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Research Article

SYNTHESIS, CHARACTERIZATION AND EVALUATION OF 2, 4-THIAZOLIDINE-2, 4-DIONES NOVEL ANALOGUES FOR ANTICANCER POTENTIAL

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ABSTRACT

Compounds with halogen group substitution on aromatic ring exhibited promising activity. Compound 3i with the 2,3-dichloro group at the phenyl ring attached to heterocyclic thiazolidine-2,4-dione showed potent activity against HeLa cells when compared with reference drug adriamycin. Substitution at R with electron withdrawing groups such as chloro, bromo, iodo in compounds 3a, 3b, 3f, 3g and 3i showed increase in activity. The electron donating groups such as methoxy, ethoxy, methyl, ethyl and hydroxy substituted compounds 3c, 3e, 3j, 3l, 3m, 3o, 3p, 3r showed decrease in activity. The compound 3i with 2, 3-dichloro substitution on the phenyl ring exhibited IC50 value of 0.007 µM better than other substitutions. Compounds 3n with 3-NO2 groups showed significant improvement in activity. Compound 3h with 3-CN group substitution on the phenyl ring exhibited intermediate potency in the series. Constitutively, 3j and 3k containing 3-hydroxy and 3,4-di hydroxy groups attached to phenyl ring showed decrease in activity compared to other derivatives of the series, attributed to the presence electron withdrawing group decrease the potency. Here compound 3i which consist halogen group substitution on aromatic ring showed potent activity against HCT-8 cells when compared with reference drug adriamycin. Substitution at R with electron withdrawing groups such as 4-Cl, 3-Br, 4-Br and 2,3di-Cl (0.097, 0.056, 0.012, 0.011 µM, consecutively). Substitution at R with electron donating groups such as -4OCH3, 2, 5 di OCH3, 4C6H5O-, 3-OH, 3,4-di-OH, 4-Me, 3,4di Me, 4-NH2 and -4OC2H5 were showed decreased in activity against HCT-8 cells.

Keywords: Anticancer Agents, 2, 4- Thiazolidine-2,4-one, Chloroacetic Acid, IC50, HeLa cells.

INTRODUCTION

Cancer is the second leading cause of death globally and was responsible for around 8.8 million deaths in 2015. Globally, nearly 1 in 6 deaths is due to cancer. Approximately 70% of deaths from cancer occur in low and middle-income countries. Presently in India, it is a major cause of morbidity and mortality. Cancer cases, as well as mortality, are increasing rapidly among Indian women, primarily because of low awareness and late detection. Data showed that India accounts for the third highest number of cancer cases among women after China and the US, with a 4.5-5% growth rate annually [1, 2]. When a cell becomes uncontrolled with irregular growth may be responsible for cancer. It can affect almost any part of the body. External factors such as tobacco, infectious organisms, and an unhealthy diet, and internal factors, such as inherited genetic mutations, hormones, and immune conditions are the main cause of cancer. These factors may act mutually or in a series to cause cancer.

Data (2012-2014) collected from population-based cancer registries (PBCR) and hospital based registries showed that breast and cervical cancers are prominently found in Indian women. The northeast part of the country reported the highest number of cancer cases in both males and females. Breast cancer is the number one cancer, which estimates about 1.5 lakh (over 10 percent of all cancers) new cases in 2016. Tobacco

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users accounted for about 30 percent of all cancers in males and females [3].

Despite the huge efforts to implement novel chemotherapeutic strategies for the treatment of different types of cancer, this disease remains one of the major concerns worldwide. Consequently, there is an urgent need to find unexplored classes of substances with selective action against cancer cells. The regulation of the cell proliferations and apoptotic pathways associated with cell death is known as an important approach to understand a great variety of medical illnesses, including cancer [4, 5]. Therefore, the identification of cell-cycle regulators and apoptotic stimuli to combat cancer cells represents an attractive strategy to the discovery and development of potential antitumor agents [6, 7].

1.3. Thiazolidinediones

- Heterocyclic compounds play an important role in cancer therapy. Thiazolidinediones (TZDs) have been reported to be a potential scaffold which derived from five membered thiazole ring system. TZD ring consist of three carbon atoms, one nitrogen atom, and one sulfur atom with two double bonded oxygen at 2 and 4 positions is of considerable interest in different areas of medicinal chemistry [8]. Literature survey revealed that TZD is one of the important novel heterocyclic ring system has therapeutic importance and when combined with other heterocyclic rings produce wide range of biological activities such as anti-diabetic [9], anti-inflammatory [10], anti-oxidant [11], anti-tubercular [12], anti-microbial [13], anticonvulsant [14] and cytotoxic activities [15] (Figure: 1). For the exploration of novel and highly active therapeutic compounds the combination of two pharmacophores into a single molecule is an interesting, effective and mostly used direction in modern medicinal chemistry. When two pharmacophores of different oriantation binds with different molecular targets or with two distinct sites on the same molecular target could be beneficial for the treatment of cancer [16-18].

