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Design, Synthesis, and characterization of a novel Ciprofloxacin-Antioxidant mutual prodrugs

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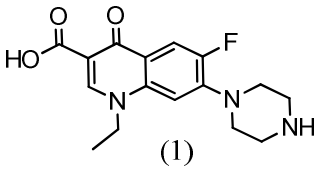
ABSTRACT

A novel Prodrugs (Compounds I and II) have been designed, and synthesized, in which ciprofloxacin has been linked to two different anti-oxidants using chloroacetylchloride as spacer. These prodrugs have been characterized by various physico-chemical methods like melting points, R_f values, and FT-IR spectrum.

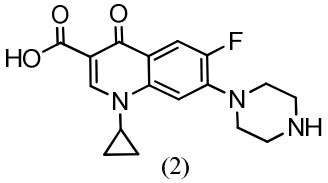
Keywords: Ciprofloxacin, Antioxidants, Prodrugs.

INTRODUCTION

Infection described as the invasion of a host organism's bodily tissues by disease causing organisms, their replication, and the response of host tissues to these organisms and the toxins they produce [(1)]. Infectious diseases are among the most lethal afflictions plaguing human societies [(2)], and they are remain a pressing problem worldwide, because microbes have combat prophylaxis or therapy longer than any other form of life [(3)].The only way to combat infectious diseases is by chemotherapy using antibacterial agents and antibiotics. Antibacterial agents have been used for more than 70 years in the treatment of such diseases. These agents possess great potential to treat affected patients. The usage of antibiotics has become widespread around the world because of their significant effectiveness on bacteria and other micro-organism agents [(4)]. However, due to their uncontrolled use, bacteria have evolved resistance against large groups of these agents [(5)]. This situation has led to a reduction in effectiveness of conventional therapy (antibiotics). Among one of the most important synthetic antibacterial agents are Fluoroquinolones which are used for treatment of serious bacterial infections. They exhibit broad-spectrum activity by inhibiting bacterial DNA replication for both Gram-negative and Gram-positive bacteria [(6)]. Since their discovery a large number of analogues have been synthesized, such as norfloxacin (1),pefloxacin, and ciprofloxacin (2), [(7,8)]. They are potent bactericidal, with broad spectrum action against many clinically vital pathogens which are responsible for variety of infections comprising gastrointestinal infections, urinary tract infections (UTI), sexually transmitted diseases (STD), respiratory tract infections (RTI) and are also clinically useful against infections of skin, prostatitis and bones and penicillin resistant sexually transmitted disease [(9,10)].



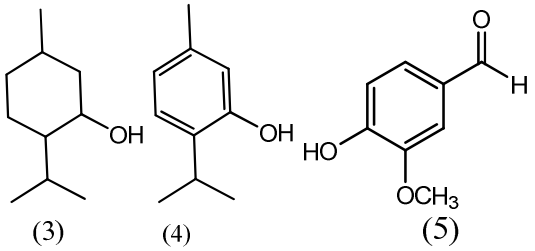
(1)



(2)

Despite of their significant advancements in the antimicrobial therapy, the resistant problem remains to be solved for most of these drugs [(11)]. A potential approach to overcome the resistance problem is to design novel and ingenious agents. The development of new antibiotics can be achieved from derivatives of known antimicrobial agents or by identification of novel agents that are active against previously unexploited targets [(12)]. One approach to overcome

the resistant problem is the synthesis of new mutual pro-drugs, which mean pharmacologically inactive compounds that are transformed by the mammalian system into an active substance via either chemical or metabolic means. Mutual pro-drugs involve two moieties that possess pharmacological activities when they are hydrolyzed in mammalian cells[13].The active moiety selected may has the same biological activity similar to that of the parent drug and thus may give synergistic effect, or this moiety may has some further biological action absent in the parent compound, thus giving some additional benefits[14, 15]. One of the most important compounds that will be utilized in this approach are the natural anti-oxidants, as menthol (3), thymol (4), vanilla (5), and guaiacol. These compounds can be bind with members of quinolones to synthesize new chemical agents to overcome the resistant problems[16].

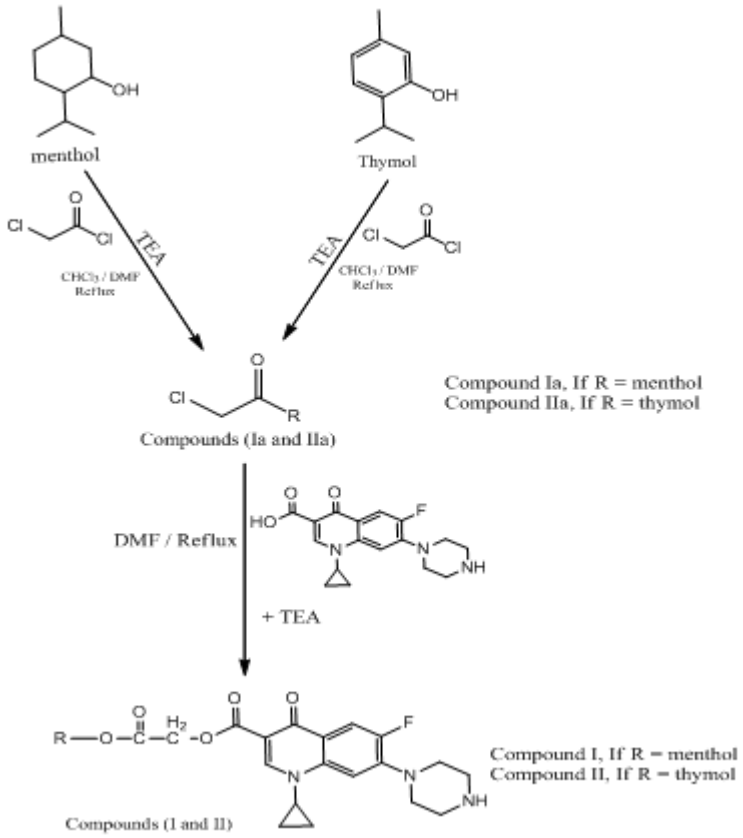


(3) (4) (5)

