Preparations, Reactions and Biological Activities of 1,3,4-Thiadiazole Derivatives: Reviewing Study

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الخلاصة

تعتبر حلقة 4,3,1- ثياديازول واحدة من أهم وأشهر الحلقات الخماسية غير متجانسة الحلقة الموجودة في العديد من المنتجات الطبيعية المتنوعة والعوامل الطبية. تظهر حلقة 4,3,1- ثياديازول طيفًا واسعًا ومتنوعًا من الأنشطة الدوائية مثل مضادات الالتهاب ومضادات الميكروبات ومضادات الصرع ومضادات الأورام والمسكنات ومضادات الفيروسات ومضادات السرطان ومضادات السل إلخ. النشاط الواسع والقوي للثياديازول ومشتقاته جعلها مركبات مهمة نشطة حيويا ومن هذه الأهمية ، جاءت محاولة كتابة هذه المراجعة لتسليط الضوء على تفاعلاتها وطرق تحضيرها وكذلك تطبيقاتها الدوائية .

Summary

1,3,4-thiazole ring consider one of most important and common from five membered heterocycle compounds present in many from variety natural products and medical agents. The 1,3,4-thiadiazole ring exhibit variety wide spectrum from pharmacological activities such as anti-inflammatory, antimicrobial, antiepileptic, antineoplastic, analgesic, antiviral, anticancer and as antitubercular etc. The wide and vigorous activities for thiadiazole ring and also their derivatives make them a bioactive important compounds and from this importance the attempt to write this review came to highlighted about their reactions, their synthesis methods and also their pharmacologically applications.

Keywords: 1,3,4-Thiadiazole , Chemical reactions , Biological activity, Drug .

1. Introduction

Thiadiazole is one of the classes of aromatic five-membered heterocyclic compounds containing more than two heteroatoms , one sulfur atom and two nitrogen atoms. In nature thiadiazoles can be occurs in four isomeric forms (Figure 1) [(1)]

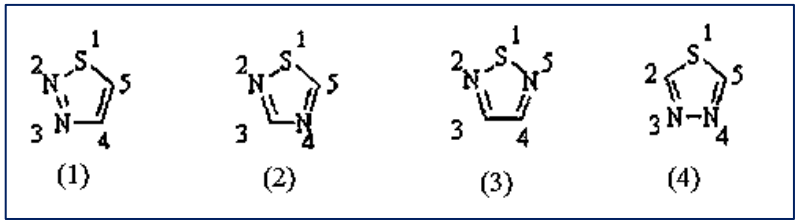


Fig. 1 Types of thiadiazoles

1,3,4-thiadiazole and their derivatives is well known due to a great interest of to their great pharmaceutical and industrial applications. Appearance the sulfur drugs , then discovery the mesoionic compounds led to the greatly accelerated rate of interest and also progress in this field[(2)]. The 1,3,4-thiadiazole ring can be classified to three subcategories: (1) Aromatic system containing neutral thiadiazole (4). (2) Mesoionic system (4a), which can be define as a five membered heterocyclic compounds, which are neither covalent nor polar (3) Non aromatic system for example, (4b) , (4c) and also (4d) Figure2[(3)]