Drug Design

The drug is most commonly an organic small molecule that activates or inhibits the function of protein, which is beneficial to the treatment of different diseases. Classical drug discovery was exclusively based on observation of natural phenomena and consequences of relieved distress. Drug design is the creative process of finding new remedies based on the knowledge of a biological target. The approaches and steps typically encountered in the modern rational drug design, includes target identification, lead discovery, and lead modification. The subsequent steps required for drug development prior to regulatory approval includes pharmacokinetics, preclinical studies, clinical trials, and intellectual property issues.

The average cost of developing new drug molecules and the time taken to market them is extremely higher. We can reduce the time to develop new drugs, but cannot reduce the cost factor. The cost of these drugs increased by inclusion of new high throughput research technologies and for an increase in the number of studies required for new drug molecules. This cost effect reduces the number of new drugs coming to market. The reason behind this may be due to lack of knowledge about the target molecules. In the drug design process enzymes are frequently the target of choice because of their involvement in various biochemical pathways in human physiology. Even with enzymes, there can be problems in obtaining their structural information. Sometimes it is difficult to isolate or produce sufficient quantities of the target enzyme to study it directly [19]. These obstacles hinder the successful entry of drug candidates into the market. Therefore, there is an essential demand for efficient methods that could enhance the drug discovery process.

Approaches of QSAR methodology

Various hypotheses are introduced in the generation of QSARs techniques. These include

Extra thermodynamic approach (Hansch Analysis)

It is linear free energy-related approach which is divided into two classes.

Linear Models

Corwin Hansch, (1969) has given the significance of lipophilicity, presented as the octanol-water partition coefficient (P), on biological activity. Lipophilicity determines the compounds bioavailability which is the amount of compound that gets to the target site. The equation (univariate relationship) for the linear model is given by:

$$\log 1/C = a \log P + b$$

Where, C is the molar concentration of a compound that produces a standard response (e.g., LD_{50}, ED_{50}, IC_{50}, EC_{50} etc.) with other data, it was observed that correlation were improved by combining Hammett's electronic parameters and Hansch's measure of lipophilicity using an equation such as:

$$\log 1/C = k1\pi + k2\sigma + k3$$

Where σ is the Hammett substituent parameter and π is defined analogously to σ.

Non-Linear Models

In the failure of linear system of hydrophobicity it is extended to non linear model with the inclusion of logP2 value in the QSAR equation. This is a parabolic equation which defines many membranes must be traversed for compounds to get to the target site, and

those with greatest hydrophobicity will become localized in the membranes they encounter initially. Thus, an optimum hydrobhobicity may be found in some test systems.

The Hansch method [20] uses combination of lipophilic, electronic and occasionally steric substituent parameters to correlate changes in chemical structures with changes in biological response. It is usually expressed mathematically as:

$$\log 1/C = \Delta Gh + \Delta Ge + \Delta Gs + \text{constant}$$

$$\log 1/C = \text{alog}P - \text{blog}P2 + c\sigma + dEs + \text{constant}$$

Where LogP is logaritham of partition coefficient, σ is the Hammett electronic constant and Es is the Taft steric constant. a, b, c and d are the coefficients determined by multiple regression analysis top fit the biological data.

In literature review, several methods has been reported for the synthesis of 2, 4-thiazolidine-2,4-diones, but most of them are very complicated, having longer reaction time and require very advanced synthetic technology. The chemicals & reagents which are required for the synthesis are not easily available andtoo expensive. So in the present investigation, it is decided to synthesize different 2, 4-thiazolidinedione derivatives by efficient, cost effective, environmentally friendly technique.

MATERIALS & METHODS

Reagents and solvents

The chemicals used for the experimental work were procured from various chemical units such as Merck India Ltd., CDH (central drug house), Sigma - Aldrich, SD fine etc. The commercially available solvents and reagents were of LR and AR grade and purified before their use in different reaction.

- **MELTING Point –** Melting points of the compounds were determined in open glass capillaries using melting point apparatus and are uncorrected.
- **TLC –** Thin layer chromatography was performed on ready-made Aluminum backed TLC GF254 plates as well as on microscopic slides (2 x 7.5 cm) coated with silica gel G and spots were visualized by exposure to iodine vapors and UV radiation.
- **IR-** Infrared spectra of all compounds were recorded in FTIR on 8400S Shimadzu Fourier Transform spectrophotometer from KBr. The IR spectrum of compounds recorded in the region 4000-400 cm^{-1} on a Shimadzu FTIR spectrometer.
- **^{1}HNMR -** The proton magnetic resonance spectra were recorded on Bruker 400 MHz instrument in solvent (DMSO-d_6, $CHCl_3$). The chemical shift is given in δ (ppm) downfield from tetramethylsilane (TMS) as internal standard. Splitting patterns were designated as follows: s: singlet; d: doublet; t: triplet; m: multiplet
- **Mass-** Mass spectra were obtained on LC-MS Spectrometer using Model Q-ToF Micro Waters.

Scheme for synthesis

The synthetic work carried out during present investigation has been described in the following scheme.

