INTERNATIONAL JOURNAL OF PHARMACEUTICS & DRUG ANALYSIS
VOL.5 ISSUE 5, 2017; 161 – 176 ; http://ijpda.com; ISSN: 2348-8948

Review Article

Review On Chemistry And Pharmacological Significance Of Triazole Derivatives

Sonawane M.D.*, Narwate B.M.,

Darandale A.S.

Department of Pharmaceutical chemistry

MES's College of Pharmacy, Sonai, Tal –Newasa, Dist- Ahmednagar, Maharashtra, India-414105

Date Received: 8th May 2017; Date accepted:

12th May 2017; Date Published: 13th May 2017

Abstract

Triazole constitutes an important class of biologically active heterocyclic compounds that have received a great deal of attention of chemists, biologists, technologists and other specialists since their discovery. In recent years, antiviral, anti-inflammatory, anti-fertility, anti-tubercular activity, antimicrobial activities, anti-cancer and anti-corrosion properties of triazoles have been published. Triazole is a unique moiety that is responsible for various biological active ties. This article highlighted Chemistry and research work of many researchers reported in literature for different pharmacological activities on synthesized Triazole.

Keywords: Triazole, heterocyclic compound, reactivity, application, Pharmacological properties

Introduction

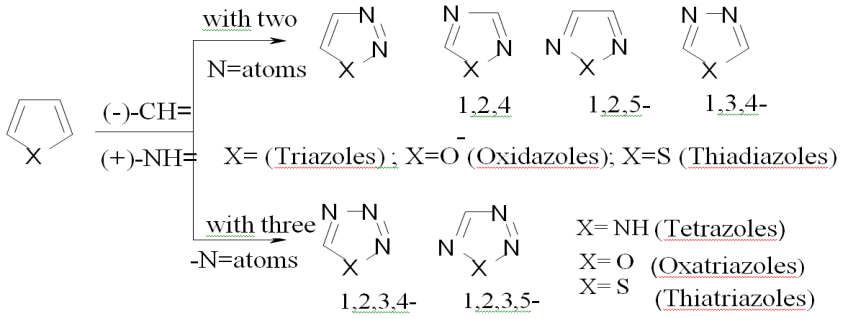
Heterocyclic chemistry is a separate field of organic chemistry with long history and future prospects. Life is totally dependent on the heterocyclic compounds, such as purine and Pyrimidine bases (building unit of DNA and RNA). Now a days, the heterocyclic chemistry brings reagents and synthetic methods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

During the past decades, the human population affected with life-treating infectious diseases caused by multidrug-resistant gram-positive and gram-negative pathogen bacteria increased an alarming level around the world. Due to this reason, new classes of anti-bacterial agents with novel mechanisms are crucible need to combat with the multidrug-resistant infections. In the past years, some azoles derivatives were developed as new anti-microbial agents, for instance, linezolid and eperezolide are currently used for the treatment of multidrug-resistant gram-positive infections. There are number of antimicrobial compound containing a 1, 2, 4-triazole ring in their structures such as fluconazole, itraconazole, ravuconazole and posaconazole that are important anti-fungal drugs. Triazole constitutes an important class of biologically active heterocyclic compounds that have received a great deal of attention since their discovery. The considerable biological importance of triazole has stimulated a lot of interest in its derivatives. 1,2,4-triazoles, being an important pharmacophores have a wide range of therapeuticpropertieslike anti-bacterial,anti-fungal,anti-mycobacterial,anti-viral,anti-inflammatory,anti-convulsant &anti-depressant[10].

In the year 1855, Bladin gave the name "Triazole" to the carbon-nitrogen ring system $C_2H_3N_3$ and described the derivatives of the class. Till date a number of triazole derivatives have entered the medicinal world as powerful therapeutic agents. Still, if we talk about broad spectrum triazole derivatives, we could not help to name even a few. So, the ongoing research is focused on developing triazole derivatives with broad spectrum of antimicrobial activity.

a. Five Member Heterocyclic:

Five membered heterocyclic with more than two heteroatom are considered to be derivative from pyrrole, furan and thiophene by the replacement of methane group (-CH=) by pyridine type nitrogen (-N=) atom from different position and are named as



(25) Heterocycles with more than two heteroatomes

(i) **Basicity**: The base strength generally decreases with increasing the number of nitrogen atom because of inductively electron-withdrawing effect of the pyridine-type nitrogen atoms (diazinesare the weaker base than pyridine).The additional nitrogen atoms in these heterocyclic, therefore,have base weakening effect as a result of which these systems are with lower basicity.

(ii)**Acidity**: The acidity of the ring system increases with the number of nitrogen atoms as tetrazoles are more acidic than triazole. Triazoles are comparable with phenol in acidic strength, while 1*H*-tetrazoles behaves as an acid (acetic acid). The positions of nitrogen atoms (orientation) do not affect considerably the acidic strength as 1, 2, 3- triazole is slightly more acidic than 1, 2, 4-triazole. But the effect of orientation on acidity is much less than the effect of total number of nitrogen atoms.

(iii) The tendency of the ring system towards electrophilic attack falls off with the introduction of additional pyridine type nitrogen atoms. Triazoles, oxadiazole and thiadiazole are therefore, resistant towards electrophilic attack and undergo electrophilic substitutions only if powerful electron-releasing substituents are present.

(iv)The introduction of pyridine type nitrogen atoms in the ring system affects the ease of quaternization. The quaternization of triazoles, oxadiazoles, thiazoles and stetrazoles requires stronger reagent and reaction conditions[10].

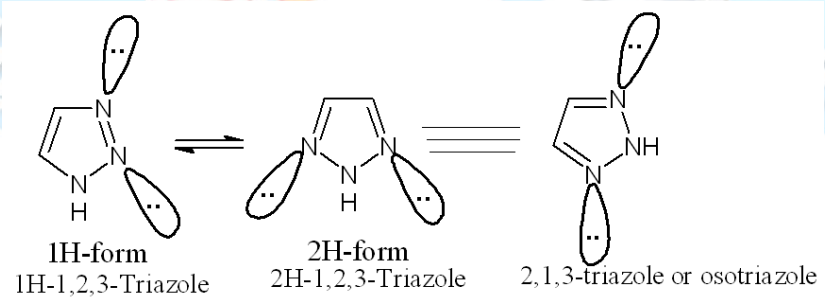
1.2. Types of Triazole:

A) 1, 2, 3-Triazoles

B) 1, 2, 4-Triazoles

A) 1, 2, 3-Triazoles:

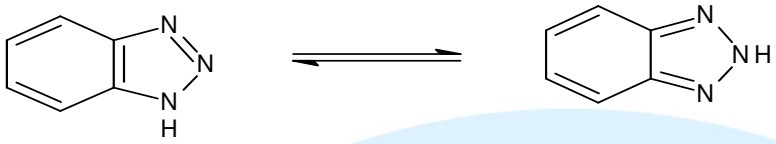
1, 2, 3-Triazoles is planner five membered heterocyclic system with two carbon and three nitrogen atom (one pyrrole-type and two pyridine –type) in the 1-, 2-,and 3,-position. It was also name as v-triazole (v-for vicinal) to distinguish it from s-Triazole (s for symmetrical) [11**].**



(26) (27) (28)

The fusion of a benzene ring with 1, 2, 3-triazole result into Benzotriazole. Which are named and numbered as

shown in below structures [12].



