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Emerging Heterocyclic Compounds for the Management of Prostate Cancer

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Abstract

Background: This review is an overview of emerging heterocyclic compound classes that might give a safe and effective treatment for prostate cancer.

Main body: Most heterocyclic compounds or heterocyclic fragments present in most of the anticancer pharmaceuticals presently in market and are versatile with unique physicochemical properties. Most of anticancer research is being capitalized on the intrinsic versatility and dynamic core of heterocyclic compounds. In this review we shall focus on moieties that are suitable for prostate cancer therapy along with addressing their biochemical modes of action, biological targets, structure-activity relationship and intrinsic drawbacks in the use of these compounds

Conclusion: These classes and their derivatives discussed here might provide a novel drug therapy for cancer treatment.

Keywords: Emerging heterocyclic, Prostate cancer (PCa), Non-androgenic drugs, Anti-proliferative agents, Cytotoxic, PC3-cells

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Background

Carcinoma of the prostate (CaP) is one of the most frequently diagnosed cancer in men worldwide. Prostate cancer-specific cause is not clear till date. Dihydrotestosterone and testosterone are the main androgenic hormones involved in the initiation and development of the disease. In vitro studies using the AR+ human prostate cancer cell line, LNCaP, provided the first evidence that structural alteration in the AR is responsible for prostate cancer. Along with identifying mutated AR genes in hormone-relapsed prostate cancer cases, increment of the AR gene in recurrent prostate tumors was also reported. Increased levels of androgen receptors usually increase sensitivity towards androgen (circulating) leading to tumor growth. Generally, Two main classes of anti-androgens are clinically used. Some steroidal agents are used as anti-androgens like cyproterone, oxendolone and spironolactone (Figure 1). However, their clinical application has been limited mainly due to poor oral bioavailability, lack of tissue selectivity, poor pharmacokinetic properties, and numerous side effects that might include hepatotoxicity, androgenic effects feminizing side effects (like gynecomastia and loss of libido). Moreover, their rigid steroid backbone does not provide wider structural modifications for new drug development. Non-steroidal anti-androgens are the current pharmacological treatment of choice for progressive androgen-dependent prostate cancer as monotherapy or adjuvant castration/ luteinizing hormone-releasing hormone (LHRH) agonists blocks the production of endogenous testosterone.

The non-steroidal ligands are effective for clinical and therapeutic applications as they lack cross-reactivity with steroidal receptors, eliminating unwanted side effects. Moreover, these show improved oral bioavailability compared to their steroidal counterparts and are also open for structural modifications. The propionanilide derivatives were first developed as non-steroidal anti-androgens and included flutamide (Eulexin), hydroxyflutamide, nilutamide, and bicalutamide (Casodex) (Figure 2). However, the clinical application of these is mainly limited because of hepatotoxicity after long-term administration. The drawbacks of these anticancer drugs emphasize the need to develop new candidates with high anti-prostate cancer activity and low adverse effects. In recent years development of various scaffolds as novel anti-prostate cancer agents have been reported. Lately, abiraterone acetate (Zytiga) in combination with prednisone was approved by FDA for the castration-resistant prostate cancer (CRPC) from the steroidal anti-androgen class, whereas Medivation (MDV3100) and Orteronel (TAK-700) are novel potential agents from the non-steroidal anti-androgen class.[1,2]

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Main Text

Heterocycles are one of the main structural components of several anticancer drugs available in the market nowadays. Their frequency in anticancer drug designing can be mostly attributed

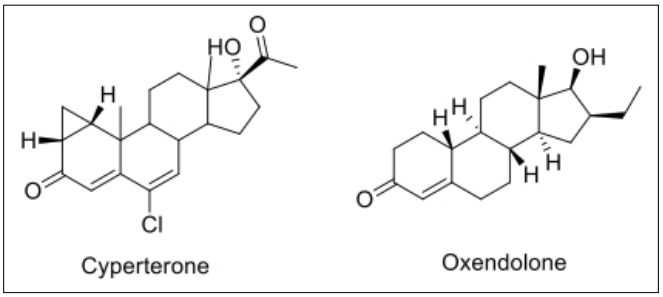


Figure 1: Steroidal Androgens

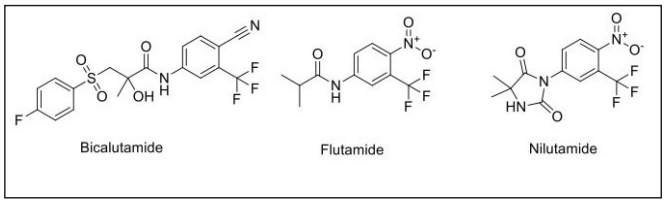


Figure 2: Non-Steroidal Antiandrogens

as they are extremely common in nature, with a vast number of cellular processes and mechanisms evolving in the ability to interact with them. Their adaptability means various metabolic pathways and multiple cellular processes in cancer pathology might be very susceptible to heterocycle-based drugs. In this review, we will be looking at some of the emerging heterocyclic compounds that can be implicated in prostate cancer therapy (that may be on the market or in development), and we will also discuss some of the properties that make them extremely valuable as anti-prostate drugs and are considered the beneficial for the same.[3]

