Microwave Assisted Synthesis, Characterization and Antimicrobial Activity of Some Odorant Schiff Bases Derived from Naturally Occurring Carbonyl Compounds and Anthranilic Acid

Prasoon Kumar Kaushik[1], V. K. Varshney[1], Pawan Kumar[2], Pallavi Bhatia[3], S. V. Shukla[4]

[1]Chemistry Division, Forest Research Institute, Dehra Dun, India,
[2]Chemical Sciences Division, CSIR-Indian Institute of Petroleum, Dehradun, India,
[3]Forest Pathology Division, Forest Research Institute, Dehra Dun, India,
[4]Fragrance & Flavor Development Center, Makrandnagar, Kannauj, India

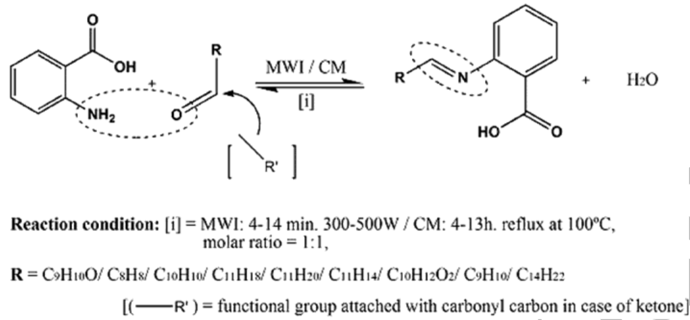
Corresponding author V. K. Varshney, E-mail: vinay.varshney5@gmail.com

Abstract

Nine odorant Schiff bases namely 2-(4-methoxybenzylideneamino) benzoic acid**,** 2-(benzylideneamino) benzoic acid, 2-(3-phenylallylidene amino) benzoic acid, 2-(3,7-dimethyloct-2,6-enylideneamino) benzoic acid, 2-(3,7-dimethyloct-6-enylidene) aminobenzoic acid, 2-(4-isopropylbenzylideneamino)benzoic acid, 2-(3,4-dimethoxybenzylideneamino) benzoic acid, 2-(1-phenylethylideneamino) benzoic acid, 2-[(4-(2,6,6-trimethylcyclohex-2-enyl)-but-2-enylidene amino)benzoic acid were prepared by condensation of anthranilic acid with corresponding naturally occurring carbonyl compounds (anisaldehyde, benzaldehyde, cinnamaldehyde, citral, citronellal, cuminaldehyde, veratraldehyde, acetophenone and α-ionone) employing conventional and microwave irradiation methods. These compounds were characterized with the aid of elemental and spectral (FT-IR, ^{1}H NMR and ^{13}C NMR) analysis. Microwave irradiation method was efficient in terms of reduced reaction time, solvent use, and increased yields of these compounds without affecting their olfactory characteristics. These Schiff bases also exhibited olfactory characteristics for various fragrance compositions and varied

antimicrobial activity against *Aspergillus niger*, *Penicillium chrysogenum*, *Staphylococcus aureus* and *Escherichia coli*.

Graphical Abstract



KEYWORDS: Schiff bases, anthranilic acid, olfactory property, antimicrobial activity, microwave irradiation

INTRODUCTION

Nature has served as a guide towards the design of novel aroma molecules for their use in various fragrance and flavour (F&F) applications [1]. In spite of the use of more than 3000 odoriferous compounds of diverse chemical structures in F&F industry, creation of new odorant molecules in augmenting the aroma of compositions for perfumery, flavor or new extended applications is intensive [2, 3]. Schiff bases (azomethines / anils / imines) having azomethine group (-CH=N-) belong to a group of compounds which possess varied biological activities including antimicrobial, anticancer, antineoplastic, antiviral, antitumour, anti-HIV, antitubercular, anticonvulsant, anthelmintic, antiplatelet, antimalarial, antibiotics, anti-inflammatory, diuretic, and analgesic [5-15]. Besides, Schiff bases are also well known in flavoring and perfumery due to their odor characteristics [16].

Several Schiff bases are reported to exhibit floral, fruity odors, namely of the citrus type and, more particularly, reminiscent of the odor of the orange-flower [17]. Schiff bases are also known to be useful as intermediates in producing other fragrance materials [18, 19].

