Review Article

Chemotherapy of breast cancer by heterocyclic compounds

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ABSTRACT

Heterocyclic compounds are generally scattered in nature and occupy a prominent location in medicinal chemistry as pharmaceuticals and drug intermediates. They play a widespread role in the metabolism of living cells, and clinically used to treat diverse sicknesses. The healing significance of heterocyclics has created a much interest in the synthesis of latest heterocyclic machine instructions to look at the sulphur and nitrogen condensed biodynamic. Reviews of the pharmacological pastime of 1,2,4-triazole derivatives are presented. a few bi-heterocyclic compounds incorporating a 1,3,4-thiazole and 1,2,four-triazole ring are presented as antimicrobial dealers.1,2,4-triazole derivatives template is a privileged fragment in cutting-edge medicinal chemistry thinking about its wide pharmacological spectrum and liking for various bio-targets. It is among the usually occurring heterocyclic nuclei in many marine in addition to herbal plant merchandise possessing a wide variety of biological packages.

Keywords: Heterocyclic compounds; breast cancer; chemotherapy; apoptosis; triazole.

INTRODUCTION

Cancer is the second leading reason of loss of life in the human being after cardiovascular diseases. These days, hundreds of thousands of cancer patient's stretch their life due to early identity and respective treatment[1]. Most of cells are specialized and they've a particular form and feature that suits them to the function they play within the body. Normal cells are growing beneath controlled mechanisms, contact inhibition, in one organized layer and differentiated cells. The basic difference between most cancers cells and regular cells are uncontrolled cell proliferation, decreased cell differentiation, capacity to invade surrounding tissue, and capacity to establish new increase at ectopic sites[2]. Regular cells can input the cell cycle for approximately 50 times and then die, whilst most cancers cellular can enter the cycle repeatedly. The nuclei of most cancers cells are enlarged and have a peculiar quantity of chromosomes within the frame. Cancer cells divide to form an abnormal mass of cellular called tumors, which invades and destroys the neighboring tissues. There are two kinds of tumor; benign tumor that is a disorganized encapsulated mass but does not invade adjacent tissue. The second type is malignant tumor, which encompass an odd out of control cell proliferation with partial or frequently complete loss of organization. Often in the developed disease stages, malignant tumors invade surrounding tissues[3]. Cancer is a complex genetic ailment caused ordinarily by environmental factors. The cancer-inflicting agents (carcinogens) can be found in meals, water, air, chemicals, and in sunlight that human beings are exposed to[4].Any chemical that generate an alternate within the DNA series is called a mutagen which they are also carcinogens. Most cancers result from mutation in a single normal cell. However, mutation also can rise up from mistakes made through DNA polymerase during DNA replications[5]. Bishop et. al. (1987) stated that cancer happens in different forms, in different tissues and organs, and frequently develops in different forms even in a single tissue[6]. The primary stage inside the improvement of most cancers is the transformation of ordinary cell to cellular that differentiates abnormally through cell division[6]. The second level is the metastasize of most cancers cells to the alternative organs of frame, making it tough to cope with one cell because it starts to develop someplace else inside the body[7]. Kundsonet. et. al. (2010) studied cell growth and controlled division by biochemical pathways using signals from inside and outside the cell[8]. Disrupted manipulate may be caused by genetic alterations of growth controlling genes, viral infection, expanded stimulation growth factors, or a combination of these elements[8].

Cell division cycle

Cell division takes place by an elaborate series of events, whereby chromosomes and different components are duplicated and evenly allotted into two daughter cells. It's exceptionally ordered and tightly regulated procedure that causes irreversible and unidirectional modifications in the cell state. It is been identified that unicellular organisms like yeast exist inside, the cell cycle continuously growing and dividing under appropriate environmental conditions. Although the identical takes place with some cancer cells, most cells in multi cellular organisms aren't cycling. Significant fractions of these cells, inclusive that who have already differentiated, are not (generally) able to proliferation[8]. Cells could be

divided into four predominant phases. S phase, DNA synthesis period, is separated from mitosis by an interval of several hours, called G2. Similarly, the period between the end of mitosis and the beginning of S is called G1. The eukaryotic cell cycle may be divided into fundamental levels: Inter-phase, comprising gap 1 (G1), synthesis (S) segment and gap 2 (G2), and M section, composed of primary events, nuclear division (Mitosis) and cytoplasmic occasions as shown in Figure 1[9].

