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DESIGN AND CYTOTOXIC ACTIVITY OF THIAZOLIDINONES *VIA* ONE-POT, THREE COMPONENT REACTION UNDER MICROWAVE AND TRADITIONAL METHOD

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ABSTRACT. Treatment of sulfamethoxazole (SMZ) (**1**) with different aromatic aldehydes **2a-f** within few minutes (5-8 min) afforded the corresponding Schiff bases **3a-f** which were subjected to react with thioglycolic acid (**4**) under refluxing toluene/dimethlformamide (DMF) in (1:1) ratio for 12-17 h, yielded *N*-(5-methylisoxazol-3-yl)-4-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)benzenesulfon- amide derivatives **5a-f**. On the other hand, the same products **5a-f** were obtained when SMZ (**1**) was treated with a mixture of the same aromatic aldehydes **2a-f** and thioglycolic acid **4** *via* one-pot, three-component reaction under microwave irradiation. The key advantages of this process were high yields 79-88%, shorter reaction times 6-11 min., easy work-up, and problems associated with toxic solvent use (cost, safety, pollution) were avoided. The structures of newly compounds were elucidated by elemental and spectral analyses. Three compounds **5a**, **5b** and **5f** were tested for cytotoxicity against four human cancer cell lines MCF-7, HePG2, HCT 116 and 116 PC-3. Compound **5b** exhibited the most potent cytotoxic properties on HePG2 and PC-3. Furthermore, it showed inhabitory effect against MCF-7 and HCT 116 cells.

KEY WORDS: Sulfamethoxazole, 4-Thiazolidinones, Schiff bases, Multicomponent reaction, Microwave, Traditional methods and cytotoxicity

INTRODUCTION

In recent year, chemists are interested to applied modern techniques in organic synthesis. One of these important techniques is the use of microwave irradiation for many reasons such as environmentally friendly, easy work-up, reduce time from hours to minutes, in addition to afford higher yield compared to traditional methods [1-4]. Moreover, One-pot multi-component reactions are the most important application in organic synthesis due to the possibility of achieving high synthetic efficiency, exceptional synthetic efficiency, high selectivity, and procedural simplicity [1-6]. 4-Thiazolidinones are an important group of heterocyclic compounds, which possess a wide range of pharmaceutical and biological applications such as antiviral [10], anticancer [11, 12], antimycobacterial [13], antimicrobial [14-16], analgesic and anti-inflammatory activities [17-20]. Recently, many diseases have spread for various reasons, one of the most dangerous diseases spread all over the world is cancer which caused by the excessive growth of cells in the body in an uncontrolled manner. Recently, there have been many developments in the treatment of cancer disease because cancer is the most common cause of human death according to the World Health Organization. Unfortunately, the number of patients

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is increasing all over the world, especially in developed countries. There are many common cancer treatments such as surgery, radiotherapy, and chemotherapy. Chemotherapy drugs is the major areas in current efforts to treat cancer [21]. Therefore, the researcher team tries to find new compounds that may be later promising to treat cancer. From previous studies, we conclude that thiazole can be used in many therapeutic cases, such as cancer treatment [20, 21]. Therefore, the teamwork decided to use sulfamethoxazole as a starting material for the synthesis of some new compounds that may be used for treatment of cancer. This study deals with the design and synthesis of new thiazole derivatives scaffold as promising anti-cancer.