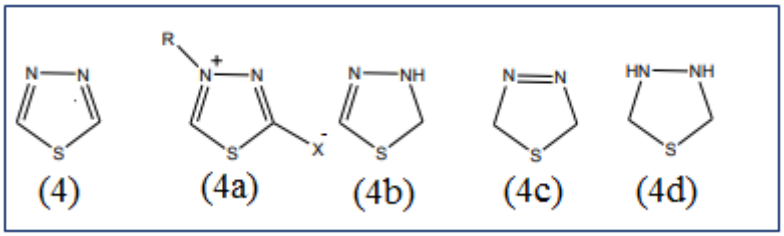


Fig. 2 Subclasses of thiadiazole

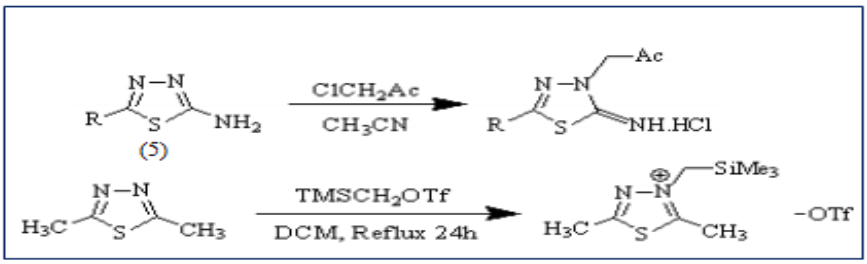
2.Reactions of 1,3,4-thiadiazole

1,3,4-thiadiazole can be undergoes following kinds of chemical reactions

2.1. Reaction of electrophilic attack at nitrogen

The electrophilic attack that occurs at nitrogen atom may be lead to produce 1,3,4-thiadiazol-2-(3H)-ones or 1,3,4-thiadiazolium salts depending on the tautomeris

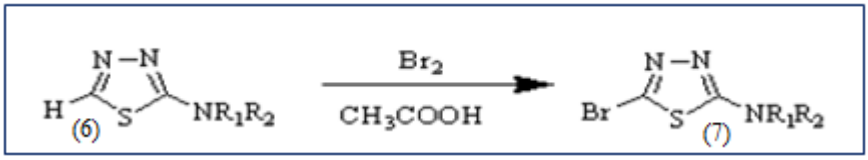
ability of the substituent at C-2 or C5 . N-alkylated thiadiazolimine can be prepare from reaction of compound (5) and chloroacetone and reaction of 2,5-dimethyl-1,3,4-thiadiazole with trimethylsilyl methyl trifluoromethane sulfonate to yield 1,3,4-thiadiazolium salts[4]



Scheme1. Reaction of electrophilic attack at nitrogen

2.2. Reaction of electrophilic attack at carbon

Carbon atoms within 1,3,4-thiadiazole are characterized by low electron density such as nitration , sulphonation ,acetylation and halogenations reactions do not take place normally , this is can be occurs by rearrangement of intermediate N-acylthiadiazolium salts. Chlorinated or brominated 2-halo-5-substituted thiadiazoles can be produce by radical halogenation. Compound (7), scheme (2) can be prepare from reaction of compound (6) and bromine in acetic acid[5]

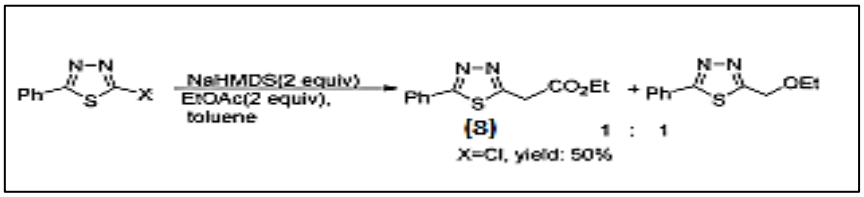


Scheme 2. Preparation of halo-thiadiazole

2.3. Reaction of nucleophilic attack at carbon

The 1,3,4-thiadiazoles can be undergoes nucleophilic reactions at the carbon atoms which are characterized by electrondeficient nature , therefore, halo-substituted thiadiazoles consider highly activated and can be react with a wide range from nucleophiles. The synthesis of 2-substituted thiadiazoles can be occurs by carbon-based nucleophiles for example, malonate. Compound (8) can be obtained from

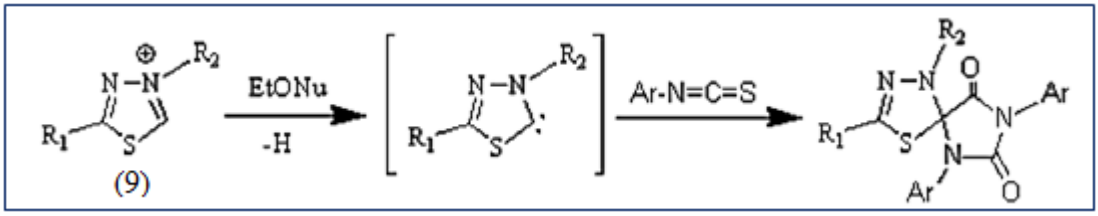
reaction of 2-chlorothiadiazole with ethyl acetate and in presence of sodium hexamethyldisilazane (NaHMDS)[6]



