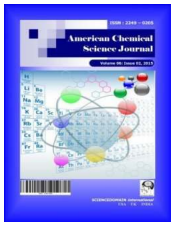

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Synthesis, Characterization and Antimicrobial Activity of Some New Heterocyclic Compounds Incorporating Pyridazine Moiety

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Authors' contributions

This work was carried out in collaboration between all authors. Author FMAS designed the study and wrote the protocol. Author NFAG performed the statistical analysis and managed the analyses of the study. Author NTAD wrote the first draft of the manuscript and managed the literature searches. Authors MIEG and HN performed the experiments. All authors read and approved the final manuscript.

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ABSTRACT

A series of heterocyclic compounds incorporating pyridazine moiety **(1-24)** were synthesized and evaluated for antimicrobial activities Gram- positive bacteria, Gram- negative bacteria and Yeast. Compounds **2b, 2c, 6, 7 and 10** were tested under antimicrobial activities as MICS. The results illustrated that among the synthesized compounds as a lead compound with good antimicrobial activity.

Keywords: Pyridazine; α,β- unsaturated compounds; antimicrobial activity.

1. INTRODUCTION

The synthesis of novel pyridazinone derivatives and investigation of their chemical and biological activities have gained more importance in recent years. Pyridazines and pyridazinones show wide spectrum of biological activities in the literature as potent inodilators [1,2], vasorelaxants [3-5]

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and potent cardiotonic agents [6-8]. They showed also anticonvulsant activity [9-11], vasodilatory [12,13] and antihypertensive [14] activities. They also possess antimicrobial [15,16], anti-inflammatory [17-20], anti feedant [21], herbicidal [22], anti nocieceptiv [23] and antihypertensive activities [24,25]. Some of 6-aryl-3(2H)pyridazinones are well known as potent analgesics [26], antiplatelet [15,27,28] and anticancer agents [29] as well as other anticipated biological [30] and pharmacological properties.

In view of the above mentioned findings and as continuation of our efforts for the synthesis of new candidates that may be of value as antitumor and/or antibacterial agents, we report here in the synthesis of some new pyridazinone derivatives and we focused on the formation of a ring system on the pharmacophoric pyridazinone residue.

2. MATERIALS AND METHODS

2.1 General Conditions

All melting points were determined on an electro thermal apparatus and are uncorrected. IR spectra (KBr) were recorded with Perkin Elmer Spectrum RXIFT-IR systems. ^{1}HNMR were measured with a Varian Gemini 200 MHz instrument using TMS as internal standard and mass spectra were measured with a Shimadzu GC–MS–QP 100 EX mass spectrometer.

2.2 Synthesis

2.2.1 Synthesis of 6-(3,4-dichlorophenyl)-4,5-dihydropyridazin-3(2H)one 1 according to the literature [31]

hydrazinolysis of 4-(3,4-dichlorophenyl)-4-oxo-butanoic acid in boiling butanol to give the corresponding 6-(3,4-dichlorophenyl)-4,5-dihydro pyridazin-3(2H)-one **1** in good yield [31].

2.2.2 Synthesis of 4-arylidene-6-(3,4-dichlorophenyl)-4,5-dihydropyridazin-3(2H)-one 2a-d

To (0.01 mole; 2.43 gm) of **1** in 30 ml of (0.1 M) alcoholic potassium hydroxide (which was prepared by dissolving 3 gm of potassium hydroxide in 30 ml of absolute ethanol), different aldehyde namely 3-nitrobenzaldehyde, 2-chlorobenzaldehyde, 4-methoxybenzaldehyde and/or furfural were added, with strong stirring by using magnetic stirrer, the mixture was allowed to reflux for 3 hrs. A mixture of water and conc. HCl was added drop by drop until gave precipitate. The solid that separated was recrystallised from the proper solvent to give **2a-d**.

2a: Pale yellow, 80% yield, m. p. 210℃; analysis for $C_{17}H_{11}N_3O_3Cl_2$ (376) M Wt, [Requires: 54.25; H, 2.92; N, 11.17; Cl, 18.88. Found: C, 54.35; H, 3.00; N, 11.00; Cl, 18.66]. IR (cm^{-1}): 3204 (NH), 1657 C=O, 1590 (C=N) 513(C-Cl).

2b: Yellow crystals, 71% yield, m.p.220℃; analysis for $C_{17}H_{11}N_2OCl_3$ (365.5) M Wt, [Requires: C, 55.81; H, 3.01; N, 7.66; Cl, 29.14. Found: C, 55.75; H, 3.00; N, 7.70; Cl, 29.00]. IR (cm^{-1}): 3125 (NH), 1651(C=O), 1600 (C=N), 547(C-Cl).

2c: Yellow crystals, 99% yield, m.p.180℃; analysis for $C_{18}H_{14}N_2O_2Cl_2$ (361) M Wt, [Requires: C, 59.83; H, 3.87; N, 7.75; Cl, 19.66. Found: C, 59.66; H, 4.00; N, 8.02; Cl, 19.00]. IR (cm^{-1}): 3142 (NH), 1688 (C=O), 1600(C=N), 527(C-Cl). ^{1}H - NMR δ: 8.6(s, 1H, NH), 7.8-7.0 (m,7H,Ar-H). 3.8(s,3H,OCH_3),7.0(s,1H,=CH),2.4(s,2H,CH_2). ^{13}C-NMR: δ 114.2,114.4,127.4, 128.7,130.4, 130.7,133.5,133.7,138.1(C-Ar), 141.3(C=N),159.9(C-O-CH_3), 162.7(C=O),CH_2(128.4), 55.9(CH_3). MS: m/z 361 (M^+, 0.13 %), m/z 268 (100%).

2d: Yellow crystals,78% yield, m.p.116℃; analysis for $C_{15}H_{10}N_2O_2Cl_2$ (321) M Wt, [Requires: C,56.07;H,3.11; N,8.72;Cl,22.11. Found; C, 56.00; H, 3.00; N, 8.90; Cl, 22.00]. IR (cm^{-1}): 3203(NH), 1679(C=O), 1602(C=N), 588(C-Cl).

2.2.3 Synthesis of 5 – (3,4 – dichlorophenyl) – 3 – (4 – methoxyphenyl) – 3,3a,4,7 – tetrahydro – 2H – pyrazolo [3,4-c] pyridazine 3.

To (0.01 mole; 3.61 gm) of **2c** was added hydrazine hydrate (0.01 mole; 0.5 ml). The reaction mixture was fused for 4 hrs. The mixture is cooled to room- temp, poured onto water. The solid was collected by filtration, and recrystallized from ethanol to give **3.**

3: Yellow crystals, 66%yield, m.p.232℃; analysis for $C_{18}H_{16}N_4OCl_2$ (375)M Wt, [Requires: C,57.60; H,4.26; N,14.93; Cl,18.93. Found: C,58.00;H,4.30;N,15.00;Cl,18.70]. IR

(cm^{-1}): 1605 C=N, 2844-2923 CH (aliphatic, aromatic), 3166 (NH) . MS: m/z 374(3.6% M^+), m/z 56.7(100%).

