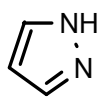
CHAPTER V

Systhesis of Pyrazole,

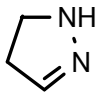
Triazole, Thiazolidinones

INTRODUCTION AND LITERATURE SURVEY:

Pyrazole derivatives constitute an interesting class of organic compounds, which are associated with diverse chemical and pharmacological properties. Pyrazoline have received considerable attention in recent years. Pyrazoline derivatives occupy a unique place in field or medicinal chemistry due to a wide range or biological activities exhibited by them.

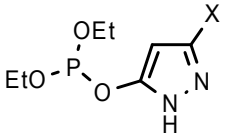


pyrazole



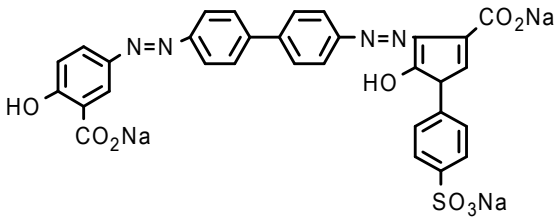
pyrazoline

Pyrazole derivatives have found application in the agrochemical field as insecticides o, o- Diethyl o-[3-methyl-5-pyrazolyl] phosphate (a) & o, o- Diethyl o-[3-methyl-5-pyrazolyl] phosphorothioate (b).



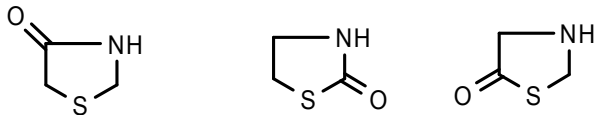
a) X=O
b) X=S

5- Pyrazolone derivatives have found many application as cotton azo dyes because even if they were more expensive intermediates.



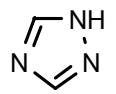
Thiazolidinones are the derivatives of thiazolidine, which belongs to an important group of heterocyclic compounds. Thiazolidinones, with carbonyl group at 2, 4 or 5 have been subject to extensive study in the recent past. Numerous reports have appeared in the literature, which highlight their chemistry and use. Diverse biological activities such as bactericidal, pesticidal, fungicidal, insecticidal, anticonvulsant, anti-tuberculosis, anti-inflammatory, antithyroidal, potentiation of pentobarbital induced of sleeping time, etc., have been found to be associated with thiazolidinone derivatives.

In recent years several new methods for the preparation of thiazolidinone derivatives and reactions have been reported in the literature. Thiazolidinones, in the presence of various reagents, undergo different types of reactions to yield other heterocyclic compounds, e.g., thiazole, benzothiophenes, triazinones etc. These advances warrant reviewing the chemistry and biological properties of various 4-thiazolidinones.

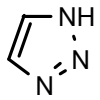


Triazole is one of a class of organic heterocyclic compounds containing a five membered ring structure composed of three nitrogen

atoms and two carbon atoms. The simplest member of the triazole family is triazole I itself, white to pale yellow crystalline solids with a weak characteristic odour, soluble in water and alcohol, melts at 120°C, boils at 260°C. Triazole and its derivatives are used for biological activities such as antiviral, antibacterial, antifungal and anti tuberculosis. Mostly 1, 2, 4-triazole I and 1, 2, 3-triazole II are very important in pharmaceutical industry. Heterocycles bearing symmetrical triazole ring I is reported to show a broad spectrum of biological.

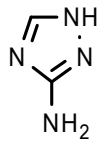


1, 2, 4 triazole

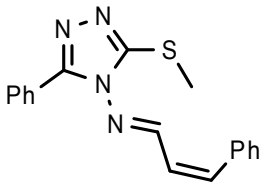


1, 2, 3 triazole

The derivative of triazole ring is based on the phenomenon of bioisosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen atom yields triazole analogue. Out of the two triazoles 1, 2, 4-triazole has wide variety of activity. The first synthesized clinical useful 1,2,4-triazole which is known as 'amitrole'III.Some novel 1, 2, 4-triazole IV act as internal standard inhibitors for nitric oxide synthase in rat plasma and urine.