MATERIALS AND METHODS

Experimental

Entirely reagents and anhydrous solvents were of analytical grade and supplied from (ReidalDehean Germany; Sigma-Aldrich Germany; BDH England). Melting points (uncorrected) were determined by capillary tube method by Thomas hover apparatus (England). R_f values were determined through using ascending thin layer chromatography, on DC-Kartan SI Alumina 0.2 mm to ensure the purity and progress of the reaction, using methanol: benzene (50:50) as mobile phase. Determination of FT-IR spectra done by using FT-IR spectrophotometer, at college of pharmacy, kufa university, by using KBr discs. CHN microanalysis has been done in college of science-Jordan university, by using Euro EA 3000 elemental analyzer (Italy).



Scheme 1: Synthesis of the compounds Ia, IIa, I and II

Steps of synthesis of all compounds are presented in scheme 1. Antioxidants (menthol and thymol) firstly coupled with chloroacetylchloride in presence of TEA, to give compounds Ia and IIa. Then coupling reaction of ciprofloxacin with compounds Ia and IIa result in synthesis of compounds I and II respectively.

Chemistry:

Coupling reaction of antioxidants with chloroacetylchrolide:

Antioxidant (12.7mmol), was dissolved in DMF:$CHCl_3$ (50:50) mixture (40 ml), then TEA (1.77 ml, 12.7mmol) was added. The reaction mixture was stirred on ice bath,chloroacetylchloride (1 ml, 12.7mmol in 10 ml $CHCl_3$) was added drop wise with continuous stirring over a period of one hour, followed by refluxing of the mixture for three hours. Then excess cold water was added, and the precipitated compound was filtered, and recrystallized from ethanol, to provide compounds Ia and II. The percent yield, physical appearance, and R_f values were given in table (1), and FT-IR spectrum was given in table 2.

Coupling reaction of ciprofloxacin with compounds Ia and IIa.

A mixture of compound Ia or IIa (9.1mmol), and ciprofloxacin (9.1mmol), were dissolved in DMF (25 ml), then TEA (1.3 ml, 9.1mmol), was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated; the residue was triturated with acetone and recrystallized from methanol. The percent yield, physical appearance, and R_f values were given in table 1, and FT-IR spectrum was given in table 2. CHN Calculated for compound I: C, 66.01; H,7.26; N, 7.96. Found: C, 66.03; H, 7.36; N, 7.07. CHN Calculated for compound II: C, 66.78; H,6.18; N, 8.06. Found: C, 67.01; H, 6.12; N, 8.17

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RESULTS AND DISCUSSION

Mutual esterprodrugs of ciprofloxacin with antioxidants (menthol and thymol) were synthesized by the scheme that shown above. They were subjected to physico-chemical characterization, the data are shown in Table 1, and their structures were confirmed by the FT-IR spectroscopy, and were represented by Table 2. IR spectra of compound I showed the characteristic absorption band for ester C=O stretching at 1747 cm^{-1}, while compound II showed C=O stretching at 1734cm^{-1}, thus confirmed the formation of ester bonds in the synthesized prodrugs.

Table 1: Physicochemical properties of the synthesized compounds

Compounds	Empirical Formula	Molecular weight	Description	% Yield	Melting point ^oC	R_f values
Ia	$C_{12}H_{21}ClO_2$	232.75	Deep brown crystals	50.3	198-201	0.75
IIa	$C_{12}H_{15}ClO_2$	226.7	Pale yellow powder	70	240-243	0.89
I	$C_{29}H_{38}FN_3O_5$	527.63	Brown crystals	84	234-236 d	0.7
II	$C_{29}H_{32}FN_3O_5$	521.58	Pale yellow crystals	77	310-313 d	0.92

Table 2: FT-IR spectra of the synthesized compounds

Compounds	Bands (cm^{-1})	Interpretation
Ia	2972	C-H stretching vibration of alkane
	1747	C=O stretching vibration of ester
	1226	C-O stretching vibration of ester
I	3352	N-H stretching vibration of piperazinyl group
	2981	N-H stretching vibration of secondary amine.
	1747	C=O stretching vibration of ester
	1651	C=O stretching vibration of quinolone.
IIa	2970 and 2939	C-H stretching vibration of alkane
	1741	C=O stretching of ester
	1581 and 1479	C=C stretching vibration of aromatic
II	3024	C-H stretching of aromatic
	2927	N-H stretching vibration of secondary amine
	1734	C=O stretching vibration of ester
	1685	C=O stretching vibration of quinolone

CONCLUSION

The designed products have been synthesized efficaciously as shown in scheme **1** and their structures were confirmed, using infrared spectroscopy (FT-IR spectra), elemental microanalysis (CHN) and their purity was confirmed by their physical data (melting points and Rf values).

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