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Full Paper

Eco-friendly Synthesis, Spectral Correlation Analysis, and Antimicrobial Activities of Substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines

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Abstract: In the present study, a series of ten substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have been synthesized by condensation of 3-nitrophenylhydrazine with various substituted benzaldehydes using SiO_2-H_3PO_4 catalyst under solvent free condition. This method involves shorter reaction time (5-10 minutes) with excellent yield (80-90%). The structures of the synthesized (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines have been characterized by their physical constants, UV, FT-IR and NMR spectral data. The characterized UV, FT-IR and NMR spectral data have been correlated with Hammett constants using single-linear and multi-linear regression analysis. From the results of single-linear and multi-linear regression analysis the effect of substituents on the spectral data have been discussed. The antimicrobial activities of all the (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have been tested using Bauer-Kirby method.

Keywords: antimicrobial activity; SiO_2-H_3PO_4; solvent-free synthesis; spectral correlation; substituent effect

1. INTRODUCTION

Now-a-days solvent-free approach to the synthesis of molecules becomes an interesting one. Since the majority of solvents are either toxic or inflammable, they cause serious consequences during synthesis. In many cases, the solvent-free approach involves improves selectivity, reduces reaction time, simplifies separation, and purification of products where compared to the conventional methods [1-5]. The development of greener methods is a major challenge in synthetic chemistry. Among the several advantages of green chemistry, the reduction or replacement of volatile organic solvents from the reaction medium is of utmost importance [6, 7]. Due to the increasing environmental and economical concern in the recent years, it is now essential for chemists to search for as many new environmentally benign methods as possible. The aims of green chemistry [8] are the prevention of wastes and the generation of substances with little or no toxicity to humans and the environment, in order to maximize atom economy. This can be achieved only if the final product is synthesized by avoiding the use of solvents whether they are harmful or not.

Green chemistry is used for designing chemical products and processes by reducing or eliminating the use of harmful chemicals and/or generating hazardous substances. Various green chemistry methods involving stirring, phase transfer catalyst, ionic liquid and many more techniques like microwave techniques include approaches for the creation of ‘‘benign-by-design’’ synthetic methods which are now accepted worldwide [9]. Processes designed by green routes help in the promotion of resource and efficient utilization of energy. They involve low level of waste and hence the processes are becoming economically and environmentally beneficial.

Hydrazone-containing azomethine –NH─N=CH─ protons constitute an important class of compounds for development of new drugs. Many researchers had synthesized such type of compounds [10] as target molecules and evaluated their biological activities. Hydrazones was reported to possess

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antimicrobial [11], antitubercular [12, 13], anticonvulsant [14], analgesic [15], anti-inflammatory [16], antiplatelet [17], anticancer [18, 19], antifungal [20], antiviral [21], antitumoral [22, 23], antibacterial [24] and antimalarial [25] activities. In recent years, environmentally benign synthetic methods have expected considerable attention and some solvent-free protocols have been developed [26, 27]. Schmeyers *et al.* reported the solid-state synthesis of various kinds of benzylidene aniline derivatives by grinding together solid anilines and solid benzaldehydes [28]. Varma *et al.* reported the clay-catalyzed synthesis of imines and enamines under solvent-free conditions using microwave irradiation [29]. There has been a large emphasis, both in the chemical industry and in academic research, on the development of environmentally benign solvents and reaction conditions. This is largely owed to the fact that traditional solvents, such as volatile organic solvents, have been implicated in a number of environmental problems [30].

In the present work, we report the synthesis of (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine derivatives using grinding method. The reactions have been carried out by grinding together equivalent amounts of the appropriate substituted aldehyde and 3-nitrophenylhydrazine in the presence of SiO_2-H_3PO_4 in a porcelain mortar, under solvent-free conditions. Grinding for about 5-10 minutes led to a colored solid mass of the crude product. The completion of the reaction was checked by TLC. Purification was carried out by simple Buchner filtration, washing with cold water, and crystallization from ethanol solvent to give the respective (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine derivatives. This method is simple and effective in terms of its short reaction time, excellent yields, and the formation of a single product. The various spectral data of these (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines have been utilized for studying the substituent effects through Hammett correlations. The antimicrobial activity of all the (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds tested for Bauer-Kirby method.

2. MATERIAL AND METHODS

Physical Measurement

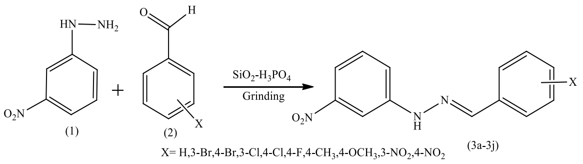
All the chemicals used in the present investigation were purchased from Sigma–Aldrich and E-Merck chemical companies. Melting points were determined with open glass capillaries on SUNTEX melting point apparatus and are uncorrected. The UV absorption spectrum of all the synthesized (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines were recorded in SHIMADZU-1650 spectrophotometer (λ_{max}, nm) in spectral grade ethanol. Fourier-transform infrared spectra (KBr, 4000–400 cm^{-1}) were recorded as KBr pellets on SHIMADZU-2010 Fourier transform spectrometer. Bruker AV400 NMR spectrometer operating at 400 MHz has been used for recording ^1H spectra and that operating at 100 MHz for recording ^{13}C spectra in $CDCl_3$ solvent using TMS as internal standard.

