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Synthesis and biological evaluation of new 4-thiazolidinone derivatives of flurbiprofen

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Abstract: In this study, the synthesis and characterization of 2-(2-fluorobiphenyl-4-yl)-*N*´-[(substituted methylene]propanehydrazides **(3a-s)** and 2-(2-fluoro-[1,1'-biphenyl]-4-yl)-*N*-(5-methyl-2-(substituted aryl)-4-oxothiazolidin-3-yl)propanamides **(4a-s)** are described and also the antiproliferative effect of the compounds on HT-29, HeLa, A549 and MCF-7 cancer cell lines is investigated. Additionally, mouse embryonic fibroblast cells NIH3T3 were also evaluated to determine the selectivity. The results showed that the identified compounds did not cause any toxicity against NIH3T3 cell line. Moreover, *N*-(2-(3,5-Bis(trifluoromethyl)phenyl)-5-methyl-4-oxothiazolidin-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **(4h)** had the most growth inhibitory effect (55.97% inhibition) on HT-29 colorectal adenocarcinoma cell line.The results obtained from the study show that the compound **4h**, which has no cytotoxic effect on normal cells, may be an alternative in the treatment of colon cancer.

Keywords: Hydrazone; 4-thiazolidinone; MTT; antiproliferative activity; flurbiprofen.

1. Introduction

Cancer, characterised by uncontrolled and pathological proliferation of abnormal cells, is the second main reason of death after cardiovascular diseases in developing and advanced countries.[1] Even though there are numerous techniques such as chemotherapy and radiotherapy, toxic effect and drug resistance restriction the success effects most of the time.

4-Thiazolidinone scaffold is an advantageous molecular modification for indicating chemical capabilities in biologically active compounds due to various activities like anticancer,[2–4] antimycobacterial,[5] antiviral,[6,7] antibacterial,[8,9] analgesic[10] and antidiabetic[11] that are even found in FDA-approved drugs (Figure 1).

Hydrazones have received remarkable interest due to their broad spectrum and metabolic profile.[12–14] These structures have been exhibited a wide spectrum of biological effects including anticancer effects.[15–23]

Flurbiprofen is a nonsteroidal anti-inflammatory drug (NSAID) and some researches have reported that this drug and its structural derivatives exhibit anticancer activities against colorectal, breast, lung, and cervical cancer cell lines. [24-27] In this context, our research group reported the synthesis

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of 2-(2-fluorobiphenyl-4-yl)-*N´*-[(substituted phenyl/5-nitro-2-furyl)methylene]propane hydrazides and 2-(2-fluoro-4-biphenylyl)-*N*-(2-substituted-4-oxo-1,3-thiazolidine-3-yl)propanamides via flurbiprofen and evaluated their anticancer activities.[28] However, there was no literature on the synthesis and antiproliferative potential of 5-methyl-4-thiazolidinones derived from flurbiprofen. We tried to replace the –H with $–CH_3$ on the 4-thiazolidinone ring and reported the findings of their biological activities.

Regarding this point together with the aim of exploring new cytotoxic agents, we synthesized a series of hydrazide-hydrazone and 5-methyl-4-thiazolidinone derivatives starting from flurbiprofen and evaluated the effects of these compounds on HT-29 (colorectal adenocarcinoma), HeLa (human cervical carcinoma), A549 (human lung adenocarcinoma), MCF-7 (human breast cancer) cell lines and NIH3T3 (mouse embryonic fibroblast) cell line at 10 µM concentration.

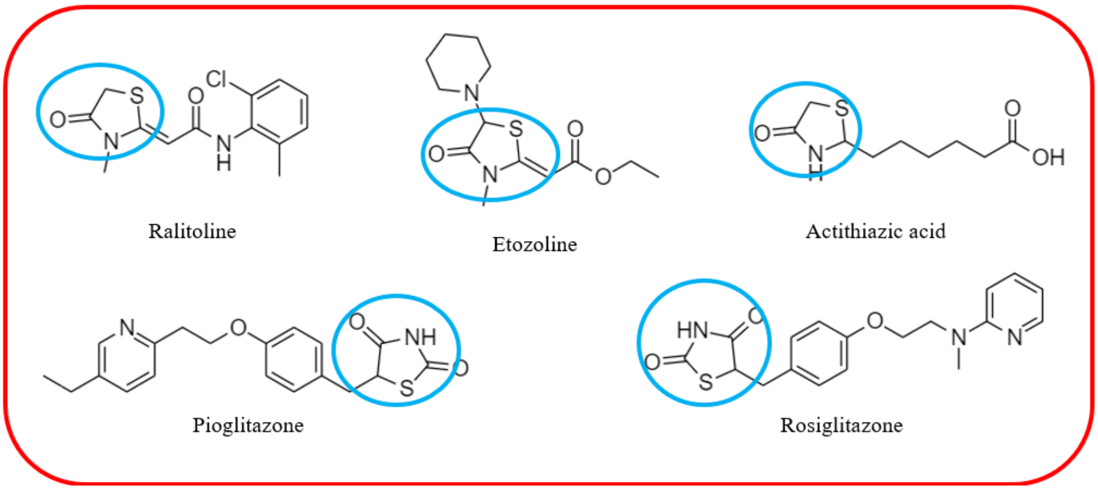


Figure 1. Some marketed drugs containing 4-thiazolidinone ring

2. Experimental

2.1. Chemical Material and Apparatus

All the reagents used were analytical reagent grade. Melting points were determined on a Thermo Scientific 9300 apparatus and are uncorrected. FTIR spectra were recorded on a Shimadzu FTIR 8400S spectrometer and frequencies are expressed in cm^{-1}. NMR spectra were recorded on a BRUKER AVANCE 300 spectrometer operating 300.00 MHz (^{1}H) and 75.0 MHz (^{13}C) in deuterated solvent. Elemental analyses were determined on CHNS-932 (LECO) analyzer.

2.2. Chemistry

*2.2.1. General procedure for the Preparation 2-(2-fluorobiphenyl-4-yl)-N´-[(substituted methylene]propanehydrazides **(3a-s)***

The methyl 2-(2-fluorobiphenyl-4-yl)propanoate **(1)** and compound **2** were prepared as per the reported method.[29, 30] A mixture of 2-(2-fluoro[1,1'-biphenyl]-4-yl)propanehydrazide **(2)** (1.0 eq.) and various aldehydes (1.0 eq.) in ethanol were refluxed in the presence of glacial acetic acid for 3-6 h. After cooling to the room temperature, the precipitate was filtered, washed with water, dried, and recrystallized from ethanol.

