

STRUCTURE ACTIVITY RELATIONSHIP: ANTIOXIDANT POTENTIAL OF SOME NOVEL SCHIFF BASES CONTAINING BENZOPHENONE MOIETYGHULAM FAREED^{1,2*}, MUHAMMAD ALI VERSIANI², NIGHAT AFZA¹, NAZIA FAREED², LUBNA IQBAL¹, AND MEHREEN LATEEF¹¹Pharmaceutical Research Center, PCSIR Laboratories Complex Karachi, Karachi-75280, Pakistan, ²Department of Chemistry, Federal Urdu University of Arts, Science and Technology, Gulshan-e-Iqbal, Karachi-75300. Sindh, Pakistan. Email: fareedchm@yahoo.com

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ABSTRACT

An efficient and facile condensation of 2-aminobenzophenone with different carbonyls yields novel Schiff bases (**1-11**) in the presence of dodecatungstosilicic acid / P₂O₅ in solvent free conditions. The products were obtained in high yield on grinding the reaction mixture for 1-3 minutes. The structures of the products were characterized using spectroscopic techniques and elemental analysis. DPPH radical scavenging activity of all the compounds was carried out using BHA as a standard. Compound (**3**) showed 51% antioxidant potential while all other compounds were found to have moderate to mild antioxidant activity ranging from 20-48%.

Keywords: Antioxidant activity, Schiff bases, Dodecatungstosilicic acid, P₂O₅, DPPH

INTRODUCTION

Bimolecular condensation of primary amine with a carbonyl group yields a versatile class in the organic synthesis, which is known as Schiff Base or Imines. It has numerous appliances in the field of biological, inorganic and analytical chemistry [1-5]. Organic reagents play vital role in modern analytical devices in order to enhance the selectivity and sensitivity of optical and electrochemical sensors as well as in many chromatographic methods[6-8]. Schiff bases have excellent features and structural similarities among these reagents. The facile method of preparation and synthetic simplicity of imines enables to design suitable structural properties[9-10]. In coordination chemistry, azomethine moiety form complexes with a variety of metals[11-12]. Imines have broad applications as organic intermediates for the preparation of pharmaceutical, or rubber additives[13] and protecting agent for amino group in organic synthesis[14]. They have also used as liquid crystals[15] and in polymer chemistry[16]. Schiff bases have broad applications in biological field including antitumor[17], antioxidant[18], antifungal [19], antibacterial[20-24], herbicidal[25], antiproliferative[26], anticonvulsant[27], antimalarial[28], and anticancer activity [29].

In view of the wide applications of imines, we also wish to report herein the synthesis, characterization, scavenging activity of novel Schiff bases (**1-11**), which were synthesized using 2-aminobenzophenone with a variety of carbonyls in the presence of dodecatungstosilicic acid / P₂O₅ as a catalyst under solvent free conditions [30-31] (**Scheme 1 & Table 1**). The structures of the synthesized compounds were elucidated using spectroscopic data and elemental analysis.

MATERIALS AND METHODS

The melting points were taken in capillary using Gallenkamp MF-370 melting point apparatus and are uncorrected. ¹H-NMR was recorded on Bruker AV-300 operating at 300 MHz using dimethyl sulfoxide (DMSO) with trimethyl silane (TMS) as an internal standard. IR spectra were recorded on Nicolet Avatar 300 DTGS. EIMS spectra were recorded on Finnigan MAT-311. Elemental analysis was performed on a Carlo Erba Strumentazione- Mod-1106, Italy. The purity of compounds was determined by using thin layer chromatography (TLC) which were pre-coated silica gel glass plates (Kieselgel 60, 254, E. Merck, Germany) and were visualized by UV at 254 and 365 nm or by iodine vapors.

