CHEMISTRY OF 1,2,4-TRIAZOLES IN CURRENT SCIENCE

EDITORS

Prof. Dr. Haydar Yüksek

Assoc. Prof. Dr. Murat Beytur

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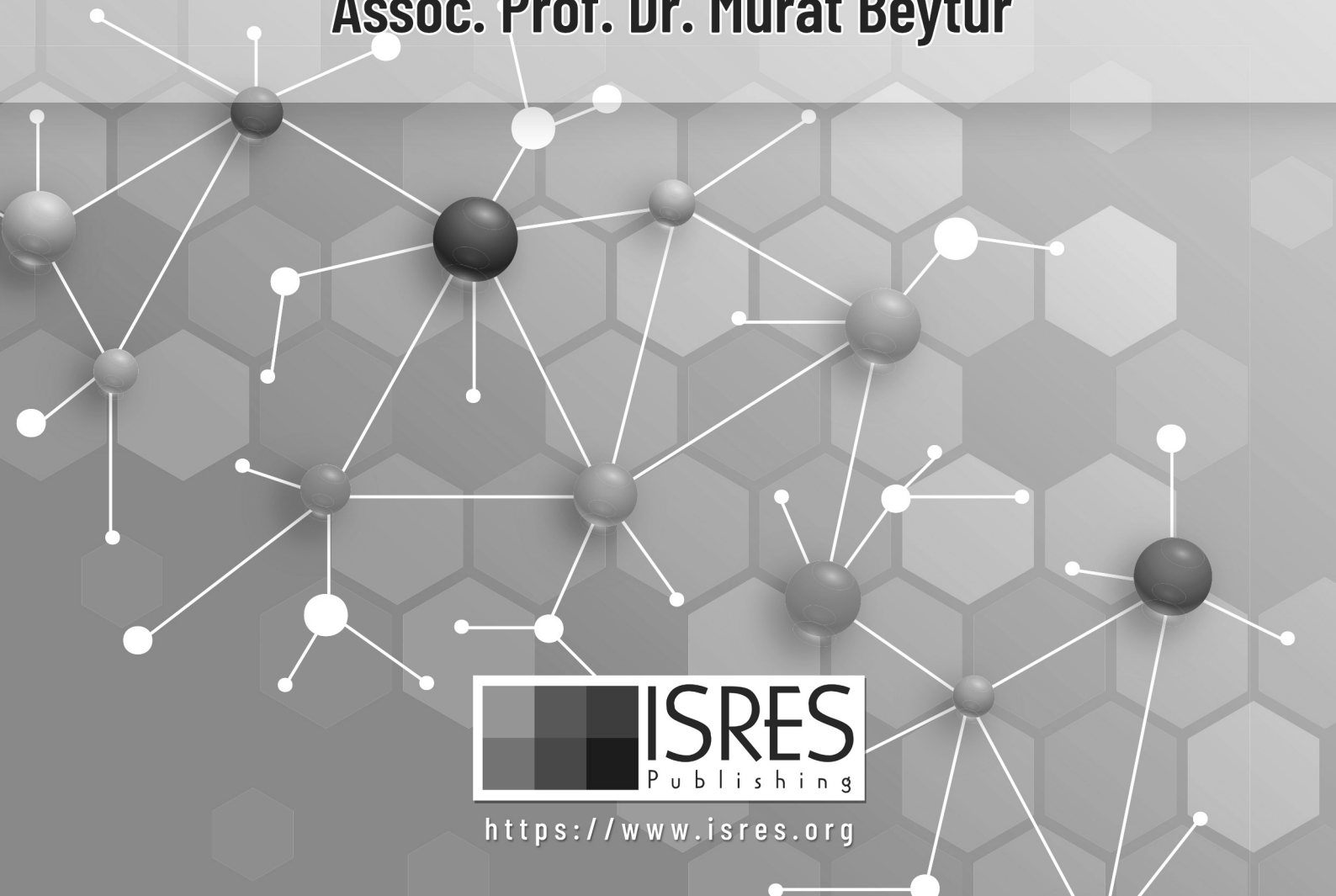

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Prof.Dr. Haydar YÜKSEK
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Assoc. Prof. Dr. Murat BEYTUR

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PREFACE

Chemistry of 1,2,4-Triazoles in Current Science is a book consisting of 11 chapters in the field of Organic Chemistry. The purpose is to inform the readers about the various operations with the 1,2,4-triazole compounds. In this book, many recent studies for 1,2,4-triazole compounds in organic chemistry were studied, and it sheds light on those who are interested in 1,2,4-triazole chemistry such as synthesis, antioxidant, antibacterial, anticancer, antifungal, molecular docking, complex studies, theoretical properties, QSAR studies, and chiral compounds. We hope that the book will be useful to scientists and readers who are interested in 1,2,4-triazole chemistry and to all those who want to improve themselves in this field. All submissions were conducted by at least two referees. Chemistry of 1,2,4-Triazoles in Current Science was published by ISRES Publishing.

December 2022

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CHEMISTRY OF 1,2,4-TRIAZOLES IN CURRENT SCIENCE

CHEMISTRY OF 1,2,4-TRIAZOLES IN CURRENT SCIENCE

Chemistry of 1,2,4-Triazoles in Current Science is published annually from the selected papers invited by the editors.

This edition consists of 11 sections related to the Field of Organic Chemistry.

All submissions are reviewed by at least two reviewers.

The purpose of the book is to provide readers with a scientific peer-reviewed publication on 1,2,4-triazole chemistry in the field of Organic Chemistry.

Chemistry of 1,2,4-Triazoles in Current Science is published by ISRES Publishing.

SYNTHESIS OF 1,2,4 TRIAZOLE COMPOUNDS

Hilal MEDETALİBEYOĞLU
Kafkas University

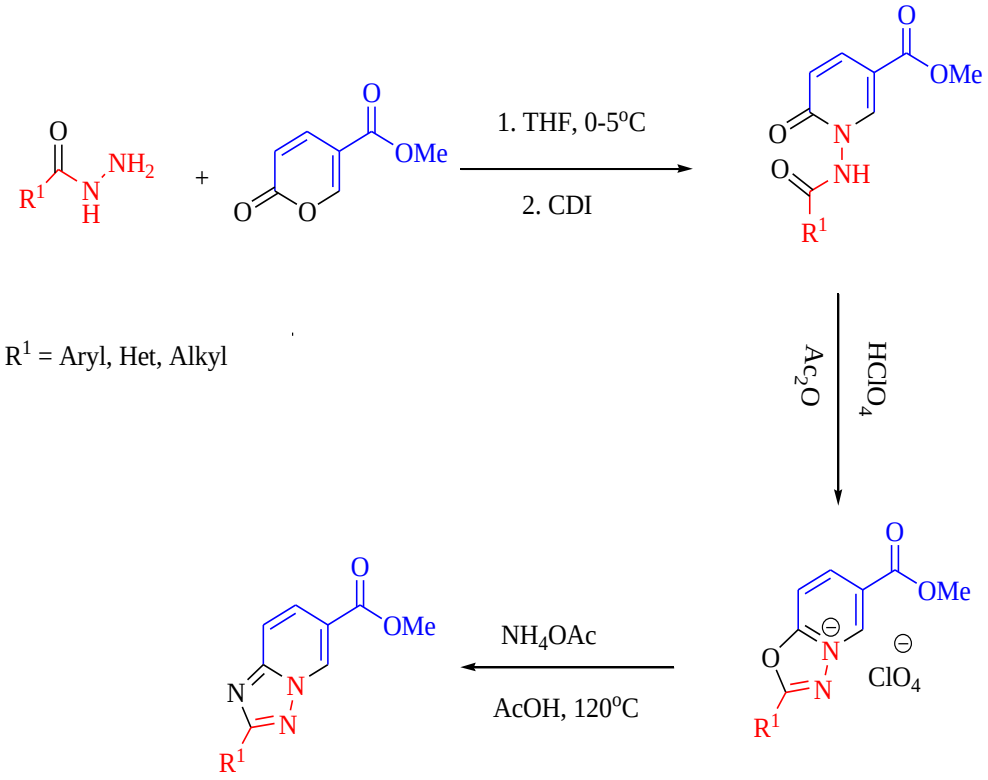
Gül KOTAN
Kafkas University

Synthesis of 1,2,4 Triazole Compounds

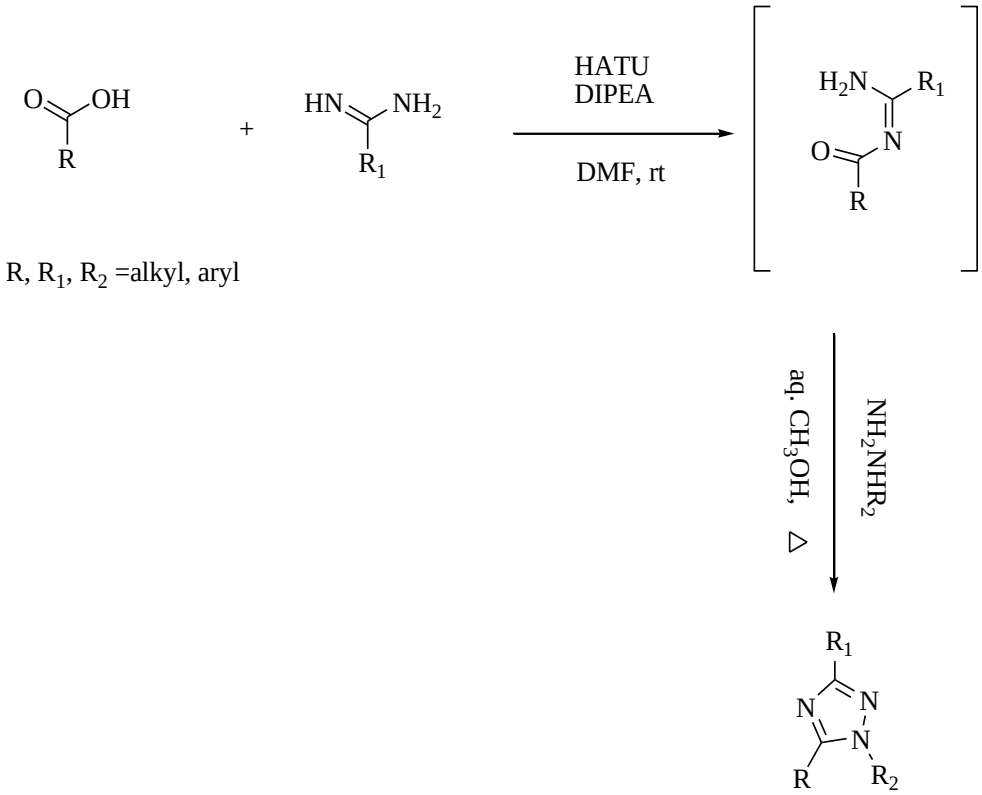
As highly privileged heterocyclic scaffolds, 1,2,4-triazoles have many uses in the fields of biology, pharmacology, and materials science (Gulyaev et al., 2021; Brandt et al., 2007; Cai et al., 2022; Cetin et al., 2018; Chawla et al., 2022; Kotan et al., 2020; Li et al., 2018; Matsuzaki et al., 2021; Medetalibeyoglu, 2022; Medetalibeyoğlu et al., 2022; Medetalibeyoğlu & Yüksek, 2021; Mermer & Boulebd, 2023; Mucha et al., 2023; Bogdan & Wang, 2015; Sanina et al., 2022; Todoulou et al., 1994; Sedash et al., 2012; Wang & Wudl, 2010; Yin et al., 2023; Yunusova et al., 2018; Zhang et al., 2020; Zhang et al., 2008; Zhang et al., 2017). Among medicinal chemists, there is a lot of interest in compounds with significant biological activity, including antihypertensive, antibacterial, and antifungal properties (Abuelizz et al., 2019; Bekircan et al., 2022; Chawla et al., 2022; Chen et al., 2019; Erensoy et al., 2023; Gavara et al., 2022; Liu et al., 2013; Madhu Sekhar et al., 2018; Mazur et al., 2019; Mohassab et al., 2017; Muzaffar et al., 2021; Sadeghian et al., 2023; Siddiqui et al., 2011). There were 1,2,4-triazole scaffolds in valuable drugs like maraviroc, sitagliptin, triazolam, and deferasirox. Furthermore, 1,2,4-triazoles, which have many possible uses, have been investigated as adaptable ligands for metal coordination (Bahemmat et al., 2015; Bazhina et al., 2022; Dong et al., 2012; Geetha et al., 2020; Haasnoot, 2000; Heidari et al., 2021; Kumari et al., 2022; Lässig et al., 2010; Liu et al., 2017; Prozorova et al., 2020; Tahli et al., 2011; Wang et al., 2012; Wang et al., 2014; Yu et al., 2022; Zha et al., 2022; Zhang et al., 2017).

Moloney et al. produced a feasible three-step synthesis of a series of fused bicyclic s-[1,2,4]triazolo[1,5-a]pyridines one utilizing unique intermediates derived from inexpensive, commercially accessible hydrazides and methyl cumulate. This approach was noteworthy in

forming dihydrazide intermediates without the need for oxidative N-N bond formation during 1,2,4-triazole synthesis. Because the crystalline oxadiazolium salts remove impurities, further purification of the dihydrazides was found to be unnecessary beyond simple separation. The oxadiazolium perchlorate salts demonstrated outstanding moisture stability which is unusual for these compounds (Moloney et al., 2017).

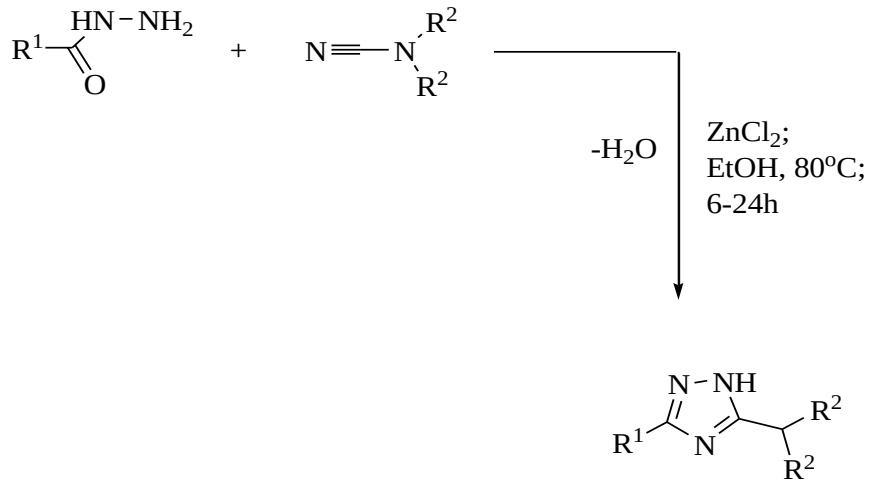


Castanedo and his colleagues demonstrated rapid and highly regioselective access to a wide range of 1,3,5-trisubstituted 1,2,4-triazoles. The components of this convenient one-pot reaction are carboxylic acids, monosubstituted hydrazines, and primary amidines. HATU is an essential component of the reaction for the coupling of peptide reagents to form acylamide intermediates with diisopropylethylamine (DIPEA) as a base in DMF. The final 1,2,4-triazole molecule might comprise a variety of substituents at position 5 (Castanedo et al., 2011).

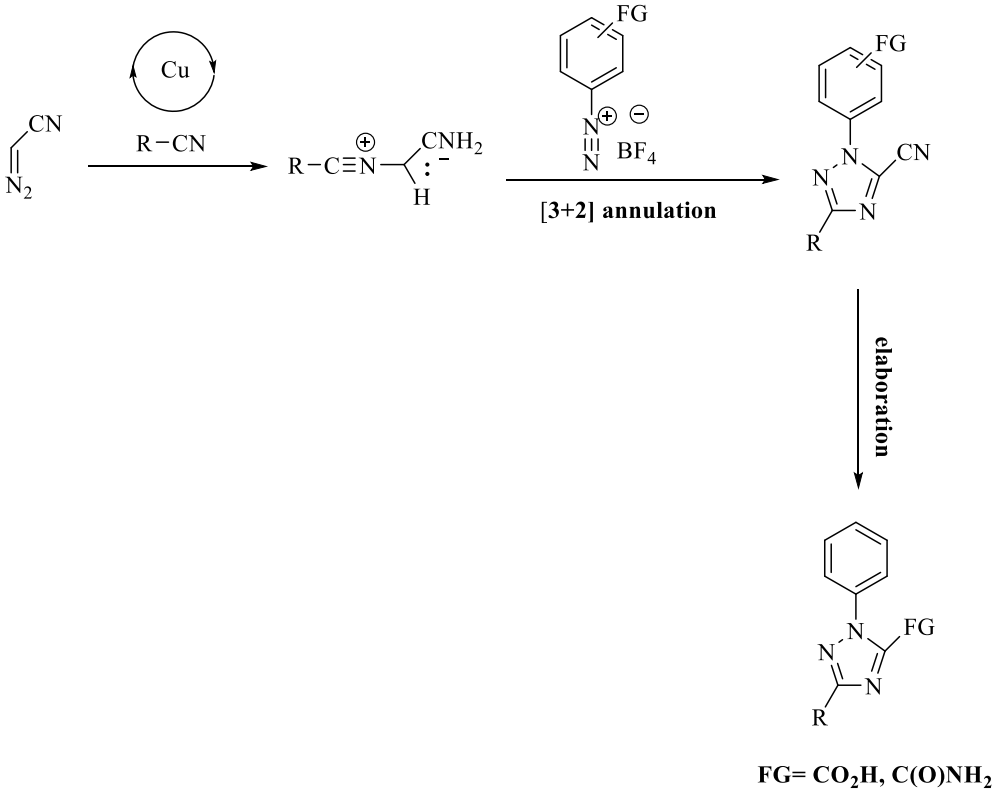


R, R_1, R_2 =alkyl, aryl

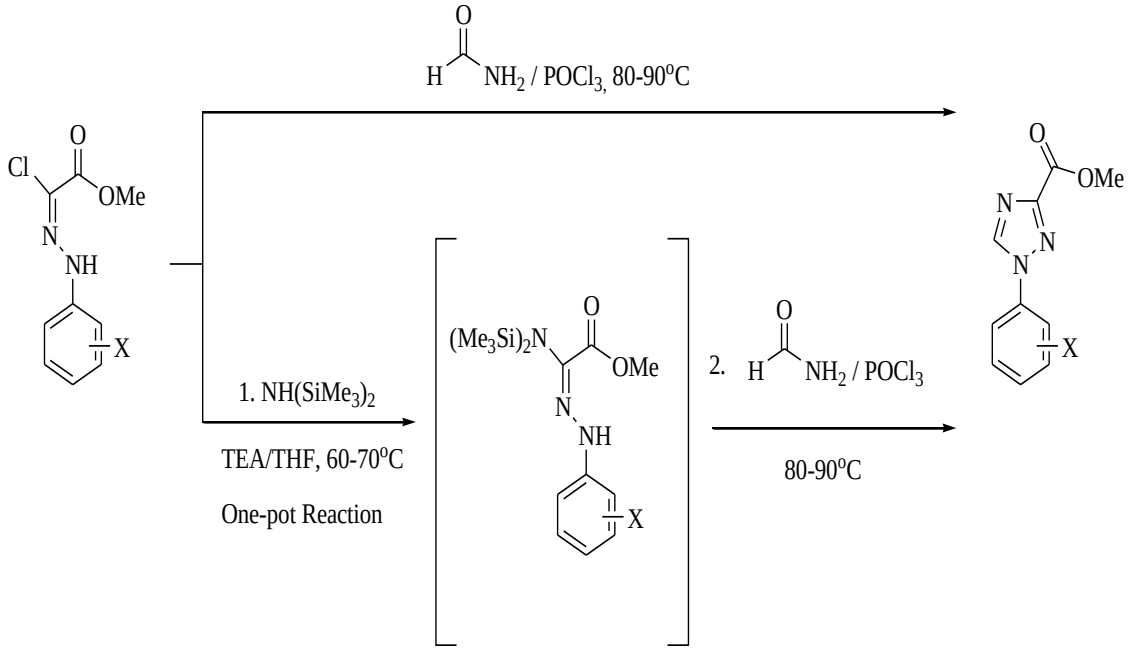
Yunusova et al. report a unique and very effective synthetic approach for producing 3-dialkylamino-1,2,4-triazoles formed from dialkylcyanamide coupling and Zn^{II}-catalyzed acyl hydrazide. The Zn^{II}-catalyzed process starts with the formation of $[Zn\{RC(=O)NHNH_2\}_3](ZnCl_4)$ complexes. It was discovered that the electronic effects of the acyl hydrazide unit substituents did not influence the reaction rate or yield of the target triazoles, while steric hindrances reduced the reaction rate without altering the yield of the heterocycles (Yunusova et al., 2018).



Zhou et al. have discovered an approach for the regioselective synthesis of 1-aryl-5-cyano-1,2,4-triazoles that is Cu-enabled and makes use of the tricomponent, [3+2] annulation reaction that combines nitriles and 2-diazoacetonitriles with aryldiazonium salts. Novel bidentate ligands for asymmetric catalysis and structurally various bioactive compounds may be synthesized using this procedure due to its versatility in gram-scale synthesis, chemical modifications to the nitrile moieties, and access to chiral bis(cyano-triazole)-1,1′-naphthalene (Zhou et al., 2021).

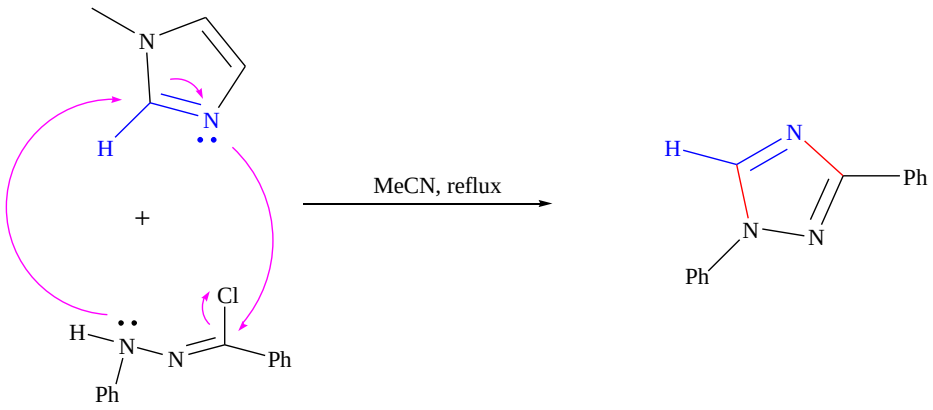


Tsai et al. have devised two straightforward one-pot procedures for synthesizing methyl 3-carboxylate-1-aryl-1H-1,2,4-triazoles, including the two-stage stepwise cascade synthetic procedure and the direct one-pot reaction. In the presence of nitrilimines and Vilsmeier reagent, methyl 3-carboxylate-1-aryl-1H-1,2,4-triazoles were successfully obtained at normal heating conditions (Tsai et al., 2019).

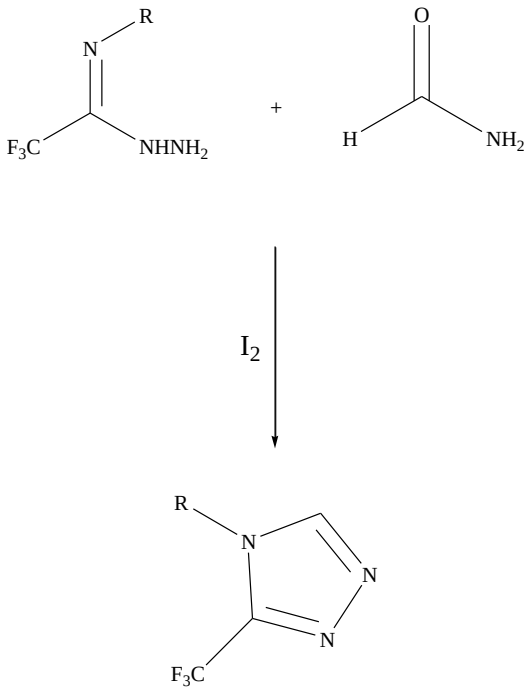


X= H, *o*-, *m*-, *p*-F, *o*-, *m*-, *p*-CF_3, *m*-, *p*-Cl, *m*-, *p*-Me, *p*-Br, *p*-OMe, and 3,4-di-Cl

Yavari and Khaledian have developed an easy-to-use one-pot, two-component method for synthesizing 1,3-disubstituted 1,2,4-triazoles utilizing easily accessible *N*-Methylimidazole (NMI) and hydrazonoyl chlorides. Nucleophilic substitution of hydrazonoyl chloride with NMI (*N*-Methylimidazole) was observed as the first step of the process. This unusual formal [3+2] cycloaddition, followed via two C-N bond cleavage, resulted in a variety of structurally different 1,3-disubstituted-1H-1,2,4-triazoles. Transformations proceeded without significant sensitivity to steric or electronic hindrance factors, and five-membered 1,2,4-triazole rings were obtained in yields ranging from 71% to 96% (Yavari & Khaledian, 2020).

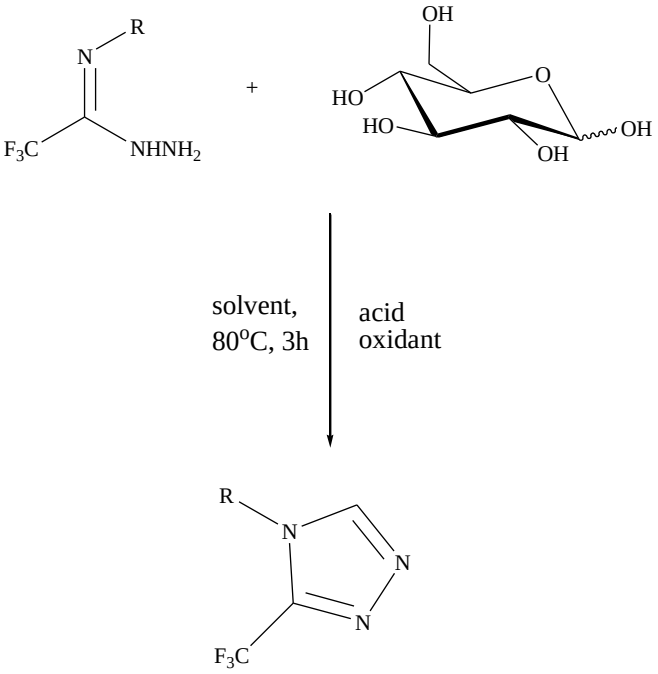


Lu et al. have developed a metal-free approach for synthesizing 3-trifluoromethyl-1,2,4-triazoles via I_2-mediated oxidative cyclization of trifluoroacetimidohydrazides by utilizing DMF, a common solvent, as the carbon source. It is observed that the desired 1,2,4-triazole products' methine units are obtained from both the *N*-methyl and *N*-acyl forms of DMF. Lu et al. stated that this method's benefits include easy access to reagents, simple operation, a wide range of substrates, and insensitivity to air and moisture (Lu et al., 2022).



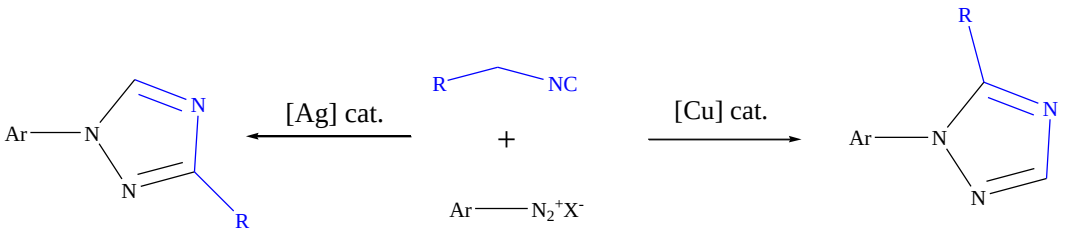
A straightforward and facile method for synthesizing 3-trifluoromethyl-1,2,4-triazoles via metal-free oxidative cyclization of trifluoroacetimidohydrazides utilizing D-glucose has been described by Lu et al. It was observed that the protocol could be used with the easy-to-find and renewable D-glucose as the C1 synthon, which has a wide range of substrates, and mild reaction

conditions and can be scaled up. They stated that the current study broadens the applications for compounds obtained from biomass in creating functionalized heterocycles (Lu et al., 2021).

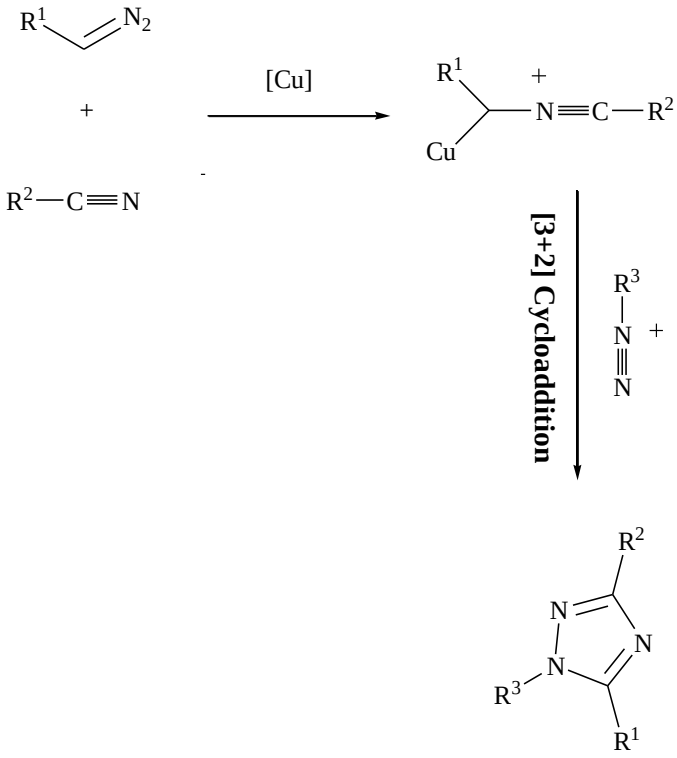


R= 4-*t*-BuPh

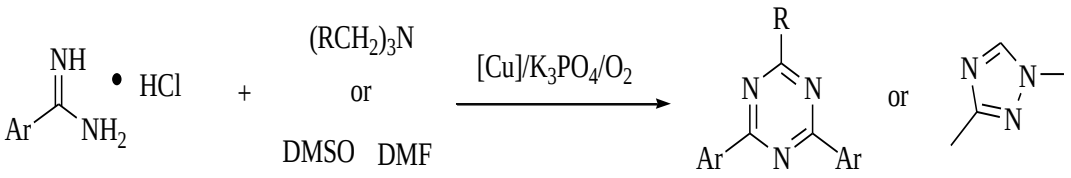
Liu et al. have reported the first catalyst-controlled methodology for the regioselective [3+2] cycloaddition of isocyanides with diazonium salts, which, under mild conditions, provides a practical method for the design of 1,2,4- triazoles in high yield from a variety of functionally diverse substrates. Under Ag(I) catalysis, 1,3-disubstituted 1,2,4-triazoles were synthesized selectively and in high yield, while 1,5-disubstituted 1,2,4-triazoles were produced by Cu(II) catalysis. Liu et al. developed these catalytic methods that give controlled, modular, and easy access to 1,2,4-triazole moieties with good efficiency, a wide range of substrates, and good compatibility with functional groups (Liu et al., 2018).



Li et al. have demonstrated a copper-catalyzed intermolecular [3+2] cycloaddition that affords 1,2,4-triazoles in medium to high yields by trapping an intermediate nitriles ylides species via the diazonium salt. They showed that this methodology offers a facile and effective strategy to generate structurally diverse 1,2,4-triazoles from readily available starting materials in a one-step manner under mild conditions. Their preliminary results have displayed that diazonium salts were the source of two N atoms for the target 1,2,4-triazoles scaffolds. Mild conditions, operational simplicity, and ready accessibility have characterized this copper-catalyzed three-component reaction, providing access to 1,2,4-triazoles with various substitution patterns (Li et al., 2018).

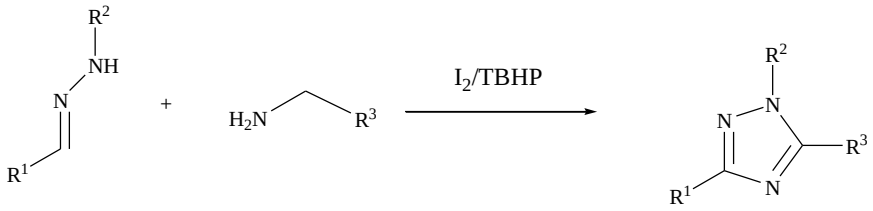


Huang et al. have described a very effective catalytic [Cu]/O2 system for obtaining 1,2,4-triazoles from amidines through oxidative functionalization of the C(sp^3)-H. To efficiently synthesize 1,3-disubstituted 1,2,4-triazoles obtained from amidines with trialkylamines, DMF, and DMSO as the reaction members, a simple and adaptable catalytic system involving copper catalyst, O_2 as the oxidant, and K_3PO_4 as the base have been devised. The method has been reported to provide significant synthetic bias and flexibility for synthesizing multi-nitrogen heterocycles from amidines. All of these have been observed to make the synthesis procedure attractive and fascinating (Huang et al., 2015).

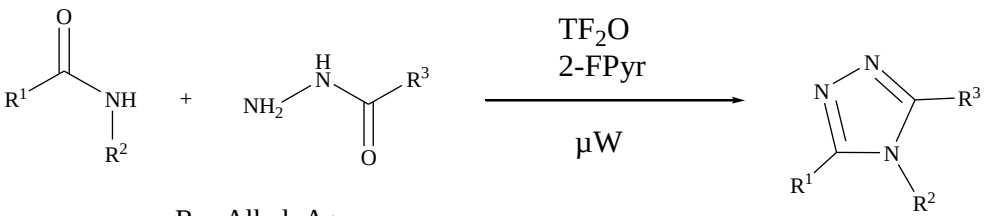


(R=H, aryl, alkyl)

Chen et al. have devised a very appealing approach for the quick and effective synthesis of compounds with 1,2,4-triazole scaffolds from hydrazones and amines via a metal-free intermolecular mechanism under aerobic oxidative conditions. It has been noted that the reaction proceeds via a cascading process of C−H functionalization, the formation of double C-N bonds, and oxidative aromatization. The methodology is reported to have easily accessible starting reagents, general and favorable operating conditions, a wide substrate coverage, and high yields (Chen et al., 2016).

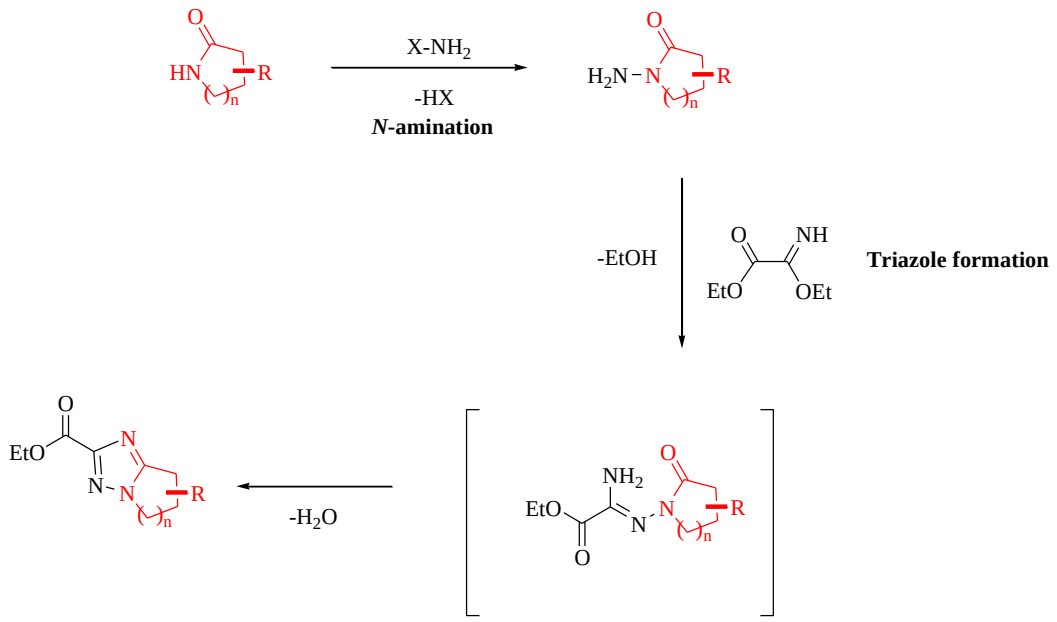


Bechara et al. have devised a general method for synthesizing 3,4,5-trisubstituted 1,2,4-triazoles from hydrazides and secondary amides via trifluoroanhydride activation followed by microwave-induced cyclodehydration. The procedure has been utilized to synthesize a range of 3,4,5-trisubstituted 1,2,4-triazoles with distinct alkyl/aryl substitution sequences (Bechara et al., 2015).

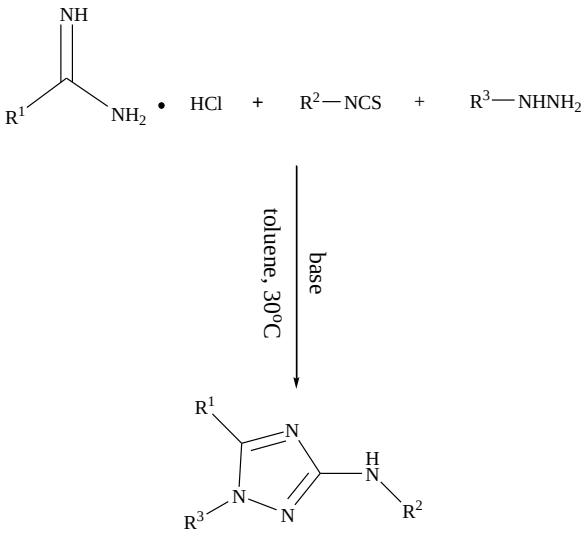


R = Alkyl, Ar

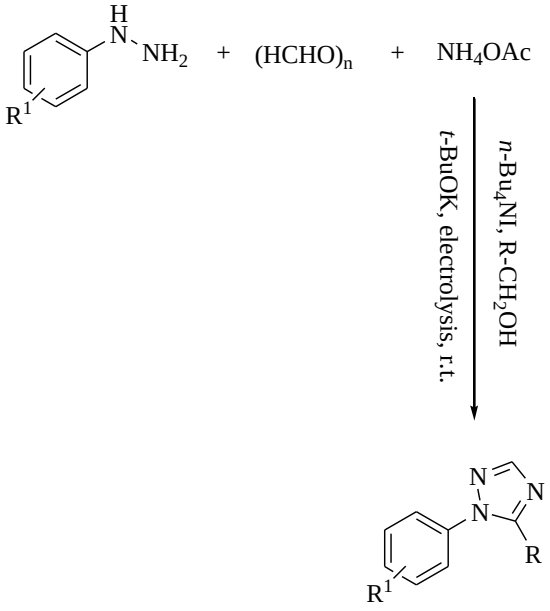
Nguyen and Hong discovered a two-step approach for synthesizing polycyclic 1,2,4-triazoles from lactams. This method involves an N-amination with HOSA, which was then followed by a cyclocondensation with ethyl 2-ethoxy-2-iminoacetate that was available for purchase. Semi-saturated triazoles with various functional groups and ring diameters have been produced utilizing this approach (Nguyen & Hong, 2021).



Guo et al. proposed an oxidant- and metal-free three-component desulfurization and deamination condensation of isothiocyanates, amidines, and hydrazines to synthesize structurally different completely substituted 1H-1,2,4-triazol-3-amines. The reaction is designed without the use of external catalysts, ligands, oxidants, or metals. This cyclization process [2+1+2] involves C–S and C–N bond cleavage, forming new C–N bonds in one pot. This study reported the synthesis of some fully substituted 1H-1,2,4-triazole-3-amines with this transformation, which has advantages such as a wide variety of substrates, environmental friendliness, mild reaction conditions, and applications in gram scale (Guo et al., 2021).

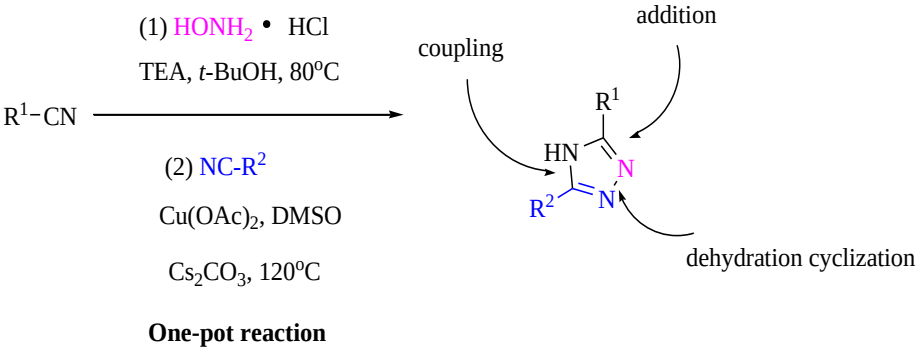


Yang and Yuan discovered a facile electrochemical approach for synthesizing 1-aryl and 1,5-disubstituted 1,2,4-triazoles, which were obtained from NH_4OAc, aryl hydrazines, alcohols, and paraformaldehyde. Employing a reactive iodide radical or I_2 and NH_3 electrogenerated in situ, it was possible to create a broad range of 1,2,4-triazole derivatives in excellent to good yields without the need of solid oxidants and transition-metal catalysts, and with little effort at room temperature (Yang & Yuan, 2018).

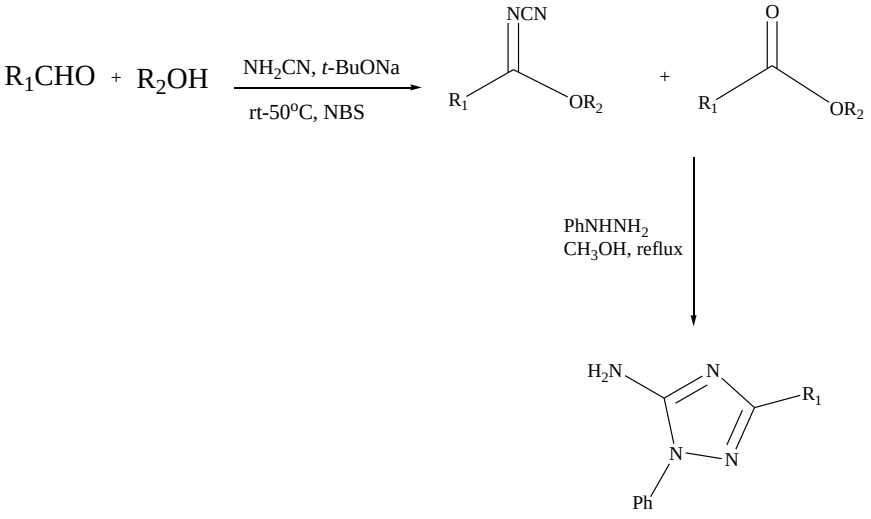


Xu et al. have devised a facile and efficient one-pot process catalyzed by copper to produce 1,2,4-triazole derivatives. In this procedure, nitriles and hydroxylamine hydrochloride, both easily accessible, are used as starting materials, while an affordable form of $Cu(OAc)_2$ is used as the catalyst. The catalytic cycle was completed without the need for an inert environment.

The corresponding 1,2,4-triazole derivatives were reportedly formed in medium to high yield in the one-pot reactions by sequentially intermolecular adding hydroxylamine to one nitrile to amidoxime, treating the amidoxime with another nitrile using a copper catalyst, and undergoing intramolecular dehydration cyclization without the addition of ligands or additives. It has been highlighted that the new strategy can tolerate a wide range of functional groups, including ether, C-Cl bonds, nitro, and N-heterocycles, and that it surpasses previous procedures economically and practically. Hence, it allows the design of a wide range of valuable compounds (Xu et al., 2015).

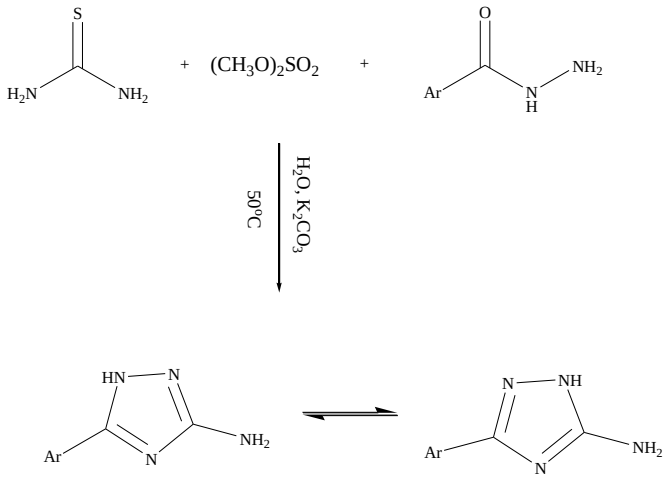


Yin et al. devised an efficient one-pot process for the cyanoimidation of aldehydes by utilizing cyanamide. The reaction took place with the NBS acting as an oxidant without the aid of a catalyst. In the next process, N-cyanobenimidate underwent cyclization reactions to produce 1,2,4-triazoles in high yields (Yin et al., 2009).

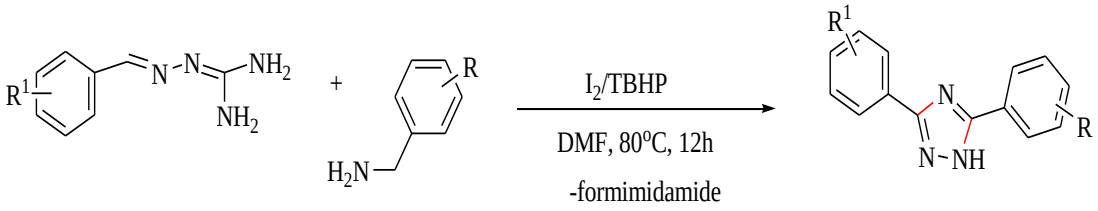


Beyzaei et al. proposed a method for efficiently synthesizing 3(5)-substituted 1,2,4-triazol-5(3)-amines in the presence of K_2CO_3 as an effective base through a one-pot synthesis involving

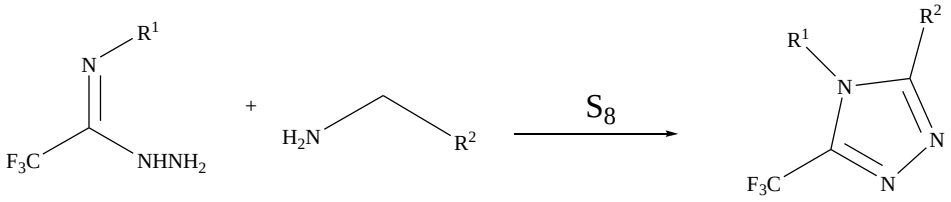
thiourea, dimethyl sulfate, and different hydrazides. It is noted that 1,2,4-triazole derivatives were produced under moderate circumstances and in accordance with certain green chemistry principles. Without additional purification, the products have been readily separated in 83-95% yields (Beyzaei et al., 2019).



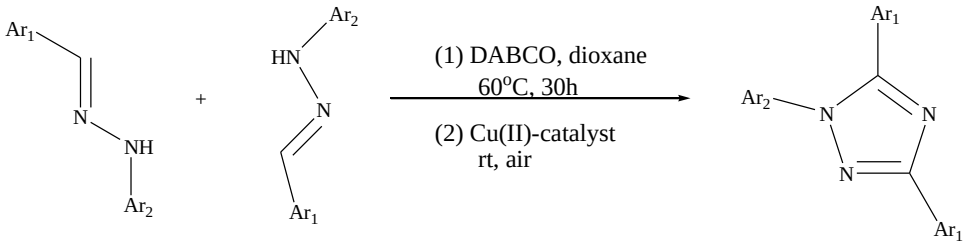
Wani et al. have discovered an effective approach for the straightforward, suitable, transition metal-free one-pot synthesis of 3,5-disubstituted-1,2,4-triazoles employing diaminoazines and benzylamines as substrates. This reaction has produced triazoles with symmetric and asymmetric substituents at moderate reaction conditions. In comparison to other approaches, it has been noted that this method offers products with a more extensive substrate range, faster production, and generally higher yields (Wani et al., 2021).



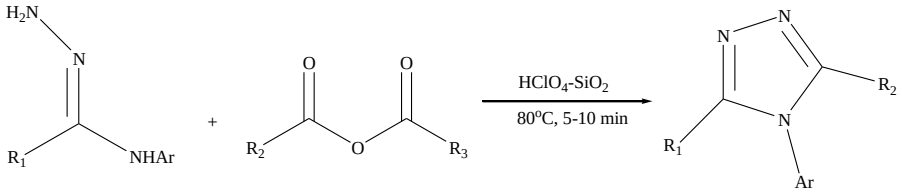
Lu et al. have developed a method for directly synthesizing 5-trifluoromethyl-1,2,4-triazoles in medium to good yields employing the elemental sulfur-mediated oxidative cyclization of aliphatic amines and trifluoroacetimidohydrazides. In this reaction, sulfur functions as a traceless oxidizer. It is noted that the metal-free procedure is distinguished by easily accessible reagents, a wide range of substrates, and promising applications (Lu et al., 2022).



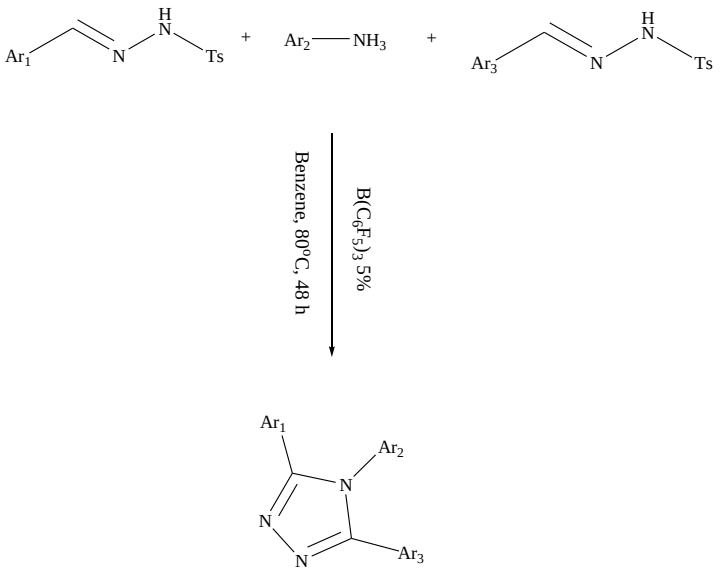
Tian et al. produced 1,2,4-triazole via decarboxylating and cyclizing 2-aryl-2-isocyanate from aryl diazonium salts. Using 1,4-diazocyclic [2,2,2]octane (DABCO) as a weak base was critical in this metal-free reaction (Tian et al., 2021).



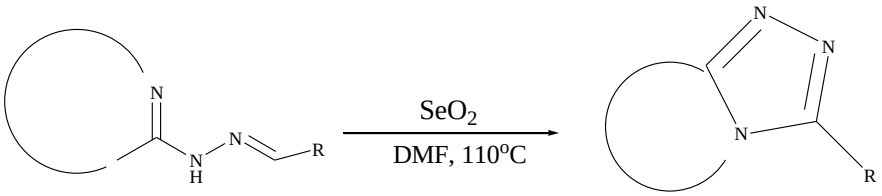
Siddaiah et al. discovered that using $HClO_4$-SiO_2 as a catalyst, 1,2,4-triazole compounds may be synthesized at 80°C with medium to high yields (55-95%). The amide hydrazone and anhydride substituents exhibit excellent tolerance under optimal conditions, and the $HClO_4$-SiO_2 catalyst was able to be recycled at least three times continuously (Siddaiah et al., 2011).



A metal-free catalytic approach for dehydrogenation cyclization based upon $B(C_6F_5)_3$ was disclosed by Guru et al. $B(C_6F_5)_3$ started a nucleophilic attack on the hydrazine part of the molecule, which was followed by amination, intramolecular cyclization, and dehydrogenation to make 3,4,5-trisubstituted-1,2,4-triazole with an 85% yield. This reaction pathway was characterized by its absence of oxidants, green economy, mild conditions, and selectivity providing a feasible platform for catalytic chemical transformation without the need for transition metals (Guru et al., 2019).



Zheng et al. described an effective and practical approach for generating 1,2,4-triazoles via the oxidative cyclization of hydrazones through the use of SeO_2. Through intramolecular oxidative cyclization between selenium dioxide and heterocyclic hydrazones, a series of fused 1,2,4-triazoles are formed. Based upon these compounds, which have a moderate to excellent yield of 1,2,4-triazolo [4,3-a] pyrimidines, 1,2,4-triazolo [4,3-a] pyridines, and 1,2,4-triazolo-[4,3-a] quinoxalines the straightforward application of this method was confirmed (Zheng et al., 2015).



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ANTIOXIDANT PROPERTIES OF 1,2,4-TRIAZOLES

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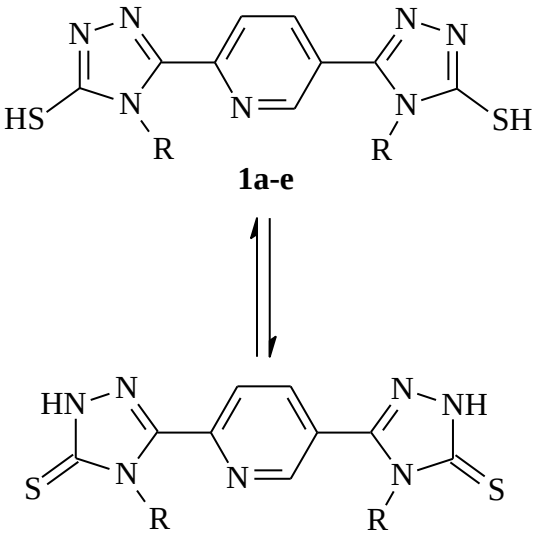
Antioxidant Properties of 1,2,4-Triazoles

In recent years, interest in endogenous and exogenous antioxidants that delay or prevent the oxidation of biomolecules has been increasing. The production of synthetic antioxidants that do not harm the organism and their effects on oxidant-antioxidant balance in biological systems are being investigated (Hussain et al., 2003). Endogenous chemicals formed from exogenous and metabolic reactions can form highly reactive free radicals. Oxygen-origin radicals can oxidize biomolecules to cause cell damage and cell death. Oxidative stress plays an essential role in the pathology of diseases. Excessive production of reactive oxygen species (ROS) and insufficient antioxidant capacity cause various physio-pathological events in organisms such as inflammation, diabetes, genotoxicity, and cancer (McClements & Decker, 2000). Moreover, there are claims that oxidative stress plays a crucial role in tissue damage related to various diseases such as cancer, rheumatoid arthritis, osteoporosis, polycystic ovarian syndrome, Alzheimer's, and Parkinson's (Harmankaya et al., 2021; Phaniendra et al., 2015). Many natural or synthetic antioxidants, known as exogenous, are believed to affect health and disease prevention positively (Harmankaya & Harmankaya, 2022).

Considering that 1,2,4-triazole fused heterocycles have antioxidant properties besides some other biological activities, in this section different 1,2,4-triazole derivatives are discussed in terms of their antioxidant abilities.

Bulut et al. synthesized a novel 1,2,4-triazole-3-thiol series (Figure 1) and evaluated them for *in vitro* antioxidant activity. Among the synthesized compounds, the derivative 1a substituted with the aromatic phenyl group showed the highest DPPH$^{\cdot}$ scavenging activity, while bulk substituted 1e showed the least activity (Bulut et al., 2018).

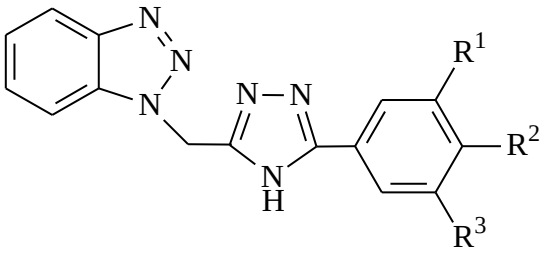


1a-e

a: R=phenyl
b: R=ethyl
c: R=3-methoxyphenyl
d: R=1-naphtyl
e: R=3-(4-morpholino)propyl

Figure 1. 5,5′-pyridine-2,5-diylbis (4-substituted 4*H*-1,2,4-triazole-3-thiol) series (Bulut et al., 2018).

Some new 1-(((aryl)-3-yl)-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazoles have been synthesized and then evaluated for their antimicrobial and antioxidant activities. The study reported that the presence of the -*OH* group at the *para* positions in 2a and 2b (Figure 2) made these compounds good antioxidants due to possible extended conjugation after hydrogen radical abstraction (Chand et al., 2018).



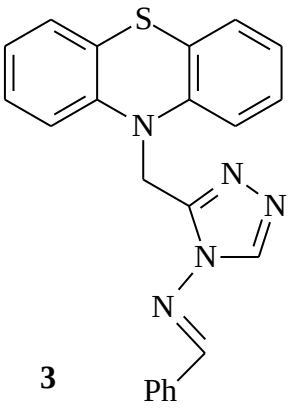
2

2a R^1=H, R^2=OH, R^3=OCH_3
2b R^1=R^3=H, R^2=OH

Figure 2. 1-Substitue-4*H*-(1,2,4)-triazol-5-ylmethyl)-1*H*-benzotriazoles (Chand et al., 2018).

A series of novel 5-((10*H*-phenothiazin-10yl)methyl)-4-(substitutedbenzylidene-amino)-4*H*-1,2,4-triazole-3-thiol derivatives (3a-i) synthesized. All the novel compounds (Figure 3) were screened for their *in vitro* antioxidant activity by using nitric oxide, hydrogen peroxide, and

DPPH· scavenging assays. Compounds 3d, 3e and 3i showed potent antioxidant activity (Maddila et al., 2015).



3

a: Ph=4-Br
b: Ph=4-Cl
c: Ph=4-F
d:Ph=4-MeO
e: Ph=4-OH
f: Ph=2,4-Cl
g: Ph=2,5-Br
h: Ph=3,5-F
i: Ph=3,5-MeO

Figure 3. 5-((10*H*-Phenothiazin-10yl)methyl)-4-(substitutedbenzylideneamino)-4*H*-1,2,4-triazole-3-thiol compounds (Maddila et al., 2015).

Ünver et al. prepared novel tiophene-1,2,4-triazole-5(3)-ones (Figure 4) and evaluated their antioxidant capacity by ferric reducing antioxidant power (FRAP) assay and DPPH radical scavenging assay. The results revealed that all the compounds were active in FRAP assay, while thiosemicarbazide derivatives (4a-d) were very active and triazole-thiol derivatives (5a-d) and Schiff bases 6d and 7d showed low activity in DPPH· scavenging assay (Ünver et al., 2014).

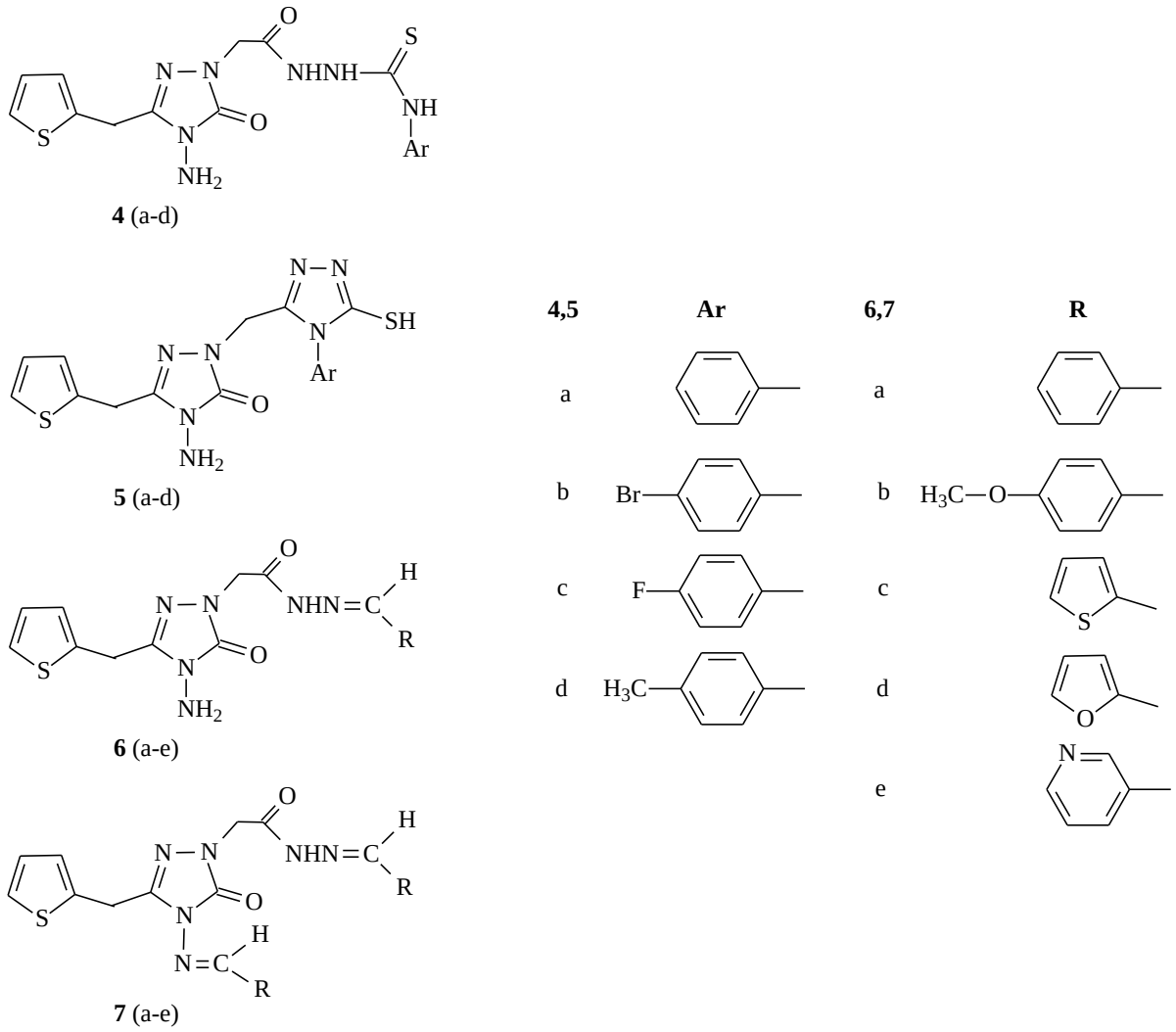


Figure 4. Structures of compounds 4, 5, 6 and 7 (Ünver et al., 2014).

Cetin and Gecibesler synthesized a series of 1,2,4-triazole derivative compounds (Figure 5) substituted with groups of phenol and pyridine and screened their antioxidant properties by various antioxidant assays to determine the effect of substituted functional groups to 1,2,4-triazole rings. The present study demonstrated that phenol and pyridine substituted 1,2,4-triazole compounds would be a better perspective in developing antioxidant agents (Cetin & Gecibesler, 2015).