Preparation of SiO_2–H_3PO_4 catalyst

In a 50 mL Borosil beaker, 3 g of silica and 3 mL of orthophosphoric acid have been taken and mixed thoroughly with glass rod at room temperature. This mixture has been heated on a hot air oven at 100℃ for 1 h, cooled to room temperature, stored in a borosil bottle and tightly capped [31].

General procedure for synthesis of substituted (E)-1-benzylidene-2-(3-nitrophenyl)hydrazines

A mixture of appropriate 3-nitrophenylhydrazine (2 mmole), substituted benzaldehyde (2 mmole) and SiO_2–H_3PO_4 (0.5 g) was thoroughly ground with a pestle in an open mortar at room temperature for 5-10 minutes. The initial syrupy reaction mixtures get solidified within 3-5 minutes. The completion of the reaction was monitored by use of TLC. After the completion of the reaction 10 mL of dichloromethane was added and the organic layer separated by filtration, yielding solid product on evaporation. The solid, on recrystallization with ethanol, afforded glittering orange solid. The insoluble catalyst has been recycled by washing with ethyl acetate (10 mL) followed by drying in an air oven at 100°C for 1h and reused for further reactions. The general reaction of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines is as shown in Scheme 1.



Scheme 1. Synthesis of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines.

3. RESULTS AND DISCUSSION

In the present research work, we adopt a mild, efficient, high yielding process for the synthesis of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines from different aromatic aldehydes with 3-nitrophenylhydrazine in SiO_2-H_3PO_4 catalyst under solvent-free condition. This method involves shorter reaction time with excellent yield (87-95%). This catalyst was reused for further reaction runs in the synthesis of the parent hydrazine with equal molar quantities of 3-nitrophenylhydrazine (2 mmole) benzaldehyde (2 mmole) and SiO_2–H_3PO_4 (0.5 g) catalyst (entry **3a**). In this reaction, the first run gave 90 % product. The second, third and fourth runs gave 89.5 % product. The fifth run gave 89% product. There is no appreciable change of percentage of product observed in these reaction runs. It is noteworthy to mention that the green route method requires simple work-up procedure involving simple filtration to isolate the products as they are insoluble in water. The physical constants of synthesized (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines shown in Table-1**.**

Table 1. Physical constants of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines**.**

Entry	X	m.p (°C)	Mol. formula	Mol. weight	Yield (%)
3a	H	198-199 198 [32]	$C_{13}H_{11}N_3O_2$	241	90
3b	3-Br	124-125	$C_{13}H_{10}N_3O_2Br$	320	88
3c	4-Br	144-145	$C_{13}H_{10}N_3O_2Br$	320	92
3d	3-Cl	120-121	$C_{13}H_{10}N_3O_2Cl$	275	95
3e	4-Cl	124-125	$C_{13}H_{10}N_3O_2Cl$	275	91
3f	4-F	122-123	$C_{13}H_{10}N_3O_2F$	259	94
3g	4-CH_3	123-124	$C_{14}H_{13}N_3O_2$	255	89
3h	4-OCH_3	126-127	$C_{14}H_{14}N_3O_3$	271	87
3i	3-NO_2	168-169	$C_{13}H_{10}N_4O_4$	286	93
3j	4-NO_2	172-173	$C_{13}H_{11}N_4O_2$	286	92

Uv–Vis spectral study

The recorded ultraviolet absorption maximum λ_{max} C=N (nm) values of all the substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds are presented in Table-2. This data has been correlated with different Hammett substituent constants and Swain-Lupton's *F* and *R* parameters using spectral correlation analyses according to the approach of John Shorter [33]. The results of single regression analyses [33] are presented in Table-3.

Table 2. The UV, FT-IR, ^1H and ^{13}C spectral data of substituted (*E*)-1-benzylidene-2-(3nitrophenyl)hydrazines.

Entry	X	UV λ_{max} (nm)	IR ν(C=N) (cm^{-1})	NMR δ^1H (CH=N) (ppm)	NMR $\delta^{13}C$(C=N) (ppm)
3a	H	348.0	1618.28	7.950	148.84
3b	3-Br	355.0	1618.28	7.822	147.80
3c	4-Br	353.5	1614.42	7.945	145.39
3d	3-Cl	352.5	1620.21	7.934	147.75
3e	4-Cl	353.5	1610.56	7.945	149.43
3f	4-F	348.0	1616.35	7.949	147.69
3g	4-CH_3	346.5	1612.49	7.939	149.40
3h	4-OCH_3	351.5	1604.77	7.930	147.85
3i	3-NO_2	349.5	1618.28	7.939	155.82
3j	4-NO_2	403.5	1570.06	7.997	156.63

Table 3. Results of correlation analyses of UV λ_{max} (nm), νC=N (cm^{-1}) IR, NMR δ^1H (ppm) CH=N and $\delta^{13}C$ (ppm) C= N of (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines with Hammett substituent constants and Swain-Lupton's *F* and *R* parameters.