Scheme 3. Reaction of nucleophilic attack at carbon

2.4. Reaction of nucleophilic attack at hydrogen bonded for carbon

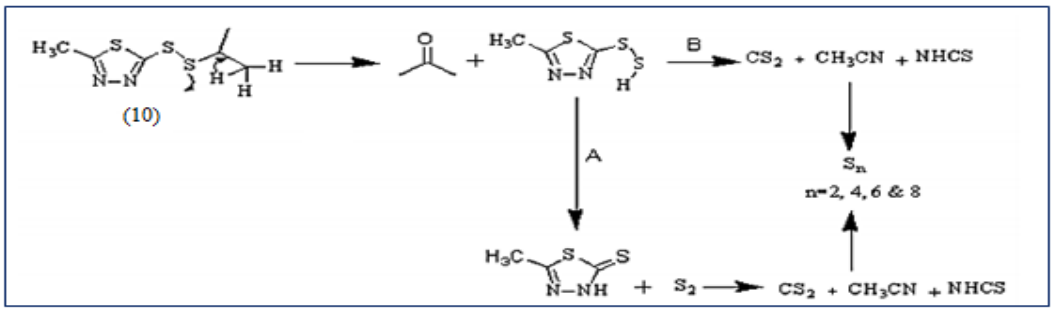
5-substituted and unsubstituted thiadiazole can be undergo reaction with alkylating agent and give salts(9) ,which in turn undergoes deprotonation to yield of carbene, which consider intermediate in preparation of spirocyclic compound[7]



Scheme4. Reaction of nucleophilic attack at hydrogen

2.5. Unimolecular thermal and photochemical reactions

The1,3,4-Thiadiazole frequently undergo to photochemical fragmentation. High vacuum pyrolysis for compound (10) between ambient and 900°C produced 2-methylpropene, thiadiazole, CH_3CN ,HNCS, CS_2 in addition to sulfur species. The β-hydrogen elimination may be its cause in presence of 2-methylpropene. This reaction would result to disulfanyl which also fragment further by two major ways. [A] the bimolecular fragmentation yield S_2 and thiadiazole, which higher than 5000℃ decomposes to CH_3CN, HNCS, CS_2 and sulfur . [B] would lead to direct elimination for S_2 from the disulfanyl to produce HNCS and CH_3CN[8]

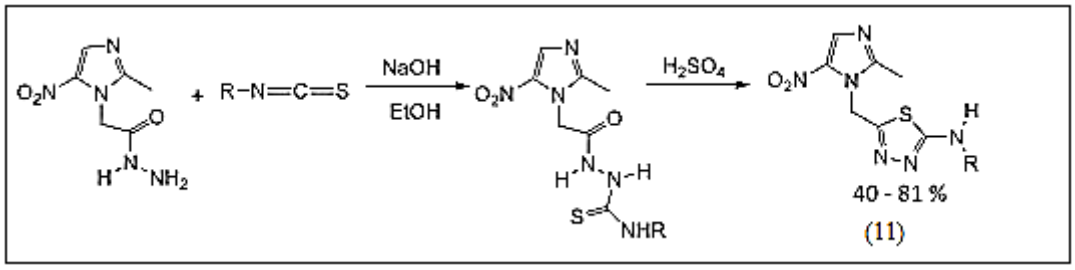


Scheme 5. Unimolecular thermal and photochemical reactions

3. Preparation Methods

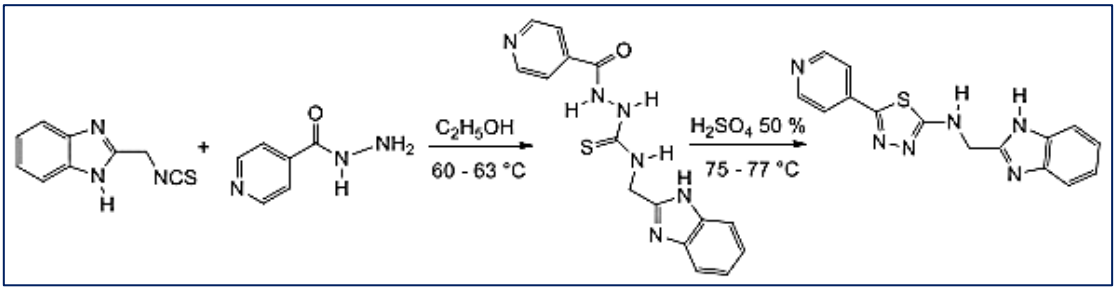
3.1. Preparation Method by acylhydrazine

