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Synthesis and Antiproliferative Activity of Novel Thiazolidine and Azetidinone Derivatives

Kabilan C[1]*, Shankar D[1], Alagarsamy V[2] and Asiya Parvin A[3]

[1]Department of Pharmacy (SCBT), SASTRA University, Tirumalaisamudram, Thanjavur 613 401, Tamil Nadu, India
[2]Medicinal Chemistry Research Laboratory, MNR College of Pharmacy, Sangareddy 502 294, Gr. Hyderabad, Andhra Pradesh, India
[3]Department of Biotechnology, Anna University, Chennai 600 003, Tamil Nadu, India

ABSTRACT

Alteration in cell differentiation and proliferation leads to an increase in tumor cells in the body. Recent advances in tumor genesis and metastasis have provided the opportunity to design novel compounds that rationally act on cancer cells. Cancer research steps forward because of the key role of heterocyclic moieties which are present in chemotherapeutic compounds. These heterocyclic compounds are capable of reversing the process of carcinogenesis and also inhibiting the growth of tumor cells. In the present study, a series of novel thiazolidine and azetidinone derivatives were synthesized and evaluated for their antiproliferative activity. One of the synthesized compounds V (N-sulphonic acid substituted derivative of azetidinone) exhibited significant inhibitory activity against the proliferation of MCF-7 breast cancer cell lines than the other compounds.

Keywords: antiproliferative activity, thiazolidines, azetidinones.

Corresponding author

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INTRODUCTION

Alteration of the genes which regulate cell growth and differentiation results in the transformation of a normal cell into a cancer cell. In recent cancer research, the focus has shifted to the synthesis of target specific agents. Some heterocyclic compounds have been synthesized as chemotherapeutic agents, which are capable of reversing the process of carcinogenesis and also inhibiting the growth of tumor cells by binding with specific target proteins. Cancer research steps forward because of the key role of heterocyclic moieties which are present in chemotherapeutic compounds. From the discovery of the penicillin derivatives, beta-lactam ring is considered as an alkylating agent, which binds and inhibits specific target proteins. Azetidinone moiety can bind and modify the activity of protease enzymes like serine (1) and cysteine proteases (2, 3). By this activity of azetidinone moiety, this may prove successful in antiviral and anticancer therapy. In cancer therapy, beta-lactam moiety plays a major role by binding with tubulin receptor or PSA (Prostate Specific Antigen). A contact inhibition property of the cell plays an important role in cancer therapy. Gosalvez has reported that TAC increases the contact inhibition properties in tumor cells, which potentiate the reverse transformation process in tumor cells (4). According to this study thiazolidine heterocyclic moiety has been focused on as a novel cancer drug design. The chemotherapeutic compounds containing thiazolidine and azetidinone heterocyclic moieties inhibit or control the growth of tumor cells by changing the physiological properties (reverse transformation) of the cell or binding with specific proteins like tyrosinase (5), PSA (Prostate Specific Antigen) and tubulin receptor.

In the recent cancer research, we have been focusing on novel compounds which control the tumor cell growth as well as minimum cytotoxic effects. In the present study, a series of novel thiazolidine and azetidinone derivatives were synthesized and tested for their antiproliferative activity.

EXPERIMENTAL SECTION

Material and Methods

Reaction courses were monitored by TLC on silica gel precoated F254 Merk plates and developed plates were examined by UV (254nm) chamber, iodine chamber and ninhydrin solution. Column chromatography was performed with a Merk 200 mesh silica gel. ^{1}H-NMR spectra were measured on Bruker400MHz, using TMS as an internal standard. Mass spectra were measured on ESI-MS. The chemicals were purchased from Sigma Aldrich.

