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Synthesis of some 4- substituted-1- phenylpyrazole-5-one derivatives and study their biological activity

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Abstract

In this study, a series of 4-[4-(3-Bromo-2oxo-4- substituted-phenylazetidin-1-yl) phenyl amino]-1,2-dihydro-2-ethyl-3- methyl-1- phenylpyrazole-5-one (IVA-H) was synthesized by Cyclocondensation of various Schiff bases of 4-[(4-aminophenyl) amino]-1-ethyl-5-methyl-2-phenyl-1,2 -dihydro-3H-pyrazol-3-one with bromo- acetyl bromide in presence of triethylamine. various Schiff bases were synthesized by condensation of 4 -[(4-aminophenyl) amino]-1- ethyl-5-methyl-2- phenyl-1,2-dihydro - 3H-pyrazol-3-one with various arylaldehydes (IIA-H). The structures of synthesized compounds were confirmed by Mass, IR, ¹H NMR, and elemental analyses. In addition, the synthesized compounds were screened for their antimicrobial activities against *S. aureus*, *P. aeruginosa*, *B. subtilis*, *E.coli* and *C. albicans*, *A. niger* (Fungi). The results revealed that some of the obtained compounds exhibit anti-bacterial activity, that showed significant activity when compared with that of the commercially available.

Keywords: Phenylpyrazole-5-one, Schiff base, Anti-bacterial activity, Antifungal agent.

Introduction

Compounds derived 4- substituted phenylpyrazole-5-one have continued to receive considerable attention due to their pharmaceutical importance and high biological activity [1-3]. They also enjoy a range of applications as a substructure in dye chemistry and synthesis [4]. Hydrazones and other Schiff bases are among the most studied 4- substituted phenylpyrazole-5-derivatives, more so considering the fact that molecules with hydrazine moiety have been noted for their biological activity [5], especially as potential inhibitors for many enzymes [6]. The interest in the chemistry of 4- substituted phenylpyrazole-5-one Schiff bases stems from their interesting legating ability due to the presence of multi electron rich donor atoms [7-9]. This is augmented by their tendency to exist in various tautomeric structures [10-12]. The ability of this class of compounds to form coordination compounds with a wide range of transition metals has been utilized in analytical chemistry, where they have been used as effective chelating and extracting reagents for many metal ions [13-15]. The literature is replete with studies of 4- substituted phenylpyrazole-5-one Schiff bases and their obtained complexes. However, the studies of biological activities of these compounds and their complexes is largely restricted to studies on microorganism. Some reports are available on study their anticancer properties [16, 17]. The heterocycles compounds are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity [18]. The most widely used antibiotics such as penicilline, cephalosporine, c, aztreonam, thienamycine and the nocardicines all contain β -lactam rings [19]. The long-term use of β -lactam antibiotics exerts selective pressure on bacteria and permits the proliferation of resistant organisms [20]. A comparative study of current antibiotics with those from previous decades shows an alarming increase in bacterial resistance to β -lactam antibiotics [21]. The development of several synthetic and semi synthetic β -lactam antibiotics by the pharmaceutical industry was due to the growing resistance of bacteria towards the β -lactam antibiotics and the need for medicines with a more specific antibacterial activity [22]. An interesting group of β -lactams are the monocyclic β -lactams, which molecules that do not contain another ring fused to the β -lactam one. Azetidinones, which are part of the antibiotic structure, are known to exhibit interesting biological activities [23]. A large number of 3-bromo monocyclic β -lactams possess powerful antibacterial, antimicrobial, anti-inflammatory, anticonvulsant and antitubercular activity [24-28]. They also function as enzyme inhibitors and are effective on the central nervous system [29]. Antipyrene Derivative was reported in literature

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as antitumor [30], antimicrobial [31], antiviral [32] and analgesic drugs [33]. In this paper, we report synthesis and characterization of 4-[4-(3-bromo-2-oxo-4-substituted-phenylazetididin-1-yl) phenyl amino]-1, 2-dihydro-2-ethyl-3-methyl-1-phenylpyrazole-5-one. Antimicrobial activity of synthesized compounds was discussed.

