Synthesis and Antimicrobial Study of Linked Heterocyclics Containing Pyrazole-pyrimidine-thiazolidin-4-one

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A new series of linked heterocyclics, 3-[4-(4-chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(aryl/heteryl)-1,3-thiazolan-4-ones (6a—j), has been synthesized by the one-pot cyclo-condensation of 4-(4-chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinamine (5), aryl/heteroaryl aldehyde and thioglycolic acid. The structures of the synthesized compounds have been confirmed *via* IR, ^{1}H-NMR, ^{13}C-NMR, MS and elemental analyses. Further, all the newly synthesized compounds 6a—j have been assayed for their antimicrobial activity against Gram-positive and Gram-negative bacteria and fungi. The compounds containing moieties like 4-nitrophenyl (6c), 3-nitrophenyl (6d), 4-dimethylaminophenyl (6g), 2-furyl (6i) and 1,3-benzodioxole (6j), at 2-position of thiazolidin-4-one ring exhibited good inhibitory activity against all the tested organisms.

Key words thiazolidin-4-one; pyrimidine; antimicrobial activity

Pyrimidines have a unique place and have contributed significantly to biological and medicinal fields.[1)] Pyrimidine ring systems containing substituted six membered ring exhibit anticancer and herbicidal activities.[2,3)] In recent years pyrimidine derivatives have received significant attention owing to their diverse range of biological properties, particularly, antitubercular[4)] and calcium channel blockers.[5)] 3-Azido-3-deoxythymidine (AZT),[6)] a pyrimidine derivative, has been found to be a potent antiviral agent against human immunodeficiency virus (HIV) type 1 *in vitro*, and has found to decrease mortality and opportunistic infections in patients with AIDS. Similarly, there has been a considerable interest in the chemistry of thiazolidin-4-one ring system, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities.[7)] Thiazolidin-4-one ring also occurs in nature; thus actithiazic acid isolated from *Streptomyces* strains exhibits highly specific *in vitro* activity against *Mycobacterium tuberculosis*.[8)] Thiazolidin-4-one derivatives are also known to exhibit diverse bioactivities such as anti-convulsant,[9)] antidiarrheal,[10)] anti-platelet activating factor,[11)] anti-histaminic,[12)] anti-diabetic,[13)] cyclooxygenase (COX) inhibitory,[14)] Ca^{2+}-channel blocker,[15)] platelet activating factor (PAF) antagonist,[16)] cardioprotective,[17)] anti-ischemic,[18)] anti-cancer,[19)] tumor necrosis factor-α antagonist[20)] and nematicidal activities,[21)] On the other hand, pyrazole and their derivatives exhibit significant biological activities such as antidepressant,[22)] inhibitors of protein kinases,[23)] antiagreegating,[24)] antiarthritic[25)] and cerebroprotectors.[26)] Some aryl pyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory,[27)] COX-2 inhibitory[28)] activator of the nitric oxide receptor and soluble guanylate cyclase activity.[29)]

In view of these reports and in continuation of our ongoing research on the synthesis of new heterocyclic derivatives,[30—36)] it was thought of interest to accommodate pyrimidine, pyrazole and thiazolidin-4-one moieties in a single molecular frame work and to obtain new heterocyclic compounds with potential biological activity. In the present study we report the synthesis and antimicrobial evaluation of some new 3-[4-(4-chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(aryl/heteryl)-1,3-thiazolan-4-ones.

Results and Discussion

Synthesis The compound **1** on cyclo-condensation with phenyl hydrazine in ethanol at reflux for 3 h gave the 3,5-dimethyl-1-phenyl-1*H*-pyrazole (**2**) in 90% yield. Formylation of **2** with *N*,*N*-dimethylformamide (DMF) in phosphorous oxychloride, at reflux for 1 h, gave the 3,5-dimethyl-1-phenyl-1*H*-4-pyrazolecarb-aldehyde (**3**) in 86% yield. The compound **3** on Claisen condensation with 4-chloroacetophenone in ethanol, in the presence of 60% aq. KOH, at room temperature for 6 h, afforded the (*E*)-1-(4-chlorophenyl)-3-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-propen-1-one (**4**) in 72% yield. The cyclo-condensation of **4** with guanidine hydrochloride, in the presence of aq. NaOH, in ethanol at reflux for 6 h, afforded the 4-(4-chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinamine (**5**) in 75% yield. Further, the one-pot cyclo-condensation of **5** with aryl/heteroaryl aldehyde and thioglycolic acid, in the presence of $ZnCl_2$ in toluene at reflux temperature for 5 h, produced 3-[4-(4-chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(aryl/heteroaryl)-1,3-thiazolan-4-ones (**6a**—**j**) in good yield (Chart 1, Table 1). Chemical structures of all the newly prepared compounds were confirmed by their elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and MS spectral data.

