

## 2-AMINO-1,3,4-THIADIAZOLE DERIVATIVES AS POTENTIAL ANTI-*HELICOBACTER PYLORI* AGENTS – AT A GLANCE

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### Abstract

*Helicobacter pylori* is a major human pathogen that causes gastric and extra-gastric complications and infects around 50% of the global population. Gastric cancer is a serious consequence of *H. pylori* infection. About 89% of all gastric cancers can be attributed to this pathogen. Treatment is indicated for all infected patients, as a strategy to knock down the risk of gastric malignancy. Due to the high level of antimicrobial resistance, new medicines are needed to treat *H. pylori* infection. This paper presents 2-amino-1,3,4-thiadiazole derivatives which exhibited anti-*H. pylori* effect. Some of the reported compounds showed higher activity compared to standard drugs, making the 2-amino-1,3,4-thiadiazole core a possible pattern for future anti-*H. pylori* agents.

### Rezumat

*Helicobacter pylori* este un agent patogen major care provoacă complicații gastrice și extra-gastrice și infectează aproximativ jumătate din populația lumii. Cancerul gastric este o consecință gravă a infecției cu *H. pylori*. Aproximativ 89% dintre toate tipurile de cancer gastric pot fi atribuite acestui agent patogen. Tratatamentul este indicat tuturor pacienților infectați, ca strategie de reducere a riscului de cancer gastric. Datorită nivelului ridicat de rezistență antimicrobiană, sunt necesare noi medicamente pentru tratarea infecției cu *H. pylori*. Acest articol prezintă derivați de 2-amino-1,3,4-tiadiazol care au manifestat efect anti-*H. pylori*. Unii dintre compușii raportați au demonstrat activitate superioară medicamentelor standard, făcând din fragmentul de 2-amino-1,3,4-tiadiazol un posibil model structural pentru viitori compuși cu activitate anti-*H. pylori*.

**Keywords:** *Helicobacter pylori*, 2-amino-1,3,4-thiadiazole, antimicrobial resistance, anti-*H. pylori* activity, inhibitory concentration

### Introduction

*Helicobacter pylori* is a Gram-negative spiral-shaped, microaerophilic microorganism identified in 1982 in human gastric mucosa. Gastric colonization with *H. pylori* can lead to gastrointestinal tract disorders such as chronic active gastritis, gastric and duodenal ulcers, indigestion and malignancies such as gastric mucosa-associated lymphoid tissue (MALT) B-cell lymphoma and gastric adenocarcinoma [1, 3, 16, 21]. In addition, *H. pylori* infection can lead to systemic complications: idiopathic thrombocytopenic purpura, iron-deficiency anaemia, vitamin B12 deficiency, coronary artery and neurodegenerative diseases, as well as gall bladder disorders (e.g., cholecystitis and cholelithiasis) [3, 6, 38]. The prevalence of *H. pylori* infection differs from country to country. Inadequate hygiene conditions and the level of development of the country are considered to be risk factors for *H. pylori* infection and therefore this infection is a feature of the socio-economic and health status of a community [3, 44]. Recent studies have shown an overall prevalence of 44.3% for *H. pylori* infection worldwide, with a higher prevalence

in developing countries, where 50.8% of the population is *H. pylori* positive, compared to industrialized countries where the prevalence of infection is less than 40% (34.7%). The highest prevalence was observed in Nigeria (89.7%), while the lowest rate was recorded in Yemen (8.9%). In Europe, the highest infection rate was found in Serbia (88.3%) and the lowest in Belgium (11.0%) [44]. *Helicobacter* species are well adapted to the highly acidic (pH < 2) inhospitable gastric environment and this makes *H. pylori* one of the most successful human pathogens. Iatrogenic transmission through the endoscope is possible, but person-to-person contact is the most accepted transmission route [3, 6, 40].

### *H. pylori* infection and gastrointestinal tract malignancy

One of the most serious consequences of *H. pylori* infection is gastric cancer, and statistics show that about 89% of all gastric cancers can be attributed to it [11]. Although the mechanism is not clearly understood, *H. pylori* infection is an important risk factor for gastric malignancy development [1, 38]. Therefore in

1994, the World Health Organization (WHO) included this bacterium in group I of human carcinogens [6, 16, 23, 36, 41].

