Revista Virtual de Química
ISSN 1984-6835

Artigo

Synthesis of 1,3,4-Thiadiazole Derivatives and Microbiological Activities: A Review

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Rev. Virtual Quim., **2019**, *11* (3), 806-848. Data de publicação na Web: 6 de maio de 2019

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Síntese de Derivados de 1,3,4-Tiadiazol e Atividades Microbiológicas: Uma Revisão

Resumo: A resistência bacteriana associada a diferentes antibióticos é uma limitação para o tratamento de infecções e isto tem estimulado o desenvolvimento de novos agentes antimicrobianos. Neste aspecto, novos derivados de 1,3,4-tiadiazol-2,5-dissubstituídos, os quais apresentam diversificada atividade biológica, têm sido o foco de vários projetos de pesquisa nos anos recentes. Este artigo destaca as principais metodologias para a síntese deste heterociclo utilizando acilidrazinas, ditiocarbazatos, tiossemicarbazidas, 1,3,4-oxadiazóis. Adicionalmente, derivados de 1,3,4-tiadizol-2,5-dissubstituídos com ação antimicrobiana são reportados.

Palavras-chave: Tiadiazol; tiosemicarbazida; bioatividade; antimicrobiano; tiosemicarbazona.

Abstract

Bacterial resistance associated to different antibiotics is a limitation for the treatment of infections and this has stimulated the development of new antimicrobial agents. In this aspect, novel 2,5- disubstituted-1,3,4-thiadiazole derivatives, which present a diversified biological activity, have been the focus of various research projects in recent the years. This article highlights the main methodologies for the synthesis of this heterocycle using acylhydrazines, dithiocarbazates, thiosemicarbazides, 1,3,4-oxadiazoles. Additionally, 2,5-disubstituted-1,3,4-thiadiazole derivatives with antimicrobial action are discussed.

Keywords: Thiadiazoles; thiosemicarbazide; bioactivity; antimicrobial; thiosemicarbazone.

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DOI: 10.21577/1984-6835.20190058

Volume 11, Número 3 Maio-Junho 2019

Revista Virtual de Química
ISSN 1984-6835

Synthesis of 1,3,4-Thiadiazole Derivatives and Microbiological Activities: A Review

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Recebido em 19 de setembro de 2018. Aceito para publicação em 4 de março de 2019

1. Introduction

Heterocyclic compounds play an important role in biological processes, especially heterocycles that contain nitrogen, because of their wide use in medicinal scaffolds for active agents.[1] The 1,3,4-thiadiazole nucleus, which makes up the azole group, is a versatile pharmacophore and exhibits a wide variety of biological activities. In addition to the 1,3,4-thiadiazole (**1**), there are three other isomers: 1,2,3-thiadiazole (**2**), 1,2,4-thiadiazole (**3**) and 1,2,5-thiadiazole (**4**) (Figure 1).[2-6]

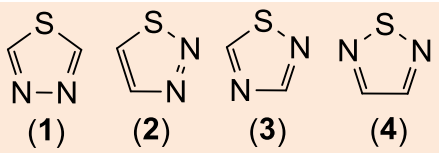


Figure 1. Structure of the thiadiazole isomers

The thiadiazole core can be employed as a bioisostere for other heterocycles, for example oxadiazoles. In this case, the substitution of the oxygen atom for sulfur maintained the biological activity and increased the led to the maintenance of

biological activity and an increase in lipophilicity.[7,8] Among the different azole heterocycles, 1,3,4-thiadiazoles have aroused much interest as can be seen from the large number of different synthetic methodologies reported in the literature. Furthermore, these compounds have very diversified biological properties,[6-15] including: antifungal,[16] anti-inflammatory,[17] antibacterial,[18] antiparasitic,[19] antioxidant,[20] antidepressant,[20] anticonvulsivant,[21] diuretic,[22] and antitumoral agents (Figure 2).[23]

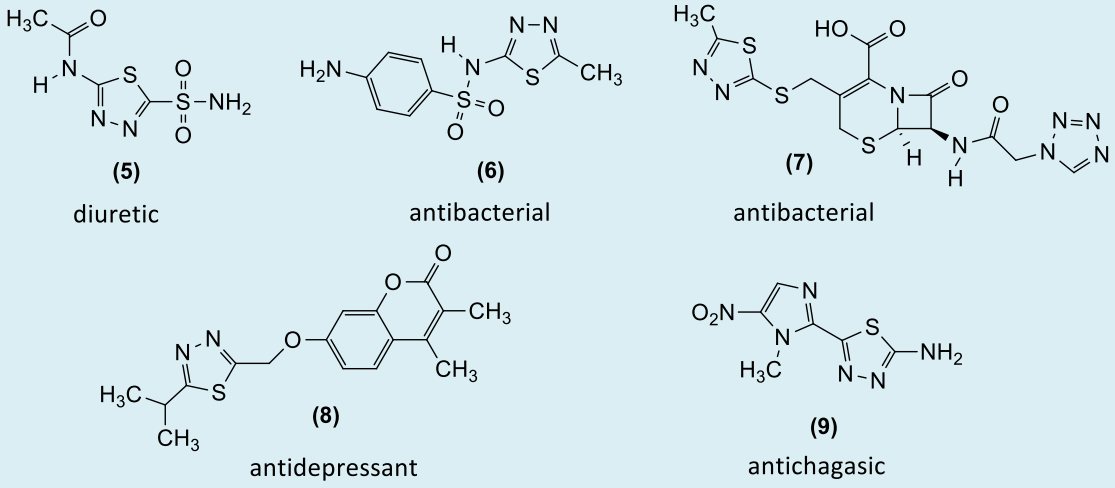


Figure 2. Examples of bioactive compounds containing 1,3,4-thiadiazole

Certain derivatives of this class, such as acetazolamide (**5**), sulfamethiazole (**6**), cefazolin (**7**), atibeprone (**8**) are already commercialized (Figure 2).[3,21,24] The drug megazol (**9**) was considered a possible alternative for the treatment of Chagas's disease, however, it has been shown to be very mutagenic, discouraging the continuity of the research.[19,25]

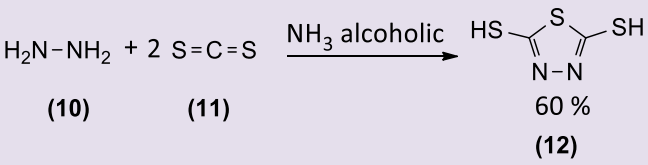
Currently microbial resistance to drugs is a concern in Medicinal Chemistry, which can be due to gene transfer or excessive drug usage. Over the last few decades there has been an increase in drug resistance and in the detection of hospital-acquired infections caused by multidrug resistant strains and this situation is considered a public health problem. This drug resistance has compromised the treatment of infectious diseases and at the same time has stimulated the search for new bioactive substances. The antibacterial and antifungal properties associated with the thiadiazole nucleus have been widely researched.[10,26,27] Futhermore various synthetic methodologies to produce thiadiazole derivatives have been reported.[26,27]

This report reviews the evolution of the main syntheses of 1,3,4-thiadiazole derivatives, as well as examples of thiadiazole structure with antimicrobial activity reported over the years.

2. Methodologies for the Synthesis of 1,3,4-Thiadiazole

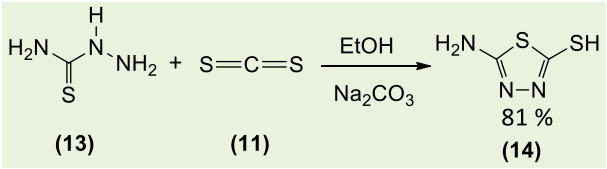
Since the late XIX century different reactions involving 1,3,4-thiadiazoles have been reported in the literature.[28-35] One of the first authors to report a synthesis of a thiadiazole was Bush in 1894,[29] who reacted hydrazine sulfate and carbon disulfide in the presence of an alcoholic solution of potassium hydroxide. According to Losanitch,[29] the development of 1,3,4-thiadizole chemistry is linked to the discovery of hydrazines. The treatment of the hydrazine salt of 2,5-dithiol-1,3,4-thiadiazole with concentrated

hydrochloric acid formed the compound **12**. Losanitch adapted this method for the synthesis of the heterocycle **12**, which was obtained with a 60 % yield from the treatment of carbon disulfide (**11**) with hydrazine hydrate (**10**) in the presence of alcoholic ammonia (Scheme 1).[29]



Scheme 1. Synthesis of 2,5-dithiol-1,3,4-thiadiazole

In a subsequent study, Petrow *et al.* (1958) reported a reaction between thiosemicarbazide (**13**) and carbon disulfide (**11**) which produced compound **14** in a yield (81 %) higher than that of Losanitch (60 %) (Scheme 2).[36]



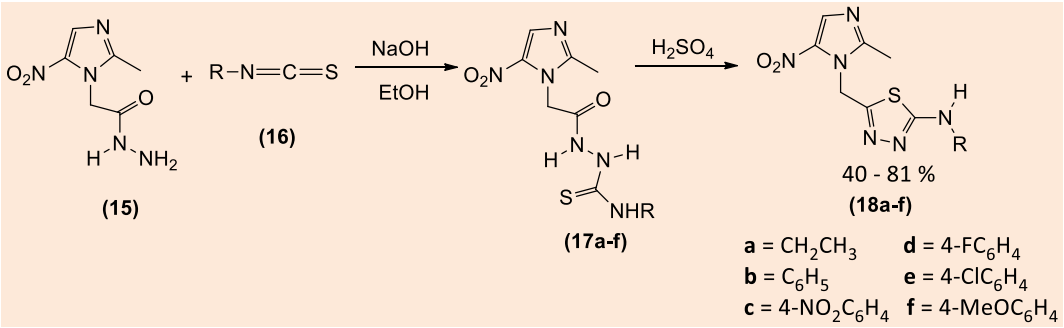
Scheme 2. Synthesis of thiadiazole from thiosemicarbazide and carbon disulfide

Among the different substitution patterns obtained for the 1,3,4-thiadiazole the compounds derived from 2-amino-5-substituted-1,3,4-thiadiazoles have been the focus of different publications.[37-39] Usually, these derivatives are available via basic routes through cyclization of acylhydrazines, dithiocarbazates, thiosemicarbazides, thiosemicarbazones or transformation of 1,3,4-oxadiazoles.

2.1. From acylhydrazines

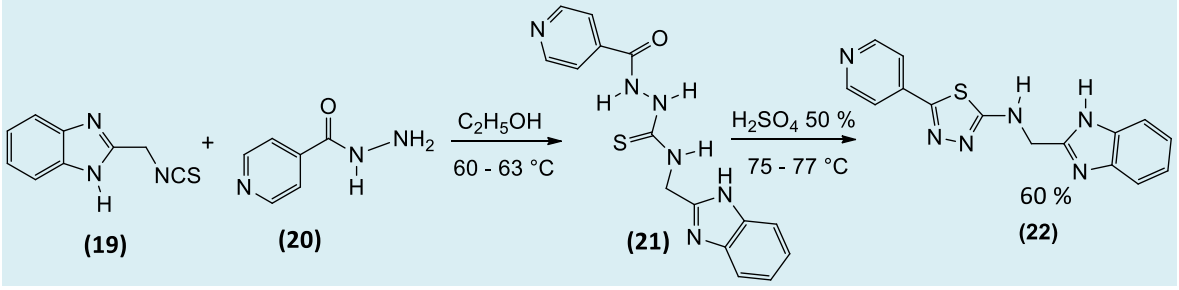
In general, the reactions between acylhydrazide and sulfur reagents (CS_2, isothiocyanate or dithiocarbamates) for thiadiazoles synthesis consists of two or more steps,[40-42] where the first is to synthesize the relevant thiosemicarbazides or dithiocarbazides which can then be converted into thiadiazoles.

