

Synthesis, Characterization and Cytotoxic Studies of New Thiazolidinones



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Abstract

A new series of substituted aromatic thiazolidinones [1-4] were synthesized by the reaction of acetophenone and its derivatives [5-8] with hydrazine hydrate and mercaptoacetic acid in absolute ethanol in one pot manner. The striking feature of this reaction is the formation of hydrazone in situ which in turn undergoes the cyclization with mercaptoacetic acid, leading to the formation of new thiazolidinones. Thus, the thiazolidinone ring closes at carbonyl carbon, by the attack of sulfur of mercaptoacetic acid moiety, preferentially from the front (β , axial) so that the nitrogen has an equatorial orientation (α , equatorial) to avoid steric repulsion, giving minimum steric hindrance. The new compounds were characterized by spectral (IR, ¹H NMR, ¹³C NMR, MS) and analytical methods. The new compounds were screened for cytotoxicity (MTT assay) as well as genotoxicity (Comet assay) studies against different cancer cell lines, during which the new compounds depicted potential anticancer behaviour.

Introduction

Heterocycles have been accredited with a great amount of attention over the years by medicinal chemists for drug discovery. The interesting structural and stereochemical features of the heterocyclic compounds provide additional fascination to the researchers and thereby alterations in the skeleton have been envisaged to discover new chemical entities with a potential to afford some promising drugs of the future. The incorporation of a heterocyclic ring like thiazolidinone, thiazole or a heteroatom in the heterocyclic backbone affects the chemical properties of a heterocycle and often results in useful alterations in its biological activities [1]. Therefore, researchers are on a continuous pursuit to design and produce better heterocyclic derivatives, by following natural models. The discovery of several biologically active heterocyclic derivatives with their wide applications in therapy has also brought about an interesting interest [1]. Thiazolidinones which is an important class of heterocyclic compounds are classified as doubly unsaturated five membered heterocyclic compounds contain one nitrogen, one sulphur and three carbon atoms including a carbonyl group. Thiazolidinones have been reported to show versatile pharmacological activities. They have been reported as COX-1 inhibitor [2], anti-inflammatory [3], antiproliferative [4,5], antihistaminic [6], anti-HIV [7,8], hypnotic [9], anaesthetic [10], antifungal [11], anthelmintic [12] and antiviral [13] agents as well as CNS [14] stimulants. 4-thiazolidinones and their derivatives [15] exhibit unusually high

activity against Mycobacterium tuberculosis. Recently, a number of 4-thiazolidinones derivatives found to exhibit highly potent and selective anti-Platelet activating factor activity both *in vitro* and *in vivo* [16]. 2-Arylimino-4-thiazolidinone derivatives have also showed antibacterial [17,18], antifungal [19] and anticonvulsant activities [20,21]. Keeping in view the applications of heterocycles and in continuation of previous work [22] we herein report the synthesis and anticancer studies of aromatic appended thiazolidinone derivatives.

Experimental

Chemistry

All the melting points were determined in degrees Celsius on a Kofler apparatus and are uncorrected. The IR spectra were recorded on KBr pellets with Perkin Elmer RXI Spectrophotometer and values are given in cm^{-1} . ¹H and ¹³C NMR spectra were run in CDCl_3 on a JEOL Eclipse (400 MHz) instrument with TMS as internal standard and values are given in ppm (δ). Mass spectra were recorded on a JEOL SX 102/DA-6000 Mass Spectrometer. Thin layer chromatography (TLC) plates were coated with silica gel G and exposed to iodine vapors to check the homogeneity as well as the progress of reaction. Petroleum ether refers to a fraction of boiling point 60-80°C. Sodium sulfate (anhydrous) was used as a drying agent. All the chemicals were purchased from Merck India and were used after distillation.

