Synthesis of novel highly substituted pyrimidines bearing furanyl thiazole nucleous

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ABSTRACT. A series of novel highly substituted pyrimidines bearing furanyl thiazole nucleous have been synthesized. In which reaction of guanidine nitrate with ketene dithioacetals **3c** produced substituted pyrimidines **4d** which further treated with various aromatic aldehydes to afford title compounds **5(a-t)**. The chemical structures of the synthesized compounds were elucidated by ^1H NMR, ^{13}C NMR, FT-IR, elemental analysis, and mass spectral data.

1. INTRODUCTION

At very early period in the history of organic chemistry, pyrimidines ('m-diazine') were known as the breakdown products of uric acid. The first pyrimidine derivative to be isolated was alloxan in 1818 by *Brugnatelli*, oxidizing uric acid with nitric acid [1]. The name pyrimidine (combination of words pyridine and amidine) was first applied by Pinner. Pyrimidines are the most important six membered heterocyclic containing 2 nitrogen atoms at position 1 and 3. It is isomeric with two other forms of diazene. Nucleic acid hydrolysis produces several pyrimidines (uracil, thymine and cytosine). Of the 2 types of nucleic acid DNA and RNA, cytosine is found present in both DNA and RNA, while uracil present only in RNA and thymine only in DNA [2].

Pyrimidine derivatives are well known for their pharmacological activities. Various drugs containing pyrimidine nucleus were synthesized and used as anticancer agents like 5-Fluorouracil (5-FU), Tegafur and Thioguanine [3]. An interest in pyrimidine derivatives as anticancer agents has led to the preparation and anticancer activity evaluation of hundreds of such molecules. For example, 2- cyanopyrimidines [4], hydrazino pyrimidine-5- carbonitriles [5], 1,3-dialkylated-pyrimidin- 2,4-diones [6] and 4-anilino-2-(2-pyridyl). Pyrimidines were evaluated as a new class of potent anticancer agents [7]. Also, pyrimidine derivatives were found to possess several pharmacological properties like antibacterial agents [8-10], including antiviral [11], antiallergic [12], hypoglycemic [13, 14] and diuretic [15].

A number of methods have been reported for the synthesis of pyrimidine derivatives [16-25]. Here we report the synthesis of novel highly substituted pyrimidines bearing furanyl thiazole nucleous. The constitutions of all the products were confirmed using ^1H NMR, ^{13}C NMR, FTIR, and elemental analysis.

2. EXPERIMENTAL

Required all reagents were obtained commercially. Solvents were purified and dried before being used. All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminium plates precoated with silica gel, 60F₂₅₄, 0.25 mm thickness) (Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions, purity and homogeneity of the synthesized compounds; eluent-hexane:ethyl acetate: (2:8). UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds are within $\pm 0.4\%$ of theory specified. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm^{-1} . ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-*d*₆ on a Bruker Avance 400F (MHz)

spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using solvent peak as internal standard at 400 MHz and 100 MHz respectively. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan).

2.1 Synthesis of *N*-(4-(furan-2-yl)thiazol-2-yl)-4-methyl-3-oxopentanamide (**2b**)

A mixture containing the 4-(furan-2-yl)thiazol-2-amine **1a** (10 mmol), methyl isobutyrylacetate (10 mmol), and catalytic amount of potassium hydroxide (10 %) was reflux at 110°C for the approximately 16-18 h. The reaction was monitored by TLC. After completion of reaction, the solvent was removed under *vacuo* when the reaction was completed. The solid or oil was crystallized from methanol to give pure product **2b**.

2.2 Synthesis of ketene dithioacetals **3c**.

A 100mL conical flask equipped with magnetic stirrer and septum was charged with a solution of *N*-(4-(furan-2-yl)thiazol-2-yl)-4-methyl-3-oxopentanamide **2b**, (10 mmol) in DMF (10 mL). Dried K₂CO₃ (10 mmol) was added and the mixture was stirred for 2 h at room temperature. CS₂ (30 mmol) was added and the mixture was stirred for an additional 2 h at room temperature. Methyl iodide (20 mmol) was added at 0-5 °C and the mixture was stirred for 4 h before being poured onto water (40 mL). The precipitated crude product was purified by filtration followed by crystallization from EtOH. When the product was oil, the organic phase was extracted with Et₂O (3 × 10 mL). The combined organic extracts were washed with H₂O (2 × 10 mL), dried (MgSO₄), and concentrated in *vacuo* to afford ketene dithioacetals directly used for the next step.

2.3 General procedure for the synthesis of substituted pyrimidines **4d**

To a well stirred mixture of guanidine nitrate (10 mmol) and sodium methoxide or sodium ethoxide (20 mmol) in methanol or ethanol was added the solution of ketene dithioacetals **3c** (10 mmol) in methanol or ethanol within 10-15 min. The resulting reaction mixture was further stirred at rt for 15 min. then, reflux the reaction mixtures for 7h on water bath. After completion of the reaction, the mixture was poured onto ice cold water. Thus, the obtained solid was filtered, wash with water and dried it and crystallization from EtOH to afford analytically pure products **4d**.

