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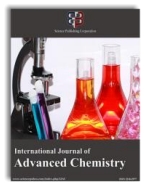

Synthesis and antimicrobial activities of some (*E*)-N′-1-(substituted benzylidene)benzohydrazides

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Abstract

About ten substituted (*E*)-N′-1-(substituted benzylidene) benzohydrazides have been synthesized. They are analyzed by their analytical, ultra violet (UV), Fourier transform-IR (FT-IR) and nuclear magnetic resonance (NMR) spectral data and evaluated by antimicrobial activities such antibacterial and antifungal activities.

Keywords: *(E)-N '-1-(substituted benzylidene) benzohydrazides; UV; IR and NMR spectra; Antimicrobial activities; Gram-positive and negative bacteria.*

1. Introduction

Some benzohydrazides derivatives were known to have a wide variety of pharmacological actions such as antimicrobial (Kirilimi et al. 2008), antiarrhythmic (Bourgery et al. 1981) and antitumor (Galal et al. 2009). Many of the benzohydrazides are both natural and synthetic were known to exhibit various biological activities including antimalarial (Li et al. 1995), anti-inflammatory (Ballesteros et al. 2010), antioxidant (Anto et al. 1995; Mukerjee et al. 2001), antileishmanial (Nielsen et al. 1998), antifungal (Nielsen et al. 1998) and antibacterial (Osorio et al. 2012) activities.

In human body free radicals containing elements may act as significant role in the basis of the life and antimicrobial evaluation involved by their valuable effects in so many types of organisms (Demir et al. 2009). Direct attack against cellular constituents are found to be responsible for many diseases including central nervous systems, AIDS and cancer (Ebrahimzedh et al. 2008, El-Sabbagh & Rady 2009) because of free radicals containing more unpaired electrons that make then extremely unstable.

The compound of organic hydrazones are considered by the presence of a –COCHNH=CH– group in the molecule. These compounds are have very high extensive biological activities because their adaptable coordination chemistry characteristics of hydrazone molecules (Raparti et al. 2009, Mangalam et al. 2010, Naskar et al. 2010, Wang et al. 2011).

Hydrazones are also reported to show various biological activities like antimicrobial (Cukurovali et al. 2006), anti-mycobacterial (Mamolo et al. 2003; Govindasami et al. 2011), anti-convulsant (Dimmock et al. 2000), anti-analgesic (Lima et al. 2000), anti-inflammatory (Salgin et al. 2007), anti-platelet (Silva et al. 2004), anti-tumoral activities (Savini et al. 2004), antiviral (Gaikwad et al. 2012), antimalarial (Hassan et al. 2012), anticancer (Rollas et al. 2002, Capilla et al. 2003), anti-tubercular (Abdel-Aal et al. 2006, Janin 2007), anticonvulsant (Bijew 2006), antiplatelet (Salgin et al. 2007), antiviral (Kesel 2011), antioxidant (Osman et al. 2012, Jaishree et al. 2008, Devasagayam et al. 2008), anticancer (Mor et al. 2011), neuro-protective (Rostom et al. 2009), herbicidal (Samadhiya & Halve 2001) and antiproliferative (Nawrocka et al. 2006) activities. In addition, literature survey of hydrazones to possess anti-cancer (Terzioglu and Gursoy 2003, Zhang et al. 2004, Boga et al. 2009, El-Sabbagh & Rady 2009) and anti-HIV properties (Rahman et al. 2005, Xia et al. 2008, Nerkar et al. 2009, Vicini et al. 2009, Wardakhan et al. 2013, Kaushik et al. 2010, Menendez et al. 2012). The heterocyclic compounds containing hydrazone functionality playing a significant role in deciding the extent of their pharmacological properties (Dilworth 1976). The interesting studies of aryl hydrazones are occur in chemistry of coordination. The metal coordination complexes of aryl hydrazones are survey reported to act as enzyme inhibitors and are useful due to their pharmacological applications. Schiff base hydrazones act as a determination of certain transition metals (Gallego et al. 1979, Kim et al. 1996, Patil & Sawant 2001, Reddy & Chandrasekhar 2001) in spectroscopic method and selective metal extracting agent in analytical chemistry.

