Synthesis a Series of 1,3,4-Thiadiazole Derivatives and Investigate Their Biological Activity

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Abstract

Eight compounds of new 1,3,4-thiadiazole biologically active for the series1,4-di(5-(4-substitutedphenyldiazenyl)-1,3,4-thiadiazol-2-yl) benzene were prepared through the reaction of terephthalic acid with thiosemicarbazide .The product was coupled with substituted benzene through a diazotization reaction. The synthesized compounds (٢-٩) were identified using the analytical and spectral means. The biological activity for those compounds was investigated against three types of bacteria Escherichia coli (Gram negative bacteria), Enterobacter (Gram- negative bacteria) and Staphylococusaurens (Gram-negative).

Keyword: Thiadiazol, biological active compounds, diazotization reaction

تحضير سلسله جديدة من مشتقات ١,٣,٤ ثاياديازول والتحري عن فعاليتها البايلوجية

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الخلاصة

تم تحضير ثمانية مركبات ٤,٣,١- ثاياديازول جديدة فعالة بيولوجيا تنتمي لسلسلة مركبات 1,4-di(5-(4-substitutedphenyldiazenyl)-1,3,4-thiadiazol-2-yl)benzene)وذلك من خلال مفاعلة حامض التريفثاليك مع ثايوسيمي كاربازايد ثم تفاعل (diazotization) الناتج مع بنزين معوض. تم تشخيص المركبات المحضرة بالوسائل التحليلية والطيفية، وتم دراسة الفعالية البايولوجية لهذه المركبات (2-9) باستخدام وسط زرعي لبعض انواع البكتيريا.

مفاتيح الكلمات : الثاياديازول ، المركبات الفعالة بيولوجيا، تفاعل الثايودايزيشن.

Introduction

The resistance towards available drugs is rapidly becoming a major worldwide problem due to the conditioning of various virus and bacteria to current chemical used for treatments. The need to design new chemical compounds to overcome this problem has become one of the most important areas of research nowadays. Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities. Thiadiazole moiety acts as a hydrogen binding domain and two – electrons donor system. It also acts as constrained pharmacophore. Many drugs containing thiadiazole nucleus are available in the market such as acetazolamide, methazolamide, sulfamehazole, etc.

It was shown that substituted 1,3,4-thiadiazoles exhibit antimicrobial [1] and antituberculer [2-4] activities , while other compounds act on the CNS as anticonvulsants [5-7] or as antidepressant and anxiolitic [8] agents. A family of selective 1,3,4-thiadiazoles phosphodiestreas inhibitors [9] , and selective orally active cyclooxygenase inhibitors were reported[10].

Moreover, many reports indicate that acylthiosemicarbazides and their corresponding cyclized 1,3,4 thiadiazole derivatives possess anti- inflammatory [11-13] and analgesic [14] activities. 1,3,4 – Thiadiazoles are thus a group of heterocycles whose derivatives are important in drugs industry, medicine and agriculture [13,15-21].Accordingly, in continuation of our work in this area [22-27] , a variety of heterocyclic derivatives have been prepared from saccharide derivatives, involving some new thiadiazole, oxathiazoles , and their chemistry and effect of the derivatives on the enzyme tyrosinase was studied [28-31] , which is the rate limiting step in melanin biosynthesis [32] .

Members of this ring system have found their way into such diverse application as pharmaceuticals, oxidation inhibitors, cyanine dyes and metal complexion agents. The literature review showed that the thiadiazole nuclei have antimicrobial, anti–inflammatory, anticancer, anticonvulsant, antidepressant, antioxidant, radio protective, and anti-leishmanial activities [33-34].

The aim of this work is to synthesis new series of 1,3,4-thiadiazole which are expected to show biological activity.

Experimental

Instrumental

The FTIR spectral data were recorded on FTIR-8300 Fourier Transform Infrared Spectrophotometer *SHIMADZU* using potassium bromide disc doublebeam UV-VISIBLE spectrophotometer. Melting points (^{o}C) were recorded on hot stage Gallen Kamp melting point apparatus and were uncorrected. NMR spectra were recorded on Jeol and spectrometer at 400 MHz for ^{1}H.

The IR spectral data and the study of physical properties were done at the Department of Chemistry, College of Education for Pure Science, Diyala University.

1. Synthesis of 1,4-di(-2-amino-1,3,4-thiadiazol)-5-yl-benzene (1)

A mixture of appropriate terephthalic acid (0.01mol) and (1.82g, 0.02 mol) of thiosemicarbazide with (5mL) of phosphorus oxychloride was refluxed gently for (5 hrs.). After cooling (50mL) of water was added, the mixture was then refluxed for (7hrs.) and filtrated, neutralized with potassium hydroxide. The Precipitate was washed with water and recrystallized from (ethanol-water) to give compounds **(1)**.

