Harshita Sachdeva*, Rekha Saroj, Sarita Khaturia and Diksha Dwivedi

Operationally simple green synthesis of some Schiff bases using grinding chemistry technique and evaluation of antimicrobial activities

Abstract: Operationally simple condensation of DL-alanine amino acid with substituted aromatic aldehydes/heterocyclic aldehyde occurs to afford Schiff bases in quantitative yield under organic solvent-free conditions efficiently in the presence of water as a green solvent. The operational simplicity, environmentally friendly conditions and high yield achieved are major benefits that meet the requirements of green production, including saving energy and high efficiency. Structural assignments are based on spectroscopic data. The compounds have also been screened for antibacterial and antifungal activities and most of the Schiff bases have shown potent antibacterial and antifungal activity.

Keywords: antibacterial activity; antifungal activity; green solvent; grindstone technology; microwave irradiation; Schiff bases.

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1 Introduction

Amino acids are molecules containing an amine group, a carboxylic acid group and a side chain that varies between different amino acids. These molecules are particularly important in biochemistry, where this term refers to α-amino acids with the general formula H_2NCHR-COOH, where R is an organic substituent. In chemistry, Schiff bases find versatile use [1]; some of them are the basic units in certain dyes, whereas some are used as liquid crystals. In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds. Schiff bases appear to be important intermediates in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate [2]. Schiff bases are used as starting materials for the synthesis of various bioactive heterocyclic compounds like 4-thiazolidinones, 2-azetidinones, benzoxazines and formazans. They possess diversified biological activities such as antitubercular [3], anticancer [4], antibacterial [5–11], antifungal [12], analgesic [13], CNS depressant [13], anti-inflammatory [14], anticonvulsant [15], insecticidal [16] and plant growth inhibitory [17] activities. Schiff bases are active against a wide range of organisms, for example, *Candida albicans*, *Escherichia coli*, *Staphylococcus aureus*, *Bacillus polymxa*, *Trychophyton gypseum*, *Mycobacterium*, *Erysiphe graminis* and *Plasmopara viticola*. One of the important roles of Schiff bases is as an intermediate in the biologically important transamination reaction. They are used as a protective agent in natural rubber [18] and an amino protective group in organic synthesis.

The discovery and development of antibiotics are among the most powerful and successful achievements of modern science and technology for the control of infectious diseases [19]. However, the increasing microbial resistance to antibiotics necessitates the search for new agents with potential effects against pathogenic bacteria. The most magnificent advances in medicinal chemistry have been made when heterocyclic compounds played an important role in regulating biological activities.

Extensive investigations in the field of Schiff bases have been reported. Naik and Desai have synthesized Schiff bases under microwave irradiation within 2–3 min in the presence of 20 ml of methanol [20]. Several methods