Frequency	Constant	r	I	ρ	s	n	Correlated derivatives
λ_{max} (nm)	σ	0.868	333.03	28.03	13.93	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	σ+	0.851	336.71	17.15	15.05	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	σ_I	0.798	328.42	28 .43	15.79	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	σ_R	0.845	344.92	38.83	15.18	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	F	0.832	330.28	22.82	16.31	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	R	0.871	345.54	31.30	15.36	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
ν C=N	σ	0.904	1614.71	16.90	14.36	9	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2
	σ+	0.905	1534.71	3 .70	10.74	9	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2
	σ_I	0.842	1535.16	0.43	10.90	10	H, 3-Br , 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	σ_R	0.811	1534.53	-5.85	10.83	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	F	0.791	1535.36	0.06	10.90	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	R	0.808	1534.67	-3.49	10.87	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
δ CH=N	σ	0.809	7.93	0.01	0.04	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	σ+	0.806	7.93	0.06	0.04	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	σ_I	0.804	7.93	0.08	0.04	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	σ_R	0.822	7.94	0.08	0.04	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	F	0.809	7.92	0.01	0.04	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	R	0.821	7.94	0.04	0.04	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
δ C=N	σ	0.906	148.31	6.45	2.94	8	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3
	σ+	0.904	149.26	3.31	3.40	8	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3
	σ_I	0.837	147.63	5.57	3.52	10	H, 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	σ_R	0.906	151.43	11.73	2.79	8	H,3-Br,4-Br,3-Cl,4-Cl,4-CH_3,3-NO_2, 4-NO_2
	F	0.834	147.84	4.85	3.57	10	H, 3-Br , 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3, 4-OCH_3, 3-NO_2, 4-NO_2
	R	0.906	151.58	9.28	2.92	8	H, 3-Br , 4-Br, 3-Cl, 4-Cl, 4-CH_3, 3-NO_2, 4-NO_2

r = correlation coefficient; ρ = slope; I = intercept; s = standard deviation; n = number of substituents

While seeking Hammett equation employed, for the correlation analyses, involving the UV absorption maximum is as shown in equation (1).

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

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

The UV spectral correlation analysis of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds reveals that all the substituents have shown poor correlations (r < 0.900) [34-39] with Hammett substituent constants namely σ, σ^+, σ_I, σ_R and Swain-Lupton's *F* and *R* parameters [40]. This is attributed to the weak polar, inductive, resonance and field effect of the substituents to predict their reactivity through resonance as per the conjugative structure shown in Figure 1**.**

All the correlations regarding UV spectral data shows positive ρ values. This positive ρ value indicates the operation of normal substituent effects. In view of the inability of the Hammett constants to produce individually satisfactory correlations with the UV absorption maximum values, the authors think that, it is worthwhile to seek multi-correlation analysis of Hammett σ_I and σ_R constants and Swain-Lupton's [40] *F* and *R* parameters. The multi-correlation analyses have shown much better correlations for all the substituents and are shown in the following equations (2) and (3).

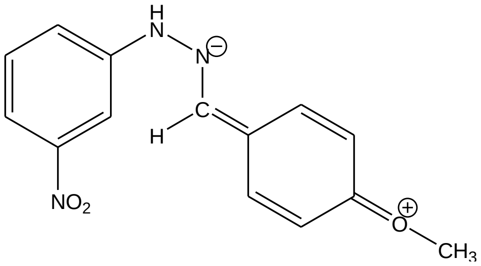


Figure 1. The resonance-conjugative structure.

$$\lambda_{max}(\text{nm}) = 344.75(\pm10.19) + 24.56(\pm8.43)\sigma_I + 35.10(\pm11.98)\sigma_R \qquad \ldots(2)$$
$$(R = 0.912,\ n=10,\ P>90\%)$$
$$\lambda_{max}(\text{nm}) = 335.91(\pm9.98) + 24.05(\pm8.78)\,F + 32.25(\pm10.18)\,R \qquad \ldots \qquad (3)$$
$$(R = 0.952,\ n=10,\ P>95\%)$$

IR Spectral study

The assigned infrared νC=N (cm^{-1}) stretching frequency values of all the substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds are presented in Table-2**.** These IR frequency νC=N (cm^{-1}) values are correlated with different Hammett substituent constants and *F* and *R* parameters using single-linear and multi-linear regression analyses [34-39]. The results of the statistical analysis [40] are presented in Table-3. In this correlation the structure parameter Hammett equation employed is as shown in given equation (4).

