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Synthesis and Antimicrobial Studies of 6-Aryl and 6-Anilino Benzo[a]phenoxazinones

Simon Sani Ocholi, Efeturi Abraham Onoabedje, and Samuel Attah Egu

ABSTRACT

Palladium catalyzed Suzuki-Miyaura (SM) and Buchwald – Hartwig (BH) cross-coupling reactions of some phenoxazines are reported. The precursor 9,11-diamino-6-chloro-7-oxa-8,10,12-triaza-benzo [a] anthracen-5-one was prepared by anhydrous base mediated reaction of 2,5,6-triamino-pyrimidin-4-ol and 2,3-dichloro-1,4-naphthoquinone in methanol. The molecular structures of the synthesized compounds agreed with UV/visible, FT-IR, ^{1}H-NMR, MS and elemental analysis data. Using Ciprofloxacin and Ketoconazole as reference drugs, the compounds were screened against six (6) micro-organisms, viz: *Listeria ivanovii, Staphylococcus aureus, Klebsiellapneumoniae, Escherichia coli, Candida albicans and Aspergillusniger*and were found to show significant activity against *L.ivanovii and E. coli* bacteria.

Keywords: Benzo[a]phenoxazinone, Buchwald–Hartwig, Suzuki-Miyaura, Cross-coupling, Palladium, Phenoxazine, Phenothiazine,.

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S. S. Ocholi
Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, Enugu State, Nigeria.
(email: simonocholi.so@gmail.com)
E. A. Onoabedje*
Department of Pure and Industrial Chemistry, University of Nigeria, Nsukka, Enugu State, Nigeria.
(email: efeturi.onoabedje@unn.edu.ng)
S. A. Egu*
Department of Pure and Industrial Chemistry, Kogi State University, Anyigba, Nigeria.
(email: attahegu@gmail.com)
Corresponding Author

I. INTRODUCTION

Antimicrobial resistance (AMR) threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi [1]. Infectious diseases are the third leading cause of death in the developed countries [2]. One of the ways to curb drug resistance is to discover new drugs and this has generated avid interest for search for new antimicrobial agents.

Phenoxazine and phenothiazine scaffolds are pharmacophores to diverse derivatives that possess biological activities. They possess antimicrobial, antimalarial, antiviral, multi drug resistance reversal, anti inflammatory, anticancer, and immunosuppressive properties [3].

Despite the fact that numerous linear and angular phenoxazine and phenothiazine compounds have been reported, the synthesis and biological study of the phenyl and anilino derivatives of 9,11-diamino-6-chloro-7-oxa-10,12-diaza-benzo[a]anthracene-5-one is largely unexplored. This prompted the synthesis of phenyl and anilino derivatives of 9,11-diamino-6-chloro-7-oxa-10,12-diazo-benzo[a]anthracene-5-one, using Pd catalysis and evaluating their antimicrobial activity.

II. RESULTS AND DISCUSSION

Most literature reports on the synthesis of angular phenoxazines and phenothiazines involved the reaction between O-aminophenol, O-aminopyridinol or aminonaphthol with 1,4-naphthoquinone derivatives in anhydrous basic media [4-6]. The synthesis of the compounds of interest, arylazabenzo[a]phenozazin-5-one and anylazabenzo[a]phenothiazin-5-one occurred in four steps. The first, the nitration of 2,4-diamino-6-hydroxypyrimidine gave 2,4-diamino-5-nitro-6-hydroxypyrimidine, **2**. Secondly. compound **2** was reduced to provide 2,5,6-triamino-pyrimidin-4-o1, **3** which in the third step was coupled with 2,3-dichloro-1,4-naphthoquinone to form 9,11-diamino-6-chloro-7-oxa-8,10,12-triaza-benzo [a] anthracene -5-one, **5** in good isolated yield after recrystallization (Fig I).