### Current pharmacotherapy for *H. pylori* infection

Treatment of *H. pylori* infection comprises antibacterial agents such as macrolides (clarithromycin, azithromycin) and beta-lactam antibiotics (amoxicillin), nitroimidazoles (metronidazole, tinidazole), fluoroquinolones (levofloxacin, ciprofloxacin), tetracycline, rifabutin or furazolidone. In addition, *H. pylori* appears to be very susceptible to bismuth compounds both *in vivo* and *in vitro*. In infected patients, triple or quadruple therapies combining antibiotics, proton pump inhibitors and bismuth compounds have resulted in *H. pylori* eradication rates of over 80% [16]. According to the American College of Gastroenterology (ACG), clarithromycin-based triple therapy that combines clarithromycin with amoxicillin and a proton-pump inhibitor (14 days) is the first-line treatment recommended for the areas where the level of clarithromycin resistance is low, followed by bismuth-based quadruple therapy consisting of bismuth, tetracycline, metronidazole and a proton-pump inhibitor (10 - 14 days). There is no significant difference between these two therapies in terms of the percentage of patients in whom *H. pylori* was eradicated [5, 6]. When the first two therapies fail, one of the following five recommended treatment regimens could be used: concomitant therapy (clarithromycin, amoxicillin, metronidazole and a proton-pump inhibitor for 10 - 14 days), sequential therapy (amoxicillin and a proton-pump inhibitor for 7 days, then clarithromycin, metronidazole and a proton-pump inhibitor for 7 days), hybrid therapy (amoxicillin and a proton-pump inhibitor for 7 days, then amoxicillin, clarithromycin, metronidazole and a proton-pump inhibitor for 7 days), levofloxacin-based triple therapy (levofloxacin, amoxicillin and a proton-pump inhibitor for 10 - 14 days) or fluoroquinolone-based sequential therapy (amoxicillin and a proton-pump inhibitor for 5 - 7 days, then levofloxacin, metronidazole and a proton-pump inhibitor for 5 - 7 days) [5, 6]. However, due to resistant *H. pylori* strains, there is a negative trend of efficacy and 20 - 30% of treatments have failed in recent years. New drugs were added to existing therapy regimens. Addition of rebamipide, a mucoprotective agent that induces prostaglandin synthesis in the gastric mucosa, to antimicrobial regimens gave promising results [2]. Dual therapy with vonoprazan, a new potassium competitive acid blocker and amoxicillin has led to an eradication of over 90% and could become an alternative treatment for *H. pylori* infection [35].

### 2-Amino-1,3,4-thiadiazole derivatives and the anti-*H. pylori* effect

Azaheterocycles are widely present in naturally occurring organic compounds (e.g., atropine, codeine,

morphine, quinine, rutaecarpine, toddaquinoline, etc.) as well as in synthetic and pharmaceutical products that exhibit outstanding biological activities [8, 12, 26, 28, 32, 37, 39]. Azithromycin, amoxicillin, metronidazole, tinidazole, levofloxacin, ciprofloxacin, rifabutin and furazolidone used for the therapy of *H. pylori* infection are molecule drugs containing a nitrogen-heterocycle [19, 33, 34, 42]. The thiadiazole ring is a nitrogen-sulphur five membered heterocycle that can be found as a structural unit in biologically active compounds or can be used as a valuable intermediate in the synthesis of organic compounds [29]. Thiadiazole derivatives have been studied as bioactive compounds with medical potential, fungicides and herbicides for agriculture, as well as corrosion inhibitors or chelating agents for industrial purposes [17, 27, 32]. Among the four isomeric forms of the thiadiazole ring (e.g., 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole and 1,3,4-thiadiazole), the derivatives of 1,3,4-thiadiazole have been the most studied, probably due to the multiple biological effects that these compounds exhibit [17, 27, 29]. The 1,3,4-thiadiazole ring possesses valuable properties, such as high aromaticity associated with good *in vivo* stability and low toxicity for vertebrates, including humans. The increased lipophilicity due to the sulphur atom and the ability of 1,3,4-thiadiazole derivatives to make mesoionic systems allow these compounds to cross cell membranes, providing enhanced oral bioavailability. Moreover, mesoionic systems enable these derivatives to bind strongly to biomolecules (e.g., DNA, proteins), and therefore to show various biological effects [15, 17, 24, 27, 29, 43]. Indeed, the 1,3,4-thiadiazole ring has proven biological potential, as it can be found in commercially available drugs: acetazolamide and metazolamide as carbonic anhydrase inhibitors, cefazolin, cefazedone and sulfametizole as antibacterial drugs and megazole – an antitrypanosomal agent [7, 10, 27, 29]. In addition, 2-amino-1,3,4-thiadiazole derivatives with antitumour and uricogenic potential have been reported [7, 13, 18, 43]. We already presented some 2-amino-1,3,4-thiadiazoles with antimicrobial [25, 29], anti-leishmanial [27], antitrypanosomal, antimalarial, antitoxoplasmosis [30] and antiviral activities [31]. This mini-review describes 2-amino-1,3,4-thiadiazole derivatives that exhibit anti-*H. pylori* activity.