$$\nu = \rho\sigma + \nu_o \qquad (4)$$

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

The results of the spectral correlation analyses are presented in Table-3**.** From this Table, it is evident that the infrared νC=N (cm^{-1}) stretching frequency values of all the (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds, except those with 4-NO_2 substituent, has shown good linear correlations with Hammett substituent constant σ (r = 0.904) and σ^+ (r = 0.905) parameters. The substituents that have been given exception were reducing the correlations considerably when they are included in regression. However the IR stretching frequency νC=N (cm^{-1}) values of all the (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds, have shown unsatisfactory correlations (r < 0.900) with the remaining Hammett substituent constants viz., σ_I, σ_R and *F* and *R* parameters. The unsatisfactory correlation is due to the weak polar, resonance, inductive and field effects of the substituents to predict their reactivity through the conjugative structure shown in Figure 1. All the correlations have shown positive ρ value except resonance parameters. It indicates the operation of normal substituent effect with respect to infrared stretching frequency νC=N (cm^{-1}) values in all the (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds.

Since most of the single regression analyses have shown poor correlations with Hammett constants and *F* and *R* parameters, it is decided to go for multi regression analyses. The multi-linear regression analyses of the νC=N (nm) stretching frequency values of all the (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds with inductive, resonance and Swain-Lupton's [40] *F* and *R* parameters produce satisfactory correlations as shown in equations (5) and (6).

$$\nu C{=}N\ (cm^{-1}) = 1534.07(\pm 7.98) + 1.09(\pm 0.30)\ \sigma_I - 6.02(\pm 2.79)\ \sigma_R \qquad (5)$$

$$(R = 0.912,\ n = 10,\ P > 90\%)$$

$$\nu C{=}N(cm^{-1}) = 1534.75(\pm 7.77) - 0.197(\pm 0.06)\ F - 3.50(\pm 1.71)\ R \qquad (6)$$

$$(R = 0.908,\ n = 10,\ P > 90\%)$$

NMR Spectral study

^{1}H NMR spectral study

The ^{1}H NMR spectra of all the synthesized (*E*)-1-benzylidene -2-(3-nitrophenyl)hydrazine compounds in the present investigation are recorded in $CDCl_3$ using TMS as internal standard. The signals of the imine protons have been assigned and their chemical shift values are presented in Table-2**.** The chemical shift δCH=N (ppm) values of all the (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have been correlated with Hammett substituents constants and *F* and *R* parameters using single-linear and multi-linear regression analysis [34-39]. In this correlation the structure parameter Hammett equation employed is as shown in equation (7).

$$\delta = \rho\sigma + \delta_0 \qquad (7)$$

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

The results of the statistical analysis are presented in Table-3. From this Table, it is evident that the ^{1}H NMR chemical shift δCH=N (ppm) values of all the substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds reveal that all the substituents have shown poor (r < 0.900) correlations [33-38] with Hammett substituent constants namely σ, σ^+, σ_I, σ_R and Swain-Lupton's *F* and *R* parameters [39]. The poor correlation is attributed to the conjugative structure shown in Figure 1. All the correlations have shown positive ρ values. This positive ρ value indicates the operation of normal substituent effect.

In this cause, all the single regression analyses have shown unsatisfactory correlations with all Hammett constants and *F* and *R* parameters, while seeking the multi-linear regression analyses. The multi-linear regression analysis produced satisfactory correlations with σ_I, σ_R and *F* and *R* [40] parameters. The correlated multi-linear regression equations are given in equations (8) and (9).

$$CH{=}N\ (\delta_{ppm}) = 7.94(\pm 0.03) + 0.03(\pm 0.01)\ \sigma_I + 0.04(\pm 0.01)\ \sigma_R \qquad (8)$$

$$(R = 0.995,\ n = 10,\ P > 95\%)$$

$$CH{=}N\ (\delta_{ppm}) = 7.93(\pm 0.03) + 0.01(\pm 0.005)\ F + 0.04(\pm 0.01)\ R \qquad (9)$$

$$(R = 0.995,\ n = 10,\ P > 95\%)$$

^{13}C NMR spectral study

In the present investigation, the δC=N carbon chemical shifts (ppm) of all the (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines was assigned and are presented in Table-2. The δC=N carbon chemical shifts (ppm) have been correlated with Hammett substituent constants and the results of statistical analysis [34-39] are presented in Table-3**.** From Table-3, it is evident that all the substituents except those with 3-NO_2 and 4-NO_2 substituents have shown satisfactory correlation with Hammett substituent constants σ (r = 0.906), σ^+ (r = 0.904), σ_R(r = 0.906) and *R* (r = 0.906) parameters. The remaining Hammett substituent constant σ_I and *F* parameter have shown unsatisfactory correlations (r < 0.900). This is attributed to weak polar, inductive and field effects of the substituents for predicting the reactivity on the δC=N carbon chemical shifts (ppm) through resonance as per the conjugative structure as shown in Figure 1. The substituents that have been given exception were reducing the correlations considerably when they are included in regression. All the correlations have shown positive ρ values with all the Hammett substituent constants and *F* and *R* parameters. It indicates that the normal substituent effect operates with respect to chemical shift δC=N(ppm) values in all the (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds.