Reaction Scheme

Synthesis of thiazolidine-2, 4-dione (1)

In a 250 ml three-necked flask, a solution containing 56.4g (0.6M) of chloroacetic acid in 60 ml of water and 45.6g (0.6M) of thiourea was dissolved in 60ml of water. The mixture was stirred for 15 minute till occurrence of white precipitates. To the contents of flask was now added slowly 60 ml of conc. hydrochloric acid from dropping funnel to dissolve the precipitates, after which the reaction mixture was stirred and refluxed for 10-12 hrs at 100-110˚C, on cooling the contents of flask were solidified to a mass of clusters of white needles. The product was filtered and washed with water to remove traces of hydrochloric acid and dried. It was recrystallised from ethanol.

R_f value: 0.64

Solubility: Product was soluble in water and ethyl alcohol.

Yield: 90%

M.P.: 123-125˚C.

IR (KBr) υ cm^{-1} 3156 (N-H), 3058 (Ar C-H), 1746 (C=O), 623 (C-S-C). **Annexure A**

Synthesis of (Z)-5-benzylidenethiazolidine-2, 4-dione (2)

A mixture of 2,4-thiazolidinedione 1 (2.4 g, 20 mmol), benzaldehyde derivative 2 (20 mmol), piperidine (1.4 g, 16 mmol) and ethanol (150 ml) was refluxed for 16–24 h. The reaction mixture was poured into H_2O and acidified with AcOH to give 3a–3d as solids, which were recrystallized from methanol. Completion of reaction has been confirmed using TLC using Benzene: Ethyl acetate as solvent system (3:7).

R_f Value = 0.8

Solubility: Product was soluble in ethyl alcohol.

Yield: 85%

M.P.: 173-175˚C.

IR (KBr) υ cm^{-1} 3323, 3170 (N-H), 3049 (Ar C-H), 1649 (C=O); 1H NMR (400 MHz, DMSO-d_6) δ 9.71 (s, 1H, -CHO), 8.25 (s, 1H, -N-H), 7.72 (d, J = 9.3 Hz, 2H, ArH), 7.50 (d, J = 8.0 Hz, 2H, ArH), 4.91 (s, 2H, NH_2); ESI-MS *m/z*: 165 [$(M+1)^+$, (13%)], 133 (24%, $C_8H_9O_2$), 105 (100%, C_7H_5O), 79 (22%, C_5H_3O), 63 (49%, C_5H_3).

Annexure A

Synthesis target compounds (3a to 3r)

To a solution of 2, 4-thiazolidinedione (0.1M) in DMF, formaldehyde (0.2M) was added under stirring. The reaction mixture was stirred at room temperature for

0.5hrs to complete the reaction of formaldehyde. To the solution of **secondary amine** in DMF was added drop wise and reflux for several hrs to complete the reaction. The completion of reaction monitored by TLC using solvent system chloroform: methanol (9:1). After the completion of reaction was poured in an ice cold water and filtered off and wash with hot water. Finally it was recrystallised from chloroform, ethanol to give final compound.

(5*Z*)-3-(aminomethyl)-5-(4-chlorobenzylidene)-1, 3-thiazolidine-2, 4-Dione (3a)

To a solution of 2, 4-thiazolidinedione (0.1M) in DMF, formaldehyde (0.2M) was added under stirring. The reaction mixture was stirred at room temperature for 0.5hrs to complete the reaction of formaldehyde. To the solution of **amine** in DMF was added drop wise and reflux for several hrs to complete the reaction. The completion of reaction monitored by TLC using solvent system chloroform: methanol (9:1). After the completion of reaction was poured in an ice cold water and filtered off and wash with hot water. Finally it was recrystallised from chloroform, ethanol to give final compound.

In the present study, 18 thiazolidine-2,4-dione derivatives have been synthesized which are outlined in **scheme 1**. The starting material thiazolidine-2,4-dione (1) was prepared by the reaction of chloroacetic acid with thiourea in the presence of hydrochloric acid. The compound 5-benzylidenethiazolidine-2,4-dione (2) was prepared by the reaction of 2,4-thiazolidinedione 1 (2.4 g, 20 mmol), benzaldehyde derivative 2 (20 mmol), piperidine (1.4 g, 16 mmol) and ethanol (150 ml) was refluxed for 16–24 h. The general procedure for the synthesis of final compounds (3a-3r) was reaction by 2, 4-thiazolidinedione (0.1M) in DMF, formaldehyde (0.2M) and secondary amine derivatives. The structures assigned to the compounds were supported by the results of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

Description of physical or chemical properties:

The synthesized compounds showed molecular weight within the range of Lipinski rule of five. The variation in molecular weights confirms the identity of compounds. Compound 3f showed the highest mol. wt. of the series which is 369. All compounds find with good percent yield that confirm the strength of synthetic procedures. Compounds such as 3b,, 3c, 3f, 3g, 3i, 3j, 3l, 3o, 3p, 3q and 3r showed highest percentage yield (70-90%) compared to other compounds of the series. Melting point represents the important physical properties of the compounds which show in the range of 250-350. R_f (retardation factor) value determine the fraction of an analyte in the mobile phase of a chromatographic system. The synthesized compounds show R_f value in the range 0.6 to 0.8.