Materials and Methods

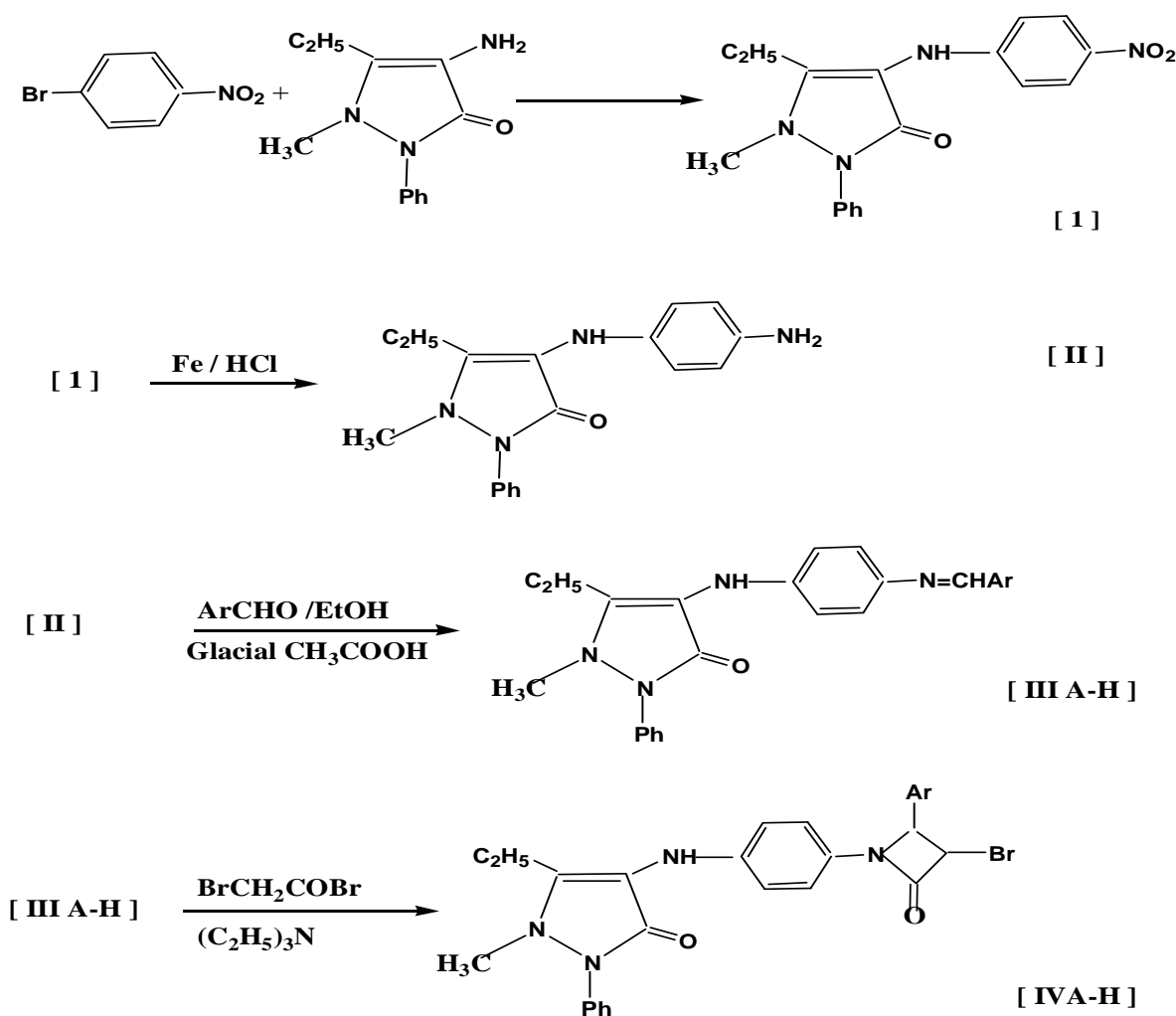
All chemical reagents used in this study were purchased from Aldrich (Milwaukee, WI, USA) and E. Merich Darmstadt, Germany. All solvents were purified according to standard procedures. All of the synthesized 4-[4-(3-bromo-2-oxo-4-substituted-phenylazetididin-1-yl) phenyl amino]-1, 2-dihydro-2-ethyl-3-methyl-1-phenylpyrazole-5-one (IV_{A-H}) were analyzed by Mass, IR, ¹H NMR, and elemental analysis. Mass spectra were recorded on Shimadzu LCMS 2010A. IR spectra were recorded on Nicolet 740 Fourier Transform Infrared (FTIR) spectrometer. ¹H NMR-spectra were recorded on a Varian Gemini 200 and 300 MHz instrument in CDCl₃ and DMSO-d₆ using Tetramethylsilane (TMS) as an internal standard. Melting Points measured using a Buchi-510 apparatus and were uncorrected. All instrumental analyses

