Original Article

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Synthesis of Deferiprone as a Widely Used Iron-Chelating Drug for the Treatment of Iron-Overload Diseases

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Abstract

Thalassemia is a genetic disease that significantly affects human health. The common treatment of thalassemia is the regular injection of red blood cell, which is associated with the accumulation of iron in different tissues of the body, and makes chelation therapy necessary. Deferiprone and deferoxamine are broadly used as iron chelating agents in the vast majority of thalassemia cases. In this study, an efficient method for the synthesis of deferiprone was used by reacting maltol with methylamine in a mixture of water and ethanol as solvent. The structure of deferiprone was assigned using different spectroscopic techniques such as IR, ^{1}H-NMR, and ^{13}C-NMR. The advantages of this pathway are simple, practical, one-pot cascade, mild condition and high yield. The statistics of the Ministry of Health of Iran show the growing trend of deferiprone drug consumption in the country. Therefore, the domestic preparation of this drug can help the pharmaceutical industry in order to reduce costs and make it available for target patients.

Keywords: Synthesis, Deferiprone, Maltol, Methylamine, Iron chelating agent.

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1. Introduction

Thalassemia and sickle cell disease are the most common inherited recessive diseases that significantly affect human health and lead to blood transfusion dependency. It is estimated that approximately 100,000 children with thalassemia are born worldwide annually, and regular blood transfusion is available only for a small percentage of these patients. A large number of these children die without treatment or due to the complications of iron overload, as a results of frequent blood transfusion (1-3).

Iron is key element for physiological function and plays a crucial role in various cellular processes such as energy production, DNA synthesis, oxygen transport, and also, in numerous other important processes that rely on the iron-containing enzymes. However, since iron is highly reactive, its overload can lead to the excessive formation of reactive oxygen species (ROS), which can subsequently result in tissue damage and ultimately death if untreated (4-6).

Considering that multiple transfusions lead to increased iron accumulation and injury to various organs including the heart, liver, and spleen, and eventually leading to death, the chelation therapy is critical in thalassemia patients. Currently, deferiprone (L1), deferoxamine (DF), and deferasirox (DFRA) are common drugs that used in the iron overload conditions (Figure 1). The combination therapy, particularly the L1/DF combination, is a common treatment approach utilized in the most thalassemia patients in many countries (1).

Deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) is an orally active iron chelator

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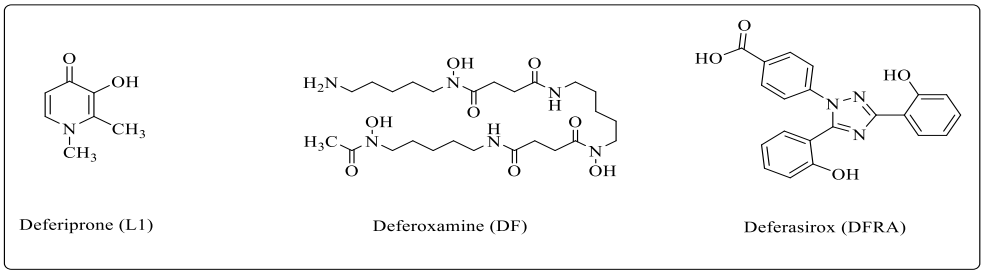


Figure 1. The chemical structures of deferiprone, deferoxamine, and deferasirox.

approved by FDA for the treatment of iron overload in patients with thalassemia and other condition. Deferiprone can cross the blood–brain barrier (BBB) and also, diffuse into almost all major organs, chelating excess iron from intracellular organelles, and transferring it to biological receptors like transferrin. Clinical trials have shown that deferiprone is safe, effective, and well-tolerated (4, 7, 8). In recent years, deferiprone consumption has become very important, which is confirmed by the statistics reported by the Ministry of Health of Iran. For example, the total production market sales value of deferiprone in 1400 was 82.59 billion Rials. In the same way, in 1401, the total production market sales value of this drug was 165.2 billion Rials for 3.8 million units. Therefore, the statistics show the growing trend of consumption of deferiprone and as a result the importance of the synthesis of this drug in the country.

In continuation of our previous works (9-11), in the present work, we synthesized deferiprone as an oral iron chelator using maltol and methylamine as starting material. This reaction was carried out with high yield in mixture of water/ethanol as solvent. Finally, IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic techniques were used to confirm the chemical structure of the synthesized deferiprone.