1H-form
1H-Benzo[d][1,2,3-triazole]
(1,2,3-Benzotriazole)
(29)

1H-form
2H-Benzo[d][1,2,3-triazole]
(2,1,3-Benzotriazole)
(30)

Tautomeric forms of Benzotriazoles

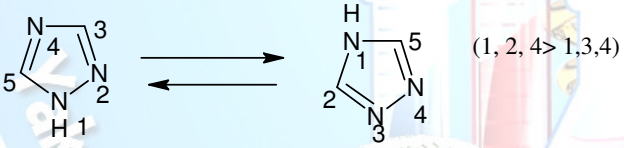
Benzotriazole exist in two tautomeric forms, but 1*H*-form predominates over the 2*H*-form. 1, 2, 3-triazoles find their applications in medicine as sedatives, anti-inflammatory, analgesic etc .**[13,14].**

B) 1, 2, 4-Triazoles:

1, 2, 4-Triazoles are cyclic hydrazidines with hydrogen atom (or substituent) on either hydrazide nitrogen (31)or on amide nitrogen (32). Parent 1, 2, 4-triazole (1*H*-form) is in tautomeric equilibrium with 1, 3, 4-triazole (1*H* form) **[15].**

1*H*-1,2,4-triazole
4*H*-1,2,4-triazole
1*H*-1,3,4-triazole

The interconversion of two tautomer forms occurs rapidly and their separation difficult, however, 1, 2, 4-triazole tautomeric is preferred over 1, 3, 4-triazole tautomer (less symmetrical 1*H*-formIs favored over symmetrical 4*H* form) **[16].**



(34) (35) (1, 2, 4> 1,3,4)

1 ,2,4triazole 1,3,4 triazole

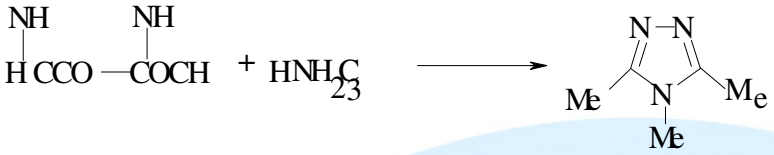
N-Unsubstituted 1, 2, 4-triazole exist in two tautomeric form (if substituent R3 and R5 are different) with the predominance of 1*H*- or 2*H*- form depending on the conditions.

(36) 1-*H* form (37) 2-*H* form

2. **Synthetic routes of Triazoles**

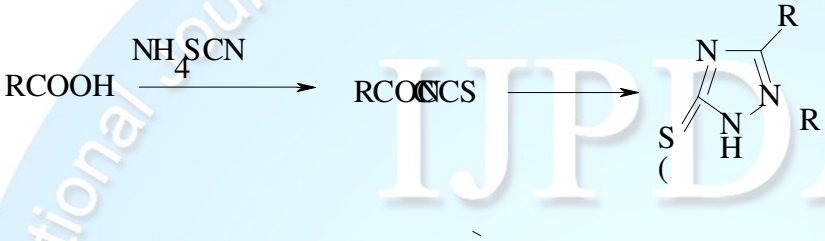
Many methods are to synthesize 1, 2, 4-triazole and its derivatives,

2.1.1From diacylhydrazide [17]



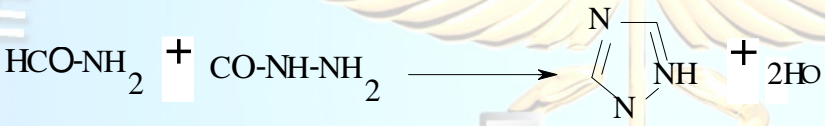
DiacylhydrazideMethanamine3,4,5-triamethyl-4*H*-1,2,4-triazole

2.2.. From acyl thiocyanates [18]



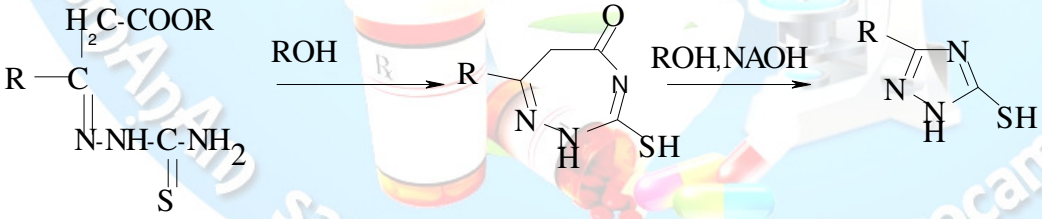
Carboxylic acid Acyl thiocyanate1,5,-disubstituted-4*H*-1,2,4- triazole-3-thiole

2.3. Triazoles may be prepared by heating acid hydrazide with amides e.g. Formylhydrazide and Formamide give triazole.**[**19]



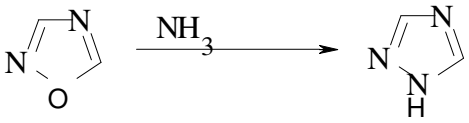
Formamide Formylhydrazide1*H*1,2,4-triazole

2.4.. From thiosemicarbazone via. 1, 2, 4- triazepines [20]



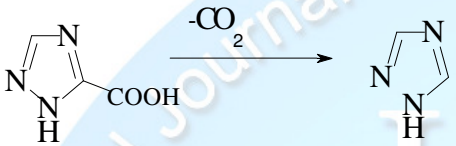
Thiasemicarbazon 1,2,4-triazepine 5-substituted-4H-1,2,4 triazole-3-thiole

2.5. From 1, 2, 4-oxidazole.[21]



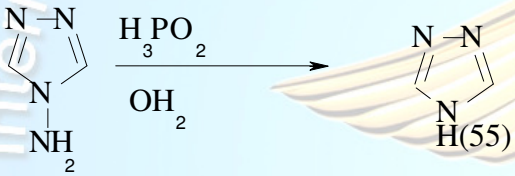
1,2,4-oxadiazole 1*H* 1,2,4-triazole

2.6.. By decarboxylation of 1, 2, 4-3(5)-carboxylic acid.[22]



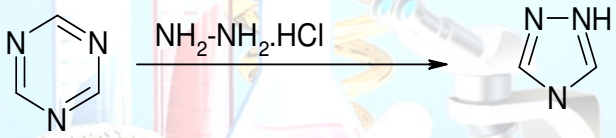
1*H*-1,2,4-triazole-5-carboxylic acid 1 *H*-1,2,4-triazole

