Pyrazole: An attractive tool for breast cancer

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BONAFIDE CERTIFICATE

Certified that this project report "**Pyrazole: An attractive tool for breast cancer**" is the bonafide work of "**PAVNI SHARMA(17SMAS102070)**" who carried out the project work under my supervision.

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TABLE OF CONTENTS

TITLE

ABSTRACT

LIST OF FIGURES

LIST OF TABLES

1. **INTRODUCTION**

2. **PYRAZOLE**

    2.1. STRUCTURE OF PYRAZOLE
    2.2. PREPARATION OF PYRAZOLE
    2.3. SAR OF PYRAZOLE
    2.4. MARKETED DRUGS BEARING PYRAZOLE

3. **OVERVIEW OF CANCER IN WORLD**

4. **PYRAZOLE ACTIVITY AGAINST BREAST CANCER (MCF-CELL LINE)**

    4.1. ABOUT BREAST CANCER
    4.2. PATHOLOGY OF BREAST CANCER
    4.3. ANTI- BREAST CANCER ACTIVITY OF PYRAZOLE

5. **CONCLUSION**

6. **REFERENCE**

ABSTRACT

Pyrazoles are a common heterocycle in the pharmaceutical industry. The pyrazole scaffold has been identified as a common moiety in a variety of pharmacologically important drug molecules, including antipyrine, ramifenazone, ibipinabant, and axitinib. They have been extensively studied by scientists and are said to have a wide range of biological activities.The aim of this article is to summarise pyrazole's basic molecular structure, as well as its preparation and structure-activity relationship. The article further delves into the various functions that pyrazole plays in anti-breast cancer action, as well as how pyrazole is developing as a promising therapeutic option for breast cancer.

LIST OF FIGURES:

1. Pyrazole structure
2. Pyrazole-derived cations and anions
3. Tautomers of unsubstituted pyrazole.
4. Pyrazoles extracted from natural products
5. Commonly prescribed marketed drugs bearing pyrazole nucleus against Breast Cancer
6. Various techniques for synthesis of pyrazole derivatives
7. Structure activity relationship of pyrazole derivatives
8. Various reported biological activities and targets of pyrazoles.
9. Pyrazoles have been linked to a range of reported biological actions and targets
10. Mechanism of Action
11. Structures of novel pyrazole and pyrazolo[1,5-a]pyrimidine derivatives showing anti-proliferative activity.
12. Structure of benzothiazole/benzoxazole and/or benzimidazole substituted pyrazole derivatives showing the highest anti-proliferative activity.
13. Novel pyrazolinyl-estran-17- one Derivatives as potent anticancer agents.
14. Novel bivalent pyrazolyl appended 1,2,3-triazoles as anticancer agents.
15. Various Compounds showing activity against MCF-7 cell lines

LIST OF TABLES

1. Various pyrazole-based clinically used drugs.
2. In vitro cytotoxic activity of the newly synthesized compounds against MCF-7 tumor cell line
3. IC50 values of the novel synthesized compound A' cell line MCF-7 using the MTT assay.

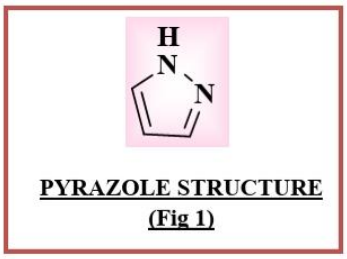
1. Introduction

For a long time, life-threatening infectious diseases have now been a chieffoundation of concern for human lives. Antibiotics, antimicrobials, and anti-infective are all terms that refer to a group of medicinal compounds that are used to treat infections. The development and testing of heterocyclic agents by means ofnew modes of action could direct to a key to the crisis at hand (1). Heterocyclic scaffolds are a central structural feature of the majority of biologically active moieties, so they play an important role in drug discovery and growth. Their versatility stems from their ability to communicate with almost any cellular system in a living organism. Researchers have been studying their interactions with various mechanistic pathways in viruses,microbes,etc in order to develop heterocyclic-based antiviral, antimicrobial, antibiotic agents. Different heterocyclic scaffolds are used in a number of FDA-approved drugs currently on the market (2 & 3).The synthesis of novel medicinal agents with extraordinary biological activities is made easier by nitrogen-containing heterocyclic compounds and their derivatives. Pyrazole is one such moiety that has received a lot of attention and has shown promise in the production of useful therapeutics (4). Pyrazole derivatives have emerged as potential therapeutics with anti-histaminic(5), antimicrobial(6), anti-depressant(7), antiviral(8), antitumor(9), and fungicide(10) properties. Medicinal chemists have observed numerous well-understood synthetic methods over the last few decades due to the diverse biological characteristics (11). As a result, in light of the importance of the pyrazole pharmacophore, the current study is conducted to provide a brief overview of how pyrazole-containing compounds act as anti-breast cancer agents as stated in recent scientific literature.

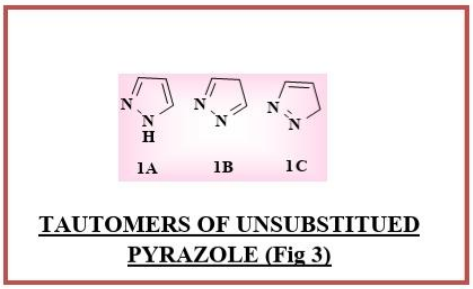
2. PYRAZOLE

2.1. STRUCTURE OF PYRAZOLE

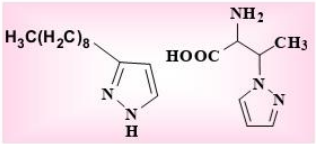
Pyrazole is an aromatic heterocyclic structure from the azole family. It's a five-membered ring of two nitrogen atoms and three carbon atoms linked together(Fig. 1).Since the unshared electrons are conjugated with the aromatic system, nitrogen atom 1 (N1) is "pyrrole-like." In the same way as pyridine structures have unshared electrons that are not compromised by resonance, nitrogen atom 2 (N2) has pyridine-like properties.Pyazoles react with both acids and bases because of the variations in nitrogen atoms(Fig.2).(12)Prototropic tautomerism is another significant structural aspect of pyrazole.Unsubstituted pyrazoles can have three tautomers, whereas monosubstituted pyrazoles can have five tautomers(Fig.3)(13). 3-n-nonyl-1H-pyrazole 3, derived from Houttuynia cordata, a common plant from tropical Asia, was the first pyrazole isolated from natural sources. Watermelon seeds contain B-(1-pyrazolyl) alanine 4(Fig.4) (14&15).