2. Material and methods

All the material was purchased from Merck Company and utilized without additional purification. The melting point of deferiprone was determined using an electrothermal 9200 apparatus and was uncorrected. The IR spectrum of deferiprone was recorded on Perkin Elmer instrument using a KBr disk. The NMR spectra were recorded on Bruker 300 MHz instrument in DMSO as solvent and TMS as the internal standard. The chemical shifts and coupling constants were reported in terms of parts per million (ppm, δ) and Hertz (Hz), respectively. The pattern of proton coupling was described as singlet (s), and doublet (d).

3. Results and Discussion

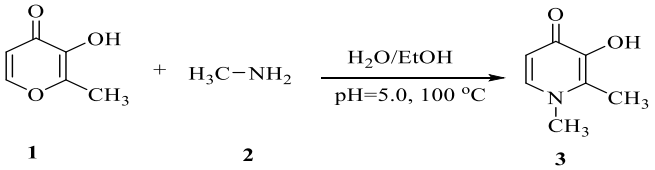
3.1. Synthesis

In a round-bottom flask, 5 mmol maltol (1) and 15 mmol methylamine (2) was dissolved in a mixture of water (20 mL) and ethanol (2 mL). Then, the pH of reaction mixture was adjusted at 5.0 using HCl (6.0 M). The reaction mixture was refluxed at 100 °C for a period of 16 h. After the completion of the reaction, the obtained precipitate was separated by filtration, dried and recrystallized from water to obtain deferiprone with 97 % yield (Scheme 1). IR, ^{1}H-NMR and ^{13}C-NMR spectra data are in good agreement with the reported data.

3.2. Characterization

The ^{1}H-NMR spectrum of deferiprone was recorded in DMSO (Figure 2), which showed two sharp singlet peaks at 2.49 and 4.00 ppm corresponding to CH_3 and N-CH_3 groups, respectively. The H_5 and H_6 protons of the pyridine-4-one ring appeared at 7.36 and 8.27 ppm as doublet peaks with J = 6.9 Hz, respectively.

^{1}H-NMR (300 MHz, DMSO-d6): 8.27 (d,



Scheme 1. Synthesis of deferiprone.

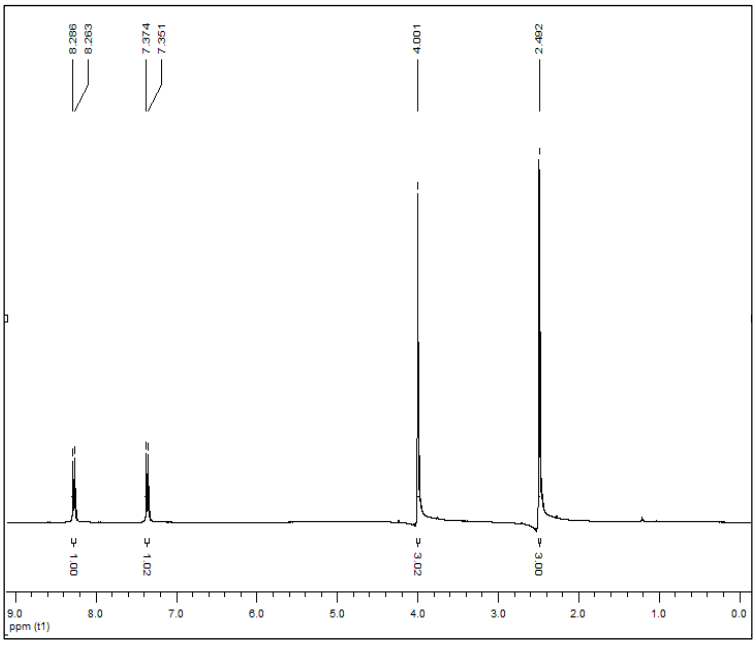


Figure 2. The ^{1}H-NMR spectrum of deferiprone in DMSO.

J = 6.9 Hz, H6), 7.36 (d, J = 6.9 Hz, H5), 4.00 (s, 3H, N-CH3), 2.49 (s, 3H, CH3).

The ^{13}C-NMR spectrum of deferiprone was also recorded in DMSO (Figure 3). The carbonyl carbon appeared as an indicator peak at 169.2 ppm. The signal at 41.4 ppm attributed to N-CH_3 group and the signals at 12.1 ppm corresponding to CH_3 group. Furthermore, the signals at 145.7, 138.4, 130.0, and 110.7 ppm assignable to another carbon in the deferiprone structure.

