

Review Article

Triazoles Synthesis & Applications as Nonsteroidal Aromatase Inhibitors for Hormone-Dependent Breast Cancer Treatment

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In the last few years, nonsteroidal aromatase inhibitors (AIs) have been emerged as promising agents for treating hormone-dependent breast cancer in postmenopausal women because of their inhibitory effect on estrogen synthesis. Indeed, these compounds can block the activity of aromatase, the enzyme that intervenes in the last steps of estrogen production pathway. Triazoles are the core structures of nonsteroidal AIs. The nitrogen atom of the triazole moiety plays a fundamental role in the aromatase functionality by interacting with the iron ions of the heme group. In general, AIs possess numerous advantages as they quench the last step of estrogen synthesis without any inhibitory effects on the production of other steroids produced via the same pathway. Some AIs as anastrozole, letrozole, and vorozole have already been approved by the Food and Drug Administration in the treatment of breast cancer. The previously mentioned compounds present severe and adverse effects as polycystic ovary syndrome (PCOS), resistance onset on long-term treatments, and a higher risk of bone fractures. This review focuses intensively on the role of AIs in the treatment of hormone-sensitive types of cancers, especially the role of triazoles as nonsteroidal AIs. Also, the review provides an overview about the chemistry of triazoles along with the different methods by which the *v*-triazoles and *s*-triazoles are synthesized.

1. Introduction

Cancer can be viewed as a collection of related diseases which are resulted from the uncontrolled division/abnormal growth of some cells of the body. Eventually, such cells will start to migrate to the other surrounding tissues causing the spreading to other parts of the body. Human cells usually develop ordinarily and divide to produce new cells as per the body needs. When cells are disrupted or grown old, they die, and new cells will be produced to take the place and function of the old ones. At the point when cancer is being developed, these vital processes break down. As a result, the cells start acting abnormally, such as harmed or old cells are still alive and survive when they are supposed to die, hence new cells are being produced without a need. These extra cells shall continuously multiply to give the growth of what is known as

tumor masses. If such masses are solid, then they are referred as tissue masses. Leukemias, cancer of the blood cells, for instance, do not produce solid masses. Tumor masses are malignant, that means they can migrate and spread into the closed tissues. Also, as these masses develop, some cancer cells may break up and migrate to other distant places in the body through the lymph system or the bloodstream to produce new tumor masses far from the first originated ones [1–3].

Breast cancer is one of the most famous leading causes of mortality in women from different age groups around the world. It is an emerging malignance. It becomes in the second position for death after the lung cancer among women. In 2021, 6.27.00 million deaths because of breast cancer were recorded by the World Health Organization (WHO). The incidence of the universal burden of breast

cancer is upgrading at a warning rate. Breast cancer affected approximately 2.5 million women annually [4] and is originated from estrogen in vast majority of postmenopausal women. About 80% of patients have hormone-responsive breast cancer [5]. The breast cancer risk is high in postmenopausal women owing to the estrogen production in the peripheral tissues, while in premenopausal women, ovaries are mainly responsible for estrogen production. In breast cancer patients, with positive estrogen receptors, estrogen plays an essential role in promoting the neoplastic breast epithelial cell growth through signaling estrogen receptor-mediated pathways. And hence, high estrogen level has been noted to increase the risk of recurrence and metastasis in the breast cancer patients with hormone-dependent types. Estrogens (estradiol and estrone) are biosynthesized from androgens (androstenedione and testosterone) by demethylation and aromatization, which are catalyzed by the rate-limiting enzyme aromatase (CYP19) [6]. Aromatase is a member of the P450 family of the monooxygenase heme proteins. It is a microsomal enzyme complex composed of two main units: one is the hemoprotein CYP19 (family of cytochrome P450), and the other is flavoprotein (NADPH) nicotinamide adenine dinucleotide phosphate-cytochrome P450 reductase. There are two fundamental strategies to block, manage, and control the progression of the hormone-dependent types of breast cancer either through binding of the estrogen receptors with receptor antagonists (ERAs like tamoxifen) or by inhibiting the estrogen production using aromatase inhibitors (AIs) [6, 7]. The AIs were found to have less side effects than the estrogen receptors antagonists because of the lack of the estrogenic effect on vasculature and uterus. Aromatase inhibitors can be categorized into two main groups according to their mechanisms of action. Type 1 is the steroid AI such as exemestane and formestane (Figure 1), which irreversibly inhibit the aromatase enzyme activity. The second type is the nonsteroidal AIs, which inhibit the aromatase activity and their inhibition effects are reversible—letrozole, vorozole and anastrozole belong to this type [8, 9]. Compared with selective estrogen receptor modulators for postmenopausal women with positive estrogen receptors treated with Tamoxifen, Arimidex alone or combined (ATAC) trials, the AIs exhibited significant results in the treatment of breast cancer. [10, 11] In spite of the fact that all available AIs either steroid or nonsteroidal types exhibited acceptable clinical effects, the long-term usage of them can lead to acquired drug resistance and considerable side effects including osteoporosis, cardiovascular disease, broken bones, and musculoskeletal and joint pain. Consequently, the investigation of novel AIs is still essential to provide alternative drugs with more favorable characters.

Triazoles are the core structure often found in the nonsteroidal AIs. Among the AIs that contain the triazole moieties are anastrozole, letrozole, and vorozole (Figure 1). Such inhibitors are approved by the “FDA” for endocrine treatment of early and advanced stages of breast cancers in postmenopausal women [12] in addition to their clinical success in the treatment of different disorders like uterine leiomyomas, endometrial cancer, endometriosis, and gynecomastia in men [13–16]. The nitrogen atom of the

triazole moiety is playing a fundamental role by interacting with the iron of the heme of the aromatase.

For instance, anastrozole is a nonsteroidal AI, in which when a heme iron is bound noncovalently to the benzyl triazole, aromatase activity is eventually stopped. Owing to this reversible interaction, anastrozole must be constantly present to inhibit the aromatase enzyme activity. Anastrozole reduces the E1S, E2, and E1 both in the mammary and periphery tissue. Anastrozole is highly selective and does not affect the biosynthesis of the androgenic precursors. In addition, anastrozole does not change the aldosterone or cortisol secretion after stimulation with adrenocorticotropic or at the baseline hormone [17, 18]. Figure 2 illustrates the mechanism of action of anastrozole.

2. Recent Investigations in the Utility of Triazoles as Nonsteroidal Aromatase Inhibitors

Despite the fact that nonsteroidal AIs are clinically successful, they have a number of disadvantages; that is they cause reproductive problems, osteoporosis, androgenic side effects, and joints pain. In addition, these molecules partially inhibit the cytochromes 2D6, 2C8/9, 1A1, 1A2, and 3A4 that are essential in the metabolism of xenobiotic which raise the drug-drug interaction. Consequently, there is a necessary to investigate structurally novel, selective, and potent AIs. Recently, the pharmacological significance of triazoles as nonsteroidal AIs has been explored by many medicinal and biochemical researchers.

