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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF NOVEL PYRIMIDO-TRIAZINE FUSED HETEROCYCLIC COMPOUNDS

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ABSTRACT:
1-Amino-6-(furan-2-yl)-4-methyl pyridine-2(1H)-thione (**1)** on condensation with chloroacetamide yield an intermediate 2-((6-(furan-2-yl)-4-methyl-2-thioxopyrimidin-1(2H)-yl)amino) acetamide **(2)** which on cyclization yield the product 3 with an active methylene group, the compound 3 reacted with diazonium salt (4a-h) of various sulfa drugs to afford, 4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene)hydrazinyl)benzenesulfa drugs derivatives **5a-h**. Synthesized compounds were characterized by IR, mass (MS), and 1H NMR spectra as well as elemental analysis. They were also screened for their *in vitro* antibacterial activity against Gram positive bacteria (*Bacillus Subtilis Staphylococcus aureus,* Gram-negative bacteria (Kllebsiella promioe, *E.coil*) and antifungal activity against plant pathogens (Botrydepladia Thiobromine Nigrosspora Sp., Penicillium Expansum, Rhizopus Nigricuns).

KEYWORDS: Pyrimidine, pyrimido-traizine, Sulfa drugs, diazonium salts, IR-NMR spectral studies, LC-MS Spectrometry, Antimicrobial activity

INTRODUCTION:

Both Pyrimidine and its derivatives are Chief classes of heterocyclic substance. They bears broad spectrum of pharmaceutical activities [i-viii]. Among its fused derivatives e.g. pyrimido-traizine have anticancer properties [ix-xiii]. Also they have anti - viral, anti – hypertensive, anti - T.B. and anti – HIV [xiv-xx]. In view of these facts the present author taught to explore the derivatives of pyrimido – triazine with furan and sulfa drug moieties. Such a type of derivatives may have good biological properties. Hence in continuous of our earlier communication [xxi], the present paper describes the pyrimidine triazole fused molecules. The research is scanned in scheme – 1.

EXPERIMENTAL SECTION:

Furanylacetone was procured from Sigma Aldrich. All other reagents were used laboratory grade.

The IR spectra of all compounds were taken in KBr pellets on a Nicolet 400D spectrometer. Proton NMR spectra were recorded on a Bruker (400 MHz) spectrometer. Deutorated DMSO was used as a solvent. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046. All the compounds were checked for their purity by TLC.

The antibacterial activities of both the series of compounds were studied against gram +Ve and –Ve bacteria shown in Table-1. The activity was measured at a conc, 50µg/ml by agar-cup plate method [xxiv]. Similar conditions using tetracycline as a control was used standard for comparison. The percentage area of inhibition of zone measured. The % age inhibition of growth of bacteria by the compounds is shown in Table-1.

The antifungal activity of both the series of compounds were measured at 1000ppm concentration in vitro Plant pathogen shown in Table-2 have been selected for study [xxiv].

GENERAL PROCEDURE

Synthesis of 1-amino-6-(furan-2-yl)-4-methyl pyrimidine-2(1H)-thione (1)

It was prepared by method reported in an earlier communication [xxi].

1-amino-6-(furan-2-yl)-4-methyl pyrimidine-2 (1H)-thione **(1)** and chloro acetamide at stoichiometric ratio in pyridine was refluxed for 4 hrs. Then resultant reaction mixture was cooled, and then poured it into ice cold water. The precipitated solid product was collected by filtration, washed with solid product with water and dried.

Synthesis of 8-(furan-2-yl)-6-methyl-1H-pyrimido[1,2-b][1,2,4]triazin-3(2H)-one (3)

The obtained product is intermediate i.e 2-((6-(furan-2-yl)-4-methyl-2-thioxopyrimidin-1(2H)-yl)amino) acetamide (2) then fused with base KOH 8-(furan-2-yl)-6-methyl-1H-pyrimido [1,2-b][1,2,4]. Then reaction mixture was cooled under tap water, then poured into ice containing conc.HCl. The solid product which precipitated was collected by filtration, washed with solid product with water, dried and crystallized from ethyl alcohol. The yield of 8-(furan-2-yl)-6-methyl-1H-pyrimido [1,2-b][1,2,4] triazin-3(2H)-one was 75 % and the product melts at 232-233ºC.For $C_{11}H_{10}N_4O_2$ (230) Calcd.: %C, 57.39; %H,4.38; %N,24.34.Found:%C,57.3 ; %H,4.3;%N, 24.3.IR(KBr)(cm^{-1}): 3340,3180 (N-H), 3080(Aromatic C-H stretch), 2848(C-H),760 (Aromatic C-H bending), 1620-1580 (Aromatic C-C stretch),1685(CO of Amide),1650(C=N),1050(C-O-C). ^{1}H NMR:8.65(s, 1H, Pyrimidine-H), 8.20-7.30(m,3H,Ar-H),2.50(s,1H,NH),3.85 (s,2H,CH_2) and 2.35 (s,3H, CH_3).

