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Chemistry of 1, 2, 4-Triazole: A Review Article

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Abstract: ***Triazole was first synthesized over a century ago, but still attracts attention of chemists, biologists, technologists and other specialists. In recent years, antiviral, anti-inflammatory, anti-fertility, anti-tubercular activity, antimicrobial activities, anti-cancer and anti-corrosion properties of triazoles have been published. This review aims to describe the structures, synthesis, reactions and spectral properties of triazoles for highlighting the future applications in several bioactive phenomena and analytical uses.***

Keywords: 1, 2, 4-Trizole, Thiole Derivatives, Applications of 1,2,4-Triazole, Synthetic approaches of 1,2,4-triazole.

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1. Introduction

Heterocyclic chemistry is a separate field of organic chemistry with long history and future prospects. Life is totally dependent on the heterocyclic compounds, such as purine and pyrimidine bases (building unit of DNA and RNA). Now a days, the heterocyclic chemistry brings reagents and synthetic methods of its own usual activity in synthesis of drugs [1], pesticides [2] and detergents [3], as well as into the correlated fields such as biochemistry [4], polymers [5, 6], Dyes [7, 8], and material sciences [9].

2. 1, 2, 4-Triazole

There is significant and continuous concern in the chemistry of five-member N-heterocycle compounds, mainly tetrazole (CH2N4), triazoles (C2H3N3), and their substituted derivatives [10]. Five-membered nitrogen heterocycle compounds are important structural fragments and considered as biologically active compounds [11-16], corrosion inhibitors [17], pesticides [18], dyes [19], acid-base indicator [20], and other industrial chemicals [21]. At 1885, Bladin was the first science who gave the name of (triazole) to the carbon nitrogen ring system (C2N3H3) and described triazoles' derivatives [22].

Triazole exists as two isomers, 1,2,3-triazoles and 1,2,4-triazoles , as shown in (Fig. 1) [10].

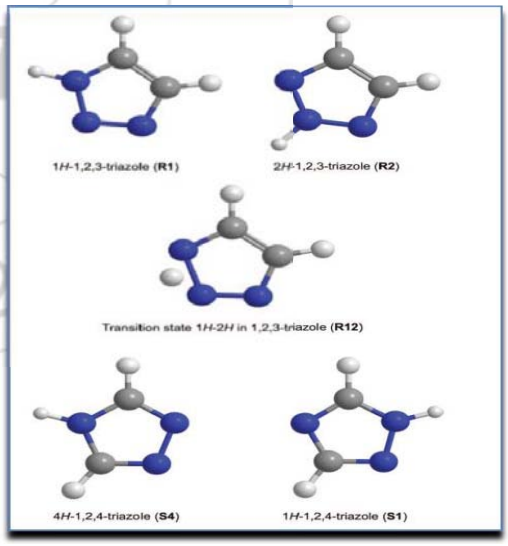


Figure 1: Triazole tautomers (R1, R2, S1 and S4) and transition state (R12) [10].

1, 2, 3-triazole is used as antibacterial [23-26], antifungal [26, 27], antioxidant [28], anti-malarial and anti-leishmanial drugs [29, 30]. 1, 2, 4-triazole is used as a factor in drug structures even more than 1,2,3-isomer. The chemical industry got attention in the synthesis of both simple and fused triazole systems [31-36] after finding that the certain triazoles have the ability of inhibiting the fog formation in photographic emulsions [37], and some others being useful

herbicides and convulsants.

3. Structural Properties of Triazoles

3.1. Aromaticity and Stability

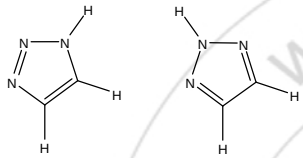
Aromaticity is the main reason of stability of triazole nucleus. An aromatic sextet is formed by donation of one π electron from each atom connected by double bonds, in addition of the remaining two electrons from a nitrogen atom [38]. Also, triazole nucleus is stabilized by resonance that it can be represented by tautomeric forms [39].

3.2. Tautomerism in Triazoles

Tautomerism is possible in both the structural isomers of triazoles.

3.2.1. Tautomerism in 1,2,3-triazoles

1,2,3-Triazoles have two tautomeric forms, 1H-1,2,3-triazole (1) and 2H-1,2,3-triazole (2) [40].



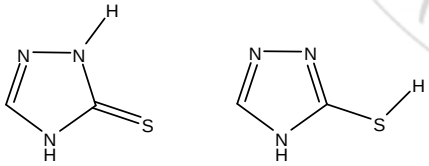
1 **2**

3.2.2. Tautomerism in 1,2,4-triazoles

1, 2, 4-Triazoles have two tautomeric forms: 1H-1, 2, 4-triazole (3) and 4H-1,2,4-triazole (4) [41]. Many studies have been indicated that is tautomer (3) more sTable than tautomer (4) [42].

3.2.3. Tautomerism in substituted-1,2,4-triazoles

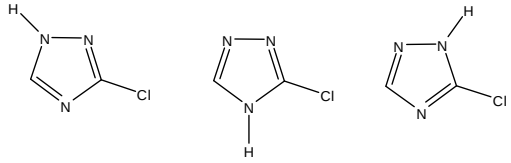
Among the substituted 1,2,4-triazoles, 3-mercapto-1, 2, 4-triazoles exist in two tautomeric forms, that is mobile hydrogen can be attached either to the nitrogen (thion form) (5) or the sulfur (thiol form) (6). Thion (5) is the predominant form [42].



5 **6**

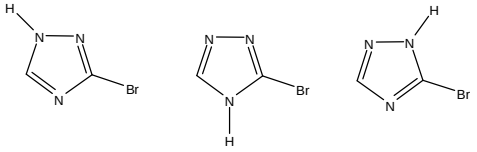
Other substituted 1, 2, 4-triazole can be exist in three tautomeric forms, such as:

1. Chloro-1,2,4-triazoles can exist as; 3-chloro-1H-1,2,4-triazole (7a), 3-chloro-4H-1,2,4-triazole (7b) and 5-chloro-1H-1,2,4-triazole (7c). Stability order of these tautomers is; 7a > 7c > 7b according to physical and theoretical studies [43, 44].