Chanamon Chamduang et al., [19] have synthesized a set of novel 13 triazole-tetrahydroisoquinoline derivatives using the Pictet-Spengler and CuAAC reaction steps. Then their aromatase inhibition activity and molecular docking were investigated. The results revealed that seven of them exhibited a significant aromatase inhibition activity ($IC_{50} = 0.07\text{--}1.9 \mu\text{M}$) comparing with ketoconazole. The triazole 2i revealed the highest inhibition activity ($IC_{50} = 0.07 \mu\text{M}$) with no effect on the normal cells. An in silico study suggested that the formation of hydrogen bonding between the methoxy group of 2i and the Thr310 residue of the aromatase enzyme may be essential for its highly potential inhibition activity (Figure 3).

The molecular docking findings of this study demonstrated that the newly investigated 1,2,3-triazole-based molecules 2a-m could bind to the aromatase enzyme active sites competitively (Figure 4).

Meanwhile, the 2D ligand protein interaction diagram (Figure 5) revealed that these compounds can interact with the target aromatase enzyme *via* different interaction types, except for the direct interaction through noncovalent binding to the heme iron of the aromatase enzyme.

Alessandra Ammazzalorso et al. [20] have synthesized a group of imidazole and triazole-based molecules and tested their human aromatase inhibition efficacy in an *in vitro* fluorescence enzymatic assay. Many derivatives exhibited excellent enzymatic inhibition activity comparing with the standard drug letrozole. Compounds with

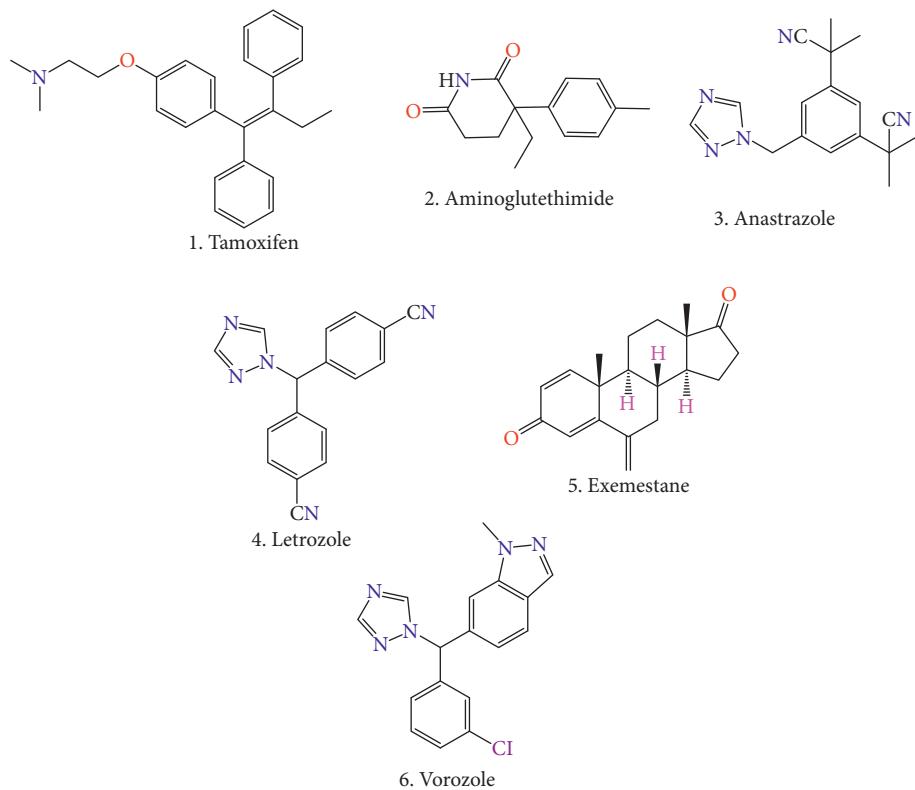
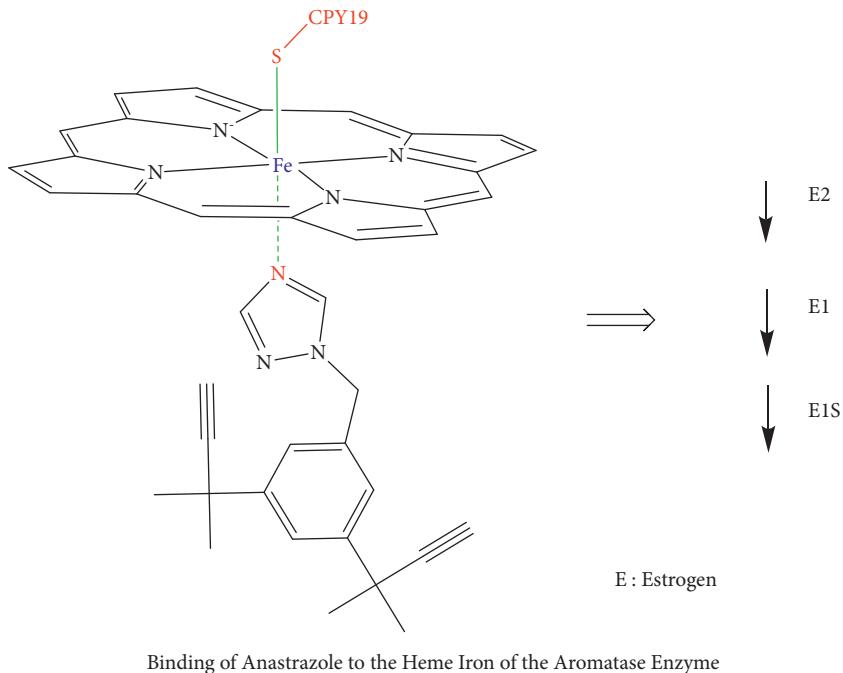


FIGURE 1: Chemical structure of the commonly used drugs for the treatment of hormone-dependent breast cancer.



Binding of Anastrozole to the Heme Iron of the Aromatase Enzyme

FIGURE 2: Mechanism of action of anastrozole.

high inhibition potency were evaluated in vitro on MCF-7 breast cancer cells by MTT assay, cell cycle analysis, and cytotoxicity assay. Also, docking studies were performed on the most promising molecules to focus the light

on the binding mode on the active sites of the human aromatase enzyme. The results of the study demonstrated the role of the newly synthesized triazole molecules as potent AIs.

