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Synthesis and anticancer studies of 1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid derivatives

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Abstract: We herein reported the SAR driven synthesis of 2, 4-Dioxo-thiazolidins with the sulphonamide groups attached to pyrrolidine ring. The anticancer activities of twelve novel thiazolidins were studied for the Human breast MCF-7, colon HCT-15 and Hepatoma Hep-G2 cancer cell lines. Compound **7e**showed descent antitumor activities when compared to *Adriamycin*(GI_{50}<0.1)for all the three tested cell lines. In addition compound **7e** exhibit total cell growth inhibition potency (TGI = 98.8) for the Human breast MCF-7 cell line. The synthesized analougs were ensured by spectral and elemental analysis.

Keywords: *2, 4-Dioxo-thiazolidins, sulphonamides, proline, MCF-7, HCT-15, Hep-G2, antitumor activities*

Introduction

Clinically cancer is known as a malignant neoplasm and is a broad group of various diseases all involving unregulated cell growth. Rapid and uncontrolled cell growth leads to malignant tumours and occupy the nearby parts of the body. In medical state of affairs, cancer leftovers a foremost challenge in the world and it is a cause of more than 20% of all deaths. About 16 million of new cancer cases per year are estimated by the end of 2020 [4]. Adverse effects of the currently available cytotoxic anticancer agents are big pain in the treatment, which ultimately, leads to the need of newer entities bearing improved anticancer properties with minor side effects.

The combination of two pharmacophores into a single molecule is an effective and commonly used direction in modern medicinal chemistry for the exploration of novel and highly active compounds. The two pharmacophores are different in the case of heterobivalent ligands. Therefore, heterobivalent ligands containing pharmacophores that bind to different molecular targets or to two distinct sites on the same molecular target could be beneficial for

the treatment of cancer [1]. Thiazolidinediones containing marketed "glitazones" occupies a unique place as insulin sensitizers for the treatment of type-2 diabetes mellitus. On the molecular level, it is well documented that the glitazones exert their antidiabetic effects through binding to the Peroxisome Proliferator Activated Receptor gamma (PPARγ), a nuclear receptor which mediates the upregulation of specific genes leading to decreased insulin resistance, In addition to their antidiabetic effects, thiazolidinediones were discovered to have potential anticancer effects dependent on or independent of their antidiabetic molecular mechanism of action [2, 3]. Different mechanisms of the anticancer effects of the glitazones have been recently reviewed [4, 5]. It was reported that the glitazones inhibit cell proliferation by arresting cell cycle progression through targeting cyclin-dependent kinase (CDK) inhibitors such as p18, p21 and p27 [6]. The thiazolidine-2,4-dione (2,4-TZD) ring is also a well-known scaffold in medicinal chemistry and has been used to develop new potential anticancer agents [7-9], such as the PI3Kα inhibitor GSK1059615 and its analogues [10]. Research into the antitumor efficacy of molecules which contain the 5-arylidene-thiazolidine-2,4-dione system has received significant attention over the last years [11-13]. A series of 5-acridin-9-ylmethylene-3-benzyl-thiazolidine- 2,4-dione analogues showed a moderate antiproliferative activity (IC50: 4.1-58 μM) against a wide panel of cancer cell lines [14]. The α,β-unsaturated carbonyl system of the 5-benzylidene-thiazolidine-2,4-dione could act as a Michael acceptor, suggesting that the alkylation of the β-position of the reactive enone system by biological nucleophiles may be one mechanism by which antiproliferative activity was exerted *in vitro*.

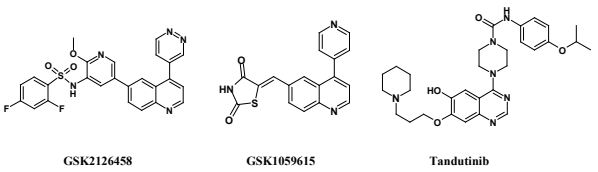


Fig.1.*Representative examples of anticancer sulfonamide, thiazolidinedione and aniline compounds*

Thiazolidinediones derivatives have been reported for broad spectrum of biological activities such as antioxidant [15], anticancer [16-18], anti-inflammatory [19-20], antimicrobial [21-22], anti-HIV [23-24], antiviral [25], anticonvulsant [26-27], and antihypertensive [28] activities. Sulfonamideplay an essential role in biological activities [29]. Combination of these two mentioned scaffolds in one molecule according seems to be a promising 'hybrid pharmacophore' approach to new anticancer agents.

Since 1,3,4-thiadiazole and thiazolidin-4-one moieties are biologically proven anticancer and antioxidant pharmacophores and substitution in these scaffolds may further enhance their activity, prompted us to undertake this problem. Moreover, the combination of two pharmacophores in a single molecule is a well established hypothesis for synthesis of more active drugs with dual activity. Thus, a series of novel sulphonamidesubstituted thiazolidine-4-oneswere synthesized and evaluated for their antioxidant and anticancer activity. In our earlier anticancer research [30] we have found that L-proline containing amide and hydrazide derivatives showed potential anticancer activities in MCF-7 and HCT-15 cell line when tested *in-vitro*. In continuation to this research here we have combine the two pharmacophores derived from the preclinical candidates of GSK, i.e. aryl sulphonamides and thiazolidinedione.