Description of IR spectra:

FT-IR spectra of synthesized compound 1, thiazolidine-2,4-dione showed characteristic peaks at υ cm^{-1} 3130 (N-H), 3047 (Ar C-H), 1737 (C=O), 619 (C-S-C), whereas compound 2 showed peaks at υ cm^{-1} 3323, 3170 (N-H), 3049 (Ar C-H), 1649 (C=O). The FT-IR spectra of compound 3a showed peaks at υ cm^{-1} 3206 (N-H), 3055 (Ar C-H), 1695 (C=O), 1546 (C=N), and 1482 (C=C). The target compound 3b showed characteristic IR peaks at υ cm^{-1} 3182 (N-H), 3062 (Ar C-H), 1658 (C=O), 1546 (C=C) and 756 (C-F). The target compound 3c showed characteristic IR peaks at υ cm^{-1} 3285 (N-H), 3057 (Ar C-H), 1678 (C=O), 1535 (C=C). The compound 3d showed characteristic υ cm^{-1}3032 (Ar C-H), 1697 (C=O), 1546 (C=C), 1278 (C-O-C). The compound 3e showed characteristic peaks at υ cm^{-1} 3032 (Ar C-H), 1658 (C=O), 1546 (C=C), 1278 (C-O-C). The compound 3f showed characteristic peaks at υ cm^{-1} 3061 (Ar C-H), 1681 (C=O), 1502 (C=C), 1276 (C-O-C), 867 (C-Br). The compound 3g showed characteristic peaks at υ cm^{-1} 3030 (Ar C-H), 1697 (C=O), 1546 (C=C), 1070 (C-Br). The compound 3h showed characteristic peaks at υ cm^{-1} 3205 (-NH_2), 3032 (Ar C-H), 1658 (C=O), 1546 (C=C). The compound 3i showed characteristic peaks at υ cm^{-1} 3240 (N-H), 3030 (Ar C-H), 2993 (Ali C-H), 1681 (C=O). The compound 3j showed characteristic peaks at υ cm^{-1} 3140 (N-H)3028 (Ar C-H), 2922 (Ali C-H), 1668 (C=O), 1543 (C=C). The compound 3k showed characteristic peaks at υ cm^{-1} 3032 (Ar C-H), 2980 (Ali C-H), 1655 (C=O), 1544 (C=C). The compound 3l showed characteristic peaks at υ cm^{-1} 3150 (N-H), 3080, 3062 (Ar C-H), 1680 (C=O), 1286 (C-O-C). The compound 3m showed characteristic peaks at υ cm^{-1} 3086 (Ar C-H), 2993 (Ali C-H), 1670 (C=O), 1546 (C=C). The compound 3n showed characteristic peaks at υ cm^{-1} 3161 (N-H), 3072 (Ar C-H), 2978 (Ali C-H), 1670 (C=O), 1533 (C=C). The compound 3o showed characteristic peaks at υ cm^{-1} 3032 (Ar C-H), 2883 (Ali C-H), 1670 (C=O), 1546 (C=C), 1280 (C-O-C). The compound 3p showed characteristic peaks at υ cm^{-1} 3113 (N-H), 3080 (Ar C-H), 2968 (Ali C-H), 1691 (C=O), 1529(C=C). The compound 3q showed characteristic peaks at υ cm^{-1} 3168 (N-H), 3084 (Ar C-H), 2941 (Ali C-H), 1680 (C=O), 1535(C=C), 1286 (C-O-C). The compound 3r showed characteristic peaks at υ cm^{-1} 3055 (Ar C-H), 2949 (Ali C-H), 1693 (C=O), 1546 (C=C), 1247 (C-O-C), 742, 680 (C-Cl)

Description of NMR spectra:

^{1}H NMR spectra peaks of the respective protons of the synthesized compounds were verified on the basis of their chemical shifts (δ), multiplicities, and coupling constants (*J*). Compounds showed two doublet at around δ 8.152, 7.952 which could be accounted for two C-H groups of *para* substituted benzene, two singlet at around δ 10.255 and 8.259 indicative of thiazolidine-2,4-dione

