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Review Article

EXPLORING POTENTIAL OF NOVEL HETEROCYCLIC COMPOUNDS AND THEIR STRUCTURE-ACTIVITY RELATIONSHIP IN PROSTATE CANCER TREATMENT

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ABSTRACT

Prostate cancer is one of the leading causes of male death globally, and its overall incidence flaunts a rising trend over the years. Currently available treatment modalities for prostate cancer suffer from severe toxicity, unpredictable efficacy, high costs, and the emergence of resistance towards anti-cancer compounds. This substantiates the need to develop novel and potent anti-proliferative agents against prostate cancer. Multiple cellular mechanisms underlie the development of prostate cancer and, thus, multiple drug gable targets. In recent years, researchers have been conducting a myriad of investigations in this direction. This work recapitulates the synthesis of 78 such molecules based on recent references. These compounds are classified and tabulated according to the moiety that they possess. Further, the review study highlights the potent member of each chemical class. In addition, the review provides fundamental insights into the design and development of such compounds through the structure-activity relationship of each series of compounds, thereby unlocking new doors for future exploration.

Keywords: Anti-cancer agents, Anti-proliferative activity, Druggable targets, Novel, Potent, Prostate cancer, Synthetic compounds

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INTRODUCTION

Cancer is a leading cause of mortality worldwide, with over 10 million deaths in 2020 [1]. According to the estimates of GLOBOCAN 2020, the predicted number of new cancer cases could reach 28.4 million in the next 20 y [2]. Prostate Cancer (PCa) is the second most common cancer in men worldwide, with an incidence rate that can go as high as 83 in 100,000 people [2, 3]. PCa being a heterogeneous disease, the diversity in clinical, spatial, morphology and molecular genetics adds to the complexity of the disease [4-6]. PCa has multifactorial etiology with a wide range of modifiable and non-modifiable risk factors [7]. Certain established factors that pose risks are elderly age, positive family history, and African ancestry [8-10]. In addition, environmental factors, dietary habits and lifestyle can have effects on risk of developing PCa and its advancement [11, 12]. Widely used treatment modalities for PCa are surgery, radiotherapy, and/or Androgen Deprivation Therapy (ADT) [13, 14]. ADT, the mainstay of treatment of metastatic hormone-sensitive PCa treatment, has high rates of relapse where PCa cells develop castration resistance and grow aggressively [15-17]. Advent of immunotherapy has tremendously revolutionized cancer treatment [18-20]. However, these novel agents suffer from drawbacks such as unpredictable efficacy, immunotoxicity and high cost [21-23]. Moreover, identifying the dominant cancer immune drivers, pose a major challenge in selecting the type of immunotherapeutic agent [24]. Hence, the quest for new drug candidates against PCa is imperative to circumvent the problems posed by currently available therapies and address unmet needs such as enhanced survival rates, minimal toxicity, improved effectiveness and lower cost. In the recent times, a wide array of molecules derived from natural sources and synthetic approaches have been tested for their potent anti-proliferative actions that can be used to treat PCa. This review study presents the preparation of significant anti-PCa compounds that are categorized based on the basic nucleus that they contain, along with the insights into their synthesis and Structure-Activity Relationship (SAR). In addition, this work identifies the most consistent and promising molecule and their targets. The reviewed compounds depict an interesting possibility to tackle PCa.

MATERIALS AND METHODS

This work reviews research articles published between 2000 to 2020 and are accessed from ScienceDirect, Scopus, Elsevier, Springer, Pubmed, web of science. The summary of preparation of potential anti-PCa compounds according to the functional group they possess as follows:

Thiazolidines and thiadiazolines

Gududuru and others reported on the synthesis of an array of 2-aryl-4-oxo-thiazolidin-3-yl amide analogues of which three 4-thiazolidinone derivatives exhibited maximum potency with an IC50 (Half-maximal inhibitory concentration) value of 39.6, 11.5 and 22.1 µM against RH 7777a cells [25].

Of the 1,3,4-thiadiazolines that were synthesized by De Monte *et al.*, N-(4-Acetyl-5-ethyl-4,5-dihydro-5-phenyl-1,3,4-thiadiazol-2-yl)acetamide was identified as the most potent agent against PC3, SKMEL-5 and SK-MEL-28 cell lines (table 1) [26].

Trifluoromethyl substituted anilide

A study carried out by Basset to *et al.* described the synthesis of trifluoromethyl substituted anilides and demonstrated three perfluorinated derivatives to exhibit the highest potency with IC50 value of 37.51, 16.28 and 7.57 µM against DU-145 cells (table 2)[28].

Dibromotyrosine analogues

Of the dibromotyrosine analogues synthesized by Sallam *et al.*, 2,6-Dibromo-1-(trans, trans-farnesyl oxy)benzene-4-acetic acid ethyl ester was identified to exhibit the highest inhibitory potency with an IC50 value of 16.5 µM (table 3)[29].

Steroid analogues

Bruno *et al.* investigated the synthesis of VN/124-1 analogs (5, 3-β-hydroxy-17-(1H-benzimidazole) androsta-5,16-diene derivatives of which 3-β-Hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-dien was identified as the most potent agent against CYP7 with an IC50 value of 47 nM [30].

A series of Platinum(II) complexes conjugated at 7αposition of 17β-acetyl-testosterone were synthesized by Fortin *et al.*, among which 17β-acetyl testosterone-7α-platinum(II) complex exhibited the highest inhibitory potency with an IC50 value of 5.2 µM against PCacell lines [31].

Bastien *et al.* synthesized 7α-testosterone chlorambucil hybrid that binds to and inhibits androgen receptor and is employed against hormone-dependent PCa [32].

Heng *et al.* described the synthesis of Nickel (II) complex with testosterone thiosemicarbazone with IC50 of 14.1±1.2, 6.6±1.7,13.8±2.2 against PC3, LNCaP, HCT 116 cell line respectively [33].

A study carried out by Shi*et al.* described the synthesis of poly substituted steroidal pyridines and identified 2-Ethoxyl-4-(pyridin-3-yl)-6-[(3'β, 17'β)-3' (hydroxyl) androst-5'-en-17'-yl] pyridine to be the most potent cytotoxic molecule with an IC50 of 1.55 μM against PC-3 cells [34].

Sethi*et al.* developed diosgenin-indomethacin pro-drugs among which 3β, 25R-Spirost-5-ene-3yl (2, 3-dimethylphenyl) aminobenzoate was reported to be the pro-drug with highest potency [35].

Preparation of azole derivatives of[17(20)E]-21-norpregnene was reported by Dalidovich *et al.* of which 3β-hydroxy-5-ene (IC50= 10μM and 42μMagainst LNCaP and PC-3 cell lines respectively) and isoxazole moieties (IC50=72μM and 67μMagainst LNCaP and PC-3 cell lines respectively) showed the highest inhibitory potency [36].

Jorda *et al.* described the synthesis of an array of galeterone derivatives such as steroid-fused azacycles of which 3b-Acetoxy-40-methylandrost-5-eno[16,17:4,5]pyrido[2,3-b] indole was a promising lead compound with IC50 value of 0.315 μM [37].

A study carried out by Komendantova *et al.* described the synthesis of steroidal 1,3,4-thiadiazines analogues and demonstrated fbruno(N-arylcarbamoyl)17 [1′,3′,4′]thiadiazine-substituted androstenesto exhibit the highest potency with IC50 value of2.1–6.6 μM [38].

Of the new steroidal imidazoles series prepared by Hou *et al.*, 20-(1′-methylimidazol-2-yl)-20-hydroxy-pregnan-4-alkene-3-oxime was identified to possess the highest potency with IC50 of 0.5 μM for AR inhibition(table 4.) [39].

1,3-diaryl-2-propen-1-ones (Chalcones)

1,3-diaryl-2-propen-1-ones (Chalcones) analogues were synthesized by Nagaraju *et al.* and identified 1,3-disubstituted-2-propen-1-ones as potent molecules with IC50 = 8.4μM (table 5) [42].