were performed at Bin Hayyan Laboratory (Aqaba Special Economic Zone- Jordan).

Experimental

1. Experimental Procedure for the Synthesis of 4-[4-(3-Bromo-2-oxo-4-substituted - phenylazetididin-1-yl)phenyl amino]-1,2-dihydro-2-ethyl-3- methyl-1- phenyl pyrazole - 5-one (IV_{A-H})

(0.02 mol) mono bromoacetyl bromide was added drop wise at room temperature to the stirred solution of (0.01 mol) substituted Schiff bases (III_{A-H}), (0.02mol) triethyl amine in 75 ml dry dioxane (Scheme 1). The reaction mixture was stirred for 45 minutes, then refluxed for 12 hours at 120 °C. After completed of reaction inferred by (TLC, eluent hexane/ ethyl acetate 30:70), the solvent was removed under reduced pressure and extracted with 50 ml ethyl acetate. Organic layer was washed in 25-30 ml water and dried over sodium sulfate. The perception was filtered off and purified by recrystallization from ethanol, which gave the 4-[4-(3-Bromo-2-oxo-4-substituted - phenylazetididin-1-yl) phenyl amino]-1,2-dihydro-2-ethyl-3- methyl-1- phenyl pyrazole -5-one (IV_{A-H}) in 65-86% yields.



Scheme 1. Roue Synthesis Compounds in this study.

Where, Ar =benzaldehyde [IV_A], p.bromobenzaldehyde [IV_B], p-fluorobenzaldehyde [IV_C], p-hydroxybenzaldehyde [IV_D], p-methoxybenzaldehyde [IV_E], o-hydroxybenzaldehyde [IV_F], o-bromobenzaldehyde [IV_G], m-nitrobenzaldehyde [IV_H].

2. Spectral Data for 4-[4-(3-Bromo-2oxo-4-substituted -phenylazetididin-1-yl) phenyl amino]-1,2-dihydro-2-ethyl-3-methyl-1- phenyl pyrazole -5-one (IV_{A-H})

4- substituted-1- phenylpyrazole-5-one (IV_A)

Solid; Molecular formula (C₂₇H₂₅BrN₄O₂), Yield: 74%, m.p: 228-230; MS(m/z) : M⁺ calculated :517.35, found 517. IR (KBr, cm⁻¹):651 (C-Br str.), 1345 (HC-N), 1614 (C=O), 1778 (C=O str.lact.ring), 3430-3445 (N-H str.). ¹H NMR (DMSO-d₆): δ (ppm) = 4.1 (1H, Ar-C-NH), 1.91 (3H, CH₃), 2.67 (3H, CH₃-N), 5.24 (1H,-N-CH-C), 5.70 (1H-CH- Br), 7.15 (9H, Ar-H, J=10Hz), 7.65 (4H-Ar-H, J=10Hz). Elem. anal. Calculated: C: 62.65%, H: 4.86%, N: 10.82%, Found: C: 62.72%, H: 4.78.3%, N: 10.74%.

