ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info

ISSN
0976-9595
Research Article

SYNTHESIS AND SPECTRAL LINEARITY STUDIES OF SOME THERAPEUTICALLY INTERESTED SUBSTITUTED HYDRAZONES

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ABSTRACT

In the present work, we report the synthesis of substituted (*E*)-2-benzylidene-1-methylhydrazines by reaction of substituted aldehydes with 1-methylhydrazine in the presence of acetic acid using as catalyst. The synthesized compounds are more than 80% yield. UV, IR and NMR spectral data have been used to identify the structure of synthesized compounds. UV, IR and NMR spectroscopic data of substituted (*E*)-2-benzylidene-1-methylhydrazines have been correlated with Hammett constants and *F* and *R* parameters using linear regression analyses. From the results the effect of substituents has been discussed. The antimicrobial assay of these (*E*)-2-benzylidene-1-methylhydrazines compounds were studied using Kirby-Bauer method.

Keywords: (*E*)-2-benzylidene-1-methylhydrazines, Correlation analysis, Effect of substituents, Synthesis, Antimicrobial activity

1. INTRODUCTION

Hydrazones are well-known compounds with interesting chemical properties which afforded diverse biological [1] and physical or medicinal applications [2]. Hydrazones are important intermediates for the preparation of nitrogen containing heterocyclic compounds [3]. They are obtained by the reaction of aldehyde and aliphatic hydrazide in acidic medium which leads to the synthesis of hydrazones. These structure fragments are mainly responsible for the physical and chemical properties of hydrazones. Both nitrogen atoms of the hydrazones are nucleophilic, although the amino type nitrogen is more reactive. The carbon atom of the hydrazone has both electrophilic and nucleophilic character [4-8]. Hydrazone compounds containing an azomethine –NH-N=CH– functional group denoted as an important class of compounds which possess broad range of biological activities [9]. For this reason, hydrazones derived from a diverse group of hetero aromatic scaffolds [10] have been successfully incorporated into some therapeutically useful drug candidates. In recent days, many hydrazone derivatives have also been known to exhibit antimicrobial [11], antimalarial [12], anti-inflammatory [13], anti-HIV [14], anticonvulsant [15], anti-hyperalgesic [16], antitubercular [17], analgesic [18], anti-inflammatory [19], antiplatelet [20] , anticancer [21], antiviral [22] and antitumoral [23] activities. They also act as insecticides, herbicides, nematocides, rodenticides, plant growth regulators, sterilants for houseflies, among other applications [24-27]. This fact is due to presence of NH-N=CH– functional group which is a pivotal role in various bioactive agents. Spectral data is useful for studying substituents effect by Hammett constants and Swain and Lupton's parameters using linear free energy relationship. Recently chemists [28-30] had synthesized hydrazones and studied linear free energy relationship and they observed satisfactory correlations using spectral data with Hammett constants and Swain and Lupton's parameters. Review of literature reveals that there is no information available regarding the study of effect of substituent of *(E)*-2-benzylidene-1-methylhydrazines. Therefore the authors have taken efforts to synthesis of (*E*)-2-benzylidene-1-methylhydrazines from 1-methyl hydrazinewith various substituted benzaldehydes by condensation reaction. The spectral data (UV, FT-IR and NMR) of *(E)*-2 benzylidene-1-methylhydrazines have been utilized for investigating the effect of substituent through Hammett correlations. The antimicrobial assay of (*E*)-2-benzylidene-1-methylhydrazines have been investigated [31] by Kirby-Bauer method.

