

Full Paper

Synthesis of New Pyrazolothiazole Derivatives from 4-Thiazolidinones

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Abstract: The synthesis of new 2,3,5,6-aryl substituted tetrahydro-2*H*-pyrazolo[3,4-*d*]-thiazoles **4a-j** as potential biologically active compounds by the cyclocondensation of phenyl hydrazine with new 5-arylidene derivatives **2a-j** of 2,3-disubstituted-1,3-thiazolidin-4-ones **1a-e** is reported.

Keywords: Cyclizations, heterocycles, fused thiazolidines

Introduction

Small ring heterocycles containing nitrogen, sulfur and oxygen have been under investigation for a long time because of their important medicinal properties. Among these type of molecules, 4-thiazolidinones have been shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, antituberculostatic, anti-HIV, antihistaminic, anticancer, anticonvulsant, antiinflammatory and analgesic properties [1-5].

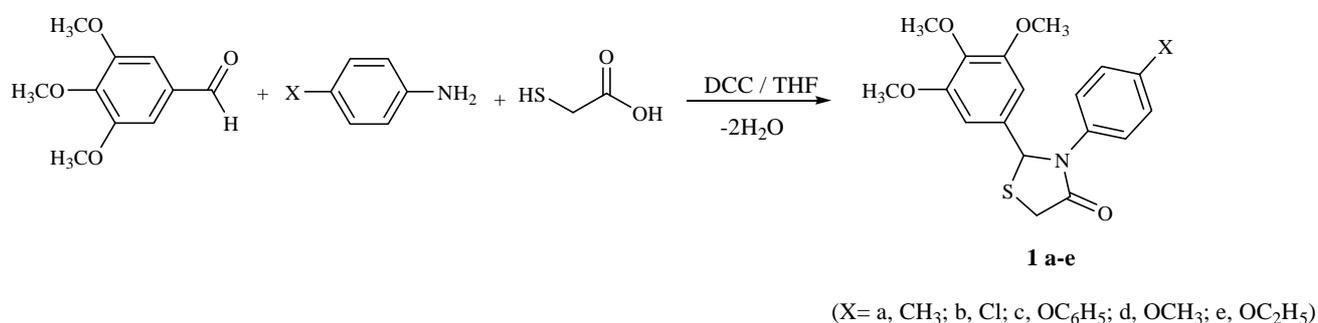
We have already reported some of our work on the synthesis, transformations and some biological properties of various 4-thiazolidinones [6-9]. Some of these compounds were screened for their antibacterial and antituberculostatic activities, and it has been found that some of them have moderate to good biological properties [8]. The biological significance of this class of compounds impelled us to continue working on the synthesis of new thiazolidine derivatives. In this study we report the synthesis

of some new tetrahydro-2*H*-pyrazolo[3,4-*d*]thiazole derivatives starting from various 4-thiazolidinones.

Results and Discussion

The target compounds were prepared starting from 4-thiazolidinone derivatives. In the first step, 4-thiazolidinones **1a-e** were synthesized by the Katti carbodiimide (DCC) mediated one-pot three-component condensation reaction of an aromatic amine, an aldehyde and a mercaptoacetic acid [10] (Scheme 1).

Scheme 1. Synthesis of 4-thiazolidinones **1a-e**.