Primary amines and carbonyl compounds (aldehydes or ketones) are widely used as substrates for the preparation of Schiff bases with biological and olfactory properties. These carbonyl compounds occur widely in nature and constitute, due to their interesting odoriferous properties, a novel group of raw materials for F&F industry. Microwave (MW) assisted synthesis of organic compounds has acquired significant importance over conventional organic synthesis in terms of reduced solvent consumption and reaction time, improved yields and easier workup matching with green chemistry approach [20]. Several Schiff bases have been synthesized using microwave irradiation and characterized [21-25].

In the present paper, we report synthesis of nine odorant Schiff bases of naturally occurring carbonyl compounds (five aromatic aldehydes - anisaldehyde, benzaldehyde cinnamaldehyde, cuminaldehyde, vertraldehyde; two acyclic terpene aldehydes - citral, citronellal; an aromatic acetophenone, and a cyclic terpenoid ketone- α-Ionone) (Figure 1) with anthranilic acid by conventional and MW assisted methods, and their characterization through elemental analysis and spectral (FT-IR, ^{1}H NMR and ^{13}C NMR) data. Their olfactory and antimicrobial properties were also examined. Anisaldehyde (4-methoxy benzaldehyde), veratraldehyde (3,4-dimethoxybenzaldehyde), acetophenone (methyl phenyl ketone) and α-Ionone (4-(2,6,6-triethylcyclohex-2-enyl) but-3-ene-2-one) occur in many essential oils. Benzaldehyde is the main, characteristic component of bitter almond oil. Cinnamaldehyde (3-phenyl-2-propenal) is the chief component of cassia oil (ca. 90 %) and Sri Lanka cinnamon bark oil (ca. 75%). Cuminaldehyde (4-isopropylbenzaldehyde) is a constituent of the essential oils of eucalyptus, myrrh, cassia, cumin and others. Citral (3, 7-dimethyl-2,6-octadien-1-al) occurs in lemon-grass oil (up to 85 %) and in *Litsea cubeba* oil (up to 75 %) while citonellal (3,7-dimethyl-6-octen-1-al) is a constituent of citronella oil (upto 45%), Backhousia citriodora oil (upto 80%) and *Eucalyptus citriodora* oil (upto 85%) [26]. Anthranilic acid (2-aminobenzoic acid) occurs in oats and being a component of the major biochemical pathway of bacteria, plant and animals is also the starting material for several other types of naturally occurring compounds.

Though, Schiff bases of acetophenone, anisaldehyde, benzaldehyde, cinnamaldehyde, citral, and citronellal with anthranilic acid have been prepared by conventional condensation method for their use as ligands for synthesis of metal complexes [27-30], to the best of our knowledge this is the first report on the MW assisted synthesis of the Schiff bases derived from acetophenone, anisaldehyde, benzaldehyde cinnamaldehyde, citral, citronellal, cuminaldehyde, α-Ionone, and vertraldehyde with anthranilic acid. Their olfactory properties and antimicrobial activity are also reported for the first time.

RESULTS AND DISCUSSION

Nine odorant Schiff bases 2-(4-methoxybenzylideneamino) benzoic acid (Sb1)**,** 2-(benzylideneamino) benzoic acid (Sb2), 2-(3-phenylallylidene amino) benzoic acid (Sb3), 2-(3,7-dimethyloct-2,6-enylidene)amino benzoic acid (Sb4), 2-(3,7-dimethyloct-6-enylidene) aminobenzoic acid (Sb5), 2-(4-isopropylbenzylideneamino)benzoic acid (Sb6), 2-(3,4-dimethoxybenzylideneamino) benzoic acid (Sb7), 2-(1-phenylethylideneamino) benzoic acid (Sb8), 2-[(4-(2,6,6-trimethylcyclohex-2-enyl)-but-2-enylidene amino)benzoic acid (Sb9) (Figure 2) were prepared from naturally occurring seven aldehydes (anisaldehyde, benzaldehyde, cinnamaldehyde, citral, citronellal, cuminaldehyde, veratraldehyde) and two ketones (acetophenone and α-Ionone) with anthranilic acid by conventional and MW assisted methods. A large number of experiments were performed to optimize the irradiation power and its duration and the optimized conditions are reported. MW irradiation resulted in no solvent consumption, reduced reaction time from 4 to 14 minutes, and improved yields from 46% to 89% over conventional method.

