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SYNTHESIS, CHARACTERIZATION AND ASSESMENT THE ANTIBACTERIAL EFFICACCY OF SCHIFF BASED COMPOUNDS GENRATED FROM ISATIN

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Abstract

Indole-2,3-dione (isatin) and its derivative have been recated with 2 and 4 substituted 1,3,4-thiadiazole derivative form Schiff bases of these compounds were synthesized in the presence of alcohol. Their chemical structure have been confirmed by mean of their IR and 1HNMR. Antimicrobial screening of synthesized compounds was done by well diffusion method against 4 pathogenic becteria and 2 pathogenic fungi. Amongst the tested compounds 5-fluoro-3-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one, 5-methyl-3-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one,and 5-nitro-3-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one exhibit significant antibacterial activity and 5-chloro-3-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one, 5-fluoro-3-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one and 5-methyl-3-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one showed favourable antifungal activity.

Key word: Isatin,Schiff base, thiadiazole , Antimicrobial activity.

Introduction

Indole-2,3-dione (isatin), an endogenous heterocyclic moiety extensively found in human tissues and bodily fluids [1]. The flexibility of indole-2,3-dione enables the synthesis of a wide range of heterocyclic compounds using several Schiff bases. Numerous of its compounds were described as having broad range pharmacodynamic properties, such as antibacterial[2-11], antiviral [12,13], analgesic and anti inflammatory [14-18], anticonvulsant [19,20], antituberculosis [21-24], anti-helminthic [25], anticancer [26-28] and anti-HIV [29-32],etc.

Heterocyclic molecules are cyclic substances that contain carbon together with other elements including nitrogen, sulfur, and oxygen.Numerous heterocyclic compounds have been shown to have medicinal value.Because of their broad-spectrum actions, thiadiazole derivatives have recently gained attention as a significant area of research. Thiadiazoles

belong to the groups of heterocycles that contain nitrogen and sulfur and are widely used as building blocks for physiologically active compounds. They are also helpful intermediates in medicinal chemistry.Thiadiazole can have four different structures: 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-thiadiazole, and 1,2,4-thiadiazole. Because of its pharmacological and biological properties, 1,3,4-thiadiazole is the most adaptable of these structures.Because to the presence of 1,3,4-thiadiazole derivatives, they display a variety of biological functions.N-C-S moiety[33].Our goal in this work is to create schiff bases using indole-2-3-dione and 1,3,4-thiadiazole derivatives in order to improve the antibacterial profile.

Experimental

All chemicals utilized were of AR grade and didn't require additional purification. Thin layer chromatography plates with a chloroform:methanol (9:1) ratio were used to test the reaction's completion, and spots were visible in the iodine chamber. The melting points were determined using open capillary tube equipment, and the results are uncorrected. Using the KBr dispersion diffuse reflectance method, IR spectra were captured on a SHIMADZU PRESTIGE IR-21. ^{1}H NMR TMS (Me4Si) was used as the internal standard while spectra were acquired on a 400 MHz JEOL JNM ECS 400 in DMSO-d6 solvent. Each and every spectrum fit the designated structure.

Synthesis of isatin and its derivative

It involves the interaction of chloral hydrate with hydroxyl amine hydrochloride in aqueous sodium sulphate to form isonitroso acetanilide. After isonitroso acetanilide was isolated, it was treated with strong sulfuric acid to make isatin.

Synthesis of thiadiazole

In 100 milliliters of ethanol, thiosemicarbazide (0.022 mol) was dissolved. Anhydrous sodium bicarbonate (0.015 mol) and carbon disulfide (0.018 mol) were then added. After being heated to 40 °C for one hour while stirring, the reaction mixture was refluxed for six to seven hours at 70 °C. Excess ethanol was removed by distilling the mixture once it had cooled. Concentrated hydrochloric acid was used to acidify the crude product. After filtering and washing with cold water, the greenish-yellow precipitate was again crystallized from hot water.

Synthesis of Schiff base

A mixture containing 0.005mole of isatin and 0.005mole of amines was well mixed and refluxed in 30 milliliters of methyl alcohol along with a small amount of glacial acetic acid for a duration of 6 hours. After the reaction mixture was cooled, the solid was extracted using filtering and repeatedly cleaned with the proper solvent before being recrystallized.

