Synthesis of some novel fluorinated 4-thiazolidinones containing amide linkages and their antimicrobial screening

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Abstract

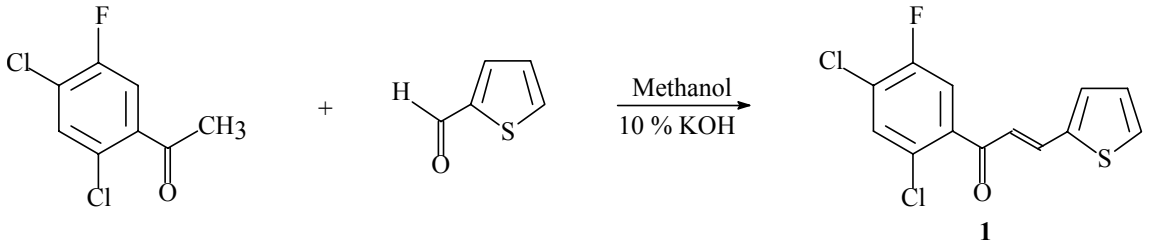
Efficient syntheses of some 4-thiazolidinones are described. A series of 2-(substituted phenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5*H*/methyl/carboxymethyl-4-thiazolidinones **5a-e,6a-e,7a-e** were prepared. The structures of the synthesised compounds were assigned on the basis of elemental analysis, IR and ^{1}H NMR spectral data. All the products were screened against different strains of bacteria and fungi.

Keywords: Schiff base, 4-thiazolidinones, antibacterial activity, synthesis

Introduction

The presence of a pyrimidine nucleus in compounds, often leads to exceptionally interesting biological and pharmacological activities. 4-Thiazolidinones have been reported to show a broad spectrum of biological activities.[1-10] The pharmacological properties of 4-thiazolidinones encouraged our interest in synthesizing several new compounds featuring various heterocyclic rings, attached to 4-thiazolidinone moieties. As a part of our aim to search for biologically active heterocycles containing sulfur and nitrogen, we have now synthesised a series of 2-(substituted phenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl) pyrimidine-2-yl-ureido]-5*H* / methyl / carboxymethyl- 4-thiazolidinones **5a-e, 6a-e, 7a-e**.

2,4-Dichloro-5-fluoroacetophenone on reaction with thiophene-2-carbaldehyde in a Claisen-Schmidt condensation[11-13] gave 1-(2,4-dichloro-5-fluorophenyl)-3-(2-thienyl)-2-propen-1-one **1** (Scheme 1), which on reaction with guanidine nitrate and 40% KOH yielded 2-amino-4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine **2** (Scheme 2) in 70% yield.



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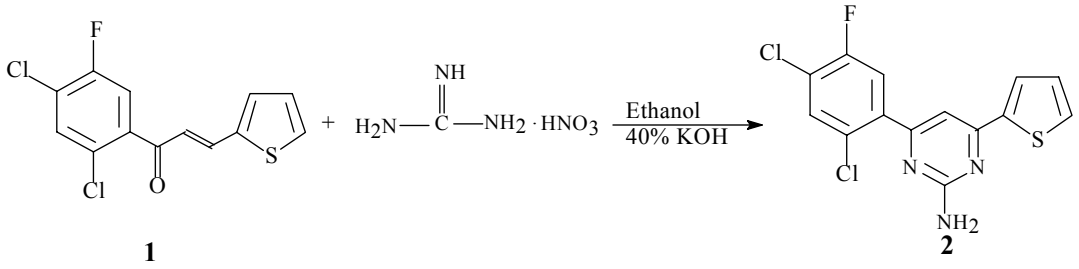
Scheme 1



