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NOVEL SYNTHESIS AND ANTICANCER SCREENING OF NEW THIOHYDANTOIN-CHALCONE CONJUGATES

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Abstract: Thiohydantoins and chalcones both are the privileged pharmacophores with significant importance in medicinal chemistry. A series of eight thiohydantoin- chalcones conjugates was synthesized and these hybrid compounds were also screened for in vitro anticancer activity. Few compounds were found active against the pathogenic bacterial strains.

Index Terms - Breast Cancer activity, chalcones, thiohydantoin, MCF-7 cell line, pharmacophores

I. INTRODUCTION

Thiohydantoins are sulfur analogs of hydantoins with one or both carbonyl groups replaced by thiocarbonyl groups[1]. Among the known thiohydantoins, 2-thiohydantoins are most notably known due of their wide applications as hypolipidemic[2] , anticarcinogenic[3] , antimutagenic[4] , antithyroidal[5], antiviral (e.g., against herpes simplex virus, HSV)[6] , human immunodeficiency virus (HIV)[7] and tuberculosis[8] , antimicrobial (antifungal and antibacterial)[9] , anti-ulcer and anti-inflammatory agents[10] , as well as pesticides[11]. Additionally, 2-thiohydantoins have been used as reference standards for the development of C-terminal protein sequencing[12,] as reagents for the development of dyes[13] and in textile printing, metal cation complexation and polymerization catalysis[14]. It is therefore not surprising that various different synthetic methods have been developed to prepare 2-thiohydantoin and its derivatives. Some of the most commonly used methods are the treatment of α-amino acids with acetic anhydride followed by ammonium thiocyanate[15] and the coupling reaction between α-amino acid derivatives and isothiocyanate [4a,12b,16] . Other preparative methods for 2-thiohydantoins include the reactions between thiourea and benzil[17] thiourea and α-halo acids[18,] oxazolinone and thiocyanate [19], amino amide and diimidazole thiocarbonate [20], and others[21]. In addition, some of the above reactions have been modified to take place under microwave irradiation[17c] and solid-phase[16a, 22] or fluorous-phase [23] supported reaction conditions. However, the above methods often suffer from one or more synthetic limitations for large-scale preparation of 2-thiohydantoin derivatives due to their use of expensive, moisture sensitive and/or highly toxic starting materials and reagents. Moreover, the methods developed for combinatorial synthesis and used to prepare 2-thiohydantoin derivatives in small quantities for purposes like biological testing may not be feasible when operated on a large scale [22d, 24]. A Thiohydantoin derivative has also been reported as herbicidal25. Bucherer reaction has also been reported for the synthesis of thiohydantoin26. Sulfenylated thiohydantoins has also been reported as fungicides. Ant diabetic hydantoins have been synthesized by Japanese scientists27. 1-3-diglycidyl-5, 5-dimethyl hydantoin has been used for primed steel plate to give a good coating for weathering, alkali, acid and water resistance28. Some thiohydantoin derivatives have been used in the treatment of blood circulation disorder29. Some thiohydantoins have been reported as inhibitors of pyrimidine biosynthesis30, 5, 5-disubstituted thiohydantoins have also been synthesized for their anti HIV activity31. Synthesis of benzylidene derivatives of 3(2, 3, 4-chlorophenyl) thiohydantoins are reported for their anticonvulsant

properties32, 1-bromo thiohydantoins is reported where transposition of halogen atom from nitrogen to 3-alkyl group is studied33. 1-N-phenyl substituted 2-thiohydantoins derivatives were synthesized by Z. Jinpei et al for their antinociceptive activity34. Acetylation of 3-substituted 1-amino-thiohydantoins has been reported35. Reaction of 5-arylidene-3-phenyl-2-thiohydantoin with 2,3,4,6-tetra-o-acetyl-a-D-gluco-pyranosyl bromide are reported. The product is arylidene-phenyl [(tetra acetyl glyco pyranosyl) thiohydantoin.36 Chalcones are one of the most important compounds. The framework 1,3-diphenylprop-2-en-1-one is well known by the generic term ‘‘chalcone,’’ a name coined by Kostanecki and Tambor37. It is also known as benzal acetophenone and benzylidene acetophenone. The chalcones has most important properties like anticancer 38, antimalarial39, antimicrobial40 and antiinflammatory41etc. 2-Hydroxy chalcones are a group of naturally occurring compounds and are used as the intermediates for the synthesis of various other flavanoids41, 42. The unsaturated carbonyl system in chalcones makes them biologically active43.Indeed,chalcones constitute an important group of natural compounds that are especially abundant in fruits (e.g., citruses, apples), vegetables (e.g., tomatoes, shallots, bean sprouts, potatoes) and various plants and spices (e.g., licorice),many of which have been used for centuries in traditional herbal medicine[44-45]

