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# Synthesis, anti-microbial evaluation and cytotoxicity bioassay of some synthesized novel pyridazine derivatives comparison to standard drugs

**Ahmed A. Fayed[1, 2*], Ahmed F. El-Farargy[3], Nabil M. Yousif[2], Farouk A. Gad[2] and Atef A. Kalmouch[4]**

*[1]Respiratory Therapy Department, Faculty of Medical Rehabilitation Sciences, Taibah University, Almadinah Almunawarah, Saudi Arabia*
*[2]Phytochemistry Department, National Research Center, Dokki, Cairo, Egypt*
*[3]Chemistry Department, Faculty of Science, Zagazig University, Egypt*
*[4]Peptide Chemistry Department, National Research Center, Dokki, Cairo, Egypt*

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**ABSTRACT**

*Pyridazines and their derivatives received tremendous attention with the recent discovery of biological activities such as anti-inflammatory, anti-epileptic, antibacterial, antibiotic, anti-depressant, anti-diabetic, anti-hypertensive, analgesic, anti-tumor, antiviral and anti-cancer.New series of pyridazine and pyrazinehave been synthesized and the structures of the new compoundswere established on the basis of [1]H-NMR, mass (ES/MS), elemental analysis and IR spectral data. In vitro anti-microbial activity (MICactivity) was evaluated and compared with standard drugs Tertacyclineand Ketoconazole. Most of the compounds in the serieshave shown very interesting anti-microbial activity against both Gram-positive and Gram-negative organisms. The detailed synthesis, spectroscopic data and pharmacological properties are reported.*

**Keywords**: pyridazine; pyrazine; triazine; Anti-microbial activity;Tertacycline.

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## INTRODUCTION

Pyridazine derivatives were used in many research fields due to their structure, stability and reactivity and their tendency to form stable compounds with useful biological properties [1]. Pyrazolopyridazines derivatives were being reported for biological and pharmacological activities such as antimicrobial [2], anti-inflammatory [3] and Inhibitors of (GSK-3) [4]. Pyridazine and pyrimidine derivatives have been previously reported to be platelet-aggregation inhibitors, α-adrenoceptor antagonists, anti-hypertensive, antinociceptive, antimicrobial and anti-parkinsonism [5-8]. Heterocyclic nitrogen compounds are responsible for the mechanism of the drug activity, for example, in Zidovudine (Retrovir®) [9]. Therefore, we are reporting here a new pyrazolopyridazine ring systems with additive effect toward the biological activities. Also, in view of these observations and in continuation of our previous work in heterocyclic chemistry [10-15], we herein are reported the synthesis of poly-functionally substituted heterocyclic systems for their antimicrobial activities.

## MATERIALS AND METHODS

### CHEMISTRY

**3,5-dihydro-4,6-dioxo-phenathro[9,10:5',6']pyrazino[2,3-d]imidazolo[2,3-b]imidazolo[2,3-f]pyridazine 4**

A mixture of **3** (0.01mol) and chloroacetyl chloride (0.02 mol) in DMF (20 ml) and few drops of piperidine was heated under reflux for 8 hours, then cooled and poured onto ice-cold water. The solid product collected and

crystallized from ethanol /DMF to give **4** as red powder in 59% yield, M.P. 291°C, IR (film): *v* = 1720 (2C=O), 1610 – 1460 (C=N) and (C=C) aromatic $cm^{-1}$; $^1$H-NMR (DMSO–$d_6$) : δ = 2.40 (S, 4H,2 $CH_2$), 7.12 – 7.64 (m, 8H, Haromatic) ppm; MS (El, 70 eV) : m/z = 392 ($M^+$, 8) and at 350 (100, base peak); Elemental analysis: ($C_{22}$ $H_{12}$ $N_6$ $O_2$) Calcd. 67.34 C, 3.08 H, 21.41 N. Found 67.31, 3.12, 21.43