1 **2**

Scheme 2

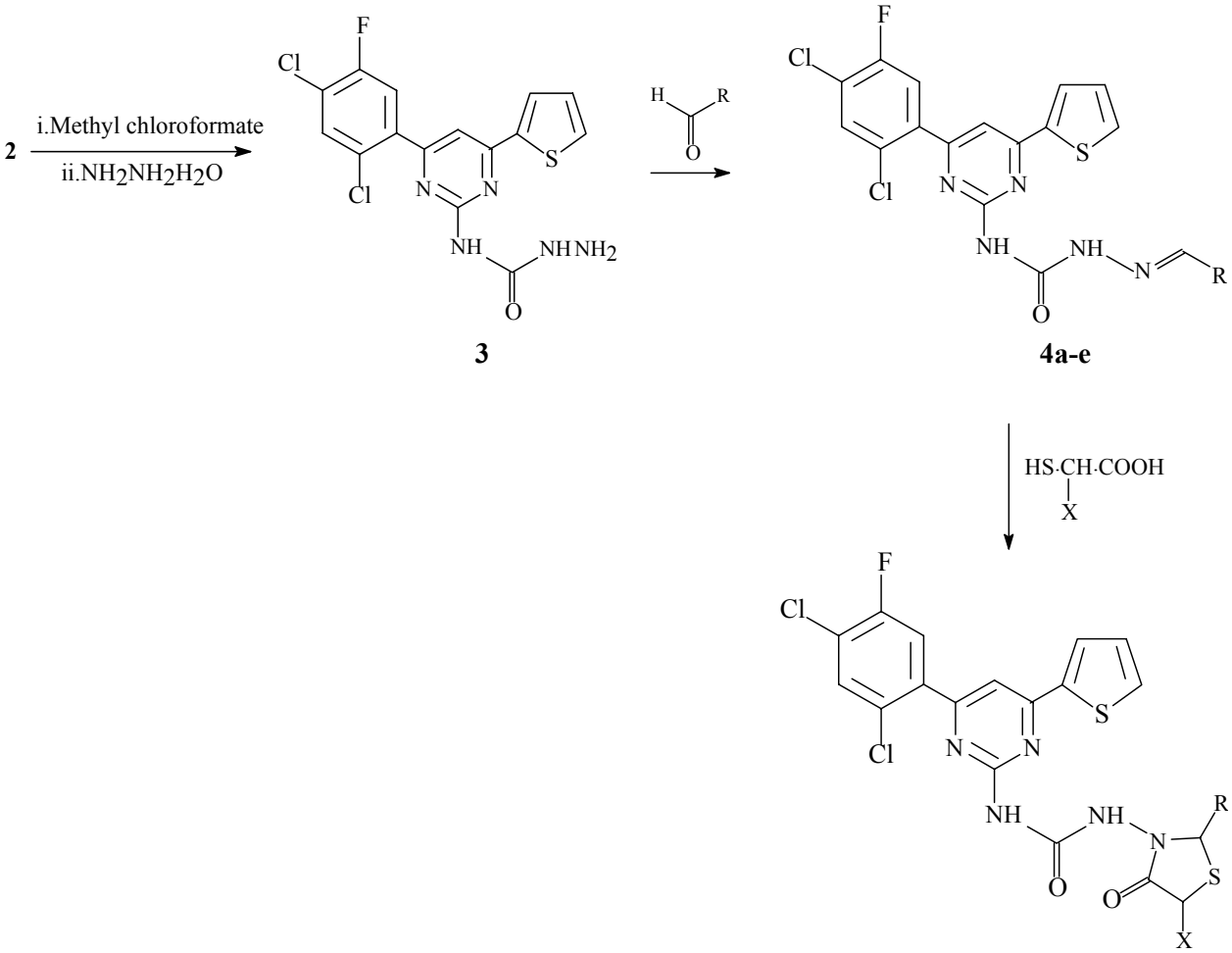
Compound **2** on further reaction with methyl chloroformate (MCF) followed by reaction with hydrazine hydrate gave 4-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidin-2-yl] semicarbazide **3** in 68% yield**.** Compound **3** on condensation with various substituted aromatic aldehydes afforded 1-(substituted benzylidene)-4-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidin-2-yl] semicarbazides **4a-e** (Scheme 3). These imines on cyclocondensation with mercaptoacetic acid (X = H), 2-mercaptopropanoic acid (X = CH_3) or mercaptosuccinic acid (X = CH_2COOH) respectively led to the formation of 2-(aryl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidin-2-yl-ureido]-5*H* / methyl / carboxymethyl-4-thiazolidinones **5a-e, 6a-e,7a-e** (Scheme 3).

Results and Discussion

The results given in Table 1 confirm that compounds with 4-thiazolidinone units are potential antibacterial agents. The structures of the synthesised compounds were confirmed by elemental analysis, IR spectra and ^{1}H NMR spectral analysis. The IR spectra of **5a-e, 6a-e, 7a-e** exhibited a band due to =CH str. (3100-3000cm^{-1}), C=C str. (1635-1495 cm^{-1}), C-H bending [1,2,4,5-substituted (900-860 cm^{-1})], C-H bending [1,4-substituted aryl (840-800 cm^{-1})], C-Cl str. (750-700 cm^{-1}), C-F str. (1100-1000 cm^{-1}), C-S-C str. (700-600cm^{-1}), C=N (ring) (1650-1580 cm^{-1}) stretching vibration band, C=O (1674 cm^{-1}, 4-thiazolidinone moiety) which indicated the presence of a pyrimidine ring and a 4-thiazolidinone ring.

The IR spectrum of **1** showed a band at 1654 cm^{-1} due to the C=O, and a band at 1642 cm^{-1} due to the C=N str. of the pyrimidine moiety and 3418 cm^{-1} due to NH_2 in compound **2**. The

appearance of band at 1610 cm^{-1} due to the -NH-CO-NH- unit in compound **3** proved the conversion of compound **2** to **3**. Similarly, the disappearance of a band at 3418 cm^{-1}(NH_2) and the appearance of a band at 1600 cm^{-1} due to C=N str. proved the conversion to compounds **4a-e**. The final structures **5a-e, 6a-e, 7a-e** were established by the disappearance of the C=N str. And the appearance of a band at 1674 cm^{-1}due to C=O str. (4-thiazolidinone).