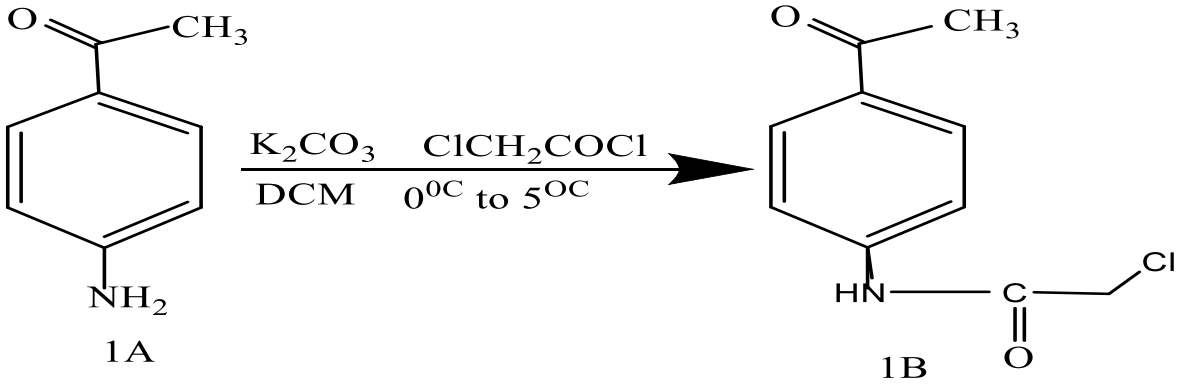
The cancer is occurs due to uncontrolled progression of normal cells. The numbers of factors influenced on the normal cell due to which the transformation of a normal cell to a cancerous cell[46]. In universe a different types of cancer are present out of which, the breast cancer is very common to the entire world and normally diagnosed in female candidates. In worldwide an estimated value for the breast cancer grasps more than one million women’s. The periodical statistical data will be observed for this disease varied widely such as in 2008, nearly about 421,000 cases were recovered for breast cancer, where as in 2009–2010, more than 49,500 women were diagnosed with breast cancer in Europe. From the breast cancer about 11,600 women’s and 75 men were died in 2010. The estimated data caused from this cancer is more than 458,000 women in 2008 worldwide. In 2008, the new cases 184,450 were appeared in persistent stages and this number varies to 230,480 in 2011 in USA. This estimated value is increases day by day and new cases (~268,600) for breast cancer was identified in women, the breast cancer also detected in men in 2019[47].

II .METHODOLOGY

The chemicals used in the synthesis were purchased from Sigma Aldrich and were used as such. Melting points of the compounds have been measured using automated melting point apparatus and are uncorrected. IR spectra were recorded in Nijol, 1H NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard. The purity of synthesized compound was check by TLC. The structural elucidation of compound was done on the basis of chemical and spectral data.

2.1 Preparation of N-(3-(4-acetyl phenyl)-2- Chloro acetamide (1B) :-

0.01mol of Para-amino acetophenone (1A) was dissolved in dichloromethane (DCM) and cooled to 0-5 ºC in ice bath. Further, 0.01 mol of potassium carbonate (K_2CO_3) were added to this reaction mixture followed by drop wise addition of 0.01 mol of Chloro acetyl chloride ($ClCOCH_2Cl$) at 0 ºC temperature. This reaction mixture was stirred at room temperature for 3 hrs. After completion of reaction, solvent was evaporated. The residue was washed with distilled water to get N-(4-acetyl phenyl)-2- Chloro acetamide (1B).