The Schiff bases were characterized by analysis of the elements (C, H and N), FT-IR, ^{1}H NMR and ^{13}C NMR spectral data. Elemental analysis of the Schiff bases was in agreement to their molecular formula assigned. The FT-IR spectra of the free aldehydes (anisaldehyde, cinnamaldehyde, cuminaldehyde, benzaldehyde, citronellal, citral, vertraldehyde), and ketones (acetophenone and α-Ionone) have a strong band at 1690-1700 cm-1 (due to carbonyl stretch), two bands of moderate intensity in the region 2700-2800 cm-1 (due to H-C=O stretch in aldehydes only), while two moderate bands at 3500 and 3580 cm-1 corresponding to N-H stretch were observed in the IR spectrum of anthranilic acid. In the IR spectra of the Schiff bases, these bands disappeared and a new band appeared in the range of 1613-1658 cm-1 attributed to the v(C=N) mode of azomethine linkage showing the condensation between the -CHO / >C=O group of the carbonyl compounds and amino group of anthranilic acid resulting in the formation of the respective Schiff base. The characteristic phenolic v(O-H) mode due to presence of a hydroxyl group in these Schiff bases were observed around 3478-3331 cm-1

The ^{1}H NMR spectra of the Schiff bases Sb1-Sb8 and Sb9 exhibit singlet of integration intensity equivalent to one hydrogen at 8.37-8.78 ppm and three hydrogens at 2.99 ppm attributed to to (-CH=N-) and to (-CH3 -C=N-) protons, respectively. A singlet at 9.78-9.98 ppm due to aromatic hydroxyl proton was observed in the spectra of all the Schiff bases. A broad signal at 8.3-8.4 ppm due to free NH_2 protons in the spectra of anthranilic acid was absent in the observed spectra of the Schiff bases which indicated the formation of the azomethine linkage. The multiplets within the 6.62-7.93 ppm range were assigned to protons belonging to aromatic rings. The spectra of Sb1 and Sb7 showed a singlet with an integration equivalent to three hydrogens at 3.90 and 3.98 ppm, respectively corresponding to the methoxyl protons. In ^{13}C NMR spectra, azomethine and carboxyl carbons of the Schiff bases appeared between 160.1-165.2ppm and 168.2-169.7 ppm, respectively. Methoxy carbons of Sb1 and Sb7 were observed at 55.6 and 56.2 ppm, respectively. Methyl carbons of the isopropoyl moiety in Sb4, Sb5 and Sb6 were found at 19.6, 25.6; 19.6, 25.6 and 23.4 ppm, respectively. Vinylic carbons of Sb3 emerged at 119.7 and 138.5 ppm. The NMR spectral assignments of the Schiff bases support the inferences drawn from the elemental and IR studies.

OLFACTORY EVALUATION

Schiff bases were evaluated for their olfactory properties in terms of their odor profile and odor strength and data are shown in Table 1.

A smaller odor diversity was observed between the Schiff bases of the aldehydes and ketones. The Schiff bases possessed an interesting profile, described as sweet floral differed in the notes and the strength, except Sb2 and Sb6 which had bitter almond and herbaceous sweet very tenacious profile, respectively. Schiff bases Sb8 and Sb9 derived from the ketones exhibited similar odor profile differed, however, in the strength. Though Sb1 of benzaldehyde and Sb7 of veratraldehyde had similar odor pofile but differed in the notes (Sb1 with fruity undertone) and the strength (Sb1 of medium and Sb7 of low strength) which could be linked to the presence of another methoxy group in Sb7. Difference in the notes of Sb4 of citral (orange blossom to fresh orange peel) and Sb5 of citronellal (fruity) could be explained on the basis of an additional double bond in citral than that in the citronellal.

Odor notes of the synthesized Schiff bases were natural and relative to those of the previously reported Schiff bases. The olfactory properties of these Schiff bases indicated their use in fragrance compositions of the varied nature.

