synthesis of new compounds from pyridazine derivatives, and preliminary pharmacological study

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***Abstract***

 In this study, pyridazine derivatives were synthesized by starting with paracetamol, also known as para hydroxy acetanilide, which does not require a prescription [1]. The reaction involved the use of metallic sodium and methanol as a solvent, resulting in the formation of p-hydroxy acetanilide sodium salt [2]. Subsequently, compound [2] was reacted with 2-chloro ethyl acetate in DMF as a solvent to yield ethyl-2-(p-acetamido hydroxy) acetate [3]. This compound was further reacted with hydrazine hydrate to obtain the corresponding hydrazide derivatives [4].

The acid anhydride derivatives, compound [4] was reacted with glacial acetic acid as a solvent, leading to the synthesis of compounds [4a-4h]. These newly synthesized compounds were then subjected to antimicrobial testing against various microorganisms, including bacterial strains, gram-negative bacteria, and fungal strains. The objective was to identify the most effective biologically active compounds.

The results of the antimicrobial activity testing can be presented graphically to provide a clear visualization of the efficacy of the synthesized compounds. Show in graphical.

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| --- |
| [3]DMF ∆ethyl-2-chloro acetate[2]MeOH ∆Na [1] [4a-4h]Different cyclic anhydride N2 H4Abs. EtOH [4]GRAPHICAL ABSTRACT  |

**Keywords**

Para-Hydroxyl Acetanilide; 1,2-diazine; Anti-fungal activity; Anti-bacterial activity

1. **Introduction**
	1. **Chemical**

 In recent years, there has been a significant focus on the compound pyridazine, a homocyclic compound with the chemical formula C4H4N2, due to its potential applications in various fields including pharmaceuticals, agriculture, materials science, and catalysts. This overview will concentrate on the synthesis of pyridazine, its biological activities, other applications, and derivatives. Pyridazine derivatives have been found to exhibit a range of biological activities such as vasodilators, cardiac therapeutics, anticonvulsants, antihypertensives1,2,3, antimicrobials4, anti-inflammatory5,6 agents, analgesics, herbicides, insecticides, and other industrial chemical activities7. Levosimendan, amibegron, indolidan, imazodan, and bemopridan are examples of pydazinones that have shown activity as therapeutic agents for the heart8.

* 1. **Biological**

 An antimicrobial refers to a substance that can either kill microorganisms (known as a microbicide) or inhibit their growth (known as a bacteriostatic agent)9. The primary categories of antimicrobial agents include disinfectants, which are non-selective agents like bleach that effectively eliminate a wide range of microbes on inanimate surfaces to prevent the transmission of diseases. Additionally, antiseptics are applied to living tissue and aid in reducing the risk of infection during surgical procedures. Lastly, antibiotics are substances that eradicate microorganisms within the body. Initially, the term antibiotic solely encompassed formulations derived from living microorganisms, but it is now also used to describe synthetic agents such as sulfonamides or fluoroquinolones. The term "antimicrobial" was originally limited to antibacterials, but it has now expanded to encompass all types of antimicrobials. Medical professionals and literature often use the term interchangeably with antibacterials. Antibacterial agents can be further classified into bactericidal agents, which kill bacteria, and bacteriostatic agents, which slow down or impede bacterial growth. However, recent advancements in antimicrobial technologies have led to the development of solutions that go beyond merely inhibiting microbial growth. Specifically, certain types of porous media have been created to effectively eliminate microbes upon contact10. Antibacterials are primarily employed in the treatment of bacterial infections. They are categorized as beta-lactams, macrolides, quinolones, tetracyclines, or aminoglycosides. The classification of antibiotics within these groups is based on their antimicrobial spectra, pharmacodynamics, and chemical composition11. Antifungals, on the other hand, are utilized to eradicate or prevent the further growth of fungi. In the field of medicine, they are commonly prescribed for infections such as athlete's foot, ringworm, and thrush. Antifungals exploit the differences between mammalian and fungal cells to effectively target fungal infections. Unlike bacteria, both fungi and humans are eukaryotes, resulting in molecular similarities between fungal and human cells. Consequently, identifying a target for antifungal drugs that does not exist in the host organism can be challenging. As a result, some of these drugs may have side effects, which can be life-threatening if not used correctly12.