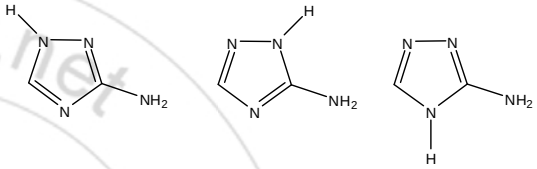
7a **7b** **7c**

2. Bromo-1,2,4-triazoles, tautomeric forms of these compounds are, 3-bromo-1H-1,2,4-triazole (8a), 3-bromo-4H-1,2,4-triazole (8b) and 5-bromo-1H-1,2,4-triazole (8c). According to the physical and theoretical studies [44], the tautomer (8a) and (8c) are of similar energy and the most stable tautomer is (8b).



8a **8b** **8c**

3. 3-Amino-1,2,4-triazole, can be exist as; 3-amino-1H-1,2,4-triazole (9a), 3-amino-2H-1,2,4-triazole (9b) and 3-amino-4H-1,2,4-triazole (9c). the stability order according to physical and theoretical studies [45] for the tautomers is; 9a > 9b > 9c.



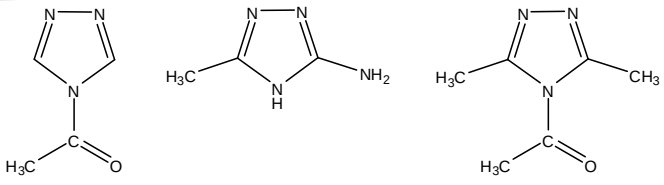
9a **9b** **9c**

4. Spectroscopy of 1,2,4-triazole

Ultraviolet (UV), infrared (IR), nuclear magnetic resonance (NMR) and mass spectroscopic studies are very informative about the structure of 1, 2, 4-triazoles and their derivatives.

4.1. Ultraviolet spectroscopy (UV)

Holam and Straub, observed that in (UV) absorption spectrum, the un-substituted 1,2,4-triazole (5) shows a very weak absorption at 205 nm. While in the case of N-acetyl-1,2,4-triazole (10), Bathochromic shift occurs with the absorption band at 221.5 nm. A similar shift in the maximum absorption of 3,5-dimethyl-1,2,4-triazole (11) appears in contrast with N-acetyl-3,5-dimethyl-1,2,4-triazole (12) [46].



10 **11** **12**

Thion-thiol tautomeric forms can also be detected by (UV) spectroscopy. That in case of 5-substituted-3-mercapto-1,2,4-triazoles, the ultraviolet spectra of an ethanolic solution of these compounds usually show two maximum absorption bands at 252-256 nm and 288-298 nm. The higher value of absorption is due to the presence of the chromophoric C=S group [47].

4.2. Infrared Spectroscopy (IR) [48]

The infrared spectroscopy is very significant in characterization of triazole compounds. The absorption bands at 1570-1550 cm-1 due to N=N and in the region of 1600-1411 cm-1 due to C=N functions are the diagnostic features. In 5-substituted-4-amino-3-mercapto-1,2,4-triazoles, thion-thiol tautomeric forms can also be identified in IR spectra by the presence of C=S absorption band at about 1258-1166 cm-1 for thion and by characteristic SH absorption band at about 2700-2550 cm-1 for thiol forms. The primary N–H stretching vibrations have been observed as two weak absorption bands near 3350 cm-1 and 3250 cm-1 have also been found supportive of thion-thiol equilibrium. Also, the appearance of N–H bands in the regions of 3200-3100 cm-1.

4.3. Nuclear Magnetic Resonance (NMR)

Both 1H and 13C NMR are important to verify the structure of the derivatives, also they are useful in synthesis of isomers. Important 13C NMR and 1H NMR chemical shifts can be shown in Table (1-2), and number of atoms can be shown in (Fig. 1) [49].

Table 2: Theoretical and experimental ^{1}H and ^{13}C isotropic chemical shifts (all values in ppm) for the 4-Amino-3-phenyl-1H-1,2,4-triazole-5(*4H*)-thione [49]

Atom	Experimental (ppm)	Calculated (ppm)
C1	128.57	121.59
C2	130.98	122.48
C3	129.03	124.31
C4	126.27	125.08
C5	129.03	124.31
C6	130.98	122.48
C7	150.02	146.66
C9	167.39	154.48
H14	7.99	6.86
H15	7.52	6.75
H16	7.48	6.07
H17	7.51	6.98
H18	8.03	8.92
H19	13.99	11.86
H20	5.78	5.15
H21	5.78	5.06

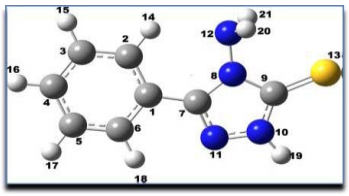


Figure 2: Molecular structure of 4-amino-3-phenyl-*1H*-1,2,4-triazole-(*4H*)-thione along with numbering of atom [49]

13C NMR is a powerful tool to characterize thion and thiol tautomers. In the spectrum of thion two values for chemical shifts are obtained, one at about 164-173 ppm for imine (C=N) and the other at 150-160 ppm for thionyl (C=S). While in thiol tautomer there is chemical shift in 50-75 ppm for (C-S) instead of thionyl group [48].

4.4. Mass Spectrometry (MS) [50]

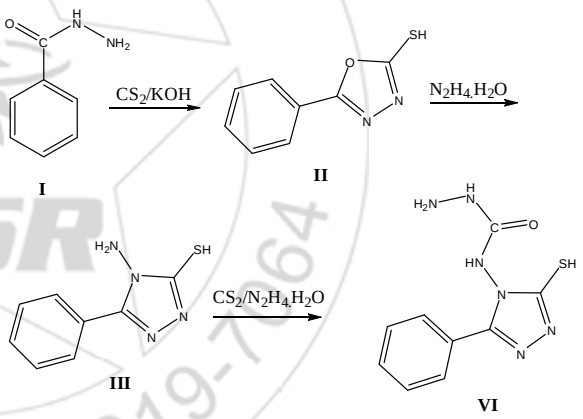
1,2,4-Triazoles have a strong molecular ion peak with the cleavage of bonds between N1–N2 and N4–C5 has been observed. In addition of N1–N2 and C3–N4 cleavage, number of atoms can be shown in (Fig. 1-2).

