Design of Ciprofloxacin Derivatives that Inhibit Growth of Methicillin Resistant *Staphylococcus aureus* (MRSA) and Methicillin Susceptible *Staphylococcus aureus* (MSSA)

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Abstract: Three derivatives of ciprofloxacin (compound B, C, and D) were constructed utilizing microwave synthesis methodology (compound D) or diazoalkane reaction in nonaqueous solvent (compounds B and C). The final structures of the derivatives featured an ester group in place of the original carboxyl group of the ciprofloxacin. These ester groups contained aliphatic single carbon (compound B), two carbon length (compound C), or three carbon length propyl ester group (compound D). The ester groups strongly affected the molecular properties of the parent ciprofloxacin. As the size of the ester group increased the formula weight, molar volume, and number of rotatable bonds increased. The Log P for these compounds were -0.701, -0.441, -0.065, 0.437 for ciprofloxacin, B, C, and compound D, respectively. Numerical values of dermal permeability coefficient (Kp) increased rapidly as length of the ester carbon chain increased. The immediate consequence of Kp increase is an increased skin penetration rate based on dose and time span of administration. Polar surface area for ciprofloxacin is 74.569 Angstroms^2, but decreases to 63.575 Angstroms^2 for all three derivatives. All three derivatives of ciprofloxacin showed zero violations of the Rule of 5, indicating these drugs would have favorable bioavailability. Compounds A, B, C, and D were placed into tissue culture with methicillin resistant and susceptible *Staphylococcus aureus* (MRSA and MSSA, respectively) to determine levels of bacterial growth inhibition. All compounds induced greater than 60 % inhibition of MSSA at concentrations as low as 15.63 micrograms/milliliter. All four compounds induced greater than 80 % inhibition of MRSA at concentratins as low as 15.63 micrograms/milliliter. Development of novel drug designs will benefit the clinical treatment of dangerous infections of MSSA and MRSA.

Keywords: Ciprofloxacin, *Staphylococcus aureus*, MRSA, MSSA.

INTRODUCTION

Ciprofloxacin is a broad spectrum fluoroquinolone drug that is a synthetic chemotherapeutic agent used in the clinical treatment of severe and life threatening infections. Ciprofloxacin is active against both gram-positive and gram-negative bacteria by interfering with DNA replication by inhibiting DNA gyrase [1]. Ciprofoxacin inhibits DNA gyrase, a type II topoisomerase, and topoisomerase IV [1]. Other bacteria inhibited by ciprofloxacin include: *Proteus mirabilis*, *Proteus vulgaris*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Neisseria gonorrhoeae.*

Methicilllin resistant *Staphylococcus aureus* (MRSA) is recognized as a world wide nosocomial pathogen and is a cause of community acquired (CA-MRSA) infections that are found world wide [2]. The liberal use of vancomycin to treat the new threat increases the potential for developing resistance by gram-positive bacteria [2]. *Staphylococcus aureus* (and *E. coli*) have been found to be among the most common hospital acquired (ie. HA-MRSA) bacteria showing high resistance rates to ciprofloxacin (82.0 %) and ofloxacin (83.4 %) [3], which are spreading rapidly across the world [4]. New designs for antimicrobials are urgently needed to treat infections of the growing number of multi-drug resistant *Staphylococcus aureus* [4,5]. Resistance to ciprofloxacin has been shown not to differ significantly between detected isolates of HA-MRSA and CA-MRSA [5]. The accessibility of antimicrobials for treatment of Neisseria gonorrhoeae is being threatened because of the rise of drug resistance, including the fluoroquinolone class [6].

Long term care facilities have been recently recognized as repositories for multi-drug resistant gram negative bacteria and that more than 80 % of detected isolates of these bacteria are resistant to ciprofloxacin and ampicillin/sulbactam [7]. The bacteria resistance to commonly used antimicrobials at long term care facilities is reducing the therapeutic options for treatment [7]. Localization of HA-MRSA at catheter sites raises concern for their implementation due to high resistance of isolates to ciprofloxacin (33%), oxacillin (34%), erythromycin (41%), and gentomicin (4.4%) [8]. Fully 50% of derived nasal swabs have been shown to contain *Staphylococcus aureus* resistant to ciprofloxacin and macrolides [9]. *Staphylococcus aureus* has been found in lower urinary tract infection isolates associated with diabetic patients [10].