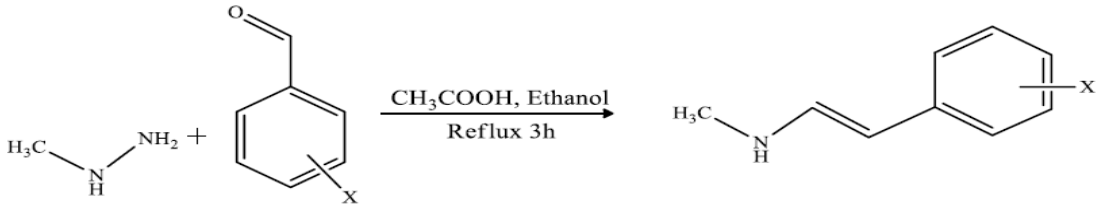
2. EXPERIMENTAL

2.1. Material

All the chemicals used in this study are of AR grade with 99% purity from Sigma-Aldrich and E-Merck chemical companies. Melting points of the all the (*E*)-2-benzylidene-1-methylhydrazines were measured on open glass capillaries melting point apparatus and are uncorrected. The absorption spectra of all the (*E*)-2-benzylidene-1-methylhydrazineshave been recorded on a SHIMADZU-1650 SPECTROMETER ($\lambda_{max,}$ nm) in spectral grade methanol. IR spectra of all the (*E*)-2-benzylidene-1-methylhydrazines compounds have been recorded on a Shimadzu FT-IR spectrophotometer and the ^{1}H &^{13}C NMR spectral studies were carried out using Bruker AV 400 MHzspectrometer.

2.2. General procedure for Synthesis of substituted (*E*)-2-benzylidene-1-methyl hydrazines

Equimolar quantities (0.01mol) of 1-methylhydrazine and substituted benzaldehyde were refluxed in a 100 mL round bottom flask for 3 h with 30 mL of absolute ethanol using 0.5 mL of glacial acetic acid (0.5 mL) as catalysis [29] as shown in Scheme-1. The reaction progress was monitored by TLC. The resultant mixture was cooled at room temperature. Then the precipitate obtained, was filtered at the filter pump and washed several times with cold water [30]. This crude product was recrystallized from ethanol and their melting points have been noted. The formation of product was confirmed by the melting point determination and spectroscopic (UV, IR, ^{1}H and ^{13}C NMR) studies as shown in Table 1.



X= H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-OCH_3, 4-CH_3, 3-NO_2, 4-NO_2

Scheme 1: Synthesis of substituted (*E*)-2-benzylidene-1-methylhydrazines

Table 1: Physical constants and spectral data (UV, IR, ^{1}H and ^{13}C NMR) of substituted (*E*)-2-benzylidene-1-methylhydrazines

Entry	X	M. F	M. W	m.p. (C)	λ_{max} (nm)	νCH=N (cm^{-1})	δCH=N (ppm)	δC=N (ppm)
1	H	$C_8H_{10}N_2$	134.18	68-69	322.00	1647.21	7.981	141.61
2	3-Br	$C_8H_9BrN_2$	211.99	81-82	319.50	1670.35	7.898	141.76
3	4-Br	$C_8H_9BrN_2$	211.99	96-97	320.00	1674.72	7.723	142.22
4	3-Cl	$C_8H_9ClN_2$	168.62	107-108	318.00	1680.00	7.899	145.44
5	4-Cl	$C_8H_9ClN_2$	168.62	110-111	317.50	1674.14	7.927	143.39
6	4-F	$C_8H_9FN_2$	152.17	81-82	315.50	1681.93	7.993	143.62
7	4-OCH_3	$C_9H_{12}N_2O$	164.20	86-87	318.50	1689.34	7.927	142.98
8	4-CH_3	$C_9H_{12}N_2$	148.20	72-73	316.00	1691.57	7.302	143.14
9	3-NO_2	$C_8H_9N_3O_2$	179.18	89-90	321.00	1674.21	8.564	139.99
10	4-NO_2	$C_8H_9N_3O_2$	179.18	93-94	321.50	1680.00	8.185	141.14

3. RESULT AND DISCUSSION

3.1. UV-visible spectral correlations

The assigned spectral (UV λ_{max}(nm)) absorptions of all the (*E*)-2-benzylidene-1-methylhydrazinesare presented in Table 1 and are correlated with Hammett sigma constants and Swain–Lupton's parameters using single and multi linear regression analysis [28-30].

