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Scope and limitations on the potent antimicrobial activities of hydrazone derivatives

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Abstract : Antimicrobial resistance of Gram-negative bacteria is a major concern and no new classes of antibiotics that are effective against this type of bacteria have been discovered since the 1960s. During the last decades, multiple approaches have been developed to combat such a bacterial resistance. However, the combination of antibiotic resistance mechanisms by bacteria and the limited number of effective antibiotics available, decreases the number of the interventions for the treatment of current bacterial infections. The solution to emerging antibiotic resistance will likely involve new therapies or new classes of antibacterial agents. For a few years now, there was a real interest in the design and synthesis of hydrazones possessing an azometine -NHN=CH- proton and constituting an important class of compounds for new drugs development as anticonvulsants, antidepressants, antitumoral agents. In this context, the design and antimicrobial evaluation of hydrazone derivatives has constituted one of the new strategies developed to fight bacterial resistance. As pointed out the range of biological activities is very broad, and this review will deal exclusively with the synthesis and use of hydrazones as antimicrobial agents and will not cover the other biological properties already well depicted in literature. Thus, we will report herein the scope and limitation of such an approach providing numerous examples demonstrating structure-activity relationships and potent interesting antimicrobial activities against both fungi, Gram-positive and/or Gram-negative bacteria.

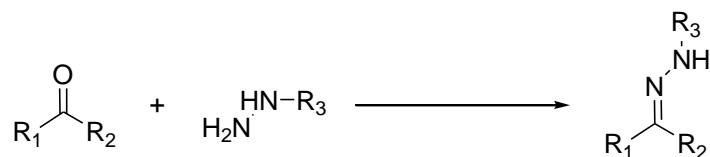
Keywords : Hydrazones, Hydrazine, Antimicrobial agents, Gram-positive bacteria, Gram-negative bacteria, Ketones, Aldehydes, Antifungal activity, Azomethine, Antimicrobial resistance, Heterocycles.

INTRODUCTION

An important interest in the design and synthesis of hydrazones possessing an azometine -NHN=CH- proton and constituting an important class of compounds for new drugs development has recently emerged.[1, 2] Since the range of biological activities is very broad this review will deal exclusively with the synthesis and use of hydrazones as antimicrobial agents excluding the other well depicted biological properties.[1-7]

Hydrazones, which general formula is R-NH-N=C, have been widely used and studied in organic chemistry. There are easily produced by condensation of a hydrazine (NH₂-NHR) with a ketone or an aldehyde (Scheme 1).

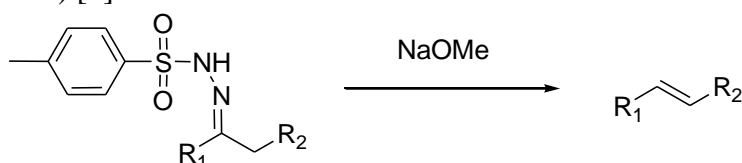
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Scheme 1

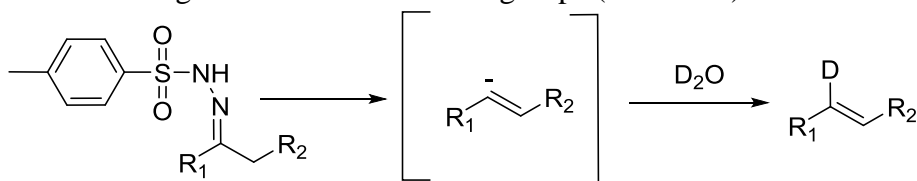
During numerous decades, this condensation has been the only way of detection of the presence of a ketone or an aldehyde group in a molecule. Moreover, hydrazones have been also involved in many reactions such as:

- The Bamford-Stevens reaction allowing the formation of a dual-link Z (Scheme 2).[8]



Scheme 2

- The reaction of Shapiro[9] which involves the elimination of a tosylhydrazone group and the formation of a double bond. It is noteworthy that during this reaction the transitional carbanion can be used to graft different functional groups (Scheme 3).



Scheme 3

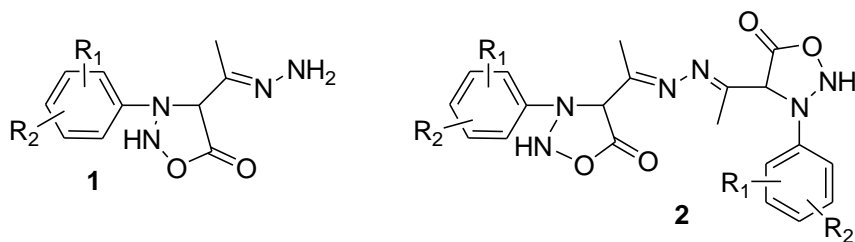
Nevertheless, although these hydrazones are well known in organic chemistry, it is only recently that researchers became interested by their biological potentialities particularly for the treatment of infectious diseases.[10]

Hydrazones as potent antimicrobial agents

As already mentioned, hydrazones possess a general formula R-NH-N=C. In the following part, we will discuss on the antimicrobial activity of different classes of hydrazones depending on the nature of the R group attached to the nitrogen atom.

1) R is a Hydrogen

In 2005, Shinge *et al.* reported the reaction of 4-acetyl-3-arylsydnone derivatives[11] with hydrazine leading to the formation of hydrazones **1** and dimers **2** in good yields and the evaluation of their antimicrobial activities against various Gram-negative bacteria and fungi (Table 1).

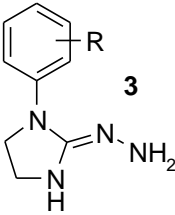


Compound	R ₁	R ₂	Diameter of inhibition (mm)			
			<i>E. coli</i>	<i>P. pyocyanous</i>	<i>R. bataticola</i>	<i>A. niger</i>
1a	H	4-Cl	29	24	13	18
1b	H	4-Br	30	22	14	18
1c	3-CH ₃	4-CH ₃	19	18	18	21
1d	4-CH ₃	3-Cl	29	21	12	13
1e	2-OCH ₃	4-Cl	31	26	11	14
1f	4-Cl	3-F	29	23	13	16
2e	2-OCH ₃	4-Cl	18	16	11	14
2f	4-Cl	3-F	21	15	13	16

Table 1. Structure and antimicrobial activities of derivatives **1a-2f**

Determination of the antifungal activity of derivatives **2** led to similar results that their parent monomers **1** (Table 1, derivatives **1e-1f** and **2e-2f**) whereas weaker activities were encountered against bacteria. Moreover, compounds possessing a chloro, bromo or fluoro substituent group exhibited antibacterial activities greater than norfloxacin reference drug. Derivative **1c** with a methyl group substitution led to an increase of the antifungal activity compared to griseofluvin. Additionally, compound **1d** possessing a methyl and halogen substituent, is slightly active against bacteria and less active against fungi compared to reference drugs.

In the same area, Sztanke *et al.* reported that derivatives **3a-3f** presented moderate to good antibacterial activities against both Gram-positive (*S. aureus*, *S. epidermidis*, *S. pyogenes*) and Gram-negative bacteria (*E. coli*) (Table 2).[12] Thus, compound **3d** bearing a 1-(4-methoxyphenyl) group appeared to be the most active compound of this series with MICs varying from 15 to 30 μ M in all cases. Nevertheless, no mechanism of action of such derivatives has still been proposed to rationalize such observations.

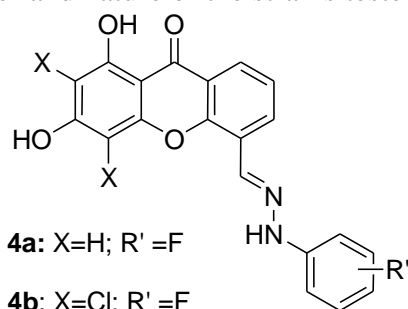


	MIC (μM)					
	3a	3b	3c	3d	3e	3f
R	H	2-CH ₃	2-OCH ₃	4-OCH ₃	2,3-CH ₃	4-Cl
<i>S. aureus</i>	41.1	39.3	37.4	29.9	37.6	29.5
<i>S. epidermidis</i>	41.1	31.4	37.4	18.7	18.8	18.4
<i>S. pyogenes</i>	65.8	78.6	74.8	59.8	75.2	59.1
<i>E. coli</i>	41.1	15.7	29.9	15.0	18.8	36.9

Table 2. Antimicrobial activities of derivatives **3a-f**

2) R is an aryl group

Most of the results presented in this part have been reported in the last twenty years demonstrating the interest and potentiality of such compounds. In 2002, Moreau *et al.* carried out the synthesis of new polyaromatic molecules **4a-4b** and have evaluated their antifungal properties against *C. albicans* and *C. krusei* strains.[13] Nevertheless, the results remain quite modest in terms of diversity with respect to the number and nature of the strains tested (Table 3).