Recently, the observations of hetero aromatic hydrazone are authenticating the association of this microorganism with various communicable diseases in human such as food-poisoning associated periodontitis (Tuazon 1995).

The above view, some information only available in literature in the previous synthesis and antimicrobial evaluations of aromatic hydrazone compounds (Rajarajan et al. 2015). Therefore the authors have taken efforts for the synthesis of (*E*)-N′-1-(substituted benzylidene) benzohydrazides to study the conformation and antibacterial and antifungal activities.

2. Experimental

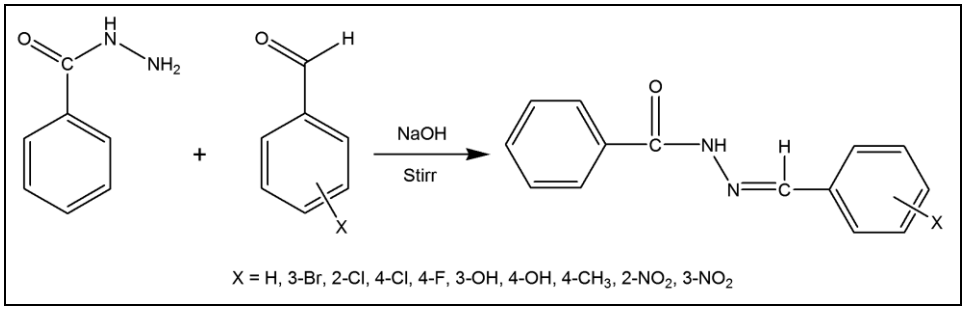
2.1. Materials and systematic methods

All the chemicals were used and purchased from Sigma-Aldrich chemical company Bangalore. All synthesized hydrazone compounds melting points are observed from uncorrected Suntex melting point instrument using open glass capillaries. The above hydrazones for UV spectra recorded using double beam-ELICO BL222 Bio-Spectrophotometer. FT-IR spectra (KBr, 4000–400 cm^{-1}) have been analyzed on AVATAR-300 FT-IR spectrophotometer. BRUKER-400 MHz NMR spectrometers has been operated for recording ^{1}H and ^{13}C NMR spectra in $CDCl_3$ solvent using internal standard as TMS.

2.2. General procedure for synthesis of (*E*)-N′-1-(substituted benzylidene) benzohydrazides

Appropriate mixture of benzohydrazide (100 mmol) and ortho, meta and para substituted benzaldehydes (100 mmol) and sodium hydroxide solution (200 mL, 0.5 M) with absolute ethyl alcohol (Scheme 1). The reactants are dynamically stirred at normal temperature maintain for 30 min (Kucukguzel et al. 2003). After complete renovation of the benzaldehydes as examined by TLC, the mixture was may allow to 20 min for undisturbed condition. By the method of filtration is used to removal of unreacted reagents. The filtrate was cleaned by distilled water. The product is recrystallized using absolute ethanol. The dried products are kept in a desiccator.

The synthesized (*E*)-N′-(1-(substituted benzylidene) benzohydrazides have been described by their physical constants, elemental analysis and spectral data. The physical constants, analytical and micro analysis data of these (*E*)-N′-(1-substituted benzylidene) benzohydrazides are shown in Table 1. The spectral data of synthesized substituted (*E*)-N′-(1-substituted benzylidene) benzohydrazides are shown in Table 2.



Scheme 1: Synthesis of substituted **(*E*)**-N′-(1-substituted benzylidene)benzohydrazides.

