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Synthesis and biological evaluation of pyrazole analogues linked with 1,2,3-triazole and 4-thiazolidinone as antimicrobial agents

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A B S T R A C T

A new series of 2-[3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-4-pyrazolyl]-3-aryl-1,3-thiazolan-4-one **5(a-i)** have been designed, synthesized and evaluated for their *in vitro* antibacterial activity against Gram positive bacteria viz. *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538p), *Micrococcus luteus* (IFC 12708) and Gram negative bacteria viz. *Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028), *Escherichia coli* (ATCC 25922) the antifungal activity against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), *Trichophyton mentagrophytes* (IFO 40996). Antibacterial evaluation indicates that compounds containing 4-methoxyphenyl **5c**, 4-fluorophenyl **5d** and 2,5-difluorophenyl **5h** groups on thiazolidinone ring showed significant activity equal to that of standard drug. The antifungal evaluation shows that compound **5c** is highly active against *A. fumigatus,* compound **5d** and **5h** were also active against *C. albicans* and *A. fumigatus.*

1. Introduction

Pyrazole is an important heterocyclic scaffold and present as main core and integral part of many naturally occurring or synthetic compounds which showed therapeutically important activities such as anticancer,[1] antidiabetic,[2] anticonvulsant,[3] analgesic,[4] antiinflammatory,[5] antiviral,[6] antimicrobial[7] and hypoglycemic.[8] The clinically used drugs which containing pyrazole as core part and exhibited various biological activities such as analgesic and antipyretic (phenazone), analgesic and antipyretic (dipyrone), anti-inflammatory, antipyretic, and analgesic (aminophenazone), anti-inflammatory, antipyretic mainly used in osteoarthritis, rheumatoid arthritis, spondylitis, Reiter's disease (phenylbutazone), chronic gout (sulfinpyrazone), and antipyretic, analgesic, antiinflammatory, mild uricosuric (oxyphenbutazone).

Similarly, the 4-thiazolidinones are derivatives of thiazolidine with a carbonyl group at the fourth position. This is a core structure in various synthetic pharmaceuticals[9-12] displaying a broad spectrum of biological activities such as sedative,[13] antiinflammatory,[14] antibacterial,[15] antifungal,[16] antitubercular,[17] analgesic and antipyretic,[18] anestetic,[19] CNS stimulant,[20] hypnotic,[21] anti-HIV and nematicidal.[22] Further, the triazole scaffold is also biologically important and exhibited various activities such as antitubercular,[23] anti-HIV,[24] antiallergenic,[25] cytostatic,[26] virostatic,[27] anticancer,[28] anticonvulsant,[29] analgesic[30] and antiinflammatory[31] activities. Triazoles are also being studied for the treatment of obesity[32] and osteoarthritis.[33] There are a number of drugs, which are containing triazole nucleus, *viz*. Fluconazole,[34] Isavuconazole,[35] Itraconazole,[36] Voriconazole,[37] Pramiconazole,[38] and Posaconazole,[39] that have been used for the treatment of fungal infections.

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Inspired by the biological profile of pyrazoles, thiazolidinones and triazole derivatives, it was thought worthwhile to design the hybrid molecules incorporating these heterocyclic rings for their varied biological activities. The present study deals with the synthesis of new 2-[3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-4-pyrazolyl]-3-aryl-1,3-thiazolan-4-one **5(a-i)** and evaluation of their antimicrobial activities.

