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Preclinical Assessment Of Nitrogen-Containing Heterocyclic Derivatives For Breast Cancer Intervention In Animal Models

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Abstract

Due to their inherent adaptability and distinctive physicochemical characteristics, the majority of heterocycle compounds and generally frequent heterocycle units found in the majority of medications now on the market have established them as genuine bases of medicinal chemistry. In addition to the medications that are now on the market, several more are being researched for their possible effectiveness in treating a variety of cancer. Specifically, these molecules inherent adaptability and dynamic core scaffold have been used in anticancer research. However, much like every other potential anticancer medication, heterocyclic compounds have drawbacks. We give a succinct summary of heterocyclic active compounds and families in this study, along with an emphasis on their primary medical uses.While examining the primary biochemical mechanisms of action, biological targets, structure-activity connections, and fundamental limitations in the utilisation of these substances, we have concentrate on those that are appropriate for cancer therapy.

INTRODUCTION

Breast cancer is the most common malignancy in women.(1) Breast carcinoma is the most frequently diagnosed carcinoma, followed by pulmonary carcinoma with 2.09 million cases.(2) Breast cancer is originates in breast tissue and they are most frequently arises from the cell surrounding lobuled and milk duct.(3)
Lobular carcinomas are the name for cancers that start in the lobules, while those originate in the ducts are called ductal carcinomas. an there are aprroximately 20+ different breast cancer types. (4) Due to current rises in incidence and repercussions on different mental, physical as well as social facets of human existence, cancer has emerged as a significant concern of the present.(5)
World Health Organisation (WHO) shows that, cancer is the third or fourth major reason for mortality in 22 countries before the age of 70 and the 1st and 2nd most common cause in of 180 nations. According to

GLOBOCAN 2020, In the twenty-first century, cancer is set to overtake all other causes of death as the main threat to increasing life expectancy throughout the world, and non-communicable diseases are now responsible for the majority of fatalities internationally. (6) The most recent statistics available from Iran's Cancer Research Centre indicates that 1400 out of the 8500 newly reported cases of breast cancer result in death per year. (7)

One in nine women will develop breast cancer over their lives.(8) Risk will raised when a person have a mother, sister or daughter who has breast cancer. But majority of people having breast cancer with no family history. The likelihood of breast cancer in men is significantly lower. Breast cancer affects one in 833 males on average, and age, genetics, obesity, alcohol use, and environmental factors appear to be the main risk factors (9).

The genes that cause breast cancer include Breast Cancer Gene 1 (BRCA1), Breast Cancer Gene 2 (BRCA2), Ataxia Telangiectasia Mutated (ATM), Human Epidermal Growth Factor Receptor 2 (HERS),and Epidermal Growth Factor Receptor (EGFR). (10) BRCA1 and BRCA2 are present in human's8 chromosome 17q21 and 13q12 respectively. BRCA1 an BRCA2 are negative regulators of cell division (anti-oncogenes). (11) HERS are present in chromosomes 17q12 and it is also called as c-erbB-2. It was initially discovered in neuroblastoma cells of rat. (12) EGFR are present in chromosomes 7p12 and it is also called as c-erbB-1. (13)

The Sixth Period in ancient Egypt has the earliest known proof of breast cancer, which goes 4200 years back. The examination of a female's bones from the Qubbet el-Hawa necropolis revealed the typical devastating devastation brought on by metastatic spread. (14)

The prominent screening technique to detect breast cancer is Mammography and some more screening techniques are Magnetic Resonance Imaging (MRI) etc. (15) There are different degrees to which cancer affects people's quality of life. Emotional consequences, mental health issues, depression, pain, therapeutic and diagnostic procedures, and social life all have a negative effect on patients life . (16)

Several medications have been granted support from the US-FDA for the treatment of breast-related cancers. Resistances frequently appear, thus new molecules are urgently required to address these issues. (17)

Finding novel applications for already available neoplastic medications in the treatment of breast cancer is increasingly crucial for creating better treatment plans and enhancing overall. (18)

NITROGEN CONTAINING HETEROCYCLIC RING –

By wide range of biological activities, heterocyclic compounds have made significant contributions to society in the form of several medications for the treatment of different diseases. They also have a major position in medicinal chemistry. (19)

1. QUINOLINE DERIVATIVES -

Quinoline is a heterocyclic, aromatic chemical that contains nitrogen as heteroatom obtained from Cinchona Alkaloids. A wide variety of biological activity can be seen by pharmacologically active compounds. (20)

Quinoline derivatives have a crucial role in medicine. It shows many activities like antifungal, antimalarial antibacterial, anti imflammatory, anticonvulsant. And quinoline molecule also used in the preparation of virucides, fungicides, biocites and many other. (21)