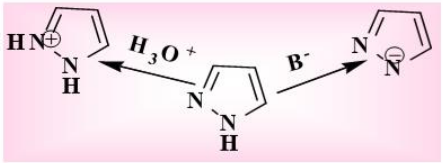
PYRAZOLE STRUCTURE (Fig 1)



TAUTOMERS OF UNSUBSTITUED PYRAZOLE (Fig 3)



PYRAZOLES EXTRACTED FROM NATURAL PRODUCTS (Fig 4)



Pyrazole-derived cations and anions (Fig 2)

Commonly prescribed marketed drugs bearing pyrazole nucleus against BREAST CANCER (Fig 5)

2.2. PREPARATION OF PYRAZOLE

Pyrazole nucleus is a molecular structure that can be used in a variety of pharmacologically effective drugs. Pyrazine's importance is due to the ease with which it can be prepared for spectacular activities. Ludwig Knorr (1883) was a pioneer in the synthesis of pyrazole and its derivatives using a variety of techniques. Annulations initiated by the condensation of a monosubstituted hydrazine with a carbonyl, such as cyclocondensation of,-unsaturated carbonyl or 1, 3- dicarbonyl compounds with hydrazines, are one of the best techniques for synthesising pyrazole rings(16). Following that, several researchers developed pharmacologically active pyrazole derivatives synthesised using both traditional and unconventional methods(Fig 6).Heller et al. proposed a one-pot pyrazole-containing compound synthesis using basic starting materials such as ketones and acid chlorides to produce 1,3-diketones. The pyrazole yields were excellent when the intermediate was reacted

with hydrazines(17).Deng et al. proposed that nitropyrazolidine was formed in substantial yields by a regioselective reaction between nitro-olefins and N- monosubstituted hydrazones(18).According to Jiang et al. Claisen condensation catalysed by MeONa/LiCl yields 4-substituted 1,5-diaryl-1Hpyrazole-3-carboxylic acids in one pot. The reaction of enolated lithium salts of diketo ester with arylhydrazine hydrochloride, trifluoroacetic in ethanol, followed by hydrolysis, yielded pyrazole derivatives in large quantities(19).In the formation of pyrazole derivatives, Hu et al. used a ruthenium (II)catalyst and dioxygen gas to introduce an intramolecular oxidative carbon-nitrogen coupling.Ruthenium (II) is a versatile catalyst that can be used to make tri- and tetra-substituted pyrazole derivatives with a broad range of functional groups(20).Wu et al. synthesised a sequence of 3,5-disubstituted pyrazoles from toluene and sodium ethoxide condensations of various tosyl hydrazine, aldehydes, and terminal alkynes at room temperature(21). In the basic medium, Zhang et al. synthesised 3,4,5-trisubstituted 1-H-pyrazole derivatives from aromatic aldehyde, vinyl azide, and tosyl hydrazine in a one-pot reaction (22) .Sha et al. devised a novel synthesis process for 3,5-diaryl-4-bromopyrazole derivatives. The 3,5-diaryl-4-bromo-3H-pyrazoles were obtained by a 1,3-dipolar cycloaddition reaction between tosylhydrazones and gem-dibromoalkenes in the presence of sodium hydroxide. The aldehyde hydrazones are used to isomerize 3,5-diaryl-4-bromo-3H-pyrazoles, yielding 3,5-diaryl-4-bromo-1H-pyrazoles(23).Harigae et al. proposed a method for making 3,5-disubstituted pyrazoles and isoxazole derivatives using reaction intermediates such as n-Buli aldehydes. Iodine and hydrazines were then added to the reaction mixture.From Nalkylated tosyl hydrazones and alkynes and t-BuOK at 0°C in pyridine(24). Kong et al. synthesised 1,3,5-trisubstituted pyrazole compounds.By reacting phenylacetohydrazide with dialkyl but-2-ynedioate in rhodium catalysts and AgOAc in MeCN(25). Li et al developed a method for the synthesis of a series of highly substituted pyrazole derivatives.(26)

Zhang et al. prepared di, tri, and tetrasubstituted pyrazole compounds in the presence of ethanol by reacting,-unsaturated carbonyl compounds such as aldehydes and ketones with hydrazine. The metal-free reaction was mediated by I2 and occurs via the oxidative formation of the CN bond. Experimentally,by transition-metal-catalyzed aerobic oxidation, the reaction was successful, regioselective, one-pot synthesis that produced the product in

excellent yields(27).In addition, Zhang et al. proposed nBu3P-catalyzed de-sulfonylative [3+2] cyclo-additions for the development of pyrazole derivatives that are basic, facile, and fast.The reactions proceeded smoothly under ideal mild temperature conditions, resulting in excellent yields of corresponding annulations products.(28)