**5,6-diamino–3,8-dioxo–phenanthro [9.10:5',6'] pyrazino [2,3-d] pyrimidino [2,3-b] pyrimidino [2,3-f] pyridazine 5**

A mixture of **3** (0.01 mol) and ethyl cyanoacetate (0.02 mol) were mixed with polyphosphoric acid (30 ml). The reaction mixture was refluxed for 6 hours. After cooling, water (30 ml) added, neutralized with sod. carbonate, and the solid product was formed by crystallization from ethanol to give **5** as green powder, in 70% yield, M.P. over 300ºC; IR (film): *v* = 3250 ($2NH_2$), 1720 (2C=O), 1610–1450 (C=N, C=C ar) $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) : δ = 5.91 (S, 2H, H-3 and H-5 ring), 7.15 – 7.68 (m, 8H,Haromatic), 11.10 (S, 4H, $2NH_2$) ppm; MS (El,70eV):m/z = 446 ($M^+$, 13), 377 (100, base peak); Elemental analysis : $C_{24}H_{14}N_8O_2$ Calcd. 64.57 C, 3.16 H, 25.10 N. Found: 64.51, 3.18, and 25.17.

**Phenannthro[9,10:5',6']pyrazino[2,3-d]-1,2,4-thiadiazolo-[2,3-b]-1,2,4-thiadiazolo[2,3-f]pyridazine-3,6-dithione 7**

Carbon disulphide (0.02 mol) was added drop wise to an ice-cold solution of KOH (0.01 mol) in ethanol (40ml) containing the compound **3**. The mixture was stirred at room temp. for 22 hours. The product obtained was employed in the next reaction without further purification. To a suspension of above potassium salt **6**, bromine (0.02 mol) and sodium carbonate (0.01 mol). The reaction mixture was refluxed for 7 hours. Then, water (30 ml) added. The solid product was collected and crystallized from ethanol to give **7** as yellow crystals, in 52% yield, M.P. over 300°C. IR (film): *v* = 1095 (C=S), 1620-1480 (C=N, C=C aromatic) $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): δ = 7.55 – 8.01 (m, 8H,Haromatic) ppm; MS (El, 70 eV): m/z = 406 ($M^+$, 54), 254 (100, base peak); Elemental analysis: $C_{20}H_8N_6S_4$ Calcd.: 52.15 C, 1.75 H, 18.29 N. Found: 52.19, 1.72, 18.21.

**4-amino-6-oxo-7H-phenanthro[9,10-e]pyrimidino[1,2-b]pyrazolo[3,4-c]pyridazine 11**

A mixture of **10** (0.01 mol), and ethyl cyanoacetate (0.01 mol), were mixted with poly phosphoric acid (30ml), the reaction mixture was refluxed 4 hours. After cooling, water (35 ml) added, neutralized with sodiumcarbonate and the solid product was formed by crystallized from ethanol to give **11** as yellow crystals, in 73% yield; M.P. over 300°C. IR (film): *v* = 3388 ($NH_2$, NH), 1670 (C-O amid), 1610–1444 (C=N and C=C aromatic) $cm^{-1}$, $^1$H.NMR (DMSO-$d_6$) : δ = 5.69 (s, $NH_2$), 7.59 – 7.90 (m, 8H, Haromatic and 1H ring H-5), 10.39 (s, NH) ppm; MS: (El, 70 eV) m/z = 352 ($M^+$, 23), 83 (100, base peak). Elemental analysis: $C_{20}H_{12}N_6O$ Calcd.: 68.17 C, 3.43 H. 2.38 N. Found: 68.23, 3.41, 2.43.

**4-oxo-6H-phenanthro[9,10-e]imidazolo[1,2-b]pyrazolo[3,4-c]pyridazine 12**

A mixture of **10** (0.01 mol) and chloroacetyl chloride (0.01 mol), in DMF (15 mL) and few drops of piperidine was heated under reflux for 6 hours, then cooled and poured onto ice-water. The precipitate obtained crystallized from DMF/ethanol to afford pure product **12** as brown powder, in 61% yield, M.P. 240ºC. IR (film) *v* = 3225 (NH or OH), 1670 (C=O amide), 1620 (C=N, C=C aromatic) $cm^{-1}$, $^1$H-NMR (DMSO – $d_6$): δ = 4.27 (S, $CH_2$), 7.74–7.96 (m, 8H, Haromatic), 11.71 (br, NH) ppm; MS: (El, 70 eV): m/z = 325 ($M^+$, base peak). Elemental analysis $C_{19}H_{11}N_5O$ Calcd.70.14 C, 3.40 H, 21.52 N. Found: 70.23, 3.36, and 21.47.

