-j** displayed the correct molecular ions ($M^{+\cdot}$) in accordance with the suggested structures. The IR spectra exhibit typical stretching absorption bands of C=O of conjugate ketone, anilide and ester groups at about 1725-1650 cm^{-1}, NH's in the region of 3470-3220 cm^{-1} and 1150, 1060 cm^{-1} attributed to SO_2 of sulfonamide group. The ^1H NMR spectra of these amidrazones DMSO-d_6 show three characteristic signals, as 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 in the range of 8.4-6.9 ppm. The ^{13}C NMR spectra exhibit characteristic signals for the Ar-C=O carbon at about 192-159 ppm and for the C=N moiety at about 143-141 ppm.

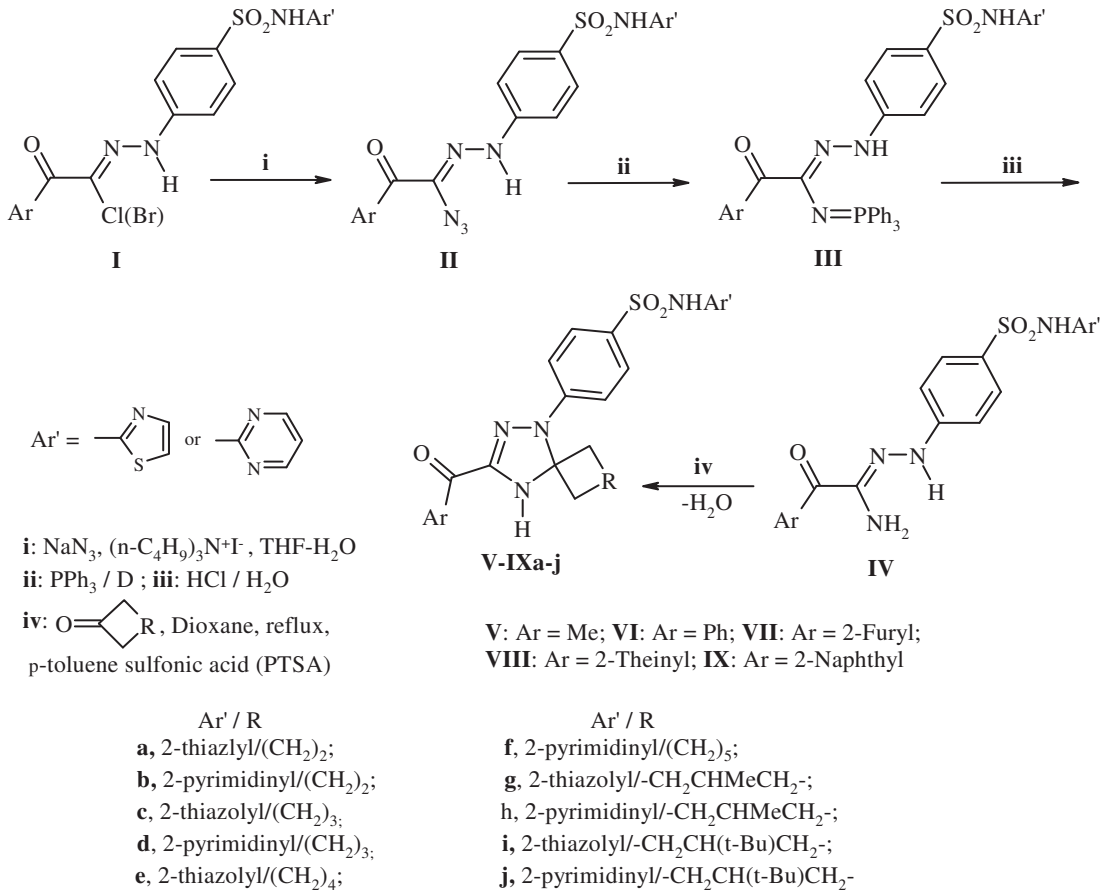

Figure. Synthetic pathway for the preparation of compounds **IV** and **V-IXa-j.**

The structural assignment of the prepared spiro 1,2,4-triazoles **V-IXa-j** was based on elemental analysis and spectral data. The electron impact (EI) mass spectra of these compounds **4a-j** displayed the correct molecular ions ($M^{+\cdot}$) in accordance with the suggested structures. 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 resonated near 3370-3350 cm^{-1}. In addition to the bands of characteristic functional groups. The ^{1}H NMR spectra of products **V-IXa-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 exhibit a characteristic singlet at 12.7-12.6 ppm due to SO_2NH proton. The ^{13}C NMR spectra display characteristic signals of the suggested structures. The signal at 90-95 ppm, which is attributed to C-5 (spiro carbon) of dihydrotriazole ring is of special significance. This is similar to reported values of spiro carbons flanked by two nitrogens in five-membered heterocycles [23,26]. The spectral data of the obtained compounds **IVa-j** are summarized in the experimental section.