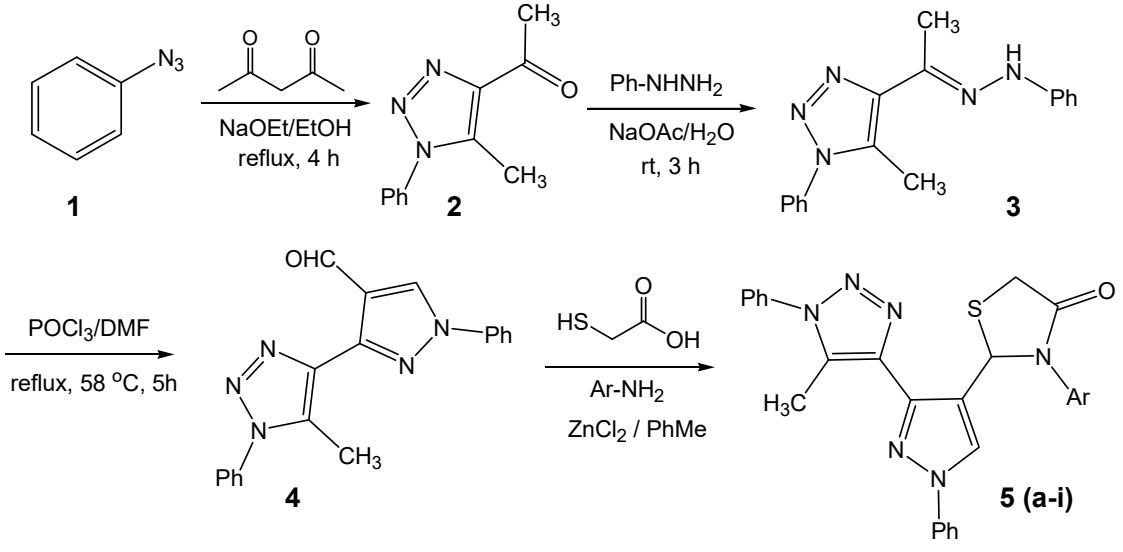
2. Results and Discussion

2.1. Chemistry

The reaction of phenylazide **1** with acetylacetone in the presence of anhydrous potassium carbonate in dimethylfomamide under stirring at reflux temperature 6-12 hours, afforded 1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-ethanone **2** in (2.39 g, 0.012 mol) 81% of yield[40], which on condensation with phenyl hydrazine hydrochloride in the presence of sodium acetate and in water under stirring at room temperature for 4 hours, furnished the 1-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-ethanone-1-phenyl hydrazone **3** in (2.32 g, 0.008 mol) 74% of yield[41]. The compounds **3** was treated with formyl solution (*N*,*N*-dimethylformamide and phosphorous oxychloride) under stirring at 55 ºC for 6 hours to afford the 3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-4-pyrazolecarbaldehyde **4** in (2.3 g, 0.007 mol) 69% of yield[41]. Further, compound **4** on condensation-cyclization with thioglycolic acid and primary aromatic amine in the presence of $ZnCl_2$ in dry toluene under microwave irradiation at 280 W for 4-7 minutes at 110ºC to afford 2-[3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-4-pyrazolyl]-3-aryl-1,3-thiazolan -4-one **5(a-i)** in 48-61% of yields (**Scheme 1**). The structures of the compounds were confirmed by their IR, NMR, MS spectral analyses.

The IR spectrum of compound **2**, the carbonyl C=O stretching frequency band observed at 1713 and C=N at 1619 cm^{-1}. The proton NMR spectrum, the methyl group on triazole ring and acetyl group appeared as a singlet at δ 2.32 and 2.50 ppm. The multiplet signal for aryl protons was observed in the range of δ 7.40-7.50 ppm. The carbon NMR spectrum, the carbons of the triazole ring were observed at δ 128.8 and 139.4 ppm. The mass spectrum showed a molecular ion peak at *m/z* 199 (M^+).

The IR spectrum of **3**, the disappearance of carbonyl C=O absorption band and appearance of C=N absorption band at 1682 cm^{-1} supported the condensation involving carbonyl group with hydrazine. Further, support obtained from the presence of an absorption band for N-H of amine at 3412 cm^{-1}. The proton NMR spectrum, the methyl protons appeared as two singlets at δ 2.14 and 2.72 ppm, the proton of NH group was observed as broad singlet at δ 8.12 ppm and the multiplet signals for the aromatic protons were observed in the range of δ 7.00-7.05 and 7.40-7.50 ppm. Further support was obtained from its carbon NMR spectrum for signals of carbons of triazole ring observed at δ 126.5 (C-5), 143.8 (C-4) ppm. The mass spectrum showed a molecular ion peak at *m/z* 291 (M^+).



5: **Ar** = a) phenyl; b) 4-methylphenyl; c) 4-methoxyphenyl; d) 4-fluorophenyl; e) 4-bromophenyl; f) 3-nitrophenyl; g) 4-nitrophenyl; h) 2,5--difluorophenyl; i) 4-hydroxyphenyl.