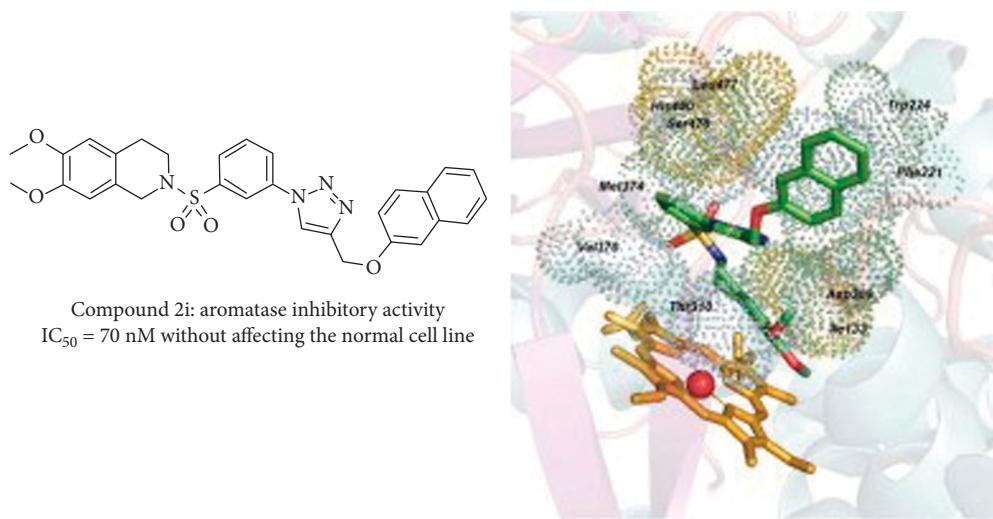


FIGURE 3: Aromatase inhibition activity of compound 2i, compound 2i binded to the active site of the aromatase enzyme. Copyright 2019. Reproduced with permission from Elsevier.

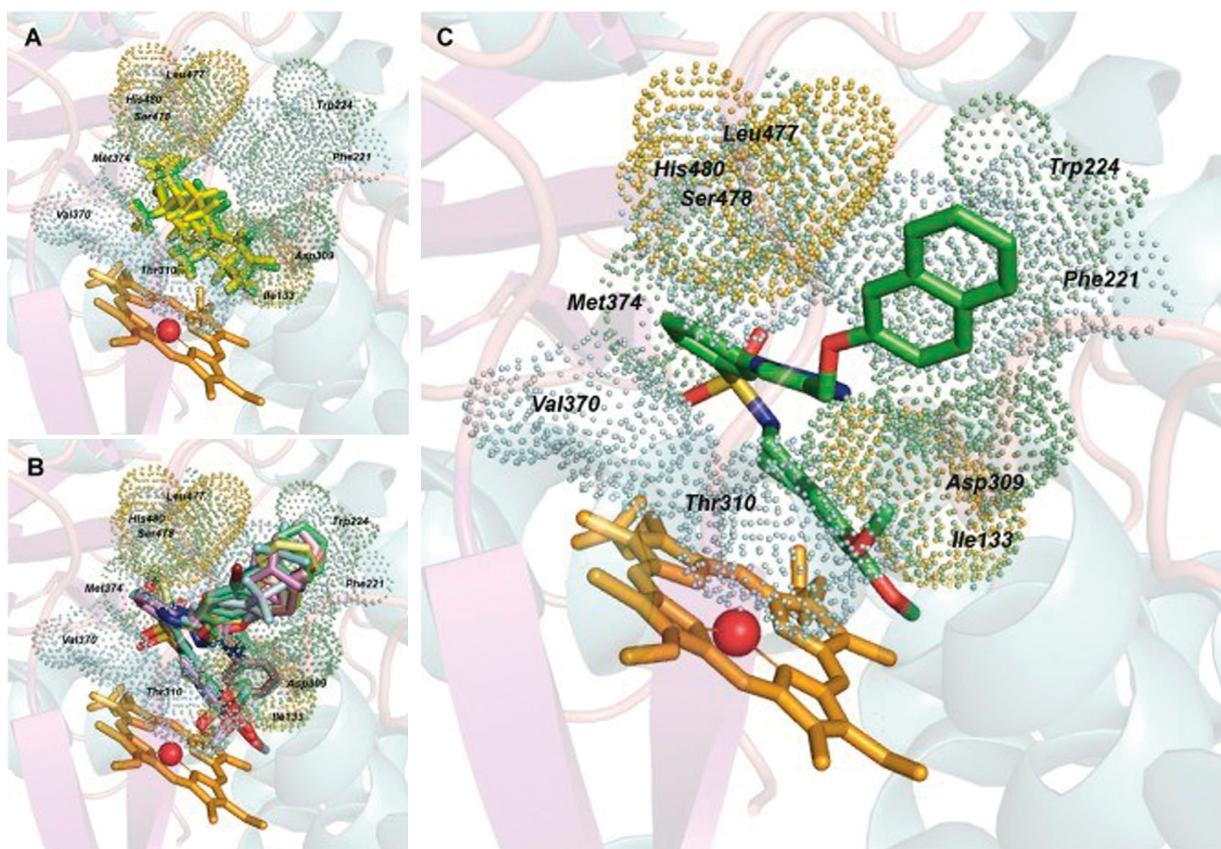


FIGURE 4: Representation of possible binding modalities of the newly investigated triazole molecules; heme and iron atoms of the active site of the aromatase enzyme are given in orange and red, respectively, the key protein residues shown as colored dotted. (a) Represents the docking of the natural substrate ASD providing $\text{RMSD} = 0.705 \text{ \AA}$. (b) Represents the newly investigated triazole molecules docked with the active site of aromatase enzyme. (c) Represents 2i occupied the active site of the aromatase enzyme. Copyright 2019. Reproduced with permission from Elsevier.

In addition, many natural products and their analogs that are not available through synthetic chemistry techniques were reported as lead nonsteroidal AIs. Natural

products such as chalcones, cinnamates, isoflavones, flavones/flavanones, and stilbenes have been demonstrated to be among the naturally occurring nonsteroidal AIs. [21–25].

