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Proceeding Paper

Synthesis, Characterization, and In-Silico Admet Studies of Some New Phenylhydrazone Derivatives as Potent for Antimicrobial Activities

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Abstract: Antimicrobial chemotherapeutic failure as a result of pathogenic resistance stain is great concern across the globe, there is need to search for an effective antimicrobial agent from synthetic sources to overcome emergent of microbial resistant in clinical practice. The phenylhydrazone derivatives were scientifically found to have wide application in area of drug discovery due to their anticancer, anti-tubercular, anti-bacterial and anti-fungal activities. Five (5) novel (E)-Substituted-N-(phenylhydrazones) derivatives' were obtained by condensation reaction between substituted acetophenone and substituted phenyl hydrazine through one step reaction, here are the five compounds, *HS1* (E)-1-(1-(4-bromophenyl)ethylidene)-2-(2,4-dinitrophenyl)hydrazine),*HS2* (E)-1-(1-(4-bromophenyl)ethylidene)-2-(4-nitrophenyl)hydrazine), *HS3*(E)-1-(4-nitrophenyl)-2-(1-(3-nitrophenyl)ethylidene)hydrazine),HS4(E)-1-(2,4-dinitrophenyl)-2-(1-(3-nitrophenyl)ethylidene)hydrazine), and HS5 (E)-1-(1-(3-nitrophenyl)ethylidene)-2-phenylhydrazine) and their structural elucidation were established on the basis of FTIR, 1D and 2D NMR spectra and the Insilco prediction of physicochemical properties found within the Lipinski's rule of five and the newly synthesized compounds were subjected to antimicrobial assessment for an in-vitro test evaluation using inhibition zone technique, MIC, MBC and MFC.

Keywords: hydrazine; hydrazone; antibacterial activity; antifungal activity; zone of inhibition; MIC; MBC; MFC

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1. Introduction

Infectious diseases caused by pathogenic agents have been a major problem to humans which account for the death of millions of people annually worldwide (Reygaert, 2018). Some of these diseases threaten the health of millions people especially where no cure or vaccine exists (Ade et al., 2020). Recently, infectious disease caused by corona virus (covid-19**)** became one of the top cause of death across the globe (Facts, 2015).

Antimicrobial resistance (AMR) possess urgent public health problem and economic challenge across the world (WHO, 2023). AMR occurs when pathogens change over time and no longer respond to antimicrobial drugs making the infection hard to treat (WHO, 2023). Misuse and overdose of antimicrobial drugs in humans result to antimicrobial drug resistance (Alberta et al., 2020).

Hydrazone are class of organic compounds formed by replacement of oxygen of carbonyl compound to carbon nitrogen double (R-CH=N-), (Ii et al., 2021). Hydrazone Schiff base compounds and their complexes have also drowned great attention last two decades due to their high level pharmaceutical potentials such as, antimicrobial, antibacterial, antifungal, anti-inflammatory etc. (Nesterkina et al., 2020).

2. Materials and Methods

Most of the glassware used for this experiments were of Pyrex product and the glassware were cleaned and rinsed with organic solvent and dried in an oven before use to avoid contamination of the products. Some of these equipment were sourced from the Department of Pharmaceutical and Medicinal Chemistry and pharmaceutical microbiology, Ahmadu Bello University (ABU), Zaria.

2.1. Reagents, Solvents and Standard Drug

The reagents were purchased from Sigma-Aldrich, Germany. All the solvents and reagents used for this research are of analytical grade and used without further purification such as, Phenyl-hydrazine, 4-bromoacetophenone, 4-nitrophenylhydrazine, Sodium hydroxide (20%), substituted Acetophenone, Hydrazine hydrate, 2,4-diphenylhydrazine, glacial acetic acid, distilled water, and some organic solvents such as methanol (Merck), ethanol absolute (Merck), n-hexane, ethyl acetate (EtOAc), chloroform ($CHCl_3$), and dichloromethane (DCM).

2.1.1. Characterization

2.1.2. Physical Appearance of Phenylhydrazone and Pyrazoline Derivatives

The color and appearance of synthesized phenylhydrazone compound and pyrazolines derivatives were observed and recorded.

2.1.3. Solubility Test of Phenylhydrazone and Pyrazoline Derivatives

The solubility of synthesized hydrazone were tested and observed in dichloromethane only while pyrazolines are soluble in dichloromethane (DCM) and dimethyl sulphoxide (DMSO).

2.1.4. Melting Point Determination of Phenylhydrazone and Pyrazoline Derivatives

All melting point of synthesized hydrazone and pyrazoline derivatives compounds were determined using a Gallenkamp melting point apparatus and were uncorrected at department of pharmaceutical and medicinal chemistry Ahmadu Bello University (A.B.U) Zaria.