General Experimental Procedure:

Preparation of Compound Ia : To a solution of cysteine amino acid (1 equiv. 8g) in dried acetone 60 mL was added 2,2-dimethoxy propane (6 equiv. 40 mL) followed by catalytic amount of PTSA and the reaction mass was stirred for 12 hours in room temperature under N_2 atmosphere. The reaction mass was concentrated under educed vacuum and later diluted with

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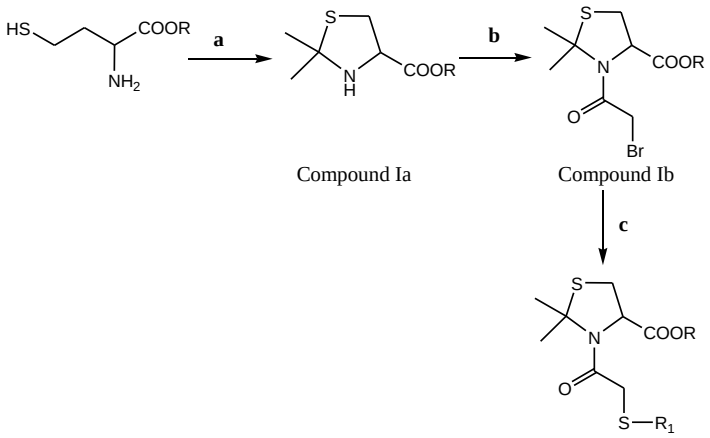
EtOAc (60 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (2 x 20mL). The organic layer was dried using anhydrous sodium sulphate, concentrated under reduced vacuum and purified using silica gel column chromatography (Gradient elution with 40:60% EtOAc in Hexane) to yield the desired thiozolidine (quanitity; yield= 85%)



Reagents and Conditions: (**a**) 2,2-Dimethoxy Propane, PTSA(cat.), Acetone, RT, 12 h; (**b**) $BrCH_2COBr$, TEA, DCM, -10 ^{O}C to -15 ^{O}C, 3h; (**c**) SH-R1, DCM, TEA, 0 ^{O}C, 3h.

Preparation of Compound Ib (Intermediate): To a stirred solution of compound I (1 equiv. 2 g) in toluene was added TEA (1.5 eqiuv. 2.2 mL) followed by $BrCH_2COBr$ (1.2 equiv. 1.1 mL) drop wise at -15 ^{o}C and the reaction mass was stirred for 3 hours under N_2 atmosphere by maintaining the temperature -10^{o}C to -15^{o}C. Brown solid mass was obtained as Compound Ib (Intermediate). Three major spots were found in TLC plate (gradient elution with 50-50% EtOAc in Hexane) under UV light. In mass spectrometry, three major molecular ion peaks were obtained. The reason behind in this problem was the reagent reacted with free –SH and $–NH_2$ groups of Cysteine. The percentage yield of the required product (compound Ib) was 30% and it was separated by preparative column chromatography.

Preparation of Compounds Ic, Id and Ie: To a stirred solution of compound Ib (intermediate) (1 equiv.) in DCM (20 ml) was added TEA (1.5 equiv.) followed by mercapto substituted heterocyclic compound (1 equiv.) and the reaction mass was stirred for 3 hours at 0^{o}C. The reaction mass was diluted with DCM (20mL) and sat. NaHCO3 solution (10mL). The organic layer separated, dried using anhydrous sodium sulphate and concentrated under reduced vacuum to yield the desired product.

Preparation of Compounds IIa, IIb, IIc and IId: To a stirred solution of mercapto substituted heterocyclic compound (1.2 equiv.) in THF (8 vol) was added $NaHCO_3$ (1.5 equiv.) and the reaction mass was stirred for 10 mins in room temperature. Water was added to the reaction mass until homogenous solution was formed. To the stirred reaction mass in THF was added AOSA (1 equiv.) and stirred for 18 hours at 50^{o}C to 55^{o}C under reflux. The reaction mass was diluted with DCM (20 mL) and sat. NaHCO3 solution (10 mL). The organic layer separated, dried using anhydrous sodium sulphate and concentrated under reduced vacuum to yield the desired

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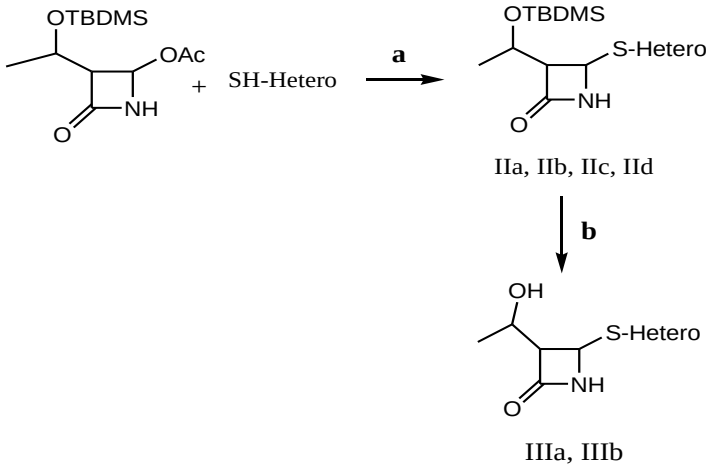
product. Purification of the crude compound over silica gel using column chromatography (gradient elution with 50-50% EtOAc in Hexane) gave the pure compound II.