Compounds	Inhibition diameter (mm)	
	<i>C. krusei</i>	<i>C. albicans</i>
4a	15	10
4b	35	15

Table 3. Structure and biological activities of compounds **4**

In the same context, Tyrkov *et al.* demonstrated that a double substitution at the nitrogen atom by two phenyl groups lead to molecules **5a-5c** possessing significant activities against Gram-positive bacteria such as *S. aureus* and *S. pneumoniae* as well as against Gram-negative *E. coli* and *P. aeruginosa* (Table 4).[14]

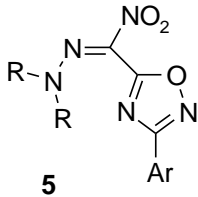
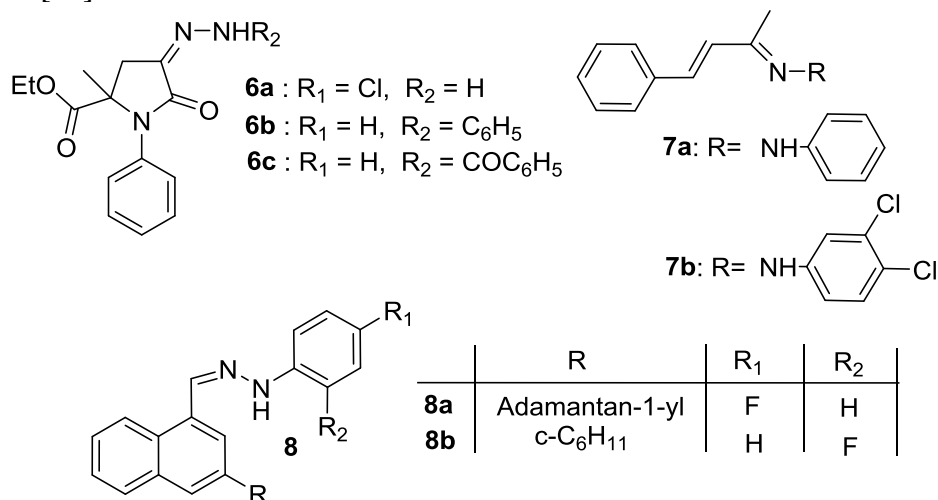
 5			MIC ($\mu\text{g/mL}$)			
Cpds	R	Ar	<i>S. aureus</i>	<i>S. pneumoniae</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
5a	C ₆ H ₅	C ₆ H ₅	7.8	7.8	3.9	7.8
5b	C ₆ H ₅	4-CH ₃ OC ₆ H ₄	7.8	7.8	3.9	7.8
5c	C ₆ H ₅	2-ClC ₆ H ₄	15.7	15.7	31.2	31.2

Table 4. Antimicrobial activities of compounds **5a-5c**

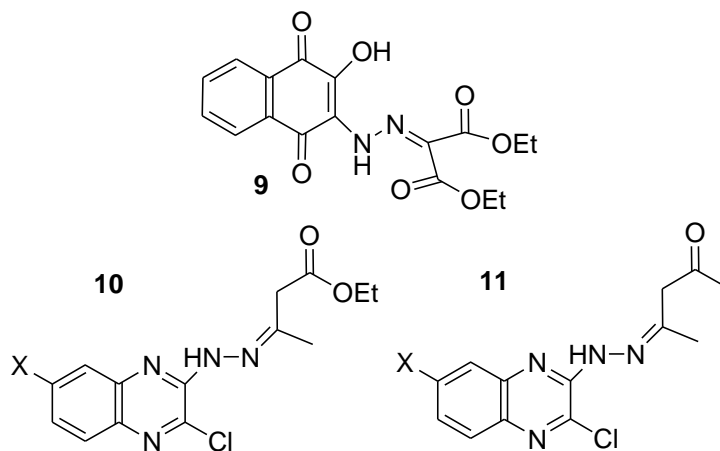
Some other compounds of interest were reported including derivatives **6a-6c**, **7a-7b** and **8a-8b** and demonstrating moderate to good biological activities (Scheme 4).[15-17] Particularly, molecules **7** and **8** present anti *Trichophyton mentagrophytes* and *Microsporum gyptem* activities with MIC less than 10 $\mu\text{g/mL}$. [15] On the other hand, some of them possessing fluorine groups can inhibit the growth of *Mycobacterium tuberculosis* at a concentration of 3.12 $\mu\text{g/mL}$. [17]



Scheme 4

3) R is a heterocyclic ring

In 2001, Oliveira *et al.* reported that hydrazones structurally more complex possess specific antimicrobial activities.



	X	MIC ($\mu\text{g/mL}$)		
		<i>E. coli</i>	<i>S. aureus</i>	<i>C. albicans</i>
9	-	>128	64	>128
10a	H	1.8	12.3	12.3
10b	Cl	1.8	12.1	12.1
11a	H	6.25	6.25	6.25
11b	Cl	6.25	1.3	6.25

Table 5. Antimicrobial activities of compounds **10-11**.

Thus, compound **9** can act against different strains of Gram-positive *S. aureus* sensitive or resistant to methicillin but with MICs ranging from 64 to 128 $\mu\text{g/mL}$. [18] On the other hand, molecules **10a**, **10b** and **11a**, **11b** present a wider spectrum of activity against both Gram-negative, Gram-positive bacteria as well as fungi (Table 5). [19] It is also noteworthy that the replacement of a hydrogen group by a chlorine one lead to an increase in terms of activity of **11b** against *S. aureus* with a MIC of 1.3 $\mu\text{g/mL}$.

In another study, Savini *et al.* have described the design of quinolyl hydrazone derivatives **12a-c** and **13a-b** presenting modest activities against *B. cereus*, *A. fumigatus* and *C. albicans* with MICs up to 100 $\mu\text{g/mL}$. [20]

Compound	Het
12a	4-Methyl-2-quinolyl
12b	4,6-Dimethyl-2-quinolyl
12c	4-Methyl-7-methoxy-2-quinolyl
13a	4-Methyl-2-quinolyl
13b	4,6-Dimethyl-2-quinolyl

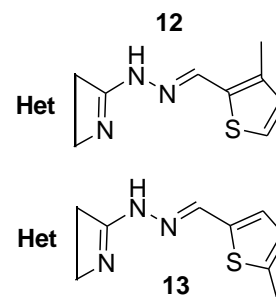
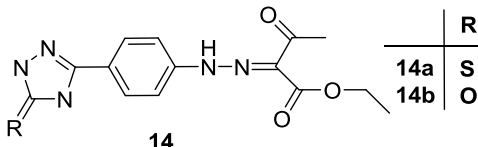


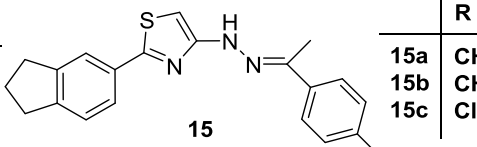
Table 6. Structure of derivatives **12-13**

Additionally, 2-arylhydrazono-3-oxobutyrates **14** (Table 6) presented antibacterial activities against Gram-positive bacteria *S. aureus* with a MIC value of 7.8 µg/mL whereas moderate ones (MICS ranging from 100 to 250 µg/mL) were encountered against Gram-negative bacteria and yeasts.[21] Surprisingly, arylhydrazone derivatives **15** and **16** possess MICs varying from 0.78 to 6.25 µg/mL against *M. tuberculosis* and present a low cytotoxicity ($120 < IC_{50} (\mu\text{g/mL}) < 180$) suggesting a potent development for a human therapeutic use.[22]



14

14a	R
14b	S O



15

15a	R
15b	CH ₃
15c	CH ₃ Cl

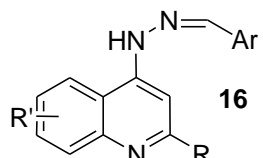
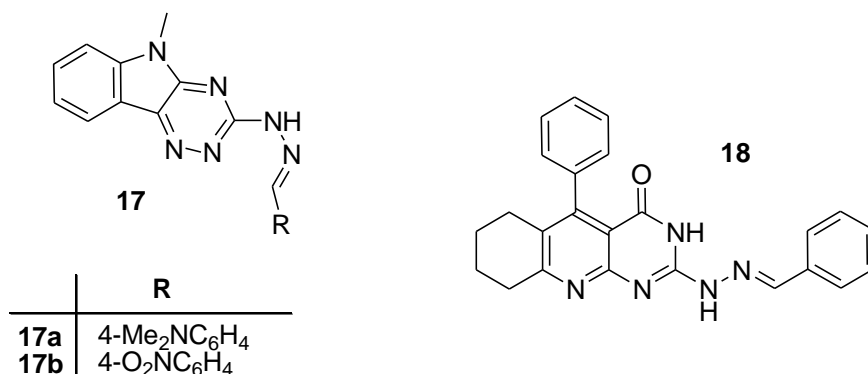
 16	R	R'	Ar	<i>M. tuberculosis</i> MIC (µg/mL)
16a	H	7-OCH ₃	4-OCH ₃ - naphthyl	0.78
16b	CH ₃	8-OCH ₃		1.56
16c		7-OC ₂ H ₅		1.56
16d		6-n-OC ₄ H ₉		0.78
16e		7-Cl		0.78

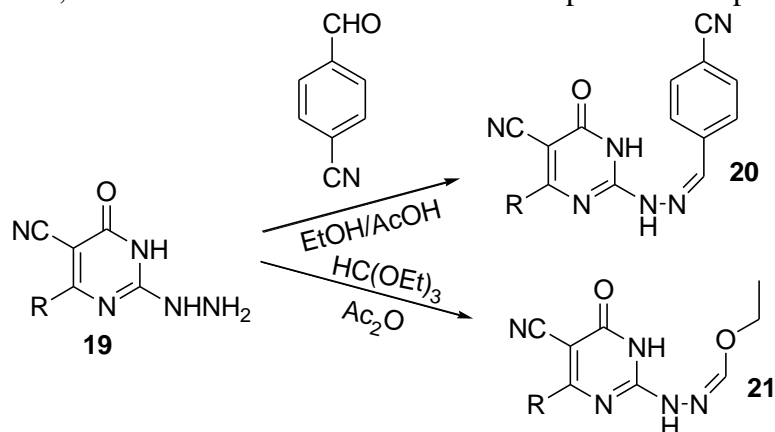
Table 6. Structure of derivatives **14-15** and antituberculosis activities of compounds **16a-16e**.