Table 1: Physical constants, yields, analytical and mass spectral data of substituted (*E*)-N′-(1-substituted benzylidene)benzohydrazides

Entry	X	MF	MW	Yield (%)	m.p. (ºC)	Mass (m/z)
1	H	$C_{14}H_{12}N_2O$	224	92	165–166	224 [M^+], 147, 134, 119, 105, 90, 77
2	3-Br	$C_{14}H_{11}BrN_2O$	303	90	138–139	303 [M^+], 305 [M^{2+}], 224, 223, 196, 181, 167, 154, 147, 105, 77
3	2-Cl	$C_{14}H_{11}ClN_2O$	258	89	141–142	258 [M^+], 260 [M^{2+}], 223, 181, 153, 147, 138, 134, 124, 120, 111, 77, 34
4	4-Cl	$C_{14}H_{11}ClN_2O$	258	91	147–148	258 [M^+], 260 [M^{2+}], 223, 181, 153, 147, 138, 134, 124, 120, 111, 77, 34
5	4-F	$C_{14}H_{11}FN_2O$	242	91	149–150	242 [M^+], 244 [M^{2+}], 223, 165, 147, 137, 134, 122, 120, 105, 95, 77, 18
6	3-OH	$C_{14}H_{12}N_2O_2$	240	93	163–164	240 [M^+], 223, 163, 147, 135, 134, 120, 106, 105, 77
7	4-OH	$C_{14}H_{12}N_2O_2$	240	94	161–162	240 [M^+], 223, 163, 147, 135, 134, 120, 106, 105, 77
8	4-CH_3	$C_{15}H_{14}N_2O$	238	89	120–121	238 [M^+], 223, 161, 147, 134, 133, 120, 104, 91, 77, 15
9	2-NO_2	$C_{14}H_{11}N_3O_3$	269	93	173–174	269 [M^+], 223, 192, 164, 149, 135, 134, 120, 105, 77, 45
10	3-NO_2	$C_{14}H_{11}N_3O_3$	269	90	165–166	269 [M^+], 223, 192, 164, 149, 135, 134, 120, 105, 77, 45

MF – Molecular formula, MW – Molecular weight, m.p. – Melting point.

Table 2: The UV, IR and NMR spectral data of substituted (*E*)-N′-(1-substituted benzylidene) benzohydrazides

Entry	X	UV (λ_{max}, nm)	IR (ν, cm^{-1})			NMR (δ, ppm)			
						^{1}H NMR		^{13}C NMR	
			C=O	C=N	N–H	N–H	C–H	C=O	C=N
1	H	323.0	1666.50	1539.20	3284.77	9.225	8.329	163.28	128.78
2	3-Br	332.0	1651.07	1539.20	3398.57	9.426	8.313	164.65	130.28
3	2-Cl	290.0	1647.21	1546.91	3188.33	9.304	8.318	166.74	132.09
4	4-Cl	323.0	1662.64	1543.05	3284.77	9.482	8.319	164.66	132.11
5	4-F	323.0	1649.14	1550.77	3201.83	9.146	8.317	162.98	132.46
6	3-OH	309.0	1645.28	1544.98	3197.98	9.331	8.518	162.86	129.87
7	4-OH	323.0	1647.21	1560.41	3197.98	9.234	7.755	164.32	131.98
8	4-CH_3	308.0	1647.21	1550.77	3197.88	9.285	8.291	165.40	143.53
9	2-NO_2	323.0	1647.21	1553.76	3182.55	9.698	8.722	163.06	432.69
10	3-NO_2	323.0	1641.42	1527.62	3383.14	9.322	8.207	164.56	133.46

3. Results and discussion

These multi-prolonged activities present in different benzohydrazides have been examined against respective microbes-bacteria's such as Staphylococcus aureus, Staphylococcus pyogenes, Micrococcus luteus, Bacillus subtilis, Klebsiella pneumoniae, Vibrio parahaemolyticus, Klebsiella oxytoca, Proteus mirabilis, Escherichia coli and Pseudomonas aeruginosa bacterial strains. And fungi such as Aspergillus niger, Mucor sp. and Trichoderma viride fungal strains.

3.1. Antibacterial sensitivity study

Antibacterial sensitivity study has been achieved using Bauer-Kirby (Bauer et al. 1966) disc diffusion method. Using sterile glass spreader the test bacterial sample (0.5 cm^3) is spread uniformly over the solidified Mueller-Hinton agar for each petri plate. The sterile forceps are used to impregnating the Whatman No. 1

filter paper with the solution of the compound in 5 mm diameter discs.