Reaction and conditions: (a) $NaHCO_3$, THF, H_2O, 50°C-55°C, 18h; (**b**) DMF, NMP, $NH_4F.HF$ 50°C-55°C, 18h.

Preparation of Compounds IIIa and IIIb: To a stirred solution of compound IIa and IIb (1 g, 1equiv.) in DMF (5 ml) was added NMP (1.5 ml) followed by $NH_4F.HF$ (5 equiv.) and the reaction mass was stirred for 12 hours at 60°C under reflux. The reaction mass was concentrated under reduced pressure to afford the crude compounds IIIa and IIIb. The crude compound was purified over preparative silica gel plate.

Preparation of Compounds IVa and IVb: To a stirred solution of compound IIIa and IIIb (1 equiv.) in DCM (8 vol) was added TEA (1.5 equiv followed by $BrCH_2COBr$ (1.2 equiv.) drop wise at -15 °C and the reaction mass was stirred for 3 hours under N_2 atmosphere by maintaining the temperature -10°C to -15°C. To this reaction mass, mercapto substituted heterocyclic compound (1.2 equiv.) was added and the reaction mass was stirred for 3 hours at 0°C. The reaction mass was diluted with DCM (20mL) and sat. $NaHCO_3$ solution (10mL). The organic layer separated, dried using anhydrous sodium sulphate and concentrated under reduced vacuum to yield the desired product. The crude compound was purified over preparative silica gel plate (Gradient elution with EtOAc and Hexane).

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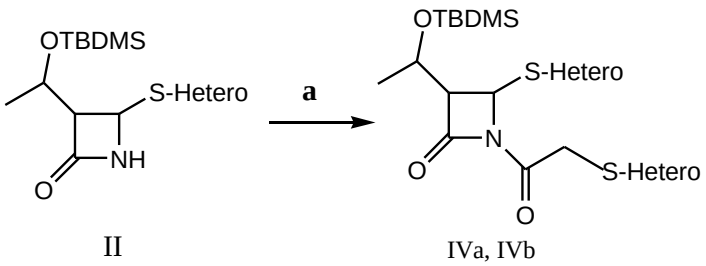
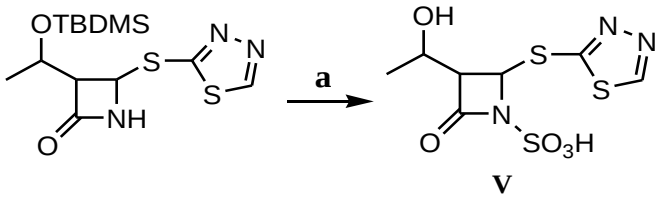


II IVa, IVb

Reaction and conditions: (**a**) (i) $BrCH_2COBr$, DCM, TEA, 3h (ii) SH-Hetero Group, 0 ^oC, 3h

Preparation of Compound V: To a stirred solution of compound IIa (1 equiv.) in DMF was added pyridine sulfonic acid and the reaction mass was stirred for 12 hours at 60^{o}C to 65^{o}C under reflux. The reaction mass was diluted with water (20 ml) and extracted with DCM (3x20 ml). The organic layer separated, dried using anhydrous sodium sulphate and concentrated under reduced vacuum to yield the desired product.



V

RESULTS AND DISCUSSION

Chemistry

Thiazolidine and its derivatives can be generated by the reaction of appropriate carbonyl compounds (aldehyde/ketone) with the Cysteine amino acid (α-aminothiols) (6). Thiazolidine ring formation occurred by imine formation followed by intra molecular cyclization (7) based on this we synthesized novel thiazolidine containing compounds and tested for their antitumor activity in MCF-7 breast cell lines. Presence of Thiazolidine moiety in compounds Ib, Ic, Id and Ie showed anti-tumor activity by enhancing the reverse transformation process and Azetidinone derivatives prepared from stable intermediate AOSA ((3S,4R)-4-Acetoxy-3-[(R)-1-(tert-butyldimethylsilyloxy)ethyl]azetidinone) (8). The Azetidinone moiety in the synthesized compounds plays a prominent role in cancer therapy by controlling the growth of tumor cells in MCF-7 cell line.

