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Syntheses, Characterization and Biological Effect Studies of Some New Heterocyclic Compounds Containing Pyrazole and Pyridazine Rings and Their Schiff Bases

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Abstract

A series of pyrazole and pyridazine derivatives and their Schiff bases were synthesized and tested for their antibacterial and antioxidant activities. The prepared compounds were analyzed using infrared, ^{1}H NMR, and mass spectrometry. Studies of the antibacterial and antioxidant compounds showed promising antibacterial and antioxidant activities.

Subject Areas

Organic Syntheses

Keywords

Pyrazole, Pyridazine, Schiff Base, Antioxidant, Antibacterial

1. Introduction

Compounds containing nitrogen, oxygen, and sulfur atoms in their cyclic structure are called heterocyclic compounds with different uses. Heterocyclic systems that include five or six atoms in their structures had a special interest in biological fields [1]. Metronidazole (2-methyl-5-nitroimidazole-1-ethanol) used as an antiamoebic and thiazolobenzimidazole derivative used as an anthelmintic are examples of the biological importance of heterocyclic compounds [2]. Another example of heterocyclic compounds is pyrazoles, which are (1,2-azoles) to be a great scaffold for synthesizing biologically active compounds, vis., antidiabetic, antipyritic activity [3]-[5]. Heterocyclic compounds with pyrazole ring showed anti-inflam-

matory [3], HeLa cervical adenocarcinoma and Fem-x melanoma [6], antimicrobial [7]-[9] antifungal [10] [11]. The azomethine group (-C=N-) is what distinguishes Schiff base compounds. They can be obtained by the reaction between primary amines and aldehydes or ketones during condensation. Schiff base compounds and some of their complexes of various types were proven to have particular organic activity, such as antiproliferative and anticorrosive effects [12]-[15]. Additionally, a noteworthy category made up of nitrogen-oxygen-sulfur Schiff base heterocyclic molecules have proven their effectiveness across multiple domains, such as anti-inflammatory effects [16], the ability to fight viruses [17], bacterial infections [18] [19], acting as antioxidants, preventing or fighting tumors or fungi and even providing relief from fever-related symptoms [20]-[26]. Hetero cyclic compounds which have pyrazole and pyridazine moiety played great importance in medicine, industry, and biochemistry, so here we synthesized novel compounds containing pyrazole and pyridine with their Schiff bases. The prepared compounds were checked out for their structures using different methods.

2. Experimental

2.1. Materials

Hydrazine hydrate, vanillin, ethyl and ethyl aceto acetate were obtained commercially from Aldrich Chemicals. The solvent was reagent grade and was used as received: dry ethanol and methanol dimethylformamide (DMF) and dimethylsulphoxide (DMSO).

Malanonitrile, piperidine and para-amino benzoic acid were obtained commercially from Aldrich and fluke Chemicals.

2.2. Instrumental

An electro thermal melting point is used in measuring melting points for the prepared compounds. All IR spectra for ligand and its metal complexes were taken on Fourier-transform infrared spectra using the KBr disc technique on a JASCO410 FTIR spectrophotometer. UV-Visible absorption spectra were measured using a Pye-Unicam 8800 a UV-Visible with a dip-type cell scanning spectrophotometer. The recording of 1HNMR spectro of the prepared compounds was performed on Varain Gemini-200 spectrometer (200 MHZ) and (300 MHZ) Al Mansoura university. Mass Spectra were recorded on a Shimadzu QP-2010 Plus Mass Spectrometer at the Micro Analytical Center, Azhar University. Microbiological analysis was carried out by the Microanalytical center, Faculty of Science, Sana'a University.

Antioxidant analysis was carried out by the Organochemical Center, Faculty of Science, Sana'a University.

2.3. Synthesis of Ethyl 4-Aminobenzoate (1) [27]

Para amino benzoic acid (5 g) was added to 95% ethanol and 5 ml of concentrated sulfuric acid in RBF. Under reflux for two hrs. the mixture was heated. Then, the

resulting solution was transferred into 500ml beaker, 60 ml of 10% sodium carbonate was added to neutraize the acidic solution. The prepared compound was extracted by ether. Add 5 ml of water and chill on ice. The white crystals are then filtered off.

2.4. Synthesis of 4-Aminobenzohydrazide (2) [28]

A solution of 10 ml of hydrazine hydrate and 4-aminoethylbenzoate (1) (1.65 g, 0.01 mol) in absolute ethanol (30 ml) was refluxed for 4 hours. The resulting precipitate is then filtered and recrystallized from ethanol.

