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تحضير وخصائص بنزو [e] إندول-٢-يلدين)-٣-(٤ ميثوكسي فنيل امينوبروبانال كعامل واعد ضد تضاعف الخلايا السرطانية

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Synthesis and Characterization of Benzo[e]Indol-2-Ylidene)-3-(4-Methoxyphenyl) IminoPropanal as A promising Agent Against Proliferation of Cancer Cells

A Thesis Submitted to
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Chapter One

Introduction

1.1 Introduction

Cancer is the world's second most prevalent cause of death, killing more than 8 million people per year; the prevalence of cancer is predicted to rise by more than 50 per cent over the coming decades(Tarver 2012). It is resulting from uncontrolled cell proliferation with an absence of cell death making abnormal cell mass or tumor, new vascularization with time, this primary tumor develops and spread to another body sites, causing metastasis then death. Cancer caused by damage or mutations in the genetic material of the cells due to environmental or inherited factors(Pérez-Herrero et al. 2015). Between 2005 and 2015, cancer cases increased by 33%. For men, the most common cancer globally was prostate cancer (1.6 million cases). Tracheal, bronchus, and lung cancer was the leading cause of cancer deaths. For women, the most common cancer was breast cancer (2.4 million cases). Breast cancer was also the leading cause of cancer deaths(Fitzmaurice et al. 2017). It is usually not possible to know exactly why one person develops cancer and another doesn't. But research providing evidence that substantial risk factors contribute only modestly (less than ~10–30% of lifetime risk) to cancer development(Wu et al. 2016).

These risk factors may act concurrently or in sequence to initiate or promote cancer arising (Am. Cancer Soc. 2020). A large percentage of tumors, including all tumors attributable to tobacco consumption and other harmful habits, may be avoided. At least 42 percent of newly diagnosed cancers in the US, around 750,000 cases in 2020, are possibly avoidable, including 19 percent of all cancers caused by smoking and 18 percent caused by a combination of excess body weight, alcohol intake, inadequate diet , and physical inactivity, according to a recent report by researchers from the American Cancer Society (ACS)(Am. Cancer Soc. 2020). PCA is the serious problem among worldwide men society, in the UK, with a

prevalence of 105 per 100 000 population, also common in northern urope and the USA (mainly in the African American population) while it is rare in China and apan. It is uncommon in India but the incidence is increasing, although the overall number of deaths from prostate cancer has declined in the past 10 years, due to the increasing use of screening methods focused on prostate specific antigen (PSA).The management paradox, though, is that while 1 in 6 men will eventually be diagnosed with prostate cancer, only 1 in 30 men with prostate cancer will die of his disease, becoming the second leading cause of cancer deaths in men.(ameson et al. 2018b).

In the second hand lung cancer (CA) had become epidemic and come up as a leading cause of cancer related death in USA and urope, killing three times much more than prostate cancer in men also twice as many women as breast cancer(ameson et al. 2018c). According to the recent statistics which illustrate the new cases in Iraq in 2018 for both sexes and all ages that 8% as lung cancer incidence and 14% of total deaths, according to the recent World Health rganization WH announced report(Iraqi Cancer Board H 2018).

Treatment against tumor still a challenge although many approval and experimental drugs with different mode of actions such as chemotherapy, radiotherapy, biological therapy and immunotherapy (Skřičková et al. 2018).

Chemotherapy is still the best way to treat many type of cancers, considering the site of it , how it big, if it is spread to other body parts and if it affects on normal body function or health (side effect)(Chabner and oberts 2005). Antioxidant can enhance the immune defenses and lower the risk of cancer and degenerative diseases by minimize cell oxygen toxicity or in ury to prevent, intercept and repair damage resulting from (S). It is work at three levels (a) **prevention** , by maintains formation

of (□□S) to the minimum level, e.g., desferrioxamine; (b) **interception**, scavenges (□□S) by using catalytic and non catalytic molecules, e.g., ascorbic acid and tocopherol; and (c) **repair**, damaged target molecules, e.g., glutathione (□ani, Chand, and □adav 2015).

Schiff bases that prepared from the condensation reaction of aromatic primary amines with aromatic aldehydes or ketones are most stable then that prepared from the condensation reaction of aliphatic primary amines with aliphatic aldehydes oraliphatic ketones. They containing a carbon nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group but not hydrogen.(□udrapal and □e 2013).Indole derivatives are an important class of organic heterocyclic which have played vital and significant role in curing so many ailments throughout the history of pharmaceuticals and medicines. Also they are one of the most attractive frameworks with a wide range of biological and pharmacological activities.(Khaledi 2012).

1.2 Aim of the study

1. To synthesizing a new Indole Schiff base.
2. To investigating the effect of synthetic heterocyclic compound new indole Schiff compound as antioxidant, acute toxicity and anti tumor on (PC-3) cell line comparing with (W□□) cell line (control).
3. A study of possible mechanisms by which new indole Schiff compound killing cancer.

Abstract:

The new indole Schiff basecompoundbenzo□e□indol-2-ylidene)-3-(4-methoxyphenyl)iminopropanal□(2P)was investigated for antioxidant, toxicity and anti-tumor ability for A549 cell, PC3 cell and W□□68 cell. 2P has antioxidant ability for IC50 (75 □g□m□) compared with control ascorbic acid (27 □g□m□). Antitumor ability for 2P was evaluated and the result was showed the viability of A549 cell and PC3 cell were decreased significantly after treated with 2P in dose dependent manner at 24,48 and 72 hours, while no toxicity effect on the W□□68 cell. The antitumor effect was through accelerated apoptosis, the alteration in nuclear morphology of PC3 cells was examined by using Hoechest staining after treated the PC3 cells with different doses (5,10,15) □g□m□.The density of the nucleus has been found to be closely linked to apoptosis and chromatin modifications..The increase in the cells membrane permeability was observed. The result was showed decreasing in the nucleus intensity and increasing in cell permeability with the increasing of concentration of 2P compound treated the cells.

□itochondria □embrane Potential is disturbed in the apoptosis by forming of permeability, this ability of 2P on the □□P of PC3 cell was studied by using of mitochondria specific dye, the □□P in the PC3 cell treated with 2P showed significant (P □0.05) reduction by decrease in the intensity of fluorescent compared with control. The effect of 2P in the treated PC3 cell for cytochrome c was detected, the result was showed that 2P activated release cytochrome c significant (P □0.05) higher that control.

After treating 2P was portioned, PC3 cell □□A material for the cell cycle process (□1, □2, and □). The result was showed that 2P break down the cell cycle progress in □1 phase (P □0.05) compared with control. The

result display there is a significant □1 step arrest in PC3 in a concentration-dependent mannerwhereas, the cells in both □2 and □ phase was reduced with an increased in the treatment. Conclusion□this result was conducted the new 2P compound has antioxidant and antitumor ability that may be used 2P a new anticancer drug.