Synthesis of 4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene)hydrazinyl)benzenesulfa drugs derivatives (5a-h)

A solution of compound 8-(furan-2-yl)-6-methyl-1H-pyrimido[1,2-b][1,2,4]triazin-3(2H)-one (3) (0.01mol) in isopropanol(30ml) and sodium acetate(50g) was stirred in cold bath and maintain temperature 0-5°C. Diazotized solution of various sulpha drugs **(4a-h)** (0.01mol) was added dropwise to this solution with good stirring. The starring was carried out untill complete reaction. The solid products were filtered off and air dried and crystallized.

4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene) hydrazinyl)benzene sulfonamide (5a): $C_{17}H_{15}N_7O_4S$(413),Yield 86%, M.P. 212 -213ºC Calcd.: %C,49.39; %H,3.66; %N,23.72;%S,7.76. Found: %C,49.3;%H, 3.6; % N, 23.7;%S, 7.7. IR (KBr) (cm^{-1}): 3372 -3180(N-H),3080(Aromatic C-H stretching), 2848 (C-H),760(Aromatic C-H bending), 1620-1580(Aromatic C-C stretching), 1685(CO of Amide),1650 (C=N), 1050(C-O-C),1365,1185 (SO_2) and 3410 (NH_2). ^{1}H NMR (400 MHz,DMSO)δ: 8.65(s, 1H, Pyrimidine-H), 8.20-6.90(m,7H, Ar-H),2.50-2.75(s,2H,NH), 2.35(s,3H, CH_3), 2.50(s,2H, NH_2).

4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene)hydrazinyl)-N-(pyrimidin-2-yl)benzene sulfonamide (5b)*:* $C_{21}H_{17}N_9O_4S$ (491), Yield 83%, M^+: 494,M.P. 217-218^{o}C, Calcd.: %C, 51.32; %H,3.49; %N,25.65;%S, 6.52. Found: %C, 51.3; %H,3.4; %N,25.6; %S,6.5. IR (KBr) (cm^{-1}): 3375-3178(N-H), 3085(Aromatic C-H stretching), 2848 (C-H), 760(Aromatic C-H bending),1620-1580 (Aromatic C-C stretching),1685(CO of Amide), 1650(C=N),1050(C-O-C) and 1365, 1185 (SO_2). ^{1}H NMR (400 MHz, DMSO) δ: 8.65(s,1H,Pyrimidine-H),8.20-6.90(m, 7H, Ar-H),2.50-2.75(s,2H,NH), 2.35 (s, 3H, CH_3),8.50-6.90(m,3H,Ar-H), 3.50 (s,1H,NH).

N-(2,6-dimethoxypyrimidin-4-yl)-4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene)hydrazinyl)benzene sulfonamide (5c): $C_{23}H_{21}N_9O_6S$ (551), Yield 80%, M.P. 226-227^{o}C,Calcd.: %C, 50.09; %H,3.84; %N, 22.86; %S,5.81. Found: %C, 50.0; %H, 3.8; %N,22.8;%S,5.7. IR (KBr) (cm^{-1}): 3375 -3178(N-H),3085(Aromatic C-H stretching), 2848 (C-H),760(Aromatic C-H bending), 1620 -1580(Aromatic C-C stretching), 1685 (CO of Amide), 1650(C=N),1050(C-O-C), 1365, 1185 (SO_2) and 1250 cm^{-1} (-OCH_3). ^{1}H NMR(400 MHz,DMSO)δ: 8.65 (s,1H, Pyrimidine-H),8.20-6.90(m,7H,Ar-H),2.50-2.75(s,2H, NH),2.35(s,3H,CH_3), 6.10(m,1H, Ar-H),3.90-4.00(s,6H,OCH_3),3.50(s,1H, NH).