Table 1: Synthesis of thiazolidines and thiadiazolines

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Thiazolidines and thiadiazolines				
a) 2-aryl-4-oxo-thiazolidin-3-yl-amides	Scheme 1: Mercaptoacetic acid, aldehydes of aromatic kind and glycine methyl ester are condensed so as to form ester intermediate which is further subjected to base catalyzed hydrolysis and subsequent reaction with suitable amines in the presence of 1-hydroxybenzotriazole monohydrate or ethylene dichloride. Scheme 2: In the presence of 4-dimethylaminopyridine as a catalyst, acid reacts with various isocyanates. Scheme 3: Product so formed is subjected to exhaustive reduction with tetrahydrofuran or borane under conditions of reflux or oxidation reaction using oxidizing agents such as potassium permanganate and hydrogen peroxide[25].	Lysophosphatidic Acid Receptor [27]	[25]	4-thiazolidinones
b) 1,3,4-thiadiazolines	Reaction between carbonyl compounds and thiosemicarbazide bathed in ethanol in the presence of acetic acid as catalyst produces thiosemicarbazone intermediates which when treated with symmetrical anhydrides (as solvent) forms 1,3,4-thiadiazolines. Subsequently, oxidation reaction is carried out using potassium permanganate in acetic acid in the presence of water and hydrogen peroxide [26].	Kinesin Eg5 ATPase	[26]	N-(4-Acetyl-5-ethyl-4,5-dihydro-5-phenyl-1,3,4-thiadiazol-2-yl) acetamide

Table 2: Synthesis of trifluoromethyl substituted anilides

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Trifluoromethyl substituted anilides:				
a) Bicalutamide derivatives	Suitable aniline when treated with methacryloyl chloride indimethyl acetamide generates phenylacrylamide intermediate when treated with hydrogen peroxide in excess and trifluoroacetic anhydride in dichloromethane yields suitable epoxides. Further, using commercial thiophenols and phenolsepoxides ring is cleaved to furnish an array of thioethers and ethers. Thioethers are oxidized by treatment with meta-chloroperoxybenzoic acid to produce suitable sulfones.	Androgen Receptor	[28]	Perfluorinated derivatives
b) Enzalutamide derivatives	Substituted anilines with acetone and trimethylsilyl cyanide follow Strecker reaction to furnish suitable cyanomines, which when treated with isothiocyanates in dimethylformamide and subsequent addition of hydrogen chloride and methanol yields desired product [28].			

Table 3: Synthesis of dibromo tyrosine analogues

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Dibromotyrosine analogues	Scheme 1: Phenolic hydroxyl group is esterified with different alkyl and aryl acid chlorides, employing N, N-dimethylaminopyridine catalyst. Scheme 2: In the presence of sodium hydride, the same phenolic hydroxyl group is esterified with different of alkyl and aryl bromides [29].	ATP binding site of VEGFR2	[29]	2,6-Dibromo-1-(trans, trans-Farnesyl oxy)benzene-4-acetic acid ethyl ester

Table 4: Synthesis of steroids analogues

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Steroid analogues				
a) VN/124-1 (TOK-001) derivatives				
i) 3-ξ-Fluoro-17-(1H-benzimidazol-1-yl)androsta-5,16-dien	Reaction of 3-β-Hydroxy-17-(1H-benzimidazol-1-yl)androsta-5,16-dien bathed in dichloromethane with diethyl aminosulfur trifluoride yields product.	Androgen Receptor	[30]	3-β-Hydroxy-17-(1H-benzimidazol -1-yl)androsta-5,16-dien
ii) 3-β-O-Mesyl-17-(1H-benzimidazol-1-yl)androsta-5,16-dien	Reaction between 3-β-hydroxy-17-(1H-benzimidazol-1-yl) androsta-5,16-diene in pyridine and methane sulfonyl chloride at a temperature of 0° C. The resulting solution is subsequently flooded over ice-water mixture so as to form precipitate of product.			
iii) 3-α-Azido-17-(1H-benzimidazol-1-yl)androsta-5,16-dien	Reaction between 3-β-O-Mesyl-17-(1H-benzimidazol-1-yl) androsta-5,16-dien in dimethylformamide and sodium azide, heated and poured into ice-water.			
iv) 3-β-O-Sulfamoyl-17-(1H-benzimidazol-1-yl)androsta-5,16-dien	Reaction between 3 β-hydroxy-17-(1H-benzimidazol-1-yl) androsta-5,16-diene in dimethylformamide and potassium tertiary-butoxide under cold conditions followed by treatment with sulfamoyl chloride in toluene. Unreacted reagents are inactivated by using water saturated with ammonium chloride. Further, the product formed is extracted with ethyl acetate.			
v) 3-β-Hydroxy-17-(1H-benzimidazol-1-yl)androsta-5-ene	Reaction of 3b-Hydroxy-17-(1H-benzimidazol-1-yl) androsta-5,16-dien in ethanol with hydrazine hydrate and acetic acid followed by heating, cooling, concentrating under vacuum and subsequent treatment with water saturated with sodium bicarbonate.			
vi) 3-β-Acetoxy-17-chloro-16-formyl-5-α-androstan-16-ene	Reaction of trans-androstane in pyridine at 0° C with acetic anhydride. A solution of 3-β-acetoxy-5 α-androst-17-one in dry chloroform is poured into cold and a uniform solution containing phosphorus oxychloride and dimethyl formamide. The resulting blend is further subjected to reflux under argon. Further, the concentrated mixture was poured onto ice, extracted using a cocktail of ethyl acetate and ether and subsequently washed with brine.			
vii) 3-β-Acetoxy-17-(1H-benzimidazol-1-yl)-16-formyl-5α-androstan 16-ene	Addition of 3-β-acetoxy-17-chloro-16-formyl-5-α-androstan-16-ene to a mixture of benzimidazole and potassium carbonate in dry dimethylformamide so as to form an admixture which is subsequently allowed to attain room temperature and subsequently flooded onto ice-cold water so as to obtain product precipitate.			
viii) 3-β-Acetoxy-17-(1H-benzimidazol-1-yl)-5 α-androsta-16-ene	3-β-Acetoxy-17-(1H-benzimidazol-1-yl)-16-formyl-5-α-androsta-16-ene is dissolved in dry benzonitrile to form a solution which is further refluxed using Palladium on activated charcoal as a catalyst, cooled to room temperature, filtrate is evaporated, and product obtained.			
ix) 3-β-Hydroxy-17-(1H-benzimidazol-1-yl)-5-α-androsta-16-ene.	Acetate of 3-β-Acetoxy-17-(1H-benzimidazol-1-yl) androstaneis dissolved in methanol in an atmosphere of inert argon gas, followed by reaction with 10% methanolic potassium hydroxide. The solution thus obtained is concentrated under diminished pressure poured onto ice water. White precipitate of the product obtained by filtration is washed and dried.			
x) 3-β-Acetoxy-17-(1H benzimidazol-1 yl)androstane	3-β-Acetoxy-17-(1H-benzimidazol-1-yl)-5-α-androsta-16-ene was dissolved in ethanol and treated with hydrazine hydrate, acetic acid and heat while the solution was continuously bubbled with air. The reaction mixture further cooled, concentrated, and poured onto ice cold water. Subsequently, water saturated with sodium bicarbonate was used to obtain precipitate of product.			
xi) 3-β-Hydroxy-17-(1H-benzimidazol-1-yl)-5-α androstane	Reaction of acetate of 3-β-Acetoxy-17-(1H-benzimidazol-1-yl)-5-α-androsta-16-ene in methanol with10% methanolic potassium hydroxide. The resulting mixture was stirred, concentrated and when poured onto ice water to obtain precipitate of product.			
xii) 17-(1H-Benzimidazol-1-yl)androsta-4,16-dien-3-one	An admixture of compounds N-methylmorpholine-N-oxide, 3-β-Hydroxy-17-(1H-benzimidazol-1-yl)-5-α-androstane and dichloromethane was prepared which was further subjected to treatment with tetrapropylammoniumperruthenate. To resulting solution, ethyl acetate was added to dilute and washed using aqueous solution of sodium chloride and sodium bicarbonate [30].			
b) Platinum(II) complexes conjugated at position 7a of 17 β-acetyl-testosterone				
Compounds	Reaction between 7 α-(E)-4-chlorobut-2-enyl-4-androsten-17b-ol-3-one acetate and specific amino acid using cesium carbonate bathed in methyl ethyl ketone	Androgen Receptor	[31]	17 β-acetyl testosterone-7 α-platinum(II) complex
i) 17β acetyl testosterone-7 α-tert-butyloxycarbonyl amino acids				
ii) 17 β-acetyl-testosterone-7 αamino acids	Reaction between 17 β acetyl testosterone-7 α-tert-butyloxycarbonyl amino acids and trifluoroacetic acid bathed in methylene chloride yields 17 β-acetyl-testosterone-7 αamino acids			
iii) 17 β-acetyl-testosterone-7 α-platinum(II) complexes	Reaction of 17 β-acetyl-testosterone-7 αamino acids with potassium tetrachloroplatinate bathed in a cocktail of water and dimethylformamide [31].			

