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Design, Synthesis, and Biological Evaluation of Anti-prostate Cancer Agent

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1] Abstract: -

In search of more effective chemotherapeutics for the treatment of castration-resistant prostate cancer. The 1,3- thiazolidine-2,4-diones possess a wide diversity of important biochemical effects and interesting pharmacological properties. 1,9-diarylnona-1,3,6,8-tetraen-5-ones bearing two identical terminal heteroaromatic rings have been successfully synthesized through Wittig reaction followed by Horner-Wadsworth-Emmons reaction. The cell proliferation assay was employed to assess their anti-proliferative effects toward both androgen-sensitive and androgen-insensitive human prostate cancer cell lines. curcumin in inhibiting prostate cancer cell proliferation. It can be concluded from our data that 1,9-diarylnona-1,3,6,8-tetraen-5-one can serve as a new potential scaffold for the development of anti-prostate cancer agents.

2] Keywords: -

Androgen receptor, prostate cancer, AR antagonist, Novel 1, 3- thiazolidine-2, 4-diones, 1,9-Diheteroarylnona-1,3,6,8- tetraen-5-ones, Synthesis, Reaction.

3] Introduction: -

The American cancers Society lately estimates that approximately 180,890 American guys can be identified as new prostate most cancers cases and that over 26,000 men will die of prostate cancer in 2016[1]. These data Imply that prostate most cancers remains the most common cancer and the second leading cause of cancer-affiliated loss of life among men in the United States of America. It is now widely recognized that most prostate cancer Patients die of castration-resistant prostate cancers because of the inevitable progression of resistance to First-line remedy with docetaxel. Prostate cancer is a leading cause of illness and death among men in Western Europe and the United States. Men with localized prostate cancer have a range of treatment options which include prostatectomy, irradiation and in some cases watchful waiting[2].

This phenomenon, known as multi-drug resistance or multiple-drug resistance (MDR) and initially described more than 30 years ago (Beck et al., 1986), is manifest as cancer cells being resistant to anti-cancer drugs that are structurally and mechanistically unrelated. MDR may present as innate/primary or it may be acquired. Innate MDR means that, from the outset, the cancer cells are already equipped to be resistant to the anti-cancer drug being used. Acquired resistance occurs when cancer cells initially respond to treatment, but develop resistance mechanisms overtime[3]. There's therefore a pressing need to search for new chemotherapeutics for this lethal disorder. The action of currently used chemotherapeutics is based on the induction of apoptosis and on the inhibition of mitosis by disturbing the cell cycle. The use of conventional cytotoxic chemotherapy methods, however, does not create larger prospects due to the lack of specificity of most drugs against cancer cells and high toxicity on healthy, rapidly dividing cells such as myelocytes, epithelial cells or gametocytes.

The dietary curcumin (1) (Figure 1) turned into chosen with the aid of us and others as lead Compound for the development of new anti-prostate cancer agents primarily based on: i) its well-documented Safety profile in human beings[4]; And ii) its properly-evidenced healing capacity in treating prostate cancer, especially for castration-resistant prostate cancer. Curcumin-based compounds with numerous lengths of central Linkers, which includes 11-atom linker, 7-atom linker, 5-carbon linker, and 3-carbon linker, have up to now been Suggested to possess comparable or increased cytotoxic and anti-proliferative efficiency towards prostate cancers cell lines, compared with curcumin. However, there may be no file available at the curcumin mimics Containing a 9-atom linker as anti-prostate cancer agent. Natural products have shown promising anti-cancer activity. They have been the mainstay of cancer chemotherapy of which flavonoids remained primary candidate Cancer is fast progressing in 21st century and is predicted to affect 22 million people by 2030. Research attributes increase in risk of contracting to

low intake of fiber diet, small consumption of fruit and green vegetables, high consumption of red meats, alcohol consumption, smoking, higher intake of salt and saturated fats, etc. Cancer is the second leading causes of mortality and morbidity after the heart diseases across the world which affected 14.1 million lives in 2012. [5]