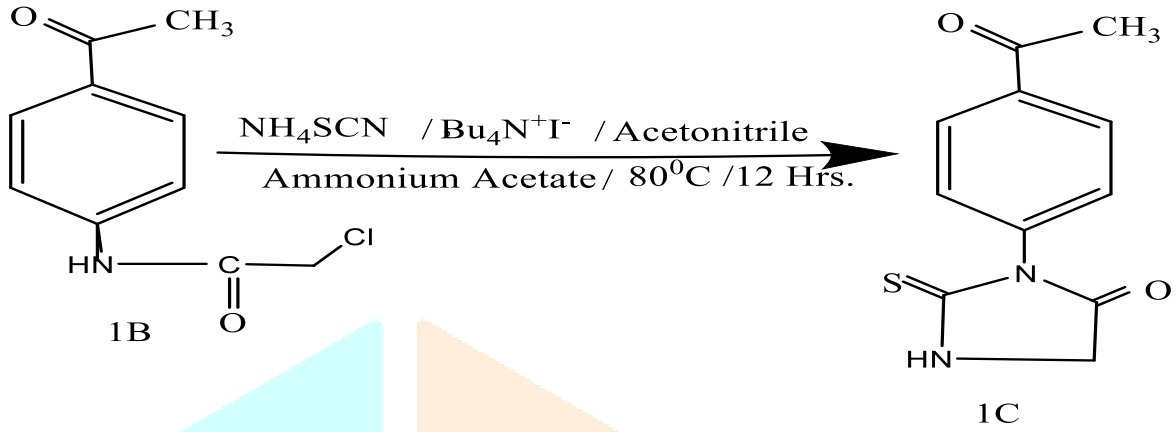
1A 1B

2.2 Preparation of N-(3-(4-acetyl phenyl) imidazolidine-2,4-dione) (1C) :-

0.01 mol of 1B was refluxed with 0.01 mol of NH_4CNS in presence of 0.01 mol of tetra butyl ammonium iodide and ammonium acetate using acetonitrile as solvent at 80 ºC for 12 hrs., after completion of reaction solvent was evaporated. The crude product N-(3-(4-acetyl phenyl) imidazolidine-2, 4-dione) 1C was extracted with ethyl acetate and was purified with column chromatography using ethyl acetate and hexane as eluent.

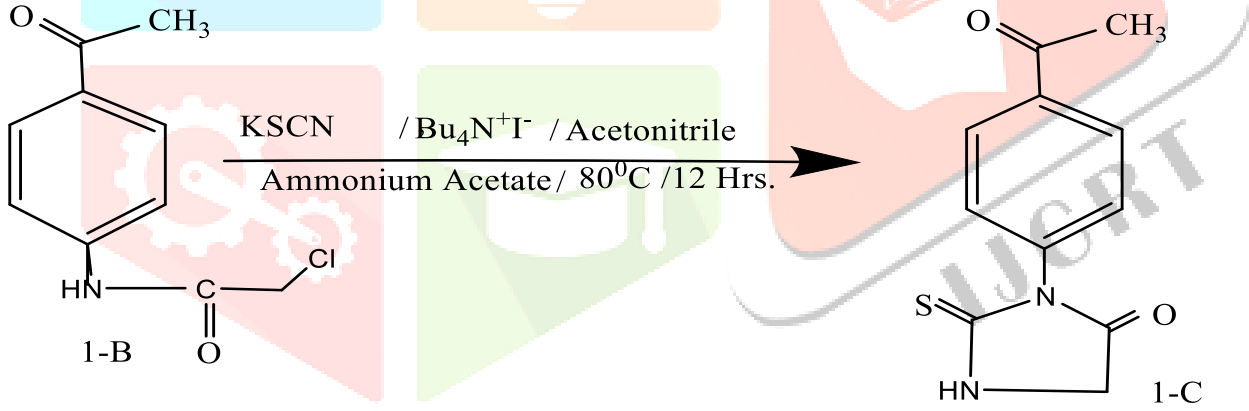
To compared the yield and texture of 1C the reaction was refluxed with two different thiocyanate with **Scheme - A and Scheme –B**

