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Synthesis and *Invitro* Anti-Cancer Evaluation of Some Novel 2, 3 Disubstituted Thiazolidinones

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Abstract

Thiazolidinone and its derivatives have high pharmacological relevance since they are available in both natural products and Pharmaceutical compounds. The main synthetic routes to thiazolidinones comprising three components such as an amine, a carbonyl group and mercapto acid. The classical method of synthesis reported may be either a one-pot three-component condensation method or a two-step process. Synthesis and anticancer activity evaluation of thiazolidinones containing benzothiazole moiety. These compounds were screened for *in-vitro* anticancer activity. The activity data exhibits that all compounds were found to show potent anticancer activity. Various substituents at C-2 and C-3 of thiazolidinone results in potent anticancer activity. Prompted by these reports, we aimed to prepare the following series of 2, 3-disubstituted- Thiazolidinone derivatives as potent anticancer agents.

Key words: Thiazolidiones, amines, carbonyl group, mercapto acid, one pot three component condensation, anticancer, benzothiazole moiety, C-2 and C-3, 2,3 –disubstituted

1. INTRODUCTION

Thiazolidinones possess a wide spectrum of biological and pharmacological activity due to the presence of nitrogen and sulfur which is considered to be responsible for the structural features to impart their activities. Despite the optimal use of available anticancer drugs (ACDs), many patients fail to experience therapeutic efficacy and others do so only at the expense of significant toxic side effects. The limitations with the conventional ACDs highlighted the need for developing newer anti-cancer agents with new, less toxic and more effective drugs are required. Thiazolidinones are five membered ring system containing sulphur and nitrogen atom, received a much attention of medicinal chemists due to their potential biological activities. Various substituents' at C-2 and C-3 of thiazolidinone results in potent anticancer activity. Prompted by these reports, we aimed to prepare the following series of 2, 3-disubstituted- Thiazolidinone derivatives as potent anticancer agents.

Hence the specific aims and objectives of the present study are,

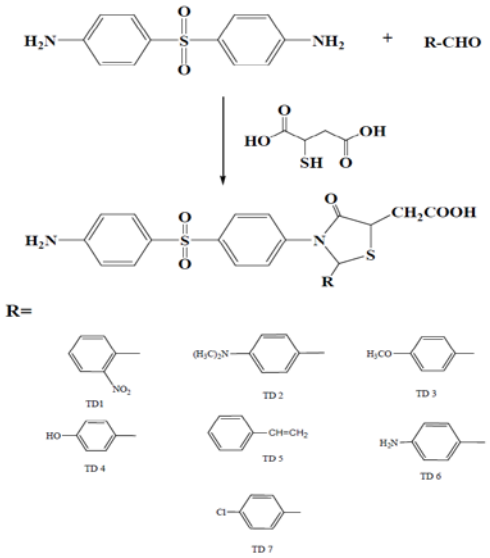
- To synthesize a series of novel 2, 3-disubstituted thiazolidinones.
- To characterize the synthesized compounds by IR, NMR, Mass spectra and elemental analysis.
- To evaluate the test compounds for anti-cancer activity by using human cervical cancer cell line (HeLa) by MTT assay method.

The title compounds are planned to synthesize by using the following synthetic routes mentioned in the following Schemes.

Scheme

Synthesis of 2-(3- (4- (4-aminophenylsulfonyl) phenyl)-2-(2-phenylsubstituted)-4 oxothiazolidin-5-yl) acetic acid **(TD1-7).**

SCHEME



Materials and methods

Melting points (mp) were taken in open capillaries on Thomas Hoover melting point apparatus and are uncorrected. The IR spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrometer. The 1H spectra were recorded on a DPX-500 MHz Bruker FT-NMR spectrometer. The chemical shifts were reported as parts per million (δ ppm) tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin-Elmer 2400 C, H, N analyzer and values were within the acceptable limits of the calculated values. The progress of the reaction was monitored on readymade silica gel plates (Merck) using chloroform-methanol (9:1) as a solvent system. Iodine was used as a developing agent. Spectral data (IR, NMR and mass spectra) confirmed the structures of the synthesized

compounds and the purity of these compounds was ascertained by micro analysis. Elemental (C,H,N) analysis indicated that the calculated and observed values were within the acceptable limits (± 0.4%). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (UK) or Spectrochem Pvt.Ltd (India) and were used without further purification.

General procedure for synthesis of 2-(5-amino-1,3,4-thiadiazol-2-yl)phenol (TD1-7)

4-(4-aminophenylsulfonyl) benzenamine (2.48gm) (0.01mol) and substituted benzaldehydes (1.47gm) (0.01mol) were dissolved in alcohol (30ml) in a 250ml round bottom flask. To this concentrated sulphuric acid (0.5ml) and dry dioxane (12ml) was added with constant stirring. To this mixture, 2-mercapto succinic acid (1.5 gm) (0.01mol) in 12ml of dry dioxane was added slowly and refluxed for 3 hr at 800C with occasional shaking. The reaction completion was monitored by thin layer chromatography. The solid mass separated was poured in to ice cold water and filtered. The solid was neutralized with one percent sodium carbonate solution, filtered and dried. The residue was recrystallized from methanol.

1. Synthesis of 3-(4-(4-aminophenylsulfonyl) phenyl)-2-(2-nitrophenyl)-4- oxothiazolidin-5-yl) acetic acid (TD1)

Yield	: 2.86 g; 81.0 %
Melting Point	: 216-218 °C
Rf Value	: 0.85 (benzene : ethylacetate(8:2))
Molecular Formula	: $C_{23}H_{19}N_3O_7S_2$
Molecular Weight	: 513(M+)
IR (KBr) cm^{-1}	: 3520 (OH), 3290 (NH_2), 3045 (Ar-CH), NO_2 (1534),1620 (C=N Str), SO_2(688) 675 (C-S-C).
^1H NMR ($CDCl_3$) δ ppm	:^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 1H, CH_2), 3.80 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H, Ar-H), 7.27-7.95 (m, *J =8.0Hz*, 8H, Ar-H).
Elemental Analysis	
Calculated	: C, 53.79; H, 3.73; N, 8.18.
Found	: C, 53.76; H, 3.71; N, 8.17.

2. Synthesis of 3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-(dimethylamino)phenyl)-4- oxothiazolidin-5-yl)acetic acid (TD 2).

Yield	: 2.86 g; 81.0 %
Melting Point	: 216-218 °C
Rf Value	: 0.85 (benzene : ethylacetate(8:2))
Molecular Formula	: $C_{23}H_{19}N_3O_7S_2$
Molecular Weight	: 513(M+)
IR (KBr) cm^{-1}	: 3520 (OH), 3290 (NH_2), 3045 (Ar-CH), NO_2 (1534),1620 (C=N Str), SO_2(688) 675 (C-S-C).
^1H NMR ($CDCl_3$) δ ppm	:^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 1H, CH_2), 3.80 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H, Ar-H), 7.27-7.95 (m, *J =8.0Hz*, 8H, Ar-H).
Elemental Analysis	
Calculated	: C, 53.79; H, 3.73; N, 8.18.
Found	: C, 53.76; H, 3.71; N, 8.17.

3. Synthesis of 3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-methoxyphenyl)-4- oxothiazolidin-5-yl) acetic acid (TD 3).

Yield	: 2.90 g; 89.0 %
Melting Point	: 245-247 °C
Rf Value	: 0.72 (benzene:ethylacetate(8:2))
Molecular Formula	: $C_{25}H_{25}N_3O_5S_2$
Molecular Weight	: 511(M+)
IR (KBr) cm^{-1}	: 3516 (OH), 3290 (NH_2), 3045 (Ar-CH), 1710 (C=O),1622 (C=NStr), 676 (C-S-C),1289 ($N(CH3)_2$),(1191)SO_2.
^1H NMR ($CDCl_3$) δ ppm	:^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 2H, CH_2), 2.85 (d, 6H,$(CH_3)_2$,3.80 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H, Ar- H), 7.27 (d, *J =7.5Hz*, 2H, Ar-H), 7.65 (d, *J = 7.0 Hz*, 2H, Ar-H), 7.95 (d, *J = 7.0 Hz*, 2H, Ar-H).
Elemental Analysis	
Calculated	: C, 58.69; H, 4.93; N, 8.21.
Found	: C, 58.67; H, 4.91; N, 8.20.

4. Synthesis of (3-(4-(4-aminophenylsulfonyl) phenyl)-2-(4-hydroxyphenyl)-4- oxothiazolidin-5-yl) acetic acid (TD 4).

Yield	: 2.68 g; 79.0 %
Melting Point	: 227-229 °C
Rf Value	: 0.78 (benzene:ethylacetate(8:2))
Molecular Formula	: $C_{24}H_{22}N_2O_6S_2$
Molecular Weight	: 498(M+)
IR (KBr) cm^{-1}	: 3516 (OH), 3290 (NH_2), 3045 (Ar-CH), 1622 (C=N Str), 676 (C-S-C), 2816 (OCH_3),
^1H NMR ($CDCl_3$) δ ppm	:^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 2H, CH_2), 3.73(s, 3H, CH_3),3.80 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H, Ar- H), 7.27 (d, *J =7.5Hz*, 2H, Ar-H), 7.65 (d, *J = 7.0 Hz*, 2H, Ar-H), 7.95 (d, *J = 7.0 Hz*, 2H, Ar-H).
Elemental Analysis	
Calculated	: C, 57.82; H, 4.45; N, 5.62.
Found	: C, 57.80; H, 4.45; N, 5.61

5. Synthesis of (3-(4-(4-aminophenylsulfonyl)phenyl)-4-oxo-2-styrylthiazolidin-5-yl) acetic acid (TD 5).

Yield	: 2.47 g; 81.0 %
Melting Point	: 197-199 °C
Rf Value	: 0.76 (benzene: ethyl acetate(8:2))
Molecular Formula	: $C_{23}H_{20}N_2O_6S_2$
Molecular Weight	: 484(M+)
IR (KBr) cm^{-1}	: 3522 (OH, broad), 3287 (NH_2), 3045 (Ar-CH), 16 (C=N Str), 675 (C-S-C).
^1H NMR ($CDCl_3$) δ ppm	:^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 2H, CH_2 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H (d, *J =7.5Hz*, 2H, Ar-H), 7.65 (d, *J = 7.0 Hz*, 2H, *J = 7.0 Hz*, 2H, Ar-H), 11.0(s, 1H, OH).
Elemental Analysis	
Calculated	: C, 57.01; H, 4.16; N, 5.78
Found	: C, 57.00; H, 4.15; N, 5.77