General Method for the Synthesis of Schiff bases 1-11

A mixture of 2-aminobenzophenone (1mmol), aromatic substituted carbonyls (1mmol) and dodecatungstosilicic acid / P₂O₅ (0.2g, 1mole% of P₂O₅ / 2-aminobenzophenone) was grinded in mortar with a pestle in solvent free conditions at room temperature for 1-3 minutes (**Scheme 1**). The reaction mixture turned pasty at the completion of the reaction. Precipitates of the Schiff bases formed upon addition of ice cooled distilled water, filtered and repeatedly washed with ice cooled water. The target molecules were obtained in excellent yields.

(2-((4-hydroxyphenyl)methylidene)amino)phenyl(phenyl)methanone (1)

Yield: 75%; m. p. 265-267 °C; Anal. Calcd. for C₂₀H₁₅NO₂: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.70; H, 4.99; N, 4.63; IR (KBr, cm⁻¹): 3400 (-OH), 2962 (C-H), 1705 (C=O), 1672 (C=N), 1596 (C=C); ¹H-NMR (300MHz, DMSO-d₆, δ / ppm): 8.70 (s, 1H, N=CH); EI-MS (m/z): 301.

(2-((3-hydroxyphenyl)methylidene)amino)phenyl(phenyl)methanone (2)

Yield: 82%; m. p. 255-257 °C; Anal. Calcd. For C₂₄H₂₂N₂O: C₂₀H₁₅NO₂: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.71; H, 5.01; N, 4.64; IR (KBr, cm⁻¹): 3400 (-OH), 2965 (C-H), 1706 (C=O), 1674 (C=N), 1595 (C=C); ¹H-NMR (300MHz, DMSO-d₆, δ / ppm): 8.71 (s, 1H, N=CH); EI-MS (m/z): 301.

(2-((phenyl)methylidene)amino)phenyl(phenyl)methanone (3)

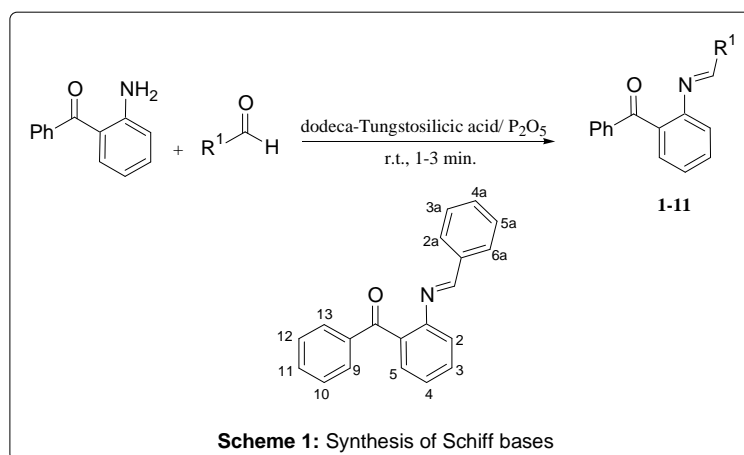
Yield: 93%; m. p. 220-222 °C; Anal. Calcd. For C₂₀H₁₅NO: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.17; H, 5.28; N, 4.90; IR (KBr, cm⁻¹): 2966 (C-H), 1709 (C=O), 1678 (C=N), 1598 (C=C); ¹H-NMR (300MHz, DMSO-d₆, δ / ppm): 8.69 (s, 1H, N=CH); EI-MS (m/z): 285.

(2-((furan-2-ylmethylene)amino)phenyl(phenyl)methanone (4)

Yield: 84%; m. p. 198-200 °C; Anal. Calcd. for C₁₈H₁₃NO₂: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.52; H, 4.74; N, 5.09; IR (KBr, cm⁻¹): 2966 (C-H), 1704 (C=O), 1675 (C=N), 1598 (C=C); ¹H-NMR (300MHz, DMSO-d₆, δ / ppm): 8.64 (s, 1H, N=CH); EI-MS (m/z): 275.