5. Synthetic Methods of 1,2,4-Triazoles

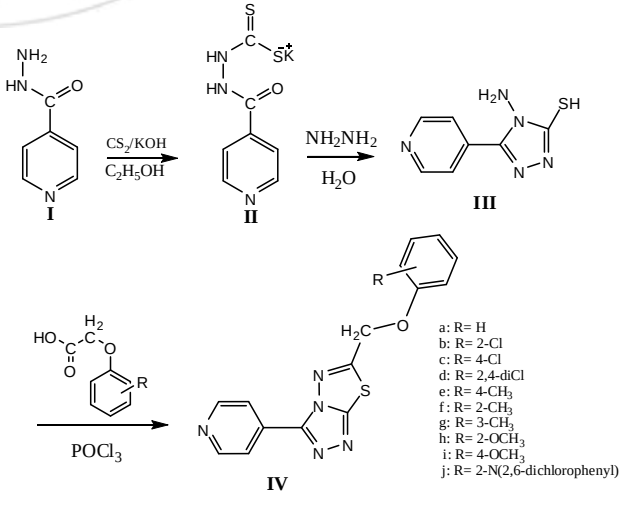
5.1. From Carboxylic Acid Hydrazide

N-(3-mercapto-5-phenyl-4H-1,2,4-triazol-4-yl) hydrazine carbothioamide (VI) prepared from the condensation of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol and thiosemi-carbazide (III) which synthesized by reaction of hydrazine hydrate and 5-phenyl-1,3,4-oxadiazol-2-ylamine (II), which in itself was synthesized from benzoic acid hydrazide (I) [51], As shown in Scheme (1).

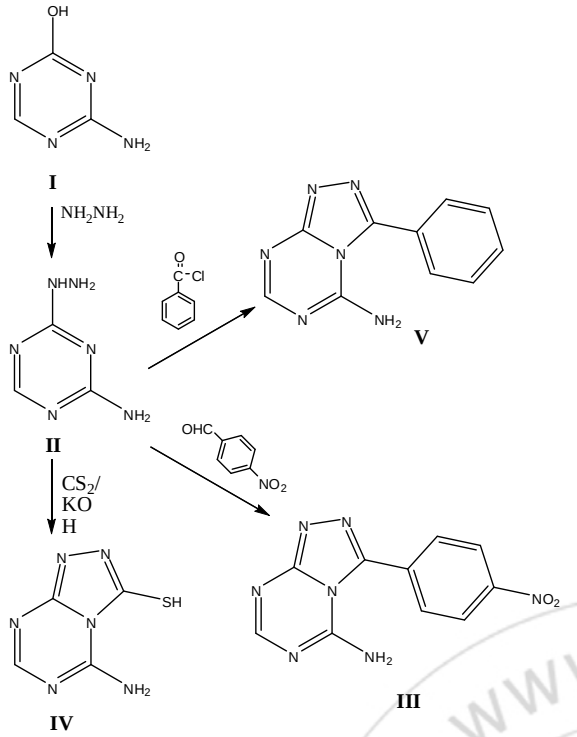
While 6-(substituted)-3-(pyridin-4-yl)-1,2,4-triazole [3,4-b] [1,3,4] thiadiazole (IV) has the synthetic root of isonicotinic acid hydrazide (I) which has been converted to potassium dithiocarbazinate (II). Then, salt (II) has been treated with hydrazine hydrate to yield 1,2,4-triazole (III), which treated with various carboxylic acids to get a series of compound (IV a-j) [52], as shown in Scheme (2).



Scheme (1): Synthesis of N-(3-mercapto-5-phenyl-4H-1,2,4-triazol-4-yl) hydrazinecarbothioamide



Scheme (2): Synthesis of 6-(substituted)-3-(pyridin-4-yl)-1,2,4-triazole[3,4-b][1,3,4]thiadiazole



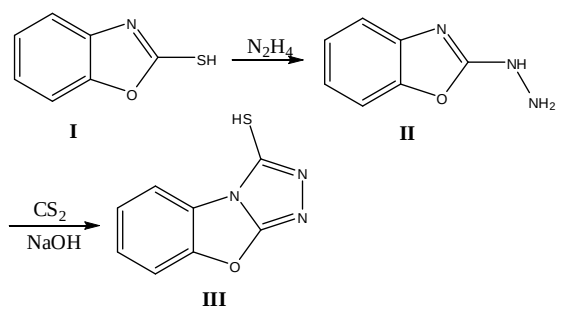
Scheme (3): Synthesis of 1,2,4-triazole derivates from 1,3,5-triazine

5.2. From 1, 3, 5-Triazine

5-amino-3-(p-nitrophenyl) [1,2,4] triazolo[4,3-a] [1,3,5] triazine (III), 5-amino[1,2,4]triazolo[4,3-a][1,3,5]triazine-3-thiol (IV), and 5-amino-3-phenyl[1,2,4]triazolo[4,3-a][1,3,5]triazine (V) were synthesized from 2-amino-4-hydrazino-1,3,5-triazine (II) which has been prepared by substitution of hydroxy group in 2-Amino-4-hydroxy-1,3,5-triazine (II) with hydrazino group [53], as shown in Scheme (3).

5.3 From Oxazole

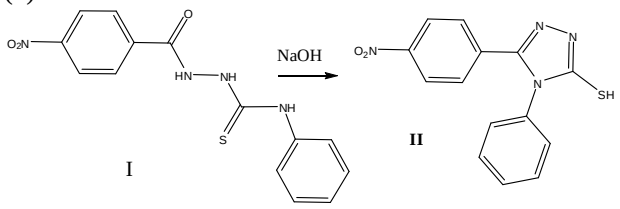
After the substitution of mecapto group in 2-meracpto benzoxazole (I) with hydrazino group to prepare 2-hydrazino benzoxazol (II), Reaction of (II) with carbon disulfide and sodium hydroxide gave 1,2,4-triazole [4,3-b] benzoxazole-1-(2H)thione (III) [54], As shown in Scheme (4).



Scheme (4): Synthesis of 1,2,4-triazole [4,3-b] benzoxazole-1-(2H)thione

5.4 From Thiosemicarbazide

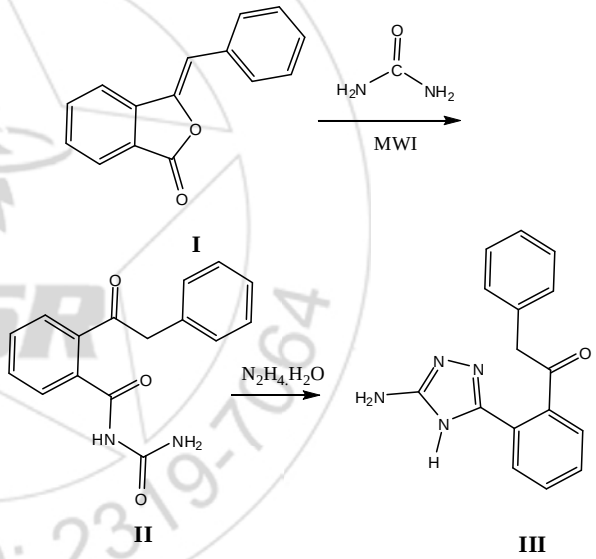
5-(4-Nitrophenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol (II) were prepared from 1-phenyl-4-(4-nitrobenzoyl)thiosemicarbazide (I) [55], As shown in Scheme (5).