**4-amino-6-phenyl-phenanthro[9,10-e]pyrimidino[1,2-b]pyrazolo[3,4-c]pyridazine 13**

A mixture of **10** (0.01 mol), benzoyl acetonitrile (0.01mol), ethanol (30ml) and few drops of piperidine was refluxed for 8 hours. After cooling, the solid product was collected and crystallized from ethanol to give **13** as green powder, in 73% yield, M.P. over 300°C. IR (film): *v* = 3410 ($NH_2$), 1610-1520 (C=N and C=C aromatic) $cm^{-1}$, $^1$H-NMR (DMSO-$d_6$), δ=6.02 (S, 1H ring H-5), 7.24-7.68 (m, 13H, Haromatic), 11.80 (br, $NH_2$) ppm; MS: (El, 70 eV): 412 ($M^+$, base peak). Elemental analysis: $C_{26}H_{16}N_6$. Calcd.: 75.71 C, 3.91 H, 20.37 N. Found: 75.58, 3.95, 20.42

**4-oxo-7H-phenanthro[9,10-e]pyrimidino[1,2-b]pyrazolo[3,4-c]pyridazine 14**

A mixture of **10** (0.01mol), ethylacrylate (0.01mol), DMF (20 ml) and drops of piperidine was refluxed for 7 hours. After cooling, the solid product was collected and crystallized from acetic acid to give **14** as yellow powder, in 60% yield, M.P. 236ºC. IR (film): *v* = 3398 (NH), 1704 (C=O), 1644-1539 (C=N and C=C aromatic) $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) : δ = 7.25 – 7.84 (m, 10H, Haromatic and 2H-pyrimidinone), 10.42 (br, NH) ppm; MS: (El, 70eV) m/z = 337 ($M^+$, 49), 283 (100, base peak). Elemental analysis: $C_{20}H_{11}N_5O$. Calcd.: 71.21 C, 3.28, 20.76. Found: 71.04, 3.15, 20.68.

**Synthesis of 15 and 16**
A solution of **10** (0.01mol) in DMF (20 ml) was added (0.01mol) benzoyl benzylidine acetonitrile and/or ethyl benzylidine cyanoacetate and piperidine (2 drops) were refluxed 4 hours. The solid products were collected to give **15** and **16** respectively.

**4-amino-5-benzoyl-6-phenyl-phenanthro[9,10-e]pyrimidino[1,2-b]pyrazo-lo [3,4-c] pyridazine 15**
Compound **15** formed as yellow crystals in 58% yield, M.P. over 300°C. IR (film): *v* = 3350 ($NH_2$), 1740 (C=O), 1620-1510 (C=N and C=C aromatic) $cm^{-1}$, $^1$H-NMR (DMSO-$d_6$): δ=7.21-7.85 (m, 18H, Haromatic), MS (El-70eV): m/z = 516 (100, base peak). Elemental analysis: $C_{33}H_{20}N_6O$. Calcd.: 76.73 C, 3.90 H, 16.26 N. Found: 76.51, 3.81, 16.42.

**4-amino-5-ethoxy carbonyl-6-phenyl-phenanthro[9,10-e]pyrimidino[1,2-b ]4-pyrazolo [3,4-c]pyridazine 16**
Compound **16** formed as green powder, in 60% yield, M.P. over 300ºC, IR (film): *v* =3424 ($NH_2$), 1769 (C=O of ester), 1650-1430 (C=N and C=C aromatic) $cm^{-1}$; $^1$H NMR (DMSO-$d_6$): δ=1.04 (t, $CH_2$), 1.90 (9, $CH_3$), 7.61-8.62 (m, 13H, Haromatic), 11.71 (s, $NH_2$) ppm; MS (El-70eV): m/z= 484 (100, base peak). Elemental analysis: $C_{29}H_{20}N_6O_2$. Calcd.: 71.88 C, 4.16 H, 17.34. Found: 71.91, 4.23, and 17.19.