However the multi-linear regression analysis of chemical shift δC=N (ppm) values of all the (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds with inductive, resonance and Swain-Lupton's [40] parameters produce better correlations as shown in equations (10) and (11).

$$\delta C{=}N(ppm) = 149.62(\pm1.89) + 4.35(\pm1.79)\sigma_I + 11.07(\pm3.45)\,\sigma_R \qquad (10)$$

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

$$\delta C{=}N(ppm) = 149.50(\pm1.84) + 5.21(\pm2.65)F + 9.48(\pm3.72)R \qquad (11)$$

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

Antimicrobial activities

Antibacterial activity

The antibacterial sensitivity assay has been performed by using Kirby-Bauer [41] disc diffusion technique. The antibacterial activities of all the synthesized (*E*)-1-benzylidene -2-(3-nitrophenyl)hydrazines are shown in Figure 2. The antibacterial activities of all the synthesized (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines have been studied against three gram positive pathogenic strains *Bacillus substilis*, *Micrococcus luteus* and *Staphylococcus aureus* and two gram negative strains *Escherichia coli* and *Pseudomonas aeruginosa*. The zone of inhibition is compared using Table-4 and the corresponding clustered column chart is shown in Figure 3. From Table-4, most of the synthesized compounds in the present investigation have shown moderate to good activity against all the five bacterial species in general.

The (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds with 4-F, 4-CH_3 and 4-NO_2 substituents have shown very good activity against *Micrococcus luteus*. The 3-NO_2 and 4-NO_2 substituted (*E*)-1-benzylidene -2-(3-nitrophenyl)hydrazine compounds have shown very good activity against *Staphylococcus aureus*. The 4-NO_2 substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compound has shown very good activity against *Escherichia coli*. The (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds with 4-CH_3, 3-NO_2 and 4-NO_2 substituents have shown very good activity against *Pseudomonas aeruginosa* species. The 4-F, 4-CH_3, 4-OCH_3, 3-NO_2 and 4-NO_2 substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have shown good activity against *Bacillus substilis*.

The 3-Cl, 4-Cl, 4-OCH_3 and 3-NO_2 substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have shown good activity against *Micrococcus luteus*. The (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds with parent (H), 3-Br, 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3 and 4-OCH_3 substituents have shown good activity against *Staphylococcus aureus*. The (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds with 4-F, 4-CH_3, 4-OCH_3 and 3-NO_2 substituents has shown good activity against *Escherichia coli*. The parent (H), 3-Cl, 4-Cl, 4-F and 4-OCH_3 substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have shown good activity against *Pseudomonas aeruginosa* species. The remaining substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have shown moderate to poor activity.

Antifungal activity

The antifungal activities of all the synthesized substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have been studied against three fungal species namely, *Aspergillus niger*, *Mucor species* and *Trigoderma viride*. The antifungal activities of all the substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have been studied and are shown in Figure 4 for Plates (1–6) and the corresponding clustered column chart is shown in Figure 5. The antifungal sensitivity assay has been performed using Kirby-Bauer [41] disc diffusion technique. The antifungal activities of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have been studied and the zone of inhibition values of the effect is given in Table-5. From Table-5 reveals that all the compounds have moderate to good antifungal activity against all the three fungal species namely *Aspergillus niger*, *Mucor species* and *Trigoderma viride*.