Mirzaei *et al*. (2008) investigated the synthesis of thiadiazoles from acylhydrazines (Scheme 3). The reaction of acylhydrazine (**15**) with substituted isothiocynate (**16**) and sodium hydroxide in ethanol yielded thiosemicarbazide (**17a-f**) which was cyclized in an acidic medium to provide *N*-substituted 2-amino-5-[(2-methyl-5-nitro-1H-imidazol-1-yl)methyl]-1,3,4-thiadiazoles (**18a-f**).[40]



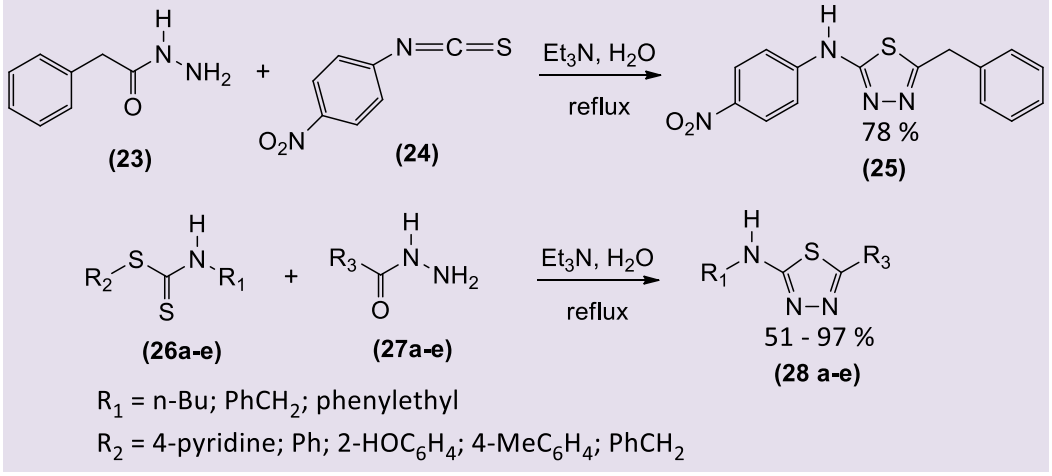
Scheme 3. Synthesis of thiadiazole from acylhydrazine and isothiocynate

Ghate *et al.* (2017) reported the synthesis of 1,3,4-thiadiazoles from isothiocynate and isoniazid in two steps (Scheme 4). At first the intermediate **21** was synthesized from 2-methylsulphonitrile-1[*H*] benzimidazole (**19**) and isoniazid (**20**), which was refluxed with 50 % H_2SO_4 to produce 1,3,4-thiadiazole derivate (**22**) with a yield of 60 %.[42]



Scheme 4. Synthesis of 1,3,4-thiadiazole from acylhydrazine reported by Ghate *et al*. (2017)

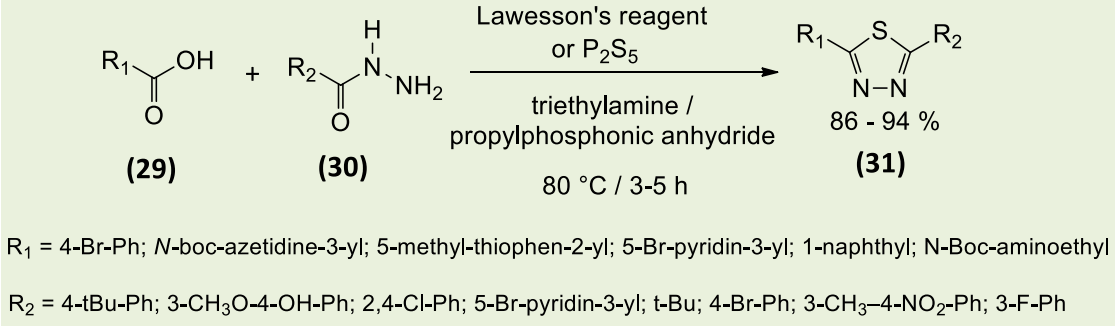
In 2010, Aryanasab[43] developed a one-pot synthesis using isothiocyanate (**24**) and acylhydrazides (**23**) to furnish 2-substituted-1,3,4-thiadiazoles (**25**) in the presence of water and triethylamine. Under the same conditions the authors used dithiocarbamates (**26a-e**) and acid hydrazides (**27a-e**) to produce **28a-e** in good yields (51-97 %) (Scheme 5).[43]



Scheme 5. One-pot synthesis of 1,3,4-thiadiazoles from acylhydrazine and the sulfur reagents

Another type of one-pot synthesis of 1,3,4-thiadiazole derivatives (**31**) from carboxylic acids (Scheme 6) was developed by Augustine *et al*. (2010).[44] According to these authors, propylphosphonic anhydride (T3P) is generally used as a coupling agent and water scavenger with low toxicity and offers several advantages over traditional reagents, such as having broad functional group tolerance, low epimerization tendency and, above all, high yields and purity. So, the main scope of the report was to evaluate the efficiency of propylphosphonic anhydride (T3P) as a reagent in one-pot synthesis.[44]

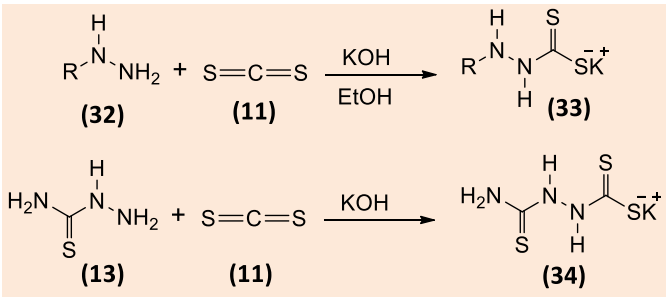
The 1,3,4-thiadiazole derivatives were synthesized from the mixture of carboxylic acid (**29**), hydrazide (**30**) and phosphorus pentasulfide (P_2S_5) or Lawesson's reagent in the presence of propylphosphonic anhydride (T3P), which has been demonstrated to be an efficient reagent for the one-pot synthesis. In most cases, the reaction proceeded with high efficiency.[44]



Scheme 6. Synthesis of thiadiazoles from carboxylic acids using propylphosphonic anhydride

2.2. From dithiocarbazates

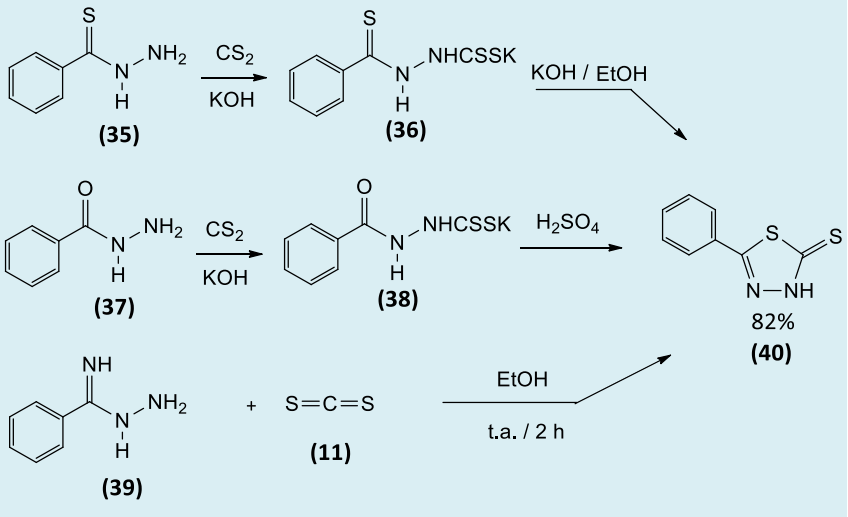
Dithiocarbazates are synthesized by carbon disulfide as the sulfur source reagent reacting with hydrazine **(32)**, hydrazides, thiosemicarbazide **(13)** or thioacylhydrazine usually under basic conditions (Scheme 7).[17]



Scheme 7. Synthesis of dithiocarbazates from hydrazine derivatives

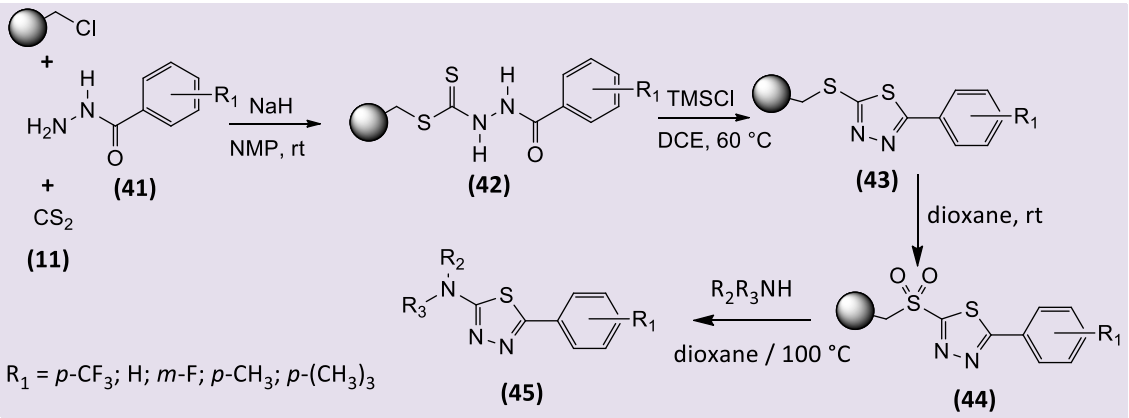
Literature reports the use of thiobenzhydrazide (**35**) and benzohydrazide (**37**) as the reagent to produce thiadiazole derivatives. Kubota and coworkers (1970)[45]described a reaction between benzamidrazone (**39**) and carbon disulfide (**11**) to obtain the thiadiazole **40** with a yield of 82 % (Scheme 8). The benzamidrazone was used by the authors due its structural similarity to **35** and **37**. The reaction conditions employed by the authors favored

the formation of **40** in a single step without the formation of the intermediate salt.[45]



Scheme 8. Synthesis of 1,3,4-thiadiazoline-5-tione derivatives

In 2010, Gong *et al*.[46] summarized several methods for solid-phase synthesis of 1,3,4-thiadiazoles using CS_2 in the presence of sodium hydride at room temperature to prepare various acyldithiocarbazate resins (**42**) and then cyclodehydrate to generate the 1,3,4-thiadiazole derivatives (**43**). They developed a simple and efficient solid-phase method able to facilitate the production of the 1,3,4-thiadiazoles and used resin as a solid support (Scheme 9).[46]



Scheme 9. Synthesis of 1,3,4-thiadiazoles using carbon disulfide and a solid support

These authors investigated various reagents for the cyclization reactions of the acyldithiocarbazates (**42**), including *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide (EDCI), *N,N*'-dicyclohexylcarbodiimide (DCC), trimethylsilyl chloride (TMSCl), *p*-toluenesulfonyl chloride (TsCl), thionyl chloride, phosphorus pentachloride, and diphenyl chlorophosphate. The results indicated that TMSCl and diphenyl chlorophosphate were the best choices for the synthesis of 1,3,4-thiadiazoles (**45**) (Scheme 9).[46] Then, to explore the diversity of this methodology, the authors used various amines to release the 1,3,4-thiadiazoles from the resin (Figure 3).[46]

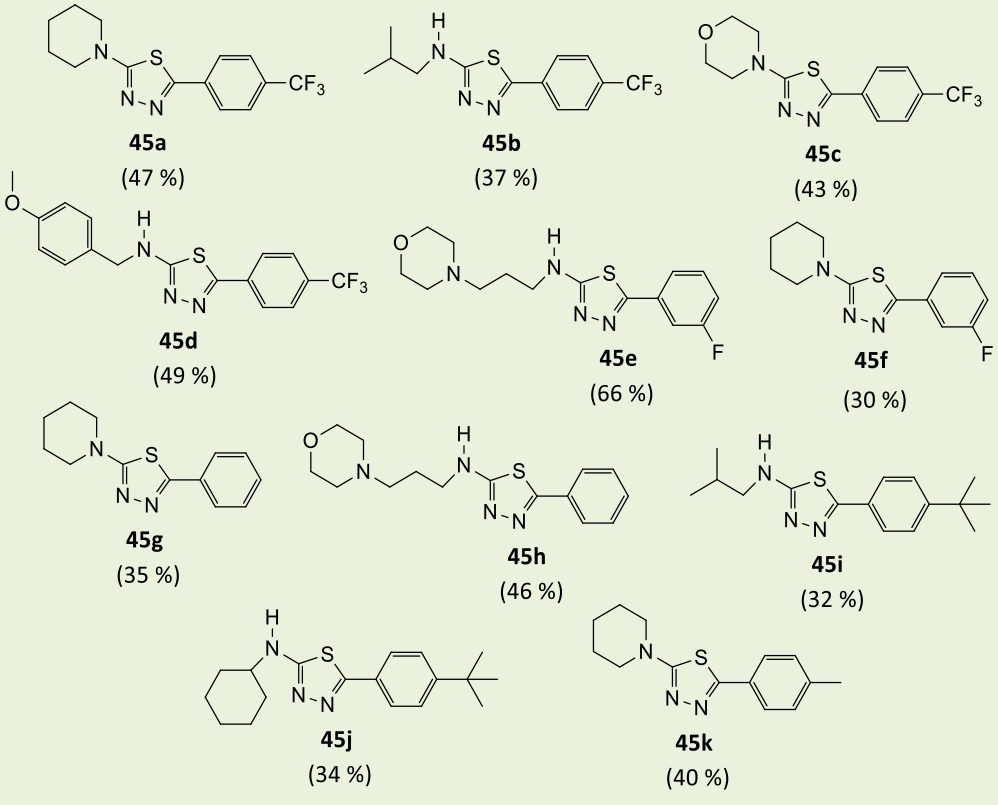
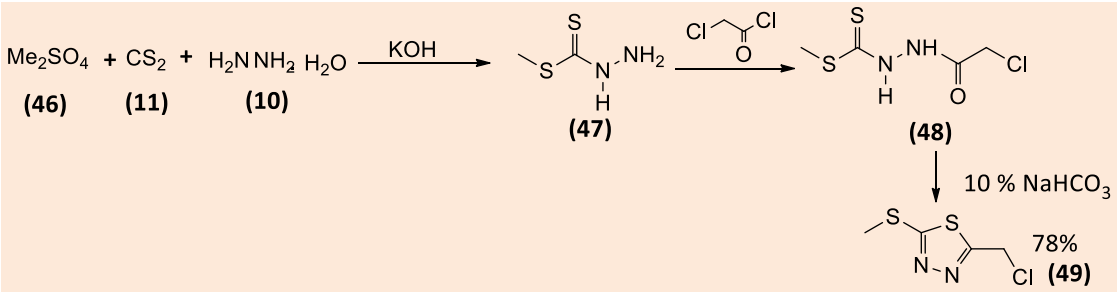


