



International Journal of Pharmaceutical Research and Development (IJPRD)

Platform for Pharmaceutical Researches & Ideas

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SYNTHESIS, CHARACTERIZATION AND *IN VITRO* ANTICANCER SCREENING OF THIAZOLIDIN-4-ONES

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ABSTRACT

A series of new thiazolidin-4-ones have been synthesized by the reaction of different substituted acetophenones with thiourea in presence of propanol to give 2-amino-4-aryl-thiazol (1) which react with chloroacetyl chloride to produce the corresponding 2-chloroacetamido-4-arylthiazoles (2). The latter was treated with potassium thiocyanate in refluxing acetone to afford the related 2-imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones (3). The synthesized compounds were characterized by spectral studies like IR, ¹H NMR and MASS spectroscopy. Anticancer evaluation of the synthesized compounds showed significant inhibition of cell by *in vitro* method using MTT assay.

Key words: Acetophenones, 2-imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones, Anticancer activity, MTT assay.

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INTRODUCTION

Thiazolidin-4-ones and their derivatives are in important class of compounds in organic and medicinal chemistry. The thiazolidin-4-one ring system is core structure in various synthetic pharmaceutical agents, showing the broad spectrum of biological activities such as anti-HIV, antitubercular, antibacterial, anticonvulsant, analgesic, antihistaminic, antidiabetic and anticancer. Thiazolidin-4-one are the derivatives of thiazolidin with carbonyl group at the 4th position and formed by the attack of sulphur nucleophile on

imine carbon followed by intramolecular cyclization with elimination of water.

The aim of the present work was to synthesized new thiazolidin-4-ones in order to find out new biologically active compound in the line of anticancer activity. Thus, synthesis of thiazolidin-4-ones has been achieved.

Cancer is the uncontrolled growth of abnormal cells in the body. Cancerous cells are also called malignant cells. so cancer is large and complex family of malignancies manifested with uncontrolled and undifferentiated cellular growth that can affect virtually every organ in the body.

Cancer begins in the body cells, which are constantly dividing and multiplying to replace old and damaged cells. Sometimes, cells begin to divide unnecessarily, forming excess tissue known as tumour.

Symptoms of cancer depend on the type and location of the cancer. For example, lung cancer can cause coughing, Cancer is a broad term used to encompass several malignant diseases. There are over 100 different types of cancer, affecting various parts of the body. Each type of cancer is unique with its own causes, symptoms, and methods of treatment. Like with all groups of disease, some types of cancer are more common than others.

Cancer is a disease of striking significance in the world today. It is the second leading cause of death after cardiovascular disease. Cancer is still considered as one of the most dreadful diseases despite the current improved methods of precautions, detections, surgery, and therapy hence prevention of cancer is the recognized goal of many activities in cancer research. Cancer is always linked to routine habits like cigarettes smoking, alcohol intake, and evening our daily diet. The diet is normally considered and consumed as a source of nutrients regardless of the consideration that it may also be one of the causes of cancer. A high intake of fat and excessive use of overheated animal foods has been related to cancer development. Therefore there is a need to discover and develop useful new lead compounds of simple structure, exhibiting optimal *in vitro* anti-tumour potency and new mechanism of action.

MATERIALS AND METHODS

Experimental: All the chemicals used in the synthesis were of analytical grade. The melting point were recorded in open capillary LAB INDIA visual melting point apparatus and is uncorrected. The IR spectra of the synthesized compounds were recorded on Shimadzu FT-IR spectrometer with potassium bromide pellets. Mass spectra were recorded on Shimadzu GCMS QP 5000. The ^1H NMR and spectra of the synthesized compounds were

recorded on AVANCE- 500 MHZ using DMSO as solvent (Chemical shift in δ ppm).

General procedure for synthesis

Synthesis of 2-amino-4-arylthiazole.

Acetophenone (0.05 mole) and thiourea (0.05 mole) was taken in a round bottom flask and dissolved in propanol (35ml) & refluxed for 2 h. The solid obtained was triturated with ethanol to remove unreacted acetophenone. To this pyridine (5 ml) was added & continued refluxed for 5 hrs. The reaction completion was monitored by TLC. After completion of reaction, the product obtained was filtered and dried. The recrystallisation was done by ethanol.