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
c) 7 α-testosteronechlorambucil hybrid	Scheme 1: Synthesis involves Nucleophilic Bimolecular type of substitution reaction. First step of synthesis involves Olefin Crossmetathesis reaction of 7 α–allyltestosterone derivative using allyl chloride and Hoveyda-Grubbs catalyst in the presence of dichloromethane to yield an intermediate 7 α-(4 chloro-but-2-enyl) testosterone. This is followed by hydrolysis reaction of acetate with hydrogen chloride in methanol and substitution reaction in the presence of chlorambucil, allyl chloride and sodium bicarbonate in a cocktail of water and dimethylformamide. Scheme 2: Hydrolysis of 7α-allyltestosterone derivative in the presence of hydrogen chloride yielded 7 α–allyl testosterone. Treatment of chlorambucil with oxalyl chloride, allyl alcohol and pyridine bathed in dichloromethane produced acid allyl ester derivative. The ester and 7-αallyl testosterone in the presence of Hoveyda-Grubbs catalyst (2nd generation) in dichloromethane yields product [32].	Androgen Receptor	[32]	----
d) Nickel (II) complex with testosterone thiosemicarbazone	Reaction between estosterone in ethanol and ethanolic thiosemicarbazide and subsequent treatment with ethanol at 78° C results in formation of a Schiff base ligand composed of testosterone, thiosemicarbazide and its nickel (II) complex [33].	Androgen Receptor and DNA binding	[33]	----
e) Poly-substituted steroidal pyridines	Scheme 1: Pregnenolone and aldehydes of aromatic kind bathed in ethanol undergoes Aldol Condensation in the presence of aluminum oxide/potassium fluoride catalyst. Resulting steroidalα, β-unsaturated ketone is treated with malononitrile and sodium ethoxide followed by acetylation reaction using acetyl chloride, triethylamine, 4-dimethylaminopyridine, methylene chloride. Scheme 2: Malononitrile in the presence of sodium ethoxide undergoes 1, 4-Michael addition reaction to form an intermediate which isomerizes to produce an enamine which, when subjected to dehydration of intramolecular kind and ambient oxidation in the presence of air yields product [34].	Androgen Receptor [40]	[34]	2-Ethoxyl-4-(pyridin-3-yl) -6-[(3'β, 17'β)-3'-(hydroxyl) androst-5'-en-17'-yl]pyridine
f) Diosgenin-indomethacin pro-drugs	Mefenamic acid and indomethacin are coupled with diosgenin in the presence of an ionic liquid N-methyl-2 pyrrolidone hydrogen sulfate to generate pro-dugs [35].	Matrix metalloproteinase-2(MMP-2) and MMP-9 [41]	[35]	3β, 25R-Spirost-5-ene -3yl (2, 3-dimethyl phenyl) aminobenzoate
g) Azole analogues of [17(20)*E*]-21-norpregnene				
i) isoxazole, 1,2,3-triazole, tetrazole derivatives of [17(20)E]-21-norpregnene	1,3-dipolar cycloaddition reaction of azides or nitrile oxides to produce nitriles or acetylenes and subsequent dehydration reaction of 17 beta-hydroxy-17beta-methylene-azoles to derivatives of norpregnene	CYP17A1	[36]	3β-hydroxy-5-ene-and isoxazole moieties
ii) 1,2,4-oxadiazole derivatives of [17(20)E]-21-norpregnene	The synthesis 1,2, 4-oxadiazoles is through the generation of acetimidamides[36].			
h) Galeterone analogues including steroid-fused azacycles				
i) Steroid-fused azacycles (benzimidazolopyrimidines ii) 17-(benzimidazol-1-ylimino) steroid derivatives iii) 16-α-(benzimidazol-2-ylamino) steroid derivatives iv) 16 α-(benzothiazol-2-ylamino) steroid derivatives	Scheme 1: Condensation reaction of 2-aminobenzimidazoles and 16-dehydropregnenolone acetate yields Azacycle fused steroids. Scheme 2: Enone undergoes Aza-Michael reaction and a subsequent electrophilic substitution employing acid as a catalyst, resulting in cyclization, spontaneously occurring dehydration, and aromatization [36].	Androgen receptor	[36]	3-β-Acetoxy-40-methylandrost-5-eno[16,17:4,5]pyrido[2, 3-b] indole
i) Steroidal 1,3,4-thiadiazines				
i) Spiro[1,3,4] thiadiazine ii) 16β-hydroxyspiro-androsteno-17,6′[1,3,4]thiadiazines iii) 17-(6′*H*-1′,3′,4′-thiadiazine-2′-carboxamide)androst-5,17-dienes	Scheme 1: The traditional nucleophilic oxirane ring opening reaction of 16β,17β-epoxypregnenolone with NH-nucleophile and subsequent aromatization-driven dehydration. Scheme 2: In the presence of a catalytic quantity of sulphuric acid, reaction between thiohydrazides with both electron-withdrawing and donating groups on the aryl moiety and16β, 17β-epoxypregnenolone yields desired product. Scheme 3: Reaction of 21-bromopregna-5,16-dien-20-one with oxamic acid thiohydrazides under mild basic circumstances to yield product [38].	Androgen receptor	[38]	(N-arylcarbamoyl) 17 [1′,3′,4′]thiadiazine -substituted androstenes
j) Steroidal imidazoles	The essential intermediates are produced by the hydrolysis of 3β-hydroxy-pregnane-5-alkene-20-one-3 acetate in the presence of potassium carbonate and its hydroxy group is protected. This intermediate undergoes nucleophilic substitution reaction with N-methylimidazole in the presence of n-butyl lithium to yield product [39].	Androgen Receptor/ CYP17	[39]	20-(1′-methylimidazol-2-yl)-20-hydroxy-pregnan-4-alkene-3-oxime

Table 5: Synthesis of chalcones

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
5. 1,3-diaryl-2-propen-1-ones (Chalcones)	Scheme 1: With 3-chloro-2-methylpropene in acetone, res acetophenone undergoes Mono-allylation reaction in the presence of anhydrous potassium carbonate and catalytic amount of sodium iodide. Subsequently, Claisen rearrangement reaction occurs with allyl–aryl ether in N, N-diethyl aniline to form rearranged product, which upon treatment with catalytic amount of p-toluenesulfonic acid in chloroform results in generation of benzofuran. Phenol undergoes benzylation with treated with benzyl bromide and subsequent cyclization upon treatment with p-toluenesulfonic acid in refluxing toluene as a catalyst. Scheme 2: Claisen–Schmidt condensation reaction of ethanone with several benzaldehydes and pyrazolaldehydesin ethanolic solution of sodium hydroxide to form 1,3-disubstituted-2-propen-1-ones [42].	Androgen Receptor [43]	[42]	1,3-disubstituted-2-propen-1-ones

Table 6: Synthesis of flavonols and flavones

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Flavonols and flavones				
a) Methoxyflavonols	Scheme 1: 20-hydroxy acetophenone and benzaldehyde undergoes Claisen-Schmidt condensation reaction to yield 20-hydroxy chalcones, which under AlgareFlynneOyamada conditions (hydrogen peroxide, sodium hydroxide) generates desirable methoxy flavonols	Androgen receptor	[44]	3,3',4',5'-Tetramethoxyflavone, 6-Fluoro-3',4',5'-trimethoxyflavonol,
b) Hydroxyflavonols	Demethylation of methoxy flavonols with boron tribromide to generate corresponding hydroxy flavonols			7-Fluoro-3',4',5'-trimethoxyflavonol
c) 4',6'-difluoro-2'-hydroxyacetophenone	Scheme 2: O-acetylation of 3,5-difluorophenol and subsequent Fries rearrangement catalysed by aluminum chloride.			
d) Tetramethoxyflavone	Scheme 3: Methylation of 3',4',5'-trimethoxy-flavonol with iodomethane generates tetramethoxyflavone [44].			
a) 3-O-substituted-3',4',5'-trimethoxyflavonols	Scheme 1: Trimethoxyflavonolsare synthesized through a four-day one-pot process employing hydroxylacetophenone and trimethoxyl benzaldehyde as the precursors. Scheme 2: Trimethoxyflavonol undergoes O-alkylation reaction with suitable alkyl halide in aprotic solvent dimethylformamide and potassium carbonate as the base to generate 3-O-alkyltrimethoxyflavonols. Scheme 3: 3', 4', 5'-trimethoxyflavonol were transformed into twelve novel 3-O-aminoalkyl-3', 4', 5'-trimethoxyflavonols in 2 steps [45].	5-alpha reductase enzyme	[45]	3',4',5'-trimethoxyflavonols and 3-O-dialkylaminoalkyl-3',4',5'-trimethoxyflavonols

Table 7: Synthesis of gold (III) alkane-diamine complexes

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Gold(III) alkanediamine complexes	Trihydrate auric acid reacts with diamine ligand equivalents to produce complexes of Gold(III) alkane-diamine [46].	thioredoxin reductase	[46]	[Au(diamine)2]3+(in PC3 cells), [Au(diamine)Cl2]+(in SGC7901 and A2780/A2780 cis cells)

Table 8: Synthesis of5-substituted-3, 4-diphenyl furan-2-ones

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
5-substituted-3,4-diphenyl furan-2-ones: a) 5-alkylidene substituted-3-phenylfuran-4-(4 methanesulfonyl phenyl)-2 ones b) Rofecoxib and its analogues	Reaction of rofecoxib or itsanalogs and anhydrous sodium carbonate in methanol andrelevant aldehyde or ketone to form precipitate of product Reaction of sodium hydroxide with phenyl acetic acid or 2-chlorophenylacetic acid or 4-fluorophenylacetic acid in dimethylformamide, followed by reaction of 2-bromo-1-(4 (methylsulfonyl) phenyl) ethanone so as to form intermediate which further reacts with diisopropylamine, acidification with hydrochloric acid, forming precipitate of product [47].	Cyclooxygenases (COXs)	[47]	3-(2-chloro-phenyl)-4-(4-methanesulfonyl-phenyl)-5-(1-methoxy-ethyl)-5Hfuran-2-one

Flavonols and flavones

Britton *et al.* reported on the synthesis of flavonols of which 3,3',4',5'-Tetramethoxyflavone, 6-Fluoro-3',4',5'-trimethoxyflavonol and 7-Fluoro-3',4',5'-trimethoxyflavonol were identified as the molecules with an excellent inhibitory potency with IC50 of 2.6, 3.3 and 4.0μM respectively [44].

