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Why Are Bat Molecules More Effective Than Chloroquine and Its Derivatives Against the Covid-19 Epidemic? Opinions and Comments

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Abstract

There is no doubt that the year 2020 remains an unforgettable era for all inhabitants of the earth due to the terrible Covid-19 outbreak and its consequences; this epidemic has confused scientists as they could not confront the challenge of its intelligence and decipher its code, especially within the cell which makes it a favorite space for its reproduction. In this paper, a design of drugs has been proposed to improve the therapeutic effects of antiviral drugs, such as reducing drug resistance and drug toxicity as well assolubility at room temperature. On the other hand,we have evaluated the therapeutic efficacy in the virology of the synthesized molecules, called Bat molecules, and compared it to that of chloroquine.

Keywords

Covid-19; Nanomaterials; Drug delivery; Chloroquine;Virology; Bat molecules

Introduction

Chloroquine and its derivatives were approved in the late 1940s to treat malaria. Hydroxychloroquine, a derivative of chloroquine, is often used to treat rheumatoid arthritis and lupus [1]. Some doctors recommend the use of these drugs in a hope to reduce the duration of Covid-19 in their patients [2]. New results may create the hope that the antimalarial drug can be used in the fight against coronavirus [3]. The undesirable effects of chloroquine are, however, numerous. Hence, some distrust among certain doctors and scientists is created regarding its massive delivery to the patients suffering from Covid-19 before the end of the discovery test. The main side effects include [4]:

- Digestive disorders with the following symptoms: nausea, vomiting, and diarrhea [5].
- Allergic reactions [6].
- Insomnia, depression, agitation, anxiety, aggression, sleep disorder, confusion, hallucination [2].
- Vision problems with blurred vision; also, rare cases of retinopathies linked to the molecular accumulation [3].
- Local pain, resembling burns, tingling, or electric shocks in the hands and feet [7].
- Hypoglycemia (hence, the probability of rigor in diabetic patients) [8].
- Hepatobiliary disorders: hepatitis occurring in particular in patients with late skin porphyria [9].

The data described in this paper is intended to provide a new method for the synthesis of new antiviral molecules, called Bat molecules, especially for coronavirus (COVID-19), and to compare its features to the chemical, physical and biological properties of chloroquine molecule [10]. The bat molecules could overcome drug resistance, thereby suggesting that the mechanism or phenomenon responsible for resistance is highly selective and structurally specific. The anti-coronavirus activity of the Bat molecule-resistant viral strains could only be due to a specific difference in the interaction with the resistance mechanisms of the virus as shown in (scheme 4 and 5).

Experimental Details

Materials and methods

Potassium hydroxide (KOH), sodium hydroxide (NaOH), sodium carbonate (Na_2CO_3), potassium bicarbonate ($KHCO_3$), nitric acid (HNO_3) urea, orcinol, ethylene glycol, ethanol, hydrochloric acid (HCl) and potassium carbonate (K_2CO_3) wereall purchased from Sigma Aldrich. Prior to use, the materials were dried under vacuum at 100°C for 2 minutes

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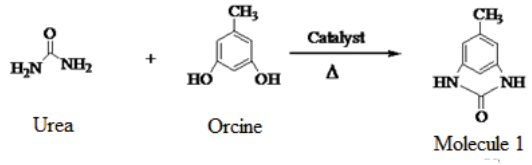


Scheme 1: Chemical structure of the novel antigen molecule (**1**) based on anti-covid-19 drugs

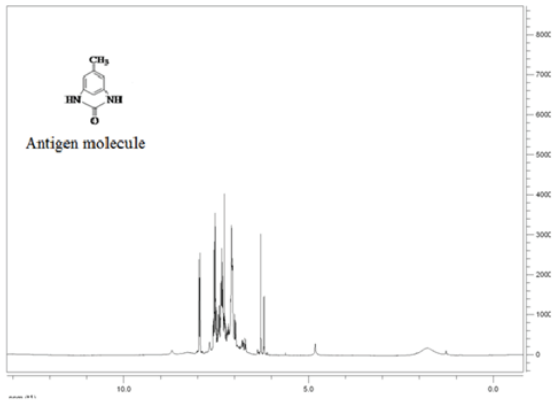


Figure 1: ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the synthesized antigen molecule **(1)**

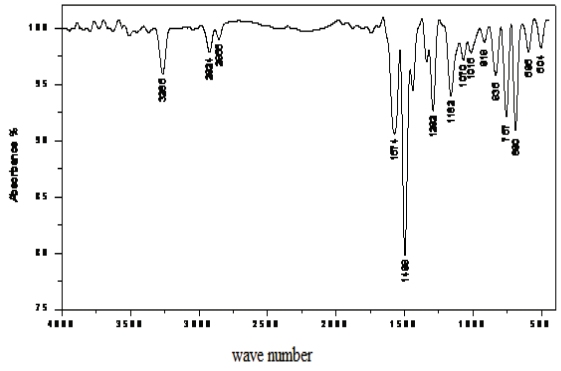


Figure 2: FTIR spectrum of the synthesized antigen molecule **(1)**

toremove residual water in the crystals [11]. The morphology and molecular structure of the samples were analyzed by using an X-ray fluorescence (XRF, Philips 1404 wavelength dispersive spectrometer) as well as a proton nuclear magnetic resonance)^{1}HNMR). ^{1}HNMR spectra were obtained by applying a 300 MHz Advance Bruker spectrometerat room temperature using tetramethylsilane (TMS) and deuterated chloroform ($CDCl_3$) as an internal standard and the deuterated solvent, respectively. In addition, a scanning electron microscope (LEO SEM 1450) was utilized to obtain SEM images. Infrared spectra (ATR absorption) were recorded on an Alpha Brucker spectrometer in the wavelength range of 4000 to 400 cm^{-1} [12].