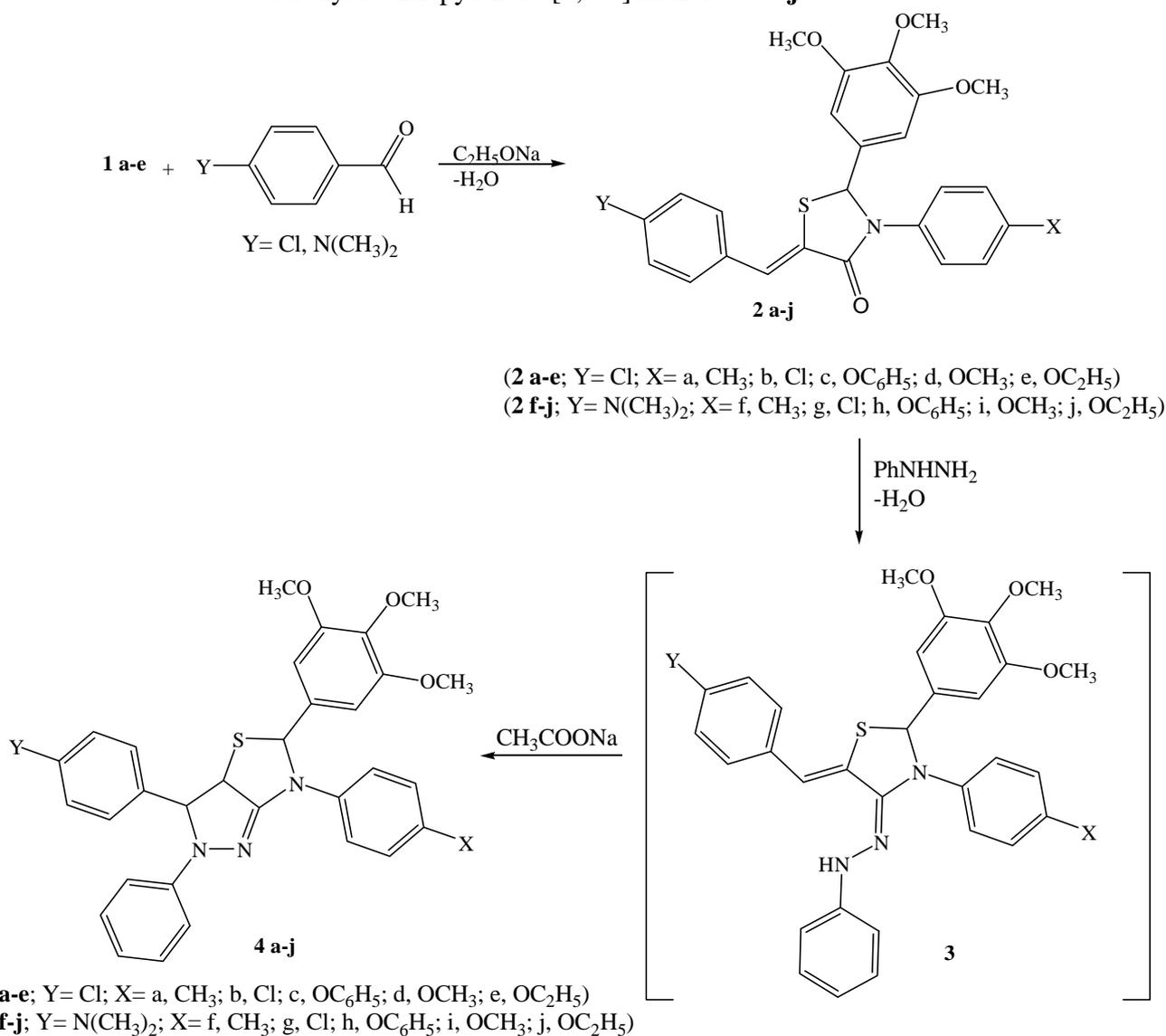
Then compounds **1a-e** were reacted with 4-chlorobenzaldehyde and 4-dimethylaminobenzaldehyde in the presence of sodium ethoxide to afford the new 5-benzylidene derivatives **2a-j** (Scheme 2). Next, compounds **2a-j** condensed with phenyl hydrazine in glacial acetic acid in the presence of sodium acetate to give products **4a-j** (Scheme 2). In a typical reaction, 5-benzylidene derivatives, sodium acetate and phenyl hydrazine were refluxed for 7-8 h in glacial acetic acid. The crude reaction mixture was filtered hot to remove any insoluble material, and cooled. Water was added to the resulting mixture which was boiled for a few minutes. Finally, the mixture was cooled to afford the crude product which was then purified by column chromatography using the appropriate solvent system. Compounds **4a-j** are presumably formed by way of the phenyl hydrazones **3**, followed by cyclization and proton transfer.

The structures of the new compounds were assigned on the basis of their analytical and spectral data. Compounds **1a-e** display in their ¹H-NMR spectra, in addition to other signals, doublets at δ 3.81-3.99 ppm due to the H_A and H_B system. In the benzylidene derivatives **2a-j**, this AB system was absent, confirming that condensation had been taken place. Regarding compounds **4a-j**, their ¹H-NMR spectra showed two doublets at δ 5.79 - 5.82 ppm due to a proton on 3a-CH and at 4.52 - 4.58 ppm, due to a proton on 3-CH, respectively. These signals demonstrate that the cyclization step had occurred.

Characteristic C=O bands appeared in the 1702-1682 cm⁻¹ region in the FT-IR spectra of the thiazolidinones **1a-e** and benzylidene derivatives **2 a-j**. In the FT-IR spectra of compounds **4a-j**, the amide carbonyl band was absent, which clearly confirmed that a cyclocondensation with phenyl hydrazine had been taken place. Besides, the C=N bands of **4a-j** were observed in the 1596-1602 cm⁻¹

region. Although the new compounds have stereogenic centers, we were not able to separate the diastereomers due to their similar R_f values.

Scheme 2. Synthesis of 5-arylidene-4-thiazolidinones **2a-j** and tetrahydro-2*H*-pyrazolo-[3,4-*d*]thiazoles **4a-j**.