2.2.4 Synthesis of 6 - (3,4-dichloro phenyl)-4-(4-methoxyhydrazinobenzylidene)-4,5-dihydro pyridazin–3 (2H) one 4a , 6 - (3,4-dichlorophenyl)-4-(4-methoxyphenylhydrazinobenzylidene)-4,5-dihydropyridazin-3 (2H) one 4b and 5-(3,4-dichlorophenyl)-2-(2,4-dinitrophenyl)-3-(4-methoxyphenyl)-3,3a,4,7-tetrahydro-2H-pyrazolo[3,4-c]pyridazine 5

To (0.01 mole; 3.61 gm) of **2c** was added, hydrazine hydrate, phenyl hydrazine and /or 2,4-dinitro (0.01 mole) in 30 ml butanol. The reaction mixture was heated under reflux for 3 hrs, cooled to room- temp. The solid was collected by filtration, and recrystallized from ethanol to give **4 a,b** and **5.**

4a: Brown crystals, 80% yield, m .p. 202℃; analysis for $C_{18}H_{18}N_4O_2Cl_2$ (393) M Wt, [Requires: C, 54.96; H, 4.58; N, 14.24; Cl, 18.06. Found: C, 55.30; H, 5.00; N, 14.30; Cl, 18.01]. IR (cm^{-1}): 3120 (NH),1680 (C=O).

4b: Yellow in 66% yield, m.p.128℃; analysis for $C_{24}H_{22}N_4OCl_2$(453) M Wt, [Requires: C,63.57; H,4.85; N,12.36; Cl,15.67. Found: C,63.01;H,4.40;N,12.00;Cl,16.00]. IR (cm^{-1}): 3267 (NH), 1683(C=O).

5: Orange crystals, 89% yield, m.p.254℃; analysis for $C_{24}H_{18}N_6O_5Cl_2$(541)M Wt, [Requires: C,53.23; H,3.32; N,15.52;Cl,13.12. Found: C, 53.00; H, 3.00; N, 16.00Cl, 13.02]. ^{1}H -NMR δ: 3.83 (s,3H,OCH_3), 2.51(d,2H,CH_2), 2.49(d,1H,CH_2-CH-CH), 2.50(1H,q,CH_2-CH-CH),11.6 (s,1H,NH) 8.88-7.04(m,10H,Ar-H).).^{13}C-NMR: δ 114.2, 114.4, 115.0, 127.4,128.7,129.0,130.4, 130.7, 132.1,133.5.133.7,137.3,146.6(C-Ar),150.6(C=NNH),158(C-O-CH_3),39.6(CH-Pyridazine),50.9 (CH-Pyrazole), CH_2(25.4), 55.9(CH_3).

2.2.5 Synthesis of 3-(3,4-dichlorophenyl)-5-(4-methoxyphenyl)-4,4a,5,6-tetrahydropyrimido [4,5-c]pyridazin-7(1H)-one 6

A mixture of **2c** (0.01 mole; 3.61 gm) and (0.01 mole; 0.6 gm) of urea was fused for 3 hours. Poured onto water, the solid that separated was collected by filtration, and recrystallized from petroleum ether (b.p.40-60˚C) to give **6.**

6: Pale yellow crystals, 50% yield, m .p. 122℃; analysis for $C_{19}H_{16}N_4O_2Cl_2$ (403) M Wt, [Requires: C,56 .57; H, 3.97; N,13.89; Cl, 17.61. Found: C, 56.68; H, 4.00; N, 14.00; Cl, 17.30]. IR (cm^{-1}): 1680 (C=O), 1598(C=N), 3198 (NH), 1459(OCH_3) .^{1}H-NMR δ: 3.83(s,3H,OCH_3), 8.63 (s,1H,NHC=O), 7.83-7.04 (m,7H,Ar-H), 8.73 (s,1H,NHC=N), 2.49(d,2H,CH_2), 2.50(d,1H, CH_2-CH-CH), 2.51(q 1H, CH_2-CH-CH). ^{13}C-NMR: δ 114.2, 114.4, 128.7,129.0,130.4, 132.0, 133.5.133.7,135.2(C-Ar), 145.3.6(C=NNH),157.3(C-O-CH_3), 165.7(C=O),55.0 (CH3), CH_2(26.4), 39.6(CH-Pyridazine), 42.8(CH-Pyrimidine). MS: m/z (402.90) (0.02%M^+), m/z (84.00) (100%).

2.2.6 Synthesis of 3-(3,4-dichlorophenyl)-5-(4-methoxyphenyl)-4,4a,5,6-tetrahydropyrimido [4,5-c]pyridazin-7(1H)-thione 7

A mixture of **2c** (0.01 mole; 3.61 gm) and (0.01 mole; 0.76 gm) of thiourea in sodium ethoxide (30ml) was refluxed for 6 hours. The solid that separated after concentration and cooling was recrystallized from petroleum ether 40-60 ˚C to give **7.**

7: Yellow crystals 50% yield, m .p. 172℃; analysis for C19 H16 N4 O S Cl2 (419) M Wt: [Requires: C, 54.41; H, 3.81; N, 13.36; S, 7.63; Cl, 16.94. Found: C, 54.50; H, 3.80; N, 13.42; S, 7.70; Cl, 16.70]. IR(cm^{-1}): 1596.24(C=N),3285.71(NH), 158.61(C=S). ^{1}H-NMR δ: 3.82 (s,3H,OCH_3), 8.63 (s,1H, NHC=S), .79-7.03 (m,7H,Ar-H), 2.51(d,2H,CH_2-CH), 2.50(q,1H,CH_2-CH-CH), 2.49(d,1H,CH-CH), 8.72(s,1H,NHCN). MS: m/z (421.00) (3.85% M^+), m/z (56.00)(100%).