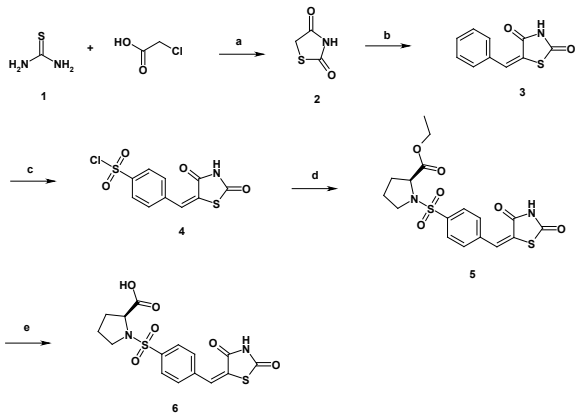
Based on the above findings, we were interested

in exploring the anticancer effects of novel thiazolidinediones analogous. Two series of thiazolidinediones with amides and hydrazides were synthesized. In the present work, the target compounds were evaluated for their cytotoxic activity against a panel of three human cancer cell lines namely breast cancer cells MCF-7, Colon cells HCT-15 and Hepatoma cells Hep-G2.

Chemistry

The targeted compounds were prepared from acid intermediate **6** as outlined in **Scheme 1**. The starting material 2,4-thiazolidinedione **2** was prepared by following the reaction of Thiourea **1** and chloroacetic acid in water with the presence of Conc. Hydrochloric acid. Knoevenagel condensation was achieved to synthesized intermediate **3** with 2,4-thiazolidinedione**2** and benzaldehyde in Toluene with the presence of piperidine. Aromatic sulfonylation was carried out on intermediate **3**under cooling to reflux condition by using chlorosulfonic acid to synthesized chloro sulfonyl intermediate **4**. L-Proline ethyl ester was introduced by replacing chloro group of 5-benzylidine-2,4-thiazolidinedione**4** in 2,4-dioxane and triethylamine to obtained the ester intermediate **5**.Acid intermediate 1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid **6**was obtained after the alkaline hydrolysis of ester intermediate **5**by using lithium hydroxide in THF-water.

Scheme 1*Synthetic route for1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid*(**6**)



Reagents and solvents: **a**.Conc.Hydrochloric acid,Water,Reflux ;**b**.benzaldehyde, piperidine, Toluene,Reflux, 3h; **c**.Chlorosulfonic acid **d.** L-proline ethyl ester hydrochloride, Et_3N, 2,4-Dioxane**e.** $LiOH.H_2O$, THF: H_2O

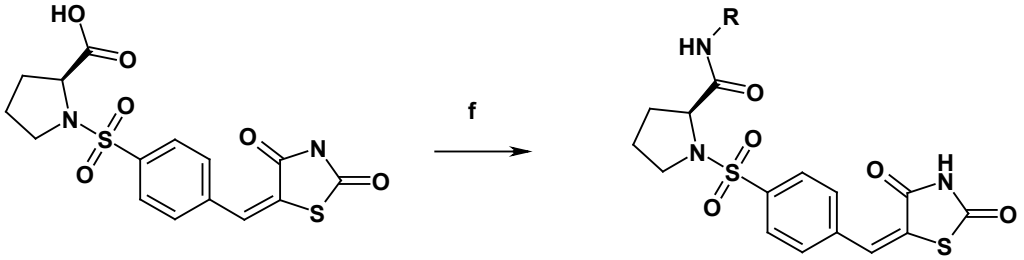
^{1}H NMR spectrum of **2** revealed the presence of singlet for one proton at δ 12.0 ppm corresponding to the NH and singlet for two protons at δ4.16 ppm corresponding to two methylene protons. Infrared (IR) spectrum of **2** showed bands at 3387 cm^{-1} (NH), 1684 cm^{-1}(C=O) and 622 cm^{-1} (C-S) groups respectively. ^{1}H NMR spectrum of **3** was identified by the characteristic multiplate of five aromatic protons at δ 7.49 to 7.62 ppm and singlet for benzylidine proton at δ 7.80 ppmfor CH proton. Chloro intermediate **4** was assigned by the shifted singlet at δ7.77 ppmfor CH proton and 2,4 thiazolidinone NH proton was shifted to δ 12.63 ppm. Crude ester intermediate**5** was used directly for hydrolysis reaction; its formation was confirmed by the ESI-MS spectrum showing *m/z*381.2. Acid intermediate **6** showed a characteristic triplet signal atδ4.14 ppm corresponding to chiral proton of L-proline and broad singlet at δ12.74 ppm for the thiazolidinedione NH proton.

Novel amide compounds **7a-f** were prepared by coupling selected amines with the acid core **6** as outlined in **Scheme 2**.Substituted aromatic and aliphatic amines were selected to evaluate the structure activity relationship among the novel analogs. Coupling reactions were performed by

using EDC.HCl and HOBt in DMF AT 25°C. Purification of the desired product was achieved by crystallization and characterized by spectral and elemental analysis.

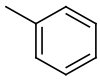
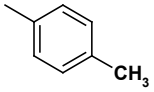
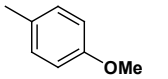
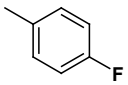
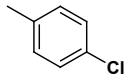
Similarly hydrazide derivatives containing aliphatic and aromatic hydrazide were also studied for anticancer activities. Synthesized compounds**8a-f** by coupling selected hydrazide

Scheme 2 *Synthetic route for1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid amides*(**7a-g**)

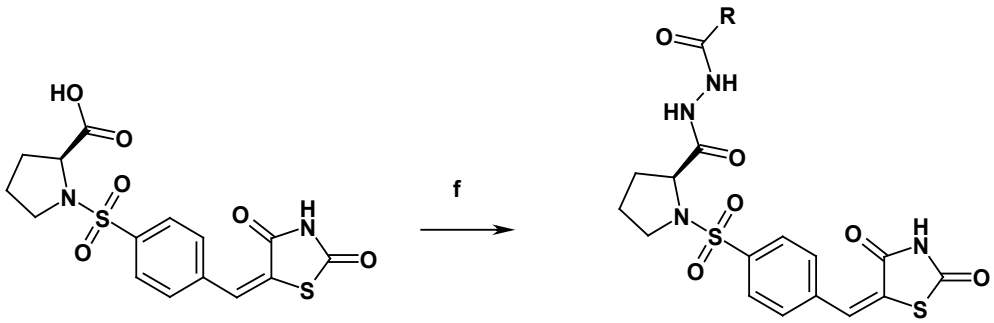


6 **7a-f**

f. R-Amine, EDC.HCl/HOBt, DMF, RT

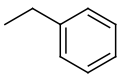
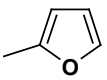
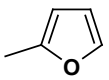
Compound	7a	7b	7c	7d	7e	7f
R						