Heterocyclic Compounds as Best Fit for Anti-prostate Agents

- It is specifically as heterocycles are most prevalent, and these represent extremely large coherent molecules having an unmatched level of flexibility in terms of the certain interactions as these can engage with various targets on cancerous cells.
- These have various enzyme binding pockets that are predisposed for interacting with heterocyclic moieties.
- Heterocycles are excellent choices when designing moities that interact with certain targets and disrupt various biological pathways (related to cell growth and development) targeted by such anticancer therapies.
- Moreover, these can be modified with additional substituents on heterocyclic rings, allowing them a broad chemical space qualifying as best starting points for anti-prostate drug development.

Because of these reasons, heterocyclic structures have played an important role in anticancer drug designing, featuring mostly anticancer drugs currently available on the market.[4]

Types of Heterocyclic Compounds used for Cancer Treatment

Nitrogen-based Heterocycles

Nitrogen-based heterocyclic compounds are of specific importance as anticancer drugs, present in almost 3/4 of the heterocyclic anticancer agents that the FDA approved. Indoles are valuable from heterocyclic nitrogen compounds, and various research has demonstrated their capability to induce cell death in cancer cell lines. Over last decades, indole and its derivatives have been demonstrated to modulate numerous biological pathways involved in cancer progression. These pathways include the disruption of cell signaling, altering normal cell cycle progression, tumor vascularisation and DNA repair mechanism alteration, and their ability to induce cellular oxidative stress leading to cell death. The earliest most important indole-based anticancer agents are vincristine and vinblastine (Figure 3)

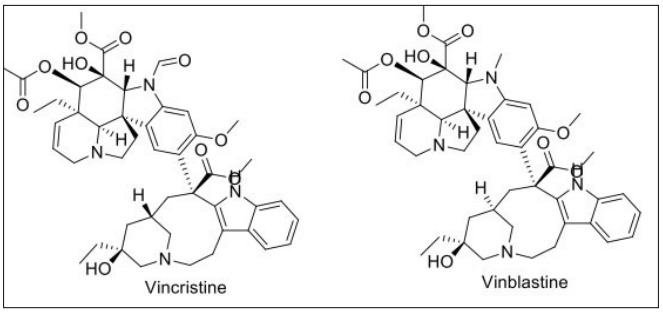


Figure 3: Structure of indole based heterocyclic agents

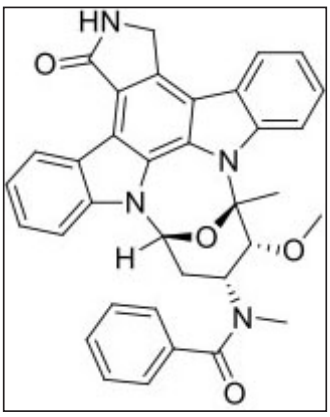


Figure 4: Structure of Midostaurin

functions by tubulin polymerization inhibition, and both still are of clinical importance today.[5]

Indolocarbazoles are a related derivative of indoles that exhibits a broad range of activities and have been in significant focus in recent years for their anti-neoplastic potential. Many indolocarbazoles have proficiency as protein kinase inhibitors, where some active protein kinases are the main factor in the malignant transformation of cells during cancer initiation. One indolocarbazole midostaurin (multi-target protein kinase inhibitor) (Figure 4), gives the idea of how relevant nitrogen-based heterocycles are for anticancer drug designing.[6]