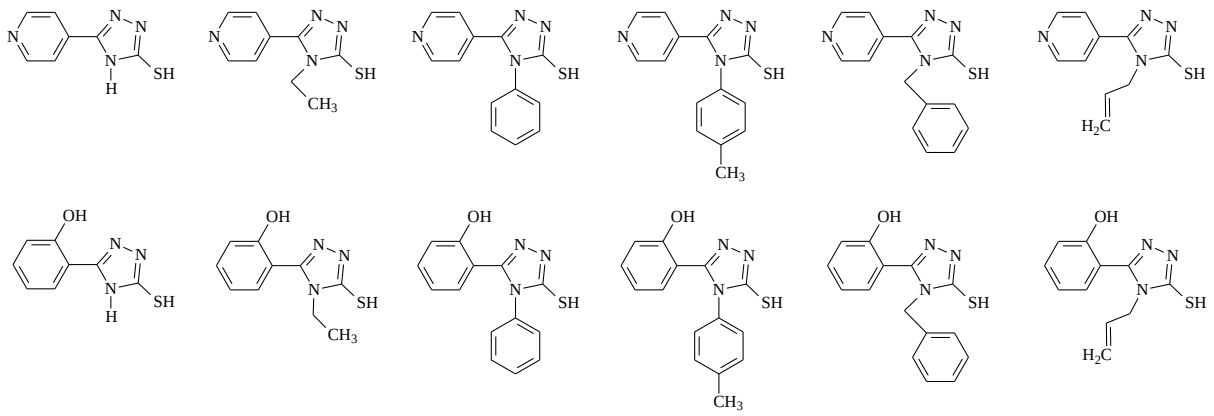


Figure 5. Structures of 1,2,4-triazole derivatives (Cetin & Gecibesler, 2015).

Yehye et al. synthesized new derivatives of the antioxidant butylated hydroxytoluene (BHT), which are Schiff base-1,2,4-triazoles as a new multipotent antioxidant series (Figure 6). The synthesized compounds were screened by DPPH radical scavenging bioassay to determine their antioxidant activities. The synthesized compounds inhibited stable DPPH free radicals at a level 10^{-4} M higher than the standard antioxidant BHT (Yehye et al., 2016).

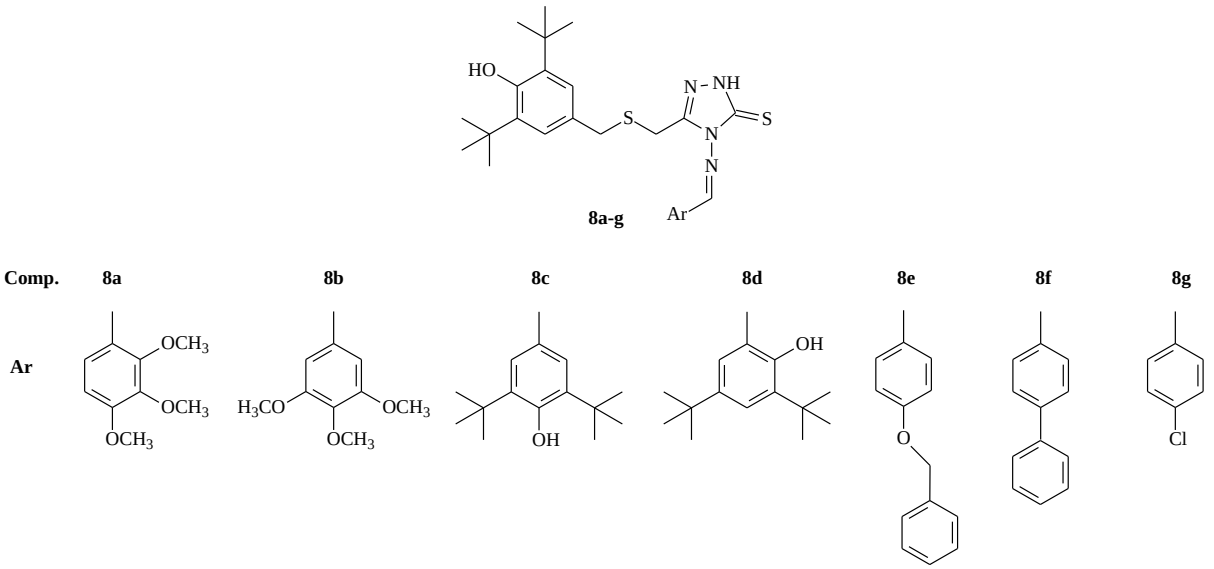
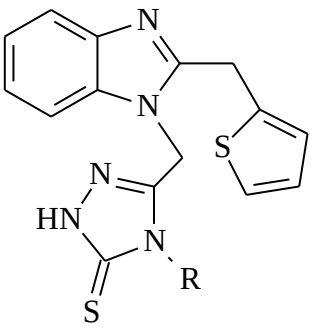


Figure 6. A novel series of 4-(Substituted benzylideneamino)-3-(3,5-di-tert-butyl-4-hydroxybenzyl thio)methyl)-1*H*-1,2,4-triazole-5(4H)-thiones (Yehye et al., 2016).

A series of 4-substitute-5-{[2-(thiophen-2-ylmethyl)-1*H*-benzimidazol-1-yl]methyl}-4*H*-1,2,4-triazole-3-thiones (Figure 7) were synthesized and their antioxidant activities were determined with Cupric Reducing Antioxidant Capacity (CUPRAC), ABTS (2,2-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)/persulfate, and DPPH (1,1-diphenyl-2-picrylhydrazyl)

assays. Compound 9f demonstrated very good antioxidant capacity in the CUPRAC method. Compounds 9a-d and 9f showed very good ABTS scavenging activity (Menteşe et al., 2015).



9

R= **a**: CH_3, **b**: CH_2CH_3, **c**: C_6H_5, **d**: *p*-C_6H_4-F, **e**: *p*-C_6H_4-Br, **f**: *m*-C_6H_4-I, **g**: *p*-C_6H_4-CH_3, **h**: *p*-C_6H_4-NO_2

Figure 7. A novel series of 4*H*-1,2,4-triazole-3-thione derivatives (Menteşe et al., 2015).

In 2014, novel triazole-thiol derivatives obtained, and their antioxidant properties was screened by DPPH· scavenging method. 4,4'-(Butane-1,4-diyl/Hexane-1,6-diyl)-bis(2-((4-(4-halogenophenyl)-5-mercapto-4*H*-1,2,4-triazole-3-yl)methyl)-5-methyl-2*H*-1,2,4-triazole-3(4*H*)-one compounds 10a / 10b / 11a / 11b (Figure 8) showed moderate activity with IC50 value of 40 ± 2.7 / 40 ± 0.9 / 36 ± 0.9 / 10 ± 0.7, respectively. BHT was used as a positive control with IC50 value of 19.8 ± 0.5 (Düğdü et al., 2014).

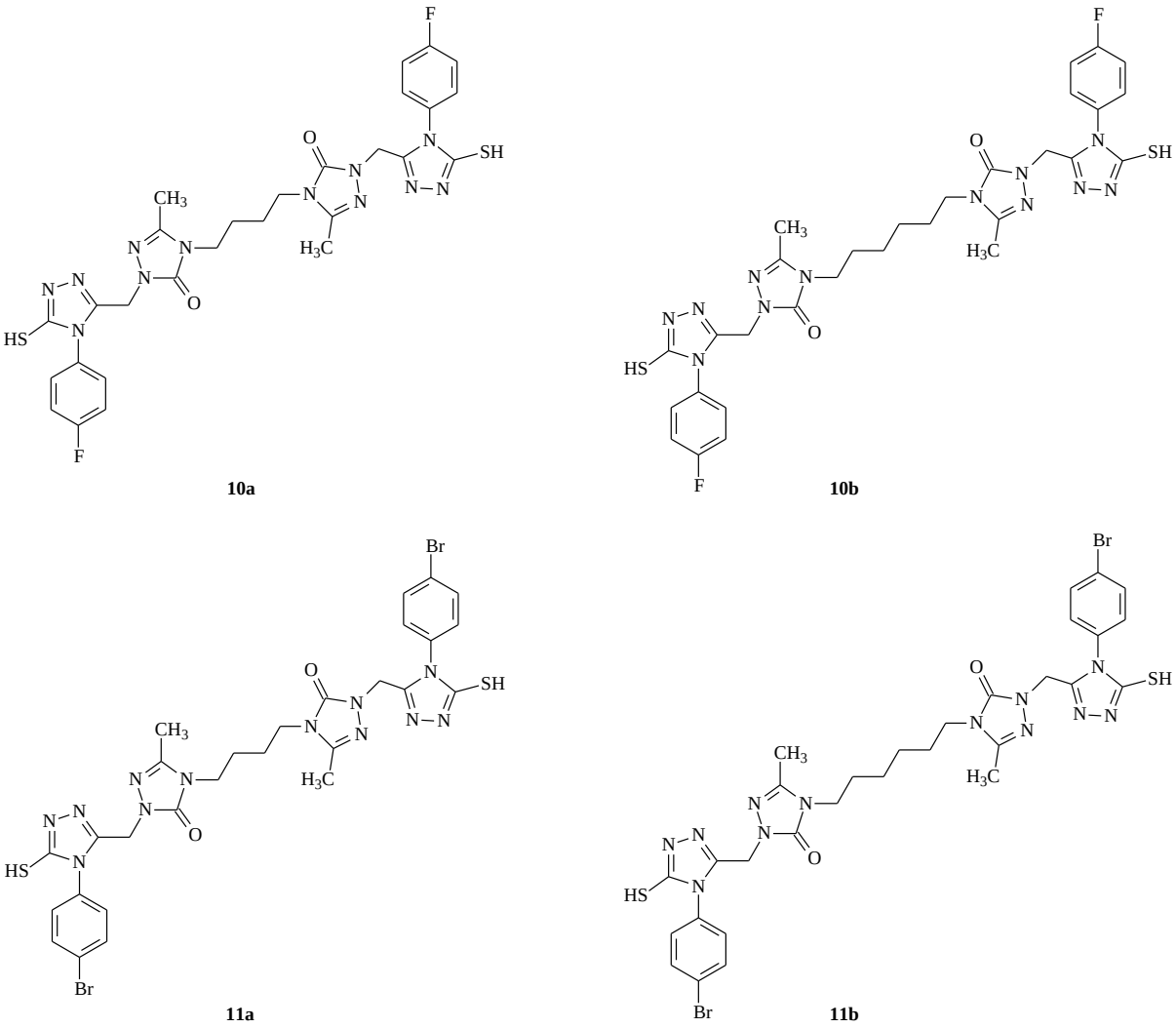


Figure 8. Structures of compounds 10a, 10b, 11a and 11b (Düğdü et al., 2014).

Barbuceanu et al. prepared a novel series of 1,2,4-triazole-3-thiones (12-14) and S-alkylated 1,2,4-triazoles (15–20) (Figure 9). The free radical scavenging activity of the compounds was carried out by DPPH· assay using ascorbic acid, *tert*-butyl-4-hydroxyanisole (BHA) and BHT antioxidant agents as the positive control. The inhibitory effect of 1,2,4-triazole-3-thiones was good, but S-alkylated 1,2,4-triazoles had a weak effect at the same concentration (Barbuceanu et al., 2014).

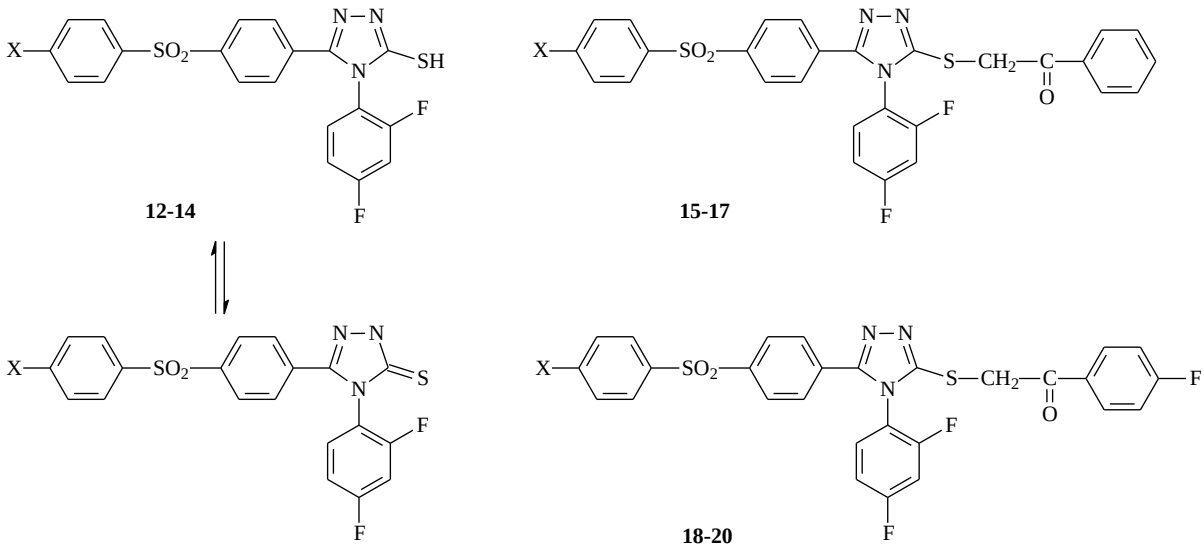


Figure 9. Novel series of 1,2,4-triazole-3-thiones (12-14) and S-alkylated 1,2,4-triazoles. X=H: 12, 15, 18; X=Cl: 13, 16, 19; X=Br: 14, 17, 20 (Barbuceanu et al., 2014).

4-Amino-3-(4-(((4-hydroxy-3,5-dimethoxybenzyl)-oxy)-methyl)-phenyl)-1,2,4-triazole-5-thione (21) and a series of its new Schiff Bases, 4-((arylidine)amino)-3-(4-(((4-hydroxy-3,5-dimethoxybenzyl)-oxy)-methyl)-phenyl)-1,2,4-triazole-5-thiones (22a-f), synthesized. Then the compounds (Figure 10) were tested for antioxidant activity by DPPH· and FRAP assays. All the compounds showed high antioxidant ability in both assays, especially compound 21. Within the Schiff bases, compound 22e exhibited higher antioxidant ability in both assays. The study was revealed that the type substituted in hydroxybenzylidene played a significant role in enhancing antioxidant ability (Hussain, 2016).

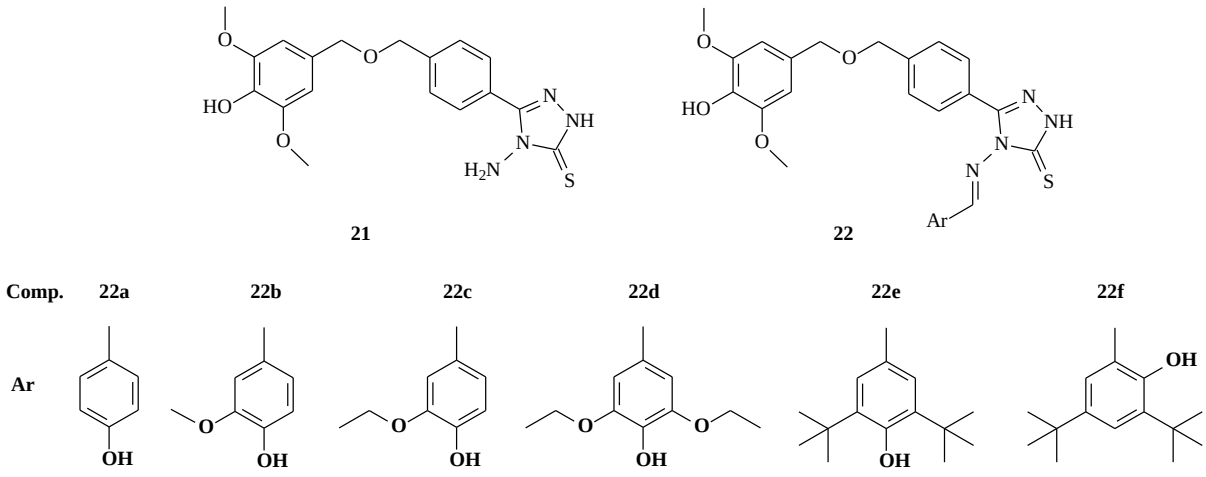
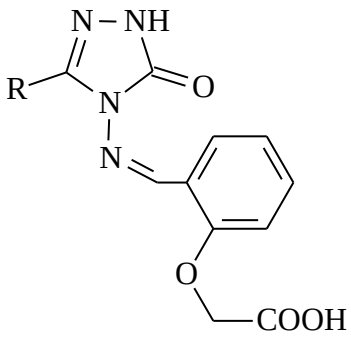


Figure 10. Structures of compounds 21, 22 (Hussain, 2016).

Çiftçi et al. synthesized a novel series of 2-[3-alkyl(aryl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl] phenoxyacetic acids (Figure 11) which were analyzed for their *in vitro* antioxidant and antibacterial properties. The compounds were also tested in the comet assay. Reducing power, free radical scavenging and metal chelating activity was used to determine the antioxidant activity. 2-(3-*p*-Methoxybenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-phenoxyacetic acid (23f) and 2-(3-*m*-chlorobenzyl-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl)-phenoxyacetic acid (23h) compounds demonstrated significant activity in the metal chelating activity, antimicrobial and comet assay tests (Çiftçi et al., 2018).

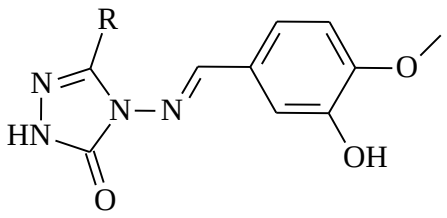


23

R= **a**: CH_3, b: CH_2CH_3, **c**: $CH_2CH_2CH_3$, **d**: $CH_2C_6H_5$, **e**: $CH_2C_6H_4CH_3$ (*p*-), **f**: $CH_2C_6H_4OCH_3$ (*p*-), **g**: $CH_2C_6H_4$.Cl (*p*-), **h**: $CH_2C_6H_4$.Cl (*m*-), **i**: C_6H_5

Figure 11. 2-[3-alkyl(aryl)-4,5-dihydro-1*H*-1,2,4-triazol-5-one-4-yl] phenoxyacetic acids (Çiftçi et al., 2018).

A series of new 3-alkyl(aryl)-4-(3-hydroxy-4-methoxybenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones were synthesized (Figure 12). The synthesized compounds were analyzed for their *in vitro* antioxidant activities using three methods. Compounds 24f and 24h showed significant activity for iron chelating and DPPH radical scavenging activity (Bahçeci et al., 2016).

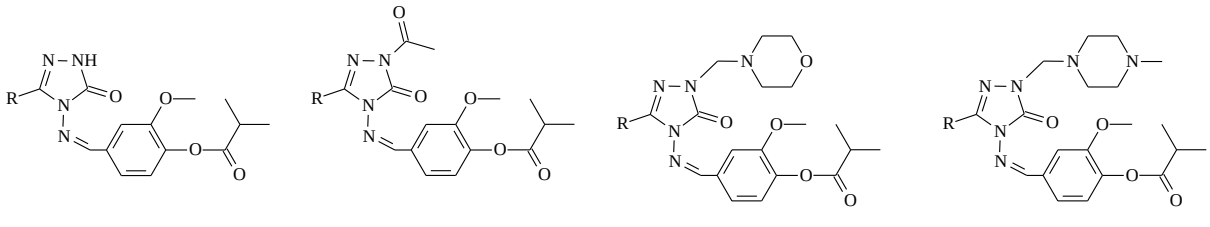


24

24	R
a	CH_3
b	CH_2CH_3
c	$CH_2CH_2CH_3$
d	$CH_2C_6H_5$
e	$CH_2C_6H_4.CH_3$ (*p*-)
f	$CH_2C_6H_4.OCH_3$ (*p*-)
g	$CH_2C_6H_4.Cl$ (*p*-)
h	$CH_2C_6H_4.Cl$ (*m*-)
i	C_6H_5
j	cyclopropyl

Figure 12. A series of new 3-alkyl(aryl)-4-(3-hydroxy-4-methoxybenzylideneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-ones (Bahçeci et al., 2016).

In 2020, some new Schiff bases and their Mannich bases (25-28) were synthesized, and *in vitro* antioxidant and antimicrobial properties of the new compounds were investigated (Figure 13). Three different methods were used for the determination of antioxidant activity. BHT, BHA, EDTA and α-tocopherol were used as the reference antioxidants. The results of some compounds were not considered as they were not significant. The scavenging effect of the compounds and references decreased in order of α-tocopherol > BHA > BHT > 28a > 25c > 25e > 27b > 25a > 25b > 25i > 28d, which were 74.9, 74.3, 65.8, 19.3, 16.0, 12.4, 9.6, 9.3, 8.2, 7.2, 5.3 (%), at the highest concentration, respectively. The compounds, except 25c-e, demonstrated a marked capacity for iron binding. Mannich bases were more active when compared to Schiff bases for all concentrations (Manap et al., 2020).

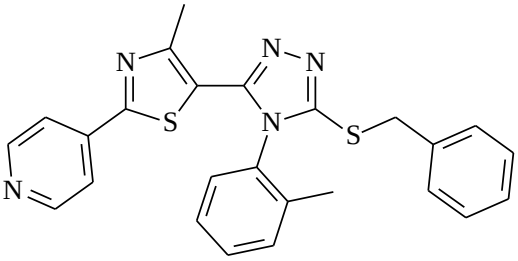


25 **26** **27** **28**

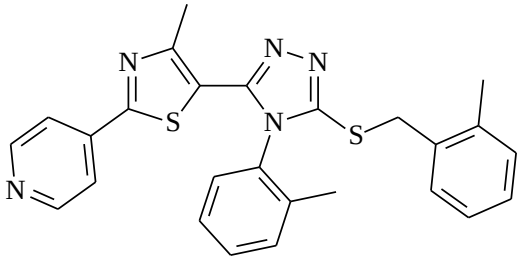
R= **a**: CH_3, b: CH_2CH_3, **c**: $CH_2CH_2CH_3$, **d**: $CH_2C_6H_5$, **e**: $CH_2C_6H_4CH_3$ (*p*-), **f**: $CH_2C_6H_4OCH_3$ (*p*-), **g**: $CH_2C_6H_4.Cl$ (*p*-), **h**: $CH_2C_6H_4.Cl$ (*m*-), **i**: C_6H_5

Figure 13. Structures of compounds 25-28 (Manap et al., 2020).

Tay et al. synthesized 63 different 5-[4-methyl-2-(pyridin-3/4-yl)thiazole-5-yl]-4-substituted-3-substitutedbenzylthio-4*H*-1,2,4-triazole derivatives and screened for their antibacterial, antifungal, and antioxidant properties. The compounds possessing 4-pyridyl moiety displayed marked antioxidant activity, especially compounds 29 and 30 (Figure 14) showed the highest antioxidant activity (Tay et al., 2022).



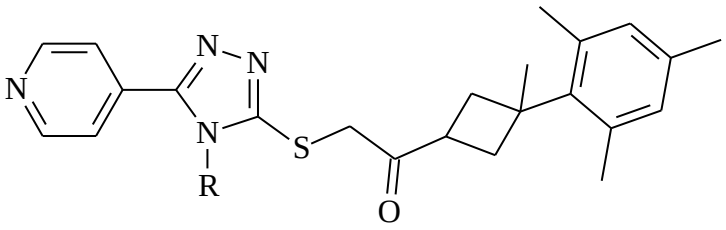
29



30

Figure 14. 5-[4-Methyl-2-(pyridin-4-yl)thiazole-5-yl]-4-(2-methylphenyl)-3-benzylthio-4*H*-1,2,4-triazole (29) and 5-[4-Methyl-2-(pyridin-4-yl)thiazole-5-yl]-4-(2-methylphenyl)-3-(2-methylbenzylthio)-4*H*-1,2,4-triazole (30) (Tay et al., 2022).

3,4,5-Trisubstituted 1,2,4-triazole sulfonyl compounds containing a cyclobutane ring (Figure 15) were synthesized and evaluated for their antioxidant, antimicrobial, and anti-cancer effects. Compounds 31c and 31e showed activity close to the reference antioxidant BHT. Compound 31d exhibited moderate activity, while compounds 31a and 31b showed the lowest activity (Koparir et al., 2022).

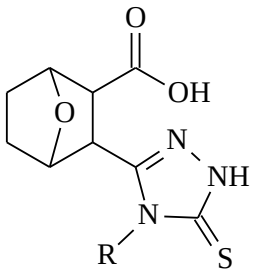


31

R= **a:** Ethyl, **b:** Allyl, **c:** Phenyl, **d:** Benzyl, **e:** *p*-Tolyl

Figure 15. Structures of compound 31 (Koparir et al., 2022).

In 2019, new norcantharidin analogs with the 1,2,4-triazole system (Figure 16) were obtained and screened for antioxidant activities. Promising activity with EC50=10.75 μg/ml presented compound 32f compared to the reference antioxidant Trolox (EC50=6.13 μg/ml) (Pachuta-Stec et al., 2019).



32

R= **a**: C_6H_5, **b**: C_6H_4.Cl (*o*-), **c**: C_6H_4.Cl (*p*-), **d**: C_6H_4.F (*p*-), **e**: $C_6H_4.CH_3$ (*o*-), **f**: CH_2CH_3, **g**: 2-(Morpholin-4-yl)ethyl

Figure 16. Norcantharidin analogs with the 1,2,4-triazole system (Pachuta-Stec et al., 2019).

Aouali et al. synthesized new imidazo[2,1-c][1,2,4]triazole derivatives and tested some of them (Figure 17) for their antibacterial, antifungal and antioxidant activities. The compounds were screened for *in vitro* antioxidant activity using DPPH· scavenging assay and exhibited significant effects compared to the reference antioxidants BHA and α-tocopherol. DPPH· scavenging capacities of the compounds were in the following order: 36 > 33 > 34 > 35. Compound 34 showed significant antifungal and antioxidant activity, suggesting a possible clinical significance (Aouali et al., 2015).

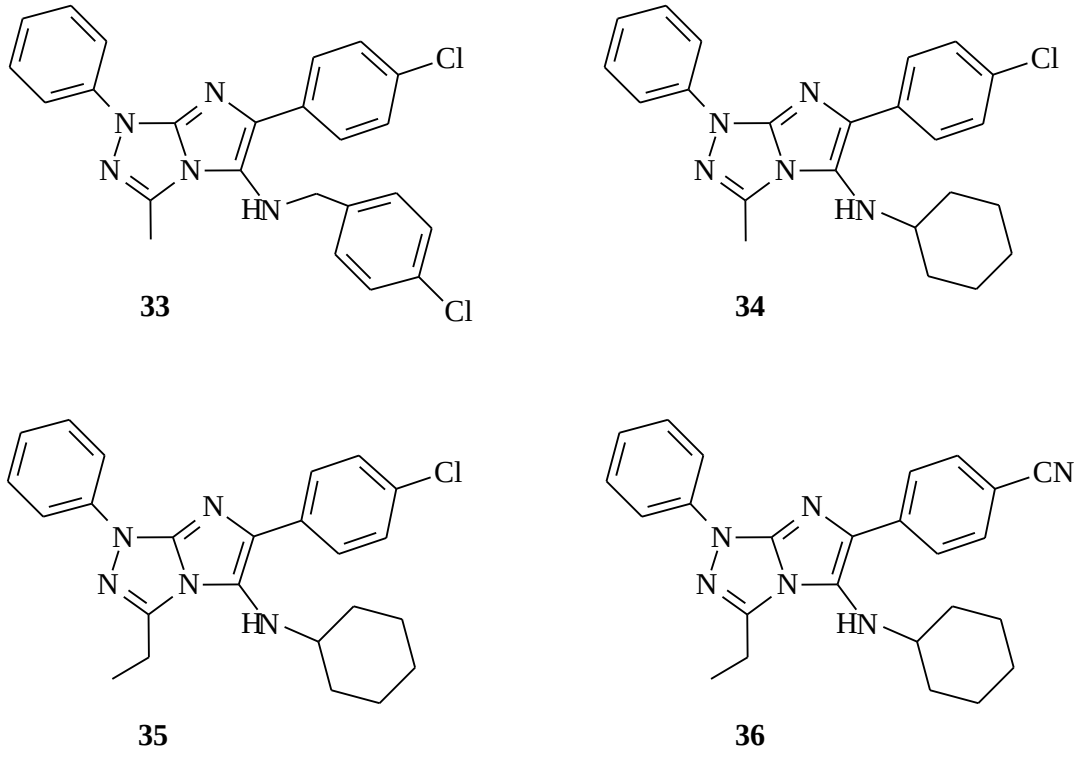


Figure 17. Structures of imidazo[2,1-c][1,2,4]triazole derivatives (Aouali et al., 2015).

Bekircan et al. obtained a series of 1,2,4-triazole derivatives containing fluorine (Figure 18) and screened them for potential antioxidant activity, and urease and xanthine oxidase inhibition activities. CUPRAC assay, 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS), and DPPH methods were used to determine the synthesized compounds' antioxidant activities. Compounds 44a and 44b displayed the highest antioxidant capacity for the CUPRAC method and showed significant DPPH radical scavenging activity. Finally, according to the CUPRAC and ABTS methods; 38a, 38b, 40a, 40b, 41a, 41b, 43a, 43b, 44a, and 44b compounds showed good antioxidant activity (Bekircan et al., 2016).

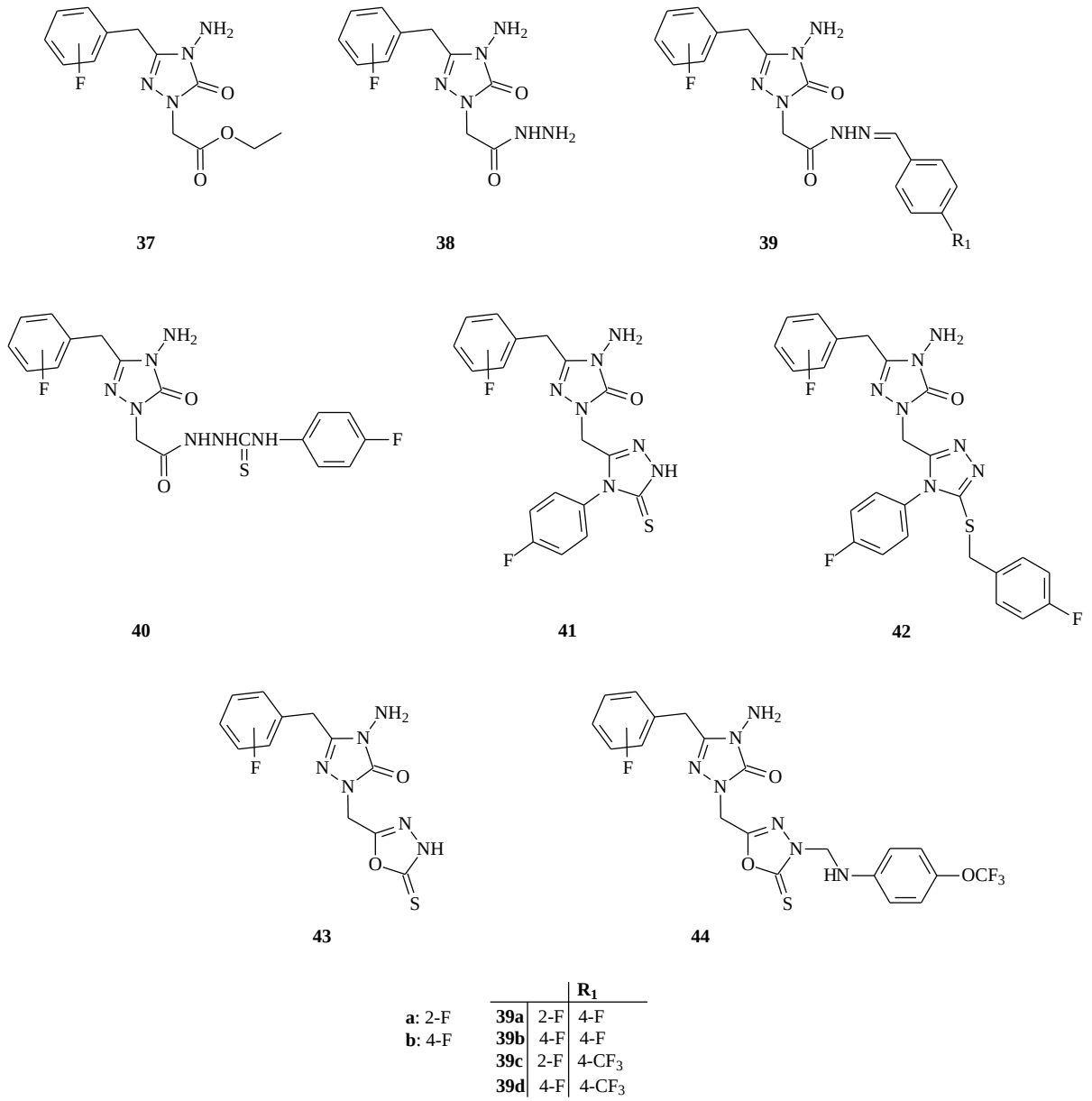


Figure 18. Structures of fluorine-containing 1,2,4-triazole derivatives (Bekircan et al., 2016).

New 1,2,4-triazole compounds (Figure 19) possessing Schiff and Mannich bases were synthesized and tested for their antioxidant and antimicrobial properties. DPPH radical scavenging and FRAP methods were carried out, and the newly synthesized compounds demonstrated antioxidant effect in both tests at various extends. Compound 46 (triazole-thiol) had the highest antioxidant activity in both assays. Moreover, as Schiff bases turned into Mannich bases, their antioxidant activities decreased, and it was determined that the type of substituent on the thiophene ring was effective on antioxidant property. The order of influence of the substituent type of the thiophene ring on the antioxidant activity was $–CH_3$ > $–NO_2$ > –Br > –H for both Schiff and Mannich bases (Ünver et al., 2016).

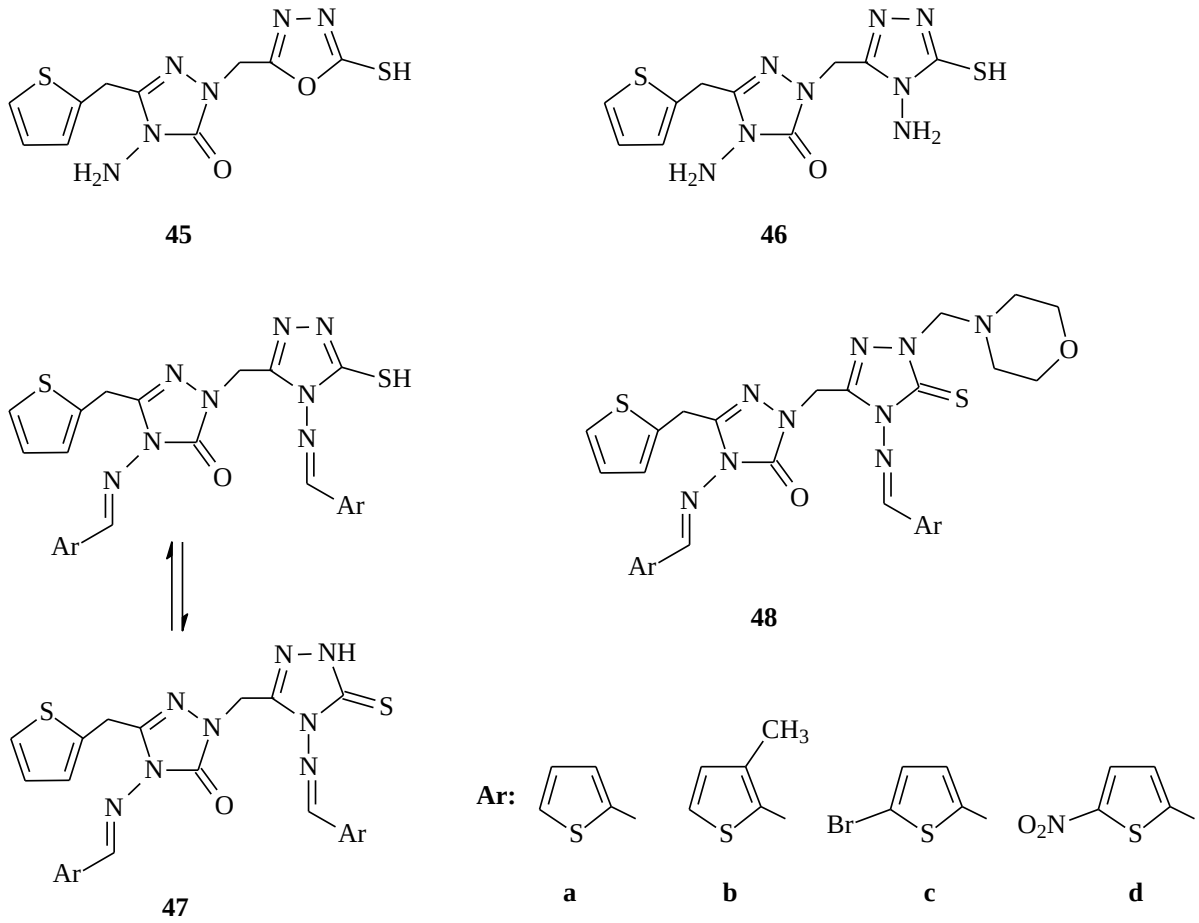
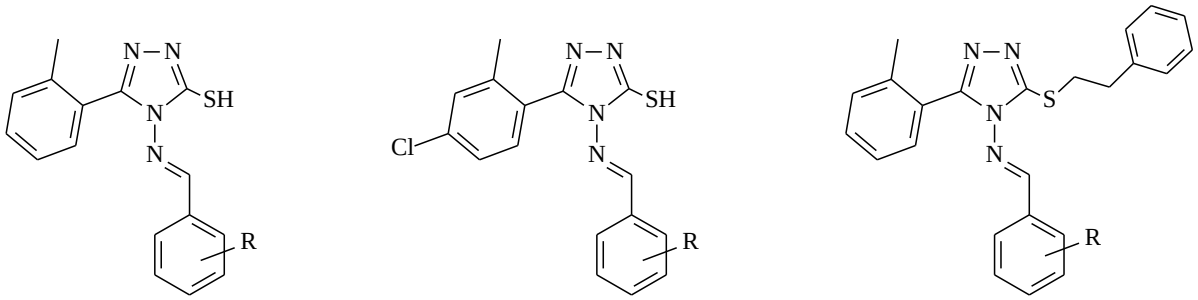


Figure 19. Structures of compounds 45-48 (Ünver et al., 2016).

A new series of 4-[(*E*)-benzylideneamino]-5-(2-methylphenyl)-4*H*-1,2,4-triazole-3-thiols (49a–h), 4-[(*E*)-benzylideneamino]-5-(4-chloro-2-methylphenyl)-4*H*-1,2,4-triazole-3-thiols (50a–i), and (*E*)-N-(benzylidene)-3-(phenethylthio)-5-*o*-tolyl-4*H*-1,2,4-triazole-4-amines (51a–h) (Figure 20) were obtained and screened for antioxidant activities by free-radical scavenging, anti-hemolytic activity, lipid peroxidation, and their protective effects against DNA oxidative damage. Compounds 50b, 50i, 51c, 51d, and 51h exhibited significant DPPH· scavenging effect with the level of inhibition between 86.8% and 94% when compared to BHT 90.4% (Aswathanarayanappa et al., 2013).

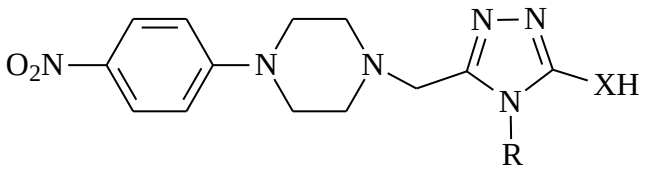


49a-h **50a-i** **51a-h**

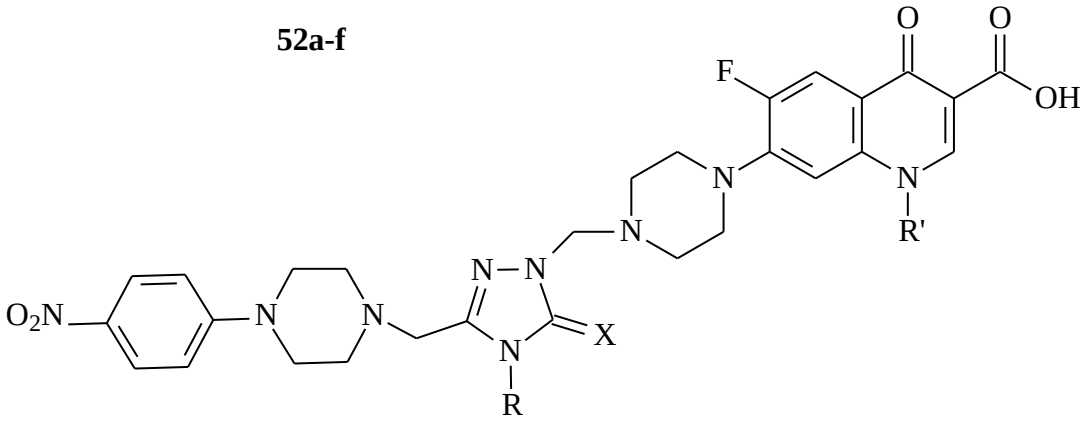
R			
49a, 50a, 51a	2,4-F	49f, 50f, 51f	3-F-4-CF_3
49b, 50b, 51b	2,5-OH	49g, 50g, 51g	4-OCH_3
49c, 50c, 51c	2-F	49h, 51h	4-$CH(CH_3)_2$
49d, 50d, 51d	3-F	50h	H
49e, 50e, 51e	5-Br-2-OH	50i	4-OH

Figure 20. New 1,2,4-triazole-based Schiff base heterocycles 49-51 (Aswathanarayanappa et al., 2013).

Menteşe et al. reported the synthesis, antimicrobial and antioxidant activity screening studies of novel hybrid molecules containing several heterocyclic pharmacophores: Fluoroquinolone, 1,2,4-triazole, 1,3,4-oxadiazole and, piperazine. DPPH·, FRAP, and CUPRAC assays were evaluated to determine the antioxidant capacity. Compounds 53j, 53d, and 53c for the DPPH· assay; 53c, 53j, and 53d for the CUPRAC assay, showed the highest antioxidant capacity values, while compounds 52b for DPPH and CUPRAC had the lowest values among the newly synthesized 1,2,4-triazole nucleus containing compounds (Figure 21) (Mentese et al., 2017).



52a-f



53a-f: R'= -C_2H_5; **53g-l**: R'= 

R, X	
52a, 53a, 53g: R= -$CH_2C_6H_5$, X=S	52d, 53d, 53j: R= -C_6H_5, X=S
52b, 53b, 53h: R= -$CH_2C_6H_5$, X=O	52e, 53e, 53k: R= -C_6H_5, X=O
52c, 53c, 53i: R= -CH_2CH_3, X=S	52f, 53f, 53l: R= -C_6H_4F(*p*-), X=S

Figure 21. Structures of compounds 52a-f, 53a-l (Mentese et al., 2017).

In 2013, 5,5'-butane-1,4-diylbis(4-ethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione and their Mannich bases (Figure 22) were synthesized and screened for their antioxidant, antifungal and antibacterial activities. Free radical scavenging activity of the synthesized compounds was determined by DPPH· assay. Compound 54 showed moderate antioxidant activity. From all the synthesized derivatives, compound 55b exhibited the lowest radical scavenging activities, while compound 55f showed the highest scavenging activities, which were better than the reference antioxidant compound. Moreover, compounds 55a, 55d, 55e, 55g, and 55h showed promising activities similar to the reference antioxidant compound (Koparır, 2013).

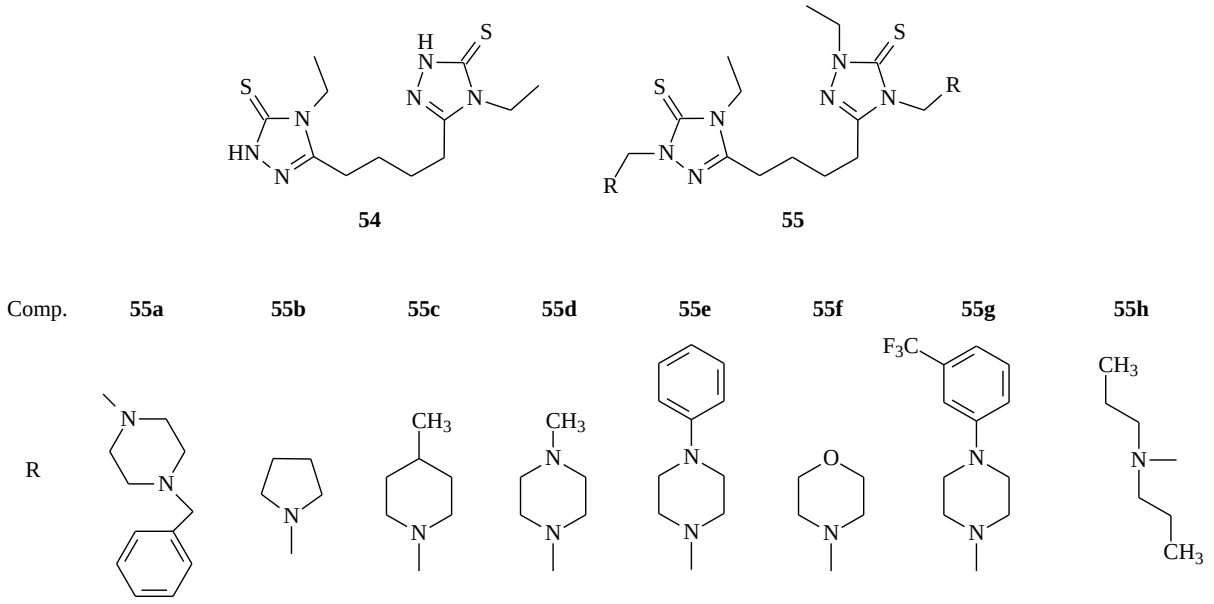


Figure 22. Structures of compounds 54 and 55 (Koparır, 2013).

In 2016, the effects of four selected 55 type compounds (Figure 22) on the levels of *in vivo* malondialdehyde (MDA) and antioxidant vitamins (A, E, C) were investigated in serum, livers, and kidneys of rats. The antioxidant effect was examined *in vitro* by determining the MDA levels in *Saccharomyces cerevisiae* cells. Moreover, the antitumor properties of the compounds were carried out against MCF-7 human breast cancer cells. 5,5'-Butane-1,4-diylbis{4-ethyl-2-((4-methylpiperidin-1-yl)methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione} (55d), 5,5'-butane-1,4-diylbis(4-ethyl-2-({4-(3-(trifluoromethyl)phenyl)piperazin-1-yl}methyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione) (55g) and 5,5'-butane-1,4-diylbis{2-((dipropylamino)methyl)-4-ethyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione} (55h) compounds' substances demonstrated significant antitumor properties, which may be indicated by good antioxidant activity, can be an indication that these compounds showed remarkable pharmacological bioactivity. Although the antioxidant effect of 5,5'-butane-1,4-diylbis(4-ethyl-2-(pyrrolidin-1-ylmethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione) (55b) was low, it was effective against breast cancer (Parlak et al., 2016).

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ANTIBACTERIAL EFFECTS OF 1,2,4-TRIAZOLES

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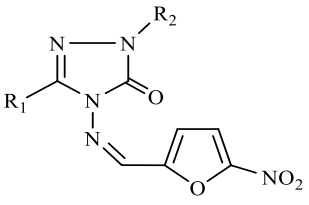
Antibacterial Effects of 1,2,4-Triazoles

Biological activity studies have increased significantly, especially in the last 20 years. While these studies are being tried on different organic compound groups, it is noticed that these studies are concentrated on heterocyclic compounds (Aktaş Yokuş et al., 2017; Beytur et al., 2019; Çiftçi et al., 2018; Yüksek et al., 2022).

Considering the academic studies, the number of studies on the antibacterial effect of 1,2,4-triazole derivatives has increased significantly since the beginning of the 2000s. In some of these studies, activities against Gram-negative and some Gram-positive bacteria were investigated. In some studies, activities against fungi have also been tried.

In a study conducted in the 1980s examining 1,2,4-triazol-3-one derivatives, 10 new compounds were synthesized (Figure 1).



1

	R_1	R_2
1a	CH_3	CH_2CO_2Et
1b	CH_3	$(CH_2)_2OH$
1c	C_2H_5	CH_2CO_2Et
1d	C_2H_5	CH_2CO_2-*n*-propyl
1e	C_2H_5	$(CH_2)_2OH$
1f	C_6H_5	CH_2CO_2-*n*-propyl
1g	C_6H_5	$(CH_2)_2OH$
1h	$p(CH_3O)C_6H_4$	CH_2CO_2Et
1i	$p(CH_3O)C_6H_4$	$(CH_2)_2OH$
1j	$p(Cl)C_6H_4$	CH_2CO_2-*n*-propyl

Figure 1. Formulas of synthesized compounds

A Gram-positive bacterial strain (*Staphylococcus aureus*) and two Gram-negative bacterial strains (*Escherichia coli* and *Pseudomonas aeruginosa*) were selected for the antibacterial activity of the 10 newly synthesized compounds. It is an important result that the activity of all synthesized compounds against Gram-positive bacteria was determined. The most interesting antibacterial activity against the selected *Staphylococcus aureus* was obtained especially in the case where the 2-hydroxy ethyl group (**1g** and **1i**) is located at the N-2 position in aromatic structures (Malbec et al., 1984).

In the early 2000s, in a study to examine the antibacterial properties of compounds containing 1,2,4-triazole ring, 1,2-bis(1,3,4-oxadiazol-2-yl)ethanes and 1,2- bis(4-amino-1,2,4-triazol-3-yl)ethanes compounds were synthesized (Figure 2).

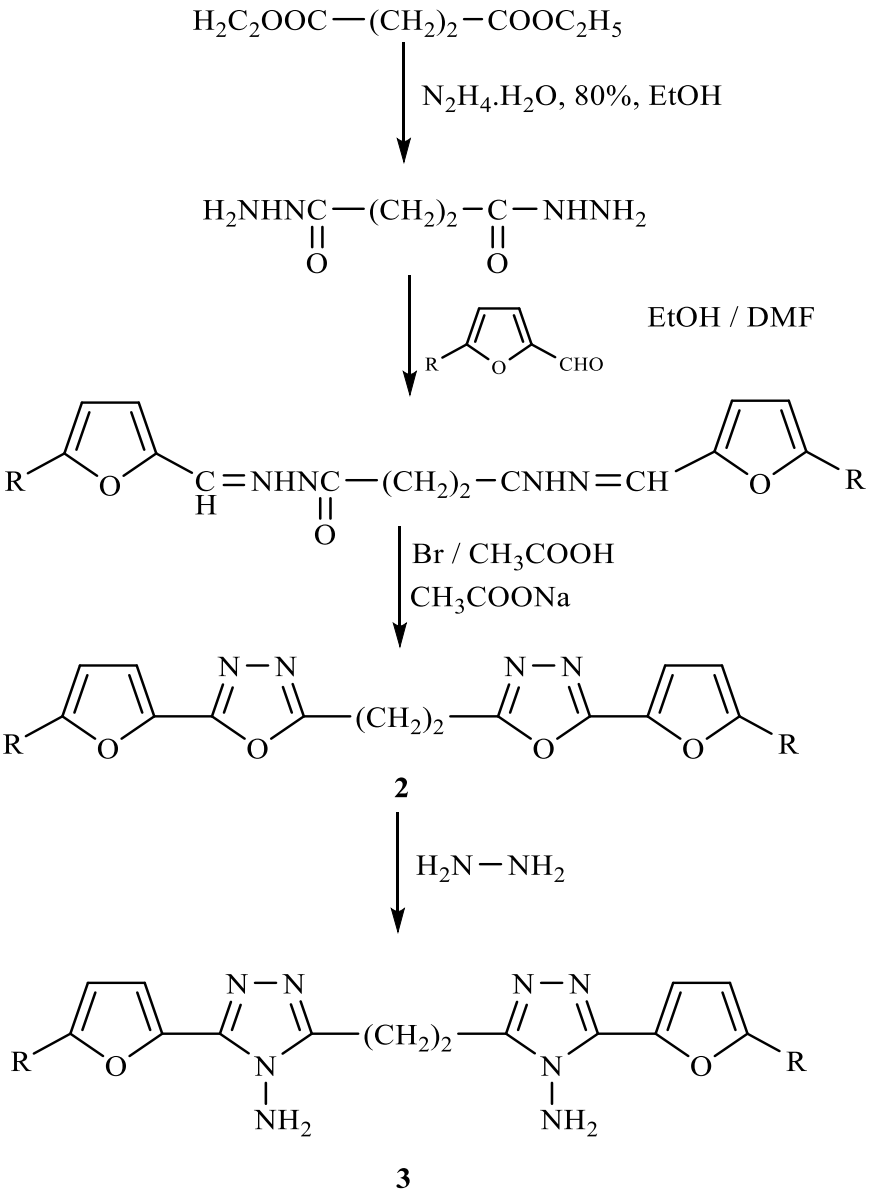


Figure 2. R= a=H, b=NO_2, c=p-nitrophenyl, d=p-chlorophenyl, e=p-bromophenyl, f=1,2,4-dichlorophenyl

When the antibacterial activity of the synthesized bis-oxadiazolylethanes (**2**) and bis-triazolylethanes (**3**) was examined, the presence of activity against selected Gram positive and Gram negative bacteria was determined. Obtaining results that compete with Furacin, which was chosen as the standard drug, was noted as an important result. The antibacterial activity results of the synthesized compounds are given in Table 1 (Holla et al., 2000).

Table 1. Antibacterial activity of bis-oxadiazolylethanes (**2** type) and bis-triazolylethanes (**3** type)

	MIC (μg/mL)			
Compound	*B. subtilis*	*S. aureus*	*P. aeruginosa*	*E. coli*
2c	6	6	6	3
2d	6	6	6	6
2e	6	6	6	12,5
3c	6	6	6	6
3e	6	6	6	6
3f	6	6	6	6
Furacin	12,5	12,5	12,5	6

In a study conducted in 2005, 1,2,4 triazole derivative compounds were synthesized and significant activities were determined especially against *S. aureus*, *S. epidermidis* and *B. subtilis* strains. The synthesis steps of the synthesized compounds are given in Figure 3.

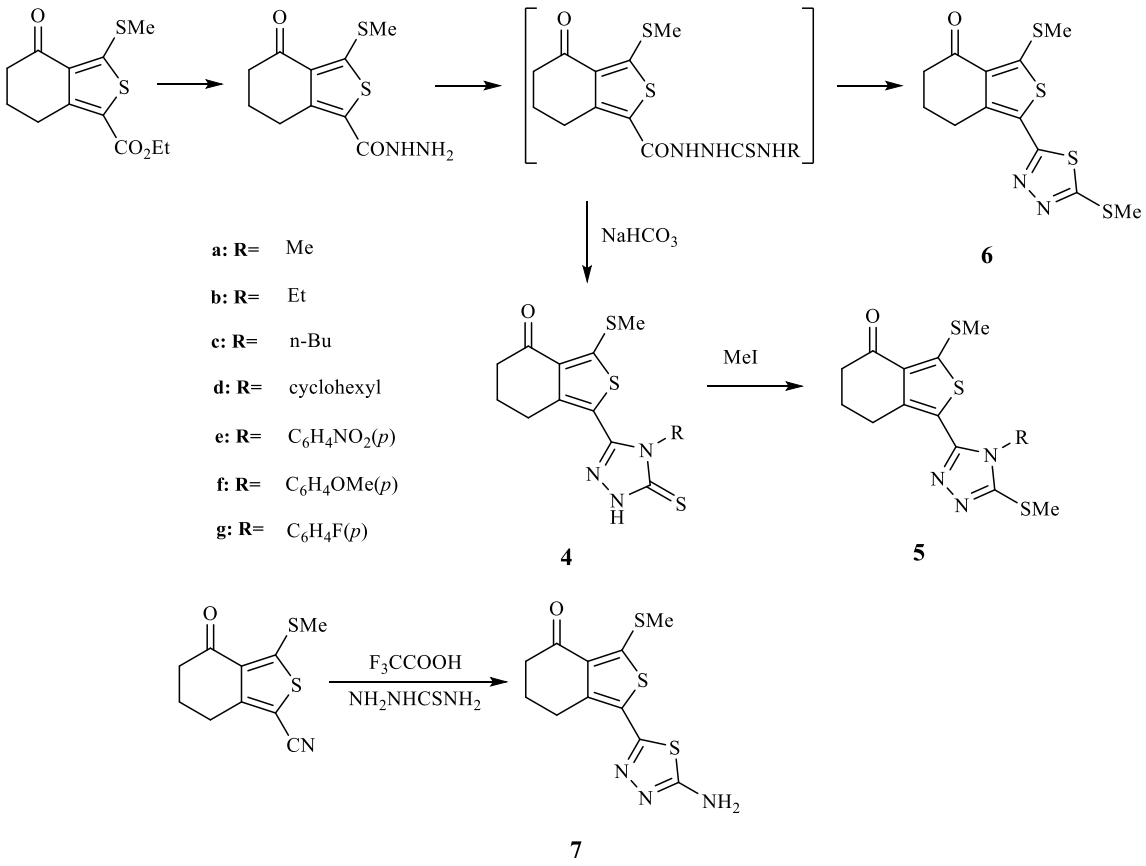


Figure 3. Reaction steps of synthesized compounds

The inhibition zone diameter values obtained as a result of the antibacterial effect examinations of the synthesized compounds are given in the table below.

Table 2. Antimicrobial effect examination data of compounds of type **4-7** (inhibition zone-mm)

Compound	*S. aureus*	*S. epidermidis*	*B. cereus*	*B. subtilis*	*P. aeruginosa*	*E. coli*	*C. albicans*	*A. niger*
4a	-	-	-	-	-	-	-	-
4b	-	-	-	-	-	-	-	-
4c	17	26	-	14	-	-	-	-
4d	-	-	-	-	-	-	-	-
4e	18	25	-	23	14	-	-	-
4f	-	-	-	11	-	-	-	-
4g	-	-	-	-	-	-	-	-
5a	-	-	-	-	-	-	-	-
5b	-	-	-	-	-	-	-	-
5c	17	26	16	16	-	-	-	-
5d	-	-	-	-	-	-	-	-
5e	18	24	12	21	14	-	-	-
5f	-	-	-	-	-	-	-	-
5g	-	-	-	-	-	-	-	-

6a	-	-	-	28	-	-	12	11
6b	-	-	-	20	-	-	13	8
6c	-	-	-	22	-	-	11	9
6d	-	-	-	-	-	-	-	12
6e	-	-	-	33	-	-	14	10
7	-	-	-	-	-	-	-	-
Genta.	23	20	28	30	27	23	NT	NT
Nitrof.	21	-	20	18	21	20	NT	NT
Amph.	NT	NT	NT	NT	NT	NT	22	22

Genta: *Gentamycin*; Nitrof: *Nitrofurantoin*; Amph: *Amphotricin*; NT: Not tested

When the antimicrobial examination results were examined, it was observed that some compounds showed moderate activity and some compounds showed high activity. Activity against Gram-positive bacteria was observed when n-butyl or p-nitrophenyl groups were present at the 4 position of 1,2,4-triazole in compounds of type **4** and **5**. No significant change was observed in the antibacterial effects of compounds **5c** and **5e** obtained from S-methylation of compounds **4**c and **4e**. No antimicrobial effect was found in **7** compounds.

It has been determined that the **6a-e** compounds obtained by changing the amino group of the **7**-type compounds have antifungal activity and a significant effect against *B. subtilis*. In addition, it was observed that compound **4e** was the most active compound against *S. aureus* and was close to the standard drug nitrofurantoin. Compounds **4c** and **5c** were found to be effective against *S. epidermidis* and compete with the standard drug Gentamicin. **6a**, **6b** and **6e** showed a significant effect against *B. subtilis*. This effect is greater for compound 6e than for Nitrofurantoin (Tehranchian et al., 2005).

In the study, in which a wide group of compounds were synthesized, 1,2,4-triazole derivatives were synthesized and Schiff Base and Mannich Bases were obtained from these compounds. This study is extremely important for comparing the antimicrobial activity of 1,2,4-triazole derivatives and Schiff Bases and Mannich Bases synthesized from them. The synthesis mechanism of the compounds synthesized in the study is given in the diagram.

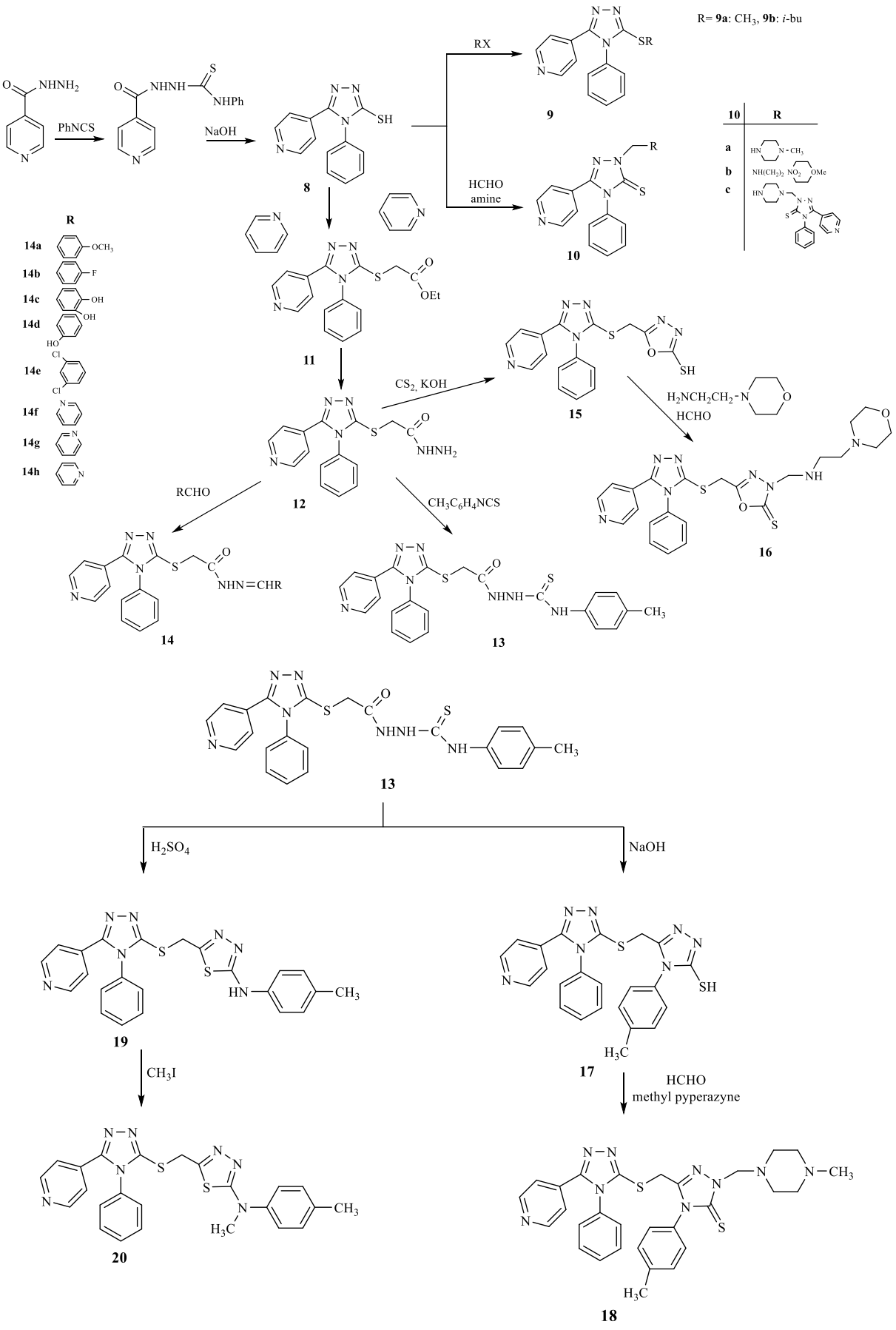


Figure 4. Synthesis mechanism of compounds **8-20**

In the study, Agar Well Diffusion Method was used for antimicrobial activity analysis. Inhibition zone diameters of synthesized compounds are given in Table 3.