Scheme 3. R = aryl; X = H (**5a-e**), CH_3 (**6a-e**), CH_2COOH (**7a-e**).

In the ^1H NMR spectrum of **1**, the signal at δ 7.1 corresponded to the COCH=CH unit. A signal at δ 6.8 for the CH (pyrimidine ring) verified the structure **2**. In the same way, the disappearance of the signal at δ 5.1 due to NH_2 and the appearance of a signal at δ 4.4 due to N=CH provided further evidence for the conversion of compound **3** into compound **4**. Finally the

disappearance of the N=CH signal and the appearance of a signal at δ 6.1 for the thiazolidinone ring CH showed the formation of compounds **5a-e, 6a-e, 7a-e**.

Table 1. Antibacterial and antifungal activity of **5a-e, 6a-e, 7a-e**

No.	Antibacterial activity				Antifungal activity	
	Diameter of Zone of Inhibition (in mm)				Diameter of the MIC in mm	
	S. aureus	*B. substilis*	*E. coli*	*P. aeruginosa*	*C. crusei*	*C. albicans*
	ATCC 6538	*ATCC 6633*	*ATCC 8739*	*ATCC 1539*	*ATCC 14243*	*ATCC 64550*
5a	++	++	++	+	++	++
5b	++	-	++	-	+	++
5c	++	+	++	+	+	-
5d	++	++	++	+	++	+
5e	+	+	+	-	+	++
6a	++	++	+	+	-	+
6b	+	+	+	-	-	+
6c	+	+	++	+	++	+
6d	++	++	+	+	++	+
6e	++	++	++	+	+	++
7a	+	++	+	-	-	+
7b	++	+	++	+	++	+
7c	+	++	+	+	++	+
7d	+	+	+	-	-	-
7e	+	+	+	+	-	++
Streptomycin	++++	++++	++++	++++	-	-
Griseofulvin	-	-	-	-	++++	++++

Diameter of zone of inhibition : (-) < 6 mm, (+) 6-12 mm, (+ +) 12-20 mm, (+ + +) 20-25 mm, (+ + + +) 25-30mm.

Diameter of the MIC: (-) 5 mm, (+) 5–12 mm, (+ +) 12–18 mm, (+ + +) 18–24 mm, (+ + + +) 24-32mm.

Antibacterial activity

All the synthesised compounds were screened for their *in vitro* antibacterial activity against *Escherichia coli (ATCC 8739)*, *Pseudomonas aureginosa (ATCC 1539)* and *Staphylococcus aureus (ATCC 6538)*, *Bacillus substilis (ATCC 6633)* bacteria using the cup-plate agar diffusion

method.[14] Streptomycin was used as reference drug. The degree of inhibition varied with the test compound as well as with the bacterium.

Against *Bacillus substilis (ATCC 6633),* compounds **5a**, **5d**, **6d**, **6e**, **7a**, **7c** exhibited good antibacterial activity, whereas compounds **5b**, **5c**, **6e**, **6c**, **7b**, **7e** showed low activity. On the other hand *Pseudomonas aureginosa (ATCC 1539)* showed poor responses to five of the prepared products. Compounds **5d**, **6d**, **7c** and compounds **5a**, **6d**, **7b** exhibited good antibacterial activity towards *Escherichia coli (ATCC 8739)* and *Staphylococcus aureus (ATCC 6538)* respectively.

On the basis of the antibacterial activity data it could be concluded that some of the compounds possess considerable antibacterial activity due to the presence of methoxy, fluoro and chloro groups. However the activity of the tested compounds is less than that of streptomycin.

Antifungal activity

The compounds were tested for their antifungal activity using *Candia crusei (ATCC 14243)* and *Candida albicans (ATCC 64550)*. For all compounds, the minimum inhibitory concentration (MIC) was taken as the lowest concentration at which there was 100% inhibition of growth compared with the growth for a drug-free control.[15] Griseofulvin was used as reference drug for comparison. The data of antifungal activity (Table 1) showed that generally, the compounds **5a, 5d, 6c, 6d, 7b, 7c** were more effective against *Candia crusei (ATCC 14243)*, while compounds **5b, 6a, 6b, 7d, 7e** exhibited low antifungal activity. Moreover, compounds **5a, 5b, 6e, 7e** demonstrated good activity against *Candida albicans (ATCC 64550).* On the basis of the antifungal activity data it could be concluded that some of the compounds possess good activity. however, none of compounds was superior to standard used against any of the fungi.