2.7. From 4-amino-1, 2, 4-triazole.[23]



4 *H*-1,2,4-triazole-4-amine 4*H*-1,2,4-triazole

2.8. From 1, 3, 5- triazole[24]

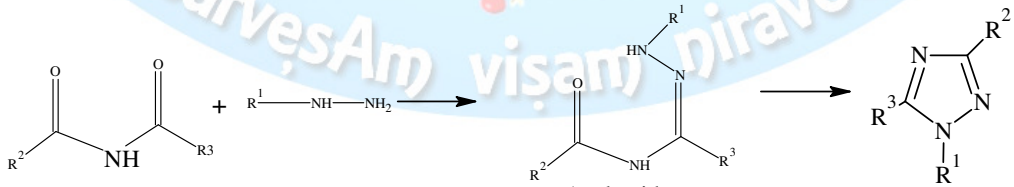


1,3,5-triazine 4*H*-1,2,4,-triazole

2.9. Synthesis:

1) From Hydrazine Derivatives:-

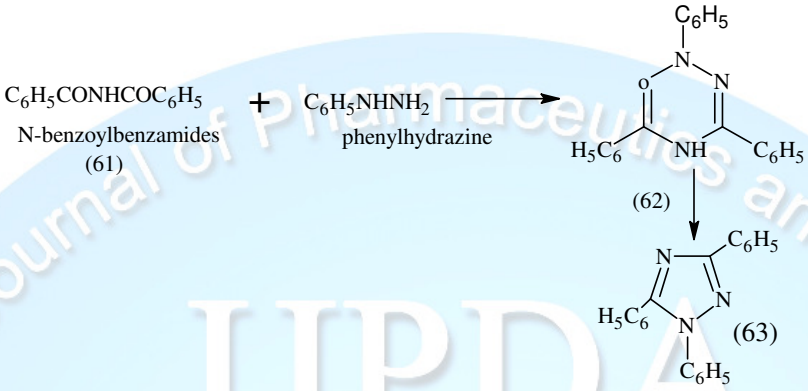
Synthesis of 1, 2, 4-triazoles involves the use of hydrazine and represented schematically **[25].**



n-acetylacetemide (58) Acylamidrazone (59) (60)

2.10. Einhorn- Brunner reaction:-

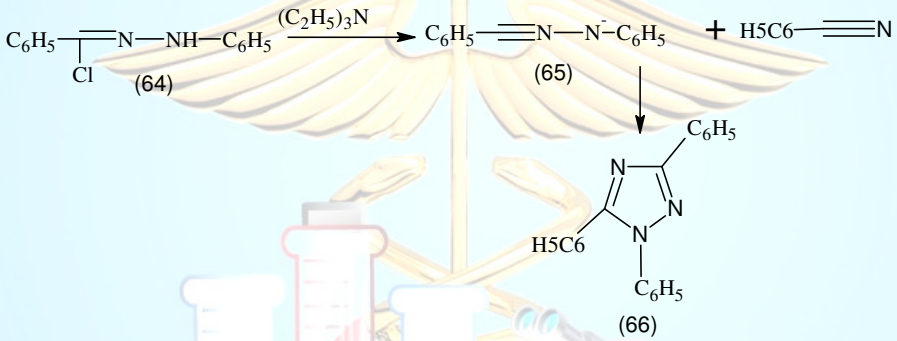
This reaction involves the condensation of diacylamines with mono substituted hydrazine's in the presence of a weak acid and proceeds via and amidrazone intermediate**. [**26]



1,3,5-triphenyl-1H-1,2,4 triazole

2.11. From Nitrilimines:

1,3-Dipolar cyclo additions of nitrilimines , obtained by dehydrohalogenationof C-halobenzylidenephenylhydrazones ,with nitriles leads to the formation of 1, 2, triazoles[27].



1, 3, 5-triphenyl-1-*H*-1,2,-triazole

3.0. Structure of Triazole:

1, 2, 4-Triazole has a planar structure with the following structural parameters.[10] 1, 2, 4- triazole is aromatic and its resonance energy has been estimated to be 205.9 KJ/mol.The calculated energy difference between two tautomer of 1, 2, 4-triazole also supports the presence of 1*H*-tautomer over the 4*H*-tautomer.[28]

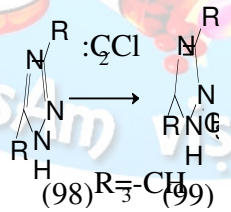


Table.No.1- triazole structural parameter

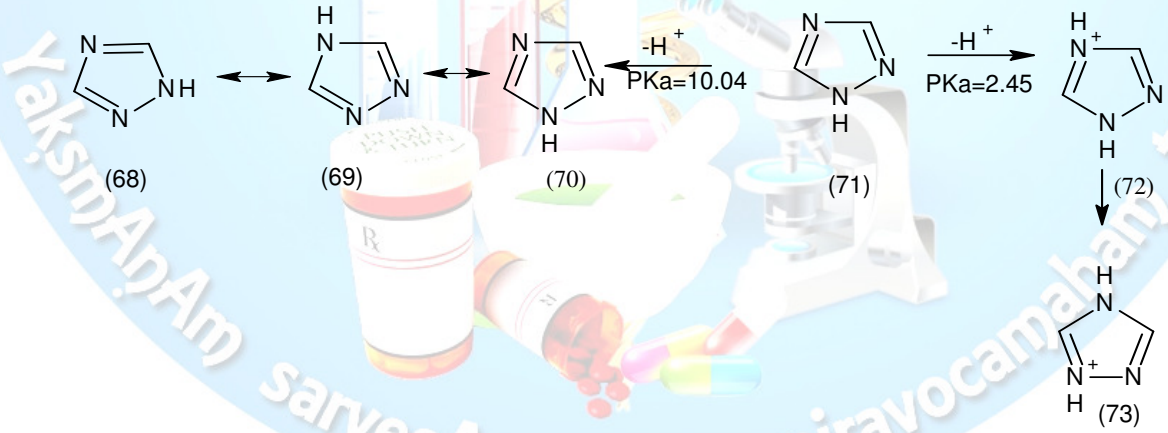
Bond	Length
N_1-N_2	1.359
N_2-N_3	1.323
C_3-N_4	1.359
N_4-C_5	1.324
N_1-C_5	1.331
N_1-H	1.030
C_3-H	0.930
C_5-H	0.930

Bond	Angel
C_5-N_1-N_2	110.2
N_1-N_2-C_3	102.1
N_2-C_3-N_4	114.6
C_3-N_4-C_5	103.0
N_4-C_5-N_1	110.1

4.0.. Reactions:

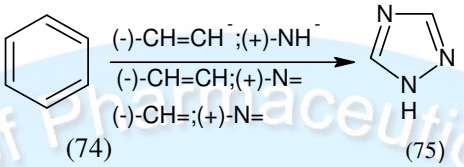
4.1. Acidity – Basicity:

1, 2, 4-Triazole is slightly less acidic (pKa = 10.04 for proton loss), but more basic (pKa = 2.4 for proton addition) than 1, 2, 3-triazole. The Basicity of 1, 2, 4-triazole is attributed to the mesomeric stabilization of the imidazolium type cation formed on protonation. Moreover, the maximum separation of protonated nitrogen's (N_1 and N_4 rather than N_1 and N_2) makes the cation most stable-



Reactivity:

1, 2, 4-Triazole is consider to be derived from benzene by replacement of - CH=CH- by –NH- and the replacement of two –CH= by two –N= atoms.