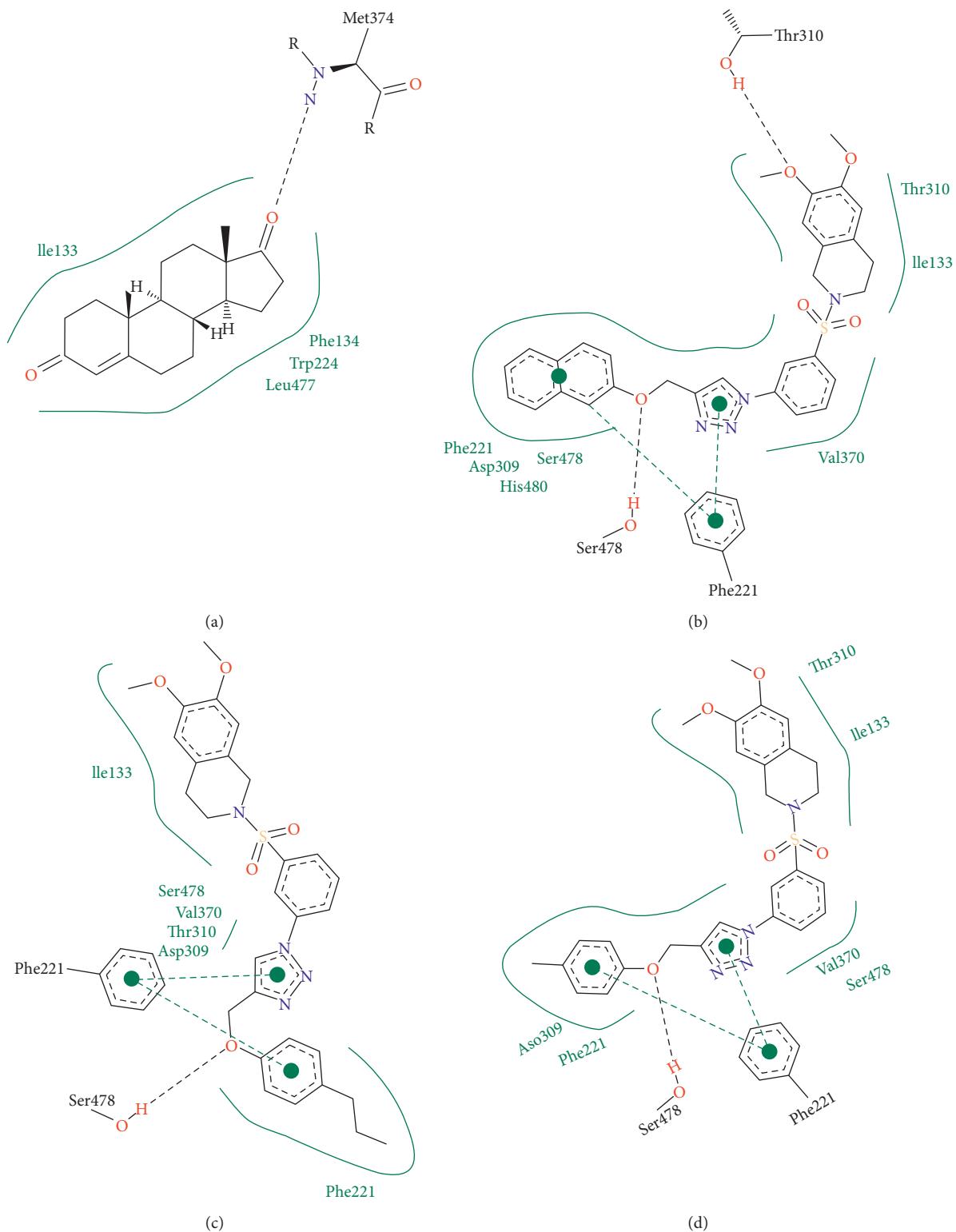


FIGURE 5: The 2D ligand protein interaction diagram. (a) Represents the 2D ligand-protein interactions of natural substrate ASD*, (b) represents compound 2i, (c) represents compound 2d, and (d) represents compound 2b. Copyright 2019. Reproduced with permission from Elsevier.

In the study by James McNulty et al. [26], a series of new class of natural product inspired cinnamyl-incorporated 1,4,5-triazole was prepared and their potencies to inhibit the

human aromatase enzyme (CYP 450 19A1) were described. The main aspect of the optimization in this study was the incorporation of aryl bromide residue at the site

corresponding to the keto groups of the androstenedione. The utility of aryl bromides as ketone bioisosteres resulted in raising the aromatase inhibition activity to 20 nM. [23, 27–33].

James McNulty et al. [27] also published another strategy for the synthesis of a novel class of 1,2,3-triazoles through a synthetic technique involving aldol reaction of benzaldehyde with methyl phenylacetate. Several triazole molecules derived from both the syn- and anti-adducts were reported to be selective potent aromatase enzyme inhibitors. The results of this study revealed that the anti-triazole acetate I and syn-triazole alcohol II) exhibited selective aromatase inhibitory activity with potency as low as 50 nM (Figure 6).

Kang et al. [34] have synthesized a series of 2-phenyl indole scaffold substituted with azole moiety at position 3. The study revealed that compound III with triazole ring system exhibited the promising aromatase inhibition activity with IC_{50} value of 0.0141 μ M comparing with the standard drug letrozole which exhibited with IC_{50} value of 0.0495 μ M (Figures 7, 8).

Pingaew et al. [35] have synthesized a novel class of 1,4-disubstituted-1,2,3-triazole incorporating sulfonamide conjugates and evaluated their aromatase inhibition efficacy (Figure 9). The study findings revealed that the meta triazole benzene-sulfonamide derivative IV having 7-coumarinyl and 6,7-dimethoxy groups on triazole and isoquinoline rings, respectively, showed the most promising aromatase inhibition activity with IC_{50} value of 0.2 μ M.

Songa et al. [36] developed a set of 4-N-nitrophenyl substituted amino-1,2,4-triazole derivatives and evaluated their aromatase inhibition efficacy. Compound V (Figure 10) revealed the most promising inhibition activity against human aromatase enzyme with IC_{50} value of 9.02 nM. The study reported that incorporation of electron-withdrawing groups at the meta position of the compound V resulted in reduction in the inhibition affinity. The output of this study demonstrated that electron-withdrawing substitution at the para position of the benzyl ring enhance the inhibition activity than electron-withdrawing groups appearing at the meta position.

El-Naggar et al. [37] reported the synthesis strategy of a new series of 1,2,3-triazole derivatives and evaluated them as potent 5- α reductase and AIs (Figure 11); compound VI revealed the most potent inhibition activity against aromatase enzyme with IC_{50} value of 0.00024 μ M. It was concluded from the study that the physical properties like molecular mass and solubility play an essential role in the inhibition potency of the tested newly investigated derivatives.

Amr et al. [38] investigated a new 2-substituted benzoxazole derivatives and evaluated their antiproliferative activity against MDB-MB-231 and MCF-7 breast cancer cell lines. The most promising compounds were tested for their aromatase inhibition activity. The 1,2,3-triazolylbenzoxazole (VII) (Figure 12) exhibited the most promising cytotoxicity against the tested cell lines and inhibited the aromatase activity with IC_{50} of 0.261 μ M.

3. Mechanism of Action of Nonsteroidal Aromatase Inhibitors

Aromatase is the rate-limiting enzyme in the biosynthesis of estrogens (estradiol and estrone) from the corresponding precursor androgens (androstenedione and testosterone) through demethylation and aromatization, which stimulate the breast cell proliferation, while the reductase unit transfer electron from NADPH to the aromatase enzyme P450. The aromatase enzyme is found in many organs such as the breast tissues, ovaries, bone, brain, and adipose tissues. The nonsteroidal AIs have the ability to inhibit or deactivate the aromatase enzyme to prevent the estrogen production which will reduce the cell proliferation (Figure 13) [39–43].

4. Synthesis of Triazoles

1,2,3-Triazoles can be classified into two main groups: 1,2,3-triazolium salt and 1,2,3-triazoles. As reflected in Scheme 1, three subclasses for 1,2,3-triazoles can be recognized based on the position of the substituents on the ring moiety.

Despite (1*H*-) and (2*H*-)1,2,3-triazoles are recognized as aromatic compounds, the (4*H*-) isomers are not. This fact appeared in the wide spread of (1*H*-) and (2*H*-)1,2,3-triazole examples and the rarity of (4*H*-)1,2,3-triazoles [44]. 1,2,3-Triazole systems are sometimes called “*v*-triazoles” to differentiate between them and the 1,2,4-triazole systems “*s*-triazoles” [45].

N-unsubstituted 1,2,3-triazoles can be recognized as (1*H*-) or (2*H*-) derivatives, as these two tautomers are in equilibrium; for simplification, they will be represented as 1*H*-triazoles (Scheme 2), as the predominate tautomer.

Strong electron-withdrawing group at N-1 in 1,2,3-triazole compounds; for example, cyano or arylsulfonyl groups are subjected to reversible ring opening which depends on temperature to form the corresponding α -diazoimine tautomers (Scheme 3). Such rearrangement is known as the Dimroth rearrangement.