Scheme (5): Synthesis of 5-(4-Nitrophenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol

5.5 From Urea

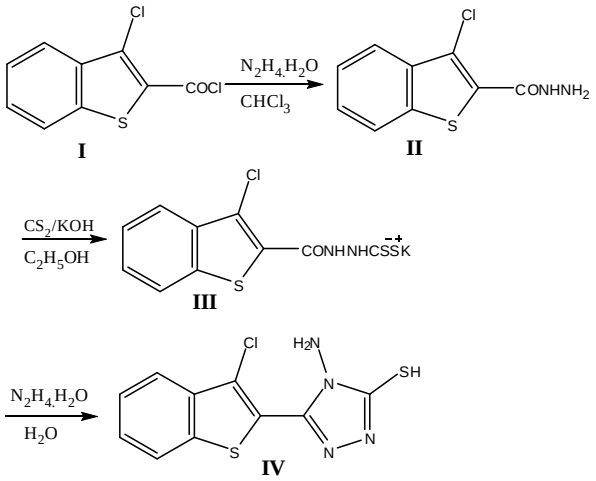
Reaction of 3-benzylidene phthalide (I) with urea under microwave irradiation (MWI) gave 1-(2-(α-phenylacetyl)benzoyl)urea (II) which reacted with hydrazine hydrate to yield 1-(2-(5-amino-4H-1,2,4-triazol-3-yl)phenyl)-2-phenylethanone (III) [56], As shown in Scheme (6).



Scheme (6): Synthesis of 1-(2-(5-amino-4H-1,2,4-triazol-3-yl)phenyl)-2-phenylethanone

5.6 From Acid Chloride

Conventional heating of 3-chloro-2-chlorocarbonylbenzo[b]thiophene (I) with hydrazine hydrate afforded the corresponding hydrazide (II). Potassium dithiocarbazate (III) was cyclized with hydrazine to afford 4-amino-5-(3-chlorobenzo [b] thien-2-yl)-3-mercapto-1,2,4-triazole (IV) [57], As shown in Scheme (7).



Scheme (7): Synthesis of 4-amino-5-(3-chlorobenzo[*b*]thien-2-yl)-3-mercapto-1,2,4-triazole

6. Applications and Biological Activities

1,2,4-Triazole and its derivatives are an imperative type of compounds which possess environmental [58], industrial [11, 17, 59], agricultural [62, 67, 69] and biological activities, including antimicrobial [60-64], antifungal [65], antibacterial [66-68], antitubercular [69], anticancer [70-72], anti-oxidant [67, 69, 73], anti-inflammatory [74, 75], antiviral [16, 76], and anticonvulsant [77] activities.

6.1. Agricultural Applications

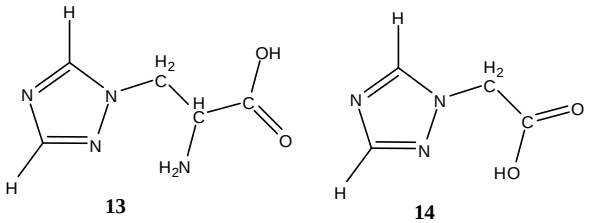
Azole derivatives have been used in the plant protection technology as pesticides [77]. In order to selectively control the growth of weeds, a wide range of azole herbicides have been developed that are exhibiting [78]:

- high level of activity
- application flexibility
- crop tolerance
- low levels of toxicity to mammals

Specifically, triazoles play an important role among this classes of heterocyclic compounds [50, 51].

Sutton *et al.* [44] have been evaluated a good *in vitro* activity of Etaconazole on fungi that causing summer disease of apple. While Amer *et al.* [49] have been determined diniconazole fungicides residues in tomatoes and green beans by capillary gas chromatography.

Schermerhorn *et al.* [79] have been determined 22 triazole compounds including parents fungicides and metabolites in apple, peaches, flour and water by liquid chromatography/tandem mass spectroscopy, and the most three common fungicides triazole are: 1,2,4-triazole (2), triazolyalanine (13), and triazolylacetic acid (14).



6.2 Pharmacological Applications

Over the last few decades, the biological and pharmaceutical properties of 1,2,4-triazoles have been formed considerable attention in their synthesis and characterization [80]. 1,2,4-Triazole and its derivatives possess widely different biological activities Figure (3).

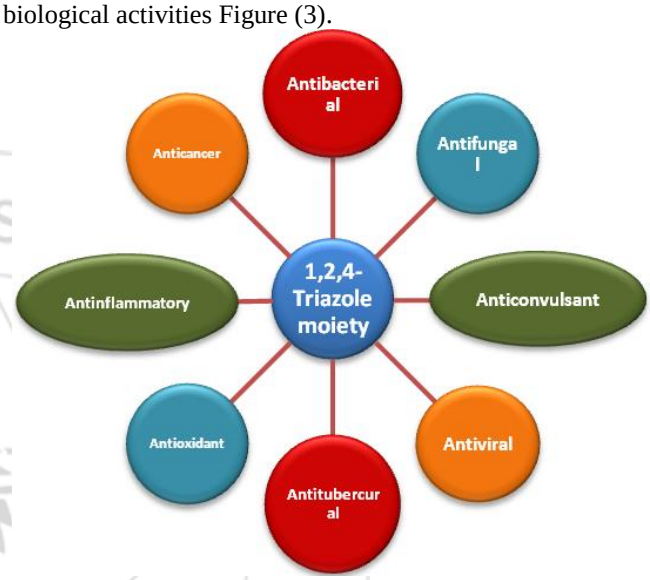
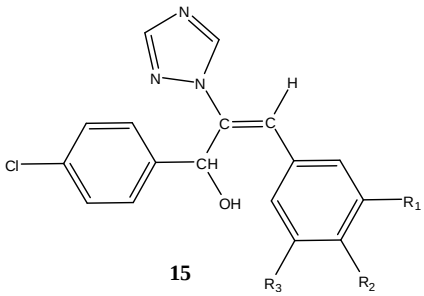