Oxygen-based Heterocycles

Oxygen-containing heterocycles are acutely used as anticancer drugs. Paclitaxel (Figure 5) is one of the main drug in cancer therapy, consisting an oxetane ring, its mechanism of action is depolymerization of microtubule polymers which results in progressive inhibition of mitosis in cancerous cells. Similar to vinblastine, it results in a decrease in cancer cell division, in turn halting cancer. Despite its benefits, numerous side effects have correlated with the drug, including hypersensitivity, hematological issues, and neurotoxicity. There have been various studies to produce more drugs like paclitaxel, having fewer side effects. Another oxygen-containing heterocyclic anticancer drug which is microtubule inhibitor, is cabazitaxel, used to treat prostate cancer. Cabazitaxel (Figure 5) is a tubulin-stabilizer, but it is in specific interest for the treatment of multidrug-resistant tumors as its resistance to cellular efflux by the p-glycoprotein efflux pumps expressed by numerous resistance cancer cells. Cabazitaxel can cross the blood-brain barrier.[7]

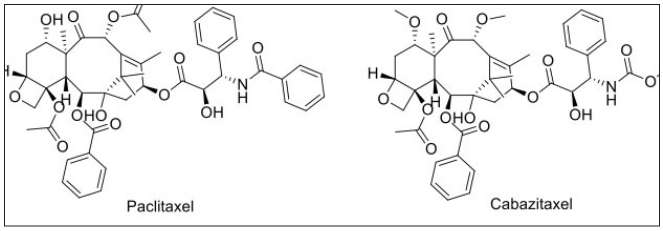


Figure 5: Structure of oxetane containing agents

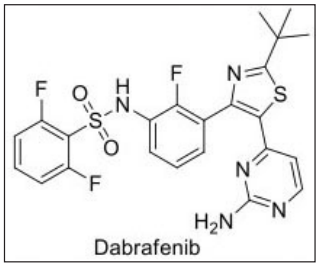


Figure 6: Structure of Dabrafenib

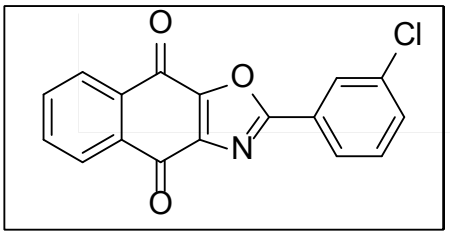


Figure 7: Structure of 2-(3-Chloro-phenyl)- naphtho [2,3-d]oxazole-4,9-dione

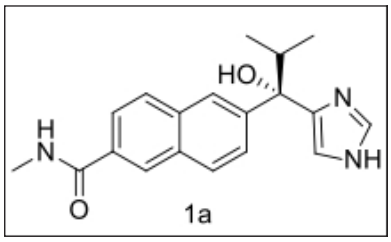


Figure 8: Structure of 1a ((S)-6-(1-hydroxy-1-(1H-imidazol-4-yl)-2-methylpropyl)-N-methyl-2-naphthamide)

Sulfur-based Heterocycles

Sulfur is one of the main components in various vitamin cofactors, sugars, and nucleic acids and also plays an essential role in the regulation of translation by the sulfuration of transfer RNA. Given its importance in biological systems, sulfur-containing heterocycles have got too much attention in the field of anticancer drugs like their oxygen- and nitrogen-based parallels. For instance, certain thiophene derivatives were checked for anti-proliferative activity against breast adenocarcinoma cells, with numerous compounds found to provide promising inhibitory effects. In addition, thiadiazole and thiazole have been important in cancer research in recent years. Dabrafenib (Figure 6) is a thiazole-containing anti-neoplastic drug molecule approved in 2013 by the FDA for use in cancer patients associated with the mutated BRAF gene.[8]

Literature Review

There are various classes of heterocyclic compounds approved or proposed for various targets in prostate carcinoma, which can be used to design new therapeutic moieties with more potency and efficacy.

2-Arylnaphtho [2,3-d]oxazole-4,9-dione Derivatives

In one in vitro anticancer assessment of these derivatives performed on androgen-dependent, LNCaP, and androgen-autonomous, PC3, human prostate malignancy cell lines. All in all, these compounds showed marginally more grounded cytotoxicity on the androgen-subordinate LNCaP than on the androgen independent PC3 prostate malignant growth cell lines. The meta substituted derivative 2-(3-Chloro-phenyl)-naphtho[2,3-d]oxazole-4,9-dione (Figure 7) has shown best cytotoxicity on both cell lines on LNCaP and PC3(IC50 0.03 μM and 0.08 μM respectively) following 5 days of presentation.[9]

Orteronel (TAK-700)