Scheme: - A Refluxed with NH_4CNS :-



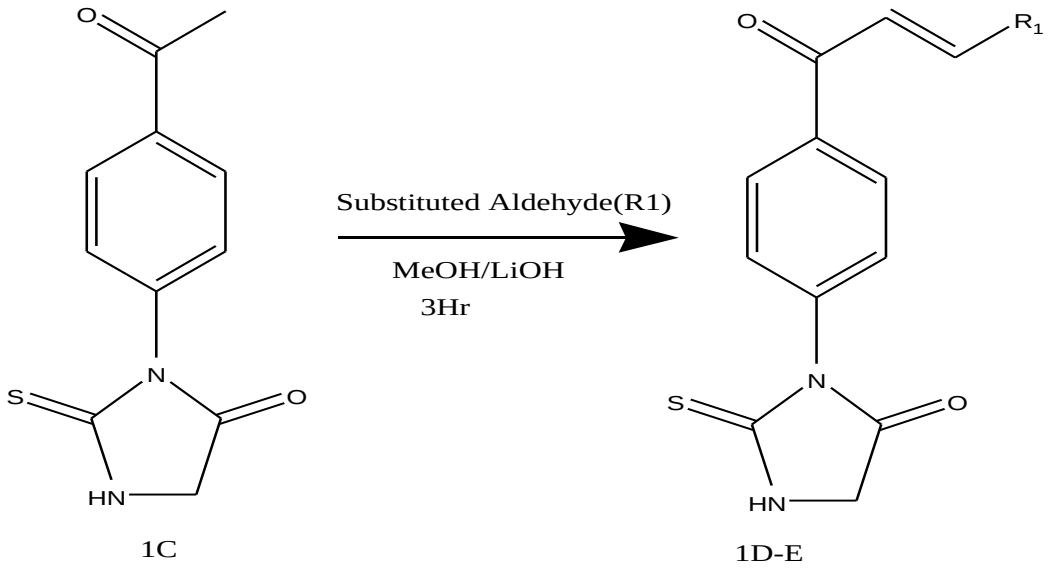
Scheme: - B Refluxed with KCNS :-

0.01 mol of 1B was refluxed with 0.01 mol KCNS in presence of 0.01 mol of tetra butyl ammonium iodide and ammonium acetate using acetonitrile as solvent at 80 ºC for 12 hrs., after completion of reaction solvent was evaporated. The crude product N-(3-(4-acetyl phenyl) imidazolidine-2, 4-dione) 1C was extracted with ethyl acetate and was purified with column chromatography using ethyl acetate and hexane as eluent.



2.3Preparation of N-(3-(4-Carboxy phenyl)-3" substituted Chalcone-Thiohydantoin Conjugates (1D-E) :-

To a well stirred solution of N-(3-(4-acetyl phenyl)- imidazolidine-2,4-dione) 1C (0.01 mol) in methanol, 0.01 mol of LiOH were added followed by the addition of 0.01 mol of corresponding substituted aromatic aldehyde. The reaction mixture was stirred at room temperature for 3 hrs. After formation of cake, keep the reaction overnight, completion of reaction, precipitate obtained was filtered washed with distilled water. The crude product obtained was purified by crystalized from methanol.