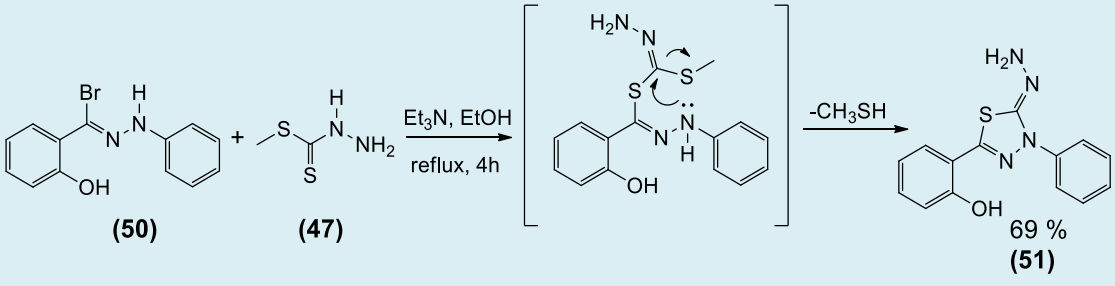
Figure 3. 1,3,4-thiadiazoles obtained and their yields

In 2011, Wang *et al.*[47] synthetized 1,3,4-thiadiazoles from dithiocarbazate. Dimethyl sulfate (**46**), carbon disulfide (**11**) and hydrazine hydrate (**10**) in the presence of potassium hydroxide reacted to generate the intermediate thiohydrazide (**47**). This intermediate reacted with chloroacetylchloride at a low temperature (-15 °C) to produce compound **48** that was cyclized in 10 % sodium bicarbonate to provide (5-methylthio-1,3,4-thiadiazol-2-yl)methylchloride (**49**) in a yield of 78 % (Scheme 10).[47]



Scheme 10. Synthesis of 1,3,4-thiadiazoles from dithiocarbazate

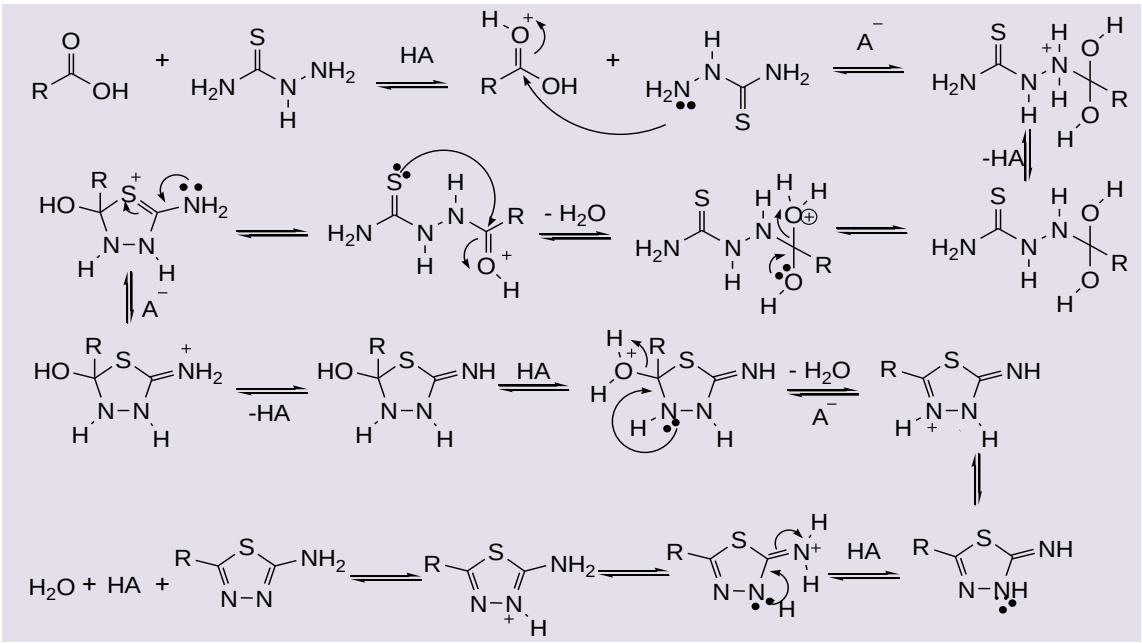
A few years later, Sayed *et al*. used the hydrazonoyl bromide (**50**) with methyl hydrazinecarbodithioate (**47**) in ethanol to obtain 3-phenyl-5-(2-hydroxyphenyl)-1,3,4-thiadiazol-2-(3-amino)-imine (**51**) as the only isolated product by the removal of hydrogen bromide and methanethiol (Scheme 11).[48]



Scheme 11. Synthesis of compound **51** from dithiocarbazate and hydrazonoyl bromide

2.3. From thiosemicarbazides

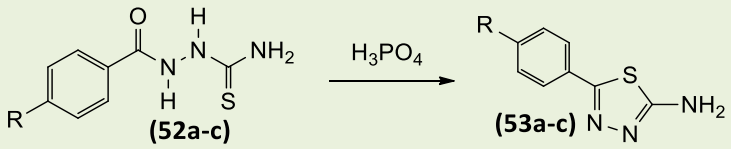
Many syntheses of 1,3,4-thiadiazoles proceed from thiosemicarbazide cyclization, which have been widely used and are efficient in the formation of thiadiazoles. This reaction occurs according to the mechanism presented in Scheme 12.[17] The proposed mechanism starts with a nucleophilic attack of the nitrogen electron pair of thiosemicarbazide to the carboxylic acid sp^2 carbon, followed of dehydration of the intermediary. The sulfur atom electron pair attacks the carbonyl causing cyclization and the intermediary formed is then dehydrated. Finally, an electron migration produces the aromatic heterocycle.



Scheme 12. Mechanism of cyclization of thiosemicarbazides[17]

The procedure performed by Hoggarth (1949) involved the treatment of thiosemicarbazide derivatives (**52a-c**) with phosphoric acid to form the thiadiazoles (**53a-c**) with yields of 30-50 % (Table1).[30]

Table 1. Synthesis of thiadiazoles from the cyclization of thiosemicarbazide derivatives

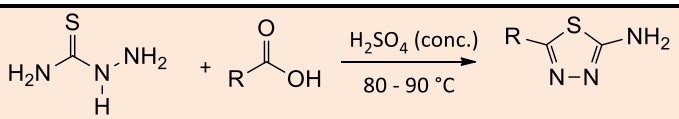


(52a-c) (53a-c)

Compound (**53**)	R	Yields (%)
a	H	40
b	-OCH_3	30
c	Cl	50

In 1959, Chubb and Nissenbaum synthesized 2-amino-5-substituted-1,3,4-thiadiazole derivatives (**55a-h**) by the reaction of a thiosemicarbazide (**13**) with carboxylic acid (**54a-h**) in the presence of sulfuric acid. The reaction was maintained at a temperature of 80-90 °C for 7 h and the products were obtained in yields of 35-80 % (Table 2).[49]

Table 2. Synthesis of thiadiazole derivatives obtained by Chubb and Nissenbaum[49]

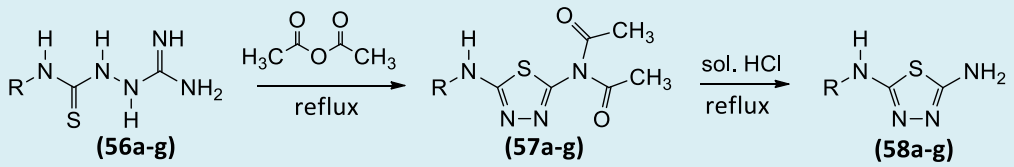


(13) (54a-h) (55a-h)

Compound (**55**)	R	Yields (%)
a	*n*-C_3H_7	80
b	*iso*-C_3H_7	70
c	*n*-C_4H_9	35
d	*iso*-C_4H_9	49
e	*t*-C_4H_9	54
f	*sec*-C_4H_9	55
g	*n*-C_5H_{11}	52
h	*iso*-C_5H_{11}	52

Years later, Kurzer and Canelle synthesized 1,3,4-thiadiazole derivatives employing a two-step methodology. This procedure involved the treatment of 1-amidinothiosemicarbazides (**56a-g**) with acetic anhydride. This reaction yielded the intermediates (**57a-g**) in yields of 38-72 %. Acid hydrolysis of these intermediates provided **58a-g** in yields of 54-85 % (Table 3).[50]

Table 3. Derivatives of 1,3,4-thiadiazoles obtained by Kurzer and Canelle[50]

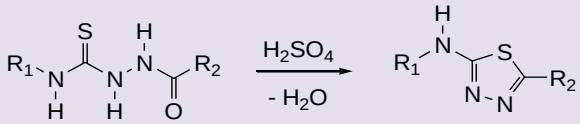


(56a-g) **(57a-g)** **(58a-g)**

Compounds	R	Yields **57a-g** (%)	Yields **58a-g** (%)
a	$(CH_3)_2CH$-	64	56
b	$(CH_3)_2CHCH_2$-	52	80
c	*p*-$CH_3OC_8H_{11}$-	40	85
d	*p*-ClC_6H_4-	72	54
e	*o*-$F_3CC_6H_4$-	38	78
f	*m*-$F_3CC_6H_4$-	64	80
g	*p*-$F_3CC_6H_4$-	56	60

Rao and Srinivasan (1970)[51]and Husain *et al*. (1986)[52]employed the same method used by Hoggarth (1949). Both authors treated aryl-thiosemicarbazide with concentrated sulfuric acid to form thiadiazoles (**59a-e**) in yields of 60-75 % and 50-55 %, respectively (Table 4).[51,52]

Table 4. Reaction of thiosemicarbazide with sulfuric acid to produce thiadiazoles



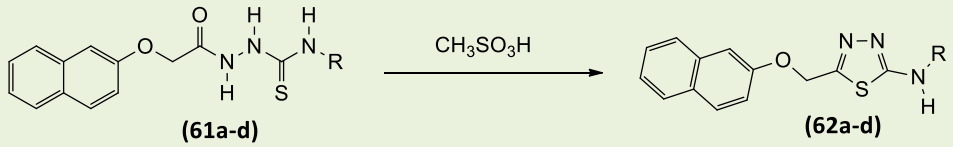
(58a-e) **(59a-e)**

Compound (**59**)	R_1	R_2	Yields (%)
a[51]	H	3,4,5-$(MeO)_3$-C_6H_2	60
b[51]	H	3,4-Cl_2-C_6H_3	72
c[51]	H	2-NO_2-C_6H_4	75
d[52]	C_6H_5	β-(CH_2O)-Naphthalene	50
e[52]	CH_3O- C_6H_4	β-(CH_2O)-Naphthalene	55

The results obtained with sulfuric acid were slightly better when compared to the results obtained by the procedure adopted by Hoggarth, using H_3PO_4. However, the compounds synthesized by Rao and Srinivasan presented better yields when compared to those of Husain et al. This difference may be related to the substitution pattern of R1, since the insertion of the phenyl group may decrease the availability of electrons in the sulfur, due to the resonance between the aromatic ring and the nitrogen.[30,51,52] However, it was not possible to compare this with the results of Chubb (1959), since the thiosemicarbazide used has no substitution.