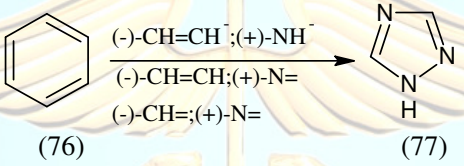
(74) (75)

Benzene 1*H*-1,2,4-triazole

The replacement of –CH=CH- in benzene by –NH- enhances the electron density and hence makes 1, 2, 4-triazole susceptible towards electrophilic attack as compared to the benzene. But the replacement of two –CH= by two –N= atoms causes the resulting 1, 2, 4-triazole to be nearly un-reactive towards electrophilic. Therefore1, 2, 4-triazole to fail to undergo nitration, sulphonation and N-oxidation. However 1, 2, 4-triazole anion undergoes alkylation and acylation very readily. 1, 2, 4-Triazoles undergo nucleophilic substitution, if substituted with electron withdrawing substituent's. The reactivity of 1, 2, 4-triazole ring towards nucleophiles is Enhanced in 1, 2, 4-triazolium cation and mesoionic 1, 2, 4-triazoles.

4.2. Reactions with Electrophiles:

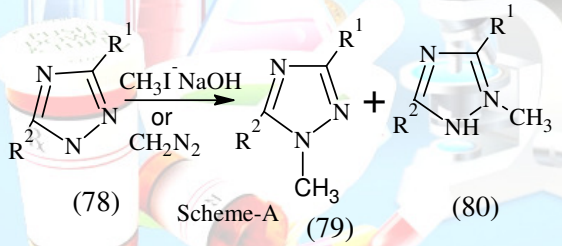
i) Electrophilic attack at Nitrogen:



(76) (77)

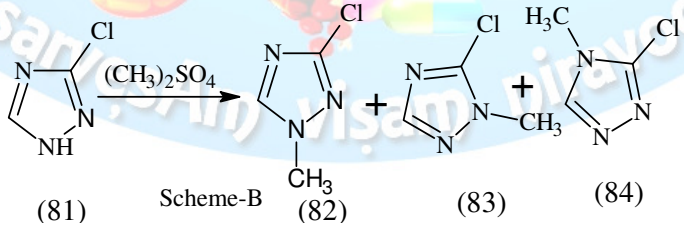
Benzene 1*H*-1,2,,4-triazole

Alkylation of N-Unsubstituted 1, 2, 4-triazoles generally occurs at N-1 rather than at N-4. If there is chance of alkylation between N-1 and N-2 due to the nature of substituent's at the positions -3 and -5, the alkylation occurs at both the positions (N-1 and N-2) with the formation of both N-alkylated products in a ratio depending on the alkylating agent (scheme -A). However, alkylation of 3-halo-1, 2, 4-triazoles with dimethyl sulphate in the absence of a base occurs at N-1, N-2 and N-4(Scheme-B).**[25]**



(78) (79) (80)

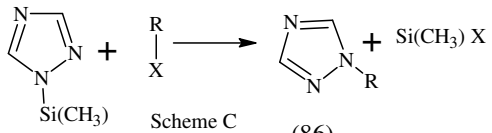
Scheme-A



(81) (82) (83) (84)

Scheme-B

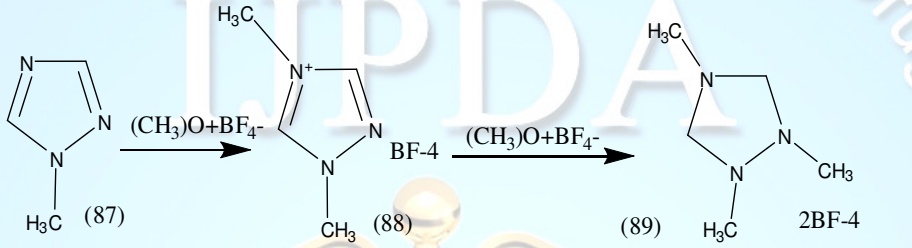
If trimethylsilyl group is present at N-1, the alkylation occurs selectively at N-2 with the removal of trimethylsilyl group (scheme-C) [28].



(85) Scheme C (86)

ii) Quaternization:

1, 2, 4-Triazoles substituted with alkyl, aryl, or acyl substituent on N-1 or N-4 undergoquaternization when treated with powerful quaternizing reagents, trialkyloxonium, tetrafluroborates. The Quaternization occurs on the nitrogen atom furthest away from the substituted nitrogen (maximum distance between substituents on annular nitrogen atoms). Thus 1, 2, 4-triazole substituted on N-1 is quaternized on N-4 and vice versa. 1- Substituted and 4- substituted 1, 2, 4-triazoles are, therefore quaternized at N-4 and N-1 positions, respectively. Di-quaternization is also possible with an excess of trimethyloxoniumtetrafluroborates [29**]**.

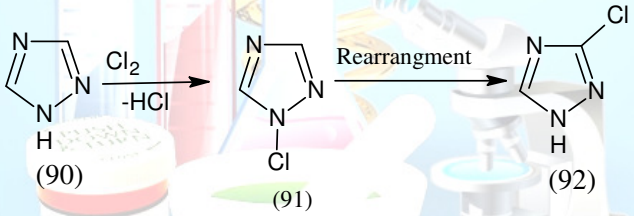


1-methyl-1*H*-1,2,4-triazole 1,4-dimethyl-1*H* -1,2,4-triazol-4-ium 1,2,4-trimethyl-1,2,4-triazolidine

ii) Electrophilic attack on Carbon:

1, 2, 4-Triazole and its C-mono alkyl derivatives fail to undergo nitration. If 1, 2, 4-triazole is substituted with an aryl group on carbon, nitration occurs on the benzene ring. But in 3-*p*-nitrophenyl-1,2,4-triazole in which benzene ring is deactivated by the nitro group, the nitration results in C-nitro derivative via N- nitro derivative.(scheme-A)**[27].**

Halogenations of 1, 2, 4-triazole is considered to proceed via N-halo-1, 2, 4-triazole with the formation of 3-halo-1, 2, 4-triazole. (Scheme-B).

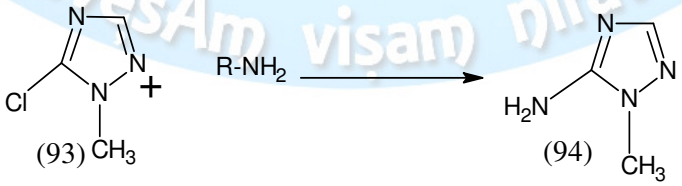


1*H*-1,2,4-triazole1-chloro-1-*H*-1,2,4-triazole 3chloro1*H*-1,2,4-triazole

Scheme-B

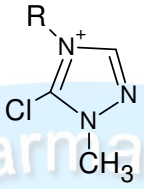
Reactions with Nucleophiles:

1, 2, 4-Triazoles substituted with halo-group at the position-3or-5 undergo nucleophilicsubstitution reactions



5-cholro-1-methyl-1*H*-1,2,4triazole1- methyl-1*H*-1,2,4-triazole-5-amine

The case of nucleophilic displacement is increased with the quaternization of nitrogen or by the presence of an additional electron-withdrawing substituent on the other ring carbon atom.