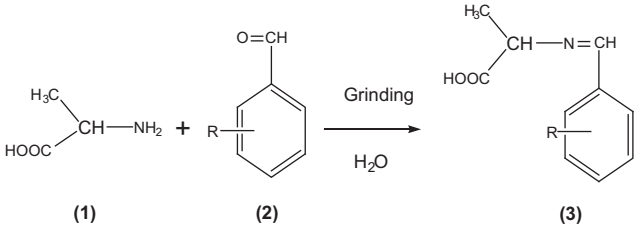
for the synthesis of Schiff bases have been reported in the literature in which Lewis acids [21–24] and materials like hydrotalcite [25] were used as catalysts. Environment-friendly methods for the synthesis of Schiff bases have been reported in the literature. Hossein et al. [26] have reported the solvent-free synthesis of Schiff base catalyzed by P_2O_5/Al_2O_3, resulting in quantitative yields of the product. Varma et al. [27] have reported the solvent-free synthesis of Schiff base under microwave conditions using montmorillonite K-10 as a solid support. The synthesis of imines catalyzed by CaO under microwave conditions has also been reported by Gopalakrishnan et al. [28]. Ravishankara et al. have reported cerium(III)-catalyzed synthesis of Schiff bases [29]. Bendale et al. have reported Schiff base synthesis by using a UV chamber and a sonicator and also by grinding method [30]. Jarrhapour et al. [31] have prepared bis-Schiff bases of isatin by a conventional method using ethanol. Tania et al. [32] reported synthesis of bis-imine Schiff bases under solvent-free conditions and also in polypropylene glycol as a recyclable reaction medium. Naqvi et al. [33] have synthesized Schiff bases using (A) water-based, (B) microwave and (C) grindstone syntheses. Uppiah et al. [34] synthesized bis-Schiff bases under solvent-free conditions. Jarrahpour and Khaili [35] reported synthesis of bis-Schiff bases of isatin and 5-fluoroisatin in a water suspension medium. Although some reported methodologies are simple and high yielding, still some have disadvantages such as prolonged reaction time, high reaction temperatures, an excess of costly dehydrating reagents/catalysts, moisture-sensitive catalysts, need for special apparatus, etc. These shortcomings led us to develop a safe, environmentally benign and more efficient method for the synthesis of biodynamic Schiff bases.

The antimicrobial and antifungal activities of various Schiff bases have also been reported [36–38]. Sahu et al. [39] reported fungi toxicity of some Schiff bases. Abdul-Gawad et al. [40] synthesized some Schiff bases and observed high antimicrobial activities. Many Schiff bases are known to be medicinally important and are used to design medicinal compounds [41–43].

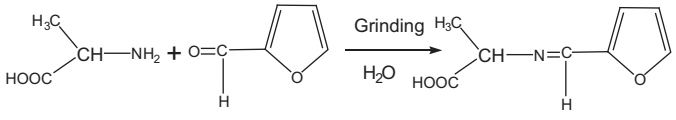
Antibacterial [44], antifungal [45], antimicrobial [46], anticonvulsant [15], anti-HIV [47], anti-inflammatory [48], and antitumor [49] activity of many biologically important Schiff base ligands have also been reported [50].

The revolutionary work of Toda et al. [51] has shown that many exothermic reactions can be accomplished in high yield by just grinding solids together using a mortar and pestle, a technique known as "grindstone chemistry", which is one of the "green chemistry techniques". Reactions are initiated by grinding, with the transfer of very small amounts of energy through friction [52]. In addition to being energy efficient, grindstone chemistry also results in high reactivity and less waste products. Such reactions are simple to handle, reduce pollution, are comparatively cheaper to operate and may be regarded as more economical and ecologically favorable procedures in chemistry [53]. Solid-state reactions occur more efficiently and more selectively than does the solution reaction, as molecules in the crystals are arranged tightly and regularly [54].

In order to broaden the scale of investigations on Schiff bases, we have now synthesized, structurally characterized and determined the antifungal and antibacterial activity of a number of amino acid Schiff bases derived from various aromatic aldehydes and DL-alanine amino acid by conventional heating, grindstone "friction-activated technology", stirring at room temperature



R=4-OCH_3, 3-OH, 4-OCH_3, 4-Cl, 4-OH, 3,4-dimethoxy, 3,4,5-trimethoxy, 2-NO_2



Scheme 1 Reaction of DL-alanine amino acid with substituted aromatic aldehydes/furfural.

and microwave irradiation methods. Data from several of the successful reactions by grinding described by Tanaka [55] led us to generalize that these reactions are all exothermic. We have concluded that after the reaction is initiated by grinding with the transfer of very small amounts of energy through friction, the reaction proceeds by itself as it is exothermic in nature.