In the IR spectra of compounds **6a**—**j**, disappearance of amine (NH_2) absorption in the region 3390—3250 cm^{-1}, which was present in the compound **5**, confirms the cyclization with the involvement of NH_2 group. In addition, the absorption bands corresponding to C=O and N–C–S of the thiazolidin-4-one ring were observed at about 1696 and 712 cm^{-1} respectively. Additional support, for the formation of thiazolidin-4-one ring, was obtained from the ^{1}H-NMR spectra; the CH_2–CO protons of thiazolidin-4-one ring appeared at 3.67—3.70 ppm, and the N–CH–S proton of thiazolidin-4-one ring appeared at 5.86 ppm. In the ^{13}C-NMR spectra, prominent signals corresponding to carbons of thiazolidin-4-one, pyrimidine and pyrazole rings, for all the compounds, were observed nearly at 39.1, 69.6 and 177.8 ppm, at

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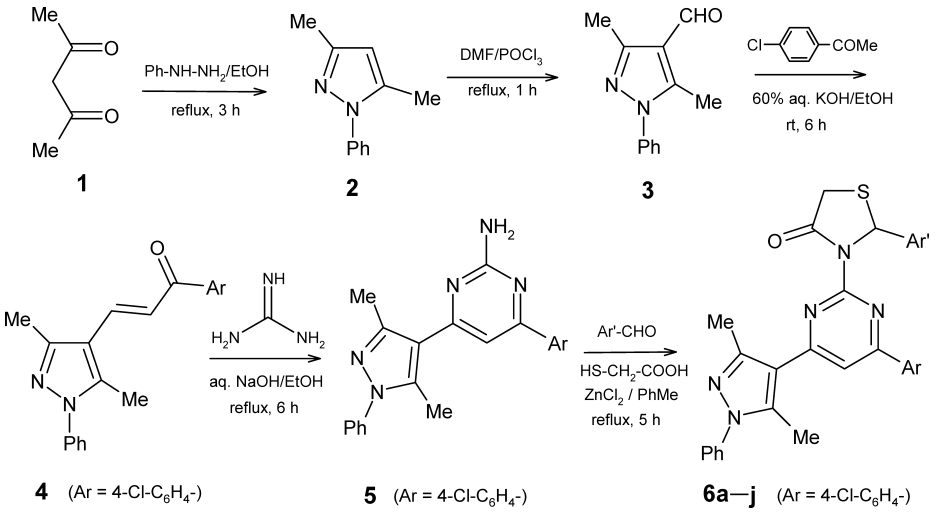

Chart 1

Table 1. Physical Charecterization of Synthesized Compounds (**2**—**6**)

Product	Ar′	Mol. formula	Yield (%)	mp (°C)
2	—	$C_{11}H_{12}N_2$	90	270—272
3	—	$C_{12}H_{12}N_2O$	86	124—126
4	—	$C_{20}H_{17}ClN_2O$	72	131—133
5	—	$C_{21}H_{18}ClN_5$	75	145—146
6a	4-(CH_3)-C_6H_4-	$C_{31}H_{26}ClN_5OS$	73	176—178
6b	4-Cl-C_6H_4-	$C_{30}H_{23}Cl_2N_5OS$	68	166—168
6c	4-(NO_2)-C_6H_4-	$C_{30}H_{23}ClN_6O_3S$	67	205—207
6d	3-(NO_2)-C_6H_4-	$C_{30}H_{23}ClN_6O_3S$	69	210—212
6e	4-(OH)-C_6H_4-	$C_{30}H_{24}ClN_5O_2S$	70	183—185
6f	2-(OH)-C_6HH_4-	$C_{30}H_{24}ClN_5O_2S$	71	177—179
6g	4-$N(CH_3)_2$-C_6H_4-	$C_{32}H_{29}ClN_6OS$	74	181—183
6h	4-(OH)-3-(OCH_3)-C_6H_3-	$C_{31}H_{26}ClN_5O_3S$	70	189—191
6i	2-Furyl	$C_{28}H_{22}ClN_2O_2S$	65	200—202
6j	5-(1,3-Benzodioxole)	$C_{31}H_{24}ClN_5O_3S$	67	194—196

121.3, 158.5, 161.7 and 174.2 ppm and at 120.6, 140.4 and 141.0 ppm respectively, are proofs of further evidence of their structures. In summary, all the newly synthesized compounds showed satisfactory spectral data consistent with their structures. Elemental analyses are also consistent with structures proposed for compounds **6a**—**j**.