Our results have shown that the sequential condensation of phenyl hydrazine and compounds **2a-f** containing carbonyl functionalities is a useful reaction for the construction of novel heterocycles of possible pharmacological interest.

Experimental

General

NMR spectra were recorded on a 400 MHz Bruker Digital FT-NMR 'Avance 400' spectrometer. Chemical shifts (δ) are on parts per million (ppm), with CDCl₃ as solvent and relative to

tetramethylsilane (TMS) as the internal reference. FT-IR spectra were recorded on Perkin Elmer FT-IR spectrometer (KBr pellets). GC-EIMS spectra were measured on a Varian SAT2100T mit GC3900 spectrometer using ionization by FAB. Melting points were measured on a Gallenkamp melting point apparatus. Silica gel 60 (Merck) was used for column separations. TLC was conducted on standard conversion aluminium sheets pre-coated with a 0.2 mm layer of silica gel. Elemental analyses were measured with a Thermo Flash Flash EA 1112 Series apparatus.

General procedure for the synthesis of 4-thiazolidinones 1a-e

p-Substituted aniline (1 mmol) and 3,4,5-trimethoxybenzaldehyde (2 mmol) were stirred in THF at an ice-bath for 5 min, followed by addition of mercaptoacetic acid (3 mmol). After 5 min DCC (1.2 mmol) was added to the reaction mixture at 0°C and the reaction mixture stirred for additional 1-3 hours at room temperature. Formed DCU was removed by filtration, filtrate was concentrated to dryness under reduced pressure and the residue was taken up with ethyl acetate. The organic layer was washed with 5 % aq. citric acid, water, 5 % aq. sodium hydrogen carbonate and then with brine. The organic layer was dried over sodium sulfate and the solvent removed under vacuum to give the crude product, which was purified by recrystallization from 2:1 petroleum ether-diethyl ether.

2-(3,4,5-Trimethoxyphenyl)-3-(4-methylphenyl)-4-thiazolidinone (**1a**). Light yellow crystals; yield 59 %; mp. 161 °C; ¹H-NMR δ: 2.29 (s, 3H, CH₃), 3.78 (s, 9H, OCH₃), 3.87, 3.93 (AB system, *J*= 9.2 Hz, 2H, 5-CH₂), 6.47 (s, 1H, 2-CH), 7.01-7.38 (m, 6H, aromatic); FT-IR: 1702 (N-C=O) cm⁻¹; Anal. Calcd for C₁₉H₂₁NO₄S (359.12): C: 63.49; H: 5.89; N: 3.90; S: 8.92. Found: C: 63.59; H: 5.92; N: 3.84; S: 8.89; MS: *m/z* 359.

3-(4-Chlorophenyl)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinone (**1b**). Yellow crystals, yield 52 %; mp. 161-162 °C; ¹H-NMR δ: 3.78 (s, 9H, OCH₃), 3.86, 3.91 (AB system, *J*= 9.2 Hz, 2H, 5-CH₂), 6.01 (s, 1H, 2-CH), 6.57-7.33 (m, 6H, aromatic) ppm; FT-IR: 1682 (N-C=O) cm⁻¹; Anal. Calcd for C₁₈H₁₈ClNO₄S (379.86): C: 56.91, H: 4.77, N: 3.68, S: 8.44. Found: C: 56.89, H: 4.79, N: 3.70, S: 8.47; MS: *m/z* 380.

2-(3,4,5-Trimethoxyphenyl)-3-(4-phenoxyphenyl)-4-thiazolidinone (**1c**). Light yellow crystals, yield 73 %; mp. 141-142 °C; ¹H-NMR δ: 3.78 (s, 9H, OCH₃), 3.86, 3.93 (AB system, *J*= 9.1 Hz, 2H, 5-CH₂), 5.96 (s, 1H, 2-CH), 6.47-7.33 (m, 11H, aromatic) ppm; FT-IR: 1683 (N-C=O) cm⁻¹; Anal. Calcd. for C₂₄H₂₃NO₅S (437.51): C: 65.88; H: 5.30; N: 3.20; S: 7.33. Found: C: 65.89, H: 5.29, N: 3.22, S: 7.36; MS: *m/z* 438.

3-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinone (**1d**). Light yellow crystals, yield 68 %; mp. 144-145 °C; ¹H-NMR δ: 3.64 (s, 3H, OCH₃), 3.78 (s, 9H, OCH₃), 3.81, 3.93 (AB system, *J*= 9.2 Hz, 2H, 5-CH₂), 5.91 (s, 1H, 2-CH), 6.47-7.24 (m, 6H, aromatic) ppm; FT-IR: 1685 (N-C=O) cm⁻¹; Anal. Calcd. for C₁₉H₂₁NO₅S (375.44): C: 60.78, H: 5.64, N: 3.73, S: 8.54. Found: C: 60.81, H: 5.67, N: 3.76, S: 8.58, MS: *m/z* 375.

