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ORIGINAL ARTICLE

Synthesis, characterization and biological activities of some azo derivatives of aminothiadiazole derived from nicotinic and isonicotinic acids

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Cyclization;
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Abstract In this study we synthesized the new compounds containing bis-1,3,4-thiadiazole **3(A–D)**$_n$ from many reaction steps (cyclization, diazotization and etherification respectively). The compounds have been characterized by melting point, FT-IR and ^{1}H NMR data. All the synthesized compounds have been evaluated *in vitro* for their antimicrobial activities against several microbes like: *Escherichia coli, Klebsiellia pneumonia, Pseudomonas aeruginosa, Serratia marscens and Staphylococcus aureus* and show that some of these compounds have very good antibacterial activity.

1. Introduction

The aminothiadiazoles have occupied an important place in drug industry. 1,3,4-Thiadiazole has wide applications in many fields. The earliest uses were in the pharmaceutical area as antibacterial drugs (Vasoya et al., 2005).

The 1,3,4-thiadiazole ring system has incorporated many substances with antibacterial, ameobicide, parasiticide and antifungal activities (Farzin and Rahil, 2008; Mohd et al., 2009). In addition, it was reported that 1,3,4-thiadiazole exhibit various biological activities possibly due to the presence of the N=C–S moiety (Holla et al., 2002).

It was also know that 3- and 4-substituted pyridines recorded pronounced antimicrobial activity such as isonicotinic acid hydrazide, which remains one of the most effective antibiotics against tuberculosis. Also, sulphanilamides effectiveness extends to acute chronic Gram negative and Gram positive infections. For example, sulfa pyridine is a chemotherapeutic agent for the treatment of pneumococcal and other bacterial infections (Osama and Salwa, 2005). There

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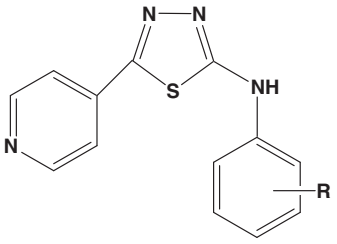
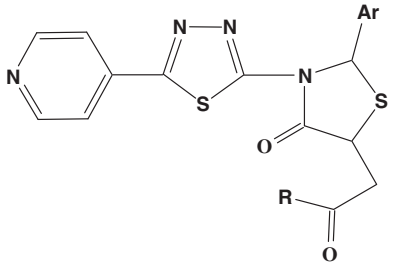
are many interesting studies on the biological activity of 2-amino-1,3,4-thiadiazole. Mohammad et al. (2009) found some derivatives of aminothiadiazole (**I**) having good anticonvulsant activity in the range of 33–100% in comparison to phenytoin, which completely inhibited the convulsions produced by an electroconvulsometer in albino mice.



R= H, *O*-CH_3, *P*-CH_3, *O*-OCH_3, *P*-Cl

(I)

Ranjina et al. (2006) synthesized a number of derivatives of aminothiadiazole containing 4-pyridyl and oxothiazolidin moieties in the same molecules (**II**).



Ar = 4- $OCH_3C_6H_4$, 4-ClC_6H_4, 3,4,5-$OCH_3C_6H_2$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, C_6H_5, 2-Furyl, 4-$(CH_3)_2NHC_6H_4$, R= phthalimidoxy.

(II)

He found that all the compounds have good antimicrobial activity but the compounds in which a nitro group is present at the Meta and Para position of the aryl ring, respectively, possess stronger antibacterial activity than others.

In this study, we designed new azo compounds containing bis-1,3,4-thiadiazole ring derived from nicotinic and isonicotinic acids in the same molecules. This type of combination and rebuilding of these heterocyclic compounds are expected to have high biological activity largely as antimicrobial agents and we compared the biological activity results of these compounds with the analogous containing the same structural units except replacing of the nicotinic and isonicotinic moieties with phenyl and cyclohexyl rings.