Scheme 1. Synthetic route for pyrazole analogues **5(a-i)**

The IR spectra of compounds **4**, the characteristic absorption of carbonyl C=O band of formyl group at 1707, C=N of pyrazole at 1677 and N=N of triazole absorption bands at 1529 cm^{-1}. The proton NMR spectrum, the formyl proton signals appeared as a singlet at δ 9.97 ppm, the methyl proton of triazole ring at δ 2.84 ppm, the other aryl proton signals as

multiplets in the regions of δ 7.30-7.40 and 8.10-8.15 ppm. The carbon NMR spectrum, the triazole ring carbons at δ 135.0 (C-5), 140.8 (C-4) and pyrazole ring carbons at 144.6 (C-3), 128.2 (C-4), 129.4 (C-5) and the formyl carbons appeared at δ 179.4 ppm. The mass spectrum showed a molecular ion peak at *m/z* 329 (M^+). The IR spectra of compounds **5a**, C=O of thiazolidinone, C=N of pyrazole and N=N of triazole absorption bands appeared at 1708, 1669 and 1533 cm^{-1}. Its ^1H NMR spectrum showed a signal at δ 7.15-7.20 and 7.35-7.45 ppm as multiplets for five and nine protons in each and a signal at δ 6.95 doublet with J = 8.7 Hz, integrating two protons assigned for aromatic protons respectively. A signal at δ 5.89 as singlet for one proton is assigned to CH-S and at δ 3.72 for two protons is assigned to the methylene group of thiazolidinone. The singlet signals at δ 2.78 for three protons are assigned to the methyl group. Its ^{13}C NMR spectrum exhibits the signal at δ 171.2 (N-CO), 61.1 (S-C-N) and 39.0 (CH_2-S) confirming its thiazolidinone ring. The triazole carbons appeared at δ 133.5 (C-5), 141.3 (C-4) and pyrazole carbons at δ 145.3 (C-3), 119.0 (C-4) and 130.8 (C-5). The mass spectrum showed a molecular ion peak at *m/z* 478 (M^+).

2.2. Antibacterial Activity

The *in vitro* antibacterial activity of compounds **5(a-i)** were evaluated against Gram +ve bacteria viz., *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538p), *Micrococcus luteus* (IFC 12708) and Gram -ve bacteria viz. *Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028), *Escherichia coli* (ATCC 25922) by broth dilution method[42]. The lowest concentration required to arrest the growth of bacteria was regarded as the minimum inhibitory concentration (MIC, µg/mL) was determined for all the compounds and presented in **Table 1**. All assays included the solvent and reference controls, Ampicillin was used as standard drug.

Table 1. *In vitro* antibacterial activity of compounds **5(a-i)**

Compound	Minimum inhibitory concentration (MIC μg/mL)					
	B. subtilis	***S. aureus***	***M. luteus***	***P. vulgaris***	***S. typhimurium***	***E. coli***
5a	12.5	25.0	25.0	—	25.0	—
5b	12.5	25.0	25.0	25.0	25.9	25.0
5c	1.56	1.56	1.56	3.12	3.12	25.0
5d	1.56	1.56	1.56	6.25	6.25	12.5
5e	12.5	25.0	12.5	—	—	—
5f	12.5	25.0	12.5	50.0	50.0	—
5g	25.0	25.0	50.0	50.0	—	—
5h	1.56	3.12	1.56	3.12	3.12	12.5
5i	25.0	12.5	25.0	50.0	50.0	50.0
Ampicillin	1.56	1.56	1.56	3.12	3.12	12.5

Note: — indicates, strains are resistant to the compound >25 μg/mL conc.

The antibacterial screening data revealed that all the tested compounds exhibited interesting biological activity, however, with a degree of variation. The structure activity relationship (SAR) studies indicates compounds containing 4-methoxyphenyl **5c**, 4-fluorophenyl **5d** and 2,5-difluorophenyl **5h** groups on thiazolidinone ring showed significant activity equal to that of standard drug against tested bacterial strains. The other compounds also exhibited considerable antibacterial activities and therefore emerged as potential molecules for their further development.