Some drugs are currently present in the market like belotecan, bosutinib, topotecan, cabozantinib, foretinib, irinotican,lenvatinib, niratinib and many more.(22)

2. INDOLE DERIVATIVE-

Indole C_8H_7N is a heterocyclic organic compound in which benzene ring is fused with pyrrole ring.(23) Indole is synthesized in the shikimate pathway from anthranilate.(24) Due to its remarkable pharmacological qualities, indole has been drawing researchers' interest and has emerged as a popular topic of research.(25) It is utilised in the discovery and design of target-based anticancer durgs.(26) And it also posses many other pharmacological activities like antimicrobial, antiviral, immflamatory etc.(27)

The indolemoeity is extensively prevalent in nature and it is found in a number of significant alkaloids, including tryptophan and auxins. (28) Treatments for several malignancies, including Hodgkin's disease, non-Hodgkin's, and prostate cancer, breast cancer involve the use of dimericmonoterpeneindole alkaloids such as vinblastine and vincristine. (29).

3. IMIDAZOLE DERIVATIVE-

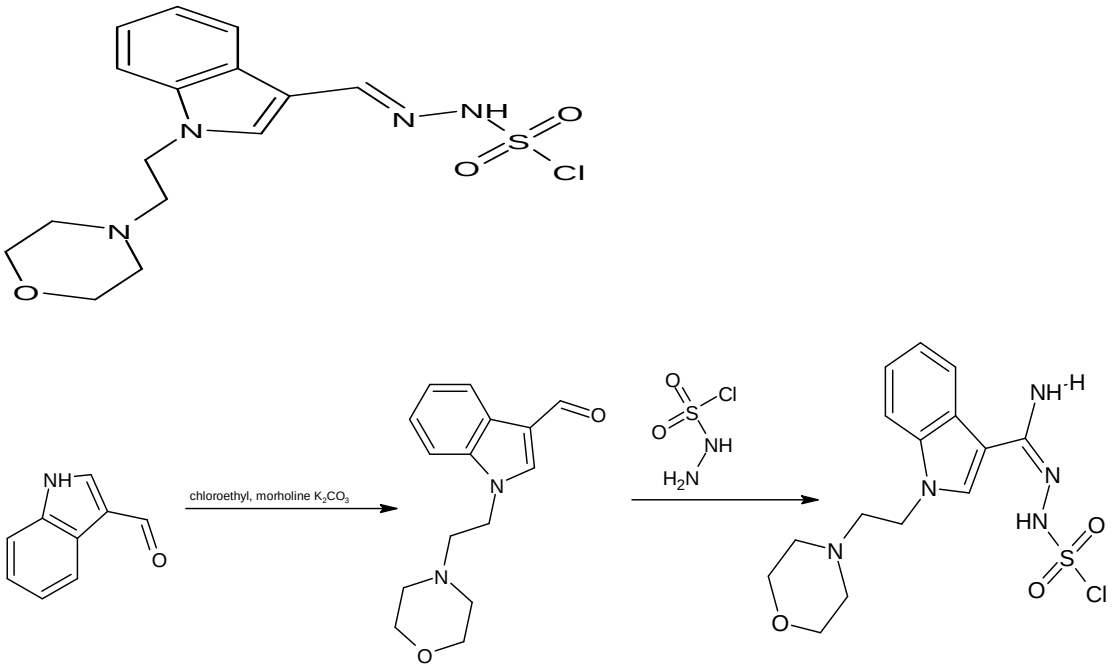
It is an alkaloid that aids as a vital role in the search for new drugs. (30) And it can be obtained from various resources.(31) Imidazole is a compound present in many existing drugs and has many therapeutic

activites. And it also possess major role as anti- cancer activity.(32) Since imidazole was discovered in the 1840s by Heinrich Debus.(33)
The investigation and modification of imidazole-based compounds possess fascinating action. Imidazoles have a several biological effects, including anti-cancer, anti-imflammatory, anti-viral, antitubercular, antiparasitic, antineuropathic and many medicinal applications. (34) Imidazoles have been employed as potent anticancer agents among all other pharmacological uses. Several imidazoles, such as temzolomide, mercaptopurine, nilotinib, dacarbazine, are now utilised in clinics to treat a variety of malignancies. These compounds show remarkable pharmacological potential to treat cancer.(35)

4. CARBAZOLE DERIVATIVE-
Carbazole is aromatic heterocyclic compound which consists of two benzene rings fused with five member containing nitrogen as hetero atom. (36) The carbazole have been the basic structure of many therapeuticically active molecules, which involves both natural and manufactured products, form more than 50 years amongst the available anti-cancer drugs.(37)
Most carbazole alkaloids come from higher plants belonging to the genus Clausena, Murraya, Micromelum all of which are members of the Rutaceae family. In addition, it is also obtained from fungus and bacteria.(38) They shows many pharmacological activites such as anticancer, anti-imflammmatory, anti-oxidant, anti-psychotic, anti-bacterial, anti-diabetics.(39)