A novel naphthyl methyl imidazole subordinate 1(6-(1-hydroxy-1-(1H-imidazol-4-yl)-2-methylpropyl)-N-methyl-2-naphthamide) and its connected structures were recognized as 17,20-lyase inhibitors. In light of the structure activity relationship around the naphthalene framework and the after-effects of a docking investigation of 1a((S)-6-(1-hydroxy-1-(1H-imidazol-4-yl)-2-methylpropyl)-N-methyl-2-naphthamide) (Figure 8) in the homology model of 17,20-lyase, the 6,7-dihydro-5H-pyrrolo[1,2-c]imidazole subordinate (+)- 3c was incorporated and distinguished as a powerful and profoundly specific 17,20-lyase inhibitor. Organic assessment of (+)- 3c at a portion of 1 mg/kg in a male monkey model uncovered stamped decreases in both serum testosterone and dehydroepiandrosterone fixations. This way, (+)- 3c (named orteronel [TAK-700]) was chosen as a possibility for clinical assessment and is presently in stage III clinical preliminaries for the therapy of emasculation-safe prostate malignancy. TAK-700 (Figure 9) is still not approved by FDA and its studies with other drugs are ongoing.[10,11]

Benzo[d]isoxazole Derivatives

The bromodomain extra-terminal (BET) family proteins have increased expanding interest as medication focuses on therapy of mutation-resistant prostate malignant growth (CRPC). In this particular study advancement, and assessment of benzo[d] isoxazole-containing derivatives as intense BET bromodomain inhibitors. Cocrystal structures of the delegate inhibitors in complex with BRD4(1) gave strong basic premise to intensify improvement. The two most intense derivatives, A (5-bromo-2-methoxy-N-(6-methoxy-3-methylbenzo[d]isoxazol-5-yl) benzenesulfonamide) and B ((R)- 5-(1-(cyclohexylmethyl)-6-(3-methylmorpholino)- 1H-benzo[d]imidazol-2-yl)benzo[d] isoxazole), (Figure 10), bound to the BRD4(1) bromodomain with Kd estimations of 82 and 81 nM, respectively. They additionally showed high selectivity over other non-BET subfamily individuals. The derivatives strongly hindered cell development, settlement arrangement, and the statement of AR, AR controlled qualities and MYC in prostate disease cell lines. Derivatives A and B likewise showed required impacts in a C4-2B CRPC xenograft tumor model in mice. These powerful and specific BET inhibitors deliver another class of mixes to improve expected therapeutics against CRPC.[12]

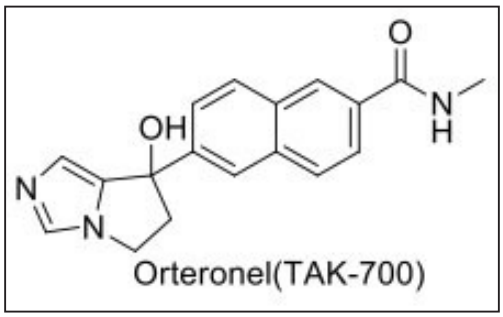


Figure 9: Structure of Orteronel (TAK-700)

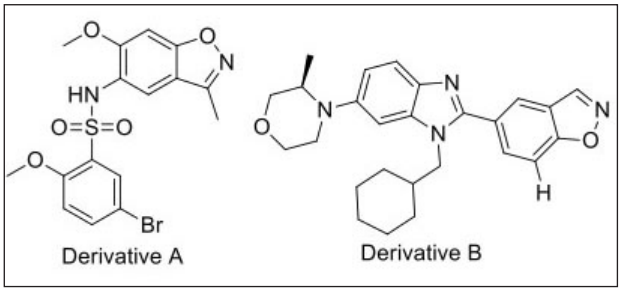


Figure 10: Structure of Derivative A and B

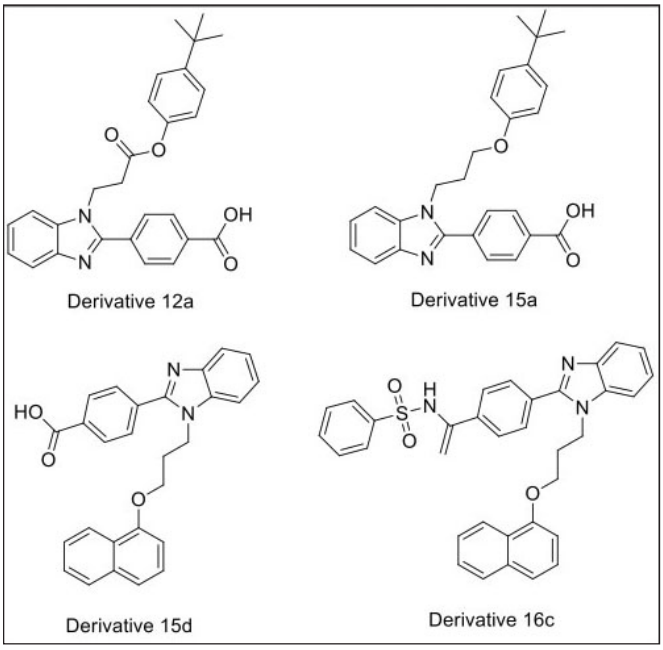


Figure 11: Structures of promising Benzimidazole derivatives as Pin1inhibitors [13]