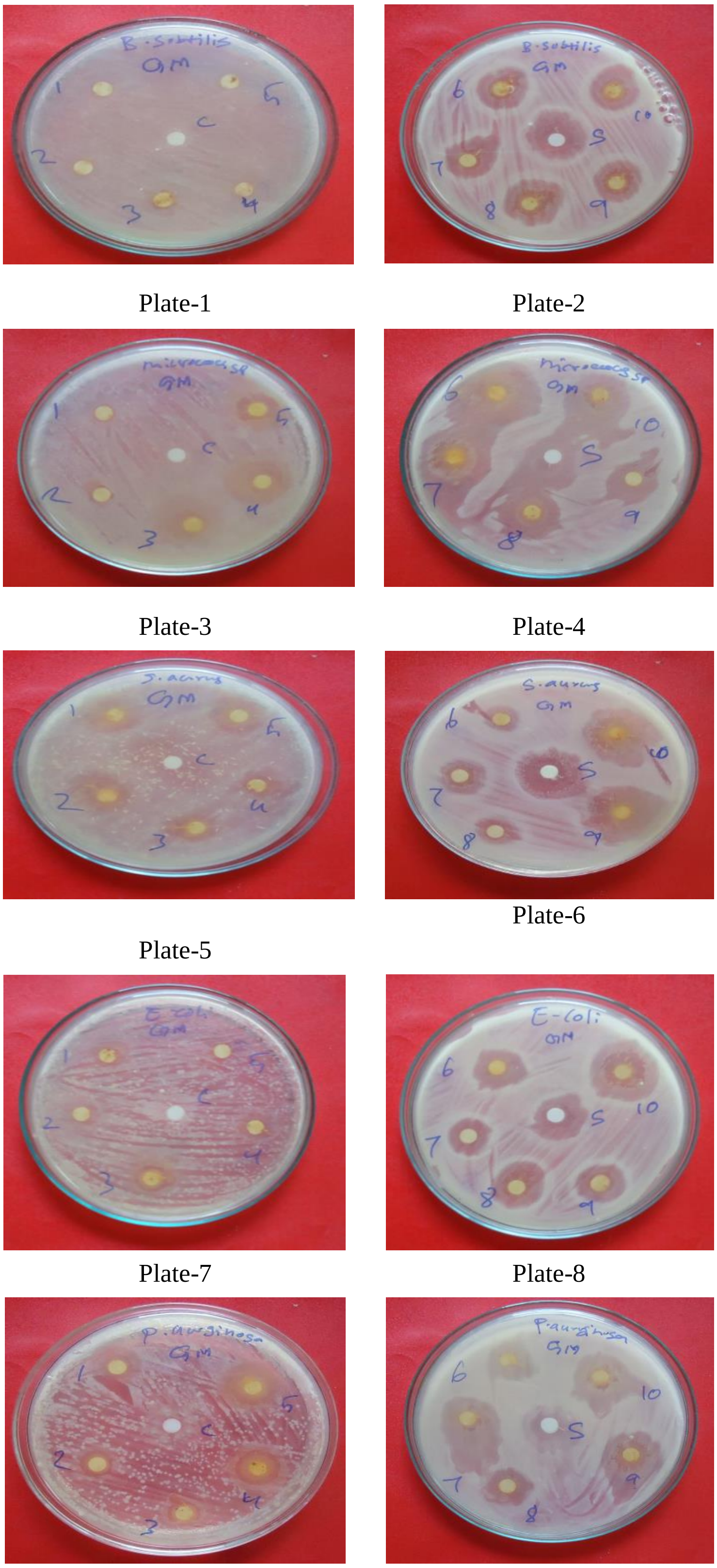


Plate-1 Plate-2

Plate-3 Plate-4

Plate-5 Plate-6

Plate-7 Plate-8

Plate-9 Plate-10

Figure 2. Antibacterial activities of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines (petri-plates).

Table-4. Antibacterial activity of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines.

Entry	**X**	**Zone of Inhibition (mm)**				
		Gram-positive bacteria		**Gram-negative bacteria**		
		Bacillus substilis	***Micrococcus luteus***	***Staphylococcus aureus***	***Escherichia coli***	***Pseudomonas aeruginosa***
3a	H	0	6	15	6	13
3b	3-Br	0	6	14	6	9
3c	4-Br	6	7	13	6	7
3d	3-Cl	0	15	12	0	15
3e	4-Cl	0	13	15	0	16
3f	4-F	16	23	14	17	18
3g	4-CH_3	17	20	16	15	20
3h	4-OCH_3	18	18	14	18	17
3i	3-NO_2	15	16	23	16	20
3j	4-NO_2	16	19	22	22	19
Standard	Ciprofloxacin	19	18	20	18	18
Control	DMSO	0	0	0	0	0