General method of synthesis of 3-amino-2-methyl-2-phenyl thiazolidinone [5-8]

Acetophenone and its derivatives [5-8] (1 mmol), hydrazine hydrate (1 mmol), mercaptoacetic acid (3.0 mmol) and few drops of conc. HCl were reflux in ethanol for 5 h. The progress and completion of the reaction was monitored by TLC. After completion of reaction, the excess solvent was reduced to three fourths of the original volume under reduced pressure. The reaction mixture was then taken in ether, washed with water and dried over anhydrous sodium sulfate. Evaporation of solvents and crystallization from methanol afforded the corresponding thiazolidinones [5-8].

3-Amino-2-methyl-2-phenyl thiazolidin-4-one [5]

Yield (68%); Mp: 149 °C; Anal. Calcd for $C_{10}H_{12}N_2O_2S$: C, 57.67; H, 5.81; N, 13.45; found; C, 57.57, H, 5.71, N, 13.34; IR (KBr) ν cm^{-1} 3215 (NH₂), 1645 (C=O), 1229 (C-N), 647 (C-S); ¹H NMR (CDCl₃, 500 MHz) δ 7.35 (s, 1H, NH₂, exchangeable with D₂O), δ 4.2 (s, 3H, CH₃), 3.36 (s, 2H, CH₂), 6.4-6.9 (m, 5H, aromatic); ¹³C NMR (CDCl₃, 125 MHz) δ 173 (C=O), 121-130 (6C, aromatic), 48 (C-N), 38 (CH₂). MS (EI): (m/z) 208 [M⁺].

3-Amino-2-methyl-2-(3'-hydroxyl) phenyl thiazolidin-4-one [6]

Yield (71%); Mp: 154 °C; Anal. Calcd for $C_{10}H_{12}N_2O_2S$: C, 57.67; H, 5.81; N, 13.45; found; C, 57.57, H, 5.71, N, 13.34; IR (KBr) ν cm^{-1} 3358 (OH), 3218 (NH₂), 1678 (C=O), 1234 (C-N), 1080 (C-O), 680 (C-S); ¹H NMR (CDCl₃, 500 MHz) δ 8.2 (s, 1H, OH, exchangeable with D₂O), δ 7.5 (s, 1H, NH₂, exchangeable with D₂O), δ 4.2 (s, 3H, CH₃), 3.38 (s, 2H, CH₂), 6.4-6.6 (m, 4H, aromatic); ¹³C NMR (CDCl₃, 125 MHz) δ 176 (C=O), 121-134 (6C, aromatic), 49 (C-N), 40 (CH₂); MS (EI): (m/z) 224 [M⁺].

3-Amino-2-methyl-2-(4'-hydroxyl) phenyl thiazolidin-4-one [7]

Yield (71%); Mp: 155 °C; Anal. Calcd for $C_{10}H_{12}N_2O_2S$: C, 57.67; H, 5.81; N, 13.45; found; C, 57.57, H, 5.71, N, 13.34; IR (KBr) ν cm^{-1} 3336 (OH), 3220 (NH₂), 1671 (C=O), 1229 (C-N), 1080 (C-O), 667 (C-S); ¹H NMR (CDCl₃, 500 MHz) δ 8.0 (s, 1H, OH, exchangeable with D₂O), δ 7.3 (s, 1H, NH₂, exchangeable with D₂O), δ 4.2 (s, 3H, CH₃), 3.35 (s, 2H, CH₂), 6.1-6.3 (m, 4H, aromatic); ¹³C NMR (CDCl₃, 125 MHz) δ 172 (C=O), 121-129 (6C, aromatic), 47 (C-N), 44 (CH₂); MS (EI): (m/z) 224 [M⁺].