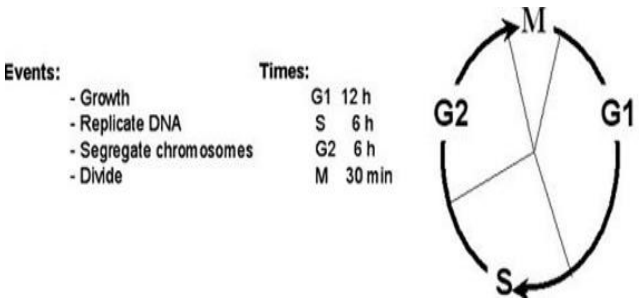


Figure 1: Organization of the cell cycle.

Apoptosis

Apoptosis is a term coined by Kerr, Wyllie and Currie in 1972[10], characterized using an ordered series of physical and biochemical reactions that are managed by means of sort of genes such P53 and Bcl-2[10].Remarkably cell dehydration is an early event for apoptosis, resulting in cytoplasmic condensation and changes in cellshape and size, that's accompanied by condensation of nuclear chromatin. Nuclear fragmentation then takes place and DNA droplets of different sizes allotted evenly throughout the cytoplasm. The nuclear fragments and other intracellular components like mitochondria are then packed and enveloped through the cell membrane and those resultants, (called apoptotic bodies), are shed from the apoptotic cell (Figure2). Aoptotic cells are phagocytized by macrophages[11].

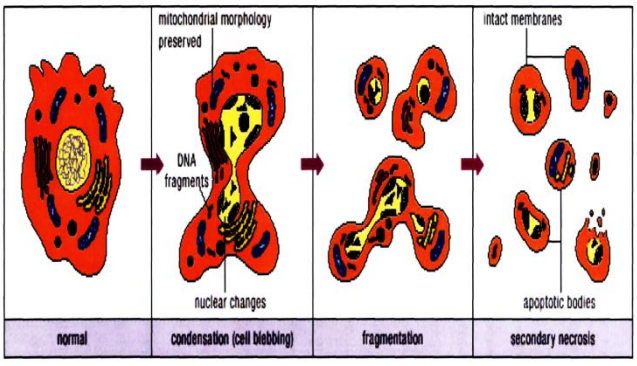


Figure 2: cellular change during apoptosis[11].

Molecular Mechanism of Apoptosis

Death-Receptor Pathway and Mitochondrial Pathway

There are two predominant cell-intrinsic pathways for inducing apoptosis, one which begins with the ligation of cellular floor demise receptors (demise-receptor pathway), and another, which involves the mitochondrial release of cytochrome C (mitochondrial pathway).The death-receptor pathway is triggered by participants of death-receptor subfamily (such as CD95)[12].Binding of CD95 induces receptor-clustering formation of a death inducing signaling complex. This complex recruits through the adaptor molecule FADD (Fas-associated death domain protein), multiple procaspase-8 molecules and results in caspase-8 activation. Some other pathway, the mitochondrial pathway is prompted significantly in response to extracellular cues and internal insults[12]. Those various response pathways converge on mitochondria, frequently thru the activation of a seasoned-apoptotic member of the Bcl-2 family such as Bax and Bid. Pro- and anti-apoptotic Bcl-2 family's members meet at the mitochondria surface, in which they compete to alter cytochrome C exit via a mechanism which it is nevertheless debated. If the pro-apoptotic camp wins, an array of molecules is released from the mitochondrial compartment. Some of the launched molecules, cytochrome C, are associated with Apaf-1 and then procaspase-9 to form the apoptosome which prompt apoptosis[13].

Crucial regulated proteins

Caspase apoptosis is a regulated physiological system leading to cell death (figure 3). Caspases, a family of cysteine acid proteases, are the vital regulators of apoptosis. Initiator caspases (including 9, 9, 10 and 12) are closely coupled to pro-apoptotic signals. Once activated, these caspases cleave and activate downstream effectors (together with 3,6 and 7), which cleave cyto skeletal and nuclear proteins. Cytochrome C launched from mitochondria is coupled to the activation of caspases-9, a key initiator[14]. Apart from caspases, members of the Bcl-2 family of proteins are important regulators of programmed cell dying pathways with members individuals that can suppress (e.g. Bcl-2, Bcl-XL). Bcl-XL exists as a 26 KDa integral membrane protein. It blocks apoptosis and thereby can also make contributions to tumor genesis by prolonging cell survival in place of by accelerating the charge of cell proliferation. Down-law of Bcl-2 can be focal step at some stages in the induction of apoptosis. Just like Bcl-2, over expression of Bcl-XL which can be induced by diverse circumstance and agents also inhibits apoptosis[15].