To prevent the collection of water droplets over the medium to keep the plates are incubated for 24 h at 37 °C temperature. The plates are visually examined after 24 h the zones of inhibition values of diameter are measured. The above procedure is followed to evaluate by triplicate results.

The antibacterial screening effect of synthesized (*E*)-N′-(1-substituted benzylidene)-benzohydrazide compounds are shown in Fig. 1. All the synthesized imines have been studied against four Gram-positive pathogenic strains S. aureus (Thirunarayanan et al. 2012), S. pyogenes (Aziz et al. 2010), M. luteus (Smith et al. 1999, Kluytmans et al. 1997), B. subtilis (Perez et al. 2000; Wei et al. 2003) and six Gram-negative strains K. pneumoniae (Lecointre et al. 1998), Vibrio parahaemolyticus (laboratory methods for the diagnosis of V. cholerae 2013), K. oxytoca (Brisse et al. 2006), P. mirabilis (Ohara et al. 2000), E. coli (Kluytmans 1997, Cornelis 2000), P. aeruginosa (Dominguesa et al. 2000, Baron 1996) for antibacterial activity. The disc diffusion method was followed 250 μg mL^{-1} concentration of Ciprofloxacin taken as the standard.

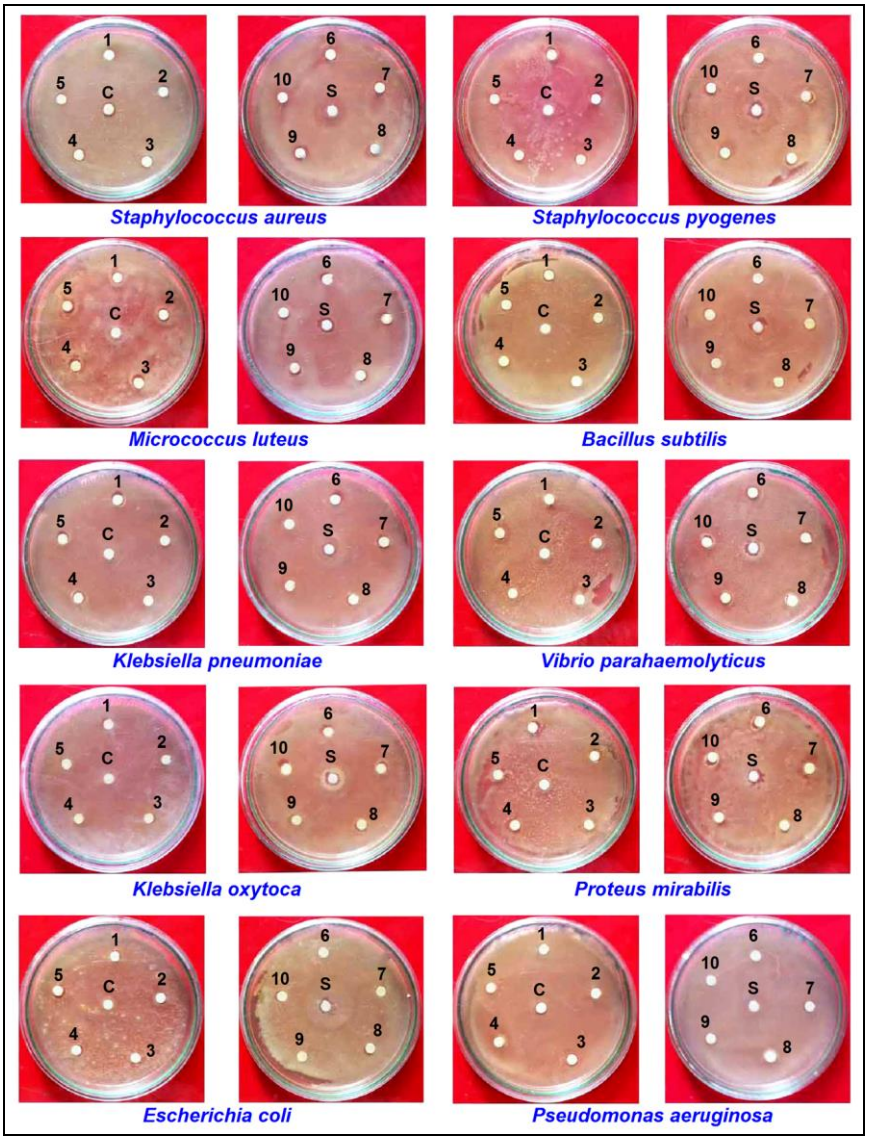


Fig. 1: Antibacterial activities of substituted (*E*)-N′-(1-substituted benzylidene) benzohydrazides. C – Control (DMSO), S – Standard (Ciprofloxacin).

