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Synthesis, biological evaluation and molecular docking study of 1-amino-2-aroylnaphthalenes against prostate cancer

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ABSTRACT

A series of functionalized naphthalene was synthesized and screened against human prostate cancer cell line (PC-3). The *in vitro* antiproliferative activity of the synthesized compounds was evaluated by monitoring their cytotoxic effects against PC-3 cells by using MTT assay. We observed that compound **5f** resulted in more than 50% cell death at 14 μM. Treatment of PC-3 cells with **5f** provides apoptosis by flow cytometry. Western blotting showed decreased expression of pro-caspase 8 and 9. Our study shows that cancer cell treated with **5f** has higher concentration of reactive oxygen species as compare to untreated sample, which facilitate cancerous cell to enter apoptosis. Exact mechanism by which ROS is generated after **5f** treatment is still under study. Molecular docking study further strengthens the results obtained from *in vitro* experiments. Compound **5f** can be considered as a promising leads for anticancer agent against prostate cancer cells due to its potent cytotoxic activity and apoptotic effect.

Prostate cancer is the fifth leading cause of cancer-related deaths in men worldwide and this disease is frequently observed in males at the age between 65 and 74 years.[1] A report in 2014 says that approximately 24 lac men in USA suffered from prostate cancer and was the cause of their mortality.[2] Prostate cancer are androgen sensitive in the beginning which respond to anti-hormonal therapy, later they turn out to be refractory and develop without androgen. This cancer is known as castrate resistant prostate cancer (CRPC), and difficult to treat. Recently, US Food and Drug Administration have approved various new molecules for the treatments of prostate cancer patients with castration resistant prostate cancer, but very few have provided survival benefits.[3,4] Recently, a review have been published on drug designing for prostate cancer.[4] Thus search of new molecules with effective therapeutic properties for prostate cancer is much more required.

Various skeletons have been studied for their anticancer properties. Some of the naphthalene based molecules like naphthalenediimide (NDI) is present in various anticancer agents and they can intercalate with DNA during the interaction.[5–9] Various molecules containing 2-aminodiaryl ketones as a main or substructure showed activity as antitubulin agents. Some of the reported compounds like Phenstatin **I** and Hydroxyphenstatine (**II**)[10] and 2-aminobenzophenone analogues (**III**) act as antitubulin agents.[11] 2-Amino-1-aroylnaphthalene and 2-hydroxy-1-aroylnaphthalene were studied for their anti-proliferative activity against human cancer cell and their activity was almost comparable to the potency of Colchicine.[12] Molecules containing aminated phenyl aryl ketones as substructure like suitably substituted 4*H*-imidazo [1,5-*a*] [1,4]-benzodiazepines and related compounds act as central benzodiazepine receptor (CBR) ligands (Fig. 1).[13] Another naphthalene based compound neotranshinlactone is reported as anticancer compound and is isolated from *Salvia miltiorrhiza*.[14–16] Since naphthalene based molecules exhibit very good anticancer activity, we became interested in the synthesis of some differently functionalized naphthalene and to study their effect against prostate cancer cell line.

In order to perform the study, we have synthesized various functionalized naphthalene by two methods. Compound **1** was synthesized by reaction of acetophenone, carbon disulphide and methyl iodide under basic conditions at low temperature. Similarly, compound **3** can be synthesized by using 2-cyanomethylbenzonitrile instead of acetophenone. Under method A, we have used

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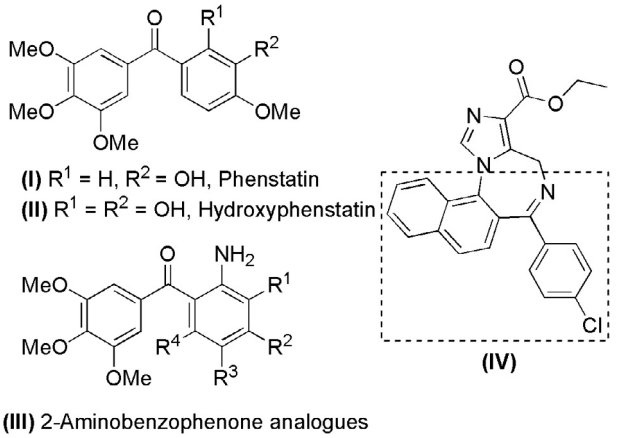


Fig. 1. Structure of phenstatin **I**, hydroxyphenstatine **II**, 2-aminobenzophenone analogues **III** 3-substituted 6-aryl-4*H*-imidazo-[1,5-*a*]benzodiazepines (**IV**).

4,4-bis-methylsulfanyl-arylethanone as a precursor and perform the reaction with 2-cyanomethylbenzonitrile under basic condition to achieve the desired product in good yield.