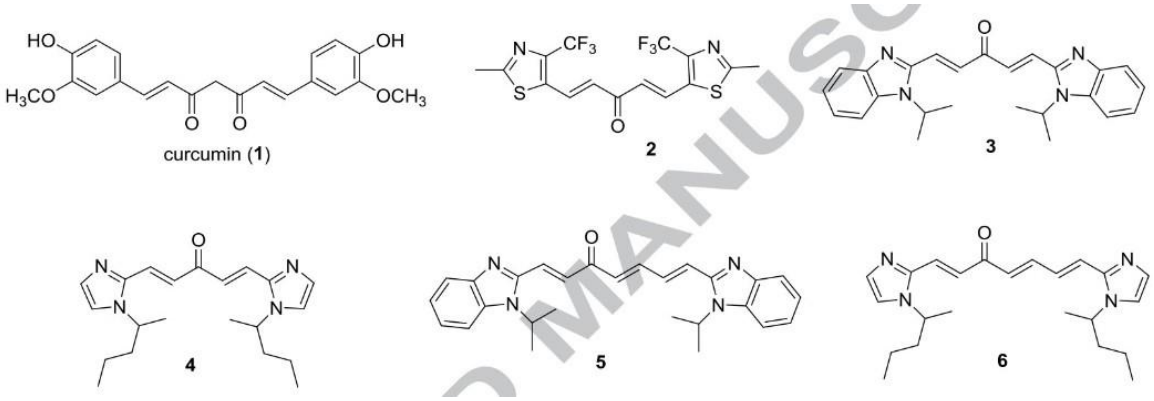


Figure 1. Structures of curcumin (1) and curcumin-based anticancer agents (2-6)

Prostate cancer (PCa) is the most usually diagnosed noncutaneous tumor and the second one main cause of cancer deaths among men in the United States. Prostate cancer (PCa) is the second most prevalent cancer in men worldwide. However, large variations in incidence rates exist between geographical regions, with a 25-fold difference between countries with the highest and lowest incidence rates. There were 307,000 deaths from PCa in 2012, and it is the fifth leading cause of death in men globally.

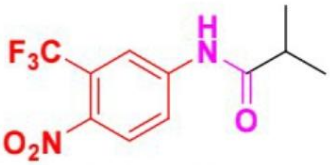
There is relatively less variation in mortality rates worldwide (10-fold variation from approximately 3 to 30 per 100,000). The mortality rates have been declining in many developed countries in part because of improved treatment. In the last 20 years, since the clinical introduction of prostate specific antigen screening (PSA), the incidence and mortality of metastatic prostate cancer lowered significantly. Although it not has been proved that the use of PSA was responsible for this lowering, in 1985 localized tumors in USA represented at most 58% of cases in USA; in the last few years, only 4% of patients had an initial presentation of the tumor with metastasis. Moreover, relative survival in five years increased exponentially, from 69% in the 70's to 96-99% in the present, concurrent with the general use of the exam (3-5). But in May 2012 the United States Preventive Services Task Force (USPSTF) published a report contrary to the use of PSA for screening of prostate cancer [6,7].

PCa growths are primitively depending on Endogenous androgens that activate the androgen receptor (AR), a member of the nuclear receptor superfamily and play a vital position in gene transcription, growth, and

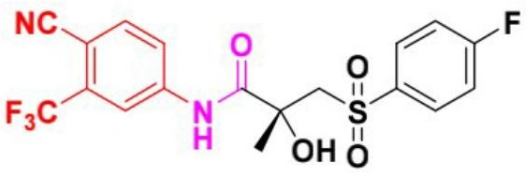
functions of the prostate as well As having outcomes on hair and pores and skin. Androgen deprivation healing procedures Are presently endorsed in conjunction with radiation remedy, also After surgical treatment or radiation if any cancers cells stay. Although screening of prostate cancer is a controversial issue mostly related to the absence or paucity of well-documented data, the diagnosis of prostate cancer at a localized stage clearly remains the only foreseeable possibility for reducing the high death rate from this disease. In fact, the remarkable progress recently achieves f treating prostate cancer discovered at a metastatic stage and to assess the potential benefits of diagnosis and treatment of the disease at a localized stage, we have started in 1989 the first prospective screening program in a randomly selected population of 60,000 men in the Quebec City area aged between 45- and 80-years using serum prostate-specific antigen [(8)].