N'-[(4-Cyanophenyl)methylidene]-2-(2-fluoro[1,1'-biphenyl]-4-yl)propanehydrazide ***(3a)***: White solid. M.p. 163-164 °C. Yield 85%. IR ν_{max} (cm^{-1}): 3184 (N-H), 2236 (C≡N), 1661 (C=O), 1626 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.43 and 1.46 (2d, 3H, J=6.9 Hz, CH_3), 3.81 and 4.79 (2q, 1H, J=6.9 Hz, $CH-CH_3$), 7.28-7.91 (m, 12H, Ar-H), 8.00 and 8.28 (2s, 1H, CH=N), 11.64 and 11.84

(2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.71, 44.01, 112.20, 115.49, 119.15, 124.46, 126.90, 127.84, 108.24, 129.04, 129.18, 131.17, 133.21, 135.33, 139.15, 145.50, 157.70, 160.96, 169.99, 175.21. Anal. Calcd. for $C_{23}H_{18}FN_3O$: C, 74.38; H, 4.88; N, 11.31. Found: C, 74.66; H, 4.93; N, 11.31.

*2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-N'-(3-phenoxybenzylidene)propanehydrazide **(3b)***: White solid. M.p. 144-145ºC. Yield 80%. IR ν_{max} (cm^{-1}): 3188 (N-H), 1661 (C=O), 1643 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.39 and 1.43 (2d, 3H, J=6.9 Hz, CH$_3$), 3.77 and 4.62 (2q, 1H, J=6.9 Hz, CH-CH$_3$), 7.03-7.52 (m, 17H, Ar-H), 7.92 and 8.20 (2s, 1H, CH=N), 11.43 and 11.64 (2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.82, 43.94, 115.26, 115.70, 119.41, 120.32, 120.68, 123.16, 124.30, 128.20, 129.07, 129.15, 130.64, 135.34, 136.66, 142.69, 143.81, 146.70, 156.64, 157.68, 160.95, 169.70, 174.81. Anal. Calcd. for $C_{23}H_{23}FN_2O_2$: C, 76.69; H, 5.26; N, 6.39. Found: C, 77.20; H, 5.20; N, 6.35.

*2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-N'-(3-(trifluoromethyl)benzylidene)propanehydrazide **(3c)***: White solid. M.p. 194-195ºC. Yield 91%. IR ν_{max} (cm^{-1}): 3192 (N-H), 1654 (C=O), 1622 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.43 and 1.46 (2d, 3H, J=7.2 Hz, CH$_3$), 3.81 and 4.74 (2q, 1H, J=6.9 Hz, CH-CH$_3$), 7.25-7.99 (m, 12H, Ar-H), 8.02 and 8.31 (2s, 1H, CH=N), 11.43 and 11.64 (2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.89, 43.95, 115.50, 122.66, 123.52, 124.31, 126.27, 127.10, 128.18, 128.25, 129.10, 129.91, 130.33, 131.08, 135.34, 135.87, 141.75, 157.70, 169.94, 175.03. Anal. Calcd. for $C_{23}H_{18}F_4N_2O$: C, 66.66; H, 4.38; N, 6.76. Found: C, 67.24; H, 4.49; N, 6.75.

*N'-(3-Bromobenzylidene)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanehydrazide **(3d)***:White solid. M.p. 148-149ºC (lit. 147-148ºC[30]). Yield 87%. IR ν_{max} (cm^{-1}): 3186 (N-H), 1651 (C=O), 1624 (C=N); Anal. Calcd. for $C_{22}H_{18}BrFN_2O.1/3H_2O$: C, 61.27; H, 4.36; N, 6.50. Found: C, 61.62; H, 4.72; N, 6.25.

*N'-(4-Bromobenzylidene)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanehydrazide **(3e)***: White solid. Yield 71%; M.p. 173-174ºC; IR ν_{max} (cm^{-1}): 3176 (N-H), 1660 (C=O), 1610 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.43 and 1.46 (2d, 3H, J=6.9 Hz, CH$_3$), 3.78 and 4.76 (2q, 1H, J=6.9 Hz, CH-CH$_3$), 7.26-7.65 (m, 12H, Ar-H), 7.94 and 8.20 (2s, 1H, CH=N), 11.47 and 11.68 (2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.74, 43.96, 124.58, 126.78, 127.07, 127.25, 128.19, 128.25, 129.13, 131.14, 132.29, 133.96, 135.35, 146.19, 157.69, 169.72, 174.93. Anal. Calcd. for $C_{22}H_{18}BrFN_2O$: C, 62.18; H, 4.27; N, 6.59. Found: C, 61.98; H, 4.46; N, 6.52.

*N'-(Benzo[d][1,3]dioxol-4-ylmethylene)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanehydrazide **(3f)***:White solid. M.p. 190-192ºC. Yield 91%. IR ν_{max} (cm^{-1}): 3182 (N-H), 1651 (C=O), 1610 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.43 and 1.47 (2d, 3H, J=6.9 Hz, CH$_3$), 3.75 and 4.74 (2q, 1H, J=6.9 Hz, CH-CH$_3$), 6.10-6.12 (m, 2H, -CH$_2$), 6.85-7.44 (m, 11H, Ar-H), 8.03 and 8.32 (2s, 1H, CH=N), 11.45 and 11.65 (2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.62, 44.09, 102.00, 109.85, 115.26, 118.56, 124.41, 124.58, 126.77, 128.19, 129.07, 131.06, 135.37, 137.72, 144.20, 146.74, 157.66, 169.55, 174.81. Anal. Calcd. for $C_{23}H_{19}FN_2O_3$: C, 70.76; H, 4.91; N, 7.18. Found: C, 70.10; H, 5.21; N, 7.06.

*N'-(2,6-Dichlorobenzylidene)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanehydrazide **(3g)***:White solid. M.p. 198-200ºC. Yield 95%. IR ν_{max} (cm^{-1}): 3203 (N-H), 1653 (C=O), 1628 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.43 and 1.46 (2d, 3H, J=6.9 Hz, CH$_3$), 3.79 and 4.67 (2q, 1H, J=6.9 Hz, CH-CH$_3$), 7.20-7.58 (m, 11H, Ar-H), 8.26 and 8.43 (2s, 1H, CH=N), 11.69 and 11.88 (2s, 1H, NH). Anal. Calcd. for $C_{22}H_{17}Cl_2FN_2O$: C, 63.63; H, 4.13; N, 6.75. Found: C, 64.21; H, 4.11; N, 6.73.

*N'-(3,5-bis(trifluoromethyl)benzylidene)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propane hydrazide **(3h)***: White solid. M.p. 130-131ºC. Yield 91%. IR ν_{max} (cm^{-1}): 3182 (N-H), 1654 (C=O), 1622 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.42 and 1.47 (2d, 3H, J=6.9 Hz, CH$_3$), 3.84 and 4.74 (2q, 1H, J=6.9 Hz, CH-CH$_3$), 7.23-8.45 (m, 11H, Ar-H), 8.13 and 8.38 (2s, 1H, CH=N), 11.77 and 12.00 (2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm:19.05, 43.90, 115.29, 121.83, 124.09, 125.44, 127.37, 128.27, 129.07, 131.00, 135.30, 137.56, 140.04, 144.04, 144.71, 170.21, 175.21. Anal. Calcd. for $C_{24}H_{17}F_7N_2O.1/2H_2O$: C, 58.66; H, 3.69; N, 5.70. Found: C, 58.86; H, 3.55; N, 5.66.

