Utilization derivatives of 4 - [4-(acetylamino)phenyl]-2 - (3,5 dimethyl - 1 H-pyrazol -1-yl)-3-hydroxy-4-oxobutanoic acid in Heterocyclic Synthesis and Study of Their Biological Activities

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ABSTRACT

The aim of this research the derivatives of 4- [4-(acetylamino)phenyl]- 2 -(3,5dimethyl- 1 H-pyrazol -1-yl)-3-hydroxy-4-oxobutanoic acid was used synthesize heterocyclic compounds. These heterocyclic compounds could be used as the main feedstock to prepare heterocyclic compounds (6,5 membred ring) including thiadiazolo, imidazole and pyridazinone derivatives. The effect of nucleophilic and electrophilic reagents on the resulting pyridazinones compounds was studied. Through preliminary analyzes of the compounds prepared in the research and spectroscopic data which obtained their structures were proved, and it have biological activities.

Keywords: acetylamino phenyl, oxobutanoic acid, imidazole, thiadiazole, imidazo thiadiazole, pyridazinon.
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1. INTRODUCTION

(2E)-4-[4-(acetylamino)phenyl]-4-oxobut-2-enoic acid has been shown that the substitution pattern on the aroyl acid molecule affects the acid and oxarin derived [1] and it is possible to reduce the activation of the double bond, Half-wave reduction potentials [2] Anillustration of some good relationships with Hammett,sigma value will be held, There are good attempts to obtain using frontier orbitals of the molecules [3] which are selective for integrase S-1360 [4] which is used as (H1V1) inhibitor [5]. Spiroindoline [6] and imidazoline [7] derivatives as well as spironolactone, are effective in treating high blood pressure without increased secretion of aldosterone [8, 9] the specific aldosterone antagonist, approved by the iunch and band administration, has been shown to have a much lower affinity for the male hormone and progesterone receptors, and this reduces the incidence of sexual disturbances [10]. A useful treatment for patients with weak heart and treating people with diabetes [11]. In particular, ketoconazole [12,13] which have been successful as antifungal agents and when spiroimidazol derivatives [14] 3-phenylamino-(substituted phenyl) isoxazolines [15]. Anti-fungal outside the body, as well as mononuclear blood cells to phytohemaglutinin A (PHA) [16]. The new class of isoxazole derivative were indicated [17]. The new oxadiazole compound, which contains the terminal carboxylic group of 3-aroyl propionic acids into oxadiazole nucleus. It is considered as agitating factors and passive at times. The antibacterial, antifungal and antitubercular activity. Also, screened for pyridazin-2-ylmethyl-2-substituted1,3,4-oxadiazole [18]. The effects on the central nervous system (CNS) of mice were studied using 1,3,4 thiaadazole derivatives [19]. Imidazolo oxazole derivatives [20] via treatment of imidazole derivatives with oxirane have been tested for antimycobacterial activity.

2. EXPERIMENTAL

A Stuart electric melting point apparatus was used to determine of all melting points. Microanalytical Center, National Research Center, Cairo, Egypt carried out all elemental analysis, FTIR (Fourier transformer infrared) Elementary Viro El Microanalysis IR spectra (KBr) have been
recorded on the FT-IR 400D infrared spectrometer using the OMNIC software and are reported to have absorption frequencies in cm$^{-1}$ and $^1$HNMR spectra recorded on the 400 MHz Bruker spectrophotometer using the internal standard TMS and the residual deuterated solvent signals $\delta= 7.26$ ppm for the CDCl$_3$ and $\delta= 2.51$ ppm for the DMSO-d$_6$. Where applicable, [DEPT 135 NMR spectroscopy has been used to assist signal allocation in the H and CNMR spectra]. The mass spectrum was recorded using the electron ionisation technique on the Shimadzu Gas chromatography mass spectra (GCMS-QP-1000 EX) mass spectrometer at 70 e.V. Homogeneity was tested by Thin layer chromatography (TLC) of all synthesized compounds.