1C 1D-E

Table 1: Synthesized Chalcone-Thiohydantoin Conjugates Compounds, M.P. and yields

Sr. No.	Compounds	R_1	M. P. (^oC)	Yield (%)
1	1E	C5H3O2	276	74%
2	1D	C6H4NO2	225	71 %

III.SPECTRAL ANALYSIS

Compound 1E

Mol. Formula $C_{18}H_{14}O_4N_2S$: Brown red amorphous solid, m.p 276 ^oC , yield 74%, Elemental analysis (%):C,61.01; H,3.98; N,7.90; O,18.06; S,9.05; IR (KBr cm-1) 3426.58 (N-H), 17.34 (C=O), 1642.5 (Ar C-H),ESI-MS[M+H]+ Calculated for **$C_{18}H_{14}O_4N_2S$**: *m/z* 354.08, 355.06; 1H-NMR (500 MHz, DMSO): δ 3.81 (2H, d, *J* = 6.8 Hz), 3.96 (2H, d, *J* = 17.7 Hz), 4.32 (2H, d, *J* = 9.7 Hz), 5.70 (1H, dt, *J* = 10.7, 9.7 Hz), 5.89-6.03 (3H, 5.96 (d, *J* = 15.8 Hz), 5.96 (d, *J* = 5.9 Hz), 5.97 (d, *J* = 5.9 Hz)), 6.36 (1H, d, *J* = 3.5 Hz), 6.63 (1H, d, *J* = 10.7 Hz), 7.01 (1H, dt, *J* = 15.8, 6.8 Hz), 7.15 (1H, d, *J* = 3.5 Hz), 9.74 (1H, s).

Compound 1D

Mol. Formula $C_{19}H_{15}O_4N_3S$: Golden yellow amorphous solid, m.p 225^oC , yield 71%, Elemental analysis (%):C,59.83; H,3.96; N,11.02; O,16.78; S,8.41; IR (KBr cm-1) 3420.58 (N-H), 17.34 (C=O), 1632.5 (Ar C-H),ESI-MS[M+H]+ Calculated for **$C_{19}H_{15}O_4N_3S$** : *m/z* 381.08, 382.08; 1H-NMR (500 MHz, DMSO): δ 3.30 (2H, d, *J* = 6.8 Hz), 3.96 (2H, d, *J* = 17.7 Hz), 4.32 (2H, d, *J* = 9.7 Hz), 5.70 (1H, dt, *J* = 10.7, 9.7 Hz), 5.90-6.06 (3H, 5.96 (d, *J* = 5.9 Hz), 5.99 (d, *J* = 15.8 Hz), 5.97 (d, *J* = 5.9 Hz)), 6.56-6.75 (3H, 6.63 (d, *J* = 10.7 Hz).

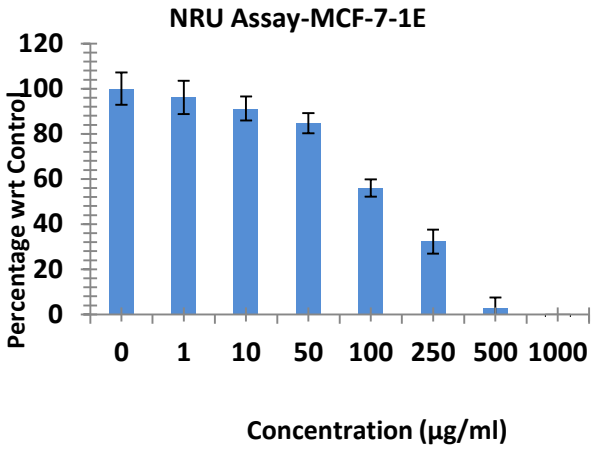
IV. BIOLOGICAL ASSESSMENT

The anti-cancer activity of synthesized compounds has been evaluated against cell lines MCF-7 (breast carcinoma cell line. Cytotoxicity of the Chalcone-thiohydantoin conjugates derivatives on MCF-7 cell line (Procured from NCCS Pune) was determined by NRU (Neutral Red Uptake) Assay. The cells (5000-8000 cells/well) were cultured in 96 well plates for 24 h in DMEM medium (Dulbecco's Modified Eagle Medium-AT149-1L) supplemented with 10% FBS (Fetal Bovine Serum - HIMEDIA-RM 10432) and 1% antibiotic solution at 37°C with 5% CO2. Next day, medium was removed and fresh culture medium was added to each well of the plate. 5 µl of Treatment dilutions (of different concentrations) were added to the defined wells and treated plates were incubated for 24 h. 100 µl of NRU (SRL Chem-36248) (40 µg/ml in PBS - phosphate buffered saline) was added to the defined wells and incubated (Heal Force-Smartcell CO2 Incubator-Hf-90) for 1 h. After that medium was removed, NRU was dissolved in 100 µl of NRU Destain solution. Finally plates were read at 550/660 nm using Elisa Plate Reader (iMark BioRad-USA). IC-50 Was calculated.