Palaska *et al*. (2002) reported the synthesis of 1,3,4-thiadiazole derivatives (**62a-d**) from the treatment of thiosemicarbazides with methanesulfonic acid. The reaction was conducted by refluxing toluene using a ratio of 1:15 of the reactants, respectively (Table 5). The authors reported low yields (15-31%) for these transformations.[53]

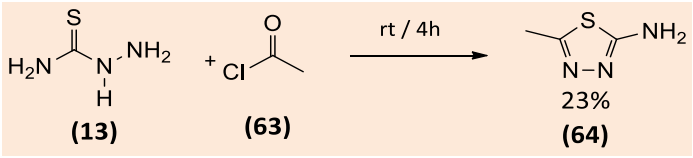
Table 5. Cyclization of thiosemicarbazide derivatives using methanesulfonic acid



Compound (**62**)	R	Yield (%)
a	C_6H_5	24
b	C_2H_5	31
c	CH_3	25
d	CH_2-CH=CH_2	15

Since then, several authors have used dehydrative cyclization of thiosemicarbazides to obtain 1,3,4-thiadiazoles. The simplicity of the reagents and the experimental conditions allowed the use of the procedures described below with yields of between 50-90 %. The most commonly used reagents were sulfuric acid and phosphorus oxychloride.[20,54-56]

In 2010, Schüttelkopf *et al*. synthetized the acetazolamide derivative (**64**) from the reaction of thiosemicarbazide (**13**) and acetyl chloride (**63**). The mixture was stirred for 4 h at room temperature and the product was obtained with yield of 23 % (Scheme 13).[57]



Scheme 13. Synthesis of 1,3,4-thiadiazole from acetyl chloride and thiosemicarbazide

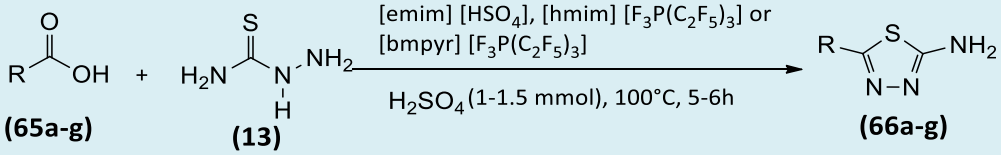
According to Epishina*et al*. (2011)[58], the methods to synthesize 2-amino-1,3,4-thiadiazoles based on the cyclocondensation of carboxylic acids with thiosemicarbazide in an acidic medium, mostly in concentrated sulfuric acid, produce good results. In some cases, $POCl_3$, $MeSO_3H$ in the presence of P_2O_5, polyphosphoric acid (PPA) and dichlorophosphate on polyethyleneglycole are used as acidic catalysts. However, they have some disadvantages, because a large amount of inorganic salts are generated in the neutralization of H_2SO_4 and the other acidic catalysts, which results in an adverse environmental impact and creates difficulties to isolate the final products. Furthermore, these reactions are suitable only for the synthesis of monocyclic compounds.[58]

The goal of these researchers was to develop a new general method for the preparation of 2-amino-1,3,4-thiadiazole derivatives. The authors evaluated carboxylic

acids (**65a-g**) and thiosemicarbazide (**13**) for the preparation of 2-amino-1,3,4-thiadiazole derivatives (**66a-g**) in ionic liquids, which have been widely employed as potential substitutes of conventional solvents for a variety of chemical processes.[58]

According to the authors, a new, simple and general method was developed based on heating of carboxylic acids, including the *N*-protected α-amino acids, with thiosemicarbazide at 100 °C in ionic liquids with the addition of H_2SO_4 in a catalytic amount (Table 6). The reaction provided **66a-g** with yields of 40–96 %.[17,58]

Table 6. Synthesis of 1,3,4-thiadiazoles using ionic liquids as the solvent

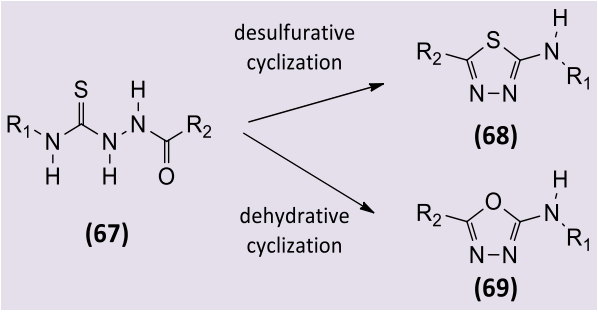


(65a-g) + **(13)** → **(66a-g)**

Compound (**75**)	R	Yield (%)
A	$PhCH_2$	92
B	Pr	73
C	Pr	76
D	CH_2NHBz	70
E	$MeS(CH_2)_2CH(NHBz)$	40
F	MeCH(NHBz)	96
G	$CH_2(NHTs)$	54

[emim] [HSO_4]: 1-ethyl-3-methylimidazolium hydrosulfate; [hmim] [$F_3P(C_2F_5)_3$]/[bmpyr][$F_3P(C_2F_5)_3$]: 1-hexyl-1-methylimidazolium and butylmethyl-pyrrolidinium trifluorotris(pentafluoroethyl) phosphates

In 2013, Yang *et al*. developed an efficient method for the regioselective synthesis of 2-amino-substituted 1,3,4-thiadiazoles or 1,3,4-oxadiazoles by cyclodehydration or cyclodesulfurization reactions (Scheme 14). Thiosemicarbazides (**67**), which serve as useful intermediates in this process, are generated by the reaction of the isothiocyanate starting material with acyl hydrazides.[59]



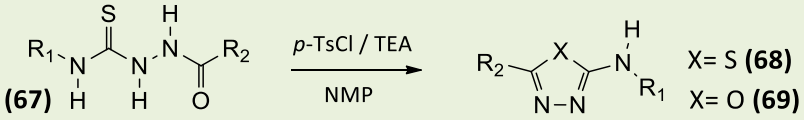
(67) → **(68)** / **(69)**

Scheme 14. Cyclization of the thiosemicarbazide

To investigate the regioselectivity of the synthesis of 1,3,4-thiadiazoles (**68a-f**), cyclization reactions of thiosemicarbazide were investigated by using various reagents, for example, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC·HCl), *p*-TsCl, TMSCl, and diphenyl chlorophosphate under various conditions.[59]

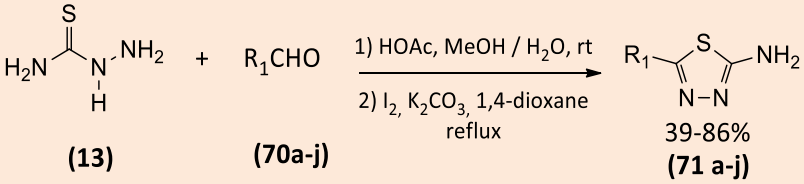
The use of EDC HCl, which is well known as a desulfurizing agent, produced 2-amino-1,3,4-oxadiazole (**69a-f**) as a major product with regioselectivity (100: 0) and a high yield (>99 %). The TMSCl, and diphenyl chlorophosphate were not efficient. On the other hand, in the case of *p*-TsCl-based cyclization, various thiosemicarbazides showed different regioselectivity depending on the substituent. The best results are presented in Table 7.[59]

Table 7. Results of the cyclization with *p*-TsCl/TEA



Compound	R_1	R_2	Ratio		Yield (%)
			68	**69**	
a	Benzyl	Ph	96	4	92
b	Benzyl	4-F-Ph	99	1	87
c	Benzyl	4-NO_2-Ph	99	1	63
d	4-methoxy-Bn	Ph	96	4	73
e	Ethyl	Ph	97	3	94
f	2,4-dimethoxy-Benzyl	4-NO_2-Ph	99	1	87

Niu *et al*. (2015) synthesized 2-amino-substituted 1,3,4-thiadiazoles (**71a-j**) via condensation of thiosemicarbazide (**13**) and the corresponding aldehydes (**70a-j**) followed by I_2-mediated oxidative C–S bond formation (Scheme 15).[60] After condensation of the thiosemicarbazide and the corresponding aldehyde, the reaction mixture was concentrated and then redissolved in 1,4-dioxane, followed by treatment with molecular iodine and potassium carbonate to form the respective thiadiazoles.[60]



Scheme 15. Synthesis of 2-amino-1,3,4-thiadiazoles employing I_2

This transition-metal-free sequential synthesis process is compatible with aromatic, aliphatic, and cinnamic aldehydes to provide a series of 2-amino-1,3,4-thiadiazole derivatives

with moderate to good yields (Table 8).[60] According to the authors, under the optimal sequential synthesis conditions, thiosemicarbazide and the corresponding aldehydes were smoothly converted into the desired thiadiazoles without purification of the condensation intermediates.[60]

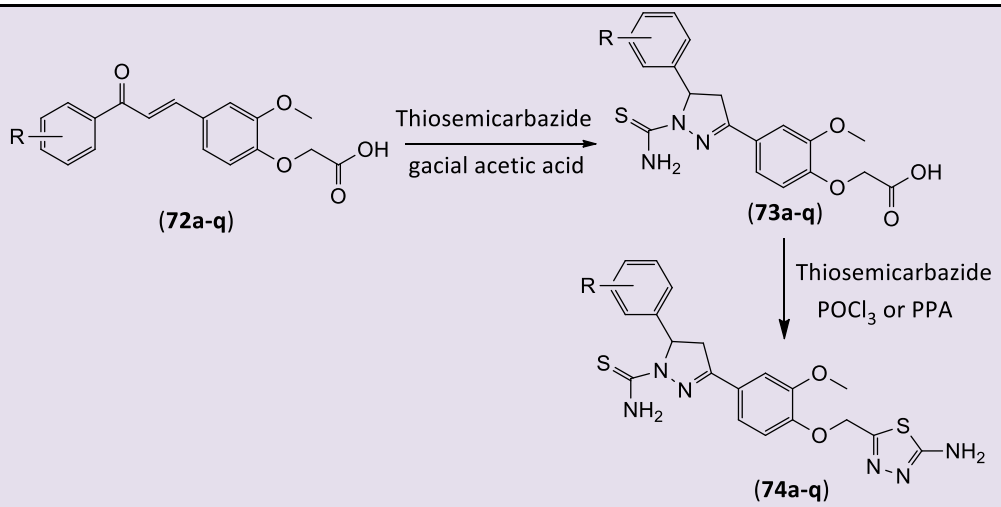
Table 8. Derivatives of 1,3,4-thiadiazoles obtained by Niu *et al*[60]

Compound (71a-j)	R_1	Yield (%)
a	*p*-CH_3-Ph	81
b	*m*-CF_3-Ph	86
c	*p*-NO_2-Ph	74
d	*p*-methoxy-Ph	54
e	*p*-Cl-Ph	60
f	*p*-CN-Ph	65
g	*o*-F-Ph	84
h	2,4-Cl-Ph	81
i	*t*-Bu	76
j	-CH_2=CH_2-Ph	39

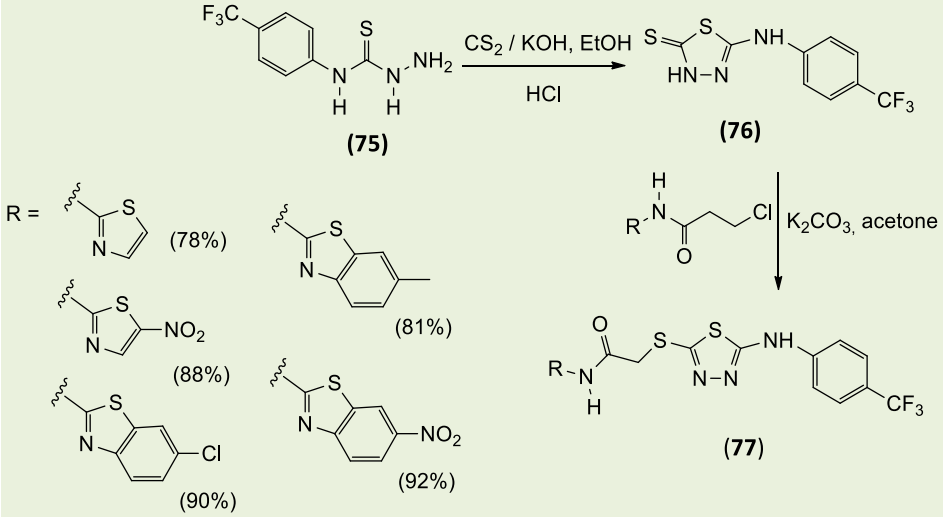
Noolvi *et al*. (2016) reacted some enones (**72a-q**) and thiosemicarbazide in the presence of glacial acetic acid and ethanol to produce the intermediates **73a-q**, which were cyclized by treating with thiosemicarbazide and $POCl_3$ or polyphosphoric acid (PPA). This last step provided **74a-q** with yields of 20 – 70 % (Table 9).[61]

In 2018, Altintop *et al*. reported the synthesis of the some thiadiazoles employing the thiosemicarbazide **75** and carbon disulfide. The intermediate **76** was synthesized by the ring closure reaction of 4-[4-(trifluoromethyl)phenyl]thiosemicarbazide (**75**) with carbon disulfide in the presence of potassium hydroxide (Scheme 16). Finally, the reaction of **76** with *N*-(aryl)-2-chloroacetamides in the presence of potassium carbonate afforded new 1,3,4-thiadiazoles (**77**) with yields between 78-92 %.[8]

Table 9. Synthesis of 1,3,4-thiadiazoles from thiosemicarbazide and $POCl_3$ or PPA

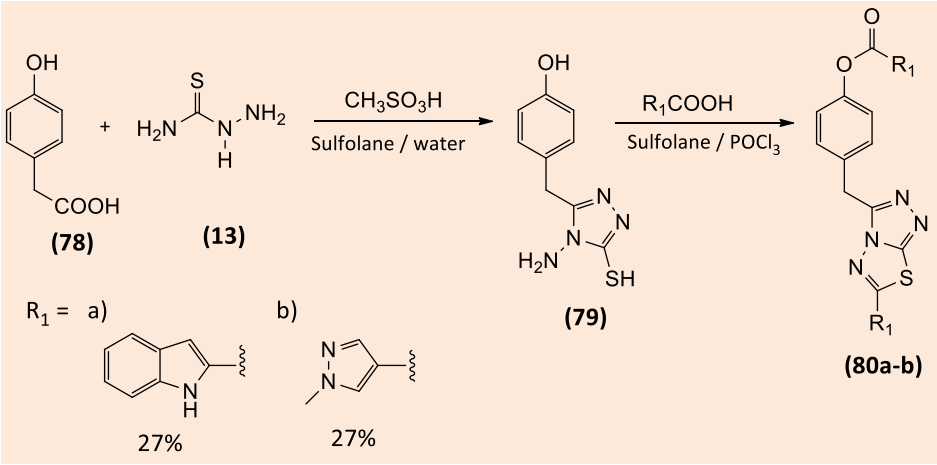


Compound (**74**)	R	Yield (%)
a	H	42
b	2-OCH_3	44
c	2,4-di-Cl	36
d	3-NH_2	26
e	3-NO_2	36
f	4-OCH_3	42
g	4-fluoro	20
h	4-NO_2	44
i	4-Br	66
j	4-CH_3	62
k	3-OH	66
l	2-OH	68
m	4-Cl	65
n	2-NH_2	59
o	2,4-di-OH	67
p	4-NH_2	70
q	2-Cl	65