Table 3. Inhibition zones of synthesized compounds

Compound	Microorganisms and effective inhibition zone diameters (mm)							
	Ec.	*Yp.*	*Pa.*	*Ef.*	*Sa.*	*Bc.*	*Ct.*	*Ca.*
8*	-	-	-	-	-	-	-	-
9a*	30	30	30	30	25	30	9	9
9b*	25	30	30	30	25	30	8	8
10a*	24	24	30	28	24	23	-	-
10b*	20	22	14	16	21	15	-	-
10c*	-	-	-	-	-	-	-	-
11*	-	-	-	-	-	-	13	13
12*	-	-	-	-	-	-	-	-
13*	-	-	-	-	-	-	7	7
14a*	24	30	30	28	28	25	-	-
14b*	30	25	38	30	30	23	-	-
14c*	-	-	-	-	-	-	-	-
14d*	30	30	30	30	25	25	-	-
14e*	-	-	-	-	-	-	-	-
14f*	42	30	40	20	24	20	-	-
14g*	8	7	-	-	-	-	-	-
14h*	-	-	-	-	-	-	-	-
15**	-	-	-	-	8	6	6	6
16**	6	-	-	-	-	-	-	-
17**	-	-	-	15	-	6	-	-
18**	-	-	-	-	-	-	-	-
19**	31	22	35	20	25	20	-	-
20**	28	16	15	7	22	17	-	-
Etanol	-	-	-	-	-	-	11	11
DMSO	-	-	-	-	-	-	-	-
Amp.	10	18	18	10	35	15	-	-
Flu.	-	-	-	-	-	-	25	25

Ec: E. coli-ATCC 25922; Yp: Y. pseudotuberculosis-ATCC 911; Pa: P. aeruginosa-ATCC 27853; Ef: E. Faecalis-ATCC 29212; Sa: S. aureus-ATCC 25923; Bc: B. cereus-ATCC 60193; Ct: C. tropicalis-ATCC13803; Ca: C. albicans-ATCC 60193; Amp: Ampicillin; Flu: Fluconazole; (-) no activity; * in DMSO; ** in ethanol.

When the compounds synthesized in the study were examined, no activity of type **8** compounds was found. Except for the **10c** compound, other Mannich Bases had a low effect on *candida* species, but gave effective results against other tested microorganisms. While a moderate effect of **11**-type compounds was observed only on *candida* species, no biological activity was found in **12**-type compounds. Low activity of **13**-type triazole derivatives was observed against *candida* species.

Low activities of the compounds obtained from the conversion of the **12**-type hydrazide structure to the **15**-type 1,3,4-oxadiazole ring were determined against *S. aureus, B. cereus, C. tropicalis* and *C. albicans*. Compounds of type **16**, which are derivatives of Mannich Base of type **15** compounds, have been found to have low activity against *E. coli*. On the other hand, the conversion of compound **13** to compound **17** did not cause a significant change in activity. Similarly, the biological activity of compound **18** was not observed. However, the effect of **19** types of compounds obtained from the reaction of **13** compounds with H2SO4 was high on bacteria except fungi. Compound **20** obtained from the methylation of compound **19** also showed a significant effect against selected bacteria.

In addition, **14a**, **14b**, **14d** and **14f** compounds of **14**-type Schiff Bases obtained from the reaction of **7**-type compounds with aldehydes had a significant effect on other bacteria except *candida* species. The effect of some of the synthesized compounds on the observed standard drugs is perhaps the most important result of the study.

Again, in a study on biological activity investigations, 6-substituted-2-amino-benzothiazole and 5-substituted-1-(1H-1,2,4-triazol-1-yl)-ethanone reacted in the presence of concentrated HCl and formaldehyde to form Mannich base. The antibacterial and antifungal effects of nine synthesized new compounds against pathogenic bacteria were investigated in vitro. The bacterial and fungal strains used for this purpose were *S. aureus, B. subtilis, P. aeruginosa, E. coli, A. niger* and *C. albicans.*

The R groups contained in the 6-substituted-benzothiazole derivative and 5-substituted-ethanone derivative contained in the 9 synthesized Mannich bases are given in Table 4.

Table 4. Substituent groups of synthesized compounds

Compound	6-substituted	5-substituted
21a	$-CH_3$	C_2H_5
21b	$-CH_3$	C_6H_5
21c	$-CH_3$	$C_6H_4CH_3$-*p*
21d	$-NO_2$	C_2H_5
21e	$-NO_2$	C_6H_5
21f	$-NO_2$	$C_6H_4CH_3$-*p*
21g	-Cl	C_2H_5
21h	-Cl	C_6H_5
21i	-Cl	$C_6H_4CH_3$-*p*

Ciprofloxacin was used as the standard drug in the antibacterial effect studies and Fluconazole was used as the standard drug in the antifungal studies. When the results are presented in a table, it is seen that the inhibition zones obtained from Gram positive and Gram negative bacteria are as in the table.

Table 5. Activity results of synthesized compounds against gram-negative and gram-positive bacteria (zone diameter-mm)

	Gram positive bacteria		Gram negative bacteria	
	S. aureus	*B. subtilis*	*E.coli*	*P. aeruginosa*
21a	06	06	08	12
21b	09	08	08	10
21c	12	08	12	06
21d	14	06	12	08
21e	04	09	14	11
21f	07	06	06	10
21g	07	08	10	11
21h	02	12	07	12
21i	07	14	20	19
Ciprofloxacin	23	21	23	23

Evaluation of results according to inhibition diameter: <5.5 mm negative effect (-); 5.5-10mm low effect (+); 11-16mm moderate effect (++); ≥17 mm high effect (+++) (Demirbaş et. al., 2004).

The zone diameter values obtained against the fungal strains used are presented in the table below.

Table 6. Activity of synthesized compounds against fungal strains

	A.niger Zone diameter (mm)	C. albicans Zone diameter (mm)
21a	12	12
21b	09	07
21c	12	12
21d	09	03
21e	10	06
21f	14	04
21g	10	14
21h	12	11
21i	11	06
Fluconazole	19	16

Evaluation of results according to inhibition diameter: <5.5 mm negative effect (-); 5.5-10mm low effect (+); 11-16mm moderate effect (++); ≥17 mm high effect (+++) (Demirbaş et. al., 2004).

The effect of **21d** and **21c** compounds against S.aureus strain is moderate. Other compounds have been found to be less effective. Against the B. subtilis strain, **21h** and **21i** compounds showed moderate effects, while the others had a low effect. When *E. coli* is considered, the effect of compound **21i** is high and close to the standard drug value. While the effect level of **21c**, **21d**, **21e** compounds was determined at medium level, the effect level of other synthesized compounds was found to be low. The effect of compound *1i* was also high in *P. aureginosa* strain. The effect of **21a**, **21e**, **21g** and **21h** compounds is moderate. The effect of other compounds was determined to be low.

The most important result obtained from the study is that the antibacterial effect of the synthesized Mannich bases is present in all compounds. The different effect values obtained are the effect of the substituent groups.

In fungi, the effect level of compounds **21a**, **21c**, **21f**, **21h** and **21i** was found to be moderate against *A.niger* strain. The effect value of other compounds is low. In *C. albicans* strain, the effect level of **21a**, **21c**, **21g** and **21h** compounds is moderate. In other compounds, the effect value is low. The absolute effect of Mannich Bases against fungi is a promising result as a compound group (Bele and Singhvi, 2009).

The mechanism of a different study on the antimicrobial activities of Schiff Bases and Mannich Bases, which contain 1,2,4-triazole, is presented in the diagram.

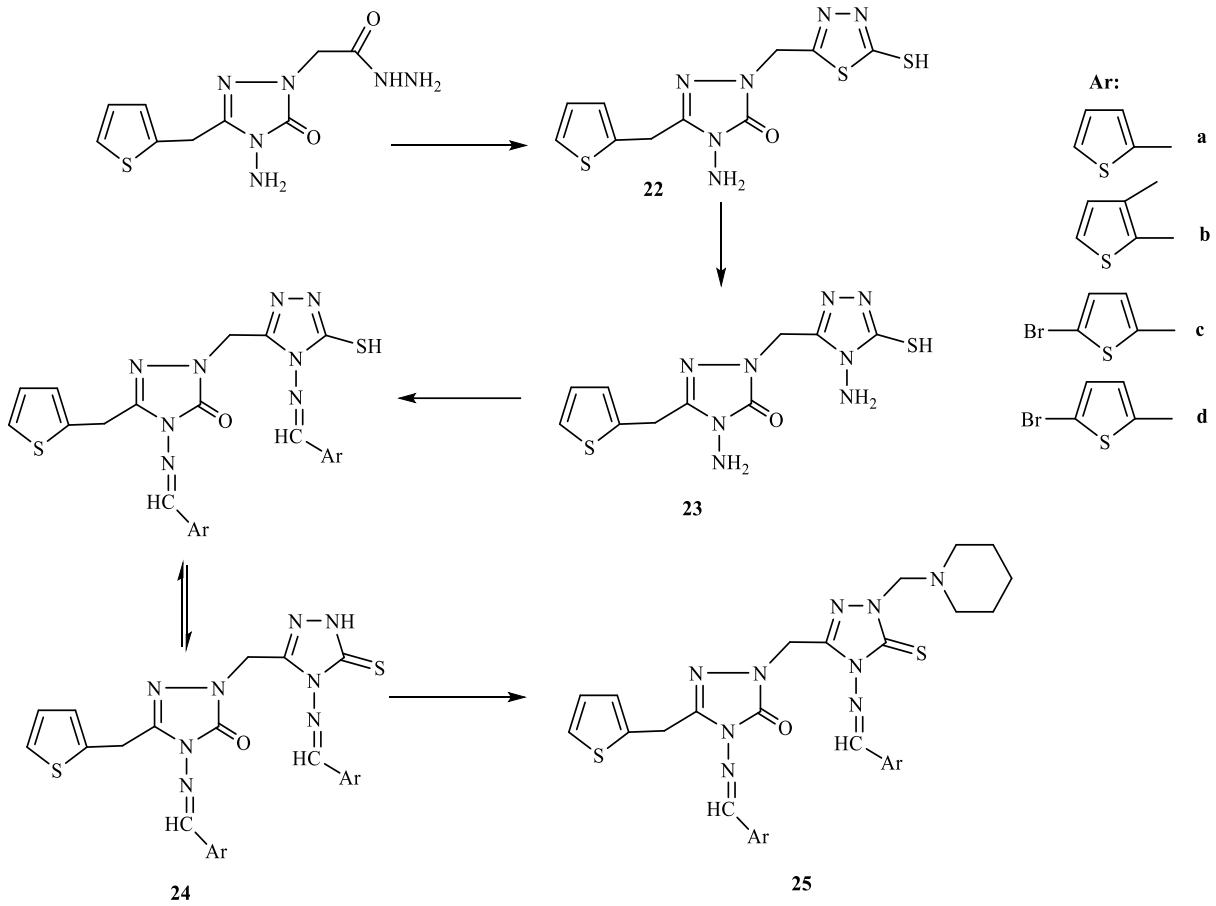


Figure 5. Reaction steps of synthesized 1,2,4-triazole derivatives, Schiff bases, Mannich bases Pathogenic Gram-negative and Gram-positive bacteria, fungi, and mycobacterium-type microorganisms were used in this large-scale study. When the results obtained from the study were presented in the form of a table, it was determined that the results were as follows.

Table 7. Antimicrobial activity results of synthesized compounds

	MIC (μg/mL)								
	Gram negative			Gram positive			Fungi		Mycobacterium
	Ec	*Yp*	*Pa*	*Sa*	*Ef*	*Bc*	*Ca*	*Sc*	*Ms*
22	125	125	125	-	-	-	125	125	-
23	-	-	500	250	-	250	125	125	62,5
24a	500	500	125	125	-	500	125	125	500
24b	-	500	500	500	-	-	500	500	500
24c	500	500	125	500	-	-	125	125	250
24d	3,9	7,8	31,25	0,98	15,6	0,98	15,6	3,9	7,8
25a	-	125	125	250	-	-	250	125	500
25b	-	500	500	-	-	-	500	500	-
25c	500	125	125	500	-	-	125	125	500
25d	31,25	31,25	62,5	7,8	62,5	15,6	31,25	31,25	15,6
Amp.	10	18	>128	35	10	15	NT	NT	NT
Strep.	NT	NT	NT	NT	NT	NT	NT	NT	4
Flu.	NT	NT	NT	NT	NT	NT	<8	<8	NT

Ec: Escherichia coli ATCC 25922; Yp: Yersinia pseudotuberculosis ATCC 911; Pa: Pseudomonas aeruginosa ATCC 27853; Sa: Staphylococcus aureus ATCC 25923; Ef: Enterococcus faecalis ATCC 29212; Bc: Bacillus cereus 702 Roma; Ms: Mycobacterium smegmatis ATCC607; Ca:Candida albicans ATCC 60193; Sc: Saccharomyces cerevisiae RSKK 251; Amp.: Ampicillin; Str.: Streptomycin; Flu.: Fluconazole; (—): no activity;NT: not tested.

All synthesized compounds were observed to have antimicrobial effects. In general, it was concluded that the activity of the synthesized compounds against Gram-negative bacteria was higher than Gram-positive bacteria. It is an important result that **24d** type Schiff Base and **25d** type Mannich Base have high efficacy against all tested bacteria, fungi and microorganisms (Unver et al., 2016).

In a recent study, 1,2,4-triazole derivatives and the antibacterial effects of Schiff and Mannich Bases obtained from these derivatives were compared. The flow chart of 27 new compounds synthesized is given below.

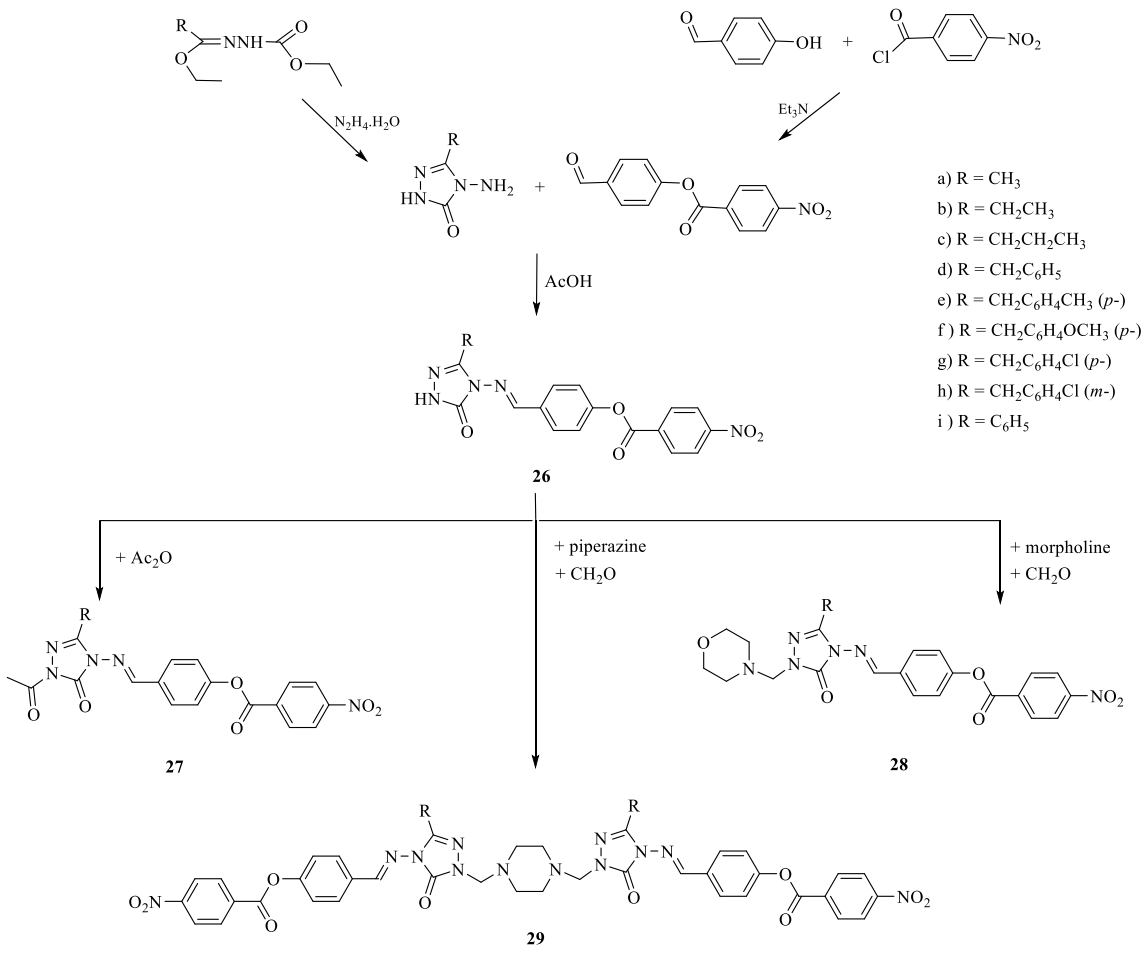


Figure 6. Reaction scheme of synthesized 1,2,4-triazole, Schiff bases, Mannich bases

The antimicrobial activity results of the synthesized compounds are given in the Table 8.

Table 8. In vitro antimicrobial activity of the compounds **3-6**.

Compound No	Microorganisms, inhibition zones (mm)					
	B. subtilis	*B. cereus*	*S. aureus*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
26a	-	-	12	-	-	-
26b	10	-	11	-	-	11
26c	-	10	-	-	-	-
26d	12	-	13	-	-	12
26e	-	9	-	-	-	-
26f	-	-	-	-	-	-
26g	11	9	-	-	-	-
26h	-	-	-	-	-	-
26i	10	-	-	-	-	13
27a	-	10	-	-	-	-
27b	-	-	-	-	-	-

27c	-	-	-	-	-	-
27d	-	-	-	-	-	-
27e	-	-	-	-	-	-
27g	-	-	-	-	-	-
27i	-	-	-	-	-	-
28a	16	13	12	-	14	14
28b	15	13	14	-	14	14
28d	13	11	12	-	11	13
28e	12	11	11	-	11	9
28g	14	12	12	-	11	9
28i	15	13	11	-	13	19
29b	-	13	11	-	11	-
29d	-	11	11	-	12	-
29f	-	9	11	-	12	13
29g	10	11	13	-	13	13
29h	-	10	11	-	13	9
Amp.	33	36	37	34	36	35
Neo.	17	17	13	16	17	16
Str.	12	12	21	10	12	11

Evaluation of results according to inhibition diameter: <5.5 mm negative effect (-); 5.5-10mm low effect (+); 11-16mm moderate effect (++); ≥17 mm high effect (+++)

The activities of the synthesized type **26** compounds against gram positive bacteria were higher than the activities against gram negative bacteria. Compounds **26b** and **26i** showed low activity against *B. subtilis*, while the effects of compounds **26d** and **26g** were moderate. Only low level activities were obtained from compounds **26c**, **26e** and **26g** against *B. cereus* strain. Moderate effects of compounds **26a**, **26b** and **26d** were detected against *S. aureus* strain, which is a common infectious agent. Type **3** compounds had no activity against *E. coli* and *P. aeruginosa* strains. Moderate effects of **26b**, **26d** and **26i** compounds were determined against *K. pneumoniae* strain as well. No actibacterial effects were observed in type **27** acetylation derivatives synthesized from type **27** compounds. Only against *B. cereus* there was a low effect of compound **27a**.

The antibacterial effects of Mannich bases obtained by using morpholine (**28** type) and piperazine (**29** type) in the presence of formaldehyde from **26** type compounds as a different compound group were also investigated. The synthesized type **28** compounds had moderate effects on all Gram-positive bacteria studied. Although there was no activity against the Gram negative bacteria *E. coli*, compounds of type **28** were moderately active against the *P. aeruginosa* strain. Compounds **28e** and **28g** showed low activities against *K. pneumoniae* strain,

while the activity of compound **28i** was high. The effect levels of other **28** type compounds were moderate.

When the antibacterial effects of the **29** types Mannich bases were investigated, it was seen that the **29g** compound had a low effect against *B. subtilis* and no effects on the others. For *B. cereus*, moderate activities were mostly obtained from the **29** type compounds. Similarly, moderate activities were determined for *S. aureus* from **29** type compounds. Type 6 compounds had moderate effects on *P. aeruginosa* strains but had no effects on *E. coli* strain. For *K. pneumoniae*, no effects were observed from compounds **29b** and **29d**. A low level of effect was determined only for **29h**, and moderate effects were seen for **29f** and **29g**. A detailed list of the newly synthesized compounds is given in Table 8 (Alkan et al., 2022).

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ANTICANCER PROPERTIES OF 1,2,4-TRIAZOLES

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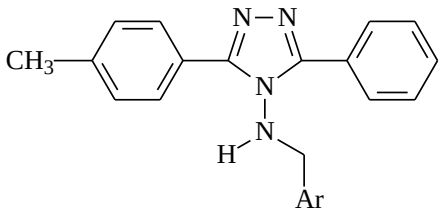
Anticancer Properties of 1,2,4-Triazoles

Cancer, one of the most serious diseases threatening human life, is characterized by the uncontrolled division of cells. There are many different types of cancer. There are claims that oxidative stress plays a crucial role in tissue damage related to various diseases such as cancer (Harmankaya et al., 2020, 2021; Harmankaya & Harmankaya, 2022). Scientists are doing various studies on this disease intensively.

Compounds bearing 1,2,4-triazole ring generally show many biological activities. In this section, the anticancer properties of various types of compounds with 1,2,4-triazole ring are discussed.

In a study by Bekircan et al., the anticancer activities of four compounds containing 1,2,4-triazole ring were investigated. Compound of 2,6-$Cl_2C_6H_3$ derivatived was found to exhibit higher anticancer activity in preliminary tests with breast cancer, non-small cell lung cancer and CNS cancer cancer cell lines. This compound has been reported to exhibit significant anticancer potential in screening tests with 60 human cancer cell lines (Bekircan et al., 2006).



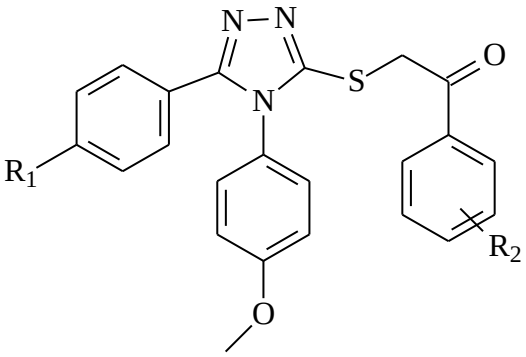
Ar= 2-OHC_6H_4, 2,4-$Cl_2C_6H_3$, 2,6-$Cl_2C_6H_3$, 3,4,5-$(OCH_3)_3C_6H_2$

Figure 1 Structure of the compounds (Bekircan et al., 2006).

In a 2011 study, a series of indolyl-1,2,4-triazoles were synthesized as anticancer agents and the cytotoxic effects of these compounds were investigated in six human cancer cell lines using 3-(4,5-dimethyldiazol-2-yl)-2,5-diphenyltetrazolium-bromide. The synthesized indolyl-1,2,4-triazole compounds have been reported to be investigated against prostate, breast and pancreatic cancer cell lines. Compounds 3-(3′,4′,5′-trimethoxyphenyl)-5-(*N*-methyl-3′-indolyl)-1,2,4-triazole and 3-(4′-piperidinyl-5-(*N*-methyl-3′-indolyl)-1,2,4-triazole carrying 3,4,5-trimethoxyphenyl and 4-piperidinyl substituents were found to have significant inhibitory effects against the cancer cell lines studied (Kumar et al., 2011).

The effect of some 1,2,4-triazole derivatives on human colon cancer appears to have been studied *in vitro* and *in vivo* in rats. According to this study, it was determined that 1,2,4-triazole derivatives have antitumor activity (Parlak et al., 2019).

A very recent study was conducted on the antiproliferative effects of 3-alkylsulfanyl-1,2,4-triazole derivatives on three human cancer cell lines, including breast cancer, lung cancer and ovarian cancer. These studied compounds were found to show moderate to promising antiproliferative activities against different cancer cell lines (Ghanaat et al., 2020).



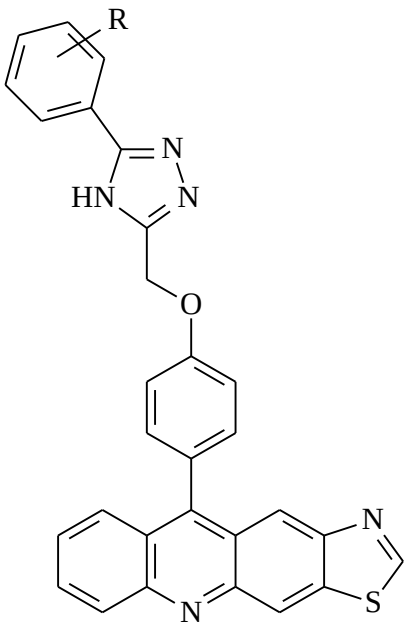
R_1= H, 3,4,5-$(OMe)_3$
R_2= H, 3,4,5-$(OMe)_3$, 4-Cl

Figure 2. 3-Alkylsulfanyl-1,2,4-triazole derivatives (Ghanaat et al., 2020).

A recent study investigated the anticancer activity of a series of novel (S)-Naproxen derivatives carrying a thiosemicarbazide/1,2,4-triazole moiety against human breast cancer cell lines (Han et al., 2022).

The antitumoral activity of 1,2,4-triazole D-ribose derivatives against T cell lymphoma cell line was investigated. Structures containing 1,2,4-triazolic ring attached to the carbohydrate moiety by sulfur have been reported in the literature to exhibit moderate anti-proliferative activity (Avanzo et al., 2012).

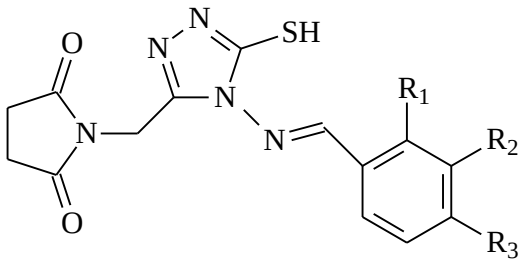
A study appears to have been made on a new series of fused acridines containing 1,2,4-triazole derivatives. All these derivatives were studied for their anticancer activities against four human cancer cell lines, including lung, breast, melanoma and colon cancers. Among these compounds, compounds bearing 3,4,5-trimethoxy, 4-chloro and 4-trifluoromethyl groups in the para position of the phenyl ring were found to exhibit the strongest anticancer activity against these four cancer cell lines (Mahanti et al., 2019).



R= H, 4-methyl, 4-methoxy, 3,4,5-trimethoxy, 4-bromo, 4-chloro, 4-fluoro, 4-trifluoromethyl, 4-nitro, 4-cyano

Figure 3. Series of fused acridine containing 1,2,4-triazole derivatives (Mahanti et al., 2019).

In a study conducted in 2017, 1,2,4-triazole-derived Schiff base and their complexes were investigated for their anticancer activities in breast cancer cell lines (Deodware et al., 2017).
It has been reported that 1,2,4-triazole derived compounds have been studied for anticancer activity against human breast cancer cell line and human cervical cancer cell line. These compounds were found to exhibit cytotoxicity to all cell lines studied (Mahar et al., 2020).



R_1= H, OH, Cl
R_2= H, OCH_3, NO_2
R_3= H, $N(CH_3)_2$, $N(C_2H_5)_2$, OCH_3, NO_2, Cl

Figure 4. *(E)*-1-((4-(arylideneamino)-5-mercapto-*4H*-1,2,4-triazol-3-yl)methyl)pyrrolidine-2,5-diones (Mahar et al., 2020).

The anticancer activity of compounds containing 4,5-diphenyloxazol-1,2,4-triazole derivatives against prostate lung cancer cell lines was investigated. Some of these have been reported to be considered promising precursor molecules for cancer therapy (Maddali et al., 2021).

In a study conducted by Parlak in 2018, the anticancer activity of [(4-substituted-5-pyridin-4yl-4*H*-1,2,4-triazol-3-yl)thio] acetic acid derivatives was investigated. These compounds have been investigated *in vitro* on human breast cancer and murine leukemia cells. It has been reported that the compounds tested in the study may have anticancer activity in different cancer series under *in vitro* conditions (Parlak, 2018).

In a study by Luo et al., 4-(3-(naphthalen-1-yl)-1-phenyl-1*H*-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-diene-3,8-dione compound has been reported that has significant *in vitro* cytotoxic activity. It has also been found that this compound suppresses breast cancer tumor growth *in vivo*. These results indicate 4-(3-(naphthalen-1-yl)-1-phenyl-1*H*-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-diene-3,8-dione compound could be a potential anticancer agent (Luo et al., 2021).

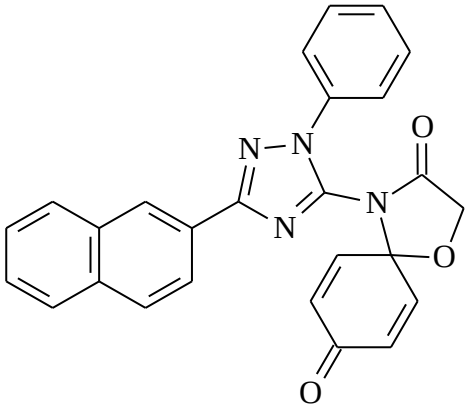
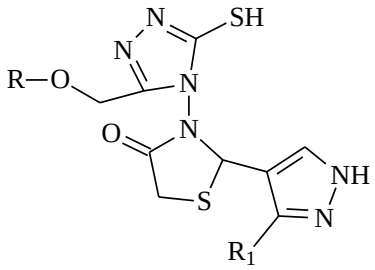


Figure 5. 4-(3-(Naphthalen-1-yl)-1-phenyl-1*H*-1,2,4-triazol-5-yl)-1-oxa-4-azaspiro[4.5] deca-6,9-diene-3,8-dione compound (Luo et al., 2021).

Compounds composed of ligands Zn^{2+}, Cd^{2+} and UO_2^{2+} with a 1,2,4-triazol ring were investigated in vitro against human hepato Carcinoma (Gaber et al., 2018).

8-substituted-[(1,2,4-triazol-3-yl)methoxy]quinoline derivatives have been found to exhibit antitumor activity. The presence of dihydro-1,2,4-triazolyl moiety in the structure shows that it positively affects the interaction of molecules with biological targets (Rashad et al., 2010).

Some of 2-(3-substituted-1*H*-pyrazol-4-yl)-3-(3-substituted-5-sulfanyl-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-ones have been reported to show anticancer activity in human breast cancer cells in a dose-dependent manner. 2-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)-3-(3-mercapto-5-(o-tolyloxymethyl)-4*H*-1,2,4-triazol-4-yl)thiazolidin-4-one compound has been determined that the presence of chlorine in the ortho position and a methyl group in the significantly increases the anticancer activity of this compound (Isloor et al., 2013).

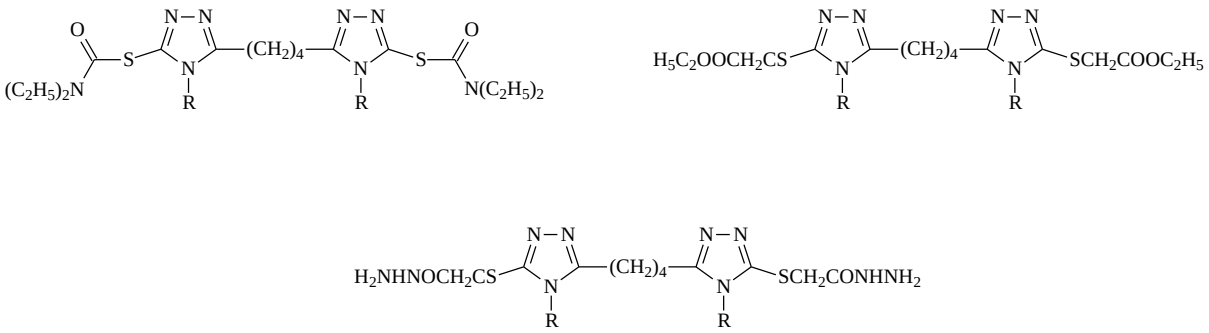


R= Phenyl, 2-methylphenyl, 4-methylphenyl, 1-naphthyl, 2-naphthyl

R_1= 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl

Figure 6. 2-(3-substituted-1*H*-pyrazol-4-yl)-3-(3-substituted-5-sulfanyl-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-ones (Isloor et al., 2013).

The *in vitro* cytotoxicity of 1,4-bis(4-substituted-5-mercapto-1,2,4-triazol-3-yl)butane derivatives was investigated. These compounds were studied for their *in vitro* cytotoxicity against three human cell lines of lung carcinoma, colon adenocarcinoma and breast cancer. As a result, it was determined that the compounds carrying *p*-tolyl and *p*-ethoxy phenyl groups as substituted groups showed more activity than other compounds (Purohit & Mayur, 2012).



R= Phenyl, *p*-tolyl, *m*-tolyl, *p*-ethoxy phenyl, cyclohexyl, *n*-butyl

Figure 7. 1,4-bis(4-substituted-5-mercapto-1,2,4-triazol-3-yl)butane derivatives (Purohit & Mayur, 2012).

Antitumor activities of *N*-substituted amides of 3-(3-ethylthio-1,2,4-triazol-5-yl)propenoic acid compounds were investigated. It was evaluated for their anticancer activities against two cancer cell lines, the human lung cancer cell line and the human breast carcinoma cell line (Pachuta-Stec et al., 2009).

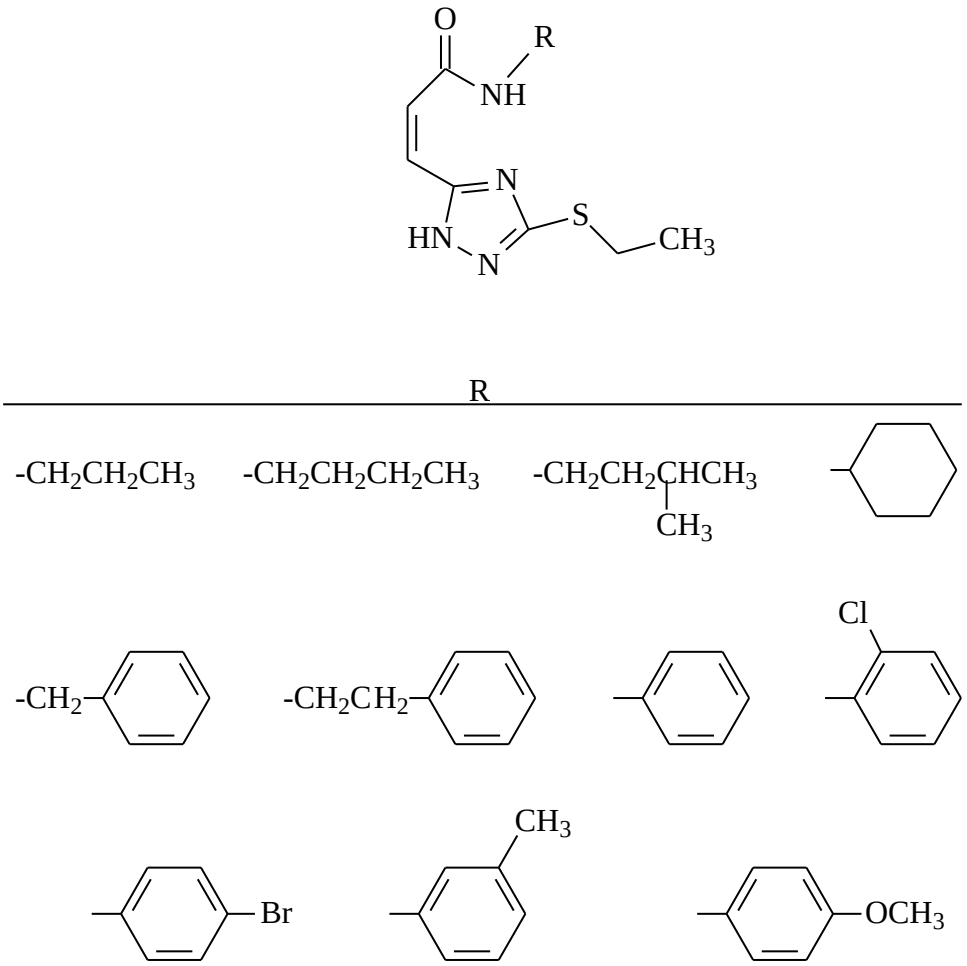


Figure 8. *N*-substituted amides of 3-(3-ethylthio-1,2,4-triazol-5-yl)propenoic acid compounds (Pachuta-Stec et al., 2009).

It is thought that some of the derivatives of phenylcarbamoylazinane-1,2,4-triazole amides may lead to the synthesis of effective drug-like molecules that can be used in the treatment of colon cancer (Saeed et al., 2022).

In a very recent study, 4-(((4-ethyl-5-(thiophen-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-6,8-dimethyl-coumarin compound synthesis was performed and cytotoxic effects of this compound on different cell lines were investigated. Research has been reported on human breast adenocarcinoma cell line, human umbilical vein endothelial cell line, and human gastric cancer cell line (Koparir et al., 2022).

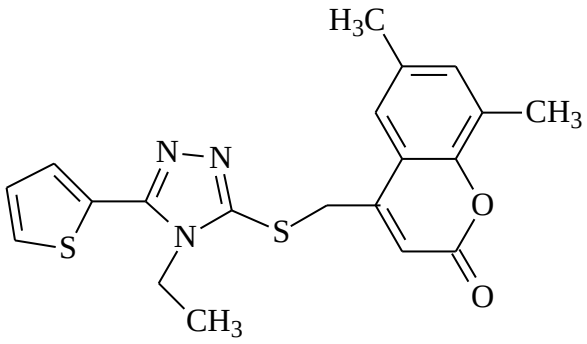
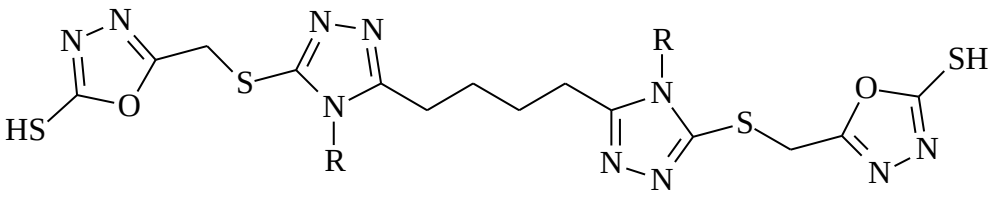


Figure 9. 4-(((4-ethyl-5-(thiophen-2-yl)-4*H*-1,2,4-triazol-3-yl)thio)methyl)-6,8-dimethyl-coumarin compound (Koparir et al., 2022).

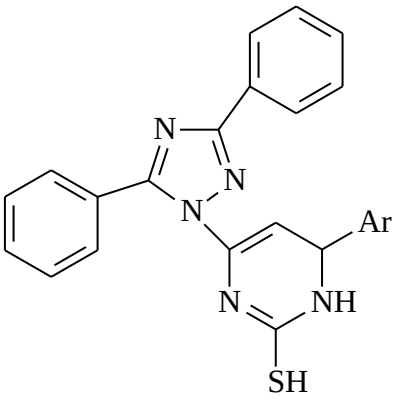
1,4-bis[5-(5-mercapto-1,3,4-oxadiazol-2-yl-methyl)-thio-4-substituted-1,2,4-triazol-3-yl]-butane series, evaluated for *in vitro* cytotoxicity potential using the standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) test. It has been tested against three human cancer cell lines: lung cancer, colon cancer, and breast cancer (Purohit et al., 2011).



R= Phenyl/*p*-tolyl/*m*-tolyl/*p*-ethoxy phenyl/cyclohexyl/*n*-butyl

Figure 10. 1,4-bis[5-(5-mercapto-1,3,4-oxadiazol-2-yl-methyl)-thio-4-substituted-1,2,4-triazol-3-yl]-butane series (Purohit et al., 2011).

The anticancer activity of 6-(substituted aryl)-4-(3,5-diphenyl-1*H*-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol compounds against 60 cell lines of different human tumors was investigated. Compounds with 4-chlorophenyl and 4-methoxyphenyl substituents were found to be active on non-small cell lung cancer (Khanage et al., 2012).

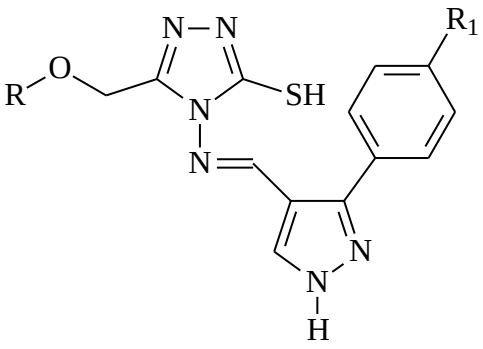


Ar= 4-chlorophenyl/2-chlorophenyl/3-nitrophenyl/4-methoxyphenyl/4-dimethyl aminophenyl phenyl/2-furyl/4-bromophenyl/4-hydroxyphenyl/2,4-dimethoxyphenyl

Figure 11. 6-(substituted aryl)-4-(3,5-diphenyl-1*H*-1,2,4-triazol-1-yl)-1,6-dihydropyrimidine-2-thiol compounds (Khanage et al., 2012).

The cytotoxicity of compounds containing 1,2,4-triazole ring containing adamantane and monoterpenoid moieties has been reported in the literature using cervical cancer and colon cancer cell lines (Munkuev et al., 2021).

In one study, the antitumor activities of Schiff base with three 1,2,4-triazole rings against Ehrlich ascites carcinoma (EAC) in Swiss albino mice were investigated. 4-({[3-(4-fluorophenyl)-1*H*-pyrazol-4-yl]methylene}amino)-5-[(2-methylphenoxy)methyl]-1,2,4-triazole-3-thiol compound has been reported to increase the survival time of infected mice (Sunil et al., 2013).



R= 4-methyl benzene, 2-methyl benzene
R_1= Cl, F

Figure 12. Structure of Schiff bases with 1,2,4-triazole ring (Sunil et al., 2013).

Azo dye ligand containing 1,2,4-triazole ring was synthesized and its *in vitro* cytotoxicity was investigated against human liver carcinoma cell line. Azo dye ligand has been found to have strong antitumor activity. It has been reported to be a promising result in terms of acceptability as an anticancer drug (El-Ghamry et al., 2018).

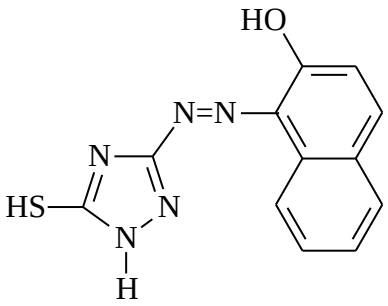


Figure 13. Structure of azo ligand (El-Ghamry et al., 2018).

Cu(II) and Ag(I) complexes of Schiff bases with 1,2,4-triazole ring were synthesized. Their cytotoxic activities against human breast cancer cell line were studied. As a result of cytotoxic activity examination, it has been reported that Cu(II) complex may be a potential anticancer agent (Abdelghany et al., 2021).

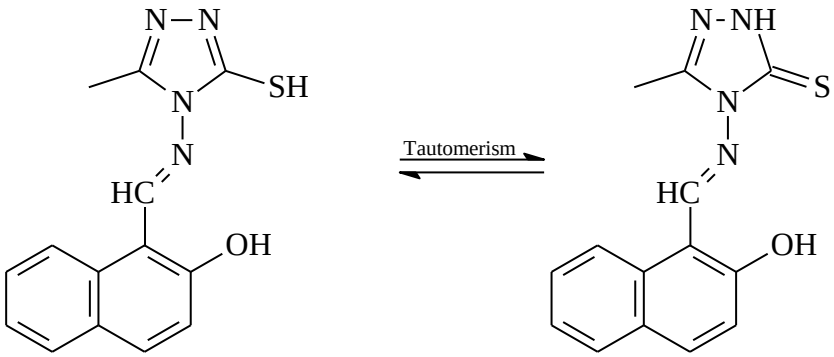
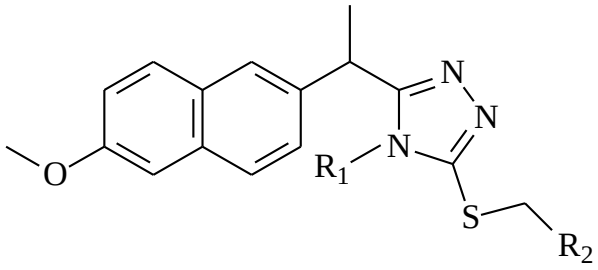


Figure 14. The proposed structure of Schiff base (Abdelghany et al., 2021).

In a study conducted in 2020, the synthesis of 4-substituted-5-(1-(6-methoxynaphtalen-2-yl)ethyl)-3-((substitutedbenzyl)thio)-4*H*-1,2,4-triazole compounds was made. These compounds have been studied against prostate cancer. (S)-3-((2,4,6-trimethylphenyl)thio)-4-(4-fluorophenyl)-5-(1-(6-methoxynaphtalen-2-yl)ethyl)-4*H*-1,2,4-triazole compound has been reported to be a potential candidate for *in vivo* prostate cancer therapy (Birgul et al., 2020).



R_1= 3-chlorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl
R_2= phenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dichlorophenyl, 2,4,6-trimethylphenyl.

Figure 15. 4-substituted-5-(1-(6-methoxynaphtalen-2-yl)ethyl)-3-((substitutedbenzyl)thio)-4*H*-1,2,4-triazoles (Birgul et al., 2020).

The cytotoxic and apoptotic activities of heterocyclic compounds with 1,2,4-triazole ring containing indole were investigated against breast cancer. The compounds have been reported to exhibit cytotoxic activity against breast cancer cells (Nafie & Boraei, 2022).

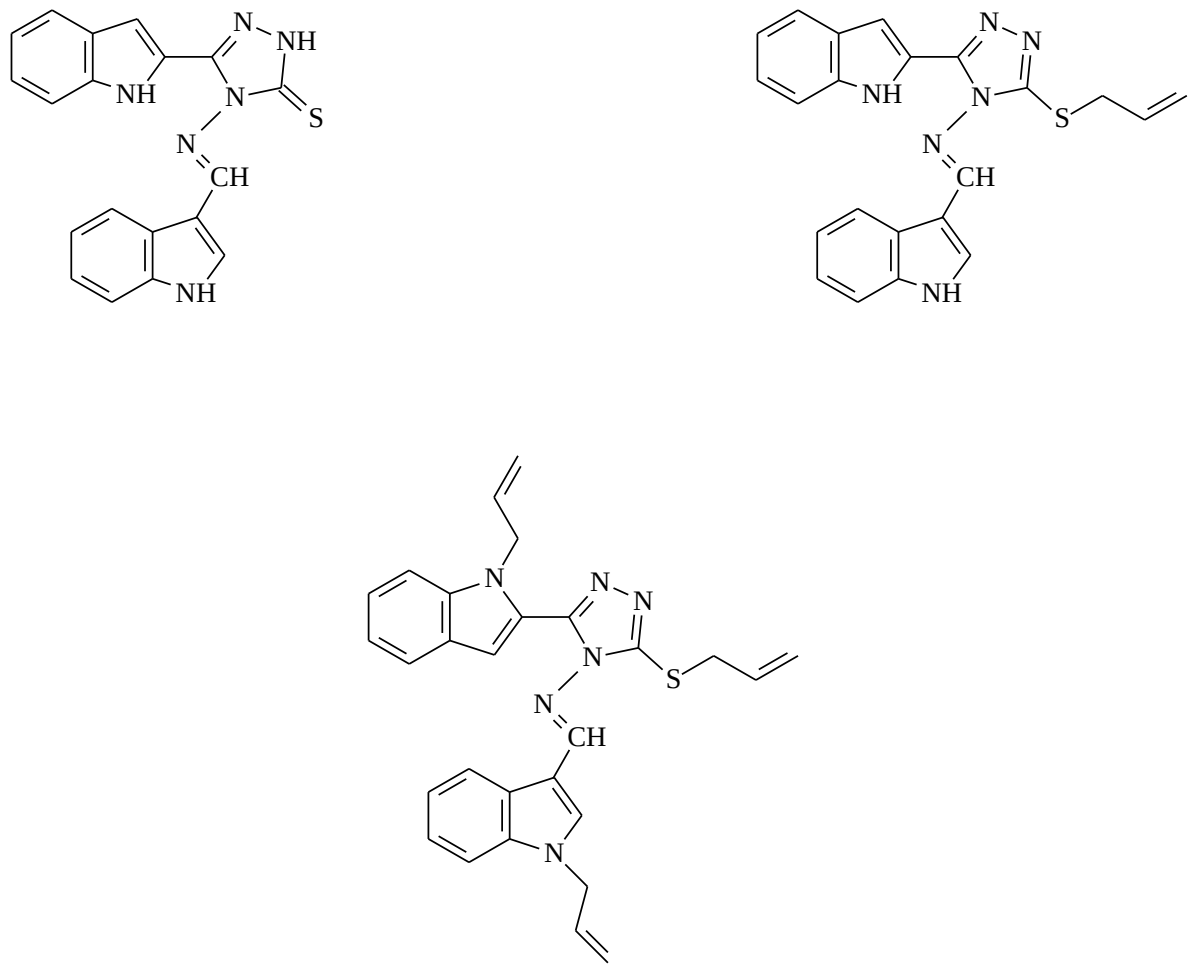


Figure 16. Structures of the compounds (Nafie & Boraei, 2022).

Three versatile half-sandwich ruthenium(II) *p*-cymene complexes carrying triazole ligands were investigated against lung adenocarcinoma and breast adenocarcinoma cells. It has been reported to show cancer cell growth inhibitory activity. These complexes have been reported to show good efficacy to kill cancer cells (Muley et al., 2021).

In a 2011 study, 3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-5-(2-fluorobenzylthio)-4-phenyl-4*H*-1,2,4-triazole has been reported that the compound may be a potential antitumor agent against liver cancer cells according to the results of apoptosis assay and Western-blot (Hou et al., 2011).

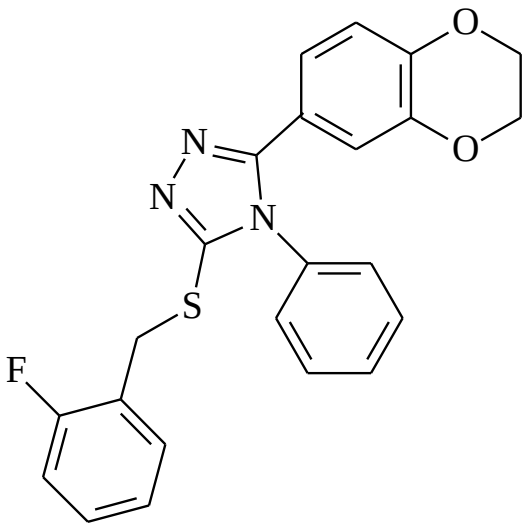


Figure 17. Structure of 3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-5-(2-fluorobenzylthio)-4-phenyl-4*H*-1,2,4-triazole (Hou et al., 2011).

4-(((4,5-Diphenyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)-1-hexadecyl-1*H*-1,2,3-triazole, 1-(4-bromophenyl)-4-(((4,5-diphenyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)-1*H*-1,2,3-triazole, and 1-(4-bromophenyl)-4-(((5-methyl-4-phenyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)-1*H*-1,2,3-triazole compounds were investigated in human colon carcinoma, human cervical carcinoma, and human breast adenocarcinoma. 4-(((4,5-Diphenyl-4*H*-1,2,4-triazol-3-yl)thio)methyl)-1-hexadecyl-1*H*-1,2,3-triazole compound were reported to be the most potent compounds tested against the human breast adenocarcinoma cell line. The other two compounds were reported to have good anticancer activity against the human breast adenocarcinoma cell line (Al Sheikh Ali et al., 2020).

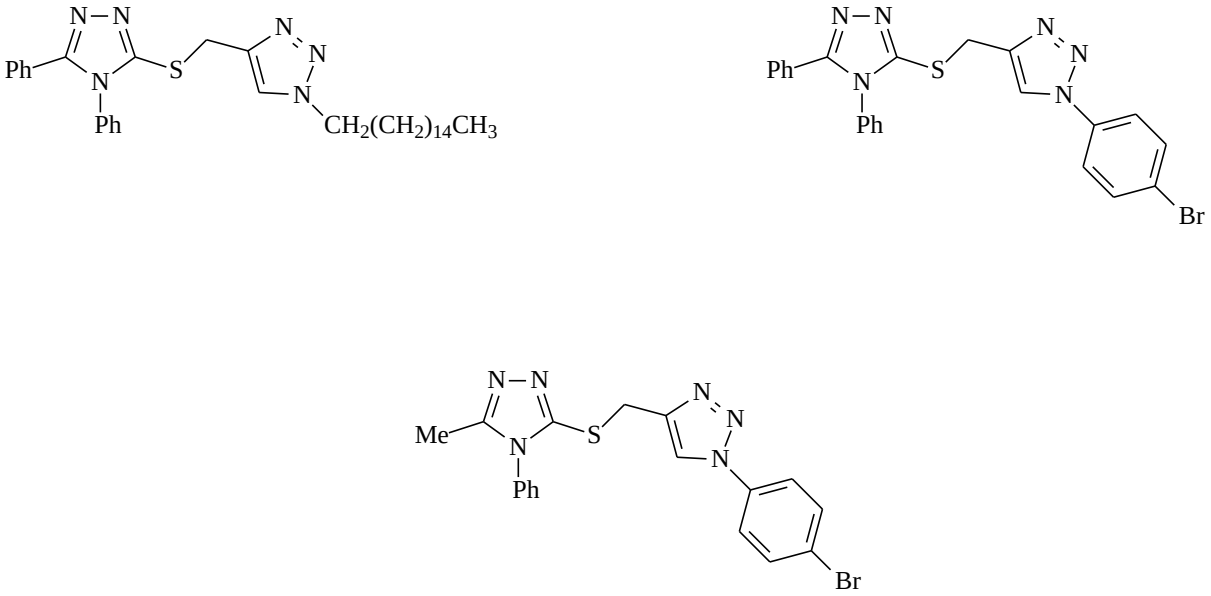


Figure 18. Structure of the compounds (Al Sheikh Ali et al., 2020).

The *in vitro* anticancer activity of compounds with a 1,2,4-triazole ring against human breast cancer cell line was investigated. The compounds have been reported to have significant anticancer activity (Desai et al., 2021).

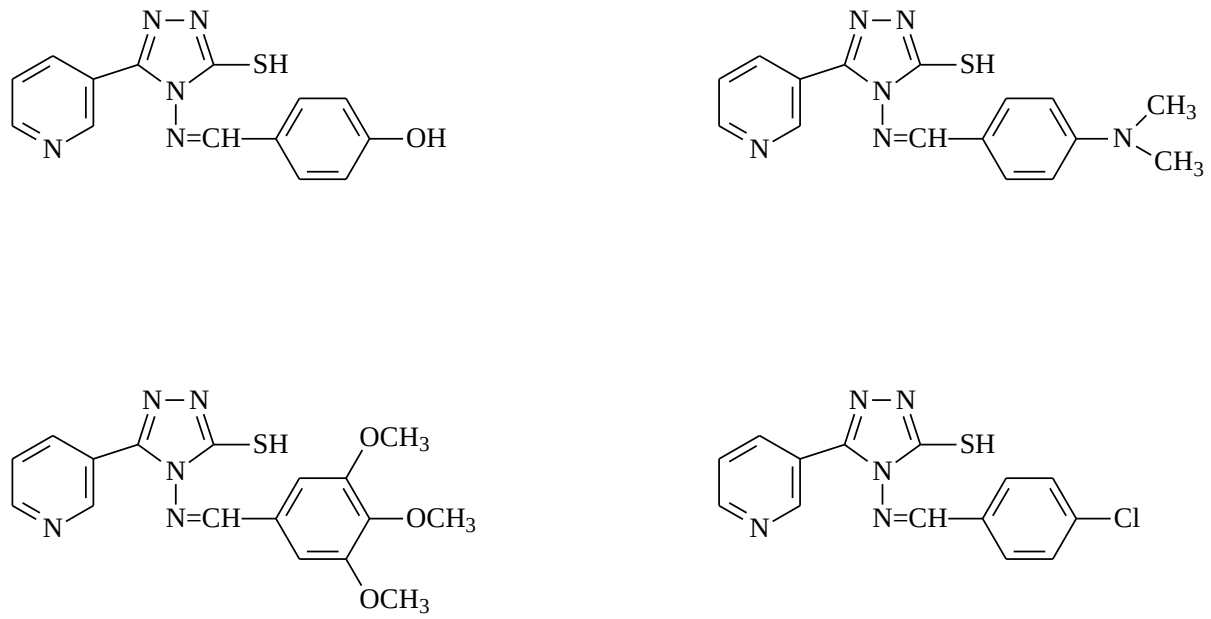
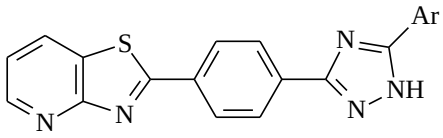


Figure 19. Structure of compounds **1**, **2**, **3** and **4** (Desai et al., 2021).

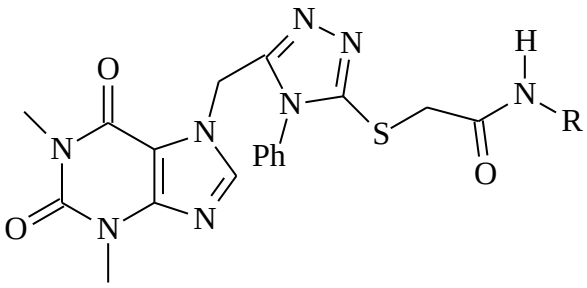
Anticancer activities of thiazolepyridine compounds combined with 1,2,4-triazole derivatives against human cancer lines including prostate cancer, lung cancer and breast cancer were investigated. Some of these compounds have been reported to exhibit significant activity (Sumalatha et al., 2020).



Ar= Pyridine-4-yl hydrochloride, 4-nitrophenyl, 3,5-dinitrophenyl, 3,4,5-trimethoxyphenyl, 3,5-dimethoxyphenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-bromophenyl, 4-cyanophenyl, 4-methylphenyl.

Figure 20. Structure of 1,2,4-triazolearyl incorporated thiazolepyridine derivatives (Sumalatha et al., 2020).

Some Mannich bases with 1,2,4-triazole ring have been reported to have antiproliferative activity on prostate, liver and breast human cancer cells (Ceylan et al., 2020).
Compounds containing 1,2,4-triazole ring with *N*-phenyl acetamide moieties were tested against lung and breast cancer cell lines for their *in vitro* potential (Shahzadi et al., 2021).



R= C_6H_5, 2,4-Cl_2-C_6H_3, 2,4-Me_2-C_6H_3, 3,4-Cl_2-C_6H_3, 4-F-C_6H_4, 2-Cl-C_6H_4, 4-Me-C_6H_4, 3,4-Me_2-C_6H_3, 4-Cl-C_6H_4, 2-F-C_6H_4

Figure 21. Structure of Thio *N*-(substituted-phenyl)acetamide derivatives of theophylline-7-acetic acid (Acefylline) (Shahzadi et al., 2021).

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ANTIFUNGAL PROPERTIES OF 1,2,4-TRIAZOLES

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Antifungal Properties of 1,2,4-Triazoles

Five-membered sp^2 hybridization compounds known as 1,2,4-triazoles have three nitrogen atoms positioned at the ring's 1, 2, and 4 locations. 4*H*-1,2,4-triazole and 1*H*-1,2,4-triazole are the two tautomeric forms (Benson & Savell, 1950). 1,2,4-triazole compounds are getting a lot of interest due to their wide-ranging effects. Most importantly, due to their wide variety of biological activity, several ring structures with a 1,2,4-triazole nucleus have been included into a number of clinically approved medications (Lemke & Williams, 2008). In addition to all these, they exhibit many biological activities such as antimicrobial (Kotan, 2021), antioxidant (Çiftçi et al., 2018), antifungal (Mi et al., 2022), anticancer (Uddin et al., 2020), herbicidal (Zhang et al., 2014), anti-inflammatory (Ayaz et al., 2020), anticonvulsant (Küçükgüzel et al., 2004). In this regard, they are actively used both in pharmacology and in medicine. Therefore, the 1,2,4-triazole ring is important for creating novel chemical heterocyclic compounds entities with distinctive structural characteristics. Furthermore, Schiff bases containing 1,2,4-triazole show many biological activities (Sun et al., 2009; Wang et al., 2016; Sztanke et al., 2008; Hu et al., 2012). In recent years, Schiff bases containing 1,2,4-triazole with very high pharmacological properties have also been added to the literature (Chohan et al. 2010). In addition, a large number of 4-amino-5-substituted-1,2,4-triazole Schiff bases have been designed and synthesized (Aktaş Yokuş et al., 2017; Jin et al., 2018; Beytur et al., 2019). These compounds were compared with the triadimephone standard and it was seen that their antifungal activities were quite good. The molecules with antifungal activity such as Rizatriptan, fluconazole and terconnazole containing 1,2,4-triazole were obtained as products (Jin et al., 2014). For this reason, the synthesis of 1,2,4-triazole Schiff bases containing

imidazole ring, halogenated benzene ring, pyridine ring, furan ring has increased (Kotan, 2015; Gürbüz et al., 2020; Kotan et al., 2022).

Fungus

Fungi are thought to have formed with the evolution of eukaryotic creatures about 1.5 billion years ago (Rogozin et al., 2003). Since their fossilization is difficult compared to vertebrates, they cannot be followed easily. Mycology is the sub-discipline of biology that studies fungi. Mycology is a new science that was advancing with the development of the microscope in the 17th century. Fungal spores were first observed by Giambattista della Porta in 1588. The work titled "Nova plantarum genera", published by Pier Antonio Micheli in 1729, provided the development of Mycology. The Dutch Christian Hendrik Persoon (1761-1836) investigated the classification of fungi in modern mycology, and Elias Magnus Fries (1794-1878) improved the classification of fungi on spore colors and properties with his microscopic research, methods still used by toxonomists today. Taxonomists have suggested that there are about 120.000 fungal species, but in 2017 there are thought to be between 2.2 and 3.8 billion species (Murthy, 2021).

Fungi are unicellular or multicellular organisms (Niklas & Skalamera, 1997). These creatures can live in all habitats, such as on land, in the sea, in plants. Some fungi can benefit their environment, they are called decomposers and take part in the cycle of carbon and other elements in nature. For example, yeast used to make bread and beer is a type of fungus (Kavanagh, 2011). This is how they grow in soil and dead plants. Others are plant parasites that cause diseases such as rust, mold and thrush (Heath & Skalamera, 1997). Fungal diseases cause significant losses in plants and, cause disease in animals and humans.