2.2.7 Synthesis of 3-(3,4-dichlorophenyl)-5-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrano[2,3-c] pyridazine-6-carbonitrile 8

A mixture of **2c** (0.01 mole; 3.61 gm), (0.01 mole; 1.13 gm) of ethylcyanoacetate and (0.04 mole; 3.08 gm) of ammonium acetate was refluxed for 6 hours. The solid that separated after concentration and cooling was recrystallized from ethanol to give **8.**

8: Yellowish crystals, yield 70%, m .p 223℃; analysis for C_{21} H_{14} N_4 O_3 Cl_2 (441) M Wt, [Requires: C, 57.14; H, 3.17; N, 12.69; Cl, 16.09. Found: C, 57.40; H, 3.25; N, 12.98; Cl, 16.47]. IR (cm^{-1}): 1572 (C=N), 2210(C≡N), 1653(C=O), 3203.95(NH). ^{1}H NMR δ: 3.31(s,3H , OCH_3), 7.07-6.84(m,7 H, Ar-H), 2.49(d,2H,CH_2), 3.78–4.12(d,2H,CH–CH-C≡N), 8.06(s,1H, NH).^{13}C-NMR: δ 113.2, 128.7, 129.2, 130.4, 133.5, 133.7, 135.2(C-Ar), 117.9(C≡N), 147.3(C=NNH), 157.3(C-O-CH_3), 175.7 (C=O),55.0(CH_3), 16.4(CH_2), 39.6(CH-Pyridazine), 31.5, 37.3, 39.8(3xCH-Pyridine),70.2 (NHCHNH). MS: m/z (427.12 M^{+2}) (4.00%), m/z (92.08) (100%).

2.2.8 Synthesis of 5-(3,4-dichlorophenyl)- 3-(4-methoxyphenyl)-2,3,3a,4,7,7a-hexahydro-1H-pyrazolo[3,4-c] pyridazin-1-carbothioamide 9.

A mixture of **2c** (0.01 mole; 3.61 gm) and (0.01 mole; 0.91 gm) of thiosemicarbazide in sodium ethoxide (30 ml) was heated under reflux for 6 hours. The solid that separated after concentration and cooling was recrystallized from petroleum ether 40-60 to give **9.**

9: Yellow crystals, 70%. Yield, m .p. 161℃; analysis for C_{19} H_{17} N_5 O S Cl_2 (434).M Wt, [Requires: C, 52.53; H, 3.92; N, 16.13; S, 7.37; Cl, 16.36. Found: C, 52.56; H, 4.00; N, 16.02; S, 7.30; Cl, 16.00]. IR(cm^{-1}): 1166(C=S), 1600(C=N), 3350- 3100 (NH_2-broad) .^{1}H-NMR δ: 3.83(s,3H, OCH_3), 8.62(s,1H, NH), 7.82-7.03(m,7H, Ar-H), 3.20(s,2H, NH_2-amide), 2.08(d,2H, CH_2-CH), 2.51-2.48(d,2H,CH-CH). MS: m/z (434.00) (0.33% M^+), m/z (58.00) (100%).

2.2.9 Synthesis of 5-(3,4-dichlorophenyl)-3-(4-methoxyphenyl)-N-(2-phenylacetyl)-3a,4-dihydro-3H-pyrazolo [3,4-c]pyridazine-2(7H)-carbothioamide 10

A mixture of **9** (0.01 mole; 4.34 gm), (0.01 mole; 1.99 gm) of phenacyl bromide in 25 ml of ethanol was refluxed for 8 hours. The solid that separated after concentration and cooling was recrystallized from ethanol to give **10.**

10: Dark brown crystals 60% yield, m.p.196℃, analysis for C_{27} H_{23} N_5 O_2 S Cl_2 (552) M Wt, [Requires: C, 58.69; H, 4.16; N, 12.68; S, 5.97; Cl, 12.86. Found: C, 58.80; H, 4.00; N, 13.00; S, 6.00; Cl, 12.94]. IR (cm^{-1}): 1686(C=O), 1607(C=N), 1169(C=S), 3208 (NH). MS: m/z (552) (1.00%), m/z 176 (100%).

2.2.10 Synthesis of 2-acetyl-6-(3,4-dichlorophenyl)-4,5-dihydropyridazin-3(2H)-one 11

Compound **1** (0.01 mole; 2.43 gm) in 15 ml of acetic anhydride was refluxed for 2 hours. The precipitate that separated on cooling was collected and recrystallized from benzene to give **11.**

11: White crystals, 50% yield, m .p 154℃; analysis for C_{12} H_{10} N_2 O_2 Cl_2 (285) M Wt, [Requires: C, 50.53; H, 3.51; N, 9.82; Cl, 24.91.Found: C, 50.50; H, 3.45; N, 10.01; Cl, 25.00]. IR (cm^{-1}): 1750(C=O), 1692(C=O), 1611(C=N), 1472(CH3).1H-NMR δ: 7.85-7.73(m, 3H, Ar-H), 3.52(s, 3H, $COCH_3$), 2.72-2.45(t, 4H, CH_2-CH_2). ^{13}C-NMR: δ 128.7,130.4,13.07, 133.5,135.7(C-Ar),145.6 (C=N), 172.3(CO CH_2),160.4(N-C=O), 24.2,32.4(CH_2 CH_2), 22.6(CH_3).

2.2.11 Synthesis of 2-(3-(2-chlorophenyl)acryloyl)-6-(3,4-dichlorophenyl)-4,5-dihydro pyridazin-3(2H)-one 12

Compound **11** (0.01 mole; 2.85 gm) in alcoholic potassium hydroxide (30 ml, 0.1 mole), was added 2-chlorobenzaldehyde (0.01 mole; 1.4 ml) with stirring. The reaction mixture was heated under reflux for 3 hrs. A mixture of water and conc. HCl was added drop wise until precipitation. The precipitate was filtered off; recrystallized from ethanol to give **12.**

12: Yellow crystals, 60% yield; m .p. 182℃; analysis for C_{19} H_{13} N_2 O_2 Cl_3 (407.5) M Wt, [Requires: C, 55.95 ; H, 3.19; N, 6.87; Cl, 26.13. Found: C, 56.03; H, 3.32; N, 6.22; Cl, 26.62]. IR(cm^{-1}): 1678(C=O), 1609(C=N).

2.2.12 Synthesis of 2-(5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)-6-(3,4-dichlorophenyl) -4,5-dihydro pyridazin-3(2H)-one 13

A mixture of **12** (0.01 mole; 4.075 gm), (0.01 mole; 0.5 ml) of hydrazine hydrate in ethanol (25 ml) was refluxed for 6 hours; the precipitate was collected and recrystallised from ethanol to give **13.**

13: White crystals, yield 60% m.p.142℃; analysis for C_{19} H_{15} N_4 O Cl_3 (421.5) M Wt, [Requires: C, 54.09; H, 3.56; N, 13.29; Cl, 25.27. Found: C, 54.20; H, 3.70; N, 13.36; Cl, 25.65]. IR (cm^{-1}): 1663 (C=O), 1599(C=N), 3193 (NH). 1H-NMR δ:3.26(s,1H,NH),7.942-7.476(7H, m, Ar-H),2.398 (2H,d,$\underline{CH_2}$-CH), 2.985(1H, t, $\underline{CH}$-CH_2) and 2.493-2.505(4H,t, CH_2-CH_2).