**Synthesis of 3-[[4-(acetylamino)phenyl] carbonyl] oxirene-2- carboxylic acid (2).**

A solution of acid 1 (0.1 mol) in methanol (25 mL) and acetone (20 mL) was reacted with 8% sodium hydroxide solution (15 mL) and hydrogen peroxide (30% 10 mL) was added drop by drop. The solution was shaken and heated at 90°C for 3 h, then allowed to stand at ambient temperature (25-30 °C) for 24 hours, then water was added and the dilute dilute hydrochloric acid (HCl) solution was acidified (pH =3). This material extracted using non polar solvent such as ether, the mixture was removed and the solid isolated from the required solvent was crystallized to give 2.
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Synthesis of 2 2-[(5-benzyl-1,3,4-thiadiazol-2-yl)amino]-3-hydroxy-4-oxo-4(4-acetaminophenyl)- butanoic acid (3).

A solution of 2 (0.01 mol) and 3,5-dimethyl-1H-pyrazole (0.01mol) oxirane derivatives in (30mL) ethanol was heated at 90°C for 3 hours under reflux. After concentration and cooling, the solid that separated was filtered off and crystallized from the necessary solvent (acetone) to give 3.

Synthesis of 4-[(5-benzyl-1,3,4-thiadiazol-2-yl)amino]-5-hyd roxy-6-(4-acetamidephenyl)-4,5-dihydropyridazin-3(2H)-one (4).

Hydrazine hydrate or phenyl hydrazine (0.01 mol) was treated with a solution of acid 4(0.01mol) in ethanol (20 mL) and heated for 3 h under reflux. The solids that separated after concentration and cooling were crystallized, supplying the pyridazinones with the required compound 4.
Synthesis 4-[(5-benzyl-1,3,4-thiadiazol-2-yl)-3-phenyacetami-de]-2,3,4,5-tetrahydropyridazin-3,5-diyl bis (chloroacetate (5)).

A solution of 4 (0.01 mol) in pyridine (30 mL) and chloroacetylchloride (0.01 mol) was refluxed for 2 h. The cooled mixture was poured on ice/cold dil. HCl. The solid that separated in ice/cold dil. HCl was crystallized, from the suitable solvent to give 5.

Synthesis of 4-[(5-benzyl-1,3,4-thiadiazol-2-yl)-3phenylacetami-de]-2,3,4,5-tetrahydropyridazin-3,5-diyl bis(hydrazinylaceta-te) (6).

The 5 (0.01 mol) solution in ethanol (20 mL) and hydrazine hydrate (01 mol) was heated for 2 hours under reflux. After concentration and cooling, the solid that separated was filtered off and crystallized from ethanol to give 6.

The schematic synthesis of thiadiazolo, imidazole and pyridazinone derivatives.
3. RESULTS AND DISCUSSION

The structure of compound 2 was inferred from.

Yield 74%. Mp 180-182 °C. Its IR(KBr) spectrum revealed strong absorption bands at 1278, 1630, 1687, 1710, (2524, 2649, 2889 different bands), (CO) 1HNMR spectrum (CDCl₃): δ 2.50 (s, 3H, CH₃), 6.92-6.98 (2dd, 1Ha and 1Hb diastereotopic protons, J=14.4 and 9.1), multiplet at 7.31–7.71 assigned for 4ArH aromatic protons, singlet 8.2 acidic proton [21-25] which exchanged in D₂O and for C₁₂H₁₁NO₅  C 57.38, H 4.41; found C 57.22, H 4.21. MS: m/z 249[M⁺], 205[M⁺- CO₂][M+H]⁺250 m/z, 163[205 -COCH₃].

The structure of compound 3 was inferred from.

Yield 62%. Mp 200-202 °C. Its IR spectrum revealed strong absorption bands at 1630, 1685, 2526, 2650, 3200, 3400 cm⁻¹ attributable to ν max of
two carbonyl group, ν NH chelated or bonded OH. The 1H-NMR spectrum of compound 3 [26] in DMSO (d6) should signals at ppm 2.4 (s, 3H, H3CCONH), 4, 12 (s, 1H), methine proton attached to nitrogen), 4.13 (s, 1H) methine proton attached to oxygen), 8.2 (brond singlet 2H, NH proton) 12.5 (broad singlet 2H, OH protons) EI-MS exhibits m/z = 440 [M+], 420 (M+ - H2O, m/z= 396 (M+ - CO2).and Anal. Calc for C21H20N4O5S C57.24; H 4.56:C57.26; H 4.54.