Thiadiazoles can be synthesized from reaction acyl hydrazide and sulfur reagents shuch as (CS_2, isothiocyanate or dithiocarbamates) , this preparation goes through two or more stages [9-11] , first reaction for synthesis of related dithiocarbazide or thiosemicarbazide , which use in preparation of thiadiazole compounds. Mirzaei et.al. were achieved preparation of thiadiazoles compound(11) from acylhydrazines as shown in Scheme (6) [9]



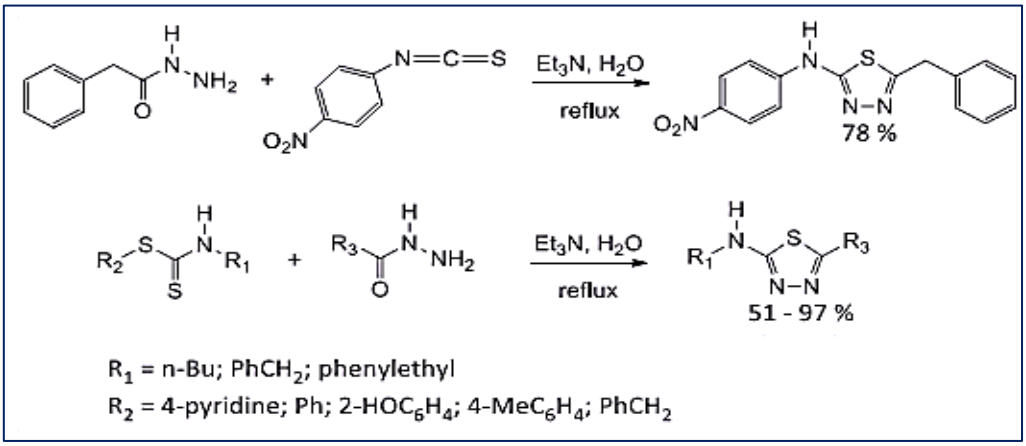
Scheme 6. Preparation of thiadiazoles by acylhydrazine

Another derivatives of thiadiazole were prepared by two steps, at first step, react of isothiocynate and isoniazid to yield the intermediate as shown in scheme (7) which then refluxed with 50 % H_2SO_4[11]



Scheme 7. Preparation of thiadiazole compounds

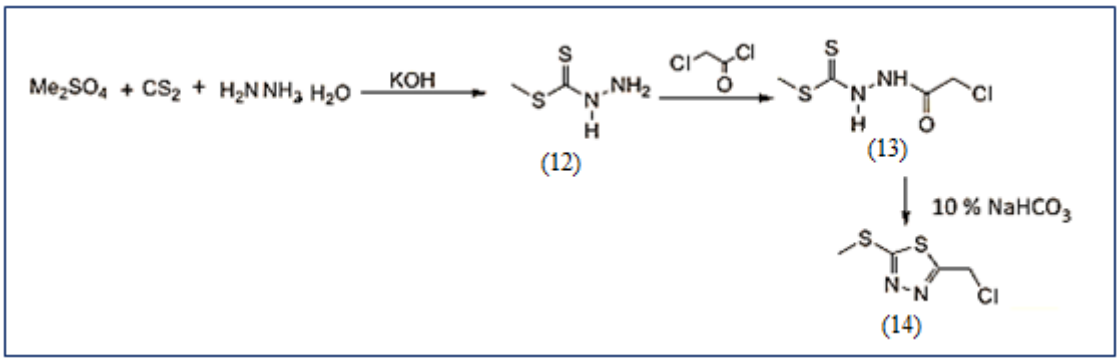
a one-pot synthesis was developed by Aryanasab for preparation of 2-substituted –thiadiazole from reaction of acylhydrazide and isothiocyanate with H_2O and Et_3N and also under same reaction conditions can be prepare 2-substituted –thiadiazole from reaction of acid hydrazide and dithiocarbamates[12]