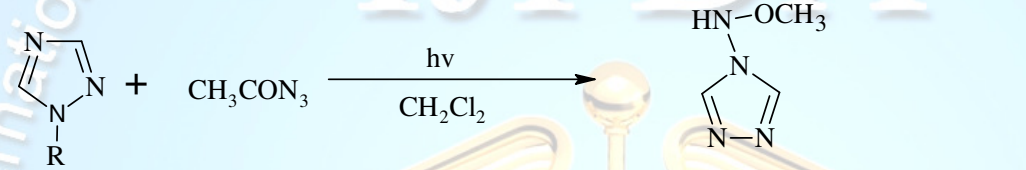
(95)

5-chloro 1-methyl1*H*-12,4-triazole

Reactions with Electron withdrawing Species:

i) Reactions with Nitrenes:

The reaction of 1-alkyl-1, 2, 4-triazoles with nitrenes, generated by irradiation of azides, results in the formation of N-imines [30].



1-methyl 1H 1,2,4 triazole

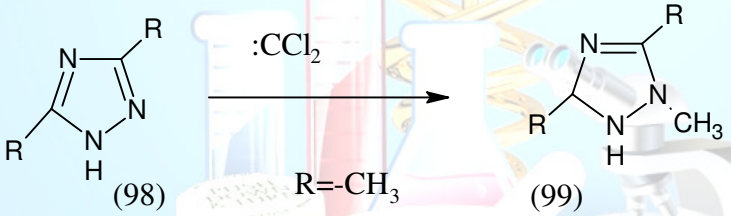
(96)

4(methoxyamino)-1-methyl-4-*H*,1,2,4triazol-1-ium

(97)

ii) Reaction with carbenes:

The reaction of 1, 2, 4-triazoles with dichlorocarbene does not proceed with the ringexpansion as in pyrazole and imidazole, but result in the formation of bis or tris-, 2, 4-triazoles [28].



(98)

3,5-dimethyl-1-*H*-1,2,4 triazole

(99)

1,3,5trimethyl-2-3dihydro-1-*H*-1,2,4,triazole

5.0 Pharmacological activities of triazole derivatives : The synthesis of high nitrogen containing heterocyclic systems has been attracted to many pharmaceutical and agrochemical industries. The triazole nucleus is one of the most important heterocycles which is a feature of natural products and medicinal agents. Triazole nucleus is enjoying their importance as being the center of activity. The nitrogen containing heterocyclics are found in abundance in most of the medicinal compounds. The triazoles are said to be the isosters of imidazoles in which the carbon atom of imidazole is isosterically replaced by nitrogen. Triazole & its derivatives have a wide range of application. The derivatization of Triazole ring is based on the phenomenon of bioisosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen triazole analogue. The triazole derivatives are versatile and have been featured in a number of clinically used drugs. The most relevant and recent studies have revealed that triazole derivatives have a broad spectrum pharmacological activities. Triazoles and its derivatives possess a great importance in medicinal chemistry and can be used for the synthesis of numer-

ous heterocyclic compounds with different biological activities. This review article covers the latest information over active triazoles derivatives having different pharmacological action. Triazole compounds are extensively used in clinic, and are currently one of the most important fields in the researches and developments of drugs the chemistry of triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. 1,2,4-triazole derivatives exhibit wide range of biological activities including Antibacterial[31-33], Anti fungal[24,35], Antitumour[36] , Antiinflammatory[37], Antitubercular[38], Hypogly caemic [39,40] , Antidepressant[41], Anti convulsant[42], Anticancer[43], Antimalaria l [44], Antiviral[45], Anti-proliferative[46], Analgesic[47] and antimigraine[48]. The first studies of 1,2,4-triazoles were concerned with structural isomerism[49]. Modern instrumental and theoretical methods achieved much success in dealing with tautomeric problems, the complexity of which is one of the enduring charms of the chemistry of 1,2,4-triazoles. Example of tautomerisation is shown by 3 Pheny l-1H-1,2,4-triazol-5-amine with 5-phenyl-1H-1,2,4-triazol-3-amine[50]

5.1 **Antibacterial and Antimicrobial Activities**: Infectious diseases have been serious and growing threatens to human health during the past few decades. The sensibility decrease to antimicrobial agents have also been increasing for a great variety of pathogens and the resistance to multiple drugs is more and more prevalent for several microorganis ms, especially for Gram-positive bacteria and some fungi. The literature survey of the recent studies done on triazole containing metal complexes indicates that they have antimicrobial activities like anti-bacterial and antifungal activities which have been summarized as given below: Vikrant S. Palekar et al, had reported synthesis of 1,4-bis(6- (substituted phenyl)-[1,2,4]-triazolo[3,4b]-1,3,4-thiadiazoles an d 4-bis(substituted phenyl)-4-thiazolidin one derivatives and screened for their anti bacterial activity. Several of these compounds showed potential antibacterial activity[51]. Nuray Ulusoy et al., establi shed a synthesis of new N-alkyli dene /arylidene-5-(2-furyl)-4-ethyl-1,2,4-triazol e-3-mercaptoacetic acid hydrazides and tested for antimicrobial activity. Above mentioned compound showed antibacterial activity against some bacteria[52]. Gabriela Laura Almajan et al, synthesized 4- (Su bstituted-arylidene)amino-5-[4-(4-Xpheny lsulfonyl)phenyl]-2-(morpholin-4-ylmthyl) -2,4-dihydro-3H- 1,2,4-triazole-3-thio ne evaluated for their anti-bacterial activity[53]. Synthesis of new 1,2,4-tri and 1,3,4-thiadiazoles were prepared by Khosrow et al. This synthesis bearing isomeric pyridyl and 1-naphthyl is reported using 1,4- disubstitutedthio semi carbazides in alkaline and acidic media, respectively. The methylthio and benzyl thio derivatives of the synthesized triazoles are also reported. All of the synthesized compounds were characterized by their FT-IR, 1H-NMR and mass spectral data. The antibacterial studies of some of the synthesized compounds against S. aureus and E. coli as MIC values are reported[54] . Synthesis of Indole-3-carboxylic acid hydrazide (2) was prepared by Abdel-Rahman et al. This synthesis was treated with aromatic aldehydes in ethanol to give the corresponding hydrazone derivatives in good yields. The indole carbohydrazide was incorporated into the 3-indolyl oxadiazoles. This synthesized compound show good antibacterial and anti-fungal activity[55]. Kiran et. al., had synthesized new organosilicon(IV) and or ganotin(IV) complexes by the reaction Me2MCl2 where (M= Si and Sn) with new ligands, 4-[(4cyano-benzylidene)-amino]-5-mercapt o-1,2,4triazole and 4-[(4-Cyano-benzyli dene)-amino]- 5mercapto-3-methyl-1,2,4-triazole in absolute methanol. The metal complexes had been proposed to have trigonal bipyramidal and octahedral geometries. This geometry was confirmed by the elemental analyses, molar conductance and spectral (UV, FT-IR, 1H, 13C, 29Si and 119Sn NMR) studies. In vitro antimicrobial activities of the compounds were evaluated. Me2Sn (L7)2 was found to possess highest antimicrobial activity[56]. Singh et al., had synthesized Zn(II) compl exes by the reactions of zinc(II) acetate with bidentate ligands of triazole Schiff bases derived from 3substituted phenyl-4-amino-5-hydrazino-1,2,4-triazole and benz aldehyde,2-hydroxyacetophenone or indo line-2,3-dione. They were characte rized by Elemental analyses, FT-IR, 1H NMR, 13C NMR and FAB mass. All these triazole Schiff bases and their complexes have also been screened for their antibacterial activities against Bacillus subtilis, Escherichia coli and antifungal activities against Colletotrichum falcatum

Aspergillus niger, Fusarium oxysporium and Carvularia pallescence by petriplates methods. The compound [ZnL11(H2O)2] is more active against all bacteria and fungi because they have additional heterocyclic ring (indoline-2,3- dione)[57] .