6. **Synthesis of (3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-aminophenyl)-4- oxothiazolidin-5-yl)acetic acid (TD 6).**

Yield	: 2.12 g; 64.0 %
Melting Point	: 245-247 °C
Rf Value	: 0.64 (benzene: ethyl acetate(8:2))
Molecular Formula	: $C_{25}H_{22}N_2O5S_2$
Molecular Weight	: 494(M+)
IR (KBr) cm^{-1}	: 3508 (OH), 3286 (NH_2), 3048 (Ar-CH), 1618 (C=N Str), 674 (C-S-C),(1510) CH=CH.
^1H NMR ($CDCl_3$) δ ppm	:^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 2H, CH_2), 3.80 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H, Ar- H), 7.21 (d, *J =7.5Hz*, 2H, Ar-H), 7.27 (d, *J =7.5Hz*, 2H, Ar-H), 7.30 (d, *J =7.5Hz*, 2H, Ar-H), 7.65 (d, *J = 7.0 Hz*, 2H, Ar-H), 7.95 (d, *J = 7.0 Hz*, 2H, Ar-H), 10.2(s, 1H, OH).
Elemental Analysis	
Calculated	: C, 60.71; H, 4.48; N, 5.66
Found	: C, 60.69; H, 4.47; N, 5.65

7. Synthesis of (3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-chlorophenyl)-4- oxothiazolidin-5-yl) acetic acid (TD 7).

Yield	: 2.32 g; 76.0 %
Melting Point	: 187-189 °C
Rf Value	: 0.72 (benzene: ethyl acetate(8:2))
Molecular Formula	: $C_{23}H_{21}N_3O_5S_2$
Molecular Weight	: 483(M+)
IR (KBr) cm^{-1}	: 3310 (NH_2, broad), 3042 (Ar-CH), 1619 (C=N Str), 672 (C-S-C).
^1H NMR ($CDCl_3$) δ ppm	:^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 2H, CH_2), 3.80 (d,1H,CH),4.08(d ,2H, NH_2), 6.34 (2, *J = 8.0 Hz*, 2H, Ar- H), 6.63 (d, *J = 8.0 Hz*, 2H, Ar- H), 7.27 (d, *J =7.5Hz*, 2H, Ar-H), 77.65 (d, *J = 7.0 Hz*, 2H, Ar-H), 7.95 (d, *J = 7.0 Hz*, 2H, Ar-H), 10.3(s, 1H, OH).
Elemental Analysis	
Calculated	: C, 57.13; H, 4.38; N, 8.69
Found	: C, 57.11; H, 4.37; N, 8.68

Chromatography Studies Of Synthesized Compounds

Thin Layer Chromatography

Thin Layer Chromatography or TLC is a solid-liquid form of chromatography here the stationary phase is a polar absorbent and the mobile phase can be a single solvent or Combination of solvents. TLC is in expensive technique and quick that can be used for determine the number of components in a mixture, verify a substance's identity, monitor the process of a reaction, determine appropriate condition for column chromatography, analyze the fractions obtained from column chromatography.

MATERIALS AND METHODS

1. Preparation of plates

Silicagel G was mixed in a glass mortar to smooth consistency with the requisite amount of water and slurry was quickly transferred to hespreader. The mixtures have been spread over the plates in thickness of 0.2mm and allow setting in to a suitable holder and after 30 minutes; plates were dried at 120^{o}C, for further activation of the absorbent.

2. Sample application

About 2 mm of absorbent from the edge of plate was removed to gives sharply defined edges. 2-5µl volumes of synthesized compounds were spotted with the help of capillary tubes, just above 1cm of the bottom of coated plates.

3. Development chamber

The chromatographic chamber was lined with filter paper dipping in to mobile phase so as to maintain the atmospheric saturation with solvent vapors in the chamber. The solvent front was allowed to rise to distance of about 12cm from the baseline on the plate was removed from the tank and allowed to dry in the air.

4. Solvent system

The choice of best developing solvent is one of the most important decisions in practical TLC by review of literature survey on by knowing nature of compounds, this solvent system used is benzene: ethyl acetate (8:2).

5. Detection of components

The spots were visualized under Iodine chamber.

Column Chromatography

Purification of synthesized derivatives was done by column chromatography.

Materials

1. Glass column of size 45cm x 3cm.
2. Silicagel for column chromatography 60-120 mesh size.
3. Eluting solvent system benzene :ethylacetate (8:2).

Preparation of column

The silica gel 60-120 mesh size was made in to slurry with the above solvent system. The bottom of the column was plugged with little glass wool. Then the slurry was poured in to the column, which is filled with solvent after two third of the column areas were filled with slurry. It was set aside for 30 minutes and eluting solvent was passed through column for several time ensure good packing of the column. After the adsorbents are settled, a filter paper was kept to prevent disturbance of the two player of the adsorbent as fresh mobile phase to be added to column for the process of elution. The fractions were collected for every 5m land analyzed for the presence of different of similar compound by running TLC and then allow evaporating to get the residue.

Pharmacological Screening

***In-Vitro* Anti-Cancer Activity**

Tissue culture has been used to screen may anti-cancer drugs since there is clear correlation between the in vitro and in vivo activities of potential chemotherapeutic agents. There is scientific justification for cytotoxicity testing in tissue, since animal models are in many ways in adequate for predicting the effects of chemicals on humans since there are many metabolic differences between species61-63. Cytotoxicity studies involve the analysis of morphological damage or inhibition of zone of outgrowth induced by the chemicals tested.

Assay For Proliferation Studies

In Vitro Anti Cancer Activity

The human cervical cancer cell line (HeLa) was obtained from national center for cell science (NCCS) pune. The HeLa cells were grown in Eagles Minimum Essential Medium containing 10% fetal bovine serum (FBS) and maintained at 37°C, 5% CO_2, 95% air and 100% relative humidity. Maintenance cultures were passaged weekly, and the culture medium was changed twice a week. Toxicity of test compound in cells was determined by MTT assay based on mitochondrial reduction of yellow MTT tetrazolium dye to a highly colored blueormazan product.

Assay for Proliferation Studies - MTT Assay

Principle

MTT [(3-(4,5-dimethyl thiazol-2yl)-2,5diphenyl tetrazolium bromide] measures the metabolic activity of the viable cells. The assay can be performed entirely in a microtiterplate (MTP). It is suitable for measuring cell proliferation, Cell viability or Cytotoxicity. The reaction between MTT and mitochondrial dehydrogenase produces water-insoluble formazan salt. This method involves culturing the cells in a 96 well microtiterplate and then incubating with MTT solution for approximately 2 hours. During incubation period, viable cells convert MTT to a water insoluble formazan dye. The formazan dye in the MTP is solubilized and quantified with an ELISA plate reader. The absorbance directly correlates with the cell number. This is applicable for adherent cells cultured in MTP.

Materials for MTT assay

- The human cervical cancer cell line (**HeLa**) Eagles Minimum Essential Medium containing 10% fetal bovine serum (FBS).
- Phosphate buffered saline (PBS)
- Dimethyl sulphoxide (DMSO)
- MTT [(3-(4,5-dimethylthiazol-2yl)-2,5 di phenyl tetrazolium bromide] CO2 incubator (WTC Binder, Germany)
- Laminar air flow cabin (Klenzaids, Chennai, India).
- Refrigerated centrifuge (Biofuge fresco, Heraeus, Germany).
- ELISA-reader (For MTP) Anthos 2010, Germany).
- Deep freezer (Polar Angelantioni Industries, Italy).
- Ultrazonic bath (Transonic [460/H], by Elma, Germany].
- Vaccum pump (Zenith [model: PDF-2-2.5], Mumbai, India).
- Pipettes (Eppendoff, Hamburg, Germany).

- Culture plates
- Centrifuge tubes
- Aerosol resistant tips
- Flat-bottomed 96-MTP
- Tissue culture grade

Cell treatment procedure

Cell treatment procedure the monolayer cells were detached with trypsin-ethylene diamine tetraacetic acid (EDTA) to make single cell suspensions and viable cells were counted using a hemocytometer and diluted with medium with 5% FBS to give final density of 1x105 cells/ml. one hundred microlitres per well of cell suspension were seeded into 96-well plates at plating density of 10,000 cells/well and incubated to allow for cell attachment at 37^0C, 5% CO_2, 95% air and 100% relative humidity.

After 24 h the cells were treated with serial concentrations of the extracts and fractions. They were initially dissolved in neat dimethylsulfoxide (DMSO) and further diluted in serum free medium to produce five concentrations. One hundred microlitres per well of each concentration was added to plates to obtain final concentrations of 100, 10, 1.0 and 0.1 µM. The final volume in each well was 200 µl and the plates were incubated at 37^0 C, 5% CO_2, 95% air and 100% relative humidity for 48h. The medium containing without samples were served as control. Triplicate was maintained for all concentrations.

Procedure

***In-vitro* anticancer screening**

The human cervical cancer cell line (**HeLa**) was obtained from National Centre for Cell Science (NCCS), Pune. The cells were grown in Eagles Minimum Essential Medium containing 10% fetal bovine serum (FBS).

For screening experiment, the cells were seeded into 96-well plates in 100µl of medium containing 5 % FBS, at plating density of 10,000 cells/well and incubated at 37 ^{0}C, 5 % CO_2, 95 % air and 100 % relative humidity for 24 hours prior to addition of samples. The samples were solubilized in Dimethylsulfoxide and diluted in serum free medium. After 24 hours, 100 µl of the medium containing the samples at various concentration (eg; 0.063, 0.125, 0.25, 0.5, 1.0 mM etc…) was added and incubated at 37^0C, 5% CO_2, 95% air and 100% relative humidity for 48 hours. Triplicate was maintained and the medium containing without samples were served as control.

