

Nematicidal Efficacy of Schiff Bases Derived from Aryl and / or Heteroaryl Carboxaldehydes

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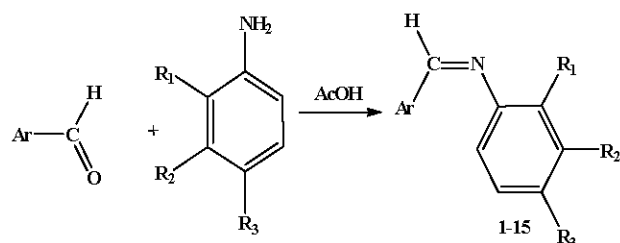
Abstract: A total of fifteen Schiff Bases (di-aryl-aldimines) **1-15** have been prepared from aryl and / or heteroaryl aldehydes with some primary aromatic amines. The synthesized Schiff bases have been screened for antinematodal activity on *Caenorhabditis Elegans*. The results were Promising and showed that all compounds under investigation have some degree of activity against *Caenorhabditis Elegans* and Schiff base **9** is the most potent.

Key words: Schiff Bases · Aryl and / or Heteroaryl Carboxaldehydes · Nematicidal Activity · *Caenorhabditis Elegans*

INTRODUCTION

Schiff bases have potential for both chemical and biological activity [1, 2]. This is due to the presence of carbon- nitrogen double bond. Schiff bases are also one of the intensively investigated classes of aromatic and heteroaromatic organic compounds. This class of compounds showed a variety of applications ranging from anticancer [3, 4], antibacterial [5-7], diuretic [8], antifungal [9-14] and antiparasitic activities [15]. They have also medicinal importance and are used in drug design due to their activity against a wide range of organisms [16-18]. They also show nematicidal activity [19-23] but could not exploited to their potential in pest control due to high temperature and long period of time required (~12-24 hours or more) for completion of the reaction [24-26]. The present investigation is one of the block building units of our

ongoing program aiming at utilization of simple and readily obtainable materials in the synthesis of different biologically active compounds [27-32]. On the other hand, development of the concept of pest management and their implementation has led to greater need for a wide range of tactics for nematode control. The latter is achieved through improvement of the growth and the yield of plants. A reduction of the nematode population in soil or in plants or a reduction of their damage led to improvement of both growth and yield of plants. As a consequence of the aforementioned facts, it was considered worth while to synthesize some Schiff bases as active pharmacophores and to get them evaluated for their nematicidal activity. So, reaction of various substituted anilines with aromatic and / or heterocyclic aldehydes in hot methanol containing a catalytic amount of glacial acetic acid yielded N- arylideneanilines [33] [cf. Scheme 1].



Scheme 1

Compd. No.	Ar	R ₁	R ₂	R ₃
1	C ₆ H ₄ (Cl)-4	H	H	H
2	C ₆ H ₄ (Cl)-4	H	H	NO ₂
3		H	H	H
4	C ₆ H ₃ (OH)(OCH ₃)-4,3	H	H	NO ₂
5	C ₆ H ₃ (OH)(OCH ₃)-4,3	H	H	H
6	C ₆ H ₅ CH=CH-	H	H	NO ₂
7	C ₆ H ₅ CH=CH-	H	H	H
8	C ₆ H ₄ (OH)-2	H	H	NO ₂
9	C ₆ H ₄ (Cl)-4	-CH=CH-	CH=CH-	H
10	C ₆ H ₃ (OH)(OCH ₃)-4,3	-CH=CH-	CH=CH-	H
11	C ₆ H ₃ (OH)(OCH ₃)-4,3	H	H	OCH ₃
12	C ₆ H ₄ (OH)-2	H	H	OCH ₃
13	C ₆ H ₄ (Cl)-4	H	H	CH ₃
14	C ₆ H ₄ (OH)-2	H	H	CH ₃
15		H	H	NO ₂

Experimental

Chemistry; Materials: All aromatic and heteroaromatic carboxaldehydes as well as primary aromatic amines were obtained commercially from Aldrich chemical company. Solvents used were of analytical grade.

