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Synthesis and Biological Activity Study of Some New Pteridine Derivatives.

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ABSTRACT

Four new pteridine derivatives compounds have been synthesized in single step by condensation of equimolar mixture of an appropriate vicinal diamine and diketone (Acenaphthenequinone). FT-IR and ^{1}H NMR spectroscopy techniques were used to identify structures of prepared compounds. The antimicrobial activity of new compounds was investigated using two bacterial species (*staphylococcus aureus*and *Escherichia coli.).* The new compound show high ability to inhibit investigated microbial.

Keywords: Pteridine derivatives, Acenaphthenequinone, Pteridine biological activity and pyrimidine.

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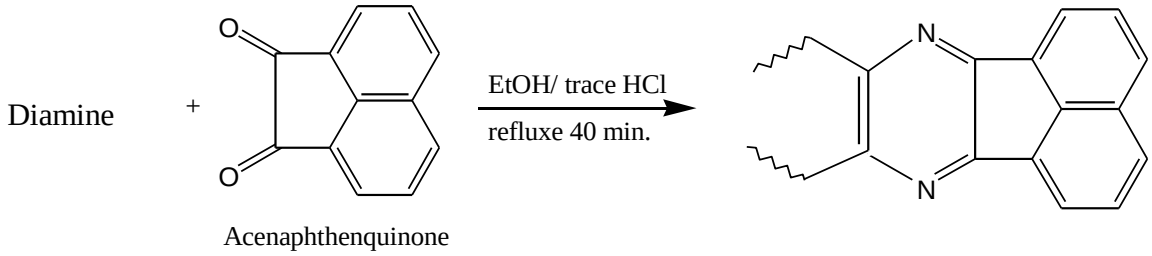
INTRODUCTION

Pteridines are heterocyclic compounds comprised of a fused pyrimidine and pyrazine ring involved in a wide range of biological functions from the color on butterfly wings to cofactors in enzyme catalysis to essential vitamins[1]. The pteridines, 5,6,7,8-tetrahydrobiopterin is the necessary cofactor of several aromatic amino acid monoxygenases, the nitric oxide syntheses and glyceryl ether monoxygenase (GEMO). Neopterin plays an essential role in the immune system and is an important biomarker in laboratory medicine for diseases such as HIV, cardiovascular disease, malignant tumors, among others[2-6]. Compounds that posses pteridine core and pyridopyrimidin have been reported to have a different biological activities like antiinflametry[7,8] , analgesic [9] , potent inhibitors for hepatitis (virus [10], Immunosuppressive activity [11], antinematocide activity [12,13] and antimicrobial activity [14-16].Bearing in mind the importance of pteridines compounds, we planned to synthesize three new acenaphthopteridine and8-chloroacenaphtho[1,2-b] pyrido [3,4-e] pyrazine as antimicrobial agent.

EXPERIMENTAL

General procedures [17, 18]

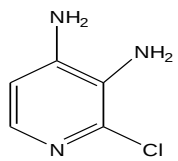
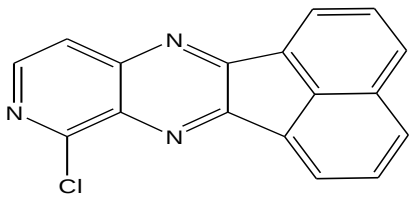
The four compounds have been synthesized in single step by condensation of equimolar mixture (2mmole) f an appropriate vicinal diamine and diketone (Acenaphthenequinone) (Scheme 1, Table 1) dissolved in 50 ml ethanol and trace hydrochloric acid (5 M) for 40 minute . The mixture was poured in to ice-water (50 ml) and the precipitate was collected. The desired compounds were obtained in good yield as air stable powder (Table 1). The reaction was followed-up by TLC using CH2Cl2-EtOAC (1:1). Purification was achieved by use of activated charcoal and occasionally column chromatography (typical, silica using mixture ofCH2Cl2:MeOHsolvent gradient from 10:0 to 9:1) was required to removed unreacted acenaphthoquinone. Melting points were uncorrected and measured by using Gallenkamp melting point apparatus.(Table 1).