After 48 hours, 15µl of MTT (5mg/ml) in phosphate buffered saline (PBS) was added to each well and incubated at 37 0C for 4 hours. The medium with MTT was then flicked off and the formed formazan crystals were solubilized in 100µl of DMSO and then measured the absorbance at 570 nm using micro plate reader. The % cell inhibition was determined using the following formula

% cell Inhibition= 100 – {(sample) / Abs (control)}× 100.

Invitro Cytotoxicity Studies on Human Cervical Cancer Cell line (HeLa)

PERCENTAGE OF CELLINHIBITION

Table No.2.

Compounds	Concentration	% Cell Inhibition	Compounds	Concentration	% Cell Inhibition
TD1	0.1 µM	1.5342	TD5	0.1 µM	1.4112
	1 µM	12.9079		1 µM	13.7176
	10 µM	30.9861		10 µM	23.8976
	100 µM	**62.8578**		100 µM	**51.3006**
TD2	0.1µM	1.0424	TD6	0.1µM	1.1895
	1µM	10.4447		1 µM	12.2646
	10 µM	22.9848		10 µM	23.6772
	100 µM	**52.8995**		100 µM	**55.0587**
TD3	0.1µM	1.4579	TD7	0.1 µM	1.3342
	1µM	11.0145		1 µM	14.6079
	10 µM	28.2358		10 µM	33.8761
	100 µM	**70.1268**		100 µM	**74.8578**
TD4	0.1 µM	1.4824			
	1 µM	11.6447			
	10 µM	29.9848			
	100 µM	**72.8995**			

Nonlinear regression graph was plotted between % Cell inhibition and Log10 concentration and IC50 was determined using GraphPad Prism software.

Statistical Analysis

All values are expressed as mean ± SEM. Data were analyzed by non-parametric ANOVA followed by Dunnett's multiple comparison tests, and other data was evaluated using Graph Pad PRISM software. A *p*-value < 0.05 was considered significantly different

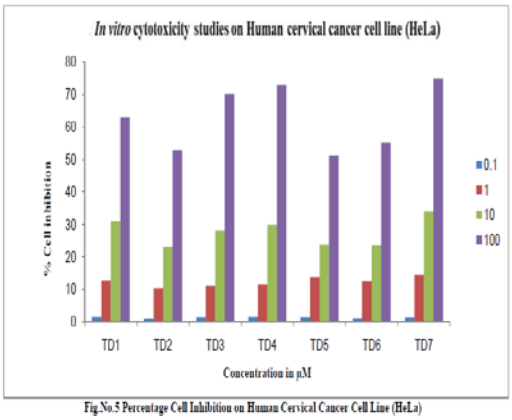
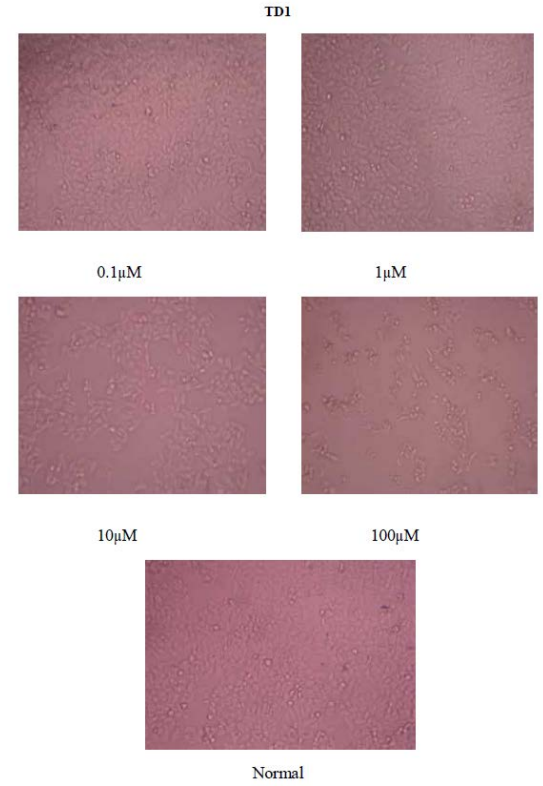
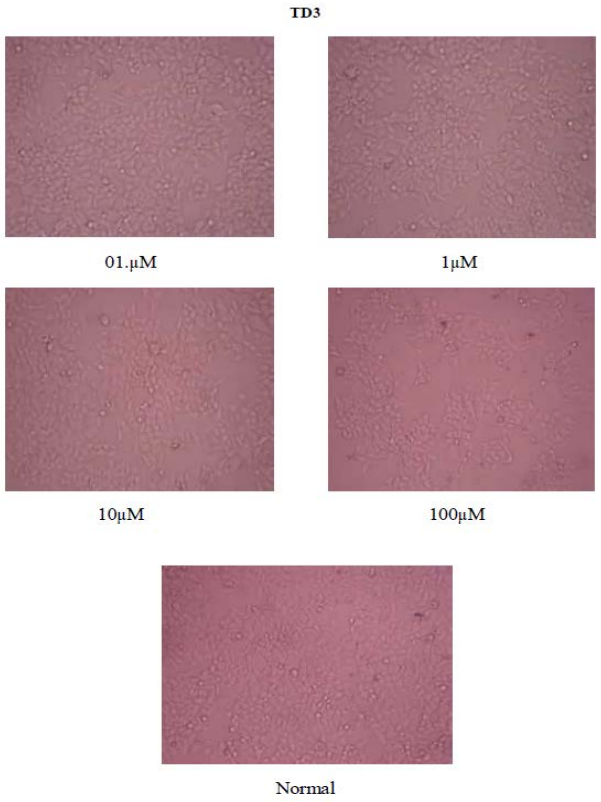
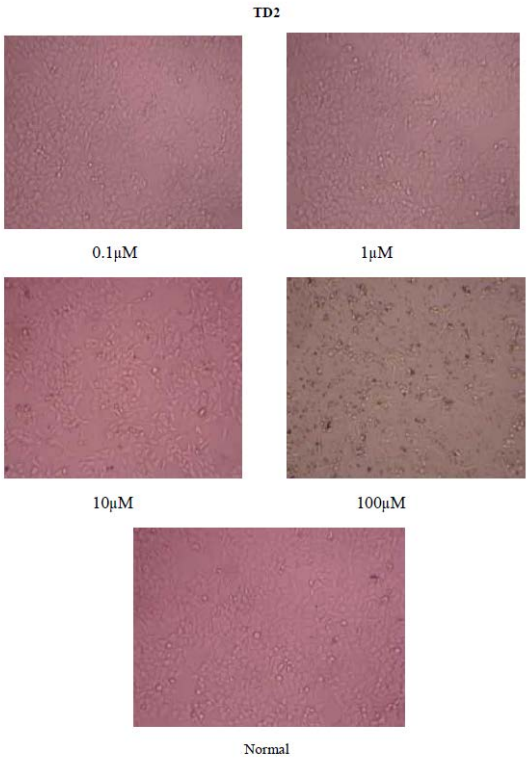
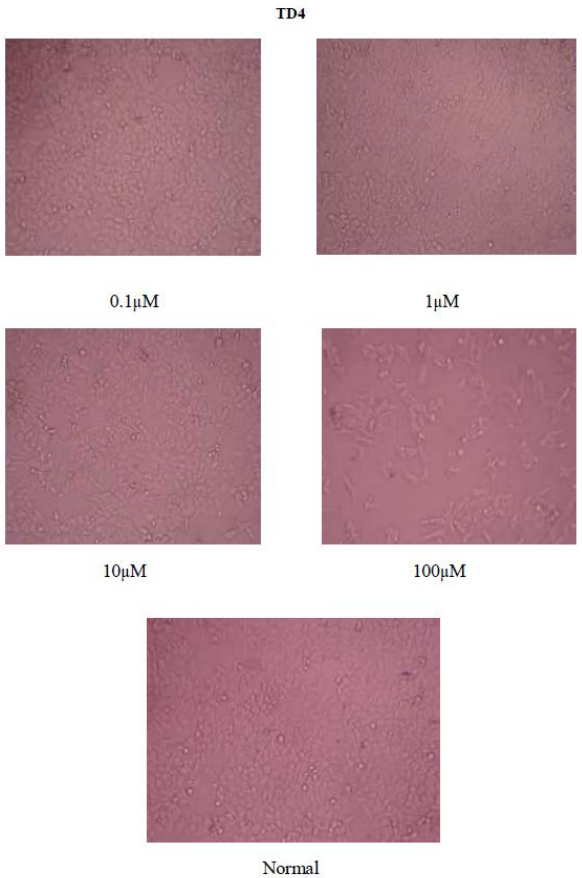


Fig.No.5 Percentage Cell Inhibition on Human Cervical Cancer Cell Line (HeLa)

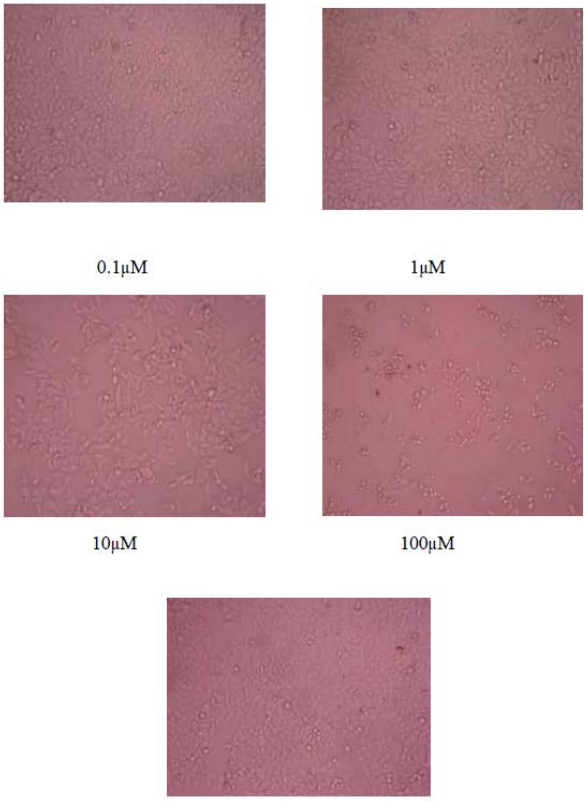

TD1
0.1µM
1µM
10µM
100µM
Normal


TD3
01.µM
1µM
10µM
100µM
Normal


TD2
0.1µM
1µM
10µM
100µM
Normal


TD4
0.1µM
1µM
10µM
100µM
Normal

TD5



TD7

TD6

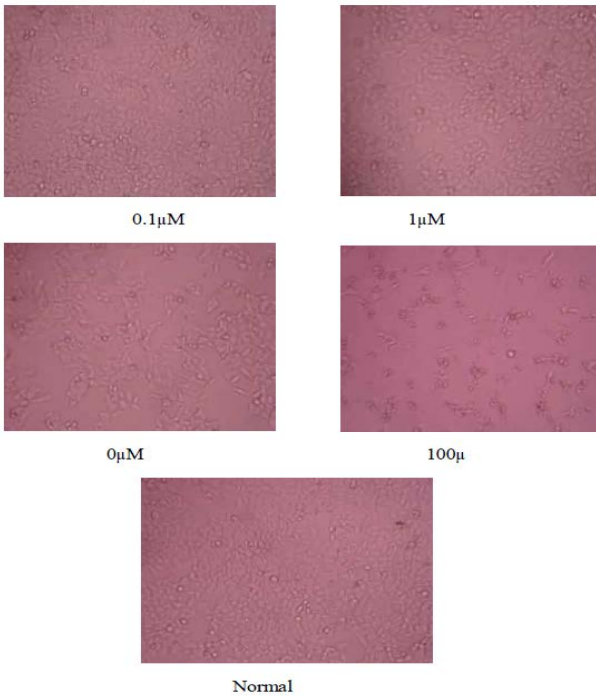


Table No.3: IC_{50} Values of Synthesized Compounds (TD1–TD7)