N-(5,6-dimethoxypyrimidin-4-yl)-4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene)hydrazinyl)benzene sulfonamide (5d) : $C_{23}H_{21}N_9O_6S$ (551), Yield 80%, M.P. 220-221^{o}C Calcd.: %C, 50.09; %H,3.84; %N, 22.86;%S,5.81. Found: %C, 49.9; %H, 3.8; %N,22.8;%S,5.8. IR (KBr) (cm^{-1}): 3380 -3175(N-H),3085(Aromatic C-H stretching), 2850 (C-H),760(Aromatic C-H bending), 1620 -1570(Aromatic C-C stretching), 1685 (CO of Amide),1650(C=N),1050(C-O-C), 1365, 1185 (SO_2) and 1248 cm^{-1} (-OCH_3). ^{1}H NMR (400 MHz, DMSO) δ:8.65(s,1H,Pyrimidine-H),8.20-6.90(m,7H, Ar-H),2.50-2.75(s,2H,NH), 2.35 (s,3H,CH_3), 6.15 (m,1H,Ar-H), 3.85-4.05(s,6H,OCH_3), 3.52(s,1H,NH).

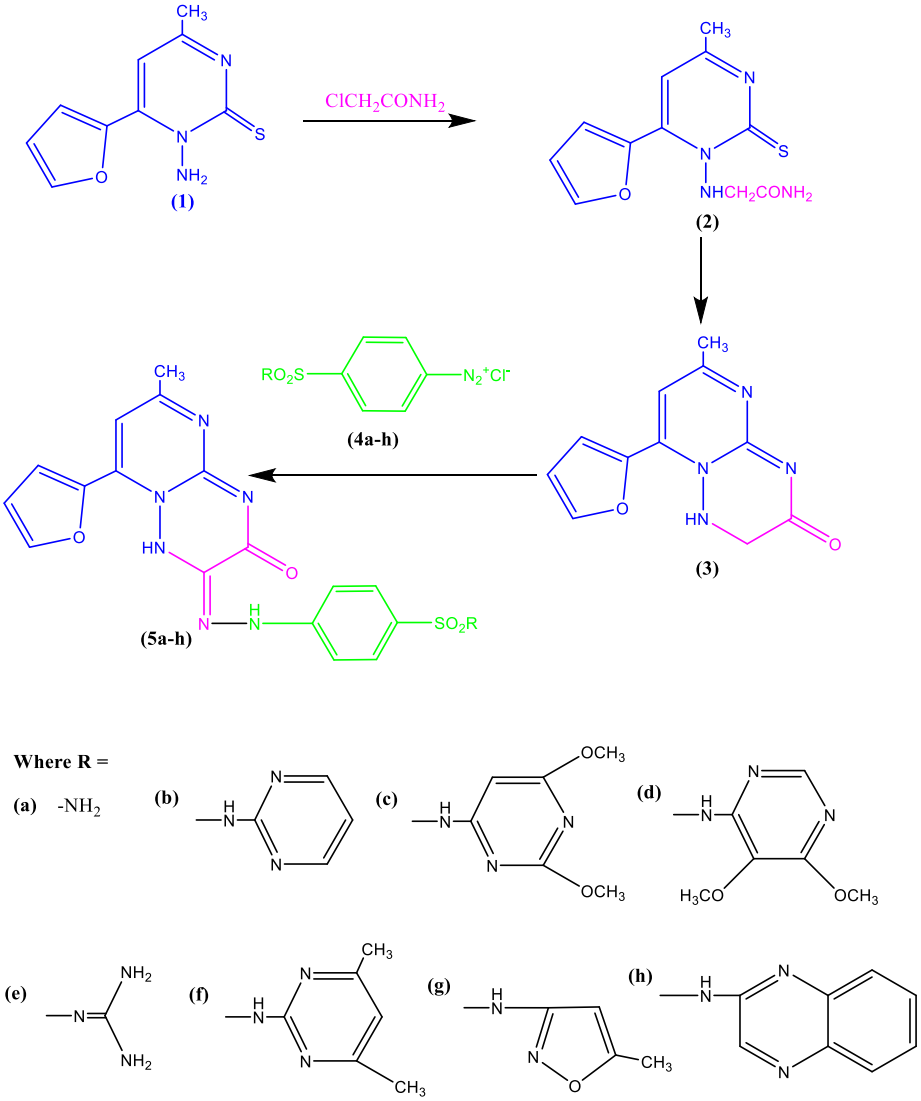
N-(diaminomethylene)-4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene)hydrazinyl)benzene sulfonamide (5e): $C_{18}H_{17}N_9O_4S$ (455), Yield 82%, M.P. 234-235^{o}C Calcd.: %C, 47.47; %H,3.76; %N,27.68;%S,7.04. Found: %C, 47.4; %H,3.7; %N,27.6;%S,7.0. IR (KBr) (cm^{-1}): 3385-3180(N-H), 3080 (Aromatic C-H stretching), 2850 (C-H),760 (Aromatic C-H bending),1620-1580 (Aromatic C-C stretching),1685(CO of Amide), 1650(C=N),1050(C-O-C), 1365, 1185 (SO_2) and 3350-3410(-NH_2). ^{1}H NMR (400 MHz, DMSO)δ:8.65(s,1H,Pyrimidine-H), 8.20-6.90(m,7H,Ar-H),2.50-2.75(s,2H, NH), 2.35 (s,3H,CH_3), 2.10(s,4H, NH_2),