3-(4-Ethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinone (1e). Light yellow crystals, yield 69 %; mp. 156-157 °C; $^1\text{H-NMR}$ δ : 1.23-1.36 (t, $J = 7.2$ Hz, 3H, CH_3), 3.77 (s, 9H, OCH_3), 3.81-3.99 (m, 4H, 5- CH_2 , OCH_2), 5.91 (s, 1H, 2-CH), 6.38-7.33 (m, 6H, aromatic) ppm; FT-IR: 1702 (N-C=O) cm^{-1} ; Anal. Calcd. for $\text{C}_{20}\text{H}_{23}\text{NO}_5\text{S}$ (389.47): C: 61.68, H: 5.95, N: 3.60, S: 8.23. Found: C: 61.70, H: 5.97, N: 3.63, S: 8.25, MS: m/z 389.

General procedure for the preparation of 5-arylidine-4-thiazolidinones 2a-j

A solution of **1a-e** (1 mmol) and 4-chlorobenzaldehyde (1 mmol) or 4-dimethylaminoaniline (1 mmol) in dry benzene (25 mL) was refluxed for about 10-12 h, in the presence of sodium ethoxide (1 mmol), cooled, poured into ice cold water and then acidified with glacial acetic acid. The benzene layer was separated, dried over CaCl_2 and evaporated in vacuo to give crude product that was purified by recrystallization.

5-(4-Chlorobenzylidene)-2-(3,4,5-trimethoxyphenyl)-3-(4-methylphenyl)-4-thiazolidinone (2a). Orange crystals; yield 53 %; mp. 174 °C (from petroleum ether-diethyl ether, 4:1); $^1\text{H-NMR}$ δ : 2.29 (s, 3H, CH_3), 3.74 (s, 9H, OCH_3), 6.46 (s, 1H, =CH), 6.74-6.83 (m, 4H, aromatic), 7.18-7.43 (m, 3H, aromatic and 2-CH), 7.51-7.53 (m, 2H, aromatic), 7.64-7.77 (m, 2H, aromatic) ppm; FT-IR: 1683 (N-C=O) cm^{-1} ; Anal. Calcd. for $\text{C}_{26}\text{H}_{24}\text{ClNO}_4\text{S}$ (481.11): C: 64.79, H: 5.02, N: 2.91, S: 6.65. Found: C: 64.74, H: 5.07, N: 2.94, S: 6.61; MS: m/z 481.

5-(4-Chlorobenzylidene)-3-(4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinone (2b). Reddish crystals; yield 41 %; mp. 184-186 °C (from petroleum ether-diethyl ether, 4:1); $^1\text{H-NMR}$ δ : 3.78 (s, 9H, OCH_3), 6.46 (s, 1H, =CH), 6.96-7.21 (m, 4H, aromatic), 7.33-7.51 (m, 3H, aromatic and 2-CH), 7.63-7.66 (m, 2H, aromatic), 7.83-7.87 (m, 2H, aromatic) ppm; FT-IR: 1691 (N-C=O) cm^{-1} ; Anal. Calcd. for $\text{C}_{25}\text{H}_{21}\text{Cl}_2\text{NO}_4\text{S}$ (502.45): C: 59.77, H: 4.21, N: 2.79, S: 6.38. Found: C: 59.80, H: 4.23, N: 2.81, S: 6.40; MS: m/z 502.

5-(4-Chlorobenzylidene)-2-(3,4,5-trimethoxyphenyl)-3-(4-phenoxyphenyl)-4-thiazolidinone (2c). Dark orange crystals; yield 44 %; mp. 168-170 °C (from petroleum ether-diethyl ether, 3:1); $^1\text{H-NMR}$ (CDCl_3) δ : 3.78 (s, 9H, OCH_3), 6.52 (s, 1H, =CH), 6.96-7.15 (m, 8H, aromatic), 7.18-7.29 (m, 4H, aromatic and 2-CH), 7.63-7.66 (m, 2H, aromatic), 7.83-7.87 (m, 2H, aromatic) ppm; FT IR (KBr): 1685 (N-C=O) cm^{-1} ; Anal. Calcd. for $\text{C}_{31}\text{H}_{26}\text{ClNO}_5\text{S}$ (560.06): C: 66.48, H: 4.79, N: 2.50, S: 5.72. Found: C: 66.50, H: 4.81, N: 2.51, S: 5.75; MS: m/z 560.