2.2.13 Synthesis of 6-(3,4-dichlorophenyl)-3,7-dihydro-2H-oxazolo[3,2-b]pyridazin-2-one 14

A mixture of **1** (0.01 mole; 2.43 gm), chloroacetic acid (0.03 mole; 2.835 gm) and anhydrous potassium carbonate (0.03 mole; 4.14 gm) in dry acetone (25 ml) was refluxed for 24 hours in water bath, cooled to room temperature, poured onto water. The precipitate was collected and recrystallized from ethanol to give **14.**

14: White crystals, 90% yield; m .p. 138℃; analysis forC_{12} H_8 N_2 O_2 Cl_2 (283) M Wt, [Requires: C, 50.88; H, 2.83; N, 9.89; Cl, 25.09. Found: C, 51.02; H, 2.63; N, 10.02; Cl, 25.00]. IR (cm^{-1}): 1693(C=O), 1572(C=N). MS: m/z (279 MI^{-3}) (0.12%), m/z (51) (100%).

2.2.14 Synthesis of 2-(3-(3,4-dichlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl)acetyl chloride 15

A mixture of **1** (0.01mole; 2.43gm), (0.01 mole; 1.13 ml) of chloro acetylchloride in ethanol (25ml) was refluxed for 6 hours. The precipitate was collected and recrystallised from benzene to give **15**.

15: Brown crystals, 95% yield; m .p. 166℃; analysis for C_{12} H_9 N_2 O_2 Cl_3 (319.5) M Wt, [Requires: C, 45.07; H, 2.82; N, 8.76; Cl, 33.33. Found: C, 45.07; H, 2.82; N, 8.76; Cl, 33.33]. IR (cm^{-1}): 1686 (C=O), 1580(C=N). 1H-NMR δ: 3.66(s, 2H, CH_2COCl). ^{13}C-NMR: δ 128.7, 130.4, 13.07, 133.5, 135.7 (C-Ar), 145.6 (C=N), 174.8(CO CH_2), 163.7(N-C=O), 24.2,32.4(CH_2 CH_2), 40.6(CH_2Cl).

2.2.15 Synthesis of 2-(2-aminooxazol-4-yl)-6-(3,4-dichlorophenyl)-4,5-dihydropyridazin-3(2H)-one 16

A mixture of **15** (0.01 mole; 3.195 gm) and urea (0.01 mole; 0.6 gm) in ethanol (25 ml) was refluxed for 10 hours, the precipitate that obtained after cooling was recrystallised from ethanol to give **16.**

16: Beige crystals, 70% yield, m.p.194℃; analysis for C_{13} H_{10} N_4 O_2 Cl_2 (325) M Wt, [Requires: C, 48.00; H, 3.07; N, 17.23; Cl, 21.84. Found: C,48.65; H, 3.27; N, 17.03; Cl, 21.32]. IR (cm^{-1}): 1680(C=O),3200-3156(NH_2).^{13}C-NMR(DMSO-d6): δ 124.2 128.7,130.4,13.07,133.5,135.7,137.5(C-Ar),145.6 (C=N) ,172.6(CO CH_2),161.5(C-NH2), 24.2,32.4(CH_2 CH_2).

2.2.16 Synthesis of 2-(2-aminothiazol-4-yl)-6-(3,4-dichlorophenyl)-4,5-dihydropyridazin-3(2H)-one 17

A mixture of **15** (0.01mole; 3.195gm), (0.01 mole; 0.76gm) of thiourea in ethanol (25ml) was refluxed for 10 hours; the precipitate was collected and recrystallized from ethanol to give **17.**

17: Pale yellow crystals, 65% yield, m.p. 160℃; analysis forC_{13} H_{10} N_4 O S Cl_2 (341)M Wt[Requires: C, 45.74; H, 2.93; N,16.42; Cl, 20.82. Found: C, 45.32; H, 3.02; N,16.04; Cl, 21.05]. IR (cm^{-1}): 1680(C=O), 3109-3206(NH_2).

2.2.17 Synthesis of 2-(3-(3,4-dichlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl)acetohy drazide 18

A mixture of **15** (0.01 mole; 3.195 gm), (0.01 mole; 0.5 ml) of hydrazine hydrate in ethanol (25 ml) was refluxed for 6 hours, the precipitate was recrystallised from ethanol to give **18.**

18: Pale yellow crystals, 75% yield, m.p.182℃; analysis for C_{12} H_{12} N_4 O_2 Cl_2 (315) M Wt, [Requires: C, 45.71; H, 3.80; N, 17.77; Cl, 22.53. Found: C, 45.65; H, 3.23; N, 17.36; Cl, 22.02]. IR (cm^{-1}): 1676(C=O), 3196 - 3325(NH_2).

2.2.18 Synthesis of 3-amino-5-(3-(3,4-dichlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl)-1,6-dihydro pyridazine-4-carbonitrile 19

A mixture of **18** (0.01 mole), (0.01 mole) of malononitrile in (25 ml) glacial acetic acid was refluxed for 8 hours, the precipitate and recrystallized from the benzene to give **19.**

19: White crystals, 55% yield, m.p.142℃; analysis for C_{15} H_{12} N_6 OCl_2 (363) M Wt, [Requires: C, 49.58; H, 3.30; N, 23.14; Cl, 19.55.Found: C, 49.02; H, 3.23; N, 23.65; Cl, 19.36]. IR (cm^{-1}): 1666(C=O), 1587(C=N), 3196, 2210(C≡N).

2.2.19 Synthesis of 3-chloro-6-(3,4-dichlorophenyl)-4,5-dihydropyridazine 20

To (0.01 mole; 2.43 gm) of **II** was added (0.01 mole; 1.535 ml) of phosphorus oxychloride. The reaction mixture was refluxed for 2 hours on water bath. Conc. HCl and cold water were added to the reaction mixture. The precipitate was collected, filtered off and recrystallised from ethanol to give **20.**

20: Brownish crystals 55% yield, m. p. 184℃; analysis for C_{10} H_7 N_2 Cl_3 (261.5) M Wt, [Requires: C, 45.89; H, 2.68; N, 10.71; Cl, 40.73. Found: C, 45.62; H, 2.85; N, 10.45; Cl, 40.36. MS: m/z 261.5, m/z 251.80(0.03%), m/z (136) (100%).

2.2.20 Synthesis of 1-(4-(6-(3,4-dichlorophenyl)pyridazin-3-ylamino)phenyl)ethanone 21

A mixture of **20** (0.01 mole; 2.615 gm) and (0.01 mole; 1.35 m) of p-amino acetophenone in ethanol (25 ml) was refluxed for 8 hours. After concentration and cooling, the solid that separated was recrystallized from ethanol to give **21.**

21: White crystals, 75% yield, m. p. 142℃; analysis for C_{18} H_{15} N_3 O Cl_2 (360) M Wt,[Requires: C, 60.00; H, 4.17; N, 11.67; Cl, 19.72. Found: C, 59.85; H, 4.06; N, 11.33; Cl, 19.26]. IR (cm^{-1}): 3218(NH), 1684(C=O). MS: m/z (350) (12.73%), m/z (173) (100%).