3-Amino-2-methyl-2-(2', 4'-dihydroxyl) phenyl thiazolidinone [8]

Yield (71%); Mp: 160 °C; Anal. Calcd for $C_{10}H_{12}N_2O_3S$: C, 49.99; H, 5.03; N, 11.66; found; C, 49.80, H, 5.00, N, 11.47; IR (KBr) ν cm^{-1} 3321, 3318 (OH), 3236 (NH₂), 1679 (C=O), 1229 (C-N), 1080 (C-O), 667 (C-S); ¹H NMR (CDCl₃, 500 MHz) δ 8.2, 8.0 (s, 1H, 2×OH, exchangeable with D₂O), δ 7.5 (s, 1H, NH₂, exchangeable with D₂O), δ 4.2 (s, 3H, CH₃), 3.44 (s, 2H, CH₂), 6.2-6.4 (m, 3H, aromatic); ¹³C NMR (CDCl₃, 125 MHz) δ 174 (C=O), 121-131 (6C, aromatic), 50 (C-N), 43 (CH₂); MS (EI): (m/z) 240 [M⁺].

Anticancer activity

Cell Lines and Culture Conditions: Human cancer cell lines used for the study were A545 (lung carcinoma cells)/ATCC (CRL-2579), MCF7 (breast cancer cells)/ATCC (HTB-22), HeLa (cervical cancer cells)/ATCC (CCL-2), HL-60 (Leukaemia cells)/ATCC (CCL-240), SW480 (colon adenocarcinoma cells)/ATCC (CCL-228), HepG2 (hepatic carcinoma cells)/ATCC (CRL-8065), HT-29 (colon cancer cells)/ATCC (HTB-38), DU145 (pancreatic cancer cells)/ATCC (HTB-81) and A549 (lung carcinoma cells)/ATCC (CCL-185) were obtained from National Cancer Institute (NCI), biological testing branch, Frederick Research and Development Centre, USA. SW480, A549, A545, HL-60, HT29, DU145 and HepG2 cells were grown in RPMI-1640 182 supplemented with 10% fetal bovine serum (FBS), 10U penicillin and 100µg/mL streptomycin at 37 °C with 5% CO₂ in a humidified atmosphere. HeLa and MCF7 cells were grown in Dulbecco's modified Eagle's medium (DMEM) 183 supplanted with FCS and antibiotics as described above for RPMI 1640. The non-cancer cells i.e. 184B5 and MCF10A breast cells were maintained in mammary epithelial basal medium supplemented with an MEGM mammary epithelial singlequot kit (Cambrex). NL-20 (normal lung cells), HPC (normal pulp cells), HPLF (periodontal ligament fibroblasts) were grown at 37 °C with 5% CO₂, 95% air under the humidified conditions. Fresh medium was given every second day and on the day before the experiments were done. Cells were passaged at preconfluent densities, using a solution containing 0.05% trypsin and 0.5 mM EDTA.

Cell Viability Assay (MTT): The in vitro cytotoxicity was measured using the MTT assay. The assay was carried out according to known protocol [23]. Exponentially growing cells were harvested and plated in 96-well plates at a concentration of 1×10^4 cells/well. After 24 h incubation at 37 °C under a humidified 5% CO₂ to allow cell attachment, the cells in the wells were respectively treated with target compounds at various concentrations for 48h. The concentration of DMSO was always kept below 1.25%, which was found to be non-toxic to the cells. A solution of 3-(4, 5-dimethylthiazolo-2-y1)-2, 5-diphenyltetrazolium bromide (MTT), was prepared at 5 mg/mL in phosphate buffered saline (PBS; 1.5 mM KH₂PO₄, 6.5 mM Na₂HPO₄, 137 mM NaCl, 2.7 mM KCl; pH 7.4) and 20 µL of this solution was added to each well. After incubation for 4 h at 37 °C in a humidified incubator with 5% CO₂, the medium/MTT mixtures were removed and the formazan crystals formed by the mitochondrial dehydrogenase activity of vital cells were dissolved in 100 µL of DMSO per well. The absorbance of the wells was read with a microplate reader (Bio-Rad Instruments) at 570 nm. Effects of the drug cell viability were calculated using cell treated with DMSO as control.