Xiang Li*et al.* developed a series of 3-O-substituted-3',4',5'-trimethoxyflavonols of which 3',4',5'-trimethoxyflavonols exhibited potent inhibitory action with IC50 values of 32.1 μM and 3-O-dialkylaminoalkyl-30,40,50-trimethoxyflavonols demonstrated amarginal improvement in inhibitory potency against proliferation of LNCaP cell lines (table 6) [45].

Gold (III) alkanediamine complexes

Mehboob *et al.* developed gold (III) alkanediamine complexes and demonstrated [Au(diamine)2]3+complex to exhibit highest potency with IC50 value of 1–6μMagainst PC3 cells and [Au(diamine)Cl2]+complex to exhibit highest efficacy in SGC7901 and A2780/A2780 cis cells (table 7) [46].

Diphenyl furanone analogues

Liu and others reported on the development of 5-substituted-3, 4-diphenyl furan-2-ones, of which 3-(2-chloro-phenyl)-4-(4-methanesulfonyl-phenyl)-5-(1-methoxy-ethyl)-5Hfuran-2-one possessed the most potent inhibitory action against PC3 (IC50 = 20μM), PC3 PCDNA (IC50 = 5 μM), PC3 SKP2 (IC50 = 5 μM) and DU145 cell lines (IC50 = 25 μM)(table 8) [47].

Aryl –pyrazol derivatives

Nakao *et al.* developed an array of 1-aryl-3,4-substituted-1H-pyrazol-5-ol derivatives of which 1-(5-methyl-1H-benzimidazol-2-yl)-4-benzyl-3-methyl-1H-pyrazol-5-ol demonstrated a potent inhibitory action against PCA-1/ALKBH3 both *in vitro* and *in vivo* (table 9) [48].

Table 9: Synthesis of1-aryl-3,4-substituted-1H-pyrazol-5-ol derivatives

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
1-aryl-3,4-substituted-1H-pyrazol-5-ol derivatives: a) 1,3,4-substituted-5-hydroxy-pyrazoles b) 1-(substituted benzimidazol-2-yl)-5-hydroxy-3-methyl-4-(subsituted benzyl) pyrazoles	Condensation reaction between N-substituted hydrazines and derivatives of ethyl acetoacetate [48].	PCA-1/ALKBH3	[48]	1-(5-methyl-1H-benzimidazol-2-yl)-4-benzyl-3-methyl-1H-pyrazol-5-ol

Emetine dithiocarbamate ester derivatives

Of the emetine dithiocarbamate ester derivatives synthesized by Akinboye *et al.*, 1-(3-Ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2Hpyrido[2,1-a]isoquinolin-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-2-carbodithioic acid (4-bromophenyl carbamoyl)-methyl ester possessed potent inhibitory action against LNCaP (IC50 = 1.698 μM), PC3(IC50 = 1.507μM), and DU145 (IC50 = 1.603 μM) cell lines (table 10) [49].

Arylpiperazine derivatives

A study conducted by Chen *et al.* described the synthesis of arylpiperazine derivatives and demonstratedN-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-1H-indole-2-carboxamide dihydrochloride (IC50 = 5.50μmol/l), N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)benzofuran-2-carboxamide (IC50 = 5.17μmol/l) and N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)benzo[b]thio-phene-2-carboxamide dihydrochloride (IC50 = 8.21 μmol/l) against DU145 cells (table 11) [50].

Silibinins

Vue *et al.* developed a series of silibinins of which 7-O-Methylsilibinin (IC50 of 10 2.76±0.18, 7.92±0.55, 2.39±0.97 against LNCaP, DU 145, PC-3 respectively) and 7-O-ethylsilibinin (IC50 of 2.58±0.07, 7.59±0.66, 3.25±0.31 against LNCaP, DU 145, PC-3 respectively) exhibited potent inhibitory action [51].

Vue *et al.* investigated the synthesis of 20-O-alkyl-2,3-dehydrosilybins and 5,20-O-dialkyl-2,3-dehydrosilybins. The study further demonstrated 5-O-heptyl-2,3-dehydrosilybin to be the most potent member of them all, having an IC50 value of less than 8 μM and potency 7 to 29 times more than silybin (table 12) [52].

Table 10: Synthesis of emetinedithiocarbamate ester derivatives

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Emetine dithiocarbamate ester derivatives	Ethanolic solution of sodium hydroxide containing salt of emetine dihydrochloride is treated with carbon disulfide and subsequently with different alkylating agents in acetonitrile to form dithiocarbamate ester derivatives of emetine [49].	Androgen Receptor	[49]	1-(3-Ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2Hpyrido[2,1-a]isoquinolin-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-2-carbodithioic acid (4-bromophenylcarbamoyl)-methyl ester

Table 11: Synthesis of aryl piperazine derivatives

Type of derivative	Type of reaction involved in synthesis	Target	Ref	Potent compound
Arylpiperazine derivatives	Scheme 1: (4-(2-(4-phenylpiperazin-1-yl)ethyl)phenyl) methanamine) in toluene reacts with corresponding acid anhydride to generate an intermediate. The solution of it is prepared to which ethyl acetate is added in a dropwise manner followed by hydrochloric acid in ethyl acetate. Scheme 2: Reaction between (4-(2-(4-phenylpiperazin-1-yl)ethyl)phenyl) methanamine bathed in dichloromethane, appropriate acid,2-(7-aza-1H benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate and N, N-diisopro-pylethylamine. The solution of the intermediate is prepared to which ethyl acetate is added in a drop wise manner followed by hydrochloric acid in ethyl acetate. Scheme 3: Reduction reaction between 2-(4-(bromomethyl) phenyl)acetic acid and borane–methyl sulfide complex, followed by nucleophilic substitution reaction occurring between intermediate so obtained and 1-phenylpiperazine with methyl cyanide as solvent in the presence of potassium carbonate, followed by reaction with 4-toluene-sulfonyl chloride along with trimethylamine using dichloromethane as solvent and 4-dimethylaminopyridine as a catalyst. Finally, treatment with various phenols in the presence of potassium carbonate to obtain product [50].	Alpha 1-adrenergic receptor	[50]	N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)-1H-indole-2-carboxamide dihydrochloride and N-(4-(2-(4-henylpiperazin-1-yl)ethyl)benzyl)benzofuran-2-carboxamide and N-(4-(2-(4-Phenylpiperazin-1-yl)ethyl)benzyl)benzo[b]thio-phene-2-carboxamide dihydr-ochloride

Table 12: Synthesis of silibinins

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Silibinins				
a) Eight 7-O-alkylsilibinins, b) Eight 7-O-alkyl-2,3-dehydrosilibinins, c) Eight 3,7-O-dialkyl-2,3 dehydrosilibinins	Selective methylation and benzylation at phenolic hydroxyl group at 7th carbon atom of silibinin in the presence of potassium carbonate and anhydrous acetone using methyl iodide and benzyl bromide [51].	Epidermal Growth Factor Receptor (EGRF) [53]	[51]	7-O-Methylsilibinin and 7-O-ethylsilibinin
i) 20-O-alkyl-2,3-dehydrosilybins and 5,20-O-dialkyl-2,3-dehydrosilybins	Under completely anaerobic conditions, silybin is converted to 7-O-benzylsilybin employing acetone solvent and equivalents of benzyl bromide and potassium carbonate. Solvent is switched from acetone to dimethylformamide and addition of benzyl bromide and potassium carbonate oxidation yields an intermediate which undergoes selective benzylation at 3-hydroxide and subsequent reaction with suitable alkyl halide using dimethylformamide as the solvent and potassium carbonate as the base to produce dibenzylsilybins that further upon treatment with ammonium formate undergoes debenzylation reaction using Palladium on activated charcoal as a catalyst.	Epidermal Growth Factor Receptor (EGRF) [53]	[52]	5-O-heptyl-2,3-dehydrosilybin
ii)5-O-alkyl-2,3-dehydrosilybins	Silybin undergoes benzylation reaction at 7thhydroxide group under complete anaerobic conditions, followed by a subsequent aerobic oxidation generates intermediate that further undergoes dibenzylation reaction occurring at 3rd OH and 20thhydroxide group to generate 3,7,20-O tribenzyl-2,3-dehydrosilybin. The intermediate thus formed undergoes alkylation reaction at of 5thhydroxide group and a subsequent global debenzylation reaction with ammonium formate using palladium carbon as catalyst to produce desired product [52].			