Current Chemotherapeutic drugs such as abiraterone, bicalutamide, cabazitaxel, and enzalutamide were practiced for the remedy of Castration-Resistant Prostate cancers (CRPC) patients. Additionally bind to the AR With excessive affinity and more potent than bicalutamide. Similarly, AR gene mutation, which include T877A and W741C/L is a critical Mechanism for castration-resistance and stays the primary undertaking in the scientific studies. there is an increasing need for the development of new therapy for prostate cancer and breast cancer with better activity profile and less toxicity. Therefore, the concept of non-steroidal, AR antagonists emerged as an attractive target to overcome these problems [(9)]. Most of the antiandrogens are derived from flutamide (1a), bicalutamide (1b), Enzalutamide (1c), nilutamide (1d). We recognized that 1,3-thiazolidine-2, 4-dione-based totally compounds, inclusive of troglitazone, ciglitazone, STG28, and OSU-CG12, bind Efficiently to the androgen receptor and have been capable of elicit hallmark Cellular response characteristics of energy restriction in LNCaP (prostate cancer). Thiazolidinediones (TZDs) are selective ligands for the nuclear transcription factor peroxisome proliferator-activated receptor (PPAR). Furthermore, the *in vivo* anticancer efficacy of troglitazone was demonstrated in a few clinical cases that involved patients with liposarcomas or prostate cancer [(10)].

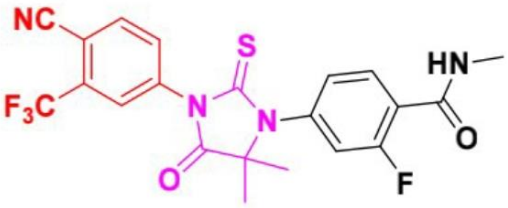
The 4-nitrophenyl group which is from the flutamide and the 1,3-thiazolidine-2,4-Dione group. To purpose at the synthesis of heterocyclic systems with potential activity against prostate cancers, we here in present an efficient regioselective synthesis of novel 1,3-thiazolidine-2,4-diones, and the compounds, have not been reported hitherto. Their Anti-prostate cancers activities. 1,3-thiazolidine-2,4-dione derivatives with the androgen receptor in opposition to prostate Cancer.



Flutamide (1a)



Bicalutamide (1b)



Enzalutamide (1c)

Nilutamide (1d)

MDV3100 is an androgen-receptor antagonist that blocks androgens from binding to the androgen receptor and prevents nuclear translocation and co-activator recruitment of the ligand-receptor complex. It also induces tumors cell apoptosis, and has no agonist activity. Because growth of castration-resistant prostate cancer is dependent on continued androgen-receptor signaling, we assessed the antitumor activity and safety of MDV3100 in men with this disease. Methods This phase 1-2 study was undertaken in five US in 140 patients. Patients with progressive, metastatic, castration-resistant prostate cancer were enrolled in dose-escalation cohorts of three to six patients and given an oral daily starting dose of MDV3100 30 mg. The final daily doses studied were 30 mg (n=3), 60 mg (27), 150 mg (28), 240 mg (29), 360 mg (28), 480 mg (22), and 600 mg (3). The primary objective was to identify the safety and tolerability profile of MDV3100 and to establish the maximum tolerated dose [11].

4] Material and method: -

1] Novel 1, 3- thiazolidine-2, 4-diones.

2] 1,9-Diheteroarylnona-1,3,6,8- tetraen-5-ones.

❖ Synthesis: -

1] Novel 1, 3- thiazolidine-2, 4-diones.

Fig 1: synthesis of Novel 1, 3- thiazolidine-2, 4-diones.