Another series of heterocyclic derivatives **17-18** were reported by Shaban[23] and El-Gazzar[24] demonstrating moderate activities against *C. albicans* and *C. glabrata* with diameter of inhibition of 8 mm. On the other hand, compound **18** appears highly active against bacteria such as *S. aureus* (16 mm), or Gram-negative bacteria *P. aeruginosa* (14 mm), *E. coli* (15 mm) or *K. pneumoniae* (18 mm).



Scheme 5

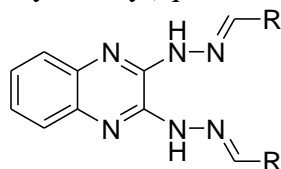
In the same context, Nassar *et al.* reported that uracil derivatives possess potent antimicrobial activities as illustrated by derivatives **19-21** easily prepared as outlined in Table 7.[25] The different compounds presented antibacterial activities against *L. monocytogenes* and were more potent than the reference drugs. Moreover, antibacterial activity of **19** was significant against Gram-negative bacteria *E. coli*, with an inhibition zone of 13 mm compared to cefoperazone.



Bacteria	Zone of inhibition (mm) antibacterial activity (1mg/mL)			
	19	20	21	Cefoperazone
<i>S. aureus</i>	8	7.5	7.5	12
<i>L. monocytogenes</i>	14	12	12	11
<i>E. coli</i>	13	9	8.5	15
<i>Y. enterocolitica</i>	-	9	-	12

Table 7. Structure and antibacterial activities of derivatives **19-21**

Recently, quinoxaline derivatives were synthesized by the reaction of *o*-phenylenediamine with oxalic acid to yield 1,4-dihydro quinoxaline-2,3-dione and then treatment with thionyl chloride to yield 2,3-dichloro quinoxaline. This was further treated with hydrazine hydrate to produce 2,3-dihydrazinyl quinoxaline which reacted subsequently with the substituted aromatic aldehyde to afford 2,3-bis(2-(substituted benzylidene) hydrazinyl)quinoxaline **22** (Scheme 6).



22a R=4FC ₆ H ₄	22c R=3ClC ₆ H ₄	22e R = 4OMeC ₆ H ₄	22g R=3,4,5 (OMe) ₃ C ₆ H ₂	22i R=4NO ₂ C ₆ H ₄	22k R=4OH3OMeC ₆ H ₃
22b R=2ClC ₆ H ₄	22d R=4ClC ₆ H ₄	22f R=3,4 (OMe) ₂ C ₆ H ₃	22h R=2 NO ₂ C ₆ H ₄	22j R=C ₆ H ₅	22l R=2OHC ₆ H ₄

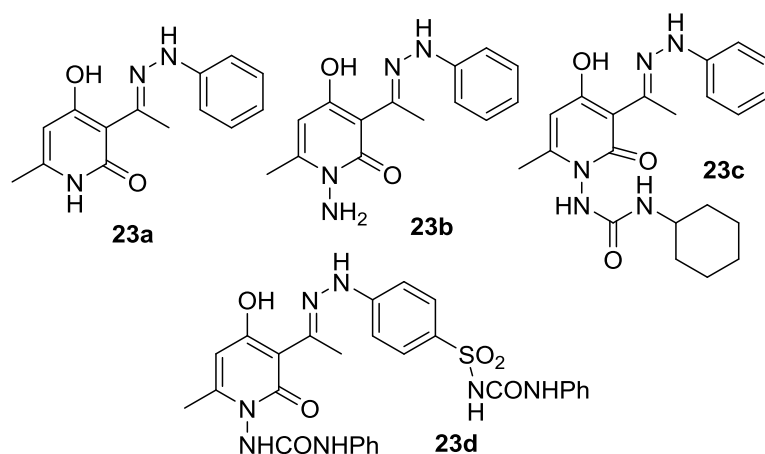
Scheme 6. Structure of the different quinoxaline derivatives **22a-22l**

The Gram-positive and Gram-negative bacteria are sensitive to most of the tested compounds, and particularly **22c**, **22d**, and **22i** presenting significant activities against both type of microbial strains than others. Whereas the compound substituted with an electron donating group or unsubstituted the phenyl ring offered a low to moderate activity against selected strains, derivatives bearing a methoxy group as a substituent of the phenyl ring undergo the least effect against selected bacterial strains (Table 8).[26]

Compounds	Gram-positive bacteria		Gram-negative bacteria	
	<i>S. pyogenes</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
22a	1.1	1.28	1.89	1.97
22b	1.09	1.12	1.37	1.84
22c	0.97	0.92	0.93	0.98
22d	1.01	1.03	0.96	1.02
22e	2.87	3.28	3.17	3.14
22f	2.97	3.31	2.97	3.48
22g	3.03	3.43	3.23	3.17
22h	2.14	1.98	1.87	2.73
22i	1.04	1.06	1.10	1.01
22j	2.89	2.91	2.76	3.01
22k	1.87	2.12	2.28	1.98
22l	1.97	2.08	1.83	1.79
Ciprofloxacin	0.97	0.89	0.93	0.96

Table 8. Antimicrobial activities of quinoline derivatives expressed as MIC (mg/mL)

Another study dealing with the synthesis of benzenesulfonylurea and thiourea derivatives of 2*H*- pyran and 2*H*- pyridine- 2- ones as antibacterial agents needs also to be mentioned. The results revealed that most of the tested compounds displayed greater inhibitory effect on the growth of the tested Gram-positive strain compared to Gram-negative ones such as *P. aeruginosa*. Moreover, few compounds were able to exert a potent antifungal activity against *C. albicans*, while all the tested compounds lacked antifungal activity against the *Aspergillus niger* fungus. A close examination of the structures of the active compounds revealed that the antimicrobial profile of the pyridine- 2- one compounds seemed to be more interesting than their corresponding pyran- 2- one isosteres, as evidenced by their MIC values (Table 9).[27]

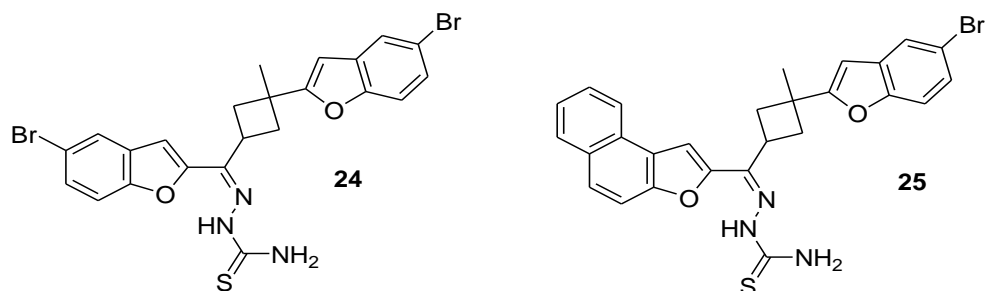


Compounds	Gram-positive bacteria		Gram-negative bacteria	
	<i>B. subtilis</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
23a	100	50	>200	>200
23b	50	50	200	>200
23c	>200	>200	>200	>200
23d	50	12.5	50	200
ampicillin	25	12.5	25	50

Table 9. Minimum Inhibitory Concentrations ($\mu\text{g/mL}$) of compounds **23a-23d**

Introduction of an amino group at position 1 of the pyridine ring as in compound **23b** resulted in significant changes of the overall antimicrobial spectrum. It showed two- fold improvement in the potency against *B. subtilis* when compared with **23a** (MIC 50 vs 100 $\mu\text{g/mL}$, respectively) whereas it revealed moderate activity against *E. coli* (MIC 200 $\mu\text{g/mL}$). Furthermore, compound **23d** produced the most potent antimicrobial activity in the current series of compounds (more potent than ampicillin (MIC 12.5 $\mu\text{g/mL}$)) against *S. aureus*, whereas its activity against *B. subtilis* and *E. coli* was 50% lower than that observed for ampicillin (MIC 50 vs 25 $\mu\text{g/mL}$, respectively).