2.1.5. UV Lamp Determination of Phenylhydrazone and Pyrazoline Derivatives

The spot was developed and viewed under UV lamp

2.1.6. In-Silico Mechanistic Studies

2.1.7. Physico Properties of the Synthesized Compounds by ADMET Analysis

The ADMET properties of the ten selected compounds were assessed using the ADMETlab platform (http: //admet.scbdd. com/webserver/ADMET prediction). The assessment was carried out for each compound's physiochemical property and found that all the compounds can be absorbed by the human intestine by submitting a SMILE format of the individual compound obtained from the chem.draw (Sanusi et al., 2023).

2.1.8. Spectroscopic Analysis

The proton magnetic resonance (1H NMR) and 13C spectral analysis were recorded on a Brucker 300 and 400 MHz instrument in DMSOd6 using tetramethylsilane (TMS) as an internal standard University of Pretoria, Republic of South Africa. The infrared spectra of compounds were recorded in an Agilent FTIR Spectrophotometer Multi-user A.B.U Zaria Nigeria.

Detailed structural analysis of the synthesized compounds were performed using Fourier Transformed Infrared Spectroscopy (FT-IR), and Nuclear Magnetic Resonance

(NMR) which include; proton (^{1}H) NMR, carbon-13 (^{13}C) NMR, Correlated Spectroscopy (COSY), HSQC and HMBC.

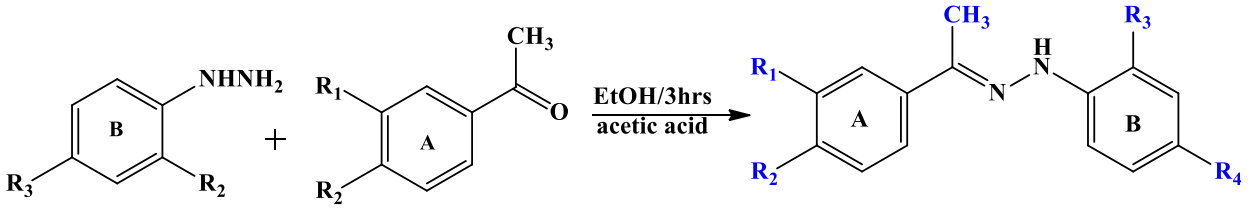
The FT-IR data are reported in terms of frequency of absorption cm^{-1} while data for ^{1}H NMR and ^{13}C NMR are reported as: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublet, m = multiplet), integration *(J).*

2.2. Chemistry

In this current research (E)-1-phenyl-2-(1-phenylethylidene) hydrazone derivatives (1–5) were obtained by following the synthetic protocols as mentioned in Scheme.1 below where an equimolar of substituted both acetophenone and phenylhydrazone were dissolved in 100mL round bottle flask contained (30 mL) of absolute ethanol with few drops glacial acetic acid as catalyst, under refluxed for 3hrs at 65–75 °C (Scheme 1) (Arshad et al., 2019). The progress of the reactions monitored by thin layer chromatography (TLC) using hexane and ethyl acetate (1:1) and the reaction mixture was filtered off using vacuum machine filtration, and dried to obtained the desire product (Moussa et al., 2020), (Fen et al., 2023).

The purity of the compounds was checked by TLC using the solvent ratio of hexane: ethyl acetate (1:1) and their structures were confirm using spectral data (IR, 1H NMR) and elemental analysis.

Chemical reaction of phenylhydrazone derivatives



I **Substituted Phenylhydrazine**

II **Substituted acetophenone**

III **Phenylhyazone derivatives**

Cpd	R_1	R_2	R_3	R_4
HS1	H	Br	NO_2	NO_2
HS2	H	Br	H	NO_2
HS3	NO_2	H	H	NO_2
HS4	NO_2	H	NO_2	NO_2
HS5	NO_2	H	H	H

Scheme 1. Synthesis of Phenylhydrazone derivatives HS1-HS5.

3. Results and Discussion

Final Product obtained were given below in Figures 1–5.

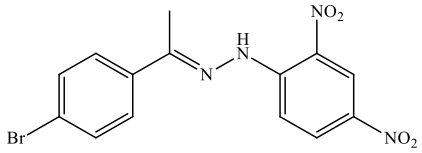


Fig.1 ((E)-1-(1-(4-bromophenyl)ethylidene)-2-(2,4-dinitrophenyl)hydrazine) .