Scheme 3 *Synthetic route for1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid hydrazide*(**8a-f**)



6 **8a-f**

f. R-Hydrazide, EDC.HCl/HOBt, DMF, RT

Compound	8a	8b	8c	8d	8e	8f
R						

with the acid core **6** as outlined in **Scheme 3**. Coupling reactions were performed by using EDC.HCl and HOBt in DMF AT 25°C. Purification of the desired product was achieved by crystallization and characterized by spectral and elemental analysis.

Biology

Antitumor activity

All the prepared target compounds **7a-f** and**8a-f** were screened for their antitumor activities against breast MCF-7 cell line and colon HCT-15 cell lines at Anti-Cancer Drug screening facility (ACDSF), Tata memorial centre, Navi Mumbai.

Experimental procedure for SRB assay [31]

The cell lines were grown in RPMI 1640 medium containing 10% fetal bovine serum and 2 mM L-glutamine. For present screening experiment, cells were inoculated into 96 well microtiter plates in 90 µL at 5000 cells per well. After cell inoculation, the microtiter plates were incubated at 37°C, 5%CO_2, 95% air and 100 % relative humidity for 24 h prior to addition of experimental drugs. Experimental drugs were solubilized in appropriate solvent to prepare stock of 10^{-2} concentration. At the time of experiment four 10-fold serial dilutions were made using complete medium. Aliquots of 10 µl of these different drug dilutions were added to the appropriate micro-titer wells already containing 90 µl of medium, resulting in the required final drug concentrations.

After compound addition, plates were incubated at standard conditions for 48 hours and assay was terminated by the addition of cold TCA. Cells were fixed *in situ* by the gentle addition of 50 µl of cold 30 % (w/v) TCA (final concentration, 10 % TCA) and incubated for 60 minutes at 4°C. The supernatant was discarded; the plates were washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (50 µl) at 0.4 % (w/v) in 1 % acetic acid was added to each of the wells, and plates were incubated for 20 minutes at room temperature. After staining, unbound dye was recovered and the residual dye was removed by washing five times with 1 % acetic acid. The plates were air dried. Bound stain was subsequently eluted with 10 mMtrizma base, and the absorbance was read on an Elisa plate reader at a wavelength of 540 nm with 690 nm reference wavelength.

GI_{50}	Growth inhibition of 50 % (GI50) calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50, drug concentration resulting in a 50% reduction in the net protein increase
TGI	Drug concentration resulting in total growth inhibition (TGI) will calculated from Ti = Tz
LC_{50}	Concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of 50% cells following treatment is calculated from [(Ti-Tz)/Tz] x 100 = -50.

Percent growth was calculated on a plate-by-plate basis for test wells relative to control wells. Percent Growth was expressed as the ratio of average absorbance of the test well to the average absorbance of the control wells * 100. Using the six absorbance measurements [time zero (Tz), control growth (C), and test growth in the presence of drug at the four concentration levels (Ti)], the percentage growth was calculated at each of the drug concentration levels. The dose response parameters were calculated for each test article. Growth inhibition of 50 % (GI_{50}) was calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth

inhibition (TGI) was calculated from Ti = Tz. The LC_{50} (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment is calculated from [(Ti-Tz)/ Tz] x 100 = -50.

Values were calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the values for that parameter were expressed as greater or less than the maximum or minimum concentration tested.

All tested compound, except **7e**(TGI =98.8), showed **TGI >100** and **LC_{50}>100** for both the breast MCF-7 and colonHCT- 15cell line.

Results and Discussion

A substituted aniline derivative often improves the activity of different pharmacophores and hence plays an important role for various SAR studies. It was also found that these substituted aniline derivatives could be potential anticancer agents [tandutinib)] **Fig 1**. With the above facts, here we have designed and prepared six novel compounds, (**7a-f**). The results of the study were tabulated in **Table 1**.The variation was brought across acid core **6** with five different anilines to get the desired derivatives (**7b–f**). In this series, 4-Fluoro aniline compound **7e** has shown remarkable inhibitory activity in MCF-7 cell line (GI_{50} = 0.1 µmol/L) with good inhibitory activities in HCT-15 cell line(GI_{50} = 56.9 µmol/L) and Hep-G2 cell line(GI_{50} = 32.2 µmol/L). All the other aniline derivatives showed very poor inhibitory activity inHCT-15 cell line.