(2-(2-fluoro-[1,1'-biphenyl]-4-yl)-N'-(2-(trifluoromethoxy)benzylidene)propanehydrazide ***(3i)***: White solid. M.p. 134-136ºC. Yield 88%. IR ν_{max} (cm^{-1}): 3194 (N-H), 1651 (C=O), 1622 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.06 (t, ethanol CH_3), 1.44 and 1.46 (2d, 3H, J=6.9 Hz, CH_3), 3.44 (m, ethanol CH_2), 3.77 and 4.77 (2q, 1H, J=6.9 Hz, CH-CH_3), 4.35 (t, ethanol OH), 7.26-7.85 (m, 12H, Ar-H), 7.99 and 8.25 (2s, 1H, CH=N), 11.50 and 11.70 (2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.79, 44.14, 115.82, 118.83, 122.29, 127.14, 127.77, 128.19, 128.49, 129.03, 131.86, 132.13, 135.34, 136.94, 140.28, 140.06, 147.13, 157.71, 169.82, 175.01. Anal. Calcd. for $C_{23}H_{18}F_4N_2O_2.1/2C_2H_5OH$: C, 63.57; H, 4.67; N, 6.18. Found: C, 63.60; H, 4.35; N, 6.46.

N'-[(4-Bromothiophen-2-yl)methylidene]-2-(2-fluoro[1,1'-biphenyl]-4-yl)propane hydrazide ***(3j)***: White solid. M.p. 203-204ºC. Yield 79%. IR ν_{max} (cm^{-1}): 3167 (N-H), 1668 (C=O), 1635 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.41 and 1.45 (2d, 3H, J=7.2 Hz, CH_3), 3.75 and 4.58 (2q, 1H, J=6.9 Hz, CH-CH_3), 7.22-7.75 (m, 10H, Ar-H), 8.07 and 8.40 (2s, 1H, CH=N), 11.49 and 11.68 (2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.62, 43.99, 109.70, 115.25, 124.09, 126.06, 126.58, 128.26, 129.07, 131.17, 132.11, 132.82, 135.34, 136.96, 157.68, 169.68, 174.53. Anal. Calcd. for $C_{20}H_{16}BrFN_2OS$: C, 55.24; H, 3.66; N, 6.60. Found: C, 55.24; H, 3.65; N, 6.59.

N'-(5-Bromo-2-methoxybenzylidene)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanehydrazide ***(3k)***: White solid. M.p. 199-200ºC. Yield 89%. IR ν_{max} (cm^{-1}): 3194 (N-H), 1676 (C=O), 1645 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.42 and 1.45 (2d, 3H, J=6.9 Hz, CH_3), 3.71-4.75 (m, 4H, CH-CH_3 and –OCH_3), 7.23-7.87 (m, 11H, Ar-H), 8.20 and 8.48 (2s, 1H, CH=N), 11.44 and 11.71 (2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.87, 44.06, 56.56, 112.91, 114.85, 115.57, 124.34, 124.92, 128.26, 129.07, 131.12, 133.79, 134.05, 135.36, 137.48, 141.12, 157.13, 160.95, 169.62, 174.87. Anal. Calcd. for $C_{23}H_{20}BrFN_2O_2$: C, 60.67; H, 4.43; N, 6.15. Found: C, 61.05; H, 4.30; N, 6.29.

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-N'-(4-methoxy-3-nitrobenzylidene)propanehydrazide ***(3l)***: Off-white solid. M.p. 219-220ºC. Yield 92%. IR ν_{max} (cm^{-1}): 3169 (N-H), 1668 (C=O), 1645 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.42 and 1.46 (2d, 3H, J=7.2 Hz, flur. CH_3), 3.79 and 4.76 (2q, 1H, J=6.9 Hz, CH-CH_3), 3.97 (s, 3H, -OCH_3), 7.41-8.21 (m, 12H, Ar-H and CH=N), 11.48 and 11.71 (2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.83, 43.91, 57.40, 115.26, 123.23, 123.80, 124.54, 126.90, 127.46, 128.25, 129.07, 131.15, 132.92, 135.36, 139.80, 145.69, 141.13, 153.46, 160.96, 169.73, 174.90. Anal. Calcd. for $C_{23}H_{20}FN_3O_4$: C, 65.55; H, 4.78; N, 9.97. Found: C, 65.81; H, 4.70; N, 9.96.

N'-(2-chloro-3-methoxybenzylidene)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanehydrazide ***(3m)***: White solid. M.p. 184-184.5ºC. Yield 92%. IR ν_{max} (cm^{-1}): 3188 (N-H), 1639 (C=O), 1622 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.43 and 1.47 (2d, 3H, J=7.2 Hz, CH_3), 3.87-4.79 (m, 4H, CH-CH_3 and -OCH_3), 7.16-7.59 (m, 11H, Ar-H), 8.39 and 8.63 (2s, 1H, CH=N), 11.60 and 11.84 (2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.78, 44.12, 56.75, 113.75, 115.83, 118.65, 122.01, 124.55, 126.90, 128.27, 129.06, 133.00, 135.35, 139.88, 155.38, 157.70, 160.96, 169.79, 175.00. Anal. Calcd. for $C_{23}H_{20}ClFN_2O_2$: C, 67.23; H, 4.91; N, 6.82. Found: C, 67.29; H, 50.76; N, 6.96.

N'-(2-Chloro-3-(trifluoromethyl)benzylidene)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanehydrazide ***(3n)***: Off-white solid. M.p. 188-189ºC. Yield 79%. IR ν_{max} (cm^{-1}): 3196 (N-H), 1660 (C=O), 1622 (C=N); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.43 and 1.47 (2d, 3H, J=7.2 Hz, CH_3), 3.80 and 4.79 (2q, 1H, J=6.9 Hz, CH-CH_3), 7.31-8.32 (m, 11H, Ar-H), 8.45 and 8.71 (2s, 1H, CH=N), 11.72 and 11.97 (2s, 1H, NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.18, 44.16, 115.63, 122.66, 124.31, 124.58, 125.06, 127.17, 128.38, 129.03, 130.84, 131.23, 135.34, 135.87, 138.49, 143.49, 157.71, 160.97, 169.98, 175.17. Anal. Calcd. for $C_{23}H_{17}ClF_4N_2O$: C, 61.55; H, 3.82; N, 6.24. Found: C, 61.47; H, 3.82; N, 6.25.

N'-[(3,4-Dichlorophenyl)methylidene]-2-(2-fluoro[1,1'-biphenyl]-4-yl)propanehydrazide ***(3o)***: White solid. M.p. 162-164ºC (lit. 166ºC[31]). Yield 83%. IR ν_{max} (cm^{-1}): 3174 (N-H), 1662 (C=O), 1606 (C=N); Anal. Calcd. for $C_{22}H_{17}Cl_2FN_2O$: C, 63.63; H, 4.13; N, 6.75. Found: C, 63.61; H, 4.02; N, 6.55.