**4,6-diphenyl-phenanthro[9,10-e]pyrimidino[1,2-b]pyrazolo[3,4-c]pyrid-azine 17**
A suspension of compound **10** (0.01mol) and benzylidine acetophenone (0.01 mol) in absolute ethanol (30 ml) containing (3 drops) of piperidine was refluxed 8 hours. The mixture was left to cool at room temperature, poured onto cold water, and neutralized with dilute HCl. The yellow solid product was filtered off and crystallized from EtOH/DMF to give **17** as yellow crystals, in 63% yield, M.P. 297°C. IR (film): *v* = 1620–1540 (C=N and C=C aromatic) $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$) : δ = 7.41 – 8.36 (m, 18H, Haromatic and H ring) ppm; MS (El-70 eV); m 1Z=473 ($M^+$, 35), 370 (100, base peak). Elemental analysis: $C_{32}H_{19}N_5$. Calcd.: 81.16 C, 4.04 H, 14.78 N. Found: 81.23, 4.12, 14.63

**Anti-microbial Activity**
The newly tested compounds were evaluated in vitro for their antimicrobial activities. The antimicrobial activities are carried out against three bacterial strains *S. aureus, S. epidermidis,E. coli* and three fungal strains *A. fumigates, A. niger and A. alternate* employing the nutrient agar disc diffusion method at 100 µg/ ml concentration[17]. DMSO was used as blank exhibited no activity against any of the used organisms. The antimicrobial activity was determined by measuring of the inhibition zone (Table 1), after 16 -20 hrs. of incubation at 37 $^0$C for bacterial strains and 3-4 days at 37 $^0$C for fungal strains. Tetracycline and Ketoconazole were used as standard drugs bacterial and fungal strains, respectively at 30 µg/ ml concentration.

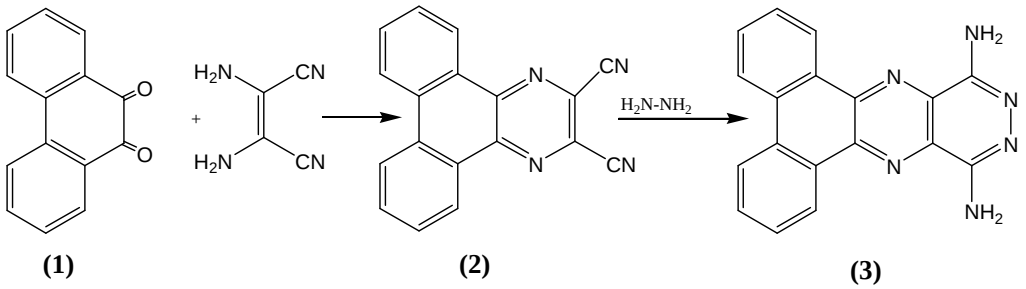
**The Minimum Inhibitory Concentration (MIC)**
A current definition of the minimum inhibitory concentration MIC is "the lowest concentration which resulted in maintenance or reduction of inoculums viability". The determination of the MIC involves a semi-quantitative test procedure which gives an approximation to the least concentration of antimicrobial agent needed to prevent microbial growth. The method displays tubes of growth broth containing a test level of preservatives, into which inoculums of microbes was added. The end result of the test was the minimum concentration of antimicrobial. The serial dilution technique [18] was applied for the determination of MIC of the tested compounds 1-6 against two species of bacterial strains *( S. aureus* and *E. coli*) and two species of fungal strains (*A. niger* and *A. alternata*). Dilution series were set up with 6.25, 12.5, 25, 50 and 100 µg/ ml of nutrient broth medium to each tube, 100 µl of standardized suspension of the test microbes ($10^7$ cells/ ml)were added and incubated at 37 $^0$C for 24 hrs (Table 2).