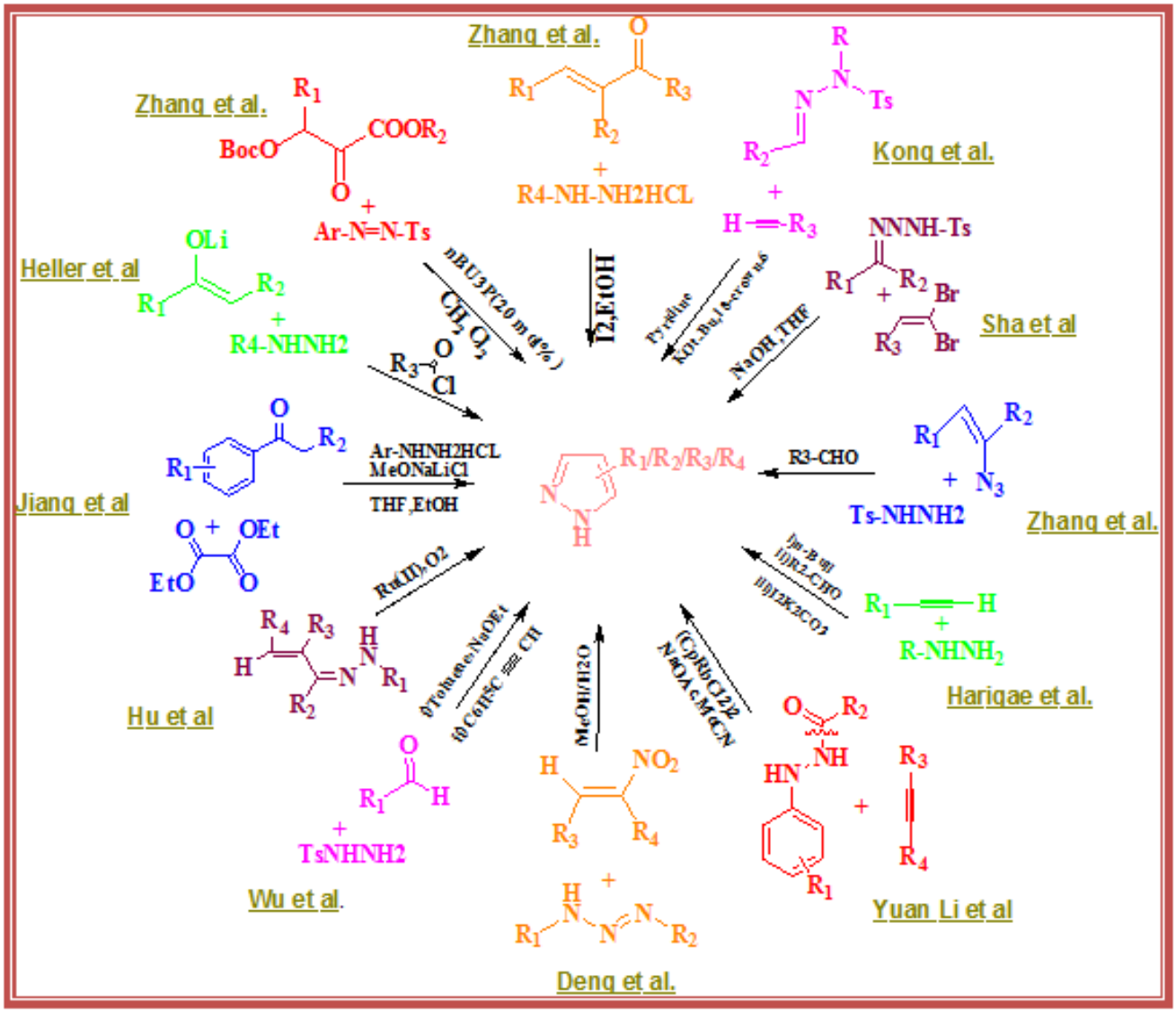


Fig 6- Various techniques for synthesis of pyrazole derivatives (29)