The Novel N-substituted thiazolidine derivatives were prepared using Cysteine. These compounds are unequivocally characterized by spectroscopic techniques. The NMR data of the final compounds are found to be in complete agreement with the reported values. The chiral

intermediate, was prepared either by the addition of bromo acetyl bromide or chloro acetyl chloride. In this process, bromoacetyl bromide was highly reactive, very sensitive and less stable compared to chloro acetyl chloride, but the reaction time drastically reduced while using bromo acetyl bromide.

Azetidinone derivatives were prepared from the standard stable intermediate (AOSA). These compounds are unequivocally characterized by spectroscopic techniques (HPLC, MASS and ^{1}H-NMR). N-substituted derivatives were prepared by the addition of bromo acetyl bromide followed by hetero compounds. The N-substitution in both moieties is responsible for stabilizing the ring.

The synthesized compounds were screened for *in-vitro* Antiproliferative activity studies at various concentrations. The percentage viability of cells was measured by MTT assay. **Table 3** and **4** shows the minimum viability percentage of the maximum Drug concentrations in µM.

Table 1: anti proliferative effects of Thiazolidine derivatives:

Compound	Concentration µM	% Cell Viability
Ia	50	73
Ib	30	62
Ic	40	65
Id	30	59
Ie	45	72

Table 2: anti proliferative effects of Azetidinone derivatives:

Compound	Concentration µM	% Cell Viability
IIa	50	85
IIb	40	77
IIIa	50	70
IVa	30	63
IVb	35	76
V	25	53

Among which the compounds in **Table 1** showed moderate activity. To optimize the ring, we incorporated bromo acetyl derivative in N-position in the thiazolidine moiety and synthesized some thiazolidine derivatives by replacing bromo atom with mercapto heterocyclic compounds and then measured its antitumor activity. We carried out this study using other novel compounds in **Table 2** containing azetidinone moiety. The N-substituted compound and N-sulfonic acid derivatives showed antitumor activity in MCF-7 breast cell lines. The synthesized compounds were characterized by NMR, MS and HPLC.

Reaction and conditions: (a) DMF, PYRIDINE-SO3H, 60^{o}C to 65^{o}C, 12 h.

Ethyl 2, 2-dimethyl-1,3-thiazolidine-4-carboxylate (Ia)

Yield, 85%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.29-1.32 (t, 3H, J= 7.16, 7.12), 1.53 (s, 3H), 1.7 (s, 3H), 2.5 (s, 1H), 3.05 (q, 1H), 3.42 (dd, 1H, J= 6.96), 4.05-4.09 (t, 1H, J= 8.16, 7.72), 4.3 (q, 2H); ESI-MS m/z 190 (M+1).

Ethyl 3-(bromoacetyl)-2,2-dimethyl-1,3-thiazolidine-4-carboxylate (Ib)

Yield, 35%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.3 (t, 3H, J= 7.16), 1.83 (s, 3H), 1.88 (s, 3H), 3.6-3.7(d, 1H, J= 10.84), 3.77 (d, 1H, J= 11), 3.29-3.49 (m, 2H), 4.25-4.30 (q, 2H); ESI-MS m/z 312 (M+1).

Ethyl 2, 2-dimethyl-3-[(pyridin-2-yl sulfanyl)acetyl]-1,3-thiazolidine-4-carboxylate (Ic)

Yield, 75%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.3 (t, 3H, J= 7.12), 1.7 (s, 3H), 1.9 (s, 3H), 3.6-4.2 (dd, J= 14.72, 14.76, 2H), 3.3 (m, 2H), 4.2 (d, 1H, J=14.76), 4.28-4.31 (q, 2H), 6.9-8.3 (m, 4H); ESI-MS m/z 341 (M+1).