Antifungal Activities

The type of stereols known as lipid particles in pathogenic fungi is argosterol. In the mammalian cell, the cell membrane is the lipid particle cholesterol. The difference in chemical properties of cholesterol and ergosterol allows us to use antifungals. The antifungal agents aim to inhibit the biosynthetic pathway of ergosterol, an important component of fungal membranes (Ozkirimli et al., 2009). Sterol 14α-demethylation constitutes an impact part of the Sterol biosynthetic pathway in eukaryotes (Nes & McKean, 1977). Cytochrome P450 sterol 14α-demethylases included in the CYP51 family within the fungal sequences were first purified from yeast in 1984 (*Sacharomyces cerevisiea*) (Yoshida& Aoyama, 1984). It has been

investigated that several plants and fungi contain more than one CYP51 gene and in recent years the CYP51 family participates in proteins found in 82 organisms (Lepesheva & Waterman, 2007). Therefore, Sterol 14α-demethylase is the primary drug target for a number of microbial infections in both plants and animals (Andes, 2004). CYP51-targeted drugs may be useful as an herbicide in crop cultivation and in the treatment of fungal diseases in humans (Warfield et al., 2014).

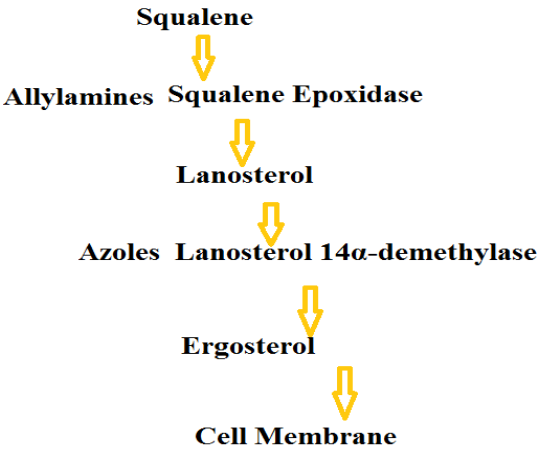


Figure 1. The biosynthetic pathway of ergosterol

Antifungal Drugs

In the synthesis of Ergosterol, firstly, Lanosterol is synthesized from squalene by the Squalene enzyme, and Ergosterol is synthesized from Lanosterol by the 14 alpha demethylase enzyme and shown in the Figure 1 (Aoyama, 2005). Allylamine (Terbinafine) blocking the Squalene Epoxidase enzyme, and Azoles (Imidazoles and Triazoles) blocking the 14 alpha-demethylase enzyme. Triazole-derived azole antifungals such as fluconazole and Voriconazole inhibit the CYP51 enzyme, thereby impairing Ergosterol synthesis (Aoyama, 2005). These antifungals are used to inhibit the growth of Ergosterol, the main Sterol found in the stolasma membrane of fungal cells. The sterol found in the animal cell membrane is called Cholesterol.

There are antifungals that inhibit the enzymes used during these transformations. The agents that effect Ergesterol synthesis are as follows. The polyene derivatives (Amphotericin B, Nystatin, Pimaricin), Azole group antifungals, i) the imidazole derivatives (such as miconazole, econazole and ketoconazole) and ii) the triazole derivatives (such as fluconazole and itraconazole, voriconazole, posaconazole), the allylamine derivatives (terbinafine, naftifine), Morpholine derivative (Amorpholine) (Sanati, 1997).

Azole group antifungals

Fungal diseases caused by pathogens are a medical problem in itself. The main ones of these pathogens are known as *Candida albicans, Aspergillus fumigatus* and *Cryptococcus neoformans (*Ostrosky-Zeichner et al., 2010; Kathiravan et al., 2012). Azole antifungals inhibit the biosynthesis of ergosterol in some fungal species such as Candida (Fringuelli et al.,1998). Because of their efficacy and lower price for most fungal infections, azoles are used worldwide as first-line antifungals for the management of systemic infections (Zavrel et al.,2017). Azoles are organic molecules consisting of a five-membered heterocyclic ring containing at least two nitrogens in their molecular structure. They are classified according to the number of nitrogen atoms in the azole ring. Azole antifungals are divided into two as imidazole and triazole derivatives (Castro et al., 2016; Chen & Sorrell, 2007; Odds et al., 2003). Imidazole and triazole antifungals were the most successful group in terms of affecting more agents in number (Ostrosky-Zeichner et al., 2010).

The triazoles (voriconazole, posaconazole, itraconazole and fluconazole,) are licensed agents used in the clinical use of invasive fungal disease. Voriconazole and Posaconazole, which represent specific advances in the understanding of structure-activity relationships, have an important place among the antifungal azoles (Ostrosky-Zeichner et al., 2010). The triazoles are effective against Cryptococcus neoformans, Candida albicans, non-albicans Candida species, and dimorphic fungus. With the exception of voriconazole and a few experimental triazoles, they are less efficacious against Candida glabrata and inert against Candida krusei among non-albicans Candida spp. Only itraconazole and voriconazole have any effect on different Aspergillus species and dematiaceous molds. Additionally effective against Fusarium spp. is voriconazole (Anaissie et al., 1995).

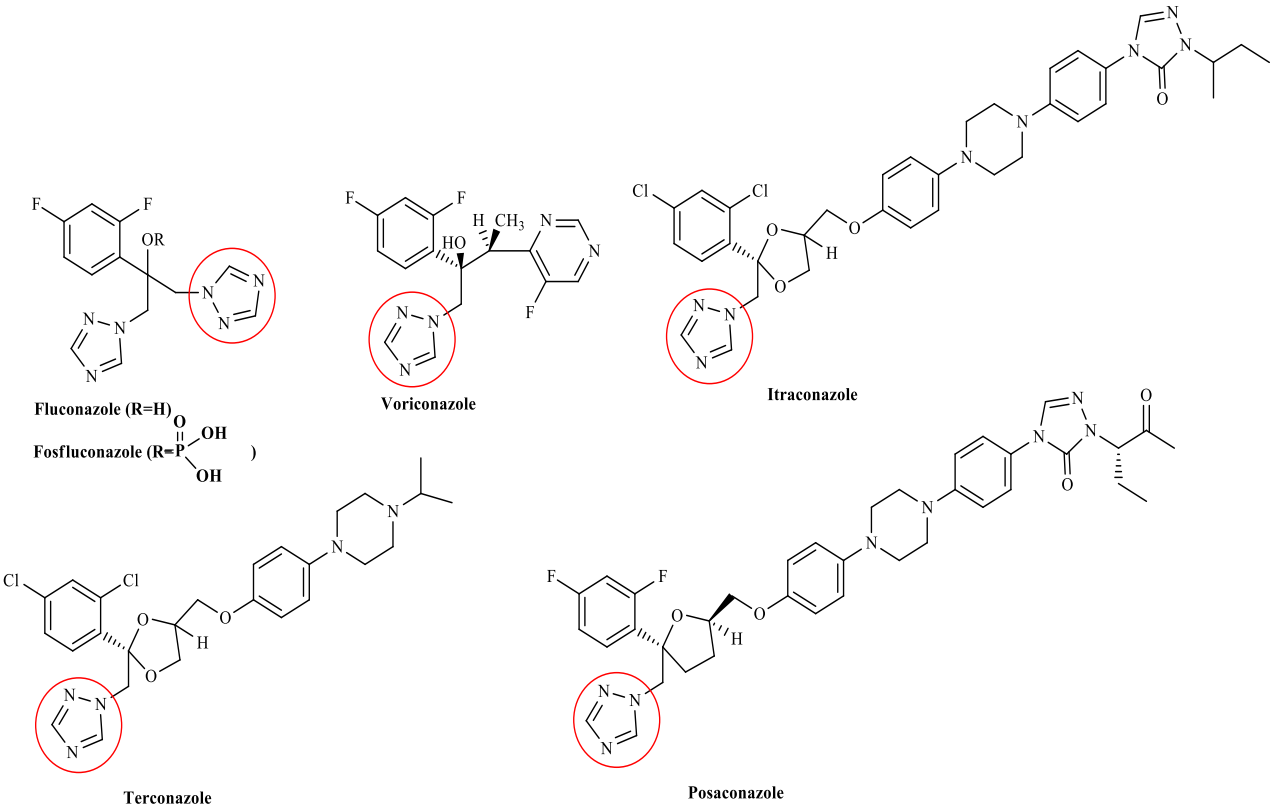
Voriconazole, a derivative of Fluconazole, is an important antifungal agent. It was first approved by the US Food and Drug Administration (FDA) in May 2002 (Jeu et al., 2003). The Voriconazole general formule is $C_{16}H_{14}F_3N_5O$ and its IUPAC name is (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol (Zhao et al., 2017) Voriconazole is highly active against fungal species such as Candida, Aspergillus and Cryptococcus and has proven to be an effective treatment for infections caused by these pathogens (Kullberg et al., 2005; Walsh et al., 2002; Herbrecht et al., 2002; Eiden et al., 2007; Singh et al., 2006; Barchiesi et al., 2015). The side effects of using voriconazole are few. The most common adverse events listed in clinical studies of a total of 1655 patients were rash

(5.3%), fever (5.7%), nausea (5.4%), visual disturbances (18.7%) and (Pfizer, New York, NY, USA).

Another antifungal agent derived from triazole is Posaconazole. It is an molecule with a broad antifungal spectrum that is widely used for the treatment of immunocompromised patients (Cornely et al., 2007; Walsh et al., 2007). The Posaconazole has antifungal activity against Candida species, the Zygomycetes species, Cryptococcus neoformans, Aspergillus and other some filamentous fungi. It is structurally a derivatives of itraconazole (Greer, 2007) The Posaconazole general formule is $C_{37}H_{42}F_2N_8O_4$ and its IUPAC name is 4-[4-[4-[4-[[(3*R*,5*R*)-5-(2,4-difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl)oxolan-3-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[(2*S*,3*S*)-2-hydroxypentan-3-yl]-1,2,4-triazol-3-one (Chen et al., 2011). It contains three nitrogen atoms in its structure, thus forming the 1,2,4 triazole ring.

Itraconazole, a triazole antifungal derivative, primarily inhibits the biosynthesis of ergosterol, an essential component of fungal cell membranes (Grant & Clissold, 1989). The Posaconazole general formule is $C_{35}H_{38}Cl_2N_8O_4$ and its IUPAC name is 2-butan-2-yl-4-[4-[4-[4-[[(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-1,2,4-triazol-3-one. It is used in the treatment of infections caused by fungi (Ahmad et al., 2001).

Fluconazole is a triazole antifungal agent that is part of the treatment for patients with a compromised immune system (Grant & Clissold, 1990). The presence of Triazole groups and 2 fluoride atoms in its structure increases the hydro-solubility and polarity of the drug, allowing it to be used in parenteral form (Debruyne & Ryckelynck, 1993) . Fluconazole is effective for treating oesophageal and vaginal candidiasis, disseminated candidiasis, oropharyngeal, as well as peritonitis, hepatosplenic candidiasis, non-neutropenic patients with candidaema, focal urinary tract infections and funguria (Kathiravan et al., 2012). The Fluconazole general formule $C_{13}H_{12}F_2N_6O$ is and its IUPAC name is 2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propan-2-ol (Ruchita et al., 2007; Sanati et al., 1997).



Fungal microorganisms

Candida albicans

Classified as an opportunistic fungus, *Candida albicans* usually causes disease in immunocompromised individuals. Candida species are yeast-type fungi. Candida albicans is the most common of the similar species (Garber, 2001) *Candida albicans* produces white patches on the skin or mucous membranes. There are many species such as *Candida glabrata*, *Candida guilliermondii*, *Candida krusei*, *Candida parapsilosis* and *Candida tropicalis* (Ellepola et al., 2000).

Aspergillus flavus

Aspergillus flavus is a saprophytic soil fungus that contaminates seed crops. It is an opportunistic fungal species that causes aspergillosis diseases as a pathogen in immunocompromised organisms. It can infect the cornea and upper tract of the eye. Like many molds, it can produce aflatoxin, a carcinogenic substance (Amaike & Keller, 2011).

Epidermophyton floccosum

It is a filamentous fungus that causes infections of the nail and skin in humans. The use of itraconazole, voriconazole, Terbinafine, and ketoconazole is effective against microorganisms that cause fungal diseases such as Epidermophyton floccosum (St-Germain & Summerbell., 2003).

Microsporum Canis

They are infectious fungi that have a low incidence in humans but are very common in animals. These fungi occur in cats and dogs. The Microsporum is the most common species in canine and feline ringworm cases (Mancianti et al., 2003).

Tricophyton mentagrophytes

Trichophyton mentagrophytes is a type of fungus that makes humans and animals sick. Such pathogenic fungi exist in different environments and infections can take all forms. T. mentagrohphytes is responsible for scaly, inflammatory fungal infections such as athlete's foot and ringworm (Gräser et al., 1999).

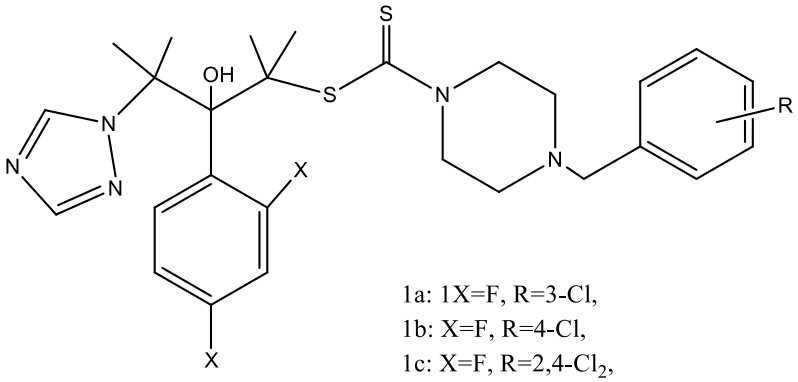
Aspelgillus fumigatus

The most frequent species isolated from the environment and found during postmortem exams is Aspelgillus fumigatus. It is primarily responsible for bone marrow transplant and cancer patients' nosocomial infections, which account for around 80% of all nosocomial infections. The remaining 20% of infections are brought on by A. j&zvus, A. niger, and A. teveus. The primary site of infection after inhaling fungal spores is typically the lung, and the chronic allergy to Aspergi/h spores and saprophytic growth (using dead or damaged tissue that has developed as a result of prior infections or injury) in pre-existing cavities, which results in the formation of so-called "fungus balls," are the most common manifestations of the disease (Koltin et al., 1997).

Antifungal Studies of 1,2,4-Triazoles

Mahmoudi et al. evaluated various 1,2,4-triazole alcohols bearing N-(halobenzyl) piperazine carbodithioate scaffold as effective antifungal agents in vitro bioassays against *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, and *Candida tropicalis*; the best activity was shown by N-(4-chlorobenzyl) derivative 1b, which Additionally, the 3-

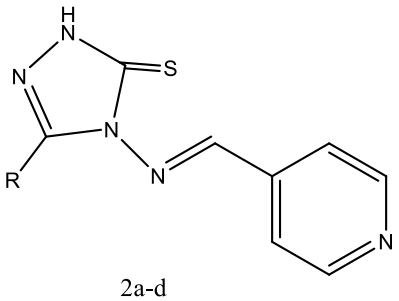
chlorobenzyl compound 1a showed high effectiveness against both Candida albicans and non-albicans species. In general, 2,4-difluorophenyl derivatives were more active than their dichlorophenyl counterparts, according to MICs. Furthermore, 2,4-difluorophenyl-carbinol was superior to the 2,4-dichlorophenyl-carbinol scaffold, according to SAR analyses. Additionally, testing against isolates resistant to fluconazole revealed that compound 21b was effective against isolates of *Candida albicans*, *Candida krusei*, and *Candida parapsilosis*, with MIC values ranging from 2 to 16 mg/mL (Mahmoudi et al.,2018)



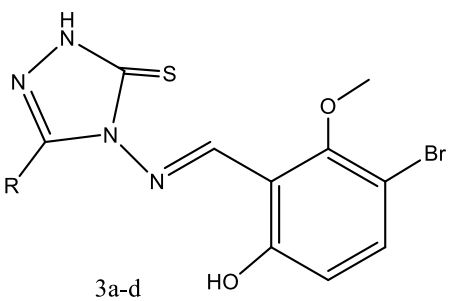
1

1a: 1X=F, R=3-Cl,
1b: X=F, R=4-Cl,
1c: X=F, R=2,4-Cl_2,
1d: X=F, R=3,4-Cl,
1e: X=F, R=4-Br,
1f: X=Cl, R=2,4-Cl_2

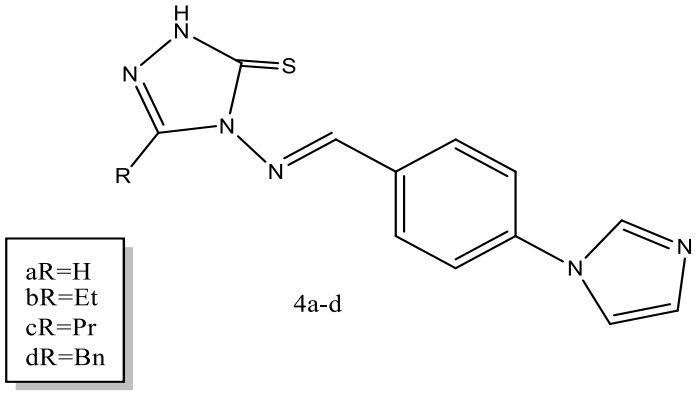
In a study by Jin et al. in 2018 (Jin et al., 2018), 1,2,4-Triazole Schiff Base derivatives were synthesized. Then, their antifungal activite test against "*Pythium solani*, *Cercospora arachidicola*, *Gibberlla saubinetii*, *Alternaria iycopersici*, *Fusarium oxysporium f. sp. niveum*, *Gibberlla nicotiancola*, *Phytophthora capsici*, *Physalospora piricola*, *hori* and *Fusarium oxysporium* f. sp. cucumber" were performed. Triadimephone was chosen as the control. The activity test was performed using the procedure in the literature (Atlas et al., 1995). In this study, it was determined that only the 4a molecule showed antifugal activity.



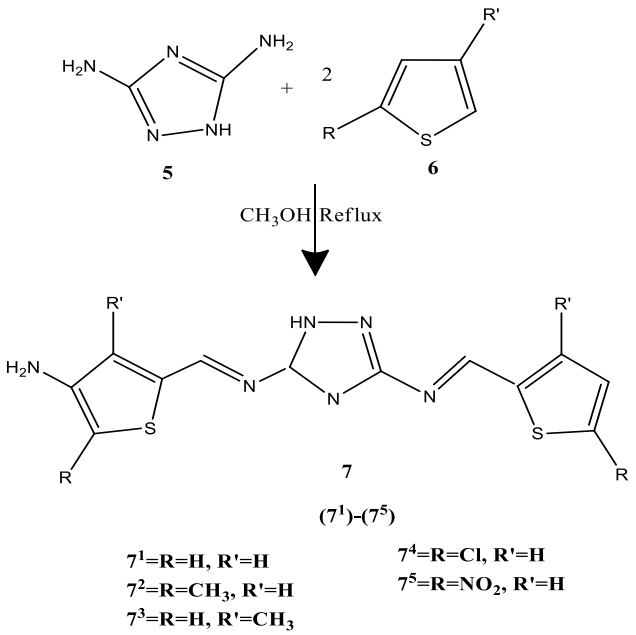
2a-d



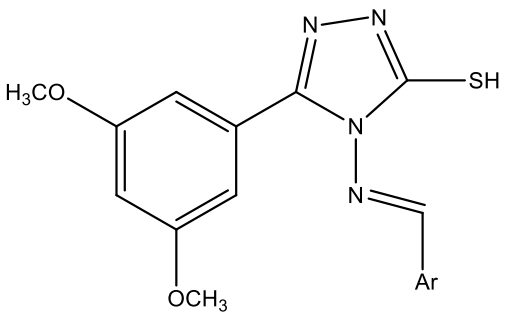
3a-d



In a study by Sumrra et al. in 2013 (Sumrra & Chohan, 2013) novel triazol-derivatives Schiff base were synthesized. The antifungal studies of compound were investigated against fungus such as *T. longifusus*, *C. albican*, *A. flavus*, *M. canis*, *F. solani* and *C. glabrata* fungal. The Miconazole and Amphotericin B were taken as standard. Antifungal test was performed according to the protocol found in the literature (McLaughlin et al., 1991). It has been determined that the ligands show different percentages of antifungal activity against different antifungal agents.



In a study by Morrthy et al. in 2017 (Moorthy et al., 2017), the antifungal activity was performed by MIC method. Amphotericin-B was determined as the standard antifungal. The antifungal activities of all the compounds were studied against *C. albicans* up to 512 µg/ml concentration. The results showed that 8a, 8b and 8f exhibit significant antifungal activity.

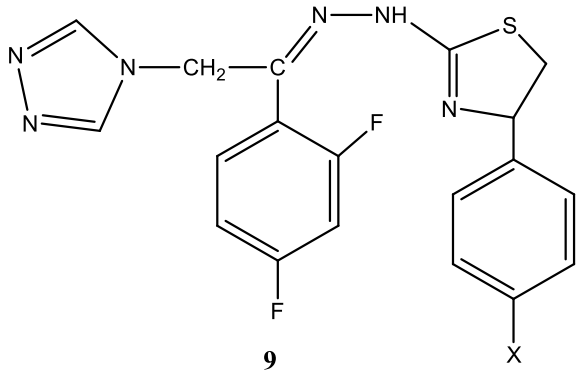


8

Ar

8a=4-Cl-C_6H_4
8b=2,4-Cl_2-C_6H_3
8c=4-OCH_3-C_6H_4
8d=C_4H_3O
8e=2,NH_2-3,4-di-CH_3-C_6H_2
8f=C_6H_4OH

In a study by Russell et al. in 2014 (Russell & Soiket, 2014) new six 1,2,4- triazol Schiff base was synthesized. The four fungal strains were selected for antifungal activity testing. These are *C. albicans*, *Colletotrichum spp*., *A. nigar* and *Fusarium spp*. The Sabouraud Dextrose Agar mediaby diffusion method (Batovska et al., 2007; Turan-Zitouni et al., 1999) was preferred for antifungal screening of compounds. Flucanazole was used as fungal control agent. The 2b and 4b were activited agains four micro-organisms. It was observed that 9b and 9d showed antifungal activity against four microorganisms and other compounds were inactive.

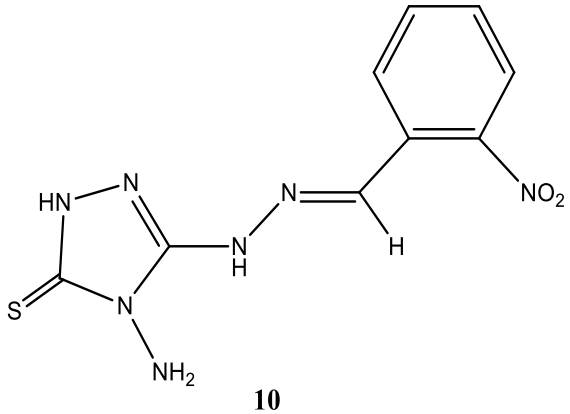


9

9a; X=Br,
9b; X=Cl,
9c; X=NO_2,
9d; X=H,
9e; X=OCH_3

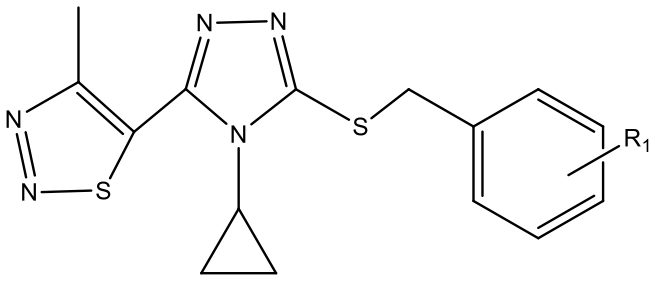
In a study by Joshi et al. in 2021 (Joshi, et al., 2018) (E)-4-amino-5-[N'-(2-nitro-benzylidene)-hydrazino]-2,4-dihydro-[1,2,4]triazole-3-thione molecule was synthesized. Antifungal activity was investigated using four fungal strains such as *Candida albicans* (ATCC 90028), *Candida tropicalis* (ATCC 750), *Candida krusei* (clinical strain) and *Candida glabrata* (clinical strain). The Agar disc diffusion test was done for activity determination (Kumar et al., 2011). The MIC results of the compound as compared with the reference fluconazole. The result of this study

showed us that, the new compound has important antifungal activity against *C. albicans* and moderate antifungal activity against *C. tropicalis*.



10

In a study by Tan et al. in 2014, triazole derivative compounds were synthesized and their antifungal activities were investigated. The *in vivo* fungicidal effects of the title compounds against *Fusarium oxysporum, Pseudoperonospora cubensis, Sphaerotheca fuligenea, Corynespora cassicola, Xanthomonas axonopod* were determined. As a control thiophanate methyl, jinggangmeisu, and zhongshengmycin were utilized. The fungicidal activity of compounds 7c, 7d, 7f, 7j, and 7k were greater than those of thiophanate methyl, jinggangmeisu, and zhongshengmycin against *P. cubensis*. Against R. solanii, none of these drugs showed overt fungicidal activity. The 7f, 7i, 7j, 7k showed fungicidal activity against F. oxysporum (Tan et al., 2014).



11a-k

R=2-ClPh, 3-ClPh, 4-ClPh, 2,4-Cl_2Ph, 3,4-Cl_2Ph, 4-BuPh, 4-OMePh, Ph, 3-CNPh, Propinyl, Heptyl

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TREATMENT METHODS FOR 1,2,4-TRIAZOLE FUNGICIDES FROM WATERS

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Treatment Methods for 1,2,4-Triazole Fungicides From Waters

Fungicides are chemical compounds that are used to efface or avert the growth of fungi or their spores. According to the origin of fungicides, Rachid Rouabhi (2010) categorized them in two main groups of fungicides; 1. Biologically based fungicides (biofungicides): Include living microorganisms (bacteria, fungi) that are antagonistic to the pathogens that induce turf disease. Examples: Ecoguard contains *Bacillus licheniformis*; Bio-Trek 22G contains *Trichoderma harzianum*. In the case of a biofungicide, the Latin name of the microbe that it contains is the generic name of the fungicide. 2. Chemically based fungicides: Synthesized from organic and inorganic chemicals, most of the fungicides that are sold throughout the world are chemically-based (Rouabhi, 2010). In addition; fungicides, protective fungicides (Copper Fungicides, Dithiocarbamates, Phthalimides, Halogenated Compounds, Sulphurous fungicides) and systemic fungicides (1. Alkylalanines, 2. Benzimidazoles, 3. Hydroxypyrimidines, 4. Carboxamides, 5. Conazole Group Fungicides (i. Imidazoles, ii. Triazines), 6. Other Derivatives) are classified into two major groups.

The pesticides and fungicides remaining on the soil surface enter the surface flow with rain water or by leaching from the ground water and other soil and then they reach water sources. Also, these chemicals can be collected from wastewater generated as a result of domestic and industrial activities. These components, which mix with the receiving waters and affect people through the food chain, must be removed from the water after use. To protect the safety of human health and aquatic ecosystems, European Union Directive has regulated the limits for individual pesticide and for the sum of all pesticides, this includes insecticides (insects),

herbicides (weeds), and fungicides (fungi), in drinking water are 0.1 µg/L and 0.5 µg/L, respectively (Liu et al., 2017).

Azole compounds are some of the most widely used fungicides worldwide and are used as anti-icing fluids, wood preservatives, and adhesives (Huang, Zhao, et al., 2022). Modern systemic fungicides are typified by the triazoles. This chemical family of fungicides, introduced in the 1980s, consists of numerous members: difenoconazole, fenbuconazole, myclobutanil, propiconazole, tebuconazole, tetraconazole, triadimefon, and triticonazole (Rouabhi, 2010). A triazole is a heterocyclic compound featuring a five-membered ring of two carbon atoms and three nitrogen atoms with molecular formula $C_2H_3N_3$. These may be of two types, the 1,2,3-triazoles or r-triazoles (Figure 1) and the 1,2,4- triazoles or s-triazoles (Figure 2) (Potts, 1961). 1,2,3-Triazoles are one of the most important nitrogen-containing five-membered heterocycles and have a wide range of applications in pharmaceuticals, supramolecular chemistry, organic synthesis, chemical biology and industry (Ali, 2020). 1,2,4-Triazole exists in two tautomeric forms known as 1*H*-1,2,4-triazole and 4*H*-1,2,4-triazole and it is very difficult to separate them due to their rapid interconversion. The 1*H*-1,2,4-triazole compounds are considered interesting heterocycles since they possess important pharmacological activities such as antifungal and antiviral activities (Al-Masoudi et al. 2006).

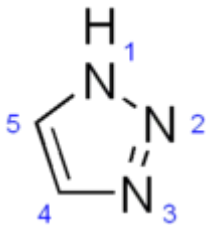

Figure 1. 1,2,3-triazole

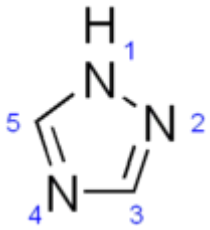

Figure 2. 1,2,4- triazole

15,519.06 Tons of triazoles and diazoles were used in 2014. For instance, in the United States, approximately 2.5 million pounds of propiconazole and 2.1 million pounds of tebuconazole

were used in agriculture purposes. The widespread application of triazoles causes them to enter aquatic environments through runoff, agricultural returns, groundwater intrusions, or through plant uptake. Therefore, triazole fungicides have been frequently detected in aquatic ecosystems all around the world. Huang et al. (2022) have tabulated the measured concentrations of triazole fungicides in waters (Huang, Jiang, et al., 2022). According to the given Table 1, levels are generally in the 100–500 ng/L range for many triazoles and many bodies of water while the levels can increase upwards of 1000 ng/L at around golf courses and in sewage effluent. These levels can cause substantial risks to environmental ecosystems and aquatic life.

Table 1. The measured concentrations of triazole fungicides in waters (extracted from the study of Huang, Jiang, et al., 2022)

Triazoles	Sampled sites	Concentration
Difenoconazole	Surface water in River Madre de Dios, Costa Rica	0.36 μg/L
Difenoconazole	Agricultural water in Thailand (Salakru, NongSua)	28 μg/L
Difenoconazole	Surface water in Malaysia (Kedah)	300 μg/L
Difenoconazole	Surface water in Victoria, Australia	0.15 μg/L
Difenoconazole	Surface water in River Meolo, Italy	0.0095 μg/L
Difenoconazole	Surface water in Jiulong River Estuary, China	0.125 μg/L
Fenbuconazole	Waterworks of Xiamen city, China	0.00022–0.00698 μg/L
Myclobutanil	River Madre de Dios, Costa Rica	0.17 μg/L
Myclobutanil	Surface waters in the Yarra catchment, VIC, Australia	>0.2 μg/L
Paclobutrazol	Surface water in Jiulong River Estuary and West Xiamen Sea, China	0.1196 μg/L
Paclobutrazol	Groundwater on golf courses throughout the United States and Canada	4.2 μg/L
Propiconazole	Banana plantation, Limon, Costa Rica	0.15–13 μg/L
Propiconazole	Influent of pharmaceutical company, Belgium	0.17–0.24 μg/L
Propiconazole	Effluent of pharmaceutical company, Belgium	0.012–0.14 μg/L
Propiconazole	Paris sewer, France	0.15–0.21 μg/L
Propiconazole	Raw municipal wastewater, Western Balkan Region	< 0.08 μg/L
Propiconazole	River Madre de Dios, Costa Rica	0.13 μg/L
Propiconazole	Effluent of wastewater treatment plants in Belgium	0.0019–0.1783 μg/L
Propiconazole	Agricultural surface water in 13 states of US	0.291–1.150 μg/L
Propiconazole	Wastewater treatment plants influents, Switzerland	0.001–0.03 μg/L
Tebuconazole	Wastewater treatment plants influents, Switzerland	0.001–0.03 μg/L
Tebuconazole	River Madre de Dios, Costa Rica	0.27 μg/L
Tebuconazole	Morcille catchment, France	0.011–6.5 μg/L
Tebuconazole	Runoff events in the west of France	81 μg/L
Tebuconazole	Stream water in Morcille River, France	175–200 μg/L
Triadimefon	Rivers in China	0.00152 to 5.22 μg/L
Triadimefon	Surface runoff in the USA	922 μg/L
Triadimenol	River Madre de Dios, Costa Rica	0.1 μg/L

The interaction degrees with the environment of the fungicides depend on their physicochemical properties. Their mobility and persistence in the soil, dissociation in water, bioaccumulation, and durability in the environment are significantly effected from the physicochemical properties. So, the physicochemical properties of triazole fungicides are very important for their environmental fate. Table 2 shows the physicochemical properties of 1,2,4-triazole fungicides such as IUPAC names, MW—molecular weight, logP—partition

coefficient, HBD—hydrogen bonds donors, HBA—hydrogen bonds acceptors, RBC—rotatable bonds count, TPSA-topological polar surface area, DT50and DT90the periods after that 50% and respectively 90% of the fungicide to be degraded. It can be concluded from Table 2 that the given 1,2,4-triazole fungicides are partly lipophilic (the median lop P is 3.35), partly flexible (the median value of the rotatable bonds is 5) and their hydrogen bonding capacity is quite low. Their lower mobility and higher sorption into soil due to their hydrophobic nature and low molecular weight may cause to the persistence of them in soil (Roman et al., 2021).

Table 2. The physicochemical properties of the fungicides (extracted from the study of Roman et al. (2021))

Fungicide Common Name	IUPAC Name	MW (g/mol)	logP	HBD	HBA	RBC	TPSA (Å²)	DT_{50} for Field Studies (Days)	DT_{90} for Field Studies (Days)
Cyproconazole	2-(4-chlorophenyl)-3-cyclopropyl-1-(1,2,4-triazol-1-yl)butan-2-ol	291.77	2.9	1	3	5	50.9	62.1–501.2 (persistent)	179–1000
Difenoconazole	1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1,2,4-triazole	406.3	4.0	0	5	5	58.4	20–265 (persistent)	68–879
Epoxiconazole	1-[[3-(2-chlorophenyl)-2-(4-fluorophenyl)oxiran-2-yl]methyl]-1,2,4-triazole	329.8	3.2	0	4	4	43.2	0.75–247.8 (persistent)	183.7–10.000
Flutriafol	1-(2-fluorophenyl)-1-(4-fluorophenyl)-2-(1,2,4-triazol-1-yl)ethanol	301.29	2.3	1	5	4	50.9	316–4089 (very persistent)	1051–13,583
Hexaconazole	2-(2,4-dichlorophenyl)-1-(1,2,4-triazol-1-yl)hexan-2-ol	314.2	3.7	1	3	6	50.9	49–200 (persistent)	NA
Metconazole	5-[(4-chlorophenyl)methyl]-2,2-dimethyl-1-(1,2,4-triazol-1-ylmethyl)cyclopentan-1-ol	319.8	3.7	1	3	4	50.9	26.6–368.5 (persistent)	102.9–1000
Myclobutanil	2-(4-chlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)hexanenitrile	288.77	2.9	0	3	6	54.5	9–58 (Moderately persistent)	637–1906
Paclobutrazol	1-(4-chlorophenyl)-4,4-dimethyl-2-(1,2,4-triazol-1-yl)pentan-3-ol	293.79	3.2	1	3	5	50.9	27.2–60.8 (persistent)	46.7–202
Propiconazole	1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1,2,4-triazole	342.2	3.5	0	4	5	49.2	15.3–96.3 (moderately persistent)	108–525
Tebuconazole	1-(4-chlorophenyl)-4,4-dimethyl-3-(1,2,4-triazol-1-ylmethyl)pentan-3-ol	307.82	3.7	1	3	6	50.9	25.8–91.6 (moderately persistent)	66–304
Tetraconazole	1-[2-(2,4-dichlorophenyl)-3-(1,1,2,2-tetrafluoroethoxy)propyl]-1,2,4-triazole	372.14	4.4	0	7	7	39.9	136–1688 (moderately persistent)	453–5606
Triadimenol	1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)butan-2-ol	295.76	3.1	1	4	5	60.2	24.1–83.7 (persistent)	76.3–423.9
Triadimefon	1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)butan-2-one	293.75	2.8	0	4	5	57	26 (non-persistent)	NA
Triticonazole	(5E)-5-[(4-chlorophenyl)methylidene]-2,2-dimethyl-1-(1,2,4-triazol-1-ylmethyl)cyclopentan-1-ol	317.8	3.1	1	3	3	50.9	36.1–242 (persistent)	329–803

Triazoles having antifungal effects inhibit the ergosterol biosynthesis, thereby interfering with the formation of fungal cell-wall. They contain about 25 commercial agrochemicals worldwide and are widely used due to their excellent antifungal activity and relatively low resistance risk. However, potential endocrine-related side effects on humans and wildlife occur owing to their large consumption because they prevent the cytochrome P450-dependent 14 α-demethylase, an enzyme counted in the biosynthesis of steroid hormones, and then disturb the balance of

androgens and estrogens. Triazoles exhibit high chemical and photochemical stability and low biodegradability, making them permanent and accumulated in the environment; so, it has been considered that they are hazardous to the environment and human health (Huang, Jiang, et al., 2022). For these reasons, the treatment process of the waters including triazoles should be developed in order to minimize the adverse effect of them. In the literature, the treatment processes such as adsorption, degradation, biodegradation, photocatalytic degradation, electrochemical oxidation, membrane filtration, and nanofiltration have been evaluated for the removal of 1,2,4-triazole fungicides. The studies in the literature about the treatment methods used for the removal of 1,2,4,-triazole fungicides from waters were summarized as follows.

The treatment methods used for the removal of 1,2,4-triazole fungicides

Adsorption

Fang et al. (2019) investigated the adsorption of three commonly used triazole fungicides namely hexaconazole (HEX), myclobutanil (MYC), and triadimenol (TRI) on pristine polystyrene (PS) particles as adsorbent. They have chosen PS as the model adsorbent material representing microplastics because it is an abundant type in wastewater treatment plants arising from pharmaceuticals and personal care products. The reason for choosing these triazole fungicides is high sales of them and also having the basic chemical structure of triazole fungicides and some characteristic groups. The linear forms of Pseudo-first order, Pseudo-second-order, and Intraparticle diffusion models were applied to the adsorption data and the results showed that Pseudo-second-order model was found to be more proper for describing the adsorption kinetics process of the three triazole fungicides on PS. Intraparticle diffusion model confirmed that adsorption and subsequent pore filling may drive the adsorption. The adsorption isotherm models of Langmuir and Freundlich were used to predict the distribution of the triazole fungicides at adsorption equilibrium between solid and liquid phases. Accordingly, it was observed that Freundlich model was more fitted to the equilibrium data indicating the heterogeneity in the adsorption process. The effects of chemical structure, particle size, pH value, and ionic strength on adsorption capacity was investigated and the results showed that the adsorption capacity of PS increased with the decrease in PS particle size and change in solution pH value and increase in salt ion strength. The discussion of the main adsorption mechanisms was further done by analyzing ATR-FTIR peaks of PS before and after adsorption and also influencing factors. Accordingly, the main mechanisms of adsorption were observed to be hydrophobic and electrostatic interactions. Furthermore, the order of adsorption and

desorption capacity of PS was HEX > MYC > TRI and also it was found that the adsorption capacity of PS for three triazole fungicides reached ug/g level. All results of this work indicated that PS can effectively adsorb these triazole fungicides with the high capacity (Fang et al., 2019).

In the study of Wang et al. (2019), the graphene was decorated by Fe_3O_4 nanoparticles and utilized as an adsorbent for the removal of ten commonly used triazole fungicides in agriculture, namely tebuconazole, hexaconazole, flutriafol, triadimenol, triazolone, epoxiconazole, penconazole, myclobutanil, paclobutrazol, and metconazole from aqueous solutions. The graphene/Fe_3O_4 NPs composite was chosen as an adsorbent due its magnetic property providing easy separation from the aqueous solution and improved adsorption capacity. The adsorption percentages of ten fungicides (20 μg/mL) ranged from 85.2% to 96.0% at the adsorbent concentration of 0.4 g/L. The effect of environmental conditions such as contact time, adsorbent amount, solution pH, and ionic strength were investigated and the results showed that the adsorption capacity of graphene/Fe_3O_4 NPs composite was not affected by the solution pH and ionic strength. The study on adsorption kinetics and thermodynamics were investigated by taking tebuconazole as an example because of the highest adsorption capacity. The pseudo-first-order and pseudo-second- order models were applied to the experimental data at different temperatures. The linear analysis results indicated that the pseudo-second-order model was more suitable to describe the adsorption of tebuconazole on graphene/Fe_3O_4 NPs composite due to the higher regression coefficients and the closeness between the calculated adsorption amount at the equilibrium ($q_{e,cal}$) and the experimental values ($q_{e,exp}$). Weber-Morris model plots exhibited multi-linearity suggesting that the whole adsorption process was limited by both external mass transfer and intra-particle diffusion. Langmuir and Freundlich isotherm models were applied to the equilibrium data of the adsorption of tebuconazole on graphene/Fe_3O_4 NPs composite and it was found that Langmuir isotherm model fitted better than Freundlich isotherm model indicating the monolayer and homogeneous adsorption process. In addition, the maximum adsorption capacity of tebuconazole onto graphene/Fe_3O_4 NPs composite was calculated as 60.2, 70.3, 80.5 mg/g at 273, 293 and 313 K, respectively. In the thermodynamic study, free energy of adsorption, enthalpy, and entropy were calculated and the results showed that the adsorption is a spontaneous, endothermic, and physisorption process. With the content of investigating the possible interactions in the adsorption, the electrostatic interaction, hydrogen bonding interaction, π- π stacking, hydrophobic interaction, and cation- π interaction

were discussed and it was concluded that π- π stacking was observed to be the dominant factor for the adsorption of tebuconazole on graphene/Fe_3O_4 NPs composite (Wang et al., 2019).

Crini et al. (2017) used two conventional activated carbons (ACs) and five non-conventional cross-linked cyclodextrin (CD)-based materials (α-CDP, β-CDP, γ-CDP, αβγ-CDP mixture, and hydroxypropyl-β-CDP) as adsorbents for the removal of triazole fungicides from aqueous mixtures of propiconazole (PROPI), tebuconazole (TEBU), epoxiconazole (EPOXI), bromuconazole (BROMU) and difenoconazole (DIFENO) which have used in wide areas such as wood industry, vegetable cultivation, horticulture, and agriculture in order to protect various products against fungal decay. The adsorption experiments were conducted at 1.0 mg/L fungicide concentration, 5.0 initial pH, 1.0 g/L adsorbent concentration, 4.0 h contact time, and 25 ^{o}C temperature using batch method. The obtained adsorption percentages for 9 adsorbents were presented in Figure 3. It was observed that the modified forms of activated carbon (M-PAC and M-GAC) were more efficient than their raw forms (PAC and GAC) and the CD-based materials regardless of triazole type. The adsorption of fungicides on AC occurs via dispersive interactions between the π electrons in the aromatic ring of the fungicides and the π electrons in the carbons, by physical adsorption in the carbon network, and by hydrogen bonding. The differences between the adsorption percentages of the commercial AC and modified AC resulted from the surface charge character. Accordingly, the AC modified with NaOH had less acidic characters than the commercial ACs, which favored adsorption process. For the adsorption of fungicides on CD-based materials, the adsorption mechanism is more complicated. The steps of surface adsorption, diffusion into polymer network, and chemisorption are considered to be effective simultaneously (Crini et al., 2017).

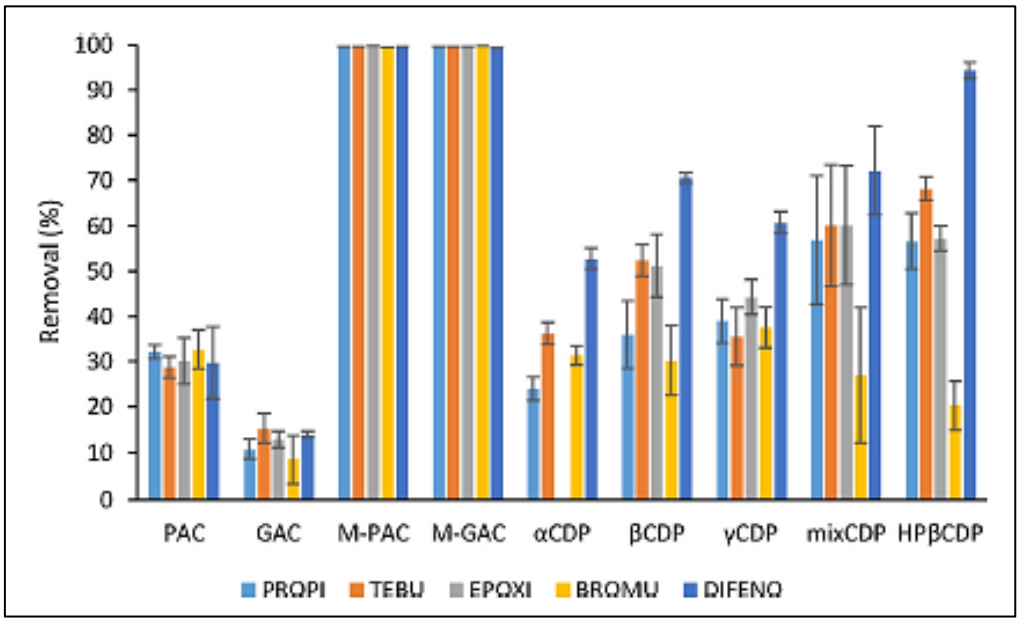

Figure 3. The adsorption percentages of PROPI, TEBU, EPOXI, BROMU, DIFENO on commercial activated carbons (Panreac powdered form (PAC) and Chemviron CA201 granular form (GAC)), activated carbons modified with NaOH (M-PAC, M-GAC), and cross-linked cyclodextrin (CD)-based materials (α-CDP, β-CDP, γ-CDP, αβγ-CDP mixture, and hydroxypropyl-β-CDP)

It was observed that the removal percentages increased as the adsorbent concentration increased due to the availability of more adsorption sites regardless of the adsorbent. Also, the removal percentages increased with contact time for all triazole fungicides, reaching an equilibrium within 3h for M-GAC and only 20 min for HPβCDP.

Table 3 showed the removal percentages of triazole fungicides in a mixture or in single solution for M-GAC and HPβCDP. It was clearly seen that there was no competition effect with the use of M-GAC while strong competition prevailed among fungicides for binding sites with the use of HPβCDP (Crini et al., 2017).

Table 3. The removal percentages of triazole fungicides in a mixture (concentration of each triazole=1.0 mg/L, 5.0 mg/L in total) or in single solution (concentration=5.0 mg/L) for M-GAC and HPβCDP (other conditions: adsorbent concentration=1.0 g/L, contact time=4h; T=25°C)

	PROPI	TEBU	EPOXI	BROMU	DIFENO
	M-GAC				
in mixture	99.7 ± 0.3	99.7 ± 0.3	99.7 ± 0.2	99.8 ± 0.5	99.4 ± 0.3
alone	99.6 ± 0.9	94.8 ± 0.9	90.6 ± 0.7	82.8 ± 0.9	99.8 ± 0.2
	HPβCDP				
in mixture	56.6 ± 1.7	68.2± 2.6	57.2 ± 1.5	20.3 ± 1.3	94.3± 1.9
alone	50.0 ± 2.1	81.0± 0.6	25.4 ± 2.3	60.7 ± 3.2	99.1± 1.4

The study of Amorim et al. (2013) was conducted in Brazil, where is the largest worldwide producer and exporter of coffee and they have studied on the pesticides used in coffee industry. One of the pesticides is epoxiconazole belongs to the class of triazoles, which is used for the control of coffee rust. 1,2,4-triazole is formed as a result of the degradation of epoxiconazole in the environment and it has environmental risk due to its being highly soluble and stable in water. It has been known that the conventional water treatment processes such as coagulation, chemical oxidation are not proper for the removal of various organic compounds such as pesticides. Therefore, in this study, adsorption was preferred for the removal of epoxiconazole due to its being relatively simple, effective, and economic feasible technique among the other removal processes used for pesticide removal like photocatalytic degradation, biogological oxidation, advanced oxidation process, aerobic-anaeorbic degradation, nano-filtartion membranes, and ozonation. Two commercial activated carbons namely charcoal-powdered activated carbon (CPAC) and bovine bone-powdered activated carbon (BPAC) were utilized as adsorbent for the removal of epoxiconazole. The results of adsorption kinetics showed that the pseudo-second-order model had higher regression coefficients and the calculated values ($q_{e,cal}$) from the pseudo-second-order model were closer to that obtained experimentally ($q_{e,exp}$). The equilibrium data of CPAC was well represented with Langmuir isotherm model while Freundlich isotherm model was found be the best fit for the equilibrium data of BPAC. Under the set experimental conditions, the removal percentages of CPAC and BPAC were found to be 76% and less than 8%, respectively. Therefore, it was observed that BPAC was not efficient

adsorbent for the removal of epoxiconazole. In the conclusion, the authors emphasized that although CPAC could be used for the removal of epoxiconazole, detailed studies should be done in order to obtain higher removal percentage and ensure the correct design of water treatment unit (Amorim et al., 2013).

Degradation

Ghauch (2008) investigated the degradation of flutriafol, a high persistent water/soil triazole pesticide, in water by zero-valent iron (ZVI) powder using a laboratory scale device consisting of a 20 ml pyrex serum vials fixed to a Vortex agitator at pH 6.6 and room temperature. Flutriafol is generally used in coffee, maize and cereals for the control of major seedborne and soil-borne diseases. Due to its high spray application rate and commonly usage on cereals, it is thought to cause water pollution. This study evaluated the usefulness of ZVI powder on the degradation of flutriafol in a phosphate buffered solution (PBS) at room temperature. The effect of iron concentration and dissolved oxygen, the observed degradation rates, the half-live of flutriafol, and the identification of some of the obtained by-products were investigated. The results showed that the half-live $t_{1/2}$ decreased from 10.8 ± 0.5 min to 3.8 ± 0.2 min as the concentration of ZVI raised from 10 to 50 g/L. According to the results of the effect of dissolved oxygen, the degradation of flutriafol occurred at a low concentration of dissolved oxygen as well as under a slightly acidic condition in the presence of an adequate buffer. Flutriafol degradation reactions progressed with first order kinetic with a half-live of about 10.8 ± 0.5 min and 3.6 ± 0.2 min at ZVI concentration of 10 g/L into oxygenated and anoxic solutions, respectively. UV–Vis spectrophotometer, a high performance liquid chromatography (HPLC) coupled with a photo diode array (PDA) and fluorescence detectors, a similar HPLC coupled with a PDA and a mass spectrometer detectors equipped with an atmospheric pressure photoionization source were used for monitoring the degradation of flutriafol and revealing by-products behaviors. Accordingly, a complete disappearance of flutriafol after 20 min of contact with ZVI, the loss of fluorescence properties of the final by-products, the defluorination of the triazole pesticide occurred via hydroxylation reaction and finally the hydrogenation of the triazole ring (Ghauch, 2008).

In the study of Saadaoui et al. (2021), the researchers investigated the degradation of two triazole pesticides (Myclobutanil and Penconazole) in aqueous solution by gamma irradiation. The effects of irradiation dose, pH, radical scavenger, and natural organic matter were examined on the removal of Myclobutanil and Penconazole. The removal percentage was acquired at least

90% at an absorbed dose of 0.575 kGy and 0.460 kGy for Myclobutanil and Penconazole, respectively. As increasing of dose, the removal percentage increases and the degradation takes place better under neutral conditions. When the concentration of humic acid was increased from 0 to 20 mg/L at a dose of 1.2 kGy, the removal percentages decreased from 100% to 40.67% and to 50% for Myclobutanil and Penconazole, respectively. When used thiourea as a radical scavenger, the degradation reaction of triazole pesticides was enhanced due to the active species like e_{aq}^- and ●H. HPLC-QTOF-MS/MS was used for the identification of the degradation by-products. Accordingly, five by-products were identified for Myclobutanil and ten for Penconazole and dominantly hydroxylation caused the formation of these by-products. A toxicity study was conducted on Wistar rats in order to evaluate the effects of these by-products, and it was found that no increase in toxicity was observed as a result of the degradation of two triazole pesticides. ^{1}HNMR analysis was conducted for the investigation of the mineralization of both pesticides by gamma irradiation and completely mineralization of both pesticides was achieved at 1.2 kGy. The overall results suggested that Gamma irradiation seems to be a promising method for the degradation of triazoles in water which can be used as recycled water (Saadaoui et al., 2021).

Zendegi-Shiraz et al. (2021) have focused on the removal of triazole fungicides namely penconazole, hexaconazole, and diniconazole via adsorbent-catalyst coupling (ACC) process. For this purpose, adsorption, degradation, and both of them were investigated separately with Ag and Fe_3O_4 as catalyst and PEG-CuO as adsorbent for the removal of the triazole fungicides. The results showed that a complete removal could not be achieved with the use of the catalyst alone, even at their high concentrations. On the other hand, the simultaneously use of PEG-CuO as adsorbent and one of the catalysts (Ag or Fe_3O_4) provided the completely removal of the triazole fungicides thanks to the ACC process. After obtained these findings, the effects of adsorbent load, catalyst load, ratio of catalyst to adsorbent, salt concentration, pH, and operating time were examined on the efficiency of ACC process for the removal of the triazole fungicides. Accordingly, the completely removal could be achieved for all triazole fungicides for 50/50 ratio of Ag/PEG-CuO as well as 30/70 ratio of Fe_3O_4/PEG-CuO. All triazole fungicides were completely removed at the absence of salt (NaCl). The optimum pH and operation time were obtained as 7.0 and 85 min, respectively. The experiments were conducted with the real fungicide polluted wastewaters obtained by washing some vegetables such as cucumber, lettuce, bell pepper, cabbage, and tomato at the optimum conditions of ACC process. The amounts of fungicide residues in vegetable wash wastewater before and after ACC process was

presented in Table 4. Accordingly, it can be concluded that the treatment of real fungicide polluted wastewaters could be effectively carried out at the obtained optimum conditions of ACC process. As a consequence, this study suggests the ACC process as a promising alternative for the removal of the triazole fungicides (Zendegi-Shiraz et al., 2021).

Table 4. The amounts of fungicide residues in vegetable wash wastewater before and after ACC process

Vegetable samples	Before treatment Penconazole Concentration (µg/mL)	Before treatment Hexaconazole Concentration (µg/mL)	Before treatment Diniconazole Concentration (µg/mL)	After treatment All fungicides Concentration (µg/mL)
Cucumber	3.25	2.59	1.49	n.q[a]
Tomato	n.q[a]	n.q[a]	n.q[a]	n.q[a]
Bell pepper	1.77	0.60	0.85	n.q[a]
Cabbage	3.50	n.q[a]	n.q[a]	n.q[a]
Lettuce	3.80	n.q[a]	n.q[a]	n.q[a]

[a]Not quantified: HPLC-UV did not detect fungicides.

Biodegradation

Liu et al. (2019) have aimed to isolate 1H-1,2,4-triazole (TZ) degrading strain from activated sludge acclimated by TZ. It was successfully done and identified as *Raoultella sp.* NJUST42. The efficiency of *Raoultella sp.* was investigated with regards to biodegradation of TZ, TOC removal, NH_4^+ release, pH increase, and biotoxicity reduction. The effects of initial TZ concentration, incubation temperature, initial pH and additional carbon source were also investigated on TZ biodegradation by *Raoultella sp.* Accordingly, the removal of TZ increased with increasing initial TZ concentration; however, it was found that TZ exhibited an inhibitory substrate at high TZ concentration. The optimum incubation temperature was observed as 30 ^oC, and too high or too low incubation temperature would adversely affect TZ biodegradation. It was also obtained that the optimum pH was 7.0 and both acidic and alkaline condition was unfavorable for TZ biodegradation. In the effect of additional carbon sources; a DT_{50} minimum value of 100.4 ± 8.4 h was obtained at the glucose concentration of 500 mg/L while that value reached a maximum value of 223.5 ± 18.4 h at the glucose concentration of 2000 mg/L, which indicated the competitive inhibition exerted by additional carbon source. As a consequence, the completely removal was achieved at incubation temperature of 30 °C, initial pH of 7.0, and initial concentration of 100 mg/L within 288 h. At these conditions, obvious TOC removal, NH_4^+ release, pH increase, biomass growth, biotoxicity reduction, and excitation emission matrix variation were also obtained. The first-order degradation kinetic model was in good

agreement with the TZ biodegradation profile by *Raoultella sp.*. HPLC/MS analysis was examined in order to explain the pathway of TZ biodegradation and it was suggested that hydroxylation, carbonylation, carboxylation, and ring cleavage were accrued and it was concluded that *Raoultella sp.* utilized TZ as the sole carbon and nitrogen source. The overall results demonstrated that the TZ biodegradation by *Raoultella sp.* could be great potential for the application in biological treatment of wastewater in practice (Liu et al., 2019).

In the study of Wu et al. (2019), co-metabolic enhancement of 1H-1,2,4-triazole (TZ), which is widely utilized as the main compound for the synthesis of triazole fungicides, biodegradation through nitrification was investigated in an activated sludge reactor. This removal method was chosen because the conventional biological process is quite unproductive for TZ removal due to highly intractable nature of TZ. The results showed the enhancement of removal of TZ, TOC, and dissolved organic matter thanks to the co-metabolic degradation of TZ in the continuous flow bioreactor. The major reason for the advanced removal performance was the enrichment of functional species related to nitrification and functional degrading species with the supplement of NH_4^+. GC/MS analysis was conducted for the identification of intermediates and five co-metabolic intermediates, including 2,4-dihydro-[1,2,4]triazol-3-one and [1,2,4]triazolidine-3,5-dione, were observed. The significant enhancement of microbial community in the co-metabolic system was proved via high-throughput sequencing analysis in the regard of richness, abundance and uniformity. This study has indicated that nitrification-assisted co-metabolism had a promising potential for the removal of intractable contaminants such as TZ from wastewater (Wu et al., 2019).

Wu et al. (2016) investigated biodegradation of 1H-1,2,4-triazole (TZ), which is broadly used in the production of insecticide, herbicide, fungicide, plant growth regulator and antitumor, antivirus and antibacterial agents, by a novel isolated strain *Shinella sp.* NJUST26. The isolation was properly done from TZ-contaminated soil and it was defined as *Shinella sp.*. The effects of pH (3.0-10), incubation temperature (20-40 ^oC), initial TZ concentration (100-320 mg/L), and additional organic carbon source (0.5-2.0 g/L yeast extract, sucrose, glucose) was examined on the biodegradation of TZ. The optimum pH and temperature were determined as 6-7 and 30 ^oC, respectively. The maximum volumetric degradation rate raised from 29.06 to 82.96 mg/L.d with increasing of initial TZ concentration from 100 to 320 mg/L, implying high tolerance of *Shinella sp.* NJUST26 towards TZ. The addition of yeast extract, sucrose, glucose at low concentration could be significantly enhanced the biodegradation of TZ by *Shinella sp.* NJUST26; however, the high concentration of additional organic carbon source negatively

affected the biodegradation. It was determined by GC/MS and HPLC/MS analysis that the main metabolites of 1,2-dihydro-3H-1,2,4-triazol-3-one (DHTO), semicarbazide, and urea formed during the TZ biodegradation. The pathway of the TZ biodegradation by *Shinella sp.* NJUST26 was as follows; TZ was firstly oxidized to DHTO, and then the cleavage of DHTO ring occurred to produce N-hydrazonomethyl-formamide, which could be further degraded to biodegradable semicarbazide and urea (Wu et al., 2016).

Satapute and Kaliwal (2016) assessed the ability of *Burkholderia* sp. strain BBK_9 for biodegradation of propiconazole (PCZ), which is a triazole foliar fungicide and used in agriculture. PCZ degrading bacterium BBK_9 strain was isolated from paddy soil and identified as *Burkholderia* sp. relying on the morphological characteristics and biochemical properties combined with 16S rRNA gene sequencing analysis. The effects of pH and temperature were investigated and the results showed that 8.89 µg/mL (89 %) PCZ was degraded at 30 ºC and pH 7.0 within 4 days. In the degradation process, PCZ acts as the sole carbon source and energy substrate, which can be used for the strain for its growth in mineral salt medium. The plasmid curing method using LD_{50} concentration was conducted in order to search the role of plasmid and in this method, three plasmids got cured in the sixth generation. Accordingly, 7.37 µg/mL PCZ could be degraded by the cured strain, indicating that there was no responsibility of the plasmid encoded gene for the PCZ biodegradation. On the other hand, it was observed that the plasmid cured cells were also a healthy competitor which has an ability to degrade the PCZ. The PCZ transformed into three important metabolites namely 1-(2,4-dich1orophenyl)-2-(1H-1,2,4-triazol-1-y1) ethanone, 1-[2-(4-chlorophenyl) ethyl]-1H- 1,2,4-triazole and 1-ethyl-1H-l,2,4-triazole during the bioconversion process. Consequently, the use of *Burkholderia* sp. strain BBK_9 for the biodegradation of PCZ is a good alternative in order to remove the contaminated pollutants providing toxic-free environment (Satapute & Kaliwal, 2016).

Photocatalytic Degradation

In the study of Lhomme et al. (2007), the degradation of cyproconazole, triazole fungicide used in agriculture, on foliage, and in cereal cultivation, by UV/TiO_2 photocatalysis in water using industrial TiO_2 coated non-woven paper. Irradiation was conducted in a cylindrical batch reactor in a thermostated tank at 25 ºC, fitted with a 25W low pressure fluorescent lamp placed vertically in a plugged tube. The described batch photoreactor was showed in Figure 4. The UV lamp was turned on to irradiate the solution including the fungicide after the adsorption equilibrium was achieved.