The comparison of zone of inhibition values are shown in Table 3 and the corresponding clustered column chart is shown in Fig. 2. Analysis the values of zone of inhibition (mm) reveals that the (*E*)-N′-(1-substituted benzylidene)benzohydrazide compounds have shown satisfactory antibacterial sensitivity against S. aureus bacterial strain. The zone of inhibition (mm) values reveals that the benzohydrazide compounds have shown satisfactory antibacterial sensitivity against S. aureus bacterial strain except 4-fluoro substituent. The inhibition zone (mm) values reveals that the benzohydrazide compounds have shown satisfactory and moderate antibacterial activity against M. luteus bacterial strain. The zone of inhibition (mm) values reveals that the benzohydrazide compounds have shown satisfactory antibacterial sensitivity against M. luteus bacterial strain except 2-chloro and 3-hydroxy substituents.

Table 3: Antibacterial activities of substituted (*E*)-N′-(1–substituted benzylidene)benzohydrazides

Entry	X	Zone of inhibition (mm)									
		SA	SP	ML	BS	KP	VP	KO	PM	EC	PA
1	H	6	6	6	7	7	–	6	7	6	6
2	3-Br	6	6	7	6	–	6	–	7	–	–
3	2-Cl	6	6	7	–	–	7	6	7	8	6
4	4-Cl	7	6	7	6	6	–	–	7	6	–
5	4-F	6	–	8	6	6	8	–	6	7	6
6	3-OH	6	7	6	–	6	7	7	7	–	–
7	4-OH	6	6	7	6	7	6	6	6	–	6
8	4-CH_3	7	7	6	6	6	–	6	6	8	–
9	2-NO_2	8	7	7	6	–	7	7	6	–	6
10	3-NO_2	6	7	7	7	–	6	7	8	7	–
Standard	Ciprofloxacin	10	10	9	12	9	8	12	10	9	8
Control	DMSO	–	–	–	–	–	–	–	–	–	–

SA – Staphylococcus aureus, SP – Staphylococcus pyogenes, ML – Micrococcus luteus, BS – Bacillus subtilis, KP – Klebsiella pneumoniae, VP – Vibrio parahaemolyticus, KO – Klebsiella oxytoca, PM – Proteus mirabilis, EC – Escherichia coli, PA – Pseudomonas aeruginosa.