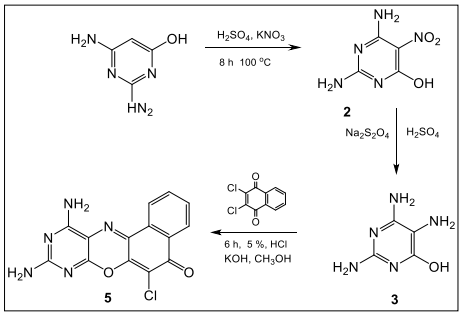

Fig 1: Synthesis of 9,11-diamino-6-chloro-7-oxa-8,10,12-triaza-benzo [a] anthracene -5-one, **5**

The fourth step (Fig II) involved the amination/arylation of 9,11-diamino-6-chloro-7-oxa-8,10,12-triaza-benzo[a] anthracen-5-one using various anilines and boronic acids under anhydrous K_2CO_3 and catalytic amount of palladium to afford highly colored products in high yields (Table 1).

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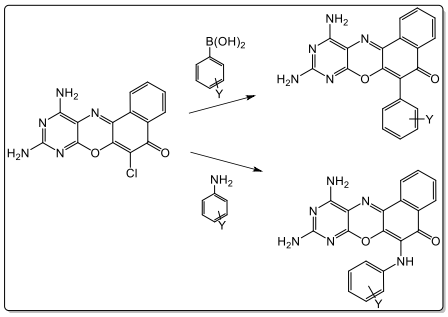


Fig.2.Synthesis of SM and BH products.

III. EVALUATION OF THE SYNTHESIZED COMPOUNDS FOR BIOLOGICAL ACTIVITY

Sensitivity test was carried out by utilizing agar-well diffusion method [7]. The synthesized compounds showed substantial activity against *L. Ivanovii* and *E. coli* only, except compound **9** which was inactive against *L. ivanovii* and *E. coli*. Also compounds **7, 8, 9** and **10** were inactive against *E. coli*. All the compounds were found to be inactive against *S. aureus*, *K. pneumoniae*, *C. albicans* and *A. niger* except compound **6** which was sensitive to *E. coli, C. albicans* and *A. niger*. In the same vein, the intermediate **5** was sensitive to the test organisms except to gram-positive bacteria.

A. Minimum Inhibitory Concentration (MIC) Determination Result

Serial dilution 5, 2.5, 1.25 and 0.625 mg/mL of each of the compounds obtained from the sensitivity test were used following the procedure outlined by Chemical Laboratory Standards Institute (CLSI) [8]. A good number of the compounds were active against the microorganisms even at low concentrations (0.01442 and 0.01567 mg/mL). Compounds **9** and **12** had the lowest MIC value (0.01442 mg/mL) and hence, most active against *L. ivanovii* (Table 3). Similarly, compound **11** was more active against *E. coli* followed by compound **12**. Compound **6** was insensitive to the test *albican* organism. All the synthesized compounds were insensitive to fungal organisms except the intermediate with a very strong activity against *A. niger*. It therefore implies that arylation/amination of postion-6 of benzo[a]phenoxazine led to the inactivation of the molecule towards fungi but enhanced its activity towards Gram-positive bacteria, especially *L.ivanovii.*

TABLE I:ARYLATION OF PHENOXAZINE AND PHENOTHIAZINEWITH BORONIC ACID DERIVATIVES

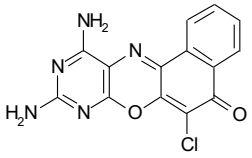
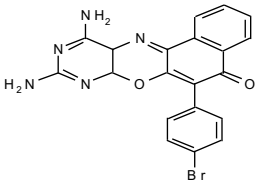
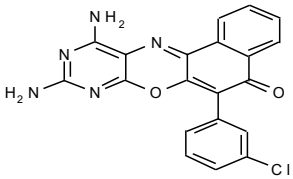
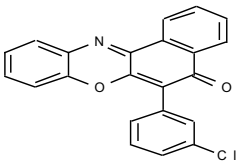
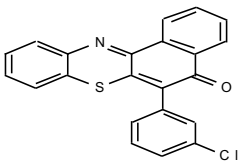
Cpd	Boronic acid	Product	Rxn time (h)	Yield (%)
5			6	89
6	$C_6H_6BBrO_2$		7	81
7	$C_6H_6BClO_2$		6	55
8	$C_6H_6BClO_2$		6	65
9	$C_6H_6BClO_2$		6	62