Tumor cell line

Baltimore laboratory had discovered the first human cell line in over 50 years ago by George Gey. This cell line become HeLa named after Henrietta Lacks, the female from whom the cellular line turned into derived, who had cervical carcinoma. Gey's vision tiled the way of cellular life way as we realize it nowadays, permitting its extensive development into a critical experimental tool in most cancers researches. One of the major reimbursements of the cultured cell lines usage in most cancers studies is that they provide an endless supply of a rather homogeneous cellular population that is capable of self-replication in standard cell culture medium[16].

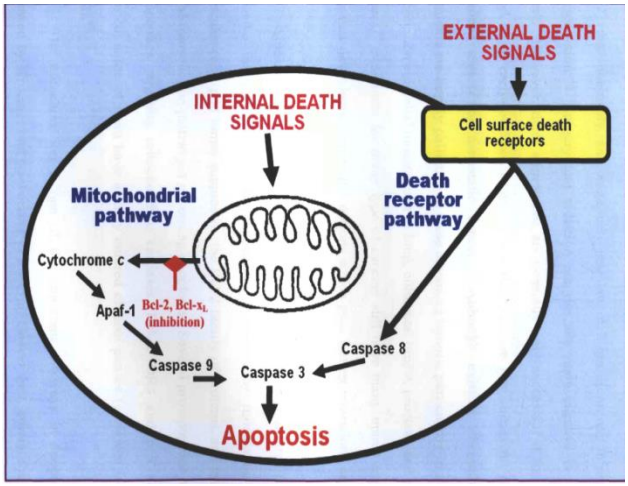


Figure 3: schematic diagram of two apoptotic pathways of caspase activation.

A number of factors Influencing Drug Responses in Tumor cell strains, like the solubility, chemical or metabolic balance, protein binding, and cell uptake, can restrict drug-induced inhibition of cell growth. Understanding of the relationship among such elements and drug structure assist in the prediction of activity of new analogues in a sequence[17].

Breast cancer

Breast cancer is one of the most commonplace and serious malignancies worldwide. Despite intensive cancer manage efforts; it stays the second leading reason of most cancers death among women[18]. MCF-7 is the acronym of Michigan most cancers foundation -7, relating to the institute in Detroit wherein the cell line was established in 1973 by Herbert Soule and co-people[19].MCF7 is a kind of most cancers originating from breast tissue, most normally from the internal lining of milk ducts or the lobules that deliver the ducts with the milk. Cancers originating from ducts are referred to as ductal carcinomas, even as those originating from lobules are known as lobular carcinomas. Breast cancer happens in humans and different mammals, at the same time as the overpowering majority of human cases arise in ladies, male breast cancers may also occur[20]. MCF-7 cells are useful in vitro breast cancer research due to the fact the cell line has retained several perfect characteristics particular to the mammary epithelium. Those encompass MCF-7 cells ability inprocessing of estrogen in estradiol form, via estrogen receptors within the cell cytoplasm. This makes the MCF-7 cellular line an estrogen receptor (ER) positive manipulate cell line[21].

Chemotherapy

Chemotherapy may be defined as the use of chemical agents in the treatment of diseases. Chemical compounds, that employed are stated to be chemotherapeutic agents. The most essential feature of suitable chemotherapeutic agents must show a excessive degree of toxicity selectivity towards a microorganism, in order that, it can be given in sufficient doses to inhibit or kill the microorganism in the course of the frame without harming the body cells. The tumor cells fighting to chemotherapeutic agent is first-rate problem in the clinical handling of cancer; so a wide array of selective and potent compounds is required to fit the growth problems related to cancer[22].Anticancer agents are can be classified into several broad groups, which are, commonly, defined according to their different mechanisms of action scheme as seen figure 4. Most chemotherapeutic agents have the potential to induce, either directly or indirectly, the potential lethal damages to tumor cells[23].These agents are classified into:-

(1) Alkylating agents and related compounds such as: Cisplatin, chlorambucil.