Table 13: Synthesis of indole derivatives

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Indole derivatives:				
i) Indeno[1,2-b]indole derivatives	Scheme 1: Indanone undergoes Fischer Indolization reaction through the formation of respective phenylhydrazones. Scheme 2: 2-nitrobenzylidenephtalide is produced either by reaction between phthalide-phosphonium bromide and 2-nitrobenzaldehyde followed by cyclization reaction or by cyclization of intramolecular type of 2-(2-nitrophenylethyl)benzoic acid. The analogues of nitrobenzylidenephtalide so formed are subjected to transformation and reduction reaction to yield desired products. Scheme 3: Reaction between ninhydrine, amines of aliphatic and aromatic kind, or enaminones of alicyclic and cyclic type producesvic-dihydroxy-indenoindolones [54].	Matrix metallo proteinases	[54]	7,7-dimethyl-5-[(3,4-dichlorophenyl)]-(4bRS,9bRS)-dihydroxy-4b,5,6,7,8,9 bhexahydroindeno [1,2-b]indole-9,10-dione
ii) Thiosemicarbazone-indole derivatives	Scheme 1: 2-(1H-indol-3-yl)ethan-1-amine reacts with carbon disulfide in the company of triethylamine. Further the compound so formed undergoes addition reaction with 4-dimethylaminopyridine and di-tert-butyl-dicarbonate to generate an intermediate, which upon treatment with hydrazine hydrate and a subsequent Schiff base condensation reaction with 5-methylpicolinaldehyde driven by acid-catalysis yields desired thiosemicarbazone-indole analogues Scheme 2: Reaction of 4-aminocyclohexane-1-carboxylic acid with 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, hydroxybenzotriazole and 2-(1H-indol-3-yl) ethan-1-amine to yield amide derivatives. Scheme 3: Reaction of substituted amines with 6-nitronicotinic acid or 4-nitrobenzoic acid in the company of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide and 1-Hydroxybenzotriazolein dichloromethane, and the subsequent reaction with hydrogen using palladium as a catalyst to generate corresponding byproducts, which are subjected to reaction similar to that of Scheme 1 [55].	Ribonucleotide reductase	[55]	(E)-N-(2-(2-methyl-1H-indol-3-yl)ethyl)-4-(2-((5-methylpyridin-2-yl)methylene)hydrazine-1-carbothioamido)benzamide

Indole derivatives

Lobo *et al.* developed derivatives of indeno [1,2-b]indole of which 7,7-dimethyl-5-[(3,4-dichlorophenyl)]-(4bRS,9bRS)-dihydroxy-4b,5,6,7,8,9bhexahydroindeno[1,2-b]indole-9,10-dione possessed strong anti-proliferative potency against PC-3 (IC50 value of 10.70±0.07μM), LNCaP (9.57±0.55μM) and MatLyLu cell line (5.96±0.28μM) [54].

Of the thiosemicarbazone indole derivatives synthesized by Xu He *et al.*, (E)-N-(2-(2-methyl-1H-indol-3-yl)ethyl)-4-(2-((5-methylpyridin-2-yl)methylene)hydrazine-1-carbothioamido)benzamide demonstrated potent inhibitory action with the IC50 value of 0.054 μM (table 13) [55].

Triazole derivatives

Mandalapu *et al.* synthesized triazole hybrids of curcumin of which (3*E*,5*E*)–1–((1–(substitutedbenzyl)–1*H*–1,2,3–triazol–4–yl)methyl)–3,5–bis(substituted benzylidene) piperidin–4–ones exhibited potent action against PC-3 (IC50 = 8.8μM) and DU-145 cell lines (IC50 = 9.5μM)[56].

Madasu*et al.* reported on the synthesis of1,2,3-triazole hybrids of myrrhanone B of which meta-hydroxy phenyl 1,2,3–triazole (IC50: 6.57±0.62 μM) and deoxyuridine 1,2,3–triazole (IC50: 10.85±0.90 μM) were found to be the most potent antiproliferative agents against PC-3 cell line (table 14) [57].

Table 14: Synthesis of triazole derivatives

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Triazole derivatives				
a) Triazole hybrids of curcumin	Reaction between substituted benzaldehydes and 4–piperidinone hydrochloride hydrate with concentrated hydrochloric acid in glacial acetic acid and subsequent alkalinization with potassium carbonate in a blend of acetone and water generates substituted benzylidenepiperidin–4–onederivatives, which further reacts with propargyl bromide in acetone. Reaction of carbon disulfide with aq. potassium hydroxide in dichloromethane yields dithiocarbamate potassium salts which in turn react with propargyl bromide in a blend of water and acetone. Further substituted benzylidenepiperidin–4–one analogues or substituted benzylidene–4–oxopiperidine–1–carbodithioate undergoes reaction with substituted benzyl azides using copper sulphate pentahydrate as catalyst and sodium ascorbate [56].	Cell survival protein Akt	[56]	(3*E*,5*E*)–1–((1–(substitutedbenz-yl)–1*H*–1,2,3–triazol–4–yl)methyl)–3,5–bis(substitutedbenzylidene) piperidin–4–ones
b) myrrhanone B-1,2,3-triazole hybrids	Propargylation followed by Huisgen's 1,3-dipolar cycloaddition reaction. Reaction of (5S,8R,9R,10S)-3-oxo-8-hydroxy-30-carboxypolypoda 13E,17E,21E-triene with propargyl bromide in company of potassium carbonate in dry acetone yields an intermediate. Parallel to this, substituted aromatic azides, deoxy uridine and protected uridine azides are prepared. Intermediate formed reacts with substituted azides in sodium ascorbate and copper sulphate pentahydrate in the water-tetrahydrofuran solution's presence [57].	Epidermal Growth Factor Receptor (EGFR) [58]	[57]	Meta-hydroxy phenyl 1,2,3–triazole and deoxyuridine 1,2,3 – triazole

Table 15: Synthesis of quinoline derivatives

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Quinoline derivatives	Scheme 1: Quinolines were oxidized using m-chloroperoxybenzoic acid in chloroform at room temperature, yielding the critical intermediate quinoline N-oxide, which was then condensed with different substituted 2-aminopyridines to generate product. Scheme 2: Under basic circumstances, methyl iodide is used to oxidise substituted 8-hydroxyquinoline that is protected by a methyl group, followed by coupling reaction with suitable pyridines and subsequent demethylation using tribromoborane in a nitrogen environment to produce thioethers. Intermediates generated through coupling, on the other hand, are hydrolyzed by strong hydrochloric acid and deprotected to yield products. Scheme 3: In the presence of triethylamine, 5-substituted 8-hydroxy quinoline reacts with methanesulfonyl chloride, and subsequent N-oxidation reaction. The intermediate formed were condensed with 2-hydroxypyridine and are further hydrolyzed with sodium hydroxide to yield the appropriate ethers [59].	PIM-1 kinase (Proviral Insertion site in Moloney murine leukemia virus)	[59]	2-(pyridine-2-amino)quinolin-8-ol

Quinoline derivatives

Of the quinoline derivatives developed by Li *et al.*, 2-(pyridine-2-amino) quinolin-8-olpossessed potent antitumor activity with IC50 value of 0.75 μM (table 15) [59].

Diheteroarylnona-tetraen-ones

Zhang *et al.* synthesized 1,9-diheteroarylnona-1,3,6,8-tetraen-5-ones, of which (1*E*,3*E*,6*E*,8*E*)-1,9-Bis(3-fluoropyridin-4-yl)nona-1,3,6,8-tetraen-5-one (IC50 value 2.36±0.56 μM, 1.21±0.43 μM, 2.43±1.31 μM against PC-3, DU145, LNCaPcell lines respectively) and (1E,3E,6E,8E)-1,9-Bis(1-(pentan-3-yl)-1H-imidazol-2-yl)nona-1,3,6,8-tetraen-5-one (IC50 value 1.14±0.12 μM, 1.78±0.13 μM, 2.17±0.2 μM against PC-3, DU145, LNCaPcell lines respectively) were the two most potent members (table 16) [60].

Boswellic acid derivatives

Li *et al.* described the synthesis of acetyl-11-keto-β-boswellic acid derivatives of which N-(2-cyano-3,11-dioxo-ursan-1,12-dien-24-oyl)-piperazine exhibited a potent inhibitory action and demonstrated IC50 value of 0.04 and 0.27 μM against PC-3 and LNCaP cell lines respectively [62].

Huang *et al.* investigated on the synthesis of ring-A modified 11-keto-boswellic acid derivatives of which 3-oxo-2-carboxylmethylene derivative of 11-keto-boswellic acid derivatives showed potent action with 0.46 μMIC50 value(table 17) [63].