5-(4-Chlorobenzylidene)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinone (2d). Orange crystals; yield 48 %; mp. 181-182 °C (from petroleum ether-diethyl ether, 4:1); $^1\text{H-NMR}$ δ : 3.63 (s, 3H, OCH_3), 3.79 (s, 9H, OCH_3), 6.47 (s, 1H, =CH), 6.96-7.09 (m, 4H, aromatic), 7.19-7.52 (m, 3H, aromatic and 2-CH), 7.63-7.67 (m, 2H, aromatic), 7.83-7.86 (m, 2H, aromatic) ppm; FT-IR: 1689 (N-C=O) cm^{-1} ; Anal. Calcd. for $\text{C}_{26}\text{H}_{24}\text{ClNO}_5\text{S}$ (497.99): C: 62.71, H: 4.86, N: 2.81, S: 6.44. Found: C: 62.74, H: 4.87, N: 2.81, S: 6.47; MS: m/z 498.

5-(4-Chlorobenzylidene)-3-(4-ethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinone (2e). Orange crystals; yield 51 %; mp. 173 °C (from petroleum ether-diethyl ether, 3:1); $^1\text{H-NMR}$ δ : 1.22-1.36 (t, $J=7.2$ Hz, 3H, CH_3), 3.78 (s, 9H, OCH_3), 3.93-3.97 (q, $J=7.2$ Hz, 2H, OCH_2), 6.45 (s, 1H, =CH), 6.94-7.11 (m, 4H, aromatic), 7.19-7.53 (m, 3H, aromatic and 2-CH), 7.63-7.68 (m, 2H, aromatic), 7.83-7.85 (m, 2H, aromatic) ppm; FT-IR: 1687 (N-C=O) cm^{-1} ; Anal. Calcd. for $\text{C}_{27}\text{H}_{26}\text{ClNO}_5\text{S}$ (512.02): C: 63.33, H: 5.12, N: 2.73, S: 6.26. Found: C: 63.36, H: 5.15, N: 2.75, S: 6.29; MS: m/z 512.

5-(4-Dimethylaminobenzylidene)-2-(3,4,5-trimethoxyphenyl)-3-(4-methylphenyl)-4-thiazolidinone (2f). Yellow crystals; yield 42 %; mp. 162 °C (from petroleum ether-diethyl ether, 4:1); $^1\text{H-NMR}$ δ : 2.31 (s, 3H, CH_3), 3.05 (s, 6H, CH_3), 3.76 (s, 9H, OCH_3), 6.42 (s, 1H, =CH), 6.76-7.22 (m, 4H, aromatic), 7.29-7.38 (m, 3H, aromatic and 2-CH), 7.45-7.49 (m, 2H, aromatic), 7.77-7.81 (m, 2H, aromatic) ppm; FT-IR: 1683 (N-C=O) cm^{-1} ; Anal. Calcd. for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_4\text{S}$ (490.62): C: 68.55, H: 6.16, N: 5.71, S: 6.53. Found: C: 68.56, H: 6.19, N: 5.73, S: 6.58; MS: m/z 491.

3-(4-Chlorophenyl)-5-(4-dimethylaminobenzylidene)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinone (2g). Red crystals; yield 32 %; mp. 156-157 °C (from petroleum ether-diethyl ether, 3:1); $^1\text{H-NMR}$ δ : 3.05 (s, 6H, CH_3), 3.78 (s, 9H, OCH_3), 6.42 (s, 1H, =CH), 6.87-6.94 (m, 4H, aromatic), 7.18-7.22 (m, 3H, aromatic and 2-CH), 7.33-7.37 (m, 2H, aromatic), 7.47-7.50 (m, 2H, aromatic) ppm; FT-IR: 1684 (N-C=O) cm^{-1} ; Anal. Calcd. for $\text{C}_{27}\text{H}_{27}\text{ClN}_2\text{O}_4\text{S}$ (511.04): C: 63.46, H: 5.32, N: 5.48, S: 6.27. Found: C: 63.49, H: 5.33, N: 5.50, S: 6.31; MS: m/z 511.