2.2. Antimicrobial activity

The standard nutrient agar disc diffusion method[35,36] was followed to determine the activity of the synthesized compounds against the sensitive organisms *Euterococci, Escherichia coli*, *Staphylococcus aureus*, *Klebsiella spp*, *Proteus spp*, as bacterial strains and two species of fungi, namely *Aspergillus niger*, *Candida albicans*. The compounds tested at a concentration of 1 mg mL^{-1} in N,N-dimethyl formamide (DMF) solution, and 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], 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. Also, the results showed the degree of inhibition varied with the tested compounds (Table). The thiazolyl and pyrimidinyl moieties generally led to 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.

Table. Antimicrobial screening results of the tested compounds

Cpd. No.	Diameter of the inhibition zone in mm*						
	Antibacterial activity					Antifungal activity	
	Euterococci	*Escherichia coli*	*Staphylo aureus*	*Klebsiella spp*	*Proteus spp*	*Candida albicans*	*Aspergillus niger*
Va	16	17	17	13	16	15	14
Vb	13	18	15	11	10	17	18
Vc	19	15	11	14	16	18	16
Vd	18	16	17	18	19	16	12
VIb	16	19	16	19	11	19	11
VIIa	13	12	14	16	17	16	19
VIIb	19	15	11	14	16	18	16
VIIIa	18	16	17	18	19	16	12
VIIIb	16	19	16	19	11	19	11
IXa	13	12	14	16	17	16	19
DMF	–	–	–	–	–	–	–

*Calculated as average of three values.

3. EXPERIMENTAL SECTION

3.1. 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 **IV** were prepared according to literature procedures [22-25]. Sodium azide, triphenylphosphine and tetrabutylammonium iodide were obtained from Fluka Chemie Company, Switzerland. Sulfathiazole, sulfadiazine, dioxane, tetrahydro-furan (THF) and triethylamine were purchased from Avocado Research Chemicals, England, and used without further purification.

3.2. Synthesis of spiro 4,5-dihyro-1,2,4-triazole derivatives V-IXa-j.

To a stirred solution of the appropriate amidrazone **IV** (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 (Va); 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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 192.3 (C=O), 169.1-116.5 (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 (Vb): 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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 192.1 (C=O), 168.19-110.6 (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 (Vc): 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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 192.4 (C=O), 168.4-116.2 (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 (Vd): 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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 191.9 (C=O), 168.25-110.4 (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 (Ve): Yield: 67%; m.p.: 178-180 ^{o}C; IR (KBr) ν_{max}: cm^{-1} 3375, 3358 (NH's), 1695 (CH_3-C=O), 1625 (C=N), 1346, 1175 (SO_2); ^{1}H NMR ($CDCl_3$): 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 ($CDCl_3$): *δ* 192.4 (C=O), 168.2-116.5 (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 (Vf): 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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 191.8 (C=O), 168.25-110.4 (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 (Vg): 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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 192.3 (C=O), 168.05-116.5 (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 (Vh): 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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 192.2 (C=O), 168.1-110.2 (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 (Vi): 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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 189.9 (C=O), 168.2-116.5 (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 (Vj): 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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 189.9 (C=O), 168.2-116.5 (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 (VIa): Yield: 66%; m.p.: 219-221 ^{o}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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 185.2 (C=O), 167.9-116.2 (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 (VIb): Yield: 67%; m.p.: 236-238 ^{o}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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 185.5 (C=O), 168.1-110.2 (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 (VIIa): Yield: 70%; m.p.: 197-199 ^{o}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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 173.6 (C=O), 168.2-116.4 (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 (VIIc): Yield: 71%; m.p.: 226-228 ^{o}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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 173.5 (C=O), 168.2-116.5 (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 (VIIIa): Yield: 72%; m.p.: 218-220 ^{o}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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 174.6 (C=O), 168.1-116.2 (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 (VIIId): Yield: 73%; m.p.: 198-200 ^{o}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 ($CDCl_3$): 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 ($CDCl_3$): *δ* 174.8 (C=O), 168.4-110.5 (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 (IXa): Yield: 61%; m.p.: 212-213 ^oC; IR (KBr) ν_{max}: cm^{-1} 3369, 3350 (NH), 1606 (Ar-C=O), 1608 (C=N), 1346, 1175 (SO_2); ^1H NMR ($CDCl_3$): 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 ($CDCl_3$): δ 185.4 (C=O), 168.0-116.2 (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 (IXb): Yield: 62%; m.p.: 165-167 ^oC; IR (KBr) ν_{max}: cm^{-1} 3367, 3355 (NH's), 1655 (Ar-C=O), 1605 (C=N), 1346, 1175 (SO_2); ^1H NMR ($CDCl_3$): 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 ($CDCl_3$): δ 185.6 (C=O), 168.2-110.4 (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.

4. CONCLUSION

New series of novel functionalized spiro1,2,4-triazols **V-IXa-j** bearing sulfonamide moiety were synthesized upon the treatment of amidrazones **Va-j** with cyclic ketones in refluxing dioxane 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 triazole ring.

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