Benzimidazole Derivatives as Pin1 Inhibitors

In one study, a series of benzimidazole derivatives were outlined and prepared (synthesized) as Pin1 inhibitors. A protease-coupled assay was utilized to check the Pin1 inhibitory potency of all prepared compounds. 13 of total prepared derivatives showed desirable Pin1 inhibitory effects with IC_{50} value <5 μM. Compounds 12a, 15b, 15d and 16c (Figure 11) depicted the most promising Pin1 inhibitory activity at a low micromolar level of about 0.33–1.00 μM in comparison with the positive control Juglone. The SARs of substituents and linker of the benzimidazole derivatives can help in further exploration of new Pin1 inhibitors.[13]

In another study to develop potent Pin1 inhibitors, a sequence of benzimidazole derivatives were drawn and synthesized. Among the derivatives, two molecules 6h((Z)-3-(1-(3-((4-bromophenyl)amino)-3-oxopropyl)-1H-benzo[d]imidazol-2-yl)acrylic acid) and 13g(2-(1-(3-oxo-3-((4-(trifluoromethyl) phenyl)amino)propyl)-1H-benzo[d]imidazol-2-yl)thiazole-4-carboxylic acid) (Figure 12) depicted a potent Pin1 inhibitory activity having IC50 values of 0.64 and 0.37 μM, sequentially.

In vitro anti-proliferative assay of six molecules showed average anti-proliferative activity against human PC-3 cells. In combination, these benzimidazole derivatives depicted great potential for further exploration as potent Pin1 inhibitors with improved properties.[14]

Thiazole-based Derivatives

As selective inhibitors of DNA-binding domain of the androgen receptor. In one study a series of thiazole-based inhibitors were prepared, checked and their SAR data was summarized for targeting specific DNA binding domain of the receptor. In this study novel compound SKLB-C2807(1-(3-(2-morpholinothiazol-4-yl)phenyl)ethanone) (Figure 13) that successfully obstructed prostate cancer cell line LNCaP/AR with an IC50 value of 0.38 μM without any conspicuous anti-proliferative effects on another cell lines PC-3 (AR-negative), SW620, MCF-7 (ER-positive) and L-O2 (non-cancerous). This thiazole derivative also significantly reduced the expression of PSA (Prostate Specific Antigen). This study lays the foundation for development of the next generation of anti-androgens.[15]

In another study, various heterocyclic thiazole derivatives were derived by synthesizing the first reaction of dimedone and elemental sulfur and phenylisothiocyanate following the heterocyclization of formed thiazole derivative by reactions with various chemical reagents. These synthesized derivatives were tested against c-Met kinase for in vitro cytotoxic activity and also against the six typical cancer cell lines (that includes A549, H460, HT-29, MKN-45, U87MG, and SMMC-7721). All targeted molecules were firstly tested against human prostatic cancer PC-3 cell line for anti-proliferative activity. Then 11 most promising compounds were again tested against tyrosine kinase, including cKit, Flt-3, VEGFR-2, EGFR, and PDGFR. 6 molecules were then selected to examine the Pim-1 kinase inhibition activity there derivatives 7a, 9d, 9k and 15c (Figure 14) depicted the highest activity.[16]

Pyrazole Derivatives

Regioselective blend of novel ring A-intertwined arylpyrazoles of dihydrotestosterone (DHT) was completed in two stages under simple response conditions. Aldol buildup of DHT with acetaldehyde managed the cost of a 2-ethylidene subsidiary regio-and sound system specifically, which was responded with various arylhydrazines within the sight of iodine by means of microwave-helped oxidative cyclization responses.[17] The 17-keto analogs of steroidal pyrazoles were likewise incorporated by straightforward oxidation to amplify the compound library accessible for pharmacological examinations and to acquire structure–movement relationship. The anti-proliferative exercises of the fundamentally related heteroaromatic mixes