Scheme16. Synthesis of 1,3,4-thiadiazoles employing thiosemicarbazide and CS_2

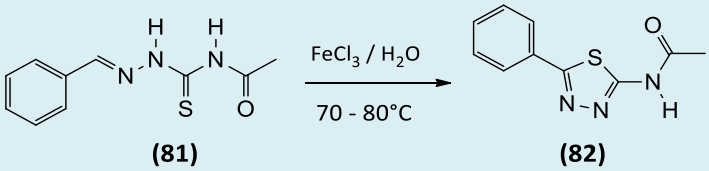
Recently, Yuan*et al*. (2018) reported the synthetic routes for the synthesis of [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives (**80a-b**). The compounds were prepared from a two-step cyclization of 2-(4-hydroxyphenyl) acetic acid (**78**) with thiocarbohydrazide (**13**) and carboxylic acids. 2-(4-hydroxyphenyl)acetic acid, hydrazinecarbothiohydrazide and methanesulfonic acid were dissolved in sulfolane/water and the solution was stirred at 90 °C for 24 h. The intermediate (**79**) obtained was then treated with carboxylic acid in sulfolane and $POCl_3$. The reaction mixture was stirred at 85 °C for 18 h. Both products were obtained in 27 % yields (Scheme 17).[62]



Scheme 17. Synthesis of [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives

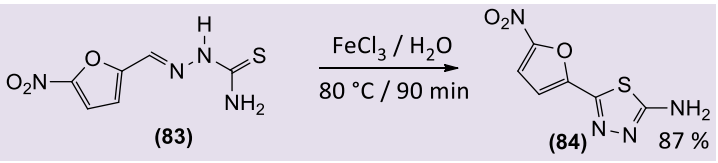
2.4. From thiosemicarbazone

Young & Eyre (1901) developed a methodology for the synthesis of 1,3,4-thiadiazole (**82**) through the oxidation of aryl thiosemicarbazone (**81**) using an aqueous solution of ferric chloride (Scheme 18). According to the authors, the oxidation of thiosemicarbazone by ferric chloride occurs under milder reaction conditions (70-80 °C) when compared to the oxidation of semicarbazone (130-140 °C).[28]



Scheme 18. Oxidation of phenyl thiosemicarbazone with $FeCl_3$ to produce 1,3,4-thiadiazoles

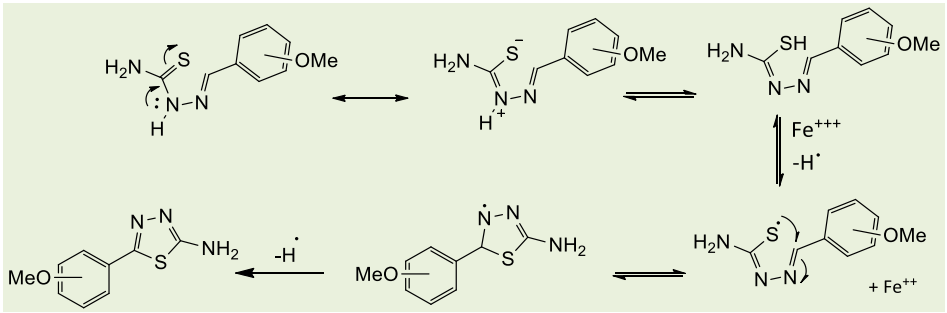
Years later, Skagius *et al.* (1960) employed the methodology developed by Young & Eyre (1901) to synthesize **84** (Scheme 19).[63] The authors reported good performance in the oxidation of 5-nitrofurfural thiosemicarbazone (**83**) with ferric chloride,[28,53,58] however when thiosemicarbazones derived from 2-furfural and 2-pyridine-carboxaldehyde were used, the yields obtained were less than 40 %. The authors associated the lower yield obtained in the reaction with furfural, compared to 5-nitrofurfural, with the nitro group which prevents the acid cleavage of the furan ring.[63]



Scheme 19. Synthesis of 1,3,4-thiadiazole with heteroaromatic substituents employing $FeCl_3$

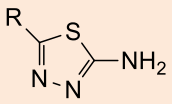
In 1970, in order to optimize the methodology, Rao and Srinivasan investigated the process of oxidative cyclization of aryl-thiosemicarbazone using ferric chloride (Scheme 20).[51]

In 1970, Rao and Srinivasan investigated the synthesis of 2-amino-5-aryl-1,3,4-thiadiazole derivatives by oxidative cyclization of aldehyde thiosemicarbanozes with ferric chloride, dehydrative cyclization of 1-acylthiosemicarbazides with sulfuric acid and direct amination of monoaryl-1,3,4-thiadiazoles using hydroxylamine hydrochloride. The authors reported more satisfactory results using a homogenous reaction mixture. In this case, the aqueous solution of ferric chloride was replaced by an alcohol solution. The authors suggested that thiosemicarbazone oxidation involved the formation of a radical intermediate (Scheme 20), giving the thiadiazole ring (**85a-f**) yields of between 44-91 % (Table 10).[51]



Scheme 20. Mechanistic scheme for the oxidation of thiosemicarbazone

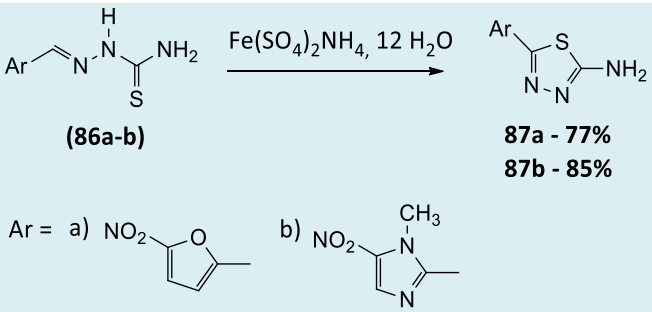
Table 10. Yield of the thiadiazole derivatives obtained by Rao andSrinivasan[51]



(85a - f)

Compound (**85**)	R	Yield (%)
a	C_6H_5	61
b	2-MeO-C_6H_4	91
c	4-MeO-C_6H_4	46
d	3,4-$(MeO)_2$-C_6H_3	65
e	2-Cl-C_6H_4	87
f	2-furil	44

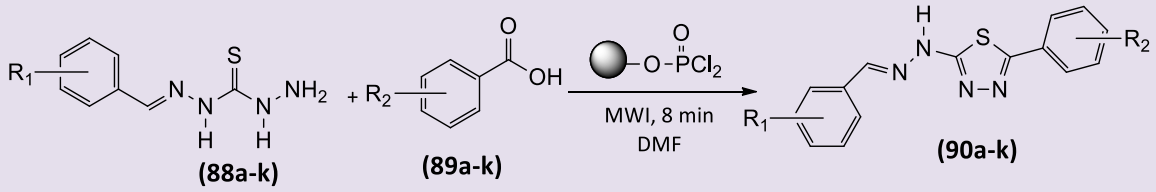
Foroumadi *et al*. (2001) reported the synthesis of 1,3,4-thiadiazoles (**87a-b**) through the oxidative cyclization reaction of 2-aryl-thiosemicarbazones (**86a-b**) using ammonium ferric sulfate dodecahydrate as the oxidizing agent. Heterocycles were obtained in yields of 77 % and 85 % (Scheme21).[64]



Scheme 21. Synthesis of 1,3,4-thiadiazoles from thiosemicarbazone and $Fe(SO_4)_2\,NH_4$

In 2008, Li *et al*. report a new route for the preparation of (un)substituted benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl) hydrazones (**90a-k**) from thiosemicarbazones (**88a-k**) and aromatic carboxylic acids (**89a-k**). These authors reported yields between 80 – 90 % when silica-supported dichlorophosphate was used as a recoverable dehydrant under microwave irradiation (Table11).[65]

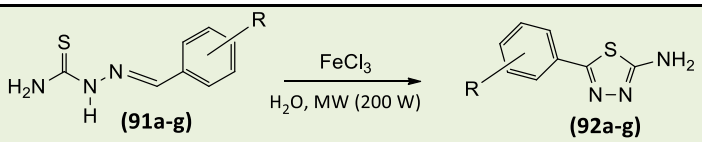
Table 11. Synthesis of benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl) hydrazones (**90a-k**)



Compound (**90**)	R_1	R_2	Yield (%)
a	H	H	90
b	H	4-CH_3O	87
c	H	2-CH_3	80
d	H	3-CH_3	84
e	H	3-Cl	84
f	H	4-Cl	82
g	4-CH_3O	H	85
h	4-CH_3O	4-CH_3O	87
i	4-CH_3O	4-Cl	83
j	4-CH_3O	3-Cl	84
k	4-CH_3O	2-CH_3	81

In 2013, Feng *et al*.[66] synthesized 2-amino-5-aryl-1,3,4-thiadiazole derivatives (**92a-g**) from the cyclization of thiosemicarbazone in the presence of $FeCl_3$. However, for more efficient and more environmentally friendly methods, the research group chose to synthesize 1,3,4-thiadiazole through microwave irradiation and ultrasound, without the use of organic solvents or acidic conditions (Table 12). The solution of thiosemicarbazone, ferric chloride and water was subjected to microwave (200 W) and ultrasound (50 W) for 3 minutes, to generate the products with 73–90 % yields (Table 12).[66]

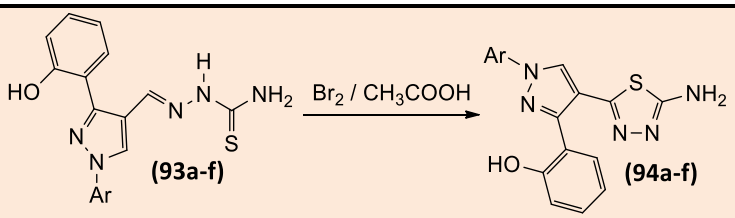
Table 12. Oxidative cyclization of thiosemicarbazones in ferric chloride using microwave irradiation



Compound (**92**)	R	Yield (%)
a	H	85
b	4-F	90
c	3-NO_2	89
d	4-Cl	85
e	2,4-Cl	84
f	4-CH_3	73
g	4-OCH_3	88

Kariyappa and Gurunanjappa (2016) reported a synthesis of novel compounds (**94a-f**) that were obtained by the oxidative cyclization of thiosemicarbazone (**93a-f**) using bromine dissolved in glacial acetic acid for 2-3 h at room temperature (Table 13).[67]

Table 13. Oxidative cyclization of thiosemicarbazones using bromine-glacial acetic acid



Compound (**94**)	Ar	Yield (%)
a	C_6H_5	82
b	4-Cl-C_6H_4	80
c	2-CH_3-C_6H_4	76
d	2-OCH_3-C_6H_4	79
e	2,4-$(CH_3)_2$-C_6H_3	78
f	2,4-$(NO_2)_2C_6H_3$	76

As can be seen, the oxidative cyclization of thiosemicarbazone is a fast and efficient methodology that provides yields of up to 90 %, as well as the cyclization by dehydration of thiosemicarbazides, and is used to date in the synthesis of 1,3,4-thiadiazoles intermediates.[10,35,67,68]

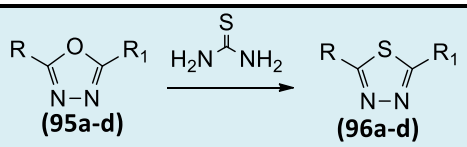
2.5. From 1,3,4-oxadiazole

An alternative methodology reported in the literature is associated with the conversion of oxadiazole to thiadiazole. The 1,3,4-oxadiazole ring is a bioisosteric analogue of the 1,3,4-thiadiazole ring. The substitution of oxygen for sulfur in the heterocyclic ring represents an example of an approach that is commonly known as bioisosterism. The idea of bioisosterism is one of the most successful techniques of bioactive compound design.[69-71]

However, the conversion of oxadiazole to thiadiazole has limited use due to the need for longer reaction times (30 h) compared to the previously reported processes, ranging from 0.5 to 7 h.