RESULTS AND DISCUSSION

Chemistry

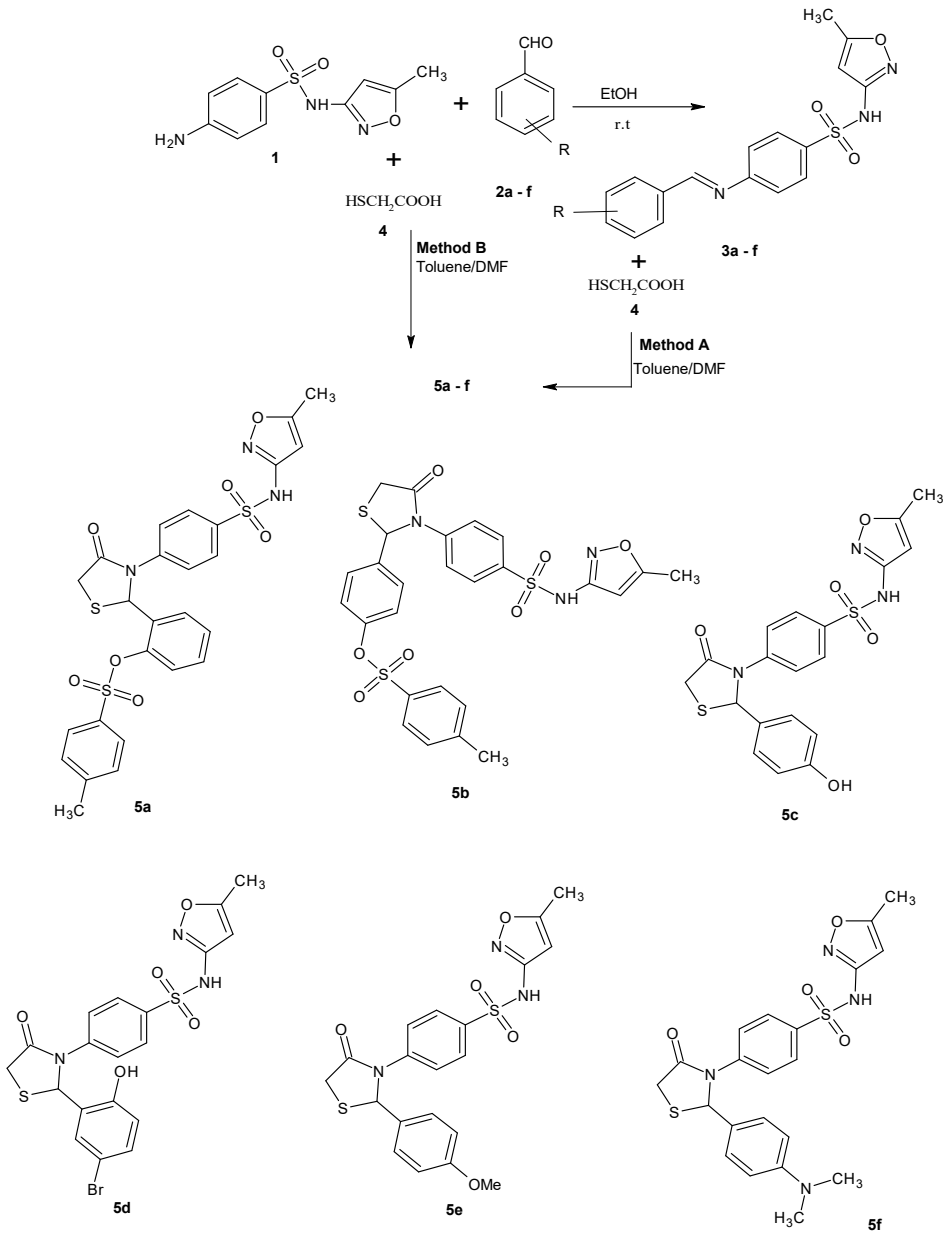
The started material sulfamethoxazole **1** was suggested to react with some aromatic aldehydes **2a-f** namely; 2-tosyloxybenzaldehyde **2a**, 4-tosyloxybenzaldehyde **2b**, 2-hydroxybenzaldehyde **2c**, 5-bromo-2-hydroxybenzaldehyde **2d**, anisaldehyde **2e**, and 4-*N,N*-dimethly edyminobenzaldeha **2f** *via* stirring in ethanol for 5-8 minutes at room temperature to afford the gorrespondinc Schiff bases **3a–f**, Scheme 1.

The structure of Schiff bases **3a-f** were established on the basis of IR, ^{1}H-NMR, ^{13}C NMR and elemental analyses. Their IR spectra showed the absence of absorption bands due to NH_2 and $C{=}O_{aldehydic}$ groups and appearance of new absorption bands in the region 1630-1645 cm^{-1} due to $CH{=}N_{str.}$ groups.^{1}H NMR (δ, DMSO-*d6*) spectra showed, beside the expected aromatic protons signals, new singlet signals in the region *δ* 8.60-8.31 ppm due to N=CH ; singlet signal at *δ* 11.29 ppm for OH group in compound **3c**; 3.83 ppm for OMe group in compound **3e**; *N*-dimethyl group at δ 3.23 ppm and in the region δ 2.44-2.27 ppm for CH_3 groups in compounds **3a,b**, respectively. Moreover, their ^{13}C NMR spectra showed the appearance of new signals at *δ* 55.88 ppm due to OMe group and the CH_3 group at *δ* 21.17 ppm, respectively. Elemental analyses of compounds **3a-f** provided the structure of the new compounds (cf. experimental).