Scheme 8. One pot preparation of thiadiazole

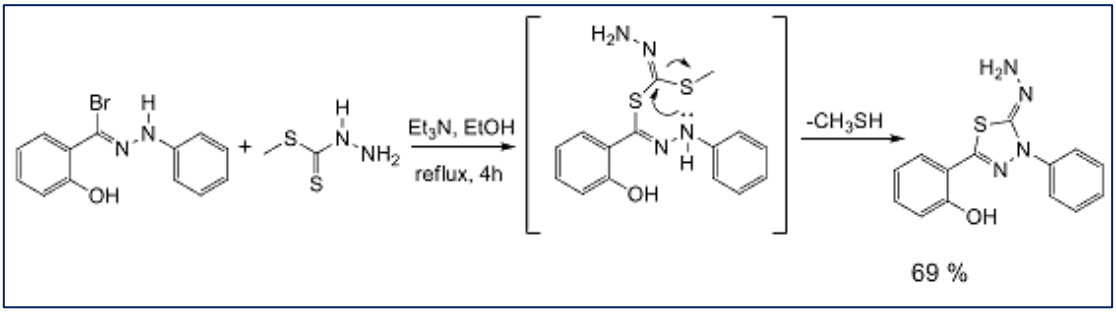
3.2. Preparation Method by Dithiocarbazate

Wang et al. were reported about synthesis of thiadiazole by dithiocarbazates, reaction of Me_2SO_4,CS_2 and hydrazine and also KOH lead to provide the intermediate (12) , which in turn react with chloroacetylchloride to yield the intermediate (13) ,which undergo of cyclization reaction in presence of $NaHCO_3$ to give compound(14)[13]



Scheme 9. Preparation of thiadiazole by dithiocarbazates

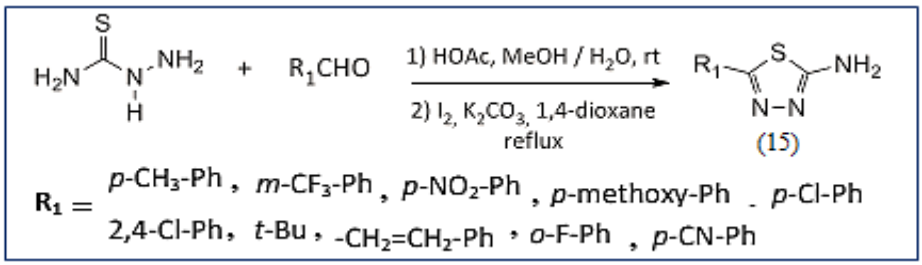
Sayed et al. achieved preparation of new thiadiazole derivative as shown in the following scheme (10) from reaction of hydrazonoyl bromide and methyl hydrazinecarbodithioate in ethanol as only product that was isolated[14]



Scheme 10. preparation of thiadiazole derivative by dithiocarbazates

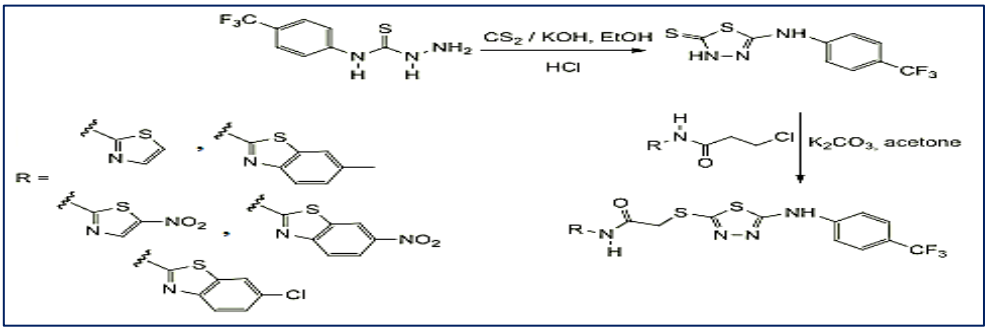
3.3. Preparation Method by thiosemicarbazide

Niu et al. had prepared of compound (15) from condensation of thiosemicarbazide with aldehyde , (Scheme 11) [15]



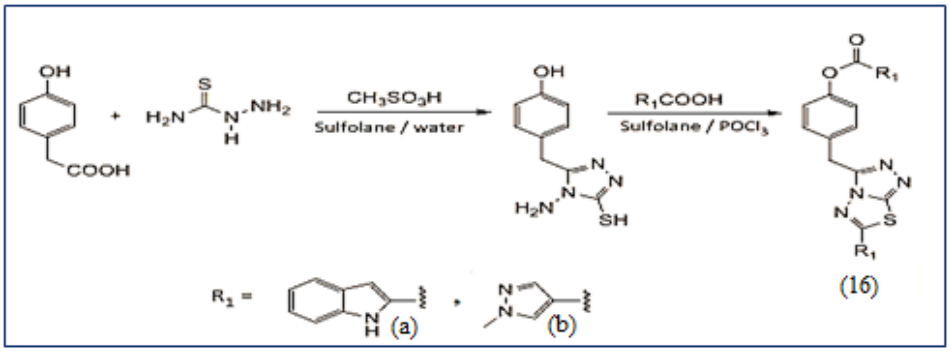
Scheme 11. Perpetration of thiadiazole using I_2

