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Green Synthesis of New Amino Acid Schiff Bases and Their Biological Activities

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Abstract: In this study, four new and two known amino acid Schiff base compounds derived from the condensation reaction of benzaldehyde, salicylaldehyde, pyrrole-2-carbaldehyde, pyridine-2-carbaldehyde, fluorene-2-carbaldehyde and terephthalaldehyde with 2-phenylglycine methyl ester hydrochloride have been synthesized by both conventional method and microwave irradiation protocol. The new compounds were characterized by FTIR, ^{1}H-NMR, LC-MS and electronic spectral studies. A comparative study between conventional heating and microwave irradiation has also been reported. Based on these results, with the microwave synthesis, the yield of the products was increased from 37% up to 96% as compared to conventional method. By microwave, reactions were completed within 5.5-8.5 minutes and the products were obtained in good to high yields, with reduced time, waste, and formation byproduct. DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging effect were performed to determine antioxidant activities of the new compounds. All of the compounds exhibited significant activities in DPPH radical scavenging.

Keywords: Antioxidant activity, green synthesis, microwave, Schiff bases.

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INTRODUCTION

Amino acids are an important class of organic chemistry which can improve pharmacological and biological properties of molecules as enhancing the lipophilicity, easing toxicity, and increasing bioavailability when these compounds are esterified and introduced to the molecular structure. Additionally, amino acids and combining molecules with them play an important role in elucidating the mechanism of transamination reaction in biological systems [1-3].

In response to the increasing industrial and biological importance of amino acid Schiff bases, many researches are directed toward the development of different methods for their preparation [4-10]. Also, the microwave synthesis of amino acid Schiff bases is of great importance in this area [11, 12].

As a green chemistry approach, microwave-assisted synthesis has been highly intriguing since last few decades by the chemists. Microwave irradiation methods used for carrying out chemical transformations are pollution free, eco-friendly, low cost, and offer high yields together with simplicity in processing and handling. The important area of green chemistry is to use non-conventional approaches of synthesis because of less or no solvent requirements, easy isolation, eco-friendly nature, less reaction time with good yield and purity of target molecules [13-15].

In this work, the synthesis of the four new and two known amino acid Schiff bases by conventional and microwave methods was aimed for the first time. Additionally, the antioxidant activities as DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging effect of synthesized compounds were aimed to investigate in this study.

MATERIALS AND METHODS

All reactions in the conventional method were carried out under the inert atmosphere of nitrogen. The solvents were purified and dried according to the standard procedures. All reagents were obtained commercially and used without further purification. The aromatic aldehydes (benzaldehyde, salicylaldehyde, pyrrole-2-carbaldehyde, pyridine-2-carbaldehyde,