N'-[2,4-Dichlorophenyl)methylidene]-2-(2-fluoro[1,1'-biphenyl]-4-yl)propanehydrazide ***(3p)***: Off-white solid. M.p. 195-196 ºC (lit. 194-195ºC[31]). Yield 74%. IR ν_{max} (cm^{-1}): 3196 (N-H), 1664 (C=O), 1622 (C=N); Anal. Calcd. for $C_{22}H_{17}Cl_2FN_2O$: C, 63.63; H, 4.13; N, 6.75. Found: C, 63.61; H, 4.02; N, 6.55.

2-(2-Fluoro[1,1'-biphenyl]-4-yl)-N'-[(4-methylphenyl)methylidene]propanehydrazide ***(3r)***: White solid. M.p. 186-187ºC (lit. 189-190ºC[31]). Yield 95%. IR ν_{max} (cm^{-1}): 3174 (N-H), 1664 (C=O), 1606 (C=N); Anal. Calcd. for $C_{23}H_{21}FN_2O$: C, 76.64; H, 5.87; N, 7.77. Found: C, 76.90; H, 5.79; N, 7.72.

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-N'-(4-hydroxy-3-methoxybenzylidene) propane hydrazide ***(3s)*** : Off-white solid. M.p. 171-173ºC (lit. 171-173ºC[31]). Yield 81%. IR ν_{max} (cm^{-1}): 3171 (N-H), 1655 (C=O), 1637 (C=N); Anal. Calcd. for $C_{23}H_{21}FN_2O_3$: C, 70.40; H, 5.39; N, 7.14. Found: C, 70,63; H, 5.59; N, 7.02.

2.2.2.General procedure for the preparation 2-(2-fluoro-[1,1'-biphenyl]-4-yl)-N-(5-methyl-2-(substituted aryl)-4-oxothiazolidine-3-yl)propanamides ***(4a-s)***

A mixture of **3a-s** (1 eq.) in dry toluene, thiolactic acid was added (10 eq.) dropwise and refluxed for 10-12 h using Dean-Stark apparatus. After evaporation, the flask content was neutralized by an addition of 5% $NaHCO_3$ until CO_2 release was completed. The precipitate was washed with water, dried, filtered and recrystallized from ethanol:water mixture (50:50).

N-(2-(4-Cyanophenyl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide ***(4a)***: White solid. M.p. 120-121ºC. Yield 74%. IR ν_{max} (cm^{-1}): 3223 (N-H), 2232 (C≡N), 1705 (C=O), 1672 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.26-1.35 (m, 3H, -CH-CH_3); 1.48-1.54 (m, 3H, thiaz. -CH_3); 3.58-3.68 (m, 1H, thiaz. C_5-H); 4.05-4.24 (m, 1H, -CH-CH_3); 5.84 and 5.89 (2s, 1H, thiaz. C_2-H); 7.00-7.87 (m, 12H, Ar-H); 10.43 and 10.49 (2s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-*d*6/TMS) δ ppm: 18.02, 20.07, 40.75, 59.80, 112.06, 115.41, 123.94, 126.92, 127.10, 128.28, 129.15, 130.87, 132.97, 135.33, 143.03, 143.43, 170.02, 172.17. Anal. Calcd. for $C_{26}H_{22}FN_3O_2S.2/3\ H_2O$: C, 66.22; H, 4.99; N, 8.91; S, 6.80. Found: C, 66.19; H, 4.74; N, 8.79; S, 6.78

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-N-(5-methyl-4-oxo-2-(3-phenoxyphenyl)thiazolidine-3-yl)propanamide ***(4b)***: White solid. M.p. 122-123ºC. Yield 68%. IR ν_{max} (cm^{-1}): 3314 (N-H), 1705 (C=O), 1669 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.27-1.36 (m, 3H, -CH-CH_3); 1.45-1.52 (m, 3H, thiaz. -CH_3); 3.63-3.69 (m, 1H, thiaz. C_5-H); 4.02-4.16 (m, 1H, -CH-CH_3); 5.74 (s, 1H, thiaz. C_2-H); 6.90-7.52 (m, 17H, Ar-H); 10.48 and 10.52 (2s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.06, 19.95, 42.54, 60.27, 115.07, 115.38, 118.42, 119.19, 119.31, 123.57, 123.96, 126.88, 128.23, 129.11, 130.46, 130.71, 135.36, 140.05, 143.16, 156.72, 157.10, 157.56, 160.82, 171.99. Anal. Calcd. for $C_{31}H_{27}FN_2O_3S.3/4H_2O$: C, 68.93; H, 5.32; N, 5.19; S, 5.94. Found: C, 69.04; H, 5.01; N, 5.17; S, 5.47.

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-N-(5-methyl-4-oxo-2-(3-(trifluoromethyl)phenyl)thiazolidine-3-yl)propanamide ***(4c)***: White solid. M.p. 110-111ºC. Yield 68%. IR ν_{max} (cm^{-1}): 3198 (N-H), 1705 (C=O), 1674 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.26-1.36 (m, 3H, -CH-CH_3); 1.50-1.55 (m, 3H, thiaz. -CH_3); 3.57-3.68 (m, 1H, thiaz. C_5-H); 4.05-4.24 (m, 1H, -CH-CH_3); 5.90 and 5.93 (2s, 1H, thiaz. C_2-H); 7.00-7.68 (m, 12H, Ar-H); 10.42 and 10.49 (2s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.03, 20.40, 42.86, 50.01, 115.39, 123.90, 124.23, 125.10, 126.13, 126.30, 127.10, 128.23, 129.07, 130.11, 130.85, 135.34, 139.37, 140.44, 143.05, 157.57, 160.88, 172.01. Anal. Calcd. for $C_{26}H_{22}F_4N_2O_2S.1/4H_2O$: C, 61.59; H, 4.47; N, 5.53; S, 6.32. Found: C, 61.26; H, 4.61; N, 5.37; S, 6.36.

N-(2-(3-Bromophenyl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide ***(4d)***: White solid. M.p. 166-167ºC. Yield 58%. IR ν_{max} (cm^{-1}): 3207 (N-H), 1701 (C=O), 1674 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.28-1.36 (m, 3H, -CH-CH_3); 1.48-1.54 (m, 3H, thiaz. -CH_3); 3.36-3.70 (m, 1H, thiaz. C_5-H); 4.02-4.19 (m, 1H, -CH-CH_3); 5.73 and 5.75 (2s, 1H, thiaz. C_2-H); 7.02-7.64 (m, 12H, Ar-H); 10.43-10.48 (m, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.12, 19.86, 42.55, 59.65, 59.89, 115.36, 122.12, 123.92, 127.11, 128.24, 129.13, 130.78, 131.09, 132.36, 135.37, 140.53, 141.53, 143.08, 157.56, 157.56, 160.82, 171.99. Anal. Calcd. for $C_{25}H_{22}BrFN_2O_2S.1/4H_2O$: C, 57.98; H, 4.38; N, 5.41; S, 6.19. Found: C, 57.94; H, 4.67; N, 5.54; S, 6.60.