2.3. Antifungal Activity

The compounds **5(a-i)** were also screened for their antifungal activity against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996) in dimethyl sulfoxide (DMSO) by broth dilution method[42]. The minimum inhibitory concentrations (MIC, μg/mL) were measured and compared with Amphotericin B (**Table 2**).

Table 2. *In vitro* antifungal activity of compounds **5(a-i)**

Compound	Minimum Inhibitory Concentration (MIC) in μg/mL			
	C. albicans	***A. fumigatus***	***T. rubrum***	***T. mentagropytes***
5a	12.5	6.25	25.0	12.5
5b	12.5	12.5	12.5	25.0
5c	3.12	1.56	3.12	12.5
5d	1.56	1.56	3.12	12.5
5e	6.25	6.25	25.0	50.0
5f	6.25	12.5	50.0	25.0
5g	12.5	12.5	12.5	25.0
5h	1.56	1.56	3.12	6.25
5i	6.25	6.25	25.0	50.0
Amphotericin B	1.56	1.56	1.56	3.12

— indicates bacteria are resistant to the compound >50 µg/mL concentration.

The antibacterial activity and structure activity relationship (SAR) studies reveals that, compound **5c** showed significant against *A. fumigatus,* compound **5d** and **5h** were also active against *C. albicans* and *A. fumigatus.*, the activity of these compounds are almost equal to the standard.

3. Conclusions

The new series of 2-[3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-phenyl-1*H*-4-pyrazolyl]-3-aryl-1,3-thiazolan-4-one **5(a-i)** have been designed, synthesized and evaluated for their antimicrobial activities. Antibacterial evaluation indicates that compounds containing 4-methoxyphenyl **5c**, 4-fluorophenyl **5d** and 2,5-difluorophenyl **5h** groups on thiazolidinone ring showed significant activity equal to that of standard drug. The antifungal evaluation shows that compound **5c** is highly active against *A. fumigatus,* compound **5d** and **5h** were also active against *C. albicans* and *A. fumigatus.*

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4. Experimental

4.1. Materials and Methods

All reagents are commercial grade and were used as supplied. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck, and compounds visualized by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported in δ ppm units with respect to TMS as internal standard and coupling constants (*J*) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer.

4.2. General Procedure

*4.2.1. Synthesis of 1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-ethanone (**2**)*

To a mixture of phenylazide **1** (0.01 mol), acetylacetone (0.02 mol) in DMF (30 mL), anhydrous K_2CO_3 (0.06 mol) was added and with stirring at reflux temperature for 6-12 hours. The reaction mixture was cooled and removed the solvent, poured into ice water and then neutralized with 5% hydrochloric acid and extracted with dichloromethane followed by purified by chromatographic column on silica gel using using petroleum ether/ethyl acetate (8:1-6:1), afforded pure compound **2** in (2.39 g, 0.012 mol) 81% of yield.

*4.2.2. Synthesis of 1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-ethanone-1-phenylhydrazone (**3**)*

To a mixture of compound **2** (0.01 mol) and phenyl hydrazine hydrochloride (0.012 mol) in water (100 mL), NaOAc (0.015 mol) was added and stirred at room temperature for 4 hours, a large amount of yellow solid emerged and was filtered and purified by recrystalization using ethyl alcohol to give pure compound **3** in (2.32 g, 0.008 mol) 74% of yield.

*4.2.3. Synthesis of 3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolecarbaldehyde (**4**)*

To a cold solution of *N*,*N*-dimethylformamide (7.5 mL), freshly distilled phosphorous oxychloride (2.5 mL) was added with stirring over a period of 30 minutes. When formylation solution was obtained, a solution of compound **3** (0.01 mol) in *N,N*-dimethylformamide (5 ml) was added and stirred at reflux temperature for 6 hours, after completion of the reaction it was poured into ice cold water and neutralized with saturated solution of NaOH, the solid emerged was filtered, washed with water and dried and recrystalized using ethyl alcohol to give pure compound **4** in (2.3 g, 0.007 mol) 69% of yield.