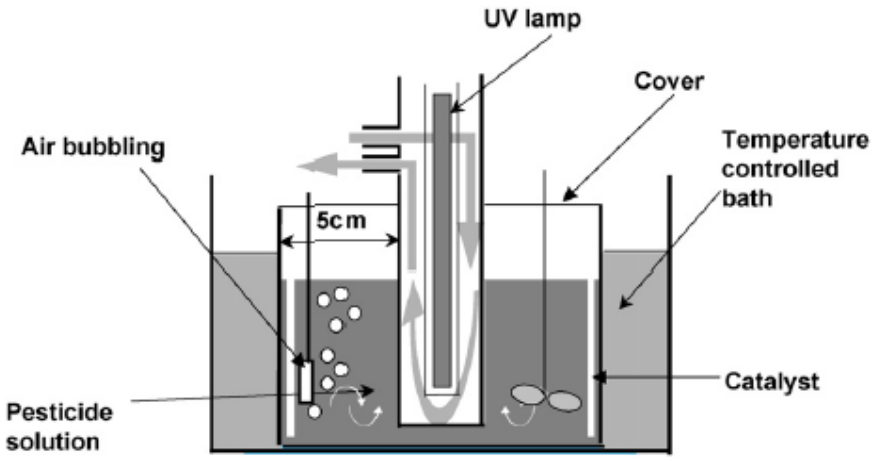

Figure 4. Batch photoreactor

The effects of dissolved oxygen on the degradation kinetics were investigated with and without air bubbling. Accordingly, even when the air bubbling was done for the forced oxygen transfer, approximately an 11% reduction in the oxygen concentration occurred. The original method considering account information obtained all along the course of the reaction for the calculation of the adsorption constant of the oxygen on TiO_2. It was determined that the calculated adsorption constant of the oxygen was quite close to the values of the degradation of cyproconazole and chlortoluron, approving the validation of the used original method. The first by-products as well as the final state of the pollutant's components such as the fate of carbon, chlorine and nitrogen were investigated. The analysis of the first by-products proposes that the hydroxyl radical attack takes place on the phenyl ring and methyl groups and on the carbon C1 of the cyproconazole before the opening of the aromatic ring. The findings of the fate of heteroatoms indicates that nitrate does not arise from ammonium oxidation, as the amount of NH_4^+ is constant, while the amount of NO_3^- increases. Ammonium and nitrate are formed differently from the nitrogen contained in triazole groups. The formation of N_2, cyanuric acid or other organic recalcitrant compounds could elucidate the lack of stoichiometric nitrogen amount. The chlorine atoms were entirely released as chloride ions. Overall result of this work indicates that TiO_2 coated on non-woven paper could be used as an efficient photocatalyst for degrading and mineralizing cyproconazole, and avoiding the toilsome filtration step, which limits the application of industrial photocatalyst process (Lhomme et al., 2007).

Zaza et al. (2001) have studied in the photodegradation of 3(5)-amino-1,2,4-triazole in aqueous solution by TiO_2 coupled to simulated sunlight. It has been known that the concentration of 3(5)-amino-1,2,4-triazole more than 0.1 µ/L causes potential pollution in surface and

groundwaters; therefore, it should be treated before discharging to receiving waters. The researchers suggest the UV plus semiconductor photocatalyst titanium dioxide as quite efficient tool for the removal of triazole herbicides in the final stages of water treatment. In this study, the irradiation was conducted with polychromatic light using heraeus apparatus equipped with xenon lamp having a spectral energy distribution similar to solar irradiation (> 290 nm). The maximum removal values of 3-amino-1,2,4-triazole in the presence of TiO_2 were achieved at pH 7.0 and the ratio 1/5 herbicide /TiO_2 (w/w). HPLC equipped with UV detector at 205 nm was used for the determination of the concentration of the remaining herbicide and metabolites. Accordingly, one metabolite was noticed and only 10% of this metabolite remained in the medium after 5 hours of irradiation. As a result, it is suggested that the photocatalysis by TiO_2 and solar light can be considered as a good alternative for the degradation of 3(5)-amino-1,2,4-triazole (Zaza et al., 2001).

In the study of Kuehr and Nunez (2007), the photocatalytic degradation of fungicide precursor of 1,2,4-triazole via TiO_2 and simulated solar radiation. A solar light simulator LS 1000W (Solar Light Co.) equipped with a xenon lamp and filters that reproduce solar UVB and UVA radiation (290–400 nm) were used. The mineralization was followed through chemical oxygen demand (COD) measurements at predetermined time intervals. The experiments were carried out at pH 8.0 because the degradation was not observed at lower pHs while the higher pHs enhanced the degradation rates. The degradation of 1,2,4-triazole progressed according to Langmuir–Hinshelwood mechanism. Accordingly, the adsorption equilibrium constants (K) and the rate constants (k) were found experimentally. As pKa increased, K values decreased while k values increased. Therefore, the rate constant related to the accessibility of the electron pair on nitrogen, but at the same time the electron pair repulsion induced by the negatively charged TiO_2 surface at pH=8.0 causes a converse effect in the adsorption equilibrium constant. These results showed that fungicides synthesized from triazole can be degraded at pH=8.0 using TiO_2 and simulated solar radiation (Kuehr & Núñez, 2007).

Electrochemical Oxidation

Han et al. (2014) have aimed to removal of triazole fungicides namely tricyclazole (TC), 1H-1,2,4-triazole (Tz) and propiconazole (PPC) via electrochemical oxidation using TiO_2-NTs/SnO_2-Sb/PbO_2 anode. Bulk electrolysis study was carried out and the results showed that the oxidation and mineralization reactions of three fungicides by HO• followed the pseudo first-order kinetic model. The oxidation rates indicated the following degradation sequence: PPC >

TC > Tz. Moreover, atom charge was calculated by semi-empirical DFT method and active sites of triazole fungicides were classified respectively. GC-MS and LC-MS/MS were used for the analysis of the intermediates. In brief, the calculation of active sites showed that N6 (0.406), N8 (0.279) and N9 (-0.303) were found to be active sites for TC and hydroxylation was first located at N8 position and then at N9 position. For Tz, the most abundant charge was observed at N5 (-0.494) and 2,4-Dichlorobenzoicacid-methylester was determined in the analysis. For PCC, it was found that C6 (0.312) was active site and the hydroxylation of C6 caused to the formation of the intermediates. Toxicity reduction of triazole fungicides solutions during the electrochemical oxidation process was evaluated and it was obtained that the acute toxicity of TC and PPC solution significantly decreased After treatment in the electrochemical oxidation reactor. Conclusively, the electrochemical oxidation method used in this study suggests a feasible and promising prospect for efficient removal of triazole fungicides from wastewaters (Han et al., 2014).

In the study of Urzua et al. (2013), the electrochemical oxidation treatment in water of three conazole fungicides, myclobutanil, triadimefon, and propiconazole, has been investigated at constant current using a boron doped diamond/stainless steel system (BDD/SS). Conazole fungicides include a triazole ring in their structure, a halogenated aromatic ring, and an alkyl chain or aliphatic heterorings and they generally used in clinical and agricultural applications. They can be evaluated for the protection of fruit, vegetable, and cereal crop as fungicides while they can be applied to treat local and systemic fungal and yeast infections in clinical purposes. For the treatment of the conazole fungicides, each solution were electrolyzed to evaluate the influence of the experimental parameters such as current, pH, and fungicide concentration on the removal of each compound and total organic carbon (TOC) reduction. Then, high performance liquid chromatography, ion chromatography and gas chromatography coupled with mass spectrometry were used for the analysis of the degradation by-products and suitable reaction pathways. Accordingly, the degradation of the conazole fungicides and their by-products is practically pH-independent and almost a complete removal of fungicides is obtained after 150–180 min. Almost complete mineralization with high efficiency was achieved at the current density of 50 mA/cm^2; also, this current density value is preferable due to the reasonable energy consumption. The pseudo first-order kinetic model was well-fitted to the electrochemical oxidation of three conazole fungicides and it was observed that the rate constants were proportional to the current in the range of 15–50 mA/cm^2, which was consistent with the raise of the adsorbed •OH at anode. Due to the parasite reactions, the rate constant

decreased at 80 mA/cm^2.According to the reaction pathways; aromatic intermediates, aliphatic carboxylic acids and Cl^- were detected previous to their complete mineralization to CO_2 while NO_3^- anions remained in the treated solution. At the obtained conditions, almost total mineralization with 94–96% TOC removal of conazole fungicides was acquired through the electrochemical oxidation using BDD/SS, which provides a practical and applicable method for the treatment of wastewater containing conazole fungicides (Urzúa et al., 2013).

Cui et al. (2017) have aimed to achieve high level standard reuse of triazole fungicides discharged water via a novel integrated system in pilot plant scale of electrochemical oxidation, upflow biological aerated filter, and electrodialysis. A novel enhanced electrochemical oxidation reactor was designed and applied as pretreatment process in order to raise the removal efficiency and make easier the recycling of the polluted waters. The flow diagram of integrated treatment system was presented in Figure 5. The anode was made of macro-porous titanium membranes electrode coated with RuO_2, while tubular and fenestrated stainless steel was used as cathodes. Four cubic meters bio-ceramic goes through bio-film colonization for 30 days which the activated sludge used to make the film was obtained from the PACT reaction tank in the same wastewater treatment plant. In the electrodialysis system, the membrane stack consisting of 40 cell pairs, i.e., 40 AEMs and 41 CEMs assembled in total and a couple of electrodes made of titanium coated with ruthenium with aid of 1% sodium chloride aqueous solution as electrode rinsing solution were used.

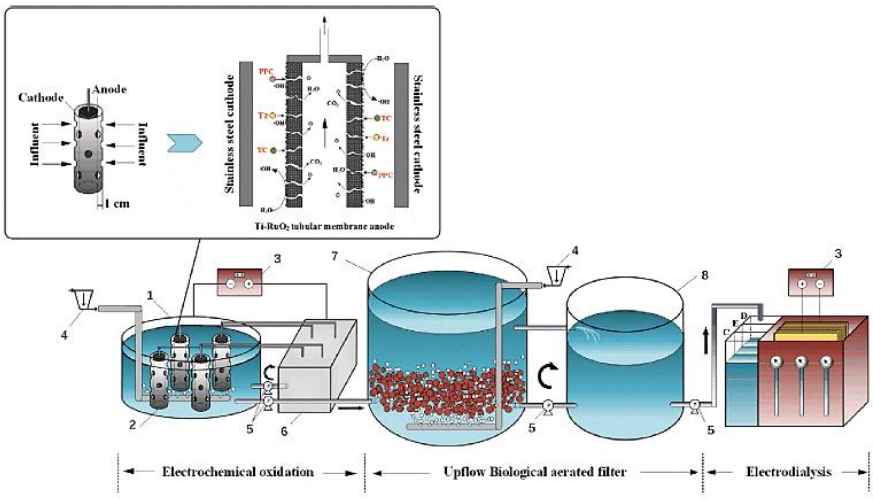

Figure 5. Flow diagram of integrated system for triazole fungicides discharged water advanced treatment (1) Electrochemical oxidation reaction tank, (2) electrode pair. (3) DC supply, (4) air compressor, (5) vertical centrifugal pump, (6) airtight stainless steel water tank, (7) upflow biological aerated filter, (8) balance tank. D: Dilute water compartment. E: Electrolyte Water Compartment. C: Concentrate water compartment

The effects of operating parameters were investigated with the discussion of economic evaluation and the optimum conditions were obtained as 5 mA/cm^2 current density, 3 m^3/h flow velocity, 5.0 pH value in the absence of supporting electrolyte. Over 90% removal from the discharged water containing the triazole fungicides was achieved at these conditions. It was thought that the remaining COD could be further raised from 250 mg/L to less than 60 mg/L thanks to the upflow biological aerated filter. Then, the electrodialysis provided the efficient removal of the salt. Lastly, a very low level of COD of 58.32 mg/L, TOC of 20.56 mg/L, $EC_{50,48h}$ of 73.1 ± 2.1%, consistent with an excellent removal of the target species of 94.19% tricyclazole, 90.11% 1H-1,2,4-triazole and 100% propiconazole, >99% salt and a low operating cost of $0.85 were achieved for the final effluent. These values meet the standard of high-level recycle for industrial water. Considering both the processing capacity and operating cost, it was concluded that this integrated system in pilot scale exhibits obvious flexibility and suitability in advanced treatment for chemical industry discharged water, especially for those with unbiodegradable organic contaminants and high salinity (Cui et al., 2017).

When the studies on the removal of 1,2,4-triazole fungicides from waters in the literature are evaluated, it has been seen that each method used has its own advantages and disadvantages. Based on these studies, the advantages and disadvantages of these methods are summarized in Table 5.

Table 5. Advantages and disadvantages of the methods used for the removal of 1,2,4-triazole fungicides from waters

Method	Adsorption	Degradation	Biodegradation	Photocatalytic Degradation	Electrochemical Oxidation
Advantages	✓ Low-cost ✓ Flexibility and simplicity of design ✓ Easy of operation	✓ Mineralization of the pollutants ✓ Rapid removal ✓ Efficient for recalcitrant molecules ✓ High reduction of chemical oxygen demand and total oxygen demand	✓ Economically attractive ✓ Efficiently elimination of biodegradable organic matters ✓ High removal of biological oxygen demand and suspended solids	✓ No production of sludge ✓ Usability of solar UV ✓ Strong light absorption of catalyst ✓ Mineralization of the pollutants ✓ No consumption of expensive oxidizing chemicals	✓ Less treatment time ✓ Less sludge production as compared to chemical and biological treatment ✓ Less land area as compared to biological process ✓ No need to add chemical for ●OH formation due to generation it from water oxidation

Disadvantages	× Requirement of adsorbent regeneration × Low selectivity × Disposal problems for used adsorbents	× Lab scale × Formation of by-productions × pH-dependence × Sludge production in some cases × Usually work in batch mode	× Inefficient for non-degradable compounds or when toxic compounds are present × Slow process × Possible sludge bulking and foaming × Generation of biological sludge and uncontrolled degradation products × Complexity of biological mechanisms, so need to have good knowledge about enzymatic process	× Formation of by-products × Lab scale × Poisoning of catalyst by organic matters × Low adsorption of organic pollutants × Low quantum yield × High cost for photo-source	× High operational cost due to high energy consumption (current density) × Electrode fouling due to oxidation of pollutants on the electrode surface × Requires post-treatment × Technical constraints

Among these methods, it can be said that the less preferred and less efficient methods are biodegradation and photocatalytic degradation due to UV stability and poorly biodegradable nature of 1,2,4-triazole fungicides. Also, the elucidation of the biodegradation mechanisms of 1,2,4-triazole fungicides is still challenge; so, research on it continues. Recently, degradation, adsorption, and electrochemical oxidation processes have appeared as possible alternatives to traditional water treatment processes for the removal of 1,2,4-triazole fungicides. High removal efficiencies can be achieved by these methods; however, as can be seen in Table 5, they have some typical drawbacks in despite of their advantages. The removal method by gamma irradiation has come to the fore among recent studies because in this method, hydroxyl radicals can be formed more easily, sufficiently and cost-effectively, without the need for power supply or addition of chemicals under irradiation. In addition, as in the studies of Zendegi-Shiraz et al. (2021) and Cui et al. (2017) separately, high removal efficiencies can be achieved with the combined methods (adsorbent-catalyst coupling process and integrated system of electrochemical oxidation, upflow biological aerated filter, and electrodialysis), as well as high recyclable water quality. Consequently, further research and development in this area are required to overcome the shortcomings of the methods used for the removal of 1,2,4-triazole fungicides and to achieve high removal efficiency with the method to be developed.

The presence of 1,2,4-triazole fungicides in water is a major problem for the environment's conservation and health. The treatment processes of them are being investigated by several methods such as adsorption, degradation, biodegradation, photocatalytic degradation, electrochemical oxidation, and so on. Although each method has its own advantages, there are also disadvantages that limit their use in the industry. So, a combination of the methods is recommended to perform water treatment perfectly. After thorough analysis of wastewater containing 1,2,4-triazole fungicides, the highest removal efficiency and recyclable water quality can be achieved by using appropriate method combinations. However, the main problem is the application of these methods to a large scale. For this purpose, future research should focus on applying these methods to treat triazole fungicide-containing wastewater, first on a pilot scale and then on an industrial scale by means of more advances in water science and engineering as well as the assistance of multidisciplinary knowledge.

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DOCKING STUDIES OF 1,2,4-TRIAZOLES

Abdülmelik ARAS

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Docking Studies of 1,2,4-Triazoles

Heterocycles are the largest class in organic chemistry. Most agrochemicals, pharmaceuticals, and additives used in industrial applications are heterocyclic in nature (Katritzky et al., 1996). Organic chemists have succeeded in discovering and developing a wide variety of heterocyclic compounds for the benefit of humanity by far. A notable structural feature of heterocycles that continues to be investigated is their ability to host substituents around a central structure. Since their first use in agriculture nearly a century ago, the chemistry of sulfur- and nitrogen-containing heterocycles has made significant advances (Katritzky et al., 2008; Maddila et al., 2013). 1,2,4-triazole is a crucial nucleus present in many compounds (Aktaş Yokuş et al., 2017; Beytur et al., 2019; Yüksek et al., 2022). The 1,2,4-triazole nucleus, which is stable against metabolism, acts as a hydrogen acceptor and donor at the active site of the receptor. Since the triazole core is polar, it can increase the solubility of the ligand and in this way significantly improve the pharmacological structure of the drug. A wide range of their derivatives are noted to have a wide spectrum of biological applications including anti-cancer activity (Kaur et al., 2016).

Molecular docking is computer-based tool that enables for prediction of whether and how small molecules bind to a macromolecular target (de Azevedo, 2019). The docking techniques, by selecting the appropriate binding position of a protein-ligand complex, complements and optimize variables such as hydrophobic, steric, and electrostatic and thus calculating their binding free energy (Adelusi et al., 2022). Due to the high time and financial needs associated with obtaining a commercial drug for the market, the computer-aided application of drug design has been accepted as a strong technology in drug discovery. In the drug discovery process, molecular modeling applications have undergone significant changes in computational abilities over the last decade. For lowering the cost and time needed for the discovery of an effective drug academic research organizations and pharmaceutical companies are using diverse

computational modeling approaches (Adelusi et al., 2022). In this chapter, we focus on reviewing molecular modeling, its applications, and its limitations in 1,2,4-Triazoles.

Characterization, molecular docking studies, and antibacterial potential assessment of the novel compounds containing the 1,2,4-triazole ring in their structure were reported by Mermer and co-authors in 2019. The synthesized derivative interaction ability with DNA gyrase was determined. To reveal the interaction mode of fluoroquinolone-1,2,4-triazole hybrids to receptors, a molecular docking application was performed. All tested compounds were seen to have excellent inhibitory potentials against DNA gyrase (E. coli) (Figure 1) (Mermer et al., 2019).

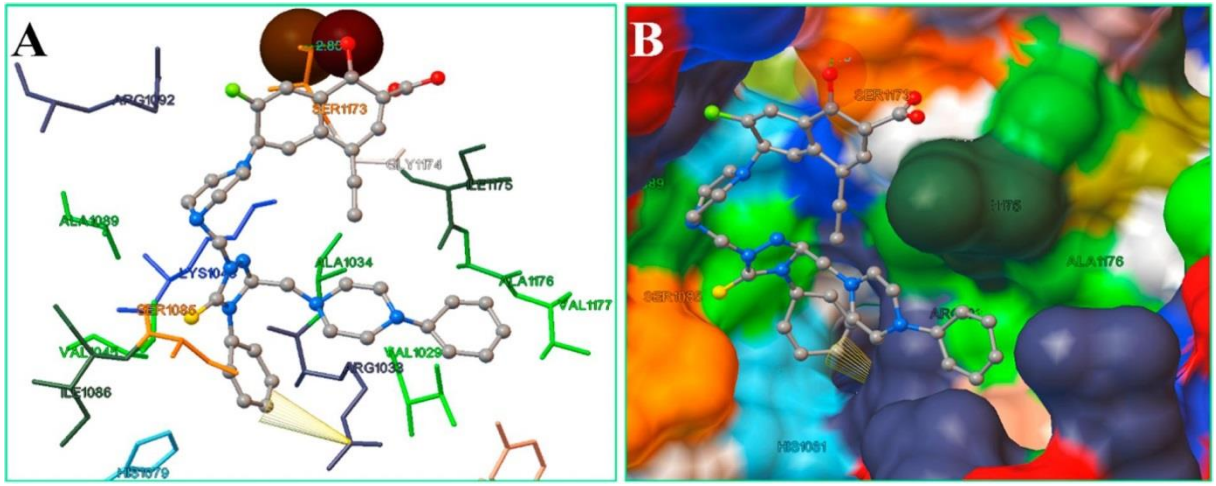

Figure 1. Interaction of most active compound to DNA Gyrase (PDB: 2XCT). and B. To DNA Gyrase (PDB: 2XCT) binding pocket (Mermer et al., 2019).

In a study, 1,2,4-Triazole-containing fifteen compounds were tested for their potential antimicrobial activities. For this, a molecular docking study was successfully applied against the topoisomerase II enzyme (PDB: 5bs8). All synthesized compounds binding energy scores were calculated between (−6.31 to −16.11 Kcal/mol) and compared with the reference moxifloxacin. Relatively lower binding interactions were observed compared to the reference moxifloxacin (Mohammed et al., 2019).

Stingacia and co-authors reported that as antimicrobial agents new vinyl-1,2,4-triazole derivatives eight compounds molecular docking studies have been performed at the active sites of E. coli DNA GyrB (PDB code: 1KZN), Thymidylate kinase (PDB code: 4HOF) and E. coli MurB (PDB code: 2Q85). The binding scores revealed that E. coli DNA GyrB 24-kDa domain in complex with clorobiocin is the most proper enzyme. For E. coli MurB 2Q85, the binding

score was changed in the range of (−5.29, −8.56 kcal/mol).The best binding score was (−8.56 kcal/mol) with compound 8 (Figure 2) (Stingaci et al., 2020).

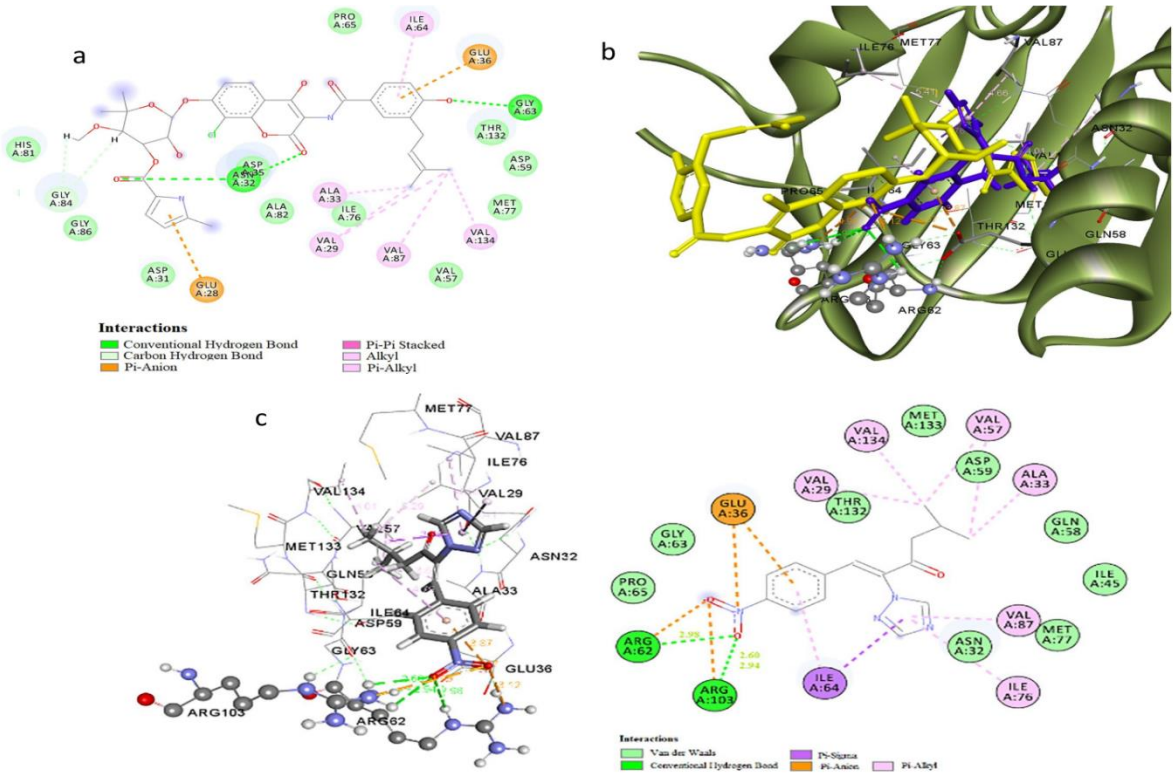

Figure 2. Docked conformation a) Clorobiocin in *E. coli* DNA GyrB, b) Compound 8 (blue) and clorobiocin (yellow) in *E. coli* DNA GyrB c) Compound 8 in *E. coli* DNA GyrB (Stingaci et al., 2020).

In 2022, Medetalibeyoğlu and co-authors applied molecular docking interactions of a series of novel 4,5-Dihydro-1H-1,2,4-triazole-5-one derivatives with AChE (PDB ID:4EY7) as target enzyme using Chimera and AutoDock Vina softwares. -12.0 kcal/mol was calculated as the highest binding energy levels of the 4g compounds with AChE target enzyme were confirmed as the best binding affinities and molecular interactions (Medetalibeyoğlu et al., 2022).

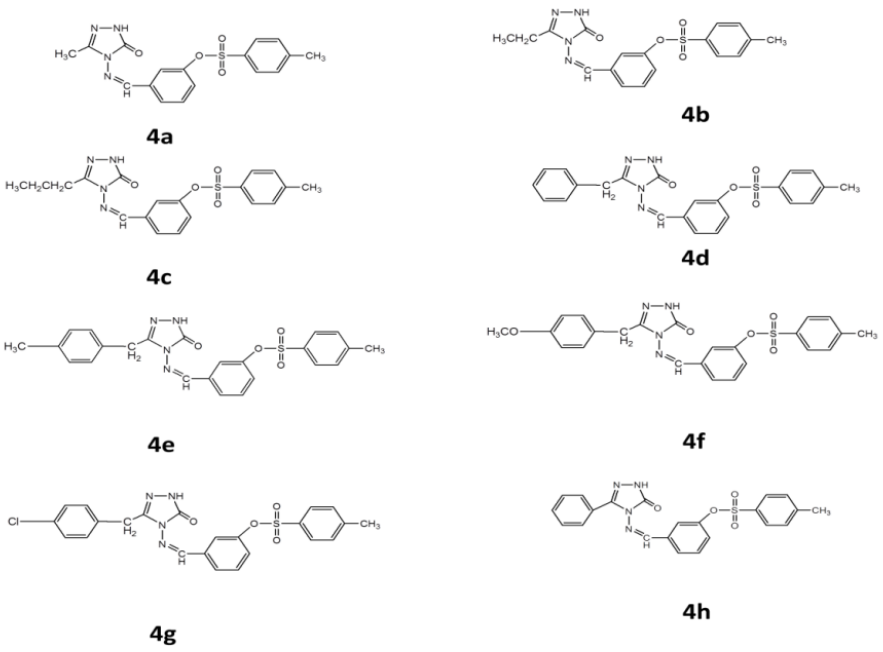

Figure 3. 4a-h compounds structures

Compounds 4a-4h binding energy scores with AChE were calculated as -10.2 kcal/mol, -10.6 kcal/mol, -10.7 kcal/mol, -12.0 kcal/mol, -11.3 kcal/mol, -8.7 kcal/mol, -12.0 kcal/mol, -11.2 kcal/mol respectively. Two compounds (4d and 4g) were firmly bound with the optimal conformation of the AChE enzyme, and their binding energy levels exceeded 12.0 kcal/mol.

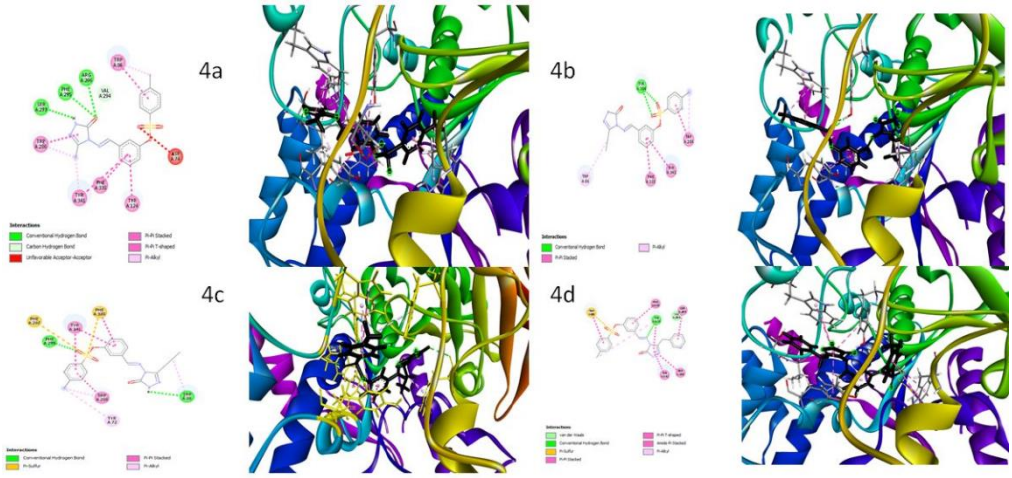

Figure 4: The interaction mode between **4a**, **4b**, **4c**, and **4d** and AChE enzyme, 3D ribbon models, and 2D view of ligand-binding residues (Medetalibeyoğlu et al., 2022)

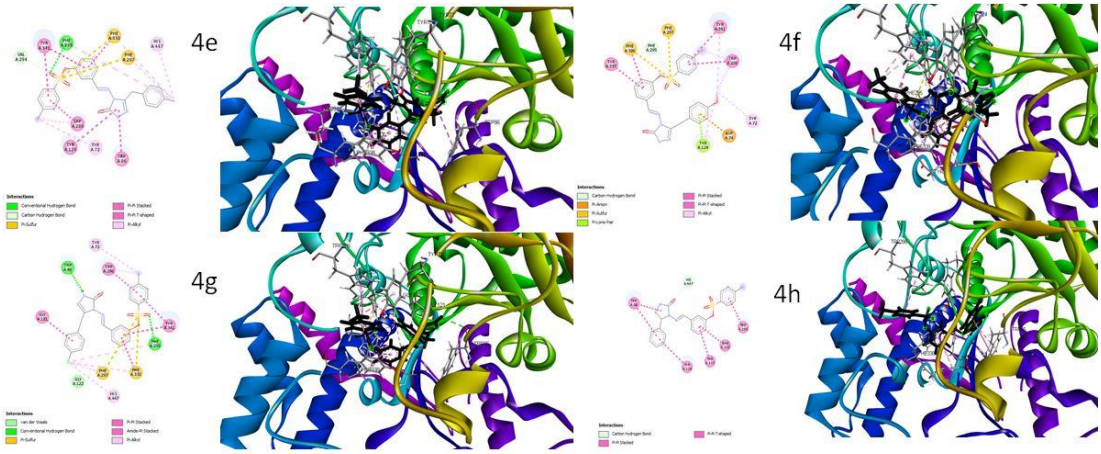

Figure 5: The interaction mode between **4e**, **4f**, **4g**, and **4h** and AChE enzyme, 3D ribbon models, and 2D view of ligand-binding residues (Medetalibeyoğlu et al., 2022)

Carbon Hydrogen, Pi-anion, conventional hydrogen bonds, Pi-Alkyl, Pi-Pi, van der Waals, Pi-sulfur, and other bonds of the compounds with enzyme-used residues were shown in the 2D views and 3D ribbon models in the Figures 4-7 (Medetalibeyoğlu et al., 2022). All novel synthesized compounds (4a-h) showed good enzyme inhibition results on AChE receptors.

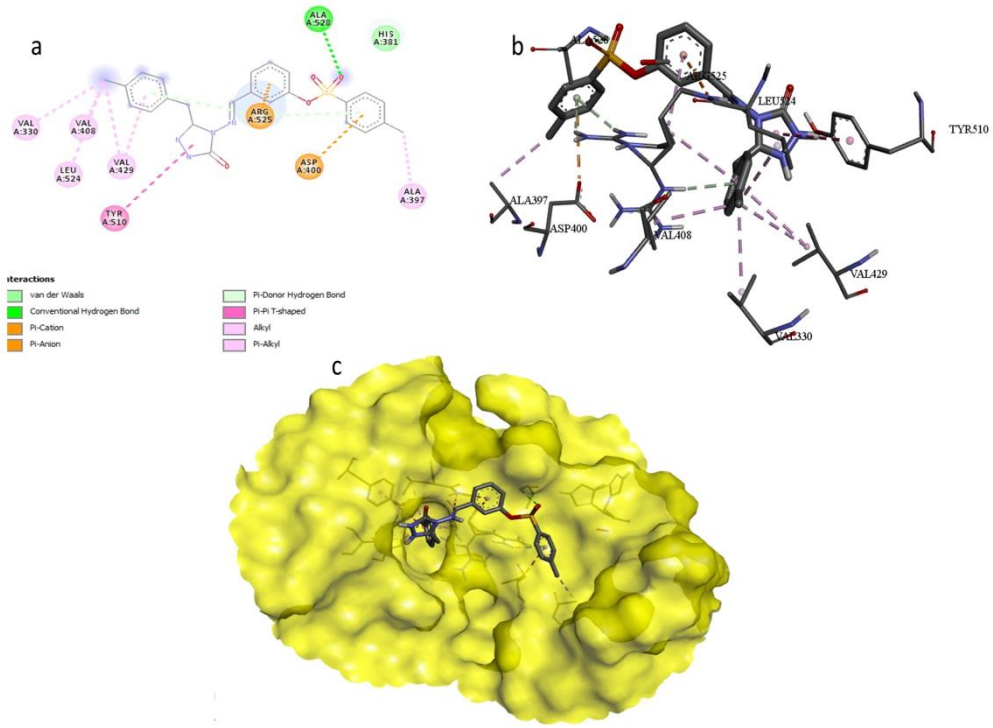

Figure 6: The interaction mode between one of most active compound **4e** and AChE enzyme

The result data have shown that inhibitor 4e formed conventional hydrogen bond, Pi-donor hydrogen bond, Pi-donor hydrogen bond, Pi-cation, Pi-anion, Pi-Pi T-shaped, alkyl, and pi-alkyl with Ala528, Arg525, Asp400, Tyr510, Ala397, Val330, Leu524, and Val429. The inhibitor 4g formed conventional hydrogen bond, Pi-cation, Pi-Sulfur, Pi-Pi Stacked, and pi-alkyl with Tyr124, Trp286, Tyr341, and His447.

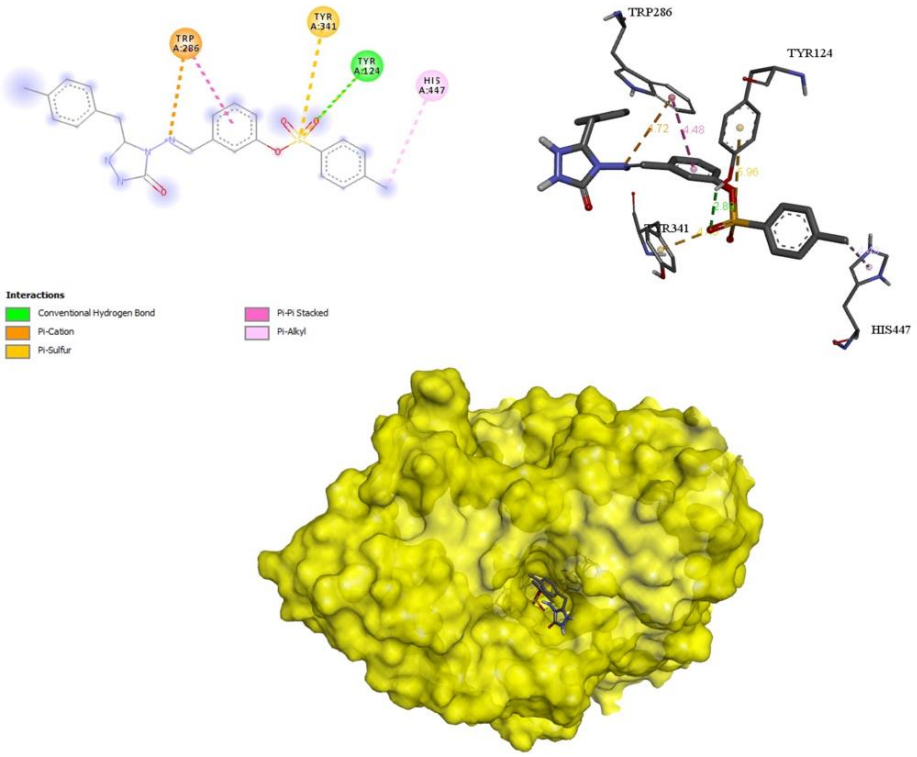

Figure 7: The interaction mode between one of most active compound **4g** and AChE enzyme

Previously, a study reported molecular docking interaction of a series novel morpholine-derived Mannich bases containing 1,2,4-triazoles with acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and glutathione S-transferase (GST) enzymes. For the performing of the molecular docking studies, catalytic active sites of three GST, AChE, and BChE enzymes were determined and chosen sites were utilized for the docking process and assessment of the best pose of the inhibitors. By using the induced-fit docking (IFD) method, inhibitors were docked into the catalytic active site of the three enzymes.

The indication diagrams have shown that inhibitor 4e formed two hydrogen bonds with His287 and Tyr124. The triazole oxygen has accepted hydrogen, while hdroxybenzyldene oxygen has donated hydrogen to the AChE enzyme residues. Metoxybenzyl and the hydroxybenzyldene aromatic ring interacted with Trp286 and Tyr72 through π-π interaction. compound 1 inhibitor

formed an aromatic hydrogen bond with four aromatic rings with Tyr124, Tyr72, Ser293, Val282, Tyr341, and Phe338. AChE enzyme active site consists of acyl and choline-binding sites. Interactions of 4e are with residues of the active sites of AChE. The enzyme was inhibited by the inhibitor by interacting with Trp286 and Tyr72 via parallel π-π interactions. Enzyme activity has been affected through the steric blockade interactions with the residues. Hydrogen bonds with His287 and Tyr124 affected enzyme inhibition (Figure 8) (Boy et al., 2021).

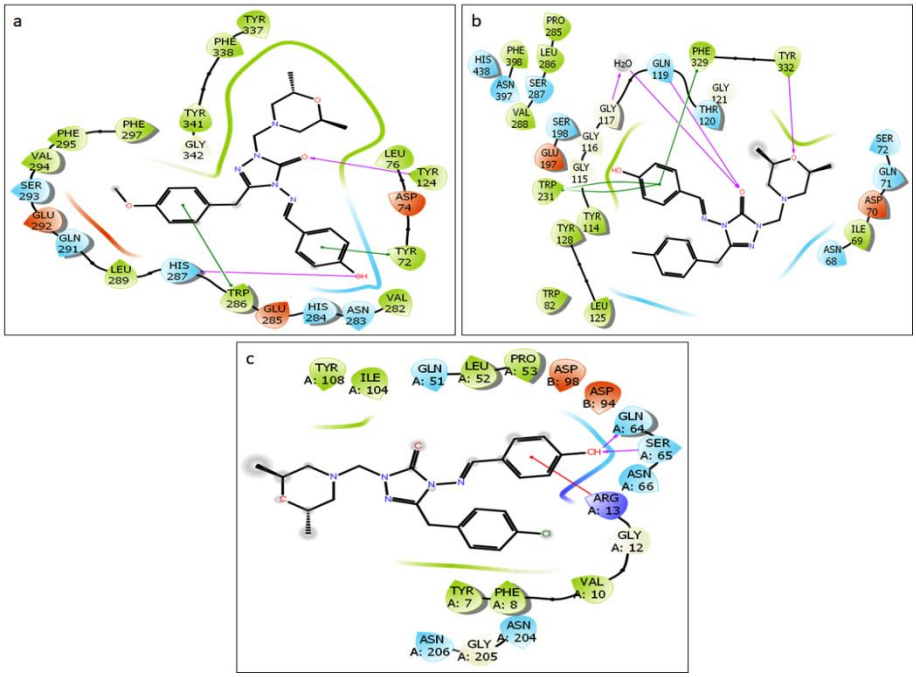

Figure 8. 2D interaction mode of most active inhibitors. a) Compound 1-AChE, b) Compound 2-BChE, andc) Compound 3-GST. Hydrogen bonds were represented as a purple arrow, π-π interactions were represented as a green line, and π-cation was represented as a red line. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article) (Boy et al., 2021).

As seen in Figure 8 c, hydroxybenzyldene through π-cation, the aromatic ring made an interaction with Arg13 and it is oxygen moiety interacted by a hydrogen bond with Ser65 and Gln64 residues of GST enzyme. Through a water bridge, a hydrogen bond was formed between chlorobenzyl moiety and Tyr108 (Figure 8c). Compound 6 as a inhibitor binding modes with GST have shown that hydroxybenzyldene moiety has participated in interactions. This result has revealed that the compound structure is a little bit big for the GST active site. Diverse G-site inhibitors showed parallel interaction with compound 4 inhibitor. Docking Scores of compounds 4-6 inhibitors with AChE, BChE, and GST enzymes were detected as -10.294 kcal/mol, -9.562 kcal/mol, and -7.112 kcal/mol, respectively (Figure 9) (Boy et al., 2021).

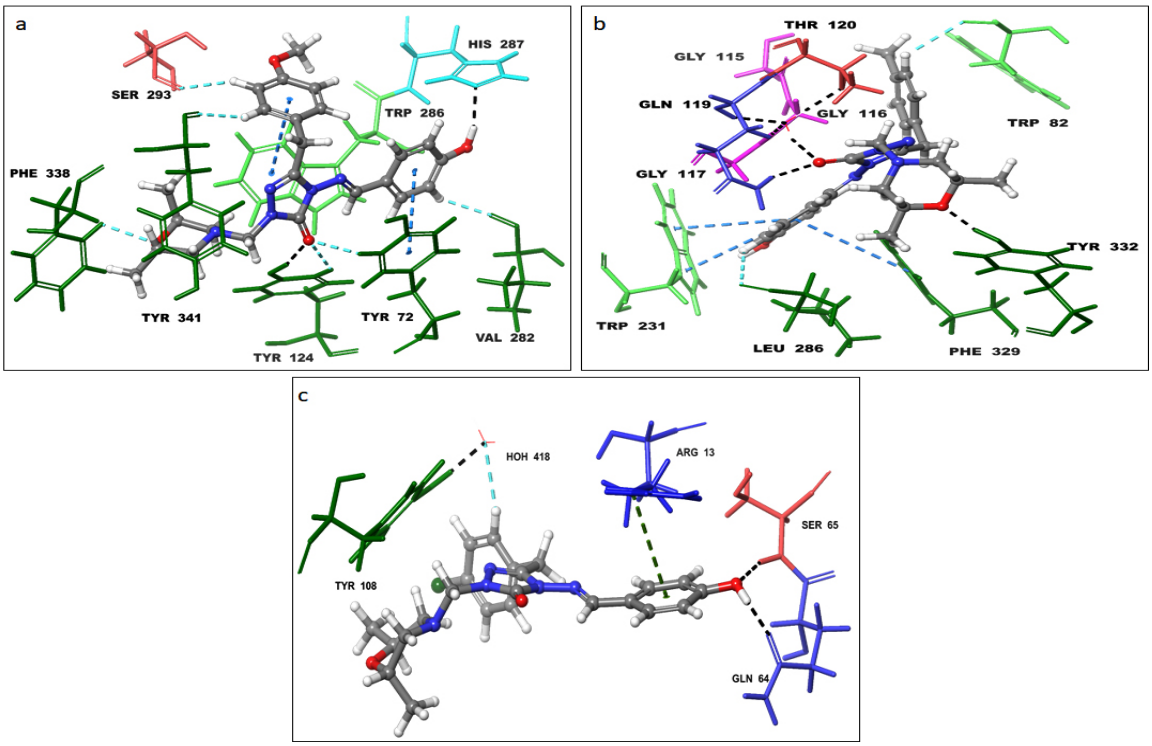

Figure 9. Detailed binding mode of most active compounds. a) Compound 5-AChE, b) Compound 4-BChE, and c) Compound 6-GST. Hydrogen bonds were represented as a black dashed line, π-π interactions were represented as a blue dashed line, π-cation was represented as a green dashed line, and aromatic hydrogen bonds were represented as a turquoise dashed line (Boy et al., 2021).

In 2019, Akın and co-workers reported Molecular docking studies of novel 2,4,5-trisubstituted-1,2,4-triazole-3-one derivative against the mushroom tyrosinase enzyme crystal structure. For analyzing the binding affinity AutoDock Vina was applied. Docking studies results indicate that the using compound as a inhibitor with the highest affinity score (−6.2 kcal/mol) strongly binds to the enzyme. The interaction of different groups in the structure of the inhibitor used with the amino acid side chains in the appropriate position in the enzyme three-dimensional structure is also important in the formation of the enzyme-inhibitor complex (Figure 10). Some of the interactions of the inhibitor compound with the enzyme active site were as follows; conventional interactions of triazole ring with His244, p-alkyl interaction of bromo phenyl ring with Val283, and p-alkyl with Val283 (Akın et al., 2019).

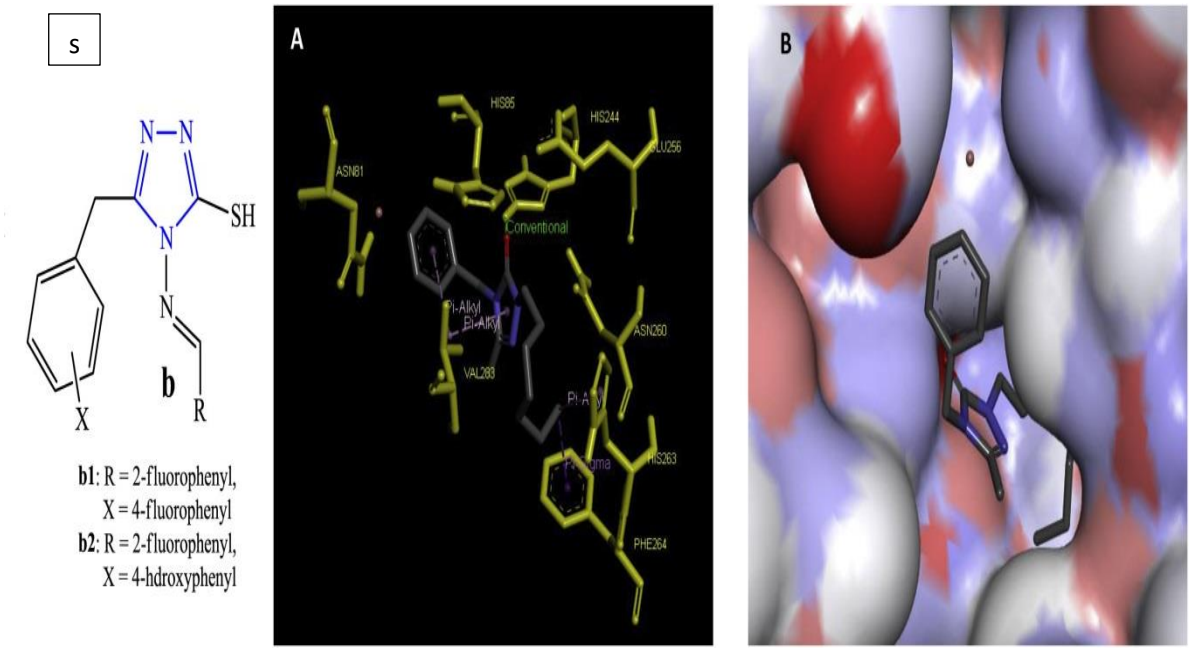

Figure 10. S) Molecular structure of 1,2,4-triazole based tyrosinase inhibitor. A) Interactions of the compounds atoms with the amino acid residues B) general projection (Akın et al., 2019).

Mohassab et al. applied a docking studies of a series of novel quinolines including 1,2,4-triazole/oxime hybrids towards the cyclooxygenases (COX-1 and COX-2) enzymes to explain compounds' possible anti-inflammatory effects. Docking applications were performed using MOE 2014 software. Inhibitors demonstrated effective anti-inflammatory properties with a low incidence of gastric ulceration, similar to that of celecoxib and indomethacin. Most of the 22 tested inhibitors revealed remarkable inhibition of COX-1 and maintained normal stomach tissue integrity. Also, docking analysis results were in agreement with promising anti-inflammatory activity when compared to indomethacin (Mohassab et al., 2017).

In 2018, Sherief and co-authors synthesized two new compounds containing 1,2,4-triazole and applied a molecular modeling study to obtain structural insights into the potential binding and possible interactions of the active compounds inside the tubulin active sites by operating Molecular Operating Environment (MOE) software. Tubulin (PDB ID: 1sa0) 3D crystal structures in complex with colchicine, were employed for docking simulation study. The overlay of the top docking poses tubulin proteins binding pockets were given in Figure 11. Docking results showed that the two compounds against tubulin set properly inside the ATP-active site engaging in two hydrogen bonds with Ser 178 and Thr 179 residues. The triazole core was extended towards the hinge region forming hydrophobic interaction with Ala 12, Lys

254, Leu 248, and Tyr 224 amino acids. Due to the high similarity of the two structures, they were in the same orientation inside the Tubulin active pocket (El-Sherief et al., 2018).

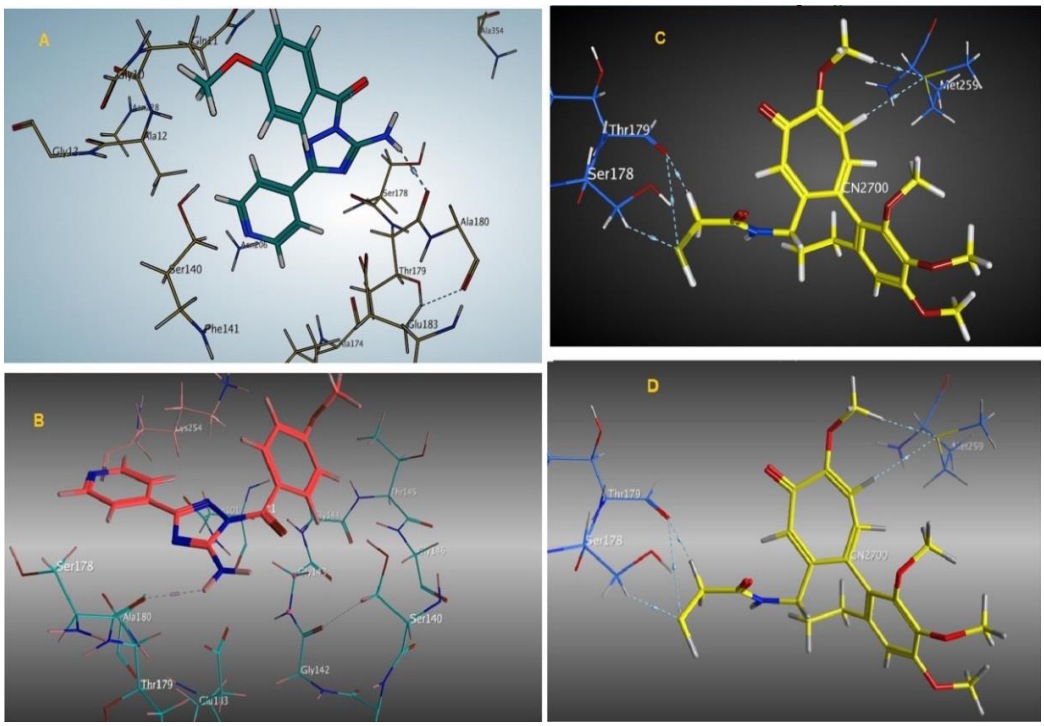

Figure 11. (A, B, C, and D) 3D overlay of the top docked poses (El-Sherief et al., 2018).

Tariq et al. tested some novel 1,2,4-Triazole-based benzothiazole/benzoxazole derivatives on p38 mitogen-activated protein kinases (MAPK) by using molecular docking studies (Tariq et al., 2018). p38 MAPK activation plays an important role in the inflammatory response. Some MAP kinase isoforms are the key regulator of the pro-inflammatory cytokines biosynthesis including TNF-α and IL-1β (Kumar et al., 2003). Also, inhibition of p38α MAP kinase blocks the production of COX-2 thereby avoiding tissue inflammation (Dean et al., 1999).

The docking scores of the newly synthesized fourteen compounds against p38α MAP kinase are calculated. All the compound's docking scores were in the range of −4.870, and −7.944. The molecules can be housed more effectively in the p38α MAP kinase active binding site because eNHCOeCH2Se (linker) flexibility. Compound 2 interacts by a hydrogen bond with hinge region MET 109 which provides the strong inhibitory activity. In the binding of compound 2 to p38α MAPK, the hydrogen bond with MET 109 seems to play an anchor role as 107–110 Amino acid residues are located at the ATP-binding site entrance. Complex 2 binding with p38α MAP Kinase, revealed that the carboxyl group and amino group which is placed between

benzothiazole and triazole ring led to two hydrogen bond interactions with LYS 53 and ASP 168 respectively (Figure 12) (Tariq et al., 2018).

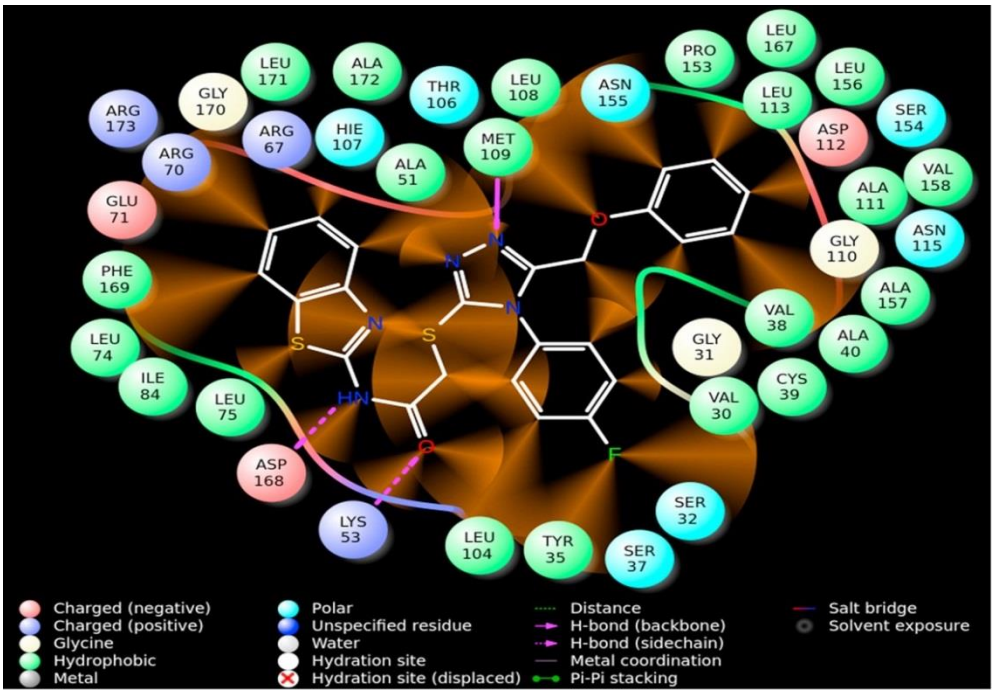

Figure 12. 2D LigPlot diagramme of compound 5b (Tariq et al., 2018).

The data detected by docking showed that electron-withdrawing para substitution on aryl moiety can result in ideal docking scores. The fluorine atom Incorporation resulted in an increase in binding affinity to the target protein receptor because it is the most electronegative element that can modify the polarity. When compared to Cl and Br, fluorine is smaller in size thereby adjusted properly at the p38α MAP Kinase receptor binding site. Compound 2 and 9 with promising molecular docking outcomes indicated that derivatives with electron-attract groups such as F at the para position can interact perfectly in the p38α MAP kinase active region (Figure 13).

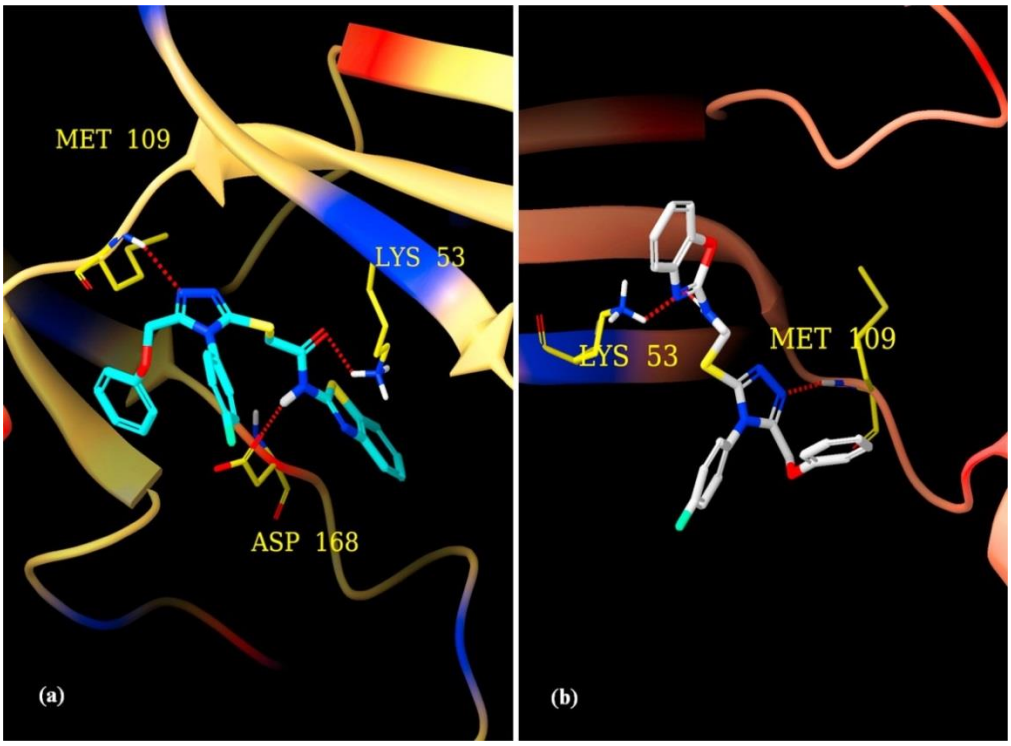

Figure 13. 3D Docked conformer of (a) Compound 2, (b) Compound 9, presented the binding site of p38α MAP Kinase receptor observing hydrogen bond interactions(Tariq et al., 2018).

In 2017, Thakkar and co-workers investigated antimalarial and antimicrobial activities analogs containing 1,2,4-triazole as DHFR inhibitor by using molecular docking interaction. To explain the binding energies potential of the active compounds containing 1,2,4-Triazole as antimalarial agents were docked against P. falciparum dihydrofolate reductase (PDB ID: 4DPD). Interactions were evaluated between the tested molecules and the Pf-DHFR enzyme. The 3D diagrams displayed the binding sites of the ligands within the receptor 4DPD. The molecules interacted with the amino acids of receptor 4DPD in the active sites through conventional carbon-hydrogen bond, van der Waals, p-sigma, hydrogen bonds, p-cation, p-anion, p-donor hydrogen bonds, p-alkyl, p-sulfur, and etc. The binding energies of these molecules were found in the range of -7.20, and 9.06 kcal/mol (Thakkar et al., 2017).

In 2021, Boy et al. reported molecular docking study of eight novel piperidine derivatives heterocyclic Schiff-Mannich base towards AChE, BChE, and GST enzymes. The physicochemical properties of tested compounds were predicted and demonstrated that eight synthesized compounds are non-toxic as rtvFG values were less than 2. They are easily absorbable orally and octanol/water partition coefficient values are well for compounds. In the light of these results, we can state that the compounds can be easily distributed from the

extracellular fluid to the tissues in case of absorption as drugs. Also, related to their moderate logBB values the characteristics of the compounds allow them to cross the blood-brain barrier. The three most active compounds binding energy scores into the active side of the structures of the enzymes were calculated. The highest binding score in the negative was picked as the best pose. The compounds binding score was −12.775 kcal/mol compound 2 with BChE, −12.095 kcal/mol binding score compound 6 with AChE, and was −9.336 binding score compound 7 with GST respectively. Depending on the calculated scores, each compounds showed very good binding to the enzymes used. Compound 6 formed hydrogen bonds with Ser293, Asn283, Phe295 and Tyr124 residues with the residue of the AChE enzyme. Compound 6 formed hydrogen bonds with Ser293, Asn283, Phe295 and Tyr124 residues, Π-cation, salt-bridge, and halogen bond interactions with Try341, Asp74, and Ser293 residues, respectively.

AChE enzyme's catalytic active site consists of two peripheral and acylation sites (Rosenberry et al., 2017). Tyr124, Trp286, Tyr341, and Tyr72 aromatic residues of the site assists to fix acetylcholine into the choline-binding pocket by orienting the acylation site (Colletier et al., 2006). AChE enzyme activity may inhibited by compound 6 complex with embarrassed the orientation of acetylcholine to the choline-binding pocket. In BChE enzyme active side, compound compound 2formed hydrogen bonds (water-mediated) with Thr120 and Asn68 residues. Compound 2 phenol moiety formed Π-Π interactions over the aromatic ring with Phe329 and Trp231amino acid residues. In the GST enzyme catalytically active side, M7 compound formed hydrogen bonds with Gln51, Tyr7, Ser65, Gly205, and Asp98 amino acid residues. Beside, formed Π-cation interaction and Π-Π interaction and with Arg13 and Phe8 residues, respectively (Figure 14-16) (Boy et al., 2021).