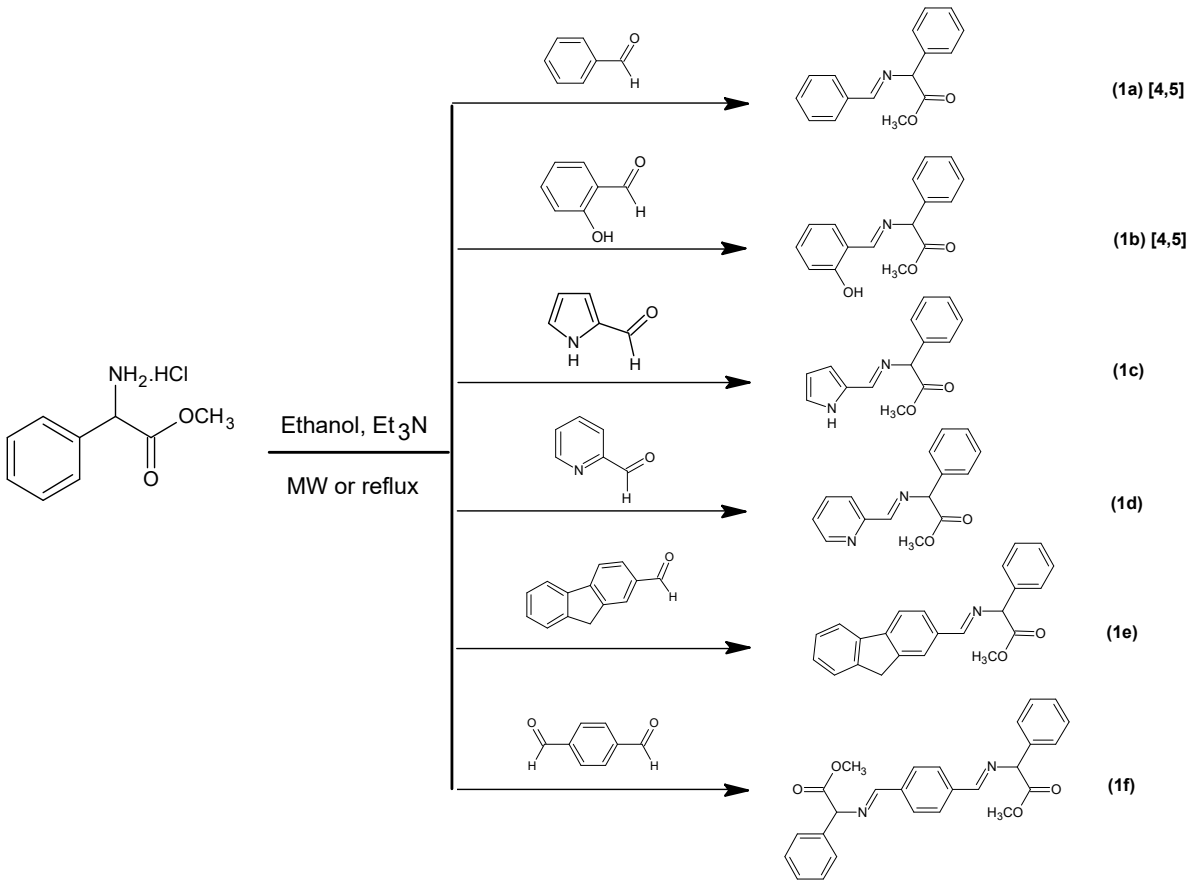
fluorene-2-carbaldehyde) were purchased from Merck Chemicals. 2-Phenylglycine methyl ester hydrochloride was provided from Aldrich, Sigma Chem.

UV-Vis spectra were recorded with a PU 8740 spectrophotometer in $CHCl_3$. The FT-IR spectra were measured on a Perkin Elmer, Spectrum One Bv 5.0 spectrometer. ^1H NMR spectra were recorded on an Agilent-NMR-vnmrs400 MHz and Varian UNITY INOVA 500 MHz spectrometers, using $CDCl_3$ as solvent and TMS as an internal standard. Mass spectra (LC-MS) were determined on an Agilent 1200 Infinity HPLC and Agilent 6460 Jet-Stream TripleQuad spectrometer (350 ^oC and 11 L/min). Column chromatography was conducted on silica gel 60. TLC was carried out on aluminum sheets precoated with silica gel 60_{F254} (Merck). Melting points were obtained with Gallenkamp Melting Point Apparatus (350 ^oC) in open capillaries with no correction.

Microwave irradiation experiments using simultaneous IR/FO temperature monitoring were performed using a Monowave 300 single-mode microwave reactor from Anton Paar GmbH (Graz, Austria). The instrument uses a maximum of 850 W magnetron output power and can be operated at 300 °C reaction temperature and 30 bar pressure.

Synthesis

The Schiff base derivatives (**1a-f)** were synthesized by the reaction of appropriate starting materials with two different methods (Scheme 1).



Scheme 1. Synthetic process of compounds (**1a-f**).

Method 1: *Conventional Method for the Synthesis of Methyl 2-[substituted methyleneamino]-2-phenylacetate (**1a-f**)*

The Schiff bases (**1a-f**) were synthesized by the condensation of appropriate aromatic aldehydes (1 mmol) and 2-phenylglycine methyl ester hydrochloride (1 mmol, in case of **1f** 2 mmol, after stirring for half an hour with Et_3N) dissolved in dry ethanol (10 mL). The resulting reaction mixture was stirred and refluxed from 4-8.5h and then allowed to cool overnight. The precipitated Schiff base was filtered, washed with cold ethanol several times, and dried in air at room temperature. The solid product was then recrystallized with ethanol [4, 11, 12].

Method 2: *Microwave Method for the Synthesis of Methyl 2-[substituted methyleneamino]-2-phenylacetate (**1a-f**)*

The suitable ratio (1:1 or 1:2) of appropriate aromatic aldehydes and 2-phenylglycine methyl ester hydrochloride (after stirring for half an hour with Et_3N) were mixed thoroughly in a grinder (Figure 1).