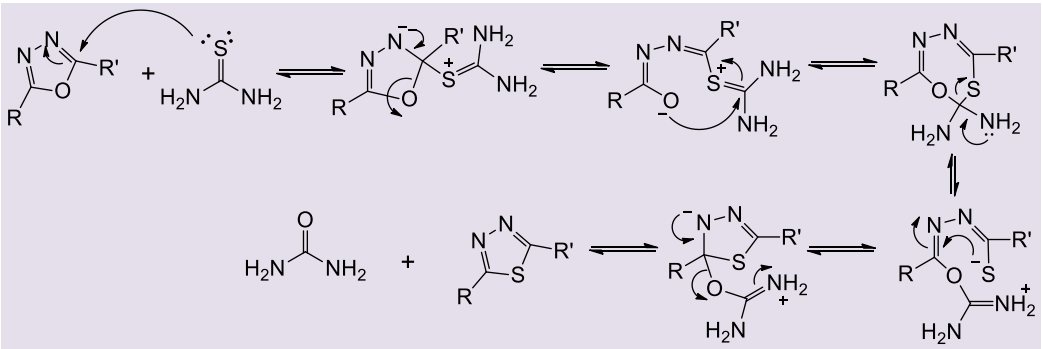
Linganna and Rai (1998) synthesized 1,3,4-thiadiazoles (**96a-d**) from the oxadiazole reaction with a solution of thiourea in tetrahydrofuran (Table 14). The authors reported yields of 55–69 %, but the reaction time was long (24-30 h).[31]

Table 14. Reaction for the conversion of aryl-1,3,4-oxadiazole to aryl-1,3,4-thiadiazoles



Compound (**96**)	R	R_1	Yields (%)
a	C_6H_5	C_6H_5	65
b	C_6H_5	(CH_3O)-C_6H_4	60
c	C_6H_5	$(CH_3O)_3$-C_6H_2	69
d	(NO_2)-C_6H_4	$(CH_3O)_3$-C_6H_2	55

According to the authors, the probable mechanism of the reaction is due to the attack of the sulfur atom from thiourea on the heterocycle followed by the ring opening, as described in Scheme 22.[31]



Scheme 22. Mechanistic scheme proposed by Linganna and Rai

Although its use is more restricted, in the last 10 years, Padmavathi and his research group have employed this methodology. Their reports showed yields between 64 – 78 %, although the reaction time ranged from 20 to 30 h.[14,38,72-74]

3. 1,3,4-Thiadiazoles: Microbiological Activities

The planning, synthesis and evaluation of the bioactivity of molecules with therapeutic potential has been the target of organic and pharmaceutical chemistry. Moreover, the heterocyclic compounds have been the focus of much research in the field of Medicinal Chemistry.[20,35,75-77]

Khalaj *et al*. (2011)[78] evaluated thiadiazole derivatives with analogous structures of linezolid (**97**) (Figure4). The results obtained were compared with the activity of linezolid and ciprofloxacin, which were used as reference antibiotics.[78]

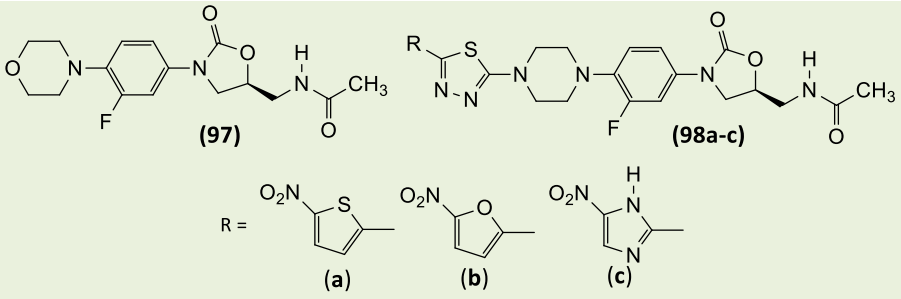


Figure 4. Thiadiazole analogous to linezolid

These derivatives (**98a-c**) were evaluated against Gram-positive bacteria (*Staphylococcus aureus ATCC 6538p, Staphylococcus epidermidis ATCC 12228, Staphylococcus warneri, Staphylococcus lentus, Staphylococcus xylosus, Staphylococcus saprophyticus, Micrococcus luteus, Corynebacterium glutamicum and Bacillus subtilis, MRSA 3, MRSA 5* and *MRSA 17*) and Gram-negative bacteria (*Escherichia coli ATCC 8739, Klebsiella pneumonia ATCC 10031* and *Pseudomonas aeruginosa ATCC 9027*).

The evaluated compounds presented MIC values similar to the reference antibiotic (linezolid - MIC> 100 µg/mL) for *Pseudomonas aeruginosa* and *Escherichia coli*. The assays employing Gram-negative bacteria presented MICs between 0.78 and 100 µg/mL. For Staphylococcus the MIC varied between 0.006 and 0.195 µg/mL. All MIC values were lower than the reference antibiotics (linezolid). The compounds were efficient against resistant strains of *Staphylococcus aureus*, which had MIC values between 0.012 and 6.5 µg/mL (Table 15).[78]

Table 15. Results of the antibacterial evaluation of compounds **98a-c**

Microorganism		Minimum Inhibitory Concentration (μg/mL)			
		98a	**98b**	**98c**	Linezolid
Gram-positive	*S. aureus*	0.098	0.012	0.098	0.781
	S. epidermidis	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

Barbuceanu *et al*. (2012) investigated biological activity of the derivatives of compounds **99a-b** and **100a-b** (Figure 5). The authors determined the MIC values for these derivatives, which were compared against the reference antimicrobials (fluconazole and amikacin).[79]

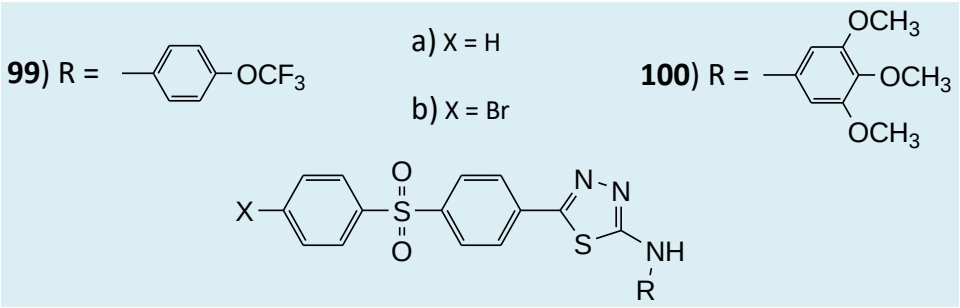


Figure 5. 1,3,4-thiadiazole class bearing diphenyl sulfone moieties with antimicrobial activity

The compounds showed antimicrobial activity (Table 16), however the concentrations presented were higher than 16 μg/mL. The best results were for *Bacillus cereus* bacteria with MIC values between 16-32 μg/mL, since the reference antibiotic (amikacin) had no activity.[79]

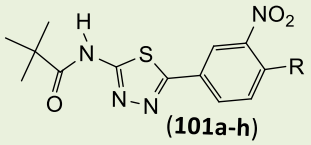
Table 16. Minimal Inhibitory Concentration of thiadiazole derivatives reported by Barbuceanu*et al*[79]

Compound	MIC (µg/mL)[a,b]							
	Sa	*Bc*	*Ec*	*Ecl*	*Ab*	*Pa*	*Ca*	*Cp*
99a	512	32	128	128	32	64	64	64
99b	512	32	128	128	32	64	128	64
100a	512	16	128	128	32	64	64	64
100b	512	16	64	128	32	64	64	64
Amikacin	2	NA	2	NA	NA	2	NT	NT
Fluconazole	NT	NT	NT	NT	NT	NT	NA	2

[a]*Sa - Staphylococcus aureus*; *Bc - Bacillus cereus*; *Ec - Escherichia coli*; *Ecl - Enterobacter cloacae*;
Ab - Acinetobacter baumanni; *Pa - Pseudomonas aeruginosa*; *Ca - Candida albicans*;
Cp - Candida parapsilosis; [b]NA = no activity; NT = not tested

Chandrakantha *et al*. (2014) evaluated *in vitro* compounds in antibacterial and antifungal studies. Antibacterial activity for the derivatives (**101a-h**) was evaluated by the well plate method (Table 17).[80]

Table 17. Results of the antimicrobial evaluation of compounds (**101a-h**)



(**101a-h**)

Compound (**101**)	R	Diameter of zone of inhibition (mm) Concentration (0.5 mg/mL)[a,b]					
		Antibacterial activity			Antifungal activity		
		Ec	*Bs*	*Pa*	*Af*	*Ck*	*Ca*
a	Morpholinyl	10	09	10	02	02	03
b	*N*-CH_3-piperazinyl	03	03	02	NA	02	02
c	4-(CF_3)-phenyl-piperidinyl	05	05	06	05	05	04
d	Cyclopentyl	04	03	02	02	02	02
e	Cyclohexyl	08	06	07	05	04	07
f	*N*-(2,4-difluorobenzyl)	03	02	02	04	05	03
g	Pyrrolidinyl	03	01	04	04	03	05
h	*N*-(4-fluoro-phenyl)	05	03	04	02	04	02
	streptomycin	17	19	15	NT	NT	NT
	fluconazole	NT	NT	NT	10	15	20

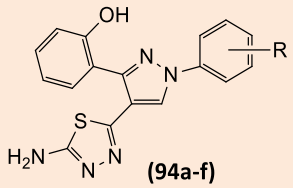
[a]*Ec - Escherichia coli; Bs – Bacillus subtillis; Pa - Pseudomonas aeruginosa; Af - Aspergillus flavus;*
Ck - Chrysosporium keratinophilum; Ca - Candida albicans;
[b]NA = no activity; NT = not tested

The compounds were tested against Gram-negative bacteria (*Escherichia coli, Bacillus subtilis* and *Pseudomonas aeruginosa*) and fungi (*Candida albicans, Aspergillus flavus* and *Chrysosporium keratinophilum*) according to Table 17.[80] The preliminary *in vitro* antimicrobial screening of new 1,3,4-thiadiazole derivatives evidenced that many of the compounds have emerged as potent antibacterial and antifungal agents with moderate activity compared to the standards.[80]

The antibacterial screening revealed that compound **101a** showed good inhibition against various of the microbial strains tested, mainly, against *Escherichia coli* compared to the reference antibiotic (streptomycin). The remaining compounds showed moderated activity against the three bacterial strains tested. In the antifungal screening, compound **101c** showed moderate activity against *Aspergillus flavus* compared with the standard drug fluconazole. Whereas other compounds showed less activity against all the microorganisms tested compared to the standards.[80]

Kariyappa and Gurunanjappa (2016)[67] performed microbial studies with various 1,3,4-thiadiazole derivatives (**94a-f**). The authors evaluated the minimum inhibitory concentration (MIC) of these derivatives using the serial dilution method. The compounds were tested against Gram-negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa*, Gram-positive bacterium, *Staphylococcus aureus* and fungi *Aspergillus niger, Aspergillus flavus* and *Candida albicans*. The antibiotics ciprofloxacin and fluconazole were used as standards for antibacterial and antifungal studies, respectively. Results of the MIC values are summarized in Table 18.[67]

Table 18. Bioactivity of 1,3,4-thiadiazole derivatives synthesized by Kariyappa and Gurunanjappa[67]



(94a-f)

Compound (**94**)	R	Minimum Inhibitory Concentration (µg/mL)[a]					
		Antibacterial activity			Antifungal activity		
		S.aureus	*E. coli*	*P.aeruginosa*	*A.niger*	*A.flavus*	*C.albicans*
a	H	25	25	50	25	25	50
b	4-Cl	12.5	12.5	12.5	12.5	25	25
c	2-CH_3	25	50	12.5	25	50	25
d	2-OCH_3	50	12.5	25	12.5	25	50
e	2,4-CH_3	50	25	25	25	25	50
f	2,4-NO_2	50	100	75	100	50	50
ciprofloxacin		25	12.5	12.5	NT	NT	NT
fluconazole		NT	NT	NT	12.5	25	25

[a]NT = not tested

The synthesized 1,3,4-thiadiazole compounds demonstrated moderate to excellent antibacterial and antifungal activity, inhibiting the organisms tested. The halogenated compound **94b** showed excellent antibacterial activity against all organisms tested and higher activity against *Staphylococcus aureus* compared to ciprofloxacin. However, the nitro compound **94f** presented the lowest activity against all the microorganisms tested.[67]

Compounds **94a** and **94d**, without substitution and containing a methoxy group, exhibited moderate activity against the fungi species tested, while the chlorinated heterocycle **94b** showed excellent activity. Compound **94f**, with nitro substitution, showed less activity against the fungi tested than the other compounds.[67]

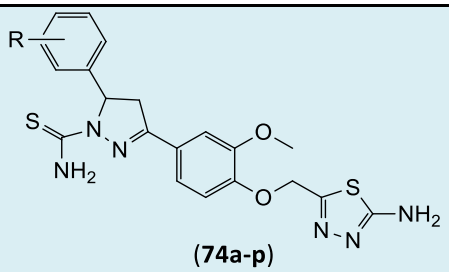
The effect of the substitution on the aromatic ring of the synthesized compounds was studied based on their results of antimicrobial activity *in vitro*. The replacement of monochloro in 1,3,4-thiadiazole, **94b,** showed good antimicrobial activity, suggesting that the *ortho*-monochloro substitution plays a very important role in hampering the cellular architecture of *Escherichia coli, Pseudomonas. aeruginosa, Staphylococcus aureus* and the fungi species *Aspergillus niger, Aspergillus flavus* and *Candida albicans*. The results suggest that **94b** could actively inhibit the growth of Gram positive (*S. aureus*) and Gram negative bacteria (*E. coli* and *P. aeruginosa*).[67]