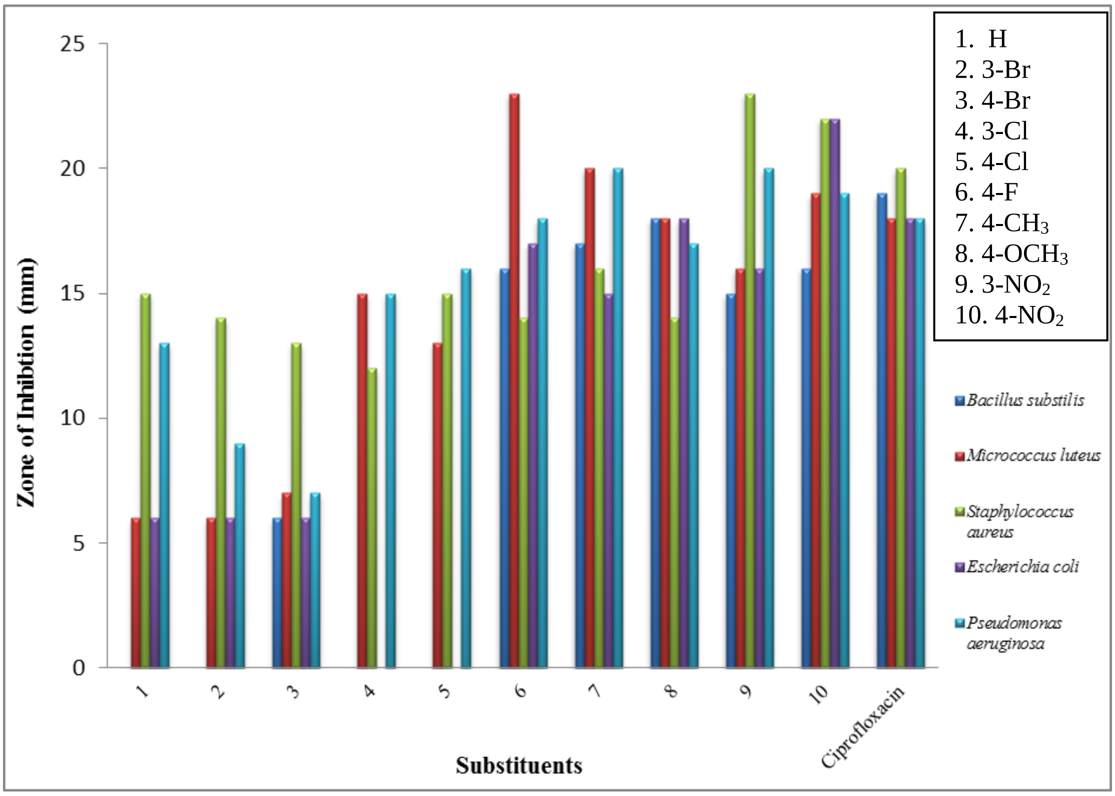


Figure 3. Antibacterial activity of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines (clustered column chart).

The 4-F substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compound has shown very good antifungal activity against *Aspergillus niger*. The 3-Br substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compound has shown very good antifungal activity against *Mucor species*. The (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines with parent (H), 3-Br, 4-Br, 3-Cl, 4-Cl, 4-CH_3, 3-NO_2 and 4-NO_2 substituents have shown good antifungal activity against *Aspergillus niger*. The parent (H), 4-Br, 3-Cl, 4-Cl, 4-F, 4-CH_3 and 3-NO_2 substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have shown good antifungal activity against *Mucor species*. The (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines with 3-Br, 4-Br, 3-Cl, 4-Cl, 4-OCH_3, 3-NO_2 and 4-NO_2 substituents have shown good antifungal activity against *Trigoderma viride*. The remaining (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines have shown moderate activity.

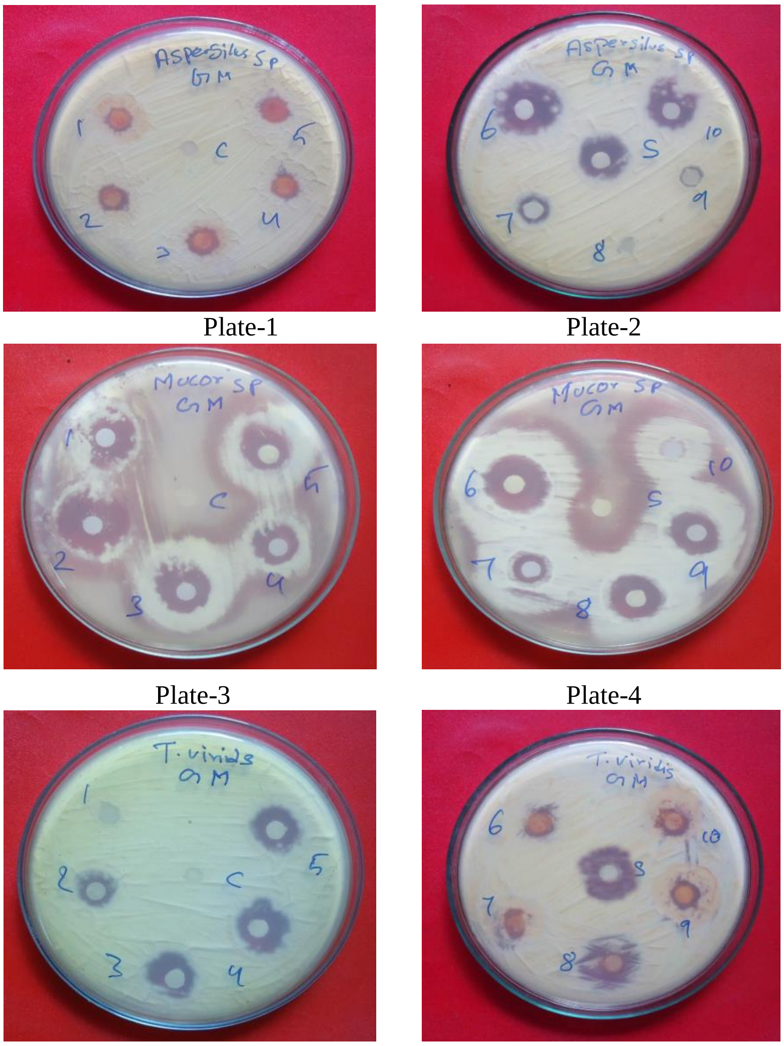


Plate-1 Plate-2

Plate-3 Plate-4

Plate-5 Plate-6

Figure 4. Antifungal activities of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines (petri-plates).

Table 5. Antifungal activity of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines.