Data Analysis: Cell survival was calculated using the formula: Survival (%) = [(absorbance of treated cells - absorbance of culture medium) / (absorbance of untreated cells - absorbance of culture medium)] × 100 [24]. The experiments were done in triplicate and the inhibitory concentration (IC) values were calculated from a dose response curve. IC₅₀ is the concentration in 'µM' required

for 50% inhibition of cell growth as compared to that of control. IC_{50} values were determined from the linear portion of the curve by calculating the concentration of agent that reduced absorbance in treated cells, compared to control cells by 50%. Evaluation is based on mean values from three independent experiments, each comprising at least six micro-cultures per concentration level.

Comet Assay (Single Cell Gel Electrophoresis)

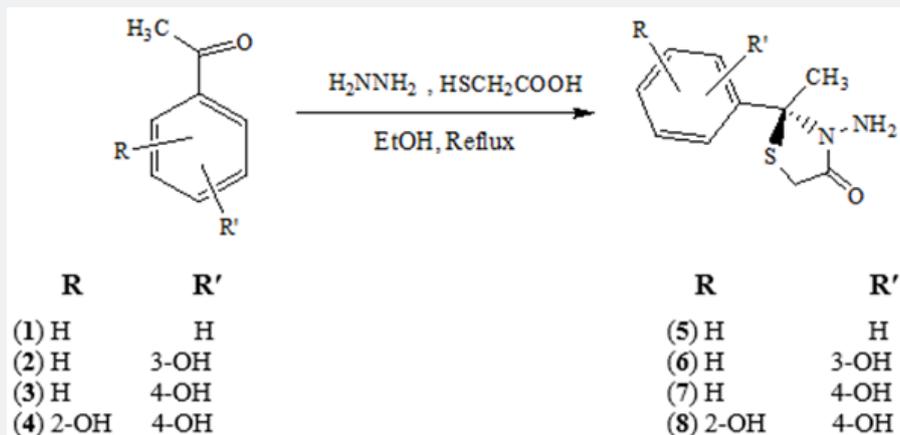
To assess the genotoxic effect of the new steroidal derivatives, comet assay [25] was performed in MCF7 cells. The MCF7 (1×10^6) cells were treated with 10, 25 and 50 $\mu\text{g}/\text{mL}$ of steroidal derivatives for 24h. The cells were then washed and 200 μL of cell suspension in low melting agarose (LMA) was layered on to the labelled slides precoated with agarose (1.5%). The slides were placed on ice for 10 min. and submerged in lysis buffer (2.5% NaCl, 100 mM EDTA, 10 mM Tris, 10% DMSO and 1% Troton X-100) at 4°C at pH 10 for more than 1 h. The slides were then equilibrated in alkaline buffer (30 mM NaOH, 1 mM EDTA) at 4°C at pH 13, electrophoresed at 0.86 V/cm at 4°C, neutralized, washed and dried. At the time of capturing the images, the slides were stained with ethidium bromide (EtBr, 150 μL 1X) and cover slips were placed over

them. For visualization of DNA-damage, EtBr-stained slides were observed under 209 objectives of a fluorescent microscope (Olympus BX-51, Japan). The images of 50-100 randomly selected cells were captured per slide using a CCD camera.