For these correlations, the Hammett equation employed for the correlation analysis, involving the UV absorption maximum is as shown in equation (1).

$$\lambda = \rho\,\sigma + \lambda_0 \quad \ldots (1)$$

where λ_0 is the frequency for the parent member of the series

The structure parameter correlation analyses are presented in Table 2. From the structure parameter correlation analysis of all the (*E*)-2-benzylidene-1-methylhydrazines except those with parent (H) and 4-OCH_3 substituents have shown much better correlation with σ and σ^+constants. All correlation except those with parent (H) and 4-F substituents have shown satisfactory correlation coefficients with σ_I and F parameters. The Hammett constants σ_R and R parameter produce satisfactory correlation except with 4-CH_3 substituent. If they are included in the regression, they reduce the correlation considerably. Hammett constants σ, σ^+, σ_I, σ_R and R parameters gave positive ρ values. This indicates that the normal substituent effects operated in all the compounds. Similarly the multi-regression analyses are produced satisfactory correlations with Swain–Lupton and F and R parameters [32]. The correlated multi regression equations are

UV (λ *max* nm)=319.78 (±1.193)+0.58 (± 0.024)σ_I+7.81 (± 2.006) σ_R … (2)

(R=0.973, n =10, P>95%)

UV (λ *max* $nm_)$=320.09 (±1.189)+0.22 (± 0.023) F+6.49 (±1.494)R …(3)

(R=0.9271, n =10, P>95%)

Table 2: Results of correlation analysis of UV (λmax nm), νC=N (cm^{-1}) IR, NMR ^{1}H NMR (δ,ppm) CH=N and ^{13}C (δ,ppm) C=N data of all the substituted (*E*)-2-benzylidene-1-methylhydrazine with Hammett substituent constants σ, σ^+, σ_I, σ_R, F and R.

Frequency	Constants	r	I	ρ	s	n	Correlated derivatives
λ max (nm)	σ	0.905	318.16	3.340	2.024	8	3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 3-NO_2, 4-NO_2
	σ^+	0.905	318.53	2.450	2.019	8	3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 3-NO_2, 4-NO_2
	σ_I	0.901	318.37	1.450	2.348	8	3-Br, 4-Br, 3-Cl, 4-Cl, 4-OCH_3, 4-CH_3, 3-NO_2,4-NO_2
	σ_r	0.907	320.03	7.905	1.624	9	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-OCH_3, 3-NO_2, 4-NO_2
	F	0.902	318.95	-.0.019	2.377	8	3-Br, 4-Br, 3-Cl, 4-Cl, 4-OCH_3, 4-CH_3, 3-NO_2,4-NO_2
	R	0.907	320.18	6.480	1.664	9	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-OCH_3, 3-NO_2, 4-NO_2
νC=N(cm^{-1})	σ	0.901	1677.69	-5.777	12.837	9	H, 3-Br, 4-Br, 3-Cl, 4-Cl,4-F,4-OCH_3,4-CH_3, 4-NO_2
	σ^+	0.902	1677.62	-7.574	12.429	9	H, 3-Br, 4-Br, 3-Cl, 4-Cl,4-F,4-OCH_3,4-CH_3, 4-NO_2
	σ_I	0.901	1673.40	7.489	12.872	9	H, 3-Br, 4-Br, 3-Cl, 4-Cl,4-F,4-OCH_3,4-CH_3, 4-NO_2
	σ_R	0.903	1673.25	-22.540	12.038	9	H, 3-Br, 4-Br, 3-Cl, 4-Cl,4-F,4-OCH_3,4-CH_3, 4-NO_2
	F	0.902	1671.89	-10.901	12.687	7	H, 3-Br, 4-Br, 3-Cl, 4-Cl,4-F, 4-NO_2
	R	0.904	1672.26	-21.479	11.740	9	H, 3-Br, 4-Br, 3-Cl, 4-Cl,4-F,4-OCH_3,4-CH_3, 4-NO_2
δCH=N (ppm)	σ	0.906	7.796	0.612	0.248	9	H, 3-Br, 4-Br, 3-Cl, 4-Cl,4-F, 4-CH_3, 3-NO_2, 4-NO_2
	σ^+	0.905	7.881	0.350	0.246	9	H, 3-Br, 4-Br, 3-Cl, 4-Cl,4-F, 4-CH_3, 3-NO_2, 4-NO_2
	σ_I	0.906	7.592	0.882	0.249	9	3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-OCH_3, 4-CH_3, 3-NO_2, 4-NO_2
	σ_R	0.903	8.021	0.593	0.311	7	H, 3-Br, 4-Br,3-Cl,4-Cl,3-NO_2, 4-NO_2