Ethyl 2-methyl-3-[(1,3,4-thiadiazol-2-yl sulfanyl)acetyl]-1,3-thiazolidine-4-carboxylate (Id)

Yield, 78%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.3- 1.34 (t, 3H, J= 7.16), 1.8 (s, 3H), 1.9 (s, 3H), 3.3-3.4 (m, 2H), 4.09-4.05 (d, 1H, J= 15.28), 4.47-4.44 (d, 1H, J= 15.32), 4.2-4.3 (q, 2H), 5.24-5.23 (d, 1H, J= 5.12), 8.9 (s, 1H); ESI-MS m/z 348 (M+1).

Ethyl 2, 2-dimethyl-3-({[4-(pyridin-2-yl)-1,3-thiazol-2-yl]sulfanyl}acetyl)-1,3-thiazolidine-4-carboxylate (Ie)

Yield, 70%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.29-1.33 (t, 3H, J= 7.16), 1.8 (s, 3H), 1.9 (s, 3H), 3.25-3.29 (m, 1H), 3.34-3.37 (d, 1H, J= 11.96), 3.99-4.03 (d,1H, J= 14.8), 4.2-4.3 (q, 4H), 7.59 (s, 1H), 7.69-7.71 (d, 2H, J= 5.84), 8.65-8.67 (d, 2H, J= 5.84); ESI-MS m/z 424 (M+1).

3*S*, 4*S*-3-[(*R*)-1-(tert-butyl dimethyl-silyloxy) ethyl-4-(pyridin-2-ylsulfanyl)azetidin-2-one (IIa)

Yield, 83%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.08 (s, 6H), 0.89-0.87 (d, 9H, J= 2.84), 1.25-1.26 (d, 3H, J= 6.24), 3.1 (m,1H), 4.3 (m, 4H), 5.51-5.52 (d, 1H, J= 2.48), 7.06 (m, 1H), 7.2 (s, 1H), 7.52-7.53 (d, 1H, J= 1.88), 8.4 (m, 1H); ESI-MS m/z 339 (M+1).

3*S*, 4*S*-3-[(*R*)-1-(tert-butyl dimethyl-silyloxy)ethyl-4-{[4-(pyridin-4-yl)-1,3-thiazol-2-yl] sulfanyl} azetidin-2-one (IIb)

Yield, 82%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.1 (s,6H), 0.87-0.91 (d,10H, J= 17.68), 1.25-1.26 (d,3H, J= 5.28), 3.29-3.30 (t,1H, J= 2.44), 4.33(s,1H), 5.69-5.70 (d, 2H, J= 2.24), 6.67 (s,1H), 7.66 (s,1H), 7.71 (d,2H, J= 4.48), 8.67 (d,2H, J= 4.47); ESI-MS m/z 422 (M+1).

3*S*, 4*S*-3-[(*R*)-1-(tert-butyldimethyl-silyloxy)ethyl-4- (1,3,4-thiadiazol-2-ylsulfanyl) azetidin- 2-one (IIc)

Yield, 85%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.1 (s, 6H), 0.89-0.88 (d, 9H, J= 2.72), 1.26-1.24 (d, 3H, J= 6.28), 3.8 (m, 1H), 4.2 (m, 1H), 6.4 (s, 1H), 6.54-6.55 (d, 1H, J= 1.4), 8.3 (s, 1H); ESI-MS m/z 346 (M+1).

3*S*, 4*S*-3-[(*R*)-1-(tert-butyldimethyl-silyloxy)ethyl-4-{2-[2-(dimethylamino)ethyl]-2*H*-tetrazole-5- sulfanyl} azetidin-2-one (IId)

Yield, 89%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.1 (d, 6H), 0.77-0.78 (s, 9H, J= 4.12), 1.14-1.13 (d, 3H, J= 4.44), 2.19 (s, 6H), 2.70-2.73 (t, 2H, J= 6.48), 3.93 (m, 1H), 4.2 (m, 3H), 6.07-6.08 (d, 1H, J= 1.76), 6.6 (s,1H); ESI-MS m/z 401 (M+1).

3-(1-hydroxyethyl)-4-(pyridin-2-ylsulfanyl)azetidin-2-one (IIIa)

Yield, 65%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.38-1.39 (d, 2H, J= 6.24), 3.36 (m,1H), 4.26-4.29 (t, 3H, J= 6.52,7.68), 4.45 (s,1H), 5.36-5.37 (d, 1H, J= 1.84), 6.32 (s,1H), 7.1 (m,1H), 7.21-7.23 (d, 1H, J= 8.14), 7.59 (m,1H), 8.39 (m,1H); ESI-MS m/z 225 (M+1).