Table 16: Synthesis of1,9-diheteroarylnona-1,3,6,8-tetraen-5-ones

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
1,9-Diheteroarylnona-1,3,6,8-tetraen-5-ones	Using potassium carbonate as base and water and ethanol as co-solvents,1,3 bis(diethyl phosphonate) acetone and (E)-3-aryl-2-propenal undergoes Horner-Wadsworth-Emmons reaction. The (E)-3-aryl-2-propenals are generated through a one to four-day Wittig reaction of the suitable carbaldedyde with (triphenylphosphoranylidene) aldehyde in dimethylformamide. Potassium carbonate was used to generate 1-alkyl-1H-imidazole-2-carbaldehydes from 1H-imidazole-2-carbaldehydes [60].	NF-κb-regulated gene products [61]	[60].	1,9-Bis(3-fluoropyridin-4-yl) 1,3,6,8-tetraen-5-one nona derivative1,9-Bis(1-(pentan-3-yl)imidazol-2-yl) 1,3,6,8-tetraen-5-onenona derivative

Table 17: Synthesis of boswellic acid derivatives

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Boswellic acid derivatives				
a) Acetyl-11-keto-β-boswellic acid derivatives	Following esterification and hydrolysis of free acid, thionyl chloride is added to chloroform to produce the suitable acyl chloride, which is subsequently treated with sodium methoxide/methanol. The protecting group was chosen to be benzyl because of the efficiency with which it could be removed using titanium tetrachloride bathed in dichloromethane. The acetate group is hydrolyzed by potassium hydroxide in methanol. Other derivatives are synthesized by reaction with 2-iodoxybenzoic acid in dimethyl sulfoxide and subsequent treatment with iodine in the presence of pyridine. Starting material for generating 2-cyano and 2-trifluoromethyl derivatives is 2-iodo analogues. Substitution reaction in the presence of cuprous cyanide bathed in N-methyl pyrrolidinone generates 2-cyano derivatives. Substituted analogues, when treated with methyl 2,2-difluoro-2-(fluorosulfonyl) acetate bathed in HMPT/DMF and cuprous iodine generates 2-trifluoromethyl analogues. Removal of benzyl group by titanium tetrachloride/methylene chloride produces free acid, which subsequently with thionyl chloride produces suitable acyl chloride. Further, product so formed undergoes condensation with several nitrogen containing heterocycles to yield amides [62].	PIN 1 (Protein Interaction with Never in mitosis A1)	[62]	N-(2-cyano-3,11-dioxo-ursan-1,12-dien-24-oyl)-piperazine
b) Ring A modified 11-keto-boswellic acid derivatives	Scheme 1: In the presence of potassium carbonate, Acetyl-11-Keto-b-Boswellic Acid derivatives (AKBA) are benzylated by treating them with benzyl bromide; subsequently, benzylated products are hydrolyzed with sodium ethoxide and further treated with 2-chloroacetyl chloride. The intermediate formed in turn is treated with amines or substituted phenols and further debenzylation with titanium tetrachloride is carried out. Scheme 2: AKBA is treated with various alcohols or amines and are subsequently subjected to series of reactions, such as hydrolysis and oxidisation using Jones' reagent, sequentially. Further, Aldol reaction of intermediate is carried out and subjected to treatment with glyoxylic acid monohydrate under basic circumstances and further substituted with benzaldehydes in the presence of potassium hydroxide, ethanol. Scheme 3: Intermediates obtained from Aldol Reaction are reacted with diethyl oxalate followed by cyclization. The resultant intermediate is then treated with hydroxylamine hydrochloride or hydrazine hydrate and subsequently subjected to ester hydrolysis [63].	PIN 1 (Protein Interaction with Never in mitosis A1)	[63]	3-oxo-2-carboxyl methylene derivative of 11-keto-boswellic acid derivatives

Indoline and Isoindoline derivatives

Among the 2-(4-phenylthiazol-2-yl) isoindoline-1,3-dione) isoindoline derivatives synthesized by Saravanan *et al.*, derivatives with 4-aromatic substituent on the 1,3-thiazole core presenting IC50 value of 5.96±1.6 μM were potent of all [64].

Kumar *et al.* developed a series of spiro-chrome no indoline-triones of which the two compounds identified to possess highest potency were 5' bromospiro[indeno[2',1':5,6]pyrano[3,2–c]chromene-7,3'-indoline]-2',6,8(7aH,12bH)-trione (IC50=0.025±0.002 μM) and 1'-allylspiro[indeno[2',1':5,6]pyrano[3',2–c]chromene-7,3-indoline]-2',6,8(7aH,12bH)-trione (IC50=0.081±0.002 μM) (table 18) [65].

Table 18: Synthesis of indoline and isoindoline derivatives

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Indoline and isoindoline derivatives				
a) 2-(4-phenylthiazol-2-yl) isoindoline-1,3-dione)isoindolinederivatives	In the presence of triethylamine, 2-bromo-1-(4-substituted phenyl)ethanone reacts with thiourea bathed in ethanol. Resulting product is further refluxed with phthalic anhydride in acetic acid [64].	Androgen Receptor	[64]	Derivatives with 4-aromatic moiety on 1,3-thiazole core
b) 10,10-dimethyl-9,10,11,11a-tetrahydro-6H spiro[chromeno [4,3–b]chromene-7,3-indoline]-2',6,8 (7aH)-triones	Reaction involving various Lewis acids and bifunctional organocatalysts. This reaction is carried out under green conditions, employing an admixture of cyclic diketone, isatins, 4-hydroxycoumarin, and β-diketone [65].	Alkaline Phosphatase	[65]	5'-bromospiro -trione and 1'-allylspiro-trione analogues

Amino-aroylnaphthalenes

Rai *et al.* developed a series of 1-Amino-2-Aroyl naphthalenes of which potent molecule 4-amino-3-aroyl/heteroaroyl-2-methylsulfanylnapthalene-1-carbonitriles presented IC50 values of 14μM (table 19) [66].

4-azaandrostenes analogues

Of the series of 4-azaandrostenes analogues synthesized by Brito *et al.*, 16E-[(4-methylphenyl) methylidene]-4-azaandrost-5-ene-3,17-dione (IC50 =28.28 μM) was identified to possess the highest inhibitory potency (table 20) [67].

Table 19: Synthesis of1-Amino-2-Aroyl naphthalenes

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
1-Amino-2-Aroyl naphthalenes	Reaction between 2-(1-cyano-2,2-bis-methylsulfanyl-vinyl)-benzonitrile and acetophenone in the presence of base generates appropriate functionalized naphthalenes [66].	cytochrome P450 receptor	[66]	4-amino-3-aroyl/heteroaroyl-2-methylsulfanylnapthalene-1-carbonitriles

Table 20: Synthesis of4-azaandrostenes analogues

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
4-azaandrostenes	Androstenedione undergoes oxidative cleavage at the enone system. Oxidative cleavage is followed by Azacyclization reaction. The intermediate thus formed undergoes Aldol Condensation with several aldehydes to yield the desired product [67].	5-alpha reductase enzyme.	[67]	16E-[(4-methylphenyl) methylidene]-4-azaandrost -5-ene-3,17-dione (in androgen-independent PC-3 cells)

Pyrazine analogues

Seo *et al.* described the preparation of a series of3,4-dihydropyrrolo[1,2-a]pyrazine of which potent molecule was identified to be (3R*,4S*)-3-(4-bromophenyl)-4-(4-fluorobenzoyl)-2-(2-oxo-2-phenylethyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-2-ium bromide with an IC50 value of 1.18±0.05 μM (table 21) [68].

Table 21: Synthesis of 3,4-dihydropyrrolo[1,2-a] –pyrazine

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
3,4-dihydropyrrolo[1,2-a]-pyrazine	In-situ imine generation from the reaction of aldehyde and ammonium acetate reacts with N-substituted pyrrole-2-carboxaldehyde. Alkylation of basic nitrogen of product so obtained forming 4-acyl-3,4 dihydropyrrolo [1,2-a] pyrazines from N-substituted pyrrole-2-carboxaldehyde with (hetero) arylaldehydes and ammonium acetate in the presence of potassium carbonate in ethanol [68].	Caspase-3	[68]	(3R*,4S*)-3-(4-bromophenyl) -4-(4-fluorobenzoyl)-2-(2-oxo-2-phenylethyl)-3,4-dihydro Pyrrolo [1,2-a]pyrazin-2-ium bromide

Table 22: Synthesis of nitrogen-containing derivatives of O-tetramethyl quercetin

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Nitrogen-containing derivatives of O-tetramethyl quercetin:				
a) 3′,4′,5,7-*O*-tetramethylquercetin b) 3,3′,4′,7-*O*-Tetramethylquercetin c) four 3-*O*-aminoalkyl-3′,4′,5,7-*O*-tetramethylquercetins	Scheme 1: Global Methylation of Rutin followed by glycoside hydrolysis Scheme 2: Manthey and Guthrie's technique for selective tetramethylation of quercetin was used. Scheme 3: Firstly, 3,4,5,7-O-tetramethylquercetin is O-alkylated with suitable dibromoalkanes. Subsequently, resulting 3-O-bromoalkyl-3,4,5,7-O –tetramethylquercetinsis N-alkylated with appropriate amines. Base and polar aprotic solvent employed in the synthesis is potassium carbonate and N, N-dimethylformamide respectively.	Androgen Receptor	[69]	5-*O*-(*N*,*N*-dibutylamino)propyl -3,3′,4′,7-*O*-tetramethyl quercetin
d) 5-*O*-aminoalkyl-3,3,4,7-*O*-tetramethylquercetins	Scheme 4: From 3,3,4,7-O-tetramethylquercetin, twenty-four different 5-O-aminoalkyl-3,3,4,7-O-tetramethylquercetins are generated [69].			

Nitrogen-containing derivatives of O-tetramethyl quercetin

Rajaram *et al.* synthesized nitrogen-containing derivatives of O-tetramethyl quercetin among which5-O-(*N*,*N*dibutylamino)propyl-3,3′,4′,7-*O*-tetramethylquercetin demonstrated potent anti-proliferative action(IC50 =0.55–2.82 μM) (table 22) [69].