Biological Properties. Antibacterial Activity All the newly synthesized compounds **6a**—**j** were assayed for their antibacterial activity against Gram-positive bacteria *viz. Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 11), and *Staphylococcus aureus* (MTCC 96), and Gram-negative bacteria *viz. Pseudomonas aeruginosa* (MTCC 741), *Klobsinella aerogenes* (MTCC 39), and *Chromobacterium violaceum* (MTCC 2625) by disc diffusion and broth dilution methods.[37] For the antibacterial assay, standard inoculums ($1—2\times10^7$ colony forming unit (c.f.u.)/ml 0.5 Mc Farland standards) were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The discs measuring 6.26 mm in diameter were prepared from Whatman no. 1 filter paper and sterilized by dry heat at 140 °C for 1 h. The sterile discs previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. The plates were inverted and incubated for 24 h at 37 °C. The inhibition zones were measured and compared with the standard drug penicillin (Table 2). For the determination of minimal inhibitory concentration (MIC), bacteria were grown over night in Luria Bertani (LB) broth at 37 °C harvested by centrifugation, and then washed twice with sterile distilled water. Stock solutions of the series of compounds were prepared in dimethyl sulfoxide (DMSO). Each stock solution was diluted with standard method broth (Difco) to prepare serial two-fold dilutions in the range of 50—0.8 μg/ml. Ten microliters of the broth containing about 10^5 c.f.u./ml of test bacteria were added to each well of 96-well microtiter plate. Culture plates were incubated for 24 h at 37 °C and the growth was monitored visually and spectrometrically. The MIC, (μg/ml) values were measured and compared with the standard drug penicillin (Table 2).

Antibacterial screening data revealed that all the tested compounds **6a**—**j** are active and showed moderate to good antibacterial activity towards all the tested strains. Compounds containing 4-nitrophenyl (**6c**), 3-nitrophenyl (**6d**), 4-dimethylaminophenyl (**6g**) and 1,3-benzodioxole (**6j**) moieties at 2-position of the thiazolidin-4-one ring exhibited potent inhibitory activity towards all the tested microorganisms. Further, the compounds containing 4-methylphenyl (**6a**) and 4-chlorophenyl (**6b**) moieties showed good activity towards *P. aeruginosa* and *C. violaceum*. **6e** containing 4-hydroxyphenyl moiety, also showed potent activity towards *B. subtilis* and *B. sphaericus*, and **6i** containing 2-furyl moiety, showed good activity towards *B. sphaericus*, *S. aureus* and *P. aeruginosa*.

Antifungal Activity Compounds **6a**—**j** were also evaluated for their antifungal activity against *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185) and *Trichophyton mentagrophytes* (IFO 40996) in DMSO by disc diffusion, broth dilution methods.[37] For the antifungal assay, Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lining. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured into each petri-dish, excess of suspension was decanted and the plates were dried by placing in an incu-

Table 2. Antibacterial Activity of Compounds (**6a**—**j**)

Compound	Minimal inhibitory concentration in μg/ml (zone of inhibition in mm)[a]					
	B. subtilis	*B. sphaericus*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
6a	26 (12)	25 (11)	26 (9)	20 (17)	30 (9)	20 (16)
6b	30 (9)	27 (10)	30 (10)	20 (16)	26 (9)	20 (14)
6c	14 (18)	18 (20)	17 (22)	18 (20)	20 (16)	17 (23)
6d	13 (17)	19 (20)	18 (22)	19 (19)	19 (20)	18 (20)
6e	18 (12)	20 (17)	30 (13)	26 (12)	25 (10)	25 (11)
6f	25 (9)	30 (10)	28 (10)	28 (10)	30 (8)	28 (13)
6g	15 (14)	18 (19)	17 (24)	20 (22)	20 (20)	18 (19)
6h	27 (10)	26 (11)	28 (10)	30 (11)	28 (10)	27 (9)
6i	30 (11)	21 (12)	20 (16)	21 (15)	28 (9)	26 (10)
6j	13 (18)	15 (15)	16 (20)	20 (22)	20 (18)	16 (17)
Penicillin	1.56 (25)	3.12 (28)	1.56 (40)	6.25 (25)	6.25 (30)	12.5 (25)

a) The values in parentheses indicate the zone of inhibition.