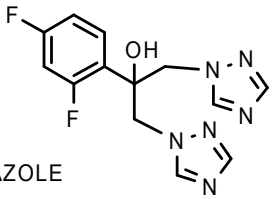
III Amitrole



IV

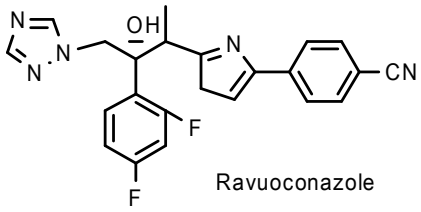
Substituted 1, 2, 3-triazoles can be produced using the azide lkyne Huisgen cycloaddition in which an azide and an alkyne undergo a 1, 3-dipolar cycloaddition reaction. It is a surprisingly stable structure compared to other organic compounds with three adjacent nitrogen atoms. However, flash vacuum pyrolysis at 500 °C leads to loss of molecular nitrogen (N2) to produce aziridine. Certain triazoles are relatively easy to cleave due to so-called ring-chain tautomerism. One manifestation is found in the Dimroth rearrangement. 1, 2, 3-Triazole finds use in research as a building block for more complex chemical compounds, such as pharmaceutical drugs like tazobactam.

Many 1, 2, 4 triazole synthesized compound were used in the treatment of tuberculosis and anti bacterial activity. Some compounds like fulconazole, Ravuconazole, Itraconazole causes bronchial arch anomalies in mice.ATZ, MTZ. NTZ triazole shows anti thyroid activity.



FULCONAZOLE

2-(2,4-Difluoro-phenyl) -1,3-bis-[1,2,4]triazol-1-yl-propan-2-ol



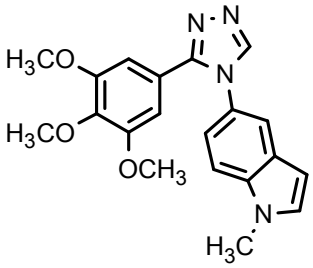
Ravuoconazole

4-{ 5-[2-(2,4-Difluoro-phenyl) -2-hydroxy-1-methyl-3-[1,2,4] triazol-1-yl-propyl]-4H-pyrrol-2-yl} -benzonitrile

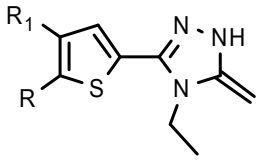
One third of the world population is infected by Tuberculosis (T.B.).T.B. is caused by Mycobacterium tuberculosis.1 Infection mostly occurs through aerosol, inhalation of droplets which contain M. t*uberculosis* bacilli and causes lung infection.2 weaker immunity persons are more likely to be infected with TB. Pathogenesis of M .Tuberculosis starts after infection which occurs in two stages. The first is an asymptomatic that can persists for many years in the host, called latent TB. The second gets activated on weakened immunity. If untreated, it may leads to death.

Exact number of cases is impossible to determine but the latest World Health Organization (WHO) survey reveals about 2 million deaths every year and 8 million new cases annually, and every third individual is either exposed to or infected by *M.tuberculosis*.5Although TB can be treated and even cured chemotherapy treatment is very lengthy and takes 6-9 months along with significant toxicity, lengthy causes poor patience compliance too.

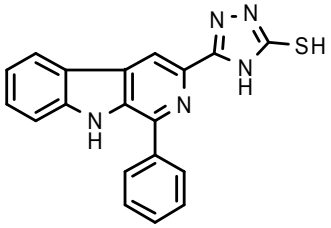
Synthesis of 1, 2, 4-triazole with potent anti proliferative and tumor activity have been reported[1].



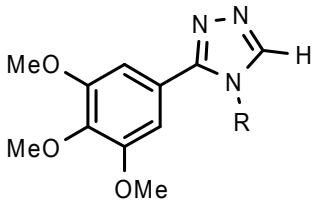
The compound 4, 5-substituted 1, 2, 4-triazole -3-thione and evaluated for their cytotoxicity have been synthesized[2].



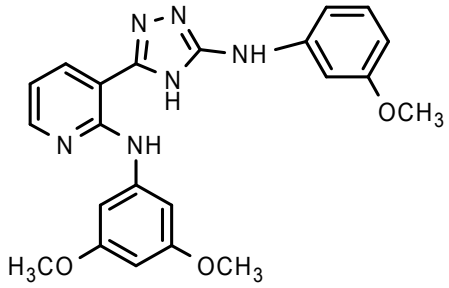
The compound 3-(5-substituted -1, 2, 4-triazole-3-yl) α- carboline derivatives have been synthesized[3].



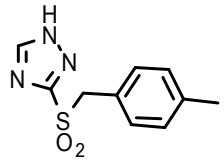
A triazole derivative which possesses highly potent triazole was synthesized[4].



1, 2, 4-triazole as a novel class of potent tubulin polymerization inhibitors was synthesized [5].