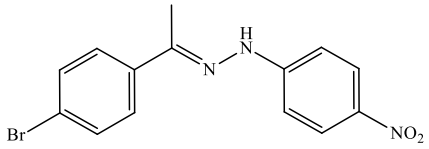


Fig.2 ((E)-1-(1-(4-bromophenyl)ethylidene)-2-(4-nitrophenyl)hydrazine) .

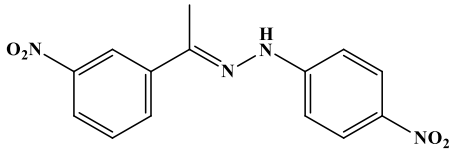


Fig.3 ((*E*)-1-(4-nitrophenyl)-2-(1-(3-nitrophenyl)ethylidene)hydrazine)

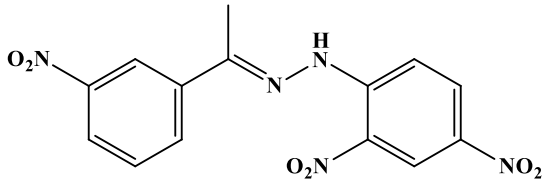


Fig.4 (*E*)-1-(2,4-dinitrophenyl)-2-(1-(3-nitrophenyl)ethylidene)hydrazine)

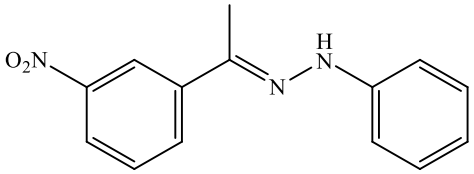


Fig.5 (*E*)-1-(1-(3-nitrophenyl)ethylidene)-2-phenylhydrazine)

3.1. Yield and Some Physical Properties of Substituted Phenyl Hydrazones

The yield and some physical properties such as, range of melting point and crystal color of the synthesized compounds are presented in Table 1

Table 1. Phenylhydrazone compounds and their characteristics.

Code	Mol. Formula	Mol. Wt. g/mol	Color	M.P. (°C)	R_f Value	Yield (%)
HS1	$C_{14}H_{11}BrN_4O_4$	379.17	Pink	213–215	0.91	40.00
HS2	$C_{14}H_{12}BrN_3O_2$	334.17	Brown	220–222	0.85	67.00
HS3	$C_{14}H_{12}N_4O_4$	300.27	Sandy-brown	213–215	0.83	67.00
HS4	$C_{14}H_{11}N_5O_6$	345.27	Yellow	210–212	0.87	89.00

HS5	$C_{14}H_{13}N_3O_2$	255.27	Reddish Brown	110–112	0.89	81.00

HS = hydrazone, Mol = molecular, Wt = weight, M.P = melting point, g/mol = gram per mole.

3.2. In-Silico Parameter of Substituted Phenyl Hydrazones

The below is the Insilico parameters of the synthesized compounds are presented in Table 2

Table 2. Insilco prediction of physicochemical parameters for phenylhydrazone derivatives.

	Lipinski's Rule Of Five							
Code	**Mol. Wt (g/mol)**	**HbA**	**HbD**	**nRB**	**LogP**	**Lipinski**	**GIA**	**BA Score**
HS1	379.17	5	1	5	5.22	Yes	High	0.55
HS2	334.17	3	1	4	4.79	Yes	High	0.55
HS3	300.27	5	1	5	4.46	Yes	High	0.55
HS4	345.27	7	1	6	4.89	Yes	Low	0.55
HS5	255.27	3	1	4	4.03	Yes	High	0.55
Cipro.	331.34	5	2	3	1.98	Yes	High	0.55
Terbinafine	291.43	1	0	4	4.88	Yes	High	0.55

(a) Molecular weight in g/mol, (b) Lipinski et al., 2001 (Mwt ≤ 500, MLogP ≤ 4.15, N or O ≤ 10, NH or OH ≤ 5 and number of rotatable bonds ≤ 10), TPS; topological surface area, GIA; gastrointestinal absorption, BA; bioavailability.

4. Conclusions

Five (5) new compounds of (E)-Substituted-N-(phenylhydrazones) derivatives were synthesized and obtained by cyclization reaction with an excellent yield of (40–89%) and all compounds were structurally characterized and confirmed by spectral analysis.

Author Contributions:

Funding:

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Conflicts of Interest:

Abbreviations

MIC: Minimal inhibitory concentration, **ZOI;** Zone of inhibition, **MBC**; Minimum Bactericidal concentration, **MFC**; Minimum Fungicidal concentration, **FTIR;** Fourier transform infrared, **NMR;** nuclear magnetic resonance, **1D;** one-dimensional, **2D**; two dimensional and **HS1-5**: synthetic hydrazone (symbolic code number)

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