Synthesis of molecule 1

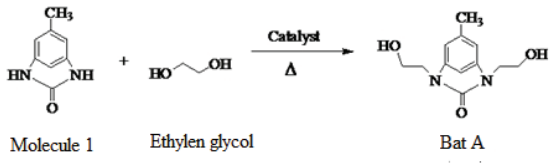
Molecule**1** was formed throughthe condensation reaction between orcinol (2 g) and urea (2 g) in ionized water (20 mL). In this reaction, a nucleophilic substitution could take place by the corresponding amine [13]. This was carried out in the presence of a molar ratio of diamine and orcine reagents, helping to avoid the formation of the terminally disubstituted diamine. After heating the mixture with the conventional method for 10 minutes, the process was continued by dilution of carbonate potassium (1 M K_2CO_3) as the catalyst. Even though the reaction completion was estimated, the yield was dependent on the solubility of the products in water during the reaction process. After the solution reduction to a small volume, the products were precipitated by the addition of cold ethanol. The pure compound was characterized by ^{1}H NMR as shown in Scheme 1 and Figures 1 and 2 [14].

Synthesis of molecule 2

The molecule called "Bat A"was prepared with slight modifications. Molecule 1 (0.05 g in 15 mL of ionized water) was added in a dropwise manner to a stirred solution of freshly distilled ethylene glycol (2 mL) in ionized water (5mL). NaOH (0.5g) as the catalyst was added to the mixture. The reaction mixture was stirred under inert atmosphere at 90°C for1 hour. The organic layer was separated and the aqueous layer was extracted with portions of cold ethanol (2 x 10 mL). The combined organic fractions were dried over anhydrous $MgSO_4$. Then,the impurities were removed under the reduced pressure to afford a brown solid. The Bat A molecule was a brown solid (1.78 g, yield 95.29%)with the chemical structure displayed in Scheme 2 and Figures 3 and 4.

Synthesis of molecule 3

The molecule called "Bat B"was prepared through a similar process to the molecule Bat A preparation. First, molecule Bat A(1.2 g in 15 mL of ionized water) was added dropwise into a stirred solution of freshly distilled carbamates (2g) in ionized water (5mL). Then, NaOH (0.75g) was introduced into the mixtureas the catalyst. The reaction mixture was stirred under inert atmosphere at 95°C for 1 hour. Portions of the cold ethanol (2 x 10 mL)were used to separate the organic layer and extract the aqueous layer. The combined organic



Scheme 2: Chemical structure of the synthesized molecule "Bat A" based on anti-covid-19 drugs

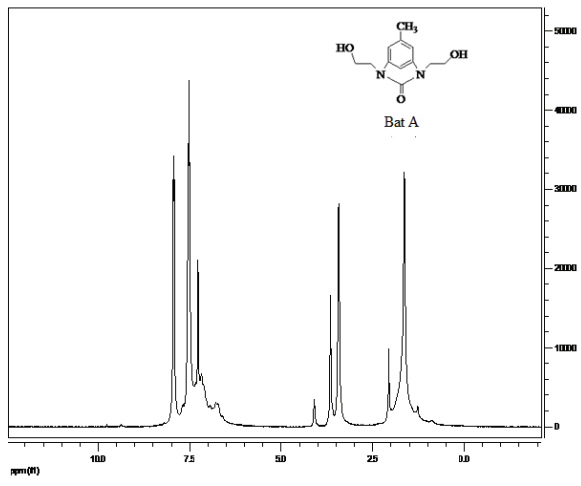


Figure 3: ^{1}H NMR spectrum of the **Bat A** molecule.

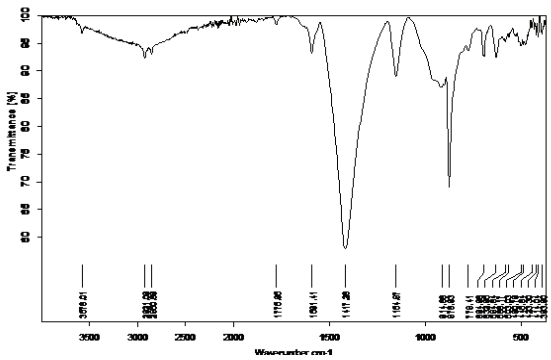
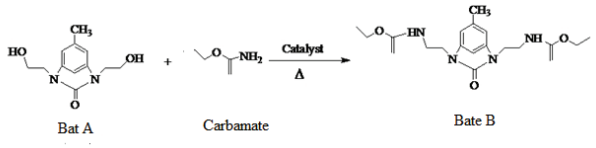