bator at 37 °C for 1 h. Using an agar punch wells were made and each well was labeled. A control was also prepared in triplicate and maintained at 37 °C for 3—4 d. The *C. albicans* was grown for 48 h at 28 °C in YPD broth (1% yeast extract, 2% peptone and 2% dextrose), harvested by centrifugation and then washed twice with sterile distilled water. *A. fumigatus*, *T. rubrum* and *T. mentagrophytes* were plated in potato dextrose agar (PDA) (Difco) and incubated at 28 °C for two weeks. Spores were washed three times with sterile distilled water and resuspended in distilled water to obtain an initial inoculums size of 10^5 spores/ml. Each test compound was dissolved in DMSO and diluted with potato dextrose broth (Difco) to prepare serial two-fold dilutions in the range 100 to 0.8 μg/ml. Ten microliters of the broth containing about 10^3 (for yeast) and 10^4 (for filamentous fungi) cells/ml of test fungi was added to each well of a 96-well microtiter plate. Culture plates were incubated for about 48—72 h at 28 °C. The inhibition zone and minimal inhibitory concentration (MIC) were determined and compared with the standard drug fluconazole (Table 3).

The antifungal screening data reveal that, most of the newly synthesized compounds were active with moderate to good antifungal activity. The compounds containing 4-dimethylaminophenyl (**6g**) and 2-furyl (**6i**), moiety at 2-position of the thiazolidin-4-one ring showed highest activity towards all the tested strains. Further, the compound **6c** containing 4-nitrophenyl moiety showed good antifungal activity towards *C. albicans*, *A. fumigatus* and *T. rubrum*. The compound **6j** containing 1,3-benzodioxole moiety also showed potent activity towards *A. fumigatus*, *T. rubrum* and *T. mentagrophytes*. The comparison of MIC values of the selected compounds **6a**—**j** and standard drug against different fungi is presented in Fig. 1.

Conclusion

A series of linked heterocyclic compounds, 3-[4-(4-chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(aryl/heteryl)-1,3-thiazolan-4-ones **6a**—**j** has been synthesized and assayed for their antimicrobial activity against Gram-positive and Gram-negative bacteria, and fungi. The compounds **6c**, **6d**, **6g**, **6i** and **6j** exhibited potent inhibitory activity towards all tested organisms.

Table 3. Antifungal Activity of Compounds (**6a**—**j**)

Compound	Minimal inhibitory concentration in μg/ml (zone of inhibition in mm)[a]			
	C. albicans	*A. fumigatus*	*T. rubrum*	*T. mentagrophytes*
6a	26 (10)	30 (9)	35 (12)	28 (16)
6b	36 (11)	32 (13)	30 (8)	40 (10)
6c	18 (17)	22 (16)	24 (16)	28 (9)
6d	22 (12)	28 (9)	32 (11)	26 (8)
6e	25 (10)	25 (8)	36 (10)	25 (15)
6f	30 (10)	32 (10)	26 (10)	30 (12)
6g	14 (23)	18 (22)	20 (18)	18 (21)
6h	30 (12)	30 (10)	40 (14)	30 (14)
6i	15 (21)	19 (20)	22 (19)	18 (23)
6j	25 (15)	20 (16)	25 (17)	22 (16)
Fluconazole	16 (22)	18 (20)	20 (22)	16 (20)

a) The values in parentheses indicate the zone of inhibition.

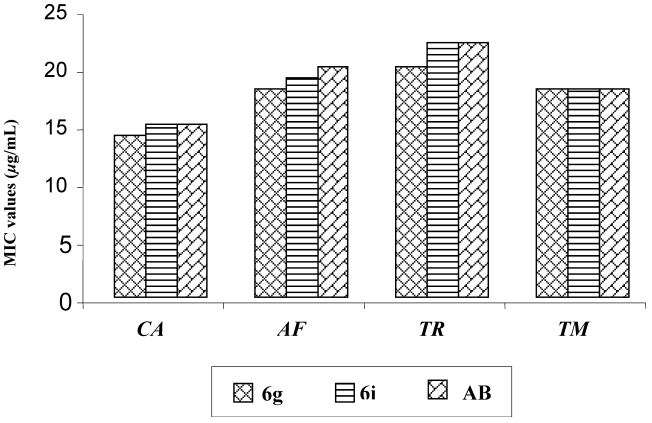

Fig. 1. Comparison of Antifungal Activity (MIC Values) of Selected Compounds and Standard Drug

Amphotericin B (AB), *C. albicans* (*CA*), *A. fumigatus* (*AF*), *T. rubrum* (*TR*), *T. mentagrophytes* (*TM*).