N-(4,6-dimethylpyrimidin-2-yl)-4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene)hydrazinyl)benzene sulfonamide (5f): $C_{23}H_{21}N_9O_4S$ **(519)**, Yield 77%, M^+: 523, M.P. 238-239^{o}C Calcd.: %C, 53.17; %H, 4.07; %N,24.26;%S,6.17. Found: %C, 53.1; %H,4.0; %N,24.2;%S,6.1. IR (KBr) (cm^{-1}): 3375-3178(N-H),3085(Aromatic C-H stretching), 2848 (C-H),760(Aromatic C-H bending), 1620-1580(Aromatic C-C stretching), 1685(CO of Amide), 1650 (C=N), 1050(C-O-C) and 1365,1185 (SO_2). ^{1}H NMR(400 MHz, DMSO) δ: 8.65(s, 1H, Pyrimidine-H),8.20-6.90(m,7H,Ar-H),2.50-2.75(s,2H, NH),2.35(s, 3H, CH_3), 6.80(m, 1H, Ar-H), 2.35-2.40(s, 6H, CH_3), 3.48(s, 1H, NH).

4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene) hydrazinyl)-N-(5-methyl isoxazol-3-yl)benzene sulfonamide thiazole (5g): $C_{21}H_{18}N_8O_5S$ (494), Yield 77%, M.P. 229-230^{o}C Calcd.: %C, 51.01; %H,3.67; %N, 22.66;%S,6.48. Found:

%C, 51.0; %H,3.6; %N, 22.6;%S,6.4. IR (KBr) (cm^{-1}): 3375-3178 (N-H),3085(Aromatic C-H stretching), 2848 (C-H),760(Aromatic C-H bending), 1620 -1580(Aromatic C-C stretching), 1685 (CO of Amide), 1650(C=N),1050(C-O-C) ,1365, 1185 (SO_2) and 1180(C-O). ^{1}H NMR(400 MHz, DMSO) δ: 8.65(s,1H, Pyrimidine-H),8.20-6.90(m,7H,Ar-H),2.50-2.75(s,2H,NH),2.35(s,3H,CH_3),6.10(m,1H, Ar-H), 2.50 (s,3H, CH_3), 3.50(s,1H,NH).

4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene)hydrazinyl)-N-(quinoxalin-2-yl)benzene sulfonamide quinoxaline (5h): $C_{25}H_{19}N_9O_4S$ (541), Yield 75%, M.P. 245-246ºC,Calcd.: %C,55.45;%H,3.54;%N,23.28;%S,5.92. Found: %C, 55.4; %H,3.5; %N,23.2;%S,5.9. IR (KBr) (cm^{-1}): 3375-3178(N-H), 3085 (Aromatic C-H stretching), 2848 (C-H), 760(Aromatic C-H bending),1620-1580 (Aromatic C-C stretching),1685(CO of Amide),1650(C=N),1050(C-O-C) and 1365, 1185 (SO_2). ^{1}H NMR (400 MHz,DMSO)δ: 8.65(s,1H,Pyrimidine-H),8.20-6.90(m, 7H, Ar-H),2.50-2.75(s,2H,NH),2.35(s,3H, CH_3), 8.10-7.75(m,5H,Ar-H), 3.55(s,1H,NH).