Staphylococcus aureus is the most important bacteria for human diseases associated with skin and mucous membrane infections. Children have been recognized as particularly important in the appearance and spread of MRSA with the

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additional hazards of relatively high rates of resistance to antibiotics [11].

Circulating strains of CA-MRSA have characteristic pathogenesis that are distinct from HA-MRSA [12]. Circulating strains of CA-MRSA behave more like strains of CA-MSSA, both of which have emerged on a global scale [12]. CA-MRSA causation of skin and soft tissue infections can be site and population specific, a scenario that amplifies problems for clinical diagnoses and treatment [13]. CA-MRSA induction of even mild skin infections does not abrogate the need for adequate hygiene because severe necrotizing fascitis and pneumonia can follow [14-16]. CA-MRSA can follow an aggressive clinical course that involves the skin and leads to the lungs [15]. Skin and soft tissue infections are the most common manifestations of *Staphylococcus aureus* among children [16,17]. Close contact among infected individuals aggravates spread of infection particularly with CA-MRSA [18-20] among children and site contamination in surgical environments [21]. High frequency of drug resistance of *Staphylococcus aureus* (including MRSA) associated with cutaneous abscesses of HIV patients has required clinical focus on chemotherapy method [22]. The observations cited clearly entails the need for new designs of therapeutic antimicrobials.

RESULTS AND DISCUSSION

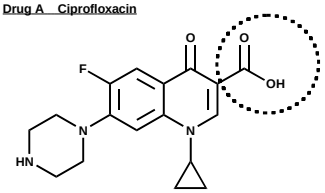
Although ciprofloxacin is presently a broad spectrum antimicrobial, the appearance of multidrug resistant pathogenic bacteria clearly exacerbates clinical application. The need for new drug designs to respond to these challenges is striking. This work presents three derivatives of ciprofloxacin which feature molecular properties that are advantageous for bioavailability in addition to effective antibacterial action against methicillin resistant and susceptible *Staphylococcus aureus*.

Ciprofloxacin as a synthetic fluoroquinolone (or quinolone) drug features a fluorine atom, 1,4-dihydroquinoline moiety, carboxyl group, and piperazine ring (see structure, Fig. **1**). The derivatives of ciprofloxacin (drugs B, C, and D) will have ester functional groups to replace the former carboxyl group of ciprofloxacin. The ester groups will alter molecular properties of the parent structure and improve skin permeation and penetration of lipid by-layers while retaining substantial levels of antibacterial activity that is at least as great as the parent ciprofloxacin or better. The structures and chemical nomenclature of derivatives B, C, and D are presented in Fig. (**1**). Note the change of the carboxyl group (inset circle) to aliphatic ester groups having one carbon (drug B) to as many as three nonbranched carbons (drug D). All other structural features of ciprofloxacin are retained in these derivatives. The methyl (B), ethyl (C), and propyl (D) ester of ciprofloxacin comprise a homologous series of antimicrobial chemotherapeutics.

The synthesis of drugs B and C was accomplished by application of diazoalkane reaction in a nonaqueous solvent system. The general process is represented in Fig. (**2**). The reactant ciprofloxacin is placed in acetonitrile (or ethyl ether) and generated diazomethane is bubbled extensively through the mixture. In the case of drug C the gas is diazoethane. After several passes the product is specifically the methyl or ethyl ester of the ciprofloxacin. In the case of drug D, microwave methodology (synthesis by microwave excitation of functional groups in solid state conditions) was applied. Initially the carbonyl carbon of ciprofloxacin (see Fig. **2**, lower) is activated by thionyl chloride ($SOCl_2$) during microwave irradiation, then the introduction of n-propanol with additional irradiation forms the final propyl ester compound.