2.4 General procedure for the synthesis of substituted pyrimidines **5(a-t)**

To a well stirred mixture of substituted pyrimidines **4d** (10 mmol) and piperidine (2 drops) in ethanol (10 mL) was added various aromatic aldehyde (10 mmol). The resulting reaction mixture was further stirred at rt for 15 min. then, reflux the reaction mixtures for 4-5h on water bath. After completion of the reaction, the mixture was poured onto ice cold water. Thus, the obtained solid was filtered, wash with water and dried it and crystallization from MeOH to afford analytically pure products **5(a-t)**.

Scheme 1 Synthetic pathway for the synthesis of 2b

Scheme 2 Synthetic pathway for the synthesis of 3c

Scheme 3 Synthetic pathway for the synthesis of 4d

Scheme 4 Synthetic pathway for the synthesis of 5(a-t)

Where $\text{R} = \text{CH}_3, \text{C}_2\text{H}_5$
 $\text{Z} = \text{Aryl Heterocycle}$

Scheme 5 Mechanism for the synthesis of pyrimidine derivatives

Table 1 Synthesis of substituted pyrimidines 5(a-t)

Entry	R	R ₁	RT(h.)	Yield %	mp °C
5a	CH ₃	H	5.0	80	150-152
5b	CH ₃	4-CH ₃	4.6	85	162-164
5c	CH ₃	3-CH ₃	4.7	83	138-140
5d	CH ₃	4-OCH ₃	4.2	86	145-147
5e	CH ₃	4-NO ₂	4.0	90	168-170
5f	CH ₃	3-NO ₂	4.3	88	161-163
5g	CH ₃	4-F	4.6	84	151-153
5h	CH ₃	4-Br	4.8	82	139-141
5i	CH ₃	4-Cl	4.8	83	169-171
5j	CH ₃	3-Cl	4.9	77	148-150
5k	C ₂ H ₅	H	4.9	81	139-141
5l	C ₂ H ₅	4-CH ₃	4.5	83	153-155
5m	C ₂ H ₅	3-CH ₃	4.7	80	164-166
5n	C ₂ H ₅	4-OCH ₃	4.3	88	180-182
5o	C ₂ H ₅	4-NO ₂	4.0	89	175-177
5p	C ₂ H ₅	3-NO ₂	4.4	87	159-161
5q	C ₂ H ₅	4-F	4.5	85	179-181
5r	C ₂ H ₅	4-Br	4.9	80	183-185
5s	C ₂ H ₅	4-Cl	4.7	79	173-175
5t	C ₂ H ₅	3-Cl	4.9	76	158-160

The required 4-(furan-2-yl)thiazol-2-amine **1a** was prepared by solid phase reaction according to literature procedure [26].

In the current study, all the pyrimidine derivatives **5(a-t)** were obtained in good yields by the reaction of various aromatic aldehydes and substituted amino pyrimidines **4d** in ethanol, using piperidine as catalyst, at reflux temperature. (Scheme 4). The mechanism (Scheme 5), in ketene dithioacetal system the carbonyl carbon and β -carbon atoms regarded as hard and soft electrophilic centers, since the carbonyl carbon is adjacent to the hard-base oxygen while the β -carbon is flanked by the soft-base methylthio groups. Thus, the binucleophile guanidine in the presence of base attacks on carbonyl carbon of systems and formed substituted amino pyrimidine **4d** product by removal of water molecule followed by methylthio as good leaving group.

The identity of the product determined by ^1H NMR, ^{13}C NMR, FT-IR spectral data, and molecular weight of some selected compounds were confirmed by mass spectrometry. ^1H NMR (DMSO- d_6) spectrum of **5a**, molecule of interest, exhibited doublet peak at δ 1.103-1.189 ppm appeared for methyl protons of isopropyl group. Also exhibited multiplet at δ 3.223-3.202 ppm appeared for methine proton and singlet at δ 3.530 ppm of aromatic methoxy group. Aromatic protons as multiplets appeared at around δ 6.845-7.562 ppm. Moreover, it exhibited two singlet peak δ 9.139 ppm appeared for methine proton and δ 10.288 ppm appeared for $-\text{NH}-$ proton. The ^{13}C NMR spectrum is in consonance with the structure assigned. In the ^{13}C NMR spectra, signals around δ 163.20 ppm are attributed to carbonyl carbons and signals around δ 110.12–141.30 ppm are attributed to aromatic carbons of compound **5a**. Moreover **5a** exhibited a distinctive signal at δ 56.20 ppm for aromatic methoxy carbon, at δ 30.65 ppm for methine carbon, at δ 21.36 ppm for methyl carbon. The IR spectrum of compound **5a** exhibited characteristic absorption band at $3,326\text{ cm}^{-1}$ for $-\text{NH}-$ group. While $3,045\text{ cm}^{-1}$ for aromatic C–H stretching and $1,688\text{ cm}^{-1}$ for carbonyl C=O stretching. The mass spectra of compounds **5a** and **5k**, molecules of interest, detected the expected molecular ion signals corresponding to respective molecular formula, i.e., mass spectra of compounds **5a** and **5k** gave molecular ion peak at m/z 447.1 ($M + 1$) and m/z 461.1 ($M + 1$) corresponding to molecular formula $\text{C}_{23}\text{H}_{21}\text{N}_5\text{O}_3\text{S}$ and $\text{C}_{24}\text{H}_{23}\text{N}_5\text{O}_3\text{S}$. The obtained elemental analysis values are in good agreement with theoretical data. Similarly, all these compounds were characterized on the basis of spectral studies. All spectroscopic data have been given in spectral data.