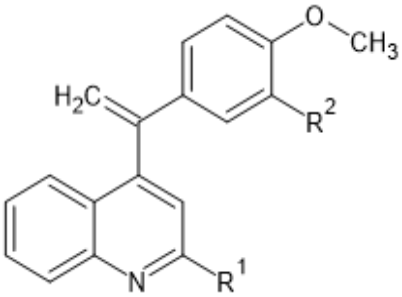
5. PYRIMIDINE DERIVATIVES-
Pyrimidine is aromatic organic compound in which nitrogen is at first position of a ring.(40) As "m-Diazine," a byproduct of the metabolism of uric acid, pyrimidines rose to prominence in the history of organic chemistry. Alloxan, the first pyrimidine derivative, was found by Brugna
telli in 1818.(41) The therapeutic effects of pyrimidine derivatives are well established in medicinal chemistry. Additionally, a number of pyrimidine derivatives have been created as chemotherapeutics. (42)
It has been reported that pyrimidine and its analogues have a great variety of biological potential, including anticancer,(43) antimicrobial, (44) antiviral (45), analgesic, (46) anti-imflammatory (47) etc.

SCHEMES
1. INDOLE -
Imran Ali *et. Al.*were synthesized novel indole based arylsulfonylhydrazides containing morpholine heterocyclic ring through multistep chemical reaction. And these compound was screened for there in vitro activity against estrogen receptor. (48)

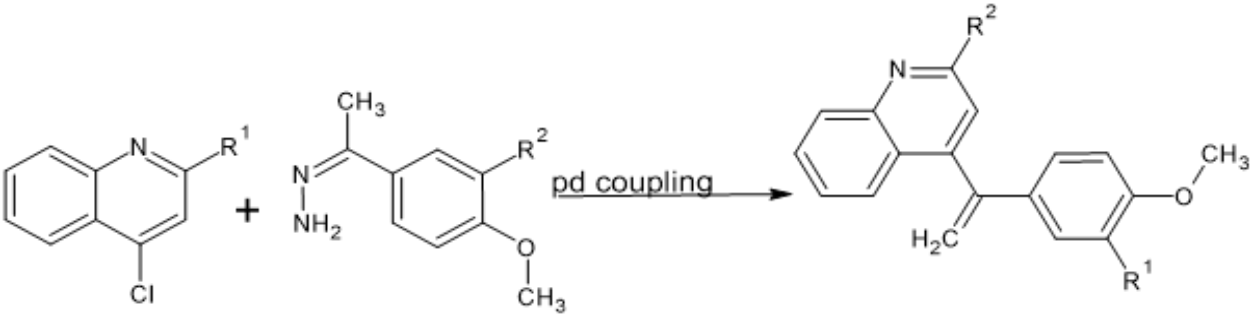


In 2018, Bugaenko*et al.* reported that the t-BuOK/DMF approach generated N-substituted indole-3-carboxylates substitutes in good yields.(49)