4.1. Synthesis of 1,2,3-Triazoles

4.1.1. Method 1: From Diazo compounds

(1) Variation 1: *Synthesis of 1,2,3-Triazoles from 2-Diazo-1,3-Dicarbonyl Compounds with Amines.* The cyclocondensation of 2-diazo-1,3-dicarbonyl derivatives with amines is a regioselective, simple old technique for the synthesis of 1*H*-1,2,3-triazole derivatives. It was modified and updated by Wolff, and his research group. Wolf had reported the production of 1,2,3-triazoles via the treatment of ethyl 2-diazo-3-oxobutanoate with phenyl hydrazine, ammonia, or semicarbazide (Scheme 4). The mechanism of this reaction involves the formation of type II α -diazoimines in situ, followed by their ring closure [46].

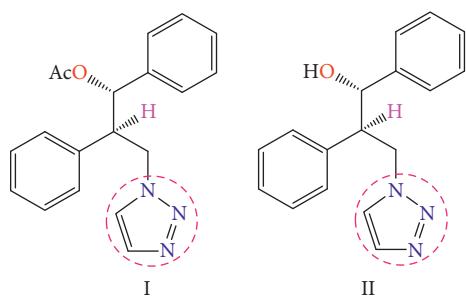


FIGURE 6: Functionalized 1,2,3-triazole derivatives as potent aromatase inhibitors (anti-triazole acetate (I) and syn-triazole alcohol (II)).

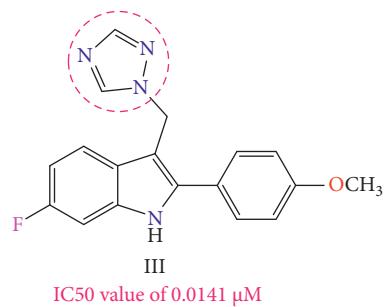


FIGURE 7: Aromatase inhibition activity of triazole bearing indole derivative (III).

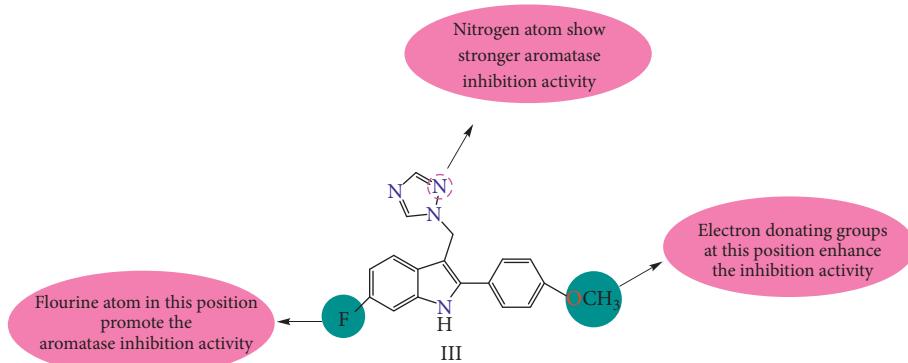


FIGURE 8: Structure-activity relationship of the triazole bearing indole derivative (III).

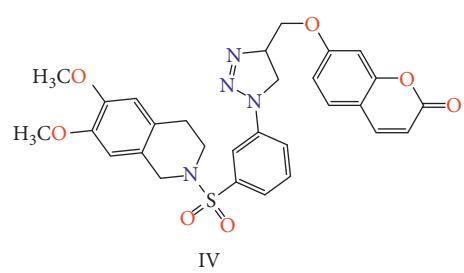


FIGURE 9: Aromatase inhibition activity of 1,4-disubstituted-1,2,3-triazole sulfonamide (IV).

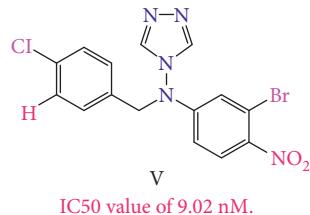


FIGURE 10: Aromatase inhibition activity of N-(3-Bromo-4-nitrophenyl)-N-(4-chlorobenzyl)-4H-1,2,4-triazol-4-amine (V).

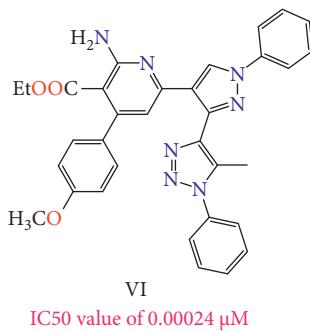


FIGURE 11: Aromatase inhibition activity of 1,2,3-triazole derivative (VI).

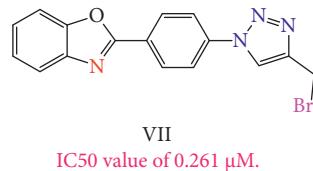


FIGURE 12: Aromatase inhibition activity of the of 2-substituted benzoxazole analogue (VII).

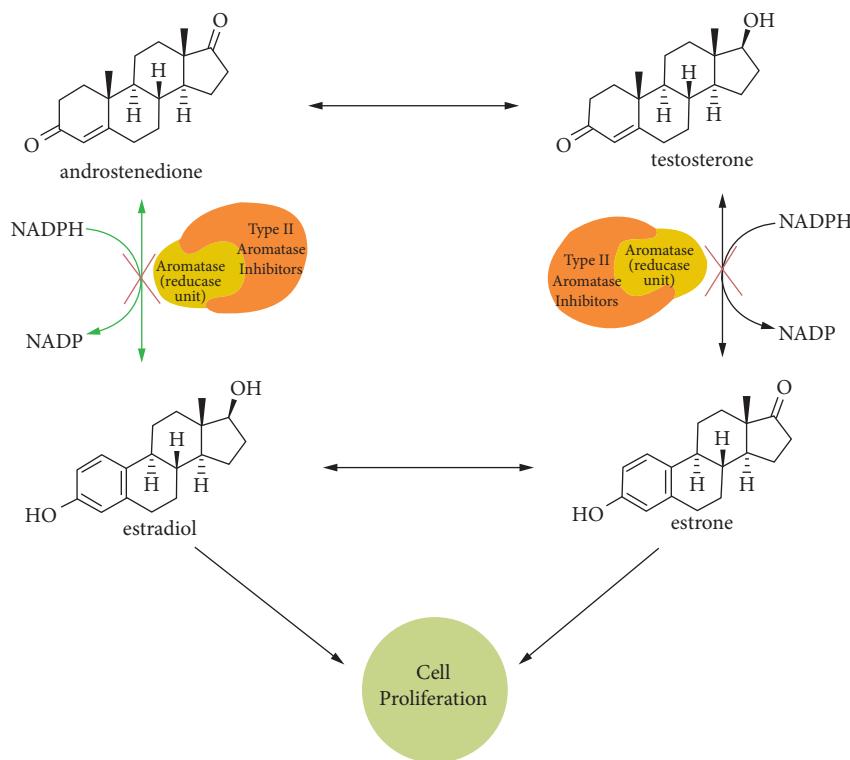
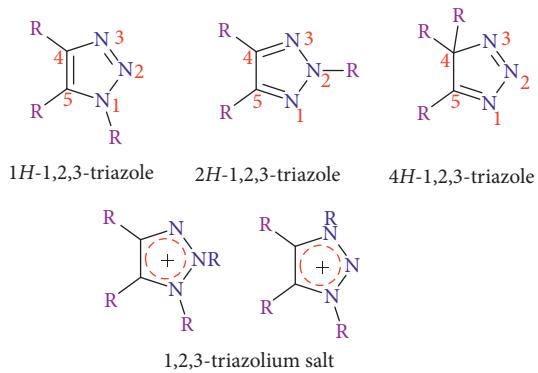
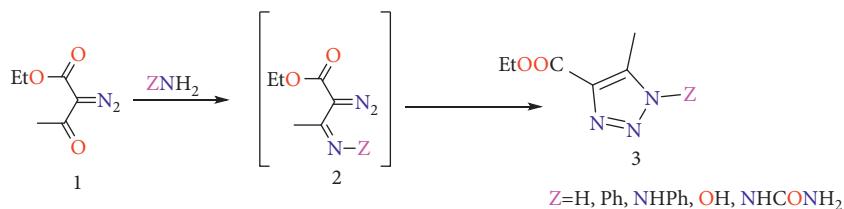


