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SYNTHESIS OF NOVEL SCHIFF'S BASES AND THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT: A new series of Schiff's base compounds were synthesized by condensation of 1-(4-amino-4 phenyl) 3-phenyl triazene-1-ol) and substituted aldehyde and gave high yields of target compounds. Antimicrobial activity of compounds has been tested against bacterial and fungal species, namely gram-positive bacteria as *S. aureus* and *S. pyogenes*, gram-negative bacteria as *E. coli* and *P. aeruginosa*, and fungal species *C. albicans* and *A. clavatus* are selected based on their clinical and pharmacological importance. Bacterial and fungal tests were performed under the same conditions using Cefixime and Griseofulvin as standard drugs. It has been found that synthesized Schiff's base has shown efficient antibacterial and anti-fungal activities. Thus they can be revealed as potent antimicrobial compounds. They are widely used for industrial purposes and also exhibit a broad range of biological activities. The structures of synthesized compounds were confirmed by TLC, melting point, Infrared spectroscopy, and proton nuclear magnetic resonance spectroscopy (^{1}HNMR) data.

INTRODUCTION: Schiff's bases, named after Hugo Schiff, are formed when, under specific conditions, any primary amine interacts with an aldehyde or a ketone [1]. Structurally a Schiff's base is an aldehyde or ketone nitrogen analogue in which the imine or the azomethane group has been substituted for the carbonyl group, and it has an ability to modulate the activities of many enzymes involved in metabolism. The pharmacophore potential of this group is due to its ability to form complex compounds with bivalent and trivalent metals found at the active core of various enzymes involved in metabolic reactions. Azomethane pharmacophore is used in the production of new bioactive molecules [2].

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Schiff's base has attracted a lot of attention due to its broad range of promising applications such as antibacterial activity [3], anti-fungal [4], anticancer [5], antidepressant [6], antioxidant, and analgesic [7]. Matar and coworkers have reported the synthesis of 3, 3-diaminodipropylamine, and different derivatives of benzaldehyde having excellent bactericidal and fungicidal properties [8]. Teran and coworkers have reported a series of new Schiff's base from 4-aminoantipyrine with excellent antibacterial, anti-fungal, leishmanicidal, and antioxidant activities for clinical applications [9]. The goal of the present research is to develop novel Schiff's bases for potential applications as antimicrobial agents. Herein, we report the preparation of Schiff's base derived from 1-(4-amino-4 phenyl) 3-phenyl triazene-1-ol), Aldehyde with reasonably good antibacterial and antifungal activities.

EXPERIMENTAL SECTION:

Material and Methods: IR spectra of the structures were recorded in KBr pellets with a Shimadzu FT-IR spectrophotometer in the 4000-

400 cm^{-1} range. The ^{1}HNMR spectra were measured at JEOL II 400 MHz from Delhi University, New Delhi. Melting points were examined in open capillary tubes.

All the chemicals used were of analytical reagent grade (AR) and of maximum purity available. All reagents were commercially available. Solvents were purified and dried according to the standard procedures**.**

General Procedure: A solution of 1-(4-amino-4 phenyl) 3-phenyl triazene-1-ol (0.1mole was dissolved in ethanol) and was added slowly to a solution of aldehyde 1a-1e (0.1 mole was dissolved in 50 ml ethanol). Stirrer the reaction mixture for 2-3 hr maintaining the reflux temperature at 75-80 °C. Cool the reaction mixture, allow to form precipitates. Filter the mass, washed with ice-cold water, recrystallizes from ethanol to afford 8-9 g 2a-2e reddish-brown shining crystals [10-13].

The molecular structure of Schiff's base is given in **Fig. 1**.

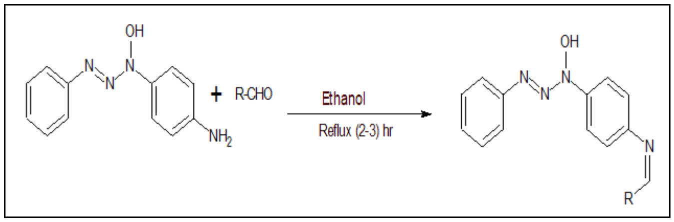
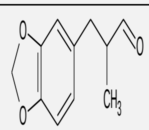
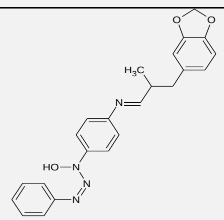
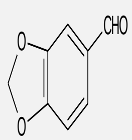
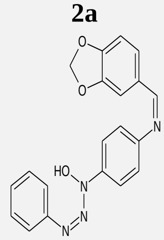
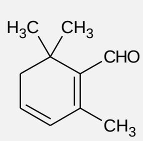
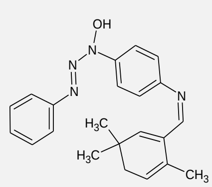
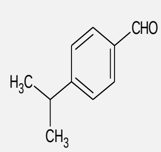
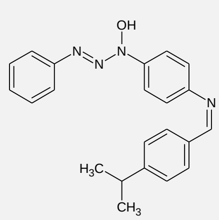
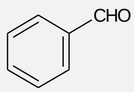
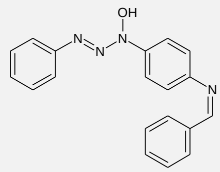