3. SPECTRAL DATA

(*E*)-2-(benzylideneamino)-*N*-(4-(furan-2-yl)thiazol-2-yl)-4-isopropyl methoxypyrimidine-5-carboxamide (**5a**)

Yellow solid, yield 80%, m.p. $150\text{--}152^\circ\text{C}$, IR (KBr, ν , cm^{-1}): 3326 (N-H Str.), 3045 (Ar C-H Str.), 1688 ($-\text{C}=\text{O}-$ Str.), ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.103-1.189 (d, 6H, $-\text{CH}(\text{CH}_3)_2$), 3.223-3.302 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.530 (s, 3H, Ar-OCH $_3$), 6.845-7.562 (m, 9H, Ar-H), 9.139 (s, 1H, CH), 10.288 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 21.36 ($\text{CH}_3\text{--CH--CH}_3$), 30.65 ($\text{CH}_3\text{--CH--CH}_3$), 56.20 (Ar-OCH $_3$), 110.12, 111.10, 112.05, 114.00, 115.60, 117.28, 119.00, 121.20, 124.30, 126.12, 128.00, 130.13, 132.45, 134.56, 136.18, 139.20, 140.23, 141.30 (Ar-C), 163.20 ($-\text{CO-NH}-$). MS(M^+): 447.14, Anal. Calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_5\text{O}_3\text{S}$ (447.51): C 61.73, H 4.73, N 15.65 Found: C 61.20, H 4.11, N 15.70%.

(*E*)-2-(4-methylbenzylideneamino)-*N*-(4-(furan-2-yl)thiazol-2-yl)-4-isopropyl methoxypyrimidine-5-carboxamide (**5b**)

Yellow solid, yield 85%, m.p. $162\text{--}164^\circ\text{C}$, IR (KBr, ν , cm^{-1}): 3343 (N-H Str.), 3035 (Ar C-H Str.), 1680 ($-\text{C}=\text{O}-$ Str.), ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.101-1.190 (d, 6H, $-\text{CH}(\text{CH}_3)_2$), 2.200 (s, 3H, Ar-CH $_3$), 3.100-3.200 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.600 (s, 3H, Ar-OCH $_3$), 6.721-7.213 (m, 8H, Ar-H), 9.100 (s, 1H, CH), 10.113 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 21.15 ($\text{CH}_3\text{--CH--CH}_3$), 24.20 (Ar-CH $_3$), 30.20 ($\text{CH}_3\text{--CH--CH}_3$), 55.20 (Ar-OCH $_3$), 108.13, 109.12,

112.00, 113.45, 114.26, 116.13, 117.64, 112.12, 122.36, 124.22, 125.20, 127.44, 129.14, 131.28, 132.00, 134.36, 136.00, 138.33 (Ar-C), 161.12 (-CO-NH-). MS(M⁺): 461.15, Anal. Calcd. for C₂₄H₂₃N₅O₃S (461.54): C 62.46, H 5.02, N 15.17 Found: C 62.20, H 4.80, N 15.18%.

(E)-2-(3-methylbenzylideneamino)-N-(4-(furan-2-yl)thiazol-2-yl)-4-isopropyl methoxypyrimidine-5-carboxamide (5c)

Yellow solid, yield 83%, m.p. 138-140°C, IR (KBr, ν, cm⁻¹): 3388 (N-H Str.), 3060 (Ar C-H Str.), 1626 (-C=O- Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm): δ 1.236-1.300 (d, 6H, -CH(CH₃)₂), 2.288 (s, 3H, Ar-CH₃), 3.223-3.300 (m, 1H, -CH(CH₃)₂), 3.700 (s, 3H, Ar-OCH₃), 6.945-7.813 (m, 8H, Ar-H), 9.212 (s, 1H, CH), 10.313 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm): 20.36 (CH₃-CH-CH₃), 24.90 (Ar-CH₃), 31.20 (CH₃-CH-CH₃), 56.00 (Ar-OCH₃), 109.15, 110.02, 112.03, 113.23, 115.00, 116.32, 117.23, 118.20, 120.45, 123.40, 125.20, 128.30, 130.22, 132.25, 135.21, 137.40, 140.11, 142.00 (Ar-C), 162.30 (-CO-NH-). MS(M⁺): 461.15, Anal. Calcd. for C₂₄H₂₃N₅O₃S (461.54): C 62.46, H 5.02, N 15.17 Found: C 62.20, H 4.80, N 15.18%.