Tables 2 show the IC 50 value of the synthesized compounds as well as reference compound Doxorubicin against breast carcinoma cell line MCF-7. Tables 3, 4, 5 and 6, show percentage viability in vitro cytotoxicity against breast carcinoma cell line MCF-7.

Table: 2

Concentration ug/mL	Viability (%)
0	100
1	96.17486
10	91.25683
50	84.69945
100	56.01093
250	32.24044
500	3.005464
1000	-177.322



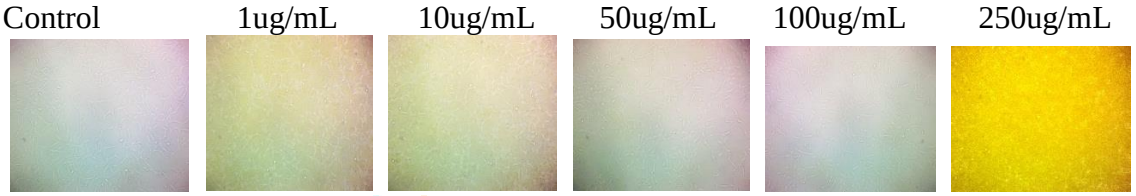
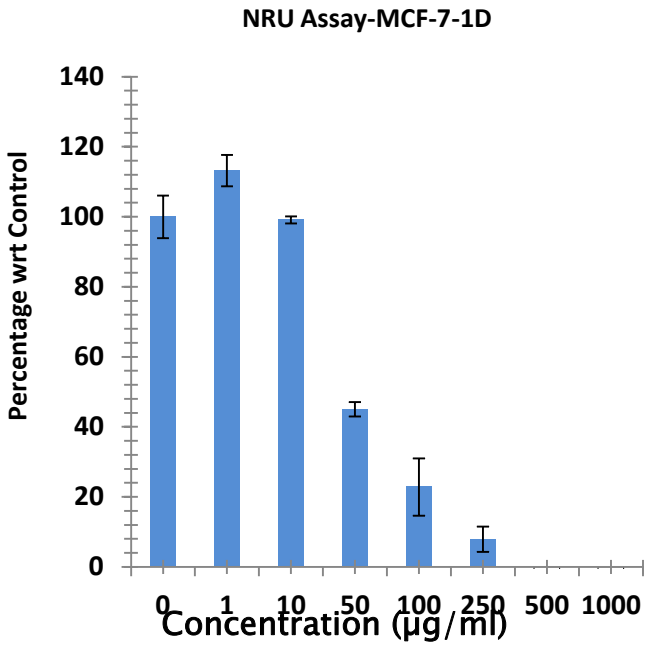
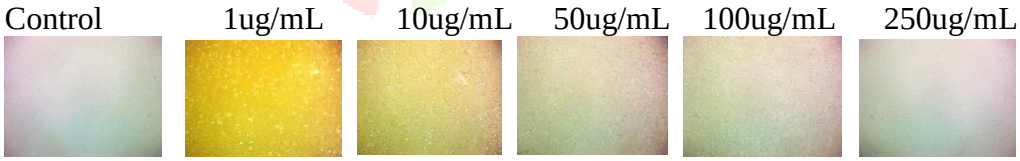


Table :3

Concentration ug/mL	Viability (%)
0	100
1	113.1579
10	99.12281
50	45.02924
100	22.80702
250	7.894737
500	15.2047
1000	47.6608





IV.RESULT AND CONCLUSION

The result evaluated that, thiohydantoin conjates shows moderate to good effect on breast cancer cell line.Therefore, much research efforts are still required to be focused on studying the substituents effects that highly enhance the drug-like properties of the thiohydantoin conjates scaffolds to reach the outmost challenges and prominent to improve human health and reduce suffering.

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