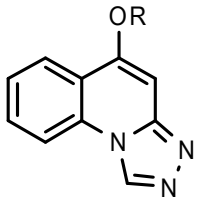


1,2,4-triazole-3-benzylsulfanyl derivatives have been synthesized[6] .



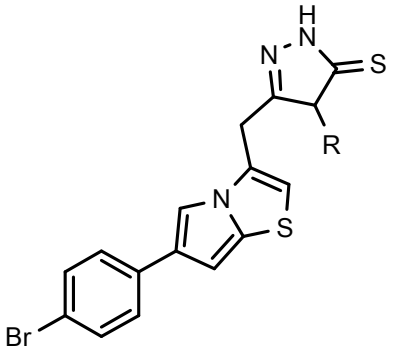
3-p-Tolylmethanesulfonyl-1H-[1,2,4]triazole

5-alkoxy-[1,2,4]triazolo[4,3-a]quinoline derivatives were synthesized and evaluated for anticonvulsant activity[7]. Their anticonvulsant activities were evaluated by the maximal electroshock test (MES) and the compound 5-hexyloxy-[1,2,4]triazolo[4,3-a]quinoline was the most potent anticonvulsant agent.

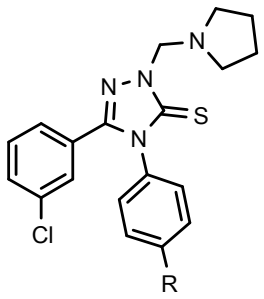


A series of 4-alkyl/aryl-2,4-dihydro-5-((6-(4- bromophenyl) imidazo[2,1-b]thiazol-3-yl)methyl)-3H-1,2,4-triazole-3-thiones,2-

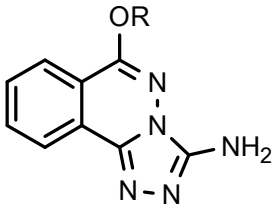
alkyl/arylamino-5-((6-(4-bromophenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-1,3,4-hiadiazoles were synthesized[8] and screened for their antibacterial and antifungal activity.



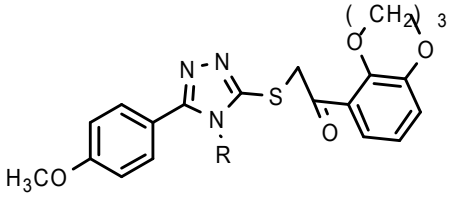
The compound 5-(3-chlorophenyl)-4-substituted-2,4-dihydro-3H-1,2,4-Triazole -3-thiones were synthesized[9] and evaluated for their antibacterial activity. Some of the compounds showed good activity.



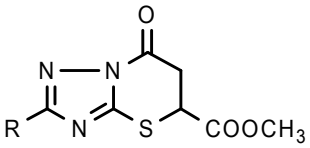
Several new 6-alkoxy (phenoxy)-[1,2,4]triazolo[3,4-a]phthalazine-3-amine derivatives and screened for their anti-inflammatory activity were synthesized[10]. Compounds (6-(2-chlorophenoxy)-[1,2,4] triazolo[3,4-a]phthalazine-3-amine) and (6-(4-aminophenoxy)-[1,2,4] triazolo[3,4-a]phthalazine-3-amine) exhibited the highest anti-inflammatory activity.



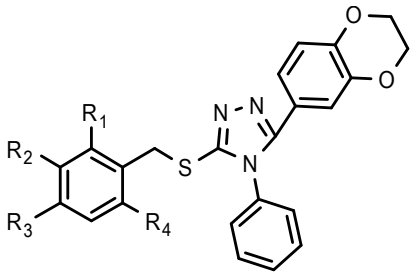
Synthesis of 5-(2-,3- and 4-methoxyphenyl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol derivatives and screened for their anti-inflammatory activity were prepared[11]. Some of compounds showed good anti-inflammatory activity.



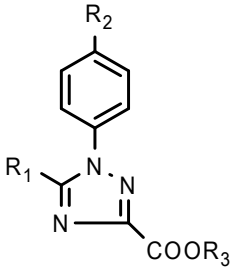
5-carbomethoxy-2-substituted-7*H*-1,2,4-triazolo[3,2-*b*]-1,3-thiazine-7-one derivatives were synthesized[12] and evaluated for their anti-inflammatory activity.



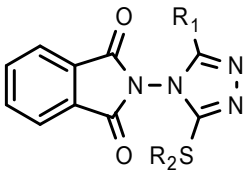
Synthesis of 3-substituted (benzylthio)-5- 2, 3-dihydrobenzo[b] [1, 4]dioxin-6-yl)-4-phenyl-4H-1,2,4-triazole and screened for antitumor activity were prepared[13] and possessed significant antitumor activity against HEPG2 cancer cell line.