General Procedure for Synthesis of Schiff Bases:

An equimolar mixture of aryl and/or hetaryl carboxaldehyde with appropriate primary aryl amine in methanol (30 mL) containing few drops of glacial acetic acid as a catalyst was heated to reflux temperature for 3-4 hours then left overnight until the product precipitated. The product was filtered off, washed with light petroleum and recrystallized from the suitable solvent [cf. Table 1]. Anhydrous dry solvents for recrystallization are recommended to avoid decomposition by hydrolysis. The crystalline solid that separated out was filtered by suction using water pump and washed with light petrol to afford the desired Schiff bases **1-15** in pure state.

Measurements: M.P were measured using a Stuart (UK) Electronic melting point apparatus. IR spectra were recorded with a thermo 330 FTIR spectrometer. ¹H- and ¹³C- NMR spectra were measured on Avance 400 Bruker

instrument using TMS as internal standard and DMSO-d₆ as a solvent. Mass spectra were measured on a MAT 312 Finnegan instrument operating at 70 eV.

Nematicidal Activity of Schiff Bases Against

Caenorhabditis Elegans: The antinematodal activity of Schiff bases was studied using *Caenorhabditis Elegans*. The *Caenorhabditis Elegans* (strain N2) and *E. Coli* (strain OP 50) were received from Caenorhabditis Genetics Center, University of Minnesota, USA. A series of synthetic Schiff bases **1-15** were tested for antinematodal activity. The *Caenorhabditis Elegans* strains N2 were maintained on NGM (3g NaCl, 2.5g peptone, 17g agar and 975 mL distilled water). After autoclaving, 1 mL cholesterol in ethanol (5 mg/mL), 1 mL M CaCl₂, 1 mL MgSO₄ and 25 mL 1M potassium Phosphate buffer plate with *E. Coli* (OP-50) as food source (stiernagle,2006) [34]. The assay was conducted in sterile 96 well plate (polystyrene, flat bottom well, coring, New York, NY, USA). Between 15 to 50 nematodes of different developmental stage (i.e. larvae-adult males and hermaphrodites) were placed in 200 μl of S medium (Seung-Hawn Jang *et al.* 2004) [35] in microtiter wells

containing 10 μ l of 5X concentrated overnight culture of *E.Coli*. Maintained at lauribroth (Berman *et al.* 1982) [36] and resuspended in S medium and test compound. Each compound was dissolved in DMSO and added to well with final concentration of 100 μ M.

The final concentration of DMSO was 1 % in the well. Control had only the equivalent volumes of DMSO alone. The animals were incubated in the laboratory at 20°C. LC50 (lethal concentration causing 50 % mortality) were evaluated after 24 and 48 hours of incubation by counting the percentage of motile and added worm under inverted microscope. All experiments were conducted in triplicate and mean percentage mortality was calculated. All compounds were tested on 100 μ M concentration. Those compounds which have shown activity were tested further for lower concentration. The test performed in triplicate and identical results obtained for each well of same concentration.

RESULTS AND DISCUSSION

Chemistry: The characterization data of the synthesized Schiff bases are listed in table 1. The structures of the prepared Schiff Bases were established and confirmed from the corresponding IR, ¹H-NMR, ¹³C-NMR and mass spectroscopy data. (cf Tables 2-5). All compounds showed in the IR spectra a strong absorption band at 1592-1637 cm^{-1} , typical of the stretching vibrations of the C=N functionality, as well as the bands corresponding to C-H stretching vibrations. The multiple signals observed in ¹H-NMR at δ 6.90 to 8.08 ppm regions are due to aromatic protons and a singlet at 8.43-9.75 ppm from the C-H protons of the CH=N groups. In ¹H-NMR the spectra of compounds **4**, **5**, **10**, **11** and **12**, signals between δ 3.50 and 4.0 ppm were attributed to -OCH₃ groups. The signals at δ 2.36 and 2.33 ppm which appeared as singlets in compounds **13** and **14** were assigned to CH₃ groups.