(2-((3-chlorophenyl)methylidene)amino)phenyl(phenyl)methanone (5)

Yield: 87%; m. p. 267-269 °C; Anal. Calcd. for C₂₀H₁₄ClNO: C, 75.12; H, 4.41; N, 4.38. Found: C, 75.14; H, 4.40; N, 4.36; IR (KBr, cm⁻¹): 2966 (C-H), 1704 (C=O), 1671 (C=N), 1592 (C=C); ¹H-NMR (300MHz, DMSO-d₆, δ / ppm): 8.66 (s, 1H, N=CH); EI-MS (m/z): 319.5.

**Table 1: Synthesis and antioxidant activity of Schiff bases 1-11**

S. No.	R ¹	R.T (min.)	Antioxidant Activity (%)	S. No.	R ¹	R.T (min.)	Antioxidant Activity (%)
1		1	29	7		3	21
2		1	30	8		3	20
3		1	51	9		1	48
4		2	30	10		2	31
5		2	40	11		3	20
6		2	20	-	-	-	-

(2-[[4-nitrophenyl)methylidene]amino]phenyl)(phenyl) methanone (6)

Yield: 90%; m. p. 233-235 °C; Anal. Calcd. For C₂₀H₂₁₄N₂O₃: C, 72.72; H, 4.72; N, 8.48. Found: C, 72.71; H, 4.70; N, 8.46; IR (KBr, cm⁻¹): 2964 (C-H), 1705 (C=O), 1675 (C=N), 1595 (C=C); ¹H-NMR (300MHz, DMSO-d₆, δ / ppm): 8.70 (s, 1H, N=CH), EI-MS (m/z): 330.

(2-[[3-nitrophenyl)methylidene]amino]phenyl)(phenyl) methanone (7)

Yield: 85%; m. p. 187-189 °C; Anal. Calcd. for C₂₀H₂₁₄N₂O₃: C, 72.72; H, 4.72; N, 8.48. Found: C, 72.70; H, 4.71; N, 8.47; IR (KBr, cm⁻¹): 2964 (C-H), 1701 (C=O), 1677 (C=N), 1598 (C=C); ¹H-NMR (300MHz, DMSO-d₆, δ / ppm): 8.69 (s, 1H, N=CH), EI-MS (m/z): 330.

(2-[[[2-nitrophenyl)methylidene]amino]phenyl](phenyl)methanone (8)

Yield: 65%; m. p. 210-212 °C; Anal. Calcd. for C₂₀H₂₁N₂O₃: C, 72.72; H, 4.72; N, 8.48. Found: C, 72.70; H, 4.71; N, 8.47; IR (KBr, cm⁻¹): 2964 (C-H), 1702 (C=O), 1678 (C=N), 1596 (C=C); ¹H-NMR (300MHz, DMSO-d₆, δ / ppm): 8.67 (s, 1H, N=CH), EI-MS (m/z): 330.

(2-[[[4-chlorophenyl)methylidene]amino]phenyl](phenyl)methanone (9)

Yield: 82%; m. p. 277-279 °C; Anal. Calcd. for C₂₀H₁₄ClNO: C, 75.12; H, 4.41; N, 4.38. Found: C, 75.12; H, 4.41; N, 4.37; IR (KBr, cm⁻¹): 2966 (C-H), 1704 (C=O), 1671 (C=N), 1592 (C=C); ¹H-NMR (300MHz, DMSO-d₆, δ / ppm): 8.66 (s, 1H, N=CH), EI-MS (m/z): 319.5.

(2-[[[4-hydroxy-3-methoxyphenyl)methylidene]amino]phenyl](phenyl)methanone (10)

Yield: 89%; m. p. 278-280 °C; Anal. Calcd. for C₂₁H₁₇NO₃: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.10; H, 5.15; N, 4.21; IR (KBr, cm⁻¹): 3402 (-OH), 2966 (C-H), 1704 (C=O), 1675 (C=N), 1598 (C=C); ¹H-NMR (300MHz, DMSO-d₆, δ / ppm): 8.71 (s, 1H, N=CH), EI-MS (m/z): 331.