2 Experimental section

2.1 General

Grinding in all the reactions was carried out in a porcelain mortar with pestle. Reagents and solvents were obtained from MERCK, Mumbai and CDH, New Delhi and are used without further purification. Melting points were determined on a Toshniwal apparatus, manufactured by Toshniwal Instruments Mfg. Pvt. Lltd., Ajmer, India. The spectral analyses of synthesized compounds have been carried out at the Sophisticated Analytical Instrumentation Facility (SAIF), Punjab University, Chandigarh, India. The purity of the compounds was checked on thin layers of silica gel in various nonaqueous solvent systems, e.g., benzene/ethyl acetate (8:2). IR spectra were recorded in KBr on a Perkin Elmer Infrared L1600300 Spectrum Two Li-Ta spectrophotometer, 09991423 power cord, India, manufactured by Perkin Elmer Life and Analytical Science, Shelton, CT, USA and ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance II 400 NMR spectrometer using deuterated dimethyl sulfoxide (DMSO-d_6) and $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference standard. The microwave-assisted reactions were carried out in Catalysts Systems Scientific Multimode MW oven with a magnetic stirrer and a reflux condenser operating at 700 W and generating 2450 MHz frequency, manufactured by Catalyst Systems, Pune, Maharashtra, India.

2.2 General procedure for the synthesis of 2-[(substituted benzylidene)-amino]-propionic acid (3a–h)

Compounds were synthesized by four different methods.

2.2.1 Method A: grindstone friction-activated synthesis

An equimolar mixture of DL-alanine amino acid (0.01 mol) and substituted aromatic aldehyde (0.01 mol) was dissolved in a minimum amount of water (0.5 ml). The mixture was then ground for 5–10 min using a mortar and pestle of appropriate size. The initial syrupy reaction mixture solidified within 20–25 min and was left overnight (8 h), washed with cold water (to remove impurities) when solid residue was separated out, which was suction filtered, washed with water, dried and crystallized from ethanol to give product **3a–h**. Ethanol used for postprocessing was distilled off and reused again.

2.2.2 Method B: stirring method

An equimolar mixture of DL-alanine amino acid (0.01 mol), substituted aromatic aldehyde (0.01 mol) and 5 ml of water was mixed in a round-bottom flask, and the mixture was magnetically stirred at room temperature (15–20°C) until the completion of the reaction [monitored by thin-layer chromatography (TLC)]. The initial syrupy reaction mixture solidified within 40–45 min. The solid mass was washed with cold water, filtered, dried and crystallized from ethanol to give the product. Ethanol used for postprocessing was distilled off and reused again.

2.2.3 Method C: conventional heating method

An equimolar mixture of DL-alanine amino acid (0.01 mol), substituted aromatic aldehyde (0.01 mol) and 10 ml of water was mixed in a round-bottom flask and refluxed for 1 h. The progress of the reaction was monitored by TLC. The crystalline product so obtained was filtered, washed with water, dried and crystallized from ethanol.

2.2.4 Method D: microwave irradiation method

An equimolar mixture of DL-alanine (0.01 mol) and substituted aromatic aldehyde (0.01 mol) containing 5 ml of water was charged into a glass microwave vessel and refluxed inside a microwave oven at 250 W. After 5–6 min, the product so formed was filtered, dried and crystallized from ethanol.

The spectroscopic characterization data of (**3a–h**) are given below.

2-[(4-Methoxy-benzylidene)-amino]-propionic acid (3a): m.p. 210°C; IR(KBr): 3091, 2924, 2736, 1622, 1593, 1464,

1302, 1201 cm^{-1}; ^1H NMR (DMSO-d_6): 1.41 (d, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.18 (q, 1H, CH), 7.07–7.51 (m, 4H, aromatic), 8.11 (s, 1H, =CH), 12.34 (s, 1H, OH) ppm. Anal. calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.58; H, 6.36; N, 6.77.

2-[(3-Hydroxy-4-methoxy-benzylidene)-amino]-propionic acid (3b): m.p. 155°C; IR (KBr): 3430, 3090, 2924, 2736, 1620, 1590, 1465, 1305, 1200 cm^{-1}; ^1H NMR (DMSO-d_6): 1.41 (d, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.18 (q, 1H, CH), 5.1 (s, 1H, OH), 7.07–7.51 (m, 3H, aromatic), 8.11 (s, 1H, =CH), 12.34 (s, 1H, OH) ppm. Anal. calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.39; H, 5.88; N, 6.30.