1. **Experimental**
	1. **Materials.**

All initial chemical compounds were sourced from Fluka or Aldrich. Melting points (MP) were determined using a Gallenkamp and a Thomas capillary freezing point apparatus, with the measurements conducted in open glass capillaries and left uncorrected. The infrared spectra of KBr discs were obtained using the SHIMAZU INFRARED-8400 Fourier transform infrared spectrophotometer. Purified and commercially available primary components and reagents were used in their entirety. 1H-NMR and 13C-NMR spectra were recorded using a 500 MHz spectrometer. The Agilent technologies model ultrashield nuclear resonance (NMR) spectra were acquired in dimethyl sulfoxide (DMSO-d6), and the chemical shifts are reported in (ppm) downfield using tetramethyl silane (TMS) as a reference. UV-vis spectra were obtained using a Shimadzu spectrophotometer and an Apel PD-303 spectrophotometer, both manufactured in Japan.

* 1. **Procedures**
		1. **Synthesis of p-hydroxy acetanilide sodium salt13.**

The reaction of N-(4-hydroxyphenyl) acetamide (also known as 4-hydroxyacetanilide) and metallic sodium produces sodium 4-(N-acetamido) phenoxide. Here are the steps involved in the reaction:

1. Place methanol (10 ml) in a round-bottom flask (50 ml), carefully add metallic sodium (0.28 g,0.011mol) and attach a reflux condenser. Connect the water tubing to the condenser ensuring that water goes in the bottom and out the top. Turn on the water so that you have a slow but steady stream of water passing through the condenser.
2. Place a heating mantle below the flask and heat the reaction mixture under reflux for fifteen mints until complete consumption of the sodium.
3. Cool the flask to room temperature. Add paracetamol (1.7 g, 0.011mol) Stir the mixture at room temperature for 30 minutes, this reaction is exothermic.
4. Filter the mixture to remove any unreacted starting materials.
5. The filtrate (Rotary Evaporator) will contain sodium 4-(N-acetamido) phenoxide and the product light white color precipitate.
6. When Fecl3 was added to the resulting solution, no color change occurred and the solution remained yellow, which is the original color of the FeCl3 solution. This indicates that there is no OH group in the solution.
	* 1. **synthesis of ethyl -****2- (p-acetamido phenoxy) acetate14.**

P-hydroxy acetanilide sodium salt (0.61 g, 0.0035 mol) and ethyl chloroacetate (0.4 mL, 0.0035 mol) were dissolved in dimethylformamide (8 mL) within a 50 mL round bottom flask equipped with a magnetic stirring bar. The resulting solution was subjected to stirring, while the temperature gradually increased to a range of 75-85 °C over a period of 12 hours. Subsequently, the reaction mixture was transferred to an ice bath and filtered using a Hirsch funnel. The resulting precipitate was then washed with cold water and subjected to recrystallization from ethanol. Table (1) presents certain physical properties of compound [3].

* + 1. **synthesis of 2- (p-acetamido phenoxy) acetyl hydrazine15.**

Compound [3] (0.6 g, 0.0025 mol.) was dissolved in (10 ml.) absolute ethanol as a solvent; hydrazine hydrate (0.08 g,0.0025 mol., 0.074 ml.) was added to the reaction mixture and refluxed for 6 hours. After cooling and pouring the reaction mixture into ice, the product was filtered, washed with ice water, and recrystallized by ethanol-water. Some of the physical properties of compound [4] in table (1)

* + 1. **synthesis of derivatives 1,2-diazine from compound [4]16.**

To a 50 mL round bottom flask, add (0.45 g, 0.002 mol) hydrazide derivative [4] and (0.002 mol) (glutaric; succinic;3-nitro phthalic, phenyl succinic; methyl succinic;2,3-dichloro malanic;3,3-tetra methylene glutaric;2,3-di methyl maleic) anhydride and reflux for (6-8 hours). The solid product obtained [4a-4h] was cooled with crushed ice, filtered, and recrystallized using ethanol and dioxane ethyl acetate. Table (1) summarizes the physical properties.