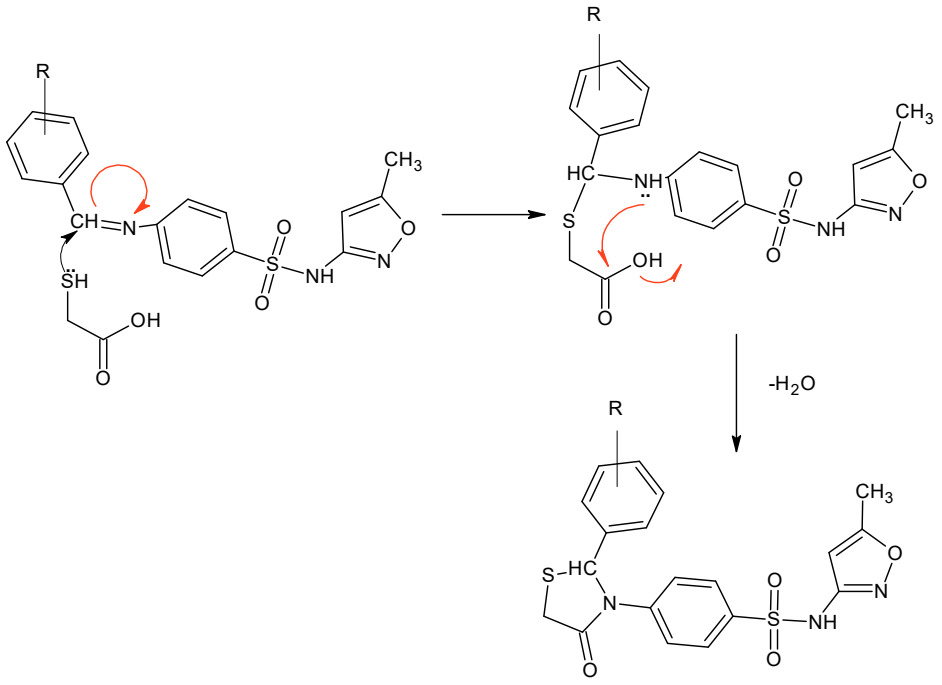
N-(5-Methylisoxazol-3-yl)-4-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)benzene derivatives **5a-f** were synthesized *via* two methods. The first method: treatment of Schiff bases **3a-f** with thioglycolic acid (**3)** under refluxing DMF/toluene for 12-17 h, in moderates 56-69%. Yield and long reaction time. The second method was deraperp as high yields, commercially available, simple, low reaction times *via* one-pot, three-component reaction of compound **1** with the same aromatic aldehydes **2a-g** and thioglycolic acid (**3)** under irradiation using microwave technique in the presence of 5 mL DMF/toluene (Scheme 1, Table 1). The key advantages of this process were high yields 79-88%, shorter reaction times 6-11 min., easy work-up, and problems associated with toxic solvent use (cost, safety, pollution) were avoided. The optimized results are summarized in Table 1.

IR spectra of compounds **5a-f** revealed the appearance of new carbonyl groups in the region 1648–1684 cm^{-1}. ^{1}H NMR (DMSO-*d6*) spectra showed, beside the expected aromatic protons signals, new doublet-doublet signals in the region δ 4.03-3.47 ppm consistent with the CH_2 groups, and singlet signal corresponding to SCH-N groups in the region *δ* 6.24-6.03 ppm. Furthermore, ^{13}C NMR spectra and elemental analyses of compounds **5a-f** provided the structure of thiazolidinone ring. For example, ^{13}C NMR spectrum of compound **5a** showed beside the expected aromatic signals the appearance of new signal at *δ* 21.58 ppm due to CH_3 group, a new signal at *δ* 60.87 ppm for the CH_2 group and at *δ* 170.11 ppm due to C=O group. Moreover, its DEPT 135 spectrum revealed the disappearance of carbonyl group and appearance of opposite side signal at *δ* 62.71 ppm for the CH_2 group.

The formation of compounds **5a-f** can be explained by the possible mechanism presented in Scheme 2.



Scheme 1. Synthesis of Schiff bases **3a-f** and 4-thiazolidinones **5a-f**.



Scheme 2. Reaction mechanism for formation of 4-thiazolidinones **5a-f.**

Table 1. Comparison of the yields and times for synthesis of 4-thiazolidinones.

Compound No.	M.W. irradiation		Conventional condensation	
	Yield %	Time (min)	Yield %	Time (h)
5a	84	11	59	17
5b	88	7	67	15
5c	87	10	56	17
5d	85	9	65	12
5e	79	8	69	15
5f	83	6	64	13

From the recorded results in Table 1, it is clear that the low consumed time and high yield of products, when green chemistry protocols (as environment friendly and economically) have been employed and it is much better compared with conventional procedure for the synthesis of 4-thiazolidinone derivatives.

