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Schiff base derivatives with morpholine and antioxidant activity

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Abstract

New Schiff base derivatives with morpholines, 4-bromo-2-(((4-morpholinophenyl)imino)methyl)phenol (**I**) and 4-bromo-2-(((2-morpholinoethyl) imino) methyl)phenol (**II**) were synthesized. The compounds **I**- **II** were characterized by spectral methods IR, and NMR spectroscopic techniques. Antioxidant activities of compounds **I** and **II** were determined by the ferric reducing ability of plasma (FRAP) assay method which is based on the reduction of Fe^{3+} -TPTZ complex to the Fe^{2+} -TPTZ complex in the presence of antioxidants and 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay methods. It was concluded that the compounds **I** and **II** had no radical scavenging activity. In the FRAP assay, higher $FeSO_4.7H_2O$ equivalent, indicating stronger antioxidant activity. Accordingly, it has been found that compound **I** has relatively high ferric reducing power ability (i.e., antioxidant activity) than compound **II**. The ability of compounds **I** and **II** to reduce iron (III) to iron (II) ions were calculated as 929 and 11 μM $FeSO_4.7H_2O$ equivalent/g sample, respectively. To summarize, the above-mentioned results indicate that compound **II** has inefficient ferric reducing activity and compound **I** has effective ferric reducing activity.

Keywords: Schiff base, morpholine, antioxidant activity, IR and NMR spectroscopy, FRAP, DPPH

1. Introduction

Antioxidants are very essential chemical substances for the human body. These substances can be produced by human body cells on their own and can be obtained through some nutrients. Antioxidants are effective protection against all diseases the use of antioxidants is intensively studied in medicinal chemistry, especially as a means for the treatment of these widespread diseases such as Parkinson, Alzheimer, heart failure and cancer, that may disturb human health.

It is also observed by experts that the antioxidant retards symptoms such as aging. Therefore, synthetic compounds are mostly studied for their antioxidant activities by using different methods [1-2]. Schiff bases which are including azomethine functional group (N=CH) possess a broad spectrum of biological activities such as antipyretic, cytotoxic, antimalarial, antipyretic, antimycobacterial, antimicrobial, anticancer, antioxidant, anti-inflammatory, antiviral, and DNA cleavage properties [3-7].

Schiff base derivatives are used in optoelectronic applications as the most important class of photochromic materials [6]. The metal complexes of Schiff bases are important compounds in inorganic chemistry for biological applications in clinical and pharmacological areas [8-10].

Morpholines have pharmacological activities such as antiemetic, antimicrobial, proteinemic, antihyperlipo, platelet aggregation inhibitory, anticancer, antiemetic, antihyperlipo, antiproliferative, and bronchodilator activity [11].

Due to their significant biological properties, Schiff base derivatives with morpholine, 4-bromo-2-(((4-morpholinophenyl)imino)methyl)phenol (**I**) and 4-bromo-2-(((2-morpholinoethyl)imino)methyl)-phenol (**II**), were synthesized and characterized by IR and NMR spectroscopic methods in this study.

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The total antioxidant capacities of **I** and **II** were analyzed by FRAP method, which is based on the reduction of Fe^{3+}-TPTZ complex to the Fe^{2+}-TPTZ complex in the presence of antioxidants and 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay methods.

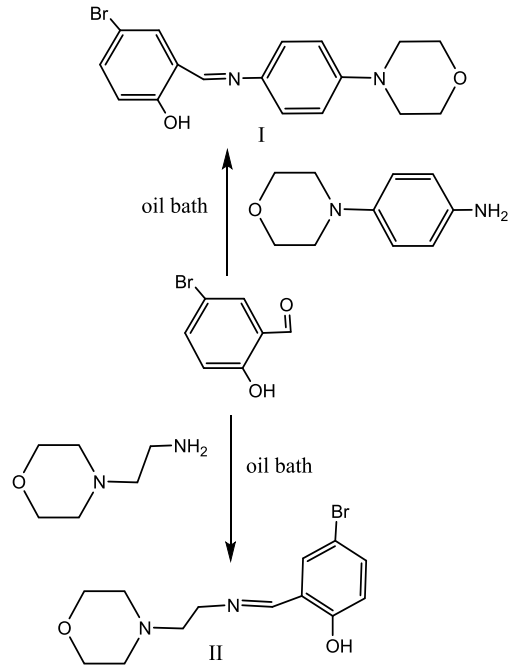
2. Experimental

2.1. Chemistry

A Varian-Mercury 400 MHz spectrometer was utilized to record the ^{1}H-NMR and ^{13}C-NMR spectra. TMS and DMSO-d_6 were utilized as an internal standard and solvent, respectively. A Perkin-Elmer FT-IR spectrometer was used to obtain IR spectra preparing KBr pellets. An electrothermal apparatus was used to determine melting points and were not verified.

2.2. Synthesis of compound II

5-bromo-2-hydroxybenzaldehyde (0.01 mol) and 2-morpholinoethan (0.01 mol) were stirred for 1 h. at 180-200 °C in the oil bath. The reaction was monitored by thin-layer chromatography (TLC). The reaction content cooled to room temperature. The obtained solid was recrystallized from a mixture of DMSO and water. The synthesis of compounds I-II is presented in Scheme 1.



Scheme 1. Synthesis pathways of compounds I-II.