❖ Reaction: -

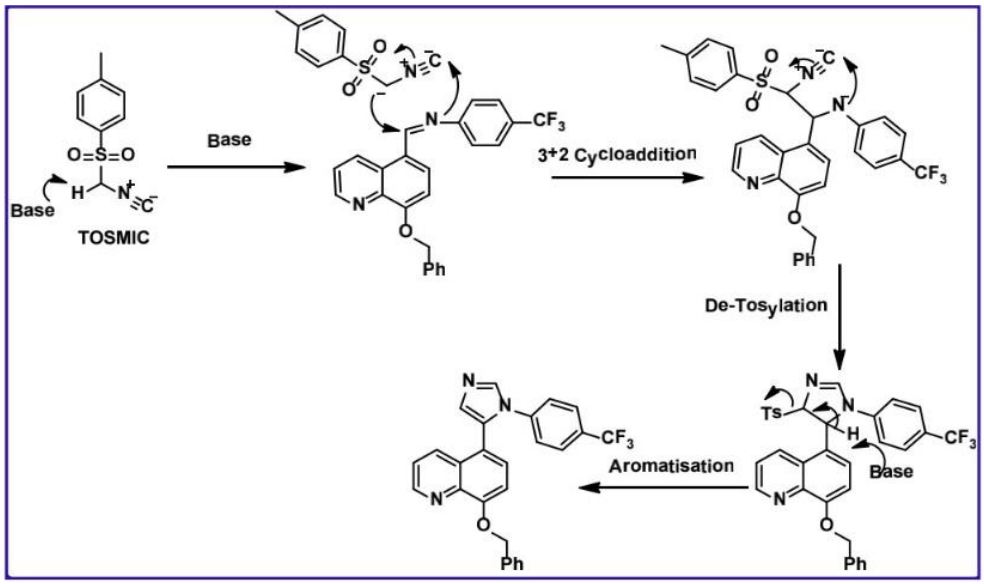


Fig 2: Reaction of Novel 1, 3- thiazolidine-2, 4-diones.

❖ **Application: -** 1] Cancer

2] Diabetes

3] Diabetes complications

4] Arthritis

5] Microbial infection.

❖ **Synthesis: -**

2] 1,9-Diheteroarylnona-1,3,6,8- tetraen-5-ones.

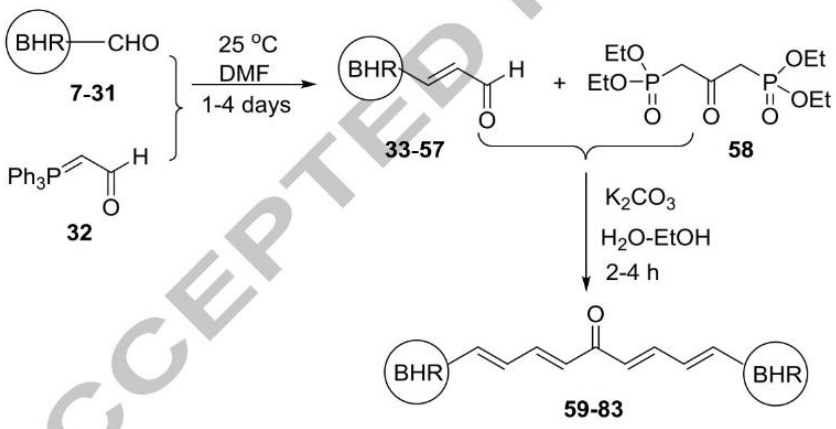


Fig: Synthesis of 1,9-Diheteroarylnona-1,3,6,8- tetraen-5-ones.