	F	0.906	7.614	0.798	0.261	9	H, 3-Br, 4-Br,3-Cl,4-Cl, 4-F, 4-OCH_3, 4-CH_3, 4-NO_2
	R	0.903	8.033	0.493	0.311	8	H, 3-Br, 4-Br,3-Cl,4-Cl,4-CH_3, 3-NO_2, 4-NO_2
δC=N (ppm)	σ	0.904	142.99	-1.998	1.433	9	H, 3-Br, 4-Br, 4-Cl, 4-F, 4-OCH_3, 4-CH_3, 3-NO_2, 4-NO_2
	σ^+	0.904	142.75	-1.317	1.469	9	H, 3-Br, 4-Br, 4-Cl, 4-F, 4-OCH_3, 4-CH_3, 3-NO_2, 4-NO_2
	σ_I	0.901	143.00	-1.200	1.598	9	H, 3-Br, 4-Br, 4-Cl, 4-F, 4-OCH_3, 4-CH_3, 3-NO_2, 4-NO_2
	σ_R	0.906	141.85	-4.887	1.207	9	H, 3-Br, 4-Br, 4-Cl, 4-F, 4-OCH_3, 4-CH_3, 3-NO_2, 4-NO_2
	F	0.847	142.89	-0.894	1.598	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-OCH_3, 4-CH_3, 3-NO_2, 4-NO_2
	R	0.905	141.83	-3.664	1.300	9	H, 3-Br, 4-Br, 4-Cl, 4-F, 4-OCH_3, 4-CH_3, 3-NO_2, 4-NO_2

r = Correlation co-efficient; ρ= Slope; I = Intercept; s= Standard deviation; n = Number of substituents

3.2. IR Spectral correlations

The recorded FT-IR C=N (ν, cm^{-1}) stretching frequencies of the synthesized (*E*)-2-benzylidene-1-methylhydrazines are presented in Table 1. This data was correlated [28-30] with Hammett substituent constants and Swain-Lupton's [32] parameters. Thus the Hammett equation may be used in the form as

$$\nu = \rho\sigma + \nu_o \quad \ldots (4)$$

where ν_o is the frequency for the parent member of the series.

The results of structure parameter statistical analyses are shown in Table 2. From Table 2, it is evident that all the Hammett constants produced satisfactory correlation with νC=N stretching frequencies except 4−OCH_3, 4−CH_3 and 3-NO_2 substituents. If they are included in the regression, they reduced the correlation considerably. All correlations gave negative ρ values are obtained. This shows that the revers substituent effect operates in all the (*E*)-2-benzylidene-1-methylhydrazines. Similarly, the multi-regression analysis of all the synthesized (*E*)-2-benzylidene-1-methylhydrazines with Swain-Lupton's parameters [32] are found to correlate satisfactorily and the correlation equations are as follows:

$$\nu cm^{-1}\ (CH=N) = 1666.86\ (\pm 8.185) - 18.43\ (\pm 2.817)\ \sigma_I + 32.00\ (\pm 4.419)\sigma_R \quad \ldots(5)$$

(R=0.955, n =10, P95%)

$$\nu cm^{-1}\ (CH=N) = 1668.21\ (\pm 8.174) + 10.10\ (\pm 2.93)\ F\ 21.08(\pm 2.51)R \quad \ldots(6)$$

(R=0.947, n =10, P>90%)

3.3. NMR Spectral study

3.3.1. ^{1}HNMR Spectral correlations

In nuclear magnetic resonance spectra, the proton chemical shifts δ CH=N (ppm) depends on the electronic environment of the nuclei concerned [28-30]. These shifts can be correlated with reactivity parameters. Thus the Hammett equation may be used in the form as

$$\delta = \rho\sigma + \delta_0 \quad \ldots (7)$$

where δ_0 is the chemical shift in the corresponding parent compound.