FIG. 1: STRUCTURE OF SCHIFF'S BESE (2A-2E)

RESULTS AND DISCUSSION: Typically, the structure of Schiff's base compounds were obtained under reflux of 1-(4-amino-4 phenyl) 3-phenyl triazene-1-ol suitable with aromatic aldehyde [1a-1e] at a 1: 1 mole ratio. The purity of the Schiff's base 2a-2e and the obtained structures were tested by TLC, melting point, FT-IR, and ^{1}H NMR. The proposed molecule's structure is represented in **Fig. 1**. 2a–2e Schiff's base compounds are novel and have not yet been reported till date in the literature.

TABLE 1: SCHIFF'S BASE STRUCTURE, MELTING POINT, MOLECULAR WEIGHT AND YIELD

Entry	R	Schiff's base	Reaction (Temp.)	Time (hr.)	M.W	M.P.	Color and shape the crystals	Yield (g)
1	 1a	 2a	75-80 °C	2-3	402	312	Reddish shining crystals	8.0
2	 1b	 2b	75-80 °C	2-3	360	326	Brownish crystals	9.0
3	 1c	 2c	75-80 °C	2-3	360	288	Reddish shining crystals	8.0
4	 1d	 2d	75-80 °C	2-3	358	346	Reddish shining crystals	8.0

5	 1e	 2e	75-80 °C	2-3	316	297	Brownish crystals	9.0

FT-IR Analysis: FT-IR spectroscopy provides information on molecular vibration or precision in transitions between vibrational and rotational energy levels in molecules. Absorption bands detected in the region of 1580-1450 cm^{-1} confirm the presence of (>C=N-) Schiff's base moiety respectively, where the bandwidth around 3750-3480 cm^{-1} confirms the presence of hydrogen-bonded $\nu_{(O-H)}$ stretching vibration. The FTIR data obtained for both Schiff bases are tabulated in **Table 2**. It is observed in the range 3500-3750 cm^{-1} which shows the presence of O-H stretching frequency (Represented in **Table 2**) [14-15].

TABLE 2: FTIR OF SCHIFF'S BASES

Schiff's base	$\nu_{(O-H)}$	$\nu_{(N=N)}$	$\nu_{(C=N)}$
2a	3734	1456	1541
2b	3550	1444	1555
2c	3652	1510	1468
2d	3525	1458	1495
2e	3710	1474	1520

^{1}H NMR analysis: ^{1}H NMR spectra of the Schiff's base structure were recorded in chloroform **Table 3**. The multiplet, which extends from δ 7.0 to δ 7.6 is equal to 13 protons present in aromatic rings. A singlet at δ 7.8-8.2 ppm is attributed to the presence of CH=N- linkage. The signal at δ 3.96 ppm corresponds to $–CH_3$ proton (3H). The 1H NMR spectra of Schiff's base provide additional support for the confirmation of the proposed structure of Schiff's base. In the ^{1}HNMR spectra of Schiff's base, Schiff's base showed a signal, ν (O-H) at 8.8-9.9 ppm.

TABLE 3: SELECTED ^{1}HNMR OF SCHIFF'S BASES

Schiff's Base	-N=CH-	Aromatic	-OH	$-CH_3$
2a	7.8-7.9	7.41-7.42 (M)	8.90- (S,1H)	3.96 (S,3 H)
2b	7.9-8.0	7.40-7.6(M)	9.80(S,1H)	-
2e	7.8-8.0	7.30-7.5(M)	9.80(S,1H)	-

Antimicrobial Activity of Schiff's Base:

Anti-bacterial and Anti-fungal Activity: [16] Bacteria strains Gram-positive bacteria as *S. aureus* and *S. pyogenes*, Gram-negative bacteria as *E. coli* and *P. aeruginosa*, and Fungal strains *C. albicans* and *A. clavatus* are selected based on their clinical and pharmacological importance. Bacterial microbes were prepared in agar / YEPD genetics using a plate-spreading process, and fungal stock culture is placed 24 hours at 37 °C in a potato dextrose agar (PDA) medium (Micro care laboratory, Surat, India), following refrigeration on 4 °C. Bacterial species were grown on Mueller-Hinton agar (MHA) plates at 37 °C (bacteria were planted in nutrient broth at 37 °C and stored in agar slants at 4°C), while yeast and fungi were planted in Sabouraud dextrose agar(SDA) and in the PDA media, respectively, at 28°C. Standard cultures were maintained at 4 °C.

Determination of Zone of Inhibition Method: [17] *In-vitro* anti-bacterial and antifungal activities were tested on a sample. Activities of a sample against two Grams (+), two Grams (-), and two fungi have been investigated by the distribution of the agar disk diffusion method. Each sample was diluted with dimethyl sulfoxides, sterilized by filtration using a sintered glass filter, and stored at 4 °C. By determining the prevention area, Gram-positive, Gram-negative, and fungal species were treated as standard antibiotics. All compounds were tested for their antibacterial and antifungal activities against Gram-positive *S. aureus*, *S. pyogenic* and Gram-negative *E. coli*, *P. aeruginosa* and fungal strains *A. clavatus* and *C. albicans*. Dilution (25 μg / ml) of the sample and standard drugs (5, 25, and 50 μg / ml) were prepared in double-distilled water using nutritious agar tubes. Mueller-Hinton's sterile agar plates were infected with bacterial infections (108 cfu) and allowed to remain at 37 °C for three hours.

Control tests were performed under the same conditions using Cefixime and Griseofulvin as standard drugs. The zones of growth inhibition around the discs were rated after 18 to 24 h of incubation at 37 °C in bacteria and 48 to 96 h for fungus at 28 °C (including disk width) on the surface of the agar around the discs, and values <8 mm were considered as not active. Antibacterial and antifungal activities of both Schiff bases are tabulated in **Tables 4** to **7**.

Agar Diffusion Test (Mueller-Hinton Test): [18] It is a test that uses antibiotic -impregnate wafers to test whether certain bacteria are susceptible to certain antibiotics. A known number of bacteria are planted on agar plates in the presence of small wafers with appropriate antibiotics. When bacteria are attacked by certain antibiotics, the cleaning area around the wafer where bacteria cannot grow is called the zone of inhibition.

TABLE 4: ANTI-BACTERIAL ACTIVITY OF STANDARD ANTI-BACTERIAL DRUG

Standard Drug	Concentration (µg/ml)	MIC in mm			
		S. pyogenes	*S. aureus*	*E. coli*	*P. aeruginosa*
Cefixime	5 µg/ml	22	19	18	20
	25 µg/ml	29	26	25	28
	50 µg/ml	33	35	36	37

TABLE 5: ANTI-FUNGAL ACTIVITY OF STANDARD ANTI-FUNGAL DRUG

Standard Drug	Concentration (µg/ml)	MIC in mm	
		C. albicans	*A. clavatus*
Griseofulvin	*5* µg/ml	*34*	*35*
	25 µg/ml	46	44
	50 µg/ml	53	55

TABLE 6: ANTI-BACTERIAL ACTIVITY OF SCHIFF'S BASE

Group	Concentration (µg/ml)	MIC in mm			
		S. aureus	*S. pyogenic*	*E. coli*	*P. aeruginosa*
2a	25 µg/ml	18	13	22	14
2b	25 µg/ml	16	18	18	13
2c	25 µg/ml	15	22	17	18
2d	25 µg/ml	20	27	18	16
2e	25 µg/ml	17	25	18	19

TABLE 7: ANTI-FUNGAL ACTIVITY OF SCHIFF'S BASES

Group	Concentration (µg/ml)	MIC in mm	
		C. albicans	*A. clavatus*
2a	25 µg/ml	20	21
2b	25 µg/ml	22	23
2c	25 µg/ml	20	21
2d	25 µg/ml	21	20
2e	25 µg/ml	22	19

CONCLUSION: Based on the results of this study, it can be concluded that a combination of 1-(4-amino-4 phenyl) 3-phenyl triazene-1-ol and aldehyde with a simple condensation process has been successfully achieved with a good mixing time of 2 to 3 hours. Both newly prepared Schiff base have shown reasonably good antibacterial and antifungal activities against various pathogenic bacteria and fungi.

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CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest regarding the publication of this article.

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