Table 1: Characterization data of Schiff Bases 1-15

Compd	Color	Molecular ^a formula (Mol. Mass)	Mp(°C) ^b (solvent of recryst.)	Yield (%)
1	Pale yellow	C ₁₃ H ₁₀ CIN[37] (215.05)	72-4 (L.P) ^c	82
2	Yellow	C ₁₃ H ₆ CIN ₂ O ₂ [38] (260.04)	140-42 (L.P)	74
3	Brown	C ₁₁ H ₆ NO [39] (171.07)	106 d (B)	79
4	Pale orange	C ₁₄ H ₁₂ N ₂ OH (272.08)	148-50 (L.P)	64
5	Pale yellow	C ₁₄ H ₁₃ NO ₂ (227.09)	155-57 (L.P)	72
6	Orange	C ₁₅ H ₁₂ N ₂ O ₂ (252.09)	133d (MeOH)	65
7	Pale brown	C ₁₅ H ₁₃ N (207.10)	100-02 (MeOH)	66
8	Orange	C ₁₃ H ₁₀ N ₂ O ₃ (242.07)	162-64 (L.P)	59
9	Pale brown	C ₁₇ H ₁₂ CIN (265.07)	107-09 (MeOH)	78
10	Brown	C ₁₈ H ₁₃ NO ₂ (277.11)	114-16 (B)	76
11	Pale Brown	C ₁₅ H ₁₃ NO ₃ (257.11)	257-59 (MeOH)	70
12	Greenish White	C ₁₄ H ₁₃ NO ₂ (227.09)	85-87 (MeOH)	67
13	White	C ₁₄ H ₁₂ CIN(229.07)	127-29 (MeOH)	79
14	White	C ₁₄ H ₁₃ NO (211.10)	96-98 (MeOH)	67
15	Pale Yellow	C ₁₁ H ₆ N ₂ O ₂ S [40] (232.03)	135-37 (MeOH)	55

a known products are given with references, the others are new.b mp's were measured using Stuart (UK) electric melting point apparatus.

c L.P = Light Petrol 60-80°C, B = Benzene, EtOH = Ethanol, MeOH = Methanol.

Table 2: IR (cm^{-1}) spectra of Schiff bases 4-14.

Compd	IR (cm^{-1})
4	1628(N=C), 1325(C-H) 3354-3480(OH) 1544, 1342 (S.NO ₂)
5	1621 (N=C), 1388(C-H) 3088 broad(OH)
6	1592(N=C), 1300(C-H) 1512, 1335(NO ₂)
7	1623(N=C), 1375(C-H)
8	1632(N=C), 1338(C-H) 1562, 1347 (NO ₂), 3150 (OH)
9	1637(N=C), 1391(C-H)
10	1621(N=C), 1381(C-H), 3048(OH)
11	1621(N=C), 2954, 1378(C-H), 3000(Broad, OH), 2954, 2982(CH ₃)
12	1637(N=C), 2964, 1362(C-H), 3610(OH), 2964, 2996 (CH ₃)
13	1622(N=C), 2929,1354(C-H), 2854, 2925(CH ₃)
14	1615(N=C), 2920, 1366(C-H), 3100(OH) 2920(CH ₃)

Table 3: ¹H-NMR of Schiff bases 4-14 (DMSO-d₆) (δ, ppm).