(2) Anti metabolites such as: methotrexate and nucleoside analogues.

(3) Anti-tumor antibiotics ((purine & pyrimidine base which are blind block of DNA, so, they prevent there substance of bowing in corporation DNA during sphere (of cell got) stopping normal development and dividing.

(4) Topoisomerase inhibitors.

(5) Mitotic inhibitors.

(6) Corticosteroids.

(7) Miscellaneous chemotherapy drugs.

(8) Other types of cancer drugs

Heterocyclic compounds

A heterocyclic compound is one which contains a ring generated from more than one kind of atom, whilst the hoop of cyclic compound is made up only of carbon atoms such compounds are called homo-cyclic compounds. Basically the molecule is an organic heterocyclic compound when there is one ring of carbon atom as minimum. All the ring atoms which are not carbon are known as hetero atoms. Nitrogen, oxygen and sulfur are taken into consideration the most hetero atoms recognized. Many heterocyclic compounds are terrific biological importance, and numerous are of significance in environmental engineering and science[25, 26]. In precept, all elements except the alkali metals can act as hetero atoms ring. Along with the type of ring atoms, their total number is important since this indicates the ring size. However, the smallest possible ring is three-membered and the most essential rings are the five- and six membered heterocyclic[27]. Organic compounds containing 5 membered heterocyclic ring like; triazole, thiadiazole and thiazolidinone have occupied unique area in the medicinal chemistry field because of their numerous biological activities such as antifungal, antimicrobial, anti inflammatory, cytotoxicity, antioxidant, antihistaminic, anti tuberculor, anticonvulsant[28-34].

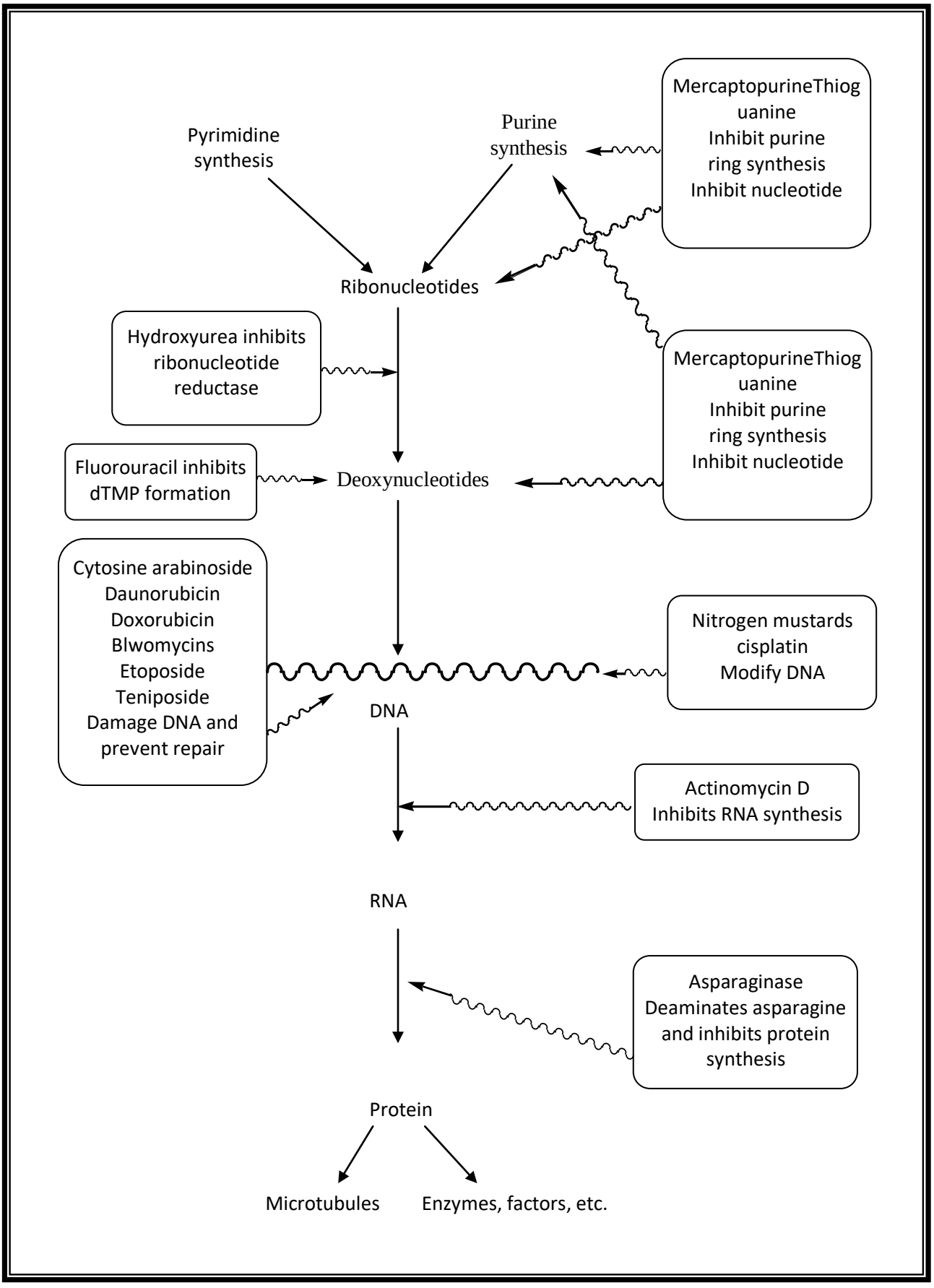
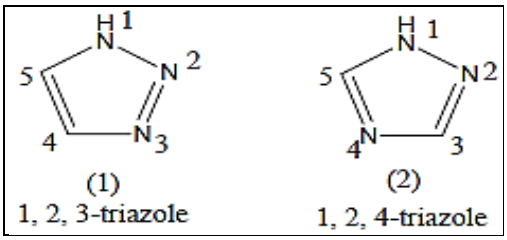