Cytotoxic activity

Three compounds **5a, 5b** and **5f** were tested for cytotoxicity against four human tumor cells (MCF-7, HePG2, HCT 116 and 116 PC-3). Using the SRB assay after 72 hours of treatment with different concentrations (0.0, 0.01, 0.1, 1, 10, 100, and 1000 µg/mL) (cell viability assay). The findings revealed that the viability of the cells decreases as the concentration of these compounds increases in all cancer cell lines (Figure 1, Table 2).

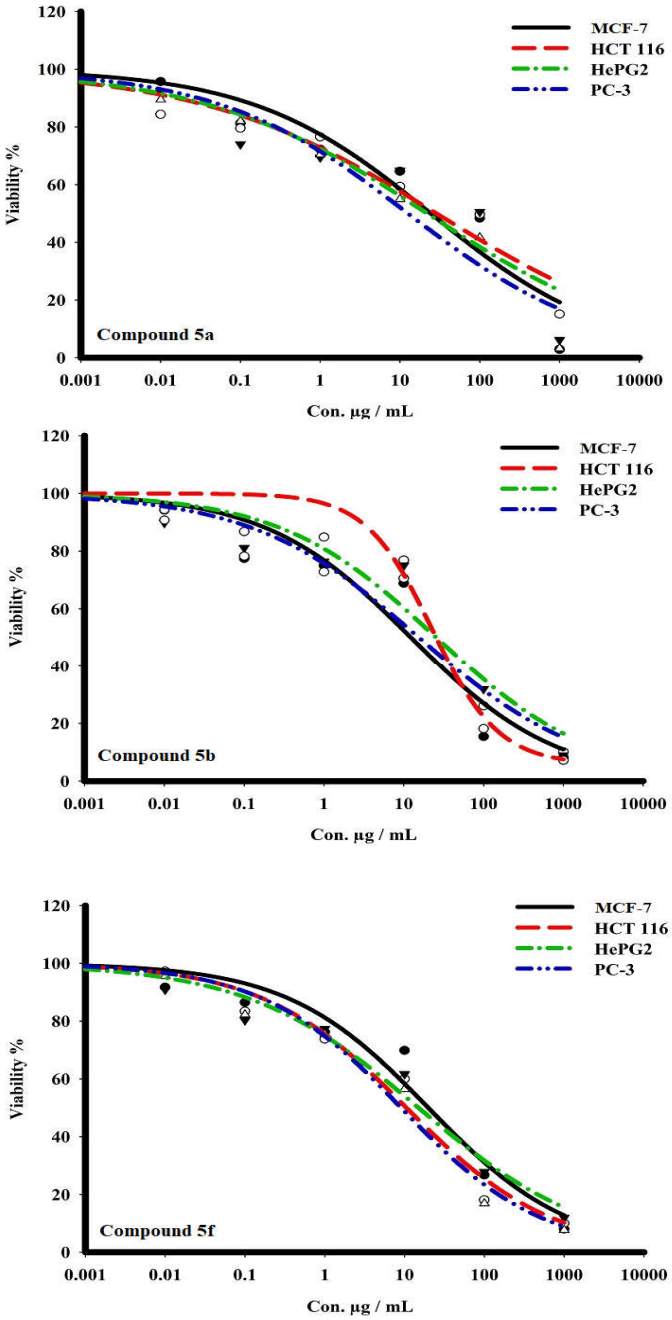


Figure 1. The toxicity responding of various tested compounds to human cancer cells MCF-7, HepG2, HCT116 and PC-3 using the SRB assay.

Compound **5b** exhibited the most potent cytotoxic properties on HePG2 and PC-3, with IC_{50s} of 13.7, 2.7 and 11.2, 0.3 µg/mL, respectively, followed by compound **5f** on MCF-7 with an IC_{50} of 11.8, 1.1 µg/mL and compound **5a** on PC-3 with IC_{50s} of 13.2, 1.2 µg/mL. Furthermore, compound **5b has** a promising inhabatory effect against MCF-7 and HCT 116 cells, with IC50s of 17.1, 0.62 and 16.5, 2.5 µg/mL, respectively, as well compound **5f** against HePG2 and PC-3 cancer cells, with IC50s of 17.3, 2.6 and 16.1, 0.8 µg/mL, respectively. Similarly, compound **5b** has a significant toxic influence on MCF-7, HePG2, and HCT 116 cells, with IC50s of 22.8, 1.9, 21.5, 2.1, and 29.1, 0.4 µg/mL, respectively, as compound **5f** on HCT 116 with IC50 27.5, 1.1 µg/mL.

Table 2. The IC_{50} (µg) of new compounds against different human solid cancer cell lines.