		Zone of Inhibtion(mm)		
Entry	**X**	***Aspergillus niger***	***Mucor species***	***Trigoderma viride***
3a	H	12	15	0
3b	3-Br	11	21	14
3c	4-Br	12	17	15
3d	3-Cl	11	14	16
3e	4-Cl	11	15	15
3f	4-F	19	17	7
3g	4-CH_3	12	12	0
3h	4-OCH_3	0	14	14
3i	3-NO_2	10	15	12
3j	4-NO_2	16	7	10
Standard	Micnazole	17	20	19
Control	DMSO	0	0	0

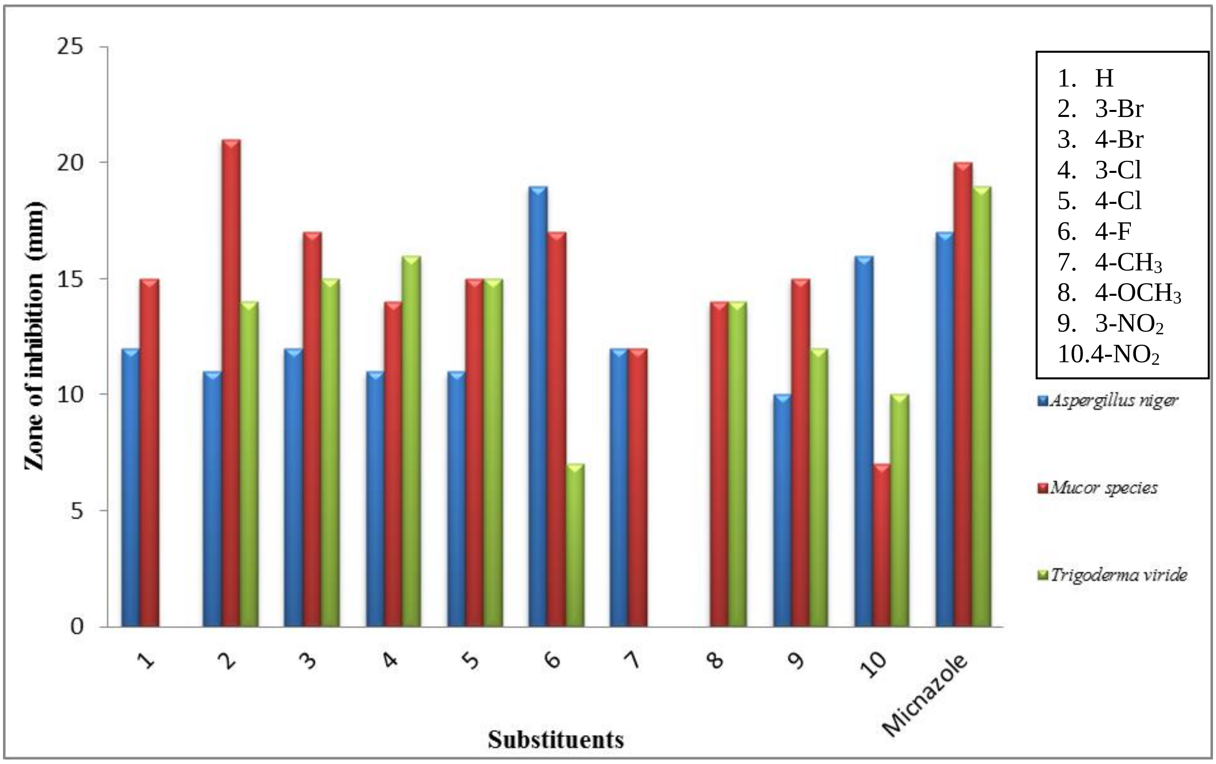


Figure 5. Antifungal activity of substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazines (clustered column chart).

4. CONCLUSION

A series of ten substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have been synthesized from various substituted benzaldehydes and 3-nitrophenylhydrazine with SiO_2-H_3PO_4 catalyst under solvent free condition. This method involves shorter reaction time (5-10 minutes) with excellent yield (80-90%). The advantages of this method include mild reaction condition, good yield, shorter reaction times, environmentally benign and of eco-friendly nature.

The synthesized substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds are characterized by their physical constants, UV, FT-IR, and NMR spectral data. The UV, FT-IR and NMR spectral data of the substituted (*E*)-1-benzylidene-2-(3-nitrophenyl)hydrazine compounds have been correlated with Hammett constants σ, σ^+, σ_I, σ_R and swain-Lupton's *F* and *R* parameters using single and multi-regression analyses. From the results of correlation analysis Hammett substituent constants σ and σ^+ produce satisfactory with FT-IR spectral data. The UV and ^{1}H NMR spectral data have shown poor correlations. The ^{13}C NMR spectral data produce satisfactory correlations with σ, σ^+, σ_R and Swain-Lupton's *R* parameters. Multi-regression analyses produce satisfactory correlations for all the Hammett substituent constants and *F* and *R* parameters. The antimicrobial activities of all the compounds have shown good to moderate activities against all the microorganisms.

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