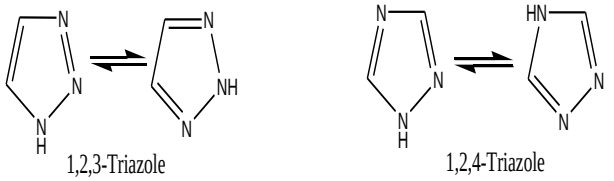
Figure 4: Sites of action of selected drugs used in the treatment of cancer [24]

Triazole

Triazole is five membered heterocyclic compound containing three nitrogen and carbon atoms. There are two form of triazole, and each has one pyrrole like nitrogen and two of pyridine like nitrogen. The call triazole turned into first given to the carbon nitrogen ring system $C_2N_3H_3$ with the byBladin who indentified its derivatives in early 1885, despite the fact that the structure stated slightly incorrect[35]. Both types of triazole have the possibility of tautomerism in 1, 2, -triazolewhich basically thesetautomers are identical[36].

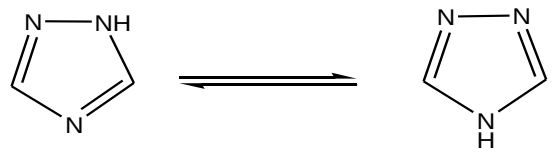


1, 2, 4-triazole nucleus stability is an inherent property of its aromatic nature. An aromatic sextet is formed via giving of one π electron from every atom joined via double bonds and the last two electrons from a nitrogen atom. Any such system is stabilized by resonance and even though the triazole nucleus may be represented through tautomeric forms. Different isomers are characterized based on the placement of the nascent hydrogen. Hence 1,2,4-triazoles are exist in two structures i.e. *1H* and *4H*[37].

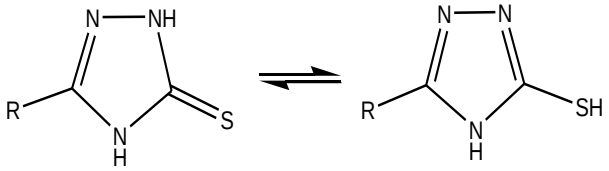


1,2,4triazol ligand has been prepared, and 1, 2, 4-Triazoles exhibit two tautomeric forms particularly [*4H*]-1,2,4-triazoles and [*1H*]-1,2, 4-triazoles .

Among of the substituted 1, 2, 4-triazoles, 3-mercapto-1,2,4-triazoles exist in two tautomeric forms due to the hydrogen labile that might be attached either to the nitrogen or the sulfur atom.