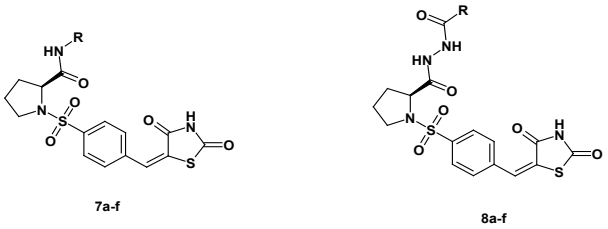


Table 1*$GI_{50}$of the tested compounds against human tumour cell line*

Compounds	R	GI_{50} (µmol/L)		
		Breast MCF-7	Colon HCT-15	Hepatoma Hep-G2
7a	Cyclohexyl	58.1	> 80	99.9
7b	Phenyl	>100	> 80	> 80
7c	4-Methyl phenyl	>100	> 80	> 80
7d	4-Methoxy phenyl	74.7	> 80	> 80
7e	4-Fluoro phenyl	**< 0.1**	24.0	32.2
7f	4-Chloro phenyl	49.0	71.8	> 80
8a	Cyclohexyl	>100	88.7	>100
8b	Phenyl	>100	>100	>100
8c	Phenyl methyl	>100	>100	>100
8d	3-Pridyl	>100	>100	>100
8e	2-Thiophenyl	>100	>100	>100
8f	2-Furyl	>100	63.5	>100
Reference	***Adriamycin***	**< 0.1**	**< 0.1**	**<0.1**

4-Chloro aniline **7f** revealed inferior activity in MCF-7 cell line than the 4-Fluoro aniline compound **7e**. 4-Methoxyaniline **7d** found to show better activity than 4-Methylaniline **7c** in MCF-7 cell line, for HCT-15 cell line and Hep-G2 cell line both are equally inferior.

Here, electron withdrawing group found to improving the potential of inhibiting the anticancer activities in MCF-7 cell line;

therefore it was observed that compound **7e** and compound **7f** are superior to compound **7c** and compound **7d**, respectively. Only compound **7e** and compound **7f** were showed notable contribution among the compounds **7a–f** in Human Colon Cancer Cell Line HCT-15. When we compare the activities of aniline **7b** with the cyclohexyl amine **7a**, we found that compound **7a** showed better inhibition in MCF-7 cell line(GI_{50} = 58.1μmol/L) and Hep-G2 cell line (GI_{50} = 99.9 μmol/L) than **7b**.In conclusion, between the three studied cell lines, compound **7e** was found to be potent for MCF-7 cell line.
Hydrazide compounds **8a-f** werealso studied for the anticancer activities inMCF-7 cell line , HCT-15 and Hep-G2 cell line. All the testedcompounds 8a–e was reportedly showed (GI_{50}> 100μmol/L) in MCF-7 cell line and Hep-G2 cell line. Compound **8a** (GI50 = 88.7 μmol/L) and compound**8f** (GI50 = 63.5μmol/L) exhibiting the anticanceractivities for the human colon HCT-15 cell line.Compound **8a** contains Cyclohexane carboxylic acid hydrazideside chain and compound **8f** was with 2-Furoic acidhydrazide side chain. Between the two series of compounds containing substitutedanilines **7a–e**andhydrazide side chains **8a–f**, it was found that substituted anilines resulted in improved activitiesin MCF-7 cell line than HCT-15 cell line and Hep-G2 cell line. Hydrazidecompounds were very poor in all the three tested cell lines.

Experimental

All the raw material were obtained commercially and used without further purification. ^{1}H NMR spectra were recorded using $CDCl_3$ and DMSO-d_6 as solvent with tetramethylsilane (TMS) as an internal standard on Varian 400-MHz instruments. Elecronspray ionization-mass pectra were recorded on LC-MS/MS Waters (Aquity) TQ detector instrument, Elemental analysis is reported from Vario Micro Elementar instrument. Melting points were taken on Veego melting point apparatus model VMP-D.

2,4-thiazolidinedione **(2)**To a solution of chloroacetic acid (60g, 0.6 mol) in 60 ml of water was added thiourea(50 g, 0.6 mol) dissolved in 60 ml of water was added. The mixture was stirred for 15 min to form a white precipitate, accompanied by considerable cooling. To the contents of the flask, 60 ml of concentrated hydrochloric acid was then added slowly from a dropping funnel, the flask was then connected with a reflux condenser and gentle heat applied to effect complete solution, after which the reaction mixture was stirred and refluxed for 8-10 h at 100-110 °C. On cooling the contents of the flask solidified to a cluster of white needles, the product was filtered and washed with water to remove traces of hydrochloric acid and dried. It was purified by recrystallized from ethyl alcohol to gave white crystalline solid (60g,Yield =85%).m.p. 122-127°C, IR (KBr disk) 3387 cm^{-1} (NH), 1684 cm^{-1} (C=O), 622 cm^{-1} (C-S).mp 123-124 °C. IR (KBr, cm^{-1}) 3250 (N-H), 1710 and 1680 (C═O). ^{1}H NMR (400 MHz, δ, ppm, DMSO-d_6) 12.00 (s, 1H, NH), 4.14 (s, 2H). ^{1}H-NMR (DMSO-d_6) D_2O Exchange experiment δ in ppm: 4.16 (s, 2H); ES-MS:*m/z*118.2 $(M+H)^+$.

5-benzylidine 2,4-thiazolidinedione **(3)** To a suspension ofbenzaldehyde (22.6g, 0.213 mol) and 2,4-thiazolidinedione (25g, 0.213 mol) in Toluene was added a catalytic amount of piperidine (1 mL). Attached a dean-stark apparatus, and the mixture was stirred and refluxed. After the complete removal of water and when the temperature reached above 110 °C, the reaction mixture was stirred for a further 3 h. On cooling, the product precipitated out from Toluene. The compound was filtered and washed with cold toluene and dry ethanol to offered 40g yellowish solid Yield 93 %.m.p. 238-243 °C, IR (KBr disk) 3360 cm^{-1} (NH), 1684 cm^{-1} (C=O), 628 cm^{-1} (C-S).IR (KBr) ν_{max}/ cm^{-1}: 3135, 3029, 1737, 1690, 1603. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.49-7.62 (m, 5H, Ar-H), 7.80 (s, 1H, CH), 12.64 (s, 1H, NH); ES-

MS:*m/z*206.3 $(M+H)^+$.