Noolvi *et al*. (2016)[61] synthesized 1,3,4-thiadiazole derivatives (**74a-p**) that were evaluated in antibacterial and antifungal *in vitro* studies using the agar diffusion method. The compounds were tested against different bacterial cultures *Staphylococcus aureus, Salmonella enterica, Vibrio cholera, Bacillus subtilis, Proteus mirabilis, Escherichia coli*V517, *Mycobacterium smegmatis, Pseudomonas aeruginosa* and one fungal culture *Candida albicans* (Table 19).[61]

Compounds **74e**, **74g**, **74h** and **74q** showed activities against all strains, while **74e** and **74h**, with nitro substitution, showed high activity against *Salmonella enterica* (93.2 % and 97 %) and *Proteus mirabilis* (80 % and 87.3 %). In addition, the results were very close to the reference antibiotic (ampicillin). Compound **74k** showed higher inhibition (87.1 %) against *Staphylococcus aureus* than the other compounds. Compound **74o** was found to be active (96.5 % inhibition) against *Escherichia coli* V517 and **74p** showed 90.2 % and 83.1 % inhibition against *Pseudomonas aeruginosa* and *Mycobacterium smegmatis,* respectively. The other 1,3,4-thiadiazole derivatives showed moderate antimicrobial activity compared to the standards.[61]

The replacement of nitro in 1,3,4-thiadiazole **74e** and **74h** showed excellent antimicrobial activity, suggesting that 3-nitro and 4-nitro substitution plays a very important role in hampering the cellular architecture of *Salmonella enterica* and *Proteus mirabilis*. In addition, the 1,3,4-thiadiazole derivatives **74e** and **74h** showed the best inhibition (83.3 % and 87.8 % and) against the fungal strain *Candida albicans.*[61]

Table 19. Bioactivity of thiadiazole derivatives evaluated by Noolvi *et al*[61]



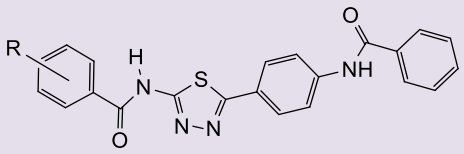
(**74a-p**)

Compound (**74**)	R	% Inhibition						
		Sa	*Se*	*Pm*	*Ec*	*Ms*	*Pa*	*Ca*
a	H	NA	NA	NA	62.9	33.7	44.7	NA
b	2-OCH_3	NA	76.8	66.6	77.0	63.9	69.4	NA
c	2,4-di-Cl	75.0	85.0	66.6	82.7	NA	NA	70.5
d	3-NH_2	NA	68.6	NA	NA	58.1	62.6	48.0
e	3-NO_2	78.5	93.2	80.0	84.4	75.5	74.6	83.3
f	4-OCH_3	NA	78.3	70.0	80.1	67.4	74.6	NA
g	4-F	75.7	76.8	77.3	87.9	72.0	83.5	77.5
h	4-NO_2	80.7	97.0	87.3	8.9	81.3	82.8	87.8
i	4-Br	NA	69.4	46.6	62.9	NA	NA	53.8
j	4-CH_3	NA	73.1	52.0	79.3	58.1	58.2	NA
k	3-OH	87.1	79.8	NA	64.6	NA	NA	55.1
l	2-OH	77.1	73.8	59.3	75.8	NA	NA	62.8
m	4-Cl	80.0	79.1	58.0	85.3	80.2	73.1	72.4
n	2-NH_2	NA	70.8	NA	88.7	70.3	75.3	62.8
o	2,4-OH	84.2	76.8	70.6	96.5	79.6	86.5	66.0
p	4-NH_2	NA	86.5	NA	83.6	83.1	90.2	51.2
ampicillin		100	100	100	100	100	100	100

Sa - Staphylococcus aureus; Se - *Salmonella enterica;* Pm - *Proteus mirabilis;*
Ec- Escherichia coli V517*; Ms - Mycobacterium smegmatis;*
Pa - Pseudomonas aeruginosa;Ca- Candida albicans

Seelam *et al.* (2016)[81] performed microbial studies of 1,3,4-thiadiazoles (**102a-k**) by the disc diffusion technique and minimum inhibitory concentration (MIC). The minimum inhibitory concentration measurement was determined for compounds that showed significant growth inhibition zones (>10mm). The activity of each compound was compared against ofloxacin and miconazole as the standard drugs. The compounds were tested against *Bacillus subtilis, Bacillus thuringiensis* (Gram positive bacteria), *Escherichiacoli* and *Pseudomonasaeruginosa* (Gram negative bacteria). There were also evaluated for their *in vitro* antifungal potential against *Candida glabrata* and *Candida tropicalis* fungal strains. The MIC values are recorded in Table 20.[81]

Table 20. Antimicrobial activity data for compounds (**102a–k**)



(102a-k)

Compound (**102**)	R	Minimum Inhibitory Concentration (μg/mL)[a,b]					
		Antibacterial activity				Antifungal activity	
		Bs	*Bt*	*Ec*	*Pa*	*Cg*	*Ct*
a	H	1	1	0.9	1	0.5	0.5
b	2-Ph	1	1	0.9	1	0.3	0.1
c	3-NO_2	0.2	>0.2	0.1	0.5	0.5	0.5
d	2-Cl	>0.1	0.4	0.1	0.5	0.2	>0.2
e	3-Cl	>0.3	0.5	0.5	0.2	1	>1
f	4-Cl	>0.2	>0.2	0.3	0.5	>0.4	0.6
g	2,3-Cl	0.2	0.2	0.1	0.4	0.9	>1
h	4-CH_3	0.8	0.5	0.5	1	>0.1	0.2
i	4-OCH_3	1	0.8	>1	0.5	>0.1	0.2
j	4-NO_2	0.2	0.7	0.4	0.5	0.5	0.5
k	4-Cl-ph	0.2	0.3	>0.1	>0.4	0.5	0.5
Ofloxacin		0.1	0.1	0.1	0.1	NT	NT
Miconazole		NT	NT	NT	NT	0.1	0.1

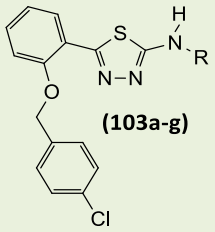
[a]*Bs - B. subtilis; Bt - B. thuringiensis*; *Ec - E. coli; Pa - P. aeruginosa; Cg - C. glabrata; Ct - C. tropicalis;* [b]NT = not tested

In general, most of the tested compounds revealed better activity against Gram-positive than Gram-negative bacteria. The antibacterial screening data showed moderate to good activity of the test compounds. Among the screened compounds, **102c, 102d, 102f, 102g** and **102k** showed a high degree activity against all the bacteria tested. The activities of these compounds were close to standard reference drugs used.

On the other hand, the antifungal screening data showed moderate activity of the test compounds, among which the screened **102b**, **102h** and **102i** showed a high degree of activity against all the microorganisms tested. The activities of these compounds were close to standard reference drugs.[81]

Radwan *et al*. (2017) synthesized a new series of 1,3,4-thiadiazole derivatives, which presented different groups (aryl, alkyl, allyl) as substituents and evaluated the antifungal property against *Candida albicans* (Table 21). The authors inserted these substituents at the C-2 position of the thiadiazole ring in order to enhance the lipophilicity and subsequently the biological activity of the compounds.[82]

Table 21. Anti-*Candida albicans* activity of compounds (**103a-g**)



(103a-g)

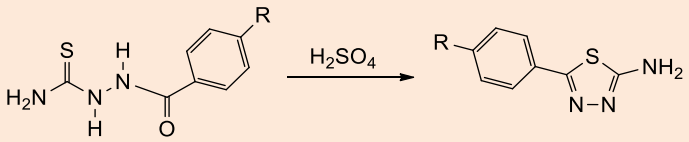
Compound (**103**)	R	Minimum Inhibitory Concentrations (MICs) - µmol/mL
		C. albicans
a	phenyl	0.16
b	allyl	0.08
c	*m*-tolyl	0.15
d	*p*-tolyl	0.15
e	*o*-tolyl	0.15
f	3-Cl-phenyl	0.14
g	*iso*-propyl	0.17
Fluconazole		0.05

The compounds (**103a-g**) had MIC values in the range of 0.08 to 0.17 µmol/mL and showed variable and promising anti-*Candida albicans* activity. The compound **103b** was found to be the most active, with a MIC value of 0.08 µmol/mL.

According to the author, the allyl substituent at position 2 of the heterocyclic ring showed higher activity than the other substituents. Basically, the small size of the allyl group is thought to be related to the high activity of the compound. For optimization of antifungal activity and in view of the results, the author suggests that further studies be undertaken starting with the compound **103b**.[82]

Upadhyay and Mishra (2017)[22] performed microbial studies of 1,3,4-thiadiazoles (**104a-h**) by the disc diffusion technique and minimum inhibitory concentration (MIC). The compounds were tested against Gram-negative bacteria, *Escherichia coli, Bacillus subtilis* and *Pseudomonas aeruginosa*, Gram-positive bacterium, *Staphylococcus aureus* and the fungi *Aspergillus niger* and *Candida albicans*. Ciprofloxacin and fluconazole were used as standards for antibacterial and antifungal studies and the results are summarized in Tables 22 and 23.[22]

Table 22. Data for antimicrobial activity of compounds (**104a-h**)



(104a-h)

Compound (**104**)	R	% inhibition					
		Antibacterial activity				Antifungal activity	
		S. aureus	*B. substilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
a	F	90.9	85.4	79.1	70.5	51.1	51.2
b	Cl	85.1	81.5	75.4	67.2	43.6	49.6
c	Br	70.3	71.5	66.4	59.9	51.9	49.6
d	I	62.8	63.8	52.3	54.1	44.3	46.3
e	CH_3	45.5	44.6	41.8	45.9	52.6	56.1
f	OH	57.0	54.6	60.5	58.2	58.6	65.9
g	OCH_3	56.2	53.1	47.0	53.3	57.9	65.0
h	OC_2H_5	64.5	63.1	53,7	46.7	57.1	61.8
Ciprofloxacin[a]		100	100	100	100	NT	NT
Fluconazole[a]		NT	NT	NT	NT	100	100

[a]Concentration - 20 µg/mL; NT = not tested

Results presented in Table 22 showed that **104a** and **104b** presented a high degree of activity against *Staphylococcus aureus* and *Bacillus substilis* (inhibition between 80 % and 91 %), which are close to the standard drugs. The compounds **104a, 104b**, **104c** and **104f** showed moderate antibacterial activity when compared to ciprofloxacin against *Escherichia coli* and *Pseudomonas aeruginosa* (59 % to 80 %). Compounds **104e** and **104g** exhibited mild inhibitory activity.[22]

The study showed that **104a** (4-fluorophenyl on C-5 of thiadiazole nucleus) produced the highest antimicrobial activity against all bacterial strains while (**104b-c**) showed significant antibacterial activity.[22]

In contrast, **104f** (R = 4-hydroxy) and **104g** (R = 4-methoxy) showed better fungal activities when compared to results against bacteria. The antibacterial activities of compounds **104e** (R = methyl) and **104g** (R = methoxy) were the lowest.[22]

Some of the compounds in the series were moderated in their action against *Aspergillus niger* and *Candida albicans*. Compounds (**104f-h**) showed better inhibitory action (57 % to 66 % inhibition), while the other compounds showed mild antifungal activities (Table 22).[22] Table 23 shows the MIC values for the most potent compounds.