The assigned CH=N chemical shifts (δ, ppm) of (*E*)-2-benzylidene-1-methylhydrazine compounds have been correlated with various Hammett sigma constants. The results of statistical analysis are presented in Table 2. From Table 3, it is evident that the ^{1}H NMR chemical shift δ CH=N (ppm) values of all substituted (*E*)-2-benzylidene-1-methylhydrazines except that with 4-OCH_3 substituent have shown satisfactory correlations with σ (r = 0.907) and σ^+ (r = 0.906) parameters. The Hammett constant σ_I parent Hand F parameters produce better correlation except that with 3-NO_2 substituent. The CH=N chemical shifts (δ, ppm) gave satisfactory correlation with Hammett's constants σ_R parameter, excluding 4-OCH_3, 4-CH_3 and 3-NO_2 substituents. The R parameter gave satisfactory correlation except with 4-F and 4-OCH_3 substituents. If they are included in the regression, they reduce the correlation considerably. All correlations gave positive ρ values this shows that normal substituent effect operates in all system. Similarly the multi-regression analysis of the entire synthesized E)-2-benzylidene-1-methylhydrazines with Swain-Lupton's

parameters [32] are found to correlate satisfactorily and the correlation equations are,

$$\delta CH{=}N(\text{ ppm}) = 7.677\ (\pm 0.168) + 0.83\ (\pm 0.033)\ \sigma_I + 0.467\ (\pm 0.013)\sigma_R \quad \ldots(8)$$

(R=0.978, n = 10, P > 95%)

$$\delta CH{=}N(\text{ ppm}) = 7.706\ (\pm 0.159) + 0.81\ (\pm 0.215)F + 0.52(\pm 0.032)R \quad \ldots(9)$$

(R=0.975, n = 10, P > 95%)

3.3.2. ^{13}C NMR Spectral correlation analysis

The recorded ^{13}C NMR C=N (δ, ppm) chemical shifts of the synthesized (*E*)-2-benzylidene-1-methyl hydrazines are presented in Table 1. This data was correlated [29-31] with Hammett substituent constants and Swain-Lupton's [32] parameters. The structure parameter correlation analyses are presented in Table 2. The C=N chemical shifts (δ, ppm) with Hammett σ, σ^+, σ_I, σ_R constants and R parameters gave satisfactory correlations except that with 3-Cl substituent. When the substituent included in the regression, they reduce the correlation considerably. All correlations gave negative ρ values are obtained. This shows that the operation of reveres substituent effect operates in all systems. Remaining Hammett constants and R parameter are failure in correlation. The failure correlation is attributed to weak inductive, field and resonance effects of substituents for predicting the reactivity on the ^{13}C NMR chemical shifts through resonance as per the conjugative structure, shown in Fig. 1.

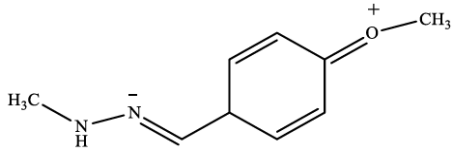


Fig. 1: Resonance conjugated structure

(*E*)-2-benzylidene-1-methylhydrazines.The multi-correlations of Swain Lupton'sparameters [32] are satisfactory and their regression equations are:

$$\delta CH{=}N\ (\text{ ppm}) = 142.13\ (\pm 0.882) - 0.67\ (\pm 0.056)\ \sigma_I - 4.78\ (\pm 0.174)\ \sigma_R \quad \ldots(10)$$

(R=967, n =10, P>95%)

$$\delta CH{=}N\ (\text{ppm}) = 142.24\ (\pm 0.909) - 1.03\ (\pm 0.181)\ F - 3.70\ (\pm 1.037)R \quad \ldots(11)$$

(R = 0.961, n =10, P95%)

3.4. Anti-microbial activity

3.4.1. Antibacterial sensitivity assay

The synthesized (*E*)-2-benzylidene-1-methylhydrazine compounds were tested for antibacterial activities against various strains by disc diffusion method [31]. For the determination of antibacterial assay, three Gram-positive pathogenic strains *Bacillus substilis, Staphylococcus aureus, Streptococcus and* two gram negative strains *Escherichia coli and P. aeruginosa* were utilized. Fig. 2 (Plates 1-10) illustrates the antibacterial activity of (*E*)-2-benzylidene-1-methylhydrazines at a concentration of 250μg/mL and the positive control (ciprofloxacin) against the pathogens subjected for analysis.