Compounds	IC_{50}% (µg/mL)			
	MCF-7	HEPG-2	HCT116	PC-3
5a	17.1 ± 0.62	13.7 ± 2.7	16.5 ± 2.5	11.2 ± 0.3
5b	22.8 ± 1.9	21.5 ± 2.1	29.1 ± 0.4	13.2 ± 1.2
5f	11.8 ± 1.1	17.3 ± 2.6	27.5 ± 1.1	16.1 ± 0.8

The toxicity responding of various tested compounds to human cancer cells MCF-7, HepG2, HCT116 and PC-3., for 72 hours, cells were incubated with variable concentrations of various three compounds (**Figure 1**.). SRB staining was used to determine cell viability and proliferation. The amount of dye binding is directly proportional to the number of viable cells. The axes reflect the concentrations of the three test substances used in the experiment, and the percentage responses of toxicity and cell survival to the concentrations are represented by bars to observe the dose-response relationship. The extent of the decrease in cell viability can vary between cell lines and compounds, indicating differences in their sensitivity to compounds.

EXPERIMENTAL

Chemistry

All commercially available reagents were purchased from Merck, Aldrich and Fluka, and were used without further purification. All reactions were monitored by thin layer chromatography(TLC) using precoated plates of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F254) and UV light (254 nm/365 nm) for visualization. Melting points were detected with a Kofler melting points apparatus and uncorrected. Infrared spectra were recorded with a FT-IR-ALPHBROKER-Platinum-ATR spectrometer, and are given as cm^{-1} using the attenuated total reflection (ATR) method.^{1}H NMR and ^{13}C NMR spectra for all compounds were recorded in DMSO-*d6* on a Bruker Bio Spin AG spectrometer at 400 MHz and100 MHz, respectively. Elemental analyses were obtained on a Perkin-Elmer CHN-analyzer model.

Cytotoxicity assay

Cell culture

The American type culture collection provided human cell lines, prostate adenocarcinoma (PC-3), breast cancer (MCF-7), hepatocellular carcinoma (HePG2) and colon cancer cell line (HCT 116) (ATCC). In a humidified, 5% (v/v) CO_2 condition, cells were incubated in RPMI-1640 enriched with (100 g/mL); penicillin (100 units/L); and heat-inactivated fetal bovine serum (10 percent v/v) at 37°C. Using the sulphorhodamine B assay, the cytotoxicity of chemical compounds was assessed against human cancer cell lines (PC-3, MCF-7, HePG2 and HCT 116) (SRB). Before

treated with the chemical compounds, 80 percent confluent proliferating cells trypsinized and cultivated in a 96 well tissue culture plate for 24 hours. Untreated cells (control) added to cells that exposed to the six various concentrations of each drug (0.01, 0.1, 1, 10, and 1000 µg/mL). They were exposed to the doses for 72 hours before being fixed with TCA (10% w/v) for 1 hour at 4 °C. After repeated washes, cells stained for ten min in the dark with a 0.4% (w/v) SRB solution. Glacial acetic acid, 1 percent (v/v), used to remove any remaining discoloration. The SRB-stained cells dissolved in Tris-HCl after drying overnight, and the color intensity quantified in a microplate reader at 540 nm. Using SigmaPlot 12.0 software, the correlation between viability percentage of each tumor cell line and chemical concentrations analyzed to determine the IC50 (drug dose that reduces survival to 50%) [22].

General procedure for synthesis of compounds 3a-f

A mixture of (2 mmole) sulfamethoxazole (**1)** (0.55 g) and of aromatic aldehydes **2a-f** namely; 2-tosyloxybenzaldehyde (**2a)**, 4-tosyloxybenzaldehyde (**2b)**, 2-hydroxybenzaldehyde (**2c)**, 5-bromo-2-hydroxybenzaldehyde (**2d)**, anisaldehyde (**2e)**, and 4-*N,N*-dimethyledyhedlaznebonima (**2f)** were irradiation using microwave technique in ethanol/TEA for 5-8 min to afford the gnidnopserroc Schiff base. The formed solid products were filtered off, washed with small amounts of ethanol, dried, and crystallized from ethanol.

*4-{[(2-(4-Methylbenzenesulfonate))methylene]amino}-N-(5-methylisoxazol-3-yl)benzene sulfon amide (**3a**)*. Mp 144 °C; IR cm^{-1}: 3117 (NH), 3076 (C–$H_{arom.}$), 1639 (CH=N), 1362 (S=O); ^{1}H NMR δ 11.65 (s, 1H, NH), 8.50 (s, 1H, CH=N) 7.95–7.04 (m, 13H, CH_{arom}), 2.44 (s, 3H, CH_3), 2.34 (s, 3H, CH_3); ^{13}C NMR δ (ppm): 165.21. 159.04, 158.42, 156.74, 155.40, 149.65, 146.79, 137.23, 136.38, 134.08, 131.19, 130.89, 130.76, 129.49, 128.85, 124.78, 121.98, 113.08, 21.65, 12.48; anal. calcd. for $C_{24}H_{21}N_3O_6S_2$ (511.57): C (56.35%), H (4.14%), N (8.21%), S (12.54%) Found: C (56.39%), H (4.17%), N (8.29%), S (12.61%).