It exhibits thione-thiol tautomeric forms shown below. This compound exists predominantly in thione form[38].



Out of its viable isomers of triazole , 1, 2, 4- triazole is (wonder nucleus) which posses nearly all biological activities types.1, 2, 4- triazole has drawn great concentration to medicinal chemists from two decade due to its wide activities variety, low toxicity and appropriate Pharmacokinetic and Pharmacodynamics profiles[39]. Literature survey reveals that 1, 2, 4-triazole derivatives exhibit extensive variety of biological activities along with Antibacterial, Antifungal, Antitumor, anti-inflammatory, Anti-tubercular, Anti-depressant, Anti-mycobacterial, Anti-malarial, Antiviral[40-48], Antioxidant[35].Several compounds containing 1,2, 4-triazole jewelry are well known as drugs as in Figure 5.For example, fluconazole is used as an antimicrobial drug, and in other hand, vorozole, letrozole and anastrozole are non-steroidal drugs used for the treatment of most cancers and loreclezole is used as an anticonvulsant[49,50].

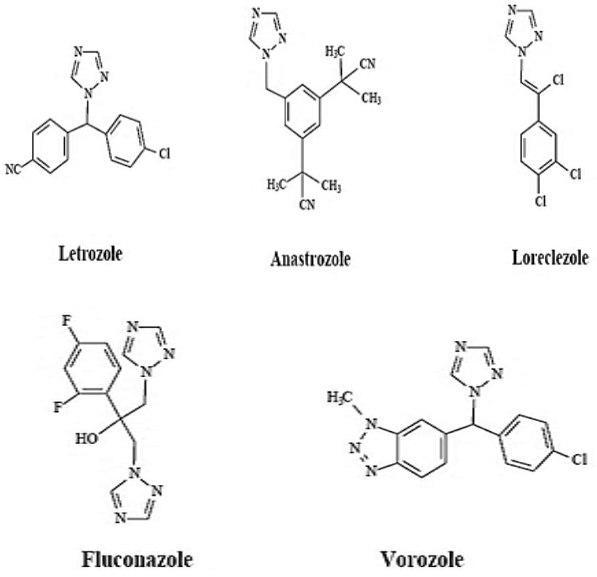
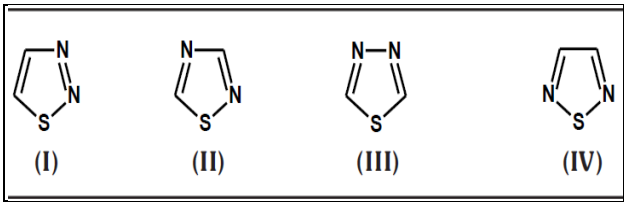


Figure 5: drugs containing 1,2,4-triazole rings

Thiadiazole

Thiadiazole is five-membered ring composed of nitrogen atoms and one sulfur atom. Consistent with their positions, thiadiazole system are categorized as 1,2,3-thiadiazoles (I) ,1,2,4-thiadiazoles (II),1, 3, 4-thiadiazoles (III)and 1,2,5-thiadiazoles(IV).



Thiadiazole moiety acts as “hydrogen binding domain” and “two-electron donor system”. It additionally acts as a limited pharmacophore[51]. In current years 1, 3,4-thiadiazole derivatives had significant attention and have been increasingly more investigated because of diverse range of biological properties. They demonstrate as antimicrobial, anti-mycobacterial,

anticancer, anti inflammatory, carbonic anhydrase inhibiting effect, antianxiety, antidepressant, antioxidant properties[52-58]. These biological activities likely because of the presence of the –N=C-S moiety that acts as two-electron donor system[59].

CONCLUSION

1, 2, four- triazole and 1, 3, 4-thiadiazole compounds have highly effective in cell line of most breast cancers (MCF-7). Most chemotherapeutic agents have the ability to result in, both directly and indirectly, potential fatal damages to tumor cells. 1, 2, four- triazole have drawn huge interest in medicinal chemists from two decades because of its wide sort of activities, low toxicity and good Pharmacokinetic and Pharmacodynamics profiles. 1, 3, 4-thiadiazole derivatives have obtained valued interest and had been increasingly more investigated because of their various ranges of biological activities.

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