AB01: 3-(1,3,4-thiadiazol-2-ylimino)-1,3-dihydro-2*H*-indol-2-one: yield 67%, M.P. 218-220°C; IR (KBr, cm^{-1}): 3425 (v, N-H), 2914 (v, Ar C-H), 1793 (v, C=O), 1685 (v, CH=N), 756 (v, C-S thiadiazole ring); ^{1}H NMR (DMSO-d$_6$, 400MHz): δ 6.87-6.89 (1H, d, Ar), 7.51-7.52 (1H, d, Ar), 7.56 (1H, d, Ar), 7.58 (1H, s, Ar-Thiadiazole), 11.08 (1H, s, NH).

AB02: 3-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one: yield 53%, M.P. 289-291°C; IR (KBr, cm^{-1}): 3050 (v, Ar C-H), 1744 (v, C=O), 1640 (v, CH=N), 3411 (v, N-H Isatin ring), 1200 (v, C-SH), 2532 (v, S-H), 706 (C-S of thiadiazole ring) ;

^{1}H NMR (DMSO-d_6, 400MHz): δ 6.87-6.88 (1H, d, Ar), 7.36-7.37(1H, d, Ar), 7.38-7.40(1H, d, Ar), 11.00 (1H, s, SH), 13.15 (1H, s, NH).

AB03:3-[(5-methyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one:Yield:58%, M.P. 260-262°C; IR (KBr, cm^{-1}): 3060 (v, Ar C-H), 3243 (v, N-H Isatin ring), 1749 (v, C=O), 1625 (v, CH=N), 743 (v, C-S thiadiazole ring), 2909-3072 (v, C-CH_3); ^{1}H NMR (DMSO-d_6, 400MHz): δ 1.86 (3H, s, CH_3), 6.85-6.87 (1H, d, Ar), 7.36-7.38 (1H, d, Ar), 7.38-7.40(1H, d, Ar), 10.99 (1H, s, NH).

AB04: 5-chloro-3-(1,3,4-thiadiazol-2-ylimino)-1,3-dihydro-2*H*-indol-2-one; Yield:69%, M.P. 254-256°C; IR (KBr, cm^{-1}): 3049 (v, Ar C-H), 3360 (v, N-H Isatin ring), 1748 (v, C=O), 1620 (v, CH=N), 745 (v, C-S thiadiazole ring), 846 (v, C-Cl); ^{1}H NMR (DMSO-d_6, 400MHz): δ 6.86-6.88 (1H, d, Ar), 7.51-7.52 (1H, d, Ar), 7.58 (1H, d, Ar), 7.56 (1H, s, Ar-Thiadiazole), 11.10 (1H, s, NH).

AB05:5-chloro-3-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one; Yield: 82%, M.P. 246-248°C; IR (KBr, cm^{-1}): 3000 (v, Ar C-H), 3499 (v, N-H of isatin ring), 1748 (v, C=O), 1626 (v, CH=N), 749 (v, C-S of thiadiazole ring), 1172 (v, C-SH), 846 (v, C-Cl), 2568 (v, S-H); ^{1}H NMR (DMSO-d_6, 400MHz): δ 6.86-6.88 (1H, d, Ar), 7.52-7.55 (1H, d, Ar), 7.56-7.58 (1H, d, Ar), 11.10 (1H, s, SH), 13.15 (1H, s, NH).

AB06:5-chloro-3-[(5-methyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one; Yield: 75%, M.P.251-254 °C; IR (KBr, cm^{-1}): 3079 (v, Ar C-H), 3239 (v, N-H of isatin ring), 1750 (v, C=O), 1620 (v, CH=N), 748 (v, C-S thiadiazole ring), 846 (v, C-Cl), 2848-3001 (v, C-CH_3); ^{1}H NMR (DMSO-d_6, 400MHz): δ 2.21 (3H, s, CH_3), 7.03-7.06 (1H, d, Ar), 8.16-8.19 (1H, d, Ar), 8.40-.8.41 (1H, d, Ar), 11.62 (1H, s, NH).