2.5. Synthesis of 4-Aminophenyl-3-Hydroxy-5-Methyl-1H-Pyrazol-1-Ylmethanone Compound PY1

A solution 13 ml of 0.1 moles of ethyl acetoacetate, 1.51 g of 0.01 moles of 4-amino-benohydrazide, and 2 ml of glacial acetic acid were heated in a water bath for a period of 4 hours with stirring from time to time with the help of a glass rod. Then, the resulting heavy reddish liquid was allowed to cool to room temperature, and then washed thoroughly with ether. Subsequently, the solid yellow powder was filtered out, dried, and recrystallized from ethanol with a yield of 46%, melting point < 300˚C.

2.6. Synthesis of (4-((4-Hydroxy-3-Methoxybenzylidene)Amino) Phenyl) (3-Hydroxy-5-Methyl-1H-Pyrazol-1-Yl) Methanone Compound PY2

A mixture of 0.151 g (0.001 moles) of vanillin and 0.217 g (0.001 mol) of compound 3 was dissolved in DMF and stirred with crystals of para toluene sulphonic acid(p-TsOH). The reaction mixture was then refluxed for a period of 24 hours, resulting in the formation of a yellow powdery precipitate which was recrystallized from ethanol with a yield of 45%. The melting point of the product was determined to be 118˚C - 120˚C.

2.7. Synthesis of Schiff Base of N-(4-Hydroxy-3-Methoxybenzylidene)-4-((4-Hydroxy-3-Methoxybenzylidene)Amino) Benzo Hydrazide Compound PD1

A yellow Schiff base compound 5 was synthesized through condensation of (0.01 mol) of vanillin and 0.02 mol in DMF (25 ml). The reaction mixture was heated for 24 hours and p-TsOH crystals were added. After evaporating the extra solvent, the yellow Schiff base precipitate was isolated and purified with diethyl ether, resulting in a yield of 86% and the melting point was 249˚C - 250˚C.

2.8. Synthesis of 5-Amino-3-(4-((4-Hydroxy-3-Methoxybenzylidene)Amino)Phenyl)-6-(4-Hydroxy-3-Methoxyphenyl) Pyridazine-4-Carbonitrile PD2

A solution of 0.419 g (0.001 moles) of compound 5 in 20 ml of absolute ethanol was mixed with 0.66 g (0.001 moles) of malononitrile in 10 ml of ethanol. 1 ml of

piperidine was then added to the reaction mixture and the concoction was refluxed for 4 hours. After cooling, the mixture was poured into 30 g of ice, and drops of concentrated HCl were added until the desired acidity was achieved. The result was a brown powdery precipitate which was then filtered and recrystallized from ethanol. The yield was 77% and the melting point was 188˚C - 190˚C.

2.9. Anti-Bacterial Evaluation

The agar well diffusion method was used to evaluate the antimicrobial activity of the prepared compounds [29].

The agar plate surface is inoculated by spreading a volume of the microbial inoculum over the entire agar surface. Then, a hole with a diameter of 5 mm is punched aseptically with a sterile cork borer, and a volume (10 ml) of the antimicrobial compound DMSO solution at a desired concentration of 1000 ppm is introduced into the well. Gentamicin was used as a positive control. The dishes were then incubated at 37˚C for 24 hours, after while zones of inhibition were measured and recorded. The antimicrobial activity interactions were analyzed by measuring the inhibition zones sizes.

2.10. Antioxidant Evaluation

The antioxidant effect study of the prepared compounds using Ferric-Bipyridine-assay (FBRC) method [30].