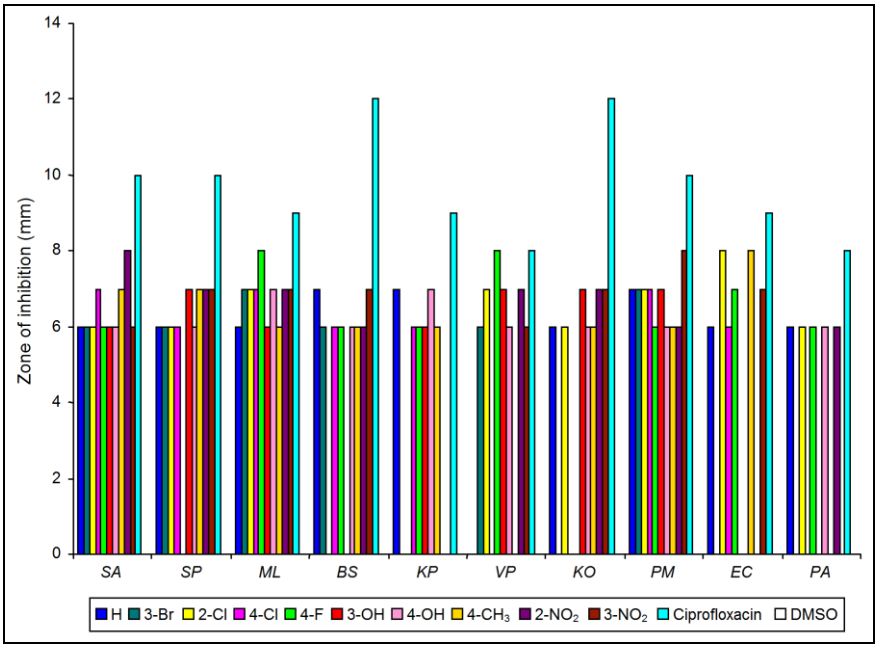


Fig. 2: Antibacterial activities clustered column chart of substituted (*E*)-N′-(1-substituted benzylidene)benzohydrazides. SA – Staphylococcus Aureus, SP – Staphylococcus Pyogenes, ML – Micrococcus Luteus, BS – Bacillus Subtilis, KP – Klebsiella Pneumoniae, VP – Vibrio Parahaemolyticus, KO – Klebsiella Oxytoca, PM – Proteus Mirabilis, EC – Escherichia Coli, PA – Pseudomonas Aeruginosa.

Analysis of the inhibition zone (mm) values reveals that the (*E*)-N′-(1-substituted benzylidene) benzohydrazide compounds have shown satisfactory antibacterial sensitivity against K. pneumoniae bacterial strain except 3-bromo, 2-chloro, 2-nitro and 3-nitro substituents. The inhibition zone (mm) values reveals that the benzohydrazide compounds have shown moderate and good antibacterial sensitivity against Vibrio parahaemolyticus bacterial strain except parent compound, 4-chloro and 4-methyl substituents. The inhibition zone (mm) values reveals that the benzohydrazide compounds have shown satisfactory antibacterial sensitivity against K. oxytoca bacterial strain except 3-bromo, 4-chloro and 4-fluor substituents. The inhibition zone (mm) values reveals that the benzohydrazide compounds have shown satisfactory and moderate antibacterial sensitivity against P. mirabilis bacterial strain. The inhibition zone (mm) values reveal that the benzohydrazide compounds have shown moderate and good antibacterial sensitivity against E. coli bacterial strain except 3-bromo, 3-hydroxy, 4-hydroxy and 2-nitro substituents. The inhibition zone (mm) values reveals that the benzohydrazide compounds have shown satisfactory antibacterial sensitivity against P. aeruginosa bacterial strain except 3-bromo, 4-chloro, 3-hydroxy, 4-methyl and 3-nitro substituents.

3.2. Antifungal sensitivity study

Antifungal activity assay has been achieved using Bauer-Kirby (Bauer et al. 1966) disc diffusion method. PDA medium is prepared and pasteurized as stated earlier. About 1 mL of the fungal species taken in a petri plate then PDA medium is poured (ear bearing heating condition).

The fungal sensitivity assay of the synthesized substituted (*E*)-N′-(1-substituted benzylidene) benzohydrazide compounds have been studied against three fungal species A. niger (Samson et al. 2001), Mucor sp. (Oswa et al. 1992) and T. viride (Ebbehog et al. 2002). The disc diffusion method was followed 250 μg mL^{-1} concentration of Miconazole taken as the standard.

The species are spreading homogenously over the plates using clockwise and anti-clockwise rotations. The test solution has been prepared by dissolving 15 mg of the substituted (*E*)-N′-(1-substituted benzylidene) benzohydrazide in 1 mL of DMSO solvent. The impregnation of discs were containing with the test solution. The medium have been permitted to solidify and kept for 24 h.