Experimental Section

General Procedures. Melting points were determined in an open capillary tube and are uncorrected. Infrared (IR) Spectra were measured on a FTIR-8400 Shimadzu spectrometer using KBr pellets. The proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Brüker Avance dpx-200 (at 200 MHz) spectrometer with $CDCl_3$ as a solvent with tetramethylsilane (TMS) as an internal reference. Chemical shifts are expressed in δ ppm. Elemental analysis of C and H was performed by Central Drug Research Institute, Lucknow and nitrogen was estimated by Kjeldhal's method,[16] results are within ± 0.4% of the theoretical value. Thin layer chromatography was carried out on silica gel (Kieselgel G; Merck) to monitor the reactions and to check the purity of the compounds. All reagents were of the highest purity available commercially.

1-(2,4-Dichloro-5-fluorophenyl-3-(2-thienyl)-2-propen-1-one 1. 2,4-dichloro-5-fluoro-acetophenone (0.01 mol) and thiophene-2-carbaldehyde (0.01 mol) were stirred in methanol (50.0 mL) at 32 ^{o}C for ½ h. Then, 10% KOH solution (3.0 mL) was added to the reaction mass and it was stirred for a further 4 h. After standing at room temperature for 24 h, the reaction mixture was added to ice-cold water and acidified with dilute HCl. The precipitate formed was filtered, washed with water, dried and recrystallized from ethanol to afford pure pale yellow product **1** in 81% yield. m.p. 92 ^{o}C; IR (KBr): =CH str. (3080 cm^{-1}), C=C str. (1517 cm^{-1}), C-H bending [1,2,4,5-substituted (889 cm^{-1})], C-H bending [1,4-substituted (848 cm^{-1})], C-Cl str. (772 cm^{-1}), C-F str. (1025 cm^{-1}), C=O (1654 cm^{-1}); ^{1}H NMR (δ,$CDCl_3$): 7.1 (1H, dd, COCH=CH), 7.3 to 7.8 (5H, m, Ar-H); Anal. Calcd. for $C_{13}H_7Cl_2OFS$: C, 51.83; H, 2.33%. Found: C: 51.87; H: 2.39%.

2-Amino-4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl) pyrimidine 2. A mixture of 1-(2,4-dichloro-5-fluorophenyl)-3-(2-thienyl)-2-propen-1-one (0.01 mol), guanidine nitrate (0.01 mol) and 40% KOH (2.0 mL) was refluxed in ethanol (50.0 mL) for 20 h. After completion of reaction, the reaction mixture was cooled to room temperature, poured into crushed ice and water and acidified with dilute HCl. The separated solid was filtered, washed with water, dried and recrystallized from ethanol to give the title compound as a white solid in 70% yield. m.p. 167 ^{o}C; IR (KBr): -NH_2 (3418cm^{-1}), C=N str. (pyrimidine moiety, 1642 cm^{-1}), C=C str. (1572 cm^{-1}), C-F str. (1056 cm^{-1}), C-Cl str. (755cm^{-1}); ^{1}H NMR (δ, $CDCl_3$): 5.15 (2H, s, NH_2), 6.7 (1H, s, pyrimidine CH), 7.3-7.9 (m, 5H, Ar-H); Anal. Calcd. For $C_{14}H_8Cl_2FN_3S$: C, 49.41; H, 2.35; N, 12.35%. Found: C, 49.46; H, 2.39; N, 12.30%.

4-[4-(2,4-Dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl] semicarbazide 3. A mixture of 2-amino-4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine (0.01 mol) and methyl chloroformate (0.02 mol) was refluxed in the presence of triethylamine for 10 h in ethanol (50.0 mL). After completion of reaction the reaction mixture poured into ice-cold water. The separated solid was acidified with dilute HCl, filtered, washed with water and dried. The dried crude was refluxed with hydrazine hydrate in toluene for 7 h. After reaction completion, the toluene was distilled under vacuum to dryness. The material was washed with water till neutral, dried and recrystallized from acetone as a white solid in 68% yield. m.p. 188 ^{o}C; IR (KBr): NH_2 (3418 cm^{-1}), C=O str. (1660 cm^{-1}), C=N str. (pyrimidine moiety, 1642cm^{-1}), NH-CO-NH (1610 cm^{-1}, urea), C-Cl str. (755 cm^{-1}), C-F str. (1056 cm^{-1}), C-S-C str. (740 cm^{-1}); ^{1}H NMR (δ, $CDCl_3$): 5.1 (2H, s, NH-N$\underline{H}_2$), 6.8 (1H, s, pyrimidine CH), 7.3-7.8 (m, 5H, Ar-H), 8.4 (1H, s, CO-NH); Anal. Calcd. for $C_{15}H_{10}N_5OCl_2FS$: C, 45.23; H, 2.51; N, 17.59%. Found: C, 45.18; H, 2.56; N, 17.52%.