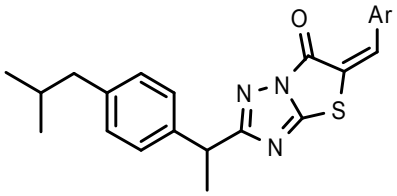
A series of mono fluoro and trifluoromethane-3, 5-disubstituted 1, 2, 4-triazoles screened for anticancer activity were synthesized[14].



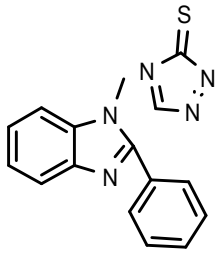
One-pot synthesis of 4-amino-5-substituted-4H-1, 2, 4-triazole-3-thiol, isobenzofuran-1, 3-dione, and various halogenated compounds lines was reported[15] and screened for antitumor activity against four human cell.



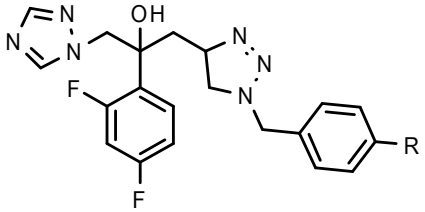
Synthesis of 6-substituted thiazolo [3,2-b]-1,2,4-triazole-5(6H)-one derivatives were synthesized[16] and these derivatives were evaluated for their anti-inflammatory activity. Some of compounds showed good anti-inflammatory activity.



Synthesis of 5-[(2-(substituted phenyl)-1H-benzimidazol-1-yl) methyl-4-methyl-2H-1,2,4-triazole-3(4H)-thiones were reported[17] and tested for antioxidant properties by using various in vitro systems.

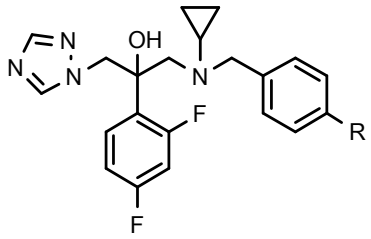


A series of 1-(1H-1, 2, 4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols was prepared[19]. The in vitro antifungal activities of all the target compounds were evaluated against eight human pathogenic fungi. Compound 5i showed the best antifungal activity.

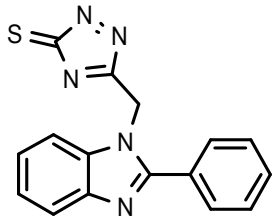


Synthesis of 1-(1H-1,2,4-triazole-1-yl)-2-(2,4-ifluorophenyl)-3-(Ncycloproyl-N-substituted-amino)-2-propanol derivatives were reported[20] and screened for their antifungal activity. Some of the title

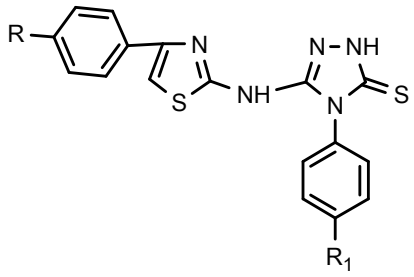
compounds had higher antifungal activity and broader antifungal spectrum than fluconazol.



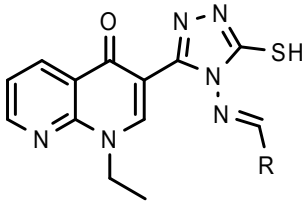
Synthesis of 5-[(2-(substitutedphenyl)-1H-benzimidazol-1-yl) methyl-4-methyl-2H-1,2,4-triazole-3(4H)-thiones was prepared[21] and tested for antioxidant properties by using various in vitro systems.



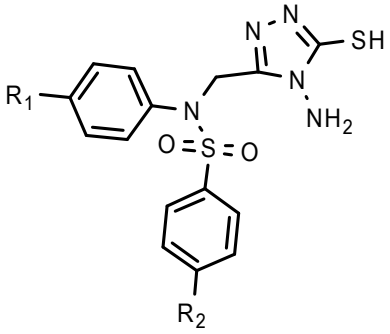
A various 3-[4-(substituted phenyl)-1, 3-thiazol-2-ylamino]-4-(substituted phenyl)-4,5-dihydro-1H-1,2,4-triazole-5-thiones were prepared[64] and screened for their anticonvulsant activity and compounds showed anticonvulsant activity.