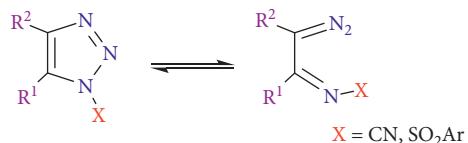
FIGURE 13: Mechanism of action of Nonsteroidal Aromatase Inhibitors. Copyright 2021. Reproduced with permission from Elsevier.



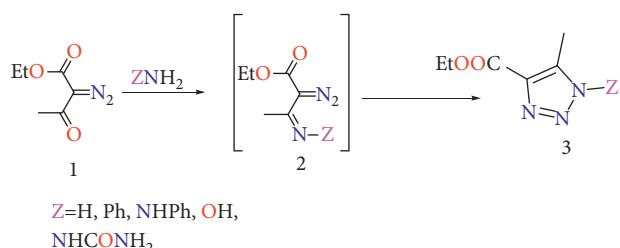
SCHEME 1: The two main classes of 1,2,3-triazoles.



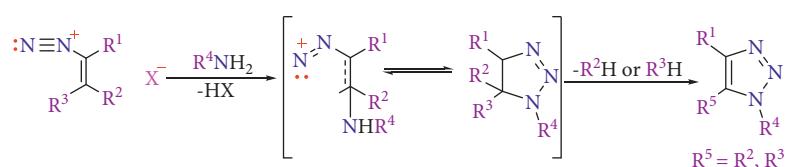
SCHEME 2: (1H-) and (2H-)1,2,3-triazole tautomers.



SCHEME 3: Effect of the electron withdrawing groups on the N-1 atom in the 1,2,3-triazoles on the ring stability.



SCHEME 4: Synthesis of 1,2,3-Triazoles from 2-Diazo-1,3-Dicarbonyl Compounds with Amines.



R^1	R^2	R^3	R^4	R^5	X	Yield%
H	OEt	OEt	H	OEt	SbCl ₆	65
H	OEt	OEt	3-morpholinopropyl	OEt	SbCl ₆	54
H	OEt	OEt	CY	OEt	SbCl ₆	62
H	OMe	4-MeOC ₆ H ₅	Furfuryl	4-MeOC ₆ H ₅	SbCl ₆	63

SCHEME 5: Synthesis of 1,2,3-triazoles from Vinyl diazonium Salts with Amines.

(2) *Variation 2: From Vinyl diazonium Salts with Amines.* Vinyl diazonium salts were reacted with amines and ammonia [46] to give 1,2,3-triazole derivatives (Scheme 5). When vinyl diazonium salts 4 were submitted to react with ω,ω' -diaminoalkanes, ω,ω' -bis(1*H*-1,2,3-triazol-1-yl)alkanes were formed [47–49].

4.1.2. Method 2: From Dichloro or Trichloroacetaldehyde Sulfonyl-Hydrazone with Primary Amines. Mesityl and tosylhydrazone of dichloroacetaldehyde (6) and trichloroacetaldehyde (8) were submitted to react with primary amines in the presence of ammonia to produce 1*H*-1,2,3-triazoles 7 and 9, respectively, in excellent yields [47] (Scheme 6).

4.1.3. Method 3: From 3-Diazo-1,3-Dihydro-2*H*-Indol-2-one Derivatives with Enaminones. β -Amino α , β -unsaturated ketones (10, $R^2 = \text{Me}$) and β -amino α , β -unsaturated esters (10, $R^2 = \text{OEt}$) were reacted with 3-diazo-indol-2-one derivatives 11 giving 1*H*-1,2,3-triazoles 12 [50–52] in excellent to good yields (Scheme 7).

4.1.4. Method 4: Synthesis of 1,2,3-Triazoles from Sulfonyl Azides with Enaminones. Tosyl and mesityl azides can play the role of diazo transfer agents to enaminones forming triazoles [50] 14 in good to excellent yields (Scheme 8).

4.1.5. Method 5: Synthesis of 1,2,3-Triazoles from Azides and Alkynes. 1,3-Dipolar cycloaddition of alkynes to azides thermally often gives the target product.

This method was initiated by Fester and Dimroth. They synthesized the parent compound through heating of a solution of acetone and acetylene with a solution of alcoholic hydrazoic acid at 100°C for 70 h [53]. With alkynes, the reaction was performed in benzene in closed vessel at temperature ranging from 90 to 135°C for 30–48 h [54] (Scheme 9).

The triazoles that are produced by this method are obtained in moderate to low yields. Also, the reactions involving substituted alkynes with electron-donating or withdrawing groups are higher in their yield and faster.

4.1.6. Method 6: From Azide Ion. Azide ions are added to alkynes to yield triazoles 20 in good yields. To obtain excellent yields, alkynes which are conjugated with electron-withdrawing groups must be used. In general, the reactions are carried out in DMSO or DMF. Sodium azides [55] are often used as source of the azide ion, but aluminum azide and lithium azide have also been utilized. The mechanism of these reactions involve nucleophilic addition of the azide ion to the triple bond of the alkyne, then 1,5-dipolar cyclization occurs to form the vinyl anion giving the final triazoles 20 [56–59] (Scheme 10).

4.1.7. Method 7: Synthesis of 1,2,3-Triazoles from Alkyl or Aryl Azides. Jiang and his research group were the first to

report the use of calcium carbide (CaC_2) as acetylene source. Such approach offers the possibility for the production of deuterated triazole derivatives when deuterium is used as a source of acetylene [60] (Scheme 11).

4.1.8. Method 8: Synthesis of 1,2,3-Triazoles from 1,3-Diketones. Aryl azides are submitted to react with pentane-2,4-dione through condensation reaction in the presence of ethanol and sodium methoxide to afford the desired triazoles 24 (Scheme 12) [37, 61–64].