(E)-2-(4-methoxybenzylideneamino)-N-(4-(furan-2-yl)thiazol-2-yl)-4-isopropyl methoxypyrimidine-5-carboxamide (5d)

Yellow solid, yield 86%, m.p. 145-147°C, IR (KBr, ν, cm⁻¹): 3339 (N-H Str.), 3012 (Ar C-H Str.), 1636 (-C=O- Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm): δ 1.080-1.125 (d, 6H, -CH(CH₃)₂), 3.125-3.206 (m, 1H, -CH(CH₃)₂), 3.589 (s, 3H, Ar-OCH₃), 3.656 (s, 3H, Ar-OCH₃), 7.230-8.120 (m, 8H, Ar-H), 9.118 (s, 1H, CH), 10.326 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm): 21.96 (CH₃-CH-CH₃), 31.00 (CH₃-CH-CH₃), 55.30 (Ar-OCH₃), 56.90 (Ar-OCH₃), 110.12, 111.20, 113.00, 114.36, 115.30, 117.00, 119.30, 121.03, 122.00, 124.56, 126.30, 127.00, 129.54, 131.02, 133.00, 135.26, 137.18, 139.00 (Ar-C), 160.36 (-CO-NH-). MS(M⁺): 477.15, Anal. Calcd. for C₂₄H₂₃N₅O₄S (477.54): C 60.36, H 4.85, N 14.67 Found: C 60.50, H 4.23, N 14.40%.

(E)-2-(4-nitrobenzylideneamino)-N-(4-(furan-2-yl)thiazol-2-yl)-4-isopropyl methoxypyrimidine-5-carboxamide (5e)

Yellow solid, yield 90%, m.p. 168-170°C, IR (KBr, ν, cm⁻¹): 3351 (N-H Str.), 3036 (Ar C-H Str.), 1681 (-C=O- Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm): δ 1.126-1.256 (d, 6H, -CH(CH₃)₂), 3.125-3.258 (m, 1H, -CH(CH₃)₂), 3.623 (s, 3H, Ar-OCH₃), 6.989-7.845 (m, 8H, Ar-H), 9.165 (s, 1H, CH), 10.126 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm): 22.26 (CH₃-CH-CH₃), 30.26 (CH₃-CH-CH₃), 56.36 (Ar-OCH₃), 111.02, 112.00, 113.36, 114.25, 116.65, 117.00, 118.30, 120.00, 122.00, 124.36, 126.30, 127.32, 128.54, 130.12, 132.25, 134.61, 135.00, 138.14 (Ar-C), 162.36 (-CO-NH-). MS(M⁺): 492.12, Anal. Calcd. for C₂₃H₂₀N₆O₅S (492.51): C 56.09, H 4.09, N 17.06 Found: C 56.15, H 4.20, N 17.01%.

(E)-2-(3-nitrobenzylideneamino)-N-(4-(furan-2-yl)thiazol-2-yl)-4-isopropyl methoxypyrimidine-5-carboxamide (5f)

Yellow solid, yield 88%, m.p. 161-163°C, IR (KBr, ν, cm⁻¹): 3377 (N-H Str.), 3042 (Ar C-H Str.), 1662 (-C=O- Str.), ¹H NMR (400 MHz, DMSO-*d*₆) δ_H (ppm): δ 1.205-1.306 (d, 6H, -CH(CH₃)₂), 3.263-3.299 (m, 1H, -CH(CH₃)₂), 3.626 (s, 3H, Ar-OCH₃), 6.366-7.526 (m, 8H, Ar-H), 9.188 (s, 1H, CH), 10.313 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-*d*₆) δ_C (ppm): 20.30 (CH₃-CH-CH₃), 31.24 (CH₃-CH-CH₃), 56.21 (Ar-OCH₃), 112.00, 113.00, 114.54, 116.03, 117.18, 119.20, 120.15, 122.00, 123.63, 125.00, 127.18, 129.30, 131.44, 132.56, 133.00, 135.18, 138.26, 140.01 (Ar-C), 162.60 (-CO-NH-). MS(M⁺): 492.12, Anal. Calcd. for C₂₃H₂₀N₆O₅S (492.51): C 56.09, H 4.09, N 17.06 Found: C 56.15, H 4.20, N 17.01%.

(E)-2-(4-fluorobenzylideneamino)-N-(4-(furan-2-yl)thiazol-2-yl)-4-isopropyl methoxypyrimidine-5-carboxamide (5g)

Yellow solid, yield 84%, m.p. 151-153 °C, IR (KBr, ν , cm^{-1}): 3380 (N-H Str.), 3030 (Ar C-H Str.), 1676 (C=O Str.), ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.236-1.300 (d, 6H, -CH(CH₃)₂), 3.120-3.201 (m, 1H, -CH(CH₃)₂), 3.712 (s, 3H, Ar-OCH₃), 7.120-8.112 (m, 8H, Ar-H), 9.201 (s, 1H, CH), 10.306 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 22.00 (CH₃-CH-CH₃), 31.56 (CH₃-CH-CH₃), 57.13 (Ar-OCH₃), 110.12, 112.30, 113.00, 114.56, 115.00, 117.03, 119.23, 120.56, 122.00, 124.50, 126.30, 127.23, 128.31, 130.54, 132.65, 135.01, 137.18, 139.20 (Ar-C), 159.18 (CO-NH). MS(M⁺): 465.13, Anal. Calcd. for C₂₃H₂₀FN₅O₃S (465.50): C 59.34, H 4.33, N 15.04 Found: C 59.22, H 4.40, N 15.26%.