N-H hydrogen and benzylidene C-H hydrogen. The compound 3a showed chemical shift δ 8.26 (s, 1H, =C-H), 8.15 (d, *J* = 1.76 Hz, 2H, ArH), 7.95 (d, *J* = 8.40 Hz, 2H, ArH), 5.11(s, 2H, NH_2), 4.23(s, 2H, -CH_2). The compound 3b showed peak around δ 8.60 (s, 1H, =C-H), 8.14 (d, *J* = 8.36 Hz, 2H, ArH), 7.94 (d, *J* = 8.40 Hz, 2H, ArH), 4.55 (s, 2H, -CH_2), 2.26 (s, 6H, -CH_3). The compound 3c showed peak around δ 7.95 (s, 1H, =C-H), 8.08 (d, *J* = 6.52 Hz, 2H, ArH), 7.89 (d, *J* = 6.44 Hz, 2H, ArH), 5.22 (s, 2H, -NH_2), 4.4 (s, 2H, CH_2), 3.83 (s, 3H, -CH3). The compound 3d showed peak around δ 8.22 (s, 1H, =C-H), 8.18 (d, *J* = 8.92 Hz, 2H, ArH), 7.91 (d, *J* = 7.16 Hz, 1H, ArH), 7.61 (d, *J* = 7.16 Hz, 1H, ArH), 4.55 (s, 2H, CH_2), 3.83 (s, 6H, -CH_3), 2.26 (s, 6H, CH_3). The compound 3e showed peak around δ 7.95 (s, 1H, =C-H), 8.06 (d, *J* = 9.96 Hz, 2H, ArH), 7.94 (d, *J* = 6.36 Hz, 2H, ArH), 7.92 - 7.57 (m, *J* = 5.92 Hz, 5H, ArH), 4.55 (s, 2H, CH_2), 2.26 (s, 6H, CH_3). The compound 3f showed peak around δ 7.95 7.96 (s, 1H, =C-H), 8.00 (d, *J* = 9.88 Hz, 2H, ArH), 7.93 (d, *J* = 6.88 Hz, 2H, ArH), 7.51 (d, *J* = 6.32 Hz, 2H, ArH), 7.12 (d, *J* = 8.00 Hz, 2H, ArH), 4.55 (s, 2H, CH_2), 2.64 (s, 4H, CH_3), 1.02 (s, 6H, CH_3). The compound 3g showed peak around δ 7.84 (s, 1H, =C-H), 8.14 (d, *J* = 7.2 Hz, 2H, ArH), 7.99 (d, *J* = 7.76 Hz, 2H, ArH), 4.55 (s, 2H, CH_2), 2.64 (s, 2H, CH_2), 2.26 (s, 3H, CH_3), 1.02 (s, 3H, CH_3). The compound 3h showed peak around δ 8.89 (s, 1H, =C-H), 8.29 (s, 1H), 8.12 (d, *J* = 7.28 Hz, 1H, ArH), 7.93 (d, *J* = 6.76 Hz, 1H, ArH), 7.64 (d, *J* = 9.44Hz, 1H, ArH), 7.55 (t, *J* = 9.68 Hz, 1H, ArH), 5.11 (s, 2H, NH_2), 4.84 (s, 2H, CH_2). The compound 3i showed peak around δ 8.84 (s, 1H, =C-H), 8.45 (d, *J* = 7.88 Hz, 1H, ArH), 8.36 (d, *J* = 6.80 Hz, 1H, ArH), 8.28 (d, *J* = 6.32 Hz, 2H, ArH), 5.11 (s, 2H, NH_2), 4.84 (s, 2H, CH_2). The compound 3j showed peak around δ 8.28 (s, 1H, =C-H), 8.05 (d, *J* = 6.56 Hz, 2H, ArH), 7.98 (d, *J* = 7.88 Hz, 1H, ArH), 7.86 (d, *J* = 7.92 Hz, 2H, ArH), 7.50 (t, *J* = 7.44 Hz, 1H, ArH), 5.11 (s, 2H, NH_2), 4.84 (s, 2H, CH_2). The compound 3k showed peak around δ 8.28 (s, 1H, =C-H), 8.23 (d, *J* = 8.48 Hz, 2H, ArH), 8.05 (d, *J* = 9.08 Hz, 1H, ArH), 7.71 (d, *J* = 7.32 Hz, 1H, ArH), 5.35 (s, 2H, OH), 4.55 (s, 2H, CH_2), 2.26 (s, 6H, CH_3). The compound 3l showed peak around δ 8.70 (s, 1H, =C-H), 8.13 (d, *J* = 12.88 Hz, 2H ArH,), 8.02 (d, *J* = 6.08 Hz, 2H, ArH), 5.11 (s, 2H, NH_2), 4.84 (s, 2H, CH_2), 2.34 (s, 3H, CH_3). The compound 3m showed peak around δ 8.28 (s, 1H, =C-H), 8.24 (d, *J* = 8.52 Hz, 1H, ArH), 8.09 (d, *J* = 8.44 Hz, 1H, ArH), 7.99 (d, *J* = 8.6 Hz, 1H, ArH), 4.55 (s, 2H, CH_2), 2.34 (s, 6H, CH_3), 2.26 (s, 6H, CH_3). The compound 3n showed peak around δ 8.30 (s, 1H, =C-H), 8.06 (s, 1H, ArH), 7.98 (d, *J* = 7.88 Hz, 2H, ArH), 7.88 (d, *J* = 8 Hz, 1H, ArH), 7.62 (t, *J* = 7.64 Hz, 1H, ArH), 5.11 (s, 2H, NH_2), 4.84 (s, 2H, CH_2). The compound 3o showed peak around δ 8.25 (s, 1H, =C-H), 8.05 (d, *J* = 9.8 Hz, 2H, ArH), 7.88 (d, *J* = 8.44 Hz, 2H, ArH), 7.78 (d, *J* = 8.36 Hz, 1H, ArH), 5.35 (s, 1H, OH), 4.55 (s, 2H, CH_2), 3.83 (s, 3H, CH_3), 2.26 (s, 6H, CH_3). The compound 3p showed peak around δ 8.38 (s, 1H, =C-H), 8.32 (d, *J* = 4.2 Hz, 2H, ArH), 8.30 (d, *J* = 4.24 Hz, 2H, ArH), 6.72 (s, 2H, NH_2), 5.11 (s, 2H, NH_2), 4.84 (s, 2H, CH_2). The compound 3q showed peak around δ 9.24 (s, 1H, =C-H), 8.53 (d, *J* = 8.92 Hz, 1H, ArH), 8.22 (d, *J* = 8.48 Hz, 1H, ArH), 8.40 (s, 1H, ArH), 5.35 (s, 1H, OH), 4.55 (s, 2H, CH_2), 2.6 (s, 6H, CH_3). The compound 3r showed peak around δ 8.81 (s, 1H, =C-H), 8.10 (d, *J* = 8.28 Hz, 2H, ArH), 7.95 (d, *J* = 6.12 Hz, 1H, ArH), 4.55 (s, 2H, CH_2), 4.09 (q, 2H, CH_2), 2.6 (s, 6H, CH_3), 1.32 (t, 3H), CH_3)