2.3. SAR of Pyrazole

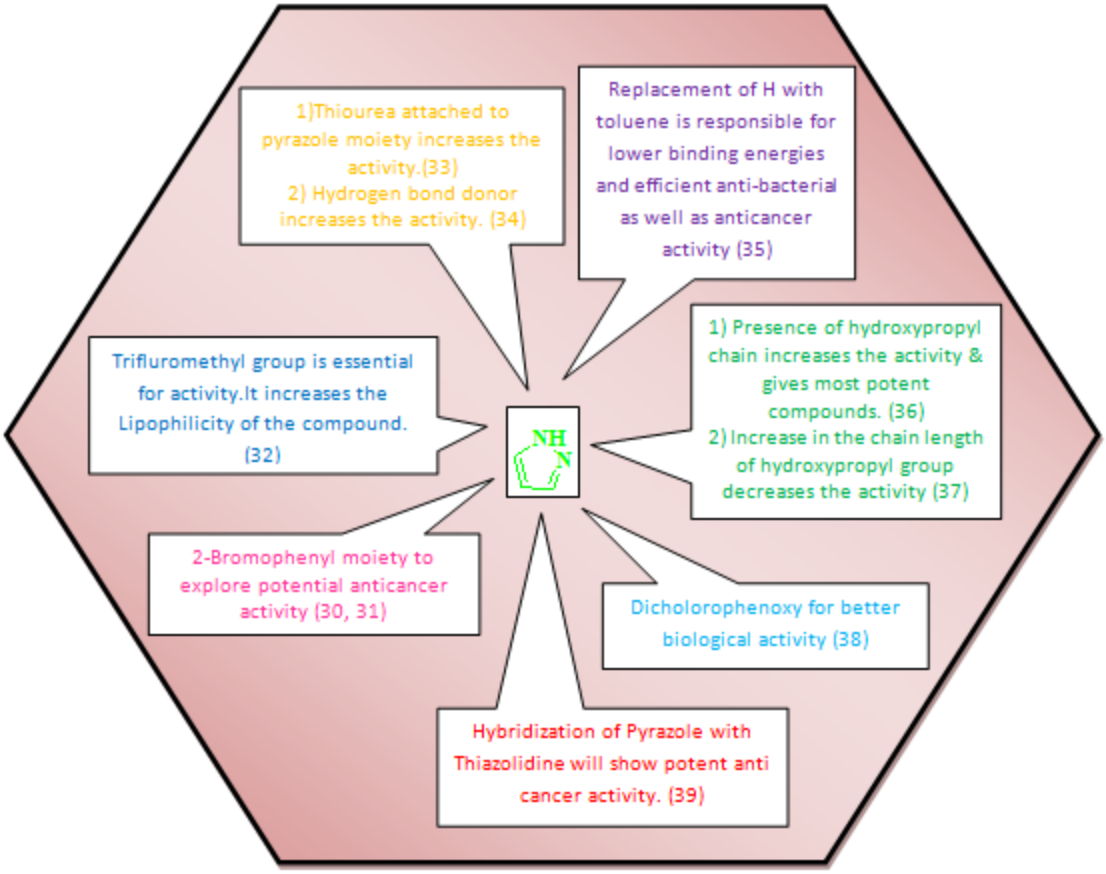


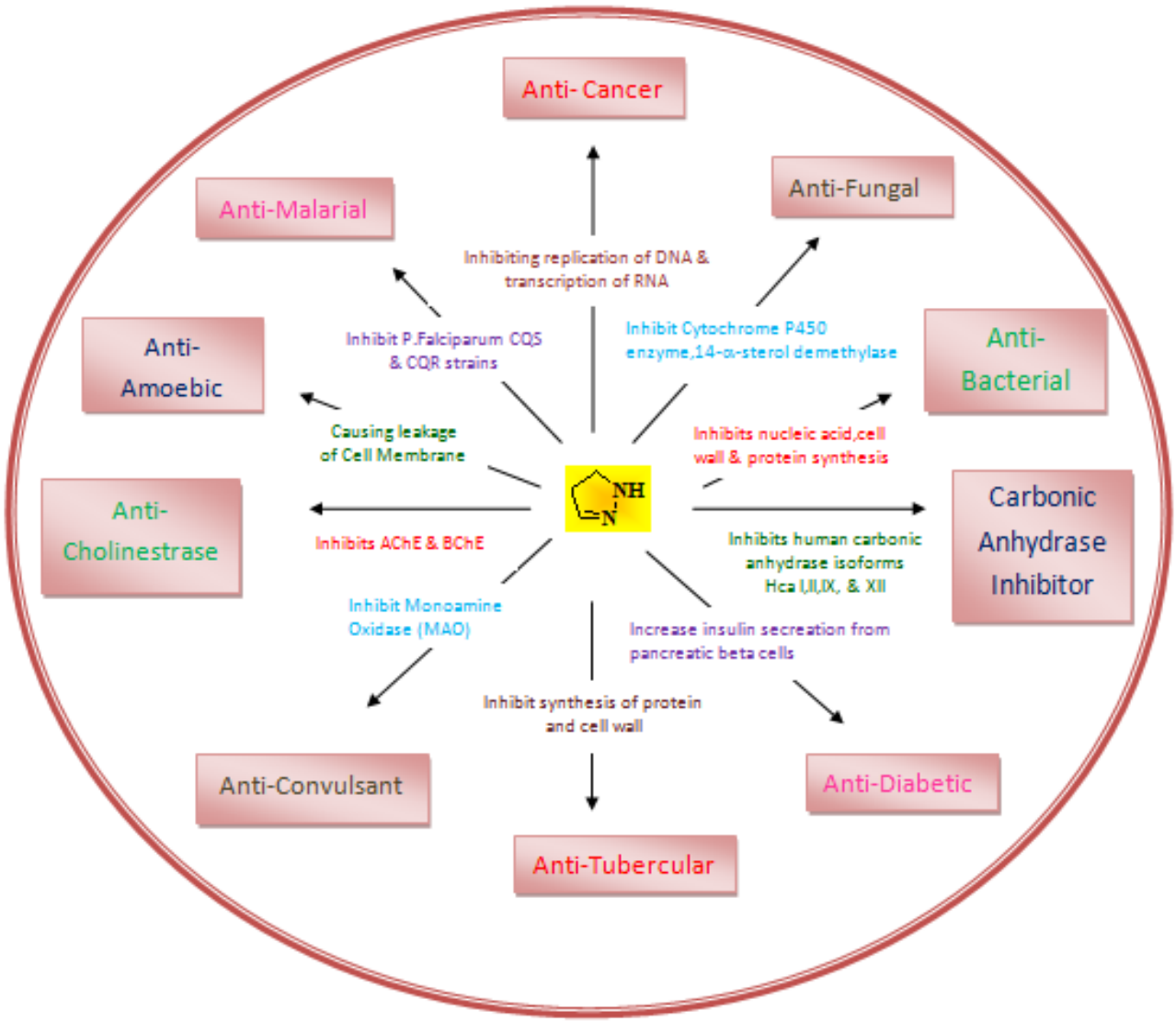
Fig 7-Structure activity relationship of pyrazole derivatives

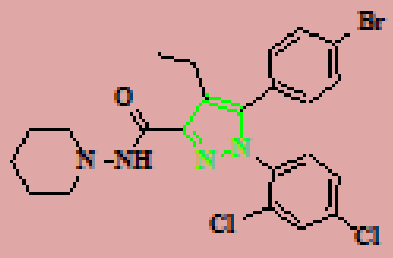
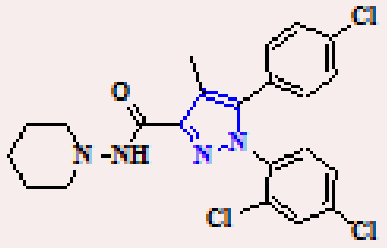
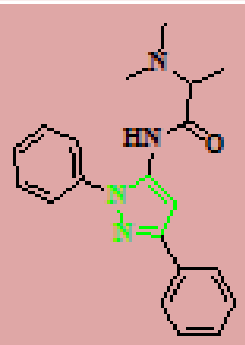
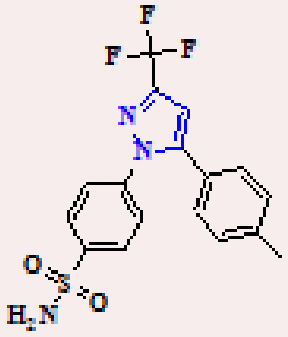
2.4. MARKETED DRUGS BEARING PYRAZOLE NUCLEUS

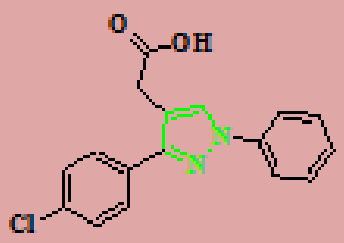
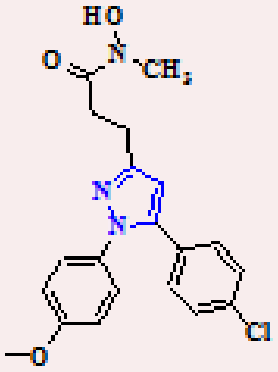
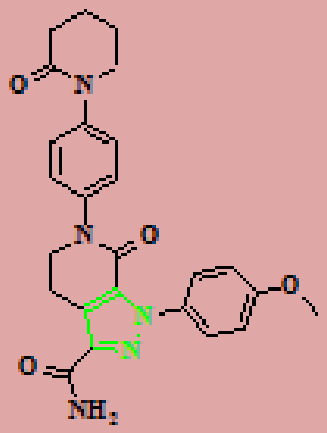
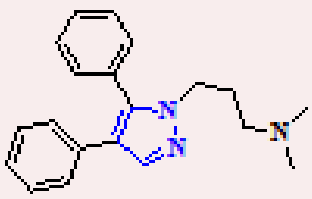
The pyrazoline ring system is a common structural function of many drugs that are used in clinical trials to treat a variety of diseases(40, 41) {Fig 10}. Anti-inflammatory drugs based on pyrazoline include antipyrine/phenazone, phenylbutazone, oxyphenbutazone, ramifenazone, morazone, and famprofazone(42,43). The pyrazoline-based drugs aminophenazone and metamizole, on the other hand, are used to deliver antipyretic and analgesic effects (44, 45). Edaravone is a clinically approved drug for the treatment of amyotrophic lateral sclerosis, a type of motor neuron disorder (ALS) (46). Sulfinpyrazone, a pyrazoline-based molecule, is an effective uricosuric medicine (Fig 8) (47) that works by enhancing uric acid excretion by urine, while Ibipinabant is a pyrazoline derivative used clinically as a selective cannabinoid CB1 receptor inverse