Scheme-1: Synthesis of 4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene)hydrazinyl)benzenesulfa drugs derivatives (5a-h)

RESULT AND DISCUSSION:

As reported in our earlier communication [xxi]. The furanyl acetone on reaction with thiosemicarbazide in presence of ethanol gives 1- amino-6-(furan-2-yl)-4-methyl pyrimidine-2(1H)-thione (1). 1 on reaction with chloroacetamide afford the intermediate 2-((6-(furan-2-yl)-4-methyl-2-thioxopyrimidin-1(2H)-yl)amino) acetamide 2. 2 on 'in situ' cyclization yield 8-(furan-2-yl)-6-methyl-1H-pyrimido[1,2-b][1,2,4]triazin-3(2H)-one (3) [xxii,xxiii]. 3 further treated with diazo salt of various sulfa drug 4a-h yield 4-(2-(8-(furan-2-yl)-6-methyl-3-oxo-1H-pyrimido[1,2-b][1,2,4]triazin-2(3H)-ylidene)hydrazinyl)benzenesulfa drugs **5a-h**. This is based on reaction of active methylene group [xxiv].

Table 1. Antibacterial Activity of Compounds (5a-h)

Comp. No.	*area of inhibition of zone (mm)*			
	Gram +ve		*Gram -ve*	
	Bacillus Subtilis	***Staphylococcus aureus***	***Kllebsiella promioe***	***E.coil***
5a	*14*	*13*	*16*	*15*
5b	*15*	*13*	*18*	*15*
5c	*17*	*14*	*18*	*16*
5d	*17*	*14*	*18*	*15*
5e	*16*	*15*	*17*	*14*
5f	*15*	*13*	*18*	*14*
5g	*15*	*15*	*18*	*16*
5h	*15*	*12*	*17*	*14*

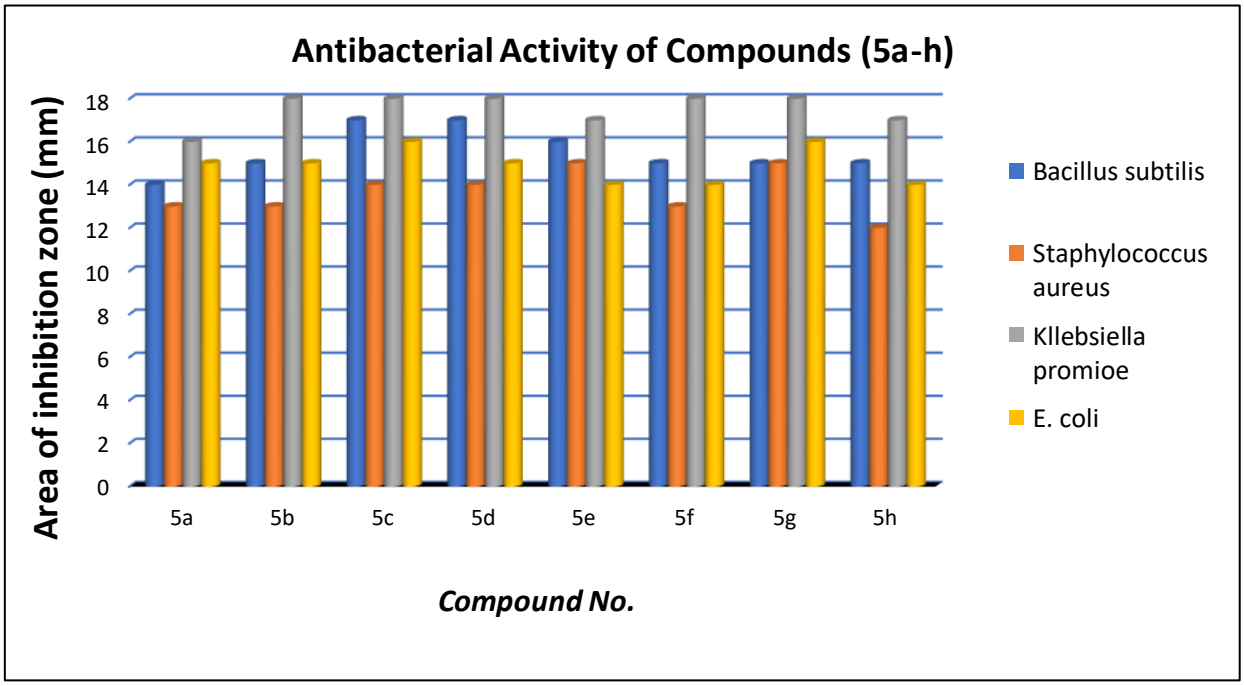


Figure 1. Antibacterial Activity of Compounds (5a-h)