(a) (b) (c) (d)

Figure 1. a) Reaction mixture without MW, b) 2 min, c) 6 min, d) 8 min, at 1200 rpm and 100 °C for compound **1f**.

The reaction mixture was then irradiated by the microwave reactor after adding 3-4 mL of dry ethanol at 850 watts and 100°C. The reaction was completed in a short time (5.5-8.5 min) with higher yields. After completion of reaction, the mixture was cooled and the separated solid was filtered and washed with cold ethanol. The resulting product was then recrystallized from ethanol [5, 16, 17].

Characterizations

The physical properties of Schiff base compounds are given in Table 1 (see Supplementary file).

The structures were characterized by using UV, FTIR, ^{1}H NMR, LC-MS spectral data. All data supported the structures of target molecules (Table 2; see Supplementary file).

LC-MS spectra confirmed the molecular weight of all the structures. The LC-MS spectrum for compound **1c** is given in Figure 2.

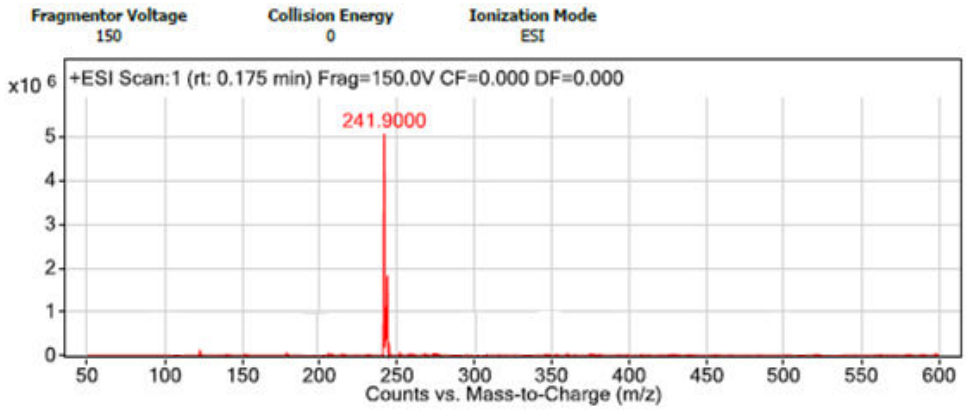


Figure 2. LC-MS spectrum for compound **1c**.

DPPH Radical Scavenging Studies

1,1-diphenyl-2-picryhyrazyl radical (DPPH•) is a stable free radical which surveys the antioxidant potential of pure compounds by an easy colorimetric method. The method is based on the guideline that accepting a hydrogen atom from the antioxidant scavenger compound DPPH• turns DPPH and the change in the color of purple to yellow is screened by spectrophotometric means at 517 nm. Higher free radical scavenging activity is designated by lower absorbance of $DPPH^{\bullet+}$ sample mixture measured at the concerned wavelength [11, 18].

According to the DPPH radical scavenging protocol, a 1-mL aliquot of the samples at determined concentration (50 µg\mL) were added to 2 mL of DPPH solution and the absorbance of DPPH reagent was determined at 517 nm after 30 min. of incubation at the dark [19].

RESULTS AND DISCUSSION

Schiff bases **1a-f** were synthesized by the condensation reaction of 2-phenylglycine methyl ester with different aromatic aldehydes under microwave assisted method as well as conventional method.

Compounds **1a-f** were completed by heating at reflux temperature in conventional method. These reactions were continued longer time than microwave method.

All reactions under microwave irradiation were performed successfully at 850 watts and 100 °C. As a result of microwave-assisted synthesis, it was observed that the reaction was completed in a short time with higher yields as compared to the conventional method.

Based on these results, with the help of microwave synthesis, the yield of product increased from 37% up to 96% as compared to conventional method. By microwave, reactions were completed within 5.5-8.5 minutes and the products were obtained in good to high yields, with reduced time, waste, and formation byproduct. The microwave assisted reactions were seen in the reaction period and yields improved significantly. The comparison study data of microwave and conventional methods are given in the Table 3 (see Supplementary file).