2-[(4-Chlorobenzylidene)-amino]-propionic acid (3c): m.p. 280°C; IR (KBr): 3090, 2925, 2736, 1620, 1592, 1465, 1302, 1205, 690 cm^{-1}; ^1H NMR (DMSO-d_6): 1.41 (d, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.18 (q, 1H, CH), 7.07–7.51 (m, 4H, aromatic), 8.11 (s, 1H, =CH), 12.34 (s, 1H, OH) ppm. Anal. calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.93; H, 4.78; N, 6.64.

2-[(4-Hydroxy-benzylidene)-amino]-propionic acid (3d): m.p. 195°C; IR (KBr): 3420, 2924, 2736, 1622, 1593, 1464, 1220 cm^{-1}; ^1H NMR (DMSO-d_6): 1.41 (d, 3H, CH_3), 4.18 (q, 1H, CH), 5.1 (s, 1H, OH), 7.07–7.51 (m, 4H, aromatic), 8.11 (s, 1H, =CH), 12.34 (s, 1H, OH) ppm. Anal. calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.37; H, 5.76; N, 7.23.

2-[(3, 4-Dimethoxy-benzylidene)-amino]-propionic acid (3e): m.p. 205°C; IR (KBr): 3091, 2926, 2735, 1622, 1595, 1464, 1302, 1200 cm^{-1}; ^1H NMR (DMSO-d_6): 1.41 (d, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.18 (q, 1H, CH), 7.07–7.51 (m, 3H, aromatic), 8.11 (s, 1H, =CH), 12.34 (s, 1H, OH) ppm. Anal. calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.93; H, 6.35; N, 5.92.

2-[(3,4,5-Trimethoxy-benzylidene)-amino]-propionic acid (3f): m.p. 210°C; IR (KBr): 3094, 2924, 2736, 1622, 1593, 1465, 1300, 1205 cm^{-1}; ^1H NMR (DMSO-d_6): 1.11 (d, 3H, CH_3), 2.52 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.18 (q, 1H, CH), 7.07–7.51 (m, 2H, aromatic), 8.11 (s, 1H, =CH), 12.34 (s, 1H, OH) ppm. Anal. calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.60; H, 6.43; N, 5.26.

2-[(Furan-2-ylmethylene)-amino]-propionic acid (3g): m.p. 185°C; IR (KBr): 3095, 2925, 2738, 1620, 1590, 1464, 1302, 1205 cm^{-1}; ^1H NMR (DMSO-d_6): 1.41 (d, 3H, CH_3), 4.18 (q, 1H, CH), 6.32–7.41 (m, 3H, aromatic), 7.50 (s, 1H, =CH), 12.34 (s, 1H, OH) ppm. Anal. calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.67; H, 5.45; N, 8.36.

2-[(2-Nitrobenzylidene)-amino]-propionic acid (3h): m.p. 195°C; IR (KBr): 3091, 2924, 2736, 1625, 1595, 1560, 1464, 1300, 1200 cm^{-1}; ^1H NMR (DMSO-d_6): 1.41 (d, 3H,CH_3), 4.18 (q, 1H, CH), 7.51–8.22 (m, 4H, aromatic), 8.11 (s, 1H, =CH), 12.34 (s, 1H, OH) ppm. Anal. calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.23; H, 4.56; N, 12.63.