The structure of compounds 4 was inferred from.

Yield 55%. Mp 212-210 Cº. IR(KBr) 1603,1687(CO), 3268 (NH) and Anal. Calc. for C21H22N6O2S : C 59.86, H 4.75; found: C 59.98, H 4.79, MS:m/z 420[M+],377[M+ -COCH3]. The 1H-NMR spectrum of compound [27-29] exhibits signals at ppm 2.5 (s, 3H H3C CO), 4.5 (s, 2H, methene protons), 6.63-7.84 (m, 9 H ArH) 8.52- 9.96 (broad singlet 4H, NH and OH protons) exchangeable in D2O).

The structure of the compound 5 was inferred from.

Yield 60%. Mp 188-190 Cº. IR(KBr) 1679,1725,1741 (CO), 3318 (NH) and Anal. Calc. for C26H26N10O2S : C 52.56 , H 4.32, N 13.50 MS:m/z533[M+ -2Cl], ,448[M+- (CH3CO+2ClCH2CO.)

The structure of the compound 6 was inferred from.

Yield 55%. Mp 220-222 Cº. IR(KBr) 1644,1708 (CO), 3320,3188 (NH2,NH).1HNMR (DMSO-d6)δ2.06(s,3H,CH3), 4.12-4.15(s,4H,2CH2-N)6.62-6.76(m,6H,2NHNH2),7.36-7.81(m,9H,Ar-Hand pyridazine), 11.36(brs,1H,NH of acetamido moiety) and Anal. Calc. for C25H30N10O5S (C 51.54, H 5.19, N 24.04; found: C 50.52, H 5.15, N 24.13).

Biological Evaluation

The antimicrobial activity of the synthesized derivatives compounds was tested using the agar diffusion assay. All compounds were tested for activity against Gram - positive and Gram-negative bacteria and selected fungi the strong activity was observed with compounds 2 the active compounds along with Tetracycline and Amphotericin as positive control The results are summarized in Table 1 These analyzes were performed at the center for Microanalysis, Faculty of science, Cairo University.
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Table (1). Antibacterial and antifungal activities of some selected compounds

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<th>Sample</th>
<th>Escherichia coli (G -)</th>
<th>Staphylococcus aureus (G +)</th>
<th>Aspergillus flavus Fungus</th>
<th>Candida albicans Fungus</th>
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<td></td>
<td>Tetracycline Antibacterial agent</td>
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<td></td>
<td>Amphotericin B Antifungal agent</td>
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استخدام مشتقات حمض 4 - [4-(أسيتاأمينو) فينيل]- 2 - (3,5 ثنائي ميثيل - 1H - بيرول -1- يل - 3- هيدروكسي-4- أكسوابيوناتويك) في تحضير مركبات غير متجانسة ودراسة تأثيراتها الحيوية.

مختار المبروك أبورزيزة، خالد احمد الفلو
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الملخص

في هذا البحث تم استخدام مشتقات حمض 4 - [4-(أسيتاأمينو) فينيل]- 2 - (3,5 ثنائي ميثيل - 1H - بيرول -1- يل - 3- هيدروكسي-4- أكسوابيوناتويك) وذلك من خلال معالجة الحمض مع 3,5 ثنائي ميثيل - 1H - بيرازول للحصول على ناتج الاضافة (3) الذي يستخدم لتحضير المركبات غير متجانسة مثل البيريدازينون والفيورانون. وأثبتت التراكيب البنائية للمركبات المحضرة بواسطة أجهزة التحاليل الدقيقة مثل الأشعة تحت الحمراء والرنين المغناطيسي وطيف الكتلة. وكانت لها نتائج إيجابية عند اختبارها بيولوجيا على بعض أنواع البيكتريا و الفطريات.

الكلمات المفتاحية: acetylamino phenyl, oxobutanoic acid, acetylamino phenyl, imidazole, pyridazinon, imidazo thiazole, thiazole thiazole.