Nitroheterocyclic derivatives such as nitrofurans (e.g., nifurtimox, nifuroxazide, furazolidone, nifuratel) and nitroimidazoles (e.g., metronidazole, tinidazole) are used in the treatment of protozoan and bacterial infections. Usually metronidazole is the first option. However, tinidazole or furazolidone have also been used for the treatment of *H. pylori* infection [21]. Considering the antimicrobial properties of the above pharmacophores, Foroumadi *et al.* [9] synthesized some 2-amino-5-(5-nitro-2-heteroaryl)-1,3,4-thiadiazoles such as **1-3** belonging to nitrofurans, nitrothiophene and nitroimidazole series. The antimicrobial activity

was determined through the paper disk diffusion method, by measuring the capability of the studied substances to inhibit the growth of *H. pylori* cultures (sensitive to metronidazole and resistant to metronidazole, respectively). The first evaluation was performed with 1,3,4-thiadiazoles at three concentrations: 8, 16 and 32 µg/disk. The results showed a very strong growth inhibition for all three derivatives at 8 µg/disk against both types *H. pylori* strains (inhibition zone > 30 mm) compared to metronidazole as a standard (8 µg/disk, inhibition zone of 18 mm and 11 mm, respectively) (Table I) [9].

Supplementary tests were done against 20 *H. pylori* strains isolated from patients, using the thiadiazole derivatives at concentrations of 32, 16, 8, 4, 2, 1 and 0.5 µg/disk. Except the concentration of 0.5 µg/disk when the compounds had only moderate activity

(average of inhibition zone > 12 mm), high activity was shown for all derivatives at concentrations of 1 - 32 µg/disk. At concentration of 8 µg/disk, all derivatives exhibited an inhibition zone with an average over 30 mm. This might suggest an activity superior to metronidazole (inhibition zone of 16.3 mm). Among the three tested compounds, the nitrofurans **1** and the nitrothiophene **2** were the most potent derivatives with equal inhibitory activity at higher concentrations and averages of inhibition zone more than 38 mm (Table II). As demonstrated for other compounds with antimicrobial activity, structure-activity relationship (SAR) studies have shown that the 5-nitro group is indispensable for the biological profile. Moreover, the anti-*H. pylori* activity depends on the type of heterocycle at C-5 of the 2-amino-1,3,4-thiadiazole fragment [9].

Table I

The growth inhibition of *H. pylori* strains by derivatives 1-3 [9]

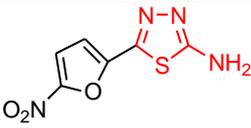
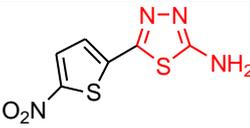
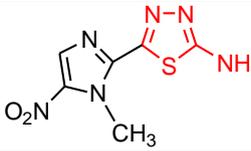
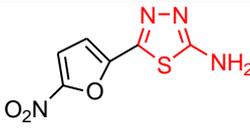
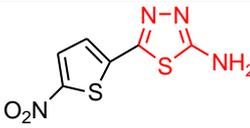
									