4- substituted-1- phenylpyrazole-5-one (IV_B):

Solid; Molecular formula (C₂₇H₂₄Br₂N₄O₂), Yield: 68%, m.p: 257-259; MS(m/z) : M⁺ calculated :596.25, found 596. IR (KBr, cm⁻¹):651 (C-Br str.), 1345 (HC-N), 1614 (C=O), 1778 (C=O str.lact.ring), 3430-3445 (N-H str.). ¹H NMR (DMSO-d₆): δ (ppm) = 4.1 (1H, Ar-C-NH), 1.91 (3H, CH₃), 2.67 (3H, CH₃-N), 5.24 (1H,-N-CH-C), 5.70 (1H-CH- Br), 7.15 (9H, Ar-H, J=10Hz), 7.65 (4H-Ar-H, J=10Hz). Elem. anal. Calculated: C: 54.26%, H: 4.06%, N: 9.32%, Found: C: 54.32%, H: 4.03%, N: 9.24%.

4- substituted-1- phenylpyrazole-5-one (IV_C):

Solid; Molecular formula (C₂₇H₂₄BrFN₄O₂), Yield: 78%, m.p: 233-235; MS(m/z) : M⁺ calculated :535.36, found 535. IR (KBr, cm⁻¹): 1310 (C-F str.), 1345 (HC-N), 1614 (C=O), 1778 (C=O str.lact.ring), 3430-3445 (N-H str.). ¹H NMR (DMSO-d₆): δ (ppm) = 4.1 (1H, Ar-C-NH), 1.91 (3H, CH₃), 2.67 (3H, CH₃-N), 5.24 (1H,-N-CH-C), 5.70 (1H-CH- Br), 7.15 (9H, Ar-H, J=10Hz), 7.65 (4H-Ar-H, J=10Hz). Elem. anal. Calculated: C: 60.52%, H:4.48%, N: 10.46%, Found: C: 60.42%, H: 4.38%, N: 10.40%.

4- substituted-1- phenylpyrazole-5-one (IV_D):

Solid; Molecular formula (C₂₇H₂₅BrN₄O₃), Yield: 80%, m.p: 242-244; MS(m/z) : M⁺ calculated :533.45, found 533. IR (KBr, cm⁻¹):651 (C-Br str.), 1345 (HC-N), 1614 (C=O), 1778 (C=O str.lact.ring), 3430-3445 (N-H str.), 3450 (O-H str.). ¹H NMR (DMSO- d₆): δ (ppm) = 4.1 (1H, Ar-C-NH), 1.91 (3H, CH₃), 2.67 (3H, CH₃-N), 5.24 (1H,-N-CH-C),5.40(1H-Ar-OH), 5.70 (1H-CH- Br), 7.15 (9H, Ar-H, J=10Hz), 7.65 (4H-Ar-H, J=10Hz). Elem. anal. Calculated: C: 60.26%, H: 4.38%, N: 10.32%, Found: C: 60.12%, H: 4.23%, N: 10.14%.

4- substituted-1- phenylpyrazole-5-one (IV_E):

Solid; Molecular formula (C₂₈H₂₈BrN₄O₃), Yield: 86%, m.p: 274-276; MS(m/z) : M⁺ calculated :532.70, found 532. IR (KBr, cm⁻¹):651 (C-Br str.), 1210 (C-O str.), 1345 (HC-N), 1614 (C=O), 1778 (C=O str.lact.ring), 3430-3445 (N-H str.). ¹H NMR (DMSO- d₆): δ (ppm) = 4.1 (1H, Ar-C-NH), 1.91 (3H, CH₃), 2.67 (3H, CH₃-N),3.80 (3H,OCH₃),5.24 (1H,-N-CH-C), 5.70 (1H-CH- Br), 7.15 (9H, Ar-H, J=10Hz), 7.65 (4H-Ar-H, J=10Hz) Elem. anal. Calculated: C: 63.12%, H:5.26%, N: 7.89%, Found: C: 63.02%, H: 5.13%, N: 7.74%.