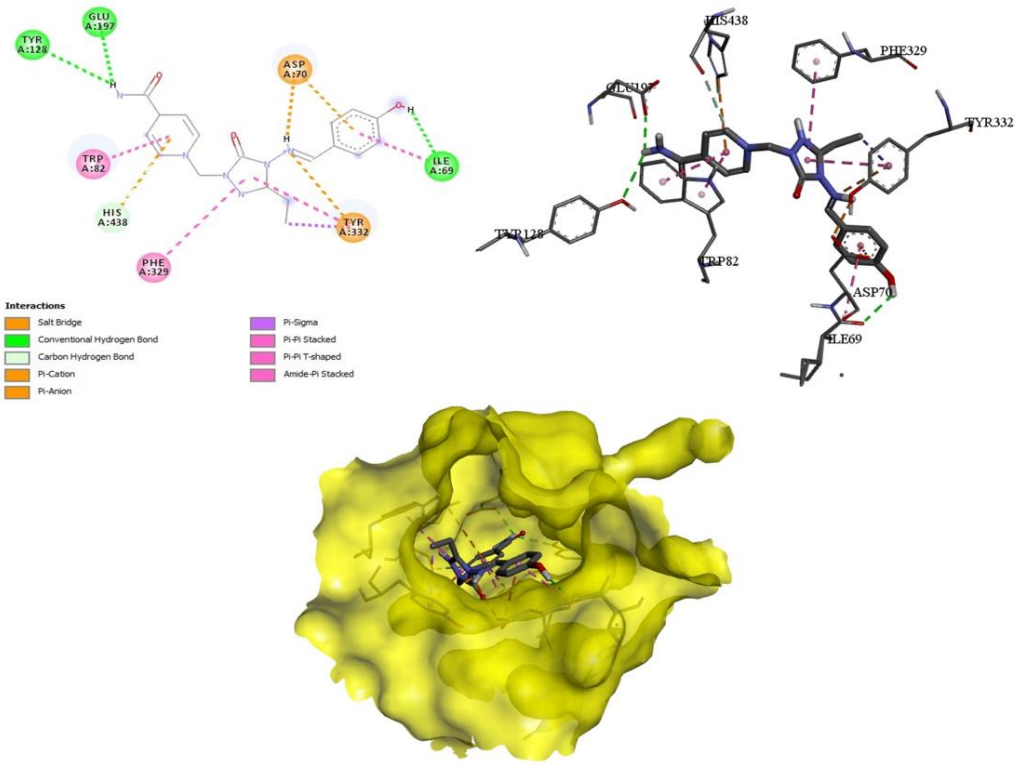

Figure 14: The interaction mode between one of most active compound 2 and BChE enzyme

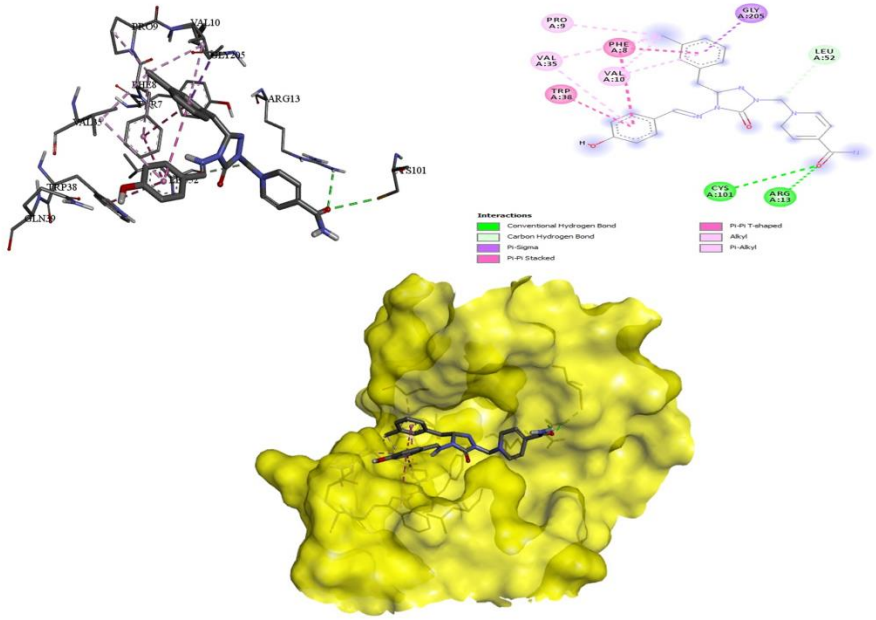

Figure 15: The interaction mode between one of most active compound 6 and GST enzyme

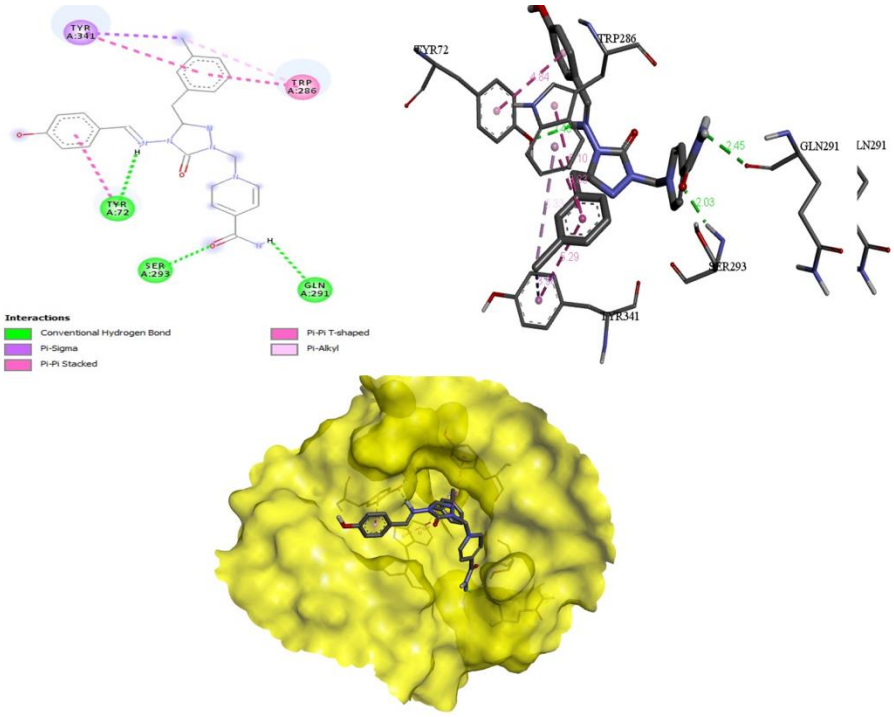

Figure 16: The interaction mode between one of most active compound 7 and AChE enzyme

Multiple computational techniques such as molecular docking protecting a vast range of time, is effectively seizing information across biological scales (Aminpour et al., 2019). Experiments; It assumes a fundamental role in science, especially in the field of drug discovery. Rich experimental results form the basis for understanding the chemistry of life. But still experiments only make sense together with models and theories. Depending on the dynamic and complex nature of chemical systems, biological systems are also complex structures. Because of these complex structures of biological systems, computer methods have become important in health and science. In the analysis of such complex structures, it is possible to understand memory and graphical features, such as computers, by using advanced tools. Computer simulations act as a bridge between processes (theory) theory and the laboratory world (experiment) (Eren and Yalçın). The core triazole ring structures with higher stabilization energies act as bridges between the interacting binding site of the enzyme and various pharmacophores. Therefore, fragment-based drug design is known to play vital roles in a wide variety of biological activities (Matin et al., 2022).

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together with their Benzo and other Carbocycl.-fused Deriv. V4 Five-memb. Rings with Two Heteroat., each with their Fused Carbocycl. Deriv. (pp. 1-13718): Elsevier.

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COMPLEX STUDIES OF 1,2,4-TRIAZOLES

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Complex Studies of 1,2,4-Triazoles

Heterocyclic aromatic compounds containing nitrogen and oxygen have gained great importance globally not only because of their prevalence in natural products, but also because of their biological (natural or synthetic antioxidants known as exogenous are believed to have positive effects on health and disease prevention (Harmankaya et al., 2020, 2021; Harmankaya & Harmankaya, 2022) photochemical, optoelectronic, theoretical, pharmacological properties and industrial importance (Beytur, 2020; Boy, Aras, et al., 2021; Boy, Türkan, et al., 2021; Koç et al., 2020; Kotan et al., 2020; Turhan Irak & Beytur, 2019; Uğurlu & Beytur, 2020). There are many studies showing that many metallo-biomolecules with N and S atoms in their structure play an important role in the coordination of metals in their active sites. Metallo-organic chemistry (Sertçelik & Durman, 2020; Sertçelik, 2021; Sertçelik et al., 2018; Sugeçti & Büyükgüzel, 2021) has an important area of research as new metal-based compounds with antibacterial and antifungal activities are needed (Scozzafava & Supuran, 2000). The presence of 1,2,4-triazole structure in ligand systems has contributed significantly to science. Recent studies of the coordination structure of 1,2,4-triazole allow the formation of polydentate binding sites, which increases the stability of the complex formed due to chelation, the effect of substituents carrying donor atoms (Burke et al., 2004; Haasnoot, 2000; Klingele & Brooker, 2003).

In recent years, many studies have been done on organotin(IV) complexes due to their important industrial and biological applications. Organotin(IV) complexes provide coordination with hetero-donor atoms through intermolecular and intramolecular interactions due to their low level of vacant 5d atomic orbitals and electron accepting ability of Sn atoms (Chandrasekhar et

al., 2002; Chaudhary et al., 2006). There are also few studies on the photo- and electroluminescent properties of Zn and Cd triazole coordination compounds (Chen et al., 2006).

The nickel complexes of 1,2,4-triazole-derived amido-functionalized N-heterocyclic carbene ligands were synthesized and structurally characterized. In particular, [1-(R)-4-N-(furan-2-yl-methyl)-acetamido-1,2,4-triazol-5-ylidene]$_2$Ni [R=Et, i-Pr and Bn] complexes were obtained by direct reaction of the corresponding triazolium chloride salts by treatment with $NiCl_2$•$6H_2O$ in the presence of K_2CO_3 as the base. Density functional theory (DFT) studies performed on these complexes revealed the highly polar character of the NHC-Ni σ-bond interaction with the corresponding molecular orbital having the maximum contribution (59-69 %) from the NHC ligand fragments while providing the minimum contribution (4 %) from the central nickel atom (Kumar et al., 2015).

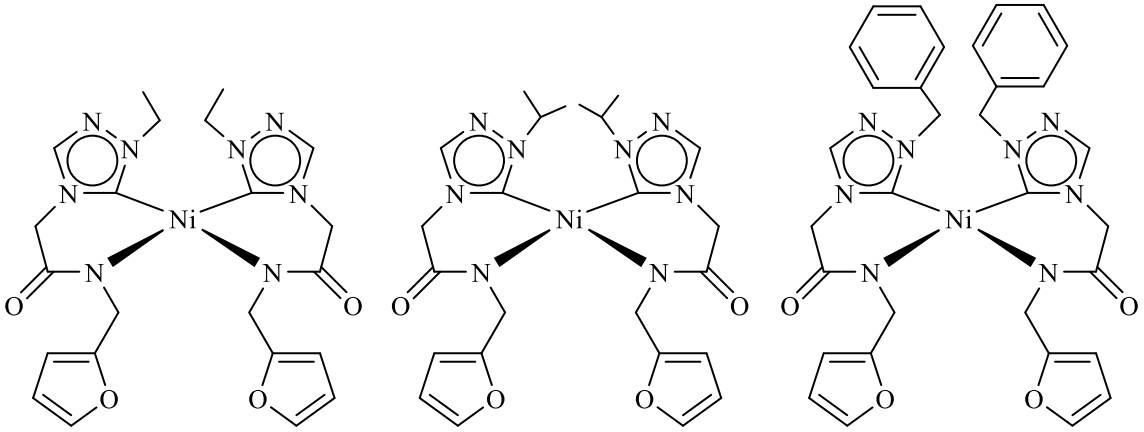

Figure 1. The nickel complexes of 1,2,4-triazole derived amido-functionalized N-heterocyclic carbene ligands (Kumar et al., 2015).

Cu(II) complexes were synthesized by reacting the at a ratio 1:1 M of newly prepared 3-R-1,2,4-triazole Schiff bases [R=H, CH_3 and C_2H_5] with $CuCl_2$•$2H_2O$ in the presence of sodium acetate trihydrate at reflux temperature. Not all synthesized complexes are electrolytes in *N*,*N*-dimethylformamide. CuO nanoparticles were synthesized by thermal decomposition of newly prepared Cu(II) triazole Schiff base complexes as solid precursors. The synthesized CuO nanoparticles were characterized using HR-TEM, FT-IR, XRD and optical properties. All Schiff bases, their Cu(II) complexes and CuO nanoparticles showed moderate activity against both pathogenic bacterial strains (*Escherichia coli* & *Staphylococcus aureus*) and weak antifungal activity (*Aspergillus flavus* & *Candida albicans*) (Aly et al., 2015).

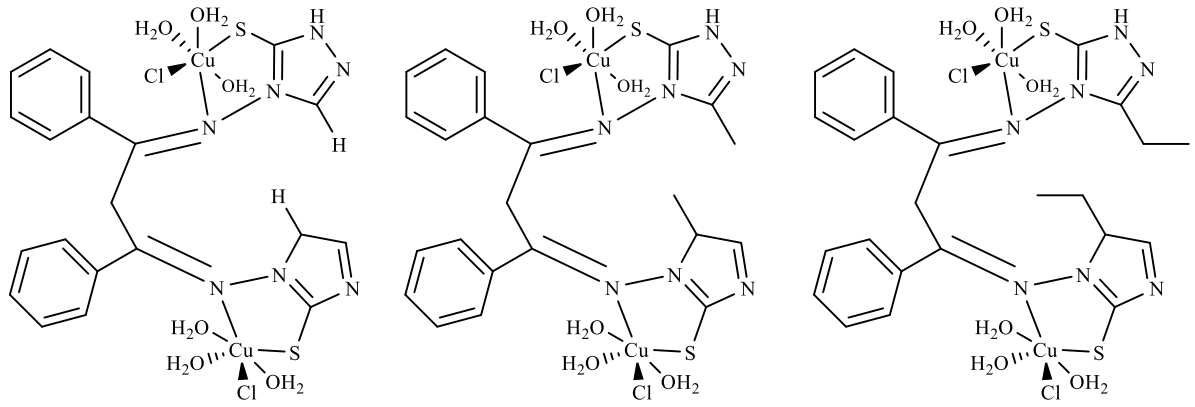

Figure 2. Cu (II) complexes of 3-R-4-amino-5-mercapto-1,2,4-triazole Schiff bases (Aly et al., 2015).

The novel triorganotin of Schiff base (E)-4-amino-3-(2-(2-hydroxybenzylidene)hydrazinyl)-1H-1,2,4-triazol-5(4H)-thion with the general formula R_3SnL complexes derived from the condensation of 4-amino-3-hydrazino-5-mercapto-4H-1,2,4-triazole and 2-hydroxy-benzaldehyde was synthesized by the sodium salt method. Spectroscopic characterization showed that in these 1:1 monomeric derivatives, that the deprotonated hydrazino-Schiff base behaves as a monoanionic bidentate coordinated along the ophenolic and nasometine and the polyhedron around the tin atom shows that it has a distorted trigonal-bipyramidal geometry. NBO analysis was performed to analyze intramolecular and intermolecular interactions leading to stabilization in the studied systems. A detailed vibration assessment was successfully performed for all complexes, and the comparative analysis between the experimental and simulated IR vibration frequencies of both complexes shows a good correlation between them. Boundary MOs have been defined for the complexes. Here, the HOMO is concentrated on the ligand moiety, and the LUMO center is concentrated around the tin atom. The synthesized complexes have showed either equivalent or better in vitro antifungal activity as compared to Schiff base with reference to Amphotericin B against *Aspergillus flavus* and *Fusarium oxysporum*. In silico, docking studies on the active site of cytochrome P450 14-α-demethylase were also performed (Joshi et al., 2019).

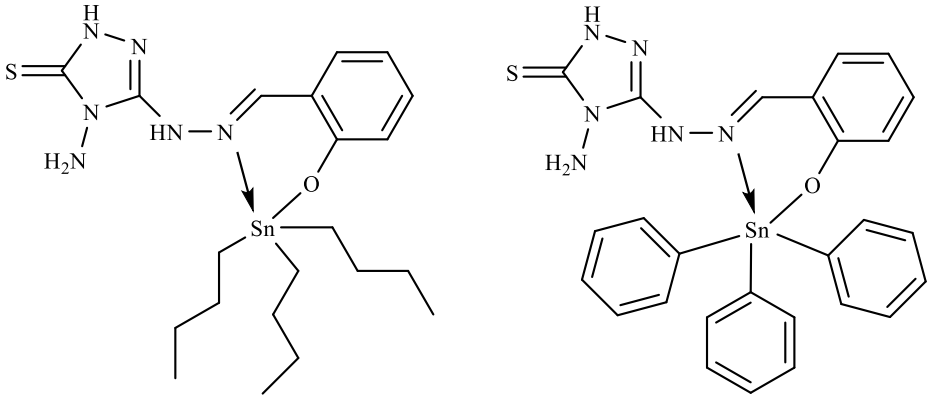

Figure 3. Triorganotin(IV) complexes of o-hydroxy schiff base (Joshi et al., 2019).

Reaction of 3-(Pyridin-2-yl)-5-(2-aminophenyl)-1H-1,2,4-triazole with salicylaldehyde or benzaldehyde gives rise to a new 1,2,4-triazole derivatives. Reactions of ligands with zinc acetate in ethanol, two new complexes are obtained with the azomethine or dihydrotriazine indolizine form of the ligands. The structures of the synthesized complexes were investigated by X-ray analysis. The complexes showed strong green-blue luminescence in the solid state. Zinc complexes synthesized with high thermal stability and high luminescence are expected to be an important agent for organic light production (Gusev et al., 2011).

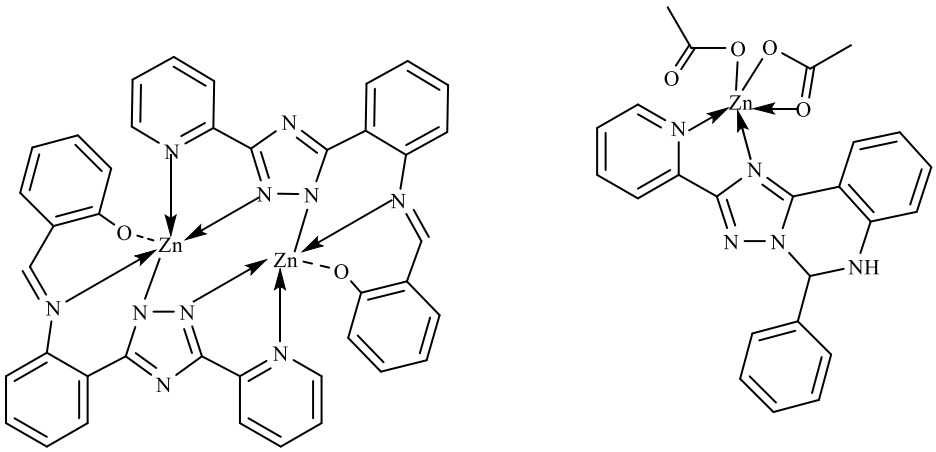

Figure 4. Zn complexes of 1,2,4-triazole (Gusev et al., 2011)

Novel triorganotin (IV) complexes with Schiff base (E)-4-amino-3-(2-(4-hydroxybenzylidene)hydrazinyl)-1H-1,2,4-triazol-5(4*H*)-thion were synthesized. It has been characterized using analytical and multiple spectroscopic techniques such as 2D-HMQC, FT-IR/Raman, NMR (^{1}H, ^{13}C, ^{119}Sn), ESI-MS spectrometry. A skewed tetrahedral geometry was determined in the Schiff base ligand. The atomic charges on the selected atoms were calculated

and the reactive regions on the surface of the molecules were evaluated by means of the molecular electrostatic potential map (MEP). A comparative analysis of the calculated vibrational frequencies with the experimental vibrational frequencies was performed and significant bands were determined. The in vitro antifungal activity of triorganotin (IV) complexes and Schiff base ligand were tested to investigate their potential antifungal activities. The results of in vitro antifungal studies against selected strains showed that both complexes showed potent inhibitory activity. Obtained bioactivity results were confirmed by in-silico molecular docking studies. Organotin complexes have attracted attention for their significant antifungal activities, but can also be considered as potential alternatives to platinum drugs used in various chemotherapies due to their low toxicity and high selectivity (Joshi et al., 2020).

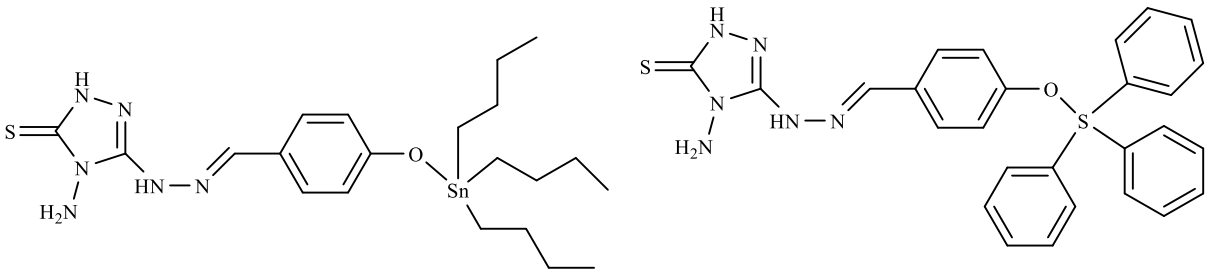

Figure 5. Triorganotin(IV) complexes of p-hydroxy schiff base (Joshi et al., 2020)

Ligands 4-phenyl-2H-1,2,4-triazol-3-thione (Hphtt), 3,30-dithiobis (4-phenyl-1,2,4-triazole) (dbpht) and [Ni](phtt)$_2$(en)$_2$] and [Cd$_2$(1-phtt)$_2$(phtt)$_2$(bpy)$_2$] (3) complexes were synthesized and characterized by various physicochemical methods. In complex Ni, the nickel center is bonded via the triazole ring nitrogen, while in complex Cd, cadmium is bonded via thiolato sulfur, forming a dimeric structure via thiolato bridging. Complexes are stabilized by various intermolecular and intramolecular hydrogen bonds. The DFT results of the optimized molecular geometry of all compounds were obtained and compared with the experimental X-ray diffraction results. Thermogravimetric analysis properties of the complexes were investigated. Its photoluminescent properties indicate that complex Cd is non-fluorescent and complex Ni has characteristic fluorescent emissions that make it a desirable target for photophysical studies and electronic applications (Dani et al., 2014).

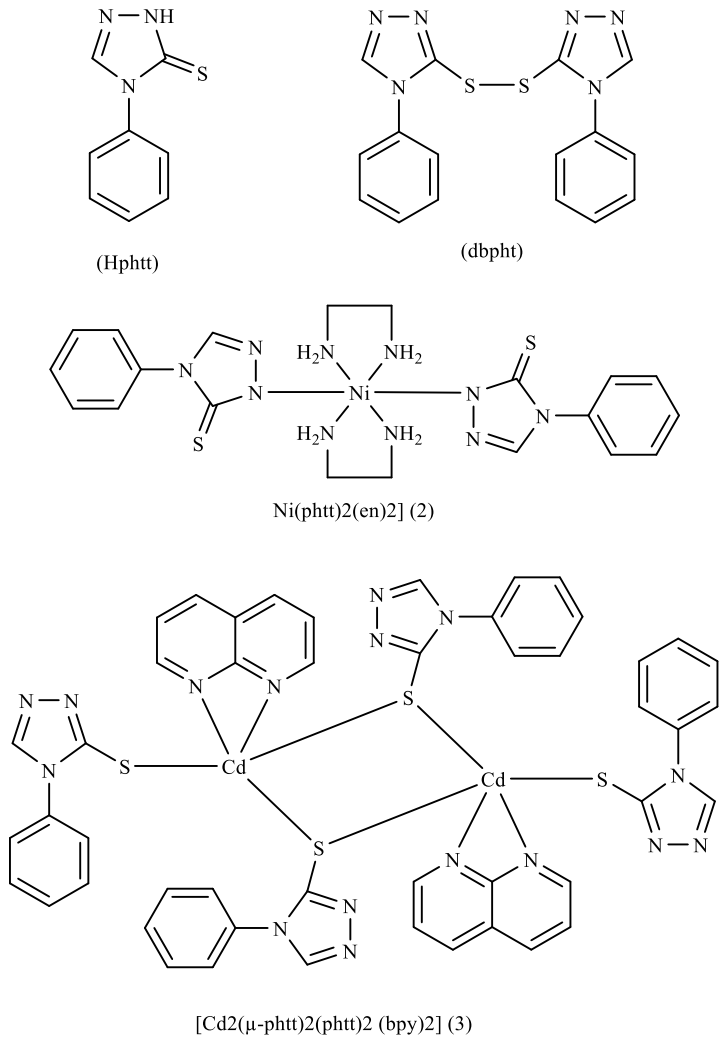

Figure 6. Syntheses of ligand and its complexes (Dani et al., 2014).

$[Ni^{II}(dpp)_2(L)_2]$ (1), $[Ni^{II}(eda)_2(L)_2]$ (2) and $[Ni^{II}(deda)_2(L)_2]$ (3) complexes was synthesized by reacting 3-pyridinyl-4-amino-5-mercapto-1,2,4-triazole with diamines and nickel (II) salt (dpp=1,3-diaminopropane, eda=ethanediamine, deda=N,N-dimethyl ethylenediamine). Three new complexes were structurally characterized by the single crystal X-ray diffraction method. Inhibitory activity of the complexes was tested in vitro against jack bean urease. Molecular docking was investigated to insert complexes into the crystal structure of jack bean urease at the active site to determine the possible mode of binding. The synthesized complexes exhibited inhibitory activities as a potent urease inhibitor. Studies of molecular docking and urease inhibitory activities of complexes against Jack bean urease have valuablely led to the development of a new urease inhibitör (Xu et al., 2014).

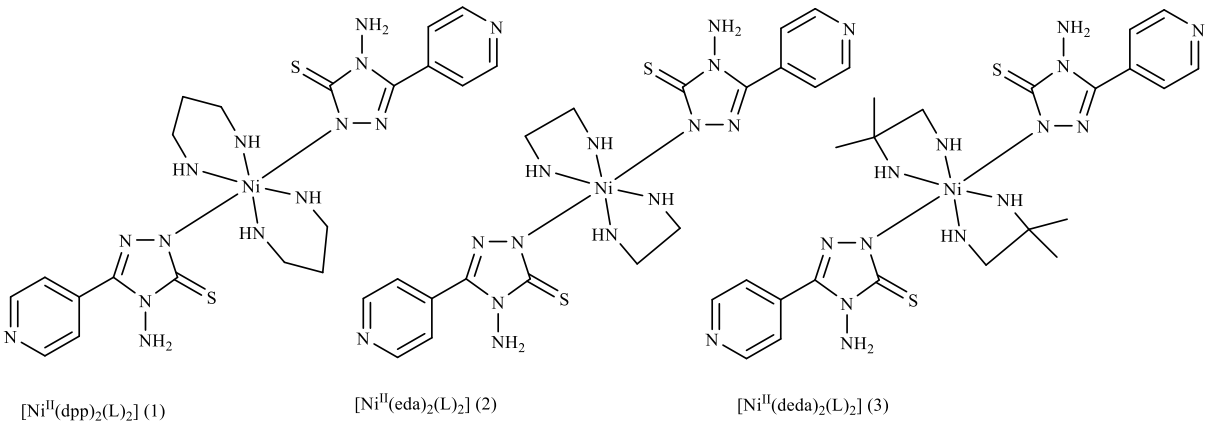

Figure 7. [NiII(dpp)2(L)2] (1), [NiII(eda)2(L)2] (2) and [NiII(deda)2(L)2] (3) complexes synthesized 3-pyridinyl-4-amino-5-mercapto-1,2,4-triazole (Xu et al., 2014).

Synthesis of three new Pd(II) complexes, $[Pd(eptu)_2]$, $[Pd(Hmmtrz)_4]Cl_2$ and $[Pd(Hmthd)_4]Cl_2 \bullet 2CHCl_3$ were investigated spectral and crystal structure research. Single crystal X-ray structures showed a warped square planar geometry with four coordinates around the Pd(II) center in these complexes. The thiourea ligand Heptu binds to the metal ion via nitrogen and sulfur atoms and behaves like a non-negative bidentate in complex $[Pd(eptu)_2]$. Triazole (Hmmtrz) and thiadiazole (Hmthd) ligands act as neutral monodentate coordinated to the metal ion via the thion sulfide in complexes. It is observed that the transition of hydrogen from sulfur to nitrogen in the ligand framework in complexes $[Pd(Hmmtrz)_4]Cl_2$ and $[Pd(Hmthd)_4]Cl_2 \bullet 2CHCl_3$ causes the ligand to form thion and coordination to the metal center in both complexes. The complexes are stabilized by inter molecular and intramolecular hydrogen bonding (Bharati et al., 2016).

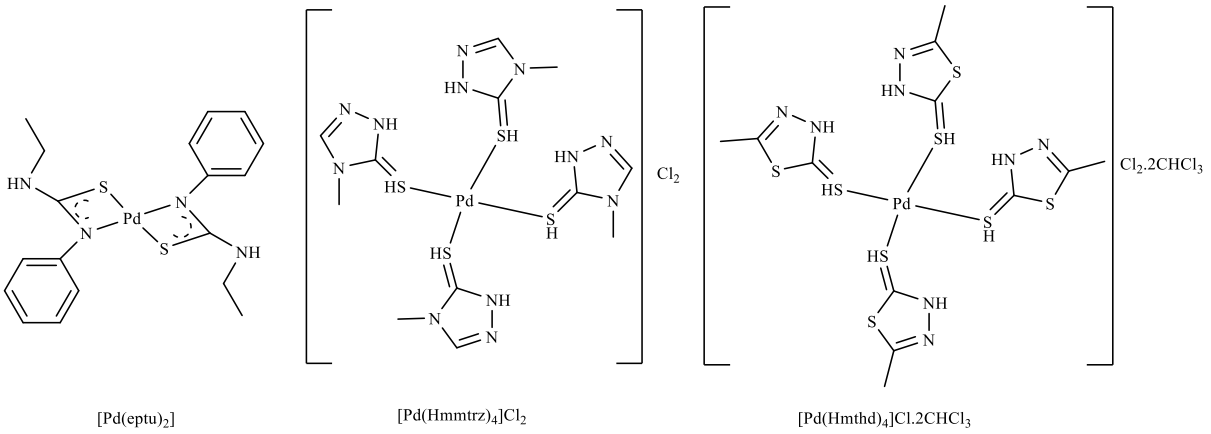

Figure 8. $[Pd(eptu)_2]$, $[Pd(Hmmtrz)_4]Cl_2$ and $[Pd(Hmthd)_4]Cl_2 \bullet 2CHCl_3$ Pd(II) complexes (Bharati et al., 2016).

Two mononuclear mixed ligand complexes $[Ni(en)_2(ppdtt)_2]•2H_2O$ and $[Cu(en)_2(ppdtt)_2]•2H_2O$ were synthesized with Hppdtt=4-phenyl-5-pyridine-4-yl-2,4-dihydro-1,2,4-triazol-3-thion and ethylenediamine (en). The studied compounds were characterized by elemental analysis, UV-Vis, IR, magnetic susceptibility, ESR, cyclic voltammetry and single crystal X-ray studies. The geometry of complexes 1 and 2 is distorted octahedral. Complexes 1 and 2 were determined to exhibit quasi-reversible redox behavior due to an electron transfer oxidation reduction. Complexes 1 and 2 crystallized in orthorhombic and monoclinic. Various types of extended hydrogen bonding provided spaces for lattice water containment in the three-dimensional supramolecular framework of the complexes (Dulare et al., 2011).

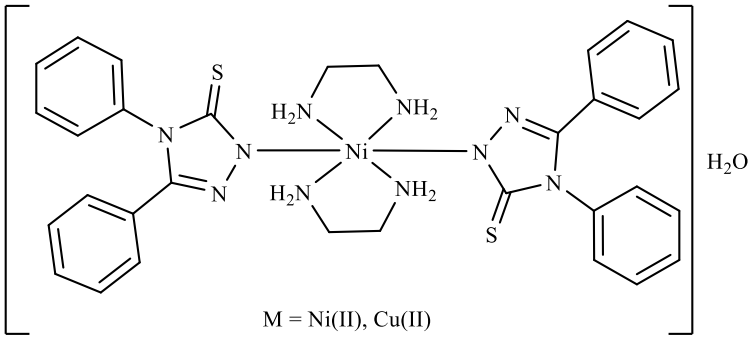

Figure 9. Two mononuclear mixed ligand complexes $[Ni(en)_2(ppdtt)_2]•2H_2O$ and $[Cu(en)_2(ppdtt)_2]•2H_2O$ (Dulare et al., 2011).

The new mixed ligand complexes $Ni(aptt)_2(en)_2]$, $[Ni(apytt)_2(en)_2]•CHCl_3$ and $[Ni(athtt)_2(en)_2]$ with 4-amino-5-phenyl-2H-1,2,4-triazol-3-thion (Haptt), 4-amino-5-(pyridin-3-yl)-4,5-dihydro-3H-1,2,4-triazole-3-thione (Hapytt) and 4-amino-5-thiophene-2H-1,2,4-triazol-3-thione (Hathtt) were prepared complexes containing en as secondary ligand. These complexes were synthesized by reacting nickel (II) acetate and triazole ligand followed by adding ethylenediamine or $[Ni(en)_2(NCS)_2]$ precursor and triazole ligand. Metal complexes were characterized with the help of elemental analysis, IR, magnetic susceptibility and single crystal X-ray data. All complexes bond with two nitrogen atoms of two triazole ligands and four nitrogens of two ethylenediamine, and the resulting complexes have distorted octahedral geometry. Due to the hard character of nickel (II), triazole ligands behave like a non-negative monodentate bound through the triazole nitrogen. The complexes contain extended hydrogen bonding that provides the supramolecular framework (Bharty et al., 2014).

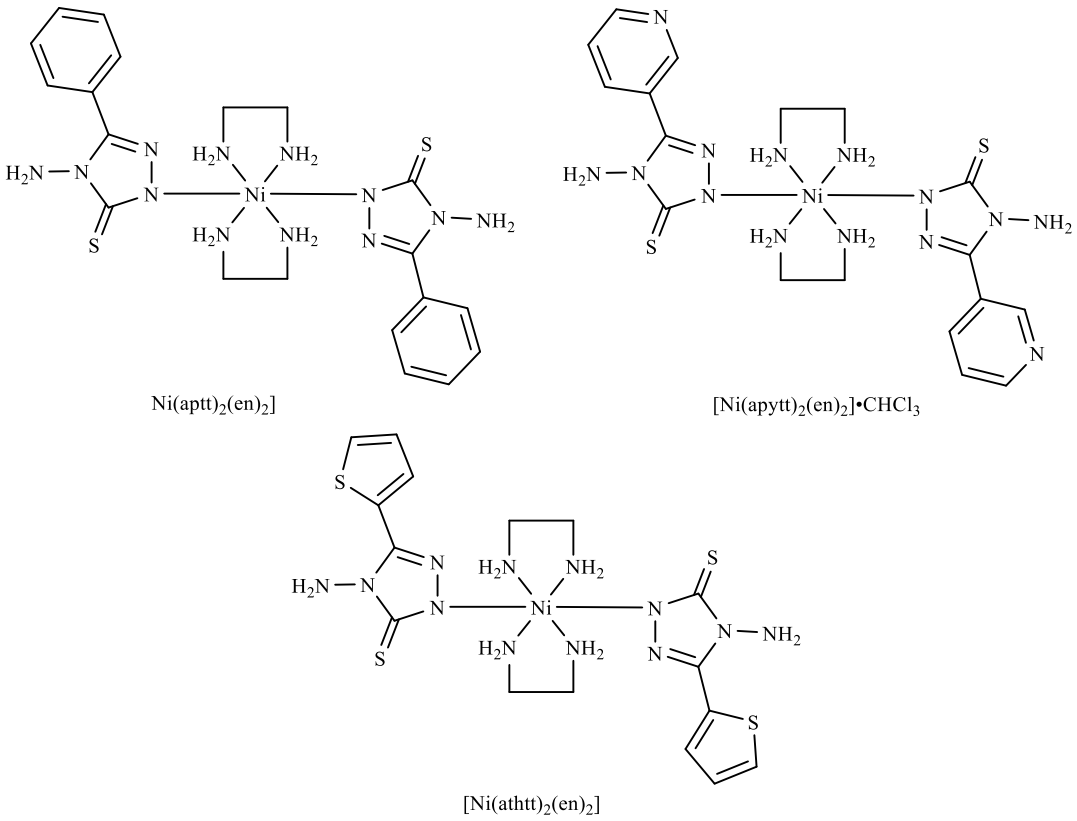

Figure 10. Ni complexes $Ni(aptt)_2(en)_2]$, $[Ni(apytt)_2(en)_2]•CHCl_3$ and $[Ni(athtt)_2(en)_{2]}$ (Bharty et al., 2014).

Five new mononuclear Pt (II) complexes with ligands 5-perfluoroalkyl-1,2,4-oxadiazolyl-pyridine and 3-perfluoroalkyl-1,2,4-triazolyl-pyridine have been reported. The structures of the synthesized complexes were characterized by a combination of elemental analysis, atomic absorption spectrometry, IR, ^1H NMR and molar conductivities. In complexes 2a and 3a, 5-perfluoroalkyl-1,2,4-oxadiazole ligands are monodentately bound to the Pt (II) ion through the pyridine ring, where the metal geometry is square planar. The 3-perfluoroalkyl-1,2,4-triazole ligands also act monodentately to the Pt(II) ion via the N2 atom of the 1,2,4-triazole ring. Five new complexes and synthesized new ligands were tested in vitro. Complexes containing the 1,2,4-triazole ring were found to be active against three interlocking tumor cell lines, but other complex was found to be much more active than ligand 2 (Rubino et al., 2016).

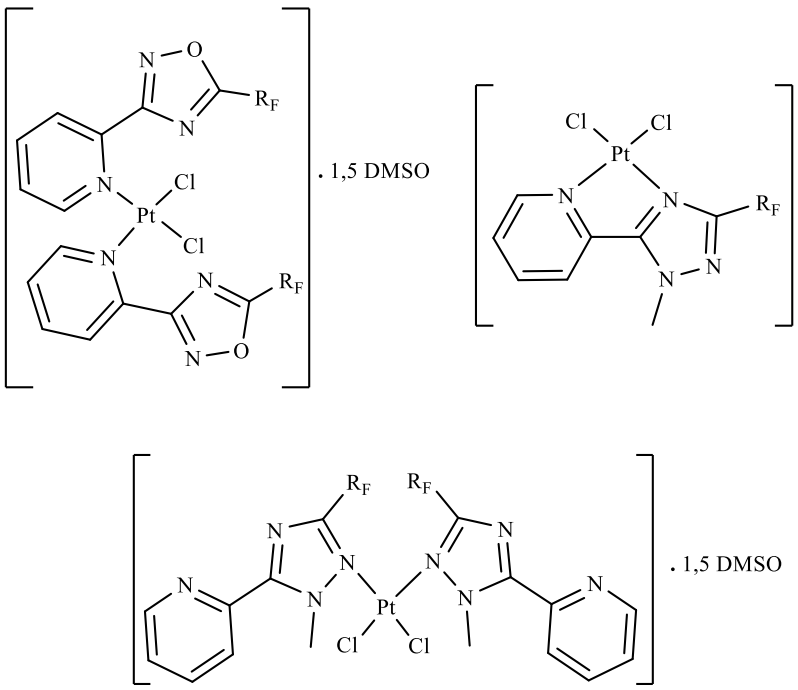

Figure 11. platinum complexes containing oxadiazole and 1,2,4-triazole moiety (Rubino et al., 2016).

The novel series of silver complexes with coumarin-substituted 1,2,4-triazole-based NHC ligands were synthesized and characterized to examine and compare their antioxidant and antihemolytic activities. Ionic 1,2,4-triazolium salts were prepared by the sequential N-alkylation method using allyl bromide and appropriately substituted 4-bromomethylcoumarine derivatives. Silver NHC complexes exhibited a linear coordination geometry with the monoclinic crystal system. The supramolecular association of the salt and the complexes proved moderate π–π stacking interactions between adjacent coumarin rings. Since the medicinal properties of silver (I) NHC complexes are well known, the existing complexes, potent antioxidant and antihemolytic properties have been studied. The bis-NHC coordinated silver hexafluorophosphate complexes showed significant DPPH radical scavenging activities (Geetha et al., 2020).

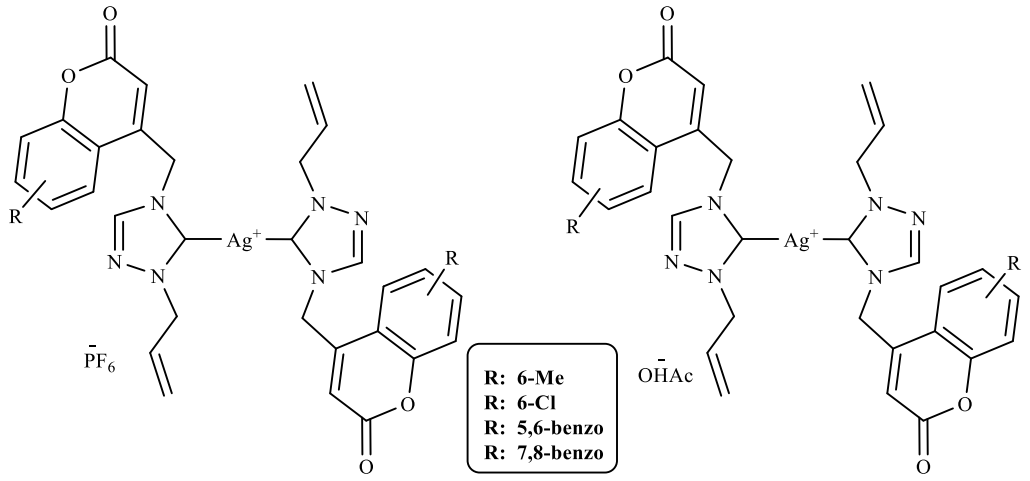

Figure 12. Coumarin and allyl substituted bis–NHC coordinated silver (I) complexes and NHC coordinated silver(I) acetate complexes (Geetha et al., 2020).

Metal complexes of cobalt (II), nickel (II) and copper (II) were synthesized with newly synthesized biologically active 1,2,4-triazole Schiff bases derived from the condensation of 3-substitute-4-amino-5-mercapto-1,2,4-triazole and 8-formyl-7-hydroxy-4-methylcoumarin. The synthesized 3-substitute-4-amino-(8-formyl-7-hydroxy-4-methylcoumarin)-5-mercapto-1,2,4-triazole Schiff bases act as tetradentate Schiff bases. The metals are coordinated to the azomethine nitrogen, lactonyl oxygen, phenolic oxygen, and sulfur atom. Analytical, IR, ESR, electronic, magnetic and thermal studies have confirmed the binding of Schiff bases to metal ions. Electrochemical investigation of Cu (II) and Ni (II) complexes can provide the degree of reversibility of an electron transfer reaction and they have a semi-reversible character. All complexes are limitedly soluble in common organic solvents, but more substantially soluble in DMF and DMSO, and are not electrolytes in DMF and DMSO. All these Schiff bases and complexes were also screened for antibacterial (*Escherichia coli, Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa and Salmonella typhi*) and antifungal activities (*Aspergillus niger, Aspergillus flavus* and *Cladosporium*) by MIC method (Bagihalli et al., 2008).

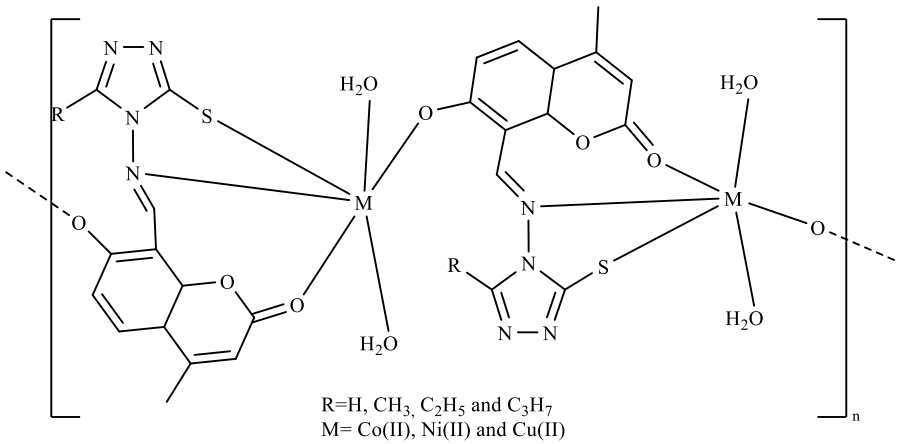

Figure 13. Proposed structure of metal(II) complexes (Bagihalli et al., 2008).

Two mononuclear and first binuclear palladium complexes containing the well-known 4-amino-3-methyl-1,2,4-triazol-5-thione moiety were synthesized and characterized. The molecular structures of the complexes were determined by X-ray diffraction studies. According to the crystal structures determined, it was found that the 1,2,4-triazole moiety acts as a bidentate chelating ligand through the sulfur and nitrogen atoms, while the deprotonated triazole moiety alone functions as a bridging agent between the two metal centers. It can simultaneously act as a bidentate chelating agent through the thiol sulfur atom and the hydrazine nitrogen atom to one metal center, and as a monodentate material through the endocyclic nitrogen atom to the other metal center. Single-crystal X-ray diffraction revealed that the packing mode of the heterocycle by the phenyl rings of the PPh3 moiety is responsible for the interesting "sandwich" effect observed (Ghassemzadeh et al., 2010).

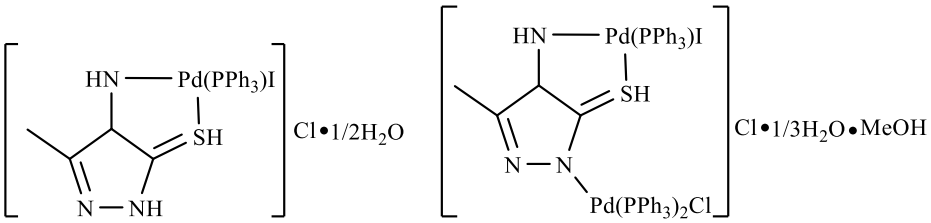

Figure 14. binuclear palladium complexes (Ghassemzadeh et al., 2010).

Synthesis, spectral characterization and luminescence properties of 3-(2-pyridyl)-1H-1,2,4-triazole-5-acetic acid ethyl ester (HL) and palladium (II) complexes were determined. The compounds $Pd(L)_2$ and $Pd_4(L)_4Cl_4$•2DMF were prepared by refluxing $Pd(HL)Cl_2$ in DMF. Molecular and crystal structures of $Pd_4(L)_4Cl_4$•2DMF were analyzed by single crystal X-ray diffraction analysis. The triazoles in $Pd_4(L)_4Cl_4$•2DMF were found to act as bidentate ligands

bridging the two palladium centers in two different ways. Therefore, the molecular structure consists of tetranuclear units of palladium ions. The luminescence properties of the ligand and its complexes are discussed (Khomenko et al., 2015).

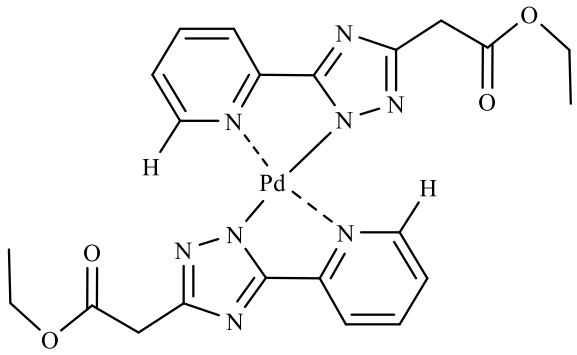

Figure 15. Structure proposed for $Pd(L)_2$ (Khomenko et al., 2015).

Two new diphenylboron containing 1,3,4-oxadiazole and two new zinc containing 1,2,4-triazole complexes was prepared in good yields by the coordination 2-(2-hydroxyphenyl)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole and 1-phenyl-3-methyl-1,2,4-triazole with triphenylboron or zinc acetate under mild conditions under mild conditions. The molecular structures of the chelated diphenylboron complexes containing 1,3,4-oxadiazole were determined by X-ray single crystal diffraction. Excited-state intramolecular proton transfer (ESIPT) rearrangements observed in ligands containing 1,3,4-oxadiazoles with the inclusion of the spectroscopic properties of all compounds were analyzed using DFT and TD DFT calculations. All complexes were found to show significant fluorescence in both polar and non-polar solvents in the blue region of the spectrum. The displayed spectral properties make these complexes important for use as blue emitters in the design of light-emitting organic diodes (Mikhailov et al., 2019).

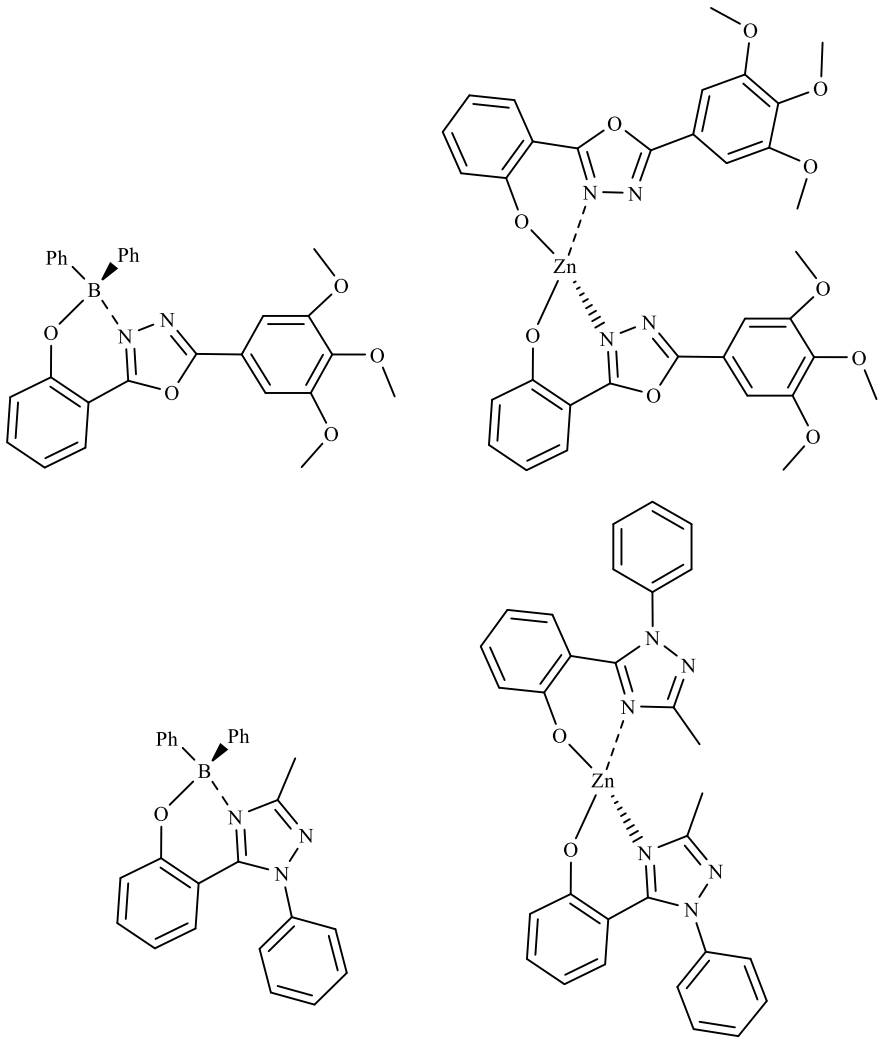

Figure 16. Two new diphenylboron containing 1,3,4-oxadiazole and two new zinc containing 1,2,4-triazole complexes (Mikhailov et al., 2019).

Two new complexes, 4-phenyl(phenyl-acetyl))-3-thiosemicarbazide (Hppt) and 4-amino-5-phenyl-1,2,4-triazole-3-thiolate (Haptt) with [Mn(ppt)2(o-phen)] and [Mn(aptt)(Cl)(o-phen)$_2$]•2Haptt•H2O new ligand containing o-phenanthroline (o-phen) as coligand was synthesized. Both complexes are six coordinated and heteroleptic with distorted octahedral geometries around the metal center. The coordination sphere of complex [Mn(ppt)2(o-phen)] is filled with two amide carbonyl oxygens and a deprotonated hydrazine nitrogen atom of two mono-negative bidentate ppt ligands and two nitrogen atoms of o-phene; each forms three five-membered chelate rings. TGA of complexes [Mn(ppt)2(o-phen)] and [Mn(aptt)(Cl)(o-phen)$_2$]•2Haptt•H_2O shows that the metal is converted to metal oxide at very high temperature. In the solid state, the crystal structure of both complexes is stabilized by various intermolecular and intermolecular interactions. To investigate possible electrochemical applications of

complexes [Mn(ppt)2(o-phen)] and [Mn(aptt)(Cl)(o-phen)$_2$]•2Haptt•H_2O, they are immobilized on a glassy carbon electrode using Nafion. The cyclic voltammetry technique is used to characterize metal complex immobilized electrodes in basic medium. Both complexes show excellent electrocatalytic activity for electrochemical oxygen reduction (Bharty et al., 2019).

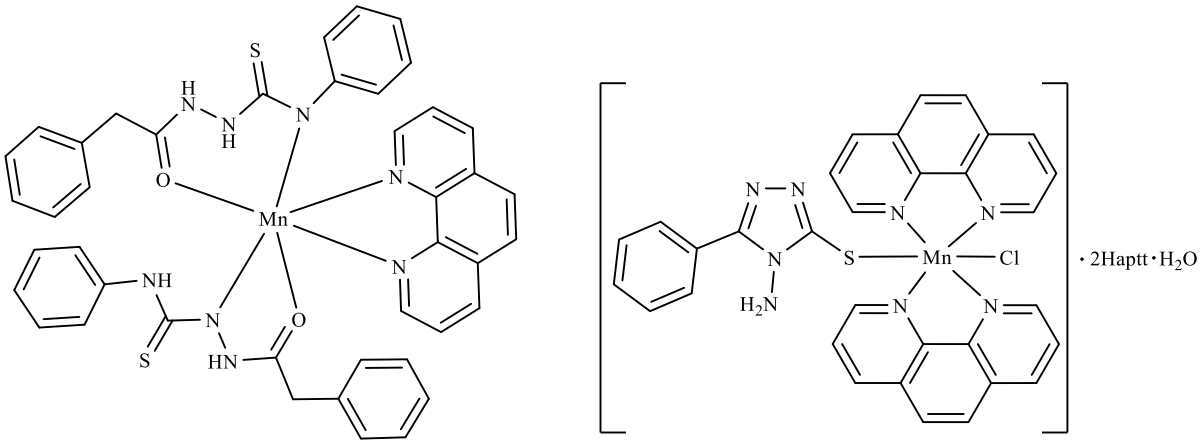

Figure 17. Two new complexes [Mn(ppt)$_2$(o-phen)] and [Mn(aptt)(Cl)(o-phen)$_2$]•2Haptt•H_2O (Bharty et al., 2019).

Cyclometallized Ir (III) complex [Ir(2,4-F_2ppy)$_2$(pyta)Cl] was successfully synthesized by reflux with 2-(1H-1,2,4-triazol-1-yl)-pyridine with Ir (III) dimer [Ir(2,4-F_2ppy)$_2$(μ-Cl)]$_2$. X-ray crystallographic study revealed that the Ir(III) ion is coordinated in a distorted octahedral geometry to a pyridine-triazole, one chloro, and two difluorophenylpyridine ligands. The crystal structure of the complex was determined and it was stated that in the solid state the complex adopts a distorted octahedral coordination environment. DFT calculations on the Ir (III) complex show that HOMO is mainly localized on the cyclometallising ligands and Ir 5d orbitals, while LUMO is located on the cyclometallising ligands, and the HOMO-LUMO energy gap is 3.86 eV. The contacts between the different units of the cyclometallized Ir(III) complex were investigated by analyzing the Hirshfeld surface and the molecular electrostatic potential surface plotted in the ground and triple excited states (Bain et al., 2020).

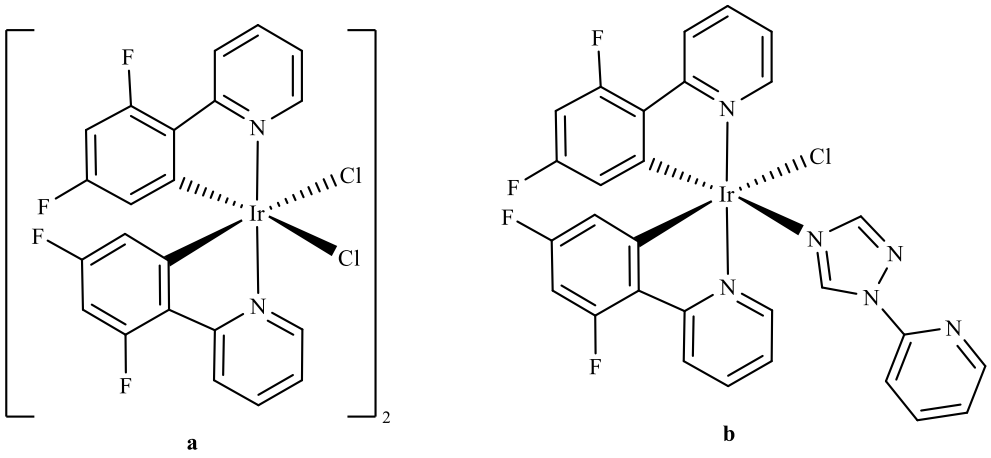

Figure 18. Cyclometallized Ir (III) complex [Ir(2,4-F_2ppy)$_2$(pyta)Cl] (b) (Bain et al., 2020).

Two neutral heteroleptic iridium(III) complexes carrying substituted pyridine 1,2,4-triazoles as auxiliary ligands were synthesized as emitters for PhoLEDs and their properties were investigated. Although the pyridine-1,2,4-triazole complex family is well known in the literature, there are few studies on their investigation as emitters for OLEDs. While sky blue devices were prepared with the fluorinated complex, blue-green devices were created with the second complex (Dumur et al., 2013).

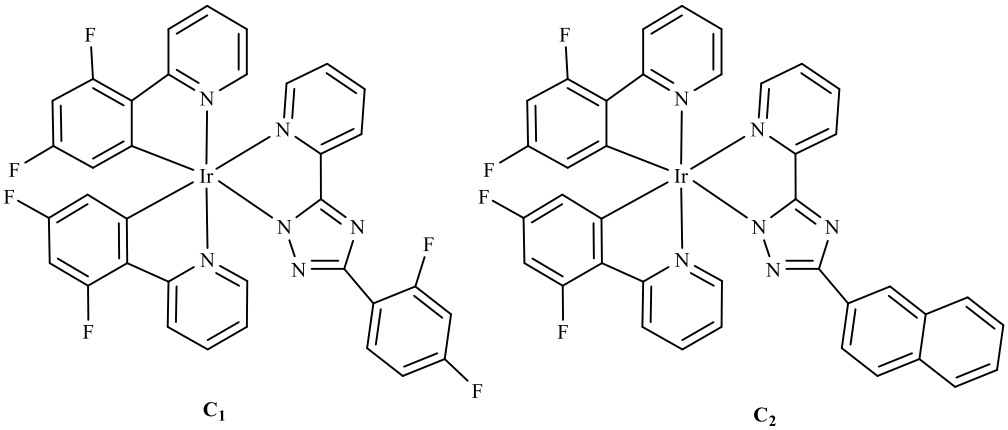

Figure 19. Two neutral heteroleptic iridium(III) complexes carrying substituted pyridine 1,2,4-triazoles (Dumur et al., 2013).

Luminescent europium complexes were obtained by the reaction of 1,2,4-triazole-3-carboxylic (trzc), pyridine-2,6-dicarboxamide (pdcam) and $EuCl_3$ solutions at different molar ratios. The synthesized europium complexes were characterized using elemental analysis, UV-vis, FT-IR spectroscopy, TGA, powder XRD studies, SEM and photoluminescence spectroscopic methods. With the aid of thermal stability data, the complexes were found to be relatively stable

at high temperature. The highest lifetime and intrinsic quantum efficiency among all complexes were determined for $[Eu(pdcam)_2(trzc)]Cl_3$. The anion detection properties of the studied Europium complexes were investigated in detail using absorption and emission spectral studies. $[Eu(pdcam)_2(trzc)]Cl_3$ (1) and $[Eu(pdcam)(trzc)_2]Cl_3$ (2) complexes were showed significant differences in luminescence upon hydrogen bonding to its F-ions. After adding different anions, UV-vis and photoluminescence spectra of Eu(III) complexes were also investigated. The anion sensing properties of europium complexes were investigated using absorption and emission spectral studies (Sengar & Narula, 2017).

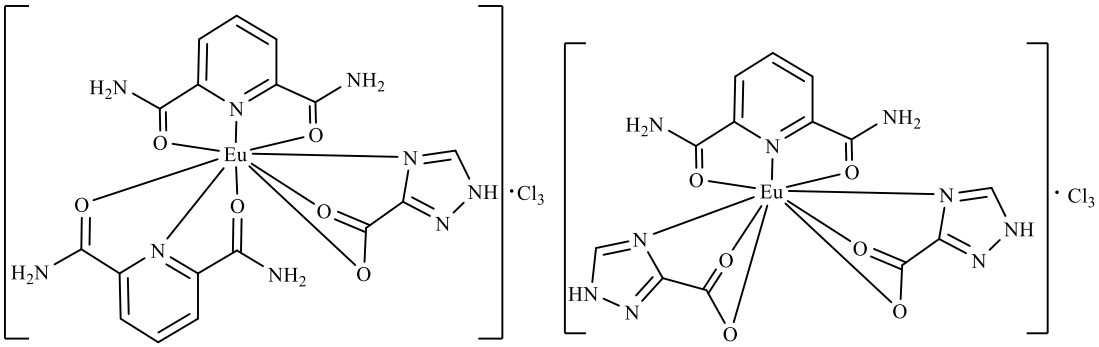

Figure 20. $[Eu(pdcam)_2(trzc)]Cl_3$ (1) and $[Eu(pdcam)(trzc)_2]Cl_3$ (2) complexes (Sengar & Narula, 2017).

A novel emissive mononuclear homoleptic Cu(I) complex of 5-tert-butyl-3-(6-methyl-2-pyridyl)-1H-1,2,4-triazole $[Cu(bmptzH)_2](ClO_4)$ were obtained by reaction of [Cu $[Cu(CH_3CN)_4](ClO_4)$ or $(PPh_3)_2(CH_3CN)_2](ClO_4)$ with the bmptzH ligand. The structural and photophysical properties of the complexes have been well studied. It was observed that Complex 1 adopts a neutral bidentate chelation coordination mode using the N atom of the pyridyl ring of bmptzH and the 4-N atom of the 1,2,4-triazolyl ring, not the 2-N and a distorted N4 tetrahedral arrangement formed by the two bmptzH chelates. It has been shown that the Cu(I) complex is highly stable and exhibits good luminescence properties in solution and solid states at room temperature as a result of the incorporation of a methyl group in the ortho-position of the pyridyl ring (Luo et al., 2017).

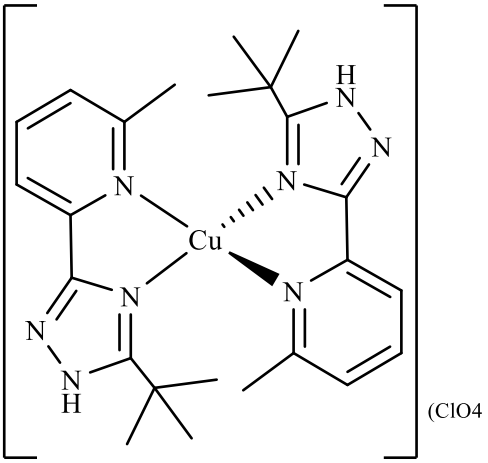

Figure 21. Cu(I) complex of 5-tert-butyl-3-(6-methyl-2-pyridyl)-1H-1,2,4-triazole $[Cu(bmptzH)_2](ClO_4)$ (Luo et al., 2017).

New Fe(III) complexes were synthesized by the reactions of Schiff base derived from 3-substituted phenyl-4-amino-5-hydrazino-1,2,4-triazole and indoline-2,3-dione with ferric nitrate. All synthesized complexes were dissolved in DMSO and DMF; shows that they are not electrolytes due to their low molar conductivity values. Elemental analysis results of the complexes show that the structures are in 1:1 stoichiometry of the $[FeLn(H_2O)(OH)]•xH2O$ type. The structural and spectroscopic properties of the synthesized complexes were investigated on the basis of elemental analysis, infrared spectra, electronic spectra, magnetic measurements, ^{1}H and ^{13}H-NMR spectra and mass spectra. According to the magnetic moment and reflection spectral studies, an octahedral geometry is formed in all the prepared complexes. FT-IR, ^{1}H and ^{13}H-NMR studies reveal that the ligand (Ln) is in the form of tautomeric enol in both cases with intramolecular hydrogen bonding. The complexes were found good antimicrobial activities when compared to their free ligands against *Staphylococcus aureus*, *Bacillus subtilis*, *Serratia marcescens*, *Pseudomonas aeruginosa* and *Escherichia coli*. When FRAP values are investigated, it shows that all compounds have ferric reducing antioxidant power (Kharadi, 2013).