(E)-2-(4-bromobenzylideneamino)-N-(4-(furan-2-yl)thiazol-2-yl)-4-isopropyl methoxypyrimidine-5-carboxamide (5h)

Yellow solid, yield 82%, m.p. 139-141 °C, IR (KBr, ν , cm^{-1}): 3360 (N-H Str.), 3078 (Ar C-H Str.), 1651 (C=O Str.), ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.165-1.206 (d, 6H, -CH(CH₃)₂), 3.212-3.314 (m, 1H, -CH(CH₃)₂), 3.623 (s, 3H, Ar-OCH₃), 7.112-8.201 (m, 8H, Ar-H), 9.213 (s, 1H, CH), 10.400 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 21.98 (CH₃-CH-CH₃), 31.25 (CH₃-CH-CH₃), 56.44 (Ar-OCH₃), 109.56, 110.23, 112.00, 115.30, 116.32, 118.00, 120.11, 121.56, 123.06, 125.66, 127.18, 129.40, 131.34, 133.00, 135.60, 137.18, 139.01, 142.00 (Ar-C), 164.00 (CO-NH). MS(M⁺): 525.05, Anal. Calcd. for C₂₃H₂₀BrN₅O₃S (526.41): C 52.48, H 3.83, N 13.30 Found: C 52.52, H 3.75, N 13.28%.

(E)-2-(4-chlorobenzylideneamino)-N-(4-(furan-2-yl)thiazol-2-yl)-4-isopropyl methoxypyrimidine-5-carboxamide (5i)

Yellow solid, yield 83%, m.p. 169-171 °C, IR (KBr, ν , cm^{-1}): 3375 (N-H Str.), 3018 (Ar C-H Str.), 1668 (C=O Str.), ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.145-1.231 (d, 6H, -CH(CH₃)₂), 3.202-3.298 (m, 1H, -CH(CH₃)₂), 3.714 (s, 3H, Ar-OCH₃), 6.982-7.858 (m, 8H, Ar-H), 9.230 (s, 1H, CH), 10.412 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 20.13 (CH₃-CH-CH₃), 31.33 (CH₃-CH-CH₃), 56.90 (Ar-OCH₃), 111.02, 112.30, 113.56, 114.00, 115.60, 117.20, 119.20, 121.04, 122.36, 125.64, 127.34, 129.36, 131.02, 133.25, 135.41, 137.25, 139.56, 141.00 (Ar-C), 162.38 (CO-NH). MS(M⁺): 481.10, Anal. Calcd. for C₂₃H₂₀ClN₅O₃S (481.95): C 57.32, H 4.18, N 14.53 Found: C 57.35, H 4.12, N 14.36%.

(E)-2-(3-chlorobenzylideneamino)-N-(4-(furan-2-yl)thiazol-2-yl)-4-isopropyl methoxypyrimidine-5-carboxamide (5j)

Yellow solid, yield 77%, m.p. 148-150 °C, IR (KBr, ν , cm^{-1}): 3369 (N-H Str.), 3026 (Ar C-H Str.), 1686 (C=O Str.), ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.156-1.236 (d, 6H, -CH(CH₃)₂), 3.124-3.215 (m, 1H, -CH(CH₃)₂), 3.715 (s, 3H, Ar-OCH₃), 6.898-7.568 (m, 8H, Ar-H), 9.228 (s, 1H, CH), 10.315 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 22.01 (CH₃-CH-CH₃), 29.98 (CH₃-CH-CH₃), 56.43 (Ar-OCH₃), 110.20, 112.30, 113.54, 115.20, 116.54, 117.00, 119.67, 121.30, 122.00, 125.36, 127.40, 128.23, 129.00, 131.50, 133.00, 135.64, 137.80, 139.02 (Ar-C), 163.00 (CO-NH). MS(M⁺): 481.10, Anal. Calcd. for C₂₃H₂₀ClN₅O₃S (481.95): C 57.32, H 4.18, N 14.53 Found: C 57.35, H 4.12, N 14.36%.

(E)-2-(benzylideneamino)-4-ethoxy-N-(4-(furan-2-yl)thiazol-2-yl)-6-isopropylpyrimidine-5-carboxamide (5k)

Yellow solid, yield 81%, m.p. 139-141 °C, IR (KBr, ν , cm^{-1}): 3397 (N-H Str.), 3025 (Ar C-H Str.), 1652 (-C=O- Str.). ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.263-1.369 (d, 6H, -CH(CH₃)₂), 1.312-1.398 (t, 3H, Ar-OCH₂-CH₃), 3.236-3.365 (m, 1H, -CH(CH₃)₂), 3.912-3.980 (q, 2H, Ar-OCH₂-CH₃), 6.563-7.569 (m, 9H, Ar-H), 9.138 (s, 1H, CH), 10.326 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 17.13 (Ar-OCH₂-CH₃), 21.20 (CH₃-CH-CH₃), 31.56 (CH₃-CH-CH₃), 59.50 (Ar-OCH₂-CH₃), 113.25, 114.32, 115.34, 117.18, 119.20, 121.00, 123.00, 125.36, 126.30, 129.20, 131.00, 133.02, 134.50, 136.21, 138.56, 139.30, 141.21, 142.00 (Ar-C), 164.20 (-CO-NH-). MS(M⁺): 461.15, Anal. Calcd. for C₂₄H₂₃N₅O₃S (461.54): C 62.46, H 4.02, N 15.17 Found: C 62.56, H 4.22, N 15.10%.