*4-{[(4-(4-Methylbenzenesulfonate))methylene]amino}-N-(5-methylisoxazol-3-yl)benzene sulfon amide (**3b**)*. Mp 148 °C; IR cm^{-1}: 3189 (NH), 3084 (C–$H_{arom.}$), 1635 (CH=N), 1360 (S=O); ^{1}H NMR *δ* 9.93 (s, 1H, NH), 8 7.74–6.06 (m, 14H, CH_{arom}+ CH=N), 2.41 (s, 3H, CH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR *δ* (ppm): 167.34, 158.67, 155.29, 153.90, 150.24, 144.09, 141.48, 136.87, 132.78, 130.15, 129.45, 127.25, 123.95, 121.98, 119,04, 117.64, 21.64, 13.97; anal. calcd. for $C_{24}H_{21}N_3O_6S_2$ (511.57): C (56.35%), H (4.14%), N (8.21%), S (12.54%) Found: C (56.41%), H (4.09%), N (8.19%), S (12.47%).

*4-{[(4-Hydroxyphenyl)methylene]amino}-N-(5-methylisoxazol-3-yl)benzenesulfonamide (**3c**)*. Mp 134 °C; IR cm^{-1}: 3415 (OH), 3214 (NH), 3079 (C–$H_{arom.}$), 1638 (CH=N), 1364 (S=O); ^{1}H NMR δ 11.29 (s, 1H, OH), 9.84 (s, 1H, NH), 8.49 - 6.02 (m, 11H, CH_{arom}+ CH=N), 2.42 (s, 3H, CH_3); anal. calcd. for $C_{17}H_{15}N_3O_4S$ (357.38): C (57.13%) H (4.23%), N (11.76%), S (8.97%) Found: C (57.19%), H (4.15%), N (11.85%), S (9.04%).

*4-{[(5-Bromo-2-hydroxyphenyl)methylene]amino}-N-(5-methylisoxazol-3-yl)benzene sulfon amide (**3d**)*. Mp 156 °C; IR cm^{-1}: 3398 (OH), 3179 (NH), 3081 (C–$H_{arom.}$), 1630 (CH=N), 1374 (S=O); ^{1}H NMR δ 10.17 (s, 1H, OH), 7.74 - 6.06 (m, 9H, CH_{arom}+ 1H, NH), 2.27 (s, 3H, CH_3); anal. calcd. for $C_{17}H_{14}BrN_3O_4S$ (436.27): C (46.80%), H (3.23%), N (9.63%), S (7.35%). Found: C (46.87%), H (3.30%), N (9.75%), S (7.31%).

*4-{[(4-Methoxyphenyl)methylene]amino}-N-(5-methylisoxazol-3-yl)benzenesulfonamide (**3e**)*. Mp 137 °C; IR cm^{-1}: 3203 (NH), 3071 (C–$H_{arom.}$), 1645 (CH=N), 1377 (S=O) ;^{1}H NMR δ 10.14 (s, 1H, NH), 8.09–6.68 (m, 10H, $CH_{arom.}$+ CH=N), 3.83 (s,1H, OCH_3), 2.55 (s, 3H, CH_3); C

(58.21%), H (4.61%), N (11.31%), S (8.63%); ^{13}C NMR δ (ppm): 161.54. 154.65, 151.24, 146.23, 146.02, 140.89, 134.65, 134.08, 130.19, 128.43, 123.87,119.54, 55.88, 21.17; anal. calcd. for $C_{18}H_{17}N_3O_4S$ (371.41). Found: C (58.28%), H (4.70%), N (11.24%), S (8.71%).

*4-([4-(Dimethylamino)phenyl]methylene]amino]-N-(5-methylisoxazol-3-yl)benzene sulfonamide (**3f**)*. Mp 176 °C; IR cm^{-1}: 3158 (NH), 3069 (C–H$_{arom.}$), 1631 (CH=N), 1376 (S=O); ^{1}H NMR δ 11.56 (s, 1H, NH), 8.07–6.85 (m, 10H, CH$_{arom.}$+ CH=N), 3.23 (s, 6H N(CH$_3$)$_2$), 2.46 (s, 3H, CH$_3$); anal. calcd. for $C_{19}H_{20}N_4O_3S$ (384.45); C (59.36%), H (5.24%), N (14.57%), S (8.34%). Found: C (59.43%), H (5.19%), N (14.68%), S (8.39%).