Experimental

General Commercial grade reagents were used as supplied. Solvents except analytical reagent grade were dried and purified according to the literature when necessary. Reaction progress and purity of the compounds were checked by thin-layer chromatography (TLC) on pre-coated silica gel F_{254} plates from Merck and compounds visualized either by exposure to UV light. Silica gel chromatographic columns (70—230 mesh) were used for separations. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded as KBr disks on a

Perkin–Elmer Fourier transform-infrared (FT-IR) spectrometer. The ^{1}H- 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 as δ ppm against tetramethyl silane (TMS) as an internal standard and coupling constants (J) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer. Elemental analyses (C, H, N) determined by a Perkin–Elmer 240 CHN elemental analyzer, are within ±0.4% of theoretical.

Typical Procedure. 3,5-Dimethyl-1-phenyl-1*H*-pyrazole (2) A mixture of acetyl acetone **1** (0.02 mol), and phenyl hydrazine hydrochloride (0.02 mol) in ethanol (20 ml) was heated under reflux for 3 h on a water bath. After completion of the reaction ethanol was evaporated, the residue was dissolved in water, neutralized with sodium bicarbonate and extracted with ether. The solvent was evaporated under reduced pressure to get the compound **2** as yellow-brown liquid. Yield 90%, bp 270—272 °C. IR (KBr) cm^{-1}: 3010, 2962, 1516, 1510. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.22 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 6.21 (s, 1H, Ar-H), 7.10—7.20 (m, 5H, Ar-H). MS *m*/*z*: 172 (M^+). *Anal.* Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.77; H, 6.95; N, 16.16.

Typical Procedure. 3,5-Dimethyl-1-phenyl-1*H*-4-pyrazolecarbaldehyde (3) To a cold solution of *N*,*N*-dimethylformamide (0.02 mol), freshly distilled phosphorous oxychloride (0.01 mol) was added with stirring over a period of 30 min. When formylation solution was obtained, a solution of compound **2** (0.01 mol) in *N*,*N*-dimethylformamide (5 ml) was added drop wise while maintaining the temperature 0—5 °C. The resulting mixture was heated under reflux for 1 h, cooled and poured with continuous stirring onto crushed ice and the formed yellow precipitate was filtered, crystallized from aqueous ethanol to get the pure compound **3** as yellow solid. Yield 86%, mp 124—126 °C. IR (KBr) cm^{-1}: 3012, 2961, 2854, 1700, 1516, 1505. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.64 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 7.15—7.25 (m, 5H, Ar-H), 9.98 (s, 1H, CHO). MS *m*/*z*: 200 (M^+). *Anal.* Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.94; H, 6.00; N, 14.02.

Typical Procedure. (*E*)-1-(4-Chlorophenyl)-3-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-propen-1-one (4) A solution of compound **3** (0.01 mol) and 4-chloroacetophenone (0.01 mol) in ethanol (20 ml) was treated with 60% aq. KOH solution (20 ml) at 5—10 °C. The reaction mixture was stirred at room temperature for 6 h. It was then diluted with water (20 ml) and extracted with diethyl ether (3×20 ml). The aqueous solution was acidified with dilute HCl. The solid obtained was filtered washed thoroughly with water and dried. The crude product was purified by crystallization from benzene : methanol (3 : 2) to get the pure compound **4** as yellow solid. Yield 72%, mp 131—133 °C. IR (KBr) cm^{-1}: 3015, 2965, 1690, 1571, 1482, 1224, 685. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.31 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 7.08 (d, J=16.2 Hz, 1H, α-H), 7.15—7.35 (m, 7H, Ar-H), 7.69 (d, J=16.2 Hz, 1H, β-H), 7.80 (d, J=7.1 Hz, 2H, Ar-H). MS *m*/*z*: 336 (M^+). *Anal.* Calcd for $C_{20}H_{17}ClN_2O$: C, 71.32; H, 5.09; N, 8.32. Found: C, 71.27; H, 5.03; N, 8.30.