N-(2-(4-Bromophenyl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide ***(4e)***: White solid. M.p. 171-172ºC. Yield 72%. IR ν_{max} (cm^{-1}): 3266 (N-H), 1705 (C=O), 1662 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.27-1.36 (m, 3H, -CH-CH_3); 1.50-1.54 (m, 3H, thiaz. -CH_3); 3.60-3.66 (m, 1H, thiaz. C_5-H); 4.04-4.17 (m, 1H, -CH-CH_3); 5.72 and 5.78 (2s, 1H, thiaz. C_2-H); 7.00-7.61 (m, 12H, Ar-H); 10.39 and 10.42 (2s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 17.97, 19.82, 42.56, 44.71, 59.90, 115.11, 122.70, 123.95, 125.78, 128.87, 128.67, 129.15, 130.86, 131.98, 135.32, 137.07, 137.81, 143.15, 160.79, 172.10. Anal. Calcd. for $C_{25}H_{22}BrFN_2O_2S$: C, 58.48; H, 4.32; N, 5.46; S, 6.25. Found: C, 58.69; H, 4.60; N, 5.35; S, 6.34.

N-(2-(Benzo[d][1,3]dioxol-4-yl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide ***(4f)***: Dark yellow solid. M.p. 177-178ºC. Yield 50%. IR ν_{max} (cm^{-1}): 3188 (N-H), 1705 (C=O), 1670 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.28-1.37 (m, 3H, -CH-CH_3); 1.46-1.53 (m, 3H, thiaz. -CH_3); 3.64-3.73 (m, 1H, thiaz. C_5-H); 4.01-4.16 (m, 1H, -CH-CH_3); 5.78-6.04 (m, 3H, thiaz. C_2-H and O-CH_2-O); 6.72-7.65 (m, 11H, Ar-H); 10.47 and 10.50 (2s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 17.89, 19.74, 42.33, 55.01, 55.36, 101.76, 109.21, 115.26, 119.11, 120.64, 121.98, 122.86, 127.00, 129.10, 129.14, 130.83, 135.35, 143.13, 145.98, 147.65, 165.68, 171.50, 172.05. Anal. Calcd. for $C_{26}H_{23}FN_2O_4S.1/4H_2O$: C, 64.65; H, 4.90; N, 5.80; S, 6.64. Found: C, 64.32; H, 4.83; N, 5.82; S, 6.31.

N-(2-(2,6-Dichlorophenyl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide ***(4g)***:White solid. M.p. 339-340ºC. Yield 80%. IR ν_{max} (cm^{-1}): 3219 (N-H), 1711 (C=O), 1676 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.24-1.36 (m, 3H, -CH-CH_3); 1.50-1.55 (m, 3H, thiaz. -CH_3); 3.62-3.75 (m, 1H, thiaz. C_5-H); 4.11-4.20 (m, 1H, -CH-CH_3); 6.40 (s, 1H, thiaz. C_2-H); 7.01-7.57 (m, 11H, Ar-H); 10.25 (bs, 1H, -CO-NH). Anal. Calcd. for $C_{25}H_{21}Cl_2FN_2O_2S$: C, 59.65; H, 4.20; N, 5.56; S, 6.37. Found: C, 59.90; H, 4.33; N, 5.42; S, 6.31.

N-(2-(3,5-Bis(trifluoromethyl)phenyl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide ***(4h)***: Light yellow solid. M.p. 220-222ºC. Yield 84%. IR ν_{max} (cm-^{1}): 3262 (N-H), 1732 (C=O), 1672 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.25-1.56 (m, 6H, -CH-CH_3 and thiaz. -CH_3); 3.57-3.68 (m, 1H, thiaz. C_5-H); 4.10-4.35 (m, 1H, -CH-CH_3); 6.04 and 6.08 (2s, 1H, thiaz. C_2-H); 6.94-8.18 (m, 11H, Ar-H); 10.43 and 10.56 (2s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.13, 20.05, 40.72, 42.68, 59.17, 114.94, 115.28, 121.73, 123.81, 125.32, 127.15, 128.22, 129.02, 131.19, 141.68, 143.07, 157.47, 167.38, 172.03. Anal. Calcd. for $C_{27}H_{21}F_7N_2O_2S.3/2H_2O$: C, 56.59; H, 3.75; N, 4.89; S, 5.59. Found: C, 56.07; H, 3.75; N, 4.67; S, 5.79.

2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-N-(5-methyl-4-oxo-2-(2-(trifluoromethoxy)phenyl)thiazolidine-3-yl)propanamide ***(4i)***: Off-white solid. M.p. 91-93ºC. Yield 81%. IR ν_{max} (cm^{-1}): 3227 (N-H), 1717 (C=O), 1668 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.25-1.36 (m, 3H, -CH-CH_3); 1.49-1.54 (m, 3H, thiaz. -CH_3); 3.39-3.68 (m, 1H, thiaz. C_5-H); 4.10-4.21 (m, 1H, -CH-CH_3); 6.08 (m, 1H, thiaz. C_2-H); 7.07-7.71 (m, 12H, Ar-H); 10.52 and 10.56 (2s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.45, 20.15, 42.64, 58.26, 63.60, 113.34, 120.92, 123.89, 125.48, 126.27, 127.15, 127.61, 128.09, 128.22, 129.09, 135.36, 145.29, 152.06, 163.76, 169.21, 172.25. Anal. Calcd. for $C_{26}H_{22}F_4N_2O_3S.H_2O$: C, 58.20; H, 4.51; N, 5.22; S, 5.98 Found: C, 58.39; H, 4.33; N, 5.25; S, 5.95.

*N-(2-(4-bromothiophen-2-yl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **(4j)***: Pale yellow solid. M.p. 119-121ºC. Yield 56%. IR ν_{max} (cm^{-1}): 3181 (N-H), 1715 (C=O), 1695 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.35-1.39 (m, 3H, -CH-CH_3); 1.47-1.54 (m, 3H, thiaz. -CH_3); 3.69-3.76 (m, 1H, thiaz. C_5-H); 4.02-4.16 (m, 1H, -CH-CH_3); 5.98 and 6.44 (2s, 1H, thiaz. C_2-H); 7.15-7.780 (m, 10H, Ar-H); 10.53 (s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.32, 20.25, 42.64, 55.56, 55.95, 108.39, 115.52, 126.33, 127.29, 126.43, 128.24, 129.19, 131.61, 135.39, 143.99, 157.69, 160.95, 171.42, 172.09. Anal. Calcd. for $C_{23}H_{20}BrFN_2O_2S_2.1/4H_2O$: C, 52.72; H, 3.94; N, 5.35; S, 12.24 Found: C, 52.58; H, 3.94; N, 5.32; S, 12.56.

