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Research Paper

SYNTHESIS, CHARACTERIZATION AND STUDY OF QUINAZOLINES AND THEIR ANTI-CANCER ACTIVITY AGAIN BREAST CARCINOMA

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4-(3*H*) -Quinazolinone are an important class of Nitrogen containing heterocycles and are reported to possess a wide spectrum of biological activities. Quinazolinone analogues are being studied by many researchers for their useful biological properties such as antibacterial, antifungal, antiviral, anticonvulsant, analgesic, anti-inflammatory, anthelmintic and antitumor activities. Cytotoxicity and genotoxicity of anticancer drugs to the normal cells are major problems in cancer therapy and endanger the risk of inducing secondary malignancy. Quinazoline derivatives occupy a pivotal position in modern medicinal chemistry and have found applications as medicines. Various researches have been performed on quinazoline and their derivatives for anticancer activity and pharmacological importance.

KEY WORDS – Nitrogen containing heterocycles , Qunazoline, Anti- Cancer, Cytotoxicity.

INTRODUCTION

Quinazoline-4(3*H*)-ones and its derivatives are versatile nitrogen heterocyclic compounds which have long been known as a promising class of biologically active compounds. Quinazolinone are excellent reservoir of bioactive substances. The stability of the Quinazoline nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents.2,3 disubstituted 3(*H*)-quinazolin-4 ones are a privileged structures frequently encountered building block moiety in approx. 150 naturally occurring alkaloids and drugs with pronounced biological activities .Various approaches toward the synthesis of quinazolin-4(3*H*)-one and 2,3 di-substituted quinazolin-4(3*H*)-one derivatives have been explored during the past years. Recent progress in quinazolinone alkaloids and related chemistry was focusing on developmentsof the synthetic methodologies and their synthetic applications. A vastnumber of quinazolinone derivatives have been synthesized to provide synthetic drugs and to design more effective medicines. Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Breast cancer is a malignant cell growth in

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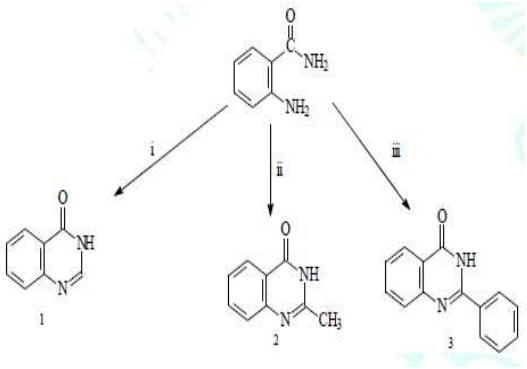
the breast. If left untreated, the cancer spreads to other areas of the body. Excluding skin cancer, breast cancer is the most common type of cancer in women in the United States, accounting for one of every three cancer diagnoses. Ninety percent of breast cancer are adenocarcinomas, which arise from glandular tissue. Within this broad category, there is a great degree of variation. For instance, there are about 30 different subtypes of adenocarcinoma. The earliest form of the disease, ductal carcinoma in situ, comprises about 15-20% of all breast cancers and develops solely in the milk ducts. The most common type of breast cancer, invasive ductal carcinoma, develops from ductal carcinoma in situ, spreads through the duct walls, and invades the breast tissue.

REVIEW OF LITERATURE

P.O. Osarumwense Synthesis And Anagesic activities of Quinazolin-4(3H)-One, 2-Methyl-4(3H)-Quinazolinone and 2–Phenyl-4(3H)-quinazolin-4(3H)–one Although numerous classes of quinazolinones have been synthesized their syntheses have the disadvantage of being multiple step reactions and time taken which are in hours and sometimes in days. However, the synthetic pathways in this study have numerous benefits for performing synthesis in organic compounds including reduced pollution, increased reaction rates, yield enhancement and cleaner chemistries. The present study has shown that the quinazolinone derivatives 1, 2 and 3 have analgesic activity with Compound 2 showing a higher activity compared to compound 1 and 3.



Fadhil Lafta Faraj, Synthesis,Characterization, and Anticancer Activity of New Quinazoline Derivatives against MCF-7 Cells The synthesized quinazolinone Schiff bases (1) and (2) establishedtheir structures by elemental analysis, spectroscopic techniques, and X-ray diffraction studies. They have shown anticancer potential against MCF7 breast cancer cells. It was found out that compounds possess the capability of inducing intrinsic and externsic apoptosis pathway, which was well regulated by caspase enzymes. Moreover, the active role of mitochondria in the cell death was confirmed by reducing the MMP, release of cytochrome c, and ROS elevation. Our results showed that compounds are promising anticancer agents. However, further research in the area of in vivo studies on the compoundsmight be vital for the development of new pharmaceuticals drugs.