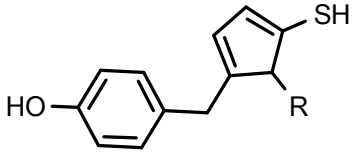
A synthesis of Nalidixic acid based Schiff bases of 4-amino-3-mercapto-1, 2, 4-triazole derivatives were synthesized[22] and screened for their antimicrobial.



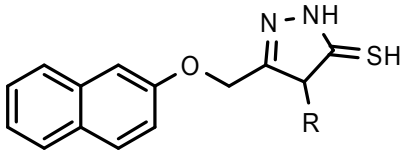
A synthesis of 3-β-[(N-benzene sulphonyl/ tosyl)-4-(un)substituted aniline] ethyl-4-amino-5-mercapto-4H-1,2,4-triazole derivatives were reported[23] and screened for their analgesic activity.



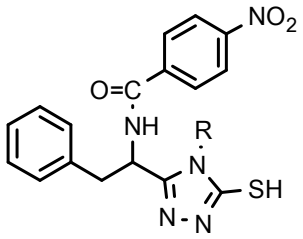
A synthesis of 5-(4-hydroxyphenyl) methyl-4-aryl/alkyl-3-mercapto-1,2,4(*H*)-triazoles was demonstrated[24] and screened for their anti-inflammatory activity.



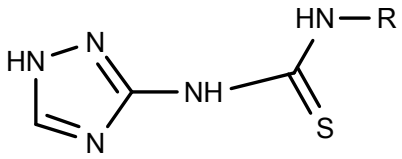
The new compound 2-(2-naphthyloxymethyl)-5-substitutedamino-1, 3, 4-Oxadiazoles and 5 - (2 -Naphthyloxymethyl) -4 -substituted-1,2,4-triazole-3 –thiones derivatives were synthesized[25] and evaluated for their anti-inflammatory activity.



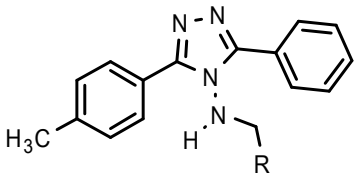
New compound 4-substituted-5-[1-(p-nitrobenzoylamino)-2-phenyl-ethyl]-3-thio-1,2,4-triazole were synthesized[26] and evaluated for their anti-inflammatory activity and established an appreciable anti-inflammatory activity that is comparable with that of other non-steroidal inflammatory agents.



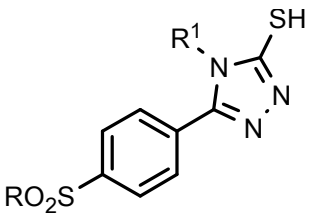
A series of 5-Amino-N-aryl/alkyl-1H-1,2,4-triazole-1-carbothioamide were synthesized[27] and selected compounds were examined for cytotoxicity, antitumor, and anti-HIV activity.



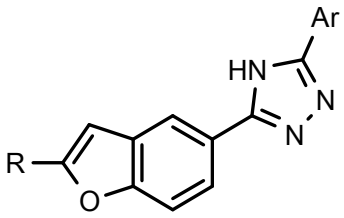
A synthesis of various 4-arylmethylenamino-4H-1,2,4-triazoles were reported[28] and screened for their anticancer activity. Some of compounds exhibited remarkable anticancer activity in 60 human cancer cell lines.



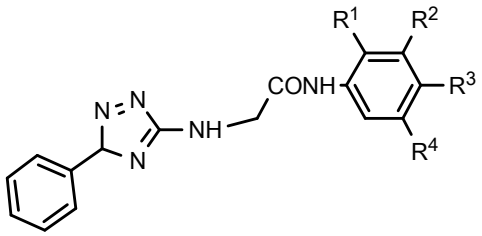
New compound 4-substituted 5-(4-phenylsulfonyl) phenyl)-1,2,4-triazole-3-thiol derivatives were synthesized[29] and assayed for the inhibition of three physiologically relevant carbonic anhydrase isozymes. Some of the compounds were potent carbonic anhydrase inhibitors.



Some novel 5-(5-substituted phenyl)-4*H*-1,2,4-triazole-3-yl-1,3-benzoxazoles were prepared[30] and evaluated for their anticonvulsant activity. Some of compounds were established as anticonvulsant agents.



N-(substituted phenyl)-2-[5-phenyl-2H-1, 2, 4-triazol-3ylamino] acetamide derivatives were synthesized [31] and tested for anticonvulsant activity by MES method.