Synthesis of 2-chloroacetamido-4-arylthiazole

A solution of 2-amino-4-aryl thiazole (0.02 mole), in dry benzene (65ml) was cooled to 0-5 °C. Chloroacetyl chloride (0.04 mole) dissolved in dry benzene (20 ml) was slowly added to the above solution with vigorous stirring. When the addition was complete, the reaction mixture was refluxed for 3 h. The reaction completion was monitored by TLC. The resulting reflux solution is kept for evaporation to obtain product which is later washed with 5% Sodium bicarbonate & water to obtain the crude product. The crude product was dried and recrystallized from ethanol.

Synthesis of 2-imino-3-(4-arylthiazol-2-yl)-4-thiazolidinone

A mixture of 2-chloro acetamido -4- aryl thiazole (0.03 mole), KSCN (0.06 mole) and dry acetone (100 ml) was refluxed for 3 h. The resulting solution is kept for evaporation to obtain crude product, excess of acetone was removed *in vacuo*. The residue was stirred with water (50 ml). The solid product was filtered, washed with water, and dried. The crude product obtained was recrystallized with ethanol.

Characterization of synthesized compounds (S1-S6)

2-Imino-3(4-hydroxy phenyl thiazol-2-yl) thiazolidin-4-one (3a)

Yield: 60.94 %, m.p. 152-154 °C, IR Spectra (cm^{-1}): 3587 (OH), 3416 (=NH), 3101(Ar-C-H), 1661(C=O), 1582 (C=N), 705 (C-S); ^1H NMR (δ ppm): 2.4 (1H,

OH), 2.4- 3.9 (2H, cyclic), 3.8 (1H, NH), 6.8-7.8 (4H of Benzene); Mass Spectra (m/z): 291.357.

2-Imino-3(4-methoxy phenyl thiazol-2-yl) thiazolidin-4-one (3b)

Yield: 90.90 %, m.p. 62-164 °C, IR Spectra (cm⁻¹): 3407 (=NH), 3070 (Ar-C-H), 2930 (O-CH₃), 1667 (C=O), 1591 (C=N), 575 (C-S); ¹H NMR (δ ppm): 2.4 (1H, cyclic), 3.9-4.1 (2H, OCH₃), 4.2 (1H, NH), 6.8-7.6 (4H of Benzene); Mass (m/z): 305.384.

2-Imino-3(4-amino phenyl thiazol-2-yl) thiazolidin-4-one (3c)

Yield: 57.21 %, m.p. 154-156 °C, IR Spectra (cm⁻¹): 3498(=NH), 3210 (-NH₂), 3098 (Ar-C-H), 1664 (C=O), 1602 (C=N), 675 (C-S); ¹H NMR (δ ppm): 2.6-2.8 (2H, cyclic), 3.9 (1H, NH), 4.2-4.4 (2H, NH₂), 8.2-8.4 (4H of Benzene); Mass (m/z): 290.373.

2-Imino-3(4-nitrophenyl thiazol-2-yl) thiazolidin-4-one (3d)

Yield: 86.41 %, m.p. (158-160 °C), IR Spectra (cm⁻¹): 3402 (=NH), 3167 (Ar-C-H), 1525(-NO₂),

1671(C=O), 1587(C=N), 670 (C-S); ¹H NMR (δ ppm): 2.6-3.9 (2H, cyclic), 4.1 (1H, NH), 7.2-8.3 (4H of Benzene); Mass (m/z): 320.355.