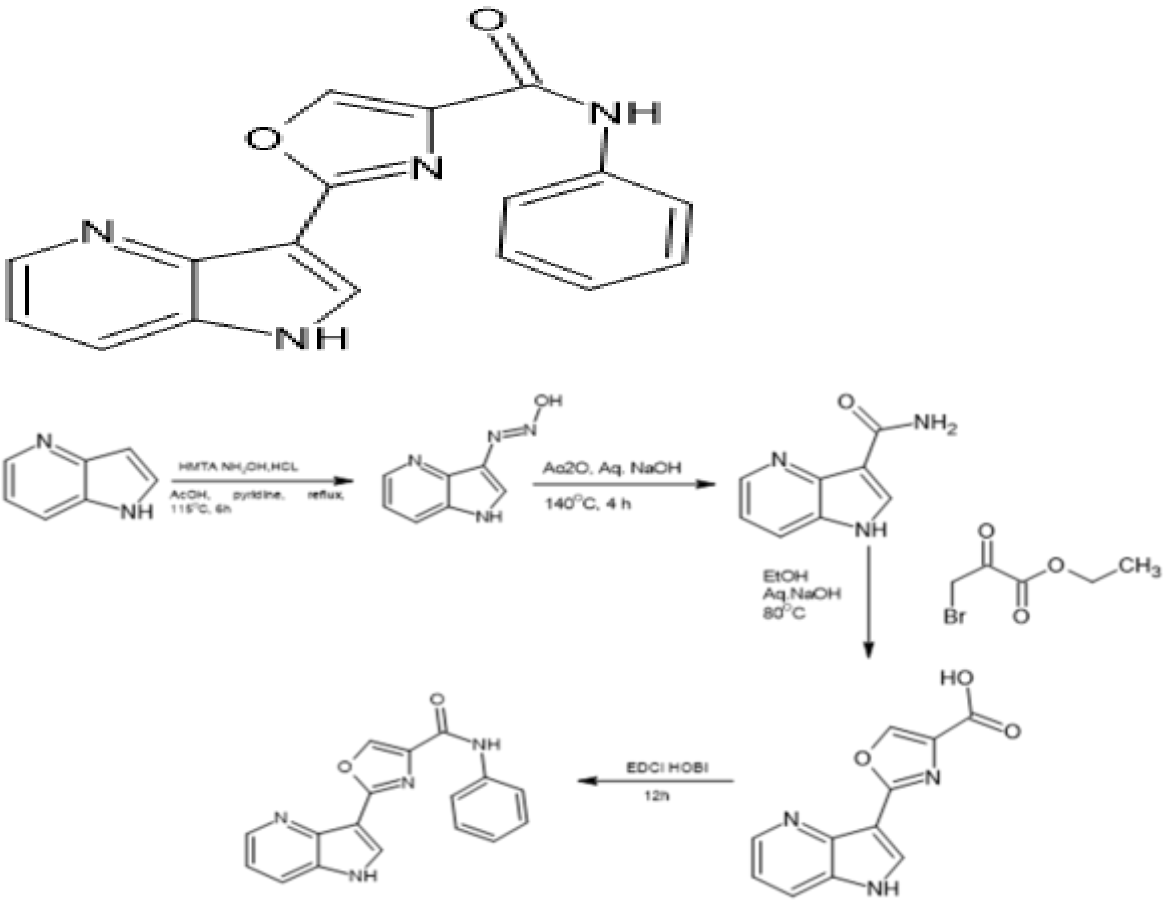
Khelifi*et al.*synthesised a unique series of isoCA-4 analogues to imitate the ability of isocombretastatin A-4 (isoCA-4) binds to the tubulin colchicine site to prevent polymerization by preventing the mitotic spindle from forming. And developing a range of novel isocombretastatin.



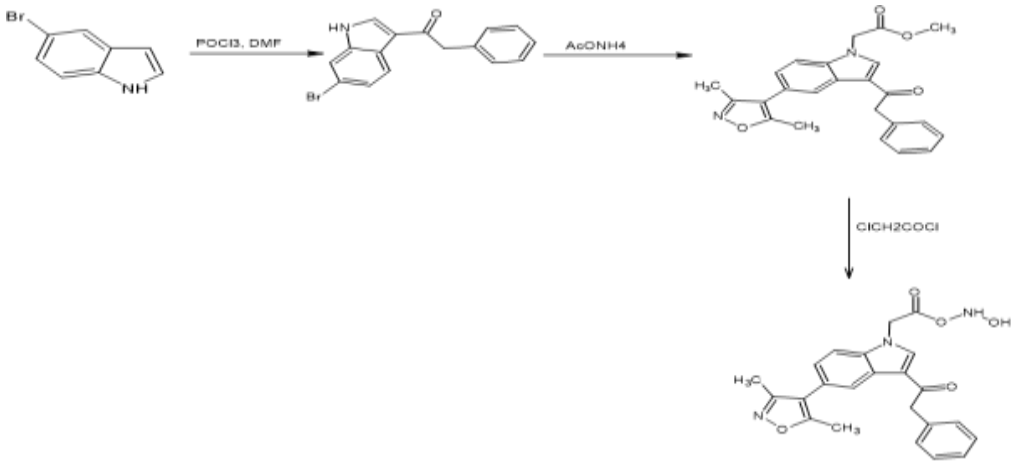
IsocoQuines 2



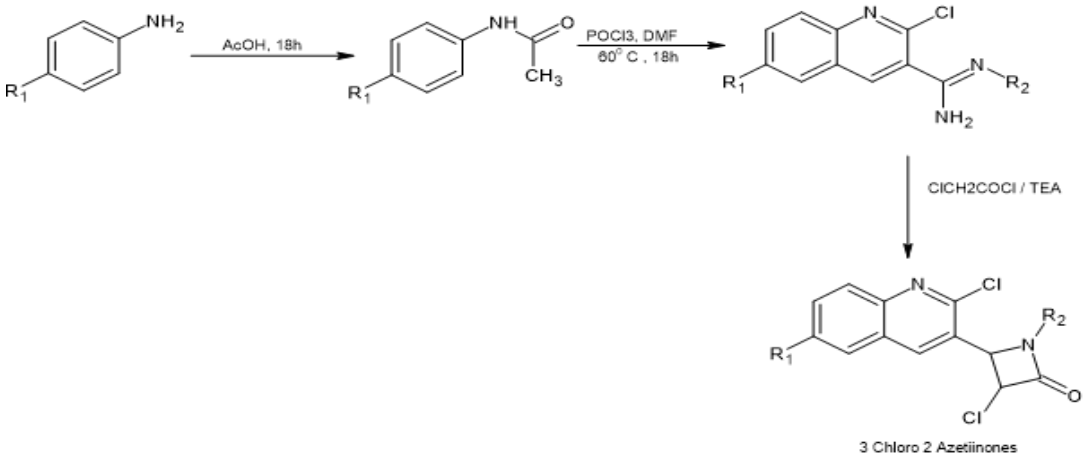
In 2019, Swammy*et al.* suggested drugs that target EGFR. They created a set of 11 amide azaindole-oxazole compounds and examined their anti-cancer properties using breast cancer cell lines. (51)