**Cytotoxicity Bioassay**
Brine Shrimp lethality bioassay [19, 20] is recent development in the assay which indicates cytotoxicity as well as a wide range of pharmacological activities (e.g. antimicrobial, anticancer, antiviral, insecticidal, pesticidal, AIDS, etc). In this method, the eggs of the brine shrimp, Artemia salina leach, were hatched for 48 hrs., to mice shrimp, 38 gm of sea salt was weighed , dissolved in one liter of distilled water, filtered off and was kept in a small tank. The eggs were then added to the divided tank. Constant oxygen supply was provided and temperature 37$^0$C was maintained for 48 hrs. to hatch and mice the shrimp called as nauplii (Larvae). The solutions of compounds 1-6 were prepared by dissolving 10 mg of each compound in 2 ml of DMSO. From this stock, a series of solution 5, 10, 20, 40 and 80 µg/ml were transferred to fifteen vials (three for each dilutions were used for each test sample and $LC_{50}$ is the mean of three values) and one vial was kept as control having 2 ml of DMSO. Then about 10 brine shrimp nauplii were applied to each of all experimental vials and control vial. The number of the nauplii that died after 24 hours was counted. The resulting data were transformed to the probit analysis for the determination of $LC_{50}$ values for the five tested compounds (Table 3).

## RESULTS AND DISCUSSION

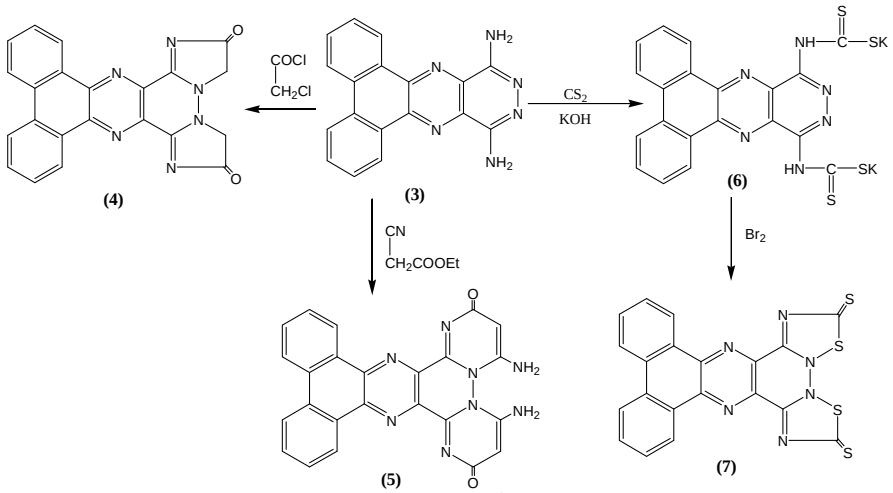
### Chemistry

In continuation of our previous work in heterocyclic chemistry, a series of novel pyridazinopyrazine derivatives have been synthesized using 2, 5-diamino-phenathro [9,10-b] pyridazino [4,5-e] pyrazine**3** which, was prepared by the condensation of phenanthraquinone**1** with diaminodicyanoethene to afford dicyanopyrazine**2** then, cyclized of compound **2** with hydrazine to afford 2,5 diamino-phenanthro [9,10-b] pyridazino [4,5-e] pyrazine**3** according to the reported procedures [16] as starting material (Scheme1).