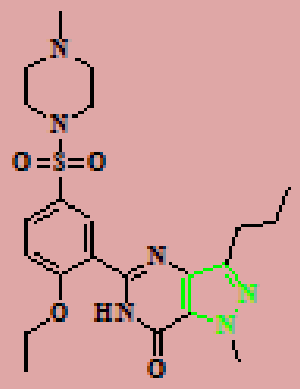
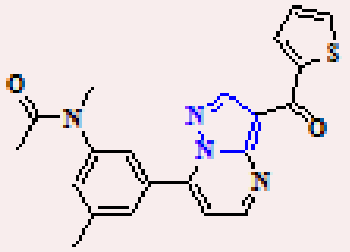
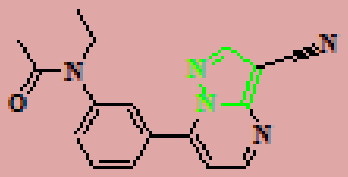
agonist (48). Axitinib is a VEGFR selective second-generation inhibitor dependent on pyrazoline that is used to treat metastatic renal cell carcinoma. It inhibits angiogenesis and causes cell death by binding to the intracellular tyrosine kinase domains of vascular endothelial growth factor receptors (VEGFRs) and lowering the amount of VEGF protein (49).

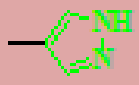
Various reported biological activities and targets of pyrazoles.(Fig. 8)(47)



Various pyrazole-based clinically used drugs. (Table 1) (50)		
Name of DRUG	Structure	Pharmacological Class
Surinabant(55)		Anti-Obesity
Rimonabant(56,57)		
Difenamizole(58)		Analgesic
Celecoxib(59)		Anti-Inflammatory

Lonazolac(53)		Non-Steroidal anti-inflammatory drug(NSAID)
Tepoxalin(54)		
Apixaban(60,61)		Anticoagulant
Fezolamine(62)		Antidepressant

Sildenafil(63,64)		Drug for Erectile Disfunction
INDIPLON(51)		ANTI-ANXIETY
ZALEPLON(52)		
Betazole(65)		H2 receptor Agonist

Fomepizole(66,67)		Antidote for methanol poisoning

3. OVERVIEW OF CANCER IN WORLD

A considerable number of novel pyrazole derivatives have recently been synthesised. (68)Because of their complex chemotherapeutic promise, pyrazole tethered heterocyclic compounds have attracted a lot of interest(69,70,71). Drugs based on heterocyclic compounds with a 1,2-diaryl substituted,pyrazole ring have often topped the list of best-selling medicinal items.Apixaban, Celecoxib, Fipronil, Remogliflazone Etabonate, Lonazolac, Tolpiprazole, Deracoxib, and several other pyrazole-based drugs are available on the market. Crizotinib and Ruxolitinib are two effective anticancer pyrazole tethered drugs(72). Celecoxib is a pyrazole tethered diaryl heterocyclic small molecule that is often used as a model(73). Celecoxib has been shown to have antitumor efficacy in animal models of prostate tumours(74,75,76). Pyrazole derivatives inhibit a number of targets, including topoisomeraseII(77-78), EGFR(79-80), VEGF,(81-82),HDAC (83-84), IGF-1R(85), AuroraA kinase(86), cMet(87), Tubulin(88), mTOR(89), B-raf(90), ROS 1(91-92), CDKs(93-94), PI3K(95), JAK2(96), and ALK(97).