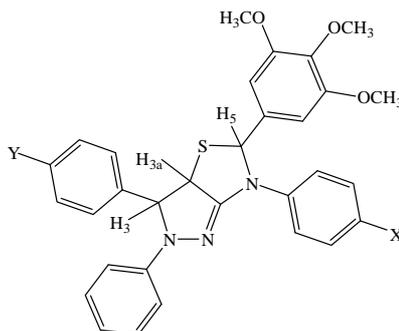
5-(4-Dimethylaminobenzylidene)-2-(3,4,5-trimethoxyphenyl)-3-(4-phenoxyphenyl)-4-thiazolidinone (2h). Orange crystals; yield 31 %; mp. 152 °C (from petroleum ether-diethyl ether, 2:1); $^1\text{H-NMR}$ δ : 3.02 (s, 6H, CH_3), 3.81 (s, 9H, OCH_3), 6.43 (s, 1H, =CH), 6.92-7.05 (m, 8H, aromatic), 7.17-7.23 (m, 3H, aromatic), 7.39-7.52 (m, 3H, aromatic and 2-CH), 7.63-7.71 (m, 2H, aromatic) ppm; FT-IR: 1691 (N-C=O) cm^{-1} ; Anal. Calcd. for $\text{C}_{33}\text{H}_{32}\text{N}_2\text{O}_5\text{S}$ (568.69): C: 69.71, H: 5.67, N: 4.93, S: 5.63. Found: C: 69.74, H: 5.69, N: 4.97, S: 5.67; MS: m/z 569.

5-(4-Dimethylaminobenzylidene)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinone (2i). Orange crystals; yield 43 %; mp. 156-158 °C (from petroleum ether-diethyl ether, 2:1); $^1\text{H-NMR}$ δ : 3.02 (s, 6H, CH_3), 3.59 (s, 3H, OCH_3), 3.81 (s, 9H, OCH_3), 6.47 (s, 1H, =CH), 6.82-7.09 (m, 4H, aromatic), 7.19-7.53 (m, 3H, aromatic and 2-CH), 7.63-7.68 (m, 2H, aromatic), 7.78-7.81 (m, 2H, aromatic) ppm; FT-IR: 1691 (N-C=O) cm^{-1} ; Anal. Calcd. for $\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_5\text{S}$ (506.62): C: 66.38, H: 5.97, N: 5.53, S: 6.33. Found: C: 66.41, H: 5.99, N: 5.56, S: 6.37; MS: m/z 507.

5-(4-Dimethylaminobenzylidene)-3-(4-ethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-4-thiazolidinone (2j). Orange crystals; yield 36 %; mp. 162 °C (from petroleum ether-diethyl ether, 4:1); $^1\text{H-NMR}$ δ : 1.24-1.38 (t, $J=7.2$ Hz, 3H, CH_3), 3.01 (s, 6H, CH_3), 3.81 (s, 9H, OCH_3), 3.91-3.95 (q, $J=7.2$ Hz, 2H, OCH_2), 6.43 (s, 1H, =CH), 6.94-7.15 (m, 4H, aromatic), 7.23-7.49 (m, 3H, aromatic and 2-CH), 7.58-7.62 (m, 2H, aromatic), 7.77-7.81 (m, 2H, aromatic) ppm; FT-IR: 1682 (N-C=O) cm^{-1} ; Anal. Calcd. for $\text{C}_{29}\text{H}_{32}\text{N}_2\text{O}_5\text{S}$ (520.65): C: 66.91, H: 6.20, N: 5.38, S: 6.16. Found: C: 66.95, H: 6.22, N: 5.41, S: 6.19; MS: m/z 521.

General method for tetrahydro-2H-pyrazolo[3,4-d]thiazoles **4a-j**

The respective benzylidene derivative, **2a-j** (1 mmol) in glacial acetic acid (10 mL), sodium acetate (1 g) and phenyl hydrazine (1 mL) were heated for 7 h. The mixture was filtered hot to remove any insoluble material, cooled, and then water was added and boiled for few minutes, then it was cooled to afford the crude product which was purified by column chromatography from *n*-hexane-ethyl acetate (2:1).



3-(4-Chlorophenyl)-5-(3,4,5-trimethoxyphenyl)-2-phenyl-6-p-tolyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (4a). Light yellow crystals; yield 49 %; mp. 143 °C; $^1\text{H-NMR}$ δ : 2.31 (s, 3H, CH₃), 3.72 (s, 9H, OCH₃), 4.58 (d, J = 11.0 Hz, 1H, 3-CH), 5.82 (d, J = 11.0 Hz, 1H, 3a-CH), 6.01 (s, 1H, 5-CH), 6.90-7.13 (m, 7H, aromatic), 7.17-7.38 (m, 4H, aromatic), 7.45-7.48 (m, 2H, aromatic), 7.64-7.77 (m, 2H, aromatic) ppm; FT-IR: 3005-3011 (aromatic), 1598 (C=N), 1256 (C-O) cm⁻¹; Anal. Calcd. for C₃₂H₃₀ClN₃O₃S (572.12): C, 67.18; H, 5.29; N, 7.34; S, 5.60. Found: C, 67.23; H, 5.21; N, 7.31; S, 5.57; MS: m/z 572.