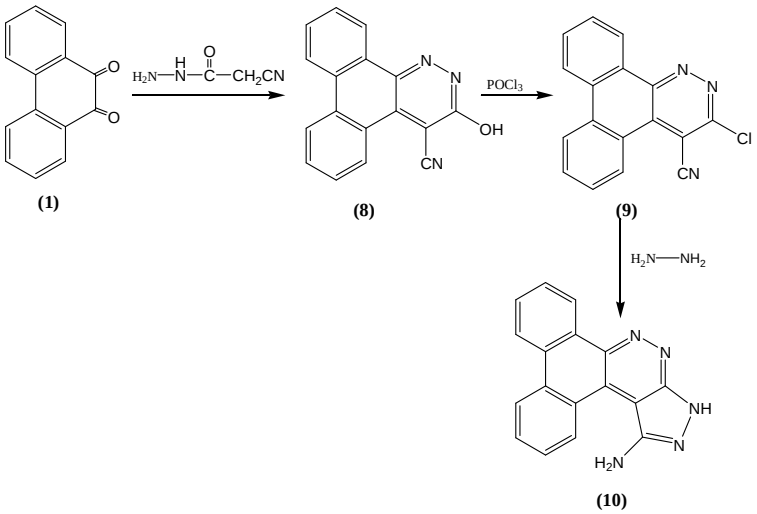

**Scheme 1: Synthetic route of compound 3**

Reaction of compound **3** with chloroacetyl chloride and ethyl cyanoacetate respectively yielded the corresponding substituted pyridazine derivatives **4** and **5** respectively. The reaction occurred by nucleophilic attack of diamino groups of pyridazine followed by cyclization and elimination of hydrogen proton to form new poly cyclic derivatives **4** and **5**. Also, compound **3** reacted with carbon-disulphide to give dipot-salt **6**, which cyclized with bromine to give thiadiazolo derivatives **7** (Scheme 2).



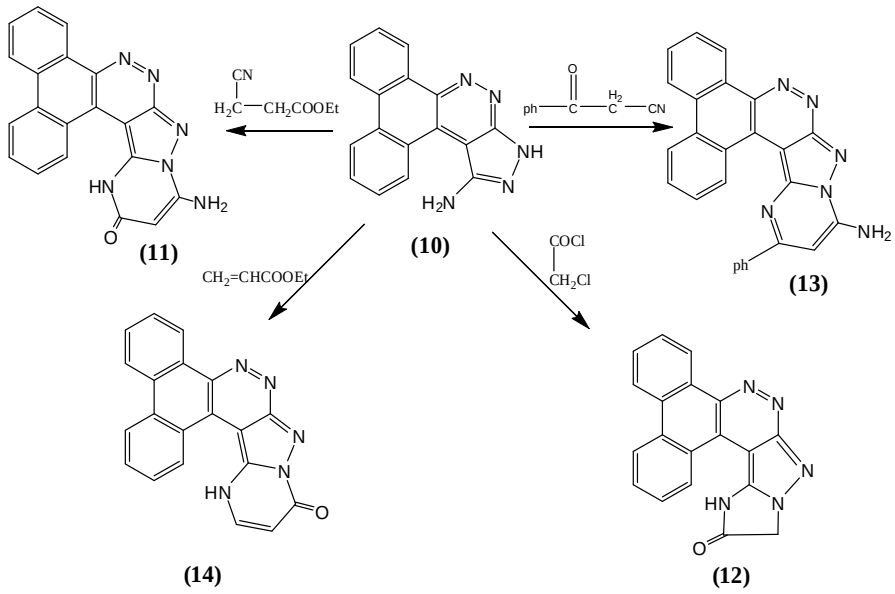

**Scheme 2: Synthetic route of compounds 4 -7**

Also, 5-amino phenanthro-[9,10-*e*]-3H-pyrazolo[3,4-*c*]pyridazine **10** was prepared by the condensation of phenanthraquinone **1** with 2-cyano ethanoic acid hydrazid to form the hydroxyl pyridazine derivative **8**, then, reaction of compound **8** with $POCl_3$ afforded chloro derivatives **9.** Reaction of compound **9** with hydrazine afforded pyrazolopyridazine **10** [16] (scheme 3).