Description of Mass spectra:

The compounds showed m/z values in their respective range. The compound 2a showed peak at *m/z* 165 and base peak at *m/z* 105. The compound 3a showed molecular ion peak at *m/z*268 and base peak at *m/z*179. The base peak of compound 3a was (((4-ethoxyphenyl)ethynyl)sulfonium). Compound 3b showed molecular ion peak at *m/z*280 with base peak at 179 and other fragment peaks at *m/z*173, 145, 125. Similarly, other derivatives of the series showed their respective *m/z* value peaks according to molecular mass of the compounds. Compound 3c showed molecular ion peak at m/z 264 with base peak at 179. Compound 3d showed molecular ion peak at m/z 322 with base peak at 179.

The synthesized compounds 3a-r were evaluated for their anti-cancer activity against selected human cancer cell line of Cervical cancer cells (HeLa) and Colon carcinoma (HCT-8) using sulforhodamine B (SRB) method. The results of anti-cancer activity are expressed in terms of growth inhibition fifty (IC50 μM) values and are shown in Table 7.8 and Table 7.9.

Compound 3i was the most potent derivative of the series against both cell lines HeLa and HCT-8 with IC50 value of 0.007 μM and 0.001 μM, consecutively. By comparing the activities of 3i with other derivatives, it was revealed that the presence of chloro group at C-2 and C-3 positions of phenyl ring confers the highest cytotoxic activity against Cervical cancer and Colon carcinoma cell lines.

Furthermore, compound 3a and 3b showed good inhibitory activity against HeLa cells with IC50 value of 0.032 μM and 0.028, consecutively. Compounds 3f, 3g, 3n, 3q showed significant improvement in activity with IC50 values of 0.028, 0.055, 0.066, 0.032, 0.148 μM, consecutively, against HeLa cells. Compounds 3d, 3h, 3k, 3l, 3m, 3p and 3r showed the lowest potency in the series with IC50 values of 3.012, 3.087, 2.016, 3.087, 4.651, 7.139 and 2.253 μM, respectively against HeLa cells. Whereas, compounds 3c, 3e, 3i, 3j and 3o showed intermediate inhibitory activities.

HCT-8 cell line study revealed that compounds 3a, 3g, 3i, 3n showed potential activity with IC50 values of 0.097, 0.012, 0.001 and 0.023 μM, respectively. Compounds 3d, 3k, 3l, 3m and 3p and showed lesser

activity with IC50 values of 10.034, 8.012, 7.045, 8.034 and 10.012 µM, consecutively, against HCT-8 cell line. The structure activity relationships (SARs) indicate that compounds having phenyl ring attached to (3a-r) thiazolidine-2, 4-dione ring were important for anti-cancer activity.

The whole molecule divided into three parts where one thiazolidine-2,4-dione ring connected with disubstituted amino group. The literature survey revealed that when thiazolidine-2,4-dione connected with di-arylamino group important for activity.