3 Results and discussion

3.1 Compound synthesis with different heat and mixing techniques

In recent years, organic research has been mainly focused on the development of green methods that involve use of alternative reaction media to replace volatile and hazardous solvents commonly used in organic synthesis [56–59]. Currently, many organic transformations are being carried out in water [60–62]. It is a unique solvent due to its being readily available, inexpensive, nontoxic, safer and environmentally benign. These wider applications and diverse potential biological activities prompted us to synthesize Schiff bases containing heterocyclic moiety under the framework of green chemistry and to ascertain their microbial activity. A literature survey reveals that although a few Schiff bases derived from amino acids have been prepared, their biological activities have scarcely been investigated. Further, there are few reports [33, 63] on their synthesis using grindstone technology. In this study, we report the synthesis and characterization of some Schiff bases using different methods for pharmacological studies (Scheme 1) (Table 1).

Hence, in continuation of our work to develop green methodologies for the synthesis of biodynamic heterocycles [64–71], herein we wish to report a highly efficient procedure for the synthesis of amino acid Schiff bases (3) in water by the reaction of DL-alanine amino acid (1) and variously substituted aromatic aldehydes/heterocyclic aldehyde (2) using grindstone chemistry technique (method A), stirring at room temperature (method B), conventional heating (method C) and microwave irradiation (method D). The results are summarized in Table 1. Comparative results of syntheses under different reaction conditions indicate that although a good yield of the product was achieved in method A compared to the other three methods B, C and D, it took a very long time to complete the reaction, i.e., grinding for 30–35 min followed by leaving the reaction mixture overnight (8 h), with yields of the products ranging from 72% to 78%. After completion of the reaction, the mixture was washed with cold water

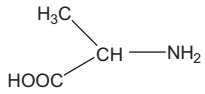
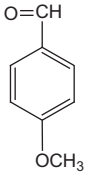
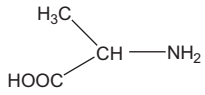
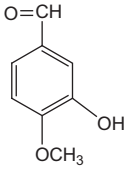
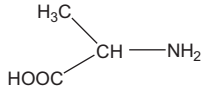
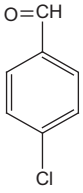
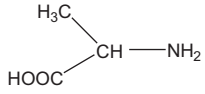
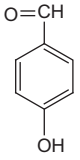
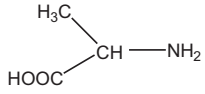
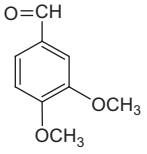
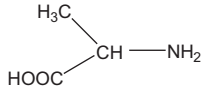
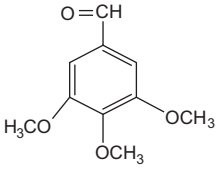
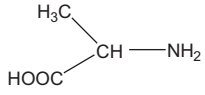
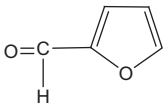
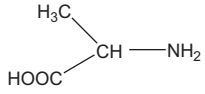
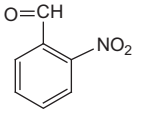
Entry	Reactant 1	Reactant 2	Method A		Method B		Method C		Method D		M.p. (°C)	Color
			Time (min)	Yield (%)	Time (min)	Yield (%)	Time (h)	Yield (%)	Time (min)	Yield (%)		
3a			35	74	40	69	1	63	6	71	210	White
3b			30	76	45	70	1	60	5	72	155	Light pink
3c			35	72	40	71	1	60	5	70	280	White
3d			30	73	40	73	1	61	6	70	195	Cream
3e			30	78	45	72	1	62	5	72	205	Cream
3f			30	76	40	71	1	62	6	71	210	Cream
3g			35	75	40	73	1	60	6	70	185	Brown
3h			35	72	40	70	1	61	5	71	195	Yellow

Table 1 Comparative results of the synthesis of compounds (**3a–h**) under different reaction conditions.
Method A, grinding method; method B, stirring method; method C, conventional heating method; method D, microwave irradiation method.