AB07:5-fluoro-3-(1,3,4-thiadiazol-2-ylimino)-1,3-dihydro-2*H*-indol-2-one; Yield: 61%, M.P. 255-257°C; IR (KBr, cm^{-1}): 2877 (v, Ar C-H), 3402 (v, N-H of isatin ring), 1733 (v, C=O), 1632 (v, CH=N), 749 (v, C- S of thiadiazole ring), 1148 (v, C-F); ^{1}H NMR (DMSO-d_6, 400MHz): δ 6.92-6.93 (1H, d, Ar), 7.47-7.49 (1H, d, Ar), 8.14-8.16 (1H, d, Ar), 7.56 (1H, s, Ar-Thiadiazole), 11.90 (1H, s, NH).

AB08:5-fluoro-3-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one; Yield:79%, M.P. 242-244°C; IR (KBr, cm^{-1}): 2970 (v, Ar C-H), 3452 (v, N-H of isatin ring), 1741 (v, C=O), 1629 (v, CH=N), 745 (v, C-S of thiadiazole ring), 2566((v, C-SH), 1144 (v, C-F); ^{1}H NMR (DMSO-d_6, 400MHz): δ 6.87-6.88 (1H, d, Ar), 7.36-7.37 (1H, d, Ar), 7.38-7.40 (1H, d, Ar), 11.00 (1H, s, SH), 12.25 (1H, s, NH).

AB09:5-fluoro-3-[(5-methyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one Yield:77%, M.P. 218-221°C; IR (KBr, cm^{-1}): 3449 (v, N-H of isatin ring), 3061 (v, Ar C-H), 2790 -2855 (v, C-CH_3), 1752 (v, C=O), 1626 (v, CH=N), 739 (v, C-S of thiadiazole ring), 1140((v, C-F); ^{1}H NMR (DMSO-d_6, 400MHz): δ 1.86 (3H, s, CH_3), 6.85-6.87 (1H, d, Ar), 7.36 (1H, d, Ar), 7.38-7.40 (1H, d, Ar), 10.99 (1H, s, NH).

AB10:5-methyl-3-(1,3,4-thiadiazol-2-ylimino)-1,3-dihydro-2*H*-indol-2-one; Yield:76%, M.P. 242-245°C; IR (KBr, cm^{-1}): 3061(v, Ar C-H), 3294 (v, N-H of isatin ring), 1752 (v, C=O), 1622 (v, CH=N), 738 (v, C-S of thiadiazole ring), 2865-2925 (v, C- CH_3); ^{1}H NMR (DMSO-d_6, 400MHz): δ 2.21 (3H, s, CH_3), 6.87-6.89 (1H, d, Ar), 7.51-7.52 (1H, d, Ar), 7.56-7.57 (1H, d, Ar), 7.58 (1H, s, Ar-Thiadiazole), 10.89 (1H, s, NH).

AB11:5-methyl-3-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one; Yield:68%, M.P. 202-204°C; IR (KBr, cm^{-1}): 3325 (v, Ar C-H), 3421 (v, N-H of isatin