TABLE II: AMINATION OF PHENOXAZINE WITH ANILINE DERIVATIVES

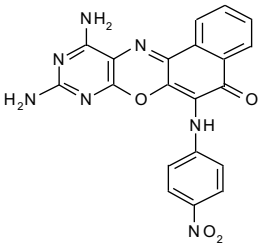
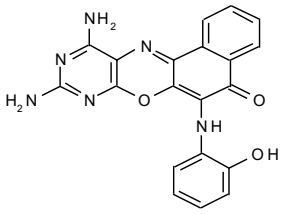
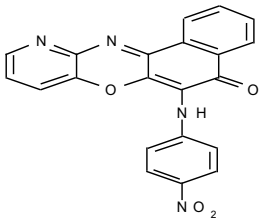
Cpd	Aniline	Product	Rxn time (h)	Yield (%)
10	$C_6H_6N_2O_2$		5	45
11	C_6H_7NO		4	65
12	$C_6H_6N_2O_2$		3	85

Table III: Minimum Inhibitory Concentration of the Compounds (mg/ml)

Compounds	Gram-positive bacteria		Gram-negative bacteria		Fungi Organism	
	S. aureus	L.ivanovii	K.pneumoniae	E.coli	C. albicans	A. niger
5	-	-	0.6990	0.13200	0.0850	0.09120
6	0.12020	0.17380	-	-	-	-
7	-	-	-	-	-	-
8	-	0.01442	-	-	-	-
9	-	0.01567	-	-	-	-
10	-	0.02121	-	-	-	-
11	-	0.01716	-	0.08385	-	-
12	-	0.01442	-	0.10320	-	-
Rf 1	0.02120	0.02130	0.0323	0.16770	-	-
Rf 2	-	-	-	-	0.06220	0.13560

IV. CONCLUSION

Suzuki-Miyaura and Buchwald-Hartwig cross-coupling reaction protocols offer excellent routes to the synthesis of new derivatives of benzo[a]phenoxazines. Compunds**8**and **12** showed pronounced activity towards Gram-positive bacteria expecially*L.ivanovii*compared to the reference drug.In addition, the dazzlingcolours of the benzo[a]phenoxazinone compounds make them applicable as potentialdyes or pigments.

V. EXPERIMENTAL SECTION

All chemicals used were of laboratory grade (Sigma-Aldrich). The melting points were determined using a Fischer John's apparatus in Chemistry Department, University of Nigeria, Nsukka and were uncorrected. UV-visible spectra were recorded on UV-2500PC series spectrophotometer using matched 1cm quartz cells in Chemistry Department, University of Nigeria, Nsukka. The IR spectra were recorded on FTIR- 8400S Fourier Transform Infrared Spectrophotometer using KBr disc (at NIPRD Abuja). ^{1}H NMR data were recorded with Brucker DPX 400 MHz spectrophotometer relative to TMS as internal standard. All chemical shifts reported in ppm (δ) and coupling constants (*J*) are reported in Hz. Multiplicity is indicated using the following abbreviations: s, for singlet; d, for doublet; t, for triplet; dd, for doublet of doublets and; m, for multiplet. The mass spectral data were obtained on a Varian 1200 Quadruple Mass and MicromassQuadro II Spectrometers. Elemental analysis was carried out on Heraeus Elemental Analyzer CHN-Rapid and the antimicrobial screening was done at the Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka.

A. 2,4-Diamino-5-nitro-6-hydroxypyrimidine.

2,4-diamino-6-hydroxypyrimidine (0.01 mg, 0.071 mmol) was dissolved in 50 mL concentrated sulfuric acid followed by portion-wise addition of potassium nitrate (0.02 mg, 0.198 mmol). The mixture was heated for 8 h with stirring while maintaining the temperature at 100 ºC. The reaction mixture was poured into crushed ice and precipitates collected by suction filtration, and residue washed with cold water and air-dried. The product was recrystallized from acetone-water to afford a light yellow solid which was obtained in 84 % yield. Mp.> 360 ºC.Lit.>400 ºC[9].