Antimicrobial Activity

In search of new and effective antimicrobial agents of natural origin, natural product derived Schiff bases have shown promise [15, 32]. Madurahydroxy lactones, occurring in *Actinomadura rubra,* derived Schiff bases were effectively inhibited *Bacillus subtilis,* *Micrococcus flavus*, *Sarcina lutea*, and *S. aureus* with MIC values ranged from 0.2 to 3.1 µg/mL [33]. Chitosan, isatin and nystatin-dextran-derived Schiff bases reported to exhibit antifungal activity against *Botrytis cinerea* and*Colletotrichum lagenarium* [34], *Microsporum audouinii*, and *Microsporum gypseum* [35], and *Candida albicans* and *C. neoformans* [36], respectively.

Antimicrobial activity of the synthesized Schiff bases was, therefore, examined against two bacteria - *Staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram –ve), and two fungi- *Aspergillus niger* and *Penicillium chrysogenum.* All the Schiff bases (Sb1-Sb9) showed moderate to good activity against the pathogenic organisms tested. The solvent used for the preparation of compound solutions (DMSO) did not show inhibition against the tested organisms (negative control). Compared to the positive control, compounds showing the zones of inhibition between 9-16 mm and > 17 mm were considered to be moderately active and highly active. Percent of activity index of tested compounds against the microorganisms are also reported (Table 2).

The MIC values (Table II) of the highly active compounds ranged between 20-30 µg/ml with 59.25-83.33% activity index while those for moderately active compounds were 40µg/ml with 39.58-77.08% activity index. Compounds Sb5, Sb6, Sb7, and Sb9 found highly active while compound Sb1, Sb2, and Sb4 found moderate active against all four microorganisms tested. Compound Sb3 was highly active against the fungi with 70.83% activity index at 30µg/ml and moderately active against bacteria with 70.37-80% activity index at 40µg/ml, however compound Sb8 was moderately active against the fungi with

75-77.08% activity index at 40μg/ml and highly active against bacteria with 74.07-82% activity index at 30μg/ml.

CONCLUSION

Microwave irradiation proved to be advantageous for preparation of nine odorant Schiff bases of naturally occurring seven aldehydes (anisaldehyde, benzaldehyde, citral, citronellal, cinnamaldehyde, cuminaldehyde, veratraldehyde) and two ketones (acetophenone and α-Ionone) with anthranilic acid in terms of reduced reaction duration (4-14 minutes), no solvent consumption and increased yield (13% - 20%) over conventional method. Elemental analysis, FT-IR ^{1}H NMR and ^{13}C NMR data supported the structures of these compounds. Olfactory attributes of these Schiff bases were not influenced by the microwave irradiation and indicative of their use in various fragrance compositions. These compounds showed moderate to good antimicrobial activity against bacteria - *Staphylococcus aureus* and *Escherichia coli*, and fungi- *Aspergillus niger* and *Penicillium chrysogenum.*

EXPERIMENTAL

General

All chemicals obtained from commercial suppliers were of highest purity grade and used without further purification. These include acetophenone (Himedia), anisaldehyde (Loba chemie), anthranilic acid (Sigma aldrich), benzaldehyde (Merck), cinnamaldehyde (Himedia), citral (Himedia), citronellal (Merck), cuminaldehyde (Sigma aldrich), α-ionone (Sigma Aldrich), vertraldehyde (Himedia), Nutrient Agar Media (Himedia) and

Potato Dextrose Agar (Himedia). Melting points were measured on open glass capillary method on Buchi Melting Point (b-540) and are uncorrected. Elemental analysis of carbon, nitrogen and hydrogen were carried out on CHN elemental analyser (Thermo Scientific). Infrared (IR) spectra were recorded at room temperature from 4000 cm^{-1} to 500 cm^{-1} with KBr pellets at a resolution of 4cm^{-1}, using Thermo-Nicolet 8700, Research spectrometer (Thermo Scientific). ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Bruker Avance-II instrument using $CDCl_3$ as solvent and tetramethylsilane (TMS) as an internal slandered. Chemical shifts (δ) are reported in ppm. The microwave assisted synthesis was performed in scientific microwave oven, (SRL-Milestone Start S Labstation for synthesis, (Operating between 140-1600W). All the reactions were carried out at power 300-500W.