Altintop et al . reacted thiosemicarbazide with carbon disulfide and with the presences of KOH, EtOH and HCl to obtain on intermediate ,which in turn react with N(substituted)-2-chloroacetamide derivatives and in presence of K_2CO_3 to provide thiadiazole [16]



Scheme 12. Preparation of thiadiazoles using thiosemicarbazide and CS_2

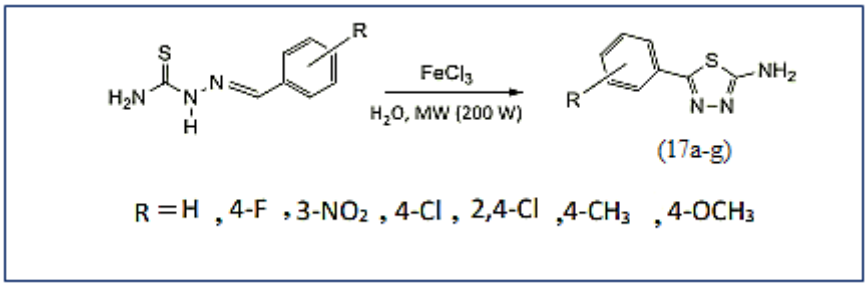
Yuanet al. synthesized the compounds (16a,b) by synthetic routes as shown in the following scheme (13), which involved cyclization of carboxylic acid with thiocarbohydrazide with presence of methanesulfonic acid and sulfolane water to yield intermediate to react in turn with another carboxylic acid to provide the target compounds [17]



Scheme 13. Preparation of thiadiazole compounds

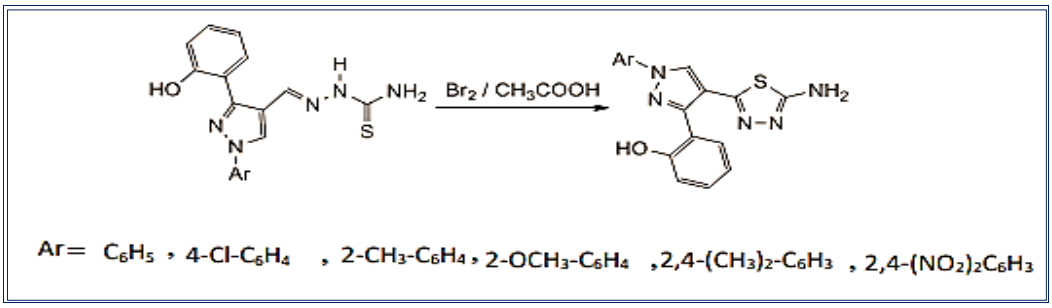
3.4. Preparation Method by thiosemicarbazone

Thiadiazole derivatives can be prepare by cyclization of thiosemicarbazone with presence $FeCl_3$ via microwave irradiation and ultrasound through 3 minutes and without use organic solvents or acidic conditions[18]



Scheme 14. preparation of thiadiazole by microwave irradiation

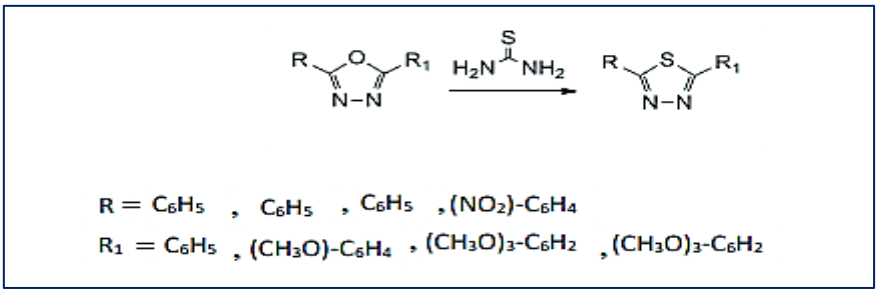
Novel compounds were synthesized by Kariyappa and Gurunanjappa by oxidative cyclization of thiosemicarbazone by Br_2 dissolved in glacial CH_3COOH through- out 2-3 hr. at room temperature [19]