3-(1-hydroxyethyl)-4-{[4-(pyridin-4-yl)-1,3-thiazol-2-yl]sulfanyl}azetidin-2-one (IIIb)

Yield, 60%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.37 (m, 1H), 2.84 (s, 1H), 3.39 (m, 1H) 5.6 (d, 1H, J= 1.88), 6.64 (s, 1H), 7.65-7.71 (m, 4H), 8.67-8.69 (d, 2H, J= 7.92); ESI-MS m/z 308 (M+1).

3*S*, 4*S*-3-[(*R*)-1-(tert-butyldimethyl-silyloxy)ethyl-1-[(1,3,4-thiadiazol-2-ylsulfanyl)acetyl]-4-(1,3,4-thiadiazol-2-ylsulfanyl) azetidin-2-one (IVa)

Yield, 65%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.12 (d, 7H, J=6.64), 0.8 (s, 11H), 1.30-1.32 (d, 3H, J= 6.24), 3.6 (s, 1H), 4.36-4.40 (d, 2H, J= 10.8), 4.63-4.67 (d, 1H, J= 16.8), 7.1 (s, 1H), 8.3 (s, 1H), 8.9 (s, 1H); ESI-MS m/z 504 (M+1).

3*S*, 4*S*-3-[(*R*)-1-(tert-butyldimethyl-silyloxy) ethyl-1-[(pyridin-2-ylsulfanyl) acetyl]4-(1,3,4-thiadiazol-2-ylsulfanyl) azetidin-2-one (IVb)

Yield, 60%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.13-0.12 (d, 6H, J= 3.12), 0.8 (s, 10H), 1.5(s,3H), 3.6 (s, 1H) 4.27-4.31 (d, 1H, J= 16.6), 4.41-4.45 (d, 1H, J= 16.6), 4.41 (d, 2H), 6.9 (t, 1H, J=6.68), 7.1-8.3 (m, 4H), 8.2 (s,1H); ESI-MS m/z 497 (M+1).

3-(1-hydroxyethyl)-2-oxo-4-(1,3,4-thiadiazol-2-ylsulfanyl) azetidine-1-sulfonic acid (V)

Yield, 72%; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.36-1.35 (d, 3H, J= 6.14), 2.24-2.25 (d, 1H, J= 3.56), 3.82 (m, 1H), 4.35 (s, 1H), 6.5 (s, 1H); ESI-MS m/z 310 (M-1).

Evaluation of Antiproliferative Effects *in vitro*

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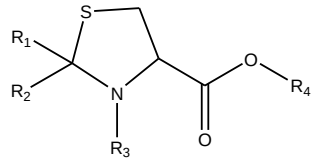
In vitro breast cancer studies were carried out in MCF-7 cells because the cell lines retain their ideal characteristics particular to the mammary epithelium. Cell culturing was done in $2.5x10^6$ cells per culture flasks, closed with a lid and placed in the incubator at 37°C with 5% CO_2. MTT assay was performed by plating the cells in 200µl media per well in a 96 well plate. This was incubated (37°C with 5% CO_2) overnight to allow the cells to attach to the walls. The drug was dissolved in DMSO, 2µl of drug added to each well and incubated (37°C with 5% CO_2) for 12, 24, 48 and 72 hrs, to allow the drug to take effect.

20µl of MTT solution (5 mg/ml of MTT in PBS) was placed on a shaking table, 150 rpm for 15 min, to thoroughly mix the MTT into the media. Again 96 well plates were incubated (37^oC, 5% CO_2) for 1-5 hours to allow the MTT to be metabolized. Resuspend formazan (MTT metabolic product) in 200 ul DMSO. Optical density was read at 560 nm and subtracts background at 670 nm. Optical density should be directly correlated with cell viability.

$$\% \text{ Cell Viability} = \frac{\text{sample absorbance} - \text{cell free sample blank}}{\text{mean media control absorbance}} \times 100$$



Antiproliferative Effects of Thiazolidine Derivatives On Breast Cancer Cell Lines (MCF-7)