*4.2.4. General procedure for the synthesis of 2-[3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolyl]-3-aryl-1,3-thiazolan-4-one **5(a-i)***

To a stirred mixture of **4** (0.001 mol), aromatic amine (0.0014 mol) and thioglycolic acid (0.015 mol) in dry toluene (5 mL), $ZnCl_2$ (0.001 mol) was added after 2 min and irradiated in a microwave oven at 280 W for 4-7 minutes at 110ºC. After cooling, the solvent was removed and extracted with ethyl acetate and purified the crude compound using column chromatography on silica gel using hexane ethyl acetate (4:6) to give pure compounds **5(a-i)** in 48-61% of yields.

4.3. Physical and Spectral Data

*1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-ethanone (**2**):* IR (KBr) ν_{max}: 3057, 2978, 1714, 1619, 1548, 1467 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.40-7.50 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.9, 29.6, 114.7, 128.8, 134.3, 139.0, 139.9, 193.1; MS: *m/z* 199 (M^+). Anal. Calcd. for $C_{11}H_{11}N_3O$ (201.22): C, 65.66; H, 5.51; N, 20.88. Found: C, 65.61; H, 5.57; N, 20.81.

*1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-ethanone 1-phenylhydrazone (**3**):* IR (KBr) ν_{max}: 3412 (O-H), 3057 (C-H, Ar), 2975 (C-H, Ali), 1682 (C=N), 1533 (N=N), 1271 (C-N) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.14 (s, 3H, CH_3), 2.72

(s, 3H, CH_3), 7.00-7.05 (m, 5H, ArH), 7.40-7.50 (m, 5H, ArH), 8.12 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8, 22.1, 114.7, 123.9, 124.8, 126.5, 126.9, 127.4, 129.0, 135.2, 142.9, 143.8, 146.7; MS: *m/z* 291 (M^+). Anal. Calcd. for $C_{17}H_{17}N_5$ (291.35): C, 70.08; H, 5.88; N, 24.04. Found: C, 70.00; H, 5.76; N, 24.01.

*3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolecarbaldehyde (**4**):* IR (KBr) ν_{max}: 3071 (C-H, Ar), 2934 (C-H, Ali), 1705 (C=O), 1677 (C=N), 1529 (N=N), 1262 (C-N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.84 (s, 3H, CH_3), 7.30-7.40 (m, 8H, ArH), 8.10-8.15 (m, 2H, ArH), 9.97 (s, 1H, CHO); ^{13}C NMR (75 MHz, DMSO-d_6): δ 19.5, 118.7, 126.9, 127.9, 128.2, 129.4, 130.4, 131.6, 132.1, 135.0, 138.1, 138.9, 140.8, 144.6, 179.4; MS: *m/z* 329 (M^+). Anal. Calcd. for $C_{19}H_{15}N_5O$ (329.26): C, 69.29; H, 4.59; N, 21.26. Found: C, 69.22; H, 4.53; N, 21.27.

*2-[3-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolyl]-3-phenyl-1,3-thiazolan-4-one (**5a**):* Yield (0.25 g) 48%; IR (KBr) ν_{max}: 3078 (C-H, Ar), 2949 (C-H, Ali), 1708 (C=O), 1669 (C=N), 1533 (N=N), 1267 (C-N), 878 (S-C-N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.78 (s, 3H, CH_3), 3.72 (s, 2H, CH_2), 5.89 (s, 1H, CH), 6.95 (d, J = 8.7 Hz, 2H, ArH), 7.15-7.20 (m, 5H, ArH), 7.35-7.45 (m, 9H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.5, 39.0, 61.1, 117.6, 119.0, 124.5, 125.7, 126.9, 127.1, 127.8, 128.7, 129.7, 129.9, 130.8, 131.8, 133.5, 137.8, 139.1, 141.3, 145.3, 171.2; MS: *m/z* 478 (M^+). Anal. Calcd. for $C_{27}H_{22}N_6OS$ (478.57): C, 67.76; H, 4.63; N, 17.56. Found: C, 67.71; H, 4.59; N, 17.52.