Scheme 15. Preparation of thiadiazoles from thiosemicarbazones

3.5. Preparation Method by 1,3,4-oxadiazole

Thiadiazole can be synthesized by the conversion of 1,3,4-oxadiazole to 1,3,4-thiadiazole by replacement of oxygen atom by sulfur atom within heterocycle, compared to previously methods, which characterized by reaction time ranging from 0.5 to 7 hr. , this conversion method consider limited method of use because of reaction time,approximately30hr[20]



Scheme16. preparation of thiadiazole from oxadiazole

4. Microbiological Activities

Khalaj et al. evaluated the biological activity of thiadiazole derivatives as antibiotics and corporation the results of biological activity with biological activity of linezolid drug (Figure3)[21]

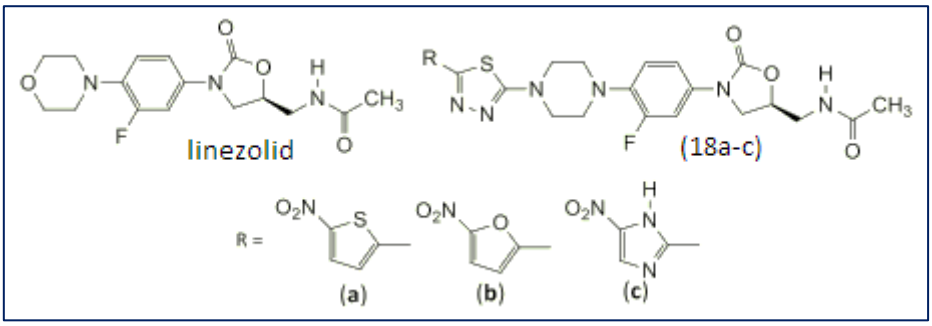


Fig. 3: Thiadiazole analogous for linezolid

Table 1: Results of antibacterial activity

Minimum Inhibitory Concentration (µg/mL)					
	Microorganism	18a	18b	18c	Linezolid
Gram positive	S. aureus	0.098	0.012	0.098	0.781
	S. epiderimidis	0.024	0.006	0.024	0.781
	S. warnei	0.049	0.006	0.006	0.781
	S. lentus	0.098	0.012	0.098	1.563
	S. xylosus	0.098	0.024	0.049	0.781
	S. saprophyticus	0.195	0.024	0.024	0.781
	M. luteus	6.25	0.391	0.195	0.781
	C. glutamicum	6.25	0.195	0.195	0.781
	B. subtilis	0.781	0.391	0.098	0.391
	MRSA 3	0.195	0.049	0.391	0.781
	MRSA 5	6.25	0.195	0.195	0.781
	MRSA 17	0.098	0.012	0.024	0.781
Gram negative	E. coli	> 100	> 100	> 100	> 100
	K. pneumonia	100	50	0.781	6.25
	P. aeruginosa	> 100	> 100	> 100	> 100

New derivatives (19-22), Figure (4) were prepared in another study then evaluated as antimicrobial and comparison the activities results with activity of ampicillin , gentamicin and amphotericin B, which used as reference drugs for positive , negative bacteria and for fungi[22]

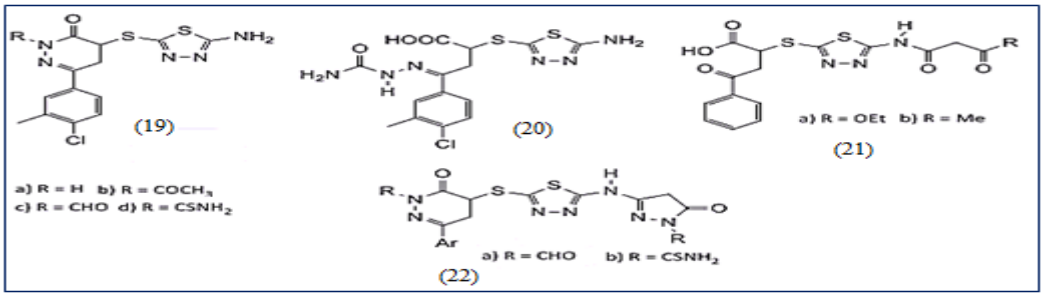


Figure 4: New derivatives of thiadiazole

Table 2:Results Antimicrobial activity of thiadiazole [22]