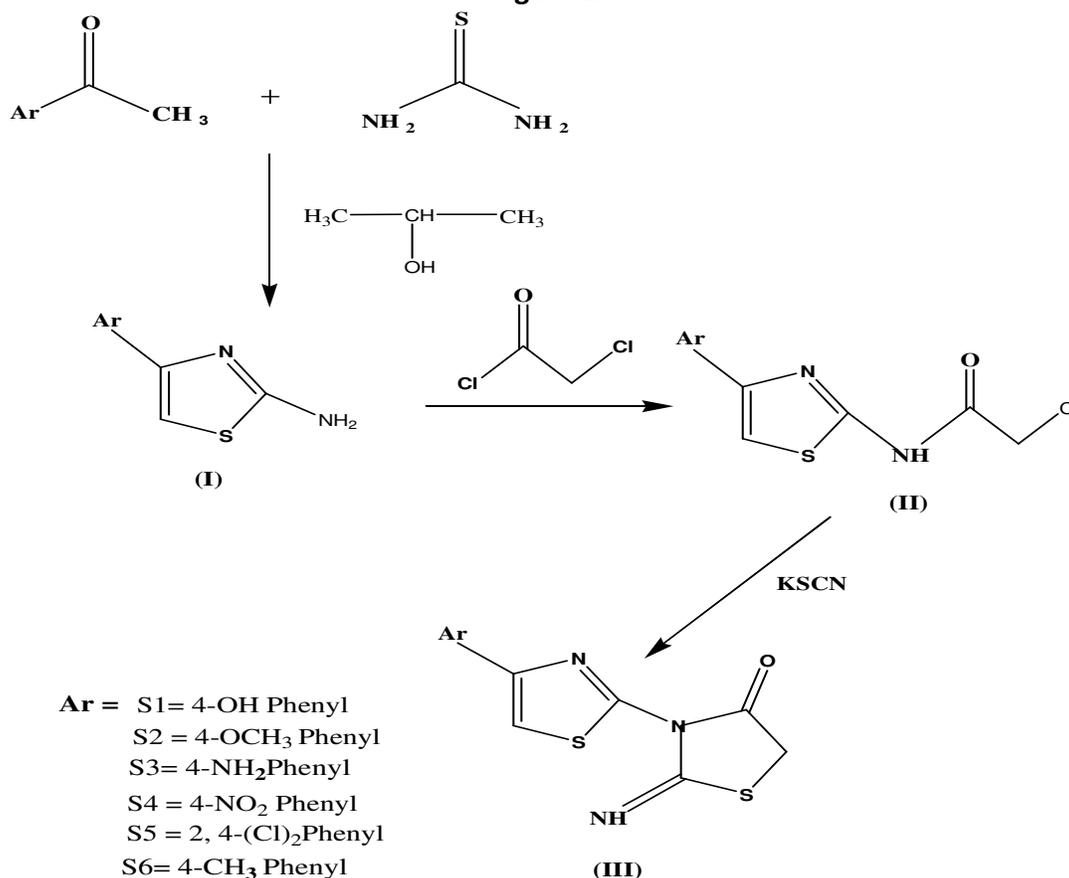
2-Imino-3(2, 4-dichloro phenyl thiazol-2-yl) thiazolidin-4-one (3e)

Yield: 97.70 %, m.p. (162-164 °C), IR Spectra (cm⁻¹): 3397(=NH), 3160 (Ar-C-H), 1778 (C=C), 1596 (C=N), 883(C-Cl), 681(C-S); NMR (δ ppm): 2.4 (1H, cyclic), 4.0 (1H, NH), 7.6-7.9 (4H of Benzene); Mass (m/z): 345.249.

2-Imino-3(4-methyl phenyl thiazol-2-yl) thiazolidin-4-one (3f)

Yield: 86.75 %, m.p. (128-130 °C), IR Spectra (cm⁻¹): 3484(=NH), 3072 (Ar-C-H), 1665 (C=O), 1601(C=N), 657 (C-CH₃), 638 (C-S); NMR (δ ppm): 1.4-1.6 (2H, cyclic), 2.4-2.7 (2H, OCH₃), 4.1 (1H, NH), 7.4-7.8 (4H of Benzene); Mass (m/z): 289.385.