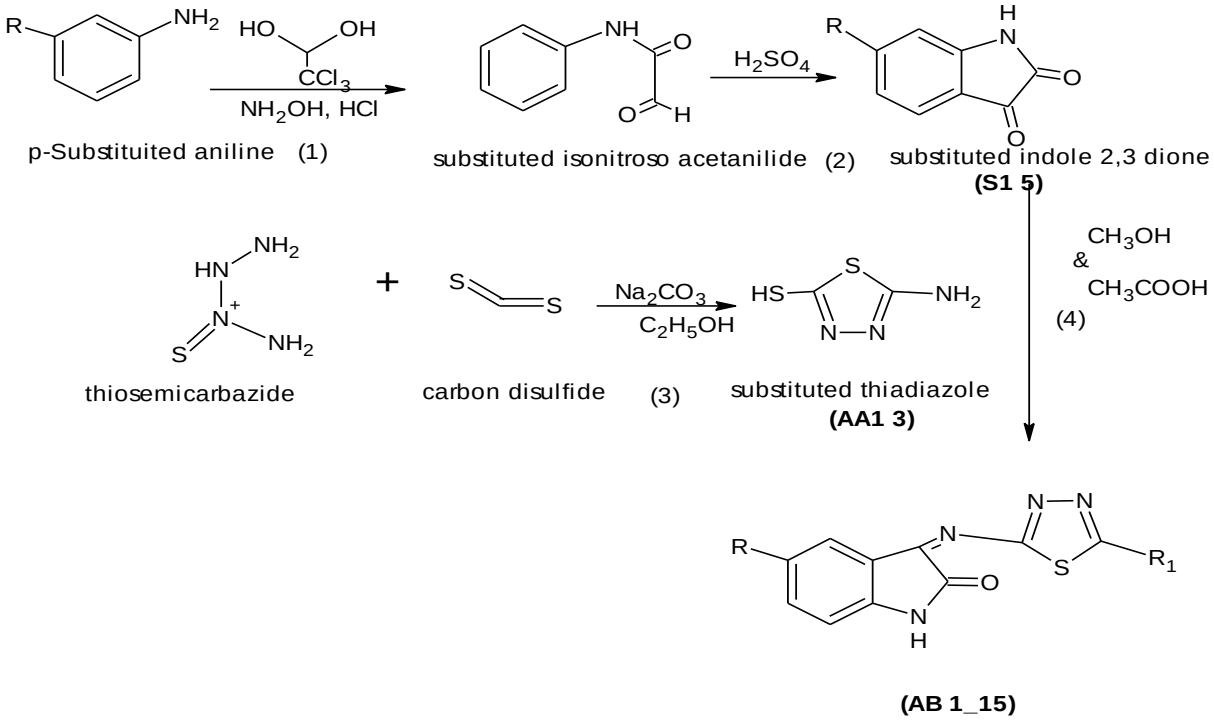
ring), 1736 (v, C=O), 1637 (v, CH=N), 1491 (v, C-S of thiadiazole ring), 2571 (v, C-SH), 2809-2914 (v, C-CH_3); ^{1}H NMR (DMSO-d_6, 400MHz): δ 2.21 (3H, s, CH_3), 6.75-6.77 (1H, d, Ar), 7.34-7.35 (1H, d, Ar), 7.36-7.37 (1H, d, Ar), 10.90 (1H, s, SH), 13.15 (1H, s, NH).

AB12:5-methyl-3-[(5-methyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one (AB12) Yield:69%, M.P. 234-236 °C; IR (KBr, cm^{-1}): 3248 (v, Ar C-H), 3287(v, N-H of isatin ring), 1747 (v, C=O), 1628 (v, CH=N), 738 (v, C-S of thiadiazole ring), 2926-3084 (v, C-CH_3); ^{1}H NMR (DMSO-d_6, 400MHz): δ 2.21 (3H, s, CH_3), 2.30 (3H, s, CH_3), 6.75-6.77 (1H, d, Ar), 7.28-7.35 (1H, d, Ar), 7.37 (1H, d, Ar), 10.89 (1H, s, NH).

AB13: 5-nitro-3-(1,3,4-thiadiazol-2-ylimino)-1,3-dihydro-2H-indol-2-one: yield 73%, M.P. 265-267°C; IR (KBr, cm^{-1}): 3336 (v, N-H of isatin ring), 3096 (v, Ar C-H), 749 (v, C-S of thiadiazole ring), 1753 (v, C=O), 1620 (v, CH=N), 1340-1471 (v, C-NO_2); ^{1}H NMR (DMSO-d_6, 400MHz): δ 7.11-7.13 (1H, d, Ar), 7.42-7.45 (1H, d, Ar), 7.96-7.98 (1H, d, Ar), 7.92 (1H, s, Ar-Thiadiazole), 11.63 (1H, s, NH).

AB14:5-nitro-3-[(5-sulfanyl-1,3,4-thiadiazol-2-yl)imino]-1,3-dihydro-2*H*-indol-2-one; Yield:85%, M.P. 198-200°C; IR (KBr, cm^{-1}): 3094 (v, Ar C-H), 3342 (v, N-H of isatin ring), 1752 (v, C=O), 1621 (v, CH=N), 750 (v, C-S of thiadiazole ring), 1128 (v, C- SH), 2615 (v, S-H), 1284-1473 (v, C-NO_2); ^{1}H NMR (DMSO-d_6, 400MHz): δ 7.03-7.05 (1H, d, Ar), 8.17 (1H, d, Ar), 8.39 (1H, d, Ar), 11.63 (1H, s, SH), 13.15 (1H, s, NH).