Typical Procedure. 4-(4-Chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinamine (5) To a mixture of compound **4** (0.01 mol) and guanidine hydrochloride (0.02 mol) in ethanol (20 ml), aq. NaOH (0.02 mol, 5 ml) was added and refluxed for 6 h (TLC, EtOAc : petrolium–ether, 2 : 1), then poured the mixture in 10% cold HCl solution (30 ml). The solid product obtained was filtered, washed with water until free from acid and recrystallized from ethanol to get the pure compounds **5** as yellow solid. Yield 75%, mp 145—146 °C. IR (KBr) cm^{-1}: 3390—3250, 3015, 1614, 1510, 1465, 685. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.43 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 5.17 (bs, 2H, NH_2), 6.92 (s, 1H, Ar-H), 7.10—7.25 (m, 7H, Ar-H), 7.75 (d, J=8.1 Hz, 2H, Ar-H). MS *m*/*z*: 377 (M^++1). *Anal.* Calcd for $C_{21}H_{18}ClN_5$: C, 67.11; H, 4.83; N, 18.63. Found: C, 67.07; H, 4.89; N, 18.65.

Typical Procedure. 3-[4-(4-Chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(aryl/heteryl)-1,3-thiazolan-4-one (6a—j) To a stirred mixture of compound **5** (0.01 mol), aryl/heteroaryl aldehyde (0.01 mol) and thioglycolic acid (0.02 mol) in dry toluene (15 ml), $ZnCl_2$ (0.01 mol) was added and refluxed for 5 h at 110 °C. After cooling, the filtrate was concentrated to dryness under reduced pressure and the residue was taken-up in ethyl acetate. The ethyl acetate layer was washed with brine, 5% sodium bicarbonate solution and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness at reduced pressure; the crude product thus obtained was purified by column chromatography on silica gel with hexane-ethyl acetate as eluent to get the pure compounds.

3-[4-(4-Chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(4-methylphenyl)-1,3-thiazolan-4-one (**6a**): Yield 73%, mp 176—178 °C. IR (KBr) cm^{-1}: 3037, 1696, 1604, 1595, 712, 690. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 3.67—3.70 (m, 2H, CH_2–CO), 5.86 (s, 1H, N–CH–S), 7.15—7.30 (m, 12H, Ar-H), 7.49 (d, J=8.1 Hz, 2H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 11.9, 13.2, 22.0, 39.1, 69.6, 120.6, 121.3, 124.0, 124.9, 125.9, 127.0, 127.5, 128.1, 134.3, 134.9, 136.5, 137.4, 139.6, 140.0, 140.4, 141.0, 158.5, 161.7, 174.2, 177.8. MS *m*/*z*: 552 (M^+). *Anal.* Calcd for $C_{31}H_{26}ClN_5OS$: C, 67.44; H, 4.75; N, 12.69. Found: C, 67.39; H, 4.78; N, 12.63.

2-(4-Chlorophenyl)-3-[4-(4-chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-1,3-thiazolan-4-one (**6b**): Yield 68%, mp 166—168 °C. IR (KBr) cm^{-1}: 3032, 1698, 1603, 1597, 712, 687. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.42 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.67—3.70 (m, 2H, CH_2-CO), 5.86 (s, 1H, N-CH-S), 7.15—7.30 (m, 12H, Ar-H), 7.48 (d, J=8.1 Hz, 2H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 11.7, 13.1, 39.2, 69.5, 120.4, 121.5, 124.7, 125.6, 126.7, 127.3, 128.0, 128.9, 133.1, 134.3, 136.6, 137.7, 139.5, 140.0, 140.9, 141.2, 158.3, 161.3, 174.1, 177.0. MS *m*/*z*: 572 (M^+). *Anal.* Calcd for $C_{30}H_{23}Cl_2N_5OS$: C, 62.94; H, 4.05; N, 12.23. Found: C, 62.90; H, 4.00; N, 12.16.