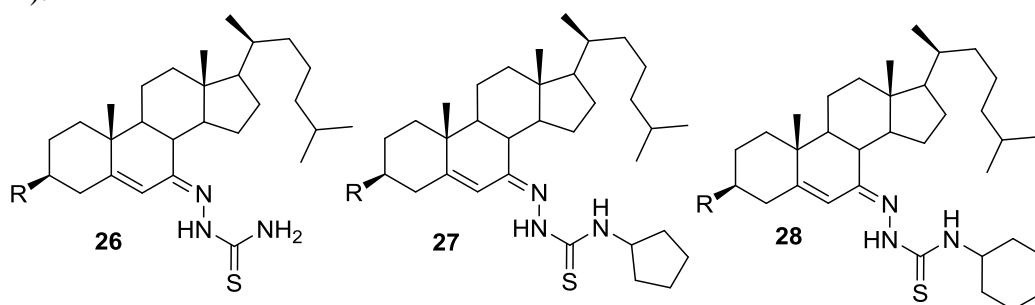
Even if numerous of them presented a weak interest in terms of encountered biological activities, it is of interest to report the design of peculiar hydrazone compounds that we can find in literature. Thus, the synthesis and evaluation of antimicrobial activities of compounds **24-25** was achieved demonstrating low activities against both Gram-positive and Gram-negative bacteria (Table 10).[28]



	Diameter (mm)				
	<i>B. subtilis</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>L. monocytogenes</i>	<i>S. aureus</i>
24	9	6	9	9	9
25	8	10	8	10	-

Table 10. Antimicrobial activities of hydrazones **24-25**

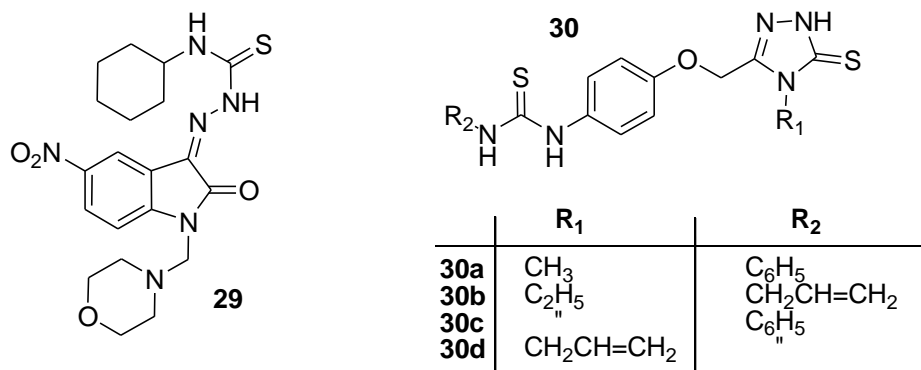
More recently, steroid hydrazone derivatives **26-28** were designed and tested against various bacteria. The results indicated that compound **26a-26b**[29] are only active against *E. coli* whereas derivatives **27-28**[30] presented MICs ranging from 32 to 128 $\mu\text{g/mL}$ against both Gram-positive and Gram-negative bacteria (Table 11).



	MIC ($\mu\text{g/mL}$)					
	26a	26b	27a	27b	28a	28b
R	CH ₃ COO	Cl	OAc	Cl	OAc	Cl
<i>S. aureus</i>	-	-	32	64	64	32
<i>S. pyogenes</i>	-	-	64	64	64	64
<i>S. typhimurium</i>	-	-	64	128	64	128
<i>E. coli</i>	128	64	32	64	32	64

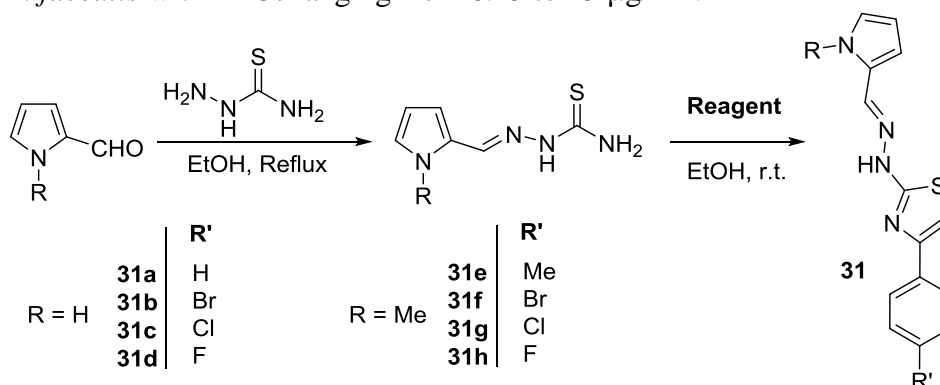
Table 11. Antimicrobial activities of hydrazones **26-28**

In 2008, new promising hydrazone anti-tuberculosis agents (**29-30**) were described in literature (Scheme 6). Thus, compounds **29** and **30** present MICs of 6.25 $\mu\text{g/mL}$ against *M. tuberculosis*. [31] Furthermore, **30d** can inhibit the growth of this microorganism by 79%. [32] Nevertheless, no more results dealing the mechanism of action or improvement of the design of such derivatives were reported until now.



Scheme 6

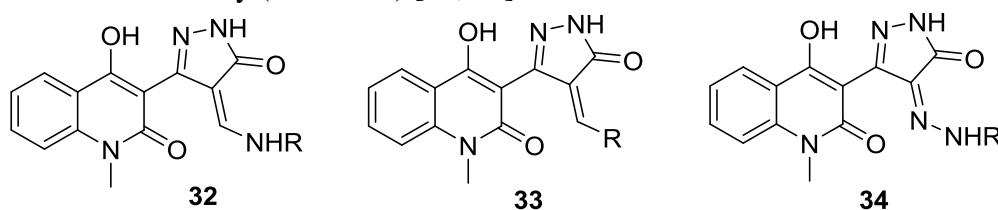
In 2012, Karaca *et al.* reported the synthesis of compounds which contain hydrazone bridged thiazole and pyrrole rings easily obtained by directly reacting pyrrole-2-carboxaldehydes with thiosemicarbazide in ethanol and subsequently condensed them with α -bromoacetophenone derivatives (Hantzsch reaction) to afford 1-substituted pyrrole-2-carboxaldehyde [4-(4-substituted phenyl)-1,3-thiazol-2-yl] hydrazones in good isolated yields (Scheme 7).[33] All the compounds were screened for their antibacterial and antifungal activities against twelve different bacteria, but they only showed good activity against *S. aureus* and *E. faecalis* with MICs ranging from 6.25 to 25 μ g/mL.



Reagent : α -Bromo-4-substituted acetophenone

Scheme 7

Derivatives of 3-pyrazolylquinolinone, in three different types; enaminones **32**, enones **33**, and hydrazonones **34**, have been also investigated for their *in vitro* antimicrobial activity (Scheme 8).[34, 35]

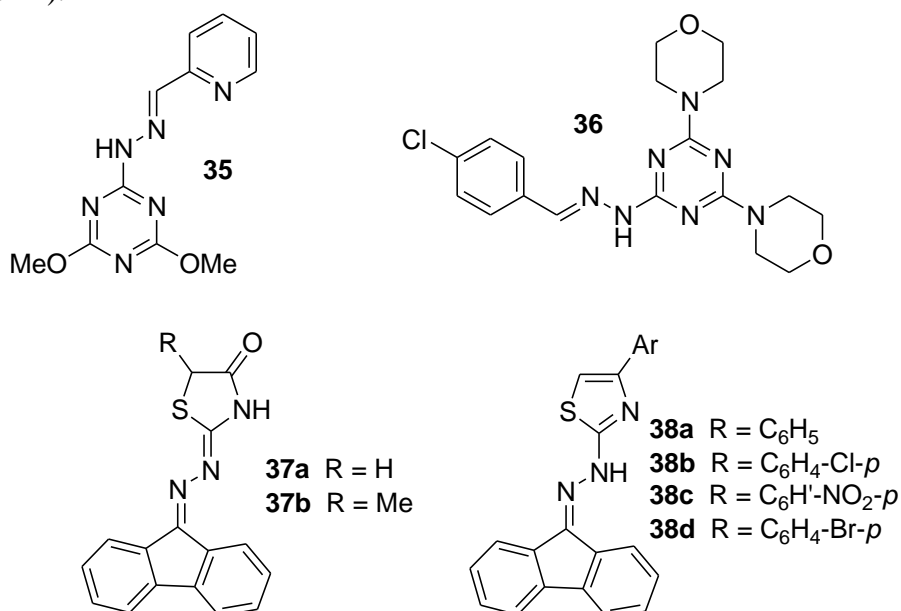


Scheme 8

The compounds were screened for their biological activities and revealed that hydrazoneones **34** possess desirable antimicrobial activity against both bacteria and fungi groups tested.

Recently, novel series of 4,6-disubstituted-1,3,5-triazines containing hydrazone derivatives **35-36** as well as fluorenyl-hydrazone-thiazoles **37-38** were synthesized employing ultrasonic irradiation and conventional heating. The ultrasonication gave the target products in higher yields and purity in shorter reaction times compared with the conventional method.[36, 37]

The biological results indicated that only compounds **35** and **36** displayed moderate biological activity against Gram-positive and Gram-negative bacteria, while fluorenyl-hydrazone-thiazoles **37-38** present interesting antifungal activities (Table 12).