*N-(2-(5-Bromo-2-methoxyphenyl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **(4k)***: Yellow solid. M.p. 111-112ºC. Yield 68%. IR ν_{max} (cm^{-1}): 3254 (N-H), 1714 (C=O), 1668 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.30-1.50 (m, 6H, -CH-CH_3 and thiaz. -CH_3); 3.64-3.66 (m, 3H, -OCH_3); 3.80 (m, 1H, thiaz. C_5-H); 4.00-4.15 (m, 1H, -CH-CH_3); 5.91-6.04 (m, 1H, thiaz. C_2-H); 6.90-7.56 (m, 11H, Ar-H); 10.58 (s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.19, 20.21, 42.53, 56.33, 56.54, 112.64, 114.05, 115.23, 123.99, 124.83, 125.74, 128.24, 129.09, 130.89, 132.92, 135.36, 143.11, 156.78, 172.13, 172.60. Anal. Calcd. for $C_{26}H_{24}BrFN_2O_3S_2.H_2O$: C, 55.62; H, 4.67; N, 4.99; S, 5.71 Found: C, 55.43; H, 4.63; N, 5.16; S, 5.70.

*2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-N-(2-(4-methoxy-3-nitrophenyl)-5-methyl-4-oxothiazolidine-3-yl)propanamide **(4l)***: Yellow solid. M.p. 108-109ºC. Yield 54%. IR ν_{max} (cm^{-1}): 3256 (N-H), 1717 (C=O), 1688 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.27-1.35 (m, 3H, -CH-CH_3); 1.49-1.54 (m, 3H, thiaz. -CH_3); 3.54-3.66 (m, 3H, -OCH_3); 3.54-3.66 (m, 1H, thiaz. C_5-H); 4.04-4.24 (m, 1H, -CH-CH_3); 5.84 (s, 1H, thiaz. C_2-H); 7.01-7.98 (m, 11H, Ar-H); 10.38 and 10.45 (2s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.19, 20.21, 42.53, 56.33, 56.54, 112.64, 114.05, 115.23, 123.99, 124.83, 125.74, 128.24, 129.09, 130.89, 132.92, 135.36, 143.11, 156.78, 172.13, 172.60. Anal. Calcd. for $C_{26}H_{24}BrFN_2O_3S_2.H_2O$: C, 55.62; H, 4.67; N, 4.99; S, 5.71 Found: C, 55.43; H, 4.63; N, 5.16; S, 5.70.

*N-(2-(2-Chloro-3-methoxyphenyl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **(4m)***: Off-white solid. M.p. 133-135ºC. Yield 85%. IR ν_{max} (cm^{-1}): 3205 (N-H), 1705 (C=O), 1663 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.28-1.37 (m, 3H, -CH-CH_3); 1.48-1.54 (m, 3H, thiaz. -CH_3); 3.59-3.69 (m, 1H, thiaz. C_5-H); 4.06-4.25 (m, 1H, -CH-CH_3); 5.77-5.82 (m, 1H, thiaz. C_2-H); 7.02-7.573 (m, 11H, Ar-H); 10.39 (s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.06, 19.91, 42.65, 59.07, 59.29, 115.05, 123.90, 126.96, 128.24, 128.76, 129.14, 126.80, 131.14, 130.17, 138.99, 140.02, 143.08, 157.55, 160.79, 171.97, 172.06. Anal. Calcd. for $C_{25}H_{21}Cl_2FN_2O_2S.1/2H_2O$: C, 58.60; H, 4.33; N, 5.47; S, 6.26 Found: C, 58.25; H, 4.49; N, 5.43; S, 6.67.

*N-(2-(2-Chloro-3-(trifluoromethyl)phenyl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **(4n)***: White solid. M.p. 161-163ºC. Yield 52%. IR ν_{max} (cm^{-1}): 3252 (N-H), 1716 (C=O), 1668 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.31-1.54 (m, 6H, -CH-CH_3 and thiaz. -CH_3); 3.66-3.70 (m, 1H, thiaz. C_5-H); 4.11-4.20 (m, 1H, -CH-CH_3); 6.18- 6.26 (m, 1H, thiaz. C_2-H); 6.98-7.68 (m, 11H, Ar-H); 10.57 and 10.66 (2s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.08, 18.87, 42.67, 51.43, 114.94, 123.72, 124.41, 128.21, 128.79, 129.00, 129.79, 130.80, 131.02, 133.04, 135.27, 142.91, 143.02, 172.18, 172.45, 172.58. Anal. Calcd. for $C_{26}H_{21}ClF_4N_2O_2S$: C, 58.16; H, 3.94; N, 5.22; S, 5.97 Found: C, 57.88; H, 3.98; N, 5.26; S, 6.51.

*N-(2-(3,4-Dichlorophenyl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **(4o)*** : White solid. M.p. 133-135ºC. Yield 52%. IR ν_{max} (cm^{-1}): 3246 (N-H), 1705 (C=O), 1662 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.28-1.37 (m, 3H, -CH-CH_3); 1.48-1.54 (m, 3H, thiaz. -CH_3); 3.59-3.69 (m, 1H, thiaz. C_5-H); 4.06-4.25 (m, 1H, -CH-CH_3); 5.77-5.82 (m, 1H, thiaz. C_2-H); 7.02-7.73 (m, 11H, Ar-H); 10.39 and 10.46 (2s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.06, 19.91, 42.65, 59.07, 59.29, 115.05, 123.90, 126.96, 128.24, 128.76, 129.14, 126.80, 131.14, 130.17, 138.99, 140.02, 143.08, 157.55, 160.79, 171.97, 172.06. Anal. Calcd. for $C_{25}H_{21}Cl_2FN_2O_2S.1/2H_2O$: C, 58.60; H, 4.33; N, 5.47; S, 6.26 Found: C, 58.25; H, 4.49; N, 5.43; S, 6.77.

*N-(2-(2,4-Dichlorophenyl)-5-methyl-4-oxothiazolidine-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide **(4p)*** : White solid. M.p. 112-114ºC. Yield 80%. IR ν_{max} (cm^{-1}): 3290 (N-H), 1717 (C=O), 1674 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.29-1.37 (m, 3H, -CH-CH_3) 1.48-1.53 (m, 3H, thiaz. -CH_3); 3.60-3.69 (m, 1H, thiaz. C_5-H); 4.08-4.18 (m, 1H, -CH-CH_3); 6.01-6.12 (m, 1H, thiaz. C_2-H); 7.00-7.66 (m, 11H, Ar-H); 10.52 and 10.59 (2s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 17.93, 20.07, 42.63, 56.62, 114.99, 123.85, 127.13, 128.24, 128.53, 129.14, 130.85, 133.87, 133.93, 134.15, 134.53, 135.36, 143.04, 171.97, 172.10, 172.34. Anal. Calcd. for $C_{25}H_{21}Cl_2FN_2O_2S.3/2H_2O$: C, 56.61; H, 4.56; N, 5.13 Found: C, 56.79; H, 4.55; N, 5.12.