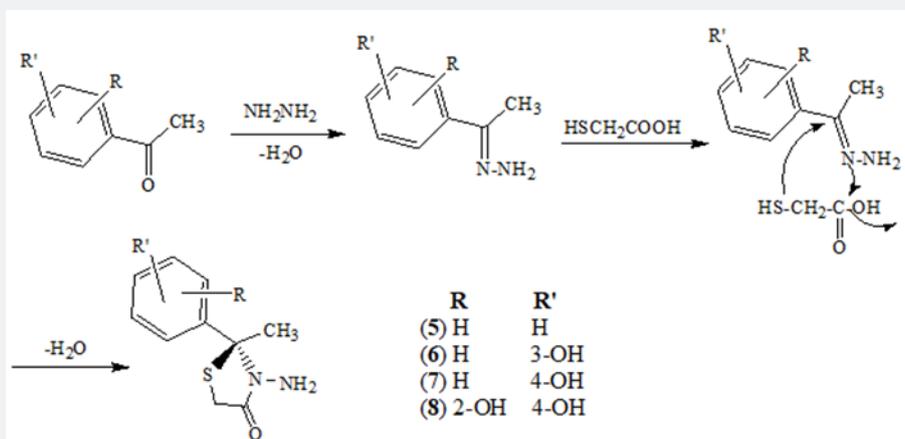
Result and Discussion

Chemistry

Development of highly functional molecules from simple building blocks has always been the curiosity of synthetic chemists. So, we here in report the convenient route for the synthesis of new thiazolidinones [5-8] by reacting acetophenone and its derivatives [1-4] with hydrazine and mercaptoacetic acid in absolute ethanol for the period of about 5 h under reflux conditions (Scheme 1) and on the completion of reaction, products were obtained in better yields (68-71%). The tentative mechanism for the formation of thiazolidinones [5-8] has been proposed in scheme 2. The mechanism depicts clearly the formation of hydrazone in situ first by simple condensation which later undergo cyclization with mercaptoacetic acid hence leads to the formation of the products [5-8]. The structures of these compounds were characterized by spectral (IR, ^1H NMR, ^{13}C NMR, MS) and analytical methods.



Scheme 1: Schematic representation for the formation of thiazolidinones[5-8].



Scheme 2: Proposed mechanism of formation 3-amino-2-methyl-2-phenyl thiazolidin-4-one derivatives [5-8].

Stereochemistry

The stereoselectivity of these thiazolidinones can be explained by considering that there is a considerable amount of steric hindrance to ring-closure from one side of the ring at Carbonyl carbon which might be explained on the basis that the sulfur atom is bulkier than nitrogen during cyclization. Thus, the thiazolidinone ring closes at carbonyl carbon, by the attack of sulfur of mercaptoacetic acid moiety, preferentially from the front (β , axial) so that the nitrogen has an equatorial orientation (α , equatorial) to avoid steric repulsion, giving minimum steric hindrance and maximum stability. This is further supported by the fact that during cyclization the nitrogen already attached to carbonyl carbon is moved towards the back (α , equatorial) side to reduce the steric hindrance, and leaving the front (β , axial) side for the attack of nucleophile to close the thiazolidinone ring. Therefore, the only product of this reaction with R stereochemistry was selectively obtained. The dreiding models also suggest the attack of sulfur from the β -side which pushes the nitrogen to the less hindered α -side. Hence the formulation of the compound as R is preferred over its isomer S.

The characterization studies showed good agreement with proposed structures of thiazolidinones [26], [5-8] (Scheme 1). In their IR spectra the presence of absorption bands in the range 3215-3236 cm^{-1} shows the presence of NH_2 while as the absorption bands at 1645-1679, 1620-1625 and 3318-3358 cm^{-1} confirm the presence of C=O & CH=CH (arom.) and OH groups, respectively in the compounds [5-8]. The presence of bands at 1229-1234 and 647-680 cm^{-1} were ascribed to C-N and C-S groups, respectively. In ^1H NMR study of the compounds [5-8], the three downfield singlets at δ 8.2-8.0, 7.3-7.5, 4.2 were ascribed to OH, NH_2 and CH_3 while as the presence of broad multiplet at δ 6.1-6.9 revealed the presence of aromatic protons. The presence of two proton singlet at δ 3.36-3.44 was ascribed to two methylene protons in ^{13}C NMR study,

the signals at δ 172-176, 121-131, 47-50 and 38-44 confirm the presence of C=O, C=C (arom.), C-N and CH_2 groups respectively in the products [5-8]. Finally, the presence of distinct molecular ion peak [M^+] at m/z : 208, 224, 224 and 240 in the MS after following the nitrogen rule, also proved the formation of compounds [5-8]. The strategy can also be applied to diverse ketones, in that way thiazolidinones may also allow further modifications on the substituted heterocyclic systems [27,28].