3,6-Bis(4-Chlorophenyl)-5-(3,4,5-trimethoxyphenyl)-2-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (4b). Yellow crystals; yield 51 %; mp. 152 °C; $^1\text{H-NMR}$ δ : 3.73 (s, 9H, OCH₃), 4.52 (d, J = 11.0 Hz, 1H, 3-CH), 5.79 (d, J = 11.0 Hz, 1H, 3a-CH), 5.99 (s, 1H, 5-CH), 6.92-7.12 (m, 7H, aromatic), 7.18-7.37 (m, 4H, aromatic), 7.46-7.51 (m, 2H, aromatic), 7.71-7.81 (m, 2H, aromatic) ppm; FT-IR: 3005-3010 (aromatic), 1596 (C=N), 1248 (C-O) cm⁻¹; Anal. Calcd. for C₃₁H₂₇Cl₂N₃O₃S (592.54): C, 62.83; H, 4.59; N, 7.09; S, 5.41. Found: C, 62.84; H, 4.61; N, 7.11; S, 5.43; MS: m/z 593.

3-(4-Chlorophenyl)-5-(3,4,5-trimethoxyphenyl)-2-phenyl-6-(4-phenoxyphenyl)-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (4c). Yellow crystals; yield 62 %; mp. 151 °C; $^1\text{H-NMR}$ δ : 3.71 (s, 9H, OCH₃), 4.56 (d, J = 11.0 Hz, 1H, 3-CH), 5.82 (d, J = 11.0 Hz, 1H, 3a-CH), 6.03 (s, 1H, 5-CH), 6.92-7.11 (m, 12H, aromatic), 7.17-7.23 (m, 4H, aromatic), 7.39-7.52 (m, 2H, aromatic), 7.63-7.71 (m, 2H, aromatic) ppm; FT-IR: 3002-3011 (aromatic), 1598 (C=N), 1250 (C-O) cm⁻¹; Anal. Calcd. for C₃₇H₃₂ClN₃O₄S (650.19): C, 68.34; H, 4.96; N, 6.46; S, 4.93. Found: C, 68.37; H, 4.98; N, 6.47; S, 4.97; MS: m/z 650.

3-(4-Chlorophenyl)-6-(4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-2-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (4d). Light yellow crystals; yield 49 %; mp. 143 °C; $^1\text{H-NMR}$ δ : 3.61 (s,

3H, OCH₃), 3.72 (s, 9H, OCH₃), 4.58 (d, J = 11.0 Hz, 1H, 3-CH), 5.81 (d, J = 11.0 Hz, 1H, 3a-CH), 6.05 (s, 1H, 5-CH), 6.90-7.08 (m, 7H, aromatic), 7.17-7.38 (m, 4H, aromatic), 7.47-7.52 (m, 2H, aromatic), 7.68-7.81 (m, 2H, aromatic) ppm; FT-IR: 3000-3010 (aromatic), 1602 (C=N), 1256 (C-O) cm⁻¹; Anal. Calcd. for C₃₂H₃₀ClN₃O₄S (588.12): C: 65.35, H: 5.14, N: 7.15, S: 5.45. Found: C, 65.37; H, 5.16, N: 7.19, S: 5.49; MS: m/z 588.

3-(4-Chlorophenyl)-6-(4-ethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-2-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (**4e**). Yellow crystals; yield 41 %; mp. 138 °C; ¹H-NMR δ: 1.23-1.37 (t, J = 7.2 Hz, 3H, CH₃), 3.71 (s, 9H, OCH₃), 3.91-3.95 (q, J = 7.2 Hz, 2H, OCH₂), 4.58 (d, J = 11.0 Hz, 1H, 3-CH), 5.82 (d, J = 11.0 Hz, 1H, 3a-CH), 6.07 (s, 1H, 5-CH), 6.92-7.11 (m, 7H, aromatic), 7.17-7.39 (m, 4H, aromatic), 7.47-7.52 (m, 2H, aromatic), 7.68-7.81 (m, 2H, aromatic) ppm; FT-IR: 3000-3009 (aromatic), 1599 (C=N), 1245 (C-O) cm⁻¹; Anal. Calcd. for C₃₃H₃₂ClN₃O₄S (602.15): C: 65.82, H: 5.36, N: 6.98, S: 5.33. Found: C, 65.84; H, 5.37, N: 6.99, S: 5.38; MS: m/z 602.

5-(3,4,5-Trimethoxyphenyl)-3-(4-dimethylaminophenyl)-2-phenyl-6-*p*-tolyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (**4f**). Yellow crystals; yield 51 %; mp. 161 °C; ¹H-NMR δ: 2.32 (s, 3H, CH₃), 2.85 (s, 6H, CH₃), 3.76 (s, 9H, OCH₃), 4.56 (d, J = 11.0 Hz, 1H, 3-CH), 5.81 (d, J = 11.0 Hz, 1H, 3a-CH), 6.02 (s, 1H, 5-CH), 6.86-7.21 (m, 11H, aromatic), 7.30-7.51 (m, 4H, aromatic) ppm; FT-IR: 3004-3010 (aromatic), 1600 (C=N), 1246 (C-O) cm⁻¹; Anal. Calcd. for C₃₄H₃₆N₄O₃S (580.75): C: 70.32, H: 6.25, N: 9.65, S: 5.52. Found: C, 70.34; H, 6.27, N: 9.67, S: 5.55; MS: m/z 581.