While in alternative method B 2-(1-cyano-2,2-bis-methylsulfanyl-vinyl)-benzonitrile was used as a starting material. Stirring mixture of 2-(1-cyano-2,2-bis-methylsulfanyl-vinyl)-benzonitrile and acetophenone under basic conditions provided the desired functionalized naphthalenes (Scheme 1). All the synthesized compounds are characterized by spectroscopic technique and the results obtained are reported earlier.[17]

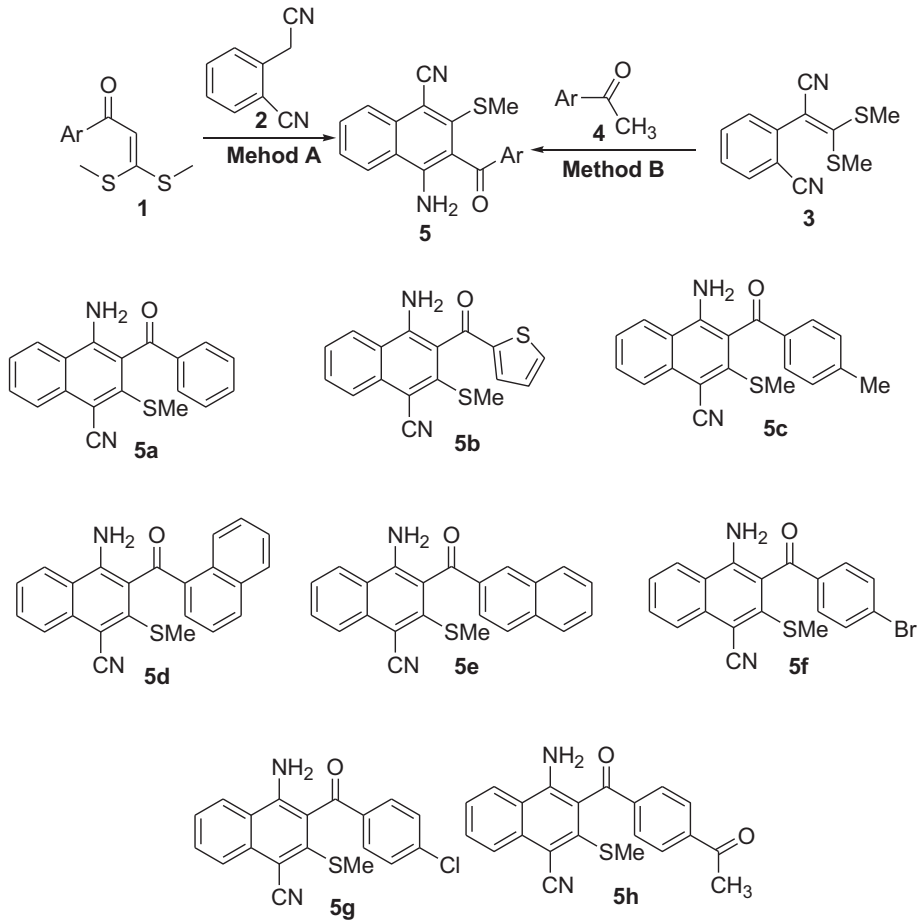
Table 1
Growth inhibition values of all the compounds measured by MTT assay.[a]

S. No.	Compound	Growth Inhibition (%)
1	5a	24.76
2	5b	23.36
3	5c	22.42
4	5d	15.88
5	5e	13.08
6	**5f**	**84.24**
7	5g	24.76
8	5h	63.97
9	cisplatin	87.27

[a] Results expressed are Mean of three independent experiments.

We have synthesized a number of compounds but on the basis of results obtained from molecular docking studies, we have selected this series (**5a**–**h**) for further studies.

The *in vitro* antiproliferative activity of synthesized compounds mentioned in Table 1 was evaluated by monitoring their cytotoxic effects on human prostate cancer (PC-3) cell line. In the initial screening **5f** emerged as a potential antiproliferative compound. At tested concentration (100 μM) compound **5f** showed 84.24% growth inhibition. For the calculation of IC_{50} value of compound **5f**, PC-3 cells were cultured with varied concentration of **5f** solubilised in DMSO. We estimated the cytotoxicity of a known anticancer drug cisplatin also on PC-3 cells as a reference compound. Due to cytotoxicity of DMSO, its concentration was kept below 0.1% throughout the experiments and also the control reaction was set with and without DMSO. After 72 h, the compound showed



Scheme 1. Synthesis of various 4-amino-3-aroyl/heteroaroyl-2-methylsulfanylnapthalene-1-carbonitriles (**5a**–**h**).