B. 2,5,6-Triamino-pyrimidin-4-ol.

To a suspension of 2,4-diamino-5-nitro-6-hydroxypyrimidine (2 mg, 0.0107 mmol) in 25 mL of boiling water was added portion wise, with stirring 5.0 mg (0.0287 mmol) of sodium dithionite. After the reaction was completed, the reaction mixture was allowed to boil vigorously for 30 min, followed by the addition of 5 mL of 9 M concentrated sulfuric acid and residue washed with cold water containing trace amount of the dithionite and air dried to obtain deep yellow solid. The crude product was recrystallized from methanol:water solution to obtain shiny yellow solid. Yield = 0.0078 mg (81 %), Mp.> 360 ºC.

C. 9,11-Diamino-6-chloro-7-oxa-8,10,12-triaza-benzo[a]anthracen-5-one.

A mixture of 2,5,6-triamino-pyrimidin-4-ol (0.0022 mg, 2 mmol) and KOH (0.0022 mg, 20 mmol) was stirred at room temperature for 0.5 h in methanol (100 mL) followed by addition of 2,3-dichloro-1,4-naphthoquinone (0.0045 mg, 20 mmol), and the entire reaction mixture was stirred at room temperature for 6 h. The solvent was distilled off in vacuum and water (50 mL) was added to the yellowish brown solid, stirred and filtered and solid further washed with 25 mL of 5 % HCl and air dried. The crude product was recrystallized from acetone-water solution after treatment with activated charcoal to give shiny yellow coloured solid. Yield = 0.0072 mg (89 %). Melting Point >360 ºC. λ_{max} 230 nm, 388.8 nm. IR 3323 (Ar-H); 1678 (C=O), 1337 (C-N).^{I}HNMR δ 8.20 (4H, m);7.70(4H, m). MS (m/e)315.19 (M^+ 10%).Anal.Calcd(found) for $C_{14}H_8ClN_5O_2$: C, 53.60 (53.45); H, 2.57 (2.46); N, 22.32 (22.30).

D. General Procedure for Suzuki-Miyaura Cross Coupling Reactions.

This was a modified method for synthesis of biaryl compounds by Tang and coworkers [10]. Dried and degassed toluene (2 mL) was added to a mixture of RX (1 mmol), $RB(OH)_2$ (1.5 mmol), K_2CO_3 (0.00058 mg, 4 mmol), $Pd_2(dba)_2$ (1 mol % Pd) and Xphos (Pd/L=1:2) in RB flask (100 mL). The mixture was flushed with nitrogen three times and stirred at 110 ºC under nitrogen for 6-8 h. It was then cooled to room temperature and partitioned between water (10 mL) and chloroform (10 mL). The organic layer was separated, dried over sodiumsulphate , filtered and concentrated in vacuo. The crude product was purified using silica gel column chromatography to provide the desired product(58 – 89 % yield).

E. Synthesis of Derivatives of 9,11-diamino-6-chloro-7-oxa-8,10,12-triazabenzo[a]anthracen-5-one.

The above general procedure was employed using 9,11-diamino-6-chloro-7-oxa-8,10,12-triaza-benzo[a]anthracen-5-one (0.0003 mg, 1 mmol), boronic acid (1.5 mmol), $Pd_2(dba)_3$ (0.00003 mg, 1 mol%), Xphos (0.0006 mg, 2 mol%), K_2CO_3 (0.0064 mg, 3 mmol) and toluene (5 mL). Purification by column chromatography (40 % EtOAc/ 60 % pet. ether eluent) provided the analytical pure titled product.

F. 9,11-Diamino-6-(4-bromo-phenyl)-7-oxa-8,10,12-triaza-benzo[a]anthracen-5-one.

4-bromophenylboronic acid (241 mg, 1.2 mmol) was utilized and the pure product was obtained as dark red solid. Yield=0.0052 mg (81 %); Mp.> 360 ºC. λ_{max} 231 nm, 339.8 nm, 478.6 nm. IR 3334 (NH_2); 3105 (Ar-H); 1645 (C=O). ^{I}HNMR δ 8.20 (4H, m); 7.50 (1H, s); 6.70 (4H ,m); 4.4 – 4.7 (4H, m). MS m/e 338.34 (M^+ 98%).Anal.Calcd (found) for $C_{20}H_{14}$ BrN_5O_2: C, 55.06 (55.02); H, 3.23 (3.19); N, 16.05 (16.00).