5.2 **Anti-Cancer Activity** Currently, the treatment for cancer primarily includes surgery and chemo therapy, but the curative effects of the existing chemotherapeutic drugs are not good enough and they have plentiful side effects. The development of more effective drugs for treating patients with cancer has been a main attempt over the past 50 years. Alias et. al., had synthesized two new complexes with formula [M(NMP.(5-(4-NitroPhenyl)-4-Amino-3-MercaptoPropen yl-1,2,4-Triazole))(H2O)3](NO3)2. 3Et OH (where M is Ni and Co(II) ions res pectively, NMP. These complexes have been characterized by spectroscopic methods such as (ultraviolet- visible and infrared), as well as to thermal gravimetric, metal analyses, micro ana lyses, conductivity, magnetic moment and molar ratio method. To measure the biologic activity and potential anticancer efficacy of these compounds, they have been compared with cisplatin on human hepatocarcinoma HepG2 cell lines in different eight concentrations (2000, 1000, 500, 250, 125, 62.5, 31.25 and 15.625 μg/ml) respectively, in the time of exposure 72 hrs. The results exhibit that the three prepared complexes i.e. ligand (NMP.TRZ) and its metal complexes have shown higher ratios cytotoxicities compared to cisplatin against HepG2 cell lines in most selected concentrations. Based on the obtained results of biological test, these compounds with L44 may be potentially being considered as good anticancer candidates for further pharmacological studies[58]. Synthesis of a series of heterocycle-fused 1,2,3-triazoles by 1,3-dipolar cycloaddition of heter ocyclic ketene aminals or N, O-acetals with sodiumazide and polyhaloisopthalo nitriles has been carried out and evaluated in vitro against a panel of human tumour cell lines.Compound 4-Methoxy-phenyl substituted 1,3, oxazo heterocycle fused 1,2,3-triazole 29 was found to be most potent derivative against A431 and K562 human tumor cell lines[59]. A new series of 3,6-disubstituted triazolo [3,4b]thiadiazole derivatives has been synthesized by simple, high yielding routes. The newly synthesized compounds were evaluated for their cytotoxic activity against a panel of 60 human cancer cell lines by the National Cancer Institute (NCI) and some of them demonstrated inhibitory effects on the growth of a wide range of cancer cell lines generally at 10−5 M level and in some cases at 10−7 M concentrations. In this assay, the anti-tumor activity of the newly synthesized compounds could not be interpreted in terms of tyrosine kinase inactivation but more likely as a relatively broad specificity for the ATP-binding domain of other kinases. The pharmacological mechanis m of action for these intriguing compounds has not, as yet, been successful [60]. A series of 4- aryliden amino-4H-1,2,4-triazole derivatives were reported by Olcay et al. This series were synthesized from the treatment of 4-amino-4H-1,2,4-triazole with certain alde hydes. Compounds were characterized by elemental analyses and 1H NMR, 13C NMR, IR and UV spectral data. In recent years, various 1,2,4-triazoles and 4,5-dihydro-1H-1,2,4-triazol-5- ones have been found to be associated with diverse pharmacological activities such as anti-convulsant, antifungal, anti-cancer, anti-inflammatory and anti bacterial[61] .

5.3 **Analgesic Activity** A series of 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid were synthesized in order to obtain new compounds with potential antiinflammatory activity, analgesic activity and lower ulcerogenic potential. All compounds were evaluated for their anti-inflammatory activity by the carrageen an induced rat paw edema test method. The compounds possessing potent anti-inflammatory activity were further tested for their analgesic, ulcerogenic and antioxidant activities. These compounds showed significant analgesic effect and at an equimolar oral doses relative to flurbiprofen were also found to be non-gastrotoxic in rats. (81.81%) than the reference drug (79.54%), low ulcerogenic potential and protective effect on lipid peroxidation[62] .

5.4 **Anticonvulsant activity** A series of novel 3-{[(substituted phenyl) methyl]thio}-4- alkyl/aryl-5-(4-aminophen yl)-4H1,2,4-triazoles and several related Schiff's bases, 3{[(sub stituted phenyl) -methyl]thio}-4 alkyl/aryl-5-{[[(s bstituted phenyl/5-nitro-2- furyl)methylene] amino]-phenyl}-4H-1,2,4-triazoles were synthesi zed for evaluation of their biological properties. Structures of the synthesized compounds were confirmed by the use of their spectral data besides elemental analysis. All com-

pounds were evaluated for their anticonvulsant activity by maximal electroshock (MES), subcutan eous pentylenetetrazole (scPTZ) and neuro toxicity (NT) screens. A number of triazole derivatives, exhibited protection after intraperitoneal administration at the dose of 100 and 300 mg/kg in one or both models employed. Some of the tested compounds showed marginal activity against M. tuberculosis H37Rv[63]. A series of 4-(4-alkoxylphenyl)-3-ethyl-4H-1,2,4- triazole derivatives was synthesized as open chain analogues of 7-alkoxyl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinolines. Th eir anticonvulsant activities were evalu ated by the maximal electroshock test (MES test) and their neurotoxicity was evaluated by the rotarod neurotoxicity test (Tox). MES test showed that 3-ethyl-4-(4-octyloxyphenyl)-4H-1,2,4-triazole 3q was found to be the most potent with ED50 value of 8.3 mg/kg and protective index (PI = TD50/ED50) value of 5.5, but compound 3r, 3-ethyl-4-(4octyloxypheny l)-4H-1,2,4- triazole, exhibited better PI value of 9.3, which was much greater than PI value of the prototype drug phenytoin. For explanation of the possible mechanism of action, the compound 3r was tested in pentylenetetrazole test, isoniazid test, thio semicarbazide test, 3-mercaptoprop ionic acid and strychnine test[64]. Several new N4-substituted triazolyl thiazoles were reported by Bineshmarvasti et al. These compound were prepared by the general method for 1,2,4- triazole ring closure. Anticonvulsant activity of compounds was measured against pentylene tetrazole-induced seizures in mice by intraperitoneal injections of different doses of the test compounds. Pretreatment of animals with flumazenil (10 mg/kg, i.p.) as a benzo diazepine receptors antagonist did not have any significant effect on anticonvulsant activity of the test compounds. These results demonstrate that the anticonvulsant activity of N4-substituted triazolylthiazole agents is not probably mediated by direct interaction with benzodiazepine receptor complex[65]. Various 3-[4-(substituted phe nyl)-1,3-thiazol-2ylamino]-4-(substituted p henyl)-4,5-dihydro-1H-1,2,4–tri azole-5-thiones has been synthesised by clubbing thiazole and triazole moieties, keeping in view the structural requirement for the pharmacophore model for anticonvulsant activity. Two compounds 1a and 1b showed significant anticonvul sant activity in both MES and subcut aneous pentylenetetrazole (sc PTZ) screen along with wide safety of margin with protective index (PI), median hypnotic dose (HD50) and median lethal dose (LD50) much higher than standard drugs[66]. A new series of 4,5-diphenyl-2H-1,2,4-triazol- 3(4H)-one were synthesized to study the effect of cyclization of the semicarbazone moiety of aryl semi carbazones on the anticonvulsant activity. All compounds were evaluated for their anticonvulsant activity in four animal models of seizures, viz. maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine (scSTY), and subcutaneous picrotoxin (scPIC)induced seizure threshold tests. The compounds were also evaluated for neurotoxicity. Eight compounds exhibited anticonvulsant activity in all the four animal models of seizure[67] .