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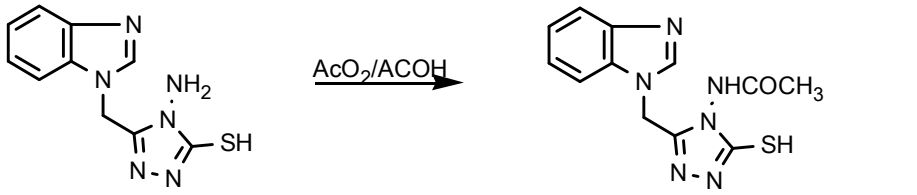
Experimental and spectral studies:

1] Synthesis of N-[3-Marcapto-5-(2-propylbenzimidiazol-1-yl methyl)-[1,2,4]triazole-4-yl] acetamide.



4-Amino-5-benzoimidazol-1-ylmethyl-4H-[1,2,4]triazole-3-thiol

N-(3-Benzoimidazol-1-ylmethyl-5-mercapto-[1,2,4]triazol-4-yl) -acetamide

10a

General method

A boiling mixture of 4-Amino-5-(2-propyl-benzimidiazol-1-yl-methyl)[1,2,4]triazole-3-thiol(0.19gm,0.001 moles) and acetic anhydride (0.19gm, 0.002moles) in glacial acetic acid (5ml) was refluxed for 4 hrs . The reaction mixture was cooled and poured in ice cold water. The formed precipitate was filtered off and recrystalised from alcohol to give the compound N-[3-Marcapto-5-(2-propyl-benzoimidiazol-1-ylmethyl) [1,2,4] triazole-4-yl]-acetamide (10a).

IR (KBr cm^{-1}) – (CH) – 3080 C =O 1700 cm^{-1} C=N 1654 cm^{-1} and C-S 1150 cm^{-1}

NMR -4H (S) aromatic 7.2

(CH_2 – CH_2 CH_3) 2H (t) = 2.4

(CH_2 – CH_2 CH_3) 2H (m) = 1.6

(CH_3 CH_2CH_2 -) 3H (t) = 0.93

-CH_2 (2H S) = 2.8

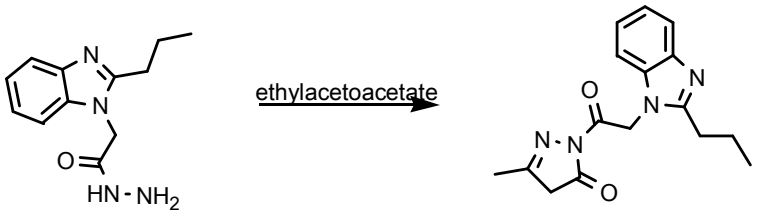
- CH_3 (3H, S) = 0.98

Table No 5.1 physical properties of [1,2,4] triazole

Solvent	M.P.	Mol form	Mol Wt	Yield	C	H	N	O	S
ethanol	130-135	$C_{15}H_{18}N_6OS$	312	70	54.53	5.49	25.44	4.84	9.70

2] Synthesis of methyl pyrazolone 1-[3-(2-propylbenzimidiazol-1-yl) propanoyl]-4,5-dihydromethyl pyrazol-3-one.

General method



(2-Propyl-benzoimidazol-1-yl) - acetic acid hydrazide
comp I

5-Methyl-2-[2-(2-propyl-benzoimidazol-1-yl) - acetyl]-2,4-dihydro-pyrazol-3-one
(10b)

A mixture of carbohydrazide (comp I) (0.6gm, 0.0028 moles) and ethyl aceto acetate (0.364gm, 0.0028moles) in ethyl alcohol (25ml) was refluxed for 4 hrs. The reaction mixture was cooled and the formed precipitate was filtered off and recrystalised and obtained compound was (10b)

IR (KBr cm^{-1}) – (CH) – 3080 C =O 1700 cm^{-1} C=N 1654 cm^{-1} and C-S 1150 cm^{-1}