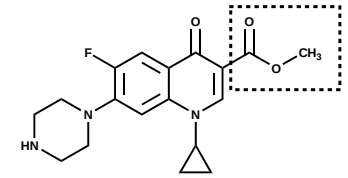
FIGURE 1

Drug A Ciprofloxacin



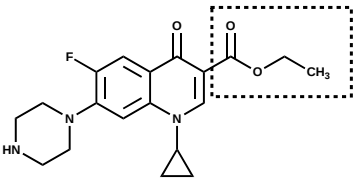
1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydroquinoline-3-carboxylic acid

Drug B Methyl derivative of ciprofloxacin



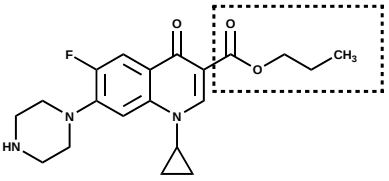
methyl 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydroquinoline-3-carboxylate

Drug C Ethyl derivative of ciprofloxacin



ethyl 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydroquinoline-3-carboxylate

Drug D Propyl derivative of ciprofloxacin



propyl 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-1,4-dihydroquinoline-3-carboxylate

Fig. (1). The molecular structures of ciprofloxacin (compound A) and derivatives B, C, and D are presented here for comparison. The parent ciprofloxacin structure contains a prominent carboxyl group (-COOH) (see inset circle0, aromatic ring, two tertiary amines, one secondary amine, and fluorine atom. Drug B is a methyl ester derivative of A, in which the carboxyl group is replaced by an ester group (see inset rectangle). Drug C is an ethyl ester derivative of A, in which the carboxyl group is replaced by an ester group (see inset rectangle). Drug D is a proply ester derivative of A, in which the carboxyl group is replaced by an ester group (see inset rectangle).

A comparison of molecular properties of ciprofloxacin to these derivatives reveals several important features gained by the formation of ester groups in place of the carboxyl group. Expectedly the modification of carboxyl to ester functional group (see Table **1**) increases molecular weight and molar

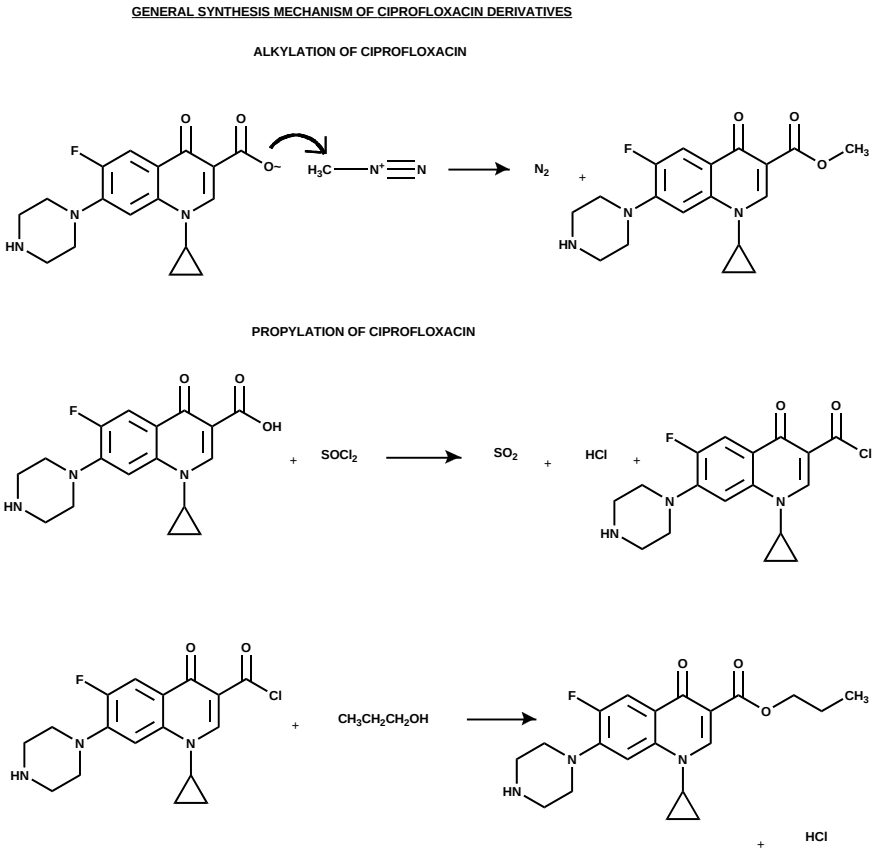


Fig. (2). Top: The alkylation of the carboxyl group initially present on the parent ciprofloxacin structure is reverted to an ester group by using diazoalkane reaction synthesis in a nonaqueous solvent. The reaction is highly selective to acidic protons of a carboxyl group and results in high yields after multiple passes. Drugs B (methyl ester) and C (ethyl ester) were synthesized by diazoalkane. Lower: The proplylation of drug D, also done by microwave methodology, was carried out by activation of the carboxyl group utilizing thionyl chloride and then followed by reaction with n-propanol.