Figure 3: Pharmacological activities of triazole moiety

6.2.1. Antibacterial Activities

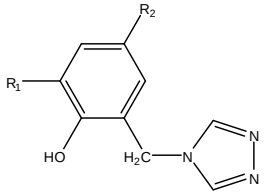
Battle against bacterial infections has resulted in the development of a wide variety of antibiotics. After years of mistreatment and overuse of antibiotics, bacteria are becoming antibiotic resistant, resulting in a potential global health disaster. It is recommended to use new antibacterial agents with enhanced broad spectrum potency. Therefore, recent efforts have been directed toward exploring novel antibacterial agents. Antibacterial drug is a chemical substance derivable from a mold or bacterium that can kill microorganisms and cure bacterial infections, Many antibiotics are now chemically modified from original compounds present naturally. They are classified in two types based on their mode of action as bactericidal agents (kill bacteria directly) and bacteriostatic agent (stop bacteria from growing) [81]. Uchil et al. [82] have been synthesized and used (substituted-(+)α-(4-chlorophenyl)-β-(phenylmethylene)-1H-1,2,4-triazole-1-ethanols) [15] as bacteriostatic agent.



a: $R_1=R_3=H$; $R_2=Cl$
b: $R_1=Br$; $R_2=R_3=H$
c: $R_1=R_2=R_3=OCH_3$
d: $R_1=R_3=H$; $R_2=SCH_3$
e: $R_1=OC_6H_5$; $R_2=R_3=H$
f: $R_1=OCH_3$; $R_2=OH$; $R_3=H$
g: $R_1=R_3=H$; $R_2=OH$
h: $R_1=R_2=OCH_2O$; $R_3=H$
i: $R_1=R_3=H$; $R_2=N(CH_3)_2$

15

While El-Zemity et al. [83] have been synthesized and evaluated the Bactericidal Potential of (1H-1,2,4-triazol-1-yl methyl)Phenols (16), N,N-dialkyl Anilines (17), and N-alkyl Anilines (18).



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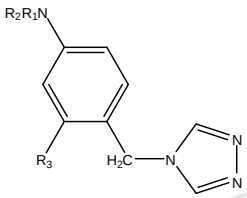
a: $R_1=R_2=H$
b: $R_1=CH_3$; $R_2=H$
c: $R_1=H$; $R_2=CH_3$
d: $R_1=i\text{-}C_4H_9$; $R_2=H$
e: $R_1=t\text{-}C_4H_9$; $R_2=CH_3$
f: $R_1=s\text{-}C_4H_9$; $R_2=CH_3$



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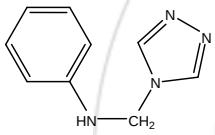
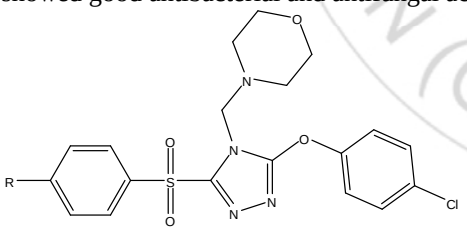
a: $R_1=R_2=R_3=H$
b: $R_1=CH_3$; $R_2=R_3=H$
c: $R_1=C_2H_5$; $R_2=R_3=H$
d: $R_1=C_2H_5$; $R_2=H$; $R_3=CH_3$
e: CH_3 CH_3 H
f: $R_1=R_2=R_3=CH_3$



18

Narayana Rao et al. [80], have been synthesized and characterized a new 1,2,4-triazole derivatives. Also, they have been evaluated the biological activity 4-[(3-(4-substituted-phenoxymethyl)-5-benzylsulfonyl)-1,2,4-triazol-4-yl) methyl]-morpholine (19) and All the title compounds showed good antibacterial and antifungal activities.



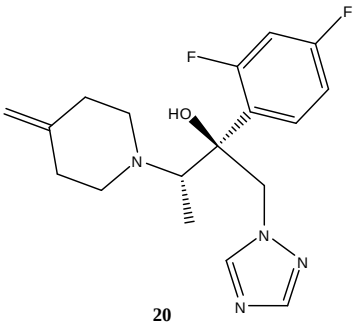
a: R= H
b: R=CH_3
c: R=OCH_3
d: R=NO_2
e: R=Cl
f: R=Br
g: R=F

19

6.2.2. Antifungal Activities

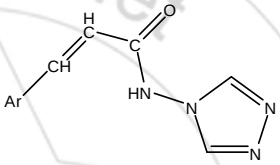
Antifungal are the class of drugs that are used to eliminate fungal infections from the human body. They work by exploiting differences between mammalian and fungal cells to eliminate fungal organism without harming the host cells. As both the cells are eukaryotic in nature so it is more difficult to design the drugs of antifungal activity with fine selections of the cells without causing any side effects [84].

The mechanism of action of triazole antifungal, was investigated with Trichophyton mentagrophytes and Candida albicans by Tatsumi et al. whom explained that Efinaconazole (20) dose-dependently decreased ergosterol production and accumulated 4,4-dimethylsterols and 4α-methylsterols. Efinaconazole induced morphological and ultrastructural changes in T. mentagrophytes hyphae that became more prominent with increasing drug concentrations. In conclusion, the primary mechanism of action of efinaconazole is blockage of ergosterol biosynthesis, presumably through sterol 14α-demethylase inhibition, leading to secondary degenerative changes [85].



20

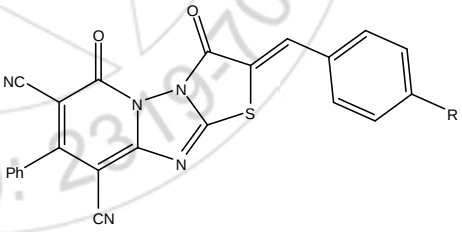
Anti (Mucor, Aspergillus Niger and Penicillium) were synthesized and characterized by Patel et al. whom prepared 3-(Substitutedphenyl)-N-(4H-1,2,4-triazol-4-yl) acrylamide derivatives (21) [86].



a: Ar=4-ClC_6H_5
b: Ar=4-$N(CH_3)C_6H_5$
c: Ar=1-Naphthalene
d: Ar=3-$OCH_3C_6H_5$
e: Ar=2-OHC_6H_5

21

Suresh et al. found that (Z)-2-(4-substitutedbenzylidene)-7-isocyano-3,6- dioxo-8-phenyl-3,6-dihydro-2H-thiazolo-[3',2':2,3][1,2,4]-triazolo[1,5-a]pyridine-9-carbon nitrile derivatives (22) exhibit good antifungal activity against Aspergillus flavus, Aspergillus fumigatus, Candida albicans, Penicillium marneffei and Trichophyton mentagrophytes [87].