The inhibition zone values of the plates have been examined and measured the diameters. The report have been documented by the triplicate and repeating the same procedure. The antifungal activities of substituted (E)-N′-(1-substituted benzylidene)benzohydrazide compounds have been studied and are shown in Fig. 3 and the inhibition zone values of the effect is given in Table 4. The clustered column chart is shown in Fig. 4.

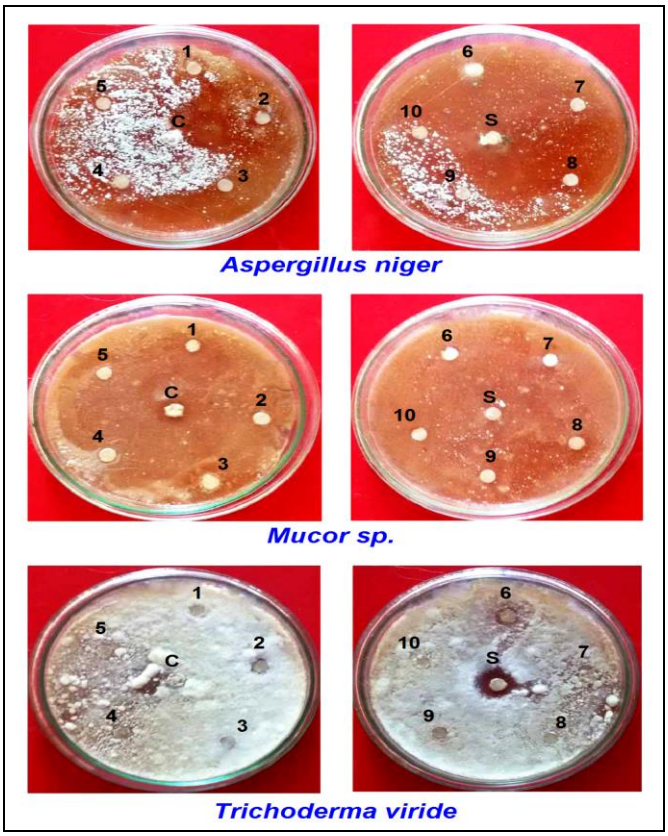


Fig. 3: Antifungal activities of substituted (*E*)-N′-(1-substituted benzylidene) benzohydrazides. C – Control (DMSO), S – Standard (Miconazole).

Table 4: Antifungal activities of substituted (*E*)-N′-(1-substituted benzylidene) benzohydrazides

Entry	X	Zone of inhibition (mm) Aspergillus niger	Mucor sp.	Trichoderma viride
1	H	6	6	–
2	3-Br	6	6	6
3	2-Cl	6	–	–
4	4-Cl	–	6	6
5	4-F	–	6	6
6	3-OH	6	6	7
7	4-OH	6	–	–
8	4-CH_3	6	6	–
9	2-NO_2	–	–	6
10	3-NO_2	6	6	–
Standard	Miconazole	7	8	10
Control	DMSO	–	–	–