COMPOUND CODE	IC_{50} (MICRO MOLAR)
TD1	45.70 µM
TD2	66.23 µM
TD3	75.26 µM
TD4	92.36 µM
TD5	68.25 µM
TD6	48.60 µM
TD7	>100 µM

Table No.4 TD1

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	1.3342	45.70	0.9995
1µM	12.6079		
10µM	33.8761		
100µM	74.8578		

TD1

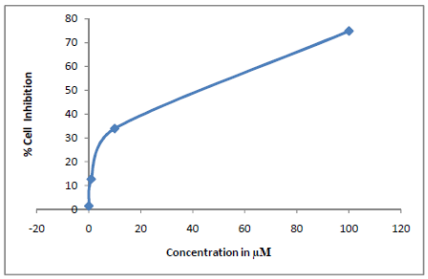


Table No.5 TD2

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	1.0424	66.23	0.9996
1µM	10.447		
10µM	22.9848		
100µM	52.9885		

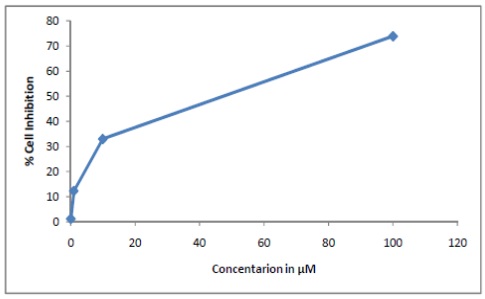


Table No.10 TD3

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	3.1895	75.26	0.9916
1µM	14.2646		
10µM	23.6772		
100µM	55.0587		

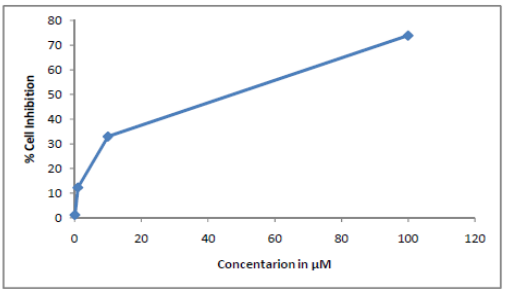


Table No.11 TD4

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	1.4315	92.36	0.9916
1µM	19.6317		
10µM	35.4864		
100µM	63.8275		

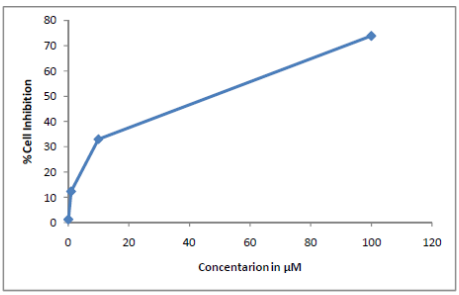


Table No.7 TD5

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	1.5342	68.25	0.9367
1µM	12.9079		
10µM	30.9861		
100µM	60.8578		

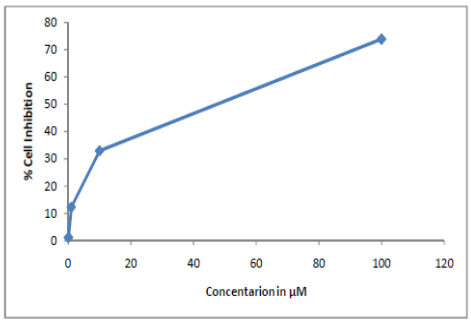


Table No.6 TD7

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	3.4112	>100	0.9907
1µM	13.7176		
10µM	33.8976		
100µM	74.8578		

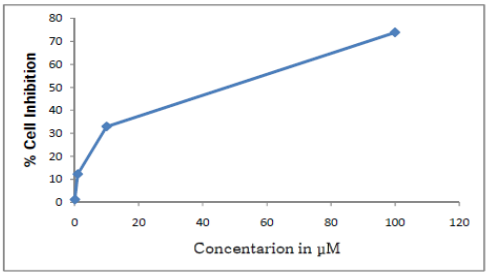
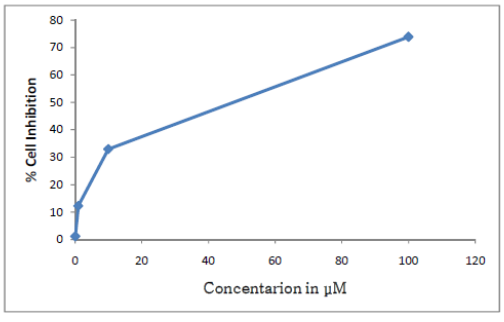
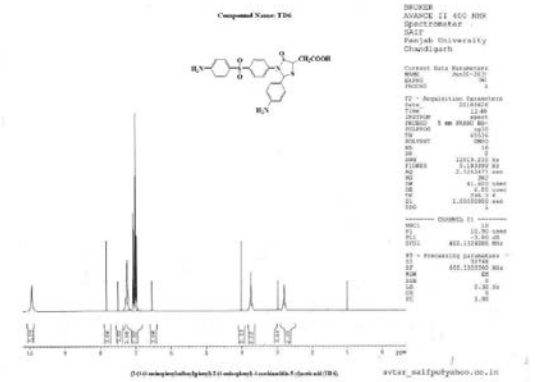
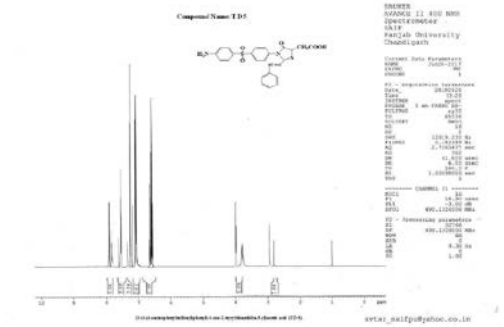


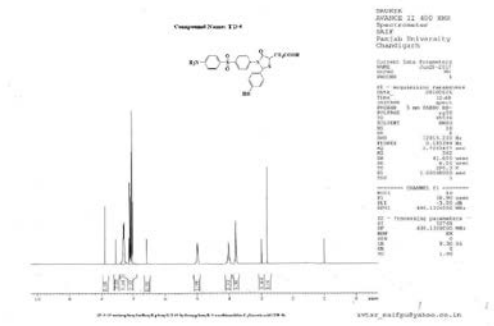
Table No.9 TD6

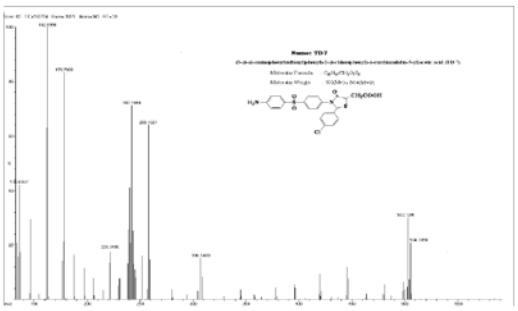
Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	1.2342	48.60	0.9916
1µM	12.3079		
10µM	32.9861		
100µM	73.8578		