(or poured onto crushed ice) and the product formed was filtered, dried and recrystallized from ethanol. However, when the reactants were stirred in water at room temperature (15–20°C), the reaction was completed in 40–45 min only, with yields of the products ranging between 69% and 73%. Compounds were also synthesized under conventional heating (method C) and microwave irradiation (method D). A yield of 70–72% was achieved within 5–6 min under microwave irradiation, which is a much shorter reaction time compared to grinding (method A). Method B

is the best of all the other three methods because a good yield was obtained in a shorter reaction time.

In summary, the present green synthetic protocol is highly efficient as it avoids the use of hazardous solvents at any stage of the reaction. The scope of the method was further studied by reacting differently substituted aromatic aldehydes/heterocyclic aldehyde, furfural, with DL-alanine amino acid (Table 1). The identity of the products obtained was confirmed by their IR and ^{1}H NMR spectral data. Our present investigation was an attempt to develop some amino acid Schiff bases taking water as a green solvent or almost organic solvent-free conditions as depicted in Scheme 1, which upholds the motto of green chemistry. This series of compounds was then subjected to *in vitro* antimicrobial activity; amongst the compounds tested, substituents with dimethoxy, trimethoxy, furan ring, NO_2 and Cl groups show significant antibacterial and antifungal activity than the unsubstituted compounds (Table 2). To conduct grindstone chemistry on a large scale, a simple and inexpensive expedient is to use a handheld electric food mixer with stainless steel rotors for grinding together the reagents in a large glass or porcelain bowl [52].

Entry	Zone of inhibition (mm)											
	Concentration (250 ppm)						Concentration (500 ppm)					
	A	B	C	D	E	F	A	B	C	D	E	F
3a	5	4	7	6	7	7	8	8	–	9	8	11
3b	4	3	6	7	–	8	–	9	**11**	**11**	7	**11**
3c	4	–	8	6	7	7	–	8	9	**10**	**12**	9
3d	–	–	–	8	8	9	9	–	9	–	11	–
3e	–	4	6	7	8	–	7	–	8	–	–	–
3f	3	4	–	7	9	9	–	8	9	**12**	–	**11**
3g	6	3	7		–	–	9	7	**11**	**11**	9	**10**
3h	7	6	6	8	7	–	8	9	**11**	–	**11**	**11**
DMSO	–	–	–	–	–	–	–	–	–	–	–	–
Streptomycin	12	10	–	12	13	12	11	–	12	13	15	14
Erythromycin	14	12	–	14	13	12	14	10	–	14	14	12

Table 2 Antifungal evaluation of the synthesized compounds (**3a–h**). A, *Aspergillus niger;* B, *Penicillium notatum;* C, *Fusarium oxysporum;* D, *Alternaria brassicicola;* E, *Chaetomium murorum;* F, *Lycopodium* sp.
Bold numbers indicate compounds showing good activity.

3.2 Antibacterial and antifungal testing

3.2.1 Antibacterial activity

The synthesized compounds **(3a–h)** were screened for their antibacterial activity against Gram-positive bacteria (*Bacillus licheniformis, S. aureus, Micrococcus luteus*) and Gram-negative bacteria (*Pseudomonas aeruginosa* and *E. coli)* by the agar well diffusion method [72]. The antibacterial activity was determined by measuring the diameter of the zone (mm) showing complete inhibition with respect to control (DMSO) and reference compounds streptomycin and erythromycin. It has been observed that all the compounds tested showed good to excellent activity against the tested bacteria (Table 3).

The results of antibacterial screening indicate that amino acid Schiff bases show more activity against *P. aeruginosa, M. luteus* and *E. coli* than *B. licheniformis* and *S. aureus*. Compound **3b** containing methoxy and hydroxyl groups in the aromatic ring was found to be more active against *M. luteus* and *E. coli* at 250 and 500 ppm concentrations. Compound **3d** containing hydroxyl groups shows good activity against *P. aeruginosa, M. luteus* and *E. coli* at 500 ppm concentration. Compound **3e** containing a dimethoxy group in the aromatic ring shows good activity against *P. aeruginosa* at 250 ppm concentration and excellent activity against *M. luteus* at 500 ppm concentration. Compound **3g** containing a furan ring shows good activity against *P. aeruginosa* at 250 ppm concentration and excellent activity against *E. coli* at 500 ppm concentration.