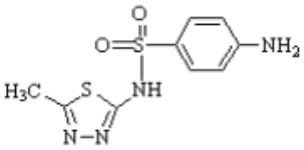
Zone of inhibition (mm) – 5 mg/mL[a,b]								
	Antibacterial activity				Antifungal activity			
No. Compound	Sp	Bs	Ec	Pa	Af	Sr	Gc	Ca
19a	21.7	23.2	20.8	NA	22.6	26.7	23.3	NA
19b	19.4	21.2	18.6	NA	20.3	19.2	20.7	NA
19c	17.9	18.2	17.7	NA	18.2	17.6	18.9	NA
19d	29.4	34.6	27.2	NA	26.4	27.3	31.2	22.4
20	24.6	28.6	23.2	NA	22.8	21.8	24.2	17.3
21a	16.0	18.3	13.0	NA	10.6	11.7	16.5	NA
21b	13.6	15.6	10.3	NA	NA	NA	NA	NA
22a	22.5	24.2	19.3	NA	19.6	20.4	23.6	NA
22b	25.1	27.4	23.4	NA	22.3	23.4	27.3	NA
Ampicillin	23.8	32.4	NT	NT	NT	NT	NT	NT
Gentamicin	NT	NT	19.9	19.9	NT	NT	NT	NT
Amphotericin B	NT	NT	NT	NT	23.7	19.7	28.7	25.4

Table 3 show results of MIC value of thiadiazole derivatives (3)[22]

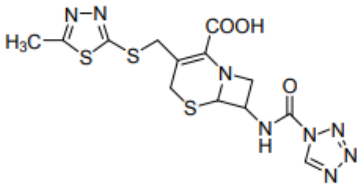
Table 3: Results Minimum inhibition concentration

Minimum Inhibitory Concentrations (MICs) - mg/ml						
	Results Antibacterial activity			Results Antifungal activity		
No.	S. pneumonia	B. substilis	E.coil	A fumigatus	S racemosum	G candidum
19d	0.60	1.25	0.60	1.25	1.25	**1.25**
21a	2.50	1.25	1.25	5.00	2.50	**5.00**
21b	2.50	2.50	2.50	NT	NT	**NT**
22b	0.60	0.60	0.60	2.50	1.25	**2.50**
Ampicillin	0.60	0.60	NT	NT	NT	**NT**
Gentamicin	NT	NT	0.60	NT	NT	**NT**
Amphotericin B	NT	NT	NT	0.60	0.60	**0.60**

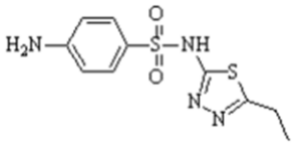
Clinically Used Drugs Containing Thiadiazole Nucleus[23]



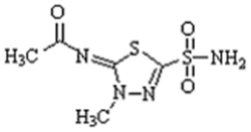
Sulphamethazole (Antibiotic)



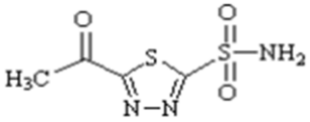
Cefazoline (Antibiotic)



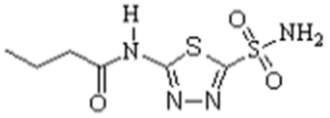
Sulfaethidole(Antibiotic)



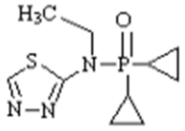
Methazolamide (Diuretic)



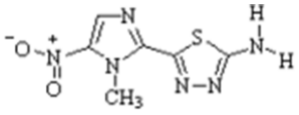
Acetazolamide (Diuretic)



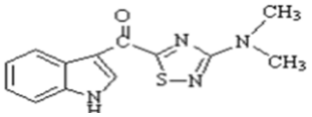
Butazolamide (Diuretic)



Azetepa (Antineoplastic)



Megazol(Antiprotozoal)



Dendrodoine(Antioxidant)

Figure 5: commercial drugs containing 1,3,4-thiadiazole

5. Conclusion

There are many methods can be used for preparation of 1,3,4-thiadiazole .1,3,4-thiadiazoles can be undergo various chemical reactions due to their chemical activity . 1,3,4-thiadiazoles have broad range from biological activities also there are many drugs contain thiadiazole moiety within their chemical structure .

References

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