*3(4-Methylphenyl)-2-[3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolyl]-1,3-thiazolan -4-one (**5b**):* Yield (0.28 g) 51%; IR (KBr) ν_{max}: 3054 (C-H, Ar), 2976 (C-H, Ali), 1710 (C=O), 1662 (C=N), 1534 (N=N), 1268 (C-N), 879 (S-C-N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 5.91 (s, 1H, CH), 7.15-7.20 (m, 6H, ArH), 7.35-7.45 (m, 9H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.5, 27.1, 39.0, 61.1, 117.6, 119.0, 126.2, 126.9, 126.9, 127.1, 127.6, 128.7, 129.7, 130.8, 131.8, 133.5, 134.0, 137.8, 139.1, 141.3, 145.3, 171.2; MS: *m/z* 492 (M^+). Anal. Calcd. for $C_{28}H_{24}N_6OS$ (492.59): C, 68.27; H, 4.91; N, 17.06. Found: C, 68.22; H, 4.88; N, 17.02.

*3(4-Methoxyphenyl)2-[3(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolyl]-1,3-thiazolan -4-one (**5c**):* Yield (0.3 g) 53%; IR (KBr) ν_{max}: 2955 (C-H, Ali), 1705 (C=O), 1663 (C=N), 1531 (N=N), 1072 (O-C), 1266 (C-N), 878 (S-C-N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.19 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 3.77 (s, 2H, CH_2), 5.82 (s, 1H, CH), 6.86 (d, J = 8.2 Hz, 2H, ArH), 7.15-7.20 (m, 4H, ArH), 7.35-7.45 (m, 9H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.5, 39.0, 58.2, 61.1, 114.3, 117.6, 119.0, 120.6, 125.8, 126.9, 127.1, 128.7, 129.7, 130.8, 131.8, 133.5, 137.8, 139.1, 141.3, 145.3, 155.2, 171.2; MS: *m/z* 508 (M^+). Anal. Calcd. for $C_{28}H_{24}N_6O_2S$ (508.59): C, 66.12; H, 4.76; N, 16.52. Found: C, 66.08; H, 4.71; N, 16.48.

*3-(4-Fluorophenyl)-2-[3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolyl]-1,3-thiazo- lan-4-one (**5d**):* Yield (0.29 g) 53%; IR (KBr) ν_{max}: 3082 (C-H, Ar), 1702 (C=O), 1660 (C=N), 1534 (N=N), 1314 (C-F), 1260 (C-N), 878 (S-C-N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.79 (s, 3H, CH_3), 3.74 (s, 2H, CH_2), 5.85 (s, 1H, CH), 7.15-7.20 (m, 6H, ArH), 7.35-7.45 (m, 9H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.5, 39.0, 61.1, 114.0, 117.6, 119.0, 125.4, 126.9, 127.1, 128.7, 129.7, 130.8, 131.8, 132.1, 133.5, 137.8, 139.1, 141.3, 145.3, 162.1, 171.2; MS: *m/z* 496 (M^+). Anal. Calcd. for $C_{27}H_{21}FN_6OS$ (496.56): C, 65.31; H, 4.26; N, 16.92. Found: C, 65.28; H, 4.23; N, 16.94.

*3-(4-Bromophenyl)-2-[3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolyl]-1,3-thiazo- lan-4-one (**5e**):* Yield (0.37 g) 58%; IR (KBr) ν_{max}: 1710 (C=O), 1671 (C=N), 1539 (N=N), 1265 (C-N), 875 (S-C-N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.76 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 5.92 (s, 1H, CH), 7.15-7.20 (m, 6H, ArH), 7.35-7.45 (m, 9H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.5, 39.0, 61.1, 117.6, 118.5, 119.0, 126.9, 127.1, 127.9, 128.7, 129.7, 130.8, 131.2, 131.8, 132.0, 133.5, 137.8, 139.1, 141.3, 145.3, 171.2; MS: *m/z* 557 (M^+). Anal. Calcd. for $C_{27}H_{21}BrN_6OS$ (557.46): C, 58.17; H, 3.80; N, 15.08. Found: C, 58.22; H, 3.76; N, 15.02.