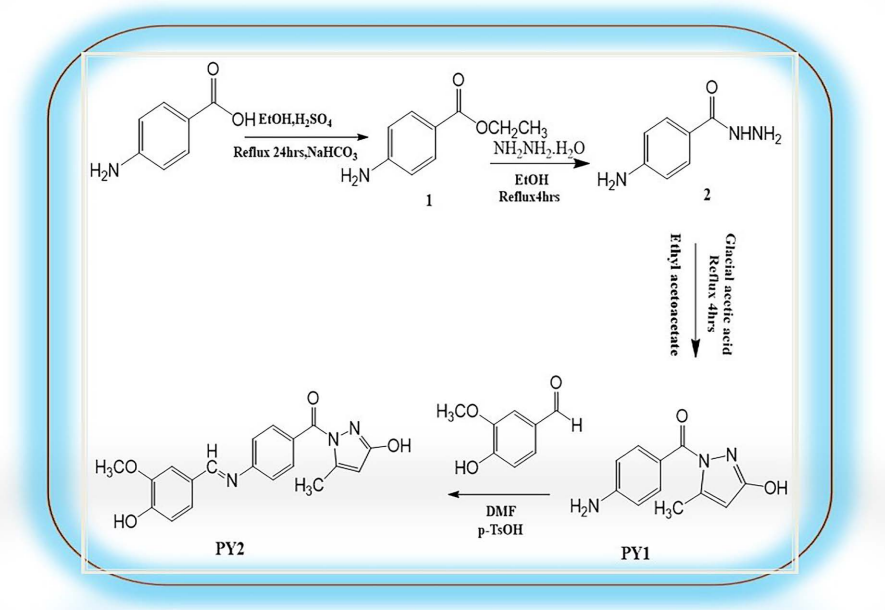
This method is based on the formation of the ferrous Fe^{2+} form of the Fe^{3+} Bipyridine complex through a reduction in low pH (4.5). Measurement of antioxidant activity by monitoring the change in absorption has been taken at 535 nm. The ferric-Bi pyridine solution consists of 2 ml of CH_3COOH/CH_3COONa buffer (300 mmol·L^{-1}) at pH = 4.5, 1 mlof Bipyridine (6.5 mmol·L^{-1}) and 1 ml of $FeCl_3{\cdot}6H_2O$ (10.07 mmol·L^{-1}). 50 µl of each compound dissolved in DMSO (0.01 mmol·L^{-1}) was added, then the volume was made up to 10 ml with deionized water. The blank solution consists of 2 ml of buffer solution (300 mmol·L^{-1}) at pH = 4.5, 1 ml of Bipyridine (6.5 mmol·L^{-1}) and 1 ml of $FeCl_3{\cdot}6H_2O$ then the volume was then made up to 10 ml with deionized water. Measurement of absorbance was taken at 535 nm with a spectrophotometer, relating to both Ascorbic acid and Gallic acid standards. The result of antioxidant power was shown as Ascorbic acid and Gallic acid Mol.l AAE^{-1} or $GAEg^{-1}$ of each compound.

3. Result and Dissection

3.1. Physical Properties of the Prepared Compounds

A new pyrazole and pyridazine heterocyclic compounds were synthesized from chemicals purchased from Aldrich and Fluka chemical. 4-aminophenyl-3-hydroxy-5-methyl-1H-pyrazo-l-yl methanone PY1 was synthesized by mixing of 4-aminobenazohydrazid, ethyl acetoacetate and glacial acetic acid and refluxing for 4 hrs to get 46% yield with (>300˚C).

Treating of PY1 with vaniline given PY2 (4-((4-hydroxy-3-methoxybenzylidene)amino)phenyl)(3-hydroxy-5-methyl-1H-pyrazol-1-yl)methanone to get 45% yield with 118˚C - 120˚C (Scheme 1).



Scheme 1. Synthesis of Pyrazol Derivative and Its Schiff base (PY1-PY2).

A mixture of valine, 4-amino phenyl benzohydrazide, and p-TsOH in DMF was refluxed for 24 hours to get PD1 86% with 249˚C - 250˚C.

Pyridazine derivative PD2 was utilized by refluxing PD1 with malono nitrile in DMF getting 77%, 188˚C - 190˚C (Scheme 2).