1-(4-Methoxybenzylidene)-4-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl] semicarbazide 4c. A mixture of 4-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidin-2-yl] semicarbazide **3** (0.01 mol) and 4-methoxybenzaldehyde (0.01 mol) was refluxed in methanol (60.0 mL) in the presence of a catalytic amount of glacial acetic acid for 10 h. After reaction completion, the reaction mass was cooled to room temperature, and poured onto ice-cold water with vigorous string. The separated solid was filtered, washed with 5% sodium bisulfite solution to remove excess aldehyde and recrystallized from chloroform as a light yellow solid in 65%

yield. m.p. 195 °C; IR (KBr): NH (3270 cm^{-1}), =CH str. (3068 cm^{-1}), C=O str. (1660 cm^{-1}), C=N str. (Schiff base, 1600 cm^{-1}), C-F str. (1056 cm^{-1}), C-Cl str. (754 cm^{-1}), C-S-C str. (741 cm^{-1}); ^{1}H NMR (δ, $CDCl_3$): 3.8 (3H, s, OCH_3), 4.4 (1H, s, N=CH-), 6.8 (1H, s, pyrimidine CH), 7.3-7.8 (m, 5H, Ar-H), 8.5 (s, 1H, CO-NH); Anal. Calcd. For $C_{23}H_{16}O_2N_5SCl_2F$: C, 53.48; H, 3.10; N, 13.56%. Found: C, 53.44; H, 3.15; N, 13.50%.

The remaining compounds were prepared by the above general method.

Preparation of 2-(4-methoxyphenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl) pyrimidine-2-yl-ureido]-5*H*-4-thiazolidinone 5c. A solution of 1-(4-methoxy benzylidene)-4-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl]semicarbazide **4c** (0.01 mol) in dry benzene (50.0 mL) and mercaptoacetic acid (0.012 mol) was refluxed for 12 h using a Dean-Stark separator. After completion of reaction, excess of benzene was distilled off and the resulting product was treated with 5% $NaHCO_3$ solution to remove unreacted mercaptoacetic acid. The separated product was washed with water, dried and recrystallized from DMF:water as a creamish white solid in 62% yield. m.p. 139 °C; IR (KBr): NH (3223 cm^{-1}), =CH str. (3068 cm^{-1}), 4–thiazolidinone moiety: C=O (1674 cm^{-1}), C=O str. (1642 cm^{-1}), C-F str. (1056 cm^{-1}), C-Cl str. (755cm^{-1}), C-S-C str. (742 cm^{-1}); ^{1}H NMR (δ, $CDCl_3$): 3.6 (1H, s, SCH_2CO, 4–thiazolidinone ring), 4.0 (3H, s, OCH_3), 6.1 (1H, s, CH of 4-thiazolidinone ring), 6.9 (1H, s, -CH, pyrimidine ring), 7.3-7.8 (m, 9H, ArH), 8.6 (1H, s, CO-NH); Anal. Calcd. for $C_{25}H_{18}O_3N_5S_2Cl_2F$: C, 50.8; H, 3.05; N, 11.86%. Found: C, 50.5; H, 3.1; N, 11.83%.

Similarly, compounds **5a, 5b, 5d, 5e** were prepared by the above general method.

2-(2-Chlorophenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido] -5*H*-4-thiazolidinone 5a.

Pale yellow solid in 67% yield. m.p. 145 °C; IR (KBr): -NH (3220 cm^{-1}), =CH str. (3064 cm^{-1}), 4–thiazolidinone moiety: C=O (1675 cm^{-1}), C=O str. (1641 cm^{-1}), C-F str. (1055 cm^{-1}) , C-Cl str. (754 cm^{-1}), C-S-C str. (741 cm^{-1}); ^{1}H NMR (δ, $CDCl_3$): 3.6 (1H, s, SCH_2CO, 4–thiazolidinone ring), 6.0 (1H, s, CH of 4-thiazolidinone ring), 6.8 (1H, s, CH, pyrimidine ring), 7.3-7.8 (m, 9H, ArH), 8.5(1H, s, CO-NH); Anal. Calcd. for $C_{24}H_{15}O_2N_5S_2Cl_3F$: C, 48.4; H, 2.52; N, 11.77%. Found: C, 48.2; H, 2.49; N, 11.73%.

2-(2-Methoxyphenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5*H*-4-thiazolidinone 5b.

White solid in 70% yield. m.p. 128 °C; IR (KBr): NH (3221 cm^{-1}), =CH str. (3068 cm^{-1}), 4–thiazolidinone moiety: C=O (1672 cm^{-1}), C=O str. (1640 cm^{-1}), C-F str. (1054 cm^{-1}), C-Cl str. (754cm^{-1}), C-S-C str. (742 cm^{-1}); ^{1}H NMR (δ, $CDCl_3$): 3.6 (1H, s, SCH_2CO, 4-thiazolidinone ring), 4.1 (3H, s, OCH_3), 6.2 (1H, s, CH of 4-thiazolidinone ring), 6.7 (1H, s, CH, pyrimidine ring), 7.3-7.9 (m, 9H, ArH), 8.4 (1H,s, CO-NH); Anal. Calcd. for $C_{25}H_{18}O_3N_5S_2Cl_2F$: C, 50.8; H, 3.05; N, 11.86%. Found: C, 50.3; H, 3.0; N, 11.89%.