4-bromo-2-(((4-morpholinophenyl)imino)methyl) -phenol (**I**) was published in literature [12].

4-bromo-2-(((2-morpholinoethyl)-imino)methyl)-phenol (**II**)**:** Yield: 83.08 %; m.p. 252-253 °C; IR (ν, cm^{-1}): 2966 (CH), 1633 (C=N), 1605 (C=C); ^{1}H-NMR (δ ppm): 2.42 (4H, t, morpholine N-CH_2), 2.60 (2H, t, N-CH_2-CH_2), 3.56 (4H, t, morpholine O-CH_2), 3.70 (2H, t, CH_2-N=CH), 6.85 (1H, d, Arom. H), 7.44-7.46 (1H, m, Arom. H), 7.65 (1H, d, Arom. H), 8.53 (1H, s, NH), 13.77 (1H, s, OH); ^{13}C-NMR (δ ppm): 52.66 (morpholine N-CH_2), 54.08 (CH_2-N=CH), 57.60 (N-CH_2-CH_2), 65.58 (morpholine O-CH_2), 108.02 (Arom. C), 118.77 (Arom. CH), 119.47 (Arom. C), 1132.83 (Arom. CH), 134.22 (Arom. CH), 160.31 (Arom. C), 164.65 (HC=N).

2.3. Determination of Antioxidant Activity

The antioxidant activities of the compounds **I** and **II** were analyzed by two commonly preferred methods (FRAP and DPPH tests), which are considered as a good indicator of the antioxidant capability of various compounds.

The radical scavenging effects of the compounds **I** and **II** against the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical were examined according to the method of Molyneux [11] with some alterations. In the presence of an antioxidant, it is based on the decolorization of the purple color of DPPH, and the change in absorbance is measured spectrophotometrically at 517 nm. A volume of 0.75 mL of 0.1 mM DPPH in methanol was mixed with an equal volume of dissolved compound solution in DMSO (at various concentrations), shaken well, kept in the dark for 50 minutes, and activity measured at 517 nm using Trolox as standard and values were revealed as SC_{50} (μg sample per mL).

The antioxidant capacities of compounds **I** and **II** were also analyzed by FRAP method, which is based on the reduction of Fe^{3+} -TPTZ complex to the Fe^{2+} -TPTZ complex in the presence of antioxidants [12]. 3 ml of freshly prepared FRAP reagent (containing TPTZ, $FeCl_3$, and acetate buffer pH: 3.6) and 100 μl of the stock solutions of compounds **I** and **II** or the blank (DMSO) were mixed in the test tube. Subsequently, absorbance values were determined at 593nm after 4 minutes of incubation at 37 °C. FRAP solution as a reagent and sample blanks were also investigated. The sum of the two measurements was subtracted to obtain the final absorbance. The last absorbance was compared with the $FeSO_4.7H_2O$ standard curve (31.25-1000 μM). The results were given as μM$FeSO_4.7H_2O$ equivalent per gram of compound. Higher $FeSO_4.7H_2O$ equivalent values

indicate higher FRAP values and this means higher antioxidant capacity.

3. Results and discussion

3.1. Chemistry

In the IR spectrum of compound **II**, while NH_2 signals belonging to starting aldehyde compound disappeared, the vibration of C=N group occurred at 1633 cm^{-1}. In the ^1H NMR spectrum of the compound **II**, proton signal belonging to N=CH was observed at 8.53 ppm as a singlet. In addition, N=CH carbon signal occurred at 164.65 ppm in the ^{13}C-NMR spectrum. Furthermore, the other NMR data also supported the structure of compound **II**.

3.2. Antioxidant Activities

In this study, FRAP and DPPH tests were implemented to calculate the antioxidant activities of compounds **I** and **II** and the results are given in Figure 1. In the DPPH test, antioxidant activities could not be determined due to the turbidity of the substances in all replicates. Therefore, it was concluded that these substances had no radical scavenging activity.

In the FRAP assay, higher $FeSO_4.7H_2O$ equivalent, indicating stronger antioxidant activity. Accordingly, it has been found that compound **I** has relatively high ferric reducing power ability (i.e., antioxidant activity) than compound **II**. The ability of compounds **I** and **II** to reduce iron (III) to iron (II) ions were calculated as 929 and 11 μM $FeSO_4.7H_2O$ equivalent/g sample, respectively. To summarize, the above-mentioned results indicate that compound **II** has inefficient ferric reducing activity and compound **I** has effective ferric reducing activity.

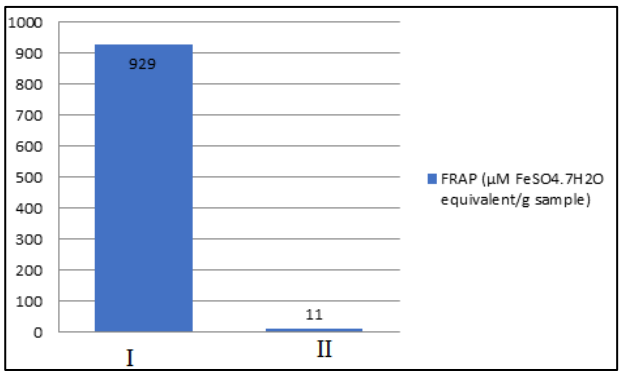


Figure 1. Ferric reducing antioxidant power (FRAP) of compounds (I-II).

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