Ruthenium (II) complexes

Grandis *et al.* developed Ruthenium (II) complexes bearing Lawsone among which[Ru(lawsone)(bis [diphenylphosphino] methane)(2,2′-bipyridine)]PF6(IC50 value of 1.9 to 4.8 μM against DU-145 and A549 cell lines respectively) and [Ru(lawsone)(bis [diphenylphosphino] methane)(1,10-phenanthroline)]PF6(IC50 values ranging from 1.3-3.0 μM against DU-145 and MDA-MB-231cell lines, respectively) exhibited the highest potency [70].

Olmo*et al.* synthesized heterofunctional ruthenium (II) carbosilane dendrons of which {[PTA(η^5-C_5H_5)RuNCPh(o-N)]-G_2-[$(CH_2)_3N(CH_3)_2]_4$}Cl (IC50 =1.8 μM in HeLa; 1.4 μM in PC-3) was identified as potent complex among all [71].

Olmo*et al.* described the synthesis of cyclopentadienyl ruthenium (II) carbosilanemetallodendrimers of which G1-{[NCPh(o-N)Ru(η^5-C_5H_5)(PTA)]Cl}$_4$ and G2-{[NCPh(o-N)Ru(η^5-C_5H_5)(PTA)]Cl}$_8$possesed potent inhibitory action with IC50 of 8.3 μM and 6.6 μMrespectively (table 23) [72].

Table 23: Synthesis of ruthenium (II) complexes

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Ruthenium (II) containing complexes:				
a) Lawsone-containing ruthenium (II) complexes:				
i) [Ru(lawsone)(bipy or phen)$_2$]PF$_6$	The precursor complex [RuCl$_2$(bipy or phen)$_2$] of cis form reacts with lawsone (law) ligand under argon atmosphere.	Death receptor-upregulates BAX and downregulates BCL-2 expression.	[71]	[Ru(lawsone)(bis[diphenyl phosphino] methane)(2,2′-bipyridine)]PF$_6$ and [Ru(lawsone)(bis [diphenylphosphino] methane)(1,10-phenanthroline)]
ii)[Ru(lawsone)([diphenylphosphino] methane)(bipy or phen)]PF$_6$	The initial generation of precursor complexes. These are generated using cis and trans forms of [RuCl$_2$(PPh$_3$)$_2$(bipy or phen)] and (diphenylphosphino)methane of toluene. The reaction mixture is a refluxedinan atmosphere provided by argon gas [71].			
a) Heterofunctionalruthenium(II) carbosilane dendrons [Ru(η^5-C$_5$H$_5$)(PTA)Cl](PTA 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decane)	Coordination of metallic centre to the focal point of dendritic wedges of different generations. Secondly, replacement of acetonitrile ligand by 1,3,5-triaza-7-Phosphatricyclo-Decane (PTA) is carried out. In a second step, without isolating the previous products a reaction of ligand exchange by PTA forms product [72].	Vasoactive Intestinal Peptide (VIP) and Growth Hormone Releasing Hormone (GHRH) receptors [73]	[72]	{[PTA(η^5-C$_5$H$_5$)RuNCPh(o-N)] -G2-[(CH$_2$)$_3$N(CH$_3$) $_2$]$_4$}Cl
b) Cyclopentadienyl ruthenium (II) carbosilanemetallodendrimers:				
i) The first generation metallodendrimer[G0{NCPh(o-N)Ru(η^5-C$_5$H$_5$)(CH$_3$CN)}]PF$_6$	Dendrimers which are functionalized with groups such as iminopyridine, G0-[NCPh(o-N)], G1-[NCPh(o-N)]$_4$ and G2-[NCPh(o-N)]$_8$ are used. Coordinating metallic centre, ligands and counterion exchange in an inert atmosphere produces suitable metallo dendrimer.	Vasoactive Intestinal Peptide (VIP) and Growth Hormone Releasing Hormone (GHRH) receptors [73]	[72]	G1-{[NCPh(o-N)Ru(η^5-C$_5$H$_5$) (PTA)]Cl}$_4$ and G2-{[NCPh(o-N)Ru(η^5-C$_5$H$_5$) (PTA)Cl}$_8$
ii) The second generation metallodendrimer[G1{NCPh(o-N)Ru(η^5-C$_5$H$_5$)(CH$_3$CN)}$_4$]PF$_6$	Synthesis following scheme similar as described above using the following reagents-dendritic ligand (II) of first generation and ruthenium precursor.			
iii) [G2{NCPh(o-N)Ru(η^5-C$_5$H$_5$)(CH$_3$CN)}$_8$]PF$_6$	Synthesis following scheme similar as described above using the following reagents-ruthenium precursor and dendritic ligand (II) of first generation.			
iv) G0-{[NCPh(o-N)Ru(η^5-C$_5$H$_5$)(PTA)]PF$_6$}$_4$	Reaction of complex[G0{NCPh(o-N)Ru(η^5-C$_5$H$_5$)(CH$_3$CN)}]PF$_6$ with 1,3,5-triaza-7 phosphoadamantane PTA ligand.			
v) G1-{[NCPh(o-N)Ru(η^5-C$_5$H$_5$) (PTA)]PF$_6$}$_4$	Reaction of complex [G1{NCPh(o-N)Ru(η^5-C$_5$H$_5$)(CH$_3$CN)}$_4$]PF$_6$ with PTA			
vi)G2-{[NCPh(o-N)Ru(η^5-C$_5$H$_5$)(PTA)]PF$_6$}$_8$	Reaction of [G2{NCPh(o-N)Ru(η^5-C$_5$H$_5$)(CH$_3$CN)}$_8$]PF6with PTA			
vii) G0-{[NCPh(o-N)Ru(η^5-C$_5$H$_5$)(PTA)]Cl}$_4$	To the complex G0-{[NCPh(o-N) Ru((η^5-C$_5$H$_5$)(PTA)]PF$_6$}$_4$ in a mixture of acetone/water, ion exchange resin is used to carry out exchange of counter ion.			
viii)G1-{[NCPh(o-N)Ru(η^5-C$_5$H$_5$)(PTA)]Cl}$_4$	To the complex G1{[NCPh(oN)Ru(η^5 C$_5$H$_5$)(PTA)]PF$_6$}$_4$ in a mixture of acetone/water, ion exchange resin is used to carry out an exchange of counterion.			
xi) G2-{[NCPh(o-N)Ru(η^5-C$_5$H$_5$)(PTA)]Cl}$_8$	To the complex G2{[NCPh(oN)Ru(η^5 C$_5$H$_5$) (PTA)]PF$_6$}$_8$ in an acetone/water, ion exchange resin is used to carry out exchange of counter ion [50].			

Table 24: Synthesis of N-heterocyclic nitro prodrugs

Type of derivative	Type of reaction involved in synthesis	Target	Ref	Potent compound
24. N-heterocyclic nitro pro-drugs:				
a) Nitro-containing triazine derivatives	A nucleophilic substitution reaction of cyanuric chloride and amines of aromatic kind such as 2,4-dinitrophenylhydrazine and 2-nitro, 3-nitro, 4-nitro, 2,4-dinitro, 3,5-dinitroaniline and is further refluxed with acetic acid.	Ssap-Ntr Bnitroreductase enzyme	[74]	Pyrimidine derivative
a) Urea derivatives of nitrophenyls and piperazine	Urea analogs of nitrophenyls and piperazine are generated by Curtius rearrangement reaction. Nitrobenzoyl chlorides react with sodium azide to produce derivatives of nitrobenzoylazide. Unstable nitrophenyl isocyanate formed via nitrogen output at temperature of reflux of toluene reacts with piperazine to yield product.			
b) Carbamate derivatives of nitrophenyls and piperazine	Rivett and Wilshire's method employes 1,4-bis (chlorocarbonyl) piperazine, which is generated through the reaction of piperazine with phosgene in pyridine and subsequent reactions at room temperature with bis(chlorocarbonyl) piperazine and nitrophenols (2-nitro, 3-nitro and 4-nitro) in dimethylformamide in the presence of sodium hydride.			
c) Pyrimidine derivative	At reflux temperature 2,4 dichloropyrimidine reacts with 4-nitroaniline in diluted hydrochloric acid to yield pyrimidine containing nitro pro-drugs [74].			

N-heterocyclic nitro pro-drugs

Güngor*e t al.* reported on the generation of N-heterocyclic nitro pro-drugs and demonstrated pyrimidine derivatives to possess highest inhibitory potency against PC3 cells (IC50 = 1.75 nMto 1.79 nM) (table 24) [74].

Dinitrobenzamide mustards

Basiri *et al.* described the synthesis of dinitrobenzamide mustards and identified mustards containing alcohol side chain counterparts as compound with maximum potency with IC50 value of 26±2 μM (table 25) [75].