	<b>1</b>	<b>2</b>	<b>3</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>1</b>	<b>2</b>	<b>3</b>
	Inhibition zone (mm)			Inhibition zone (mm)					
	Metronidazole-sensitive strain			Metronidazole-resistant strain					
	8 µg/disk	16 µg/disk	32 µg/disk	8 µg/disk	16 µg/disk	32 µg/disk			
<b>1</b>	35	45	57	37	45	52			
<b>2</b>	35	44	59	34	43	55			
<b>3</b>	34	43	55	32	41	49			

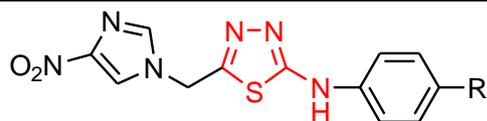
Table II

The growth inhibition of *H. pylori* strains by derivatives 1-3 [9]

									
	<b>1</b>	<b>2</b>	<b>3</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>1</b>	<b>2</b>	<b>3</b>
	Average of inhibition zone diameter (mm)								
	0.5 µg/disk	1 µg/disk	2 µg/disk	4 µg/disk	8 µg/disk	16 µg/disk	32 µg/disk		
<b>1</b>	14.2	20.6	26.6	32.3	38.4	44.1	48.0		
<b>2</b>	13.3	19.7	25.3	31.1	38.2	43.0	47.9		
<b>3</b>	12.2	18.3	23.7	29.2	32.8	36.7	42.3		

2-Amino-1,3,4-thiadiazole derivatives having an attached nitroimidazole moiety were prepared by Tafti *et al.* [36]. After evaluating their activity, SAR studies revealed that substitution of the C-2 amine group with alkyl moieties (e.g., methyl, ethyl, butyl, cyclohexyl) results in compounds lacking anti-*H. pylori* activity. The derivative **4** bearing a 4-methylphenyl group exhibited a potent anti-*H. pylori* activity. The biological tests performed at three concentrations (8, 16 and 32 µg/disk) showed moderate to strong activity (inhibition zone diameter of 19, 23 and 25 mm, respectively) against metronidazole-sensitive *H. pylori* strains with respect to standard drug, metronidazole (8 µg/disk,

inhibition zone diameter of 18 mm). The compound **4** was also very active against metronidazole-resistant *H. pylori* strains at every concentration (inhibition zone diameter of 21, 26 and 33 mm for 8, 16 and 32 µg/disk, respectively) compared to metronidazole (8 µg/disk, 11 mm). Although the nitro group typically increases antimicrobial activity, the nitro derivative **5** showed only moderate activity against both metronidazole-sensitive (16 mm diameter area) and metronidazole-resistant *H. pylori* strains (14 mm diameter area) at high concentration of 32 µg/disk [36].



R = CH<sub>3</sub> (**4**); NO<sub>2</sub> (**5**)

**Figure 1.**

The chemical structures of thiadiazole derivatives **4-5**

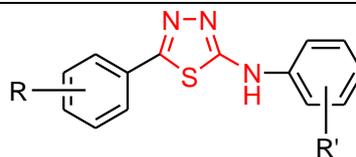
*H. pylori* produces large amounts of urease and this discovery allowed the identification of *H. pylori* infection based on the presence of urease in or on the gastric mucosa [38]. Urease is a nickel-dependent enzyme that catalyses the hydrolysis of urea into ammonia and carbon dioxide at a rate of about 10<sup>14</sup> times over the non-catalysed reaction [20]. This leads to the local neutralization of gastric acid and the establishment of a microenvironment suitable for the development of *H. pylori* [4, 20]. Moreover, the ammonia is toxic for different gastric cell lines. In addition, urease interacts with the immune system giving rise to oxidative reactions in human neutrophils, and therefore urease activity has been suggested to be the cause of gastric epithelium deterioration. Hydrogen peroxide resulted through this oxidative process can react with ammonia and gastric chloride, giving toxic monochloramine. Carbon dioxide made during urea

hydrolysis can also play a role in the survival of *H. pylori* in the stomach [4]. Urease is also liable for the development of renal diseases such as urolithiasis, pyelonephritis as well as hepatic encephalopathy, hepatic coma and catheter complications. Control of urease activity through the use of blocking agents could prevent these pathologies [20, 22].