3-[4-(4-Chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(4-nitrophenyl)-1,3-thiazolan-4-one (**6c**): Yield 67%, mp 205—207 °C. IR (KBr) cm^{-1}: 3035, 1699, 1603, 1596, 1520, 1370, 710, 686. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.40 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.67—3.70 (m, 2H, CH_2–CO), 5.86 (s, 1H, N–CH–S), 7.15—7.30 (m, 8H, Ar-H), 7.40—7.45 (m, 4H, Ar-H), 7.71 (d, J=8.6 Hz, 2H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 11.7, 13.1, 39.1, 69.4, 120.2, 121.7, 123.9, 124.1, 124.9, 127.1, 127.9, 128.8, 136.4, 137.3, 139.1, 140.0, 140.7, 141.9, 142.1, 147.0, 157.5, 161.6, 174.1, 177.4. MS *m*/*z*: 584 (M^+). *Anal.* Calcd for $C_{30}H_{23}ClN_6O_3S$: C, 61.80; H, 3.98; N, 14.41. Found: C, 61.74; H, 3.93; N, 14.36.

3-[4-(4-Chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(3-nitrophenyl)-1,3-thiazolan-4-one (**6d**): Yield 69%, mp 210—212 °C. IR (KBr) cm^{-1}: 3062, 2980, 1689, 1600, 1595, 1517, 1365, 714, 685. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.41 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.67—3.70 (m, 2H, CH_2–CO), 5.94 (s, 1H, N–CH–S), 7.15—7.30 (m, 8H, Ar-H), 7.40—7.45 (m, 4H, Ar-H), 7.80—7.95 (m, 2H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 11.8, 13.1, 39.1, 70.1, 118.8, 119.6, 120.3, 122.4, 123.9, 124.9, 127.1, 128.5, 129.1, 131.3, 136.2, 137.1, 138.0, 139.7, 140.3, 140.5, 141.2, 147.1, 158.7, 161.3, 173.2, 176.8. MS *m*/*z*: 584 (M^+). *Anal.* Calcd for $C_{30}H_{23}ClN_6O_3S$: C, 61.80; H, 3.98; N, 14.41. Found: C, 61.74; H, 3.92; N, 14.34.

3-[4-(4-Chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(4-hydroxyphenyl)-1,3-thiazolan-4-one (**6e**): Yield 70%, mp 183—185 °C. IR (KBr) cm^{-1}: 3400—3320, 3047, 2922, 1695, 1603, 1595, 715, 689. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.40 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.68—3.70 (m, 2H, CH_2–CO), 5.27 (s, 1H, OH), 5.85 (s, 1H, N–CH–S), 6.92 (d, J=8.6 Hz, 2H, Ar-H), 7.15—7.30 (m, 10H, Ar-H), 7.48 (d, J=8.2 Hz, 2H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 12.0, 13.7, 40.2, 69.5, 115.0, 121.6, 122.3, 123.9, 125.0, 126.1, 127.5, 128.1, 129.7, 136.5, 138.4, 139.2, 140.5, 140.2, 142.1, 156.3, 158.4, 161.3, 174.1, 177.2. MS *m*/*z*: 554 (M^+). *Anal.* Calcd for $C_{30}H_{24}ClN_5O_2S$: C, 65.03; H, 4.37; N, 12.64. Found: C, 65.00; H, 4.31; N, 14.66.

3-[4-(4-Chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(2-hydroxyphenyl)-1,3-thiazolan-4-one (**6f**): Yield 71%, mp 177—179 °C. IR (KBr) cm^{-1}: 3400—3300, 3027, 2922, 1696, 1600, 1592, 717, 685. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.44 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 3.66—3.70 (m, 2H, CH_2–CO), 5.87 (s, 1H, OH), 5.96 (s, 1H, N–CH–S), 6.85—6.90 (m, 2H, Ar-H), 7.15—7.30 (m, 10H, Ar-H), 7.48 (d, J=8.1 Hz, 2H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 11.2, 13.6, 39.4, 62.1, 115.2, 119.2, 120.9, 121.6, 122.3, 124.3, 125.7, 126.0, 126.7, 127.2, 128.3, 136.4, 137.4, 139.6, 140.4, 140.8, 141.0, 152.6, 158.0, 161.2, 174.1, 177.4. MS *m*/*z*: 554 (M^+). *Anal.* Calcd for $C_{30}H_{24}ClN_5O_2S$: C, 65.03; H, 4.37; N, 12.64. Found: C, 64.98; H, 4.32; N, 14.60.