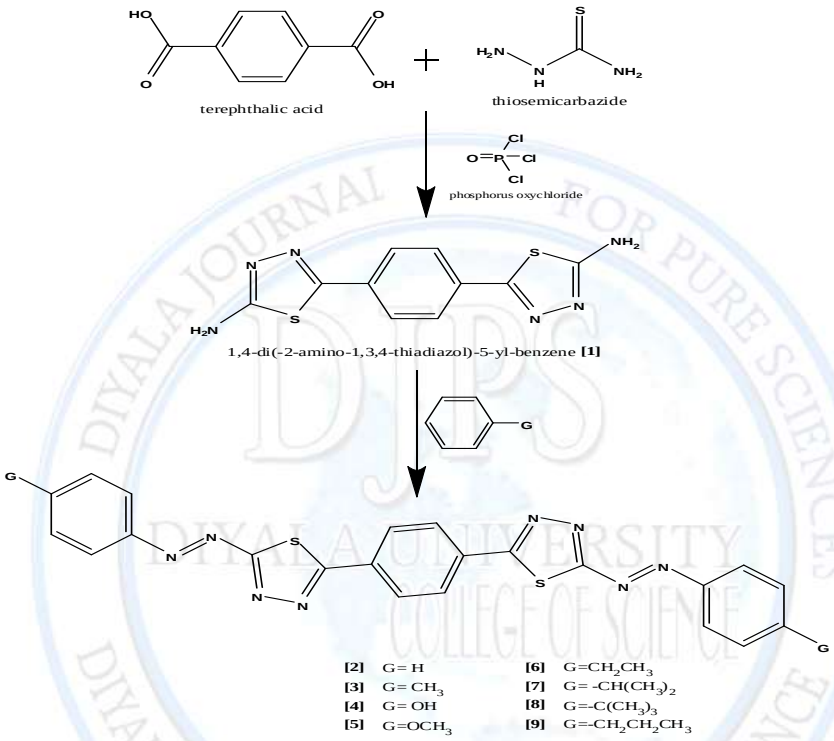
2. Synthesis of 1,4-di (5-(phenyldiazenyl)-1,3,4-thiadiazol-2-yl)benzene series (2-9):

1,4-Di(2-amino-1,3,4-thiadiazol)-5-yl-benzene (0.01mole) was dissolved in slightly acidified distilled water, a mixture of (HCl and $NaNO_2$) (0.02 mole) was added and the reaction was carried in an ice bath. Then different substituted benzene (G: *p*-CH_3, *p*-OH, *p*-OCH_3, *p*-CH_2CH_3, *p*-isopropyl, *p*-tertiary butyl, *p*-n-propyl) (0.01 mole) were used to prepare the target molecules that were filtered and purified.

Results and Discussion

1. Synthesis

Scheme 1. Synthesis scheme of 1,3,4-thiadiazoles derivatives



The precursor 1,4-di(-2-amino-1,3,4-thiadiazol)-5-yl-benzene (1) was synthesized by the reaction of terephthalic acid and thiosemicarbazide in presence of phosphorus oxachloride [35].Compound (١) was characterized based on FTIR and ^{1}H-NMR, the IR spectrum shows two strong peaks at (3140-3215) cm^{-1} related to thesymmetric and asymmetric ($-NH_2$) group absorption vibration and peak at 1620 cm^{-1} related to (C=N) of the 1,3,4-thiadiazole ring, while the ^{1}H-NMR spectrum was the chemical shift at 7.6 ppm for benzene ring and 8.2 ppm for (N-H) (figure 1).

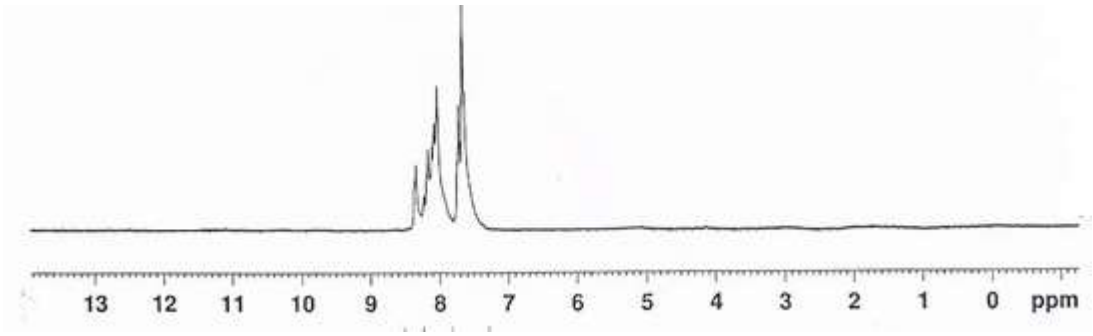


Figure 1: ^{1}H NMR Spectrum for compound 1,4-di(5-(phenyldiazenyl)-1,3,4-thiadiazol-2-yl)benzene [2]