2. Experimental

2.1. Materials and physical measurements

All starting materials and solvents were purchased from Aldrich and Fluka and used without further purification. Melting points were determined on Electro-thermal capillary apparatus and are uncorrected. The FT-IR spectra were obtained using SHIMADZU model FT-IR-8400S. ^{1}H NMR spectra were obtained on BRUKER model Ultra shield 300 MHz spectrophotometer in DMSO-d_6 solution with the TMS as the internal standard. *Note*: in some ^{1}H NMR spectra, the peaks at δ 2.5 and 3.35 are for the solvent (DMSO-d_6) and dissolved water in (DMSO-d_6), respectively.

*2.2. Preparation methods and physical data of synthesized compounds **1**(**A**–**D**)–**3**(**A**–**D**)*

*2.2.1. General procedure for preparation of 2-amino-5-(substituted)-1,3,4-thiadiazole **1**(**A**–**D**)*

A mixture of the corresponding carboxylic acid (10 mmol), thiosemicarbazide (0.91 g, 10 mmol) and phosphorous oxychloride (5 mL) was gently refluxed for 3 h. After cooling, water (25 mL) was added slowly and the reaction mixture was refluxed for 3 h and filtered. The solution was neutralized with concentrated potassium hydroxide solution and the precipitate was filtered and recrystallized from ethanol.

*2.2.1.1. 2-Amino-5-(3-pyridyl)-1,3,4-thiadiazole (**1A**).* This compound was obtained as a pale yellow powder, yield (69%), mp > 300 °C; FT-IR (KBr disk, cm^{-1}) 3308 and 3168 (NH_2), 1645 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz, δ) 9.19 (s, 1H, a-H, pyridine), 8.95 (d, 1H, d-H, pyridine), 8.62 (t, 1H, c-H, pyridine), 8.12 (d, 1H, b-H, pyridine), 7.55 (s, 2H, NH_2).

*2.2.1.2. 2-Amino-5-(4-pyridyl)-1,3,4-thiadiazole (**1B**).* This compound was obtained as a yellow powder, yield (74%), mp 239–240 °C; FT-IR (KBr disk, cm^{-1}) 3297 and 3123 (NH_2), 1641 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz, δ) 8.70 (d, 2H, HC═N, pyridine), 7.85 (d, 2H, HC═C, pyridine), 7.75 (s, 2H, NH_2).

*2.2.1.3. 2-Amino-5-(4-phenyl)-1,3,4-thiadiazole (**1C**).* This compound was obtained as an off white powder, yield (82%), mp 220–222 °C; FT-IR (KBr disk, cm^{-1}) 3320 and 3156 (NH_2), 1631 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz, δ) 7.78–7.47 (m, 5H, Ar–H), 7.43 (s, 2H, NH_2).

*2.2.1.4. 2-Amino-5-(4-cyclohexyl)-1,3,4-thiadiazole (**1D**).* This compound was obtained as a white powder, yield (91%), mp 238–240 °C; FT-IR (KBr disk, cm^{-1}) 3302 and 3117 (NH_2), 1633 (C═N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz, δ) 6.99 (s, 2H, NH_2), 1.99–1.15 (m, 11H, cyclohexyl).

*2.2.2. General procedure for preparation of 2-(p-hydroxyphenyl-azo)-5-(substituted)-1,3,4-thiadiazole **2**(**A**–**D**)*

Compounds **1**(**A**–**D**) (1.78 mmol) were dissolved by heating and stirring in (8 mL) of 85% phosphoric acid. The solution was cooled to 0 °C in an ice bath, and then concentrated nitric acid (4 mL) and a solution of sodium nitrite (0.13 g, 1.87 mmol) in (2 mL) of water was added. The mixture was stirred vigorously and maintained at below 5 °C during 10 min. Afterwards a solution of phenol (0.17 g, 1.78 mmol) in (0.5 mL) water was added dropwise with stirring. The mixture was poured into cold water (100 mL). The precipitate solid was filtered, washed several times with water and recrystallized from ethanol.

*2.2.2.1. 2-(p-Hydroxyphenyl-azo)-5-(3-pyridyl)-1,3,4-thiadiazole **2**(**A**).* This compound was obtained as a dark red powder, yield (71%), mp 246–248 °C; FT-IR (KBr disk, cm^{-1}) 3450–3095 (broad O–H group), 1432 (N═N) cm^{-1}; ^{1}H NMR