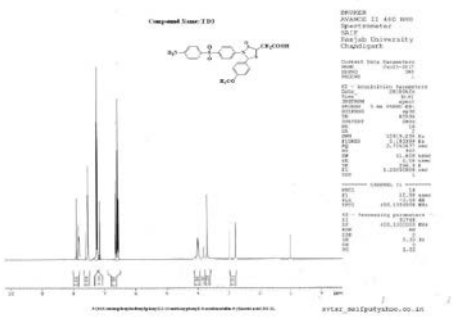


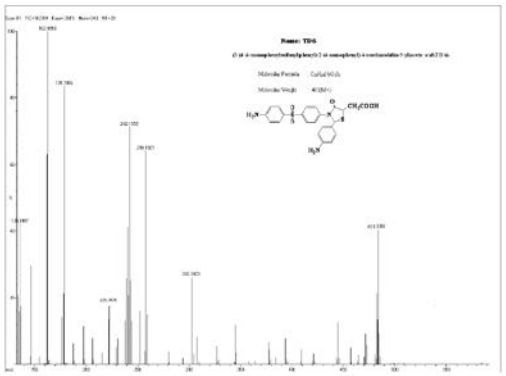


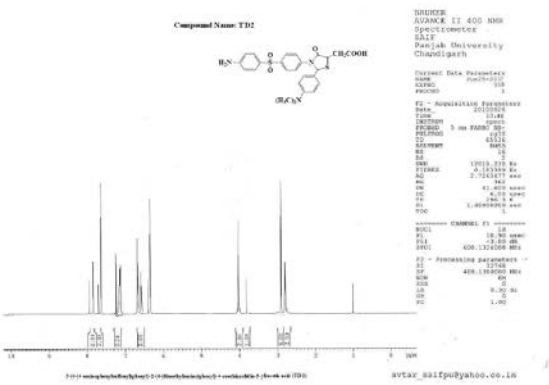


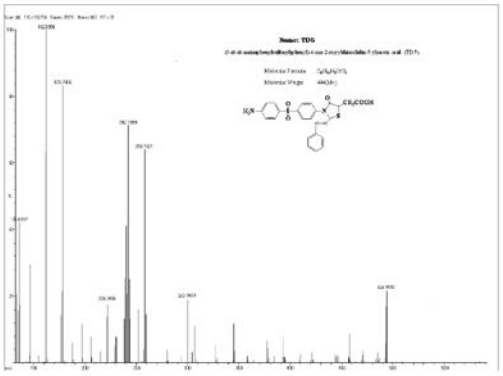


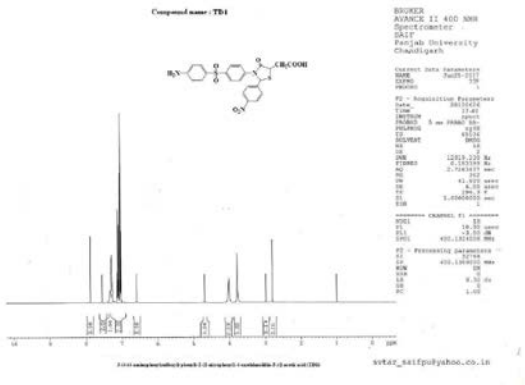


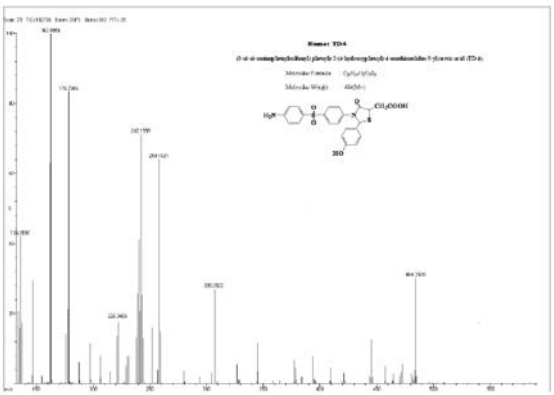


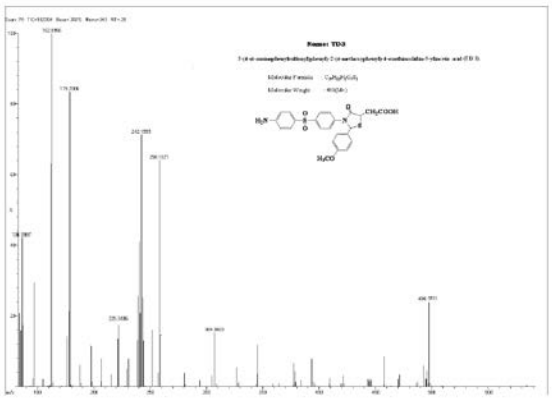


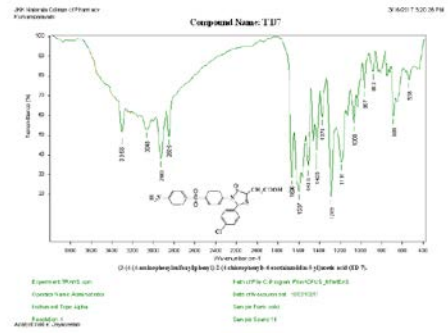


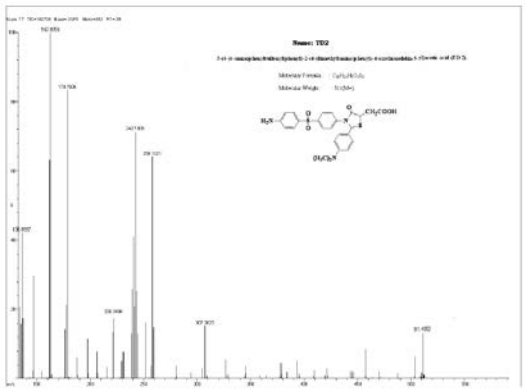


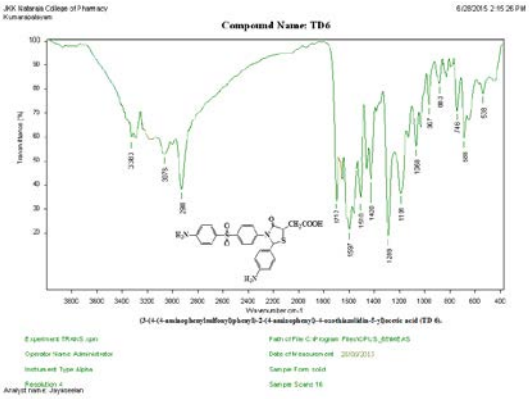







Compound Name: TD7

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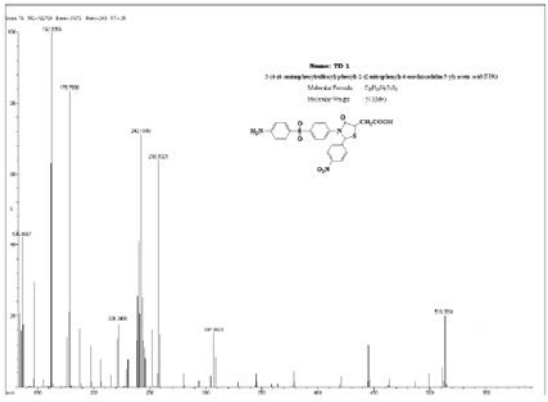
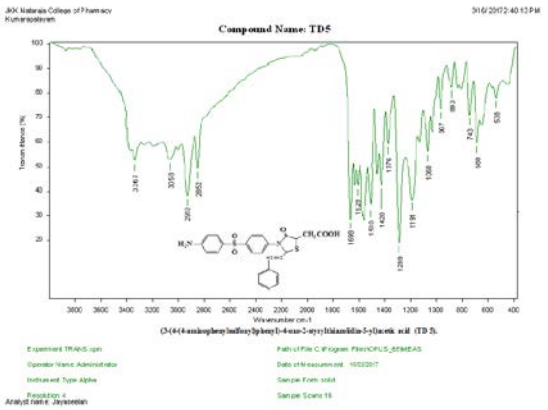
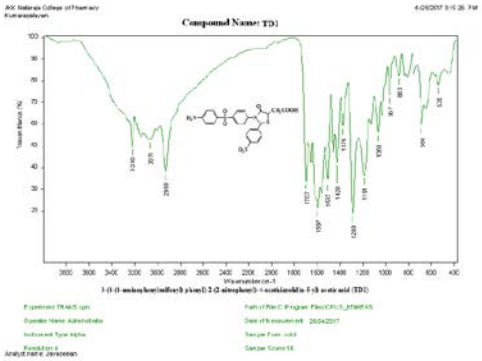
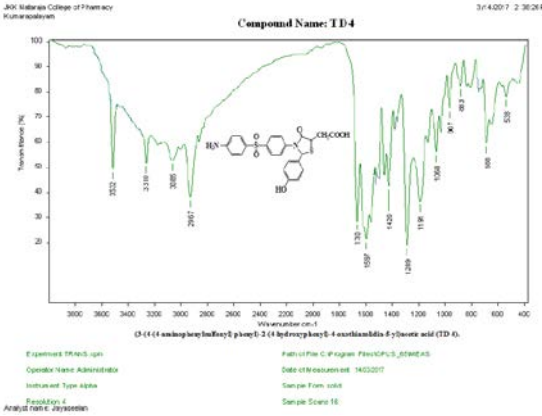
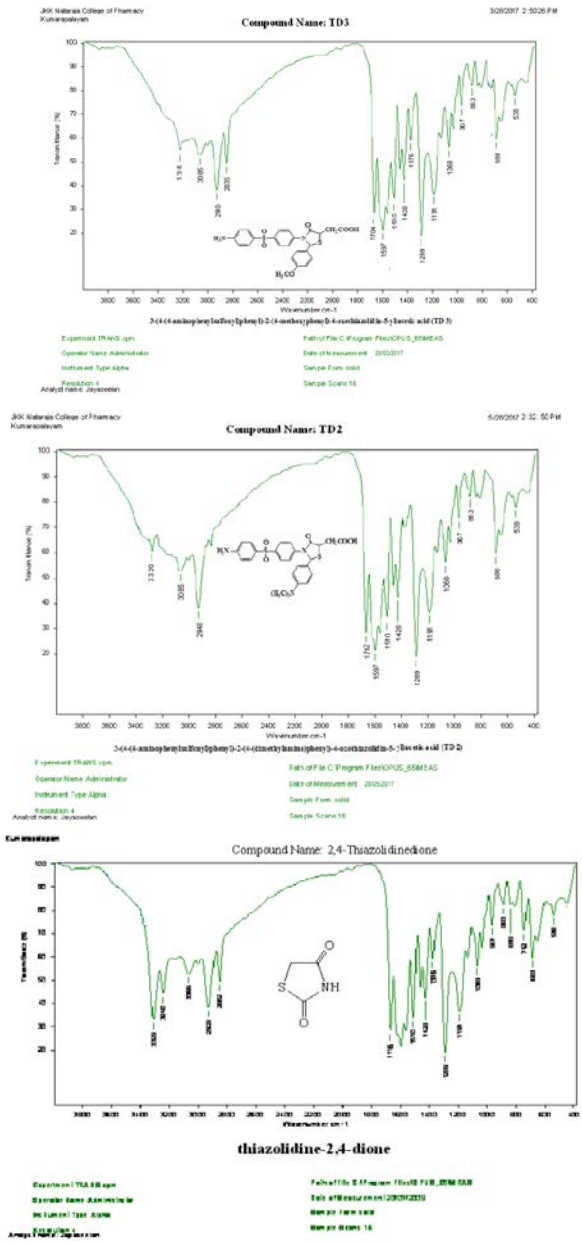



Compound Name: TD5


Compound Name: TD1


Compound Name: TD4



RESULTS AND DISCUSSION

5.1. Chemical work**:**

The results of the present work are discussed under the following heads.

Scheme**:**2-(3-(4-(4-amino phenyl sulfonyl) phenyl)-4-oxo-2- (4-substituted-phenyl thiazolidin-5-yl) acetic acid.