(2-[[[1-(2-hydroxyphenyl)ethylidene]amino]phenyl](phenyl)methanone (11)

Yield: 89%; m. p. 289-291 °C; Anal. Calcd. for C₂₁H₁₇NO₂: C, 79.98; H, 5.43; N, 4.44. Found: 79.97; H, 5.40; N, 4.43; IR (KBr, cm⁻¹): 3402 (-OH), 2966 (C-H), 1704 (C=O), 1675 (C=N), 1598 (C=C); ¹H-NMR (300MHz, DMSO-d₆, δ / ppm): 2.31 (s, 3H, CH₃), EI-MS (m/z): 315.

DPPH Radical Scavenging Activity

The antioxidant activity was assessed by measurement of scavenging ability of the isolated compounds on free radical 2, 2'-diphenyl-1-picrylhydrazyl i.e. DPPH. 90 μl of 0.3 mM DPPH solution (in ethanol) was added to 10 μl of each of the concentration of fraction, the mixture was incubated for 30 minutes at 37°C, then absorbance was measured at 517 by microtitre plate reader (Spectra max plus 384 Molecular devices USA). BHA was used as positive control. The results are depicted in (Table 1).

$$\% \text{ DPPH scavenging effect} = \frac{Ac-As}{Ac} \times 100$$

Where;

Ac = Absorbance of control (DMSO treated); As = Absorbance of Sample

RESULTS AND DISCUSSION**Chemistry**

Benzophenone moiety containing novel Schiff bases (1-11) were synthesized using bimolecular condensation reaction of 1-amino benzophenone with a variety of aromatic carbonyls in the presence of dodeca-tungstosilicic acid / P₂O₅ under solvent free conditions (Table 1). The completion of the reaction was monitored by thin layer chromatography (TLC). The synthesized products were characterized by using different spectroscopic techniques and elemental analysis.

¹H-NMR

The synthesized compounds were subjected to ¹H-NMR technique in DMSO. ¹H-NMR of all the compounds are very simple and -N=CH-Ar of all the synthesized Schiff bases appears in the region of 8.6-8.7 ppm. The free NH₂ group appears as a singlet in the region of 4-6 ppm. The absence of this signal confirmed the formation of schiff bases. In case of phenolic protons which shows hydrogen bonding with the nitrogen of Schiff bases are resonate as sharp peak. The aromatic protons appears as a multiplet in the region of 6.74-7.90 ppm depending on the aromatic substituent.

Infra Red

In FT-IR spectrum -N=C- appears in the region of 1670-1680 cm⁻¹ whereas, aromatic C=C vibrate at 1610-1600 cm⁻¹. Free NH₂ group vibrate at 3400 cm⁻¹ as a sharp two peaks. This signal was absent in

the observed infra red spectrum which indicated the formation of Schiff bases.

Antioxidant-Structure Activity Relationship

Free radicals play a very important role in the pathogenesis of various human diseases and aging. In food products free radicals also cause damage, resulting in diminish taste and shelf life. Antioxidants are therefore protecting against free radicals and save health. Mostly strong antioxidants activity is shown by polyphenols.

The aim of our study was to explore the most potent antioxidant and examine the factors that give a picture and establish the antioxidant activity with frequent comparison to various Schiff bases containing benzophenone moiety (Table 1). The results revealed that compound (3) showed highest % scavenging potential (51%) in all the screened compounds, whereas all the other synthesized compounds showed moderate to mild antioxidant activity ranging from 20-48%. Although we don't have exact classification with regard to higher or lower antioxidant activity. It is also thought that the large conjugated system and low steric hindrance in the frame work of Schiff base benefit the Schiff base to trap radicals. Compound (3) which is less sterically hindered as compared to the all screened compounds showed 51% antioxidant activity due to its low steric hindrance, while halogen (Cl) containing Schiff bases (5 and 9) showed moderate % scavenging activity i.e., 40% and 48 % respectively. The reason for their behavior may be explained in such a way that, generally electron donating group has a good ability to catch free radicals by themselves. Due to extra stabilization radical obtained compound having chlorine would have higher aptitude to trap free radical in a faster rate than the other similar compound. All the other compounds showed mild antioxidant activity.

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