3.2. Spectral Analyses of the Prepared Compounds

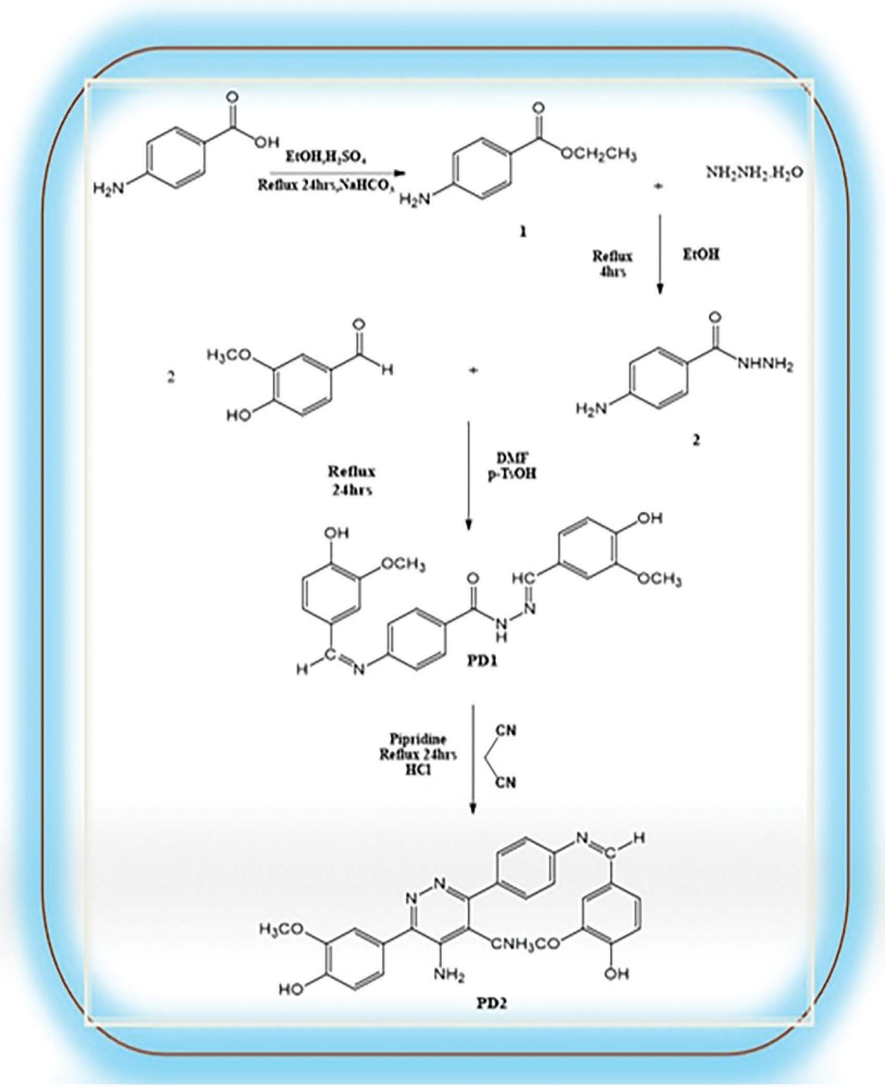
For the prepared compounds PY1 and PY2, we can find that both of them have a signal in the range (3304 - 3500) cm^{-1} and a chemical shift at 10.42 ppm (s, 1H, OH) in 1HNMR spectra for the two compounds.

In mass spectra, the main peak M^+ for (PY1 and PY2) is the same as the calculated molecular weights of both compounds.

The presence of $-NH_2$ in ^{1}HNMR spectra for PY1 at 5.81 (s, 2H, NH_2) and absence of the same group at 1HNMR spectra of PY2, also the presence of -CH=N at 8.35 (s, 1H, CH) ppm for PY2 and not for PY1 confirmed the formation of Schiff base PY2 from PY1.

Likewise, IR spectra for both compounds PD1 and PD2 showed OH groups at the range 3196 - 3244 cm^{-1}. The IR signal for the CN group at 2211 cm^{-1} for PD2 confirms the formation of the pyridazine ring

In ^{1}HNMR spectra the presence of two signals for CH=N at 8.31 ppm (s, 1H, CH) and 9.72 ppm (s,1H, CH) in PD1 and just the appearance of one CH=N at 8.60 ppm (s,1H, CH) for PD2 this confirms the use of one azomethine group in PD1 to form PD2. Also, the appearance of $-NH_2$ at 4.58 ppm.



Scheme 2. Synthesis of pyridazine derivative and its Schiff bases PD1 - PD2.

Mass spectra for PD1 and PD2 showed that the M^+ of them is the same as the calculated molecular weights for the same compounds.

3.3. Biological Activity Antimicrobial Activity of Pyrazole and Pyridazine Derivatives and Their Schiff Bases (PY1, PY2, PD1, PD2)

For *in vitro* antimicrobial activity, the investigation compounds PY1, PY2, PD1, and PD2 were tested against the bacteria Staphylococcus aureus and Staphylococcus aureus an examples of Gram-positive bacteria. Escherichia coli as example of gram-negative bacteria.gentamycin we used as a standard drug for comparison (See Table 1).

The investigation results reveal that most of the newly synthesized compounds exhibited significant activity against Escherichia coli, Staphylococcus aurous, and Salmonela Typhi bacteria. Compounds PY1 and PY2 showed more admirable

Table 1. Antimicrobial activity of pyrazole and pyridazine derivatives and their Schiff bases (PY1, PY2, PD1, PD2) (conc. 1×10^{-3} ppm) bases.