4.1.9. Method 9: Synthesis of 1,2,3-Triazoles by Ring Transformation. Several heterocyclic rings can be converted into 1,2,3-triazoles through just isomerization or other chemical modifications. For example, diazotization of iso-xazol-4-amines to give triaz-1-ols and diazotization of 5-amino-2-ols to give triaz-4-ols.

One of the most successful methods for the synthesis of 1,2,3-triazoles is through chemical transformation of 1,2,3-thiadiazoles into 1,2,3-triazoles.

Base-catalyzed isomerization of 1,2,3-thiadiazol-5-amines gives 1,2,3-triazo-5-thiols. In addition, the thermolysis of 5-alkoxycarbonylamino-1,2,3-thiadiazoles 25 in a glass test tube in the absence of solvent affords product 26 as an eco-friendly method [65] (Scheme 13).

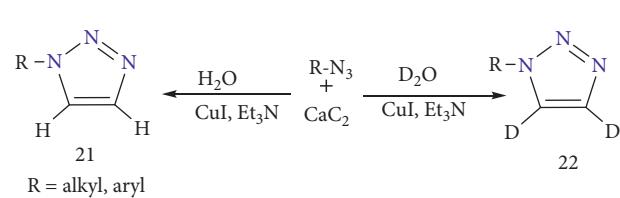
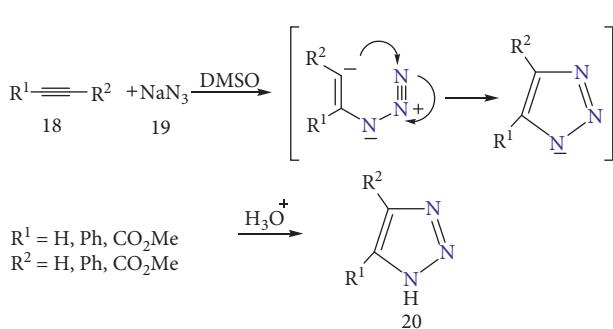
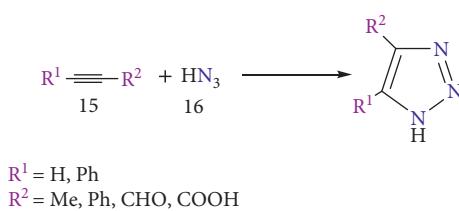
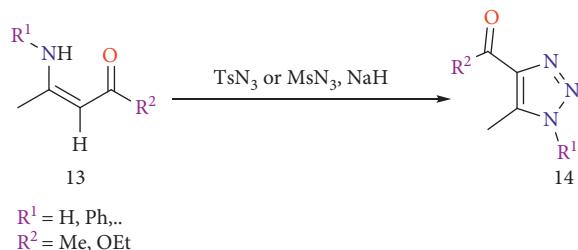
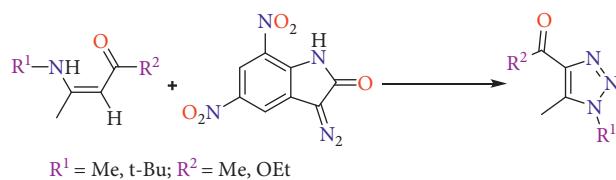
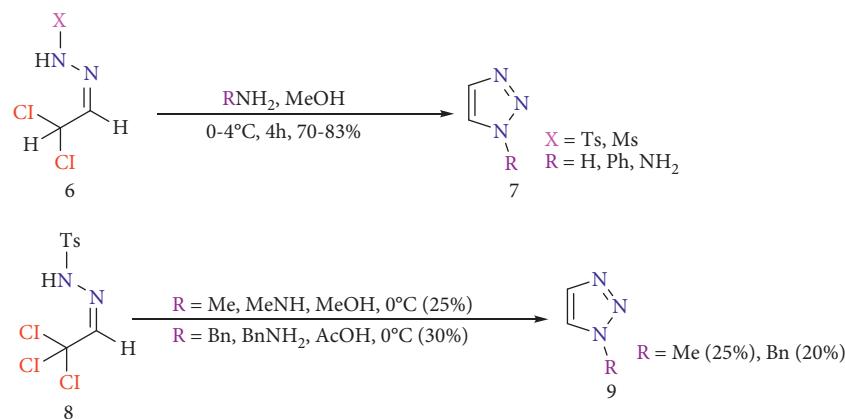
4.2. Synthesis of 1,2,4-Triazoles

4.2.1. Method 1: Synthesis of 1,2,4-Triazoles Involving Hydrazine Derivatives. The reaction of the substituted hydrazine or hydrazine with the suitable electrophile is one of the mostly used methods for the production of 1,2,4-triazoles. Examples are illustrated in Scheme 14 [66].

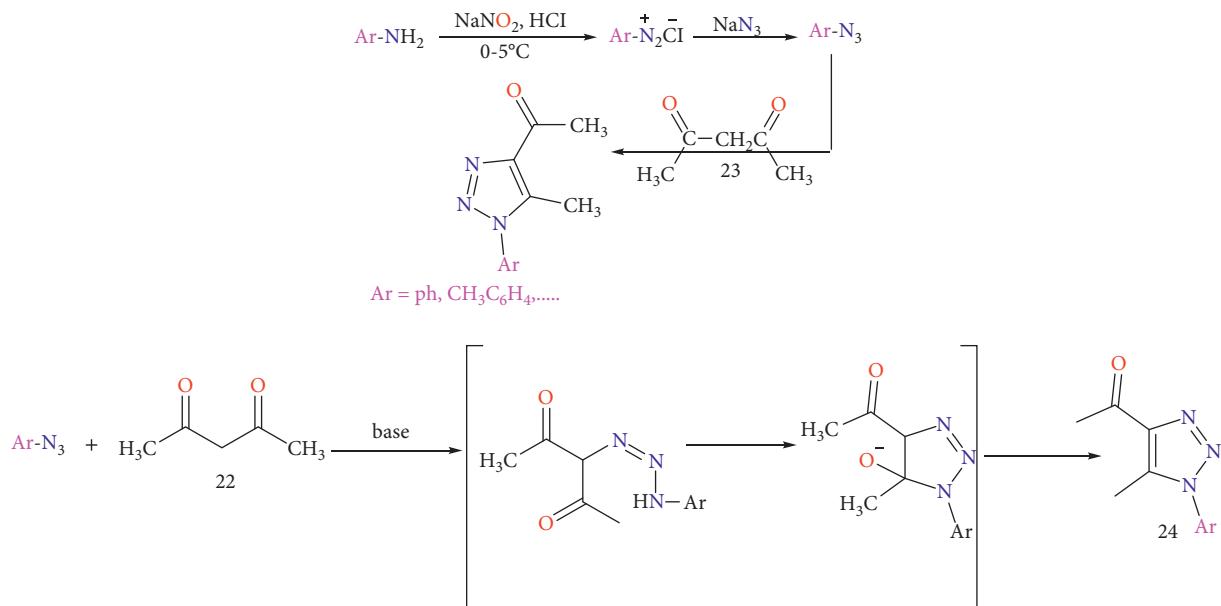
4.2.2. Method 2: Synthesis of 1,2,4-Triazoles Involving Nitrile Imines and Triazines. 1,3-Dipolar cycloaddition is one of the most famous methods that is used for the synthesis of 1,2,4-triazoles. For example, nitrile imine 32 is submitted to react with the tetrazole derivative (31, $X = \text{NH}$) to afford 33. Reaction of 31 with the tetrazole (31, $X = \text{O}$) to give 39 which on treatment with a base give triazolinone 35 [67] (Scheme 15).