**Table (1) physical properties of compounds**.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| NO. | Compounds Smiles | Chemical formula | M.Wt. | M.P. | Yield % | color | Recys. solvent |
| 2. | O=C(C)NC1=CC=C([O-]) C=C1. [Na+] | C8H8NNaO2 | 173.15 | 390 | 85 |  Light white | - |
| 3. | O=C(C)NC1=CC=C(OCC(OCC)=O) C=C1 | C12H15NO4 | 237.10 | 197-199 | 80 | Lightyellow | Ethanol  |
| 4. | O=C(C)NC1=CC=C(OCC(NN)=O) C=C1 | C10H13N3O3 | 223.23 | 155-157 | 78 | Off white | Ethanol+water |
| 4a. | O=C(CCC1) NN(C(COC2=CC=C(NC(C)=O) C=C2) =O) C1=O | C15H17N3O5 | 319.32 | 190-191 | 80 | yellow | Dioxane  |
| 4b. | O=C1CCC(N(C(COC2=CC=C(NC(C)=O) C=C2) =O) N1) =O | C14H15N3O5 | 305.10 | 185-187 | 85 | Brown  | Ethanol  |
| 4c. | O=C1N(C(COC2=CC=C(NC(C)=O) C=C2) =O) NC(C3=C1C([N+] ([O-])=O)=CC=C3)=O | C18H14N4O7 | 398.09 | 225-226 | 82 | Yellow  | Dioxane |
| 4d. | O=C1CC(C2=CC=CC=C2)C(N(C(COC3=CC=C(NC(C)=O) C=C3)=O)N1)=O | C20H19N3O5 | 381.39 | 210-212 | 75 | Brown  | ethyl acetate |
| 4e. | O=C1CC(C)C(N(C(COC2=CC=C(NC(C)=O) C=C2)=O)N1)=O | C15H17N3O5 | 319.32 | 193-194 | 80 | Gray  | Ethanol  |
| 4f. | O=C1C(Cl)=C(Cl)C(N(C(COC2=CC=C(NC(C)=O)C=C2)=O)N1)=O | C14H11Cl2N3O5 | 372.16 | 220-221 | 83 | Pale green  | Dioxane  |
| 4g. | O=C(NN(C(COC1=CC=C(NC(C)=O) C=C1)=O)C(C2)=O)CC32CCCC3 | C19H23N3O5 | 373.41 | 215-217 | 86 | Light yellow | Ethanol  |
| 4h. | O=C1C(C)=C(C)C(N(C(COC2=CC=C(NC(C)=O) C=C2) =O) N1)=O | C16H17N3O5 | 331.33 | 184-187 | 80 | Brown  | Ethyl acetate |

* 1. **Antibacterial activity tests: Screening for anti-Vibrio spp. Activity.**

 Three types of bacteria, namely **Vibrio** **alginolytic**, **Vibrio** **parahaemolyticus**, and **Vibrio** **Vulnificus**, were utilized in this study. To assess the antibacterial activity of compounds [4a-4h] against Vibrio spp., we made modifications to the disc diffusion method originally described by Gulluce17. The bacteria were cultured overnight in alkaline peptone water containing 1% NaCl at a pH of 8.4 and a temperature of 37 °C. The optical density of the bacterial suspension was adjusted to 0.5 McFarland using a DENSIMAT (Biome Rieux). Subsequently, the bacterial inoculum was swabbed onto MHI agar plates supplemented with 1% NaCl. Discs with a diameter of 6 mm, made of Whatman paper No. 3, were soaked with 10 µl/disc of the compounds' stock solutions (1 mg/ml in DMSO) and placed on the plates. The plates were then incubated at 37°C for a period of 18 to 24 hours. The inhibition zone diameters surrounding the discs were measured as an indicator of the compounds' antibacterial activity. For comparison, tetracycline (30µg/disc) was used as a reference. To determine the antibiotic susceptibility, we followed the Kirby-Bauer method and utilized Muller Hinton agar plates supplemented with 1% NaCl, as described by Ottaviani18. After incubation at 37°C for 18 to 24 hours, the inhibition zone diameters were measured using a 1 mm flat rule19.