❖ **Application: -** 1] Cancer

2] Diabetes

3] Arthritis

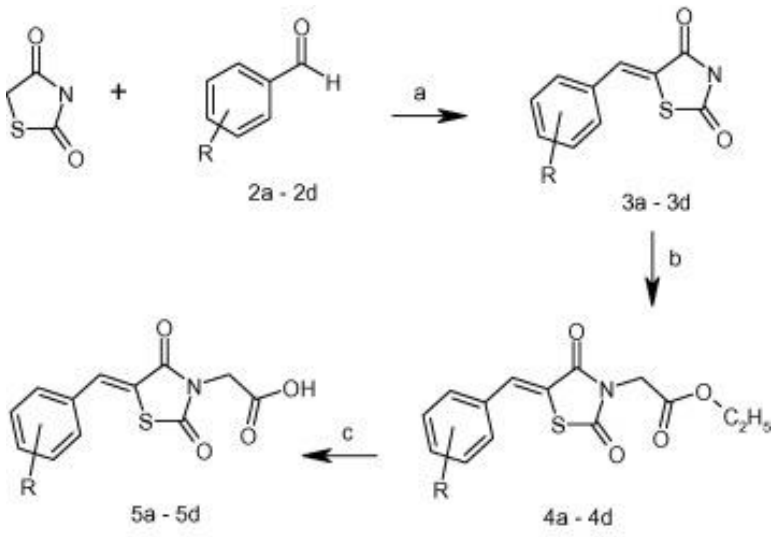
4] Diabetes complications

5] Microbial infection

5] Result and discussion: -

I] Chemistry: -

The unsaturated 1,3-thiazolidine-2,4-diones are generally more potent than their saturated compounds in the cell proliferation assay. Interestingly, it has been observed a similar trend in the euglycemic and hypolipidemic activities for some of the unsaturated thiazolidinediones[12]. The synthetic protocol of thiazolidinedione derivatives presented here is shown in Scheme. Thiazolidin-2,4-dione on reacting with benzaldehyde derivative undergoes condensation giving benzylidene thiazolidinedione **3a**–**3b** which upon *N*-Alkylation with ethyl bromoacetate furnished alkyl 2,4-dioxothiazolidin-3-ethyl ester **4a**–**4b**, ethyl ester is being converted to acid derivative **5a**–**5d** using conc. HCl and glacial acetic acid[13].



Twenty-three new and two knowns (1E,3E,6E,8E)-1,9-diarylnona-1,3,6,8-tetraen-5-ones bearing two identical terminal heteroaromatic rings have been successfully synthesized as illustrated in Specifically, these target compounds have been achieved by Horner-Wadsworth-Emmons reaction of one equivalent of 1,3-

bis(diethylphosphonato) acetone with 2.2 equivalents of the appropriate (E)-3-aryl-2-propenal, using potassium carbonate as base and employing water and ethanol (3:2, v/v) as a co-solvent.

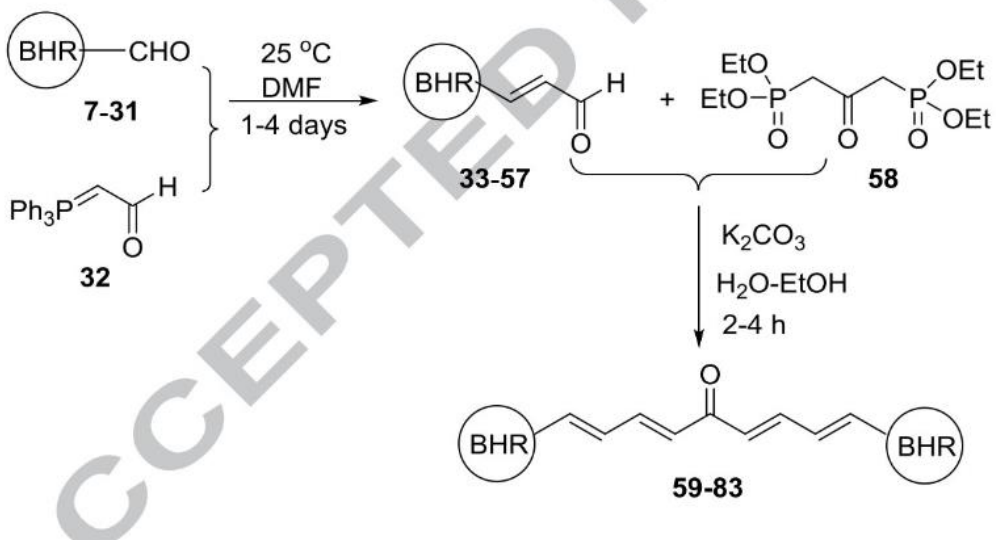


Fig: Synthesis of 1,9-diarylnona-1,3,6,8-tetraen-5-ones.

Curcumin, as the positive reference control, was prepared by ClaisenSchmidt condensation of vanillin with acetylacetone according to the procedure described in the literature [(14)].