4'-chlorosulfonyl-5-benzylidine-2,4-thiazolidinedione **(4)** To a solid 5-Benzylidine 2,4-thiazolidinedione (35g, 0.170 mol) was added Chlorosulfonic acid (45ml, 0.682 mol) at room temperature using the dropping funnel and attached condenser. The reaction was found to be exothermic. After addition of chlorosulfonic acid completed, the reaction mass was refluxed for 1 h on a water bath. The reaction was cooled and poured in a thin stream with stirring into crushed ice contained in a 1 L beaker. The product was filtered and dried.The product was purified by recrystallization from ethanol to furnish yellowish solid (35g Yield 68 %).m.p. 177-182 °C, IR (KBr disk) 3360 cm^{-1} (NH), 1684 cm^{-1} (C=O), 1120 and 1310 cm^{-1} (SO_2 sym and asym), 763 cm^{-1} (Cl), 628 cm^{-1} (C-S); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.56 (d, 2H,*J* =8.4 HzAr-H), 7.71 (d, 2H,*J* =8 Hz, Ar-H), 7.77 (s, 1H, CH), 12.64 (s, 1H, NH); ES-MS:*m/z*303.1$(M+H)^+$.

1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid ethyl ester**(5)**To a stirred solution of L-proline ethyl ester hydrochloride (12g, 0.066 mol) in Dioxane (120 ml) was added triethylamine (28 ml, 0.198 mol) followed by the drop wise addition of 4'-chlorosulfonyl-5-benzylidine-2,4-thiazolidinedione (20g, 0.066 mol) in Dioxane (100 ml) at 0°C. Allowed the reaction mixture to come to 25°C and stirred for 3h. Dioxane and other volatiles were removed under reduced pressure and residue was taken in EtOAc, washed with water, 1N HCl solution in water and saturated $NaHCO_3$ solution in water. Collected organic layers were dried over $Na_2SO_4$and removed under vacuum to yield ester intermediate as a yellowish gel (22g, 82 %)**5**. This was used without further purification. ES-MS:*m/z*411.3 $(M+H)^+$.

1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid**(6)**To a suspension of ester compound **5** (20 gm, 0.048 mol) in THF (160 ml) and water (40 ml) was added lithium hydroxide monohydrate (3 g, 0.072 mol) at 0°C, and the reaction mixture was stirred for 12 h. THF was distilled out under vacuum and to the remaining aqueous residue was added 1N HCl solution in water to adjust the solution P^H = 4, the solid was precipitated out. The solid was filtered and dried to obtained compound **6**as a yellowish solid (15g, 79%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.74 (br, s 1H, -CO-NH-CO-), 7.93 (d, 2H, *J* =8.8 Hz, Ar-H), 7.84 (s, 1H, Ar-H), 7.79 (d, 2H, *J* =8.8 Hz, Ar-H),4.12-4.15 (m,1H,-N-CH-CO), 3.14-3.22 (m, 2H, -N-CH_2-CH_2-), 1.77-1.94 (m, 3H, -N-CH_2-CH_2-), 1.58-1.61 (m, 1H, -CH_2-CH_2-CH_2-), ES-MS: *m/z*381.2 $(M+H)^-$.

1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid cyclohexylamide**(7a)**To a solution of 1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid**6**(1g, 0.0026 mol) in DMF (5ml) was added EDC.HCl (0.0.75 g, 0.0039 mol) and cyclohexylamine (0.257 g, 0.0026 mol) followed by the HOBt (0.351 g, 0.0026 mol) at 25°C. Reaction mixture was the stirred for the 6h. Quenched the reaction mixture with water (50ml), white solid was comes out was filtered, dried and washed with diethyl ether to gave compound **7a.** off white solid (0.82g, Yield= 68%); mp= 137-139 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.75 (br, s 1H, -CO-NH-CO-), 7.96 (d, 2H, *J* =8.8 Hz, Ar-H), 7.86 (s, 1H, Ar-H), 7.81 (d, 2H, *J* =8.4 Hz, Ar-H), 7.71(s, 1H, *J* =8 Hz Ar-H), 4.04-4.07 (m,1H,-N-CH-CO), 3.40-3.49 (m, 2H, -N-CH_2-CH_2-), 3.20-3.25 (m, 1H, -N-CH_2-CH_2-), 1.66-1.82 (m,6H, -CH_2-CH_2-CH_2-), 1.51-1.55 (m, 2H, -CH_2-CH_2-CH_2-), 1.09-1.27 (m, 5H, -CH_2-CH_2-CH_2-); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.1(2×C), 30.9, 48.9, 59.8, 126.4, 126.7, 128.0, 128.1, 129.0 (2×C), 129.6, 130.5 (2×C), 135.6, 137.2, 167.0,

167.4, 168.6, 169.9; ES-MS: m/z 463.X (M+H)$^+$; Anal. Calcd.for $C_{21}H_{25}N_3O_5S_2$; C, 54.41; H, 5.44; N, 9.06; Found: C, 54.45; H, 5.45; N, 9.03.

***1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid phenylamide*(7b)**yellowishsolid(0.92g, Yield= 76%); mp= 147-149 °C;^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.75 (br, s 1H, -CO-NH-CO-), 10.0 (br, s 1H, -CO-NH-), 7.99 (d, 2H, J =8.4 Hz, Ar-H), 7.83 (s, 1H, Ar-H), 7.59 (d, 2H, J =8.0 Hz, Ar-H), 7.3.7.34 (m, 2H, Ar-H), 7.05-7.09 (m, 1H,Ar-H), 4.25-4.28 (m,1H,-N-CH-CO), 3.47-3.51 (m, 1H, -N-CH$_2$-CH$_2$-), 1.87-1.93 (m, 3H, -CH$_2$-CH$_2$-CH$_2$-), 1.57-1.60 (m, 1H, -CH$_2$-CH$_2$-CH$_2$-);^{13}C NMR (DMSO-d_6, 100 MHz)δ 24.3, 29.9, 49.2, 61.5, 119.3 (2×C), 127.4, 128.2 (2×C), 129.2 (2×C), 129.4, 130.3 (2×C), 132.4, 136.1, 137.7, 137.8, 167.6, 167.8, 169.6;ES-MS: m/z 458.X (M+H)$^+$; Anal. Calcd. for $C_{21}H_{19}N_3O_5S_2$; C, 55.13; H, 4.19; N, 9.18; Found: C, 54.15; H, 4.23; N, 9.22.