2-(3,4,5-Trimethoxyphenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidin-2-yl-ureido]-5*H*-4-thiazolidinone 5d.

Pale yellow solid in 76% yield. m.p. 103 °C; IR (KBr): -NH (3223 cm^{-1}), =CH str. (3066 cm^{-1}), 4–thiazolidinone moiety: C=O (1673 cm^{-1}), C=O str. (1644 cm^{-1}), C-F str.(1054 cm^{-1}) ,C-Cl str.

(756 cm^{-1}), C-S-C str. (741 cm^{-1}); ^1H NMR (δ, $CDCl_3$): 3.5 (1H, s, SCH_2CO, 4–thiazolidinone ring), 4.0 (9H, s, 3,4,5-tri-OCH_3), 6.1 (1H, s, CH of 4-thiazolidinone ring), 6.8 (1H, s, CH, pyrimidine ring), 7.3-7.8 (m, 7H, ArH), 8.4 (1H, s**,** CO-NH); Anal. Calcd. for $C_{27}H_{22}O_5N_5S_2Cl_2F$: C, 49.8; H, 3.38; N, 10.77%. Found: C, 49.4; H, 3.41; N, 10.82%.

2-(4-Fluorophenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl) pyrimidin-2-yl-ureido] - 5*H*-4-thiazolidinone 5e.

White solid in 73% yield. m.p. 130 ^oC; IR (KBr): -NH (3223 cm^{-1}),=CH str. (3068 cm^{-1}), 4–thiazolidinone moiety: C=O (1674cm^{-1}), C=O str. (1642 cm^{-1}), C-F str. (1056 cm^{-1}), C-Cl str. (753 cm^{-1}), C-S-C str. (742 cm^{-1}); ^1H NMR (δ, $CDCl_3$): 3.7(1H, s, SCH_2CO, 4–thiazolidinone ring), 6.0 (1H, s, CH of 4-thiazolidinone ring), 6.8 (1H, s, CH, pyrimidine ring), 7.3-7.8 (m, 9H, ArH), 8.6 (1H, s, CO-NH); Anal. Calcd. for $C_{24}H_{15}O_2N_5S_2Cl_2F_2$: C, 49.82; H, 2.59; N, 12.11%. Found: C, 49.78; H, 2.64; N, 12.08%.

Preparation of 2-(4-methoxyphenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl) pyrimidine-2-yl-ureido]-5-methyl-4-thiazolidinone 6c. A solution of 1-(4-methoxy benzylidene)-4 - [4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl] semicarbazide **4c** (0.01 mol) in dry benzene (50.0 mL) and 2-mercaptopropanoic acid (0.012 mol) refluxed for 14 h using a Dean-Stark separator. After completion of the reaction, excess of benzene was removed by distillation and the product was treated with 5% $NaHCO_3$ solution to remove unreacted 2-mercaptopropanoic acid. The separated product was washed with water, dried and recrystallized from chloroform: methanol (1:1) mixture as a white solid in 72% yield. m.p. 101 ^oC; IR (KBr): NH (3223 cm^{-1}), 4–thiazolidinone moiety; C=O (1674 cm^{-1}), C=O str. (1642 cm^{-1}), C-F str. (1056 cm^{-1}), C-S-C str. (754 cm^{-1}); ^1H NMR (δ, $CDCl_3$): 1.5 (3H, d, $CHC\underline{H}_3$), 3.9 (3H, s, CH_3), 4.20 (1H, q, $C\underline{H}$-CH_3), 5.96 (1H, s, CH of 4-thiazolidinone ring), 6.8 (1H, s, CH, pyrimidine ring), 7.3-7.8 (m, 9H, ArH), 8.7 (1H, s, CO-NH) ; Anal. Calcd. for $C_{26}H_{20}O_3N_5S_2Cl_2F$: C, 51.65; H, 3.31; N, 11.58%. Found: C, 51.61; H, 3.29; N, 11.62%.

Similarly, compounds **6a, 6b, 6d, 6e** were prepared by the above general method.

2-(2-Chlorophenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5-methyl-4-thiazolidinone 6a.