6-(4-Chlorophenyl)-5-(3,4,5-trimethoxyphenyl)-3-(4-dimethylaminophenyl)-2-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (**4g**). Yellow crystals; yield 38 %; mp. 150 °C; ¹H-NMR δ: 2.89 (s, 6H, CH₃), 3.76 (s, 9H, OCH₃), 4.57 (d, J = 11.0 Hz, 1H, 3-CH), 5.81 (d, J = 11.0 Hz, 1H, 3a-CH), 6.05 (s, 1H, 5-CH), 6.83-7.26 (m, 11H, aromatic), 7.27-7.53 (m, 4H, aromatic) ppm; FT-IR: 3000-3008 (aromatic), 1600 (C=N), 1257 (C-O) cm⁻¹; Anal. Calcd. for C₃₃H₃₃ClN₄O₃S (601.16): C: 65.93, H: 5.53, N: 9.32, S: 5.33 Found: C, 65.97; H, 5.57, N: 9.37, S: 5.38; MS: m/z 601.

5-(3,4,5-Trimethoxyphenyl)-3-(4-dimethylaminophenyl)-6-(4-phenoxyphenyl)-2-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (**4h**). Yellow crystals; yield 38 %; mp. 155 °C; ¹H-NMR δ: 2.89 (s, 6H, CH₃), 3.81 (s, 9H, OCH₃), 4.56 (d, J = 11.0 Hz, 1H, 3-CH), 5.81 (d, J = 11.0 Hz, 1H, 3a-CH), 6.02 (s, 1H, 5-CH), 6.86-7.21 (m, 16H, aromatic), 7.30-7.51 (m, 4H, aromatic) ppm; FT-IR: 3004-3010 (aromatic), 1598 (C=N), 1258 (C-O) cm⁻¹; Anal. Calcd. for C₃₉H₃₈N₄O₄S (658.82): C: 71.10, H: 5.81, N: 8.50, S: 4.87 Found: C: 71.17; H, 5.83, N: 8.52, S: 4.90; MS: m/z 659.

6-(4-Methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-3-(4-dimethylaminophenyl)-2-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (**4i**). Yellow crystals; yield 42 %; mp. 158 °C; ¹H-NMR δ: 2.83 (s, 6H, CH₃), 3.55 (s, 3H, OCH₃), 3.80 (s, 9H, OCH₃), 4.56 (d, J = 11.0 Hz, 1H, 3-CH), 5.81 (d, J = 11.0 Hz, 1H, 3a-CH), 6.01 (s, 1H, 5-CH), 6.91-7.21 (m, 11H, aromatic), 7.29-7.53 (m, 4H, aromatic) ppm; FT-IR: 3002-3011 (aromatic), 1596 (C=N), 1245 (C-O) cm⁻¹; Anal. Calcd. for C₃₄H₃₆N₄O₄S (596.75): C: 68.43, H: 6.08, N: 9.39, S: 5.37 Found: C: 68.45; H, 6.11, N: 9.34, S: 5.39; MS: m/z 597.

6-(4-Ethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-3-(4-dimethylaminophenyl)-2-phenyl-3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole (**4j**). Yellow crystals; yield 41 %; mp. 143 °C; ¹H-NMR δ: 1.23-1.37 (t, *J*= 7.2 Hz, 3H, CH₃), 2.81 (s, 6H, CH₃), 3.83 (s, 9H, OCH₃), 3.91-3.95 (q, *J*= 7.2 Hz, 2H, OCH₂), 4.58 (d, *J*= 11.0 Hz, 1H, 3-CH), 5.81 (d, *J*= 11.0 Hz, 1H, 3a-CH), 6.03 (s, 1H, 5-CH), 6.89-7.23 (m, 11H, aromatic), 7.29-7.53 (m, 4H, aromatic) ppm; FT-IR: 3000-3007 (aromatic), 1600 (C=N), 1249 (C-O) cm⁻¹; Anal. Calcd. for C₃₅H₃₈N₄O₄S (610.77): C: 68.83, H: 6.27, N: 9.17, S: 5.25. Found: C: 68.85; H: 6.29, N: 9.20, S: 5.29; MS: m/z 611.

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Sample Availability: Samples of the compounds are available from the authors.