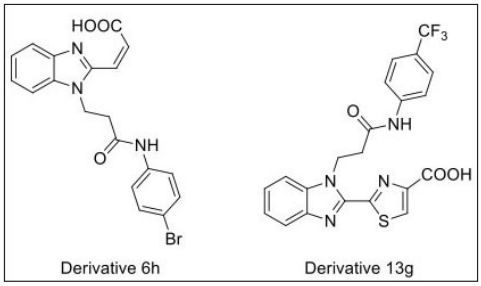


Figure 12: Structure of benzimidazole derivatives as Pin1 inhibitors[14]

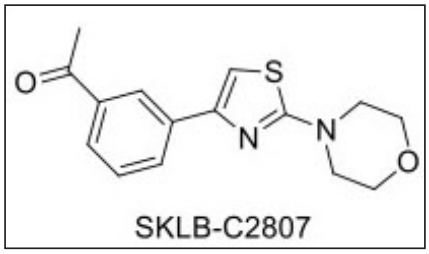


Figure 13: Structure of SKLB-C2807(1-(3-(2-morpholinothiazol-4-yl)phenyl)ethanone))

(Figure 15) were tried in vitro on human cervical and bosom adenocarcinoma cell lines (HeLa, MCF-7 and MDA-MB-231) and on two androgen-free threatening prostate carcinoma cell lines (PC-3 and DU 145). In light of essential cytotoxicity screens and IC50 evaluation, a structure-work relationship was recognized, as subordinates conveying a hydroxyl bunch on C-17 show more grounded movement contrasted with the 17-one partners. Disease cell selectivity of the subordinates was additionally decided utilizing non-dangerous MRC-5 cells. Moreover, the proapoptotic impacts of some chose subsidiaries were confirmed on androgen treatment refractive p53-inadequate PC-3 cells. The current examination infers that novel DHT-determined arylpyrazoles apply malignant growth cell explicit anti-proliferative action and initiate apoptosis in PC-3 cells.[18]

Triazole Derivative

In another study numerous 1,2,3-triazole hybrids of myrrhanone B were synthesized using Huisgen 1,3-dipolar cycloaddition reaction (regioselective Cu catalyzed) in an highly efficient manner. All these analogues were checked for their anti-proliferative activity against various cancerous cell lines including PC-3 cell lines that illustrated compounds 11 and 29 as potent anti-proliferative against PC-3 cell line. Compound 11 was having six folds more potency than parent and showed almost identical inhibitory activity as doxorubicin, On the other hand compound 29 was having four folds more potency than parent. In view of potent activity of compounds 11 and 29 they have been subjected to detailed flow-cytometry analysis. Compound 29 treated cells significantly increased the SubG1 population of cells indicative of apoptosis compared to compound 11.[19,20]

Pyridine Derivatives

In one study numerous pyridine and thieno[2,3-b]pyridine derivatives were prepared as PIM-1 kinase inhibitors.[21] 37 molecules were selected using NCI for testing initially at single

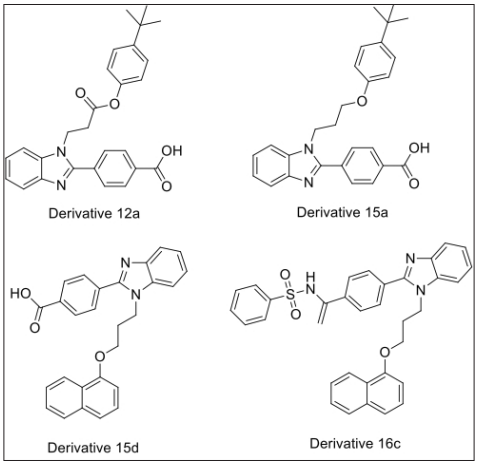


Figure 14: Structure of thiazole derivatives (derived from dimedone)

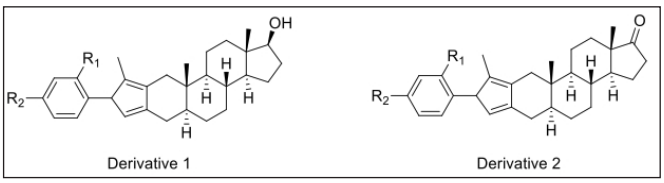


Figure 15: Structure of derivatives Dihydrotestosterone-derived ring A-condensed Pyrazoles[18]

Table 1: Name of thiazole derivatives (derived from dimedone)