* 1. **Evaluation of antifungal activity:**

 They used two types of antifungal candida: ***Candida Para psilosis*** *and* ***Candida albicans.***

The antifungal activity of the compounds under investigation was assessed using the agar-disc diffusion method. To conduct the experiment, two Candida species were cultivated on Sabouraud chloramphenicol agar plates at a temperature of 30°C for a period of 18–24 hours. Subsequently, multiple colonies exhibiting similar morphology to the clinical yeast were transferred into Api suspension medium and adjusted to a 2 McFarland turbidity standard using a Densimat (BioMerieux). The respective yeast inocula were then streaked onto Sabouraud chloramphenicol agar plates at a temperature of 30°C using a sterile swab, followed by drying. For the experiment, a sterilized 6 mm paper disc was impregnated with 10 ml (1 mg/ml) of each of the compounds being tested, which were dissolved in dimethyl sulphoxide. The treated Petri dishes were initially placed at a temperature of 4°C for a duration of 1–2 hours, and subsequently incubated at 37°C for 18–24 hours. The diameter of the transparent inhibition zone surrounding each disc was measured to assess the extent of fungal growth inhibition. To determine the susceptibility of the standard, a paper disc containing 20 mg of fluconazole was employed.

* 1. **Spectra data:**

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|  |  **FTIR:** ט (NH)=3250 cm-1, ט(C-H) arm. =3045cm-1, ט (C ט -H) alpha. = (2960,2850) cm-1, ט(C=O) amide=1665cm-1, ט(C=C) arm. = (1600,1545) cm-1, ט(C-O) =1125cm-1, Ꟙ(p-sub.) =810cm-1. |

* + 1. p-hydroxy acetanilide sodium salt [2]
		2. ethyl-2-(p-acetamido phenoxy) acetate [3].

|  |  |
| --- | --- |
|  | FTIR: ט (N-H) =3340cm-1, ט(C-H) arm. =3070cm-1, ט(C-H) alpha. = (2900,2850) cm-1, ט(C=O) ester =1735cm-1, ט(C=O) amide=1680cm-1, ט(C=C) arm. = (1500,1475) cm1, Ꟙ(CH3) = (1420 and 1375) cm-1, ט(C-O) =1225cm-1, Ꟙ(p-sub.) =845cm-1. |

1H-NMR: δ 9.71 (s, 1H, NH), 7.79-7.28 (dd, 4H, Ar-H), 5.02 (s, 2H, CH2), 4.63-4.59 (q, 2H, CH2),2.65 (s,3H, CH3) 1.64-1.61 (t,3H, CH3).

13C-NMR: δ 177.16(C13,8), 168.28(C3), 132.18(C6), 124.53(C4,2), 116.28(C5,1), 72.61(C12), 61.27(C15), 25.54(C10)14.99(C16).

* + 1. 2-(4-acetamido phenoxy) acetyl hydrazine [4].

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| --- | --- |
|  | FTIR: ט(N-H) =3345cm-1, ט(NH2) Asym. = 3345 overlaps, ט(NH2) Sym.=3330cm-1 ט (C-H) arm. =3060cm-1, ט(C-H) alpha. = (2920,2850) cm-1, ט(C=O) amide=1690cm-1, ט(C=C) arm. = (1550,1460) cm-1,ט(C-O)=1120cm-1,Ꟙ(p- sub.)845cm-1. |

1H-NMR: δ 9.37 (s, 1H, NH),8.87 (s, 1H, NH), 7.47 – 7.09 (dd, 4H, Ar-H), 5.65(s, 2H, NH2), 4.70 (s, 2H, CH2), 2.75 (s,3H, CH3).

13C-NMR: δ 176.82(C13,8), 164.67(C3), 149.31(C6), 130.19(C4,2), 119.99(C5,1), 68.59(C12), 22.66(C10).

* + 1. 1-(2-(p-acetamido phenoxy) acetyl)-1,2-diazepane-3,7-dione [4a].