3-[4-(4-Chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-[4-(dimethylamino)phenyl]-1,3-thiazolan-4-one (**6g**): Yield 74%, mp 181—183 °C. IR (KBr) cm^{-1}: 3042, 2965, 1698, 1599, 1592, 716, 686. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.42 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.91 (s, 6H, 2×N–CH_3), 3.67—3.70 (m, 2H, CH_2–CO), 5.82 (s, 1H, N–CH–S), 6.80 (d, J=8.5 Hz, 2H, Ar-H), 7.15—7.30 (m, 10H, Ar-H), 7.49 (d, J=8.1 Hz, 2H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 12.2, 13.5, 39.1, 43.6, 69.5, 111.4, 120.6, 121.3, 123.9, 125.9, 127.1, 127.5, 128.1, 130.7, 134.5, 137.1, 139.6, 140.0, 140.9, 141.9, 142.3, 158.7, 162.7, 174.6, 176.6. MS *m*/*z*: 582 (M^+). *Anal.* Calcd for $C_{32}H_{29}ClN_6OS$: C, 66.14; H, 5.03; N, 14.46. Found: C, 66.10; H, 4.98; N, 14.40.

3-[4-(4-Chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(4-hydroxy-3-methoxyphenyl)-1,3-thiazolan-4-one (**6h**):

Yield 70%, mp 189—191 °C. IR (KBr) cm^{-1}: 3350—3300, 2967, 1697, 1598, 1590, 1067, 716, 686. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.40 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 3.67—3.70 (m, 2H, CH_2–CO), 3.80 (s, 3H, OCH_3), 5.10 (s, 1H, OH), 5.83 (s, 1H, N–CH–S), 6.81 (s, 1H, ArH), 7.15—7.30 (m, 10H, Ar-H), 7.48 (d, J=8.1 Hz, 2H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 11.6, 13.5, 39.4, 54.8, 70.0, 109.8, 116.6, 118.8, 120.1, 121.5, 124.4, 125.4, 127.1, 128.7, 132.3, 136.6, 137.4, 139.6, 140.5, 141.9, 142.3, 146.4, 148.6, 158.1, 161.8, 174.2, 177.1. MS m/z: 584 (M^+). *Anal.* Calcd for $C_{31}H_{26}ClN_5O_3S$: C, 63.75; H, 4.49; N, 11.99. Found: C, 63.70; H, 4.44; N, 11.92.

3-[4-(4-Chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-2-(2-furyl)-1,3-thiazolan-4-one (**6i**): Yield 65%, mp 200—202 °C. IR (KBr) cm^{-1}: 3039, 1694, 1600, 1594, 1592, 1030, 715, 682. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.42 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.67—3.70 (m, 2H, CH_2–CO), 5.98 (s, 1H, N–CH–S), 6.30—6.40 (m, 2H, Ar-H), 7.15—7.30 (m, 8H, Ar-H), 7.45—7.50 (m, 3H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 11.9, 13.2, 39.3, 63.2, 101.8, 109.2, 120.6, 121.2, 124.4, 125.6, 127.5, 128.1, 136.5, 137.7, 139.6, 140.4, 141.3, 144.4, 158.5, 160.8, 161.7, 173.2, 176.1. MS m/z: 528 (M^+). *Anal.* Calcd for $C_{28}H_{22}ClN_5O_2S$: C, 63.69; H, 4.20; N, 13.26. Found: C, 63.63; H, 4.24; N, 13.21.

2-(1,3-Benzodioxol-5-yl)-3-[4-(4-chlorophenyl)-6-(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolyl)-2-pyrimidinyl]-1,3-thiazolan-4-one (**6j**): Yield 67%, mp 194—196 °C. IR (KBr) cm^{-1}: 3042, 1695, 1603, 1592, 1120, 717, 682. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.42 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.67—3.70 (m, 2H, CH_2–CO), 5.65—5.70 (m, 2H, O–CH_2–O), 5.85 (s, 1H, N–CH–S), 7.15—7.30 (m, 9H, Ar-H), 6.83 (s, 1H, Ar-H), 7.45—7.50 (m, 3H, Ar-H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 12.1, 13.2, 39.1, 70.1, 99.7, 105.8, 109.9, 119.1, 121.6, 122.3, 124.9, 125.9, 127.5, 128.8, 132.4, 136.5, 137.4, 139.6, 141.4, 142.0, 145.6, 147.3, 158.5, 161.7, 173.2, 176.8. MS m/z: 582 (M^+). *Anal.* Calcd for $C_{31}H_{24}ClN_5O_3S$: C, 63.97; H, 4.16; N, 12.03. Found: C, 63.92; H, 4.10; N, 12.00.

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