5.1.1 Synthesis of 2-(3-(4-(4-aminophenylsulfonyl)phenyl)-4-oxo-2-(4-substitutedphenylthiazolidin-5-yl) acetic acid.

Synthetic route depicted in scheme outline the chemistry part of the presentwork. 2-(3- (4-(4-aminophenylsulfonyl)phenyl)-4-oxo-2-(4-substituted-phenylthiazolidin-5-yl) acetic acid **(TD1-7)** were obtained by the condensation of 4-(4-amino phenyl sulfonyl) benzenamine with substituted benzaldehydes in presence of dry dioxane, concentrated sulphuric acid and ethanol. The formation of the substituted thiazolidinone was confirmed by the presence of characteristic peaks in the IR spectra. It showed characteristic peaks at around 3400 cm-1 for NH2 stretching and peak around 2900 cm-1 due to the presence of N=CH stretching. The NMR spectrum of the compounds TD1-7 showed the characteristic peak around δ 2.70 ppm for CH3 group, δ 3.00 ppm for CH2 and δ 5.70 ppm for NCH and also shows multiplet in the range of δ 6.80-8.30 ppm owing to aromatic protons. The appearance of peak due to chlorine in IR spectra around 700 -800 cm-1 and formation M+2 peak in the mass spectra. Data from the elemental analyses and molecular ion recorded in the mass spectra further confirmed the assigned structure.

5.2. Pharmacological Investigation

The anticancer screening of title compounds **(TD1-7)** were evaluated against human cervical cancer cell line (HeLa) by MTT assay method. In this assay the effective ranges of anticancer activity for compounds **TD1-7** were in the concentration of 0.1, 1.0, 10, 100 μM respectively in the human cervical cancer cell line (HeLa). Triplicate was maintained and the medium containing without samples were served as control. **TD1** (*p*-nitrophenyl) produced IC50 value 45.70 μM in case of the human cervical cancer cell line (HeLa). Relatively less value of IC50 indicates the sample has more anticancer activity. The compounds **TD1** (*p*-nitro phenyl) had shown the percentage of cell inhibition was 74.85 against the human cervical cancer cell line (HeLa) in the highest concentration, which have *p*-nitrophenyl group in the thiazolidinone nucleus. The result indicates that **TD1** (*p*-nitrophenylgroup) showed a significant anticancer activity against the human cervical cancer cell line (HeLa), when compared to that control. **TD2** (dimethyl amino group) produced IC50 value 66.23 μM in case of the human cervical cancer cell line (HeLa). Relatively less value of IC50 indicates the sample has more anticancer activity. The compound **TD2** (dimethyl amino group) had shown the percentage of cell inhibition was 52.89 against the human cervical cancer cell line (HeLa) in the highest concentration, which have dimethylamino group in the thiazolidinone nucleus. The results indicate that **TD2** (dimethyl amino group) showed a moderate anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control. **TD3** (methoxyl group) produced IC50 value 75.26μM in case of the human cervical cancer cell line (HeLa). Relatively less value of IC50 indicates the sample has more anticancer activity. The compound **TD2** (methoxyl group) had shown the percentage of cell inhibition was 52.25 against the human cervical cancer cell line (HeLa), which have dimethyl amino group in the thiazolidinone nucleus. The results indicate that **TD3** (methoxyl group) showed a less anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control. **TD4** (Hydroxyl group) produced IC50 value 92.36 μM in case of the human cervical cancer cell line (HeLa). Relatively less value of IC50 indicates the sample has more anticancer activity. The compound **TD4** (Hydroxyl group) had shown the percentage of cell inhibition was 63.82 against the human cervical cancer

cell line (HeLa) in the highest concentration, which have imidazole group in the thiadiazole nucleus. The results indicate that **TD4** (Hydroxyl group) showed a moderate significant anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control. **TD5** (vinyl group) produced IC50 value 75.26 μM in case of the human cervical cancer cell line (HeLa). Relatively less value of IC50 indicates the sample has more anticancer activity. The compound **TD5** (vinyl group) had shown the percentage of cell inhibition was 55.05 against the human cervical cancer cell line (HeLa) in the highest concentration, which have vinyl group in the thiazolidinone nucleus. The results indicate that **TD5** (vinyl group) showed a moderate significant anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control. **TD6** (*p*-amino grp) producedIC50value 48.60 μM in case of the human cervical cancer cell line (HeLa). Relatively high value of IC50 indicates the sample has more anticancer activity. The compound **TD6** (*p*-amino group) had shown the percentage of cell inhibition was 73.85 against the human cervical cancer cell line (HeLa) in the highest concentration, which have *p*-amino group in the thiazolidinone nucleus. The results indicates that **TD6** (*p*-amino group) showed a good significant anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control. **TD7** (*p*-chloro group) produced IC50 value > 100 μM in case of the human cervical cancer cell line (HeLa). Relatively high value of IC50 indicates the sample has more and significant anticancer activity. The compound **TD7** (*p*-chloro group) had shown the percentage of cell inhibition was 55.05 against the human cervical cancer cell line (HeLa) in the highest concentration, which have *p*-chloro group in the thiadiazole nucleus. The results indicates that **TD7** (*p*-chloro group) showed a more significant anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control. The best mean IC50 values were achieved with compound (**TD3, TD4, TD5** and **TD7**) with slight difference among them. Title compounds (**TD1-7**) were found to exhibit mild to moderate anticancer activities in cell lines and the results were summarized below:

☐ Compound **TD1** (*p*-nitrophenyl group) shows less activity against the HeLa (IC50 –47.50) cancer cell lines.

☐ Compound **TD2** (dimethylamino group) shows moderate activity against the HeLa(IC50 – 66.23) cancer cell lines.

☐ Compound **TD3** (methoxyl group) shows high significant activity against the HeLa(IC50 72.56) cancer cell lines.

☐ Compound **TD4** (4-hydroxl group) shows more & potent significant against the HeLa(IC50 –92.36) cancer cell lines.

☐ Compound **TD5** (vinyl group) shows the moderate activity against the HeLa (IC50 –68.25) cancer cell lines.

☐Compound **TD6** (*p*-amino group) shows less significant activity against the HeLa (IC50–48.60) cancer cell lines.

☐Compound **TD7** (*p*-chloro) shows very high and potent significant activity against theHeLa (IC50 > 100) cancer cell lines.

Among the test compounds, compound 3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4- chlorophenyl)-4-oxothiazolidin-5-yl) acetic acid (**TD7**) was found to be the most active agent which showed 74.85 percentage of cell inhibition against the human cervical cancer cell line (HeLa) in the highest concentration, which have *p*-chloro group in the thiazolidinone
nucleus.

SUMMARY AND CONCLUSION

In summary, a new series of 2-(3-(4-(4-aminophenylsulfonyl) phenyl)-4-oxo-2-(4- substituted-phenyl thiazolidin-5-yl) acetic acid were synthesized. These title compounds containing seven different substituents at C-2 and C-3 were screened for their anticancer agents. Most of the test compounds were found to exhibit significant anticancer activity against the human cervical cancer cell line (HeLa) in the highest concentration. Among the substituents at C-2, *p*-chloro phenyl substituent and at C-5 4-amino phenyl sulfonyl substitutent showed maximum potency, while 4-methoxy phenyl, 4- hydroxy phenyl and 4-
nitro phenyl substitutent showed equipotent activity but the dimethylaminophenyl, vinyl and 4-amino phenyl substituent at C-2 exhibited least activity when compare to other substituents.

The order of activity at C-2 is *p*-chloro phenyl ≥ 4-hydroxy phenyl ≥ 4-methoxy phenyl ≥ 4-nitro phenyl ≥ 4-amino phenyl ≥ dimethylaminophenyl ≥ vinyl substituents.

Among the test compounds, compound 3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-chlorophenyl)-4-oxothiazolidin-5-yl) acetic acid (**TD7**) was found to be the most active agent which showed 74.85 percentage of cell inhibition against the human cervical cancer cell line (HeLa) in the highest concentration, which have *p*-chlorophenyl group in the thiazolidinone nucleus. Hence this molecule can be selected as a lead molecule of the present study for further exploitation.

REFERENCE

1. Rogawski MA, Loscher W, The neurobiology of antiepileptic drugs, Nat Rev Neurosci,5(7), 2004, 553-564.
2. Schmidt D and Loscher W, Epilepsia, 46, 2005, 858.
3. Kwan P and Brodie M, New Engl J Med, 342, 2000, 314.
4. Dichter MA and Brodie M, New Engl J Med, 334, 1196, 1583.
5. Diurno MV, Greco G, MazzoniO,Novellino E, Calignana G, Larana A, Barberi andBolognese A, Med Chem Res, 4, 1994, 578-562.
6. Bolognese A, Diurno MV, Greco G, Mazzoni O, Novellino E, Perissutti E and Silipo C, JRecept Res, 15, 1995, 631-635.
7. Bolognese A, Diurno V, Mazzoni O, Correale G, Gomez Monterrey I and Barone V, JMol Graph Model, 54, 1999, 579-586.
8. Diurno MV, Mazzoni O, Correale G, Gomez Monterrey I, Calignano A, La Rana G andBolognese A, Farmaco, 54, 1999, 579-585.
9. Eltsov OS, Mokrushin VS, Belskaya NP, Kozlova NM, Rus. Chem. Bull., Int. Edn, 52,2003, 461.
10. Markovic R, Stodanovic M, Heterocycles, 56, 2005, 2635.
11. Cunico W, Gomes CRB, Ferreira M, Capri LR, Soares M, Wardell SMSV, Tetrahedron Lett, 48, 2007, 6217.
12. Pawar R B, Mulwad VV, ChemHeterocycl. Compound, 40, 2004, 219.
13. Ocal N, Aydogan F, Yolacan C, Turgut ZJ, Heterocycl. Chem, 40, 2003, 721.