The urease inhibitors can block the enzyme and recently much attention has been paid to the search of urease inhibitors as a new therapy for urease mediated diseases. In this regard some 2,5-disubstituted-1,3,4-thiadiazoles, such as **6-13**, have been tested as urease inhibitors in search of a skeleton where structural variations could lead to promising agents. Among the synthesized compounds, the chlorosubstituted derivatives **7** and **11** with chlorine in *ortho* and *para* position of the phenyl group were the most active with the half maximal inhibitory concentration IC<sub>50</sub> values of 313.2 μM (82.8% inhibition) and 214.7 μM (91.1% inhibition), respectively. The compound **9** showed a moderate activity (73.4% inhibition) indicating that a *meta*-nitro group on the aryl ring is favourable to biological activity (Table III). It seems that 2,6-dimethyl substituents of the aryl-amino moiety are better matched to the active site of the enzyme, leading to a good inhibition of urease. Thiourea was used as the standard drug [14].

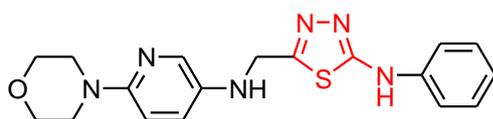
**Table III**

Structural details and urease inhibition activity of derivatives **6-13** [14]



**6-13**

	R	R'	Inhib (%)	IC <sub>50</sub> (μM)
<b>6</b>	4-CH <sub>3</sub>	2,6-(CH <sub>3</sub> ) <sub>2</sub>	27.1	—
<b>7</b>	2-Cl	2,6-(CH <sub>3</sub> ) <sub>2</sub>	82.8	313.2 ± 0.09
<b>8</b>	4-Cl	2,3-(CH <sub>3</sub> ) <sub>2</sub>	52.8	483.55 ± 1.99
<b>9</b>	3-NO <sub>2</sub>	2,4-(CH <sub>3</sub> ) <sub>2</sub>	73.4	398.2 ± 0.40
<b>10</b>	H	2,3-(CH <sub>3</sub> ) <sub>2</sub>	56.8	426.1 ± 0.00
<b>11</b>	4-Cl	2,6-(CH <sub>3</sub> ) <sub>2</sub>	91.1	214.7 ± 10.16
<b>12</b>	3-Cl	2,4-(CH <sub>3</sub> ) <sub>2</sub>	12.4	—
<b>13</b>	4-NO <sub>2</sub>	2,4-(CH <sub>3</sub> ) <sub>2</sub>	7.2	—



**14**

**Figure 2.**

The chemical structure of thiadiazole derivative **14**

2-Amino-1,3,4-thiadiazole derivative **14** containing pyridine and morpholine nuclei exhibited good urease inhibitory activity with IC<sub>50</sub> value of 6.05 ± 1.19

μM. The biological activity was increased at higher concentrations. The results indicate that this structure could be a promising scaffold for future urease inhibitors [4].

2,5-Disubstituted-1,3,4-thiadiazole derivatives **15-20** synthesized by Saleem *et al.* were evaluated for their urease inhibition activity [22]. Among the studied compounds, the derivative **16** proved to be the most active with IC<sub>50</sub> value of 1.55 μM compared to thiourea as standard drug (IC<sub>50</sub> value of 26 ± 5 μM). Other compounds showed moderate to good activity with IC<sub>50</sub> values ranging from 5.51 μM to 15 μM.

SAR studies showed that inhibitory activity depends on the nature and position of the substituents on the phenyl rings. The most active compound has a 3-methoxybenzyl group and a 2-methoxyphenylamino group as substituents of 1,3,4-thiadiazole ring ( $IC_{50}$  value of  $1.55 \pm 0.16 \mu\text{M}$ ). Changing the 3-methoxy-

benzyl substituent with the 3-methoxyphenethyl, the urease inhibition activity was reduced (derivative **17**,  $IC_{50}$  value of  $15 \pm 4 \mu\text{M}$ ). Decreased inhibitory activity was also recorded for the molecules with many methoxygroups (e.g., derivative **18**,  $IC_{50}$  value of  $10 \pm 3 \mu\text{M}$ ) (Table IV) [22].