4- substituted-1- phenylpyrazole-5-one (IV_F):

Solid; Molecular formula (C₂₇H₂₅BrN₄O₃), Yield: 72%, m.p: 255-257; MS(m/z) : M⁺ calculated :533.45, found 533. IR (KBr, cm⁻¹):651 (C-Br str.), 1345 (HC-N), 1614 (C=O), 1778 (C=O str.lact.ring), 3430-3445 (N-H str.), 3450 (O-H str.). ¹H NMR (DMSO- d₆): δ (ppm) = 4.1 (1H, Ar-C-NH), 1.91 (3H,

CH₃), 2.67 (3H, CH₃-N), 5.24 (1H,-N-CH-C),5.40(1H,Ar-OH), 5.70 (1H-CH- Br), 7.15 (9H, Ar-H, J=10Hz), 7.65 (4H-Ar-H, J=10Hz). Elem. anal. Calculated: C: 62.65%, H: 4.86%, N: 10.82%, Found: C: 62.72%, H: 4.78.3%, N: 10.74%.

4- substituted-1- phenylpyrazole-5-one (IV_G):

Solid; Molecular formula (C₂₇H₂₄Br₂N₄O₂), Yield: 72%, m.p: 264-266; MS(m/z) : M⁺ calculated :597.25, found 597. IR (KBr, cm⁻¹):651 (C-Br str.), 1345 (HC-N), 1614 (C=O), 1778 (C=O str.lact.ring), 3430-3445 (N-H str.). ¹H NMR (DMSO-d₆): δ (ppm) = 4.1 (1H, Ar-C-NH), 1.91 (3H, CH₃), 2.67 (3H, CH₃-N), 5.24 (1H,-N-CH-C), 5.70 (1H-CH- Br), 7.15 (9H, Ar-H, J=10Hz), 7.65 (4H-Ar-H, J=10Hz). Elem. anal. Calculated: C: 54.26%, H: 4.06%, N: 9.32%, Found: C: 54.32%, H: 4.03%, N: 9.24%.

4- substituted-1- phenylpyrazole-5-one (IV_H):

Solid; Molecular formula (C₂₇H₂₄BrN₅O₄), Yield: 72%, m.p: 264-266; MS(m/z) : M⁺ calculated :562.15, found 562. IR (KBr, cm⁻¹):651 (C-Br str.), 1325-1340 (NO₂), 1345 (HC-N), 1614 (C=O), 1778 (C=O str.lact.ring), 3430-3445 (N-H str.). ¹H NMR (DMSO- d₆): δ (ppm) = 4.1 (1H, Ar-C-NH), 1.91 (3H, CH₃), 2.67 (3H, CH₃-N), 5.24 (1H,-N-CH-C), 5.70 (1H-CH- Br), 7.15 (9H, Ar-H, J=10Hz), 7.65 (4H-Ar-H, J=10 Hz). Elem. anal. Calculated: C: 57.66%, H: 4.26%, N: 9.96%, Found: C: 57.52%, H: 4.13%, N: 9.84%.

Antimicrobial activity

The antimicrobial and anti-fungal activities of the synthesized compounds were determined against four bacteria *S. aureus*, *P. aeruginosa*, *B. subtilis*, *E.coli* and *C. albicans*, *A. niger* (fungi), by measuring zone of inhibition (mm). Results of the antimicrobial tests are presented in (Table 1). The antimicrobial activity was performed by Agar diffusion method at the concentration level of 250 µg/ml. Ciprofloxacin and Ketoconazole as standard drugs at concentration of 250 µg/ml. Nutrient agar was used as culture media for antifungal activity and DMSO as control.