Figure 4: FTIR spectrum of the obtained Bat A molecule **(2)**



Scheme 3: Chemical structure of the Bat B molecule based on anti-covid-19 drugs

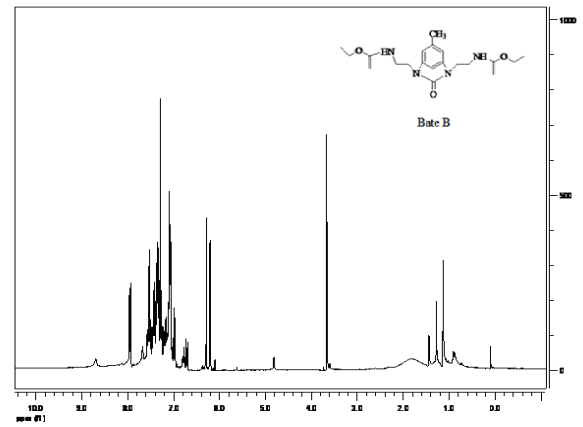


Figure 5: ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the Bat B molecule

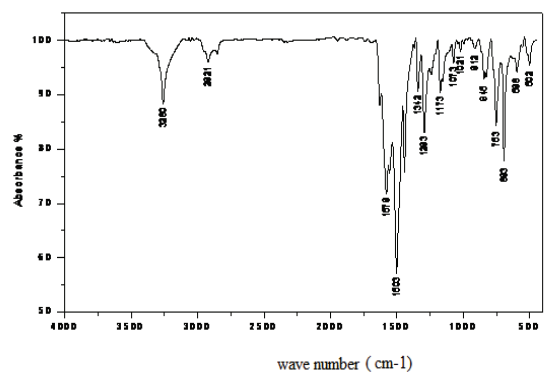
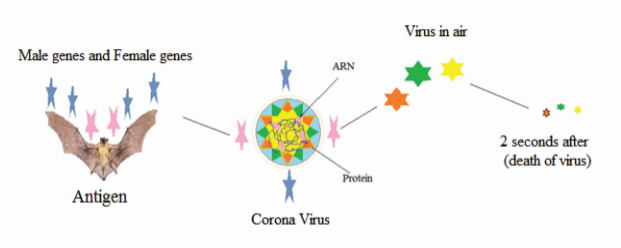
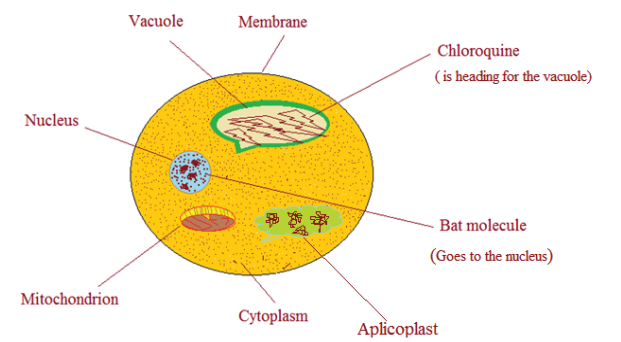


Figure 6: FTIR spectrum of the Bat B molecule



Scheme 4: Proposed mechanism of corona virus (COVID-19) under effect of bat molecules



Scheme 5: Presentation and explanation of the effect of chloroquine and the bat molecule in the cell

fractions were dried over anhydrous MgSO4 and the impurities were removed under the reduced pressure to reveal a brown solid which wasthe molecule Bat B. Scheme 3 and Figures 5 and 6 present the molecular features of the synthesized molecule Bat B (1.88 g, yield 96.02%).

Conclusions

There are many drug interactions with chloroquine-based drugs such as Nivaquine® which must be taken into account before prescription. There is also a need for close eye monitoring in the long-term patients. Regular monitoring of liver and kidney functions is, therefore, recommended. In addition, cardiac monitoring is necessary, regarding the co-prescription of chloroquine or hydroxychloroquine with Azithromycin to the patients with Sars-covid-2 (virus responsible for covid-19). Finally, chloroquine and its derivatives are so-called «narrow therapeutic margin» drugs, which means that the effective dose and the toxic dose are relatively close. In the case of overdose or improper use, they can behighly toxic. Bat molecule drugs interact with the virus in a way different from that of chloroquine. These new molecules present some advantages over the traditional chloroquine in anti-virology studies; it is safer to handle as it is non-toxic, it is soluble in water at room temperature, and its biological properties allow it to be monitored by the common equipment. Using microscopy platform, we showed that the Bat molecules could interact with virus in a manner different from that of chloroquine, which is localized in the digestive vacuole of the virus. Furthermore, the inhibited growth of chloroquine-sensitive strains is more extensively in comparison to the resistant strains against the bat molecules directly targeting the nucleus. We believe that the synthesized molecules could be valuable tools in the future drug discovery projects andso, they could be used in the treatment of virus, especially covid-19.

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