Table 23. Minimum inhibitory concentrations of the compounds with the higher percentages of inhibition reported by Upadhyay and Mishra[22]

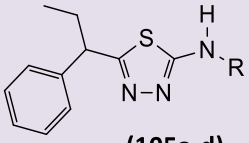
Compound (**104**)	R	Minimum Inhibitory Concentrations (MICs) - µg/mL					
		Antibacterial activity				Antifungal activity	
		S. aureus	*B. substilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*C. albicans*
a	F	20	22	24	32	44	48
b	Cl	28	26	30	36	NT	NT
c	Br	34	36	38	38	NT	NT
f	OH	36	38	40	40	34	32
g	OCH_3	NT	NT	NT	NT	42	36
Ciprofloxacin		18	20	20	24	NT	NT
Fluconazole		NT	NT	NT	NT	26	24

NT = not tested

Based on the results of antimicrobial activity *in vitro* and analysis of structure, the author suggests that substitution on C-4 of the aromatic ring linked at the C-5 position of the thiadiazole nucleus determines the antibacterial and antifungal activities. The electron withdrawing group (F, Cl and Br) at *para* position of the aromatic ring is necessary for the potency of such antibacterial agents.[22]

Gür *et al*. (2017) performed microbial studies of 1,3,4-thiadiazoles (**105a-d**) using *in vitro* antibacterial and antifungal activity tests against nine different bacteria (*Salmonella enteritidis, Salmonella typhimurium, Salmonella infantis, Salmonella Kentucky, Staphylococcus aureus, Enterobacter aerogenes, Bacillus subtilis, Escherichia coli and Enterococcus durans*) and one fungus (*Candida albicans*) using the disk diffusion method.[83] Here the synthesized 1,3,4-thiadiazole derivatives exhibited effective antimicrobial activity against S*. aureus, E. coli*, and *C. albicans*. According to the author, the 1,3,4-thiadiazole derivatives can be considered as a source of bioactive agents for pharmacological and medicinal applications. The antimicrobial activity test results are shown in Table 24.[83]

Table 24. Antimicrobial activity results for the compounds (**105a-d**)

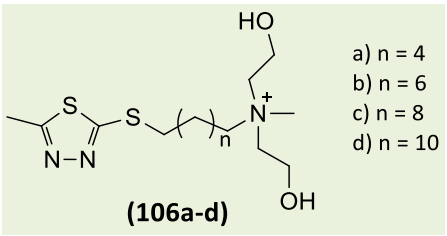


(105a-d)

Compound (**105**)	R	µL	Diameter of zone of inhibition (mm)		
			Antibacterial activity		Antifungal activity
			S.aureus	*E. coli*	*C.albicans*
a	2-CH_3-phenyl	30	NA	NA	NA
		50	13	NA	NA
		80	13	NA	NA
b	4-F-phenyl	30	NA	NA	NA
		50	9	NA	13
		80	13	NA	14
c	benzyl	30	8	NA	14
		50	12	NA	16
		80	13	NA	19
d	methyl	30	12	15	12
		50	15	15	13
		80	17	15	15

NA = no activity

In Xie *et al*. (2017), evaluated antimicrobial activities of four novel 5-methyl-1,3,4-thiadiazole-2-thiol-substituted by a group derived from *N*,*N*-bis(2-hydroxyethyl) quaternary ammonium salts (QAS) (Figure 6). The compound **106d** displayed a potent antimicrobial effect against different common pathogens (*Staphylococcus aureus, Escherichia coli, Pseudomonas. aeruginosa, Proteus vulgaris, Candida albicans, Physalospora piricola, Aspergillus niger*) and had relatively low cytotoxity against two human cell lines (HaCat and LO2), according to Table 25.[84]



(106a-d)

Figure 6. Quaternary ammonium salts with antimicrobial activity

Table 25. Minimal inhibitory concentration of thiazole containing quaternary ammonium salts

Compound (**106**)	Minimum Inhibitory Concentrations (MICs) - µg/mL						
	Antibacterial activity				Antifungal activity		
	S. aureus	*E. coli*	*P. aeruginosa*	*P. vulgaris*	*C. albicans*	*P. piricola*	*A. niger*
a	100	100	200	100	50	25	50
b	50	50	100	50	25	12.5	25
c	25	50	50	50	25	12.5	12.5
d	12.5	25	50	25	12.5	6.25	12.5

In this study, the cytotoxicity of target compounds was evaluated for human epidermal (HaCat) and human normal liver (LO2) cell lines using the MTT assay (Table 26). The IC_{50} values of **106a-b** were more than 50mg/mL for LO2 and HaCat. In addition, compounds **106c-d** also showed low IC_{50} values (more than 25mg/mL). These data demonstrated that **106a-b** were non-toxic for LO2 and HaCat. Specifically, the lower-toxic compounds **106c** and **106d** with better activities than the others might become superior antimicrobial agents.[84]

Table 26. Cytotoxicity of QASs

Compound (**106**)	IC_{50} (µg/mL)	
	LO2	HaCat
a	>100	>100
b	86.52 ± 5.33	65.38 ± 3.12
c	43.18 ± 2.67	36.87 ± 2.81
d	30.12 ± 2.32	27.03 ± 2.53

El-Badry *et al*. (2018) synthesized a novel series of 1,3,4-thiadiazolyl-sulfanyl-4,5-dihydropyridazin-3(2*H*)-ones and evaluated the antimicrobial activity against two Gram-positive bacteria (*Streptococcus pneumonia* and *Bacillus subtilis*), two Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*), and four fungi (*Aspergillus fumigatus, Syncephalastrumracemosum, Geotrichum candidum* and *Candida albicans*) (Figure 7).[27]

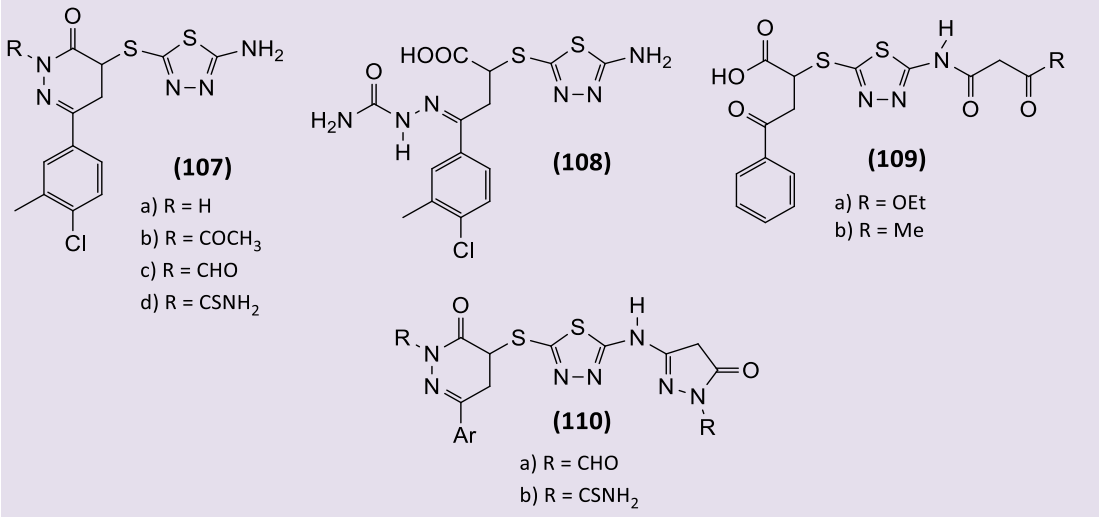


Figure 7. Novel series of 1,3,4-thiadiazolyl-sulfanyl-4,5-dihydropyridazin-3(2*H*)-ones

Ampicillin, gentamicin and amphotericin B were used as control drug standards for Gram-positive bacteria, Gram-negative bacteria, and fungi references respectively. The inhibition zones (mm) of the compounds are given below (Table 27).

Table 27. Antimicrobial activities of novel series of 1,3,4-thiadiazoles synthesized by El-Badry *et al*[27]

Compound	Zone of inhibition (mm) – 5 mg/mL[a,b]							
	Antibacterial activity				Antifungal activity			
	Sp	*Bs*	*Ec*	*Pa*	*Af*	*Sr*	*Gc*	*Ca*
107a	21.7	23.2	20.8	NA	22.6	26.7	23.3	NA
107b	19.4	21.2	18.6	NA	20.3	19.2	20.7	NA
107c	17.9	18.2	17.7	NA	18.2	17.6	18.9	NA
107d	29.4	34.6	27.2	NA	26.4	27.3	31.2	22.4
108	24.6	28.6	23.2	NA	22.8	21.8	24.2	17.3
109a	16.0	18.3	13.0	NA	10.6	11.7	16.5	NA
109b	13.6	15.6	10.3	NA	NA	NA	NA	NA
110a	22.5	24.2	19.3	NA	19.6	20.4	23.6	NA
110b	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

[a]*Sp- Streptococcus pneumonia*; *Bs- Bacillus subtilis; Ec- Escherichia coli*; *Pa- Pseudomonas aeruginosa*; *Af- Aspergillus fumigatus; Sr- Syncephalastrum racemosum; Gc- , Geotrichum candidum*; *Ca - Candida albicans;* [b]NA = no activity; NT = not tested

Compounds **107d**, **108** and **110d** showed potent activity against *B. subtilis* and their effect exceeded the control drug against *S. pneumonia* and *E. coli*. In addition, the compounds **107b**, **107c**, and **110a** demonstrated potent activity, while **109a** and **109b** were the least active against all strains. All compounds were inactive against *P. aeruginosa*.[27]

Compound **107d** was the most potent against all the fungi and its effect exceeded the control drug. Compounds **107b-c** only revealed moderate activities against *G. candidum*, while **107a**, **108**, **110a**, and **110b** were more potent. Against *C. albicans* strain, the compound **107d** was the most potent while **108** was the least effective.[27] Table 28 shows the MIC values for the most potent compounds.[27]

Table 28. Antibacterial and antifungal minimum inhibition concentration for the most potent thiadiazoles reported by El-Badry *et al*[27]

Compounds	Minimum Inhibitory Concentrations (MICs) - mg/mL					
	Antibacterial activity			Antifungal activity		
	S. pneumonia	*B. substilis*	*E. coli*	*A. fumigatus*	*S. racemosum*	*G. candidum*
107d	0.60	1.25	0.60	1.25	1.25	1.25
109a	2.50	1.25	1.25	5.00	2.50	5.00
109b	2.50	2.50	2.50	NT	NT	NT
110b	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

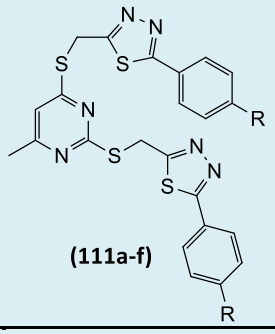
NT = not tested

Padmaja *et al*. (2018) performed microbial studies of 1,3,4-thiadiazoles (**111a-f**) by applying *in vitro* antibacterial (Gram-positive and Gram-negative) activity tests against four different bacteria (*Staphylococcus aureus, Bacillus subtilis, Klebsiella peneumoniae* and *Pseudomonas aeruginosa*) using the disk diffusion method in four different concentrations 12.5, 25, 50 and 100 µg/well (Table 29).[85]

According to the report, the results (Table 29) indicated that the tested compounds were more susceptible towards the Gram-negative bacteria than the Gram-positive ones. The compounds with chloro substituents showed slightly higher activity. In fact, **111c** and **111f** were particularly effective against *P. aeruginosa* in all the tested concentrations.[85]

The presence of chloro and nitro as substituents on the phenyl ring provides greater activity than the methyl and methoxy substituents. This may be due to the presence of more electronegative atoms, which may increase the biological potency, bioavailability, metabolic stability and lipophilicity.[85]

Table 29. Antibacterial activity of compounds (**111a-f**) using the diffusion method



(111a-f)

Compound (**111**)	R	µg/well	Diameter of zone of inhibition (mm)			
			Gram-positive		Gram-negative	
			S.aureus	*B.subtilis*	*P. aeruginosa*	*K. pneumoniae*
a	H	12.5	10	11	15	20
		25	11	13	19	21
		50	12	15	20	23
		100	13	18	24	26
b	4-CH_3	12.5	NA	8	10	14
		25	NA	10	12	16
		50	NA	11	15	18
		100	8	13	19	20
c	4-Cl	12.5	15	21	26	28
		25	17	23	29	30
		50	19	26	32	32
		100	21	29	34	35
d	4-Br	12.5	11	17	19	24
		25	13	19	23	26
		50	15	21	25	28
		100	17	24	29	31
e	4-OCH_3	12.5	NA	NA	NA	NA
		25	NA	NA	NA	NA
		50	NA	NA	8	NA
		100	NA	NA	10	13
f	4-NO_2	12.5	16	22	28	31
		25	18	24	31	33
		50	20	27	33	35
		100	23	31	35	38

NT = not tested

Table 30 shows the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of the most potent compounds. According to the author, the antimicrobials are usually regarded as bactericidal if the MBC is not greater than four times the MIC. The MBC values for **111c** and **111f** were twice the MIC values particularly against *P. aeruginosa.* In general, the compounds having electron withdrawing substituents on the phenyl ring displayed higher antimicrobial activity than the compounds with electron donating substituents.[85]

Table 30. Antibacterial minimum inhibitory and bactericidal concentration in compounds with better performance

Compound (**111**)	Minimum Inhibitory Concentrations – MICs (MBC)			
	Antibacterial activity			
	S.aureus	*B.subtilis*	*P. aeruginosa*	*K. pneumoniae*
c	50 (200)	25 (100)	6.25 (12.5)	12.5 (50)
f	50 (200)	25 (100)	6.25 (12.5)	12.5 (50)
Chloramphenicol	6.25	6.25	6.25	12.5

NA = no activity

4. Conclusion

The studies reported in this review have shown the significant importance of 1,3,4-thiadiazole and its derivatives for the design of new pharmacological compounds and treatment for bacterial infections. Thiadiazoles are a very important class of heterocyclic compounds with diverse pharmacological properties. The therapeutic potential of 1,3,4-thiadiazole is a reality, since it is present in commercial drugs, as well as the focus of different studies with relevant results; mainly for microbiological activities. The possibility of being used as a bioisostere for other heterocycles, such as oxadiazole, provides an increase in lipophilicity without causing a loss of pharmacological properties. In general terms, the synthetic methods for preparation of diverse 1,3,4-thiadiazole derivatives are very effective, allowing the design and preparations of new antibacterial agents.

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