(E)-2-(4-methylbenzylideneamino)-4-ethoxy-N-(4-(furan-2-yl)thiazol-2-yl)-6-isopropylpyrimidine-5-carboxamide (5l)

Yellow solid, yield 83%, m.p. 155-153 °C, IR (KBr, ν , cm^{-1}): 3390 (N-H Str.), 3025 (Ar C-H Str.), 1650 (-C=O- Str.). ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.100-1.200 (d, 6H, -CH(CH₃)₂), 1.212-1.298 (t, 3H, Ar-OCH₂-CH₃), 2.300 (s, 3H, Ar-CH₃), 3.200-3.300 (m, 1H, -CH(CH₃)₂), 3.900-3.980 (q, 2H, Ar-OCH₂-CH₃), 6.500-7.650 (m, 8H, Ar-H), 9.200 (s, 1H, CH), 10.213 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 18.12 (Ar-OCH₂-CH₃), 22.36 (CH₃-CH-CH₃), 25.36 (Ar-CH₃), 31.28 (CH₃-CH-CH₃), 59.66 (Ar-OCH₂-CH₃), 109.23, 110.16, 113.24, 114.00, 115.36, 116.87, 118.00, 120.33, 122.00, 124.39, 126.36, 128.45, 130.12, 132.14, 133.00, 135.26, 138.12, 140.33 (Ar-C), 163.24 (-CO-NH-). MS(M⁺): 475.17, Anal. Calcd. for C₂₅H₂₅N₅O₃S (475.56): C 63.14, H 5.30, N 14.73 Found: C 63.18, H 5.40, N 14.70%.

(E)-2-(3-methylbenzylideneamino)-4-ethoxy-N-(4-(furan-2-yl)thiazol-2-yl)-6-isopropylpyrimidine-5-carboxamide (5m)

Yellow solid, yield 80%, m.p. 164-166 °C, IR (KBr, ν , cm^{-1}): 3356 (N-H Str.), 3025 (Ar C-H Str.), 1636 (-C=O- Str.). ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.135-1.188 (d, 6H, -CH(CH₃)₂), 1.200-1.290 (t, 3H, Ar-OCH₂-CH₃), 2.420 (s, 3H, Ar-CH₃), 3.198-3.203 (m, 1H, -CH(CH₃)₂), 3.980-3.4050 (q, 2H, Ar-OCH₂-CH₃), 6.890-7.456 (m, 8H, Ar-H), 9.312 (s, 1H, CH), 10.525 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 17.88 (Ar-OCH₂-CH₃), 22.96 (CH₃-CH-CH₃), 25.30 (Ar-CH₃), 31.90 (CH₃-CH-CH₃), 60.03 (Ar-OCH₂-CH₃), 110.15, 112.20, 113.36, 115.41, 116.20, 117.18, 119.80, 121.00, 123.02, 125.00, 127.13, 129.36, 131.24, 133.02, 135.56, 137.14, 139.80, 140.96 (Ar-C), 162.30 (-CO-NH-). MS(M⁺): 475.17, Anal. Calcd. for C₂₅H₂₅N₅O₃S (475.56): C 63.14, H 5.30, N 14.73 Found: C 63.18, H 5.40, N 14.70%.

(E)-2-(4-methoxybenzylideneamino)-4-ethoxy-N-(4-(furan-2-yl)thiazol-2-yl)-6-isopropylpyrimidine-5-carboxamide (5n)

Yellow solid, yield 88%, m.p. 180-182 °C, IR (KBr, ν , cm^{-1}): 3369 (N-H Str.), 3070 (Ar C-H Str.), 1688 (-C=O- Str.). ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.145-1.256 (d, 6H, -CH(CH₃)₂), 1.290-1.326 (t, 3H, Ar-OCH₂-CH₃), 3.220-3.290 (m, 1H, -CH(CH₃)₂), 3.712 (s, 3H, Ar-OCH₃), 3.826-3.900 (q, 2H, Ar-OCH₂-CH₃), 6.713-7.621 (m, 8H, Ar-H), 9.288 (s, 1H, CH), 10.245 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 18.33 (Ar-OCH₂-CH₃), 23.00 (CH₃-CH-CH₃), 32.01 (CH₃-CH-CH₃), 56.60 (Ar-OCH₃), 59.03 (Ar-OCH₂-CH₃), 111.02, 112.21, 113.26, 115.20, 116.54, 117.80, 118.30, 120.32, 122.00, 124.53, 126.30, 128.41, 130.12, 131.23, 133.56, 135.20, 138.34, 139.21 (Ar-C), 165.21 (-CO-NH-). MS(M⁺): 491.16, Anal. Calcd. for C₂₅H₂₅N₅O₄S (491.56): C 61.08, H 5.13, N 14.25 Found: C 61.20, H 5.18, N 14.28%.