Olfactory Evaluation

Olfactory properties of the Schiff bases were studied employing standard olfactory method [31]. Sample solutions (10 wt. % in ethyl alcohol) were used to evaluate their odour properties.

Antimicrobial Activity

Antimicrobial activity of the Schiff bases was evaluated according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS, 1997) using the agar disc diffusion method. The bacterial cultures for *Staphylococcus aureus* (ATCC 259235) and *Escherichia coli (*ATCC 27853) were obtained from Microbial Type Culture Collection (MTCC), Chandigarh and fungal cultures of *Aspergillus niger* and *Penicillium* *chrysogenum* were obtained from National Type Culture Collection (NTCC), Forest Research Institute, Dehradun.

DETERMINATION OF MIC

MIC values were determined by testing performed according to the guidelines of NCCLS (Tuite, J., 1969). Solutions of the test compounds, ciprofloxacin and griseofulvin were prepared in DMSO at different concentrations of 10, 20, 30, 40, 50, 60 μg/ml to determine the MIC. All determinations were done in triplicate and found the same result.

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Table 1. Olfactory properties of the Schiff bases

Sl. No.	Schiff base	Odor profile	Odor strength
A.	**Aldehyde and Anthranilic acid**		
1.	Sb1	Sweet, floral with fruity undertones	Medium
2.	Sb2	Bitter almond	Medium
3.	Sb3	Sweet, floral, honeysuckle	Medium
4.	Sb4	Sweet floral, orange blossom to fresh orange peel	Intense
5.	Sb5	Very tenacious, sweet floral, fruity	Intense
6.	SB6	Herbaceous sweet very tenacious	Medium
7.	Sb7	Sweet-floral	Low
B.	**Ketone and Anthranilic acid**		
8.	Sb8	Heavy, sweet-floral	Medium
9.	Sb9	Heavy and very sweet-floral	Intense

Table 2. Zone of inhibition, MIC and % activity index of odorant Schiff bases

Schiff base	Bacteria Zone of inhibition (MIC)		Fungi Zone of inhibition (MIC)		*% Actevity index (bacteria)		% Actevity index (fungi)	
	E. coli	*S. aureus*	*A. niger*	*P. chrysogenum*	*E. coli*	*S. aureus*	*A. niger*	*P. chrysogenum*
Sb1	14.0 (40)	15.0 (40)	12.0 (40)	12.0 (40)	56	55.55	50.00	50.00
Sb2	11.0 (40)	11.0 (40)	9.5 (40)	10.0 (40)	44	40.74	39.58	41.66
Sb3	20.0 (40)	19.0 (40)	17.0 (30)	17.0 (30)	80	70.37	70.83	70.83
Sb4	19.0 (40)	18.5 (40)	18.5 (40)	18.0 (40)	76	68.51	77.08	75.00
Sb5	19.0 (20)	20.0 (20)	19.0 (20)	20.0 (20)	76	74.07	79.16	83.33

Sb6	15.0 (20)	16.0 (20)	18.5 (30)	18.0 (30)	60	59.25	77.08	75.00
Sb7	19.5 (30)	20.0 (30)	16.0 (20)	16.5 (20)	78	74.07	66.66	68.75
Sb8	20.5 (30)	20.0 (30)	18.0 (40)	18.5 (40)	82	74.07	75.00	77.08
Sb9	19.0 (20)	19.0 (20)	19.0 (30)	20.0 (30)	76	70.37	79.16	83.33
Ciprofloxacin	25.0 (20)	27.0 (20)	-	-	-	-	-	-
Griseofulvin	-	-	24.0 (20)	24.0 (20)	-	-	-	-
DMSO	-	-	-	-	-	-	-	-

1 - 8 mm = less active; 9 - 16 mm = moderate active; >17 mm = highly active

*% Activity index = Zone of inhibition by test compound (diameter) / Zone of inhibition by standard (diameter) x 100