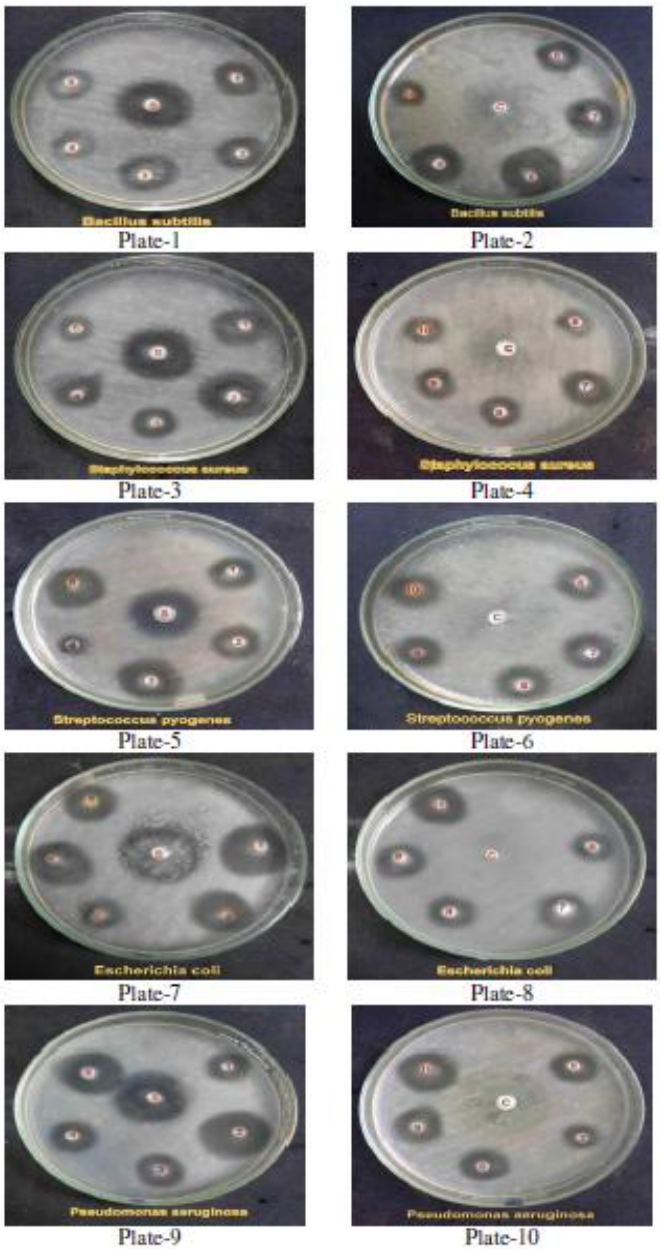


Fig. 2: Antibacterial activity of substituted (*E*)-2-benzylidene-1-methylhydrazines (petri-plates)

Table 3.Antibacterial activity of zone of inhibition values of substituted (*E*)-2-benzylidene-1-methyl hydrazine compounds

Entry	X	Zone of inhibition(mm)				
		Gram +ve bacteria			Gram -vebacteria	
		B.subtilis	*S. aureus*	*Streptococcus*	*E.coli*	*P.aeruginosa*
1	H	8	10	14	17	7
2	3-Br	8	12	12	11	13
3	4-Br	7	14	16	8	8
4	3-Cl	9	7	7	11	7
5	4-Cl	8	13	11	9	11
6	4-F	8	11	10	7	8
7	4-OCH_3	9	10	11	9	7
8	4-CH_3	12	10	10	7	9
9	3-NO_2	7	10	10	7	9
10	4-NO_2	6	11	10	10	10
Standard	Ciprofloxacin	18	18	18	20	18
Control	DMSO	0	0	0	0	0