Table 1: *In vitro* antimicrobial activity of the test compounds (IV_{A-H}) and evaluation of the inhibition zone (mm).

Compound	S. aureus	P. aeruginosa	B. subtilis	E. coli	C. albicans	A. niger
IV _A	13	11	11	10	12	11
IV _B	12	13	10	12	11	12
IV _C	14	12	13	09	10	11
IV _D	18	17	16	15	15	14
IV _E	21	20	18	17	19	18
IV _F	17	16	16	14	13	14
IV _G	11	13	10	11	12	10
IV _H	12	15	14	10	11	11
Ciprofloxacin	25	25	25	26	-	-
Ketoconazole	-	-	-	-	24	27
DMSO (cont.)	-	-	-	-	-	-

Results and Dissuasion

Cyclocondensation of various Schiff bases of 4-[(4-aminophenyl) amino]-1-ethyl-5-methyl-2-phenyl-1,2 -dihydro-3H-pyrazol-3-one with bromo- acetyl bromide in presence of triethylamine gives 4-[4-(3-Bromo-2oxo-4-substituted-phenylazetididin-1-yl) phenyl amino]-1,2-dihydro-2-ethyl-3- methyl-1- phenylpyrazole-5-one (IV_{A-H}). Synthesized compounds were confirmed by TLC, IR, ¹H NMR, and elemental analysis. Melting Points (m.p) and yields have been identified for each of these compounds. The mass spectra

showed the molecular weights apart from fragmentation profile. The spectra data (IR, ¹H NMR,) confirmed the formation of 4-[4-(3-Bromo-2oxo-4-substituted-phenylazetid-1-yl) phenyl amino]-1,2-dihydro-2-ethyl-3-methyl-1-phenylpyrazole-5-one (IV_{A-H}). All compounds are stable solids, dissolved in DMSO at room temperature. The titled compounds were confirmed by IR spectral data showing characteristic at 1345 (HC-N), 1614 (C=O), 1778 (C=O str.lact.ring), 3430-3445 (N-H str.) and 651 cm⁻¹ (C-Br). In the ¹H NMR spectra of the synthesized compounds showing characteristic δ (ppm)= 5.67 (CH₃-N), 5.70 (C-Br), 7.15 (Ar-H). Since our titled the obtained compounds are known to possess antimicrobial activity, the compounds were screened for their antibacterial and antifungal activity by known cup-plate method. Some of the obtained compounds exhibit antibacterial activity, that showed significant activity when compared with that of the commercially available. The difference in activity between the compounds which is due to the presence of substituents in the phenyl group of the molecule.

Conclusion

The heterocycles compounds are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity [18]. Several organic compounds containing a fused many membered heterocyclic ring, i.e., 3- substituted phenylpyrazole-5-ones and 4- substituted phenylpyrazole-5-ones make up a board class that attached attention in the past few years owing to its wide range of biological activities, especially antimicrobial [31]. It is interesting to note from chemical literature that various new pharmacophores like Azetidones, which are part of the antibiotic structure, are known to exhibit interesting biological activities [23]. They also enjoy a range of applications as a substructure in dye chemistry and synthesis [4]. In this study we synthesized some 4- substituted phenylpyrazole-5-ones and studied their antimicrobial activity. The yields of synthesized compounds were in the range of 65-86%. The purity of the synthesized compounds were assessed by TLC and melting points. Some compounds showed biological activity (Table 1), especially compounds (IV_{D,F,E}). Hence, it can be concluded that the 4- substituted phenylpyrazole-5-one derivatives can potentially be developed into useful, interesting heterocyclic system, with enhanced activity.

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