All the elemental and spectral features suggest that the data are consistent with the predicted structure shown in Scheme-1. The LC-MS of selected compounds shows the peak of M^+ ion which is consistent of their molecular weight. All these facts confirm the structures of **5a-h**.

Table 2. Antifungal Activity of Compounds (5a-h)

Comp. No.	Zone of Inhibition at 1000 ppm (%)			
	Botrydepladia Thiobromine	**Nigrosspora Sp.**	**Penicillium Expansum**	**Rhizopus Nigricuns**
5a	61	68	59	58
5b	63	68	61	57
5c	70	77	73	70
5d	65	71	66	66
5e	64	69	59	59
5f	63	71	69	64
5g	78	75	76	68
5h	66	74	69	63

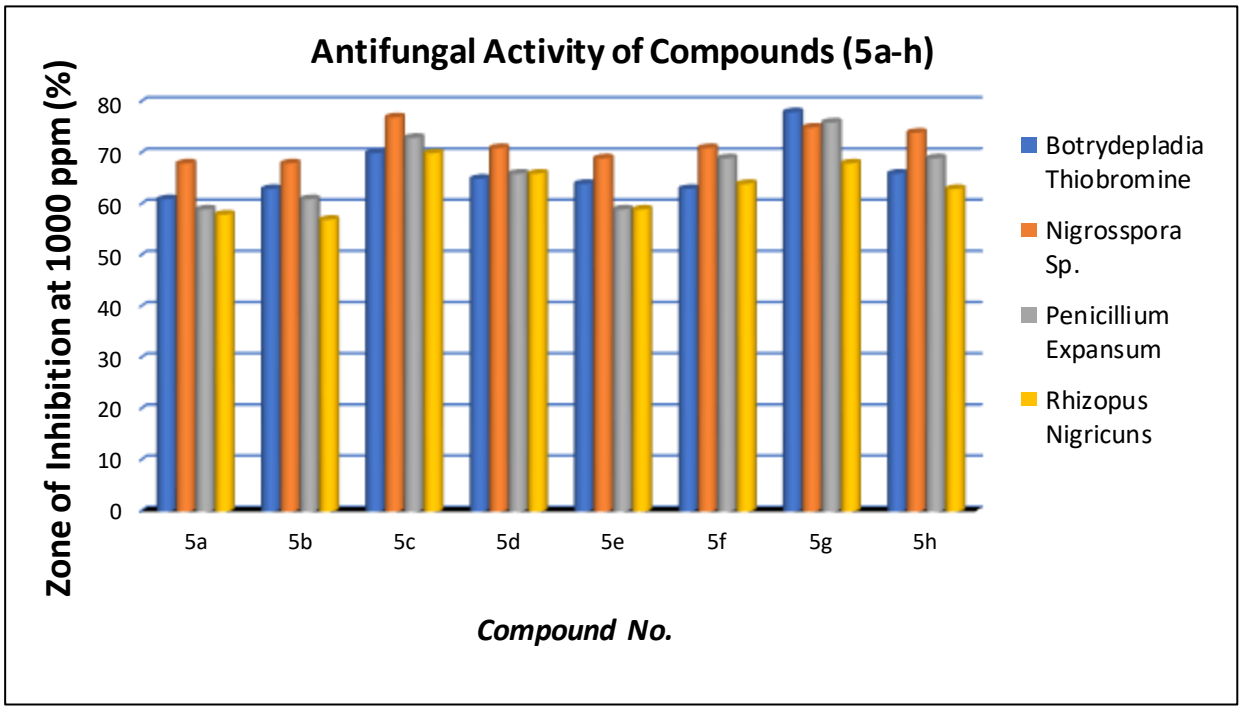


Figure 2. Antifungal Activity of Compounds (5a-h)

CONCLUSION:

The examination of antibacterial activity data reveals that all compounds toxic against microbes and the compounds **5g** and **5c** found more active against the gram-positive and

gram-negative bacteria.

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