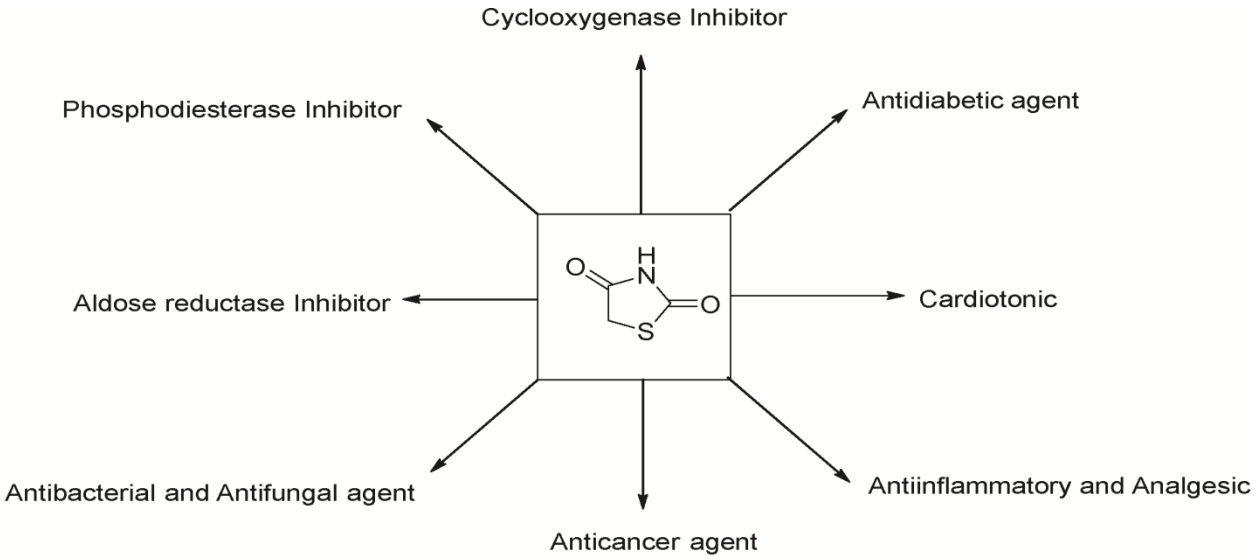
Table 1: Structure and properties such as molecular weight, yield, melting point and Rf value of synthesized compounds 3(a–r).

S. No.	Compd. No.	Mol. Wt.	Yield (%)	Melting point (˚C)	R_f
1	3a	268.717	65	220	0.7
2	3b	280.316	75	244	0.6
3	3c	264.298	86	236	0.9
4	3d	322.378	56	212	0.7
5	3e	354.423	47	190	0.6
6	3f	369.275	86	185	0.8
7	3g	355.249	76	178	0.8
8	3h	259.282	57	234	0.5
9	3i	303.162	86	207	0.7
10	3j	250.272	78	240	0.7
11	3k	294.325	65	216	0.8
12	3l	248.299	85	187	0.8
13	3m	290.379	67	227	0.7
14	3n	279.27	57	230	0.5
15	3o	308.351	86	239	0.7
16	3p	249.287	86	175	0.7
17	3q	312.77	85	198	0.7
18	3r	306.379	84	228	0.7

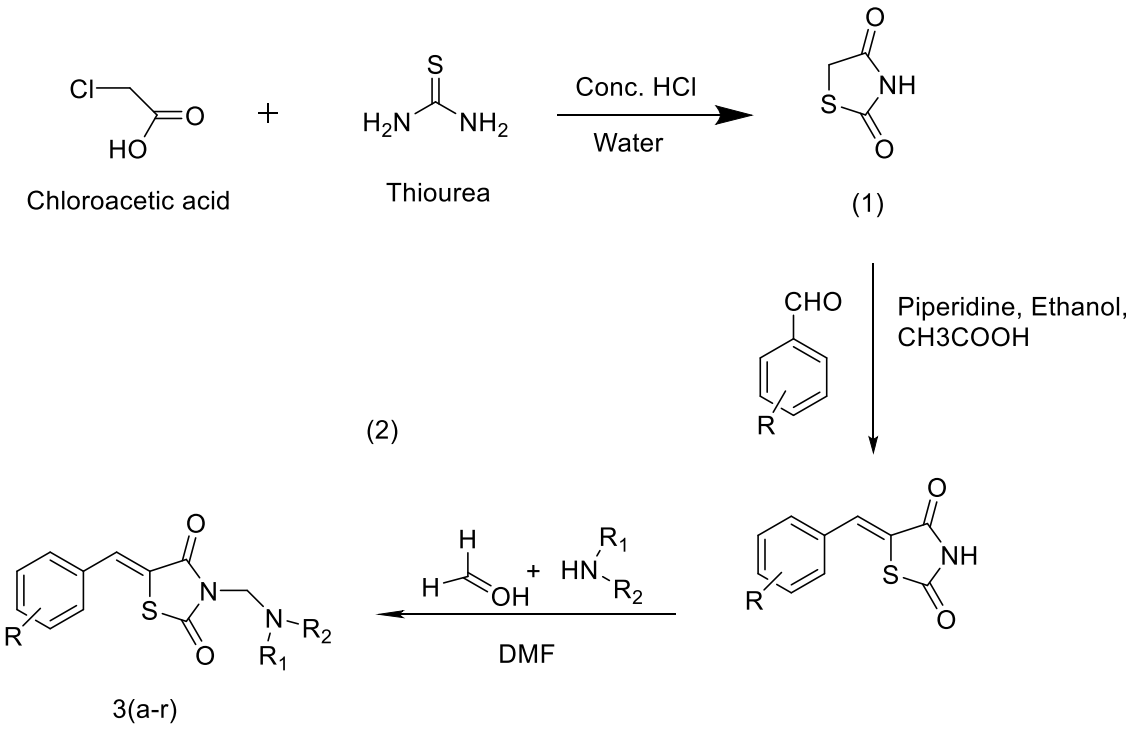
Table 2: In vitro antiproliferative activity (IC50)of synthesized compounds 3(a–r) against Cervical cancer cells (HeLa) and Colon carcinoma (HCT-8). *ADR = Adriamycin, positive control compound.