***1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid p-tolylamide*(7c)**brownish solid (0.89 g, Yield= 72%); mp= 153-155 °C;^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.62 (br, s 1H, -CO-NH-CO-), 9.91 (s, 1H, -CO-NH-), 7.98 (d, 2H, J =8.4 Hz, Ar-H), 7.85 (s, 1H, Ar-H), 7.82 (d, 2H,J =8.0 Hz Ar-H), 7.81 (s, 1H, Ar-H). 7.46 (d, 2H, J =8.4 Hz, Ar-H), 7.10 (d, 2H, J =8.4 Hz, Ar-H), 4.22-4.25 (m,1H,-N-CH-CO), 3.46-3.51 (m, 1H, -N-CH$_2$-CH$_2$-), 3.25-3.28 (m, 1H, -N-CH$_2$-CH$_2$-), 2.25 (s, 3H, -CH$_3$), 1.85-1.94 (m, 1H, -CH$_2$-CH$_2$-CH$_2$-), 1.56-1.58 (m, 1H, -CH$_2$-CH$_2$-CH$_2$-);^{13}C NMR (DMSO-d_6, 100 MHz) δ20.4, 24.3, 31.1, 49.0, 61.7, 119.4 (2×C), 127.2, 128.0 (2×C), 129.0 (2×C), 129.3, 130.5 (2×C), 132.4, 136.1, 137.4, 137.8, 167.6, 167.7, 169.6;ES-MS: m/z 472.X (M+H)$^+$; Anal. Calcd.for $C_{22}H_{21}N_3O_5S_2$; C, 56.04; H, 4.49; N, 8.91; Found: C, 56.06; H, 4.53; N, 8.94.

***1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (4-methoxy-phenyl)-amide*(7d)** brownishsolid (0.78g, Yield= 61%); mp= 161-163°C;^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.65 (br, s 1H, -CO-NH-CO-), 9.84 (s, 1H, -CO-NH-), 7.96 (d, 2H, J =8.4 Hz, Ar-H), 7.84 (s, 1H, Ar-H), 7.80 (d, 2H, J=8.8 Hz Ar-H), 7.47 (d, 2H, J=9.2 Hz, Ar-H), 6.87 (d, 2H, J=9.2 Hz, Ar-H), 4.20-4.22 (m,1H,-N-CH-CO), 3.70(s, 3H, Ar-OCH$_3$), 3.44-3.48 (m, 1H, -N-CH$_2$-CH$_2$-), 1.84-1.88 (m, 3H, -CH$_2$-CH$_2$-CH$_2$-), 1.54-1.57 (m, 1H, -CH$_2$-CH$_2$-CH$_2$-);^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.3, 31.0, 49.1, 55.1, 61.7, 113.8, 114.0, 119.7 (2XC), 127.2,128.0 (2XC), 129.3,130.5 (2XC), 131.8, 137.7, 137.8, 155.4, 167.6,167.7,169.3; ES-MS: m/z 488.X (M+H)$^+$; Anal. Calcd.for $C_{22}H_{21}N_3O_6S_2$; C, 54.20; H, 4.34; N, 8.62; Found: C, 54.23; H, 4.35; N, 8.59.

***1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (4-fluoro-phenyl)-amide*(7e)** yellowishsolid (0.98g, Yield= 79 %);mp= 154-156°C;^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.68 (br, s 1H, -CO-NH-CO-), 10.09 (s, 1H, -CO-NH-), 7.96 (d, 2H, J =8.4 Hz, Ar-H), 7.80 (d, 2H,J=7.6 Hz, Ar-H), 7.58-7.61 (m, 2H, Ar-H), 7.04-7.16 (m, 3H, Ar-H), 4.20-4.23 (m,1H,-N-CH-CO), 3.45-3.49 (m, 1H, -N-CH$_2$-CH$_2$-), 1.84-1.90 (m, 3H, -CH$_2$-CH$_2$-CH$_2$-), 1.54-1.57 (m, 1H, -CH$_2$-CH$_2$-CH$_2$-);^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.3, 31.1, 49.2, 61.7, 115.1, 115.3, 121.2, 121.3, 126.8, 127.9 (2×C), 130.2 (2×C), 130.8, 135.0, 137.0, 138.3,156.9, 159.3, 169.7 (2×C); ES-MS: m/z 476.X (M+H)$^+$; Anal. Calcd.for $C_{21}H_{18}FN_3O_5S_2$; C, 53.04; H, 3.82; N, 8.84; Found: C, 53.07; H, 3.85; N, 8.82.