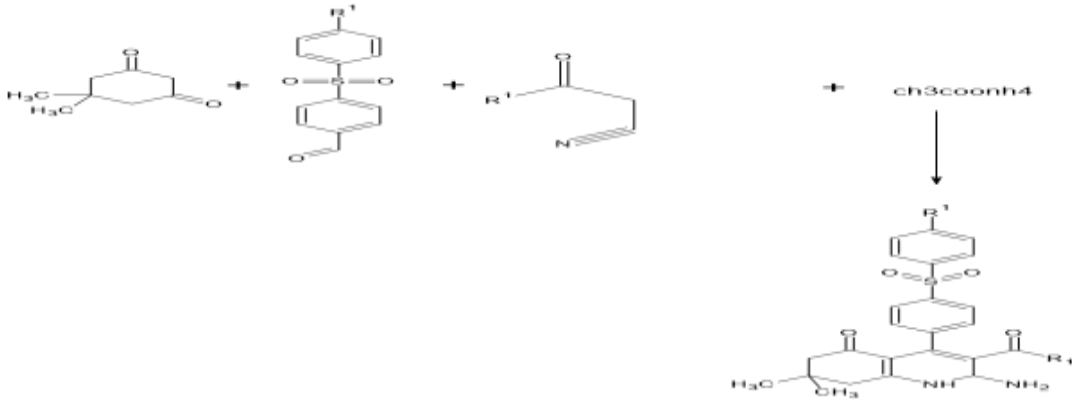
Cheng *et al.* concentrated on the synthesis of novel compounds in 2019 with the goal of developing HDAC inhibitors and anti-leukemic medicaments. They formed manyindole substitute which combine with the inhibitory actions of HDAC and BRD4 into a single molecule by employing a structure forming design process.
They also shows to be the most potent inhibitor against HDAC3, with an IC50 value of 5 nmol/L, and BRD4 with inhibition of 88% and rate at a dosage of 10 mol/L. (52)



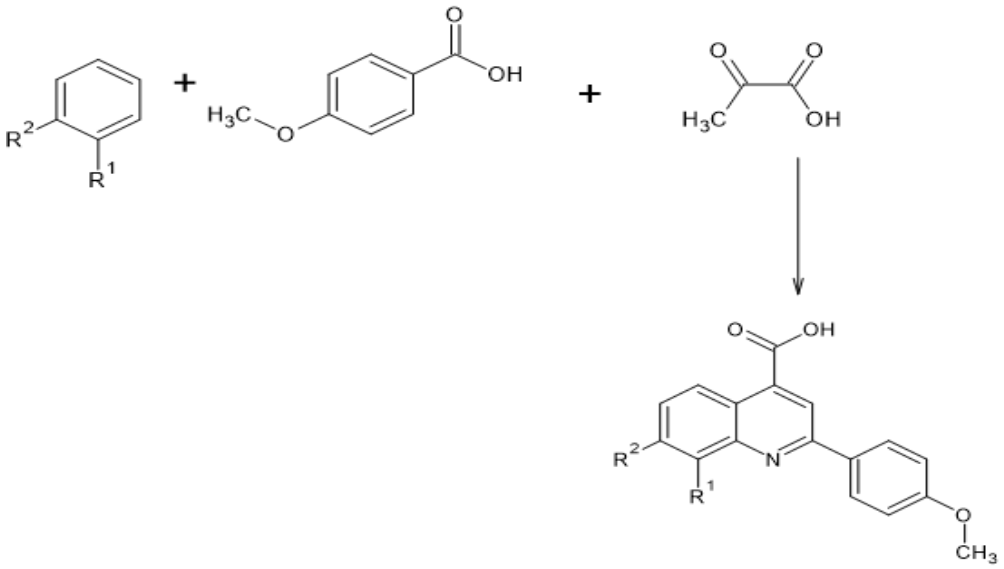
2. QUINOLINE-
Azetidinone derivatives were created by K. Govindarao *et al.* (53) as potential antibreast cancer medicines that are effective against the cell lines MDA-MB-231 and MCF7. These result in high IC50 values when compared to the typical human liver cell.