G. 9,11-Diamino-6-(3-chloro-phenyl)-7-oxa-8,10,12-triaza-benzo[a]anthracen-5-one.

3-Chlorophenylboronic acid (188 mg, 1.2 mmol) was coupled with phenyl boronic acid to obtain a dark brown solid product. Yield= 180 mg (55 %); Mp.>360 ºC.λ_{max}230.8 nm, 481nm. IR 3424 (Ar-H); 1646(C=O1377 (C-N). MS (m/e) 338.34(M^+ 100%).Anal.Calcd (found) for $C_{20}H_{12}$ ClN_5O_2:C, 61.63 (61.51); H, 3.10 (3.15); N, 3.10 (3.15).

Intermediates 6-Chloro-7-oxa-11,12-diaza-benzo[a]anthracen-5-one, 6-Chloro-benzo[a]phenoxazin-5-one and 6-Chloro-benzo[a]phenothiazin-5-one were synthesized as previously reported [11-13].

H. 6-(3-Chloro-phenyl)-benzo[a]phenoxazin-5-one.

6-Chloro-benzo[a]phenoxazin-5-one (281.5 mg, 1 mmol) was coupled with 3-chlorophenylboronic acid (187 mg, 1.2 mmol) to obtain a dark red solid product. Yield= 235 mg (65 %); Mp.> 360 ºC. λ_{max}231.2 nm, 475.4 nm. IR 3124 (Ar-H); 1663(C=O); 1336 (C-N). ^{I}HNMR δ 8.7 (4H, m); 8.38(4H, m); 7.82(4H, m).MS (m/e)358.06 (M^+ 20%) / 282.03 (M^+ 40%).Anal.Calcd (found) for $C_{22}H_{12}$ $ClNO_2$:C, 73.85(73.80); H, 3.38 (3.32); N, 3.91 (3.84).

I. 6-(3-Chloro-phenyl)-benzo[a]phenothiazin-5-one.

6-Chloro-benzo[a]phenothiazin-5-one (297.5 mg, 1 mmol) and 3-chlorophenyl boronic acid (187 mg, 1.2 mmol) were utilized and the product was obtained as dark red solid. Yield= 247 mg (62 %); Mp. 220-222 ºC. λ_{max} 231.8 nm, 389.8 nm, 472.8 nm. IR 3124 (Ar-H); 1663(C=O); 1376 (C-N) .^{I}HNMR δ 8.0 (1H, d); 7.70 (2H, m); 7.30 – 7.62 (9H, m). MS m/e 339.22(M^+ 100%).Anal.Calcd (found) for $C_{22}H_{12}$ ClNOS: C, 70.68(70.55); H, 3.24(3.30); N, 3.75 (3.60).

J. General Procedure for Buchwald-Hartwig Reaction.

Xphos (1.5 mg, 0.0032 mmol, 1 mol %) and $Pd(OAc)_2$ (2.1 mg, 0.0095 mmol, 3 mol%) were placed in a 50 mL two-neck round-bottom flask. after purging with nitrogen for 30 s, water (1 mL) and EtOH (5 mL) were added and the solution was heated for 60 s to 80 ºC. The pre-activation was followed by a colour change from yellow to dark brown. Then, the 9,11-diamino-6-chloro-7-oxa-8,10,12-triaza-benzo[a]anthracen-5-one, aniline derivative, base and 2 mL dioxane were added. The reaction mixture was heated at reflux with vigorous stirring for the indicated time. The completion of reaction was monitored by TLC, then cooled, filtered and recrystallized from water and acetone mixture.

K. 9,11-Diamino-6-(4-nitro-phenylamino)-7-oxa-8,10,12-triaza-benzo[a]anthracen-5-one.

General procedure was followed in the synthesis: Xphos (1.5 mg, 0.0031 mmol, 1 mol %) and $Pd(OAc)_2$ (2.1 mg, 0.0093 mmol, 3 mol %)were placed in a 50mL two-neck round-bottom flask. Nitrogen gas was introduced for 30 s. Water (1 mL) and ethanol (5 mL) were added and the solution was heated for 80 s at 80 ºC. The pre-activation was monitored by colour change from yellow to brown.