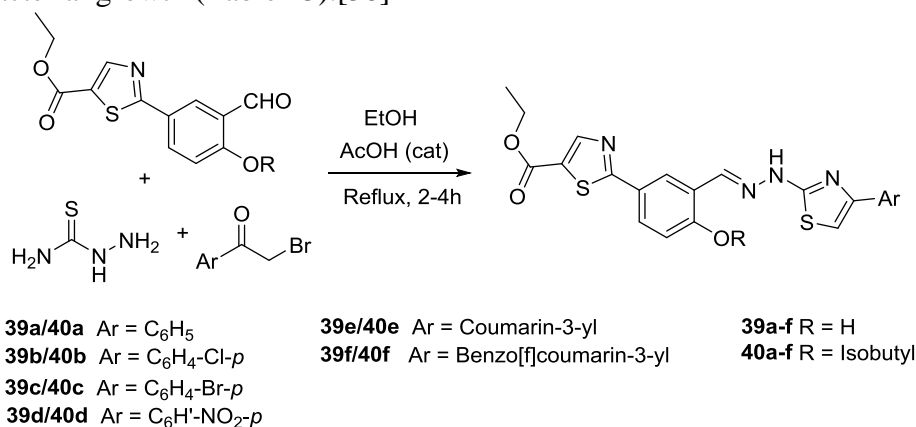


	MIC (µg/mL)							
	35	36	37a	37b	38a	38b	38c	38d
<i>S. aureus</i>	100	100	50	25	25	12.5	25	12.5
<i>B. laterosporus</i>	50	50	NT	NT	NT	NT	NT	NT
<i>E. coli</i>	NA	NA	50	6.25	25	25	25	12.5
<i>P. aeruginosa</i>	NA	NA	25	25	25	12.5	12.5	25
<i>A. niger</i>	NA	NA	25	12.5	12.5	12.5	12.5	12.5
<i>C. albicans</i>	NA	NA	25	12.5	25	50	50	50

Table 12. Antimicrobial activities of hydrazones **35-38**

More recently, Chellamella *et al.* reported the synthesis and biological evaluation as antimicrobial agents of ethyl-2-(3-((2-(4-(4-aryl)thiazol-2-yl)hydrazono)methyl)-4-hydroxy/isobutoxyphenyl)-4-methylthiazole-5-carboxylate compounds (**39a-f** and **40a-f**) by employing a one-pot multi-

component approach. The overall activity data revealed that the presence of a coumarin motif in their structure is essential for the broad-spectrum antimicrobial activity. These compounds could bind the active site of the enzyme, DNA gyrase which is responsible for the bacterial replication and thus lead to the inhibition of the bacterial growth (Table 13).[38]



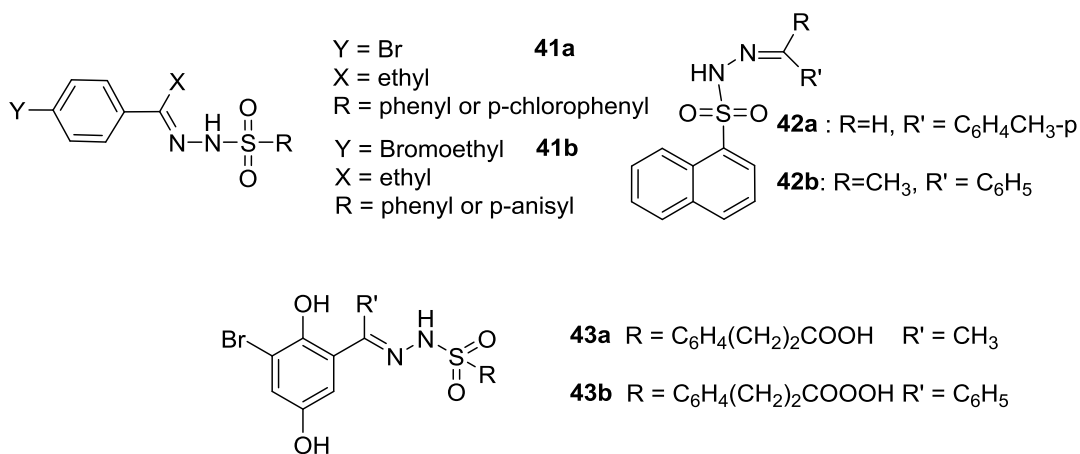
	MIC (µg/mL)				
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>C. albicans</i>	<i>A. niger</i>
39a	40	35	35	25	35
39b	35	30	25	25	50
39c	35	30	50	75	50
39d	40	30	50	50	25
39e	15	20	20	12.5	12.5
39f	15	25	20	12.5	12.5
40a	30	30	35	75	100
40b	25	25	20	75	75
40c	35	30	35	50	75
40d	25	25	30	75	75
40e	15	15	20	12.5	25
40f	20	20	20	12.5	12.5

Table 13. Structure and antimicrobial activities of derivatives **39-40**

4) Sulfonylhydrazones

Sulfonylhydrazones are hydrazones presenting the general formula: R₁R₂C=N-NH-SO₂-R₃.

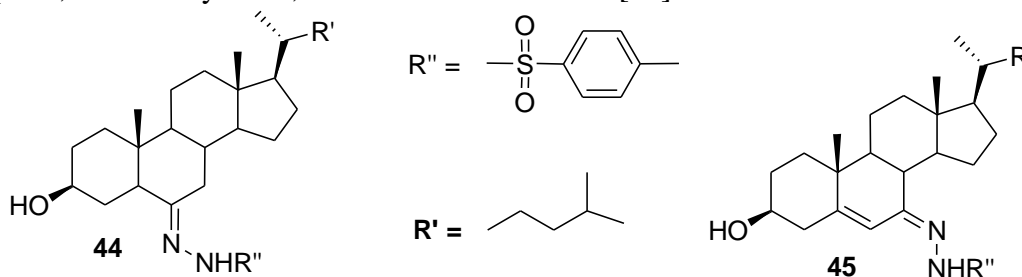
In 1984, Bhatt *et al.* have prepared the molecules **41a** and **41b** possessing antibacterial activity against *S. aureus* (inhibition diameter: 40mm) and *E. coli* (30mm), respectively.[39] In the same context, Salama *et al.* designed analogues of these molecules demonstrating the influence of the structure on their antimicrobial activities.[40] Thus, compounds **42a-42b** were identified as the best analogues active both against Gram-positive or negative bacteria and fungi (Scheme 9).



Scheme 9

On the other hand, the group of Shad reported the synthesis of hydrazones **43a-43b** active against *E. coli* and *S. aureus* with a diameter of inhibition of 29 and 27 mm, respectively. Furthermore, they are less active against *B. negaterium* with only a 12 mm diameter of inhibition encountered (Scheme 9).[41]

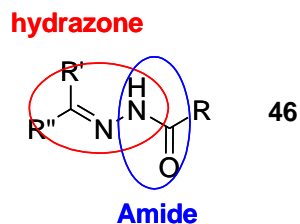
In 2004, The first cholesteryl hydrazone derivatives **44-45** were synthesized and tested for their antimicrobial activities demonstrating interesting antifungal activities especially against *C. albicans* with MICs ranging from 1.25 and 25 $\mu\text{g/mL}$ (Scheme 10).[42] Recently, antiviral activities of hydrazones of 5 α -steroids were reported highlighting the potent interest of such derivatives against polio, Rift Valley fever, and influenza A viruses.[43]



Scheme 10

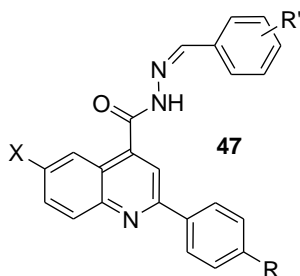
5) Ylidene hydrazone derivatives

Another class of hydrazones is constituted by ylidene hydrazone derivatives **46** possessing a hydrazone function and an amide group as illustrated in Scheme 11 and where R, R' and R'' could pertain to linear or cyclic alkyl or aryl substituents.



Scheme 11.

Metwally *et al.* reported the synthesis of derivatives **47** from quinoline and bearing various substituent groups (Table 14).[44]



	X	R	R'
47a	2-H	4-bromophenyl	2-nitrobenzylidene
47b	6-Cl	2-phenyl	4-bromobenzylidene
47c	6-Cl	4-bromophenyl	2-nitrobenzylidene
47d	6-Cl	4-bromophenyl	4-nitrobenzylidene
47e	6-Cl	4-methoxyphenyl	2-nitrobenzylidene
47f	6-Cl	4-methoxyphenyl	4-nitrobenzylidene

Table 14. Structures of hydrazone derivatives **47**.