**Table IV**

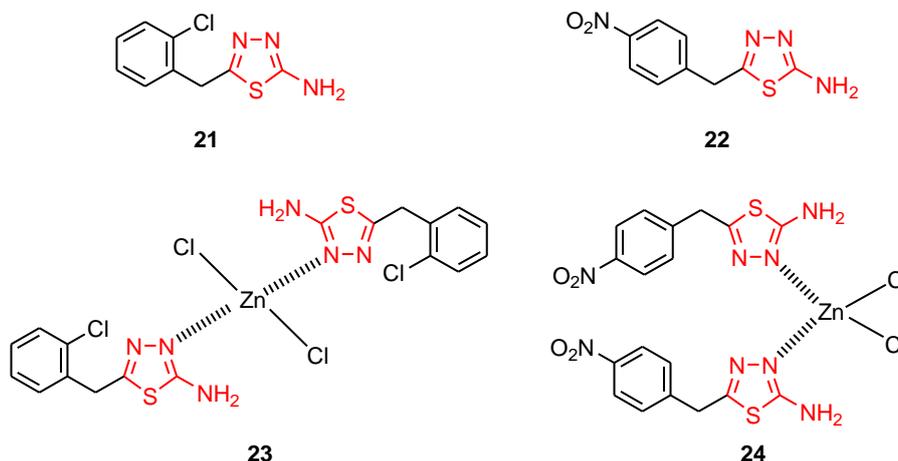
Structural details and urease inhibition activity of derivatives **15-20** [22]



	R	R'	n	$IC_{50}$ ( $\mu\text{M}$ )
<b>15</b>	3-OCH <sub>3</sub>	4-OCH <sub>3</sub>	2	$5.51 \pm 1.20$
<b>16</b>	3-OCH <sub>3</sub>	2-OCH <sub>3</sub>	1	$1.55 \pm 0.16$
<b>17</b>	3-OCH <sub>3</sub>	2-OCH <sub>3</sub>	2	$15 \pm 4$
<b>18</b>	3,4,5-(OCH <sub>3</sub> ) <sub>3</sub>	3-OCH <sub>3</sub>	2	$10 \pm 3$
<b>19</b>	3-OCH <sub>3</sub>	4-Cl	1	—
<b>20</b>	3-OCH <sub>3</sub>	4-Cl	2	—

Metal complexes have also been investigated as urease inhibitors. Zhu *et al.* [45] designed two zinc (II) complexes, **23** and **24**, with general formulae  $ZnCl_2L_2$  derived from the 2-amino-1,3,4-thiadiazoles **21** (L1) and **22** (L2) as ligands. The X-ray diffraction studies showed that zinc atom has a tetrahedral geometry being coordinated by two nitrogen atoms of the ligand and two chlorine atoms from  $ZnCl_2$ . Studies of inhibitory activities performed for ligands **21** and **22**, as well as metal complexes **23** and **24** at a concentration of

100  $\mu\text{g}/\text{mL}$  showed that, compared to acetohydroxamic acid as a reference (92.34% inhibition), ligand **21** is a weak urease-inhibitor (4.30% inhibition), whereas ligand **22** did not inhibit urease at all. Increased activity was observed for complexes **23** and **24**, with inhibition values of 14.31% and 17.8%, respectively, suggesting that metal complexes may enhance biological activity and this strategy can be used for the development of new enzyme inhibitors [45].

**Figure 3.**

The chemical structures of ligands **21-22** and thiadiazole-zinc (II) complexes **23-24**

## Conclusions

*H. pylori* is a very common human pathogen worldwide that causes a variety of disorders, from gastric and extra-gastric to very serious diseases such as malignancies. Unfortunately, *H. pylori* resistance to antimicrobial drugs is currently a global problem, and the development of resistance is associated with an

increased treatment failure rate. In this regard, finding new molecules and/or developing an anti-*H. pylori* vaccine capable of providing an acceptable eradication rate and reduced side effects would be a great advantage. Some 2-amino-1,3,4-thiadiazoles have shown promising anti-*H. pylori* effect. Additional synthetic and clinical experiments are needed to investigate the potential of

2-amino-1,3,4-thiadiazole scaffold and to develop effective healing methodologies for patients infected with *H. pylori*.

### Conflict of interest

The authors declare no conflict of interest.

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