Acenaphthenquinone

Scheme 1

Table 1: Physical properties of preparedcompounds

Symbol	diamine	Product Compounds	m.p C° of product	Yield %
A1	 3,4-diamino-2-chloropyridine	 8-chloroacenaphtho[1,2-*b*]pyrido[3,4-*e*]pyrazine	259-263 C°	93.4 %

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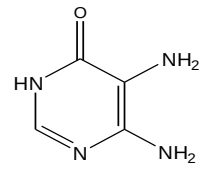
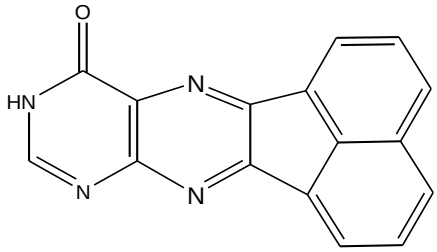
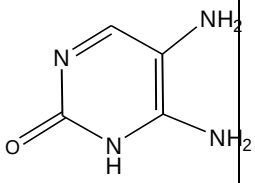
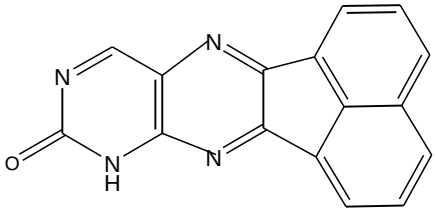
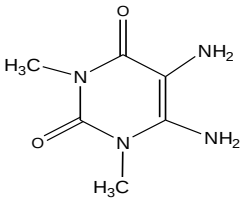
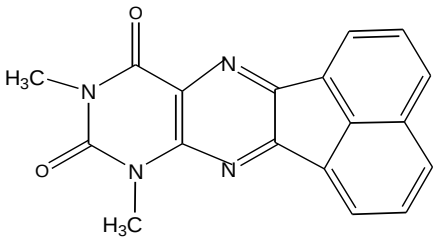
A2	 5,6-di amino-4-hydroxypyrimidine	 Acenaphtho[1,2-*g*]pteridin-1(10*H*)-one	295- 296 **C°**	90.4 %
A3	 5,6-di amino-2-hydroxypyrimidine	 Acenaphtho[1,2-*g*]pteridin-9(8*H*)-one	278-280 **C°** **Decompose**	80.8%
A4	 5,6-diamino-1,3-dimethyluracil	 8,10-dimethylacenaphtho[1,2-*g*]pteridine-9,11 (8*H,10 H*)-dione	> 310 **C°**	66.6%

Physical measurements

IR spectra for prepared compounds were measured as KBr disks using Shimadzu model FT IR-8400Sspectrometeratthe laboratory of Chemistry department in Basrah University. The ^{1}H- NMR spectra were recorded on a Bruker Biosipin Avance III spectrometer at 600 MHz in DMSO-d6 as solvent with TMS as an internal reference at the Chemistry department in Konstanz university, Germany.

Antimicrobial activity assay

The antimicrobial activity of new compounds was investigated using two bacterial species, one was Gram negative *Escherichia coli* (ATCC 25922) and the other was Gram positive *Staphylococcus aureus* (ATCC 25923).These strains were obtained thankfully from Immunology laboratory /Department of Biology/College of Science/University of Basrah. The method agar diffusion was used to estimate the biological activity**[19]**,in nutrient agar media at concentration (50 g/ L) which is used DMSO as a solvent and as a control for the disc sensitivity test. The results of biological activities are shown in Table3.

RESULTS AND DISCUSSION

I.R spectra

The spectra of this compounds show that all compounds have common peaks such as a variable intensity of aromatic C-H stretching (3010-3060 cm^{-1}), strong peaks of aromatic double bond C=C stretching (1500 -1550 cm^{-1}). The strong peak at (1610-1668 cm^{-1}) is attributed to(-unsaturated aromatic C=N

stretching)[20]. FT-IR of this compounds show additional peaks at (1110 cm^{-1}) attributed to C-Clin compound A1[20]and peak at (2950-3050cm^{-1}) attributed to asymtric and symtric stretching of (-CH_3) group in compound A4.Medium peak at (3238-3446 cm^{-1})of (-N-H) stretching of secondary amid in compounds A2 and A3. Strong peak at (1683-1714 cm^{-1}) of (-C=O) stretching in compounds A2-A4[20,21]. The peak position of (C=O) group gave us simple method to distinguish between compound A2 and A3.In compound A3 (CO) group position btween two electron donor group (-NH-CO-N=) while in compound A2(CO) group position near one electron donor group(-NH-CO-), therefore , this group (CO) in compound A3 is shifted to lower wavenumber (1683cm^{-1}) ,while in compound A2 is shiftd to higher wavenumber (1703 cm^{-1})[21].Disappearing of (CO) group stretching peak of acenaphthenequinoneat (1726cm^{-1}) in compound A1 is good evidence of preparing it.

^{1}H-NMR Spectra

Due to the existing of a large number of aromatic protons which appears in the same region, it was difficult to recognize the spin systems of each group of protons. The integrations give us useful information about the exact numbers of protons in each compound.In compound A1 8.63-8.01 (8H, m) .Compound A2 12.94 (1H, s, -NH)Sec. amid,9.95 (1H, s, -CH=N-), 8.55-7.99 (4H, m), 6.42-6.10 (2H, m). Compound A3 12.87 (1H, s, -NH) Sec. amid, 10.58 (1H, s, -CH=N-), 8.40-7.83 (4H, m), 6.65-6.63 (2H, m). Compound A4 8.50-8.29(4H, d dd, J= 12), 8.00-7.93 (2H, m), 3.75 (6H, s, -N-CH_3). Figures (1a-4a) show the 1H-NMR spectra of these compounds.