*2-[3-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolyl]-3-(3-nitrophenyl)-1,3-thiazolan-4-one (**5f**):* Yield (0.36 g) 61%; IR (KBr) ν_{max}: 3061 (C-H, Ar), 1704 (C=O), 1670 (C=N), 1560 (N=O), 1535 (N=N), 1261 (C-N), 872 (S-C-N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.71 (s, 3H, CH_3), 3.74 (s, 2H, CH_2), 5.85 (s, 1H, CH), 7.15-7.20 (m, 5H, ArH), 7.35-7.45 (m, 7H, ArH), 8.42-8.50 (3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.5, 39.0, 61.1, 115.3, 117.6, 118.0, 119.0, 126.9, 127.1, 128.7, 128.9, 129.0, 129.7, 130.8, 131.8, 133.5, 135.4, 137.8, 139.1, 141.3, 145.3, 146.1, 171.2; MS: *m/z* 523 (M^+). Anal. Calcd. for $C_{27}H_{21}N_7O_3S$ (523.57): C, 61.94; H, 4.04; N, 18.73. Found: C, 61.90; H, 4.05; N, 18.68.

*2-[3-(5-Methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolyl]-3-(4-nitrophenyl)-1,3-thiazolan-4-one (**5g**):* Yield (0.32 g) 54%; IR (KBr) ν_{max}: 3079 (C-H, Ar), 1701 (C=O), 1667 (C=N), 1559 (N=O), 1532 (N=N), 1267 (C-N), 875 (S-C-N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.77 (s, 3H, CH_3), 3.76 (s, 2H, CH_2), 5.87 (s, 1H, CH), 7.15-7.20 (m, 4H, ArH), 7.35-7.45 (m, 7H, ArH), 7.85 (d, J = 8.6 Hz, 2H, ArH), 8.12 (d, J = 8.6 Hz, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.5, 39.0, 61.1, 117.6, 119.0, 123.9, 126.9, 127.1, 127.9, 128.7, 129.7, 130.8, 131.8, 132.6, 133.5, 137.8, 139.1, 141.3, 143.1, 145.3, 171.2; MS: *m/z* 523 (M^+). Anal. Calcd. for $C_{27}H_{21}N_7O_3S$ (523.57): C, 61.94; H, 4.04; N, 18.73. Found: C, 61.89; H, 4.06; N, 18.70.

*3-(2,5-Difluorophenyl)-2-[3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolyl]-1,3-thiazolan-4-one (**5h**):* Yield (0.34 g) 59%; IR (KBr) ν_{max}: 3055 (C-H, Ar), 2978 (C-H, Ali), 1711 (C=O), 1664 (C=N), 1535 (N=N), 1266 (C-N), 875 (S-C-N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.76 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 5.92 (s, 1H, CH), 6.85 (m, 1H, ArH), 7.15-7.20 (m, 6H, ArH), 7.35-7.45 (m, 7H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.5, 39.0, 61.1, 109.0, 115.8, 116.9, 117.6, 118.2, 119.0, 126.9, 127.1, 128.7, 129.7, 130.8, 131.8, 133.5, 137.8, 139.1, 141.3, 145.3, 154.2, 165.4,

171.2; MS: *m/z* 514 (M^+). Anal. Calcd. for $C_{27}H_{20}F_2N_6OS$ (414.55): C, 63.02; H, 3.92; N, 16.33. Found: C, 63.06; H, 3.90; N, 16.30.

*3-(4-Hydroxyphenyl)-2-[3-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-1-phenyl-1H-4-pyrazolyl]-1,3-thiazo- lan-4-one (**5i**):* Yield (0.29 g) 53%; IR (KBr) ν_{max}: 3433 (O-H), 2988 (C-H, Ali), 1704 (C=O), 1664 (C=N), 1531 (N=N), 1267 (C-N), 874 (S-C-N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.74 (s, 3H, CH_3), 3.71 (s, 2H, CH_2), 5.32 (s, 1H, OH), 5.87 (s, 1H, CH), 6.89 (d, J = 8.3 Hz, 2H, ArH), 7.15-7.20 (m, 4H, ArH), 7.35-7.45 (m, 9H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.5, 39.0, 61.1, 115.7, 117.6, 119.0, 121.6, 122.8, 126.9, 127.1, 128.7, 129.7, 130.8, 131.8, 133.5, 137.8, 139.1, 141.3, 145.3, 154.1, 171.2; MS: *m/z* 494 (M^+). Anal. Calcd. for $C_{27}H_{22}N_6O_2S$ (494.57): C, 65.57; H, 4.48; N, 16.99. Found: C, 65.52; H, 4.42; N, 16.93.

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