Compound no	The volume of the sample (µml)	Gram-negative (mm)	Gram-positive	
			Staphylococcus aureus (mm)	*Salmonelatyphi (mm)*
PD1	10	14 (+3)	-	1 (+1)
PD2	10	10 (+2)	-	4 (+1)
PY1	10	6 (+2)	2 (+1)	-
PY2	10	2 (+1)	-	2.5 (+1)
Gentamycin	10	9	9	8

activity against the three types of bacteria when compared to the standard drug Gentamycin. Particularly compounds PY1 and PY2 have shown the highest zone of inhibition against Escherichia coli 1000 ppm concentration. Compound PY2 showed a moderate effect against Escherichia coli. Compound PD1 had a moderate effect on *E. coli* bacteria which was less than the standard drug Gentamycin, but it was the only compound that affected Staphylococcus aureus bacteria. Compound PD2 had less effect on the bacteria.

3.4. Antioxidant Evaluation of Pyrazole and Pyridazine Derivatives and Their Schiff bases (PY1, PY2, PD1, PD2)

The antioxidant activity for the synthesized compounds was evaluated using Ferric-Bipyridine Assay and results were summarized in Table 2.

Table 2. The calculated mol/l equivalent of GAE and AAE /1g of compounds (PY1, PY2, PD1, PD2).

Sample no		PY1		PY2		PD1		PD2	
		1	2	1	2	1	2	1	2
Equivalent ($moll^{-1}$ Ascorbic acid equivalents or Galic acid (equivalents 1^{-1} g) of substances.	Ascorbic Acid Equivalents	0.1390	0.1388	0.07848	0.07557	0.4824	0.4635	0.4368	0.4948
	Gallic Acid Equivalents	0.4054	0.4046	0.2288	0.2203	1.4064	1.3513	1.2736	1.4426
Average (x̄)	Ascorbic Acid Equivalents	0.1389		0.07702		0.4729		0.4658	
	Gallic Acid Equivalents	0.4050		0.2245		1.3788		1.3581	
SD	Ascorbic Acid Equivalents	$1.8598 * 10^{-4}$		2.0548×10^{-3}		0.0133		0.0410	
	Gallic Acid Equivalents	$5.5154 * 10^{-4}$		6.00×10^{-3}		0.03828		0.1199	
RSD	Ascorbic Acid Equivalents	1.3386×10^{-3}		0.02666		0.0283		0.0880	
	Gallic Acid Equivalents	1.3618×10^{-3}		0.0267		0.0282		0.0882	
RSD %	Ascorbic Acid Equivalents	0.13386		2.666		2.83		8.804	
	Gallic Acid Equivalents	0.1361		2.673		2.82		8.82	

All the prepared compounds showed different ranges of antioxidant activity, and this can be related to the high amount of antioxidant groups in the prepared compounds. The results presented in Table 2 showed that the highest antioxidant capacity was for compound PD1 which had the value of 0.47229 $moll^{-1}$ AAE 1 g^{-1} of compound PD1 and 1.3788 GAE·1 g^{-1} of compound PD1, this is due to the presence of many antioxidant groups like NH2 and OH, which decreased the evaluation of the free radical. Compound PD2 had the value of 0.4658 mol/l AAE/1g of PD2 and 1.3581 $moll^{-1}$ GAE·1 g^{-1} of compound PD2, which is less than its starting compound PD1, this is due to the involvement of NH_2 and NH group in cyclization formation in compound PD1 which made it less effective as an antioxidant. From Table 2, we can notice that PY1 has an antioxidant capacity of 0.1389 mol/l AAE·1 g^{-1} of compound PY1 and 0.405 $mol{\cdot}l^{-1}$ GAE·1 g^{-1} of compound PY1, those values were more than compound PY2 which had an antioxidant capacity of 0.07702 $mol{\cdot}l^{-1}$ AAE·1 g^{-1} of compound PY2 and 0.2245 $mol{\cdot}l^{-1}$ AAE·1 g^{-1} of compound PY2. Finally, we can arrange the antioxidant capacity of compounds (PY1, PY2, PD1, PD2) as follows: Antioxidant equivalents of ascorbic acid and Gallic acid compound (PD1) > compound (PD2) >compound (PY1) > compound (PY2).

Conflicts of Interest

The authors declare no conflicts of interest.

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