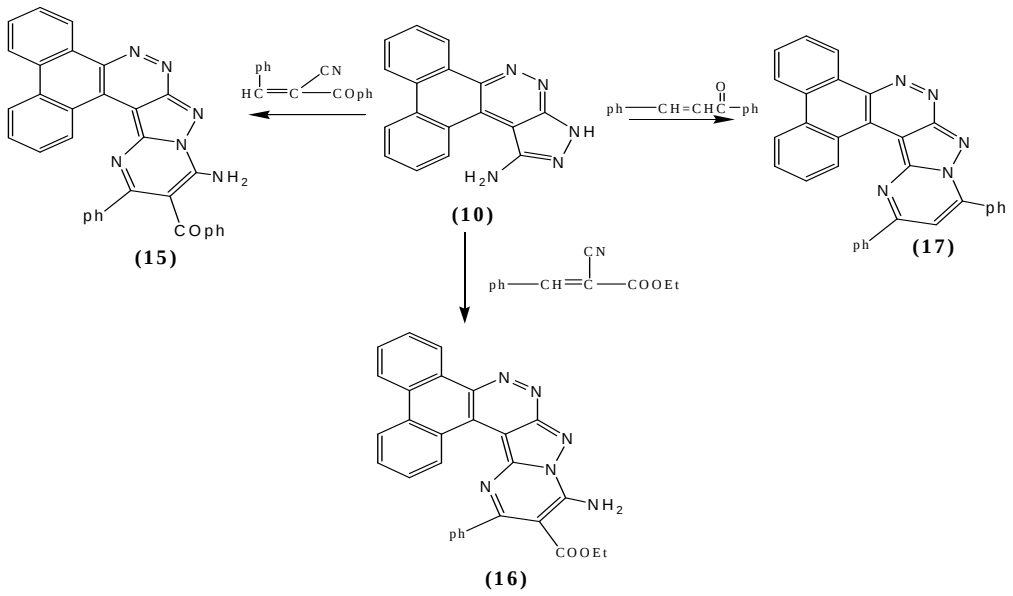
**Scheme 3: Synthetic route of compounds 8 10**

Compound **10** reacted with ethyl cyanoacetate to yield the corresponding new polycyclic pyrimidinopyrazolopyridazine derivatives **11.** This reactions occurred by nucleophilic attack of lone pair of electrons on nitrogen atom followed by cyclization. Compound **10** reacted with chloroacetyl chloride to afford new compound imidazolo-pyrazolo-pyridazine **12.** Also, reaction of compound **10** with benzoyl acetonitrile and ethyl acrylate respectively to yield the corresponding new polycyclic pyrimidino-pyrazolo-pyridazine derivatives **13** and **14** respectively (scheme 4).



**Scheme 4: Synthetic route of compounds 11 -14**

Reaction of compound **10** with benzylidine derivatives namely benzoyl benzylidine aceto nitrile, ethyl benzylidine cyanoacetate and benzylidine acetophenone respectively, afforded pyrimidinopyrazolo-pyridazine derivatives **15, 16** and **17** respectively. (Scheme 5)



**Scheme 5: Synthetic route of compounds 15 -17**

## Anti-microbial Activity

The tested compounds **4, 5, 7, 11, 12, 13, 14, 15, 16** and **17** were evaluated in vitro for their anti-microbial activity. The anti-microbial activities are carried out against three bacterial strains, *(Staphylococcus aureus,Staphylococcus epidermidis* and *Escherichia coli), and* three fungal strains (*Aspergillus* fumigates, *Aspergillus niger* and Alternaria alternate). The preliminary screening results indicated that the most compounds showed antimicrobial activity from weak, moderate to good. From the inhibition zone diameter data analysis, compounds **11, 12, 15** and **16** showed good inhibitions against all the species of bacterial but compounds **5, 13** and **14** moderate inhibitions against *A. niger* and *A.alternate*. Compounds **4, 7** and **17** showed in general weak inhibitions against all the species of bacterial and fungal strains. (Table 1)

**Table 1: The Antimicrobial activity of tested compounds at 100 µ g/ml concentrations**

| Compd. NO. | Diameter of the inhibition zone [a] (mm) | | | | | |
|---|---|---|---|---|---|---|
| | Bacteria | | | Fungi | | |
| | *S. aureus* | *S. epidermidis* | *E. Coli* | *A.Fumigates* | *A. niger* | *A. Althernata* |
| 4 | 10 | 8 | 11 | 7 | 9 | 10 |
| 5 | 12 | 10 | 13 | 14 | 11 | 13 |
| 7 | 8 | 9 | 10 | 8 | 10 | 6 |
| 11 | 20 | 18 | 22 | 19 | 18 | 19 |
| 12 | 19 | 20 | 21 | 18 | 16 | 19 |
| 13 | 13 | 14 | 16 | 15 | 12 | 16 |
| 14 | 11 | 13 | 12 | 14 | 13 | 11 |
| 15 | 24 | 21 | 25 | 18 | 17 | 20 |
| 16 | 26 | 22 | 23 | 20 | 19 | 21 |
| 17 | 6 | 9 | 6 | 7 | 8 | 10 |
| Tertacycline[b] | 27 | 25 | 29 | - | - | - |
| Ketoconazole[b] | - | - | - | 21 | 20 | 23 |