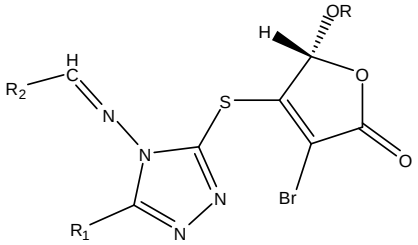


a: R=H
b: R=Cl
c: R=NO_2
d: R=OCH_3
e: R=$N(CH_3)_2$
f: R=Br
g: R=$OCOCH_3$
h: R=CH_3
i: R=$CH(CH_3)_2$
j: R=$C(CH_3)_3$

22

6.2.3. Anticancer and Antitumor Activities

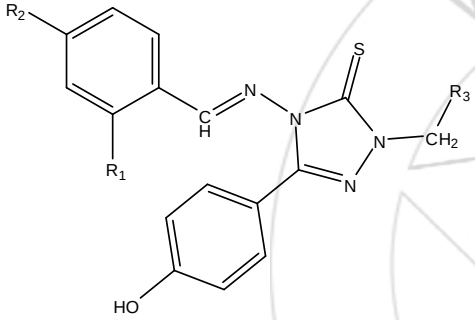
Cancer, a diverse group of diseases identified by the production and prevalence of abnormal cells, is a major global problem [88]. Therefore, the discovery and development of new effective and selective anticancer drugs are of high importance in modern cancer researches. 1,2,4-Triazole derivatives have their chance with these researches with a good results [41, 59]. Li et al., synthesized and evaluated in vitro anticancer activity of 12 hybrid 1,2,4-triazole Schiff's bases (23) bearing γ-substituted butenolide moiety [89].



23

a: R= 1-menthyl; R_1 = C_6H_5,R_2 = 4-Cl-C_6H_5
b: R= 1-menthyl; R_1 = 4-CH_3O-C_6H_5; R_2 = 4-Cl-C_6H_5
c: R= 1-menthyl; R_1 = C_6H_5; R_2 = 4-O_2N-C_6H_5
d: R= 1-menthyl; R_1= 4-CH_3O-C_6H_5; R_2= 4-O_2N-C_6H_5
e: R= 1-menthyl; R_1 = C_6H_5; R_2 = 2-furanl
f: R= 1-menthyl; R_1 = 4-CH_3O-C_6H_5; R_2 = 2-furanl
g: R= 1-menthyl; R_1 = CH_3; R_2 = 4-Cl-C_6H_5
h: R= 1-menthyl; R_1 = 4-HO-C_6H_5; R_2 = 4-CH_3O-C_6H_5
i: R= 1-menthyl; R_1 = C_6H_5; R_2 = 4-HO-C_6H_5
j: R= bornyl; R_1 = C_6H_5; R_2 = 4-Cl-C_6H_5
k: R= bornyl; R_1 = 4-HO-C_6H_5; R_2 = 4-CH_3O-C_6H_5
l: R= bornyl; R_1 = CH_3; R_2 = 2-HO-C_6H_5

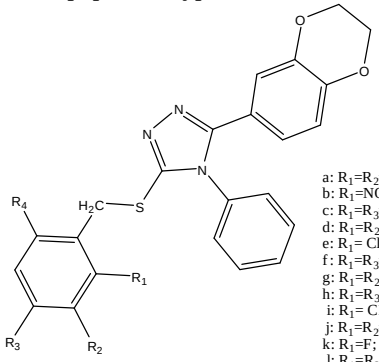
A. Anton Smith et al. have been synthesized and evaluated in vitro anticancer activity of 1,2,4-triazole derivatives (24) [72].



24

a: R_1 = R_2= Cl; R_3 = $N(C_2H_5)_2$
b: R_1 = H; R_2= NO_2; R_3 = $N(C_2H_5)_2$
c: R_1 = H; R_2 = $N(CH_3)_2$; R_3 = $N(C_2H_5)_2$
d: R_1 = R_2= Cl; R_3 = N-pyridyl
e: R_1 = H; R_2= NO_2; R_3 = N-pyridyl
f: R_1 = H; R_2= $N(CH_3)_2$; R_3 = N-pyridyl
g: R_1 = R_2= Cl; R_3 =N-morpholinyl
h: R_1 = H; R_2= NO_2; R_3 = N-morpholinyl
i: R_1 = H; R_2= $N(CH_3)_2$; R_3 = N-morpholinyl

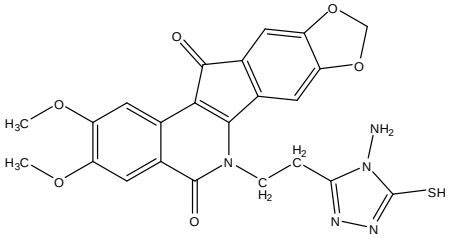
Y.-P. Hou et al. have been synthesized 1,2,4-triazole derivatives (25) that have antitumor activity with 1,4-benzodioxane fragment as a novel class potent methionine aminopeptidase type II inhibitors [70].



25

a: R_1=R_2=R_3=R_4=H
b: R_1=NO_2; R_2=R_3=R_4=H
c: R_1=R_3=R_4=H; R_2=NO_2
d: R_1=R_2=R_4=H; R_3=NO_2
e: R_1= Cl; R_2=R_3=R_4=H
f: R_1=R_3=R_4=H; R_2=Cl
g: R_1=R_2=R_4=H; R_3=Cl
h: R_1=R_3=R_4=H; R_2=OCH_3
i: R_1= CH_3; R_2=R_3=R_4=H
j: R_1=R_2=R_4=H; R_3=CH_3
k: R_1=F; R_2=R_3=R_4=H
l: R_1=R_2=R_4=H; R_3 =F
m: R_1=R_3=F; R_2=R_4=H
n: R_1=R_4=F; R_2=R_3=H
o: R_1=Br; R_2=R_3=R_4=H
p: R_1=R_3=R_4=H; R_2=Br
q: R_1=R_2=R_4=H; R_3=Br