Table 25: Synthesis of dinitrobenzamide mustards

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Dinitrobenzamide Mustards	Scheme 1: 2-chloro-3,5-dinitrobenzoic acid bathed in methanol is esterified by an acid catalyst. Further, the protected dinitrobenzoate is treated with bis(chloroethyl)amine and subsequently with aqueous potassium hydroxide in dioxane so as to cleave the methyl group, yielding benzoic acid which in turn reacts with oxalyl chloride under mild circumstances to form acid chloride. The acid chloride upon treatment with β-Alanine t-butyl ester or ethanolamine affords desirable product in situ [75].	Activation by nitroreductase enzyme followed by DNA alkylation	[75]	Dinitrobenzamide Mustards Containing alcohol side chain

Thiohydantoin derivatives

Wang *et al.* developed an array of thiohydantoin analogues of which4-(4,4-dimethyl-5-oxo-3-(1-oxoisochroman-6-yl)-2-thioxoimidazolidin-1-yl)-2(trifluoromethyl)benzonitrile demonstrated to posses potent inhibitory action with IC50 value of 1.936μM against LNCaP and 0.730μM againstLNCaP/AR(table 26) [76].

Table 26: Synthesis of thiohydantoin analogues

Type of derivative	Type of reaction involved in synthesis	Target	Reference	Potent compound
Thiohydantoin Derivatives	Suzuki coupling reaction of several boric acid or borate esters, followed by oxidation reaction using selenium dioxide at methyl group and a subsequent Pinnick oxidation to furnish appropriate carboxylic acids. Further, reduction of quinoline core so as to afford tetrahydroquinoline and formation of esters from relevant carboxylic acids is carried out. At the end, cyclization reactions yielded products [76].	Androgen Receptor	[76]	4-(4,4-dimethyl-5-oxo -3-(1-oxoisochroman-6-yl) -2-thioxoimidazolidin-1 yl)-2(trifluoromethyl) benzonitrile

Structure-activity relationship studies

Among thiazolidines, electron-donating substituent, sulfoxide or sulfone moiety conferred potent cytotoxicity to these analogues, whereas electron-withdrawing groups at ortho-position decreased their anticancer activity [25].

Incorporation of a C5-ethyl group of the thiadiazoline ring resulted in an enhanced inhibitory effects on mitosis and kinesin activity in cell lines of PC3, SKMEL-5 and SK-MEL-28 [26].

Among anilides, replacing central methyl moiety of bicalutamide with a trifluoromethyl moiety yielded derivatives with potent anti-proliferative action and superior stability with enzymes of phase 1 biotransformation while maintaining appreciable membrane permeability [28].

In dibromotyrosine derivatives, incorporation of C-1acetyl ester group conferred higher anti-migratory activity, whereas incorporation of ether group conferred higher anti-proliferative activity to these analogues [29].

In vitro SAR studies of β-hydroxy-androstadiene derivatives indicated that 3β-OH group is crucial to exert androgen receptor down-regulation. Isosteric substitution of 3β-OH moiety with fluoro group at C-3 resulted in significant reduction in this activity, whereas substitution with azido moiety completely terminated the action. Chemical alterations such as incorporation of 16-methyl alcohol or the substitution of 17-benzimidazole with purines that can be either substituted or unsubstituted led to a significant decrease in the down-regulation of androgen receptor [30].

The SAR results of poly-substituted steroidal pyridines revealed that analogues with heterocyclic rings at 4-position of the pyridine ring demonstrated superior anti-proliferative action against various tumor cell lines than phenyl-substituted counterparts. Moreover, it was deduced that the presence of an additional 4-pyridine moiety conferred appreciable growth inhibition activity to the derivatives [34].

Among norpregnene azole derivatives, compounds with 3β-hydroxy-5-ene-and isoxazole groups had the most potent inhibitory action against LNCaP and PC-3 cells. Derivatives with 3-oxo-4-ene-isoxazole groups demonstrated moderate anti-proliferative potency. Of oxadiazoles, 3β-hydroxy-5-ene-derivative was the only potent inhibitor among the series [36].

Of the chalcones synthesized by Nagaraju *et al.*, benzylated derivatives showed greater cytotoxicity than the corresponding debenzylated derivatives owing to higher lipophilicity of benzylated counterparts [42].

Findings of a study conducted on synthesis of flavonols imply that 3',4',5'-arrangement of either hydroxy or methoxy groups imparts potency to flavonols and that the methoxy derivatives have superior growth arrest activity as compared to their hydroxy counterparts [44].

The results of an investigation that involved synthesis of 3-O-substituted-trimethoxyflavonols indicates that incorporation of dipentylaminopropyl moiety increases the anti-proliferative potency as well as the ability to induce apoptosis in PC-3 cell lines. The study also concluded that potency of these derivatives could be enhanced by modifications at 3-OH group [45].

In diphenyl furanone derivatives, incorporation of fluoro group at para-position and/or chloro group at ortho-position on C-3 phenyl ring along with suitable modifications at 5 position of central furanone yields analogues with potent anti-proliferative effects [47].

An investigation on aryl-substituted-pyrazol-ol derivatives suggested that incorporating phenyl or naphthyl ring on 4 position-methyl moiety of the pyrazole ring generated potent anti-proliferative agents. Derivatives containing carboxyl moiety or those lacking the methyl group exhibited equivalent activities. Compounds with a phenyl ring

attached at the 3-position demonstrated lower activities. The removal or substitution of aromatic rings on the benzimidazole moiety resulted in weaker PCA-1/ALKBH3 inhibitors [48].

The arylpiperazine derivatives with an o-methylsulphonyl moiety on the phenyl ring possessed potent inhibitory action against LNCaP cell lines [50].

The SAR results of silibinins indicated that anti-proliferative potency of the derivatives can be enhanced by making chemical modifications on the C-7 phenolic hydroxyl moiety. Bioavalability of these analogues could be improved by incorporating suitable functional group through a linker to hydroxyl group at 7 position of silibinin and 2,3-dehydrosilibinin [51].

O-alkyldehydrosilibinins with modified hydroxyl group at either 3, 5, or 7 position have potent anti-proliferative action against androgen-sensitive PCa cell lines. However, derivatives with an enhanced ability to induce PC-3 cell apoptosis can be obtained by incorporating an alkyl group at hydroxyl group at either 5, or 7 position [52].

Results of the study on indeno [1,2-b]indole suggested that analogues with dimethyl group at 7 positions and dichloro phenyl group at 5 positions are essential features that confer anti-proliferative potency to these derivatives [54].

Among thiosemicarbazone indole derivatives, it was observed that benzamide moiety in the linker was responsible for selective cytotoxicity of these compounds. Moreover, a reduction in the potency of these analogues was seen when NNS donor was replaced with other donor chelators, indicating that NNS donor conferred significant anti-proliferative potency towards tumor cell lines [55].

The SAR results of triazole hybrids of curcumin indicated that anti-proliferative potency of the derivatives can be enhanced by incorporating 4-methyl groups at R1 position on the 1,2,3-triazole scaffold [56].

The results of the study on diheteroaryl nona-tetra enones, suggested that analogues with pyridine-4-yls and quinolin-4-yl heteroaromatic rings confer anti-proliferative potency to these derivatives [60].

The SAR results of acetyl-keto boswellic acid derivatives indicated that anti-proliferative potency of the derivatives can be enhanced by incorporating electron-withdrawing moiety on ring A and a nitrogen atom containing heterocycle at C-24 [62].

Among spiro-chromeno indoline-triones derivatives, it was observed that groups like bromo at R2 position, carbonyl available in isatin, 4-hydroxycoumarin and 1H-indene-1,3(2H)-dione support electron withdrawal thus enhance therapeutic effects of these analogues. Presence of abundance of functional groups ensures a higher bioavailability and anti-proliferative effects [65].

Among derivatives of O-tetramethyl quercetin 5-O-Aminoalkyl-3,3′,4′,7-O-tetramethylquercetins are considered to be a superior scaffold for further design and development quercetin anti-prostate drugs [69].

The SAR results of lawsone-containing ruthenium(II) complexes indicated that those containing phosphine ligand displayed potent anti-proliferative action by enhancing lipophilicity of the complex, thereby increasing its cytotoxicity against various tumour cell lines [70].

Among N-heterocyclic nitro pro-drugs, it was observed that para-nitrosubstituted piperazine-urea moiety and ortho-nitrosubstituted piperazine-carbamate moiety conferred significant anti-proliferative potency to these pro-drugs [74].

The SAR results of dinitrobenzamide mustards indicated that insertion of a carboxylic acid group into the construct of dinitrobenzamide mustard yields agents with superior hypoxia-selectivity than their alcohol counterparts [75].

The development and spread of particular cancer cells can be prevented by targeted treatment [77]. Fewer efficacies in the present cancer therapy, patient non-compliance, drug resistance and uncertainty of current candidates in a clinical trial have led to the need for the development of potential anticancer agents [78-80].

CONCLUSION

This present review summarizes the synthesis of significant anti-PCa agents their SAR studies and reflects current advancements and attempts in the field of cancer research. This review work intends to provide a basic insight into the design and development of novel molecules against PCa; thereby paving the way for future exploration.

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CONFLICT OF INTERESTS

The authors confirm that there is no conflict of interest related to the manuscript.

AUTHORS CONTRIBUTIONS

Kavana Krishna Nayak was involved in writing the manuscript, conducting the literature search, and interpreting the results. Lalit Kumar was involved in supervision, critical review, and literature search. Ruchi Verma contributed by providing the idea, designing the study, supervising, performing critical reviews, writing and editing the manuscript, conducting the literature search.

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