*2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-N-(5-methyl-4-oxothiazolidine-2-(p-tolyl)-3-yl)propanamide **(4r)***: White solid. M.p. 143-145ºC. Yield 72%. IR ν_{max} (cm^{-1}): 3234 (N-H), 1703 (C=O), 1674 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.26-1.35 (m, 3H, -CH-CH_3); 1.49-1.54 (m, 3H, thiaz. -CH_3); 2.22-2.31 (s, 3H, tolyl –CH_3); 3.57-3.68 (m, 1H, thiaz. C_5-H); 4.01-4.15 (m, 1H, -CH-CH_3); 5.71 and 5.77 (2s, 1H, thiaz. C_2-H); 7.16-7.55 (m, 12H, Ar-H); 10.36 (s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 17.97, 18.91, 21.19, 42.47, 60.27, 60.87, 115.42, 123.98, 127.01, 128.47, 129.11, 129.43, 130.83, 134.35, 135.38, 139.12, 143.16, 171.93, 172.09, 172.21. Anal. Calcd. for $C_{26}H_{25}FN_2O_2S.1/2H_2O$: C, 68.25; H, 5.73; N, 6.12; S, 7.01 Found: C, 68.81; H, 5.50; N, 6.32; S, 6.77.

*2-(2-Fluoro-[1,1'-biphenyl]-4-yl)-N-(2-(4-hydroxy-3-methoxyphenyl)-5-methyl-4-oxothiazolidine-3-yl) propanamide **(4s)***: Off-white solid. M.p. 70-72ºC. Yield 80%. IR ν_{max} (cm^{-1}): 3240 (N-H), 1709 (C=O), 1666 (C=O); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.27-1.35 (m, 3H, -CH-CH_3); 1.48-1.54 (m, 3H, thiaz. -CH_3); 3.66 (s, 3H, –OCH_3); 3.76 (s, 1H, thiaz. C_5-H); 3.99-4.11 (m, 1H, -CH-CH_3); 5.64- 5.74 (m, 1H, thiaz. C_2-H); 6.64-7.55 (m, 11H, Ar-H); 9.31 (s, 1H, -OH); 10.34 (s, 1H, -CO-NH). ^{13}C-NMR (75 MHz) (DMSO-d_6/TMS) δ ppm: 18.20, 20.68, 42.44, 55.80, 55.95, 60.97, 112.14, 115.61, 121.54, 124.04, 126.89, 127.61, 128.24, 129.10, 130.85, 135.38, 143.13, 147.97, 148.10, 157.57, 160.82, 172.01. Anal. Calcd. for $C_{26}H_{25}FN_2O_4S.H_2O$: C, 62.64; H, 5.46; N, 5.62; S, 6.03 Found: C, 62.42; H, 5.02; N, 5.75; S, 5.93.

2.3. Biological Assay

2.3.1. Cell Culture

Human breast cancer cell line MCF-7 (ATCC®, HTB22™), human colon cancer cell line HT-29 (ATCC®, HTB-38™), human lung cancer cell line A549 (ATCC®, CCL-185™), human cervical carcinoma cell line HeLa (ATCC®, CCL2™), and mouse fibroblast embryonic cell line NIH3T3 (ATCC®, CRL-1658) were maintained in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% FBS (Fetal bovine serum), 1% L-Glutamine and penicillin/streptomycin (Gibco) at 37°C in a humidified incubator with 5% CO_2.

2.3.2. Cell Viability Assay

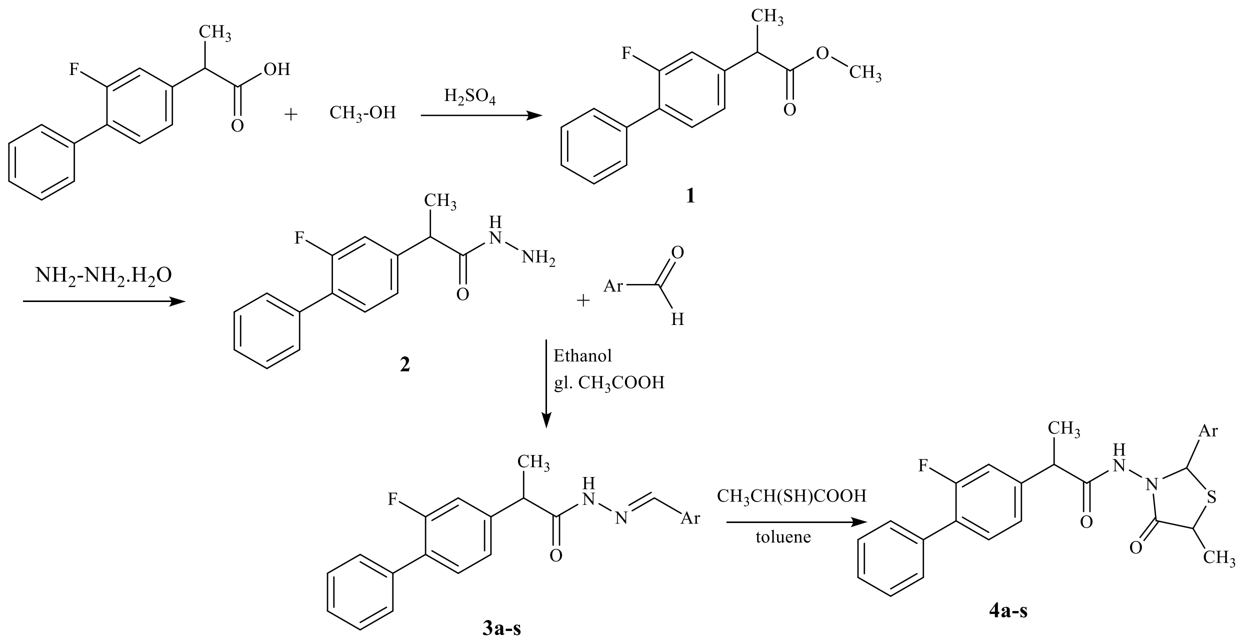
Cell viability was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay following the procedure of Kulabaş et al.[32] Viability was calculated as follows:

Cell Viability (%)= $(A_{treatment} - A_{blank})/(A_{control} - A_{blank}) \times 100\%$ (where, A = absorbance).

3. Results and Discussion

3.1. Chemistry

The general methods for synthesis of target hydrazone and 4-thiazolidinone derivatives are depicted in Scheme 1. The starting methyl (±) (R,S)-2-(2-fluorobiphenyl-4-yl)propanoate **(1)** synthesized using known methods from (±) (R,S)-flurbiprofen[29] easily reacted with hydrazine hydrate in ethanol yielding (±) (R,S)-2-(2-fluorobiphenyl-4-yl)propanehydrazide **(2)**.[28-30] Based on the condensation reaction of **2** and substituted aldehydes in the presence of acetic acid, (±) (R,S)-2-(2-fluorobiphenyl-4-yl)-*N´*-[(substituted methylene]propanehydrazides ***(3a-s)*** were obtained. Finally, 2-(2-fluoro-[1,1'-biphenyl]-4-yl)-*N*-(5-methyl-2-(substituted aryl)-4-oxothiazolidin-3-yl)propanamide derivatives **(4a-s)** were synthesized by the treatment of **3a-s** with a large excess of thiolactic acid ((R,S)-2-mercapto propionic acid) in the presence of toluene.[28] The compounds **(3d, 3o, 3p, 3r, 3s)** have been previously synthesized and reported in the literature.[30, 31] while the other compounds are the original compounds reported in this study. In this study, the structures characterization of original compounds were studied by FT-IR, NMR and elemental microanalysis and their antiproliferative activities were evaluated using MTT assay.