AB15:3-[(5-methyl-1,3,4-thiadiazol-2-yl)imino]-5-nitro-1,3-dihydro-2*H*-indol-2-one Yield:63%, M.P. 240-242 °C; IR (KBr, cm^{-1}): 3126 (v, Ar C-H), 3336 (v, N-H of isatin ring), 1756 (v, C=O), 1618 (v, CH=N), 748 (v, C-S of thiadiazole ring), 2781-2845 (v, C- CH_3), 1337-1467 (v, C-NO2); ^{1}H NMR (DMSO-d_6, 400MHz): δ 2.21 (3H, s, CH_3), 7.03-7.05 (1H, d, Ar), 8.17-8.18 (1H, d, Ar), 8.39-.8.41 (1H, d, Ar), 11.62 (1H, s, NH).



Scheme -1

Where R=H,Cl,F,CH_3,NO_2

R_1 =H,SH, CH_3

Antimicrobial activity: The newly synthesized isatin schiff bases' in vitro antibacterial activity was tested using the well diffusion method, which has been previously described [33]. In order to determine if the synthesized schiff bases have antibacterial or antifungal properties against Candida albicans (MTCC-183), Aspergillus niger (MTCC-277), Escherichia coli (MTCC-452), Staphylococcus aureus (MTCC-3160), and Klebsiella pneumonia (MTCC-432), they were examined. The tested sample's 10, 20, and 30 µg/mL concentrations were compared to both the strains of bacteria and fungus. As typical medications, fluconazole and ciprofloxacin were utilized, along with zone of inhibition after being incubated for 24 hours at 37^0C, was investigated.

Result and discussion

Novel synthesized Schiff bases of isatin **,**3-(1,3,4-thiadiazol-2-ylimino)-1,3-dihydro-2*H*-indol-2-one (AB01-15) were obtained from reaction sequences present in Scheme –I .Initially substituted isatin were created by reacting substituted anilines with chloral hydrated, sodium sulphate and hydroxylamine hydrochloride, prepared intermediate reacted with sulphuric acid to get desired compounds (S1-5). Thiosemicarbazide was dissolve in ethanol than added anhydrous sodium bicarbonate and carbon disulfide, heated 40 °C and refluxed for hours, resulted in the formation of substituted thiadiazole(AA1-3) . later on Schiff base of isatin were obtained by refluxed with amines along with methyl alcohol and small amount of glacial acetic acid(AB01-15). The newly synthesized compounds were confirmed by IR and 1H NMR spectral analysis.In IR spectrum, a sharp and strong band at 1733-1793 cm-1 was observed, which confirmed the presence of carbonyl (C=O) group. An absorption band at 1618-1637 cm-1 was observed which confirmed the CH=N (imine) group of Schiff base.

TABLE-1

ANTIMICROBIAL ACTIVITY OF SOMESCHIFF BASES OF INDOLE-2-3-DIONE (**AB01-15**)

		Zone of inhibition (mm)					
Sample code	Conc. (µg/mL)	Gram-positive bacteria		Gram-negative bacteria		Fungi	
		S. aureus	*B. subtilus*	*E. coli*	*K. pneumoniae*	*C. albicans*	*A. niger*
AB01	10	6±0	6±0	6±0	6±0	7±0	6±0
	20	6±0	7±0	6±0	6±0.94	9±0.57	7±0.5
	30	7±0	7±0	6±±0.5	6±0.47	10±0.5	7±0.57
AB02	10	8±0.5	6±0	6±0	6±0.47	7±0	6±0
	20	9±0.47	6±0	7±0.94	7±0.94	8±0.5	6±0
	30	10±0.94	7±0.94	7±0	9±0.57	9±0.47	6±0.47
AB03	10	7±02	6±0	6±0	8±0.84	6±0	6±0
	20	8±0.57	6±0	6±0	14±0.94	7±06	6±0
	30	9±0.59	7±0.92	9±0.5	15±0.52	7±0.92	7±0.44
AB04	10	6±0	6±0	6±0	6±0.47	6±0	6±0
	20	7±0	7±0.86	7±0.57	7±0.86	6±0	6±0.57
	30	8±0.5	8±0	7±0.47	8±0.94	6±0.57	7±0.86