Table 1. Molecular Properties of Ciprofloxacin and Derivatives

Drug	Log P	Polar Surface Area (Angstroms^2)	Molecular Weight	Number of Oxygens and Nitrogens	Number of Hydroxyls and Amines	Violations of Rule of 5	Number of Rotatable Bonds	Kp (cm/hour)	Molar Volume (cm^3)
A, Ciprofloxacin	-0.701	74.569	331.35	6	2	0	3	2.87E-05	226.7
B, Methyl-Cipro	-0.441	63.575	345.37	6	1	0	4	3.83E-04	252.1
C, Ethyl-Cipro	-0.065	63.575	359.40	6	1	0	5	7.01E-04	268.6
D, Propyl-Cipro	0.437	63.575	373.43	6	1	0	6	1.29E-03	285.1

volume.Additionally the presence of lengthening aliphatic ester branch increases the lipophilic nature of the drug as indicated by the steadily increasing numerical values of the partition coefficient Log P (ie. From -0.441 of B to 0.437 of D). The increase of Log P values indicates a steadily increasing solubility of the drug into the lipid by-layers of the cellular membrane of the bacteria and presumably increased penetration into the microbe. Increased penetration by the ciprofloxacin derivative into the target bacteria would enhance efficacy of the drug. The number of oxygens and nitrogens (hydrogen bond acceptors) as well as hydroxyls (-OH) and amine (-NH_n) (hydrogen bond donors) remain the same for the derivatives as for ciprofloxacin. A reduction in the polar surface area of the derivatives compared to ciprofloxacin parent would enhance bioavailability of the drug [23] whereas the increase in formula weigh and number of rotatable bonds would not be beneficial. Drug movement across the transcellular direction and by passive interaction should not have a polar surface area greater than 120 Angstroms^2 [23]. Altogether the properties of the derivatives still support favorable bioavailability for clinical application, as assertion auspicated by the determination that drugs B, C,

and D show zero violations of the Rule of 5 [24]. The Rule of 5 states that poor permeation is more likely when a drug possesses more than 5 hydrogen bond donors, formula weight greater than 500, Log P greater than 5, and more than 10 hydrogen bond acceptors [24]. None of these criteria describe drugs A, B, C, and D. Values of polar surface areas for B, C, and D suggests that greater than 60% of orally administered dose would be absorbed by the intestinal system [25]. Other investigators have reported that drugs having 10 or fewer rotatable bonds and polar surface area less than 140 Angstroms^2 will have good bioavailability [26]. These two criteria are fulfilled with all three ester derivatives of ciprofloxacin presented in this work. Therefore drugs B, C, and D are expected to show favorable bioavailability.

The comparison of B, C, and D to ciprofloxacin in terms of bacterial inhibition and specifically inhibition of MRSA and MSSA, all drugs were placed into tissue culture similarly. Results presented as percent inhibition of colony forming units (CFU) are presented in Fig. (**3**). Derivatives B, C, and D showed striking and comparable inhibition of both MRSA and MSSA as did ciprofloxacin. The inhibition of MSSA by ciprofloxacin (drug A), B, C, and D was near total (100%) at concentration as little as 15.63 micrograms/milliliter. This was followed at essentially 100 % inhibition by CFU at all concentrations above 15.63 μg/mL. These results suggest that ester forms of ciprofloxacin form a potent advent group of fluoroquinolone type chemotherapeutics to augment the clinical treatment of serious diseases previously managed by ciprofloxacin. This extends the number of fluoroquinolone compounds available to clinical workers. In addition, the results of similar testing with MRSA (see Fig. **3**) demonstrated that derivatives B, C, and D are comparable to ciprofloxacin inhibiting bacterial growth. Over 80 % inhibition by CFU was observed for all drugs at concentration of 15.63 microgram/milliliter. At all concentrations above 15.63 μg/mL the derivatives induced greater than 80 % inhibition. Again, these results extends the number of fluoroquinolone compounds available to clinical workers. The profound inhibition of MRSA and MSSA coupled with enhancement of choice molecular properties via ester group modification provide clinical antimicrobials having a diverse, but highly effective, antimicrobial activity.