2.2.21 Synthesis of 2-Bromo-1-{4-[4-bromo-6-(3,4-dichloro-phenyl)-pyridazin-3-ylamino]-phenyl}-ethanone 22

A mixture of **21** (0.01mole; 3.6gm) and bromine (0.02 mole; 3.2ml) in 10ml glacial acetic acid are stirred for 3 hours. The precipitate was collected and recrystallized from ethanol to give **22.**

22: Pale yellow crystals, yield 66%, m .p. 150℃; analysis for C_{18} H_{11} N_3 O Br_2 Cl_2 (516) M Wt, [Requires: C, 41.86; H, 3.48; N, 8.13; Cl, 13.75; Br, 31.00.; Found: C, 42.06; H, 3.33; N, 8.00; Cl, 14.02; Br, 29.95]. IR (cm^{-1}): 1664 (C=O), 1599(C=N), 3361(NH), 586(C-Br). ^{1}H-NMR δ: 5.05(s, 1H, NH), 4.64(s, 2H, $COCH_2$).

2.2.22 Synthesis of 2-(4-(4-bromo-6-(3,4-dichlorophenyl)pyridazin-3-ylamino)phenyl)-6H-1,3,4-thiadiazin-5-amine 23

A mixture of **22** (0.01 mole; 4.39 gm), (0.01 mole; 0.91 gm) of thiosemicarbazide in ethanol (25 ml) was refluxed for 6 hours, then collected the precipitate and recrystallised from ethanol to give **23.**

23: Yellow crystals, 60% yield, m .p. 145℃; analysis for C_{19} H_{13} N_6 S Cl_2Br (508) M Wt, [Requires: C, 44.88 ; H, 2.55 ; N, 16.53; S, 6.29Cl, 13.97; Br, 15.74.;Found: C, 45.03 ; H, 2.36; N, 16.25; S, 6.85Cl, 14.23; Br, 15.33]. IR (cm^{-1}): 1612(C=N), 3313-3245(NH_2). 1H- NMR δ: 6.90 (2H,s,CH_2), 6.99(s,1H,CH-pyridazine ring), 8.12(s,1H,NH), 5.54(s,2H,NH_2).

2.2.23 Synthesis of [4-(2-Amino-thiazol-4-yl)-phenyl]-[4-bromo-6-(3,4-dichloro-phenyl)-pyridazin-3-yl]-amine 24

A mixture of **22** (0.01 mole; 4.39 gm), thiourea (0.01 mole; 0.76 gm) in ethanol (25ml) was refluxed for 6 hours, the solid obtained was collected and recrystallised from ethanol to give **24.**

24: White crystals, 50%yield, m.p. 156℃; analysis forC_{19} H_{12} N_5 S $BrCl_2$ (493) M Wt, [Requires: C,46.24; H,2.43; N,14.19; S, 6.49; Br, 16.22 Cl,14.40.; Found: C,46.66; H,2.74; N,14.02; S, 6.65; Br, 16.54; Cl,14.40]. IR (cm^{-1}): 1599(C=N), 3361-3176(NH_2). ^{1}H-NMR δ: 8.13-7.77(m,8H, Ar-H), 6.57(s,1H,CH-thiazole ring), 4.64(s,1H, NH), 5.76(s,1H,NH_2).

3. RESULTS AND DISCUSSION

3.1 Chemistry

In this investigation, a series of new pyrazole, pyridine, oxazole thiazole, thiadiazine and pyrimidine, fused and /or attached to pyridazine moiety were designed, synthesized (Schemes 1–3), and biologically evaluated for their in vitro

antimicrobial activity. Thus, the reaction of 4-oxo-4-(3,4-dichlorophenyl)-2-butenoic acid with hydrazine hydrate in ethanol afforded 6-(3,4dichlorophenyl)-4,5-dihydro pyridazin-3(2H)-one **1**[31]. The introduction of two strong electron withdrawing atoms (two chloro) into the aromatic moiety of the butanoic acid has increased the electrophilicity of the carbon carbonyl at position 4 which resulted in obtaining good yield of the corresponding pyridazinone.

Treatment of 6-(3,4-dichlorophenyl)-4,5-dihydropyridazin-3(2H)one **1** with different aldehydes namely 3-nitrobenzaldehyde, 2-chlorobenzaldehyde, 4-methoxybenzaldehyde and/or furfural under Claisen reaction conditions gave the corresponding arylidene derivatives **2a-d** [32-35].

6 - (3,4-dichlorophenyl) – 4-arylidene -4,5 - dihydropyridazin-3(2H) one derivative **(2a-d**) were used as the key intermediate in the synthesis of the desired fused heterocyles incorporating pyridazine moiety via their interaction with hydrazine derivatives and active methylene compounds as shown in scheme 1. Thus, fusion of 6 - (3,4-dichlorophenyl) - 4 - (4 – methoxy- benzylidene) - 4,5 - dihydropyridazin-3(2H) one **2c** with hydrazine hydrate afforded the corresponding5 - (3,4 -dichlorophenyl)- 3- (4-methoxyphenyl) - 3,3a,4,7-tetrahydro- 2H-pyrazolo [3,4-c] pyridazine **3** while its reaction with hydrazine hydrate, phenyl hydrazine and /or 2,4-dinitrophenyl hydrazine in boiling butanol has produced 6 - (3,4 - dichlorophenyl) - 4 - (4-methoxyhydrazinobenzylidene)-4,5-dihydropyridazin-3(2H)one **4a,** 1-(4-(4-methoxyphenylhydrazinobenzylidene)-6-(3,4-dichloro phenyl)-4,5-dihydropyridazin-3(2H)one **4b** and 5-(3,4-dichlorophenyl)-2-(2,4-dinitrophenyl)-3-(4-methoxyphenyl)-3,3a,4,7-tetrahydro-2H-pyrazolo[3,4-c]pyridazine **5** [36-41], respectively.

The infrared spectrum of **3** indicated absorption band at 3166 cm^{-1} attributable to ɣNH but devoid the presence of ɣ C=O. While the infrared spectra of **4a, 4b** indicated absorption bands at 3120-3267 cm^{-1},1680-1683cm^{-1}ɣ attributable to NH,ɣ C=O but devoid the presence of ɣ C=O in compound **5**.