3.2.2 Antifungal activity

Antifungal activity was determined by cup plate method [73] at concentrations of 250 and 500 ppm against *Aspergillus niger, Penicillium* sp., *Fusarium oxysporum, Alternaria brassicicola, Chaetomium murorum, Lycopodium* sp. by measuring the zone of inhibition in mm. The antifungal activity was determined by measuring the diameter of the zone (mm) showing complete inhibition with respect to control (DMSO) and reference compound streptomycin and erythromycin. Compound **3b** containing methoxy and hydroxyl groups in the aromatic ring and **3g** containing a furan ring shows good activity against the fungi *F. oxysporum, A. brassicicola* and *Lycopodium* sp. Compound **3h** containing the NO_2 group shows good activity against *F. oxysporum, Chaetomium murorum* and *Lycopodium* sp. at 500 ppm. Compound **3f** containing a trimethoxy group shows excellent activity against *A. brassicicola* and *Lycopodium* sp. It has been found that Schiff bases possess effective antifungal activity. The presence of NO_2 (**3h**), Cl (**3c**) and a furan ring (**3g**) enhances fungicidal activity against *F. oxysporum, C. murorum, Lycopodium* sp. and *A. brassicicola* (Table 2).

Results of antibacterial and antifungal screening are in accordance with the data reported in the literature [74];

Entry	Zone of inhibition (mm)									
	Concentration (250 ppm)					Concentration (500 ppm)				
	A	B	C	D	E	A	B	C	D	E
3a	5	4	6	9	9	9	6	–	7	–
3b	6	5	5	**10**	**10**	8	9	7	**10**	**11**
3c	–	7	–	–	8	4	9	4	–	9
3d	9	9	–	8	–	**10**	8	–	**10**	**11**
3e	**10**	–	–	9	–	8	4	6	11	3
3f	6	–	8	7	8	7	–	9	9	**12**
3g	**10**	9	7	–	7	3	9	9	–	**11**
3h	–	–	–	9	–	3	–	8	6	5
DMSO	–	–	–	–	–	–	–	–	–	–
Streptomycin	11	–	13	12	13	11	–	12	12	15
Erythromycin	14	12	–	14	–	14	10	–	12	14

Table 3 Antibacterial evaluation of the synthesized compounds (**3a–h**).
A, *Pseudomonas aeruginosa*; B, *Bacillus licheniformis*; C, *Staphylococcus aureus;* D, *Micrococcus luteus;* E, *Escherichia coli*. Bold numbers indicate compounds showing good activity.

all the synthesized Schiff bases of DL-alanine amino acid have shown good activity against the tested microbes. Among these Schiff bases, compounds bearing the trimethoxy group (**3f**), dimethoxy group (**3e**) and furan ring (**3g**) have shown excellent activity against the tested bacteria and fungi.

4 Conclusion

Stirring at room temperature and microwave irradiation methods, i.e., methods B and D, are much simpler and faster than methods A and C. All the reported methods are consistent with a green chemistry approach as reactions are carried out in water and no organic solvent is needed (except for crystallization). Moreover, method A (grindstone technology) is energy efficient as no external heating is required. The use of water as a green solvent offers a convenient, nontoxic, inexpensive reaction medium for the synthesis of Schiff bases. This procedure is economical and milder and includes cleaner reactions as well as a simple experimental and workup procedure, which makes it a useful and attractive process, and is also consistent with the green chemistry theme, which affords good yields. It has been found that Schiff bases possess effective antibacterial and antifungal activity. Among these Schiff bases, compounds bearing the furan ring and groups like trimethoxy, dimethoxy, hydroxyl, nitro and chloro groups in the aromatic ring have shown excellent activity against the tested bacteria and fungi.

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