Synthesized compounds **1a-f** were characterized by UV, FTIR, ^{1}H NMR and LC-MS spectral data. The UV-Vis electronic spectra of the Schiff bases showed absorption bands that could be attributed to π-π^* and n-π^* electronic transitions. Maximum wavelength values of Schiff bases have been shown in Table 2 (see Supplementary file). The FTIR spectra showed that the band of C=N imine stretching vibration appeared for the Schiff bases in the range of 1608-1653 cm^{-1}. The ^{1}H-NMR spectra of **1a-f** showed the characteristic chemical shifts in $CDCl_3$. The singlet signals at 2.11-2.18 ppm were attributed to the protons of the OCH_3 moiety, the multiplet signals at 6.58 to 7.98 ppm showed aromatic protons. The most important singlet signals at 8.51-8.65 ppm were attributed to protons of the CH=N groups.

All the compounds **(1a-f)** showed good free radical scavenging activity by inhibiting DPPH radical in a concentration-dependent manner. Figure 3 depicts the percentage for antioxidant activity of the synthesized compounds at the concentration of 50 µg/mL.

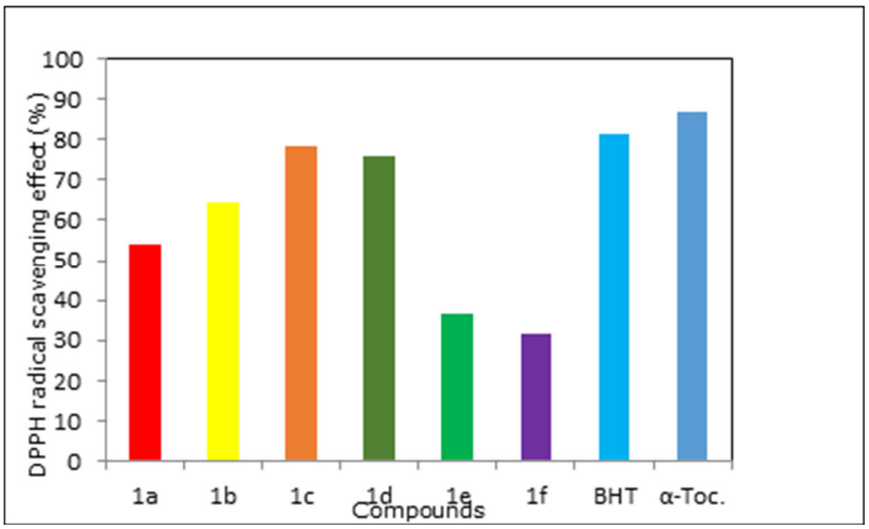


Figure 3 DPPH· scavenging effect (%) of the Schiff bases (**1a-f**).

Compound **1c,** with pyrrole ring, exhibited the best antioxidant activity of 78.27% which is similar to that of reference antioxidants, butylated hydroxytoluene (BHT) and α-tocopherol. Several positive correlations were observed among the structure and antioxidant activities.

ACKNOWLEDGEMENT

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Öz ve anahtar kelimeler

Yeni Amino Asit Schiff Bazlarının Yeşil Yöntemle Sentezi ve Biyolojik Aktiviteleri

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Öz: Bu çalışmada, dört yeni ve iki bilinen amino asit Schiff bazı bileşikleri benzaldehit, salisilaldehit, pirol-2-karbaldehit, piridin-2-karbaldehit, fluoren-2-karbaldehit ve tereftalaldehit ile 2-fenilglisin metil ester hidroklorürü arasındaki kondensasyon reaksiyonundan geleneksel ve mikrodalga yöntemleriyle sentezlenmiştir. Yeni bileşikler FTIR, ^{1}H-NMR, LC-MS ve elektronik spektral çalışmalarla karakterize edilmiştir. Geleneksel ısıtma ve mikrodalga uyarması arasında karşılaştırma yapılmış ve bildirilmiştir. Bu sonuçlara göre, mikrodalga sentezi ile ürünlerin verimi %37'den %96'ya yükselmiştir Mikrodalga ile, tepkimeler 5,5-8,5 dakika arasında tamamlanmış ve ürünler iyi ve yüksek verimlerle, azalmış durumdaki reaksiyon süresi, atık ve yan ürünler ile ele geçmiştir. DPPH (2,2-difenil-1-pikrilhidrazil) radikal süpürme etkisi de yeni bileşiklerin antioksidan aktivitesi belirlenmiştir. Bütün bileşikler etkili bir biçimde DPPH radikal süpürme özelliği göstermektedir.

Anahtar Kelimeler: Antioksidan aktivite, yeşil sentez, mikrodalga, Schiff bazları.

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