Compd.	¹ H-NMR
4	9.45 (s, 1H, -OH, exchangeable), 8.36 (s, 1H, benzylideneimine H), 8.08-6.90 (m, 7H, Ar-H), 3.80 (s, 3H, -OCH ₃).
5	9.75 (s, 1H, -OH, exchangeable), 8.43 (s, 1H, -CH=N), 7.52-6.88 (m, 8H, Ar-H), 3.84 (s, 3H, -OCH ₃).
6	8.10 (m, 1H, -CH=N), 7.60-6.95 (m, 11H, Ar-H and olefinic H).
7	8.25 (d, 1H, benzylideneimine H, J = 5.36 Hz), 7.54-7.07 (m, 12H, Ar-H and olefinic H).
8	12.27 (s, 1H, OH, exchangeable), 8.99 (s, 1H, -CH=N), 8.32-6.98 (m, 7H, Ar-H).
9	8.73 (s, 1H, benzylideneimine H), 8.09-7.23 (m, 11H, Ar-H).
10	9.76 (s, 1H, OH, exchangeable), 8.53 (s, 1H, benzylideneimine H), 8.29-6.92 (m, 10H, Ar-H), 3.89 (s, 3H, -OCH ₃).
11	9.60 (s, 1H, OH, exchangeable), 8.44 (s, 1H, -CH=N), 7.49-6.86 (m, 7H, Ar-H), 3.83 and 3.76 (2s, 6H, 2 -OCH ₃).
12	13.38 (s, 1H, OH, exchangeable), 8.59 (s, 1H, benzylideneimine H), 7.36-6.89 (m, 7H, Ar-H), 3.82 (s, 3H, -OCH ₃).
13	8.41 (s, 1H, -CH=N), 7.83-7.11 (m, 8H, Ar-H), 2.36 (s, 3H, -CH ₃).
14	13.19 (s, 1H, OH, exchangeable), 8.94 (s, 1H, -CH=N), 7.63-6.93 (m, 7H, Ar-H), 2.33 (s, 3H, -CH ₃).

Table 4: Mass spectrometry of Schiff bases 4-14.

Compd.	m/z (% Relative abundance)
4	272 (M ⁺ , 4.25), 227 (2.34), 139 (4.85), 138 (70.25), 107 (76.60), 92 (48.80), 91 (6.91), 65 (100.00).
5	227 (M ⁺ , 98.26), 211 (21.66), 166 (14.45), 154 (7.12), 139 (5.12), 104 (22.42), 77 (100.00).
6	252 (M ⁺ , 27.28), 251 (M-1) ⁺ , 83.41), 205 (56.73), 178 (4.88), 149 (4.88), 138 (54.55), 115 (70.16), 92 (48.50), 91 (47.95), 65 (100.00).
7	207 (M ⁺ , 33.52), 206 (M-1) ⁺ , 100.00), 178 (3.25), 128 (13.57), 115 (18.72), 77 (90.33).
8	242 (M ⁺ , 96.65), 212 (13.38), 195 (37.11), 167 (29.72), 151 (5.91), 120 (44.48), 76 (100.00).
9	267 (M+2) ⁺ , 20.42), 266 (M+1) ⁺ , 20.79), 265 (M ⁺ , 60.68), 230 (2.89), 202 (3.48), 154 (23.00), 127 (100.00), 77 (29.47), 51 (9.14).
10	277 (M ⁺ , 100.00), 261 (7.13), 216 (6.07), 204 (5.90), 178 (3.99), 154 (19.97), 127 (80.53), 101 (11.97), 85 (44.01), 83 (69.57), 77 (27.60).
11	257 (M ⁺ , 100.00), 242 (85.72), 227 (3.73), 198 (5.24), 170 (15.75), 154 (7.33), 134 (6.16), 115 (7.02), 77 (4.02), 64 (19.33).
12	228 (M+1) ⁺ , 16.62), 227 (M ⁺ , 100.00), 212 (71.79), 183 (4.33), 154 (3.40), 128 (5.33), 105 (3.08), 77 (55.04), 65 (38.15).
13	231 (M+2) ⁺ , 30.49), 230 (M+1) ⁺ , 33.41), 229 (M ⁺ , 90.60), 193 (2.89), 165 (4.57), 150 (2.05), 118 (22.99), 91 (100.00), 77 (9.79), 65 (61.60).
14	211 (M ⁺ , 100.00), 210 (M-1) ⁺ , 76.87), 167 (6.29), 120 (12.86), 118 (8.68), 91 (80.65), 65 (74.49).