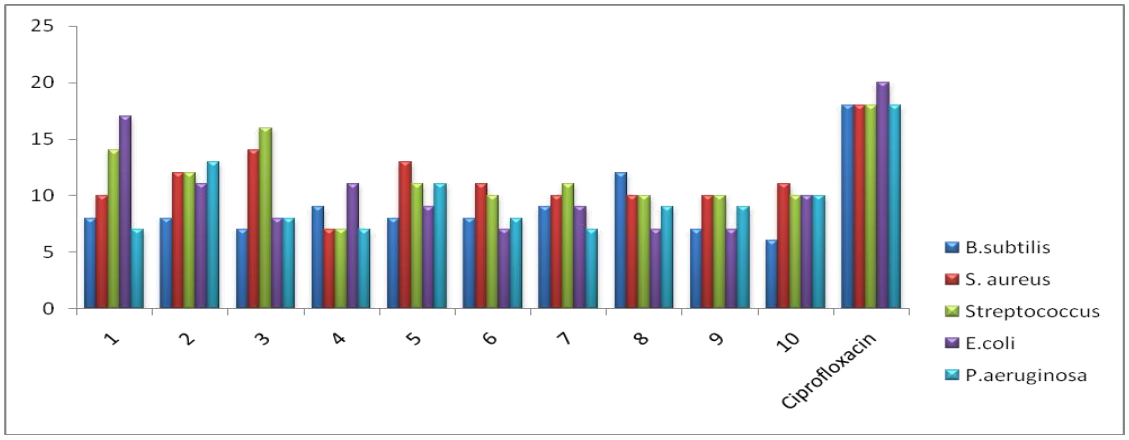


Fig. 3: Antibacterial activity of substituted (E)-2-benzylidene-1-methylhydrazine compounds (cluster Colum chart)

The corresponding clustered column chart is shown in Fig.3**.** The diameter of each zone of inhibition was measured and the results are given in Table 4. The 4-CH_3 substituted hydrazones have shown good activity against *B. subtilis*. The 3-Br, 4-Br and 4-Cl substituted compound has shown good activity against *S. aureus.* The parent, 3-Br and 4-Br substituted compound has shown good activity against *Streptococcus pyogenes*. The H and 3-Br have very good activity against *E.coli* and *P. aeruginosa*.

3.4.2. Antifungal sensitivity assay

The synthesized substituted (*E*)-2-benzylidene-1-methylhydrazines have been studied antifungal activities against three fungal species namely, *A. niger, M. species* and *T. viride*. The Kirbye-Bauer disc diffusion technique [31] has been followed and amphotericin-B was used as the standard. The screening effects of antibacterial activity of synthesized (*E*)-2-benzylidene-1-methylhydrazines are shown in Fig 5 (Plates 1-10). The comparisons of zone of inhibitions are shown in Fig.4**.** The observed zone of inhibition values are given in Table 4. The parent compound (H), 3-chloro and 4-nitro substituted compounds have shown good anti-fungal activity against *A.niger*. The 4-methoxy and 4-nitro substituted compounds have shown good activity against *M. species*. The 3-Cl, 4-F, 4-OCH_3, 3-NO_2 and 4-NO_2 substituted compound has also shown good activity against *T. viride*. Remaining substituted (*E*)-2-benzylidene-1-methylhydrazines have shown moderate anti-fungal activity against three fungal species.

Table 4: Antifungal activity of zone of inhibition values of substituted (*E*)-2-benzylidene-1-methylhydrazines

Entry	X	Zone of inhibition (mm)		
		A. flavus	*A. niger*	*T. viride*
1	H	11	8	10
2	3-Br	10	7	10
3	4-Br	9	8	9
4	3-Cl	11	8	11
5	4-Cl	9	8	10
6	4-F	10	8	11
7	4-OCH_3	10	11	12
8	4-CH_3	9	9	9
9	3-NO_2	10	10	15
10	4-NO_2	11	13	11
Standard	Amphotericin-B	18	18	20
Control	DMSO	-	-	-