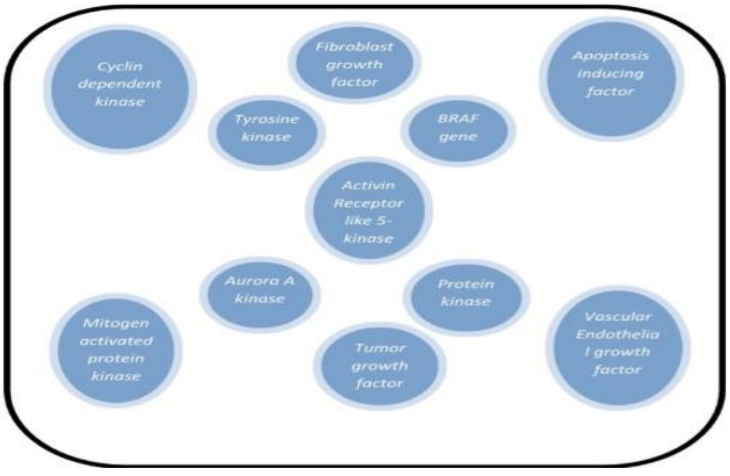


Fig. 9
Targets for pyrazole as anti-cancer agents

4. PYRAZOLE ACTIVITY AGAINST BREAST CANCER (MCF-7 CELL LINE)

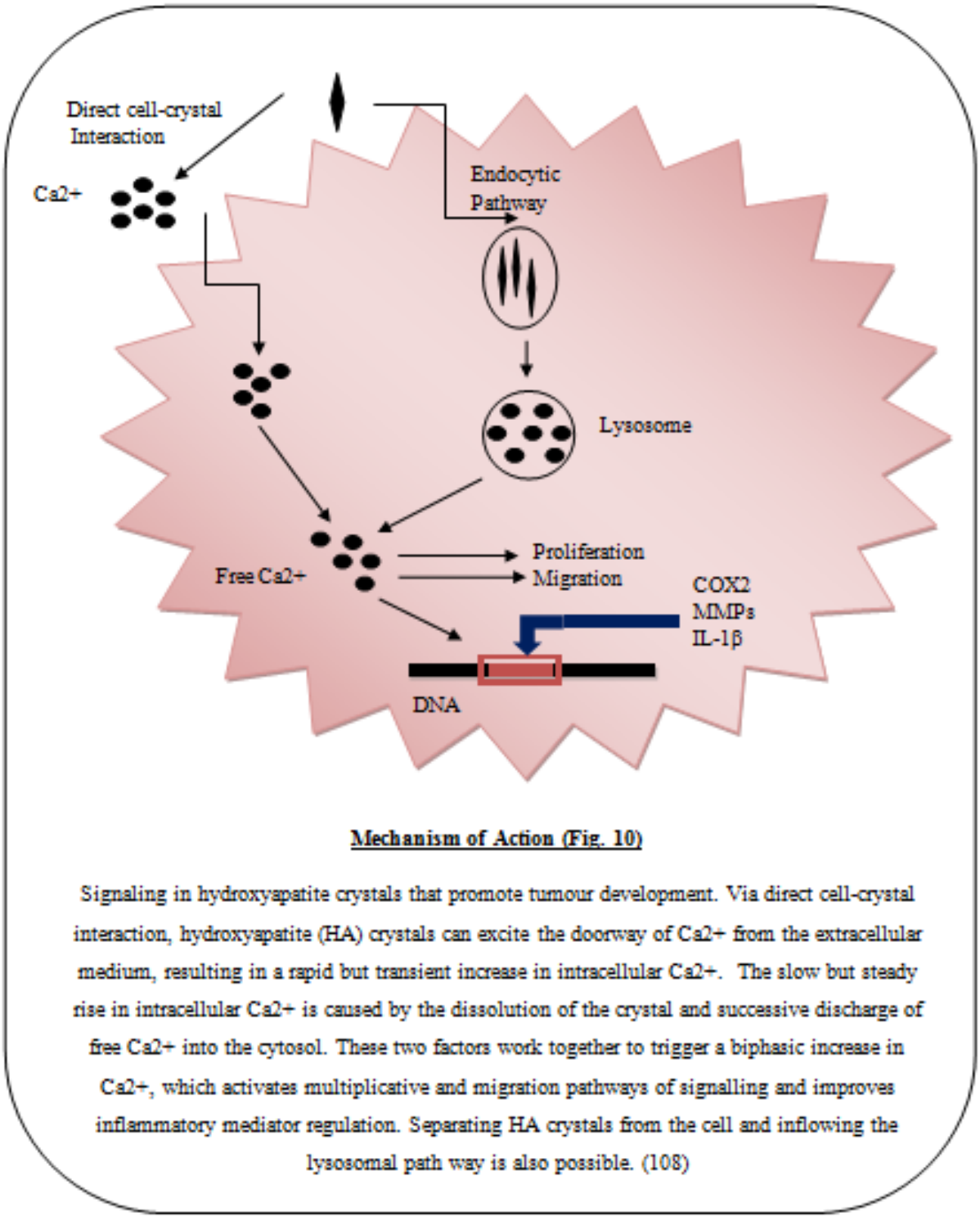
4.1. ABOUT BREAST CANCER

Breast cancer is a complex molecular disease and the most prevalent cancer in women in the U.S. and Western Europe worldwide, with every 8th or 9th woman affected during her lifetime. Although mortality is diminishing due to advancements in both diagnostic and clinical methods, breast cancer is now the second most common cause of cancer death in women.(98-101)Neoplastic cells vary from normal body cells, according to the oncology of breast cancer. Normal tissues of the body have minimal growth promotion and regulation which seeks to sustain the structure and functions of the body. However, cancer cells have extensive and chronic propagation without any external stimulation.(102,103)Continuous progress in our understanding of the molecular biology of breast cancer progression has helped us reveal innovative pathway-specific targeted therapeutics, and the advent of such beneficial therapeutics is currently driving the need for 'patient-tailored' molecular-based treatment strategy(104).Breast cancer mainly consists of three tumor subtypes classified according to the expression of the estrogen or progesterone receptor, the amplification of the ERBB2 gene and the triple-negative (tumors missing all 3 reviewed molecular markers).The three subtypes have distinct risk profiles and treatment planning. Optimal treatment for each condition depends on the tumor subtype, the anatomical level of cancer, and patient expectations (105).

4.2. Pathology of Breast cancer

Breast cancer metastasis is characterized by a multi-step cascade which can be subdivided across distinct phases.Removal of tumor cells from the primary tumor, presumably after an epithelial-mesenchymal (EMT) transition.Proliferation and intrusion of tumor cells into neighboring tissues. Transendothelial displacement of tumor cells to vessels (known as intravasation) approaching the blood as circulating tumor cells (CTCs).Survival of the CTC in the circulatory system.Arrest of CTCs at secondary sites and extravasation as dispersed tumor

cells (DTCs).The propagation of DTCs in distant tissues to facilitate colonization and proliferation of metastases.(106,107)



Mechanism of Action (Fig. 10)

Signaling in hydroxyapatite crystals that promote tumour development. Via direct cell-crystal interaction, hydroxyapatite (HA) crystals can excite the doorway of Ca2+ from the extracellular medium, resulting in a rapid but transient increase in intracellular Ca2+. The slow but steady rise in intracellular Ca2+ is caused by the dissolution of the crystal and successive discharge of free Ca2+ into the cytosol. These two factors work together to trigger a biphasic increase in Ca2+, which activates multiplicative and migration pathways of signalling and improves inflammatory mediator regulation. Separating HA crystals from the cell and inflowing the lysosomal path way is also possible. (108)

5. ANTI- BREAST CANCER ACTIVITY OF PYRAZOLE

In 2019, Ghada M.E. Ali et al. designed, tested, and synthesised a number of new pyrazole and pyrazolo[1,5-a]pyrimidine derivatives to see whether they could inhibit CDK2/cyclin A2 in vitro.The aim of the cytotoxicity test was to see how responsive and selective tumour and normal cells were to the targeted molecules. Using the MTT assay, all newly synthesised compounds were tested for anticancer activity against the human breast cancer cell line MCF-7.The composites A and B(Fig. 11) had the highest activity against the cancer cell line MCF-7 among the newly synthesised derivatives, with IC50 values of 14.12 M for 92 and 10.05 M for 93, according to the IC50 results shown in Table 2.Mohamed A. Abdelgawad (2017) prepared and synthesised a new sequence of substituted benzothiazole / benzoxazole and / or benzimidazole derivatives for their possible anti-cancer action against breast carcinoma MCF-7 in order to create new antiproliferative agents.The compound A'(Fig. 12) has an IC50 of 6.42.Among the synthesis series, 2-acetyl-4-[(3-(1Hbenzimidazol-2yl) phenyl] hydrazono-5-methyl-2,4-dihydropyrazol-3 has the highest efficacies against MCF-7 cells.(109)