Anticancer Activity

The cytotoxicity of thiazolidinones 5-8 (341-344) was studied by MTT assay [23]. The data reported in Table 1 suggest that compound 5-8 (341-344) showed different levels of cytotoxicity. During the screening, the potential behaviour was depicted by the compounds against given cancer cells. The compound 6 showed $\text{IC}_{50} = 9.63\mu\text{mol L}^{-1}$ (HT-29), $9.73\mu\text{mol L}^{-1}$ (MCF7), $11.45\mu\text{mol L}^{-1}$ (A549). Compound 7 also depicted minimum IC_{50} value in the range of $12.79\mu\text{mol L}^{-1}$ (HT-29) and $10.60\mu\text{mol L}^{-1}$ (MCF7) while compound 5 showed minimum $\text{IC}_{50}=9.11\mu\text{mol L}^{-1}$ (A545) and $15.26\mu\text{mol L}^{-1}$ (HepG2) cell line. From the Table 1 it is clear that the IC_{50} for compound 6 against A549 and HeLa cells was found to be 11.45 and $11.72\mu\text{M L}^{-1}$ which is close to the IC_{50} of Cisplatin 12.0 and $9.43\mu\text{M L}^{-1}$, respectively against the same cells. IC_{50} for compound 6 against HeLa cell line was found to be $11.72\mu\text{M L}^{-1}$ which were also close to the IC_{50} of Cisplatin 9.43 against the same cell line. Similarly IC_{50} for compounds 5 and 6 against HepG2 was found to be 11.26 and $13.56\mu\text{M L}^{-1}$ which is also near to IC_{50} of Cisplatin 9.8 against same cell line. It can be concluded that compound 6 and 7 showed potential in vitro cytotoxicity against A549, HeLa, HepG2 and A545 cell lines by depicting IC_{50} close to that of Cisplatin, thus can be considered as potential cytotoxic agents. Compound 5-8 also showed marked cytotoxicity against HL-60 and HepG2 cell lines by showing IC_{50} less than standard drug, 5-fluorouracil.

Table 1: The IC_{50} of compounds [5-8] against cancer cells. 5-FU = 5-Fluorouracil.

Comp.	$\text{IC}_{50}(\mu\text{M L}^{-1})$							
	Lung A545	Breast MCF7	Cervical HeLa	Leukaemia HL-60	Colon SW480	Hepatic HepG2	Colon HT-29	Lung A549
5	9.11	27.39	15.13	>50	26.11	15.26	17.12	16.31
6	13.45	9.73	11.72	20.17	12.81	11.01	9.63	11.45
7	16.53	10.60	17.37	28.34	>50	24.37	12.79	20.64
8	17.24	21.33	14.22	>50	>50	13.56	14.87	22.31
Cisplatin	8.9	9.3	9.43	7.83	3.52	9.80	7.24	12.0
5-FU	15.4	15.3	16.32	>50	15.17	>50	9.79	12.8

Comet Assay

To understand the apoptotic degradation of DNA, the compound 5-8 were screened against MCF7 in comet assay. There was dose-dependent increase in the tail length when cells were treated with compound 5-8. Compound 6 presented maximum apoptotic DNA damage among the three thiazolidinone studied, which is in accordance with its maximum cytotoxicity as seen in

MTT assay. The quantified increase in DNA damage suggested that the thiazolidinone derivative 6 induced dose-dependent fragmentation of chromosomal DNA leading to apoptosis. The images of comet assay for control, cells treated with compound 5-8 ($50\mu\text{g/mL}$) are depicted in Figure 1. Slides were analysed for parameter like tail length (TL), using image analyzer CASP software version 1.2.2. The results of the assay for tail length are shown in Figure 2.