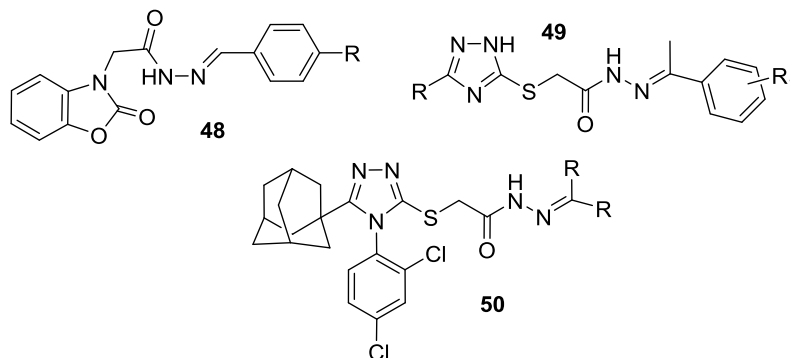
It has been observed that these compounds presented no activity against Gram-positive bacteria such as *S. aureus* (MIC > 200 µg/mL), while MICs are ranging from 25 to 50 µg/mL against *E. coli* and *C. albicans* (Table 15). These activities against *E. coli* and *C. albicans* are as same as reference drugs. It may also point out that these molecules do not present any haemolytic activity. The authors concluded that the nature of the substituents and substitution pattern on the quinoline ring may have a considerable impact on the observed antibacterial and antifungal activities of the considered hydrazones, para substitution appearing to be more beneficial for activity compared to the ortho one (Table 15). As an improvement of such studies, Shruthi *et al.* have recently reported that such compounds were found to be active against bacterial strains including *Acinetobacter baumannii*, *Escherichia coli* and *Staphylococcus aureus*. [35]

	MIC (µg/mL)	
	<i>E. coli</i>	<i>C. albicans</i>
47a	25-50	25-50
47b	100	25-50
47c	25-50	50-100
47d	25-50	50

47e	25-50	25-50
47f	25-50	25

Table 15. Antibacterial activities of hydrazone derivatives **47**

Some other compounds **48-50** demonstrated antifungal activities (Table 16). Particularly, compounds **48a** and **48d** possess a MIC of 128 µg/mL against three different *Candida* strains.[45-47]



MIC (µg/mL)					
	R		<i>C. albicans</i>	<i>C. Krusei</i>	<i>C. parapsilosis</i>
48a	H		128	128	128
48b	Br		64	256	128
48c	Cl		128	256	256
48d	CH ₃		128	128	128
48e	OCH ₃		128	128	512
49a	H	4-NO ₂	100	100	100
49b	CH ₃	4-NO ₂	100	100	200
49c	C ₂ H ₅	4-Cl	100	100	200
49d	C ₂ H ₅	4-NO ₂	100	100	200
50a	(CH ₂) ₃		365	-	-
50b	(CH ₂) ₄		365	-	-
50c	(CH ₂) ₅		-	-	-

Table 16. Antifungal activities of compounds of **48-50**.

In 2001, Chornous *et al.* have synthesized hydrazone derivatives **51** possessing a hetero-nitrogen-ring but these molecules demonstrated moderate antibacterial activities against *S. aureus* and *E. coli* (Table 17).[48]

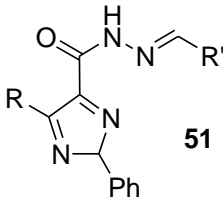
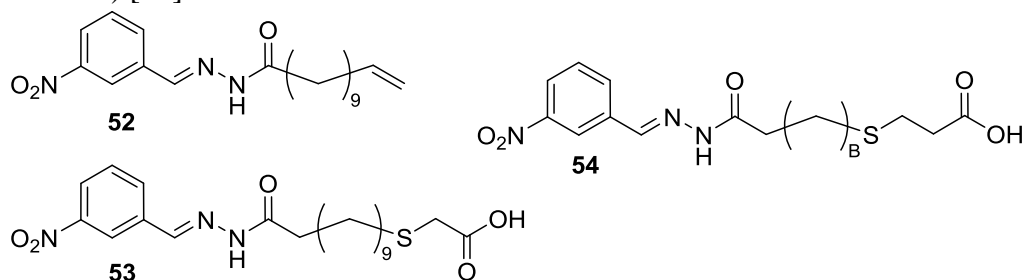
		R	R'	MIC ($\mu\text{g/mL}$)	
				<i>S. aureus</i>	<i>E. coli</i>
 51	51a	4-FC ₆ H ₄	HOC ₆ H ₃	62.5	250
	51b	4-FC ₆ H ₄	5-nitrofur-2-yl	62.5	>500
	51c	4-C ₂ H ₅ C ₆ H ₄	5-nitrofur-2-yl	31.2	>500
	51d	Thienyl-2-yl	5-nitrofur-2-yl	62.5	500

Table 17. Antibacterial activities of compounds **51**.

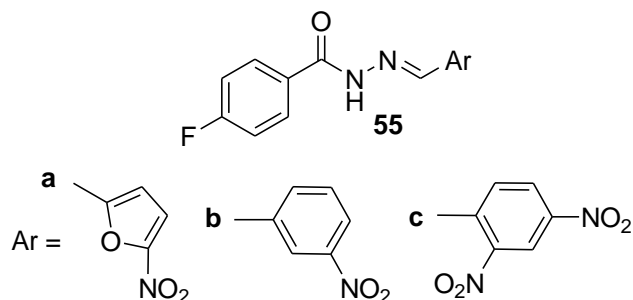
Rahman *et al.* have also prepared hydrazones bearing long linear alkyl chains terminated by a carboxylic acid or allyl group. All these molecules do not possess any activity against *C. albicans* but are efficient against both Gram-positive and Gram-negative bacteria with diameters of inhibition varying from 10 to 20 mm (Table 18).[49]



	diameters of inhibition (mm)				
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>
52	-	-	19	-	-
53	12	12	10	14	-
54	18	15	14	20	-

Table 18. Antibacterial activities of compounds **52-54**.

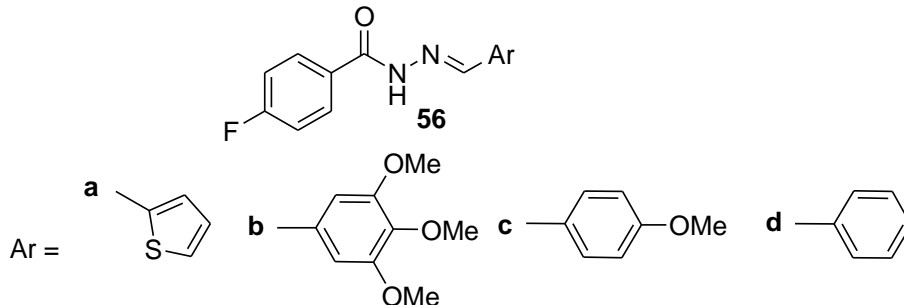
Another study of interest needs to be mentioned and was reported by Rollas *et al.* who performed the synthesis of analogues **55a-c** possessing nitroaryl or furyl groups. These compounds are very active against Gram-positive *S. aureus* bacteria with MICs ranging from 2 to 8 $\mu\text{g/mL}$ whereas high MICs were encountered against yeasts and Gram-negative bacteria (Table 19).[50]



	MIC ($\mu\text{g/mL}$)			
	<i>S. aureus</i>	<i>C. albicans</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
55a	2	62.5	250	250
55b	8	125	125	125
55c	4	125	125	125

Table 19. Antimicrobial activities of compounds **55a-55c**.

In the same area of research, Rao[51], Kursun[52] and Fahmy[53] have performed the synthesis of various analogues of derivatives **56a-d** demonstrating also moderate to good antibacterial and antifungal activities against Gram-positive bacteria and fungi with diameter of inhibition ranging from 0 to 17 mm depending on the considered microorganisms (Table 20).

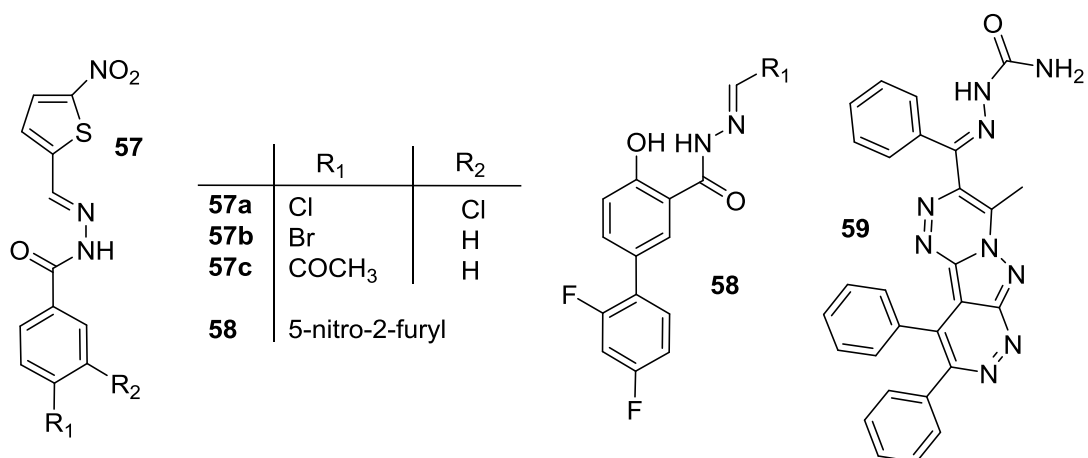


	Diameter of inhibition (mm)				
	<i>B. subtilis</i>	<i>S. aureus</i>	<i>P. notatum</i>	<i>A. niger</i>	<i>C. utilis</i>
56a	8*	7*	0	0	0
56b	0	0	10*	0	12*
56c	11*	11**	12*	16*	17*
56d	10	9	9	14	13

*significant **highly significant

Table 20. Antimicrobial activities of compounds **56a-d**.