***1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid (4-chloro-phenyl)-amide*(7f)** yellowishsolid (1.1 g, Yield= 85%);mp= 163-165°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.70 (br, s 1H, -CO-NH-CO-), 10.18 (s, 1H, -CO-

NH-), 7.96 (d, 2H, *J* =8.4 Hz, Ar-H), 7.95 (s, 1H, Ar-H), 7.83 (d, 2H, *J* =8.4 Hz, Ar-H), 7.61(d, 2H, *J* = 9.2 Hz,Ar-H), 7.35 (d, 2H, *J* =8.8 Hz, Ar-H), 4.24-4.25 (m,1H,-N-CH-CO), 3.45-3.50 (m, 1H, -N-CH$_2$-CH$_2$-), 1.84-1.94 (m, 3H, -CH$_2$-CH$_2$-CH$_2$-), 1.55-1.58 (m, 1H, -CH$_2$-CH$_2$-CH$_2$-); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.2, 31.0, 49.3, 61.7,115.3,123.0 (2×C), 126.7, 127.2, 127.9 (2×C), 129.1 (2×C), 130.7, 136.6, 137.0, 138.3, 156.9, 159.3, 169.7 (2×C); ES-MS: m/z 492.1 (M+H)$^+$; Anal. Calcd.for $C_{21}H_{18}ClN_3O_5S_2$; C, 51.27; H, 3.69; N, 8.54; Found: C, 51.30; H, 3.67; N, 8.52.

***Cyclohexanecarboxylicacid N'-{1-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carbonyl}-hydrazide*(8a)** To a solution of 1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid**6**(1g, 0.0026 mol) in DMF (5ml) was added EDC.HCl (0.0.75 g, 0.0039 mol) and cyclohexyl carboxylic acid hydrazide (0.369 g, 0.0026 mol) followed by the HOBt (0.351 g, 0.0026 mol). Allowed the reaction mixture tostir for 6h. Quenched the reaction mixture with water (50ml), white solid was comes out was filtered, dried and washed with diethyl ether to gave compound **7a.** off white solid (0.94 g, Yield= 72 %);mp= 173-175°C;^{1}H NMR (DMSO-d_6 400 MHz) δ 12.76 (br, s 1H, -CO-NH-CO-), 9.90 (s, 1H, -CO-NH-NH-), 9.79 (s, 1H, -CO-NH-NH-), 7.97 (d, 2H,*J*=6.4 Hz, Ar-H), 7.87 (s, 1H, Ar-H), 7.80-7.82 (d, 2H, *J* =8.4 Hz, Ar-H), 4.16-4.19 (m,1H,-N-CH-CO), 3.42-3.45 (m, 1H, -N-CH$_2$-CH$_2$-), 3.17-3.23 (m, 1H, -N-CH$_2$-CH$_2$-), 2.16-2.21 (m,1H, -CH$_2$-CH$_2$-CH$_2$-), 1.55-1.91 (m, 9H, -CH$_2$-CH$_2$-CH$_2$-),M 1.13-1.37 (m, 5H);^{13}C NMR (DMSO-d_6, 100 MHz) δ24.1(2×C),31.0, 49.0, 53.3, 60.0, 126.8, 127.8, 128.1(2×C), 128.9, 129.6, 130.6(2×C), 131.6, 137.2, 137.6, 160.3, 167.1, 167.5, 170.7;ES-MS: m/z 507.3 (M+H)$^+$; Anal. Calcd.for $C_{22}H_{26}N_4O_6S_2$; C, 52.16; H, 5.17; N, 11.06; Found: C, 52.14; H, 5.15; N, 11.09.

***BenzoicacidN'-{1-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carbonyl}-hydrazide*(8b)**off white solid (1g, Yield= 79 %); mp= 187-189 °C;^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.52 (br, s 1H, -CO-NH-CO-), 10.49 (s, 1H, -CO-NH-NH-), 10.08 (s, 1H, -CO-NH-NH-), 7.99-8.01 (d, 2H, *J* = 8 Hz, Ar-H), 7.60-7.91 (m, 5H, Ar-H), 7.48-7.53 (m, 3H, Ar-H), 4.26-4.29 (m,1H,-N-CH-CO), 3.45-3.48 (m, 1H, -N-CH$_2$-CH$_2$-), 3.20-3.32 (m, 2H, -N-CH$_2$-CH$_2$-), 1.83-1.92 (m,2H, -CH$_2$-CH$_2$-CH$_2$-), 1.60-1.63 (m, 1H, -CH$_2$-CH$_2$-CH$_2$-);^{13}C NMR (DMSO-d_6, 100 MHz)δ24.2, 28.9, 55.6, 58.3,126.8 (2×C) , 127.8 (2×C), 128.1(2×C), 128.8 (2×C), 129.6, 130.6(2×C), 131.6, 137.2, 137.6, 160.3, 167.2, 167.4, 170.7; ES-MS: m/z 501.4 (M+H)$^+$; Anal. Calcd.for $C_{22}H_{20}N_4O_6S_2$; C, 52.79; H, 4.03; N, 11.19; Found: C, 52.74; H, 4.06; N, 11.16.

***1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid N'-phenylacetyl-hydrazide*(8c)** yellowish solid (1.0 g, Yield= 78%); mp= 193-195°C;^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.74 (br, s 1H, -CO-NH-CO-), 10.21 (s, 1H, -CO-NH-NH-), 10.03 (s, 1H, -CO-NH-NH-), 7.77-7.96 (m, 5H,Ar-H), 7.26-7.29 (m, 2H, Ar-H), 7.20-7.23 (m, 1H,-C=CH-), 4.13-4.16 (m, 1H,-N-CH-CO), 3.45 (s, 2H, -CO-CH$_2$-Ar-), 3.14-3.19 (m, 1H, -N-CH$_2$-CH$_2$-), 2.71-2.75 (m, 1H, -CH$_2$-CH$_2$-CH$_2$-), 1.78-1.86 (m, 3H, -CH$_2$-CH$_2$-CH$_2$-), 1.52-1.55 (m, 3H,-CH$_2$-CH$_2$-CH$_2$-); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.1, 25.1(2XC), 25.3, 28.9, 29.1, 30.9, 41.8,48.9, 59.8, 126.9, 128.0, m129.5, 130.5(2XC), 137.2, 137.7, 137.7, 167.2, 167.5, 169.8, 173.9; ES-MS: m/z 515.4 (M+H)$^+$; Anal. Calcd.for $C_{23}H_{22}N_4O_6S_2$; C, 53.69; H, 4.31; N, 10.89; Found: C, 53.73; H, 4.37; N, 10.86.