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| --- | --- |
|  | FTIR: ט(N-H) = (3550,3350) cm-1, ט(C-H) arm. =3060cm-1, ט(C-H) alpha. = (2920,2850) cm-1, ט (C=O) amide=(1702,1680) cm-1,ט(C=C)arm.=(1550,1475)cm-1,ט(C-O)=1165cm-1,Ꟙ(p-sub.)850cm-1. |

1H-NMR: δ9.85(s, 1H, NH), 9.50 (s, 1H, NH), 7.67 – 7.39 (dd,4H, Ar-H), 4.70 (s, 2H, CH2), 2.58 – 2.55 (t, 4H, CH2), 2.37 (s,3H, CH3), 1.88-1.80 (Q, 2H, CH2).

13C-NMR: δ 183.31(C7,3), 171.54(C21,10), 165.66(C14), 153.42(C17), 132.25(C19,15), 121.16(C17,14), 66.79(C12), 35.26(C6,4),27.31(C23), 18.38(C5).

* + 1. **1-(2-(p-acetamido phenoxy) acetyl) tetrahydro pyridazine-3,6-dione** [4b].

|  |  |
| --- | --- |
|  | FTIR: ט(N-H) = (3500,3450) cm-1, ט(C-H) arm. =3060cm-1, ט (C-H) alpha. = (2950,2825) cm-1, ט (C=O) amide= (1710,1690) cm-1, ט(C=C) arm. =( 1600,1475)cm-1,ט(C-O)=1225cm-1,Ꟙ(p-sub)=830cm-1. |

1H-NMR: δ 9.67 (s, 1H, NH), 9.37 (s, 1H, NH), 7.47 – 7.09(dd, 4H, Ar-H), 4.70 (s, 2H, CH2), 2.66 – 2.62 (t, 4H, CH2)2.10(s,3H, CH3).

13C-NMR: δ 179.13(C1,4), 172.67(C20), 164.71(C13), 157.62(C16), 144.46(C18,14), 132.25(C17,15), 66.48(C11), 34.08(C3,2), 29.90(C22).

* + 1. 2-(2-(p-acetamido phenoxy) acetyl)-8-nitro-2,3-dihydro phthalazine-1,4-dione [4c].

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|  | **FTIR:** ט (NH)=3550 overlaps cm-1, ט(C-H) arm. =3060cm-1, ט (C ט -H) alpha. = (2950,2850) cm-1, ט(C=O) amide= (1720,1685) cm-1, ט(C=C) arm. = (1600,1470) cm -1, ט(NO2Asym.) =1530cm-1, ט(NO2Sym.) =1340cm-1, ט(C-O) =1125cm-1, Ꟙ(p-sub.) =850cm-1. |

1H-NMR: δ 9.74 (s, 1H, NH), 9.25 (s, 1H, NH), 7.45-7.13 (dd, 7H, Ar-H), 4.77 (s, 2H, CH2)2.24(s,3H, CH3).

13C-NMR: δ 184.21(C1,4), 174.60(C16,27), 160.11(C23), 154.04(C20), 151.13(C9), 142.46(C5), 134.50(C10), 131.27(C22,24), 127.10(C21,25), 124.82(C6,8), 121.35(C7), 64.24(C18), 29.90(C29).

* + 1. **1-(2-(p-acetamido phenoxy) acetyl)-5-phenyltetrahydro pyridazine**

**-3,6-dione [4d].**

|  |  |
| --- | --- |
| **A chemical structure with numbers and letters  Description automatically generated** | **FTIR:** ט(N-H) = (3555,3325) cm-1, ט(C-H) arm. =3100cm-1, ט(C-H) alpha. = (2950,2825) cm-1, ט(C=O) amide= (1705,1680) cm-1,ט(C=C)arm.=(1600,1475)cm-1,ט(C-O)=1220cm-1,Ꟙ(p-sub)=835cm-1. |

1H-NMR: δ 9.84 (s, 1H, NH), 9.33 (s, 1H, NH), 7.44 – 7.30 (m, 9H, Ar-H),4.71-4.68(d, *2H*, CH2), 2.95-2.92 (t, 1H, CH), 2.70 (s, 2H, CH2),2.15(s,3H, CH3).