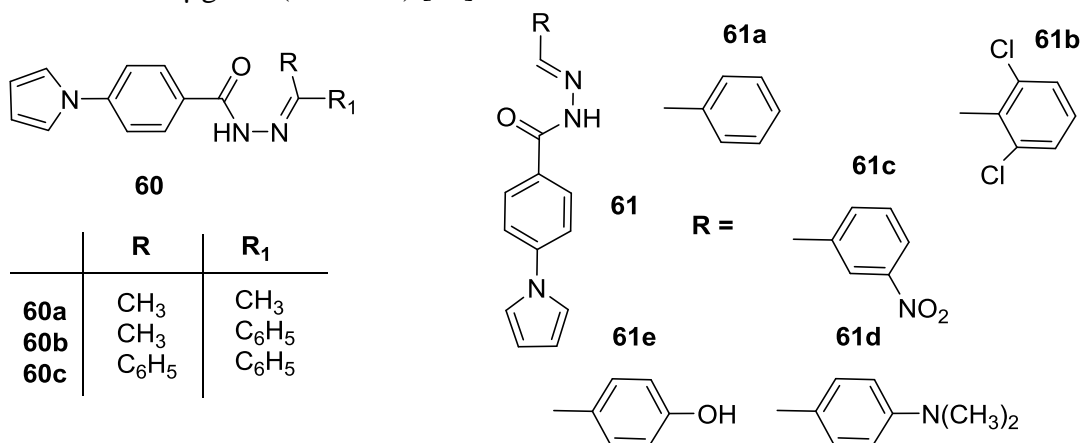
In 2007, numerous parent derivatives such as **57a-c**, **58** and **59** have been prepared presenting interesting antibacterial activities against a large panel of bacteria (Scheme 12).[54]



Scheme 12

It is noteworthy that **57c** possesses the best MICs of 0.11 and 1.27 µg/mL against two different strains of *S. aureus*, respectively. Otherwise, the derivative **58** presents moderate activities against *B. subtilis* (75 µg/mL), *S. epidermis* (18.75 µg/mL), *E. coli* (75 µg/mL) and *S. aureus* (37.5 µg/mL) whereas hydrazone **59** presents a weak activity against all these pathogens.[55] Furthermore, **58** inhibits the growth of *M. tuberculosis* by 34% at a concentration of 6.25 µg/mL.

In 2007, Joshi *et al.* reported the synthesis of N'-(arylidene)-4-(1H-pyrrol-1-yl) benzohydrazide **60-61** and their moderate to good antimicrobial activities typically against *M. tuberculosis* with some derivatives **61b** and **61e** possessing MICs of 32.5 µg/mL (Table 21).[56]

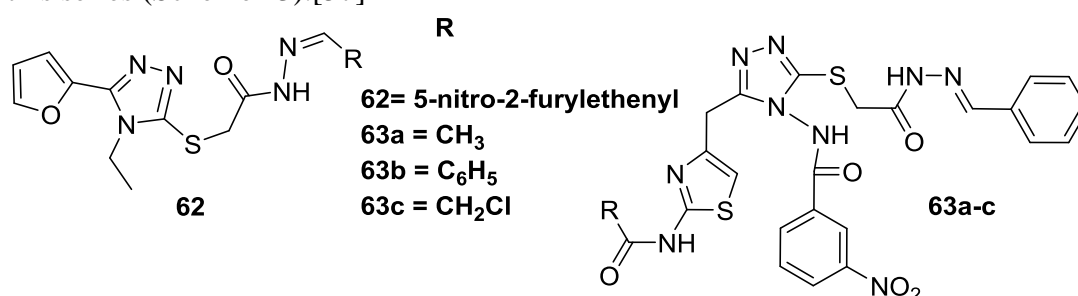


	MIC (µg/mL)					
	<i>S. aureus</i>	<i>E. faecalis</i>	<i>M. tuberculosis</i>	<i>K. pneumoniae</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
60a	250	125	62.5	250	125	62.5
60b	250	125	62.5	125	125	62.5

60c	500	250	62.5	125	125	62.5
61a	250	250	125	125	125	125
61b	125	125	31.25	125	62.5	62.5
61c	500	500	62.5	500	500	62.5
61d	250	125	62.5	125	250	125
61e	125	125	31.25	125	62.5	62.5

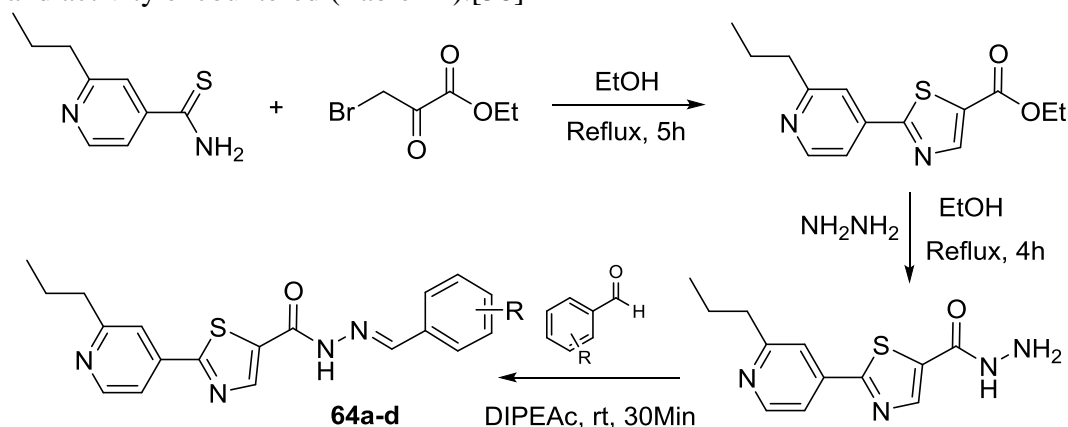
Table 21. Antibacterial activities of compounds **60-61**

The design of derivatives **62** and **63** led to products active against *M. tuberculosis* with MICs varying from 0.39 to 15 μ M, **63b** being the most active compound of this series (Scheme 13).[57]



Scheme 13

Recently, Muluk *et al.* reported the synthesis of new pyridyl and thiazolyl clubbed hydrazone derivatives **64** displaying moderate antimicrobial activities and suggesting that the design of new parent derivatives could improve the selectivity and activity encountered (Table 22).[58]

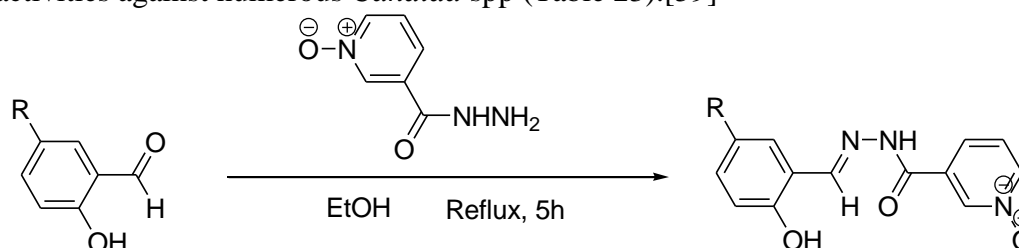


	R	MIC (μ g/mL)		
		<i>B. subtilis</i>	<i>E. aerogenes</i>	<i>C. albicans</i>
64a	3, 5-Cl	90	170	150
64b	4-Cl	260	120	280
64c	3-Cl	120	150	250

64d	2-NO ₂	75	85	210
Streptomycin	-	25	30	NA
Fluconazole	-	NA	NA	30

Table 22. Structure and antimicrobial activities of compounds **64a-64d**.

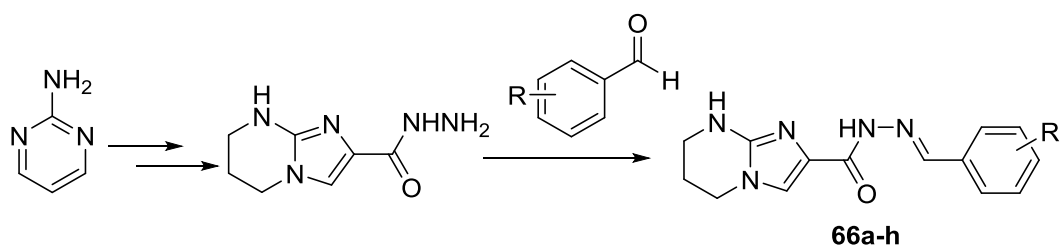
To further dissect the structural features necessary to inhibit azole-resistant fungal species, Backes *et al.* have recently performed the synthesis of a new class of modified salicylaldehyde derivatives and subsequently identified a series of modified pyridine-based hydrazones **65a-f** possessing fungicidal and antifungal activities against numerous *Candida* spp (Table 23).[59]



	R	MIC ₈₀ (µg/mL)			
		<i>TW1</i>	<i>TW17</i>	<i>C. albicans</i> ATCC10231	<i>C. albicans</i> ATCC48435
65a	H	31	31	31	16
65b	Me	16	16	16	31
65c	MeO	62	31	16	4
65d	Cl	31	31	16	4
65e	Br	8	8	16	4
65f	NO ₂	4	2	8	4

Table 23. Structure and antimicrobial activities of compounds **65a-65f**.