*General procedure for synthesis of compounds **5a-f***

Method A (traditional method). A mixture of Schiff bases **3a-f** (2 mmol) and thioglycolic acid (2.2 mmol) in dry toluene and DMF (1:1, molar ratio), 30 mL) was refluxed for 7-11 h., and the water formed during the reaction was removed by Dean-Stark apparatus. After the completion of reaction (progress was checked by TLC), the reaction mixture cooled and washed with dilute solution of sodium bicarbonate to remove unreacted acid. The organic layer separated, toluene was removed by rotary evaporator, the solid product was collected and purified by crystallization from ethanol.

Method B (microwave method). An equimolar amount (1 mmol) of sulfamethoxazole (**1**), (2 mmol), aromatic aldehyde (2 mmol) in dry toluene- DMF (5 mL) was allowed to irradiate in a MW oven for 10-14 min, then thioglycolic acid (2 mmol) was added. The mixture allowed to irradiate in a MW oven for approve time as shown in Table 1 After the completion of reaction (progress was checked by TLC), the reaction mixture was cooled and washed with dilute solution of sodium bicarbonate to remove unreacted acid. The organic layer separated, toluene was removed by rotary evaporator, the solid product was collected and purified by crystallization from ethanol.

*4-[(2-(4-Methylbenzenesulfonate))-4-oxoisothiazolidin-2-yl]-N-(5-methylisoxazol-3-yl)benzene sulfonamide (**5a**)*. Mp 187 °C; IR (ATR) cm^{-1}: 3197 (NH), 3097 (C–H$_{arom.}$), 2987, 2926 (C–H$_{aliph.}$), 1675 (C=O), 1367 (S=O); ^{1}H NMR δ 11.36 (s, 1H, NH), 7.92–6.59 (m, 13H, CH$_{arom.}$), 6.09 (s, 1H, N–CH–S), 4.01-3.86 (dd, 2H, CH$_2$), 2.45 (s, 3H, CH$_3$), 2.39 (s, 3H, CH$_3$); ^{13}C NMR δ (ppm): 171.10, 149.24, 146.36, 131.50, 130.65, 129.29, 128.51, 127.31, 126.68, 125.76, 125.18, 124.68, 122.83, 98.12, 62.90, 33.18, 21.21; DEPT 135; 130.65, 130.61, 129.29, 128.51, 126.67, 125.76, 125.17, 122.83, 122.78, 62.71, 33.13, 21.58. Anal. calcd. for $C_{26}H_{23}N_3O_7S_3$ (585.67) C (53.32%), H (3.96%), N (7.17%), S (16.42%). Found: C (53.39%), H (4.05%), N (7.24%), S (16.53%).

*4-[(4-(4-Methylbenzenesulfonate))-4-oxoisothiazolidin-2-yl]-N-(5-methylisoxazol-3-yl)benzene sulfonamide (**5b**)*. Mp 214 °C; IR cm^{-1}: 3187 (NH), 3065 (C–H$_{arom.}$), 2974, 2965 (C–H$_{aliph.}$), 1677 (C=O), 1362(S=O), 1176; ^{1}H NMR δ 7.83–7.01 (m, 14H, CH$_{arom+}$1H, NH), 6.24 (s, 1H, N–CH–S), 3.93-3.78 (dd, 2H, CH$_2$), 2.44 (s, 3H, CH$_3$), 2.21 (s, 3H, CH$_3$); ^{13}C NMR δ (ppm): 171.41, 170.84, 157.81, 146.83, 142.02, 136.98, 131.99, 130.98, 130.57, 128.82, 128.52, 128.56, 127.84, 124.84, 121.99, 95.87, 58.14, 21.67, 12.50; DEPT 135; 150.13, 148.20, 141.13, 138.03, 131.20, 130.03, 60.57,21.14, 20.47. Anal. calcd. for $C_{26}H_{23}N_3O_7S_3$ (585.67); C(53.32%), H(3.96%), N(7.17%), S (16.42%). Found: C (53.41%), H (4.09%), N (7.27%), S (16.59%)

*4-[2-(4-Hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzene sulfon amide (**5c**)*. Mp 189 °C; IR cm^{-1}: 3412 (OH), 3187 (NH), 3065 (C–H$_{arom.}$), 2974, 2965 (C–H$_{aliph.}$), 1684 (C=O), 1362 (S=O); ^{1}H NMR δ 13.09 (s,1H, OH), 12.41 (s, 1H, NH), 8.17–6.76 (m, 9H, CH$_{arom.}$), 6.15 (s, 1H, N–CH–S), 4.03-3.99 (dd, 2H, CH$_2$), 2.45 (s, 3H, CH$_3$); ^{13}C NMR δ (ppm):