B. A. Baviskar et al. have been synthesized clubbed triazolyl indeno [1,2-C]isoquinolines (26) as anticancer agent [71].

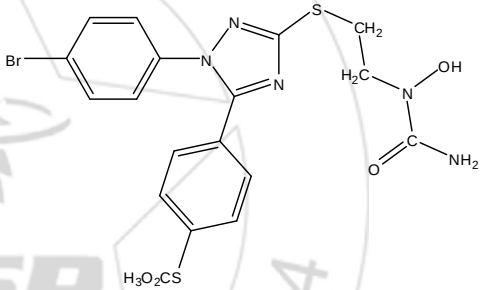


26

6.2.4. Anti-inflammatory Activities

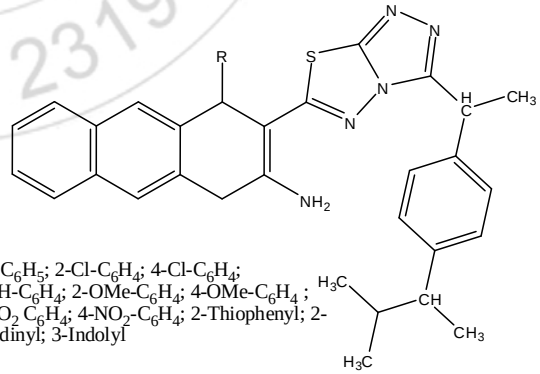
Therapeutic use of non-steroidal anti-inflammatory drugs (NSAIDs) which are used in treatment of a number of arthritic diseases is limited because of their side effects, such as, gastrointestinal haemorrhage and ulceration. So, new drugs having effective anti-inflammatory activity with minimum side effects have been developed [75].

A series of hybrids from diaryl-1,2,4-triazole and N-hydroxyurea (27) were synthesized, evaluated as novel anti-inflammatory agents, and displayed promising analgesic activity in acetic acid-induced writhing response and hot-plate assay, by Jiang et al. [90].



27

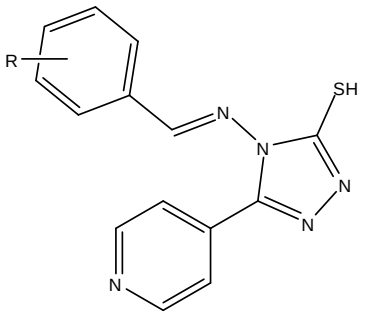
Subbarao et al. have been evaluated a good anti-inflammatory activities of novel series of 1,2,4-triazolo [3,4-b] [1,3,4] thiadiazoles (28) [91].



R = C_6H_5; 2-Cl-C_6H_4; 4-Cl-C_6H_4; 4-OH-C_6H_4; 2-OMe-C_6H_4; 4-OMe-C_6H_4 ; 2-NO_2 C_6H_4; 4-NO_2-C_6H_4; 2-Thiophenyl; 2-Pyridinyl; 3-Indolyl

28

Murti et al. have been characterized the anti-inflammatory activity of 4-(Substituted benzylideneamino)-5-(pyridin-4-yl)-4H-1,2,4-triazol-3-thiol derivatives (29) [92].



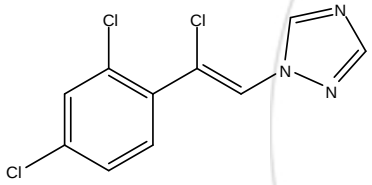
29

R = 4-Cl, 3-OH, 4-OCH_3, 2-NO_2, 4-$N(CH_3)_2$

6.2.5. Anticonvulsant Activities

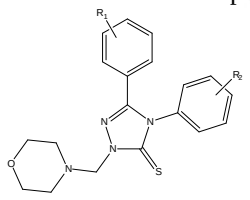
Anticonvulsants are drugs that avoid or decrease the severity and rate of seizures in various types of epilepsy. The different types of anticonvulsants may proceed on different receptors in the brain and have different forms of action [93]. 1,2,4-triazole derivatives considered as a good anticonvulsants such as alprazoam (39).

Wingrove et al. put forward a hypothesis that the activity of loreclezole (30) (second-generation antiepileptic drug) is dependent on the interaction between the triazole moiety and the amide group of asparagine (Asn-289), which is located on the β2 subunit of the GABAA receptor [94].



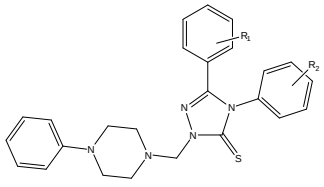
30

Plech et al. have been Studied on the anticonvulsant activity and influence on GABA-ergic neurotransmission of 1,2,4-triazole-3-thione based compounds (31), (32), and (33) [95].



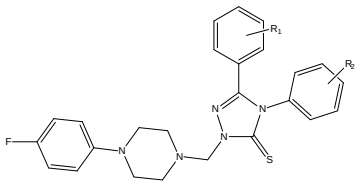
a . R_1= 3 -Cl, R_2= 4-B r
b . R_1= 3 -Cl, R_2= 4-C H_3
c , R_1= 4 -Cl, R_2= 2-B r
d . R_1= 4 -Cl, R_2= 4-B r

31



a , R_1= 3 - Cl, R_2 = 4- Br
b . R_1= 3 - Cl, R_2= 4- CH_3
c , R_1= 4 - Cl, R_2= 2- Br
d . R_1= 4 - Cl, R_2= 4- Br

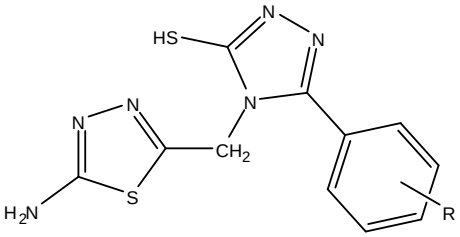
32



a . R_1= 3 -Cl, R_2= 4- Br
b . R_1= 3 -Cl, R_2= 4-CH_3
c . R_1= 4 -Cl, R_2= 2- Br
d . R_1= 4 -Cl, R_2= 4- Br

33

D. Kumudha et al. synthesized and evaluated anticonvulsant and CNS depressant activity of some 1,3,4-thiadiazoles having substituted 1,2,4-triazole moiety (34) [96].



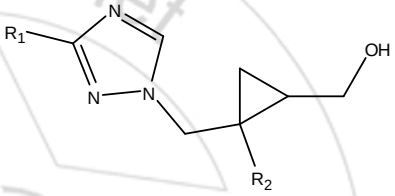
34

R= H; 2-Cl; 3-CH_3; 4-CH_3

6.2.6. Antiviral Activities

Antiviral drugs are a class of medication used specifically for treating viral infections. specific antivirals are used for specific viruses [97].