Compound	R1	R2	R3	R4	% Cell Viability
Ia	CH_3	CH_3	H	C_2H_5	73
Ib	CH_3	CH_3	$COCH_2$-Br	C_2H_5	62
Ic	CH_3	CH_3	$COCH_2$-C_5H_4SN	C_2H_5	65
Id	CH_3	CH_3	$COCH_2$-$C_2HS_2N_2$	C_2H_5	59
Ie	CH_3	CH_3	$COCH_2$-$C_8H_5S_2N_2$	C_2H_5	72

Table 3: *In-Vitro Activity* of Thiazolidine Derivatives

Synthesized Thiazolidine and Azetidinone Derivatives

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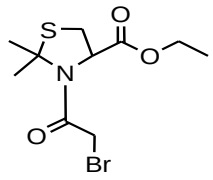
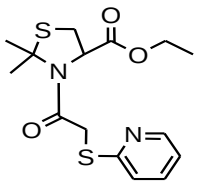


Ib



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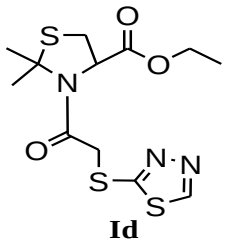

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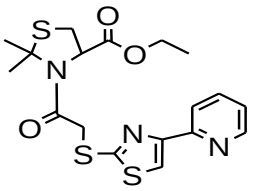

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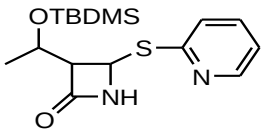
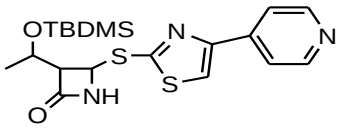


IIa



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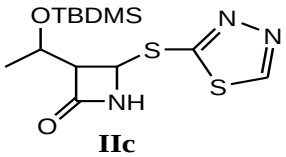
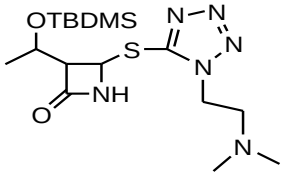


IIc



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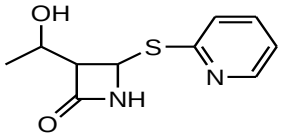
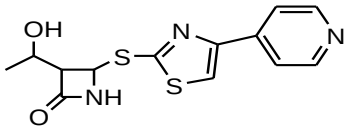
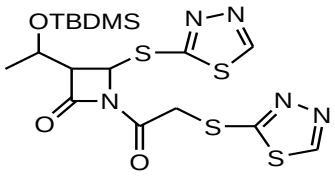


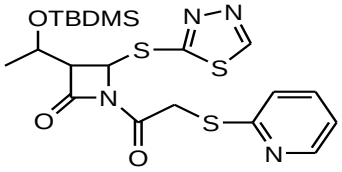
IIIa



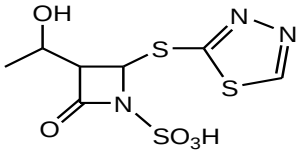
IIIb



IVa

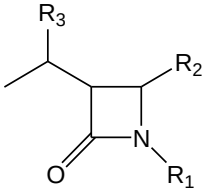


IVb



V

Table 4: *In-Vitro Activity* of Azetidinone Derivatives



Antiproliferative Effects of Azetidinone Derivatives On Breast Cancer Cell Lines (MCF-7)				
Compound	R1	R2	R3	% Cell Viability
IIa	H	C_5H_4SN	OTBDMS	85
IIb	H	$C_2HS_2N_2$	OTBDMS	77
IIc	H	$C_8H_5S_2N_2$	OTBDMS	NT
IId	H	CH_3	OTBDMS	NT
IIIa	H	C_5H_4SN	OH	70
IIIb	H	$C_8H_5S_2N_2$	OH	NT

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Iva	$COCH_2$-$C_2HS_2N_2$	$C_2HS_2N_2$	$COCH_2$-$C_2HS_2N_2$	63
IVb	$COCH_2$-$C_8H_5S_2N_2$	$C_2HS_2N_2$	$COCH_2$-$C_8H_5S_2N_2$	76
V	SO_3H	$C_2HS_2N_2$	OH	53

From the *in-vitro* studies of the synthesized compounds, compound Ib (N-substituted bromo acetyl derivative of thiazolidine) and compound Id showed 62% and 59 % of cell viability respectively at 30µM concentrations. N-sulfonic acid substituted derivative of azetidinone derivatives (Compound V) showed 53% viability at 25µM concentration.

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