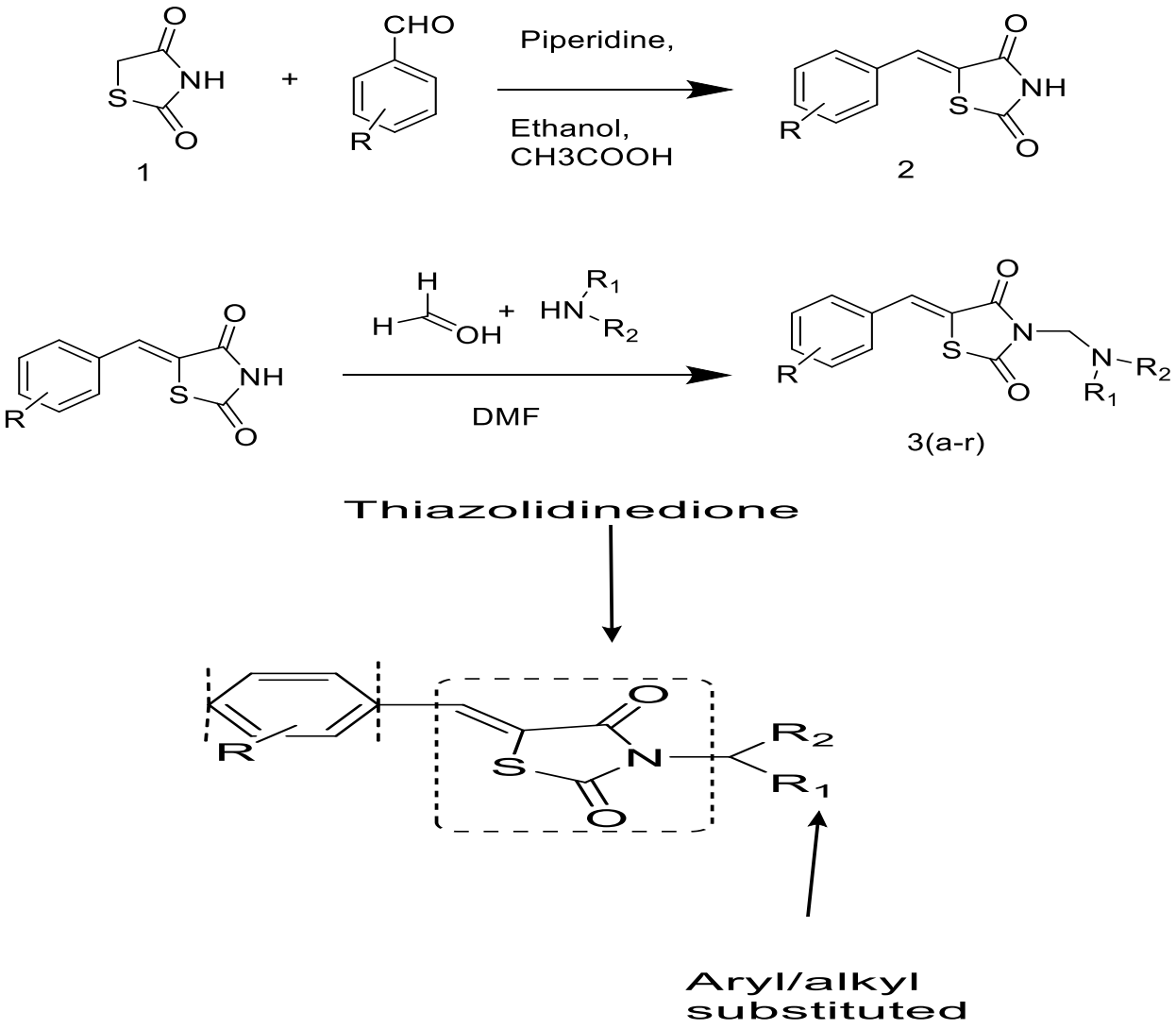
S.No.	Compd. No.	HeLa (µm) (Cervical cancer cells)	HCT-8 (µm) (Colon carcinoma)
1	3a	0.012	0.097
2	3b	0.028	> 25
3	3c	1.028	1.085
4	3d	3.012	10.034
5	3e	1.097	> 25
6	3f	0.055	0.056
7	3g	0.066	0.012
8	3h	3.087	0.123
9	3i	0.007	0.011
10	3j	1.572	4.065
11	3k	2.016	8.012
12	3l	3.087	7.045
13	3m	4.651	8.034
14	3n	0.032	0.023
15	3o	1.031	3.076
16	3p	7.139	10.012
17	3q	0.148	0.234
18	3r	2.253	5.012
Adriamycin		0.0001	0.0023

Role of thiazolidine-2, 4-diones in wide range of biological activities.



Reaction Scheme





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