Table 5: ¹³C-NMR (DMSO-d₆) (δ, ppm) of Schiff Bases 4-14.

Compd	¹³ C-NMR
4	160.0, 154.2, 152.4, 147.3, 146.3, 131.0, 125.5, 125.2, 123.2, 115.9, 112.3, 56.1.
5	160.2, 152.4, 152.0, 147.3, 131.1, 129.9, 127.2, 125.5, 122.3, 115.9, 112.3, 56.1.
6	163.7, 158.6, 146.4, 135.2, 133.3, 128.5, 128.5, 127.9, 125.2, 123.2, 119.8.
7	163.7, 152.4, 135.2, 133.3, 130.0, 128.6, 128.5, 127.9, 127.2, 122.3, 119.9.
8	161.1, 160.0, 154.2, 146.4, 132.4, 132.1, 125.2, 123.2, 121.4, 120.5, 117.8.
9	160.0, 151.9, 136.6, 135.0, 134.5, 130.5, 128.9, 128.6, 128.3, 127.8, 126.8, 126.3, 115.2.
10	160.0, 152.2, 151.9, 147.9, 147.3, 135.0, 131.1, 128.5, 128.3, 127.8, 126.7, 126.3, 125.5, 115.9, 115.1, 112.3, 56.1.
11	159.9, 159.1, 152.4, 147.3, 144.3, 131.1, 125.5, 115.9, 115.6, 122.1, 112.3, 56.1, 55.8.
12	161.1, 160.1, 159.1, 144.3, 132.4, 132.1, 122.1, 121.4, 120.4, 117.8, 115.5, 55.8.
13	160.1, 149.1, 136.9, 136.5, 134.5, 130.6, 130.3, 128.9, 122.2, 21.3.
14	161.1, 159.9, 149.1, 136.8, 132.4, 132.1, 130.3, 122.2, 121.4, 120.5, 117.7, 21.3.

Table 6:

Compound No.	LC50 (μM)	Compound No.	LC50 (μM)
1	100	9	8
2	>100	10	50
3	95	11	>100
4	>100	12	85
5	>100	13	55
6	45	14	90
7	40	15	>100
8	>100		

In the DEPT spectra of compounds **1-15**, there are no peaks at 189.0-196.0 ppm due to CHO group and the observed peaks were shifted to ~160.0-163.0 ppm which were attributable to HC=N group.

Nematicidal Activity: Among the Schiff bases tested, compounds **1, 3, 6, 7, 9, 10, 12, 13, 14** showed LC50 in the range of 8-100 μM against *Caenorhabditis elegans*.

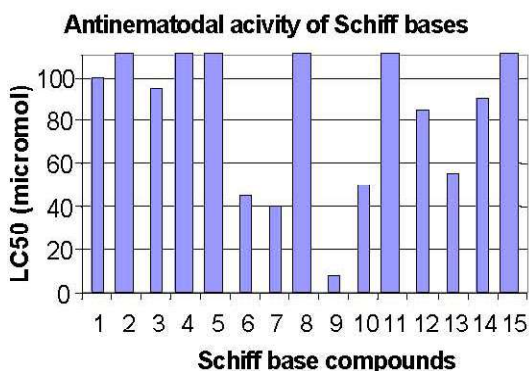


Fig. 1:

The compounds **2, 4, 5, 8, 11, 15** showed $LC_{50} > 100 \mu M$. Schiff base **9** was the most potent with $LC_{50} 8.0 \mu M$ (Table 6 and Figure 1). SAR analysis indicated influence of biphenyl group present in compound **9** on antinematodal activity.

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