Derivative	*Chemical name*
7a	2-chloro-N-(8-cyano-5,5-dimethyl-3-phenyl-2-thioxo-2,3,4,5-tetrahydrothieno[3′,2′:3,4]benzo[1,2-d]thiazol-7-yl)acetamide
9d	7-((3-chloro-4-(4-chlorophenyl)-5-cyano-6-hydroxy-4H-pyran-2-yl)amino)-5,5-dimethyl-3-phenyl-2-thioxo-2,3,4,5-tetrahydrothieno[3′,2′:3,4]benzo[1,2-d] thiazole-8-carbonitrile
9k	ethyl 7-((3-chloro-4-(4-chlorophenyl)-5-cyano-6-hydroxy-4H-pyran-2-yl)amino)-5,5-dimethyl-3-phenyl-2-thioxo-2,3,4,5-tetrahydrothieno[3′,2′:3,4] benzo[1,2-d]thiazole-8-carboxylate
15c	7-(4-chlorophenyl)-8-imino-5,5-dimethyl-3-phenyl-2-thioxo-2,3,4,5,7,8-hexahydrothiazolo[5,4-f]cinnoline-9-carbonitrile

Table 2: Derivatives of Dihydrotestosterone-derived ring A-condensed pyrazoles

S. No.	*Derivative 1*	*Derivative 2*	R_1	R_2
1.	1a	2a	H	H
2.	1b	2b	CH_3	H
3.	1c	2c	H	CH_3
4.	1d	2d	CH_3	CH_3
5.	1e	2e	H	OCH_3
6.	1f	2f	H	F
7.	1g	2g	H	Cl
8.	1h	2h	H	Br
9.	1i	2i	H	CN
10.	1j	2j	H	NO_2

dose of 10 μM using NCI 60 cell line panel. Molecule 5b(2-amino-4-(4-chlorophenyl)-6-(2,5-dihydroxyphenyl)nicotinonitrile) (Figure 16) illustrated potent anticancer activity and was examined twice in five-dose assay that gave confirmation about its potent antitumor activity against all tested cell lines except 6 where moderate sensitivity was observed. This molecule was transferred to NCI biological evaluation for its activity. Most active molecules (a total of 5 molecules) from each series were tested for their PIM-1 kinase inhibitory activity out of which molecule 8d(6-(2-hydroxy-5-methoxyphenyl)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile) (Figure 16) was the most potent one.[22]

Novel Olean-28, 13β-lactams

γ-Lactam is a chief structural moity in numerous natural products (biologically active) and in some of the synthetic pharmaceutical molecules.[23] However, till now there is no successful approach for construction of γ-lactam ring straight from natural rigid polycyclic amides. There is a report of a simple methodology for synthesizing a group of olean28,13β-lactams from their respective amides, enhanced by reagent 2,3-dichloro-5,6- dicyanobenzoquinone (DDQ) by an intramolecular dehydrogenative C–N coupling reaction using radical ion mechanism.[24] In the study, biological evaluation of derivatives showed that the most active lactam 10h (Figure 17) illustrated potent anti-proliferative activity against cancerous cells but a less inhibitory activity on noncancerous cells in vitro. In addition, this molecule specifically prevented the growth of implanted prostate cancer during in vivo studies. Moreover, 10h enhance cell cycle arrest and apoptosis and also down-regulation of the AKT/mTOR signaling in DU-145 cells and it was more stable in rat plasma and human liver microsomes in comparison with CDDO-Me and is having a little hERG channel inhibitory activity. Overall 10h might be a potential antiprostate cancer agent.[25]

18β-glycyrrhetinic Acid Derivatives

In a study various combinations (conjugates) of 18β-glycyrrhetinic acid derivatives with 3-(1H-benzo[d]imidazol-2-yl)propanoic acid (Figure 18) prepared to act as Pin1 inhibitors. Most of these compound showed improved Pin1 inhibitory activity against prostate cancer cells in comparison to parent moities. Most potent of these against PC-3 were having IC50 values of 7.80 μM and 3.52 μM. SAR indicated that both structures at ring C of glycyrrhetinic acid and provides required length of linker between GA skeleton and benzimidazole moiety which in turn improved the activity of the moieties. Thus, these compounds might represent a novel anti-proliferative agent working through Pin1 inhibition.[26,27]

AKBA (3-acetyl-11-keto-boswellic acid) Derivatives

A study reported with designing, preparation, and SAR study of novel ring A modified AKBA derivatives as Pin1 inhibitors.[28] Many derivatives depicteded superior Pin1 inhibitory activities in comparison to parent moity. Most promising compound 10a(IC50=0.46 μM) (Figure 19) inhibited Pin1 along with this it also has anti-proliferative effect against PC-3 cells with GI50=1.82 μM. SAR showed that modifications in ring A is having significant impact on its activity. Compound 10a might be potential anti-prostate cancer agent through Pin1 inhibition.[29,30]