Thereafter, 9,11-diamino-6-chloro-7-oxa-8,10,12-triaza-benzo[a]anthracen-5-one (314 mg, 1 mmol), 4-nitroaniline (166 mg, 1.2 mmol), K_2CO_3 (193.2 mg, 1.4 mmol), and dioxane (2 mL) were added. The reaction mixture was reflux with vigorous stirring for 5 h. After monitoring the reaction to completion by TLC, it was cooled, filtered and recrystallized from acetone and n-hexane to give a dark brown solid in 190 mg.

Yield= 45 %; Mp.> 360 ºC. λ_{max} 231.2 nm, 339.8 nm, 418 nm. IR 3423 (NH_2); 3190 (Ar-H); 1651(C=O); 1076(C-N). ^{1}HNMR δ 8.20 (4H, d); 7.50 (1H, s); 6.70 (4H, d); 4.4 (4H, m). MS m/e 339.22(M^+ 100%) .Anal.Calcd (found) for $C_{20}H_{13}N_7O_4$:C, 57.83 (57.80); H, 3.15 (3.11); N, 23.60 (23.55).

L. 9,11-Diamino-6-(2-hydroxy-phenylamino)-7-oxa-8,10,12-triaza benzo[a]anthracen-5-one.

In line with the general procedure, Xphos (1.5 mg, 0.0031 mmol, 1 mol%) and $Pd(OAc)_2$ (2.1 mg, 0.0093 mmol, 3 mol%) were placed in a 50 mL two-neck round-bottom flask. Nitrogen gas was introduced for 30 seconds. Water (1 mL) and ethanol (5 mL) were added and the solution heated for 60 s at 80 ºC. The pre-activation was monitored by colour change from light yellow to dark brown. Thereafter, 9,11-diamino-6-chloro-7-oxa-8,10,12-triaza-benzo[a]anthracen-5-one (314 mg, 1 mmol), 2-hydoxyaniline (131 mg, 1.2 mmol), K_2CO_3 (193.2 mg, 1.4 mmol), and dioxane (2 mL) were added. The reaction mixture was heated at reflux with vigorous stirring for 3 h 45 min. After reading the completion by TLC, it was cooled, filtered and recrystallized from acetone and methanol solution to give a black solid obtained in 207 mg.

Yield= 65 %. Mp. > 360 ºC. λ_{max} 230.2 nm, 389.8 nm, 478.6 nm. IR 1662(C=O); 1463 (C-O-C); 1377 (C-N). ^{1}H NMR 8.0 (1H, s); 7.9 (1H, s);7.7 (1H, d); 7.6 (1H, d); 7.30 (2H, m); 6.80 (1H, s); 6.30 (1H, d); 5.20 (1H, s); 2.8 (5H, m).Anal.Calcd (found) for $C_{20}H_{14}N_6O_3$: C, 62.17 (62.22); H, 3.65(3.68); N, 21.75(21.81).

M. 6-(4-Nitro-phenylamino)-7-oxa-11,12-diaza-benzo[a]anthracen-5-one.

Following the general procedure, Xphos (1.5 mg, 0.0031 mmol, 1 mol %), and $Pd(OAc)_2$ (2.1 mg, 0.0093 mmol, 3 mol%) were placed in a 50 mL two-neck round-bottom flask. Nitrogen gas was introduced for 30 s. Water (1 mL) and ethanol (5 mL) were added and the solution was heated for 60 sec at 80 ºC. The pre-activation was monitored by colour change from light yellow to dark brown. Thereafter, 6-chloro-7-oxa-11,12-diaza-benzo[a]anthracen-5-one (281 mg,1 mmol), 4-nitroaniline (165.74 mg, 1.2 mmol), K_2CO_3 (193.2 mg, 1.4 mmol) and dioxane (2 mL) were added. The reaction mixture was heated and refluxed with vigorous stirring for 2 h 30 min. After monitoring the reaction to completion by TLC, it was cooled, filtered and recrystallized from water and acetone mixture to give a black solid, obtained in 154 mg.