II] Anti-proliferative effects toward three prostate cancer cell lines: -

To evaluate the in vitro anticancer potential of the synthesized 1,9-diarylnona-1,3,6,8-tetraen-5-ones we first determined their antiproliferative activity toward both androgen-sensitive (LNCaP) and androgen-insensitive (PC-3 and DU145) human prostate cancer cell lines using the WST-1 cell proliferation assay. Curcumin was employed as a positive control for comparison in the parallel experiment. Among the series of compounds tested, eighteen out of twenty-five 1,9- diarylnona-1,3,6,8-tetraen-5-ones. antiproliferative potency than curcumin in three prostate cancer cell models suggesting that 1,9-diarylnona-1,3,6,8-tetraen-5-one can serve as a new potential scaffold of Antiprostrate cancer agent[(15)]. This is different from another two promising scaffolds, (1E,4E)-1,5- diheteroarylpenta-1,4-dien-3-ones and (1E,4E,6E)-1,7-diaryl-1,4,6-heptatrien-3-ones

that we previously reported, in which ortho pyridyl confers greater cytotoxic and antiproliferative potency than para pyridyl in various prostate cancer models[16].

III] Structure Activity Relationship: -

The structure activity relationship of the compounds relates the features of a chemical structure associated with the property, effect, or biological activity. The compounds with either a chloro or trifluoro group at R1 and cyano or nitro at R2 have higher binding affinity than the other combination[17].

Also, the standard drugs, Flutamide, Nilutamide and Enzalutamide indicate that cyclic amide or thioamide groups are an essential for higher AR binding affinity. Recent studies on 4-(4-Benzoylaminophenoxy) phenol derivatives as AR antagonists highlight the importance of the two-phenyl coupled through ether linkage[18].

6] Biological Evaluation: -

I] Antioxidant Activity: -

The antioxidant activities of the new chemical entities (NCEs) were determined along with the reference standards by radical scavenging assay, total reduction capability and Nitric Oxide (NO) radical scavenging assay. The reducing capacities of a compound may serve as a significant indicator of its potential antioxidant activity[19]. The presence of reductants in the tested samples cause the reduction of the Fe3+/ferricyanide complex to the ferrous form (Fe2+) and the yellow color of test solution changes into green and blue colors depending on the reducing power of antioxidant capacity. The DPPH free radical is a stable free radical and the reduction capability of DPPH radicals was determined by the decrease in its absorbance at 517 nm induced by the compounds having antioxidant potential. These effects can be attributed to non-scavenging

role of antioxidants including induction of apoptosis, growth arrest, inhibition of DNA synthesis and modulation of signal transduction pathways. In regard of curcumin antitumoral properties, several studies were conducted on cervical cancer. Cervical cancer cell lines were often used as a preferred carcinogenic model to understand molecular targets and mechanism of curcumin action. Here are reported all the in vitro and in vivo advances for the use of curcumin in the treatment of prostate cancer [(20)].

II] Anticancer Activity: -

The human prostate cancer cell lines and non-cancerous cell line (3T3), were used for the cytotoxicity studies. In the previous studies, we have observed up to 10 µM activity against prostate cancer cell lines from the oxobenzimidazoles derivatives. In recent studies, it was reported that gal suppressed castration resistant and enzalutamide-resistant prostate cancer growth in vitro and also blocked nuclear translocation and decreased AR dependent genes[(21)].

7] Conclusion: -

In summary, twenty-five symmetric 1,9-diarylnona-1,3,6,8-tetraen-5-ones with two identical nitrogen's containing terminal heteroaromatic rings have been synthesized. Eighteen 1,9-diarylnona-1,3,6,8-tetraen-5-ones exhibit significantly improved antiproliferative potency as compared with curcumin. This indicates that (1E,3E,6E,8E)-1,9-diarylnona-1,3,6,8-tetraen-5-one can serve as a potential scaffold for further exploration of the therapeutic potential for the treatment of prostate cancer. Our findings also suggest that para pyridyls and quinolin-4-yl serve as favorable heteroaromatic rings for the enhanced potency of this new scaffold.

In the present study, a series of 1,3-thiazolidine-2,4-dione analogs were synthesized and evaluated for their in vitro antioxidant and anticancer activities. The combination of receptor-ligand based screening was utilized to identify novel androgen receptor antagonists. The anti-proliferative activity of thiazolidinediones and standard (bicalutamide) were tested in LNCaP and PC-3 prostate cancer cell lines. All the compounds showed

compliance with the standard range of known drugs ADME properties. We, further, intend to carry out in vitro and in vivo AR binding studies for the active compounds.

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