Figure 1



Scheme: Synthesis of thiazolidin-4-ones

ANTICANCER ACTIVITY

All the synthesized compounds were tested for *in vitro* anticancer activity. The cytotoxicity study was carried out by MTT assay method and anticancer screening of title compounds were evaluated against the Human Cells Line {Human Colorectal cell line (HCT116)} at different concentrations of 0.1 μM , 1.0 μM , 10 μM , 100 μM in DMSO

RESULTS AND DISCUSSION

All the title Compounds (S1–S6) were found to exhibit mild to moderate anticancer activities in the human colorectal cells line (HCT 116) and the result was summarized in Table 1 and Fig 2.

Table 1 Percentage of toxicity in HCT116 cell line

S. N	COMPOUNDS	TEST CONC. (μM)	PERCENTAGE OF TOXICITY	
			HCT116	IC 50
1	Hydroxyphenyl	0.1(μM)		IC 50 =24.68
		1.0(μM)	14.2248	
		10(μM)	20.6180	
		100(μM)	27.8636	
2	Methoxyphenyl	0.1(μM)	19.2860	IC 50=14.70
		1.0(μM)	25.8391	
		10(μM)	36.1747	
		100(μM)	55.1411	
3	Aminophenyl	0.1(μM)	3.4629	IC 50=15.91
		1.0(μM)	11.8273	
		10(μM)	32.3921	
		100(μM)	67.6078	
4	Nitrophenyl	0.1(μM)	18.9578	IC 50=9.447
		1.0(μM)	27.1101	
		10(μM)	39.8977	
		100(μM)	56.8415	
5	Dichlorophenyl	0.1(μM)	20.2450	IC 50=4.895
		1.0(μM)	33.3510	
		10(μM)	53.9158	
		100(μM)	71.4970	
6	Methylphenyl	0.1(μM)	11.2940	IC 50=1.724
		1.0(μM)	32.5512	
		10(μM)	47.8950	
		100(μM)	65.6362	

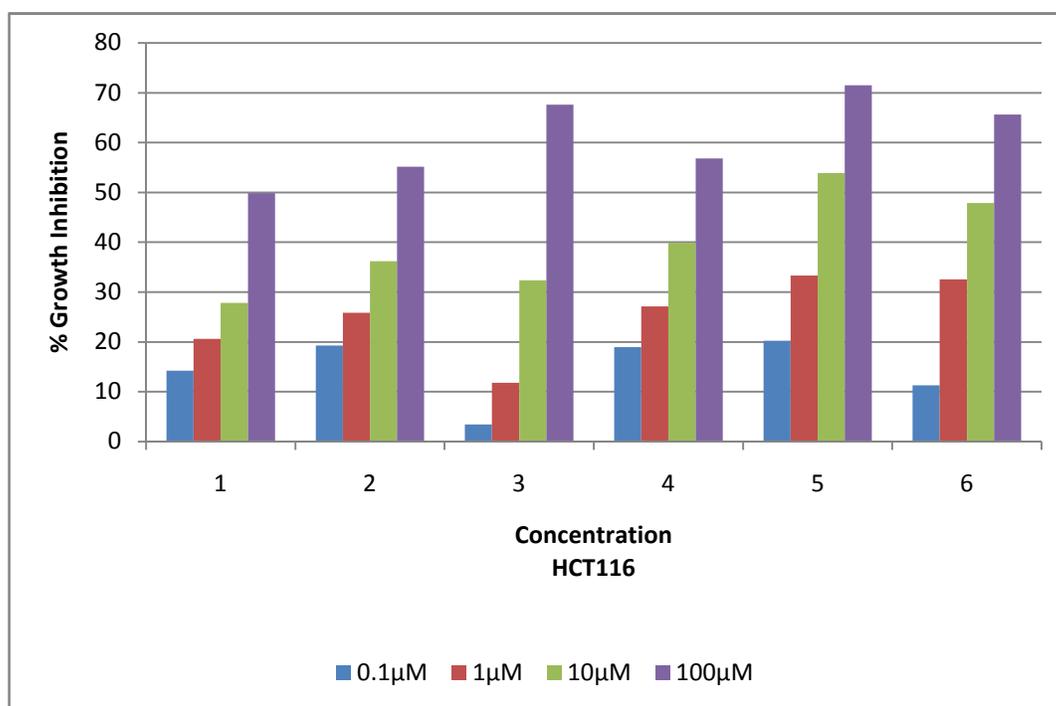


Fig 2 TGI of synthesized compounds for HCT 116

CONCLUSION

A series of thiazolidin-4-ones were successfully synthesized and tested for their *in vitro* anticancer activity. overall conclusion made for synthesized compounds are most of the compounds were more active against human colorectal cells line (HCT 116). whereas S5, S3 and S6 were found to exhibit good anticancer activity in HCT116 cell line when compared to S1, S2 and S4. The maximum activity is showed in S5.