NMR -4H (S) aromatic 7.2

(CH_2 – CH_2 CH_3) 2H (t) = 2.4

(CH_2 – CH_2 CH_3) 2H (m) = 1.6

(CH_3 CH_2CH_2 -) 3H (t) = 0.93

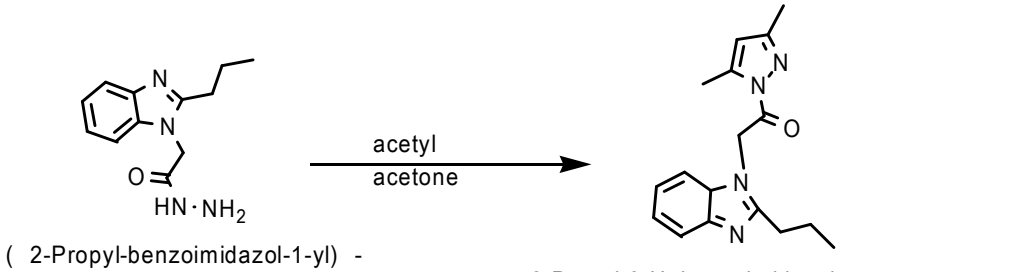
-CH_2 (2H S) = 2.8

- CH_3 (3H, S) = 0.98

Table No. 5.2 Physical properties of dihydro methyl pyrazolone

solvent	M.P.	Mol for	Mol Wt	Yield	C	H	N	O
ethanol	187-190	$C_{17}H_{22}N_4O_2$	314	75	64.95	7.05	17.82	10.18

3] Synthesis of dimethyl pyrazole.



(2-Propyl-benzoimidazol-1-yl) - acetic acid hydrazide

comp I

2-Propyl-3a\-benzoimidazole; compound with 1-(3,5-dimethyl-pyrazol-1-yl) -propan-1-one

(10c)

General method

A mixture of carbohydrazide (comp I) (0.6gm, 0.0028 moles) and acetyl acetone (0.364gm, 0.0028moles) in ethyl alcohol (25ml) was refluxed for 4 hrs. The reaction mixture was cooled and the formed precipitate was filtered off and recrystalised and obtained (10c)

IR (KBr cm^{-1}) – (CH) – 3080 C =O 1700 cm^{-1} C=N 1654 cm^{-1} and C-S 1150 cm^{-1}

NMR -4H (S) aromatic 7.2

(CH_2 – CH_2 CH_3) 2H (t) = 2.4

(CH_2 – CH_2 CH_3) 2H (m) = 1.6

(CH_3 CH_2CH_2 -) 3H (t) = 0.93

-CH_2 (2H S) = 2.8

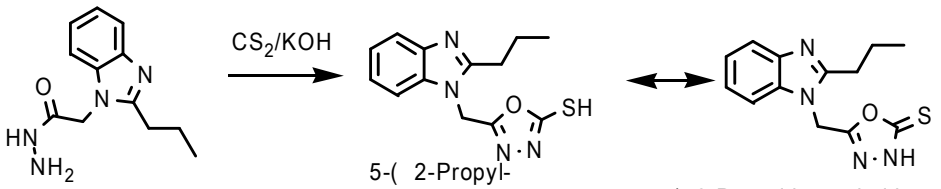
- CH_3 (3H, S) = 0.98

Table No. 5.3 Physical properties of Dimethyl pyrazole

solvent	M.P.	Mol for	Mol Wt	Yield	C	H	N	O
ethanol	180-185	$C_{17}H_{22}N_4O_2$	312	70	69.2	7.74	17.93	5.12

4] Synthesis of 3-Dimethyl amino methyl-5-(2-propyl-benzimidiazol-1-ylmethyl)-3H[1,3,4]oxadiazole-2-thione from 2-propyl -3H-benzimidiazole hydrazide.

Step I

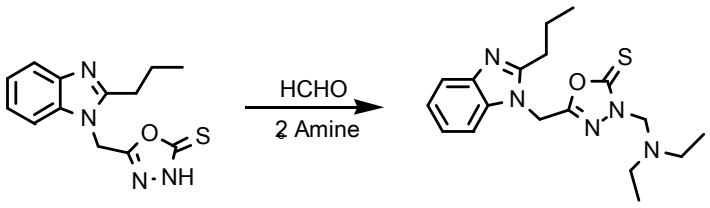


(2-Propyl-benzoimidazol-1-yl) - acetic acid hydrazide
comp I

5-(2-Propyl-benzoimidazol-1-ylmethyl) - [1,3,4]oxadiazole-2-thiol

5-(2-Propyl-benzoimidazol-1-ylmethyl) -3H- [1,3,4]oxadiazole-2-thione

Step II



5-(2-Propyl-benzoimidazol-1-ylmethyl) -3H- [1,3,4]oxadiazole-2-thione

R=NEt_2, Morpholine etc.