Yield= 85 %. Mp. , 129-131ºC. λ_{max} 230.4 nm, 288.4 nm, 389.6 nm, 409.8 nm. IR 3370 (NH_2); 3095 (Ar-H); 1646(C=O); 1377 (C-N). ^{1}H NMR 8.75 (2H, m); 8.40 (2H, m); 7.80 (6H, m); 7.25 (1H, s).MS m/e 339.22(M^+ 100%).Anal.Calcd (found) for $C_{21}H_{12}N_4O_4$:C, 65.63(65.82); H, 3.15 (3.03); N, 14.58 (14.35).

N. Antimicrobial Screening

All the synthesized compounds (**5-12**) were screened for their antimicrobial activities at concentration 10 mg/mL in agar media [9]. Using Ciprofloxacin an antibacterial agent and Ketoconazole, an antifungal agent as reference drugs. The compounds were screened against six (6) micro-organisms; namely,*Listeria ivanovii, Staphylococcus aureus, Klebsiellapneumoniae, Escherichia coli, Candida albicans* and *Aspergillusniger*.

O. Minimum Inhibitory Concentration (MIC) Testing:

Agar cup diffusion method was applied to determine the minimum inhibitory concentration (MIC) of the synthesized compounds, Ciprofloxacin and ketoconazole as standard drugs. Serial dilution of the synthesized compounds was prepared from 10 mg/mL solution of the phenoxazines to give 5, 2.5, 1.25, 0.625 mg/mL. Four drops of each dilution were added to the corresponding cup previously marked out in the seeded microorganisms and the agar (MHA) plate. The cork borer used to make the cup is 8 mm in diameter. The plates were incubated at 37 ºC for 24 h for bacteria and 48 h for fungi tests. The diameter of zone of inhibition was measured and the value subtracted from the diameter of the borer (8 mm) to give the inhibition zone diameter (IZD). The graph of IZD^2 against the log of concentration was plotted for each plate containing a specific compound and a microorganism. The anti-log of the intercept on x-axis gave the MIC. The procedure was repeated for ciprofloxacin and ketoconazole reference drugs.

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AUTHORS' BIOGRAPHY

Simon Sani Ocholi was born on the 27th September 1987 in Ejegbo, Ankpa LGA of Kogi State, Nigeria. He attended University of Agriculture, Makurdi (2012-2015) where he obtained his Bachelors' degree in chemistry. He then proceeded to the prestigious University of Nigeria, Nsukka (2016-2019) where he obtained his M.Sc in organic chemistry. He has a passion for synthetic/medicinal organic Chemistry.

Efeturi A. Onoabedje completed his Ph. D in Organic Chemistry in 2014 from the University of Nigeria, with a research stint in Cardiff University, Cardiff, Wales, UK. His Ph.D research focused on application of metal catalysis in functionalisation of phenothiazine and phenoxazine scaffolds. He is a recipients of Petroleum Technology Development Fund (PTDF) Ph.D Scholarship (2012) and CSIR-TWAS Post-Doc Fellowship (2017) Awards. Dr. Onoabedje is presently a Senior Lecturer in the Department of Pure & Industrial Chemistry, University of Nigeria, where he teaches courses in organic chemistry and carries on research in the design and synthesis of anti-infective agents.

Dr. Samuel Attah Egu obtained his Ph.D in organic chemistry in 2016 from the University of Nigeria. During his Ph.D research, he investigated the synthesis of novel heterocyclic compounds, e.g., quinolinequinone, using a transition-metal based approach. He is a recipients of Tertiary Education Trust Fund (TETFUND) Ph.D Scholarship (2013) and TWAS-ICCBS Post-Doc Fellowship (2018) Awards. He also had Laboratory experience in Cardiff University in 2014. Dr. Egu has published articles in reputable journals and is presently a Lecturer in the Department of Pure & Industrial Chemistry, Kogi State University, Anyigba, Nigeria, where he teaches courses in organic chemistry and carries out research in the design and synthesis of bioactive heterocycles.