ACKNOWLEDGMENT

J.K.K. Nattaraja college of pharmacy is acknowledge highly for providing all necessary facilities for this work.

REFERENCES

- 1) Ilango K, Valentina P. Text book of Medicinal chemistry. 5th edition, 2007; vol-II: preface.
- 2) Vijay V, Khurana L. A review on antimicrobial activity of 4-thiazolidinone derivatives. Int. J. Res. Pharm. Sci. 2011; (1): 17-27.
- 3) Shiradkar MR, Ghodake M, Bothara KG. Synthesis and anticonvulsant activity of clubbed thiazolidinone-barbituric acid and

thiazolidinone-triazole derivatives. ARKIVOC. 2007; 58-74.

- 4) Bhambi D, Sharma C, Salvi VK, Talesara GK. Synthesis and pharmacological studies of some phthalimidoxy substituted spiro-thiazolidinone derivatives of isatin. Indian. J. Chem. 2009; 48B: 1006-1012.
- 5) Patel D, Pate N. Synthesis and characterization of some new thiazolidinone containing coumarin moiety and their antimicrobial study. Arch. App. Sci. Res. 2010; 2(6): 68-75.
- 6) Mulay A, Ghodke M, Nikalje AP. Exploring Potential of 4-thiazolidinone: A Brief Review. Int. J. Pharm. Pharma. Sci. 2009; 1(1): 47-64.
- 7) Singh TP, Sharma PK, Kaur KK, Mondal SC. Pharmacological evaluation of thiazolidinone Derivatives: A Prespective Review. Der. Pharma. Chemica. 2011; 3(1): 194-206.
- 8) Sharma R, Nagda DP, Talesara GL. Synthesis of various isoniazido thiazolidinones and their imidoxy derivatives of potential biological interest. Arkivoc. 2006; (i): 1-12.
- 9) Ceylan M. Synthesis and antimicrobial activity of some new 3-substituted benzyl-5-(4-chloro-2-piperidin-yl - thiazol-5-yl-

- methylene)-thiazolidine-2, 4-dione derivatives. Turk. J. Chem. 2006; (30): 355-360.
- 10) Chavan AA, Pai NR. Synthesis and antimicrobial screening of 5-arylidene-2-imino-4-thiazolidin ones. Arkivok. 2007; 148-155.
- 11) Vagdevi HM, Vaidya VP, Latha KP, Padmashali B. Synthesis and pharmacological examination of some thiazolidinone derivatives of naphtha furan. Indian. J. Pharm. Sci. 2006; 68: 719-725.
- 12) Patel KH, Mehta AG. Synthesis of novel azetidinone and thiazolidinones derivatives and evaluation of their antimicrobial efficacy. E. J. chem. 2006; 11(3): 103-109.
- 13) Handan A, Oznur A, Seher I. Synthesis of Mannich bases of some 2, 5-disubstituted 4-thiazolidinones and evaluation of their antimicrobial activities. Turk. J. chem. 2005; 29: 425 -435.
- 14) Shah TJ, Desai KA. Synthesis of some novel fluorinated 4-thiazolidinones containing amide linkages and their antimicrobial screening. Arkivok. 2007; 218-228.
- 15) Bhoot DP, Khunt RC, Shankhavera VK. Synthesis of some new heterocyclic compounds. J. Sci. Isla. Rep. Iran. 2006; 17(4): 323-325.
- 16) Monk A. Feasibility of high flux anticancer drug screen using a diverse panel of cultured human cell lines. J. Nat. Canc. Inst. 1991; 83: 757-766.