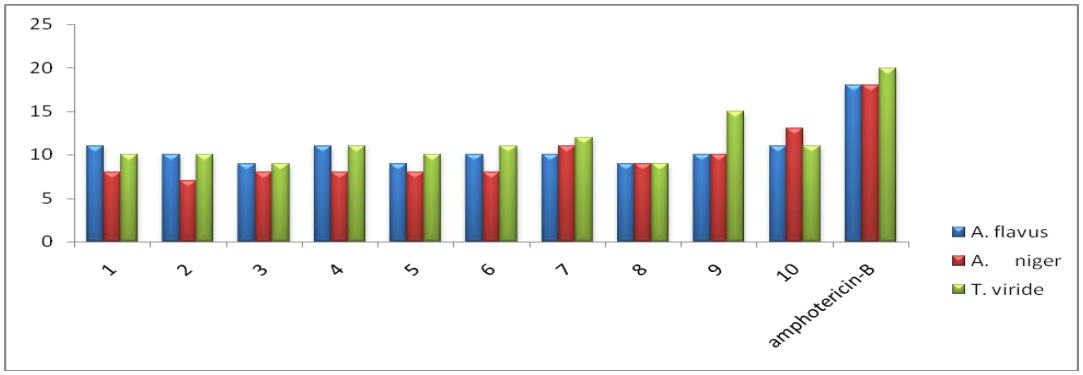


Fig. 4: Antifungal activity of substituted (E)-2-benzylidene-1-methylhydrazines

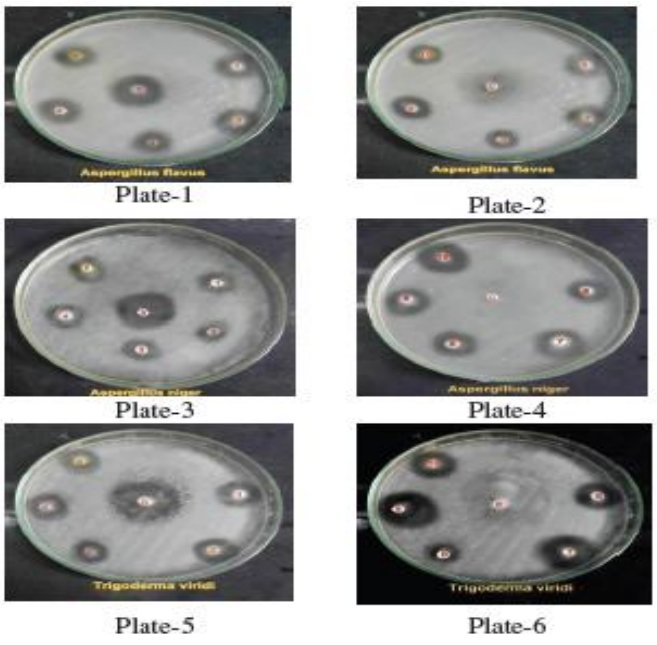


Fig. 5: Antifungal activity of substituted (E)-2-benzylidene-1-methylhydrazine compounds

4. CONCLUSION

In this investigation, ten number of substituted (*E*)-2-benzylidene-1-methylhydrazines have been prepared by condensation method. The yields of the products have been obtained more than 90 %. Synthesized compounds have been identified by UV, IR and NMR spectral analysis. The assigned UV λ_{max}(nm), IR νC=N(cm^{-1}) and NMR δ(ppm) spectral data with respect to CH=N and C=N have been correlated with Hammett constants and Swain Lupton's parameters using spectral correlation (single and multi) analyses. The single regression analysis gives satisfactory correlations with all the Hammett substituent constants whereas the multi-linear regression analysis gives satisfactory correlations with all the Hammett substituent constants and Swain Lupton's (F and R) parameters. The antibacterial activities of the synthesized (*E*)-2-benzylidene-1-methylhydrazines have been studied using three gram-positive microbes namely *Bacillus subtilis*, *Staphylococcus aureus* and *Streptococcus* and

two gram-negative microbes *Escherichia coli* and *Pseudomonas aeruginosa*. The antifungal activities of the synthesized (*E*)-2-benzylidene-1-methylhydrazines have also been studied using three fungal species namely *A. flavus, A. niger and T. viride*. A good antibacterial activity has been possessed by some of the substituted (*E*)-2-benzylidene-1-methylhydrazines on the microorganisms. Some of the substituted (*E*)-2-benzylidene-1-methylhydrazines have shown moderate antifungal activities.

5. REFERENCES

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