14. Neuenfeldt, PD, Drawanz BB, Siqueira GM, Gomes CRB, Wardell SNSV, Flores AFC,Cunico W, Tetrahedron Lett , 51, 2010, 3106.
15. Bolognese A, Correale G, Manfra M, Lavecchia A, Novellino E, Barone V, Org. Biomol.Chem, 2, 2004, 2809.
16. Pratap UR, Jawale DV, Bhosle MR, Mane RA, Tetrahedron Lett, 52, 2011, 1689.
17. Mali JR, Pratap UR, Netankar PD, Mane RA, Tetrahedron Lett, 50, 2009, 5027.
18. Bolli MH, Abele S, Binkert C, Bravo R, Buchmann S, Bur D, Gatfield J, Hess P, Kohl C,Mangold C, Mathys B, Menyhart M, Meuller C, Nayler O, Scherz M, Schmidt G, SippelV, Steiner B, Strasser D, Treiber A, Weller TJ, Med. Chem, 53, 2010, 4198.
19. Moghaddam F M, Hojabri LJJ, Heterocycl. Chem, 44, 2007, 35.
20. Ottana, R, Maccari R, Barreca ML, Bruno G, Rotondo A, Rossi A, Chiricosta G, Di Paola R, Sautebin L, Cuzzocrea S, Vigorita MG, Bioorg. MedChem. 13, 2005, 4243.
21. Johnson MR, Fazio MJ, Ward DL, Sousa LR, J. Org.Chem, 48(1), 1994, 83 -94.
22. Graciet JC, Niddam, V, Gamberoni, M,Trabaud, C, Dessolin J, Medou M, Mourier N, Zoulim F, Bore lC, Hantz O, Camplo M, Chermann JC, Kraus, JL, Bioorg. Med Chem. Lett.6(1), 1996, 1775-1781.
23. Singh SP, Parmar SS, Raman K, Chem. Rev. 81,1981, 175.
24. Andrade AMC, Lima WT, Rocha MPA, Lima MCA, Galdino SL, Barbosa Filho JM, Goes AJS, Pitta IR, Boll. Chim. Pharmaceutica,141, 2002, 428.
25. Akerblom E, 2-aminothiazolin-4-one and 2-iminothiazolidin-4-one derivatives part II tautomerism, Acta Chemica Scandinavica, 21, 1967, 1437-1442.
26. Lesyk RB, ZimenkovskyBS,Curr Org Chem, 8, 2004, 1547
27. Fuschigami T, Narizuka S, Konno A, J. Org.Chem, 57, 1992 , 3755
28. Nishimoto SI, Hatta H, Ueshima H, Kagiya TL, J. Med Chem,35, 1992, 2712.
29. SubbaRaoYV,Choudary BM, Synth. Commun,21,1991 ,1163.
30. Maccari R, Barreca ML, Bruno G, Rotondo A, Rossi A, Chiricosta G, Di Paola R, Sautebin L Cuzzocrea S, Vigorita MG, Bioorg. Med Chem. 13, 2005 4243.
31. Cava MP, Levinson MI, Tetrahedron,41, 1985, 5061.
32. Souza MV, Ferreira SB, Mendonca JS, Costa M, Rebello FR, Quim. Nova,28, 2005, 77.
33. Berseneva VS, Tkachev AV, Morzherin YY, Dehaen W, Luyten I, Toppet S, Bakulev VA, J. Chem. Soc, 1 ,1998 , 2133.
34. Tenorio RP, Carvalho CS, Pessanha CS, Lima JG, de Faria AR, Alves AJ, Melo EJ, Goes AJS, Bioorg.Med Chem. Lett,15, 2005, 2575.
35. Aquino TM, Liesen AP, Lima JG, Silva RE, Lima VT, Araújo JM, Goés AJ, Abstracts of the 29th Annual Meeting of the Brazilian Chemical Society, Waters Lindóia, Brazil, 2006.
36. Cunico W, Gomes C R B, Ferreira M, Capri LR, Soares M, Wardell SM, SV, Tetrahedron Lett, 48, 2007, 6217.
37. Neuenfeldt PD, Drawanz BB, Siqueira GM, Gomes CR, Wardell SNS, Flores AF C, Cunico W, Tetrahedron Lett,51, 2010, 3106.
38. Pratap UR, Jawale DV, Bhosle MR, Mane RA, Tetrahedron Lett, 52, 2011, 1689.
39. Mali JR, Pratap UR, Netankar PD, Mane RA, Tetrahedron Lett, 50, 2009, 5027.
40. Bolli MH, Abele S, Binkert C, Bravo R, Buchmann S, Bur D, Gatfield J, Hess P, Kohl C, Mangold C, Mathys B, Menyhart M, Meuller C, Nayler O, Scherz M, J. Med. Chem , 53, 2010, 4198.
41. Moghaddam FM, Hojabri LJ, Heterocycl. Chem, 44, 2007, 35.
42. Lidstrom P, Tierney J, Wathey B and Westman J, Tetrahedron, 56, 2001, 55-60.
43. Tej Rakish Singh, Pramod Kumar Sharma, Preet Kanwal Kaur, Sombhu Charan Mondal and Amitgupta, Der Pharmed Chemica, 3(1), 2011, 194-206.
44. Singh SP, Parmar SS, Raman K and Stenberg ,Chemistry and biological activity of thiazolidinones, Chem Rev, 81, 1981, 175-203.
45. Cunico W, One pot synthesis of 2-isopropyl-3-benzyl-1,3-thiazolidin-4-ones and 2- phenyl-3-isobutyl-1,3-thiazolidin-4-ones from valine, arylaldehydes and mercaptoacetic acid, Tetrahedron Letters, 48, 2007, 6217-6220.
46. Chizhevskaya II, Khovratovich NN and Kharchenko RS, Investigation of the mobility of methylene group hydrogen atoms in some derivatives of 2-iminothiazolidin-4-one, Khimiya Geterotsiklicheskikh Soedinenii, 3(4), 1967, 642-646.
47. Christensen J, Vestergaard M, Mortensen PB, Sidney's P, Agerbo E, Convulsion and Risk of Suicide. A population-based case-control study, Lancet Neurol. 6(8), 2007, 693- 698.
48. Foldvary-Schaefer N, Wyllie E. Epilepsy. In: Goetz C, Textbook of Clinical Neurology. 3rd ed. Philadelphia, PA. Saunders Elsevier. 2007, 52.
49. Freeman JM, Kossoff EH, Hartman AL, The ketogenic diet. One decade later, Pediatrics, 119(3), 2007, 535-543.
50. Jette N, Hemming K, Hutton JK, Marson AG, Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database Syst Rev, 16(3), 2008, 141-147.
51. Johnson MV, Seizures in childhood. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF.Nelson Textbook of Pediatrics.18th ed., Philadelphia, PA. Saunders Elsevier. 2007, 586-590.
52. Krebs PP, Psychogenic epileptic seizures, Am. J. Electro neurodiagnostic Technol, 47(1), 2007, 20-28.
53. Krumholz A, Wiebe S, and Gronseth G, Practice Parameter: Evaluating an apparent unprovoked first seizure in adults (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society, Neurology, 69(21), 2007, 1996-2007.
54. Kwan P, Brodie MJ, Emerging drugs for epilepsy, Expert Opin Emerg Drugs, 12(3), 2007, 407-422.
55. Leone MA,Solari A, Beghi E, Treatment of the first tonic-clonic seizure does not affect long-term remission of epilepsy, Neurology, 67(12), 2006, 2227-2229.
56. Salanova V, Worth R, Neurostimulators in Epilepsy, Curr Neurol Neurosci Rep, 7(4), 2007, 315-319.
57. Spencer SS, Seizures and epilepsy. In: Goldman L,Cecil Medicine. 23rd ed. Saunders. 2007, 231-240.
58. Tomson TV and Hilesmaa, Epilepsy in pregnancy. British Medical Journal, 13(35), 2007, 769-773.
59. Kwan P and Brodie M, New Engl. J. Med, 342, 2000, 314.
60. Hauptman A, Luminal Epilepsie. Munchen Med Wochenschr, 59, 1912, 1907-1909.
61. Daniel Glossman-Mitnik, Computational Study of 3,4-Diphenyl-1,2,5-Thiadiazole 1-Oxide for Organic Photovoltaics. National Journal of Chemistry, 24, 2006, 596-607.
62. Denny, WilliamA, The design and development of anticancer Drugs. Chemical Process in NewZealand, edtion 1, 1995, 22.
63. Atlanta, Ga, Cancer Facts and Figures, American Cancer Society, 2,2011,58-65.
64. Monforte P, Grasso S, Chimirri A, FenechG, Zappala M, Monforte AM, antitumor activity of series of 2-alkyl-3 -[2-(1, 3, 4-thiadiazolyl)]-4-thiazolidinones, Farmaco Sci, 43(10),1988, 851-856.
65. Duane D Miller, VeeresaGududurú, EunjuHurh, and James T Dalton,Synthesis, SAR and antiproliferative activity of 2-aryl-4-oxo-thiazolidin-3-yl-amides for prostate cancer, Bioorganic and Medicinal Chemistry Letters, 14, 2004, 5289-5293.
66. Roman Lesyk, Havrylyukdmytro, MosulaLudmyla, Zimenkovsky ,Synthesis of novel 4-thiazolidinone derivatives, Eur J Med Chem, 2004, 545-553.
67. StefaniaCarotti, Rosaria Ottana, Rosanna Maccari, Ida Landini, GiuseppaChiricosta, Barbara Caciagli, Mari Gabriella Vigorita, Enrico Mini, In vitro antiproliferative activity of 4-thiazolidinones against human colon cancer cell lines, Bioorganic and Medicinal Chemistry Letters, 15, 2005, 3930-3933.
68. Amanysayed Maghraby, Mahmoud Mohamed Bahgat, Mogeda Emam Heiba, Andreas Ruppel and Omar Abd-elfattah Mohamed Fathalla, Synthesis of series of new 4-oxo-2- thioxo- 1, 2, 3, 4-tetrahydropyrimidine derivatives with an incorporated thiazolidinone moiety for their possible serine protease and cercarialelastase inhibitory effects, Arch
Pharm Res, 28(9),2005, 1002-1012.
69. Benaka Prasad SB, Chandrappa S, Vinaya K, Ananda Kumar CS, Thimmegoeda NR, Rangappa KS, Synthesis of a series of novel 5-(4-methyl benzylidene)-thiazolidine-2, 4- dione derivatives with different substituted aromatic sulfonyl chlorides and alkyl halides for their invitro anti proliferative activity, Invest New Drugs, 26, 2008, 437-444.
70. Shuhong Wu, Hongyu Zhou, Shumeizhzi, Aifeng Liu, Ying Sun, Rongshi Li, Ying Zhang, Sean Ekins, Peter W Awaan, Binliang

Fang, Bin Zhang and Bing Yan, The synthesis, structure activity relationship, cytoselective toxicity and anti-cancer activity of pharmacophore of thiazolidinone derivatives, J Med Chem, 51(5), 2008, 1242-1251.