Infections of *Staphylococcus aureus* often make their presentation in the form of skin or soft tissue contagion [16-20]. Although beginning as skin infections, MRSA or MSSA can travel to the lung tissue and result in formation of pneumonia [14-16]. More effective drugs are necessary to prohibit the advancement of these infections to other organs. A notable action of the replacement of the carboxyl group by ester functional groups is the profound increase in the rate of skin penetration, which is affirmed by the dermal permeability coefficient Kp. Measuring the rate (as cm/hour) of a dose administered as a topical agent, the Kp for B, C, and D are exceedingly greater than the Kp for the ciprofloxacin parent (see Fig. **4**). Beginning with ciprofloxacin (see Table **1**) the Kp numerical value jumps more than one-order of magnitude to 0.000383 cm/hour for drug B. Values of Kp for C and D are greater yet than ciprofloxacin and drug A. Clearly the modification of ciprofloxacin to an ester compound substantially improves the potential of topical usage which is an advantage for treating skin based infections of MRSA and MSSA. This would significantly improve the prognosis of limiting extent and damage of *Staphylococcus aureus* infections. Advantages of an effective topical agent for skin based incidents of MRSA or MSSA include: 1) Drug application is directly to site of bacteria; 2) Decreased chance of allergic reaction to drug; 3).

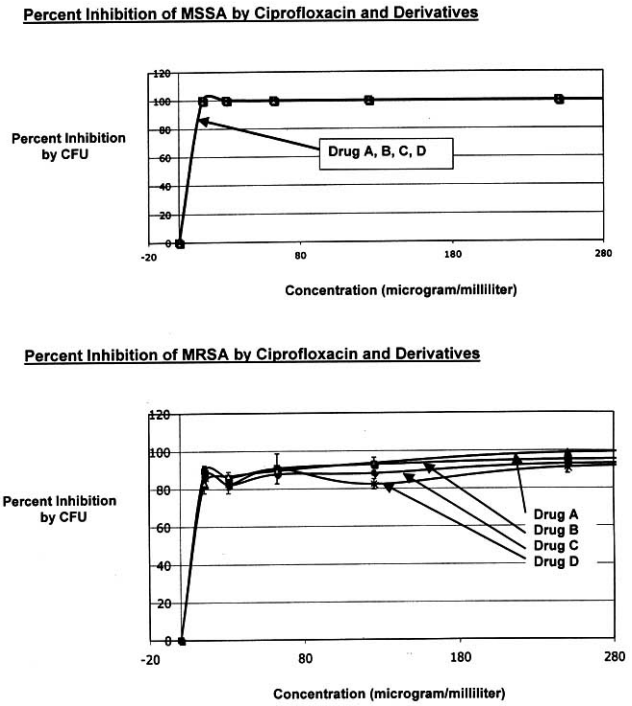


Fig. (3). Comparison of MSSA and MRSA growth inhibition induced by ciprofloxacin (A) and ester derivatives B, C, and D. Top: A very strong growth inhibition of MSSA is demonstrated by all compounds of this study. The growth inhibition measured by colony forming units (CFU) for all compounds is greater than 80 % at concentrations starting at 15.63 micrograms/milliliter and higher. Essentially drugs A, B, C, and D are identical in their performance and strong inhibition of MSSA is achieved. Lower: Again in the case of MRSA all compounds induce greater than 80 % inhibition of MRSA as measured by colony forming units. All concentrations of A, B, C, and D induce strong inhibition, starting at 15.63 micrograms/milliliter.

Decreased chance of drug-drug interaction; 4) Ease of use; and 5) Rapid response following clinical presentation. These results present stark assertions that ester forms of ciprofloxacin have considerable potential as chemotherapeutics for the clinical treatment of dermal and non-dermal infections of MSSA and/or MRSA.