***Nicotinic acid N'-{1-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carbonyl}-hydrazide*(8d)** brownish solid (0.88g, Yield= 68 %); mp=

201-203°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.76 (br, s 1H, -CO-NH-CO-), 10.73 (s, 1H, -CO-NH-NH-), 10.19 (s, 1H, -CO-NH-NH-), 9.05 (s, 1H, Pyridine-H), 8.76 (d, 1H, *J*= 3.6Hz, Pyridine-H), 8.24(d, 1H, *J*= 7.6Hz, Pyridine-H), 7.99(d, 1H, *J*= 6.4 Hz, Pyridine-H), 7.82-7.84 (m, 3H, Ar-H), 7.53-7.57 (m, 1H, -C=CH-), 4.26-4.29 (m, 1H,-N-CH-CO), 3.33-3.49 (m, 1H, -N-CH$_2$-CH$_2$-), 3.20-3.25 (m, 1H, -CH$_2$-CH$_2$-CH$_2$-), 1.84-1.93 (m, 3H, -CH$_2$-CH$_2$-CH$_2$-), 1.60-1.63 (m, 1H, -CH$_2$-CH$_2$-CH$_2$-) ; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.2, 28.9, 55.6, 58.3, 115.9, 125.1, 126.7 (2×C), 127.2 (2×C), 129.5, 130.7, 138.0, 138.3, 142.0, 148.3, 153.7, 167.2, 167.5, 169.8, 173.9; ES-MS: m/z 502.4 (M+H)$^+$; Anal. Calcd.for $C_{21}H_{19}N_5O_6S_2$; C, 50.29; H, 3.82; N, 13.96; Found: C, 50.33; H, 3.87; N, 13.98.

Thiophene-2-carboxylicacid N'-{1-[4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carbonyl}-hydrazide **(8e)** yellowish solid (1 g,Yield= 76 %);mp= 189-191°C;^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.76 (br, s 1H, -CO-NH-CO-), 10.52 (s, 1H, -CO-NH-NH-), 10.10 (s, 1H, -CO-NH-NH-), 7.95-8.05 (m, 2H,Ar-H), 7.82-7.87 (m, 5H, Ar-H), 7.18-7.20 (m, 1H,-C=CH-), 4.22-4.26 (m, 1H,-N-CH-CO), 3.44-3.48 (m, 1H, -N-CH$_2$-CH$_2$-), 3.18-3.24 (m, 1H, -N-CH$_2$-CH$_2$-), 1.82-1.96 (m, 3H, -CH$_2$-CH$_2$-CH$_2$-), 1.59-1.62 (m, 1H, -CH$_2$-CH$_2$-CH$_2$-); ^{13}C NMR (DMSO-d_6, 100 MHz)δ24.1, 30.9, 48.9, 59.8, 126.4, 126.7, 128.0, 128.1, 129.0 (2×C), 129.6, 130.6(2×C), 135.6, 137.2, 137.7, 167.0, 167.4, 168.6, 169.9;ES-MS: m/z 507.3 (M+H)$^+$;Anal. Calcd.for$C_{20}H_{18}N_4O_6S_3$; C, 47.42; H, 3.58; N, 11.06;Found:C, 47.45; H, 3.54; N, 11.02.

1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid N'-(furan-2-carbonyl)-hydrazide**(8f)** off white solid (0.94 g, Yield= 74%); mp= 192-194°C;^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.75 (br, s 1H, -CO-NH-CO-), 10.37 (s, 1H, -CO-NH-NH-), 10.04 (s, 1H, -CO-NH-NH-), 7.98-8.00 (d, 2H,*J*=8.4 Hz, Ar-H), 7.87-7.89 (d, *J*=8.4 Hz, 2H, Ar-H), 7.82-7.84 (d, *J*=8 Hz, 1H,-C=CH-),7.24-7.25 (d, 1H, *J*=3.2 Hz,Ar-H), 6.65-6.66 (dd, 1H, *J*=2 Hz, *J*=1.6 Hz,Ar-H), 4.24-4.26 (m, 1H,-N-CH-CO), 3.43-3.47 (m, 1H, -N-CH$_2$-CH$_2$-), 3.19-3.25 (m, 1H, -N-CH$_2$-CH$_2$-), 1.81-1.93 (m, 3H, -CH$_2$-CH$_2$-CH$_2$-), 1.59-1.62 (m, 2H, -CH$_2$-CH$_2$-CH$_2$-); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 24.1, 31.2, 48.9, 59.8, 111.9, 113.6, 126.4, 126.7, 128.0, 128.1, 129.6, 130.6 (2×C), 146.1, 147.2, 137.7, 167.0, 167.4, 168.6, 169.9; ES-MS: m/z 491.3 (M+H)$^+$;Anal. Calcd.for$C_{20}H_{18}N_4O_7S_2$; C, 48.97; H, 3.70; N, 11.42;Found:C, 48.93; H, 3.74; N, 11.46.

Conclusion

A series of novel 1-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonyl]-pyrrolidine-2-carboxylic acid derivatives were synthesized by a facile six step procedure. Their structures were characterized by spectral and elemental analysis. The preliminary bioassay results imply that some of the compounds exhibit first-rate tumor cell inhibitory activity against human Breast MCF-7, Colon HCT-15 and HepatomaHep-G2 cell lines. Compound **7e**was the new finding from this research work and it will be studied further in near future.

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