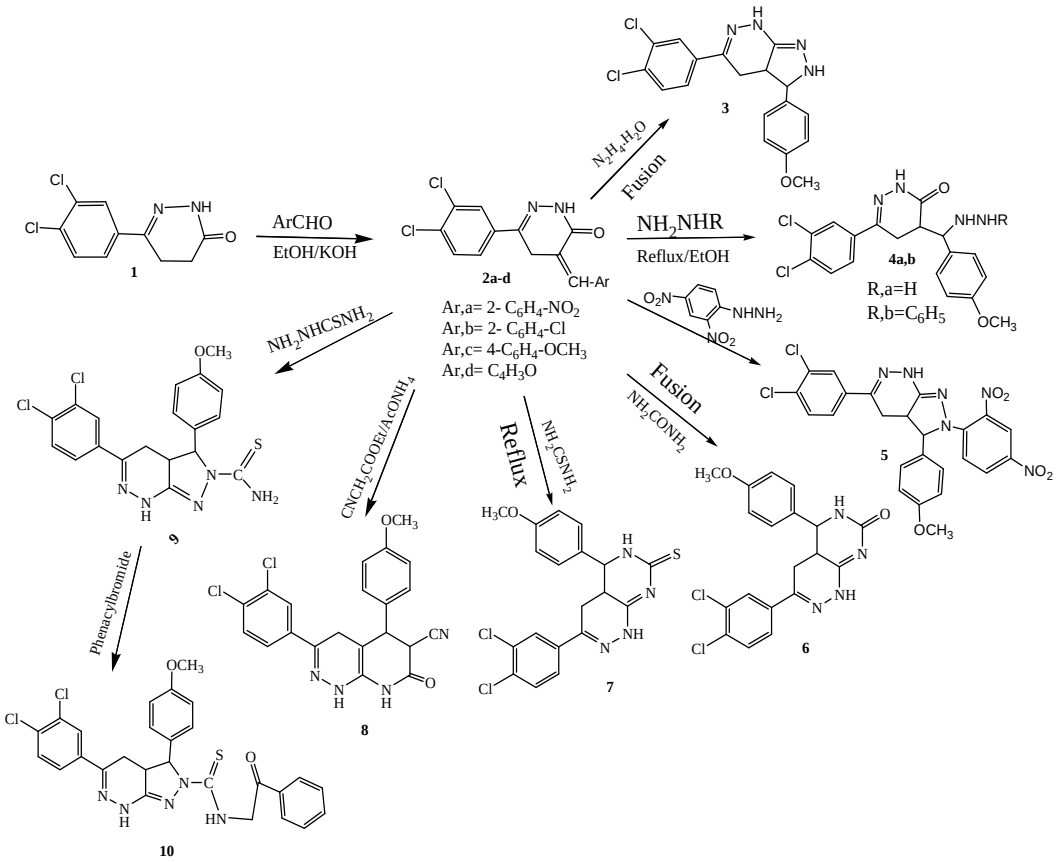
Fusion of **2c** with urea afforded the corresponding 3- (3,4-dichlorophenyl) -5- (4-methoxyphenyl) - 4,4a,5,6-tetrahydropyrimido [4,5-c] pyridazin -7(1H) - one **6** while its reaction with thiourea in sodium ethoxide afforded 3-(3,4-dichlorophenyl)-5-(4-methoxyphenyl)-4,4a,5,6-tetrahydropyrimido[4,5-c]pyridazine-7(1H)-thione **7** [41].

Also, fusion of 6-(3,4-dichlorophenyl)- 4-(4-methoxy-benzylidene)-4,5-dihydropyridazin-3(2H) one **2c** with ethyl cyanoacetate in the presence of ammonium acetate afforded 3-(3,4-dichlorophenyl)-5-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrido[2,3-c]pyridazine-6-carbonitrile **8** [41]. Its IR spectrum showed absorption band at 2210 attributable to ɣC≡N. The molecular structure of compound **8** was established by ^{1}H NMR spectrum, which exhibited the presence of signals at δ 3.78–4.12(d, 2H, CH–CH-C≡N).

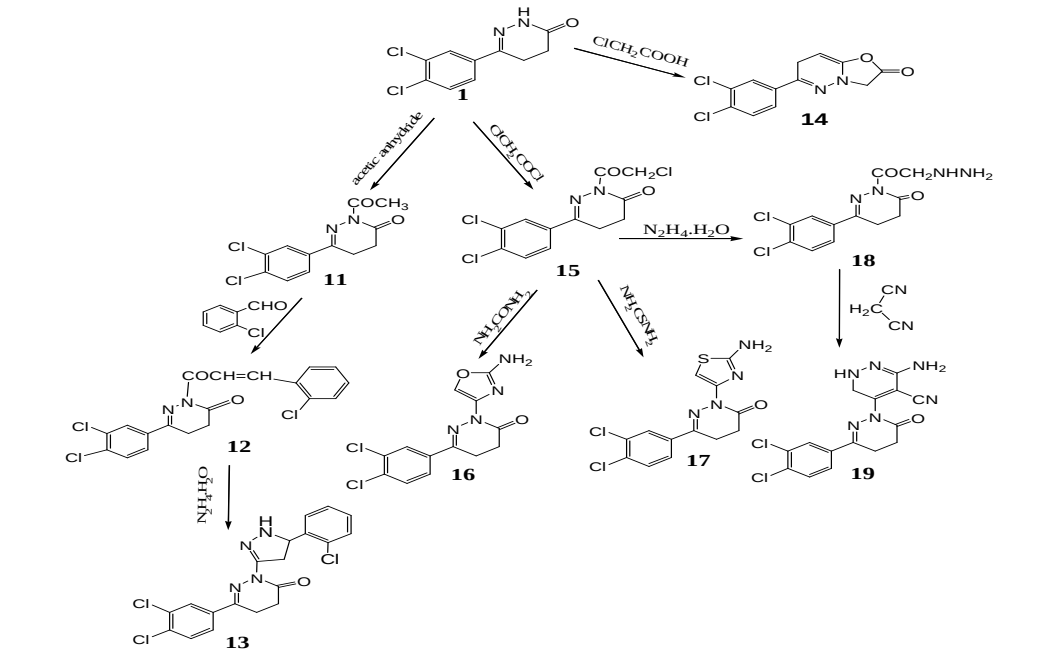
On the other hand, the reaction of 6 - (3,4-dichlorophenyl)- 4 - (4-methoxybenzylidene) - 4,5- dihydropyridazin-3(2H)-one **2c** with thiosemicarbazide yielded the corresponding 5-(3,4-dichlorophenyl)-3-(4-methoxyphenyl)-2,3,3a,4,7,7a-hexahydro-1H-pyrazolo[3,4-c] pyridazine-1-carbothioamide **9** [42]. Its IR spectrum showed absorption bands at 1166, 3350- 3100(broad) attributable to ɣC=S,ɣ NH_2. The ^{1}H-NMR(DMSO-d_6) of **9** showed signal bands at δ 3.20(s,2H, NH_2-amide).