(E)-2-(4-nitrobenzylideneamino)-4-ethoxy-N-(4-(furan-2-yl)thiazol-2-yl)-6-isopropylpyrimidine-5-carboxamide (5o)

Yellow solid, yield 89%, m.p. 175-177°C, IR (KBr, ν , cm^{-1}): 3380 (N-H Str.), 3076 (Ar C-H Str.), 1672 (C=O Str.). ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.145-1.236 (d, 6H, $-\text{CH}(\text{CH}_3)_2$), 1.300-1.356 (t, 3H, Ar-OCH $_2$ -CH $_3$), 3.230-3.298 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.890-3.980 (q, 2H, Ar-OCH $_2$ -CH $_3$), 7.125-8.230 (m, 8H, Ar-H), 9.321 (s, 1H, CH), 10.336 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 19.12 (Ar-OCH $_2$ -CH $_3$), 23.01 (CH $_3$ -CH-CH $_3$), 30.21 (CH $_3$ -CH-CH $_3$), 58.30 (Ar-OCH $_2$ -CH $_3$), 112.03, 113.05, 114.00, 116.31, 117.80, 119.20, 121.04, 123.00, 125.46, 127.41, 129.50, 131.54, 133.00, 135.62, 137.41, 139.80, 140.13, 141.00 (Ar-C), 159.12 (CO-NH-). MS(M^+): 506.14, Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{N}_6\text{O}_5\text{S}$ (506.53): C 56.91, H 4.38, N 16.59 Found: C 56.85, H 4.42, N 16.62%.

(E)-2-(3-nitrobenzylideneamino)-4-ethoxy-N-(4-(furan-2-yl)thiazol-2-yl)-6-isopropylpyrimidine-5-carboxamide (5p)

Yellow solid, yield 87%, m.p. 159-161°C, IR (KBr, ν , cm^{-1}): 3378 (N-H Str.), 3056 (Ar C-H Str.), 1670 (C=O Str.). ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.203-1.280 (d, 6H, $-\text{CH}(\text{CH}_3)_2$), 1.320-1.356 (t, 3H, Ar-OCH $_2$ -CH $_3$), 3.254-3.298 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.920-4.00 (q, 2H, Ar-OCH $_2$ -CH $_3$), 7.123-8.225 (m, 8H, Ar-H), 9.312 (s, 1H, CH), 10.378 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 18.01 (Ar-OCH $_2$ -CH $_3$), 22.19 (CH $_3$ -CH-CH $_3$), 31.98 (CH $_3$ -CH-CH $_3$), 60.01 (Ar-OCH $_2$ -CH $_3$), 111.00, 112.03, 114.01, 116.24, 117.30, 118.32, 120.21, 122.25, 124.10, 126.14, 127.30, 129.31, 131.20, 133.04, 135.24, 136.48, 138.30, 140.24 (Ar-C), 164.30 (CO-NH-). MS(M^+): 506.14, Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{N}_6\text{O}_5\text{S}$ (506.53): C 56.91, H 4.38, N 16.59 Found: C 56.85, H 4.42, N 16.62%.

(E)-2-(4-fluorobenzylideneamino)-4-ethoxy-N-(4-(furan-2-yl)thiazol-2-yl)-6-isopropylpyrimidine-5-carboxamide (5q)

Yellow solid, yield 85%, m.p. 179-181°C, Anal. IR (KBr, ν , cm^{-1}): 3388 (N-H Str.), 3041 (Ar C-H Str.), 1646 (C=O Str.). ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.189-1.212 (d, 6H, $-\text{CH}(\text{CH}_3)_2$), 1.250-1.300 (t, 3H, Ar-OCH $_2$ -CH $_3$), 3.198-3.256 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.950-4.023 (q, 2H, Ar-OCH $_2$ -CH $_3$), 6.890-7.450 (m, 8H, Ar-H), 9.313 (s, 1H, CH), 10.378 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 17.20 (Ar-OCH $_2$ -CH $_3$), 22.96 (CH $_3$ -CH-CH $_3$), 32.00 (CH $_3$ -CH-CH $_3$), 61.30 (Ar-OCH $_2$ -CH $_3$), 110.23, 112.03, 113.24, 115.00, 117.31, 119.20, 121.04, 123.65, 125.40, 127.41, 129.50, 131.02, 133.06, 135.40, 137.50, 139.00, 140.12, 142.05 (Ar-C), 165.00 (CO-NH-). MS(M^+): 479.14, Calcd. for $\text{C}_{24}\text{H}_{22}\text{FN}_5\text{O}_3\text{S}$ (479.53): C 60.11, H 3.62, N 13.96 Found: C 59.95, H 3.64, N 13.80%.