The target compounds (2-9)1,3,4-thiadiazoles derivativeswere synthesized by diazotization reaction of 1,4-di(-2-amino-1,3,4-thiadiazol)-5-yl-benzene with benzene and other substituted benzene compounds (*p*-CH_3, *p*-OH, *p*-OCH_3, *p*-CH_2CH_3, *p*-isopropyl, *p*-tertiary butyl, *p*-n-propyl).The physical properties of the target molecules as shown in (table 2). The authenticity of the product was confirmed by spectral data (FTIR) shown in (table 1).

Table 1: The FTIR (KBr cm^{-1}) spectrum data (stretching vibrations) for the compounds (2-9).

Substituent G	Comp.	O-H	C-H aromatic	C-H aliphatic	C=N	N=N
H	2	-	3080	2955	1615	1600
***p*-CH_3**	3	-	3110	2987-3000	1610	1550
***p*-OH**	4	3356	3112		1689	1560
***p*-OCH_3**	5	-	3024	2990-2866	1684	1580
***p*-C_2H_5**	6	-	3100	2980-2890	1643	1581
***p*-i-pro**	7	-	3103	298-2885	1647	1555
***p*-t-Bu**	8	-	3050	2995-2810	1644	1548
***p*-n-pro**	9	-	3090	2985-2880	1656	1588

Table 2: The physical properties of the compounds (2-9).

Com. No.	M.P. (^{o}C)	% Yield	IUPAC Name
2	200	90	1,4-di(5-(phenyldiazenyl)-1,3,4-thiadiazol-2-yl)benzene
3	220	85	1,4-di(5-(4-methyl phenyldiazenyl)-1,3,4-thiadiazol-2-yl)benzene
4	300	87	1,4-di(5-(4-hydroxy phenyldiazenyl)-1,3,4-thiadiazol-2-yl)benzene
5	198	80	1,4-di(5-(4-methoxy phenyldiazenyl)-1,3,4-thiadiazol-2-yl)benzene
6	208	77	1,4-di(5-(4-ethyl phenyldiazenyl)-1,3,4-thiadiazol-2-yl)benzene
7	210	79	1,4-di(5-(4-isopropyl phenyldiazenyl)-1,3,4-thiadiazol-2-yl)benzene
8	209	78	1,4-di(5-(4-tert-butyl phenyldiazenyl)-1,3,4-thiadiazol-2-yl)benzene
9	200	98	1,4-di(5-(4-n-propyl phenyldiazenyl)-1,3,4-thiadiazol-2-yl)benzene

2. Biological activity

The antibacterial activity results are given in figure (3-4).The synthesized 1,3,4-thiadiazoles derivatives exhibit various antibacterial activities which can make those compounds useful for the target application . The compounds [2-9] have been screened for their antibacterial activity by agar growth technique against three types of bacteria Escherichia coli (Gram negativebacteria), Enterobacter (Gram-negativebacteria) and Staphylococusaurens (Gram-negative). Each compound was dissolved in DMSO to give a final concentration of 0.01 mg/ml. From the data obtained, all the compounds (3, 7, 8, and 9) have the highest activity against E. coli (G-ve) and Enterobacter (G-ve) than others, in case of compounds (2) and (5) show no activity against E. coli and Enterobacter while with Staphylococusaurens, compounds (3, 4,6, 7 and 9) shows the higher activity than others.

Table 3: Biological Activity of compounds (2-9)

	2	3	4	5	6	7	8	9
Escherichia coli	+	+++	++	+	++	+++	+++	+++
Entrobacter (G)$^-$	+	+++	+++	++	+++	+++	++	+++
Candida albicans	_ _ _	+++	++	+++	+++	++	+++	+++

Note:

- = Inactive

+ = slightly active inhibition zone <5 mm

++ = Moderately active inhibition zone <5 mm

+++ = Highly active inhibition >12 mm

All the compounds 3 , 7,8 and 9were found to be highly active against Escherichia coli (G $^-$) while the compounds (3 , 4 , 6 and 7) were found to be highly active against Entrobacter (G $^-$) . But the compounds (3, 5,6,8 and 9) were found to be highly active against Candida albicans. But the compound (4) and (7) were found to be med active against Candida albicans.

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