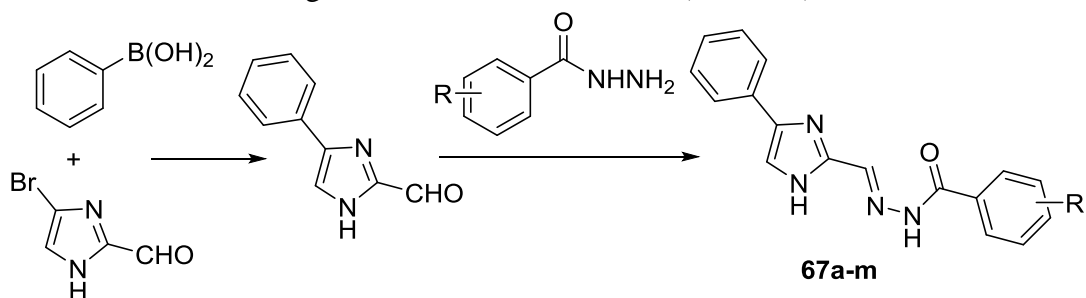
Condensation of 5,6,7,8-tetrahydroimidazo[1,2-a]-pyrimidine-2-carbohydrazide with various aromatic aldehydes in ethanol at reflux led to the generation of hydrazone derivatives **66** in 80–92% yield. Compounds **66d**, **66e** and **66f** exhibited excellent antibacterial activity with zone of inhibition 30–33 mm against *E. coli* and *S. aureus*. These compounds also exhibited excellent antibacterial activity with zone of inhibition ranging from 22 to 25 mm against *P. aeruginosa* and *S. pyogenes* (Table 24).[60]



		Zone of inhibition of compounds 66a-f			
		Concentration used 250µg/mL of DMSO			
	R	<i>E. coli</i> MTCCC443	<i>P. aeruginosa</i> MTCC424	<i>S. aureus</i> MTCC96	<i>S. pyogenes</i> MTCC442
66a	4-F	25	19	24	17
66b	2-CF ₃	27	20	23	18
66c	3-CF ₃	26	19	23	17
66d	4-CF ₃	33	24	29	24
66e	4-OCF ₃	30	25	30	22
66f	4-OCHF ₂	30	23	31	22
66g	2,4-F	20	16	19	13
66h	3,4-F	21	15	19	14

Table 24. Structure and antimicrobial activities of compounds **66a-66h**.

In another work, the synthesis of imidazole hydrazone derivatives **67a-m** and their evaluation against *A. niger*, *S. aureus*, *S. pyogenes*, *E. coli* and *P. aeruginosa* resulted in moderate to good antimicrobial activities (Table 25).[61]

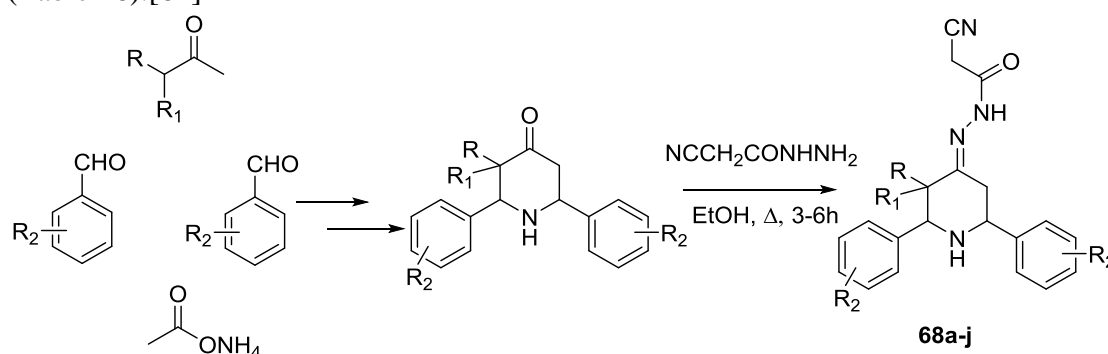


		Zone of inhibition of compounds 67a-m				
		Concentration used 250µg/mL of DMSO				
	R	<i>E. coli</i> MTCCC443	<i>P. aeruginosa</i> MTCC424	<i>S. aureus</i> MTCC96	<i>S. pyogenes</i> MTCC442	<i>A. niger</i> MTCC282
67a	H	26	24	18	17	26
67b	4-OH	28	27	24	25	30

67c	4-Br	15	13	-	-	22
67d	4-Cl	14	12	-	-	21
67e	4-F	25	23	25	23	28
67f	4-SO ₂ CH ₃	30	30	26	25	31
67g	3-NO ₂	25	24	18	19	28
67h	3-Cl	14	12	-	-	21
67i	2-Br	13	13	-	-	20
67j	2-I	15	14	-	-	18
67k	2,5-F	28	27	20	20	30
67l	3,5-Cl	15	15	-	-	17
67m	2,4-Cl	14	13	-	-	16

Table 25. Structure and antimicrobial activities of compounds **67a-m**.

Pilai *et al.* have recently described the stereoselective synthesis of a series of novel cyanoacetyl hydrazones of 3-alkyl-2,6-diarylpiperidin-4-ones **68a-j** demonstrating interesting antibacterial activities against *E. aerogenes* and some fungal strains (Table 26).[62]

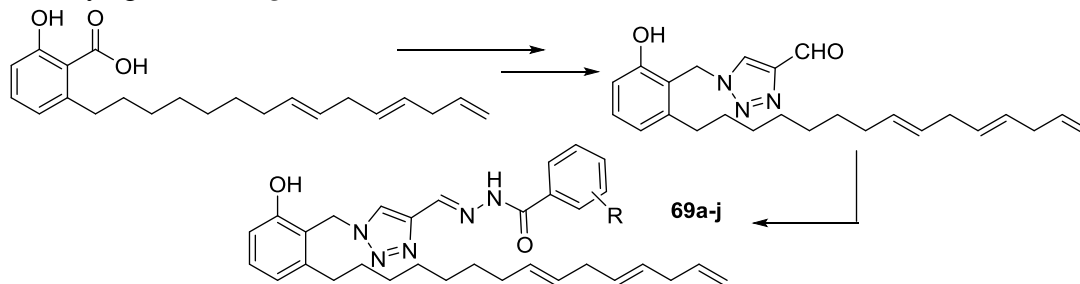


		Zone of inhibition of compounds 68a-j			
		Concentration used 250µg/mL of DMSO			
	R/R₁/R₂	<i>E. coli</i>	<i>E. aerogenes</i>	<i>S. aureus</i>	<i>C. albicans</i>
68a	Me/H/H	–	34	–	9
68b	Et/H/H	–	–	–	6
68c	Me/Me/H	–	14	–	19
68d	Me/H/ <i>p</i> -Me	11	11	12	–
68e	Me/H/ <i>p</i> -OMe	9	12	–	12
68f	Me/H/ <i>o</i> -Cl	12	9	–	–
68g	Me/H/ <i>m</i> -NO ₂	14	11	–	12
68h	Me/H/ <i>p</i> -F	–	–	16	8
68i	Me/H/ <i>p</i> -Cl	–	–	–	7

68j	Me/H/ <i>p</i> -Br	–	–	16	28
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Table 26. Structure and antimicrobial activities of compounds **68a-j**

Another example to be cited deals with the synthesis of hydrazone derivatives of anacardic acid linked with 1,2,3-triazole ring and exhibiting strong antifungal activity against *A. niger* and *C. albicans* (Table 27).[63]



		Zone of inhibition of compounds 69a-j	
		Concentration used 250 µg/mL of DMSO	
	R	<i>A. niger</i>	<i>C. albicans</i>
69a	H	16	15
69b	4-OMe	13	12
69c	4-Cl	17	18
69d	4-OH	26	23
69e	3,4,5-OMe	27	24
69f	2,5-Cl	19	19
69g	3,5-Cl	20	20
69h	Me/H/ <i>m</i> -NO ₂	25	24
69i	4-F	24	22
69j	2,5-F	26	24

Table 27. Structure and antimicrobial activities of compounds **69a-j**

CONCLUDING REMARKS

Numerous different approaches have been depicted for the design and synthesis of hydrazones presenting interesting antimicrobial activities. It also remains clear that this class of compounds is still too neglected as outlined in a previous review highlighting their use as metal ligands for the formation of hydrazone-transition metal complexes possessing interesting biological, analytical and catalytic applications.[64]

CONFLICT OF INTEREST

None declare

ACKNOWLEDGEMENT

None declare

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