

Due to infectious diseases caused by bacterial pathogens each year millions of people die worldwide, and at any one time hundreds of millions of people are disabled keeping children away from school and preventing adults from working. Although most of the casualties have been noticed in developing countries where health budgets are unrealistically small, no country is safe from infectious diseases, especially in the world of rapid air travel and hospital infections which are now a leading cause of death in some industrialized countries.

Since the discovery of nalidixic acid by George Leshner in 1962 over ten thousands analogues have been synthesized from which four generations of chemotherapeutics with broad spectrum of antibacterial activities have emerged. Fluoroquinolones are broad-spectrum antibiotics (effective for both gram-negative and gram-positive bacteria) that play an important role in treatment of serious bacterial infections, especially hospital-acquired infections and others in which resistance to older antibacterial classes is suspected.

The expression of resistance to antimicrobial agents is the logical and inevitable of using these agents to treat human infections. There are many ways in which microorganisms develop resistance to antibiotics and chemotherapeutic agents and different resistance mechanisms may interact to increase the level or spectrum of resistance of an organism. It is clear that bacteria and fungi will continue to develop resistance to currently available drugs by either new mutations or the exchange of genetic information, i.e., putting old resistance genes into new hosts. Confronted with the problem of antibacterial resistance to fluoroquinolones and side effects of the existing drugs, researchers in academia and pharmaceutical industry have pursued several approaches to identify new multitarget inhibitors. The most common strategies include: (i) combination therapy, (ii) single pharmacophore multi-target inhibitors, and (iii) dual action hybrid antibiotics.

Thus, in recent years the concept of “dual action drugs” has been gaining popularity in medicinal chemistry and medicine. Since a single drug is not always able to adequately control the illness, the combination of drugs with different pharmacotherapeutic profile may be needed, and therefore, drugs incorporating two different pharmacophoric groups in a single molecule with the intention of exerting dual drug action have been developed. For example, one of the hybrid parts may be incorporated to counterbalance the known side effects associated with the other hybrid part, or to amplify its effects through action on another biological target. Interestingly, the fluoroquinolone antibiotics linked to another antibacterial agent represent the most widely investigated class of hybrid compounds.

The main objective of this project is to design and prepare a series new dual acting antibacterials incorporating a fluoroquinolone drug and a fluorescent triazolium compound, aimed at evaluating the hypothesis that a new class of hybrid antibacterial agents can be obtained that exhibit the following unique dual antimicrobial mechanism of action: (i) perturbation of the lipid bilayer of the bacterial cytoplasmic membrane and the outer membrane of Gram-negative bacteria due to presence of quaternary ammonium group, and (ii) inhibition of DNA gyrase / bacterial topoisomerase IV elicited by fluoroquinolone portion. Fluorescent properties of these hybrid agents should allow the observation of their fate in the bacterial cell. The presence of permanent positive charge in the structure of such hybrid agents should prevent their distribution to the brain after intravenous administration, and thus, reduce the side effects elicited by fluoroquinolones in the central nervous system.