Figure 1. Naturally occurring carbonyl compounds

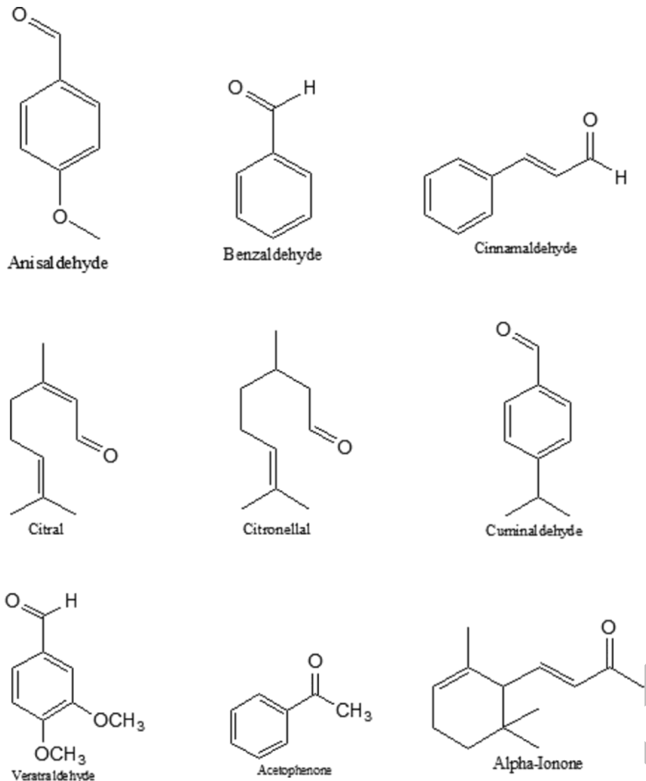
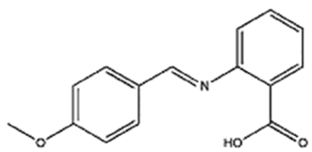
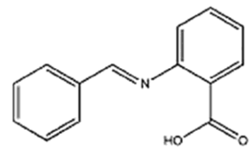


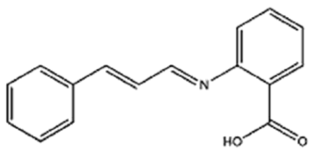
Figure 2. Structures of the synthesized odorant Schiff bases


2-(4-methoxybenzylideneamino)benzoic acid

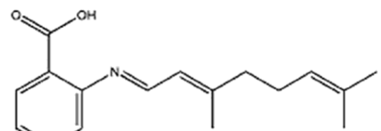
(Sb1)


2-(benzylideneamino)benzoic acid

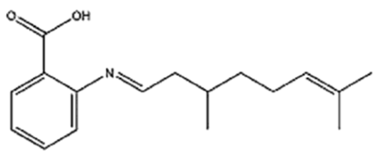
(Sb2)


2-(-3-phenylallylidene)amino)benzoic acid

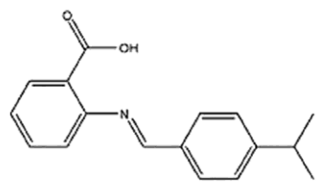
(Sb3)


2-((-3,7-dimethyloct-2,6-enylideneamino)benzoic acid

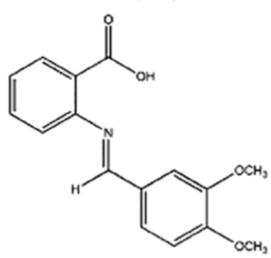
(Sb4)


2-(3,7-dimethyloct-6-enylidene)amino benzoic acid

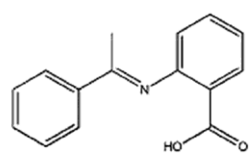
(Sb5)


2-(4-isopropylbenzylideneamino)benzoic acid

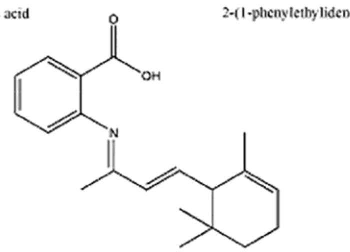
(Sb6)


2-(3,4-dimethoxybenzylideneamino)benzoic acid

(Sb7)


2-(1-phenylethylideneamino)benzoic acid

(Sb8)


2-4-(2,6,6-trimethylcyclohex-2-enyl)but-2-enylideneamino)benzoic acid

(Sb9)