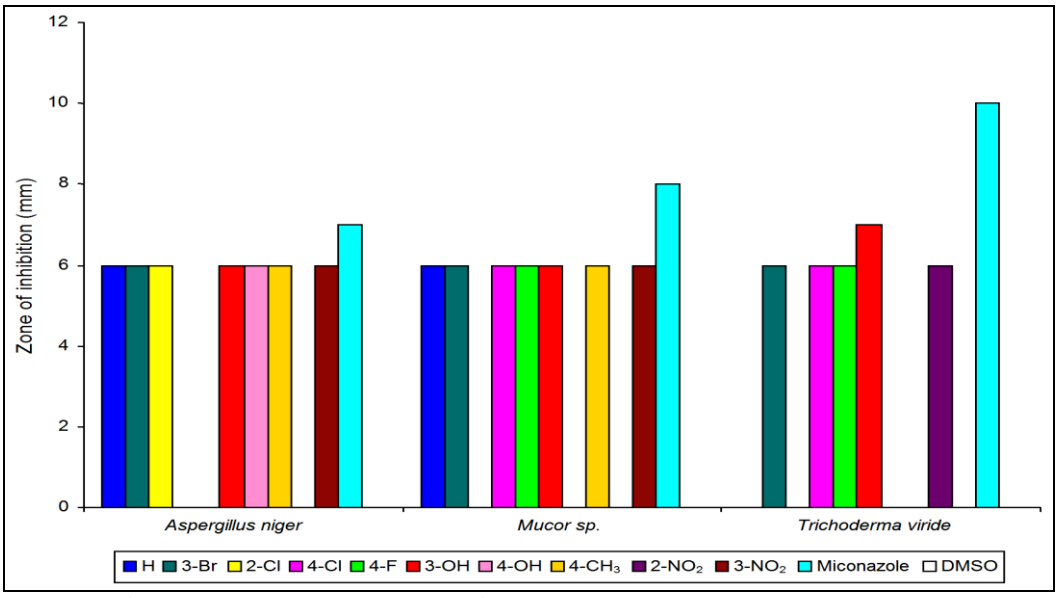


Fig. 4: Antifungal activities clustered column chart of substituted (*E*)-N′-(1-substituted benzylidene) benzohydrazides.

Analysis of the inhibition zone values (mm) values reveals that the (E)-N′-(1-substituted benzylidene)benzohydrazide compounds have shown good antifungal sensitivity against A. niger fungal species except 4-chloro, 4-fluoro and 2-nitro substituents. The zone of inhibition (mm) values reveals that the benzohydrazide compounds have shown satisfactory antifungal activity against Mucor sp. fungal species except 2-chloro, 4-hydroxy and 2-nitro substituents. The zone of inhibition (mm) values reveals that the benzohydrazide compounds have shown satisfactory antifungal activity against T. viride fungal species except parent compound, 2-chloro, 4-hydroxy, 4-methyl and 3-nitro substituents.

4. Conclusions

The series of ten numbers of substituted (E)-N′-(1-substituted benzylidene)benzohydrazide compounds had been synthesized by condensation of benzohydrazides and substituted benzaldehydes. These synthesized substituted (E)-N′-(1-substituted benzylidene)benzohydrazide compounds have been categorized by their physical constants, spectral data. The parent and 4-methyl substituted (E)-N′-(1-substituted benzylidene)benzohydrazide compounds have antibacterial activities against all bacterial strains except V. parahaemolyticus and P. aeruginosa bacterial strains. The 3-bromo and 3-hydroxy substituted (E)-N′-(1-substituted benzylidene)benzohydrazide compounds have antibacterial activities against all bacterial strains except K. pneumoniae, K. oxytoca, E. coli and P. aeruginosa bacterial strains. The 4-chloro substituted (E)-N′-(1-substituted benzylidene)benzohydrazide compound have antibacterial activities against all bacterial strains except K. oxytoca and P. aeruginosa bacterial strains. The 4-fluoro substituted (E)-N′-(1-substituted benzylidene)benzohydrazide compound have antibacterial activities against all bacterial strains except S. pyogenes and K. oxytoca bacterial strains. The 4-hydroxy substituted (E)-N′-(1-substituted benzylidene)benzohydrazide compound have antibacterial activities against all bacterial strains except E. coli bacterial strain. The 2-nitro substituted (E)-N′-(1-substituted benzylidene)benzohydrazide compound have antibacterial activities against all bacterial strains except K. pneumoniae and E. coli bacterial strains. The 3-nitro substituted (E)-N′-(1-substituted benzylidene)benzohydrazide compound have antibacterial activities against all bacterial strains except K. pneumoniae and P. aeruginosa bacterial strains. The synthesized (E)-N′-(1-substituted benzylidene)benzohydrazide compounds have shown good antifungal sensitivity against A. niger fungal species. The parent, 3-Br, 4-Cl, 4-F, 3-OH, 4-CH_3 and 3-NO_2 substituted benzohydrazide compounds have shown good antifungal activity against Mucor sp. fungal species and the 2-Cl, 4-OH and 2-NO_2 substituents are inactive. The 3-OH substituted benzohydrazide compound shows good antifungal activity against T. viridie fungal species and the remaining compounds show satisfactory antifungal activity.

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