170.11, 168.38, 150.09, 144.56, 141.18, 139.76, 131.86, 130.02, 127.46, 126.13, 123.34, 122.35, 60.87, 33.18, 21.58. Anal. calcd. for $C_{19}H_{17}N_3O_5S_2$ (431.48) C(52.89%), H (3.97%), N (9.74%), S (14.86%). Found: C (52.94%), H (4.07%), N (9.86%), S (14.93%).

*4-[2-(5-Bromo-2-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl) benzene sulfonamide (**5d**)*. Mp 203 °C; IR cm^{-1}: 3345 (OH), 3164 (NH), 3092 (C–$H_{arom.}$), 2962, 2953 (C–$H_{aliph.}$), 1682 (C=O), 1357 (S=O); ^{1}H NMR δ 12.14 (br,1H, OH), 11.08 (s, 1H, NH), 8.04–6.76 (m, 8H, $CH_{arom.}$), 6.24 (s, 1H, N–CH–S), 3.51-3.47 (dd, 2H, CH_2), 2.43 (s, 3H, CH_3); ^{13}C NMR δ (ppm): 174.32, 167.13, 151.57, 147.15, 144.61, 141.05, 138.12, 136.35, 134.00, 132.16, 130.08, 127.20, 125.16, 124.99, 123.57, 62.02, 21.58. Anal. calcd. for $C_{19}H_{16}BrN_3O_5S_2$ (510.38); C (44.71%), H (3.16%), Br (15.66%), N (8.23%), S (12.57%). Found: C (44.71%), H (3.16%), N (8.23%), S (12.57%), Br (15.66%).

*4-[2-(4-Methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzene sulfon amide (**5e**)*. Mp 186 °C; IR cm^{-1}: 3175 (NH), 3067 (C–$H_{arom.}$), 2971, 2965 (C–$H_{aliph.}$), 1667 (C=O), 1361 (S=O); ^{1}H NMR δ 11.09 (s, 1H, NH), 8.05–6.57 (m, 9H, $CH_{arom.}$), 6.03 (s, 1H, N–CH–S), 3.89 (s, 3H, OMe), 3.49-3.47 (dd, 2H, CH_2), 2.41 (s, 3H, CH_3); ^{13}C NMR δ (ppm): 170.83, 157.80, 146.83, 143.71, 142.19, 140.69, 139.29, 134.67, 132.24, 130.15, 129.27, 124.76, 122.37, 121.45, 64.68, 60.36, 21.57. Anal. calcd. for $C_{20}H_{19}N_3O_5S_2$ (445.51) C (53.92%), H (4.30%), N (9.43%) S (14.39%). Found: C (53.78%), H (4.37%), N (9.39%), S (14.46%).

*4-[2-(N,N-Dimethylphenylamino)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzene sulfonamide (**5f**)*. Mp 217 °C; IR cm^{-1}: 3197 (NH), 3084 (C–$H_{arom.}$), 2993, 2972 (C–$H_{aliph.}$), 1648 (C=O), 1367 (S=O); ^{1}H NMR δ 10.86 (s, 1H, NH), 8.05–6.57 (m, 9H, $CH_{arom.}$), 6.08 (s, 1H, N–CH–S), 3.30(s, 6H, NMe_2), 3.80-3.78 (dd, 2H, CH_2), 2.43 (s, 3H, CH_3); ^{13}C NMR δ (ppm): 171.65, 154.61, 148.14, 145.81, 142.08, 138.14, 138.03, 135.61, 134.14, 133.04, 132.72, 130.36, 127.90, 125.26, 121.45, 62.57, 21.45. Anal. calcd. for $C_{21}H_{22}N_4O_4S_2$ (458.55) C (55.00%), H (4.84%), N (12.22%), S (13.99%). Found: C (54.97%), H (4.94%), N (12.31%), S (14.06%).

CONCLUSION

New series of 4-thiazolidinones were synthesized *via* two methods, traditional method and microwave technique which is a simple and efficient protocol strategy (multicomponent reaction). The advanced of this method are mild reaction, low cost, expeditious, and an environmentally method. These compounds are promising anticancer cell and characterized by spectral techniques. The cytotoxicity of three compounds **5a, 5b** and **5f** were tested against four human cancer cell lines MCF-7, HePG2, HCT 116 and 116 PC-3. Compound **5b** exhibited the most potent cytotoxic properties.

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