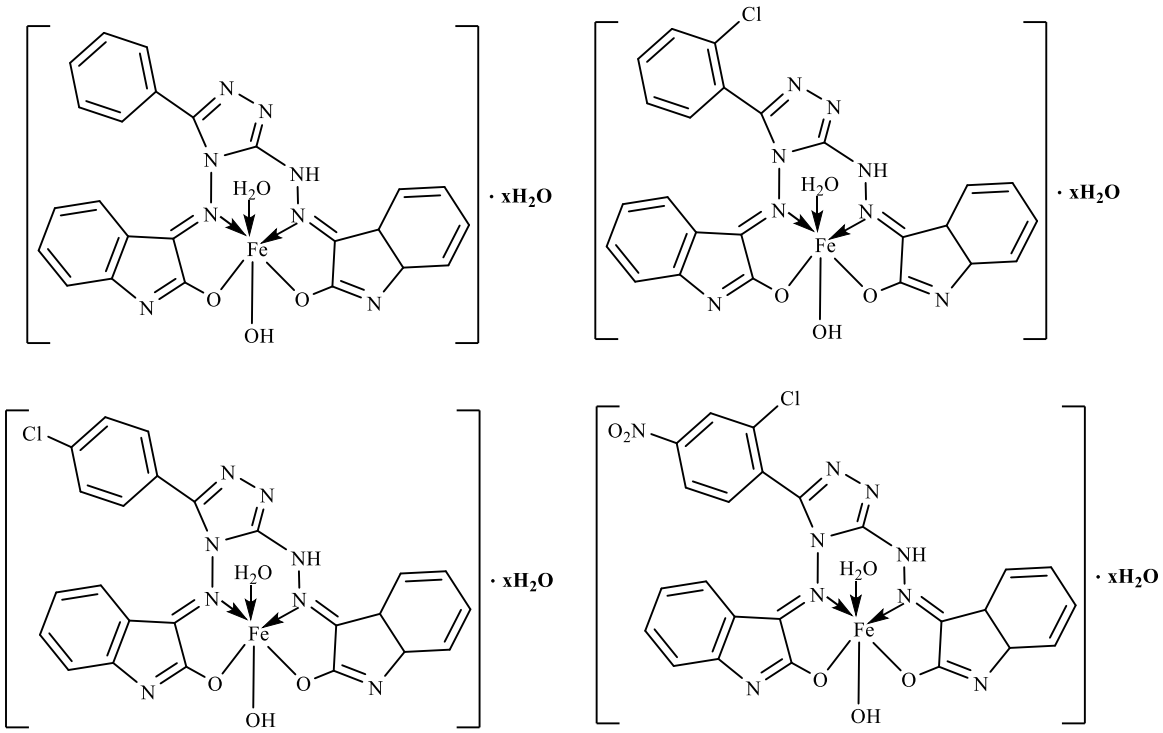

Figure 22. Fe(III) complexes synthesized Schiff base derived (Kharadi, 2013).

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THEORETICAL STUDIES OF 1,2,4-TRIAZOLES

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Theoretical Studies of 1,2,4-Triazoles

Computational chemistry is the atomic and molecular modeling of chemistry in computer environment by using theoretical chemistry methods derived from physics principles such as quantum mechanics, molecular mechanics and molecular dynamics. Scientists need to calculate very cheaply and quickly by computers without the need for physical experiments that can be achieved by working in laboratories. Physicists and chemists have preliminary information about the structure of drugs before synthesis by making calculations on the computer and enable them to determine the desired properties in the drug. Molecule Modeling software provides convenience to those dealing with chemistry. With these programs, molecules can be observed from different angles by rotating them on the computer screen, their isomers and geometric structures can be understood, their energies can be calculated, UV, IR, NMR spectra can be drawn, and even MO diagrams can be accessed (Beytur et al., 2019; Beytur & Avinca, 2021; Gumus & Turker, 2012; Lienard et al., 2015; Rai et al., 2008; Sertçelik, 2021). In addition to experimental methods, computational chemistry methods are also used in the determination of corrosion inhibitors. The activity of an inhibitor, several quantum chemical parameters, can be calculated theoretically without the need for experimentation. The quantum chemical parameters generally used in theoretical studies on corrosion are atomic charges and molecular orbital energies (Karelson et al., 1996; Li et al., 2011).

DFT and HF methods used in theoretical calculations have been widely used in many references in recent years (Karunakaran & Balachandran, 2012; Suvitha et al., 2014). The functional density theory (DFT) method can calculate the physicochemical properties of the investigated molecules at the microscopic level with great precision and low processing cost (Marinho et

al., 2021; Raviprabha & Ramesh S. Bhat, 2019). Density Functional Theory (DFT) can be used to achieve geometric optimization of organic molecule. In addition, infrared (IR) spectra can be simulated and Frontier Molecular Orbitals (FMO) created for electronic characterization and for quantum chemical computations to determine the properties of the molecule as a nucleophile or electrophile parameters (Braga et al., 2016; Kotan et al., 2020; Uğurlu & Beytur, 2020). Ethyl-2-(4-amino-5-oxo-3-(thiophen-2-yl-methyl)-4,5-dihydro-1,2,4-triazol-1-yl) acetate compound was optimized using DFT/ 6–311++G(d,p) basis set and the B3LYP method. Structural parameters of the compound were calculated from the optimized molecular shape. The molecular structure of the related compound was determined by X-ray analysis and compared with experimental data. Theoretical vibration frequencies and NMR chemical shift values were obtained theoretically with the same method and basis set. In addition, molecular electrostatic potential (MEP) map and Mulliken atomic charges were calculated. Structural and spectral data obtained from the theoretical study were compared with the experimental data. Structural parameters and method and basic function selection were found to be appropriate (Çelik & Ünver, 2022).

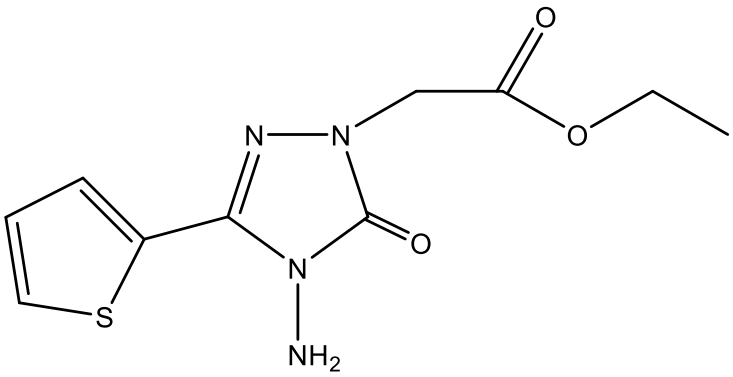

Figure 1. Structure of ethyl-2-(4-amino-5-oxo-3-(thiophen-2-yl-methyl)-4,5-dihydro-1,2,4-triazol-1-yl) acetate compound (Çelik & Ünver, 2022)

4-((4-Ethyl-5-(thiophen-2-yl)-4H-1,2,4-triazol-3-yl)thiomethyl)-7,8-dimethyl-2H-chromen-2-one synthesized by condensation 4-ethyl-5-(thiophen-2-yl)-4H-1,2,4-triazol-3-thiol and 4-(chloromethyl)-7,8-dimethyl-2H-chromen-2-one with medium acetone. The molecular shape was experimentally characterized using FT-IR, ^{1}H- and ^{13}C NMR spectroscopy. The Gaussian 09 program at the B3LYP/cc-pVDZ level of the DFT theory was used to generate the optimized structure of the compound, IR vibrational frequencies, ^{1}H- and ^{13}C NMR chemical shifts, Mulliken atomic charges and HOMO-LUMO energies. Obtained theoretical FT-IR, ^{1}H- and ^{13}C

NMR spectroscopy results were compared with experimental data. Theoretical and experimental results were found to be compatible. The proposed molecular structure is supported by both theoretical and experimental evidence. Dipole moment, hardness, softness, electronegativity, electrophilicity index, nucleophilicity index and chemical potential as electronic structural parameters for the prepared compound were calculated. In addition, the ratio of electrons transferred was calculated to determine the interaction between the iron surface and organic molecules (Parlak et al., 2022).

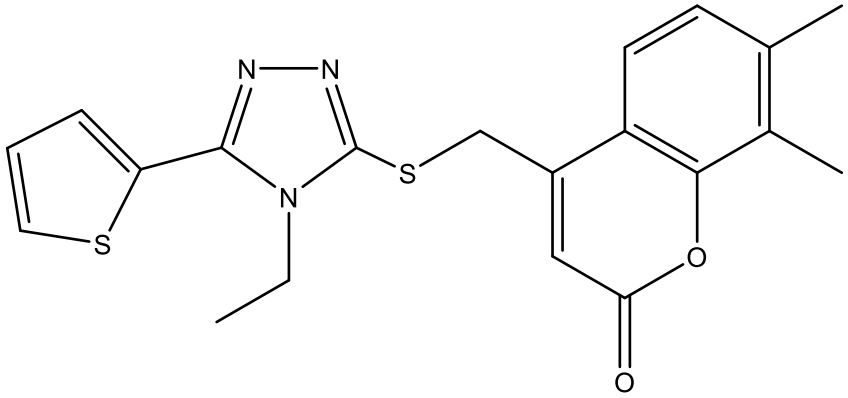

Figure 2. Structure of 4-((4-ethyl-5-(thiophen-2-yl)-4H-1,2,4-triazol-3-yl)thiomethyl)-7,8-dimethyl-2H-chromen-2-one (Parlak et al., 2022)

The N-Aroyl-1,2,4-triazoles TACl and TAM were regioselectively obtained in excellent yields through an efficient N-acylation reaction of 3-amino-5-methylsulfanyl-1H-1,2,4-triazole with aroyl chlorides. The structures of N-aroyl-1,2,4-triazoles were investigated by single-crystal X-ray diffraction and it was observed that their crystal structures were characterized by dimer formation via N–H N bonds. The supramolecular assembly depends on the type of linkages between the dimers and these vary markedly with para-substituted groups on the aroyl group. The ionization potential, electron affinity, electronegativity, electrophilicity index, hardness and chemical potential properties, which were calculated directly with the HOMO and LUMO energies, were determined. In addition, molecular electrostatic potential maps of both molecules showing a negative region on the N2 atom instead of the exocyclic amino group of the 1,2,4-triazole ring were calculated. Vibratory spectral analysis was performed for the N-aroyl-1,2,4-triazoles TAM and TACl using infrared spectroscopy in the range of 400-4000cm^{-1}. The fundamental vibrational frequencies and the intensity of the vibrational bands were evaluated using the density functional theory (DFT) basis set with the standard B3LYP/6–31G(d,p)

method, and a very good agreement was found between the observed and calculated frequencies (Moreno-Fuquen et al., 2021).

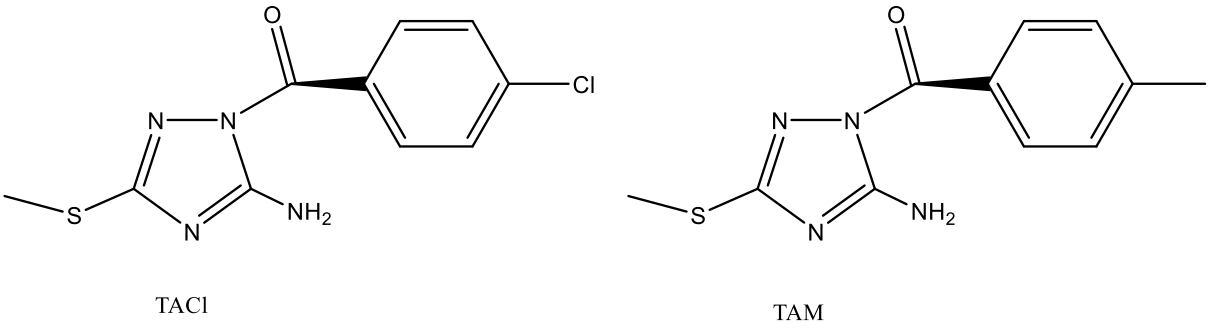

Figure 3. Structure of the N-Aroyl-1,2,4-triazoles TACl and TAM (Moreno-Fuquen et al., 2021)

An enantiomerically pure triazole derivative, (+)-(R)-5-[1-(benzenesulfonamido)-2-phenylethyl]-4-phenethyl-2,4-dihydro-3H-1,2,4-triazole-3 -thion was successfully synthesized in high yield and characterized by spectroscopic techniques (FT-IR and UV-Vis) and single crystal X-ray diffraction analysis. Hirshfeld surface (HS) analysis revealed the nature of intermolecular contacts, fingerprint plots and molecular surface contours. DFT calculations were performed on an isolated molecule in the gas phase using the B3LYP/6–31G(d,p) basis set. The DFT results of the related molecule for the geometric parameters were found to be compatible with the X-ray data. The stability of the molecule resulting from hyperconjugative interactions, charge delocalization was analyzed using natural bond orbital analysis (NBO), and nonlinear optical properties were investigated in the the study (Başaran et al., 2022).

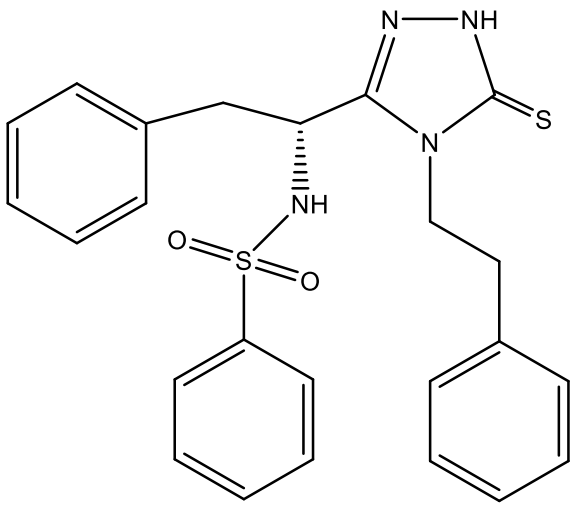

Figure 4. Structure of (+)-(R)-5-[1-(benzenesulfonamido)-2-phenylethyl]-4-phenethyl-2,4-dihydro-3H-1,2,4-triazole-3-thion (Başaran et al., 2022)

{Bis-4-[(3-alkyl-5-oxo-1H-1,2,4-triazol-4(5H)-yl)-imino-methyl]-phenyl} [1,10-biphenyl]-4,40-disulfonates were synthesized by reaction of 3-alkyl-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones (T) and bis-(4-formylphenyl) [1,10-biphenyl]-4,40-disulfonate. The structures of these compounds were determined by IR and NMR spectral methods. Corrosion inhibitory activities of related compounds were investigated using quantum mechanical methods. Parameters such as the energy of highest occupied molecular orbital, the energy of the lowest unoccupied molecular orbital, the energy gap and the dipole moment, which are related to the corrosion efficiency of organic compounds with molecular geometry, and especially the electronic properties examined, were determined using the density function theory method. Using these calculation results, properties such as hardness, softness, electronegativity values were calculated. In addition, quantum chemical parameters such as the fraction of electrons transferred between the iron surface and 4,5-dihydro-1H-1,2,4-triazol-5-one derivative compounds were also Calculated (Beytur et al., 2019).

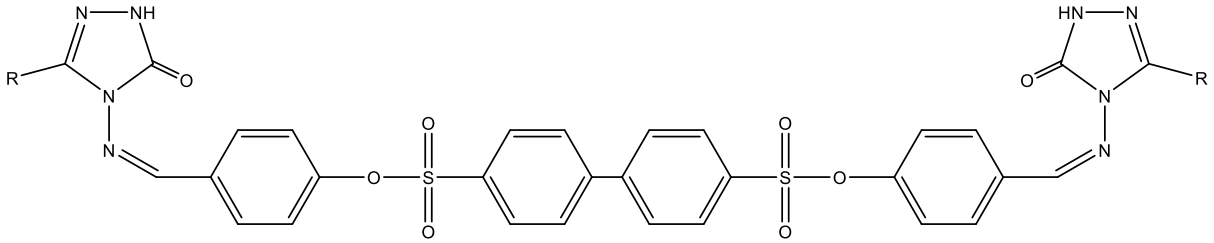

Figure 5. Structure of {Bis-4-[(3-alkyl-5-oxo-1H-1,2,4-triazol-4(5H)-yl)-imino-methyl]-phenyl} [1,10-biphenyl]-4,40-disulfonates (Beytur et al., 2019)

3-Subtitued-4-(3-methyl-2-thienylmethyleneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one compounds were synthesized by the reaction 4-amino-(3-substıtued)-4,5-dihydro-1*H*-1,2,4-triazole-5-ones and 3-methylthiophene-2-carbaldehyde. The spectroscopic, electronic, geometric, nonlinear optical properties of titled molecules have been simulated. UV-visible absorption spectra data were calculated by using TD-DFT method in ethanol. Calculation of FT-IR frequencies was performed for the related compounds. The frequencies recorded with the DFT/B3LYP and DFT/B3PW91 methods were compared with the experimental values and it was determined that the B3LYP values were closest to the experimental values. From the optimized structure, ^{13}C-NMR and ^{1}H-NMR chemical shift values were calculated according to the GIAO method using the Gaussian 09W program package in a DMSO solvent environment. It has been seen that the results obtained are compatible with the experimental data. Finally, electronic properties of synthesized molecules such as ionization potential, electron affinity, energy gap, electronegativity, molecular hardness, molecular softness, electrophilic index, nucleophilic index and chemical potential were calculated from HOMO and LUMO energies using DFT/B3LYP and DFT/B3PW91 methods (Beytur & Avinca, 2021).

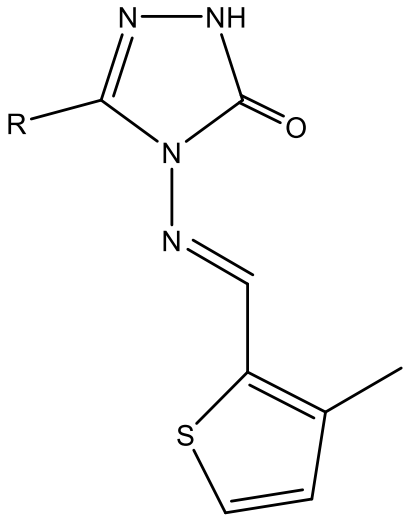

Figure 6. Structure of 3-Subtitued-4-(3-methyl-2-thienylmethyleneamino)-4,5-dihydro-1*H*-1,2,4-triazol-5-one compounds (Beytur & Avinca, 2021)

Corrosion inhibition of mild steel by 3,5-bis(n-pyridyl)-4-amino-1,2,4-triazoles in molar perchloric acid was investigated by gravimetric and electrochemical impedance spectroscopy techniques at 30 °C. 2-PAT, 3-PAT and 4-PAT were obtained with 65%, 95% and 92% protection efficiencies, respectively. It has been determined that the inhibitory properties of n-PAT change with concentration. A significant correlation between inhibition efficiency and

quantum chemical parameters was obtained using the quasi-experimental quantitative structure-activity relationships (QSAR) approach (Lebrini et al., 2008).

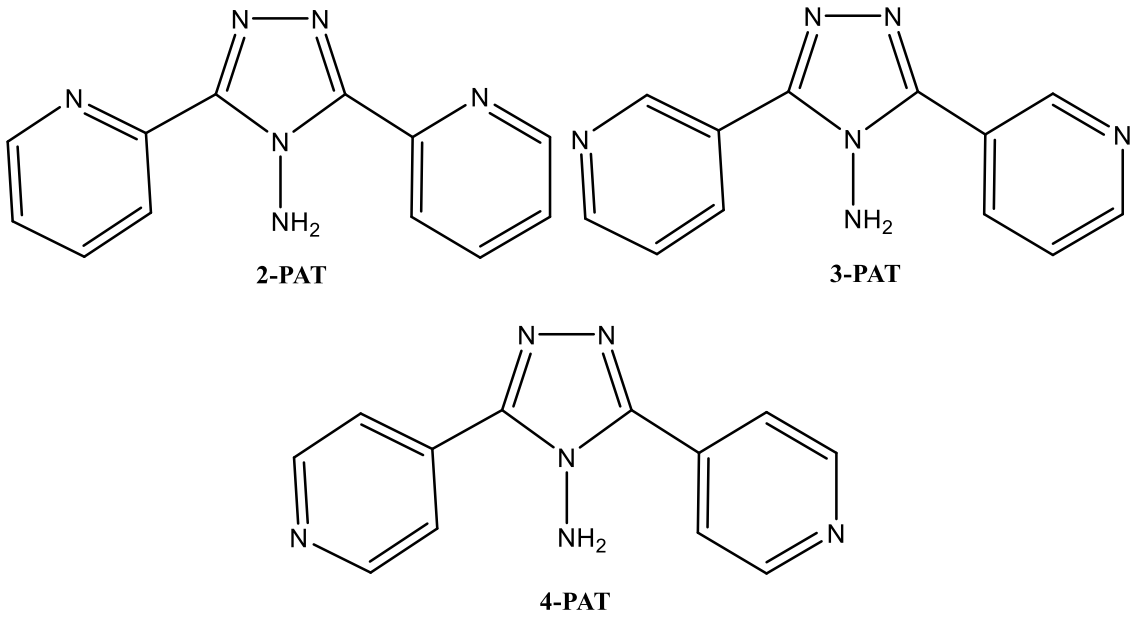

Figure 7. Structure of 3,5-bis(n-pyridyl)-4-amino-1,2,4-triazoles (Lebrini et al., 2008)

The inhibitory effect of 3-amino-1,2,4-triazole-5-thiol (3ATA5T) in 0.5 M HCl on carbon steel (CS) was investigated by electrochemical impedance spectroscopy. The compound of interest was investigated by potentiodynamic measurements at various concentrations and temperatures. According to the obtained results, it was determined that there is a harmony between the experimental and quantum computing parameters. Potential zero charge results determined that the CS surface was positively charged in the presence of 3ATA5T. Quantum chemical calculations showed that the potential zero charge measurements were in agreement with the experimental values (Mert et al., 2011).

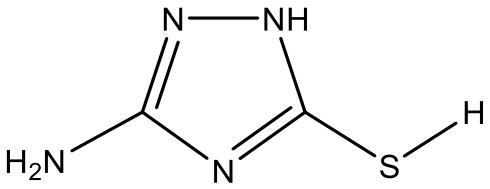

Figure 8. Structure of 3-amino-1,2,4-triazole-5-thiol (3ATA5T) (Mert et al., 2011)

The 5-propyl-4-amino-1,2,4-triazol-3-thion required for the study was obtained experimentally. The structure of the synthesized compound was characterized by spectroscopic (FT-IR and ^{1}H NMR) and structural (single crystal X-ray diffraction) techniques. Geometric parameters of the studied molecule were calculated by HF and DFT (B3LYP) method and analyzed with experimental data. The results showed that the calculated geometric parameters obtained by B3LYP/6-311G+(d,p) method had a better agreement with the experimental data than HF method. FT-IR and 1H NMR spectrum data were analyzed experimentally and theoretically. The theoretically calculated results were compared with the experimental data and found to be compatible with the FT-IR and ^{1}H NMR spectra. The energy gap value between HOMO and LUMO was calculated and the data obtained predicts that charge transfer from the benzene ring to the triazole ring can occur. NBO values were calculated from the optimized structure of the 5-propyl-4-amino-1,2,4-triazol-3-thion molecule using density functional theory (Jin et al., 2014).

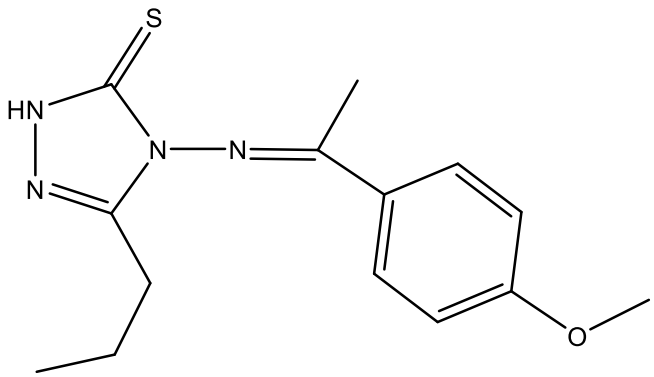

Figure 9. Structure of The 5-propyl-4-amino-1,2,4-triazol-3-thion (Jin et al., 2014)

The electronic structure, molecular properties and vibrational spectra of the 3-(adamantan-1-yl)-4-(4-chlorophenyl)-1H-1,2,4-triazole-5(4H)-thion compound, a new derivative of 1,2,4-triazol-5(4H)-thion were investigated by density functional theory. The hydrogen bonded dimer of the related compound was studied theoretically with the 6-311++G(d,p) diffused and polarized basis set using B3LYP, M06-2X and X3LYP methods. Intermolecular hydrogen bonding was determined using NBO analysis of the studied compound. The experimental FT-IR and FT-Raman spectra of the investigated compound were found to be compatible with the spectral data obtained by the DFT/B3LYP method. The dipole moment, molecular electrostatic potential surface and nonlinear optical properties such as and polarizability, first order static hyperpolarizability of the compound were calculated. The UV-Vis spectrum of the cap

molecule was calculated theoretically. The TD-DFT method was used to calculate the six lowest excited states and their excitation energies (Al-Tamimi, 2016).

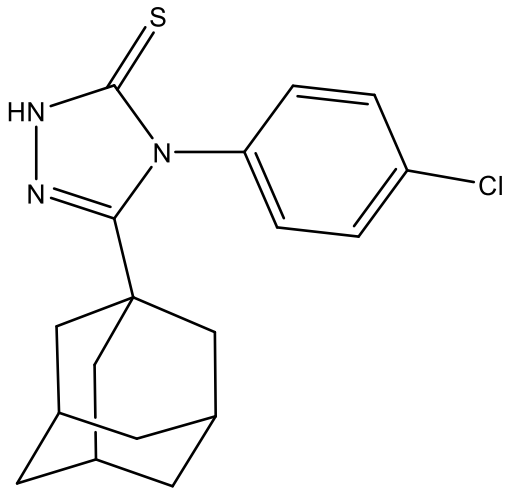

Figure 10. Structure of 3-(adamantan-1-yl)-4-(4-chlorophenyl)-1H-1,2,4-triazole-5(4H)-thion compound (Al-Tamimi, 2016)

4-allyl-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazol-3-thione was synthesized and its structure was investigated by IR-NMR spectroscopy and single-crystal X-ray diffraction. Molecular geometry obtained from X-ray experiment, vibration frequencies, 1H and 13C chemical shift values using gauge including atomic orbital (GIAO) of the compound were calculated using Hartree-Fock (HF) and density functional method (DFT/B3LYP). To determine the conformational conformity, the molecular energy profile of the studied compound was obtained by HF/6−31G(d) and (DFT/B3LYP) calculations. Additionally, frontier molecular orbitals (FMO), molecular electrostatic potential (MEP) and thermodynamic parameters were obtained by HF and DFT functional methods (Cansız et al., 2012).

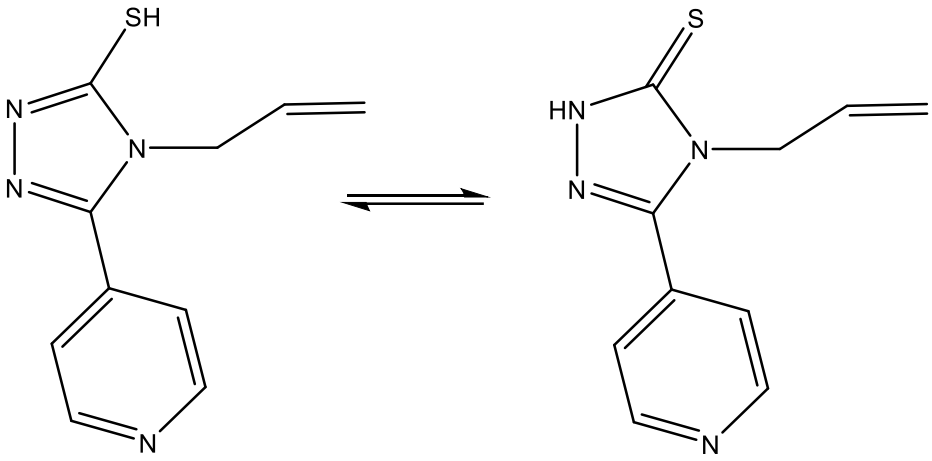

Figure 11. Structure of 4-allyl-5-pyridin-4-yl-2,4-dihydro-3H-1,2,4-triazol-3-thione (Cansız et al., 2012)

4-(4-Methoxyphenethyl)-3,5-dimethyl-4H-1,2,4-triazole was obtained from the reaction of 2-(4-methoxyphenyl)ethanamine with ethyl N'-acetylacetohydrazonate. The structure of the synthesized compound was characterized by IR, 1H/13C NMR, mass spectrometry, elemental analysis, analysis of X-ray crystallography and theoretical methods. The molecular geometry and vibrational frequencies of the relevant compound in the ground state were determined using the density functional method (B3LYP) with the 6-31G(d) basis set. The obtained data proved that the optimized geometry can reproduce the crystal structure well and that the theoretical vibration frequencies are in good agreement with the experimental values. The predicted nonlinear optical properties of the corresponding compound were determined and it was observed that urea was greater in value. The molecular electrostatic potentials and frontier molecular orbitals values of the compound were performed at the B3LYP/6-31G(d) theory level of DFT calculations (Düğdü et al., 2013).

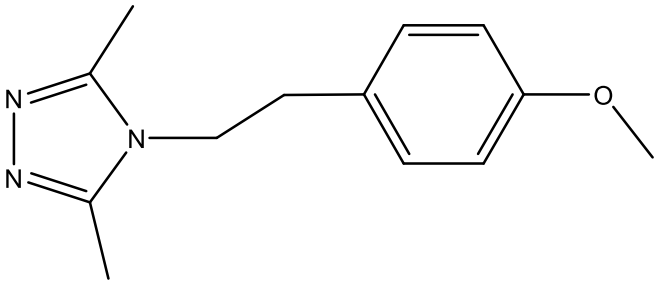

Figure 12. Structure of 4-(4-Methoxyphenethyl)-3,5-dimethyl-4H-1,2,4-triazole (Düğdü et al., 2013)

Experimental and theoretical vibrational frequencies of a newly synthesized 4-benzyl-3-(thiophen-2-yl)-4,5-dihydro-1H-1,2,4-triazole-5-thion molecule, a potential anti-inflammatory agent, were determined. Experimental Laser-Raman (4000-100 cm^{-1}) and FT-IR spectra (4000-400 cm^{-1}) of the molecule in the solid phase were obtained. The theoretical vibration frequencies and geometric parameters such as bond lengths, bond angles and dihedral angles of the optimized molecule were determined by density functional theory method (DFT/B3LYP). Types and evaluations of vibration frequencies were made with potential energy distribution (PED) analysis using VEDA 4 program. At the same time, the highest occupied molecular orbital (HOMO) energy, lowest unoccupied molecular orbital (LUMO) energy and other related molecular energy values of the 4-benzyl-3-(thiophen-2-yl)-4,5-dihydro-1H-1,2,4-triazole-5-thion molecule were calculated with the same theoretical calculations (Sert et al., 2014).

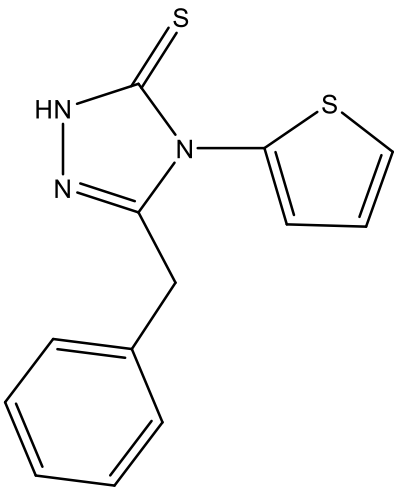

Figure 13. Structure of 4-benzyl-3-(thiophen-2-yl)-4,5-dihydro-1H-1,2,4-triazole-5-thion molecule (Sert et al., 2014)

Optimization study was carried out for the synthesis of 1,2,4-triazole-Schiff base derivatives. The reaction was carried out for a certain time in a microwave reactor using solvents such as ethanol, methanol or THF. By monomode microwave reactor in water, parameters such as temperature, time and solvent were changed to ensure that the reaction efficiency was at a high rate. The structures of the synthesized 1,2,4-triazole-Schiff base derivatives were characterized by FT-IR, NMR and MS. To determine the molecular geometry, electronic properties and chemical reactivity of the synthesized compounds were theoretically made DFT (density functional theory) and AIM (atoms in molecules) studies (Mermer & Boulebd, 2023).

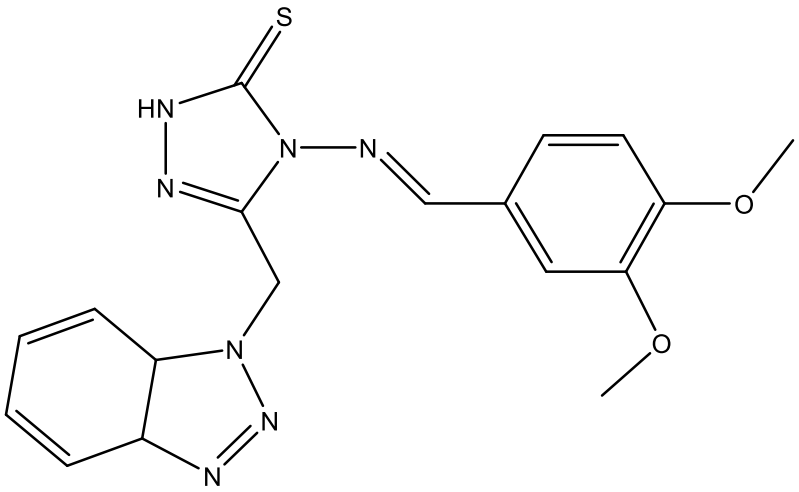

Figure 14. Structure of 1,2,4-triazole-Schiff base derivative (Mermer & Boulebd, 2023).

Various tautomers of 3-amino-1,2,4-triazole were calculated by FT-IR and FT-Raman spectrometry combined with quantum chemical theoretical calculation using PCM solvent model and normal mode analysis. Significant wavelength difference and Raman density patterns in solids and different solvents were obtained. Utilizing these data, NNH···N≤ on the five-membered N-heterocyclic ring is induced by hydrogen bond perturbation through hydrogen bonds. Thanks to the ground state proton transfer reaction mechanism in the five-membered N-heterocyclic ring, it was determined that there is intermolecular hydrogen bonding between the 3AT and protonic solvent molecules (Meng et al., 2018).

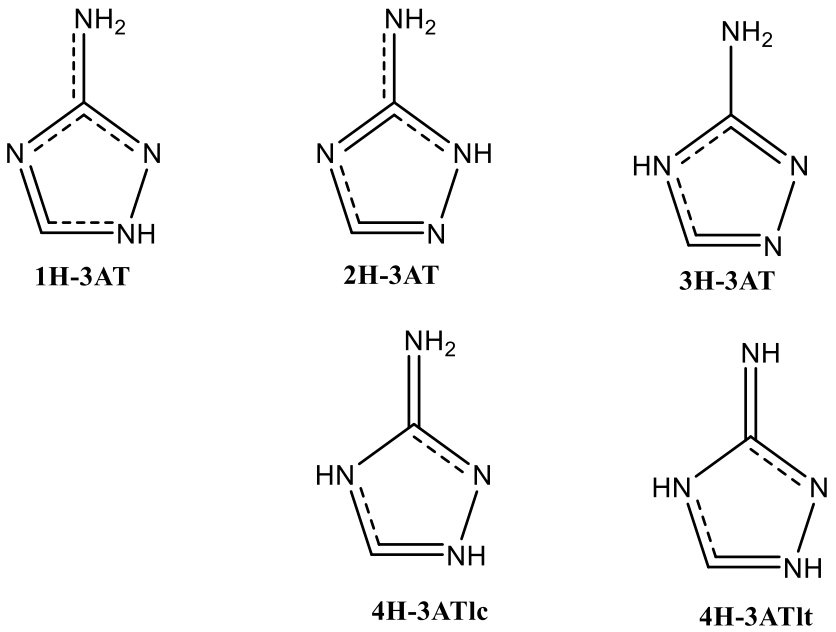

Figure 15. Various tautomers of 3-amino-1,2,4-triazole (Meng et al., 2018)

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PROPERTIES OF CHIRAL 1,2,4-TRIAZOLES

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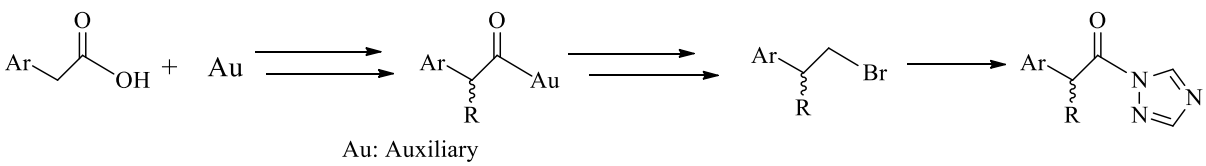
Properties of Chiral 1,2,4-Triazoles

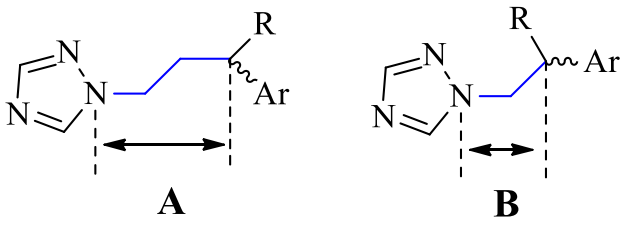
Chirality is generally a very popular feature that works in many fields. It is an important factor in the chemicals used in agriculture, especially in the field of pharmacy and in many areas of our lives. The reason for this is that the system in which life exists is very closely related to chirality. Many biologically active substances, whether synthetic or natural, have chiral structures. In addition, the triazole derivative has a wide range of studies in many compounds. In this section, a study is presented about what features these two very special structures have when they come together.

The triazole compounds belonging to the group of demethylase inhibitor (DMI) fungicides represent a large and important well-known fungicide species used in agriculture to control a wide variety of fungi in fruits and vegetables. Penicillium digitatum is one of the most common pathogens causing green mold rot in Citrus species and can be found in many parts of the world. In the study, both the in vitro antifungal activities of the chiral *β*-arylalkyl-1*H*-1,2,4-triazole derivative against Penicillium digitatum and the binding activity of P. digitatum (PdCYP51) to the CYP51 protein were studied. Molecular models were studied and also docking studies with chiral triazole were performed. As a result of the study, the in vitro inhibitory activities of the R- and S-enantiomers have been seen in good agreement with the suitable binding activities in cultured cells (Cao et al., 2011)

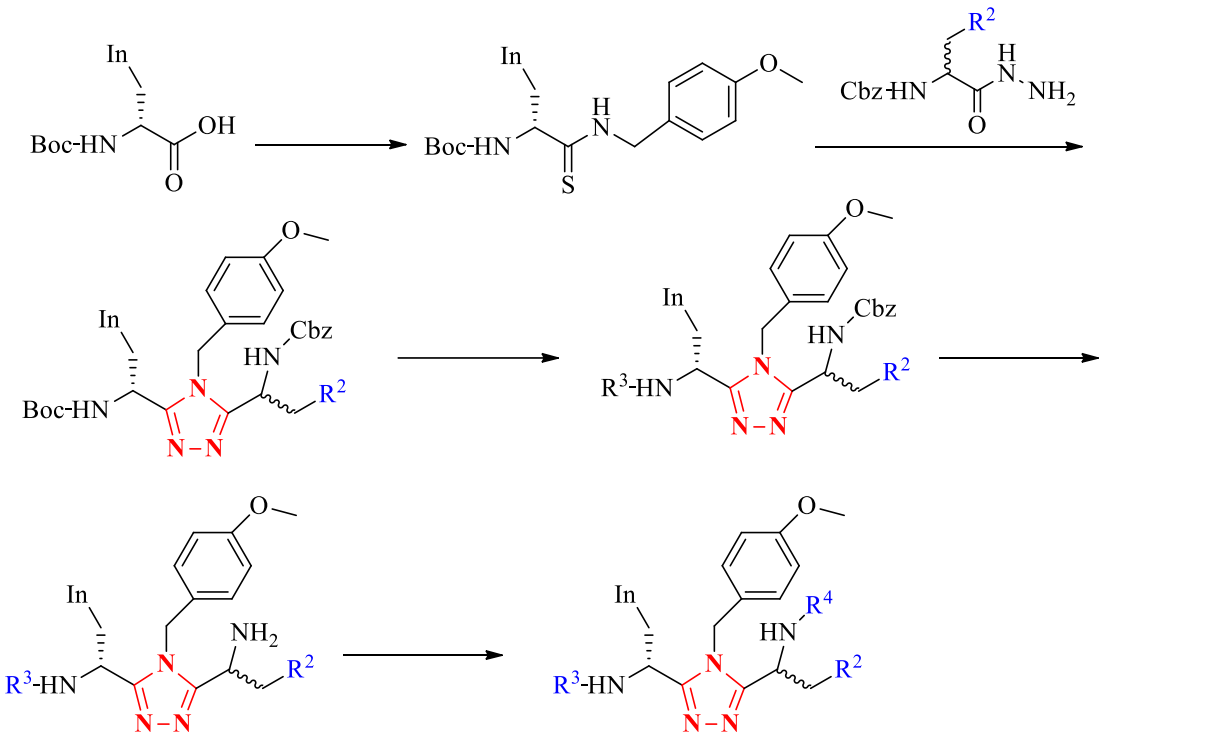


Au: Auxiliary

As a result of the study, it is estimated that the chiral β-arylalkyl-1*H*-1,2,4-triazole derivative B series shows better activity than the chiral *r*-aryl-1*H*-1,2,4-triazole derivative A. These two series of chiral triazole derivatives are similar in chemical structure and differ only in the length of the alkyl chain between the aryl group and the triazole moiety (Cao et al., 2011).

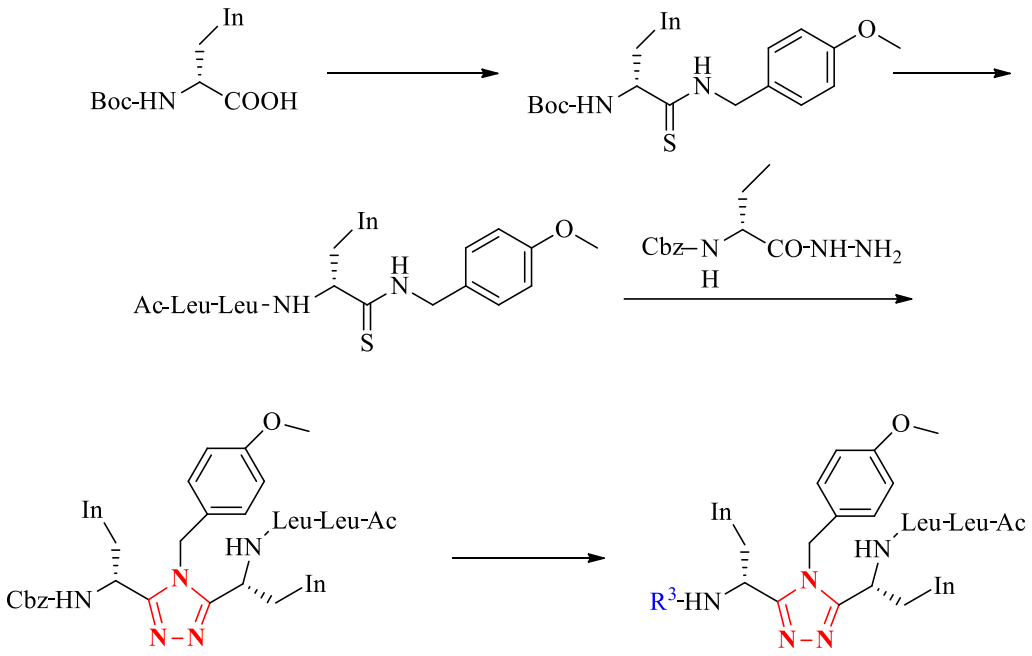


In a cyclic AMP response element CRE-luciferase reporter gene assay, triazole-bearing compounds obtained during the study were examined for their affinity to GHS-R1a, their capacity to induce intracellular calcium mobilization, and confirmation of their agonist/antagonist character. It has been shown by compounds with an indole group as R2 that compounds with the R configuration of the new chiral center have ligands with a higher affinity than those with the S configuration of this carbon. In two functional assays, each of these agents exhibited receptor antagonistic effects. The R configuration for the new chiral center contained the best compounds in the series, providing good affinities and strong biological activity (Maingot et al., 2016).



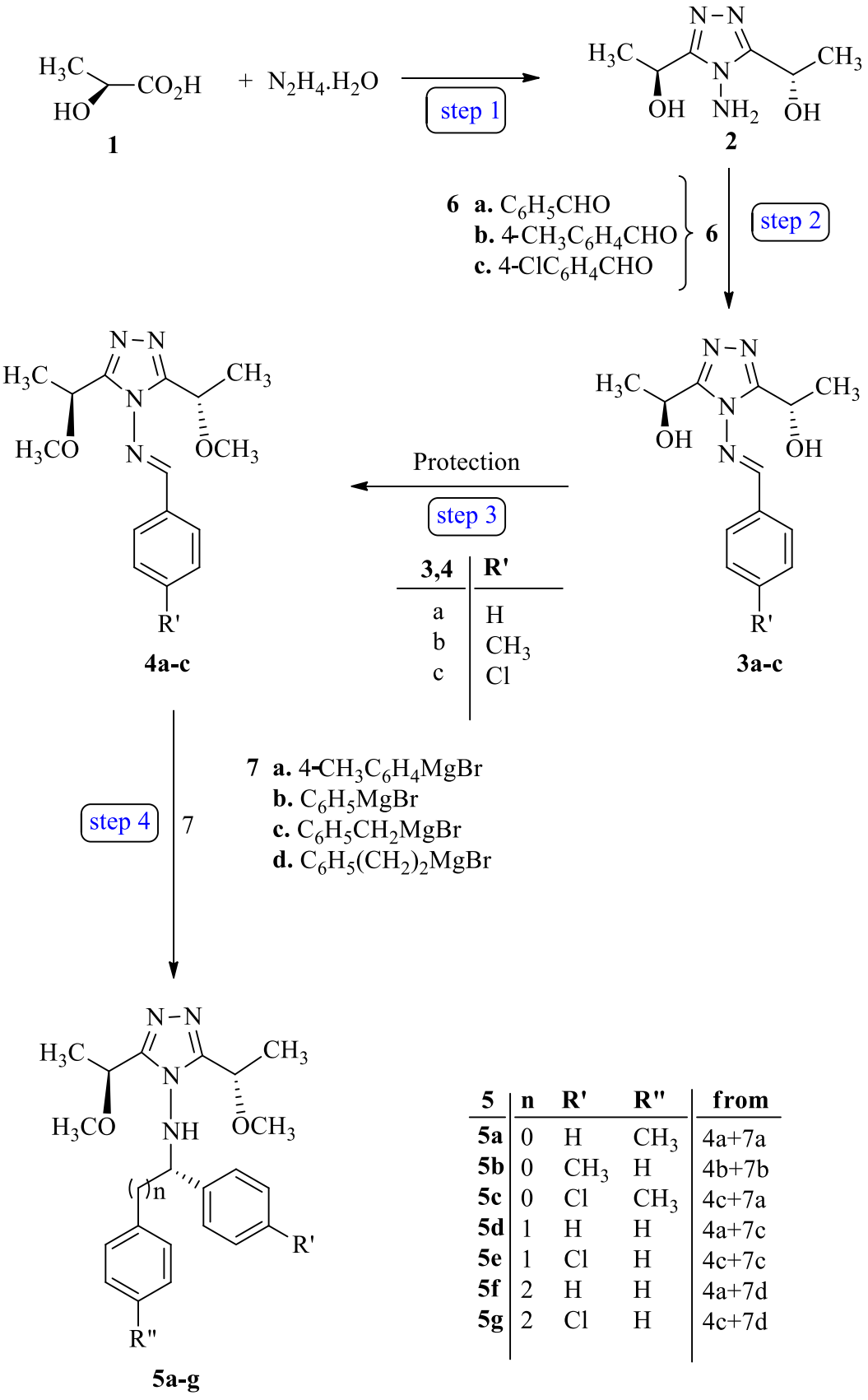
R²= Phenyl, indol
R³= Aib (pyridin-2-yl)carboxyl, 4,6-difluoro(pyridin-2-yl)carboxyl, 3,4-dihydro-2H-pyran-6-carboxyl, 2-hydroxylacetyl, (s)morpholine-2-carboxyl
R⁴=CHO, CH_3CO

In the continuation of this study, the corresponding tripeptide containing a thioamide bond with the 1,2,4-triazole structure was obtained and six different acylating groups were included in its N-terminal part. Then, the reactions were carried out with appropriate structures to reach the target compounds. As a result of the study, the following evaluations can be made; The possibility has been observed that the incorporation of a second chiral center at position 3 of the 1,2,4-triazole scaffold may result in potent ligands offering good to high affinities for the receptor. The presence of an amino function in the chiral center led to the extension of the C-terminal portion of the molecule and the incorporation of the Leu-Leu dipeptide sequence, which is included in the identified potent inverse agonists. In short, it has been seen that the trisubstituted 1,2,4-triazole scaffold carrying a second chiral center may be an alternative for generating more diverse molecules and obtaining high affinity ligands (Maingot et al., 2016).



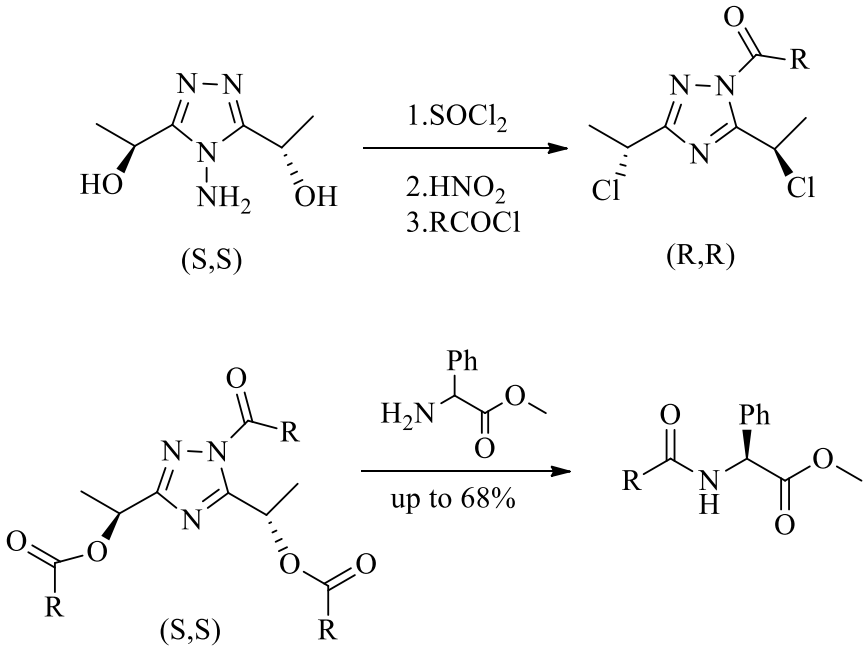
R^3= Aib (pyridin-2-yl)carboxyl, 2-hydroxylacetyl, (s)morpholine-2-carboxyl, 2-Hydroxyl-2-methylpropionyl, Isonipecotyl, Lys.

Here, the use of this new C2-symmetric triazole as a chiral aid for the nucleophilic1,2-addition reaction of Grignard reagents to the CN double bond of hydrazone 4 is reported. Protection of the free hydroxyl groups is successfully accomplished by reacting the hydrazones 3 with sodium hydride and methyl tosylate using DMF as solvent, to generate the corresponding protected chiral hydrazones 4 in excellent yields 88-98% (Katrizky et al., 1996).

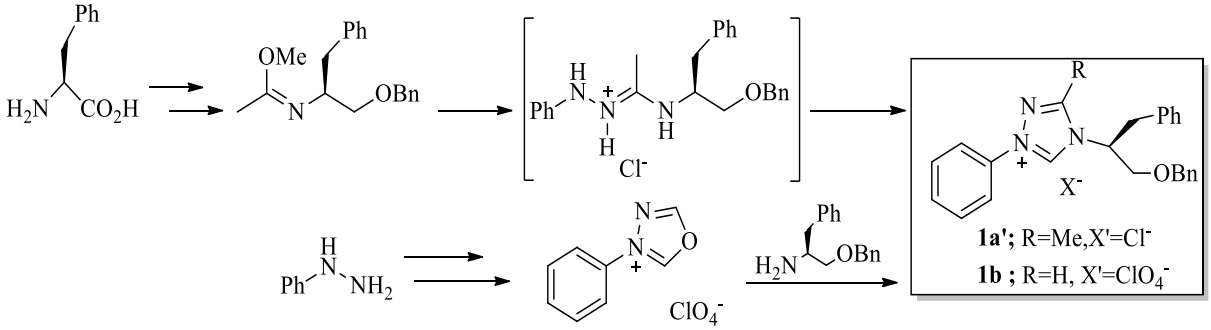


5	n	R'	R''	from
5a	0	H	CH_3	4a+7a
5b	0	CH_3	H	4b+7b
5c	0	Cl	CH_3	4c+7a
5d	1	H	H	4a+7c
5e	1	Cl	H	4c+7c
5f	2	H	H	4a+7d
5g	2	Cl	H	4c+7d

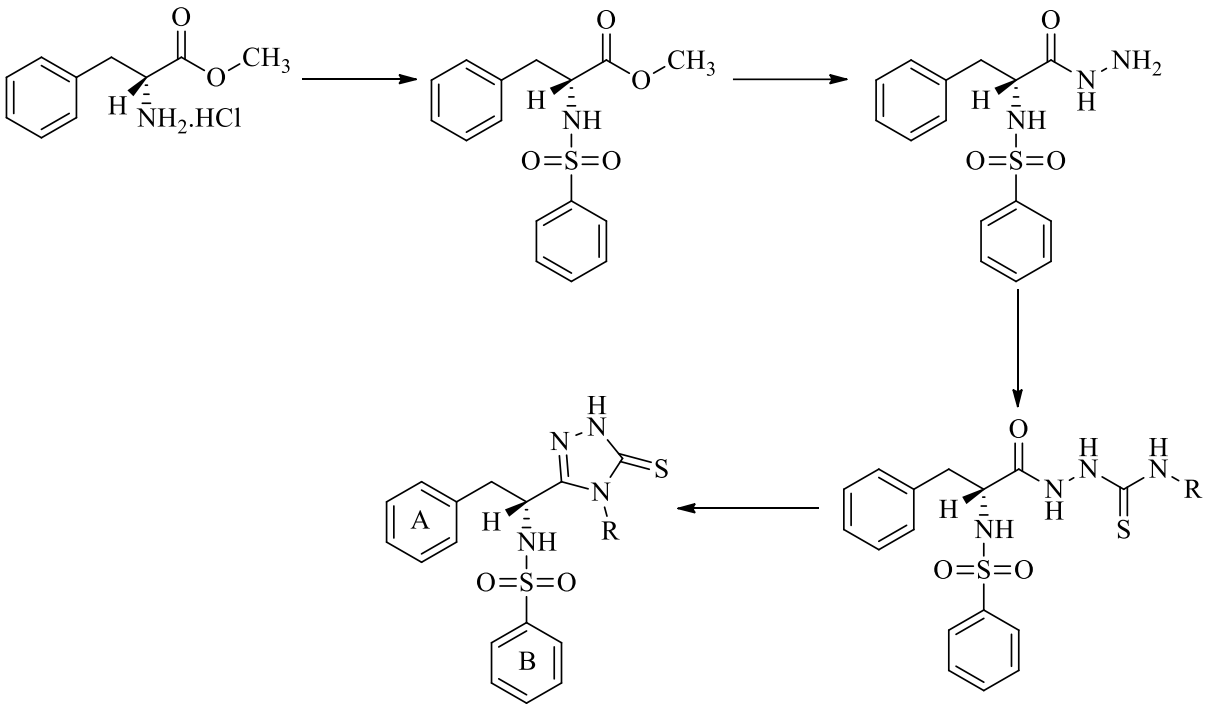
Chiral 1,2,4-triazoles are encouraging reagents for chiral acylation; In the study given below, a good yield of enantiomeric excess is achieved for triazole compounds.This study also revealed stereospecific control of the amino group upon substitution of a beta hydroxy group with thionyl chloride (Katritzky et al., 2010).



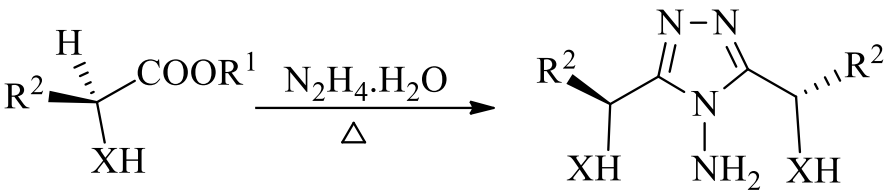
Chiral 1,2,4-triazolium NHC salt precursors Ia' and Ib are presented in another study to demonstrate the benefits of chiral 1,2,4-triazole derived compounds and their potential as catalysts in stereoselective reactions (Strand et al., 2012).



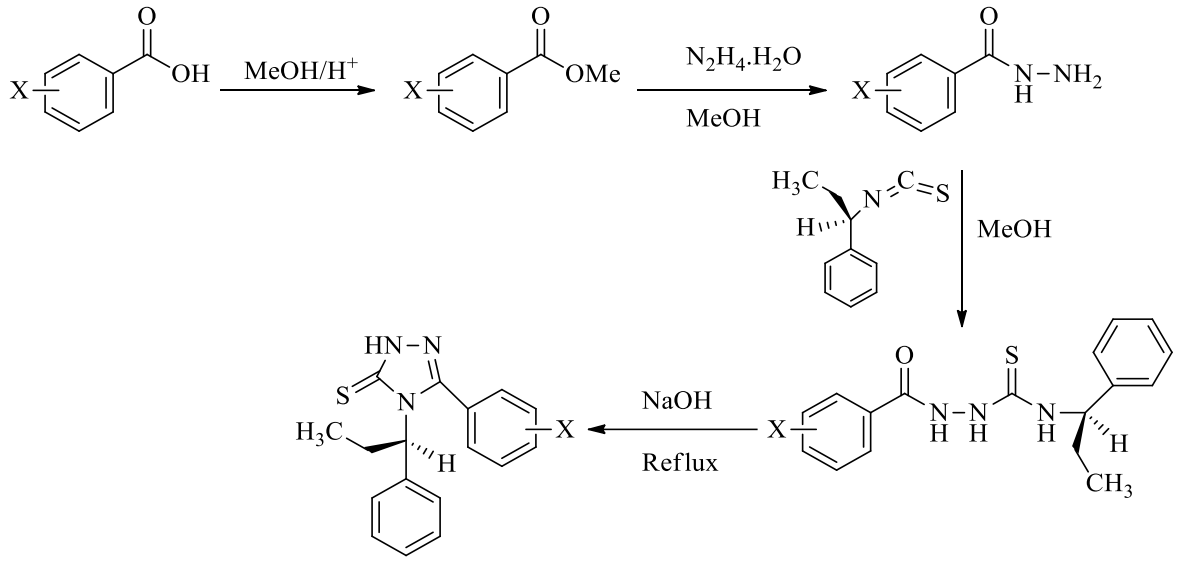
The combination of chiral N-sulfonylated α-amino acid group with a 1,2,4-triazole-3-thione core was designed in studies on the development of new effective and broad-spectrum homochiral compounds that can be used for the treatment of viral infection (Başaran et al., 2016).



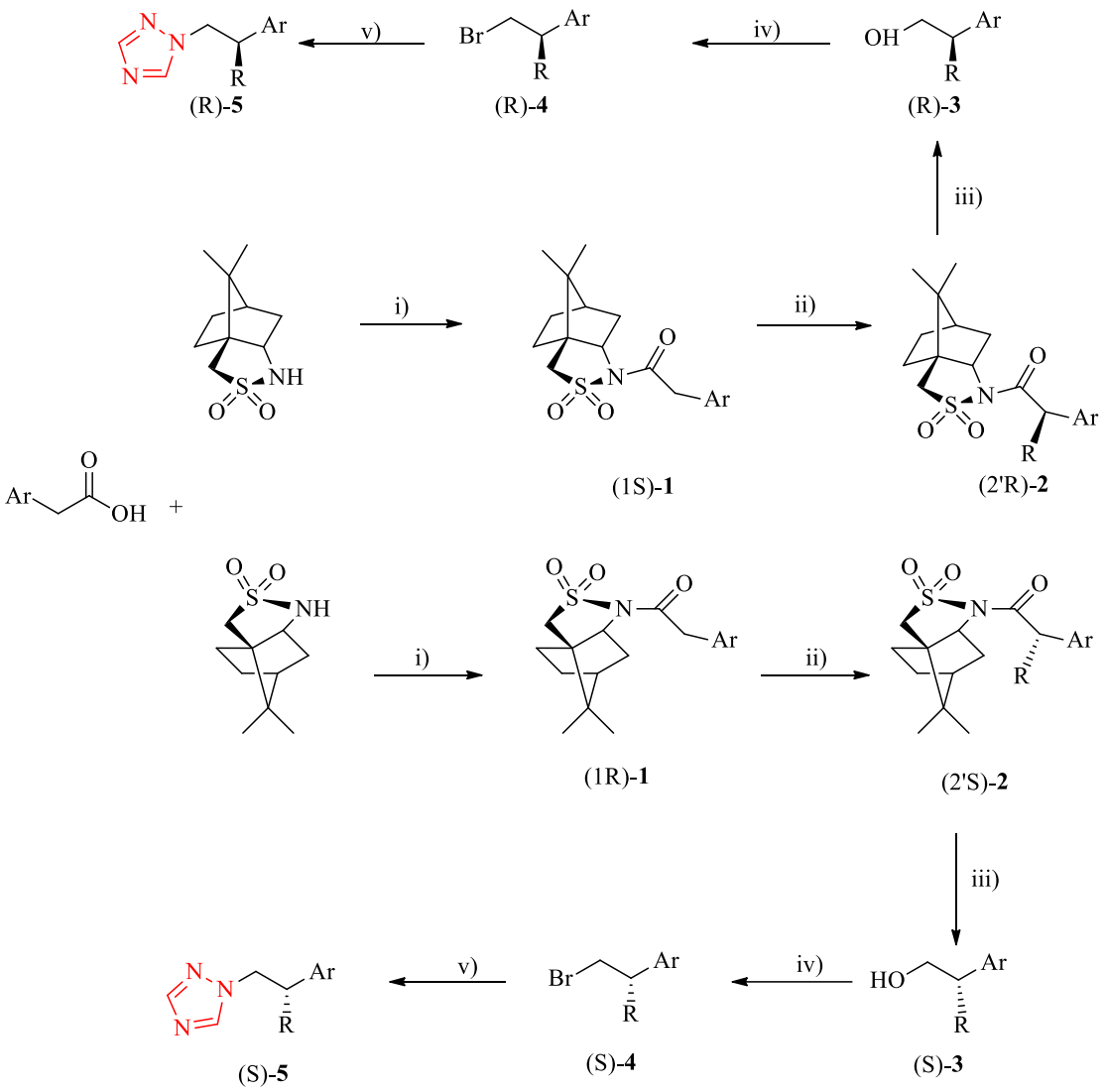
A few novel chiral synthons established on the 4-amino-1,2,4-triazole moiety have been arranged by the condensation reaction of optically active α-hydroxy- and α-aminoacids with hydrazine (Martínez-Díaz et al., 1994)



When a chiral drug interacts with a chiral receptor site; the two enantiomers of the drug interact differently and might caus to varied impacts. In this regard, studies have been conducted to examine the synthesis of some chiral 5-aryl-4-(1-phenyl)propyl-1,2,4-triazol-3-thiones in terms of their urease inhibition and antimicrobial activity properties (Serwar et al., 2009).