Colorless solid in 68% yield. m.p. 121 ^oC; IR (KBr):-NH (3220 cm^{-1}), 4–thiazolidinone moiety; C=O (1674c m^{-1}), C=O str. (1641 cm^{-1}), C-F str. (1052 cm^{-1}), C-S-C str. (752 cm^{-1}); ^1H NMR (δ, $CDCl_3$): 1.6 (3H, d, $CHC\underline{H}_3$), 3.6 (1H, s, SCH_2CO, 4-thiazolidinone ring), 4.2 (1H, q, $C\underline{H}$-CH_3), 5.9 (1H, s, CH of 4-thiazolidinone ring), 6.7 (1H, s, CH, pyrimidine ring), 7.3-7.8 (m, 9H, r-H), 8.6 (1H, s, CO-NH). Anal. Calcd. for $C_{25}H_{17}O_2N_5S_2Cl_3F$: C, 49.3; H, 2.79; N, 11.5%. Found: C, 49.7; H, 2.75; N, 11.53%.

2-(2-Methoxyphenyl)-3 -[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl) pyrimidine-2-yl-ureido]-5-methyl-4-thiazolidinone 6b.

Off white solid in 61% yield. m.p. 152 ^oC; IR (KBr): NH (3223 cm^{-1}), 4–thiazolidinone moiety; C=O (1672cm^{-1}), C=O str. (1640 cm^{-1}), C-F str. (1056 cm^{-1}), C-S-C str. (754 cm^{-1}); ^1H NMR (δ, $CDCl_3$): 1.7 (3H, d, $CHC\underline{H}_3$), 4.0 (3H, s, OCH_3), 4.3 (1H, q, $C\underline{H}$-CH_3), 5.8 (1H, s, CH of 4-thiazolidinone ring), 6.8 (1H, s, CH, pyrimidine ring), 7.3-7.7 (m, 9H, ArH), 8.5 (1H, s, CO-

NH); Anal. Calcd.for $C_{26}H_{20}O_3N_5S_2Cl_2F$: C, 51.65; H, 3.31; N, 11.58%. Found: C, 51.68; H, 3.28; N, 11.55%.

2-(3,4,5-Trimethoxyphenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5-methyl-4-thiazolidinone 6d.

Light yellow solid in 79% yield. m.p. 123 ^oC; IR (KBr):-NH (3222 cm^{-1}), 4–thiazolidinone moiety: C=O (1672cm^{-1}), C=O str. (1641 cm^{-1}), C-F str. (1053cm^{-1}), C-S-C str. (753 cm^{-1}); ^1H NMR (δ, $CDCl_3$): 1.6 (3H, d, CHC<u>H</u>$_3$), 3.9 (9H, s, 3,4,5-tri-OCH_3), 4.2 (1H, q, C<u>H</u>-CH_3), 5.8 (1H, s, CH of 4-thiazolidinone ring), 6.7 (1H, s, CH, pyrimidine ring), 7.3-7.8 (m, 7H, ArH), 8.7 (1H, s, CO-NH) ; Anal. Calcd. for $C_{28}H_{24}O_5N_5S_2Cl_2F$: C, 50.6; H, 3.61; N, 10.54%. Found: C, 50.57; H, 3.58; N, 10.59%.

2-(4-Fluorophenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5-methyl-4-thiazolidinone 6e.

White solid in 68% yield. m.p. 141 ^oC; IR (KBr):-NH (3224 cm^{-1}), 4–thiazolidinone moiety: C=O (1673cm^{-1}), C=O str. (1640 cm^{-1}), C-F str. (1055 cm^{-1}), C-S-C str. (752 cm^{-1}); ^1H NMR (δ, $CDCl_3$): 1.6 (3H, d, CHC<u>H</u>$_3$), 4.2 (1H, q, C<u>H</u>-CH_3), 5.7 (1H, s, CH of 4-thiazolidinone ring), 6.9 (1H, s, CH, pyrimidine ring), 7.4-7.8 (m, 9H, ArH), 8.6 (1H, s, CO-NH); Anal. Calcd. for $C_{25}H_{17}O_2N_5S_2Cl_2F_2$: C, 50.67; H, 2.87; N, 11.82%. Found: C, 50.71; H, 2.84; N, 11.87%.

2-(4-Methoxyphenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5-carboxymethyl-4-thiazolidinone 7c. A solution of 1-(4-methoxy benzylidene)-4-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl] semicarbazide **4c** (0.01 mol) in dry benzene (50.0 mL) and mercaptosuccinic acid (0.012 mol) was refluxed for 13 h using Dean-Stark separator. After completion of reaction, excess benzene was removed by distillation. The resulting product was treated with 5% $NaHCO_3$ solution to remove unreacted mercaptosuccinic acid. The separated product was washed with water, dried and recrystallized from chloroform/acetone as a pale yellow solid in 76% yield. m.p. 136 ^oC; IR (KBr): NH (3223 cm^{-1}), 4-thiazolidinone; C=O (1674 cm^{-1}), C=O str. (1642 cm^{-1}), C-F str. (1056 cm^{-1}), C-Cl str. (758 cm^{-1}), C-S-C str. (740 cm^{-1}); ^1H NMR (δ, $CDCl_3$): 2.6 (1H, d, CH_ACOOH), 3.0 (1H, d, CH_BCOOH), 3.9 (3H, s, OCH_3), 6.2 (1H, s, CH of 4-thiazolidinone ring), 6.9 (1H, s, CH, pyrimidine ring), 7.3-7.9 (m, 9H, ArH), 8.6 (1H, s, CO-NH); Anal. Calcd. for $C_{27}H_{20}O_5N_5S_2Cl_2F$: C, 50.0; H, 3.08; N, 10.8%. Found: C, 50.03; H, 3.04; N, 10.83%.