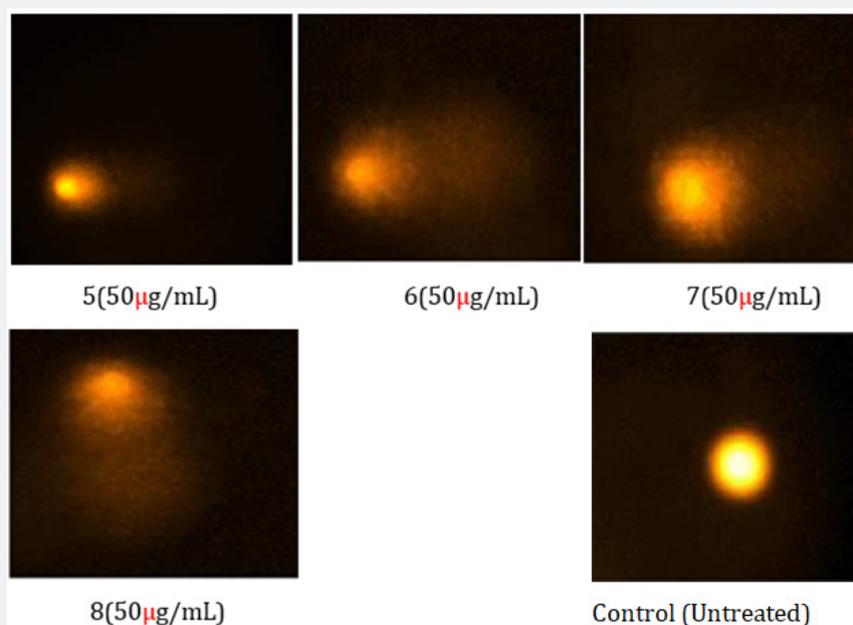


Figure 1: Detection of DNA damage in MCF7 cells. Treated cells (24h) were layered over agarose gel, lysed, electrophoresed in alkaline buffer and stained with propidium iodide.

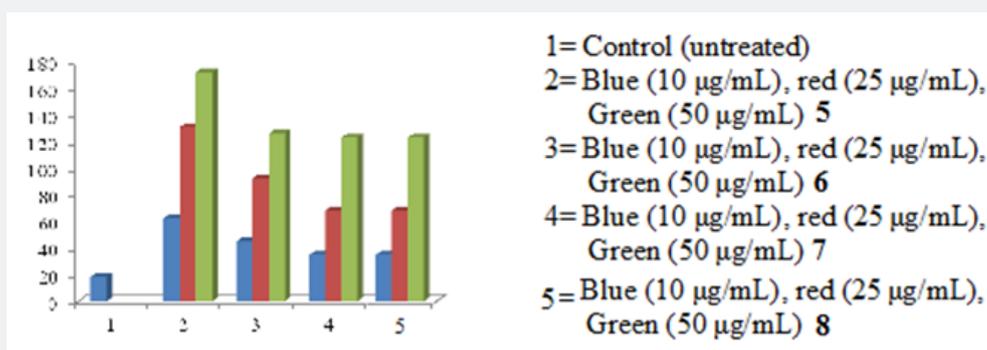


Figure 2: Comparing the effect of thiazolidinones (5-8) on the tail length in comet assay.

Conclusion

The operationally simple reaction for convenient synthesis of thiazolidinones was successfully developed. The reaction got completed in almost 5 h and on completion; potential yields were obtained. This strategy offered a very straight forward, one-pot and efficient method for access to new thiazolidinones. The compounds successfully revealed the cytotoxic and genotoxic behaviour against the different cancer cell lines. In conclusion, the present study showed that this one pot synthesized compounds can be used as a template for future development through modification and derivatization to design more potent and selective anticancer agents.

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