AB05	10	10±0.57	9±0.94	8±0.5	6±0	8±0.47	6±0
	20	11±0.47	11±0.57	10±0.57	6±0.5	12±0.57	7±0.47
	30	16±0.5	14±0.5	13±0.94	7±0.86	13±0.5	8±0.94
AB06	10	7±0	6±0	6±0	8±0.86	6±0	6±0
	20	8±0.5	6±0	6±0	14±0.94	7±0	6±0
	30	9±0.57	7±0.94	9±0.5	15±0.57	7±0.94	7±0.47
AB07	10	6±0	6±0	6±0	6±0	7±0	6±0
	20	7±0	7±0.83	7±0.55	7±0.83	6±0	6±0.55
	30	8±0.5	8±0	7±0.44	8±0.92	10±0.5	7±0.54
AB08	10	9±0.57	12±0.94	11±0.94	11±0.47	8±0.94	7±0.86
	20	11±0.57	14±0.57	13±0.5	12±0.86	11±0.5	8±0.47
	30	13±0.5	18±0.5	16±0.57	17±0.86	20±0.57	9±0.57
AB09	10	6±0	6±0	6±0	6±0	7±0	6±0
	20	6±0	7±0	6±0	6±0.94	9±0.57	7±0.5
	30	7±0	7±0	6±±0.5	6±0.47	10±0.5	7±0.57
AB10	10	6±0	6±0	6±0	6±0.47	6±0	6±0
	20	7±0	7±0.86	7±0.57	7±0.86	6±0	6±0.57
	30	8±0.5	8±0	7±0.47	8±0.94	6±0.57	7±0.86
AB11	10	9±0.5	7±0.94	7±0.94	6±0	7±0.57	6±0.5
	20	11±0.57	10±0.57	10±0.5	7±0	8±0.47	7±0.47
	30	14±0.94	13±0.5	12±0.47	7±0.57	12±0.47	7±0.5
AB12	10	6±0	6±0	6±0	6±0.47	6±0	6±0
	20	7±0	7±0.86	7±0.57	7±0.86	6±0	6±0.57
	30	8±0.5	8±0	7±0.47	8±0.94	6±0.57	7±0.86
AB13	10	6±0	6±0	6±0	6±0	7±0	6±0
	20	7±0	7±0.83	7±0.55	7±0.83	6±0	6±0.55
	30	8±0.5	8±0	7±0.44	8±0.92	10±0.5	7±0.54
AB14	10	11±0.57	8±0.57	6±0	7±0.57	6±0	6±0
	20	13±0.5	10±0.5	6±0.5	11±0.47	7±0	6±0.5
	30	15±0.47	15±0.94	6±0	12±0.94	8±0.94	8±0.47
AB15	10	6±0	6±0	6±0	6±0	7±0	6±0
	20	7±0	7±0.83	7±0.55	7±0.83	6±0	6±0.55
	30	8±0.5	8±0	7±0.44	8±0.92	10±0.5	7±0.54
Ciprofloxacin	10	25±0.47	12±0.5	22±0.47	23±0.47	---	---
	20	29±0.47	17±0.74	26±0.47	26±0.47	---	---
	30	34±0.47	20±0.15	30±0.47	28±0.47	---	---
Fluconazone	10	---	---	---	---	26±0.86	17±0
	20	---	---	---	---	30±0.74	24±0.5
	30	---	---	---	---	32±0.57	30±0

Antibacterial activity: all novel synthesized compounds exhibit antibacterial activity. the tested compounds AB08 showed good antibacterial activity against gram positive and gram

negative bacterial strain, AB14 exhibit good antibacterial activity against gram positive bacterial strain and also showed activity against *K. pneumoniae*, AB11 compound showed good antibacterial activity against gram positive and gram negative bacteria, AB06 compound exhibit good antibacterial activity against *K. pneumoniae* ,AB05 compound also showed good antibacterial activity. Other all compounds exhibit mild to moderate inhibition against all bacterial strain.

Amongst the 15 newly synthesized Schiff bases, compounds AB05,AB08,and AB11 exhibit better antifungal activity against *C. albicans*, other compounds exhibit mild activity (Table-1)

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