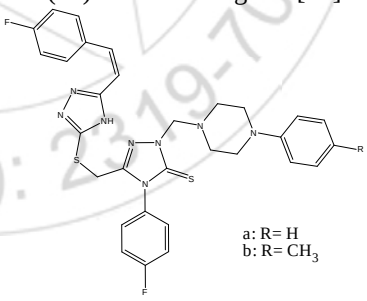
K. Benci et al. were synthesized and evaluated 1,2,4-triazole acyclic cyclopropane nucleoside analogues (35) [98].



35

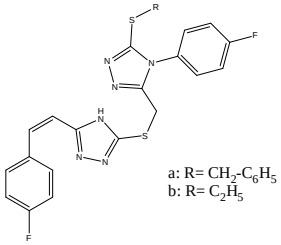
a: R_1=H, R_2=CH_2OH
b: R_1=CH_2OH, R_2=CH_2OH
c: R_1=$CONH_2$, R_2=CH_2OH
d: R_1=$CONH_2$, R_2=$CONH_2$

A. Abou-zeid et al. were used 1,2,4-traizole derivatives (36) and (37) as antiviral agents [99].



a: R= H
b: R= CH_3

36



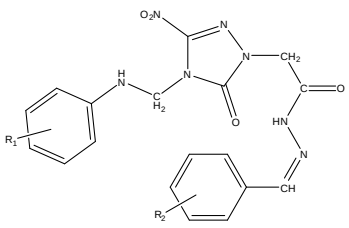
a: R= CH_2-C_6H_5
b: R= C_2H_5

37

6.2.7. Antitubercular Activities

Tuberculosis is still a major treat to mankind. The increasing problem of Multi-Drug Resistant-tuberculosis has focused attention on developing new drugs that are not only active against drug resistant tuberculosis, but also shorten the lengthy therapy. There is urgent need and significant interest in developing new tubercular drugs. In developing new tubercular drugs, it is essential to think about which targets in the tubercule bacillus are good drug targets. Several recent reviews on this topic are already available [96, 100, and 101].

M. Maste Meenaxi et al. were studied the antitubercular activity of 1,2,4-triazole derivatives (38) [69].



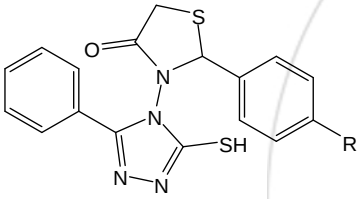
38

a: R_1= 4-NO_2; R_2= 2,4-dichloro
b: R_1= 3-NO_2; R_2= 2,4-dichloro
c: R_1= 4-NO_2; R_2= 4-CH_3
d: R_1= 4-NO_2; R_2= 2-Cl
e: R_1= 4-NO_2; R_2= 4-OCH_3
f: R_1= 4-NO_2; R_2= 4-OH
g: R_1= 4-NO_2; R_2= 3,4-dimethoxy
h: R_1= 4-NO_2; R_2= 3,4-dichloro
i: R_1= 4-NO_2; R_2= 4-Cl
j: R_1= 4-NO_2; R_2= H
k: R_1= 3-NO_2; R_2= 3,4-dichloro
l: R_1= 3-NO_2; R_2= 4-OH
m: R_1= 4-NO_2; R_2= 4-NO_2

6.2.8. Antioxidant Activities

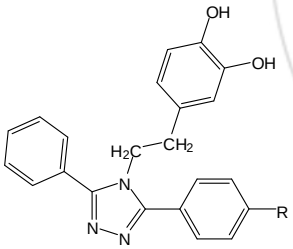
Damage to cells caused by free radical is supposed to play an essential role in the aging process and in disease development. antioxidants are our first line of protection against free radical damage, The antioxidants became even more critical with amplified exposure to free radicals. pollution, cigarette smoke, drugs, illness, stress and even exercise can increase free radical exposure [102].

A. Abdul Hameed and F. Hassan have been synthesized and evaluated antioxidant activity of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol derivatives (39) [73]. K. Sancak et al. found that tri-substituted triazole (40) and (41) possess highly potent antioxidant properties [103].



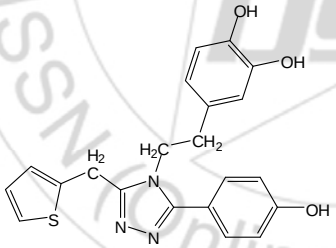
39

a: R= $N(CH_3)_2$
b: R= Br



40

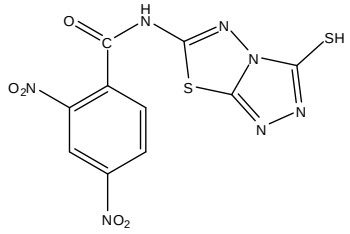
R= H; OH



41

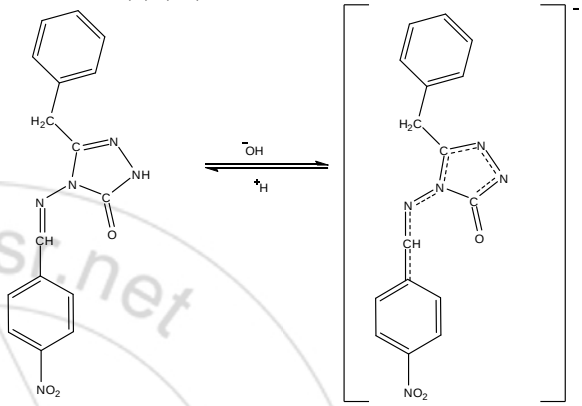
7. Industrial Applications

Some selected triazoles have been used as light emitting diodes (Electroluminescent devices) [104]. Many types of triazole have been used to increase the efficiency of cooling fluids (lubricant oil), such as 2-mercapto-1,2,4-triazole-2,4-dinitrobenzamide (42) [11].



42

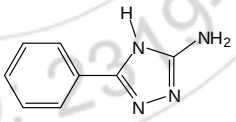
Also, triazole have been used as acid-base indicator because it shows reversible, clear colour change, sharp and low relative error (RE~1.4%) in the pH range 8.5-10.1, As shown in Scheme (8) (20).



Colorless (HIn) Yellow-Green (In^-)

Scheme (8): Resonance structures of 3-benzyl-4-p-nitrobenzylidenamino - 4,5-dihydro-1,2,4-triazole-5-one, Whereas In = indicator

Some triazole systems have extensive use in the separation of silver from other metal cations in liquid membrane systems [105]. In addition, these compounds are used as synthetic dyes and bleaching agents [106], It also they are used as non-ionic surfactants [107]. Moreover, triazoles (43) have also been reported as inhibitors of corrosion of aluminum in hydrochloric acid solution [17].



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