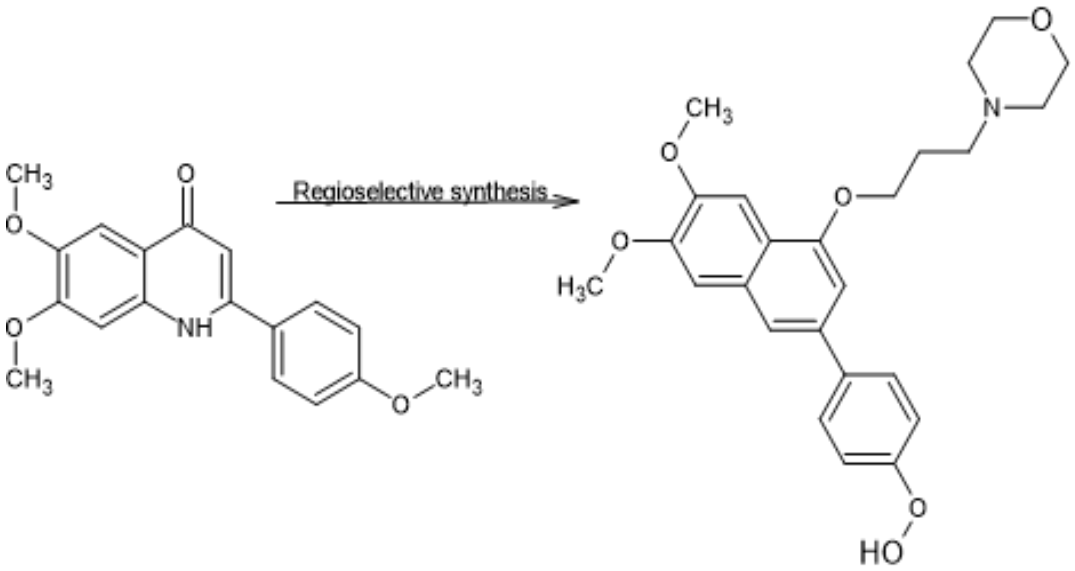
Mohamed Mokhtar and others (54) designed green synthesis of quinolinone derivatives which targets multi-receptor tyrosine kinases using the MCF-7 cell line. They utilized a copper nanoparticle catalyst that has been coated with chitosan under ultrasonic irradiation.



5-(Imidazolylmethyl)-2-Aryl-Quinoline analogues as Aromatase Inhibitors were reported by Ghodsi et al. in 1955. Quinolines 8a-g's toxicity to MCF-7 and T47D cell lines was evaluated.



Elbadawi *et al*. (56) synthesized a4-alkoxyTopoisomerase I which is inhibited by -2-aryl-6,7-dimethoxyquinolines derivative and halogen benzoyl chloride derivatives. And these activity is performed on mice cell line 4T1. And they found positive result against it.

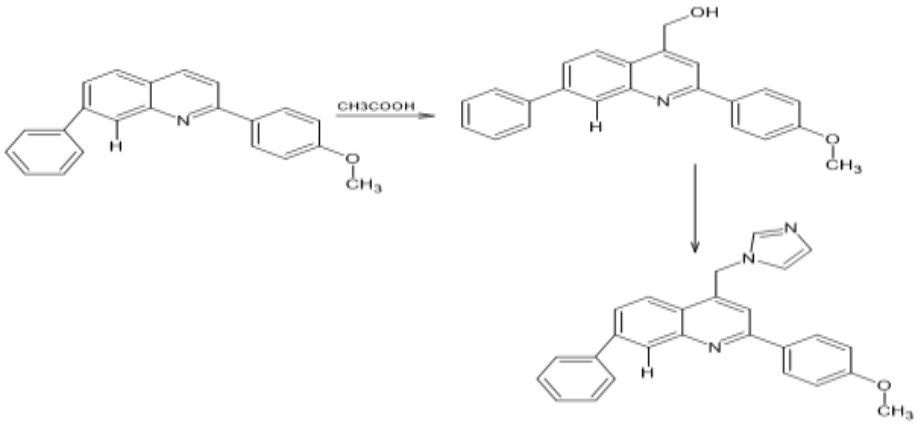


7H Chromeno quinoline derivatives and 7,12-dihydrodibenzo naphthyridine were synthesised by R.A. Kardile *et al.* in 1957. They found dibenz naphthyridinone, indenoisoquinoline, indeno quinolone and indeno quinoline against C57MG cell line of mice. (57)

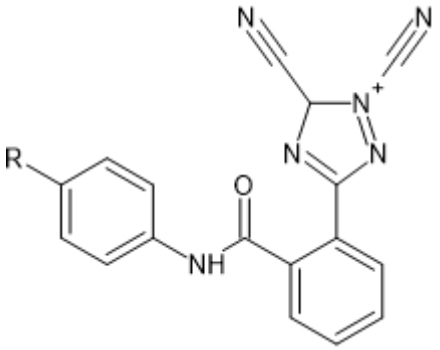
3. IMIDAZOLE DERIVATIVE-

Deryaosmaniye and other (58) developed a derivatives of aromatase inhibitors. Here the thiazolylhydrazone group inhibits MAO-B and the azole group binds to the HEM group of the enzyme to inhibit aromatase.