Compound	-Ar	Compound	-Ar
a	4-cyanophenyl	**j**	4-bromothiophen-2-yl
b	3-phenoxyphenyl	**k**	5-bromo-2-methoxyphenyl
c	3-(trifluoromethyl)phenyl	**l**	4-methoxy-3-nitrophenyl
d	3-bromophenyl	**m**	2-chloro-3-methoxyphenyl
e	4-bromophenyl	**n**	2-chloro-3-(trifluoromethyl)phenyl
f	benzo[d][1,3]dioxol-4-yl	**o**	3,4-dichlorophenyl
g	2,6-dichlorophenyl	**p**	2,4-dichlorophenyl
h	3,5-bis(trifluoromethyl)phenyl	**r**	p-tolyl
i	2-(trifluoromethoxy)phenyl	**s**	4-hydroxy-3-methylphenyl

Scheme 1. Synthesis of the title compounds **3a-s** and **4a-s**

The structures of the target compounds **3a-s** and **4a-s** were elucidated by FT-IR and NMR spectral studies and elemental analysis. The FT-IR spectra of all the synthesized compounds displayed characteristic absorbtion band for N-H, C=O and/or C=N groups.

According to literature, the hydrazones may exist as Z/E geometrical isomers about imine bonds and cis/trans amide conformers.[33,34] ^{1}H-NMR spectra of compounds **3a-s** display two sets of singlets each belonging to the –CH-CH_3, -NH and =CH protons in DMSO-d_6, indicating the presence of cis/trans conformers (see Figure S2).

The synthesis of thiazolidin-4-one moiety was evident by the presence of frequency ranged from 1699-1732 cm^{-1} characteristic C=O group at the 4th position. The proton resonance at 5.71-6.44 ppm in the spectra were attributed to 4-thiazolidinone C2-H position.[35,36] Generally, two sets of singlet or multiplet signals were determined for most of the protons of the thiazolidinones, and this is because of the magnetically inequivalent protons on chiral center.[36]

3.2. Biological Assay

3.2.1. Antiproliferative Activity

The antiproliferative activity of all the synthesized hydrazone and thiazolidinone compounds were evaluated in vitro against four human cancer cell lines (the colorectal adenocarcinoma cell line HT-29, the cervical carcinoma HeLa cells, the lung cancer cell line A549, as well as the breast cancer cell line MCF-7) at 10 μM concentration. In addition, cytotoxicity results against mouse fibroblast cell line NIH3T3 (ATCC®, CRL-1658™) at 10 μM dose of compounds **3a-s** and **4a-s** were given in Table 1 and these compounds appeared to be safe towards NIH3T3 fibroblasts.

Table 1. Cytotoxicity and antiproliferative activity of compounds **3a-s** and **4a-s** in selected cancer cell lines

Comp.	**% proliferation (at 10 μM)**					**Comp.**	**% proliferation (at 10 μM)**				
	HT-29	**HeLa**	**A549**	**MCF-7**	**NIH3T3**		**HT-29**	**HeLa**	**A549**	**MCF-7**	**NIH3T3**
3a	100.49	106.06	95.58	93.28	128.83	**4a**	86.75	102.78	96.77	92.63	110.46
3b	99.34	98.56	104.50	89.99	122.45	**4b**	88.15	95.96	93.11	79.31	103.02
3c	95.31	95.38	79.36	92.37	94.56	**4c**	84.12	87.98	82.77	82.51	80.84
3d	91.36	105.48	97.79	85.49	103.32	**4d**	88.15	97.98	91.29	99.24	89.33
3e	94.90	104.71	99.22	84.66	117.86	**4e**	69.96	109.52	94.97	85.42	95.72
3f	93.09	101.83	94.45	86.92	111.82	**4f**	74.16	101.06	82.14	84.76	84.28
3g	90.04	99.13	95.81	88.13	109.78	**4g**	77.53	102.60	86.66	87.13	92.63
3h	72.59	100.38	65.27	69.41	90.56	**4h**	44.03	85.67	78.09	72.56	78.18
3i	90.88	124.28	125.13	88.87	118.03	**4i**	87.00	87.79	84.97	83.25	82.60
3j	88.67	116.86	102.47	66.02	97.62	**4j**	98.77	99.81	95.31	86.25	87.51
3k	93.56	97.64	114.65	90.13	109.35	**4k**	85.10	100.87	133.44	96.08	78.11
3l	88.37	101.81	105.63	96.44	115.82	**4l**	87.33	89.71	93.78	88.46	89.26
3m	82.46	105.42	108.88	92.88	119.64	**4m**	92.35	85.38	98.02	84.73	82.46
3n	88.53	103.20	105.13	87.97	120.92	**4n**	78.68	74.90	80.56	76.89	79.93
3o	87.93	88.17	75.61	85.08	71.68	**4o**	94.57	99.13	84.41	82.30	75.02
3p	82.18	80.68	94.55	76.48	114.2	**4p**	87.41	86.83	87.34	90.21	82.25
3r	92.60	116.40	94.14	92.29	107.06	**4r**	90.62	96.15	114.68	110.85	77.96
3s	89.71	93.94	88.24	66.51	115.39	**4s**	97.20	87.50	116.92	99.28	90.18

According to data, the most active compound was identified as compound *N*-(2-(3,5-bis(trifluoromethyl)phenyl)-5-methyl-4-oxothiazolidin-3-yl)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamide (4h) by 55.97% inhibition in HT-29 cell line. This compound was observed non-toxic to NIH3T3 mouse fibroblast cells with high survival rate (78.18%). Other remarkable inhibitions were observed with compounds *N'*-(3,5-bis(trifluoromethyl)benzylidene)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanehydrazide **(3h)** (34.73% inhibition vs. A549), *N'*-[(4-bromothiophen-2-yl)methylidene]-2-(2-fluoro[1,1'-biphenyl]-4-yl)propanehydrazide **(3j)** (33.98% inhibition vs. MCF-7) and 2-(2-fluoro-[1,1'-biphenyl]-4-yl)-*N'*-(4-hydroxy-3-methoxybenzylidene)propanehydrazide **(3s)** (33.49% inhibition vs. MCF-7) at 10 µM concentration.

4. Conclusion

In this present study, we have described the synthesis and identification of flurbiprofen hydrazones and 4-thiazolidinones which were tested for antiproliferative activity against HT-29, HeLa, A549 and MCF-7 cancer cell lines. NIH/3T3 fibroblast proliferation was also tested and cell proliferation was found to be between 128.83% and 71.68%, which means that all the compounds were nontoxic. Among these derivatives, non-toxic compound **4h** caused significant decrease (55.97%) in HT-29 colorectal adenocarcinoma cell proliferation at 10 µM concentration. Regarding these flurbiprofen analogs, we can conclude that the replacement of 4-thiazolidinone ring with 5-methyl-4-thiazolidinone ring did not condiderably affect the activity.

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Conflict of interest statement

The authors declared no conflict of interest.

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