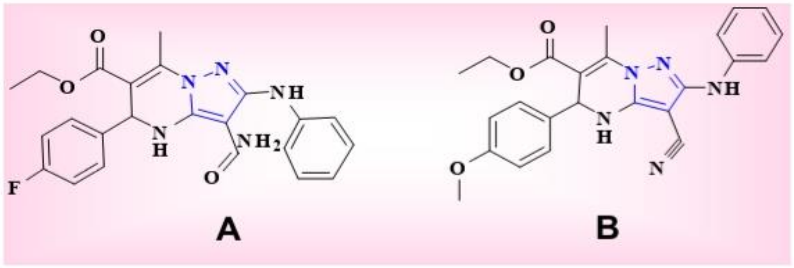


Figure11: Novel pyrazole and pyrazolo[1,5-a]pyrimidine derivative structures with anti-proliferative action.

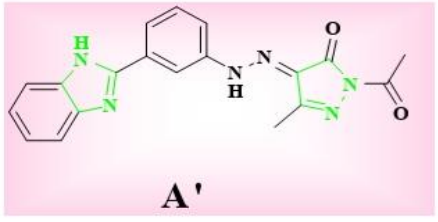


Figure 12: The highest anti-proliferative efficacy was seen in benzothiazole/benzoxazole and/or benzimidazole substituted pyrazole derivatives

COMPOUNDS	IC50(µM) value of MCF7
A	14.12
B	10.05
DOXORUBICIN	0.44

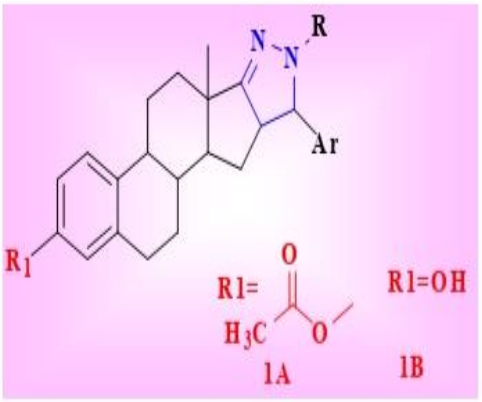
Table 2:In vitro cytotoxic activity of the newly synthesized compounds against MCF-7 tumor cell line

COMPOUNDS	IC50 ±SD(µM) MCF-7
A'	6.42 ± 1.34
DOXORUBICIN	2.11 ± 0.04

TABLE 3: IC50 values of the novel synthesized compound A' cell line MCF-7 using the MTT assay.

The structural modification of estrone, a powerful 17b-HSD1 inhibitor, resulted in the discovery of compounds with significant antiproliferative properties but no hormonal effects. Based on these findings, Amr et al. engineered and synthesised a series of novel pyrazolinyl-estran-17-one derivatives, which were then tested for anti-breast cancer activity in vitro and in vivo. The results of an in vitro cytotoxicity assay performed on the MCF-7 cell line revealed that all of the tested derivatives were cytotoxic at nanomolar levels. Compounds 1A & 1B(Fig 13), in particular, showed the most cytotoxic potential against MCF-7 cells, with IC50 values ranging from 43 to 56 nM, while compound 1B was the most potent candidate, with an IC50 of 43+/-0.58 nM. The derivatives had a significant impact on the development of the tumour volume in an in vivo analysis using a xenograft breast cancer animal model. After 12 days, treatment with the most potent compound 1A decreased the growth of tumour volume by around 87.0 percent.(110)

Figure 13: Novel pyrazolinyl-estran-17- one derivatives as potent anticancer agents.



The synthesis, molecular docking, and evaluation of novel bivalent pyrazolinyl-1,2,3-triazoles as potential VEGFR inhibitors and anticancer agents were identified by Abd-Rabou et al. Compounds displayed a modest wide spectrum of anti-cancer activity against MCF-7 and HepG2 cell lines in an in vitro evaluation of human hepatocellular carcinoma, colorectal cancer, and breast cancer (MCF-7) cell lines. Compound 3A had excellent anticancer activity against the MCF-7 breast cancer cell line (IC 50 = 32.26 mg/mL), which was equivalent to fluorouracil (IC 50 = 30.00 mg/mL), while compound 2 was the most effective candidate against the HepG2 cancer cell line (IC50 = 57.06 mg/mL), but it was less potent than the standard drug fluorouracil (IC50 = 33.5 mg/mL). The active site of the VEGFR-2 tyrosine kinase receptor was studied using molecular docking tests of compounds 2, 3A-B, (Fig 14) and 5-fluorouracil. The findings showed that compounds had higher affinity for the receptor site than 5-fluorouracil, with compound 2 emerging as the most promising candidate with a binding score (Delta G) of-10.8 kcal/mol.(111)

Figure 14: Novel bivalent pyrazolyl appended 1,2,3-triazoles as anticancer agents.