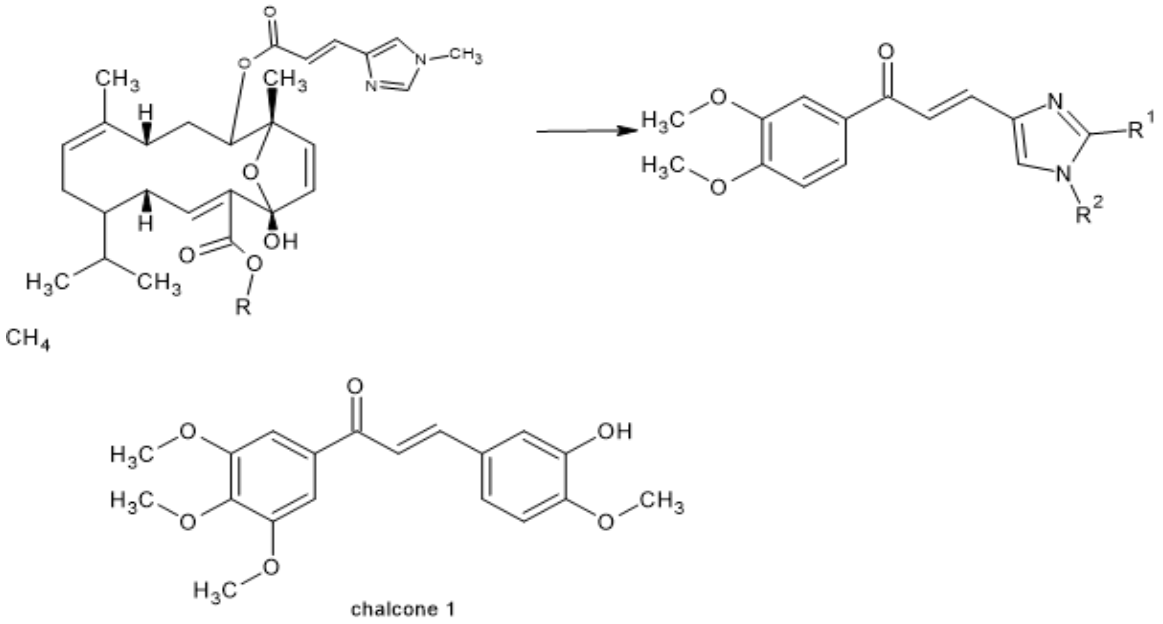
The main reason behind developing this combination was to minimize the ngative effects of aromatase inhibitor caused by patient with breast cancer having lower oestrogen level while also preventing the effect of aromatease inhibitor on dopaminergic neurons.



M. shaheermalik*et Al*. (59)developed a novel N-phenylbenzamidederivatives , In order to understand binding affinity at the molecular level. The this derivative were then exposed to molecular docking. To gain a better understanding of the interactions at the receptor level, molecular dynamic simulations were also conducted. Additionally, computational research was done on the derivatives' molecular descriptors and drug-likeness characteristics.