3-Diethylaminomethyl-5- (2-propyl-benzoimidazol-1-ylmethyl) -3H-[1,3,4]oxadiazole-2-thione
10d-10f

General Method

A mixture of paraformaldehyde (0.9g 0.001M) and the appropriate secondary amines like diethyl amine, Morpholine, dimethyl aniline (0.015M) was refluxed for 2 hours in absolute ethanol (50 ml) then added to the reaction and observed the paraformaldehyde are completed soluble then added mixture of (1.05g, 0.004moles) of carbohydrazide (comp I) in 20 ml of ethanol, then the reaction mixture refluxed for 4 hours. Then the reaction mixture is concentrated and separated product was filtered and recrystalised from Chloroform / Pet.Ether to give corresponding compounds (10d-10f).

IR (KBr cm^{-1}) – (CH) – 2991 C =O1180 cm^{-1} C=N 1654 cm^{-1} and C-S 1150 cm^{-1}

NMR - 4H (S) aromatic 7.2

(CH_2 – CH_2 CH_3) 2H (t) = 2.4

(CH_2 – CH_2 CH_3) 2H (m) = 1.6

(CH_3 CH_2CH_2 -) 3H (t) = 0.93

-CH_2 (2H S) = 2.8

- CH_3 (3H, S) = 0.98

Table N0. 5.4 physical properties of Oxadiazole-2-thione

	R	M.P	Mol formula	%Yld	C	H	N	S
1	NEt_2	207-210	$C_{17}H_{23}N_5OS$/345	65	59.1	6.71	20.27	13.48
2	MORPHOINE	180-185	$C_{17}H_{23}N_5O_2S$/359	60	56.8	5.89	19.48	17.83
3	Dimethyl aniline	240-245	$C_{24}H_{30}N_4O_2S$/438	68	65.7	6.89	12.77	7.31

RESULT AND DISCUSSION:

1] Synthesis of N-[3-Marcapto-5-(2-propylbenzimidiazol-1-yl methyl)-[1,2,4]triazole-4-yl] acetamide.

The synthesis of triazole thiols from acetahydrizide (comp I) was reacted with CS_2 in presence of KOH to form 5-(2-propyl benzimidiazole-1-ylmehyl)-[1, 3, 4] Oxadiazole -2-thiol was obtained. Then the compound 5-(2-propyl benzimidiazole-1-ylmehyl)-[1, 3, 4] Oxadiazole -2-thiol was treated with hydrazine hydrates obtained 4- amino -5-(2-propyl benzimidiazole-1-yl methyl)-4H-[1, 2, 4] triazole -3-thiol. A mixture of 4-Amino-5-(2-propyl-benzimidiazol-1-yl-methyl) [1, 2, 4] triazole-3-thiol and acetic anhydride was heated in presence of acetic acid for four hours, after completion of reaction cool the reaction and monitored by TLC. The reaction mixture poured in ice formed solid precipitate. Then solid product was filtered and recrystalised from alcohol to give the compound N-[3-Marcapto-5-(2-propyl-benzoimidiazol-1-yl methyl) [1, 2, 4] triazole -4-yl]-acetamide.

2] Synthesis of methyl pyrazolone 1-[3-(2-propylbenzimidiazol-1-yl) propanoyl]-4,5- di hydro methyl pyrazol-3-one.

Carbohydrazide (comp I) was allowed to react with ethyl aceto acetate and acetyl acetone in presence of ethanol to obtained corresponding methyl pyrazole derivative and dimethyl pyrazole respectively.

3] Synthesis of 2-propyl -3H-benzimidiazole compound with 3-propionyl thiozolidin-4-one.

The synthesis of triazole thiols from acetahydrizide (comp I) was reacted with CS_2 in presence of KOH form 5-(2-propyl benzimidiazole-1-ylmehyl)-[1, 3, 4] Oxadiazole -2-thiol was obtained. One of the earliest discovery concerning the utility of Mannich bases intermediates in drug synthesis. Carbohydrazide was allowed to undergo the Mannich reaction with different secondary amines namely, diethyl amine, Morpholine etc. In absolute ethanol to give compounds 3-diethyl amino methyl -5-(2-propyl-benzimidiazol-1-ylmethyl)-3H-[1, 3, 4]oxadiazole-2-thione. A mixture of paraformaldehyde and the appropriate secondary amines like diethyl amine, Morpholine, dimethyl aniline was refluxed for 2 hours in absolute ethanol ,then added to the reaction and observed the paraformaldehyde are completed soluble then added mixture of carbohydrazide in of ethanol ,

then the reaction mixture refluxed for 4 hours. Then the reaction mixture is concentrated and separated product was filtered and recrystalised.

Conclusion:

All newly synthesized compounds 10a, 10b, 10c showed moderate to mild antimicrobial activity. These findings concluded that the titled compounds have the property to kill the microbes in some extent when compared with standard drugs.

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