The remaining compounds **7a, 7b, 7d, 7e** were synthesised by the same procedure.

2-(2-Chlorophenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido] -5-carboxymethyl-4-thiazolidinone 7a.

White solid in 67% yield. m.p. 129 ^oC; IR (KBr): -NH (3219 cm^{-1}), 4-thiazolidinone: C=O (1674 cm^{-1}), C=O str. (1640 cm^{-1}), C-F str. (1052 cm^{-1}), C-Cl str. (756 cm^{-1}), C-S-C str. (741 cm^{-1}); ^1H NMR (δ, $CDCl_3$): 2.65 (1H, d, CH_ACOOH), 2.85 (1H, d, CH_BCOOH), 6.1 (1H, s, CH of 4-thiazolidinone ring), 6.8 (1H, s, CH, pyrimidine ring), 7.3-7.8 (m, 9H, ArH), 8.7 (1H, s, CO-NH); Anal. Calcd. for $C_{26}H_{17}O_4N_5S_2Cl_3F$: C, 47.8; H, 2.60; N, 10.72%. Found: C, 47.77; H, 2.55; N, 10.77%.

2-(2-Methoxyphenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5-carboxymethyl-4-thiazolidinone 7b.

Creamish white solid in 64% yield. m.p. 132 ^{o}C; IR (KBr): -NH (3222 cm^{-1}), 4-thiazolidinone:C=O (1672cm^{-1}), C=O str. (1641 cm^{-1}), C-F str. (1052cm^{-1}), C-Cl str.(753cm^{-1}), C-S-C str. (741 cm^{-1}); ^{1}H NMR (δ, $CDCl_3$): 2.6 (1H, d, CH_ACOOH), 2.9 (1H, d, CH_BCOOH), 4.0 (3H, s, OCH_3), 6.2 (1H, s, CH of 4-thiazolidinone ring), 6.8 (1H, s, CH, pyrimidine ring), 7.3-7.8 (m, 9H, ArH), 8.5 (1H, s, CO-NH); Anal. Calcd. for $C_{27}H_{20}O_5N_5S_2Cl_2F$: C, 50.0; H, 3.08; N, 10.8%. Found: C, 50.05; H, 3.1; N, 10.85%.

2-(3,4,5-Trimethoxyphenyl-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5-carboxymethyl-4-thiazolidinone 7d.

Almost white solid in 66% yield. m.p. 119 ^{o}C; IR (KBr): -NH (3221 cm^{-1}), 4-thiazolidinone: C=O (1672cm^{-1}), C=O str.(1643 cm^{-1}), C-F str.(1053 cm^{-1}), C-Cl str.(753cm^{-1}), C-S-C str. (742 cm^{-1}); ^{1}H NMR (δ, $CDCl_3$): 2.6 (1H, d, CH_ACOOH), 3.0 (1H, d, CH_BCOOH), 4.1 (9H, s, 3,4,5-tri-OCH_3), 6.2 (1H, s, CH of 4-thiazolidinone ring), 6.8 (1H, s, CH, pyrimidine ring), 7.4-7.8 (m, 7H, ArH), 8.7 (1H, s, CO-NH); Anal. Calcd. for $C_{29}H_{24}O_7N_5S_2Cl_2F$: C, 49.15; H, 3.38; N, 9.88%. Found: C, 49.11; H, 3.34; N, 9.91%.

2-(4-Fluorophenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2-thienyl)pyrimidine-2-yl-ureido]-5-carboxymethyl-4-thiazolidinone 7e.

Off-white solid in 81% yield. m.p. 142 ^{o}C; IR (KBr): NH (3223 cm^{-1}), 4-thiazolidinone; C=O (1674 cm^{-1}), C=O str. (1640 cm^{-1}), C-F str. (1055 cm^{-1}), C-Cl str. (756 cm^{-1}), C-S-C str. (743 cm^{-1}); ^{1}H NMR (δ, $CDCl_3$): 2.6 (1H, d, CH_ACOOH), 2.9 (1H, d, CH_BCOOH), 6.1 (1H, s, CH of 4-thiazolidinone ring), 6.7 (1H, s, CH, pyrimidine ring), 7.4-7.9 (m, 9H, ArH), 8.7 (1H, s, CO-NH); Anal. Calcd. for $C_{26}H_{17}O_4N_5S_2Cl_2F_2$: C, 49.05; H, 2.67; N, 11.0%. Found: C, 49.11; H, 2.71; N, 11.04%.

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