4.2.3. Method 3: Synthesis of 1,2,4-Triazole Transformation of Other Heterocyclic Systems. The formation of triazoles from non-triazole rings often involve nitrogen substitution by another heteroatom in a five-membered ring system. Usually, the process includes nucleophilic opening of the heterocyclic ring, followed by the ring closure and the loss of the other atoms. New material in this area may be appeared later on as is reported by Polya [68] Few examples are mentioned in Scheme 16.

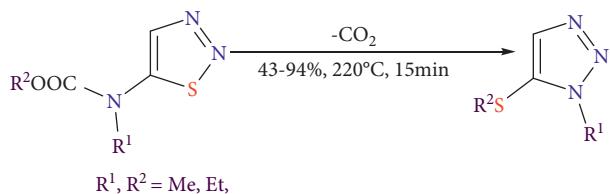
4.2.4. Method 4: Synthesis of 1,2,4-Triazoles Utilizing Microwave Irradiation. Microwave irradiation is a widely utilized strategy for a rapid synthesis of many useful organic



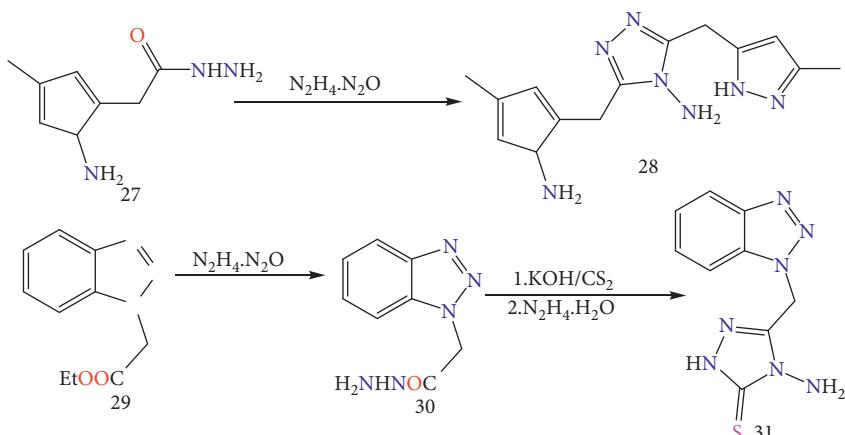
compounds with high selectivity and good yields [69]. Microwave is established to be a technique to heat chemicals rapidly without any overheating. In addition, it is reported in some research work the specific nonthermal effects of



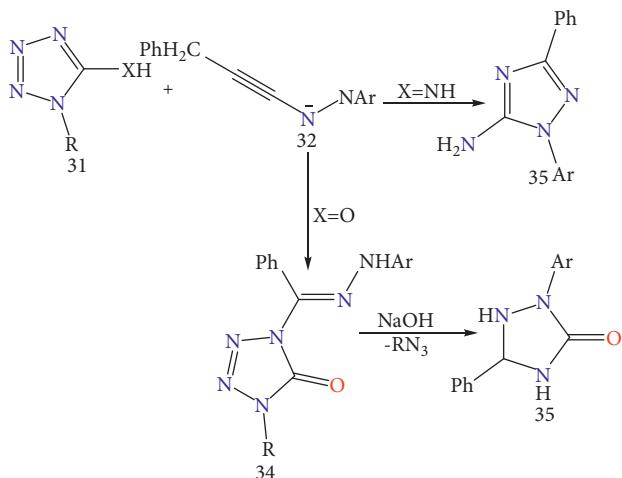
SCHEME 12: Synthesis of 1,2,3-Triazoles from 1,3-Diketones & the mechanism of the reaction.



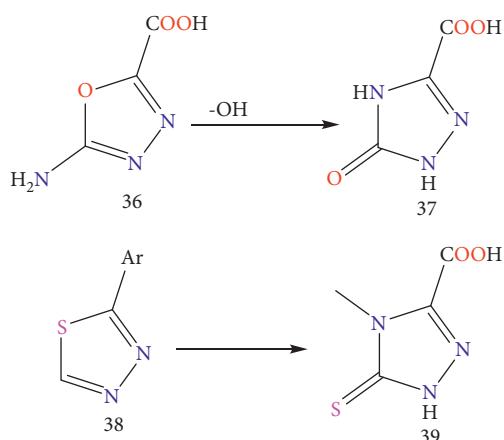
SCHEME 13: Synthesis of 1,2,3-Triazoles by Ring Transformation.



SCHEME 14: Synthesis of 1,2,4-Triazoles Involving Hydrazine Derivatives.



SCHEME 15: Synthesis of 1,2,4-Triazoles Involving Nitrile Imines and Triazines.



SCHEME 16: Synthesis of 1,2,4-Triazole Transformation of Other Heterocyclic Systems.

$\text{NH}_2\text{NH}_2\cdot 2\text{HCl}$ in the presence of excess of hydrazine hydrate in ethylene glycol under microwave irradiation (Scheme 17).

5. Conclusions and Future Prospects

Anastrozole, letrozole, and vorozole are known as modern third-generation AIs that block the biosynthesis of the estrogen effectively without affecting the steroidogenic pathways. They exhibited a significant efficacy and offering a greater potency and selectivity of aromatase inhibition than the prototype AIs of the first and second generations. The available data suggest that letrozole achieves a significant longer duration of response than megestrol and amino-glutethimide [74].

Binding mode of the triazoles as aromatase inhibitors is based on protein ligand interaction and docking studies.

The triazole of the ligand pointed towards the heme group in the aromatase enzyme active site and coordinated to the heme iron through its N-4 atom. Also, two π -cation interactions are observed, one of which between triazole and porphyrin of the heme group [74]. Although, AIs either steroidal or nonsteroidal types exhibited remarkable clinical effects, the long-term usage of them can lead to acquired drug resistance and considerable side effects including osteoporosis, cardiovascular disease, broken bones, and musculoskeletal and joint pain. Hence, the investigation of novel AIs is still essential to provide alternative drugs with more favorable characters.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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SCHEME 17: Synthesis of 1,2,4-Triazoles Utilizing Microwave Irradiation.

microwaves. Sometimes, the microwave irradiation effects are thought to be only certain forms of heat techniques.

Kappe *et al.* [70] have utilized this technique mostly for the synthesis of their organic moieties. In addition, Molteni and Ellis [48, 71, 72] have reported the work performed from 1994 regarding microwave-assisted synthesis of heterocycles and the formation of heterocycles through reactions in which a heteroatom is directly involved in the process of bond formation. By using the microwave irradiation technique, many 1,2,4-triazoles have been indexed recently.

Bentiss *et al.* [73] have prepared (3,5-disubstituted 4-amino-1,2,4-triazoles) 41 by reacting nitrile derivatives 40 with

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