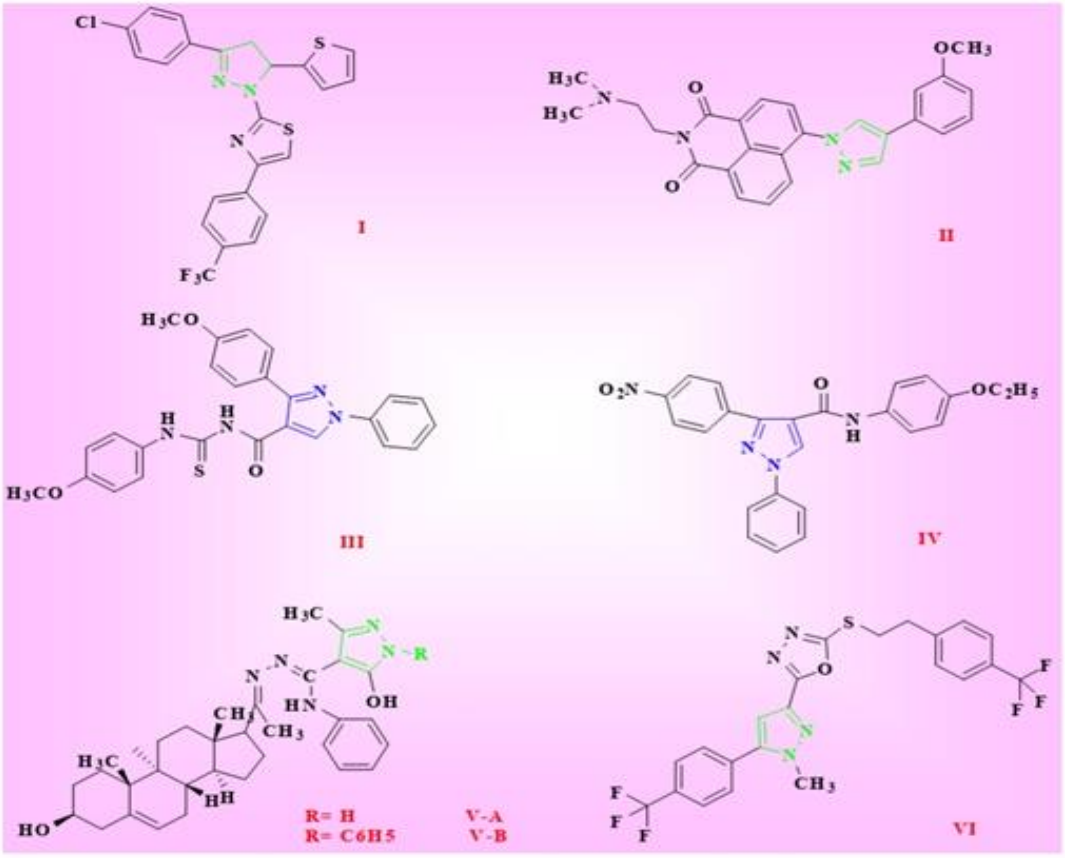
Zhang synthesised a series of novel 3-(1H-indole-3-yl)-1H-pyrazole-5-carbohydrazide derivatives and tested them for cytotoxicity using the MTT method against four human cancer cell lines: A549, HepG-2, BGC823, and BT474. When analysed using the flow cytometry process, one of the synthesised compound 19 was found to arrest the cell cycle at the S level (109). A library of S-substituted-1,3,4-oxadiazole nuclei carrying N-methyl-4-(trifluoromethyl) phenyl pyrazole moiety was designed using a combinatorial chemistry technique. When compared to Doxorubicin as a reference drug, the synthesised molecules were tested for in vitro cytotoxic activity using the MTT assay, and the results revealed compound 20 to be the most promising anticancer agent, with an IC50 value of 15.54 mM in MCF-7 cells . Mohareb et al. synthesised heterocyclic steroids, such as Pregnenolone pyrazoles, and investigated their cytotoxic profile against three human tumour cell lines: MCF-7 breast cancer, NCI-H460 nonsmall cell lung cancer, and CNS cancer (SF-268). The results were measured using the SRB assay. The study's findings revealed that some of the compounds studied, such as 33, had much stronger inhibitory effects on the three tumour cell lines than doxorubicin. (112)

Zhao et al. identified compound I as the most active anticancer agent with IC50 of 0.12 and 0.16 μM against WM266.4 and MCF-7 cell lines respectively. Li et

al. developed a new sequence of 4-pyrazolyl-1,8-naphthalimides and tested their antitumor activity in vitro. Compound II, with an IC50 value of 0.51 M against MCF-7 cells, outperformed the others in the sequence in terms of cytotoxicity. Sun et al. developed several derivatives of pyrazole coupled with a thiourea moiety and looked for inhibitory action against cyclin dependent kinase (CDK). Compound III was found to be the most effective CDK2 inhibitor, with an IC50 of 25 nM, and it also inhibited tumour cell proliferation in three cancer cell lines, namely H460, MCF-7, and A549, in the micromolar range of 0.75 to 4.21 M. (112) Li et al. created a new class of N,1,3-triphenyl-1H-pyrazole-4-carboxamide analogues and tested their anticancer activity as well as Aurora-A kinase binding ability.As per the results,it was found that, compound IV was the most active molecule against HCT116 and MCF-7 cell lines with IC50 values of 0.39 ± 0.06 μM and 0.46 ± 0.04 μM respectively. With an IC50 value of 0.16± 0.03 M, the compound outperformed the other molecules in terms of Aurora-A kinase inhibition. (113)

Pregnenolone was used as a prototype by Mohareb et al. to design and produce steroidal anticancer compounds.Pregnenolone thiosemicarbazone derivatives were synthesised first, and then heterocyclized into pyrazolyl semicarbazidoandrostane derivatives. The newly synthesised molecules were tested for antiproliferative activity against three human cancers: MCF-7 breast adenocarcinoma, NCIH460 non-small cell lung cancer, and CNS cancer (SF-268). Compounds V-A and V-B had significantly higher inhibitory effects against all three cancer cell lines than the gold standard, doxorubicin. (114)Puthiyapurayil et al. planned and developed a novel combinatorial library of S-substituted-1,3,4-oxadiazole carrying N-methyl-4-(trifluoromethyl)phenyl pyrazole moiety. The MTT assay was used to assess their cytotoxic potential in vitro. Compound VI, with an IC50 value of 15.54 M against MCF-7 cells, was found to have important anti-proliferative activity among the synthesized compounds.(115)(Fig. 15).

Fig. 15- Various Compounds showing activity against MCF-7 cell lines



6. Conclusion

Pyrazole is an N- heterocycle with five members that can be used in a variety of chemotherapeutic active agents. The discovery of biomolecules containing the heteroaromatic pyrazole has piqued interest. This study emphasised the importance of this portion in the discovery and advancement of potential drug candidates for a variety of diseases, particularly cancer. The first section of this study summarises the chemical methods for obtaining pyrazole derivatives and related products, as well as the biochemical experiments that have been conducted on them. Under view of, this research project we note that modern evidence on pyrazole and its metabolites, as well as hybrid pyrazoles, has been conducted to better elucidate the rationale of action of this family of substances. Implementations of this group in different clinical strains have shown positive potential, especially in the human breast cancer cells {MCF-7}. Since findings in this area are growing, treatment strategies involving members of this heterocycle family may be detected in the nearish term.

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