Conclusion

Due to their versatility in nature along with in their structural and chemical diversity, heterocyclic compounds play an extremely essential role in anti-prostate drug discovery. The use of heterocyclic molecule provides identification to numerous potential eminent drug candidates, and assists in the drug development process that leads in saving time, money and resources. Various classes like 1,2,4-oxadiazoles, 2-Arylnaphtho [2,3-d]oxazole-4,9-dione derivatives, Thiazole-based derivatives, Benzimidazole derivatives as Pin1 inhibitors illustrated anti-prostatic activity and these are having numerous sites that can be utilized for preparing or discovering drugs with high potency and specificity. These classes and their modifications can be utilized for development of remarkable anti-proliferative agents for prostate carcinoma.

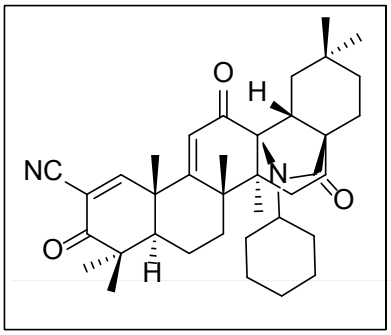


Figure 17: Structure of 10h promising anti-prostate cancer agent(Olean-28, 13β-lactam)

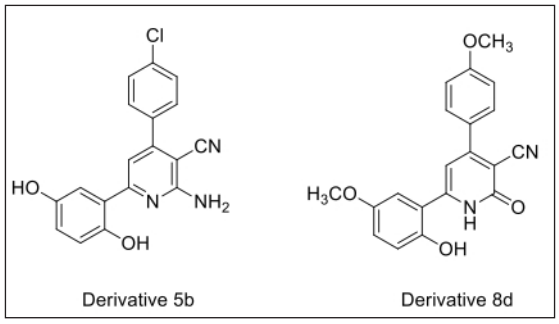


Figure 16: Structures of pyridine derivative showing anti-prostate activity[22]

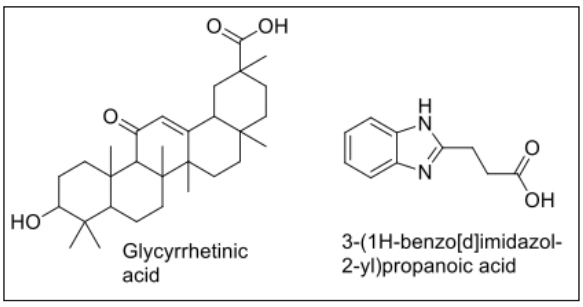
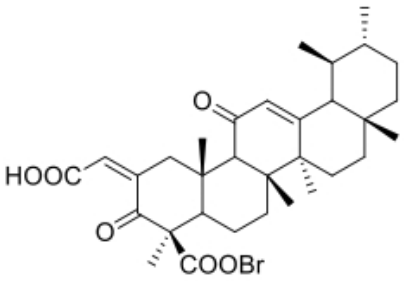


Figure 18: Structure of Glycyrrhetinic acid and 3-(1H-benzo[d] imidazol-2-yl)propanoic acid



10a

Figure 19: Structure of AKBA (3-acetyl-11-keto-boswellic acid) derivative

Abbrevations

- **CaP-** Carcinoma of Prostate
- **PCa-** Prostrate Cancer
- **AR-** Androgen Receptor
- **LNCaP-** Lymph Node Carcinoma of the Prostate
- **FDA-** Food and Drug Administration
- **DNA-** Deoxyribonucleic Acid
- **RNA-** Ribonucleic Acid
- **BET family-** Bromodomain and extra-terminal family
- **PC-3-** Prostate cancer Cell line
- **IC_{50}-** Half maximum inhibitory concentration
- **PSA-** Prostate Specific Antigen
- **MYC-** Master Regulator of Cell Cycle Entry and Proliferative Metabolism
- **CRPC-** Castration Resistance Prostate Cancer
- **Pin-1-** Peptidylprolyl Cis/Trans Isomerase, NIMA-Interacting 1
- **SAR-** Structure Activity Relationship
- **AKT/mTOR-** Protein Kinase B/ mammalian target of rapamycin
- **VEGFR-** Vascular Endothelial Growth Factor Receptor
- **EGFR-** Epidermal Growth Factor Receptor
- **PDGFR-** Platelet-derived Growth Factor Receptor
- **AKBA**- 3-acetyl-11-keto-boswellic acid

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