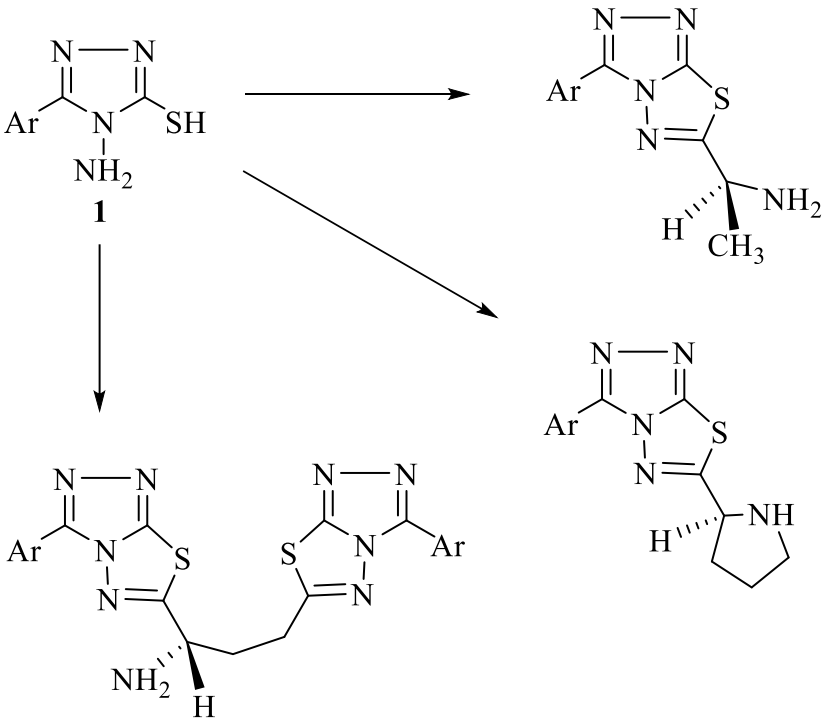


A number of chiral triazole derivatives have been synthesized as potential antifungal agents. In these studies, the compounds were obtained with very high yields. As a result of the studies, most of the synthesized compounds showed significantly higher fungicidal activities than the commercial agent triadimefon against Fusarium oxysporium, Dothiorella gregaria, Botrytis cinereapers, Colletotrichum gossypii, Rhizoctonia solani and Gibberella zeae species. Again in these studies, some enantiomers were found to show significant differences in activity (Lu et al., 2011).

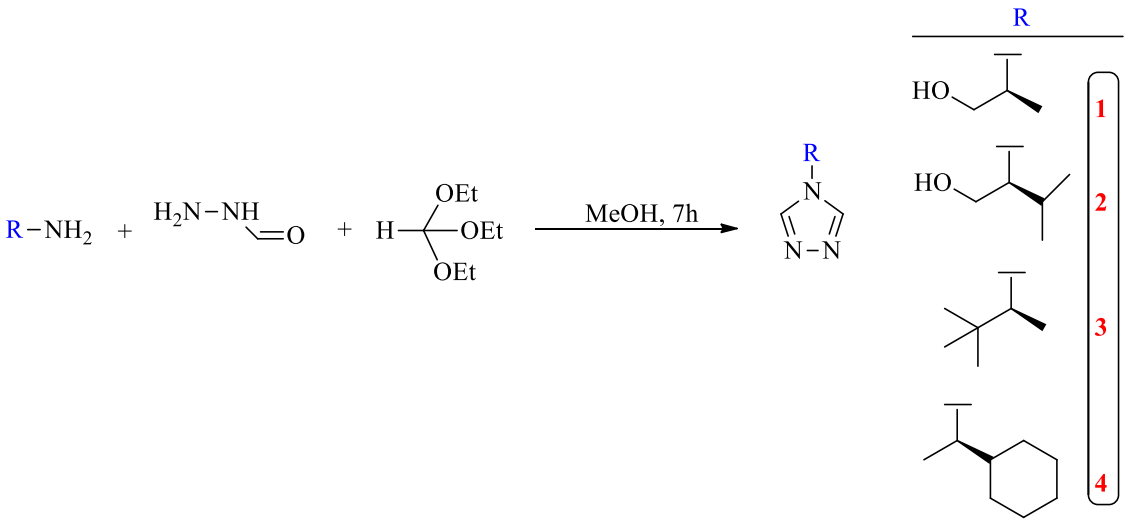


i) 1. Et_3N; 2. Me_3CCOCl, toluene, 80-110°. ii) 1.BuLi, THF, -78°; 2. hexamethylphosphori triamide (HMPA)/RX (MeI, PrI, BuI, $PhCH_2Br$, $CH_2=CHCH_2Br$). iii) $NaBH_4$, aq, THF. iv) HBr. v) 1H-1,2,4-Triazole, K_2CO_3, MeCN, reflux, 5-7h.

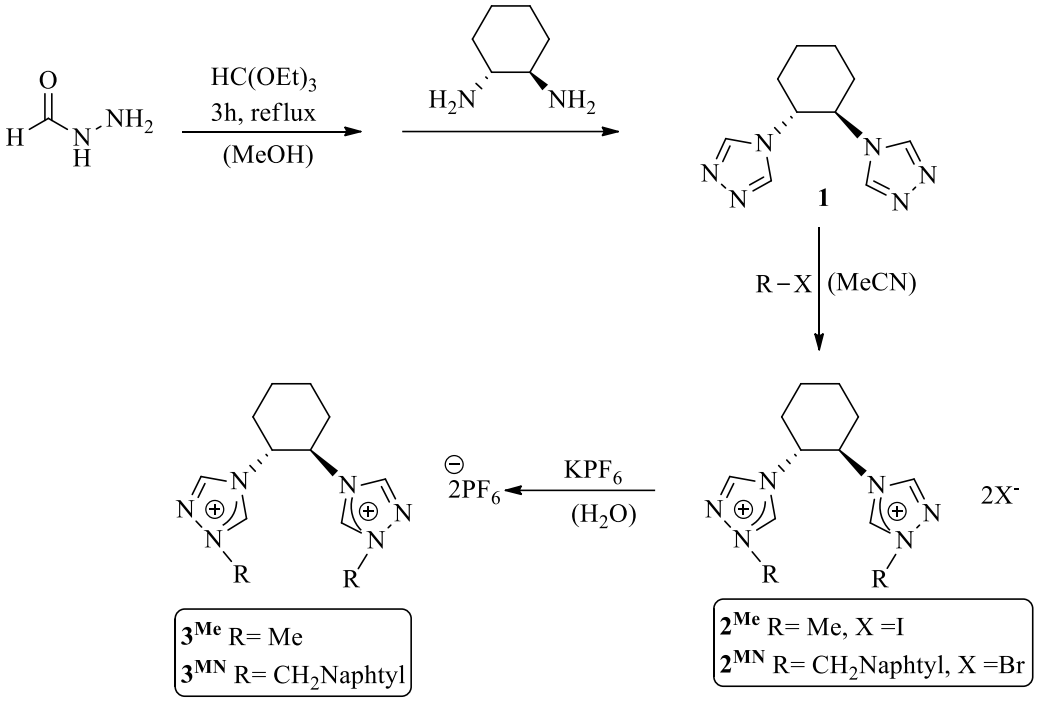
The effect of stereospecificity is a well-known fact in the biological activity of enzyme inhibitors and drug efficacy in compounds that bind to receptors. In recent years, nitrogen-containing heterocyclic compounds have received great attention due to their biological activities. Likewise, S-Triazoles and 1,3,4-thiadiazoles are also widely used. They are known to exhibit a wide spectrum of biological activity. In this study, some new compounds were synthesized to examine the relationship between stereochemistry and the performance of antibiotics. Antibacterial studies of the compounds have been done and it has been seen that it gives positive results when compared to penicillin as standard (Shi et al., 2001).



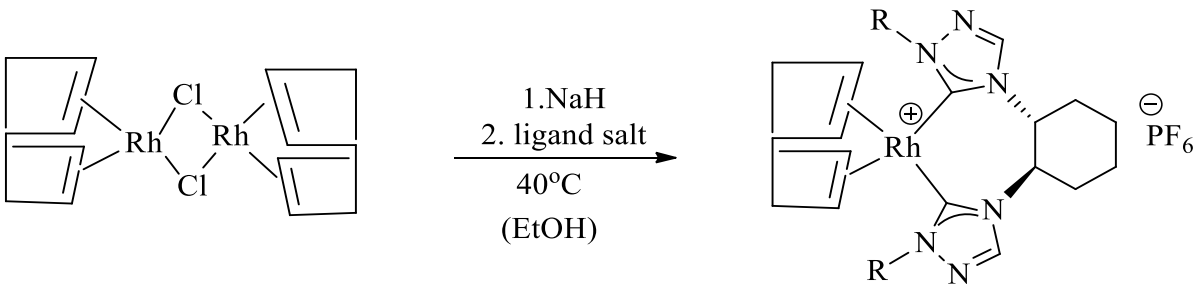
1,2,4-Triazoles also appear as drugs and ligands that are actively used to form coordination structures. Elaboration of pharmaceutically important homochiral molecules, studies for medical applications, and synthesis of stereoselective catalysis, chiral ligands is a crucial step for the construction of advanced materials. Therefore, in this study, its characteristic chiro-optical properties were investigated and its suitability for the elaboration of chiral exchangeable nanoparticles and composites and for the magnetic stereoselective detection of alcohols was investigated (Gural'skiy et al., 2017).



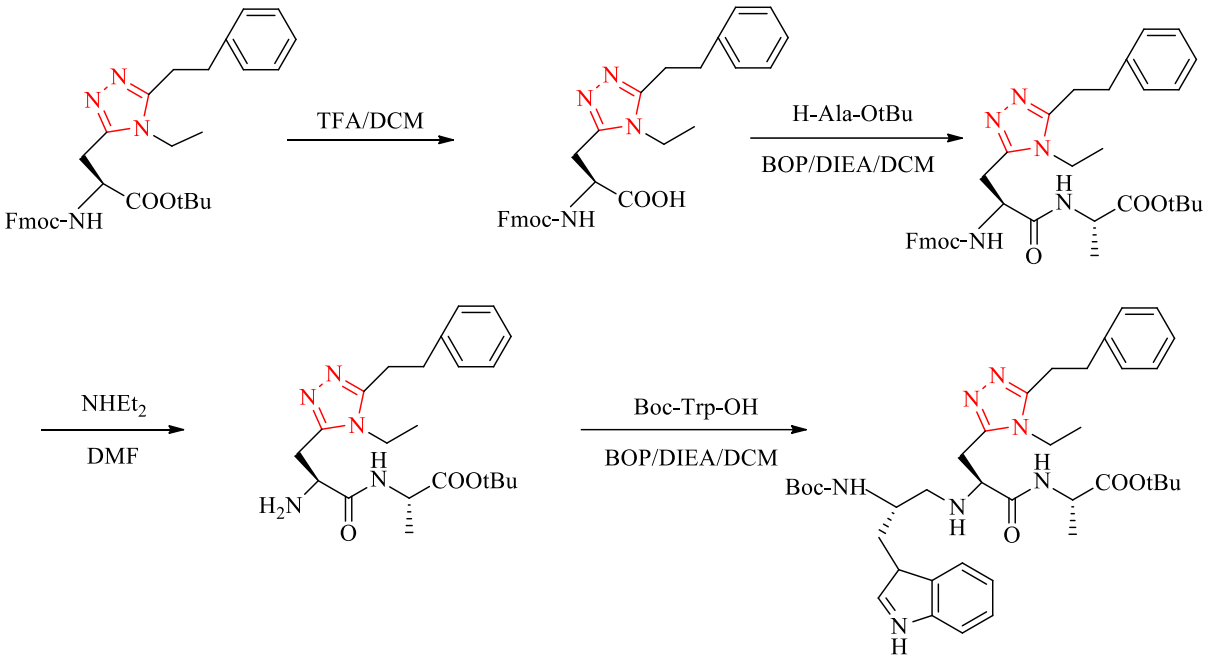
In this part, a study was carried out to obtain chiral bistriazolium salts starting from chiral R,R-(-)-1,2-diaminocyclohexane. They have been successfully applied as enantioselective catalysts for the hydrogenation of prochiral olefins in good yields.



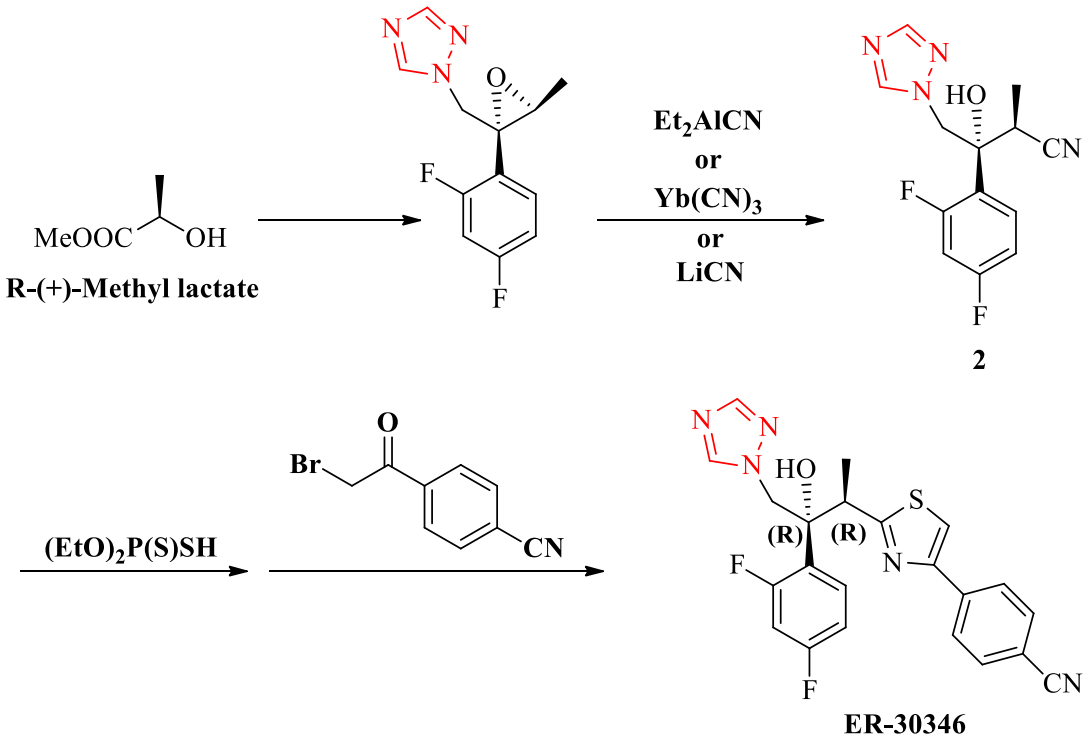
In the continuation of this synthesis, two new chiral biscarbene rhodium(I) complexes were obtained. The properties of the new chiral ligands and their suitability for various catalytic applications are being investigated (Riederer et al., 2011).



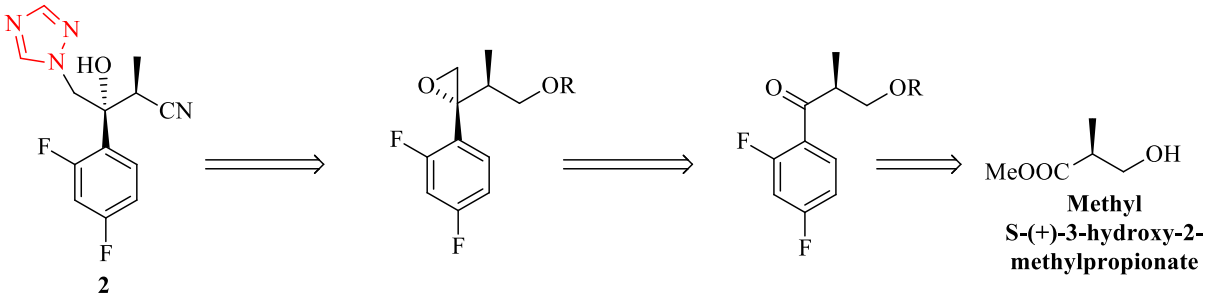
It was obtained by using N- and C-protected aspartic or glutamic acids in the synthesis of unnatural α-amino acids containing 3,4,5-trisubstituted 1,2,4-triazole heterocycles in their side chains. Through this study, it was found that it is possible to produce amino acids containing 1,2,4 triazole rings. It seems possible to synthesize many more new compounds with a wide variety in this structure.(Blayo et al., 2011).



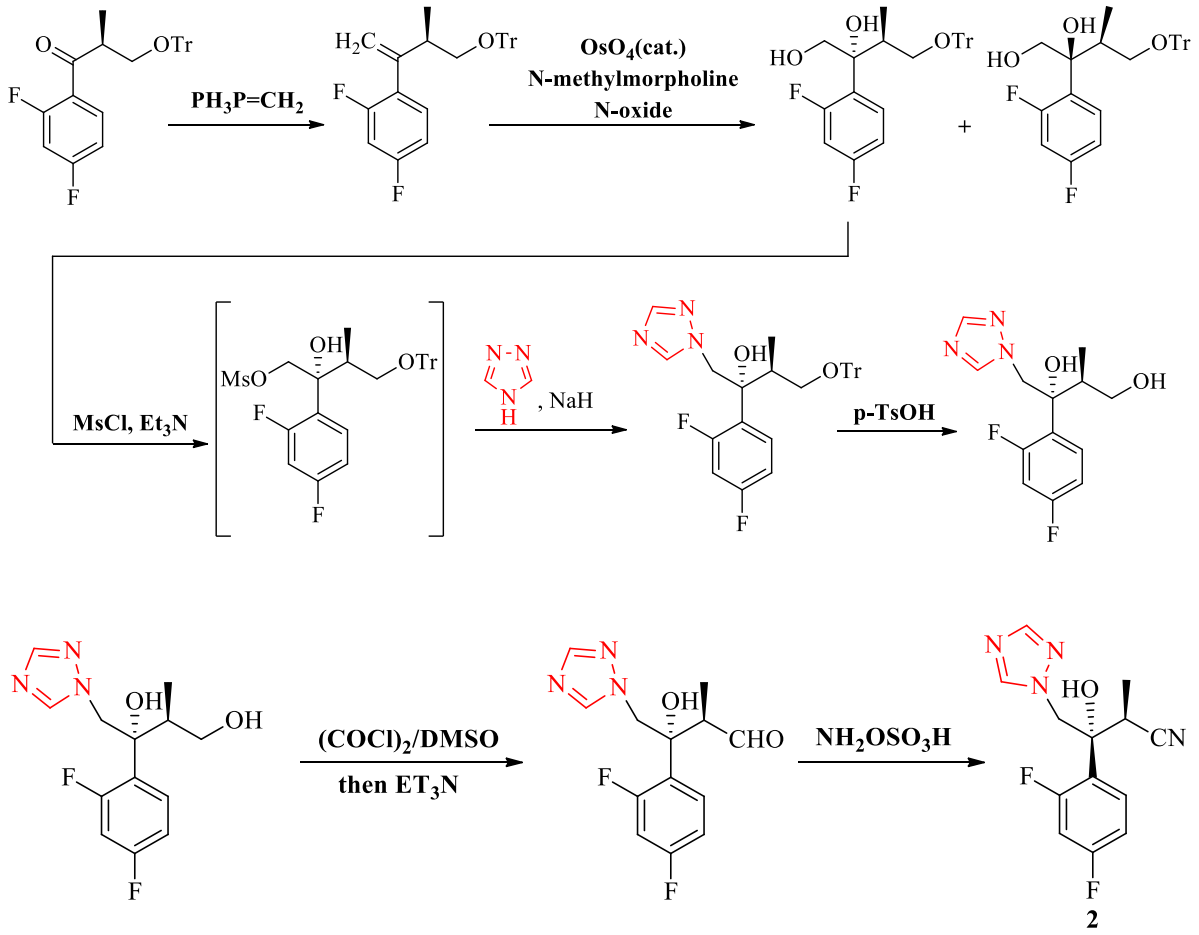
As another example of a study involving triazole groups, we can give the following; We can give a new synthetic route for compound 2, an intermediate for obtaining ER-30346, a triazole antifungal agent, from a commercially available chiral compound, methyl S-(+)-3-hydroxy-2-methylpropionate (Kaku et al., 1998).



As mentioned in the previous paragraph, we chose commercially available methyl S-(+)-3-hydroxy-2-methylpropionate as the chiral starting material. A retrosynthetic analysis is shown below.



As a result of studies, a new synthetic route has been found starting from the commercially available compound to compound 2, which is a key intermediate for the new antifungal triazole ER-30346.



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QSAR STUDIES OF 1,2,4-TRIAZOLES

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QSAR Studies of 1,2,4-Triazoles

The QSAR Method

The QSAR method is an application developed using data analysis tehcniques to design new bioactive compounds especially new effective drugs. With quantitative structure activity relationship (QSAR) method, the relationship between chemical structure and biological activties can be determined by using some descriptors (Tropsha, 2010).

The quantitative structure activity relationship (QSAR) method was founded by Corwin Hansch and until today, ıt has developed, diversified (Cherkasov et al., 2014). Actually, a study of several alkaloids using equations was published by Crum-Brown and Fraser in 1868, and it is noteworthy for being the first generation description of a quantitative structure-activity connection. The study of Cantor on the narcotic activity of several substances marked the beginning of systematic QSAR. The numerous research conducted throughout the development of the QSAR approach has led to its current status. The Hammet Technique was modified in 1956 to account for the steric, resonance and polar effects of the substituent in aliphatic molecules (Muhammad et al., 2018). Nowadays, various QSAR techniques are used and QSAR has become one of the most widely used techniques to analyze the physical and biological characteristics of compounds. This method has developed over 60 year by ongoing advancements, multidisciplinary discoveries, and community-driven innovations (cherkovs et al., 2014). The QSAR models have a wide range of applications for determining the potantiel effects of chemical substances on ecological and human health. In fact, indirectly, the QSAR method is fruquently used in academic, industrial and governmen instıtutes worldwide. In addition, pharmaceutical chemistry is most significant application of the QSAR.

One of the numerous goals of QSAR studies is to predict the bioactivity of compounds by describing their physicochemical characteristics. Another goal is to evaluate and understand how a chemical reaction in a chain of substances works.

These purposes can be listed as follows.

- The production of pharmaceuticals for use in human health and agriculture is quite expensive and takes roughly 10 years (Tüzün, 2013). In other words, QSAR techniques have the potential to significantly reduce the time and effort needed for the designe of new medications.
- In drug designe processes, drug candidates are tested on experimental animals, who endure excruciating suffering. Animal experiments might be minimized using QSAR techniques.
- The chemical contamination is another serious problem. The amount of experimental investigations in industrial and pharmaceutical chemistry is decreased as a result of QSAR research (Puzyn et al., 2010).

The quantitative structure-activity relationship (QSAR) approach is computer application that link a collection of structural or property descriptors of a chemical substance to determine its biological activity.

A theoretical molecular descriptor associates topological, geometrical, and quantum chemical indices of molecules. The molecular descriptors used in QSAR/ QSPR model development are generally releated to structural and quantitative properties such as size, shape, symmetry, complexity, branching, cyclicity, stereoelectronic character of molecule (Hawkins et al., 2001). The QSAR model found process consists of data preparation, data analysis and model validation. These processes are very important for any QSAR modeling. In the first step, a molecular dataset is chosen, molecular descriptors are calculated and the QSAR technique is chosen for the statistical methods of data analysis and correlation. In the second step for QSAR model process, descriptor set is designed according to biological activity. There are several different computer programs and methods that used for this step. In all of the methods, biological activities serve as the dependent variables, while descriptors serve as the independent variables. The third step in the construction of a QSAR model, the model validation process, determines predictive potential and consequently, its capacity to define the biological activities of untested substances (Golbraikh et al., 2003).

Internal and external validation are the two different types of validation techniques utilized in QSAR models. In each stage of internal model validation, one compound from the datas set is randomly discarded, and the remaining compounds are then used to build the model. The resulting model is used to forecast the deleted compound's action. Also the effectiveness of the generated model's predictive power are evaluated via external validation (Muhammad et al., 2018)

Many computational approaches in used QSAR prosess are depend on the complexity of the data. These processes include two-dimensional (2D), three-dimensional (3D), and higher dimensional techniques. The conformational configurations of atoms in space are insensitive to 2D-QSAR, and 3D-QSAR provides knowledge about the positions of atoms in three spatial dimensions. Comparative molecular field analysis, often known as CoMFA, is a technique that uses effective 3D-QSAR models. The CoMFA method is a QSAR technique constructed to link a molecule's geometric, steric, and electrostatic characteristics with its biological functions. In 3D-QSAR methods, the active conformation is a minimal energy conformer but 4D-QSAR method is quite different from 3D-QSAR methods, The active conformer of each compound in the investigated chemical series is defined as the minimal energy conformer within the values, and all conformers are taken into consideration when calculating activity in 4D-QSAR (Tüzün 2013). In the 4D-QSAR genetic algorithms provide a collection of automatically docked orientations and conformations for each molecule.

Table 1. Various stages of QSAR model development (Veerasamy et al., 2011)

1. **Prepearing The Molecules for The QSAR Study**
- Partial charges
- Conformations
- Aignments
- Training and Test Set

2. **Calculte Values for All Descriptors for All ligands in Training Set**
- Traditional 2D
- 3D (CoMFA,CoMSIA)
- 4D-QSAR

3. **Select Descriptors**
- By Hand
- Stepwise MLR
- Simulated Annealing
- Genetic algorithm

4. Create Model Using Training Set

- Multiple Linear regression
- Principal Compenent Analysis
- Partial Least Squares
- Neural Networks

5. Validation

- (Internal, externel)

In 5D and 6D-QSAR, respectively, the fifth (protein flexibility) and sixth (entropy) dimensions are seen as the induced-fit possibilities of ligands following binding to the active site and solvation models (Veerasamy et al., 2011).

In medicinal chemistry investigations, the concept of molecular similarity is frequently used for new sentenceses. Molecules with similar properties may show similar bioactivity. In short, molecules with same chemical or structural properties generally react similarly in biological assays. It is crucial for this approach to perform that the right molecular parameters (descriptors) and analytical techniques (metrics) be chosen for the calculation of molecular similarity.

Pharmacophores are bioactive molecules used in drug design that are ordered geometrically to (at least conceptually) complement the receptor site. These configurations of molecular characteristics are thought to be important for biological activity. Pharmacophore models are typically formed from six different feature types: hydrogen-bond donors, hydrogen-bond acceptors, basic groups, acidic groups, aromatic groups, and hydrophobic groups (Glen & Adams, 2006).

1,2,4-Triazoles

1,2,4-Triazoles are aromatic heterocylic compounds with three nitrogens and two carbons

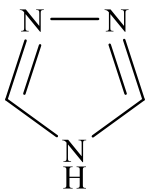


Figure 1. The Structure of 1,2,4-Triazole

According to investigations of the literature, heterocylic compounds exhibit a variety of biological features and are found in many drugs. The triazoles are substances with heterocylc structure and the ability to generate their many derivatives. For this reason, it has become the

focus of new drug candidate studies for the treatment of many diseases such as various cancer diseases (Dixit et al., 2006). For example, 1,2,4-triazol Schiff Base derivatives have demonstrated anti-fungal (Odds et al.,1985; Chai et al., 2011), anti-microbial (Çiftçi et al.,2018; Manap, 2022), anti-oxidant (Kardaş et al., 2016), activities; methal based triazole derivatives have demonstrated anti-oxidant, anticancer (Deswal et al., 2022) anti-fungal (Rodriguez-Fernandez et al., 2006), and anti-bacterial (Al-Radadi et al., 2020; Sumrra et al., 2020), anti-tümör (El-Metwaly et al., 2020). In addition , triazol and its derivatives are found in a variety of medications, including alprazolam, trazodone (an antidepressant), rizatriptan (an antimigrane medicine), and hexaconazole (an antifungal medication) (hyptonic, sedative and tranquilizer drug) (Lass-Flörl, 2011).

Some QSAR Studies of 1,2,4-Triazoles Derivatives

In reported study, 1,2,4-triazole-5-substituted carboxylic acid bioisosteres were synthesized and tested for in vitro URAT1 inhibitor activity (IC50) by the using 3D-QSAR method. This study results especially shown that all of 19 new triazole compounds, N-(pyridin-3-yl)methanesulfonamide derivative of triazole displayed highly potent URET 1 inhibitor for treatment of gout diseas (Wu et al., 2019).

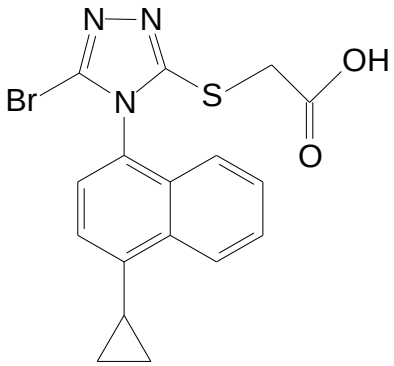


Figure 2. Lesinurad (structure of approved URET1 inhibitor) (Wu et al., 2019).

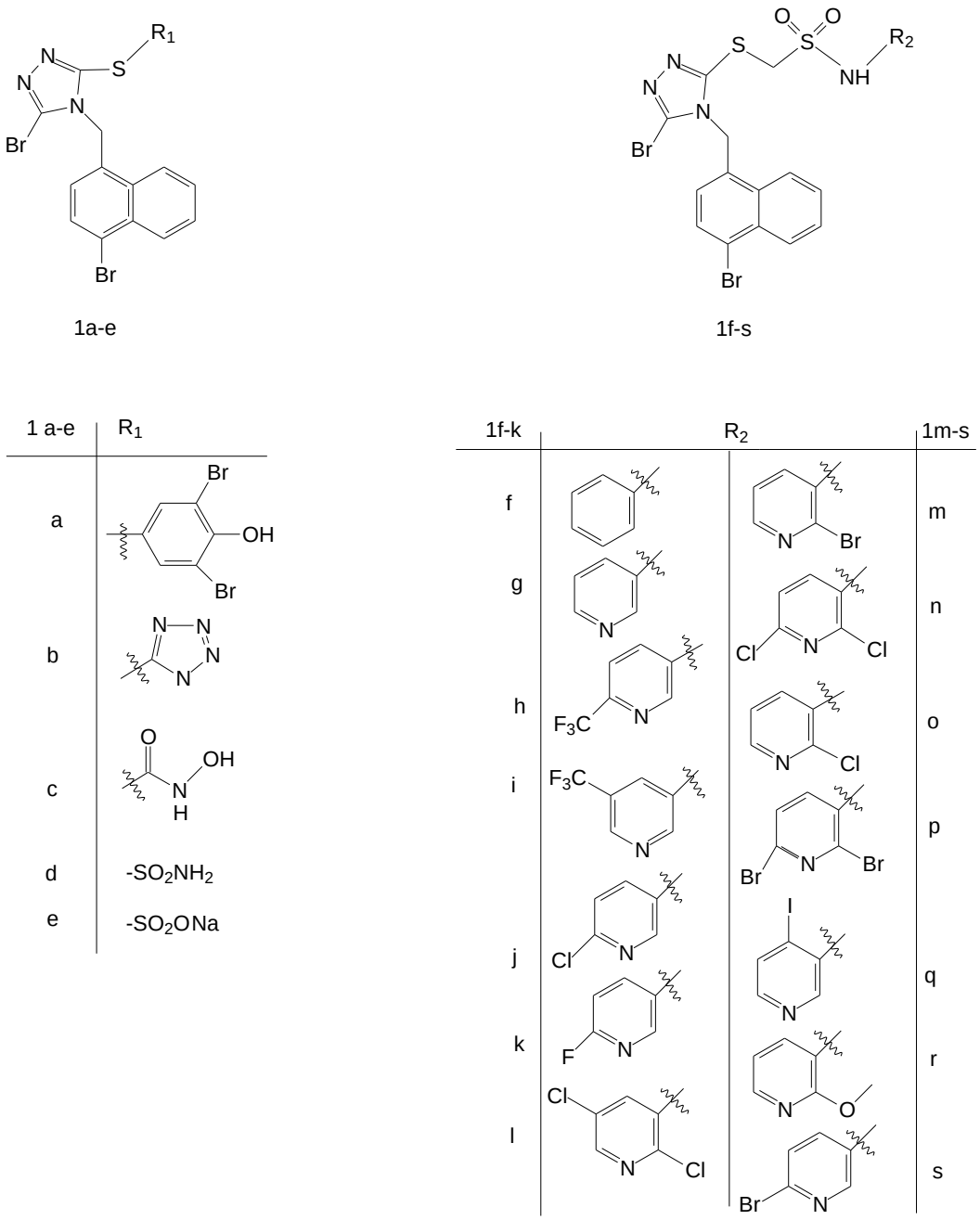


Figure 3. Structures of 1a-e and 1f-s compounds synthesized in study (Wu et al., 2019)

In "A revıew synthesıs, evaluatıon and qsar study of substıtuted 1, 2, 4-trıazole nucleus" study, Singh et al. collected data of triazole derivatives and investigated QSAR analysis. The QSAR regression data were obtained to predict the anticancer biological activity against the human pancreatic cancer cell line (Panc-1) of 1,2,4-triazole derivatives. According to obtained results, triazole compounds with different R grup may be used as descriptor for the development of predictive QSAR models (Singh et al., 2020).

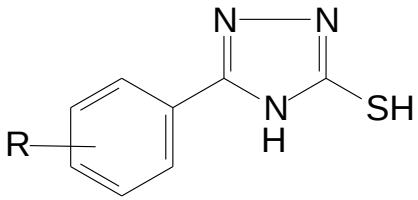
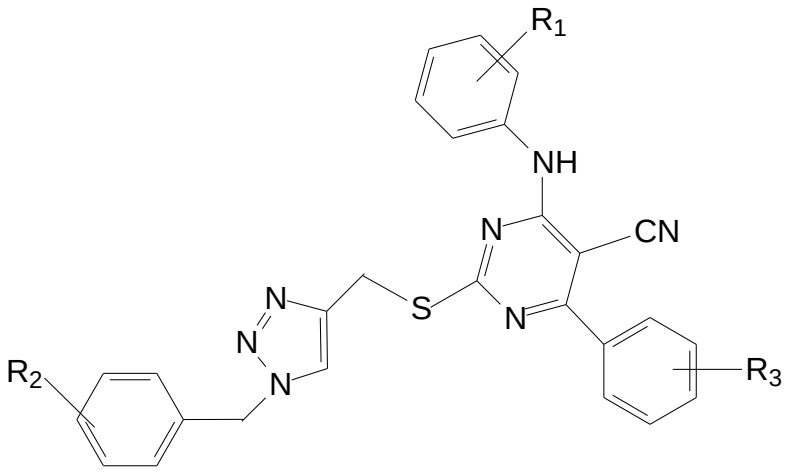


Figure 4. Structure of 1,2,4-triazole-3-thiol derivatives containing different R group (Singh et al., 2020).

Adegoke et al. synthesized 1,2,3-triazole-pyrimidine derivatives and investigated anticancer activities of 1,2,3-triazole-pyrimidine derivatives against human esophageal carcinoma (EC-109) by using the DFT-QSAR method. The results obtained from QSAR method were compared with experimental values. The evaluated results shown that the experimental and predicted inhibition efficiency (IC 50) of 1,2,3-triazole-pyrimidine gave good correlation results for generated a novel QSAR model equation for human esophageal carcinoma (EC-109) through multiple linear regression (Adegoke et al., 2020).



Compounds	R_1	R_2	R_3	Compounds	R_1	R_2	R_3
1	*p*-OCH_3	*o*-Cl	H	11	*o*-CH_3	*o*-Cl	H
2	*m*-CF_3	*o*-Cl	H	12	*o*-F	*p*-CH_3	H
3	*o*-Cl	*o*-Cl	H	13	*p*-CH_3	*p*-CH_3	H
4	*p*-Cl	*o*-Cl	H	14	*o*-Cl	*p*-CH_3	H
5	*m*-Cl	*o*-Cl	H	15	*p*-CH_3	*o*-Cl	H
6	*o*-OCH_3	*o*-Cl	H	16	*p*-CH_3	*o*-Cl	*p*-$CH(CH_3)_2$
7	*m*-CH_3	*o*-Cl	H	17	*o*-OCH_3	*o*-Cl	*p*-$CH(CH_3)_2$
8	*m*-NO_2	*o*-Cl	H	18	*p*-CH_3	*o*-Cl	*p*-CH_3
9	*o*-F	*o*-Cl	H	19	*p*-CH_3	*o*-Cl	*m,p,o*-triOCH_3
10	*p*-F	*o*-Cl	H	20	*p*-CH_3	*o*-Cl	*p*-Cl

Figure 5. Structure of 1,2,3-triazole pyrimidine derivatives with different R_1, R_2 and R_3 grups (Adegoke et al., 2020).

In this study, Elmchichi et al. collected the data of A, B, and C type triazole derivatives to reveal the relationship between physicochemical properties and anti-cancer effects of the compounds. The researcers randomly divided these compounds two parts as learning set, test set. After that, they studied anti-pancreatic cancer activity of compounds using QSAR method which calculates 11 different descriptor with different statistical methods (Elmchichi et al., 2020).

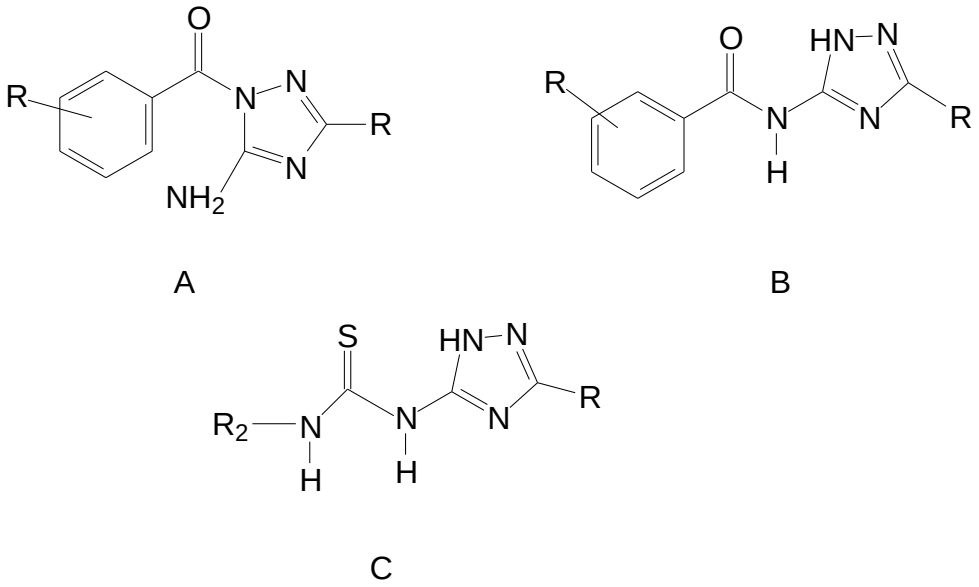


Figure 6. Structures of A, B and C type 1,2,4-triazole derivatives (Elmchichi et al., 2020)

In the "Synthesis, crystal structure and 3D-QSAR studies of antifungal (bis-)1,2,4-triazole Mannich bases containing furyl and substituted piperazine moieties" study, Yan Zhang et al., reported that a series of piperazine-containing 3-(furan-2-yl)-1,2,4-triazole Mannich bases and bis-Mannich bases were synthesized and some compound's anti-fungal activities were evaluated using the CoMFA set of 3D-QSAR method. According to data reported, steric and electrostatic field are two important factor for compound's bioactivity or deactivity (Zhang et al., 2018).

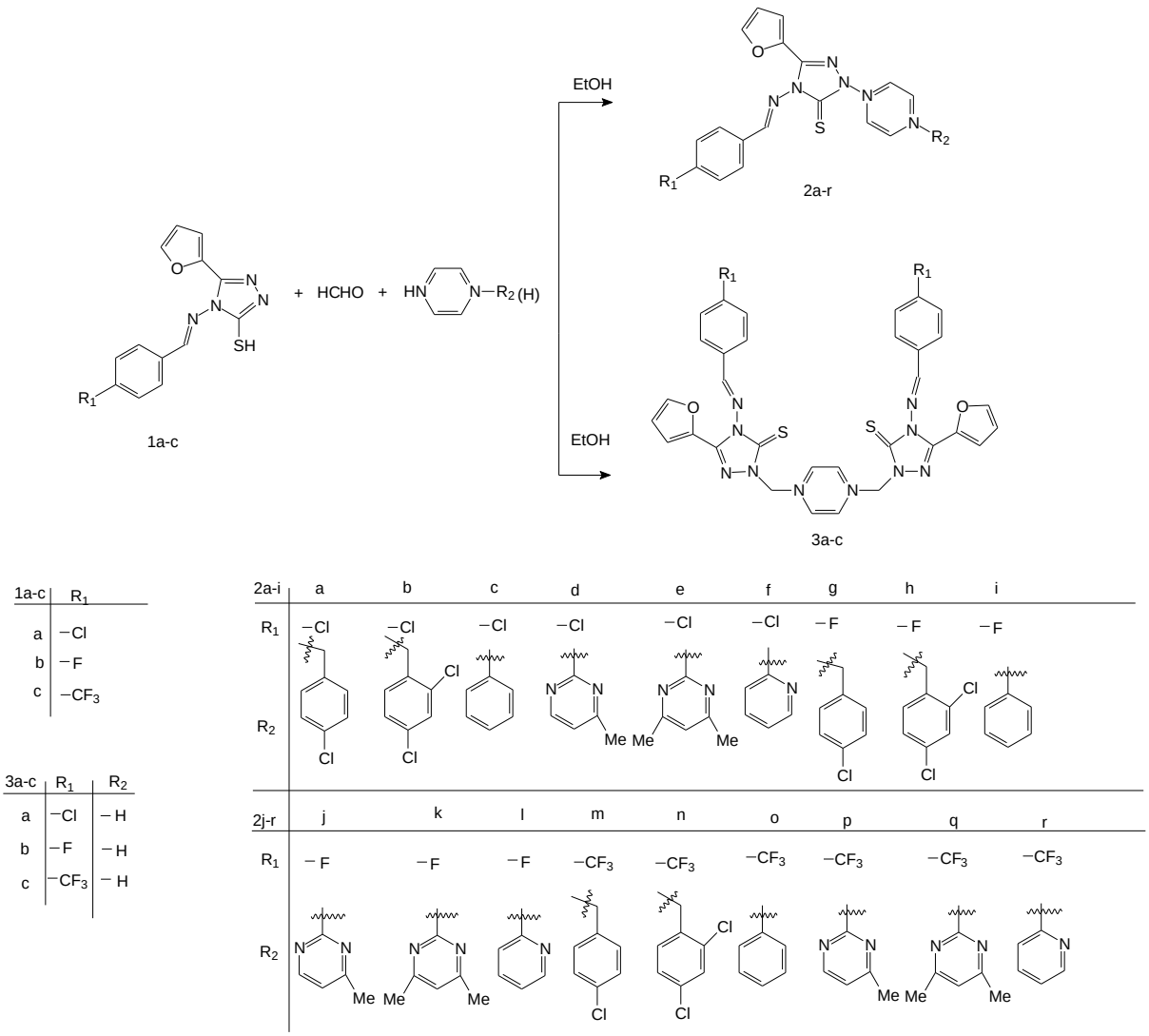


Figure 7. Structures of Schiff Bases and Mannich Bases of triazoles derivatives (Zhang et al., 2018)

In this study releated 3D QSAR method of 1,2,4-triazole derivatives, Hong-jin Tang et al. investigated to analyze the SAR for 1,2,4-triazole derivatives as XOR inhibitors by select a data set of 48 3,5-dipyridyl-1,2,4-triazole derivatives with XOR inhibitory activity from the work of Nagata Osamu et al. In this study. The steric, electrostatic, and hydrophobic fields for each compounds were obtained using (CoMSIA) model and the obtained data were evaluated especially the relationship of the in terms of the bioactivity of molecule. According to results that the steric, electrostatic, and hydrophobic fields play an important role in bioactivity of compounds (Tang et al. 2016).

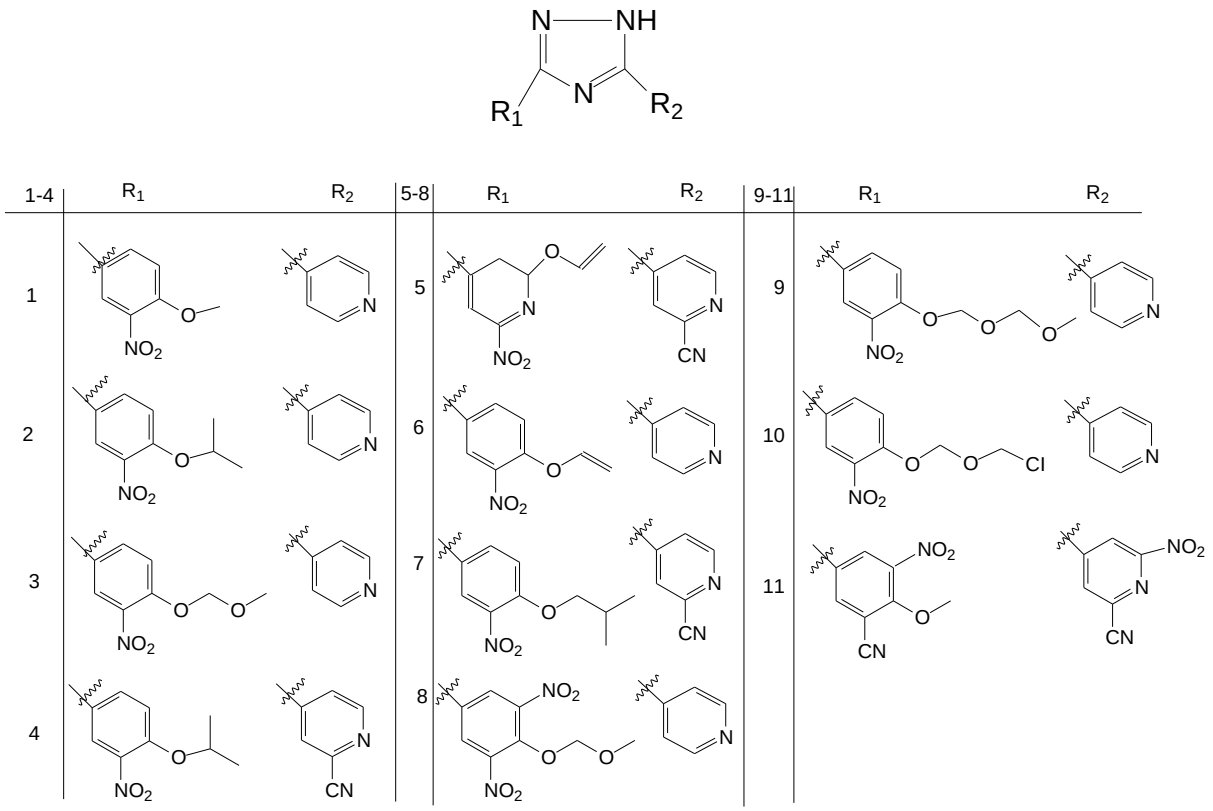


Figure 8. Structures of new designed 3,5-dipyridyl-1,2,4-triazole derivatives (Tang et al. 2016)

Mehta1 et al. used 4H-1,2,4-triazole derivatives to design of new anticancer agents by using QSAR method. In this reported work, a set of 51 molecules of 3,4,5-trisubstituted-4H-1,2,4-triazole derivatives were used for 3D-QSAR studies to designe dual tankyrase inhibitors as Wnt signaling antagonist. Two data set of triazole derivatives were used in study. First data set was training set (39 molecules) and second set was used test set (12 molecules). The data of compounds were obtained from literatüre and CoMFA, CoMSIA, and HQSAR models were applied for QSAR study. The results of study shown that QSAR methods employe for the design of different bioactive triazole derivatives (Mehta et al., 2020).

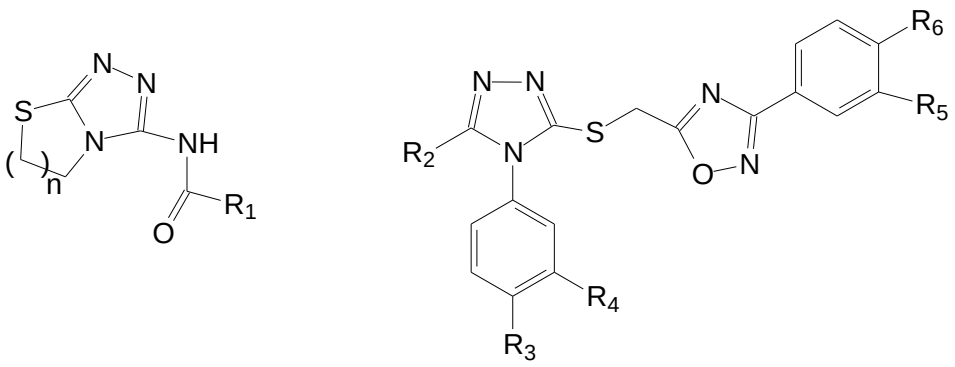
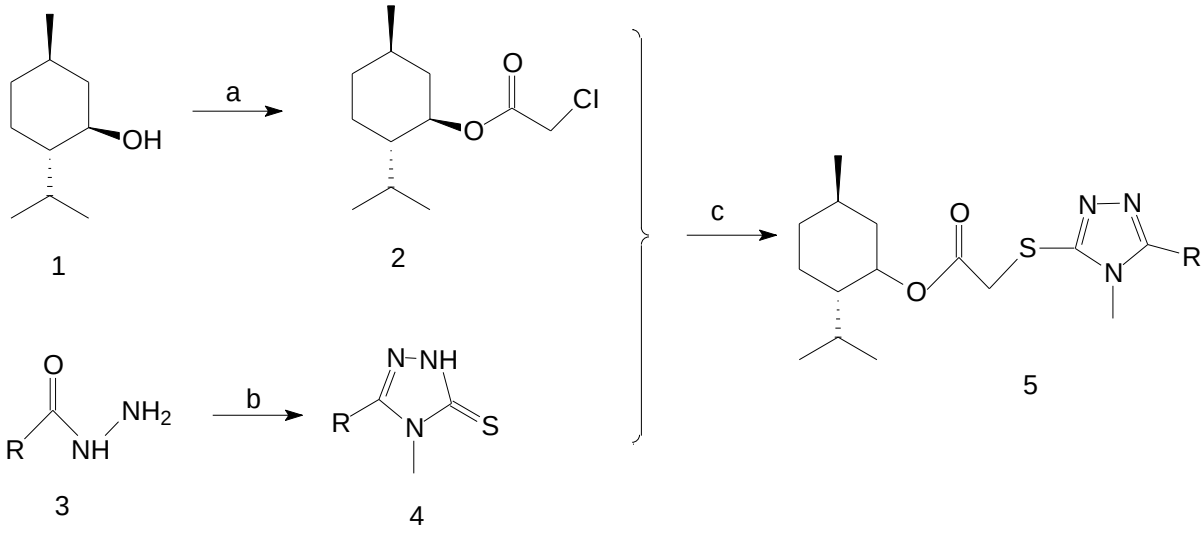


Figure 9. Training set and test set of 3,4,5-trisubstituted-4H-1,2,4-triazole derivatives (Mehta et al., 2020)

In a QSAR study of triazole derivatives, a seri of menthol derivatives containing 1,2,4-triazole-thioether were synthesized and examined anti-fungal properties against tested fungal by experimental studies. In addition, QSAR analysis studies were performed using the CoMFA /3D-QSAR method to design new antifungal compounds against fungals (Huang et al.,2021).

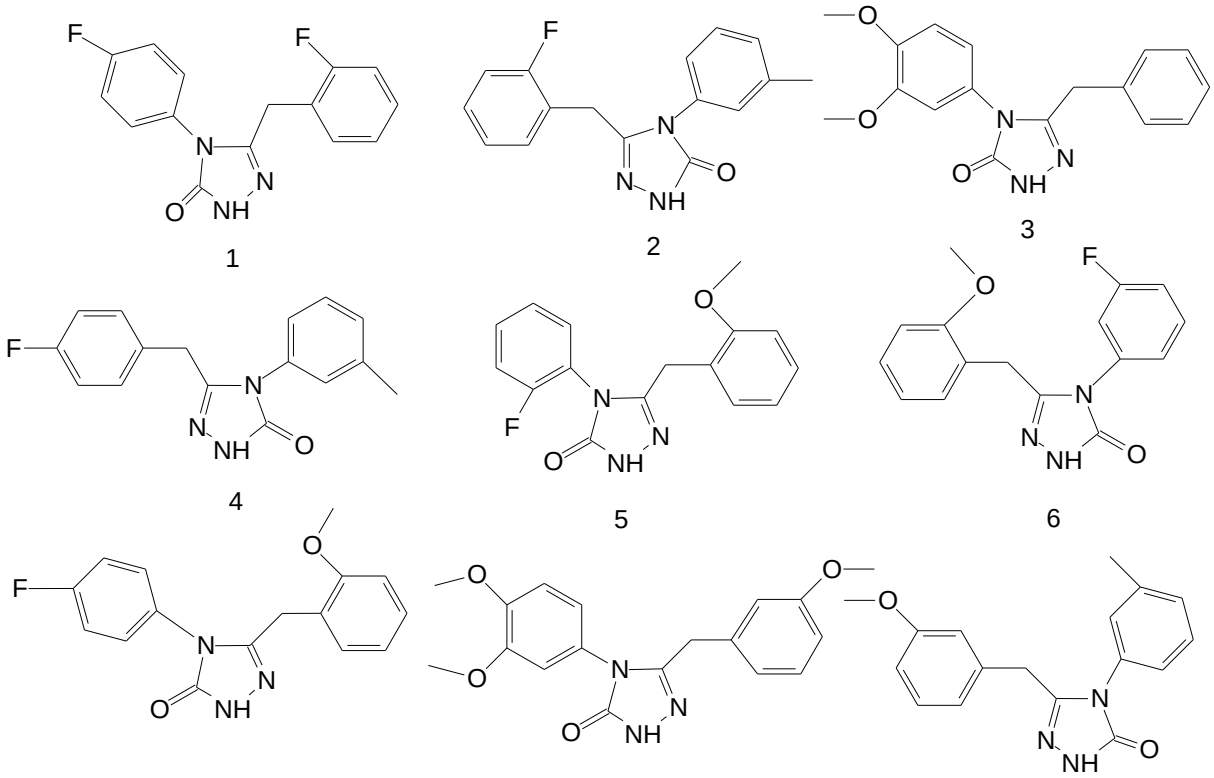


5a: R=Ph; 5b:R=o-CH_3 Ph; 5c: R=*p*-CH_3 Ph; 5d: R=o-OCH_3 Ph; 5e:R= *p*-OCH_3 Ph; 5f: R= o-F Ph; 5g: R= m-F Ph; 5h: R= *p*-F Ph; 5i: R=o-CI Ph; 5j: R= m-CI Ph; 5k: R= *p*-CI PH; 5l: *p*-Br Ph; 5m: R= o-l Ph; 5n: R= *p*-l Ph; 5o: R=o-CF_3 Ph; 5p: R= m-CF_3 Ph; 5q: R= *p*-OH Ph; 5r: *p*-OH Ph; 5s: R= o-NH_2 Ph; 5t: R= *p*-NH_2 Ph; 5u: R=p-$C(CH_3)_3$ Ph; 5v: R= m, p-OCH_3 Ph; 5w: R= m, m-OCH_3 Ph; 5x: R= α-furyl; 5y: R= α-thienly; 5z: R=β-pyridl

Figure 10. Synthesis of 5 type 1,2,4-triazole-thioether derivaties

Dahmani et al., studied to develop the a-glucosidase inhibition activity of triazol derivatives using QSAR method. The researcers built a computational model to develop a new QSAR model using different physio-chemical descriptors such as electronic descriptors (LUMO

(ELUMO) and HOMO (EHOMO) energies, partial atomic charges (q)) and topological descriptors (polarizability (Pol), molar refractivity (MR), partition coefficient octanol/water (log P), molar volume (MV), surface area grid (SAG), molar weight (MW)), geometric descriptors (solvent accessible hardness and potential). Looking at the results of study, good correlation were seemed between experimental data and predicted pIC50 values. Actually, ıt can be said that, this model can be use succesfully to predict the a-glucosidase inhibitory activity of similar triazole derivatives (Dahmani et al., 2021).



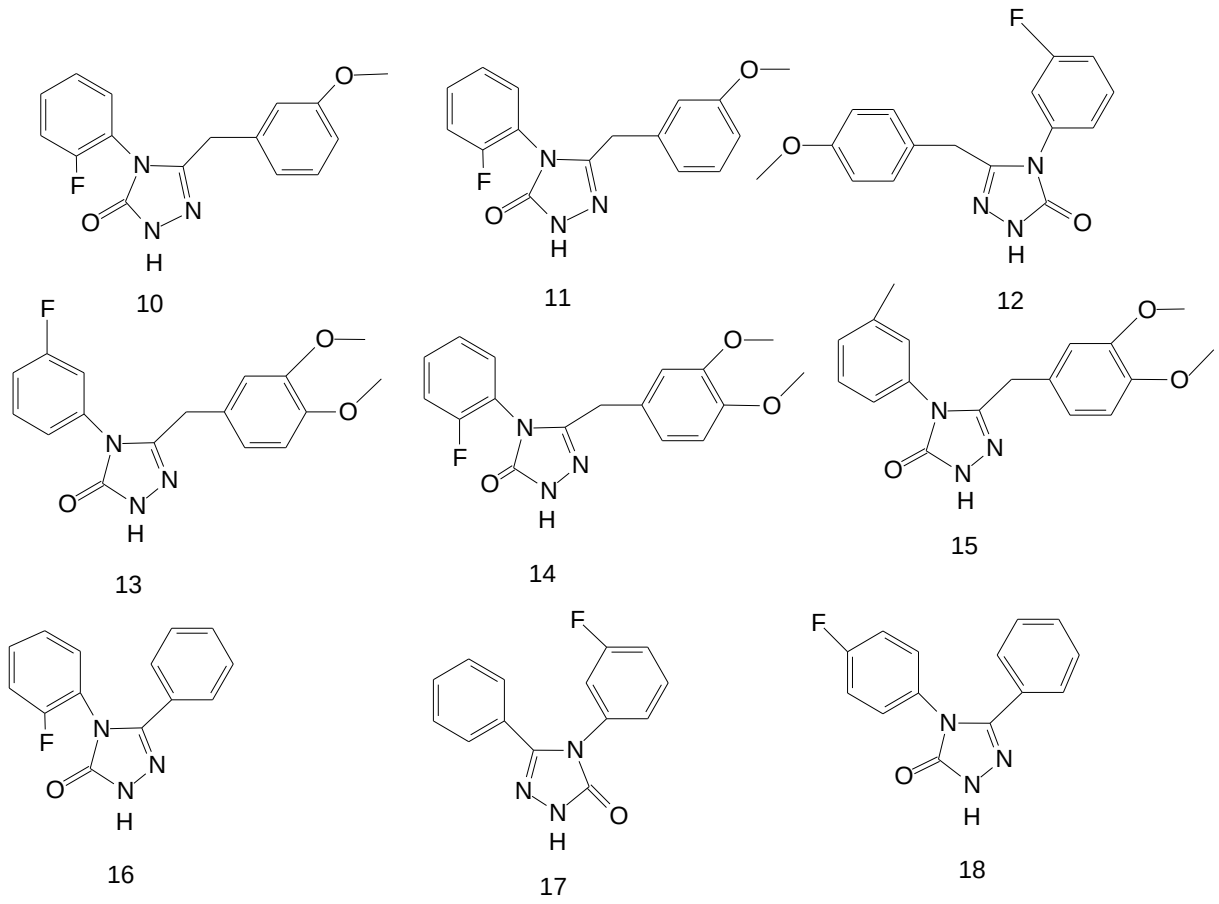
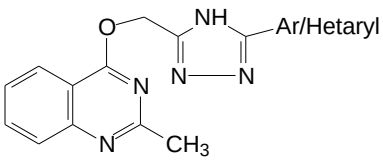
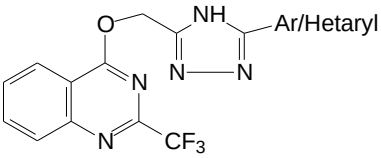


Figure 11. Structure of the investigated **18** 1,2,4-triazol-5(4H)-one derivatives.

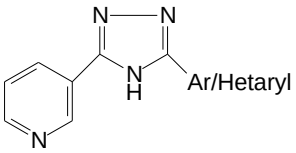
In the "Synthesis and QSAR studies of some novel disubstituted 1,2,4-triazole as antimicrobialagents" study of Pande & Jain, they synthesized disubstituted 1,2,4-triazole derivatives and established reliable quantitative structure activity relationship (QSAR) model to understand the relationship between chemical structure properties and the bioactivity properties of synthesized compounds. In this study, statistical parameters for antibacterial activity and anti-fungal activity of compounds were calculated and evaluated comparing experimental data of compounds. Acording to results obtained from QSAR study molecule-bound halogen, methoxy group and heterocyclic structures are very important for bioactivty of molecule (Pande & Jain, 2014).



1a-k



2a-k



3a-k

Compounds	Ar	Compounds	Ar	Compounds	Ar
1a	$-C_6H_5$	2a	$-C_6H_5$	3a	$-C_6H_5$
1b	$4\text{-}FC_6H_4$	2b	$4\text{-}FC_6H_4$	3b	$4\text{-}FC_6H_4$
1c	$4\text{-}ClC_6H_4$	2c	$4\text{-}ClC_6H_4$	3c	$4\text{-}ClC_6H_4$
1d	$4\text{-}BrC_6H_4$	2d	$4\text{-}BrC_6H_4$	3d	$4\text{-}BrC_6H_4$
1e	$4\text{-}OHC_6H_4$	2e	$4\text{-}OHC_6H_4$	3e	$4\text{-}OHC_6H_4$
1f	$4\text{-}CH_3C_6H_4$	2f	$4\text{-}CH_3C_6H_4$	3f	$4\text{-}CH_3C_6H_4$
1g	$4\text{-}OCH_3C_6H_4$	2g	$4\text{-}OCH_3C_6H_4$	3g	$4\text{-}OCH_3C_6H_4$
1h	$3,4\text{-}(OCH_3)_2C_6H_3$	2h	$3,4\text{-}(OCH_3)_2C_6H_3$	3h	$3,4\text{-}(OCH_3)_2C_6H_3$
1i	$3,4,5\text{-}(OCH_3)_3C_6H_2$	2i	$3,4,5\text{-}(OCH_3)_3C_6H_2$	3i	$3,4,5\text{-}(OCH_3)_3C_6H_2$
1j	2-Furanyl	2j	2-Furanyl	3j	2-Furanyl
1k	2-Thiophenyl	2k	2-Thiophenyl	3k	2-Thiophenyl

Figure 12. Structures of disubstituted 1,2,4-triazole derivatives (Pande & Jain, 2014)

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