Treatment of 5- (3,4-dichlorophenyl) -3- (4-methoxyphenyl) -2,3,3a,4,7,7a-hexahydro -1H-pyrazolo [3,4-c] pyridazine -1- carbothioamide **9** with phenacyl bromide in boiling ethanol afforded the corresponding 5-(3,4-dichlorophenyl)-3-(4-methoxyphenyl)-N-(2-phenylacetyl)-3a,4-dihydro-3H-pyrazolo[3,4-c]pyridazine-2(7H)-carbothioamide**10** [43]. Its IR spectrum showed the presence of C=O, C=S and NH functional groups which proves the formation of open not cyclic compound.

Reaction of 4,5-dihydro-6-(3,4-dichlorophenyl)-pyridazin-3(2H)-one**1** with acetic anhydride in the presence of glacial acetic acid afforded the corresponding 2-acetyl-6-(3,4-dichlorophenyl)-4,5-dihydropyridazin-3(2H)-one **11** [44,45] (scheme 2) which was reacted with 2-chloro benzaldehyde under Clasien conditions to give 2-(3-(2-chlorophenyl)acryloyl)-6-(3,4-dichlorophenyl)-4,5-dihydropyridazin-3(2H)-one **12** [32-35]. The infrared spectrum **11** showed strong absorption band at 1750, 1472 attributable to ɣC=O acetyl, ɣCH_3. Also the structure of **11** was elucidated by 1H NMR spectrum, which exhibited signals at δ 3.52(s, 3H, $COCH_3$).



Scheme 1. Heterocycle synthesis from 4-(arylidenee)-6-(3,4-dichlorophenyl)-4,5-dihydro pyridazin 3(2H)-one



Scheme 2. Functionalizations of 4,5-dihydro-6-(3,4-dichlorophenyl)-pyridazin-3(2H)one **1**

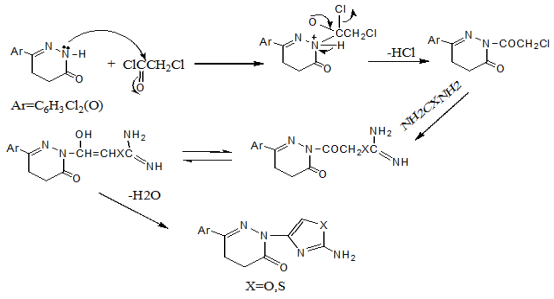
Interaction of **12** with hydrazine hydrate in ethanol under reflux afforded hydrazine derivative **13** [36-41]. The 1H NMR spectrum of **13** showed disappearance of the signal assigned to CH=CH group and appearance of new signal at δ 3.26(s, 1H, NH) pyrazolyl moiety.

Also, reaction of 4,5-dihydro-6-(3,4-dichlorophenyl)-pyridazin-3(2H)-one **1** with chloroacetic acid in dry acetone containing K_2CO_3 gave the corresponding 6-(3,4-dichlorophenyl)-3,7-dihydro-2H-oxazolo[3,2-b]pyridazin-2-one **14** [46] while its reaction with chloroacetylchloride under reflux in ethanol afforded the corresponding 2-(3-(3,4-dichlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl)acetyl chloride **15** [47].

The infrared spectrum of **14** showed absorption band at 1693 attributable to ν δ–lactone. The infrared spectrum of **15** was devoid the presence of NH, The 1H NMR spectrum of **15** showed disappearance of the signal assigned to NH group and appearance of new signal at δ 3.66 for (s,2H, CH_2COCl).

Interaction of **15** with urea and/or thiourea in boiling ethanol afforded the corresponding oxazole 2-(2-aminooxazol-4-yl)-6-(3, 4-dichlorophenyl)-4, 5-dihydropyridazin-3(2H)-one **16** and thiazole 2-(2-aminothiazol-4-yl)-6-(3,4-dichlorophenyl)-4,5-dihydropyridazin-3(2H)-one **17,** respectively [48]. The infrared spectra of **16**, **17** showed absorption band at 3200-3156 νNH_2.

Reaction takes place according to following mechanism:-



Hydrazinolysis of **15** gave 2-(3-(3, 4-dichlorophenyl)-6-oxo-5, 6-dihydropyridazin-1(4H)-yl) acetohydrazide **18** which reacted with malononitrile in glacial acetic acid under reflux for 8 hrs. to afford 3-amino-5-(3-(3,4-dichlorophenyl)-6-oxo-5,6-dihydropyridazin-1(4H)-yl)-1,6-dihydro pyridazine-4-carbonitrile **19** [49]. The infrared spectrum of **18** showed absorption bands at 1676, 3196 -3325 attributable to ν C=O, ν $NHNH_2$. The infrared spectrum of **19** showed absorption band 2210 attributable to νC≡N**.**

The behavior of 4,5-dihydro-6-(3,4-dichlorophenyl)-pyridazin-3(2H)-one **1** towards nucleophilic reagents like $POCl_3$ gave 3-chloro-6-(3,4-dichlorophenyl)-4,5-dihydropyridazine **20** [50] (scheme 3), with substitution of the enolic hydroxyl group. The infrared spectrum of **20** was devoid the presence of C=O, NH and showed absorption band at 598cm^{-1} attributable to ν C-Cl while its ^{1}H-NMR (DMSO-d_6) spectrum showed disappearance of signal for (NH, OH) proton.

The structure of **20** was confirmed chemically by its reaction with p-amino acetophenone in ethanol to afford the corresponding 1-(4-(6-(3,4-dichlorophenyl)pyridazin-3-ylamino) phenyl)ethanone**21.** Infrared spectrum of **21** showed absorption band at 3218 attributable to ν NH and devoid the presence of νC-Cl.

Treatment of 1-(4-(6-(3,4-dichlorophenyl)pyridazin-3-ylamino) phenyl)ethanone **21** with bromine /acetic acid gave the corresponding 2-Bromo-1-{4-[4-bromo-6-(3,4-dichloro-phenyl)-pyridazin-3-ylamino]-phenyl}-ethanone **22.** The ^{1}H-NMR (DMSO-d_6) spectrum of **22** showed signals at δ 5.05 (s, 1H, NH), δ 4.64(s, 2H, $COCH_2$) and disappearance of (CH_3) protons.

Reaction of **22** with thiosemicarbazide and /or thiouerea afforded the corresponding 2-(4-(4-bromo-6-(3,4-dichlorophenyl)pyridazin-3-ylamino)phenyl)-6H-1,3,4-thiadiazin-5-amine **23** and 4-(2-aminothiazol-4-yl)-phenyl]-[4-bromo-6-(3,4-dichloro-phenyl)-pyridazin-3-yl]-amine **24** respectively. The infrared spectrum of compound 23 showed absorption band at 3313-3245 attributable to ν NH_2. 1H NMR spectrum of **23** revealed the presence of new singlet signal at δ 6.90 δ assigned to CH_2 protons for thiadiazine moiety, δ 6.99(s,1H,CH-pyridazine ring) and 8.12(s,1H,NH) and δ 5.54(s, 2H, NH_2). Its 1H-NMR (DMSO-d_6) spectrum showed signals at δ 6.57(s, 1H, CH-thiazole ring), δ 4.64(s, 1H, NH), δ 5.76(s, 1H, NH_2).