71. Rosanna Maccari, Rosaria Ottana, Rosella Ciurleo, Paolo Paoli, Michela Jacomelli, Giampaolo Manao, Giido Camici, Christian Laggner, Thierry Langer, Synthesis of 4-(5- arylidene-4-oxo-2-phenylimino thiazolidin-3yl)-methyl benzoic acids and screened their inhibitory activity against human PTP1b and LMW-PTP enzymes, Bioorganic and Medicinal Chemistry, 17, 2009, 1928-1937.
72. Zimenkovsky, Havrylyuk, DmytroBorys, lesyk Roman, Synthesis of novel non fused thiazolidinone as potent anticancer agents, Phosphorus, sulfur, silicon and the related elements, 184 (3), 2009, 638-650.
73. HavrylyukDmytro, MosulaLudmyla, Zimenkovsky, BorysVasylenko, OlexanderGzella, Andrzej, Lesyk Roman, Synthesis and anticancer activity evaluation of 4-thiazolidinones containing benzothiazole moiety, Eur J Med Chem, 2010, 871-875.
74. Kaminskyy DV, Lesyk RB, The structure-anticancer activity relationships among 4- azolidinone-3-carboxylic acid derivatives, Biopolymers and Cell, 26(2), 2010, 136-145.
75. IvannaSubtelne, DmytroAtamanyuk, EwaSzymanska, KatarzynaKiec -kononowicz, BorysZimenkovsky, OlexandrVasylenko, AndrzejGzella, Roman Lesyk, Synthesis of 5- arylidene-2-amino azolones and evaluation of their anticancer activity, Bioorganic and Medicinal Chemistry, 18, 2010, 5090-5102.
76. Maity TK, Nagalakshmi G, Maiti BC, the synthesis, characterization and antiproliferative activity of 2-(substituted phenyl)-5-methyl-3-pyridin-4yl-1, 3-thiazolidinones, Int J Pharm Tech Res, 3(2), 2011, 707-718.
77. Zhengming Li, Yuxin Li, Wei Chen, Xiaoping Yang, Guanping Yu, Mingzhen Mao, Yunyun Zhou, Tuanwei Liu, Synthesis and anti-tumor activity of series of regioselective 3-thiazolidine acetic acid derivatives, Chem Biol Drug Des, 78, 2011, 969-978.
78. Ping Gong, XinZhai. Wei Li, Dong Chem, Ruiwei Lai, Jun Liu, Design and synthesis of 2-iminothiazolidin-4-one moiety-containing compounds as potent anti-proliferative agents, Archive der Pharmazie, 64, 2012, 2011-2016.
79. Pattan K, Mohammad Imran, Parikh AR, Maiti BC, synthesis and antidiabetic activity of 2-amino [5(-4-sulfonyl benzylidine) -2, 4-thiazolidindione] -7- chloro -6- fluro benzothiazole, Molecules, 7, 2005, 178-184.
80. Firake BM, Firake SD, Chaudhari RY, Patil VR, Synthesis and pharmacological activity of series of N-aryl/alkyl substituted pyridine thiazolidinones, Asian J Research Chem, 2(2), 2009, 157-161.
81. Suroor Ahmad Khan, Mohammad Imran, Mohammad Shahar, Synthesis of 2-substituted phenyl-3-(4-1-naphthyl)-1, 3-thiazolyl-amino -4-oxo thiazolidin-acetic acid derivatives as anti-hyperglycemic activity, Acta Poloniae Pharmaceutica, 66(1), 2009, 51-56.
82. Vipan Kamboj, Prabhakar Verma, Synthesis of 3-(4-alkyl/aryl substituted)-4-oxo-1, 3- thiazolidin-2-ylidene acetohydrazide for their anti-diabetic activity, Acta Pharmaceutica Sciencia, 52, 2010, 411-415.
83. Birendra Shrivastava, Pankaj Sharma, Lamba HS, Jaya Sharma, Lokesh Sharma,Synthesis of 5-substituted-1, 3-thiazolidin-4-ones as anti-hyperglycemic activity, Pharmacie Globale (IJCP), 3(9),2010,1-6.
84. DeepthiKini, ManjunathGhate, Synthesis and oral hypoglycemic activity of series of 3-(5- methyl-2-aryl-3-thiazolylamino)-4-thiazolidinone coumarin derivatives, E-Journal Chem, 8(1),2011, 386-390.
85. Farid Badria, Omaima Mohamed abdElhafez, Ezz El Din Ahmed Mohamed El Khrisy, Alaa El Din Mohamed Fathy, New thiazolidinone and oxadiazoline coumarin derivatives and their antiviral activity, cytotoxicity and SAR studies, Arch Pharm Res, 26(8), 2003, 686-696.
86. Anna Maria Monforte, Angela Rao, Alba Chimirri, Stefania Ferro, PietroMonforte, Maria Zappala, Synthesis of benzimidazole and thiazolidinone derivative as HIV-1 RT inhibitors, Arkivoc, 5, 2004, 147-155.
87. Zappala, Angela FG, Manjunath S, Synthesis of 1,3-thiuazolidinones with dihalogen and
pyrimidine substitution as its HIV-1 reverse transcriptase inhibitors, Chem Bio and Drug Design, 69(3), 2004, 264-270.
88. Dharmarajan Sriram, Perumal Yogeeswari, Ashok Kumar TG, Microwave-assisted synthesis and anti-YFV activity of 2, 3-diaryl-1, 3-thiazolidin-4-ones, J Pharm Pharm Sci, 8(3), 2005, 426-429.
89. Ravindra K Rawl, Ashutosh Kumar, Mohammad Imran Siddidi and Setu B Katti, Molecular docking studies on 4-thiazolidinones as HIV-1 RT inhibitors, J Mol Model, 13,2007, 155-161.
90. RavichandranVeerasamy, Abhishek Jain, Krishnan S Kumar, Harish Rajak, Ram Agarwal, Synthesis and biological evaluation of thiazolidinone derivatives as potent antiviral agents, Chem Bio and Drug Design, 78(3), 2011, 464-470.
91. EvelinBoshra, Abdulla Mohammed Asiri, Syntesis of new heterocyclic thiazolidines with acaricidial, insecticidal and bactericidal actitivty, Arkivoc, 2, 1989, 47-55.
92. HamedEad, Nadia H metwalli, Nagwa M Morsi, Synthesis and antimicrobial activity of 5-(2-thienylmethylene) derivatives of thiazolidin-4-one by cyclo-addition reactions, Arch Pharm Res, 13(1), 1990, 5-8.
93. Afaf K Ansary, Adel A Elgendy, Salwa Elmeligie ,Aly Ahmendy, Synthesis of Quinoxaline derivatives containing thiazolidinone residue as a potent antibacteial and antifungal agent, Arch Pharm Res, 18(1), 1995, 44-47.
94. Sayed R, Aly AA, Synthesis and biological activity of 2-[2-carboxymethylthio-2-(4- chlorophenyl) ethyl]-2-(4-chlorophenyl)-4-thiazolidinone, Chem Pap, 60(1), 1999, 56-60.
95. Ulusoy U, Ergen N, Ekinci AC, Ozer H, Synthesis, Characterization and anticonvulsant evaluation of bis-4-thiazolidinones, Monatshefte fur Chemie, 127, 1996, 1197-1202.
96. AyselGursoy, NalanTerzioglu, Synthesis and isolation of new Regioisomeric-4- thiazolidinones and their anticonvulsant activity, Turk J Chem, 29, 2005, 247- 254.
97. Kailash G, MahendraR, Shiradhar, Mangesh Ghodake, Bothara Shashikant V, Bhandari,
Ana Nikalje, Kalyan Chakravarthy Akula, Nisheeth C Desai, Prashant J Burange, Synthesis and anticonvulsant activity of clubbed thiazlolidinone-barbituric acid and thiazolidinone-triazoles, Arkivoc, 10(14), 2007,58-74.
98. Huger MH, Shingalapur RV, Kallapa M, Rangappa SK, Synthesis of 4-thiazolidinones containing 2-mercapto benzimidazoles for their anticonvulsant activity, Eur J Med Chem, 45, 2010,1753-1759.
99. Saxena KK, Kaur H, Kumar S, Vishwakarma SP, Sharma M, Kumar A, Synthesis and anticonvulsant activity of novel substituted thiadiazolylazetidinonyl derivatives, Eur J Med Chem, 45, 2010, 2777-2783.
100. Rangappa S, Ramya V, Shingalapur Kallappa M, Hosamani Keri, Mallinath H, Hugar, Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies of benzimidazole pharmacophore, European Journal of Medicinal Chemistry, 45, 2010, 1753–1759.
101. Ganesh Akula, BethiSrinias, MattaVidyasagar, Saikrishna Kandikonda, Synthesis of 3- (1H-benzimidazol-2-yl amino)-2-phenyl-1, 3-thiazolin-4-one as potential CNS depressants, Int J Pharm tech Res, 3(1),2011, 211.
102. Tejprakash Singh, Pramod Kumar Sharma, Sambhu Charan Mondalc and Nitin Kumar,
Synthesis, characterization and anticonvulsant activity of novel thiazolidinone derivatives, J Chem Pharm Res, 3(5), 2011, 609-615.
103. Nikalje, Mangesh Ghodke, Anna Pratima G, Firoz Kalam Khan, Design and synthesis of 2-(1,3-dioxoisoindolin-2-yl)-N-(4-oxo-2-substituted thiazolidin-3-yl) acetamide derivatives as potential anticonvulsant agents, European Journal of Medicinal Chemistry, 46, 2011, 5448-5455.
104. Indulatha VN, Gopal N, Jayakar B, Anticovulsant activity of some novel N-(oxo-2(aryl substituted) thiazolidin-3yl-carboxamides, Rjpbcs, 3(1), 2012, 315-322.