Aisha Youssif Hassan Helali, Marwa Taha Mostafa Sarg, Makarem Mohamed Said Koraa,

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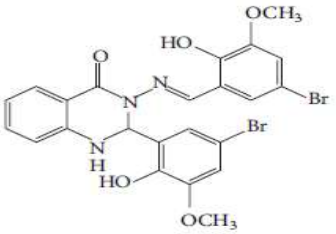
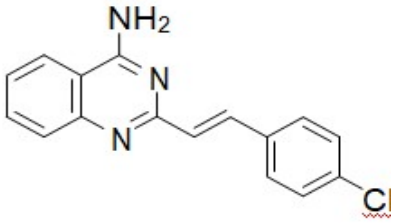
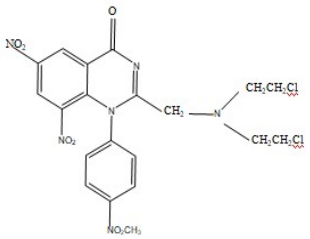


Mona Said Fathy El-Zoghbi Utility of 2-Methyl-quinazolin-4(3*H*)-one in the Synthesis of Heterocyclic Compounds with Anticancer Activity Compound and exhibited very potent anticancer activity against both Hep-G2 and MCF-7 cell lines. However, compounds showed remarkable anticancer activity against liver Hep-G2 cell line, while compound exhibited potent anticancer activity against MCF-7 cell line. Docking was performed for the five most active anticancer compounds and on the two enzymes; thymidylate synthase and di-hydrofolate reductase in a trial to predict their mode of action as anticancer drugs. Also, the compounds show several interactions with both enzymes but they exhibit strong interactions with dihydrofolate reductase enzyme, mainly compounds giving rise to the conclusion that they might exert their action through inhibition of both enzymes but mainly DHFR enzyme.



Govindaraj have synthesized 2-{[Bis-(2-chloroethyl) amino] methyl}- 6, 8-dinitro-1- (4-substituted ethyl)-1H-quinazolin-4-one derivatives(66). The synthesized compounds were screened for their anticancerous activity by short-term in-vitro antitumor activity and in-vivo anticancer activity by body weight analysis, mean survival time and percentage increase in life span methods in Swiss albino mice bearing DLA $1x10^6$ cells/ml. They have found that quinazolinon-2-methyl nitrogen mustard with either a nitro or chloro group at para phenyl position is a most potent anticancer compound. As they show significant increase in the MST and also good % ILS when compared with the control, i.e., mice treated with CMC. Hence they have concluded that the 1, 6, 8- trisubstituted quinazolinones with a nitrogen mustard moiety connected through a methylene group at position 2 are effective in mice bearing Dalton's Lymphoma Ascites.



Therapeutic potential of qunazoline derivatives as anticancer agents:

Quinazoline derivatives as protein kinase inhibitors. kinases constitute the most important human en- zyme class that controls the sequence of events such as cell cycle progression, cell division, and cell

proliferation. The protein kinases, when expressed in mutated, unregulated forms or when produced in abnormally high levels, are capable of transforming normal cells into cancer cells and thus play important roles in tumorigenesis. Protein kinases not only control cell division but also support the angiogenesis process that is required for tumor growth and metastasis. In the early 2000s, discovery of erlotinib and gefitinib as anticancer drugs encouraged researchers to investigate 4-anilinoquinazoline compounds, which led to the development of new and promising compounds such as lapatinib, vandetanib, and afatinib. In previous studies, several patents and articles have been published that discuss the feasibility of the anilinoquinazoline scaffold for the development of tyrosine kinase inhibitors (TKIs).

Quinazoline derivatives with anticancer activity:

In view of the importance of quinazoline derivatives plus the tendency of some of these molecules to develop resistance. Synthesized novel quinazoline derivatives with the purpose of finding a more potent compound. A series of new 4,6-di-substituted quinazoline derivatives were synthesized and screened for anti-inflammatory and anticancer activities against U937 leukemia cell lines. The anti-inflammatory activity of these com- pounds was moderate to poor. However, all of the com- pounds in this series exhibited a noteworthy decrease in cell viability with reference to concentration. The cytotoxic activity of compound was in the micro molar range, very close to that of the standard positive control drug (etoposide), and exhibited maximum activity. It was assumed that the maximum activity of was a result of the presence of iodine and L-phenylalanine at positions 6 and 4 of the quinazoline nucleus, respectively.

AIM & OBJECTIVE:

In the pharmaceutical field, there has always been and will continue to be a need for new and novel chemical entities with diverse biological activities. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesizing pharmacologically interesting compounds of widely different composition.

We must always continue to search for drugs which exhibit clear advantages over the already existing respective drugs. Such advantages may be:

- A qualitative or quantitative improvement in activity,
- A partial or total absence of undesirable side effects,
- A lower toxicity,

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- More nutritive value,
- Improved stability and
- A decrease in production cost.

PLAN OF WORK

Part A - 2-methyl-quinazolin-4(3H)-one

Part B - 2-(4-Chlorostyryl)quinazolin-4(3H)-one

Part C - 4-chloro-2-(4-chlorostyryl)quinazoline

Part D - 2-(4-chlorostyryl)-4-hydrazinyl quinazoline

1. PhysicochemicalStudies

- Melting point determination
- Thin layer chromatography (TLC)
- Rotational and Vibrational absorption spectra (IR)
- Nuclear Magnetic Resonance spectra (1H-NMR and 13C-NMR)

2. Pharmacological Studies

- Anticancer activity

SUMMARY AND CONCLUSION

In summary, an efficient, catalyst-free, multi component strategy for synthesis of 2-methyl-quinazolin-4(3H)-one, 2-(4-Chlorostyryl) quinazolin-4(3H)-one, 4-Chloro-2-(4-chlorostyryl) quinazoline and 2-(4-Chlorostyryl)-4-hydrazinyl quinazoline was developed. These synthesized compounds were found to exhibit considerable in vitro anti-cancer activity. Compounds exhibited very potent anticancer activity against both Hep-G2 and MCF-7 cell lines. However, compounds showed remarkable anticancer activity against liver Hep-G2 cell line, while compound exhibited potent anticancer activity against MCF-7 cell line.

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