5.5. **Antifungal activities** Yasemin et al. prepared a new series of 1-(2-hydroxy-2- phenyl-ethyl)-3-thiophen-2-ylmethyl-4-[arylidene-amino]- 4,5-dihydro-1H-[1,2,4]triazole-5-ones and 1-(2-hy droxy-2 phenyl-ethyl)3-thiophen-2-yl me thyl-4-[aryl-amino]4,5- dihydro-1H-[1,2,4] triazole-5-ones from 2-(1-ethoxy-2-(thio phen-2-yl)ethylidenehydrazinecarbox ylate and hydrazine hydrate. The newly synthesized compounds were screened for their antifungal activity. The derivatives of compound exhibited significant antifungal activity[68] . Bijul lakshman synthesized twenty eight derivative of 4-amino-5-substituted aryl-3mercapto-1,2,4-triazoles and these compoun ds have been tested in vitro against Rhizoctonia solani, Sclerotium rolfsii, Fusarium oxysporum, Pythium aphanidermatum, Puccinia recondite and Bipolaris sorokiniana . the compound exhibits highest activity again st Puccinia recondite(ED50 = 12 mg/ ml) and the compound exhibits highest activity against Bipolaris sorokiniana (ED 50= 27 mg/ml)[47]. Monikaet and co-workers synthesized derivative of the 9-substituted-3-aryl-5H,13a-H-quinolino[3, 2f] [1,2,4] triazolo[4,3-b][1,2,4]triaze pines from the 5-aryl-3,4- diamino-1, 2,4-triazols and 2-chloro-3-formylquinolines using catalytic amount of p-TsOH and N,N-dimethyl formamide as an energy transfer medium using microwave heating as well as solvent using oil-bath and the synthesized compounds were screened for antifungal activity against Aspergillus flavus, Aspergillus niger, Rhizopus species and Penecillum notatum species by paper disc technique against two

concentration 500µg/ml and 1000µg/ml. the compounds showed excellent anti-fungal activity against Aspergillus niger and Penecillum notatum at 500µg as well as and 1000µg[69] . Yan Zou et al, prepared a series of 1-(1H-1,2,4- triazol-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2- propanols. The in vitro antifun gal activities of all the target compounds were evaluated against eight human pathogenic fungi. Compound showed the best antifungal activity[49] . Xiaoyun Chai et al, synthesized a series of 1-(1H-1,2,4- triazol-1-yl)-2-(2,4-di fluoro phenyl)-3-[(4-substituted trifluoromethyl phenyl)-piperazin-1-yl]-propan-2-ols and evaluated for their antifungal activity. Some of the compounds showed excellent anti-fungal activity[70] .

6.0 **Conclusion** Triazole is a unique moiety that is responsible for various biological activities. This article highlighted basic chemistry and research work of many researchers reported in literature for different pharmacological activities on synthesized triazole compounds. Triazole compounds have finalized much significance as they have also been explored for their diverse biological activities. Different new and potent compounds will prepared to explore more effective and potent molecule by substitution of different atoms or groups on Triazole ring with different pharmacological activities.

7.0. References:

1. A. Kamal., MA. Syed, & SM. Mohammed. "Theraputic Potential of Benzothaizole," A Patent Review (2010- 2104). Informa healthcare, 25 (3), 335-349, 2015.
2. A. Bretschnider, E. Franken, U. Gőrgens, M. Füsslein, A. Hense, J. Kluth, HG. Schwarz, A. Kohler, O. Malsam, A. Voerste, & A. Becker, Heterosyclic Compounds as Pestisides. United states: Patent Application Publisher, 2014.
3. P. Gourdon, JH. Andersen, KL. Hein, M. Bublitz, BP. Bendersen, X. Liu, L. Yatime, M. Nyblom, TT. Nielsen, C. Olsen, JV. Møller, P. Nissem, & JP. Morth, "HiLiDe-Systematic Approach to Membrane Protein Crystallization in Lipid and Detergent. Cryst," Growth Des., 11 (6), 2098-2106, 2011.
4. P. Yang, PA. Martos, & B. Barrett, "Symposium Introduction: 2014 North American Chemical Residue Workshop," J. Agric. Food Chem., Just accepted manuscript. 2015.
5. K. Fuji, S. Tampa, K. Shono, A. Sugie, & A. Mori, "Murahashi Coupling Polimerization: Nickel (II)-N- Heterocyclic Carbene Complex-Catalyzed Polycondensation of Organolithium Species of (Hetero)arenes," J. Am. Chem. Soc., 135 (33), 12208- 12211, 2013.
6. Y. Andrei, "Introduction: Small Heterocycles in Synthesis," Chem. Rev., 114 (16), 7783, 2014.
7. Y. Hau, S. Chang, D. Huang, X. Zhou, X. Zhu, J. Zhao, T. Chen, WY. Wong, & WK. Wong, "Significant Improvement of Dye-Sen
8. J. Burschca, A. Dualeh, F. Kessler, E. Baranaoff, N. Crevey-Ha, C. Yi, MK. Nazeeruddin, & M. Grätzel, "Tris(2-(1H-pyrazol-1-yl)pyridine) cobalt (III) as p- Type Dopant for Organic Semiconductor and Its Application in Highly Effecient Solid-State Dye- Sensistized Solar Cells," Am. Chem. Soc., 133 (45), 18042-18045, 2011.
9. V. Thottempudi, F. Foroohar, DA. Parrish, & JM. Shreeve, "Tris(triazolo)benzene and Its Derivatives: High-Density Energetic Materials," Angew. Chem. Int. Ed. Engl., 51 (39), 9881-9885, 2012. sitized Solar Cell Performing Using Simple Phenothiazine-Based Dyes," Chem. Mater., 25 (10), 2146-2135, 2013.
10. Goldstein P, Ladell J, Abovitz C, *Acta Crystallography.* (1969) 25:135.
11. Dewar M.S., Morita T, *Journal of American Chemical Socity.*(1969)91: 796.
12. Bernaridini A.,Viallefont P., Danius J., Romestant M.L., Soulami., *Bull. Soc. Chem.* (1975) 647.
13. Gasparini J.P., Gassend R., Mire J. C., Eulgerio*J. Organomet Chem.* (1980) 141:188.
14. Olofsan R.A., Kendal R.V.., *Journal of Organic Chemistry*. (1970) 35:2246.
15. Habraken C.L., Cohn-Fernandes., *J. Chem. Soc. Chem. Commun.*(1972) 37.
16. Timpe H.J., "*Advance Hetrocyclic Chemistry*". (1974) 17: 213.
17. Desai K.R.,*Green Chemistry Microwave Synthesis*, First Edition, Himalaya Publication House, India (2005) 1.
18. Galema S.A., Halstead B.S., Mingos D.M.,*Chem. Soc. Rev.*(1998) 2:213-232.