Table 1. Response of various microorganisms to some synthesized compounds in vitro culture. (Mean* of zone diameter, nearest whole mm.)

Organism	Gram- positive bacteria				Gram- negative bacteria				Yeasts and Fungi**			
Organism	Gram- positive bacteria				Gram- negative bacteria				Yeasts and Fungi**			
	Staphylococcus aureus (ATCC25923)		Bacillussubtilis (ATCC 6635)		Salmonella typhimurium (ATCC 14028)		Escherichia (ATCC 25922)		Candida albicans (ATCC 10231)		Aspergillus fungus	
Conc. / Sample	1 Mg/ml	0.5 Mg/ml	1 Mg/ml	0.5 Mg/ml	1 Mg/ml	0.5 Mg/ml	1 Mg/ml	0.5 Mg/ml	1 Mg/ml	0.5 Mg/ml	1 Mg/ml	0.5 Mg/ml
1	0	0	8	7	0	0	12	8	0	0	8	7
2b	14.3	0	17.3	0	15.2	0	14.2	0	17.3	0	20.2	0
2c	0	0	0	0	0	0	0	0	18	14	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	12.1	0	13.6	0	12.3	0	11.2	0	14.3	0	16.1	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	16.3	0	19.3	0	17.4	0	16.2	0	20.9	0	18.6	0
11	0	0	11	8	9	8	14	10	11	7	14	12
18	10	7	11	10	11	8	10	7	22	18	12	9

• Low activity = Mean of zone diameter ≤ 1/3 of mean zone diameter of control.

• Intermediate activity = Mean of zone diameter ≤ 2/3 of mean zone diameter of control.

• High activity = Mean of zone diameter > 2/3 of mean zone diameter of control.

** = Calculate from 3 values.*

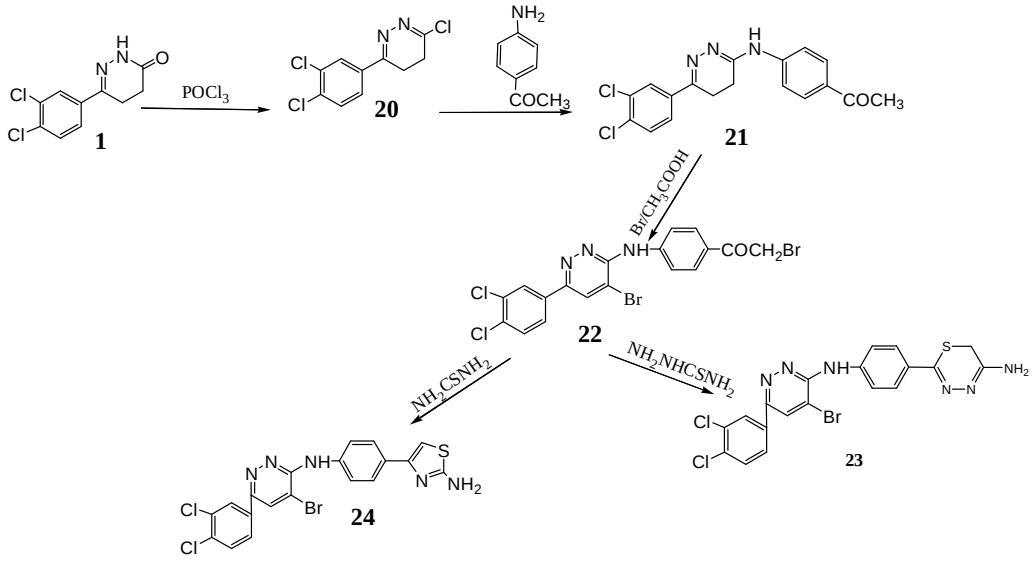
*** = identified on the basis of routine cultural , morphological and microscopical characteristics.*

0 = No effect

3.2 Antimicrobial Activity

The compounds **1, 2b, 2c, 6, 7, 9, 10, 11 and 18** were screened for their antimicrobial activity against the bacteria Staphylococcus aureus, Bacillus subtilis(Gram-positive bacteria), and Salmonella typhimurium, Escherichia coli (Gram-negative bacteria) in addition to the yeast Candida albicansand fungus Aspergillus fumigatus following the filter paper disc technique. Ampicillin, Gentamicin and Amphotericin B were taken as standard drugs. The synthesized compounds and reference drugs were dissolved in dimethyl formamide (DMF) at 1 mg/ml. Antimicrobial activity was determined by measuring the diameter of the inhibition zone after an incubation for 24 h at 37℃ and the activity of each compound was compared with its respective reference drug as a positive control. The results are listed in Table 1. The antimicrobial activity showed that all compounds were active against tested microorganisms except compounds1, **2c, 9** and **6.** Compounds **2b, 7, 10, 11** and **18** were most active in comparison to Amphotericin B, which was taken as a standard antifungal drug.

On the similar manner compounds **2b, 2c, 6, 7** and **10** were tested for their antimicrobial activity as MICS (µg/ml)of tested samples against tested microorganisms. The results are listed in Table 2.



Scheme 3. Heterocyclization reactions with 22

Table 2. Antimicrobial data (at MIC) of the investigated compounds

Organism	Gram- positive bacteria		Gram- negative bacteria		Yeasts and Fungi**	
	***Staphylococcus aureus* (ATCC25923)**	***Bacillussubtilis* (ATCC 6635)**	***Salmonella typhimurium* (ATCC 14028)**	***Escherichia* (ATCC 25922)**	***Candida albicans* (ATCC 10231)**	***Aspergillus fungus***
Conc. / Sample	**100 µl**	**100 µl**	**100 µl**	**100 µl**	**100 µl**	**100 µl**
2b	62.5	31.25	62.5	63.5	15.63	1.95
2c	125	125	125	125	125	31.25
6	125	62.5	125	125	31.25	3.9
7	125	62.5	125	125	62.5	31.25
10	31.25	3.9	15.63	31.25	3.9	0.98

#: Chloramphencol in the case of Gram – positive, Cephalothin in the case of Gram – negative bacteria and cycloheximide in the case of fungi

4. CONCLUSION

The research study reported the successful synthesis and antimicrobial activity of new pyrazole, oxazole, pyridine, thiazole, thiadiazine, and pyrimidine derivatives bearing pyridazine moiety. The antimicrobial activity study revealed that some of the tested compounds showed moderate to good antibacterial activity and some of the tested had antifungal activities against pathogenic strains.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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