[a]*15mm or less weak inhibition, 16-20mm:moderate inhibition, 20mm or more good inhibition*
[b]*The concentration of used standard drugs was 30 µ g/mL*

**Table2: The minimum inhibitory concentration (MIC, µg/ml)of tested compounds 11, 15 and 16**

| The selected organisms | The minimum inhibitory concentration (MIC) | | | |
|---|---|---|---|---|
| | **11** | **15** | **16** | Standard[a] |
| *S. aurous* | 50 | 50 | 50 | 6.25 |
| *E. coli* | 25 | 12.5 | >100 | 12.5 |
| *A. niger* | 50 | 2.5 | >100 | 6.25 |
| *A. althernata* | 50 | >100 | 25 | 6.25 |

[a]*Tetracycline and Ketoconazole were used as standard drugs against bacterial and fungal strains, respectively.*

## The Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC, µg/ ml) of the most active compounds **11**,**15** and **16** against two species of bacteria (*S. epidermidis* and *E. coli*) and also two species of fungi (*A. niger* and *A. alternate*) were

determined (Table 2). Compounds **11**, **15**and **16** demonstrated good inhibitions against the selected bacterial and fungal strains.

**Cytotoxicity Activity**

The $LC_{50}$ values of tested compounds **11**, **15**and **16** were found to be 2.36, 4.52 and 1.93µg/ ml, respectively (Table 3). The standard drug Bleomycin has $LC_{50}$ value at 0.62 g/ml. The lowest $LC_{50}$ value was found in the case of compound **15** indicating higher cytotoxicity than the other compounds. Compounds **11** and **16** showed potent biocidal activity against brine shrimp due to their lower cytotoxicity that agreement with preliminary anti-microbial screening and the minimum inhibitory concentration (MIC).

**Table3: Cytotoxicity activity of tested compounds 11, 15 and 16**

| Comp. No | 95% confidence limite ppm | | | Regression Equation | $X^2$(df) |
|---|---|---|---|---|---|
| | $LC_{50}$ | Lower | Apper | | |
| 11 | 2.36 | 2.14 | 5.22 | Y=3.45 + 1.73 X | 3.42 (2) |
| 15 | 4.52 | 3.95 | 9.31 | Y=3.16 + 2.16 X | 0.46 (2) |
| 16 | 1.93 | 1.31 | 3.57 | Y=4.25 + 1.49 X | 0.37 (2) |
| Bleomycin[a] | 0.62 | 0.38 | 0.74 | Y=3.14 + 1.65 X | 0.51 (2) |
| Gallic Acid[a] | 3.52 | 2.15 | 5.18 | Y=3.93 + 1.62 X | 1.32 (2) |

[a]*Bleomycin and gallic acid were used as standard drugs in cytotoxicity activity.*

## CONCLUSION

The objective of the present study was to synthesize and investigate the anti-microbial activity of new thiazolo pyrimidine derivatives. The starting materials **3** was synthesized and carried out to synthesize imidazolopyridazinopyrazine derivative **4, 6** and thiadiazolopyridazinopyrazine derivative **7** respectively. Pyrazolopyridazine **10** was prepared and carried out to synthesize pyrimidinopyrazolopyridazine derivatives **11,** imidazolopyrazolopyridazine **12** andpyrimidinopyrazolopyridazine derivatives **13** and **14**respectively. Also, compound **10** carried out to synthesize pyrimidinopyrazolopyridazine derivatives **15, 16** and **17** respectively.The newly tested synthesized compounds **4, 5, 6, 7, 11, 12, 13, 14, 15, 16, 17** and the standard drug Tetracycline and Ketoconazole were found to exhibit essentially equipotent antimicrobial activity**.**

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