19. Horikoshi S., Hamamura T., Kajitani M., Yoshizawa-Fujita M.,SerponeN.*Org. Process Res. Dev*.(2008) 12:1089-1093.
20. Kenkre V.M., skalaLM.W., Weiser; Katz J.D. *Mater J., Sci.* (1991) 26: 2483.
21. Ramesh P.D. Vaidyanatha B.M., GanguliK.J.J.,Rao; J. Mater Res. (1994) 2: 3025.
22. Xu X., Yang W., Liu J., lin L.,Adv Master (2000) 3:195.
23. Pileni M.P., Langmuir (1997) 13: 3266.
24. JA He; VallluziR.,Yang K, DolukhanyanT.,Sung C.,KurnaiJ., S\TripathyL.Chem Mater (1999) 11:3299.
25. Samuelson; LBalogh; D Tomalia; Chem Mater (1999) 11: 3268.
26. W Li; Ruan L.,MeitanZhuanhua (1992) 22:87
27. Matursievicz H., Anal Chem(1999) 71 :3145
28. Roszel P.W., US 20 26103 ChemAbstr.; 117,177752
29. Kasai T., Abe S., Kanbayashi S., Okada S.,JP (2000) 34:114.
30. Lee K.Y., Case E.D.,Asmussen J., Mater.J., Res. Innovat.(1997) 1: 101.
31. Varvarason A, Tantili-Kakoulidou A, Siatra-Papastasikoudi T, Tiligada E, Arzneim Forsch, 2000, 50, P. 48-54.
32. Gokce M, Cakir B, Earl K, Sahin M. ,Arch Pharm, 2001,334:,P.279-283.
33. Pintilie O, Profire L, Sunel V, Popa M, Pui A. J Agric Food Chem ,2000;,50,P. 48-54.
34. Zan XI, Lai LH, Ji GY, Zhon ZX.. J Agric Food Chem , 2002,50,P. 3757-3760.
35. Chem H, Li Z, Han Y.,J Agric Food Chem ,2000, 48, P.5312-5315.
36. Passannanti A, Diana P, Barraja P, Mingoia F, Lauria A, Cirrincione G. Heterocycles,1998, 48, 1229.
37. Hosur MS, Talwar R. Ind J Pharm Sci, 1993, 55: 86.
38. Udupi RH, Kulkarni VM, Purushottamachar P, Srinivasalu NJ. Indian Chem Soc 2002,79: 381.
39. Mhasalkar MY, Shah MH, Nikam ST. J Med Chem ,1971, 14(3), 260-262.
40. Mullican MD, Wilson MW, Connor DT, Dyer RD,. J Med Chem, 1993, 36, 1090-1099.
41. Mhasalkar MY, Shah MH, Nikam ST, Deliwda ,J Med Chem.1980, 13(4): 672-676.
42. Ilkay K, Sevim R. Farmaco, 2004, 55(11), 893.
43. Holla SB, Veerendra B, Shivananda MK. Eur J Med Chem. 2003, 38, 759.
44. Jilino M, Stevens FG. J Chem Soc Perkin Trans, b; 1677.
45. Diana GD, Nitz J. J EP, 566199, 1993, Vol ,2,610- 620.
46. Manfredini S, Vicentini CB, Manfrini M, Bianchi N, Rutigliano C, Mischiati C, Gambari R et al. Bioorg Med Chem. 2000, 8, 2343.
47. Shenone S, Bruno O, Ranise A, Bondavalli W, Falcone G, Bioorg Med Chem. 2001, 9, P.2149-2153.
48. Hart C. Am Chem Soc. 1999, 2: 20-31.
49. Ed. A. R.Katritzky, C. W. Rees, pergamon press Ltd., Oxford, (1984) P. 773
50. Dolzhenko AV, Tan GK, Koh LL, Chui WK, Acta Cryst. 2009, 65: 125.
51. Palekar V.S., Damle A.J., Shukla S.R. Eur. J. Med Chem. 2009; 44: 5112–5116
52. Nuray U., Aysel G., Gulten O., Il Farmaco 2001; 56: 947–952.
53. Gabriela L.A., Stefania F.B., E. Almajan, Draghici C., Saramet G. Eur. J. Med Chem. 2009; 44: 3083–3089.
54. Z Khosrow; F Khalil; T Taraneh; RS Mohammad. Turk. J. Chem., 2004, 28, 95 - 100.
55. A Abdel-Rahman; H Farghaly. J. Chin. Chem. Soc., 2004, 51, 147-156.
56. Kiran S, Parvesh P, Yogender K, Chetan S, Int J Inorg Bioinorg Chem, 3, 2013, 57-64.
57. Singh A K, Pandey O P, Sengupta S K. Spect Acta Part A: Mol Biomol Spect, 85, 2012, 1-6.
58. Mahasin Alias, Ameena N. Seewan, Carolin Shakir, Farooq I. Mohammad., Int J Pharm, 4, 2014, 126-132.
59. Yan S, Liu Y, Chen Y, Liu L, Lin J, Bioorganic and Medicinal Chemistry Letters, 20, 2010, 5225–5228
60. Ibrahim DA, European Journal of Medicinal Chemistry, 44, 2009, 27762781.
61. O Bekircan; B Kahveci; M Kucuk. Turk. J. Chem., 2006, 30, 29-40.
62. Suroor A. Khan, Mohammad Amir, European Journal of Medicinal Chemistry, 43; 2008; 2688-2698.
63. I˙lkay Küçükgüzel, Sq. Güniz Küçükgüzel, IL Farmaco 59; 2004; 893–901.
64. Jing Chen, Xian-Yu Sun, Bioorganic & Medicinal Chemistry 15; 2007; 6775–6781.
65. M Bineshmarvasti; M Sharifzadeh; AR Jalilian; K Soltaninejad; and A Shafiee. Daru., 2003,11(2), 74.

66. Siddiqui N, Ahsan W, European Journal of Medicinal Chemistry, 45, 2010, 1536–43.
67. Shalini M, Yogeeswari P, Sriram D, Stables JP, Biomedicine Pharmaco therapy, 63, 2009, 187-193.
68. Y. Univer, E. Dugdu, K. Sancak and S. A. Karaoglu., Turk J Chem., 2009, 33, 135.
69. M. Gupta, S. Paul and R. Gupta., Journal of Chemistry., 2010, 49B, 475.
70. Zou Y., Zhao Q., Liao J., Chai X.,Mingjuan X., Bioorg. Med. Chem. Lett.2012; 22:2959–2962. 50.
71. Chai X., Zhang J., Yongbing Cao, Y. Zou, Wu Q., Zhang D., Jiang YEur.i2011; 46: 3167-3176.