Hydrophobic drugs with high partition coefficients are preferentially distributed to hydrophobic compartments such as lipid by-layers of cells while hydrophilic drugs (low partition coefficients) preferentially are found in hydrophilic compartments such as blood serum [27]. The lengthening of the aliphatic carbon chain of the ester substituent induces a numerical increase of Log P values. The derivatives of ciprofloxacin B, C, and D have increased solubility in hydrophobic compartments, such as the bacterial cell membrane. The relationship of ester substituent size and Log P is presented

in Fig. (**5**). As the length of the ester substituent increases, so does the Log P and Kp numerical values of the derivatives B, C, and D. This work shows that alteration of the molecular structure of ciprofloxacin preserves the antibacterial activity as well as modifies molecular properties so that the clinical potential and types of administration of these novel drug designs is diversified.

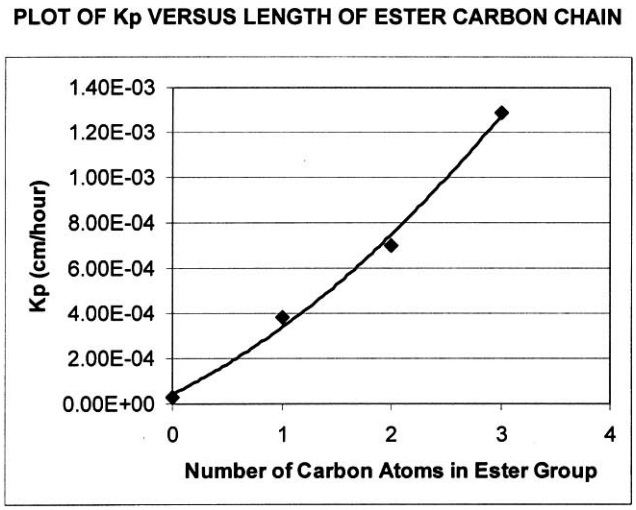


Fig. (4). As the number of carbon atoms within the aliphatic ester group increases so does the Kp numerical value for compounds B, C, and D. The rapid increase in Kp value clearly indicates a substantial increase in the rate of skin penetration by compounds B, C, and D compared to the parent ciprofloxacin. Measured as centimeters per hour these results indicate an improved capability to treat skin and soft tissues infections by MRSA and MSSA.

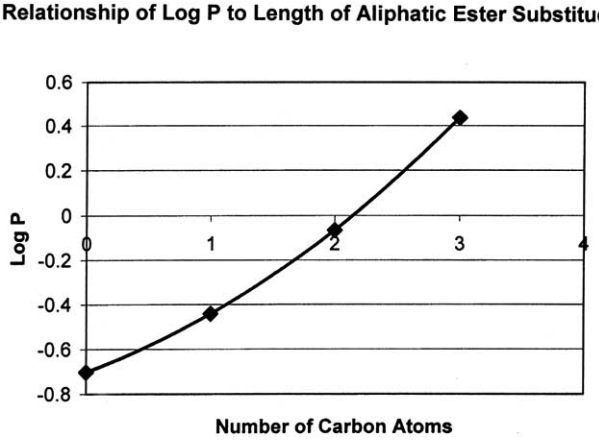


Fig. (5). As the length of the aliphatic ester substituent increases the Log P value for the drug increases. As Log P increases the solubility of drug in the lipophilic by-layer of cell membranes also increases. Increase of Log P correlates with increase of Kp and the number of carbon atoms in the ester substituent increases. Drug A (ciprofloxacin) has no carbon ester atoms, drug B has one carbon, drug C has two carbon atoms, and drug D has three carbon atoms.