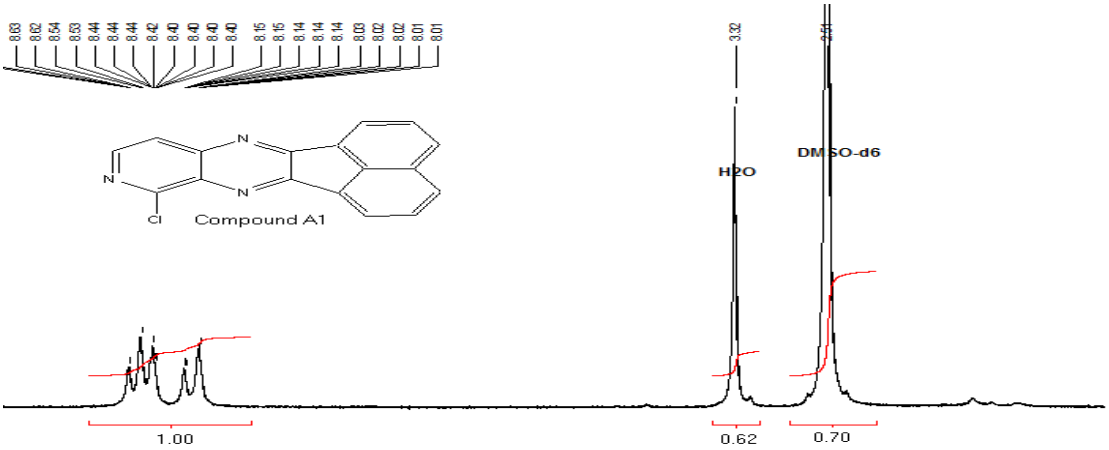


Figure 1a: ^{1}H-NMR Spectrum of Compound A1

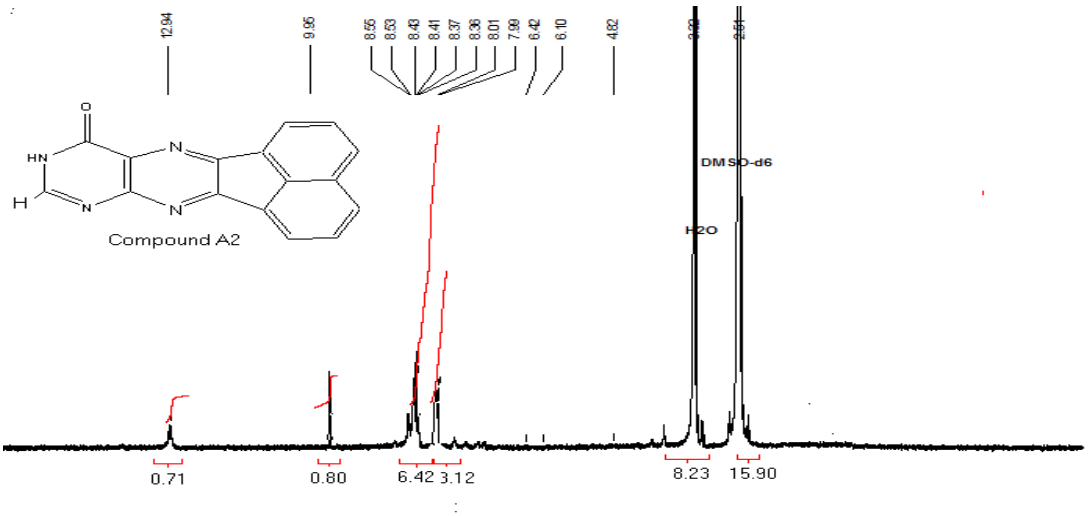


Figure 2a: ^{1}H-NMR Spectrum of Compound A2

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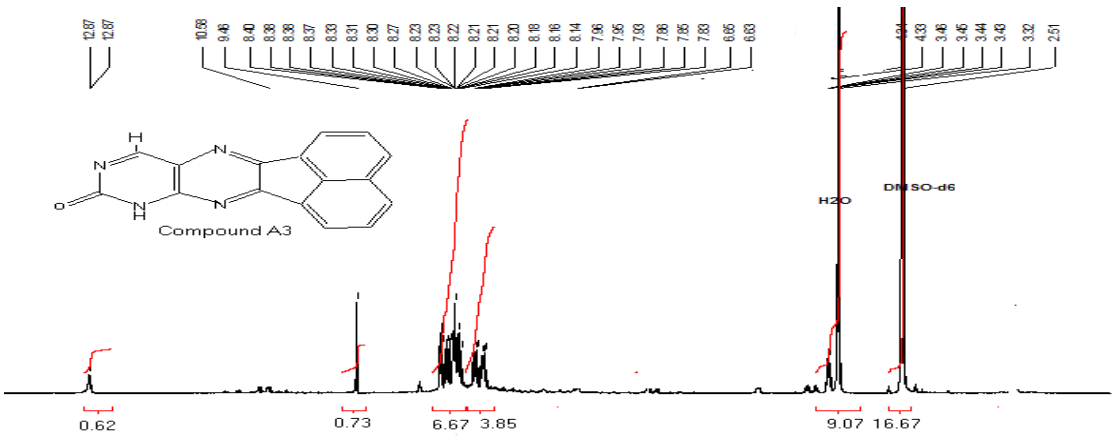

Figure 3a: ^{1}H-NMR Spectrum of Compound A3

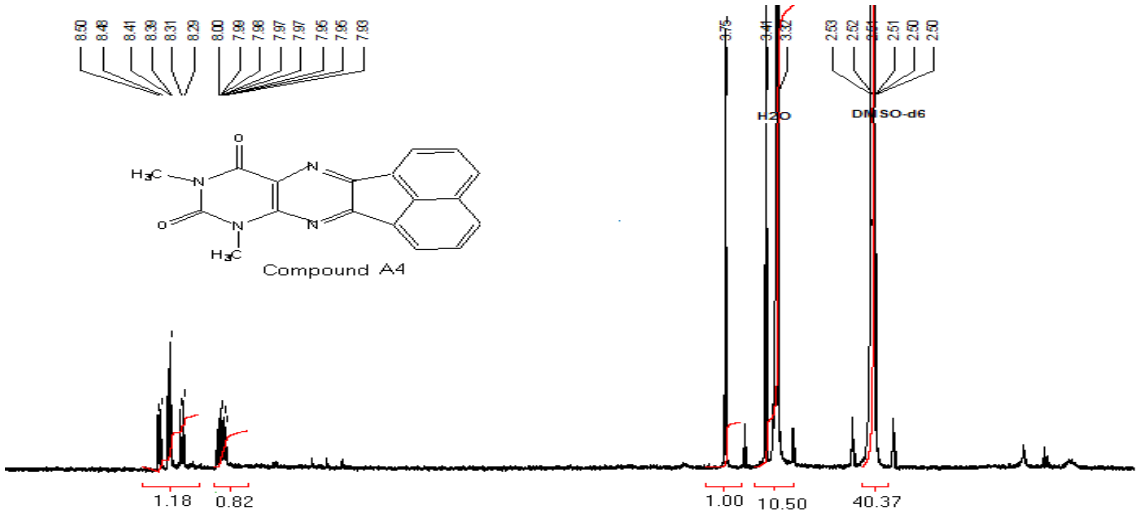

Figure 4a: ^{1}H-NMR Spectrum of Compound A4

Antimicrobial activity assay

The results of biological activity against two types of bacterial (staphylococcus aureus and Escherichia coli.) are shown in Table 2.

Table 2: The result of biological activity

compounds	Inhibition zone in mm	
	E. coli.	*St.aureus*
A1	18	26
A2	30	33
A3	20	23
A4	26	32

The biological activity exhibited by the four compounds was higher against gram-positive bacteria (*S.aureus*) as compared with gram-negative bacteria (*E.coli*). It is generally accepted that bacterial outer envelope is responsible for the different microbial responses to biocides challenges. Cytoplasmic membrane in

Gram negative bacteria is composed essentially of a phospholipids bilayer with embedded proteins; it is semi permeable and regulates the transfer of solutes and metabolites in and out of the cell cytoplasm. It is also associated with several important enzymes involved in various cell metabolic functions[20].

In Gram-negative bacteria, passage across the outer membrane (OM) depends upon the chemical nature of the inhibitor, hydrophilic compounds utilizing the porin channels (hydrophilic route) and hydrophobic compounds, enter via the hydrophobic route. Nevertheless, passive diffusion was the rout by which biocides pass through the staphylococcal cell wall which might explain the higher susceptibility of *S.aureus* to the series applied in the present study [20, 21].

In general, Compound A2 is more active than the other compounds against the two types is very clear on its activities. The compound A2 is more active against the two types of bacterial, while compound A3 became less active (Table 2). A remarkable reduction in the activity of compound A1 has occurred when the Diamine was changed from pyramidin ring to pyridine ring against *E.coli*. A slight increase in the activity has occurred against *S.aureus* in compound A1 compared with compound A3. A slight change was detected in the activity between compound A2 and A4 against *S.aureus* (Table 2).

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