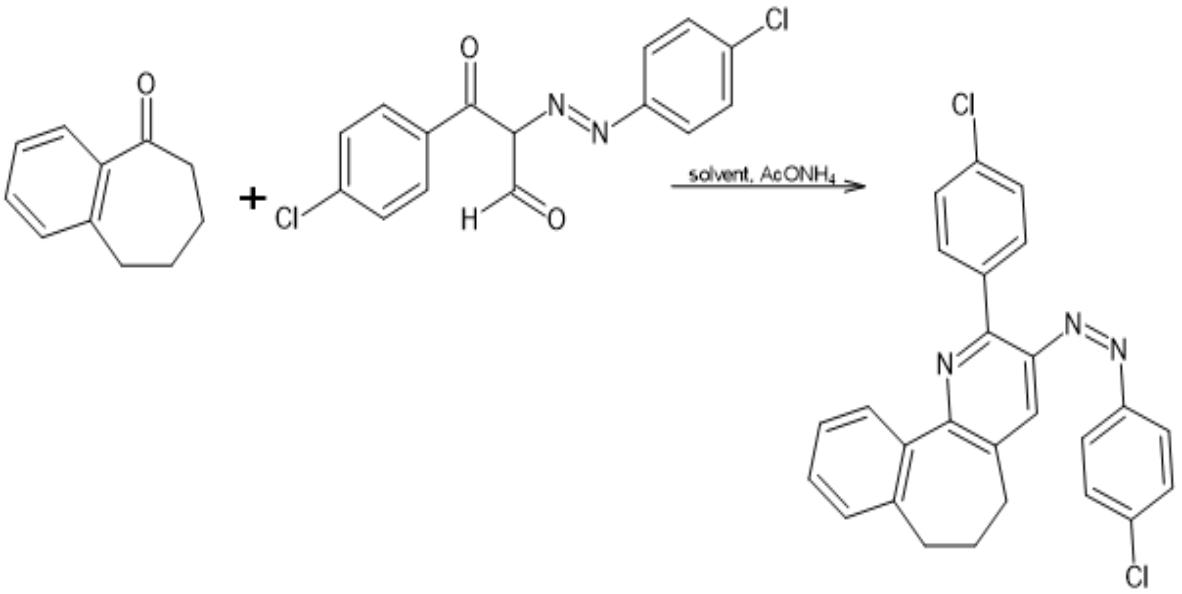


Sara rahimzadehOskuei*et Al*.(60) developes a novel imidazole-chalcone derivatives which fight against cancer cells (MCF-7) , and human hepatocellular carcinoma cells (HEPG2) and adenocarcinoma human alveolar basal epithelial cells (A549).

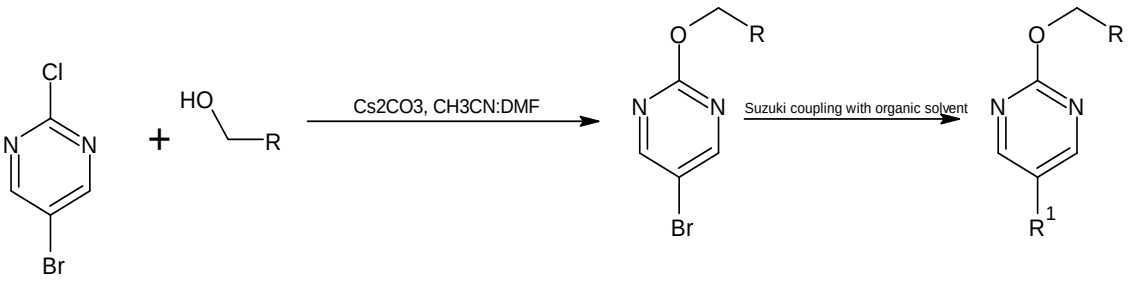


4. PYRIMDINE-

Behbehani*et al*. (2020) have developed a unique synthetic platform that employs a fresh, useful, and efficient method to generate considerably substituted pyridine systems. Making use of the MTT.The first cytotoxicity examination of these synthetic 10-pyridine derivatives was performed using a colorimetric test on human malignant cell lines, MCF-7 (breast cancer). All 10 of the pyridine derivatives showed considerable cytotoxic characteristics in experiments on malignant A549 and MCF-7 cells.The study's result indicates that the compounds indicated above might serve as appropriate main sources for upcoming research on the creation of anticancer medications. (61)



OntedduSurendranathaand his associate have published a research detailing a prouctive method for the synthesis of 2,5disunbstitute pyrimidine. Suzuki produced the required ,5disubstitutedpyrimidines by combining 2 substituted benzyloxy-5-bromopyrimidines with different aryl boronic acids in water at 80^0 C WITH 0.5 M aq. In turn, 2-benzyloxy-5-eous Na_2CO_3. And a catalytic quality of PdCl2(PPh3)2. Bromopyrimidines were produced via the reaction of substituted benzyl alcohols and 2-chloro-5-bromopyrimidine in CH3CN:DMF (1:1) in the presence of Cs2CO3. A small number of 2,5-disubstituted pyrimidines have shown a modest degree of cytotoxicity in vitro against the HeLa cell line. (62)



R AN R1 : Aryl, hetroaryl

CONCLUSION:

Heterocycles appear to be involved in a number of metabolic biochemical processes in cells. Because of their reactivity with tissues and cells, these molecules regulation is so strictly regulated that any disruption may be linked to disease disorders. In order to upset the delicate equilibrium in cells, synthetic cyclic compounds used as anticancer medicines resemble natural ligands and substrates. Through boosting lipophilicity, polarity, or other physicochemical qualities, heterocyclic compounds or heterocyclic fragments also contribute significantly to improving the pharmacokinetics and pharmacodynamics aspects of anticancer

medicines. Because heterocycles are found in most marketed medications, they are therefore significant in today's drug design.

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