13C-NMR: δ 178.85(C1,4), 174.68(C26,15), 162.96(C19), 159.66(C22), 134.18(C20,24), 128.44(C21,23), 126.78(C9), 125.13(C14,10), 120.76(C13,11), 116.31(C12), 69.06(C2), 48.89(C3), 37.37(C17), 26.51(C28).

* + 1. **1-(2-(p-acetamido phenoxy) acetyl)-5-methyltetrahydro pyridazine**

**-3,6-dione [4e].**

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|  | **FTIR:** ט(N-H) = (3550,3350) cm-1, ט(C-H) arm. =3060cm-1, ט(C-H) alpha. = (2950,2850) cm-1, ט(C=O) amide= (1695,1680) cm-1, ט(C=C) arm. = (1600,1475) cm-1,Ꟙ(CH3)=(1450 |

and 1345) ט(C-O) =1190cm-1, (p-sub) =835cm-1.

1H-NMR: δ 9.73(s, 1H, NH), 8.77 (s, 1H, NH), 7.45 – 7.39 (m, 4H, Ar-H), 4.13 (t, 1H, CH), 3.25 (d, 2H, CH2), 2.74 (s, 2H, CH2), 2.11 (s, 3H, CH3)0.95(s,3H, CH3).

13C-NMR: δ 184.88(C1,4), 176.45(C10,21), 166.29(C14), 160.54(C17), 134.14(C15,19), 126.34(C16,18), 67.62(C3), 38.02(C2), 35.58(C12), 25.97(C23), 17.22(C9).

* + 1. N-(2-(p-acetamido phenoxy) acetyl)-4,5-dichloro-1,2-dihydro pyridazine -3,6-dione [4f].

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|  | **FTIR**: ט(N-H) = (3500,3350) cm-1, ט(C-H) arm. =3070cm-1, ט(C-H) alpha. = (2950,2825) cm-1, ט(C=O) amide= (1720,1690) cm-1, ט(c=c) alkene=1660cm-1, ט(C=C) arm. = (1550, 1460) cm-1, ט(C-O) =1190cm-1, Ꟙ(p-sub) =835cm-1, Ꟙ(C-Cl) =750cm-1**.** |

**1H-NMR:** δ 9.86 (s, 1H, NH), 9.39 (s, 1H, NH), 7.46 – 7.11 (dd, 4H, Ar-H), 4.73 (s, 2H, CH2)2.17(s,3H, CH3).

**13C-NMR:** δ 182.09(C1,4), 169.81(C11,22), 154.98(C15), 150.28(C18), 143.43(C16,20), 131.07(C17,19), 120.59(C2,3), 66.64(C13), 26.88(C24).

* + 1. **N-(2-(p-acetamido phenoxy) acetyl)-8,9-diazaspiro [4.6] undecane -7,10-dione [4g].**

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| --- | --- |
|  | FTIR: ט(N-H) = (3445 overlaps) cm-1, ט(C-H) arm. =3070cm-1, ט(C-H) alpha. = (2950,2850) cm-1, ט(C=O) amide= (1706,1690) cm-1, ט (C=C) arm. = (1550, 1450) cm-1, ט(C-O) =1190cm-1, Ꟙ(p-sub) =830cm-1.  |

**1H-NMR:** δ 9.78 (s, 1H, NH), 9.34 (s, 1H, NH), 7.42 – 7.17 (dd, 4H, Ar-H), 4.68(s, 4H, CH2), 2.79 (s, 2H, CH2), 2.54 (t, 4H, CH2), 2.17(s, 3H, CH3), 1.27(Q, 4H, CH2).

**13C-NMR:** δ 180.35(C7,10), 174.06(C14,25), 153.02(C18), 147.95(C21), 128.44(C19), 120.76(C23), 116.32(C22,20), 66.40(C11,6), 46.43(C16,5), 44.53(C1,4), 40.59(C2,3), 23.31(C27).

* + 1. **N-(2-(p-acetamido phenoxy) acetyl)-4,5-dimethyl-1,2-dihydropyridazine -3,6-dione [4h].**

|  |  |
| --- | --- |
|  | FTIR: ט(N-H) = (3560,3350) cm-1, ט(C-H) arm. =3070cm-1, ט(C-H) alpha. = (2920,2825) cm-1, ט(C=O) amide= (1995,1680) cm-1, |

ט(c=c) alkene=1650cm-1, ט (C=C) arm. = (1570, 1460) cm-1, Ꟙ(CH3) =1412 and1375 cm-1, ט(C-O) =1195cm-1, Ꟙ(p-sub) =850cm-1.