(E)-2-(4-bromobenzylideneamino)-4-ethoxy-N-(4-(furan-2-yl)thiazol-2-yl)-6-isopropylpyrimidine-5-carboxamide (5r)

Yellow solid, yield 80%, m.p. 183-185°C, IR (KBr, ν , cm^{-1}): 3388 (N-H Str.), 3025 (Ar C-H Str.), 1684 (C=O Str.). ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.201-1.250 (d, 6H, $-\text{CH}(\text{CH}_3)_2$), 1.300-1.326 (t, 3H, Ar-OCH $_2$ -CH $_3$), 3.200-3.300 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.856-3.900 (q, 2H, Ar-OCH $_2$ -CH $_3$), 7.450-8.500 (m, 8H, Ar-H), 9.321 (s, 1H, CH), 10.188 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 17.90 (Ar-OCH $_2$ -CH $_3$), 21.06 (CH $_3$ -CH-CH $_3$), 30.23 (CH $_3$ -CH-CH $_3$), 59.00 (Ar-OCH $_2$ -CH $_3$), 108.36, 110.56, 112.36, 114.01, 116.20, 117.01, 118.70, 120.31, 122.00, 124.30, 126.31, 128.34, 130.21, 132.01, 134.01, 136.07, 138.00, 139.14 (Ar-C), 163.00 (CO-NH-). MS(M^+): 539.06, Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{BrN}_5\text{O}_3\text{S}$ (540.43): C 57.51, H 3.07, N 21.34 Found: C 57.45, H 3.22, N 21.20%.

(E)-2-(4-chlorobenzylideneamino)-4-ethoxy-N-(4-(furan-2-yl)thiazol-2-yl)-6-isopropylpyrimidine-5-carboxamide (5s)

Yellow solid, yield 79%, m.p. 173-175°C, IR (KBr, ν , cm^{-1}): 3365 (N-H Str.), 3053 (Ar C-H Str.), 1698 (C=O Str.). ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.201-1.250 (d, 6H, $-\text{CH}(\text{CH}_3)_2$), 1.290-1.302 (t, 3H, Ar-OCH $_2$ -CH $_3$), 3.202-3.298 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.900-4.00 (q, 2H, Ar-OCH $_2$ -CH $_3$), 6.980-7.625 (m, 8H, Ar-H), 9.321 (s, 1H, CH), 10.412 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 17.88 (Ar-OCH $_2$ -CH $_3$), 21.01 (CH $_3$ -CH-CH $_3$), 32.22 (CH $_3$ -CH-CH $_3$), 58.96 (Ar-OCH $_2$ -CH $_3$), 111.01, 112.00, 114.02, 116.53, 117.20, 118.30, 120.45, 122.00, 124.36, 126.31, 127.01, 129.30, 131.20, 133.00, 135.01, 137.03, 139.41, 140.21 (Ar-C), 164.36 (C=O-NH-). MS(M $^+$): 495.11, Anal. Calcd. for C $_{24}$ H $_{22}$ ClN $_5$ O $_3$ S (495.98): C 58.12, H 4.47, N 14.12 Found: C 58.18, H 4.20, N 14.06%.

(E)-2-(3-chlorobenzylideneamino)-4-ethoxy-N-(4-(furan-2-yl)thiazol-2-yl)-6-isopropylpyrimidine-5-carboxamide (5t)

Yellow solid, yield 76%, m.p. 158-160°C, IR (KBr, ν , cm^{-1}): 3326 (N-H Str.), 3038 (Ar C-H Str.), 1683 (C=O Str.). ^1H NMR (400 MHz, DMSO- d_6) δ_{H} (ppm): δ 1.156-1.200 (d, 6H, $-\text{CH}(\text{CH}_3)_2$), 1.220-1.300 (t, 3H, Ar-OCH $_2$ -CH $_3$), 3.220-3.280 (m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.890-3.941 (q, 2H, Ar-OCH $_2$ -CH $_3$), 6.980-7.500 (m, 8H, Ar-H), 9.365 (s, 1H, CH), 10.421 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO- d_6) δ_{C} (ppm): 19.03 (Ar-OCH $_2$ -CH $_3$), 22.78 (CH $_3$ -CH-CH $_3$), 32.10 (CH $_3$ -CH-CH $_3$), 60.21 (Ar-OCH $_2$ -CH $_3$), 110.20, 112.03, 114.00, 115.32, 116.36, 117.12, 119.30, 121.01, 123.00, 125.03, 127.41, 129.30, 131.40, 132.01, 135.04, 137.00, 139.06, 140.25 (Ar-C), 165.00 (C=O-NH-). MS(M $^+$): 495.11, Anal. Calcd. for C $_{24}$ H $_{22}$ ClN $_5$ O $_3$ S (495.98): C 58.12, H 4.47, N 14.12 Found: C 58.18, H 4.20, N 14.06%.

4. CONCLUSION

Here, we report the synthesis of substituted pyrimidines bearing furanyl thiazole nucleus. It means the method produced a single scaffold with furan, thiazole and pyrimidine heterocyclic systems.

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