CONCLUSION

Ciprofloxacin is a broad spectrum antimicrobial and has seen the substantial increase in the number of MRSA and MSSA isolates across the globe. Many infections of *Staphylococcus aureus* are manifested through skin and soft tissue infections of children and patients in long term care facilities. This work presents three ester derivatives of ciprofloxacin that show very strong inhibition of MRSA and MSSA. The three ciprofloxacin derivatives B, C, and D induced greater than 80 % growth inhibition of both MRSA and MSSA beginning at concentrations of as little as 15.63 micrograms/milliliter. The replacement of the carboxyl group of in the parent ciprofloxacin by ester groups increased molar volume, formula weight, and number of rotatable bonds, but decreased the polar surface area from 74.569 Angstroms^2 of ciprofloxacin to 63.575 Angstroms^2 for the derivatives. All three derivatives of ciprofloxacin showed a substantial increase in the rate of skin penetration as indicated by Kp numerical values. The ester derivatives would then be expected to have greater penetration and higher efficacy in the treatment of *Staphylococcus aureus* infections of skin and soft tissues. These promising features of ciprofloxacin ester compounds clearly indicate a substantial potential for the clinical treatment of MRSA and MSSA.

EXPERIMENTAL

Reagents and Instrumentation

Chemicals and reagents were obtained from Aldrich Company (P.O. Box 2060, Milwaukee, WI 53201). Infrared spectroscopy use a Mattson Galaxy FTIR in dimethylsulfoxide dried over molecular sieves.

Molecular Modeling

Molecular modeling and molecular properties were determined by utilizingChemSketch v. 5 (90 Adelaide Street West, Toronto, Ontario M5H 3V9,Canada), Molinspiration (Liscie Udolie 2, SK-841 04 Bratislava, SlovakRepublic). Values of Kp were determined by DERMWIN U.S. Environmental Protection (copyright (c) 2000 U.S. Environmental Protection Agency).

Bacterial Strains and Growth Conditions

Methicillin resistant *Staphylococcus aureus* strain MRSA252 and methicillin sensitive strain MSSA476 were kindly provided by Dr. Greg A. Somerville, University of Nebraska, Lincoln, NE. *Staphylococcus* cultures were grown by suspending a single colony with normal morphology on tryptic soy (BD Biosciences) agar in 30 ml of tryptic soy broth (TSB). Serial dilutions were made 1:2 in 25 cm^2 culture flasks (Sarstedt) and cultures were grown in a final volume of 15 ml. Cultures were incubated at 37ºC overnight with shaking. Cultures at early stationary phase (OD_{630} 2-4) were used to inoculate flat bottom 96-well plates (Sarstedt) with 10^6 bacteria in a final volume of 100 µl of TSB with variousconcentrations of the test compounds added previously. After 5 h of incubation at 37ºC the optical density (OD) and colony forming units (CFU) were determined for all cultures. OD were determined at 630nm using a Dynatech Revelation 2.0. CFU were determined through microdilution by plating 20 µl of each dilution on Luria Broth (Difco) agar plates.

Synthesis of Ciprofloxacin Derivatives

All reagents be kept dried and free of water. All glassware used in synthesis must be clean and dry. For methylation of ciprofloxacin (compound B): Place 20 milligrams of ciprofloxacin into 15 mL of dried acetonitrile, then bubble diazomethane through the mixture three to five passes (diazomethane generated by placing 5 molar NaOH onto 1-methyl-3-nitro-1-nitrosoguanidine). For ethylation of ciprofloxacin (compound C): Place 15 milligrams of ciprofloxacin into 10 mL dried acetonitrile, then bubble diazoethane through the mixture four to six passes (diazoethane generated by placing 5 molar NaOH onto 1-ethyl-3-nitro-1- nitrosoguanidine). For propylation of ciprofloxacin (compound D): Place 15 milligrams of ciprofloxacin into a clean dry glass reaction tube. Place 15 microliters of $SOCl_2$ into the vessel and microwave briefly for 30 seconds. Then add 100 microliters of n-propanol and microwave up to 60 seconds. Allow to cool and remove excess alcohol by vacuum. Keep products dry and store at -10^{o}C. For ciprofloxacin the carboxyl group gives a noticeable bands in I.R. spectra at about 3000 cm^{-1}, 1700 cm^{-1}, 1400 cm^{-1}, 1300 cm^{-1}. For the methyl ester (drug B) peaks at about 1725 cm^{-1} and 1150 cm^{-1} are indicative. For the ethyl ester (drug C) peaks about 1750 cm^{-1} and about 1250 cm^{-1}. For drug D the propyl ester derivative peaks at 1750 cm^{-1} and 1200 cm^{-1}.

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