**1H-NMR:** δ 9.74 (s, 1H, NH), 9.21 (s, 1H, NH), 7.45 – 7.24 (dd, 4H, Ar-H), 4.64 (s, 2H, CH2), 2.02 (s, 3H, CH3), 1.21 (s, 6H, CH3).

**13C-NMR:** δ 176.96(C1,4), 172.17(C11,22), 157.37(C15), 153.93(C18), 123.06(C16,20), 121.79(C17,19), 114.23(C2,3), 65.88(C13), 28.38(C24), 17.22(C9,10).

1. **Result and discussions.**

 Pyridazine derivatives have been synthesized from paracetamol, an over-the-counter compound, by reacting it with sodium metal in methanol as a solvent. The resulting product is compound [[2](https://link.springer.com/article/10.1007/s00044-015-1398-5)], as shown in equation (1).



Equation (1).

Compound [[3](https://link.springer.com/article/10.1007/s00044-015-1398-5)] was synthesized by reacting compound [[2](https://www.mdpi.com/1420-3049/14/9/3676)] with ethyl chloroacetate in DMF as a solvent, as illustrated in Equation (2).



Equation (2).

Hydrazine hydrate is added in batches to the compound [3] to produce hydrazine derivatives [4]. The solvent is absolute ethanol, as shown in equation (3).



Equation (3)

Pyridine derivatives [4a-4h] are synthesized by reacting hydrazine derivatives with anhydride derivatives (succinic anhydride, 3-nitrophathlic anhydride, phenyl succinic anhydride, methyl succinic anhydride, glutaric anhydride, 2,3-dichloro malonic anhydride, 3,3-tetrametyl glutaric anhydride, 2,3-dimethyl maleic anhydride) in the presence of glacial acetic acid as a solvent and electrophilic activator, as shown in equation (4).



Equation (4)

 The objective of this investigation was to examine the pharmacological efficacy of pyridazine derivatives as antimicrobial agents. Several compounds demonstrated notable drug effectiveness in comparison to the reference compound employed in the study. Among the prepared compounds, Compound [4c] exhibited the most pronounced pharmacological effectiveness as both an antifungal and antibacterial agent. This can be attributed to its capacity to form the greatest number of hydrogen bonds and van der Waals forces within its hydrocarbon components, in addition to the presence of a potent pulling group. Table No. (2) presents additional compounds containing withdrawing and donating groups.

**Table (2): Bacterial and fungal inhibition zone in (mm) for prepared compounds.**

|  |  |
| --- | --- |
| *Compounds* *No.* |  *Zones of growth inhibition(mm)*  |
| ***Vibrio alginolytic*** | ***Vibrio vulnificus*** | ***Vibrio parahaemolyticus*** | ***Candida Parapsilosis*** | ***Candida albicans***  |
| Tetracycline | 25 | 20 | 22 |  \_ |  *\_* |
| Fluconazole | \_ | \_ | \_ | 16 | 22 |
| Control DMSO | -ve | -ve  | -ve | -ve | -ve |
| 4a | 15 | 16 | *15* | *14* | *16* |
| 4b | *14* | *12* | *16* | *10* | *9* |
| 4c | *26* | *21* | *21* | *17* | *20* |
| 4d | *17* | *16* | *18* | *11* | *16* |
| 4e | *19* | *20* | *13* | *14* | *18* |
| 4f | *21* | *19* | *17* | *15* | *20* |
| 4g | *17* | *14* | *18* | *14* | *15* |
| 4h | *22* | *21* | *15* | *18* | *19* |

1. **Conclusion**

 The researchers developed new pyridazine derivatives and characterized them through diverse methods, including Fourier-transform infrared spectroscopy and Nuclear magnetic resonance (1H, 13C). Additionally, they examined the physical characteristics of these substances and evaluated their effectiveness against bacterial and fungal infections.

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