^{13}C-NMR (75 MHz, DMSO-d6): 169.2, 145.7, 138.4, 130.0, 110.7, 41.4, 12.1.

The IR spectrum of deferiprone was reported in Figure 4. According to Figure 4, C-H aliphatic, C=O, and OH stretching vibrations are well visible. For example, the OH stretching vibration appeared at the ~ 3148 cm-1region and C=O vibration appeared around ~ 1571 cm^{-1}.

4. Conclusion

In conclusion, we have prepared deferiprone from both commercially available maltol

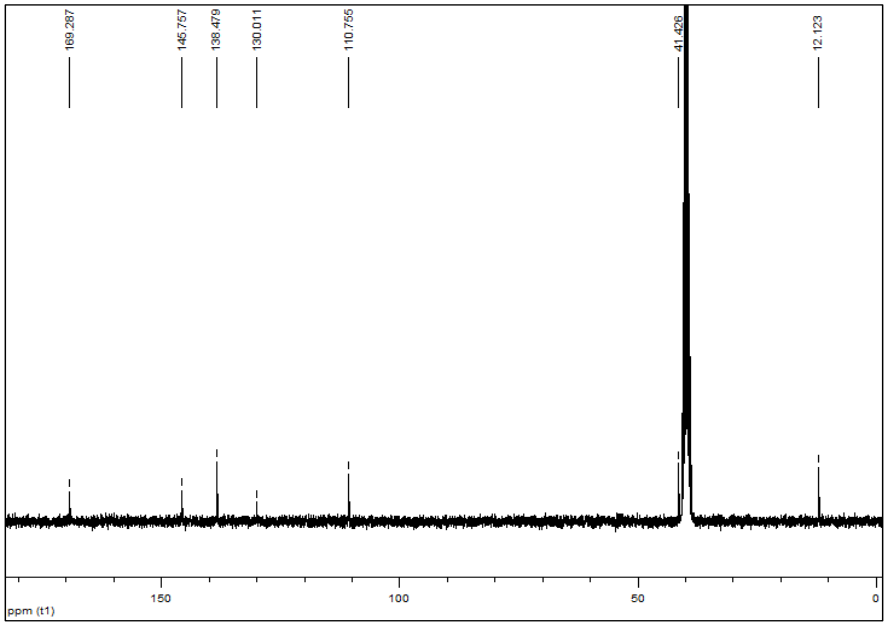


Figure 3. The ^{13}C-NMR spectrum of deferiprone in DMSO.

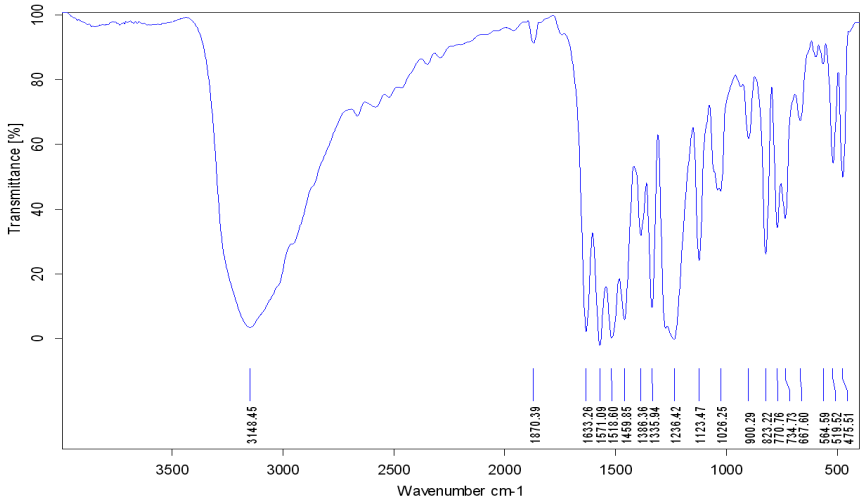


Figure 4. The IR spectrum of deferiprone.

and methylamine. The reaction of the starting materials maltol and methylamine was carried out in a mixture of water and ethanol at pH=5.0 as solvent with high yield. These specific pH conditions effectively prevent the polymerization of maltol, as a one of the starting materials. This prevention of polymerization plays a key role in enhancing the reaction yield, up to about 97 %. Finally, the spectroscopic techniques such as IR, ^{1}H-NMR, and ^{13}C-NMR were used to confirm the chemical structure of prepared deferiprone. According to the growing trend of deferpirone consumption in Iran, the synthesis of this drug is important for thalassemia patients.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

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