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Original article

Design, synthesis, and evaluation of novel fluoroquinolone–flavonoid hybrids as potent antibiotics against drug-resistant microorganisms

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ABSTRACT

Based on a rationally conceived pharmacophore model to build a multi-target bacterial topoisomerase inhibitor, twenty-one fluoroquinolone–flavonoid hybrids were synthesized. Some obtained hybrids show excellent antibacterial activity against drug-resistant microorganisms with narigenin–ciprofloxacin being the most active, showing 8, 43, 23 and 88 times better activity than ciprofloxacin against *Escherichia coli* ATCC 35218, *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 25923 and *Candida albicans* ATCC 90873, respectively. Drug accumulation and DNA supercoiling assays of two active analogues revealed potent inhibition of both the DNA gyrase and efflux pump, confirming the desired dual mode of action. Molecular docking study disclosed that the introduced flavonoid moiety not only provides several additional interactions but also does not disturb the binding mode of the floxacin moiety. Our data also demonstrated that development of antifungals is possible from fluoroquinolones modified at C-7 position.

1. Introduction

Antibiotics have a long history, beginning in the 1930s and earlier, during which several distinct drug classes were discovered and numerous improved analogues were made available [1]. Fluoroquinolones, broad-spectrum antimicrobial agents, are among the most attractive drugs in the anti-infective chemotherapy field [2]. These antibiotics target the bacterial type II topoisomerase enzymes (DNA gyrase and topoisomerase IV) which are essential, ubiquitous enzymes involved in bacterial cell growth and division [3]. However, quinolone-resistant microbes are rapidly spreading in hospitals and the community. In fact, antibiotic drug resistance has become a growing problem across the globe over the past several decades. Microbe develop drug resistance through various mechanisms, such as overexpression of drug efflux transporters like multidrug and toxic compound extrusion (MATE) transporters [4,5], changes in the target sites of antibiotics [6], optimization of the enzyme (such as β-lactamase) activity resulting in inactivation of antibiotics [7], spontaneous chromosomal mutations [8], and horizontal transfer of genetic elements [9]. Inhibition of the activity of drug efflux transporters appears to be a promising approach for restoring the activity of a drug that is the substrate of these efflux pumps [10].

Flavonoids are a class of plant phenolic compounds that are widely found in fruits, vegetables, seeds and herbs. A large number of human and animal studies show that flavonoids exert beneficial effects in the prevention of many diseases, including cancer, cardiovascular disease and neurodegenerative disorders [11]. Because of their considerable health related effects, flavonoids become the subjects of much medical and biological research as investigators try to find more biological properties and mechanisms [12]. Recently, some flavonoids received much attention due to their unique biological properties in the modulation of multidrug resistance [13]. Iris L. K. Wong et al. reported that apigenin homodimers (**I**) (Scheme 1) can modulate the efflux pump P-glycoprotein activity in human cancer [14]. Subsequently, tetramethylscutellarein (**II**) and sarothrin (**III**) were reported as potent inhibitors of bacterial NorA efflux pump [15,16]. Not coincidentally, several other flavonoids (naringenin (**IV**) [17], quercetin (**V**), kaempferol (**VI**) [18],

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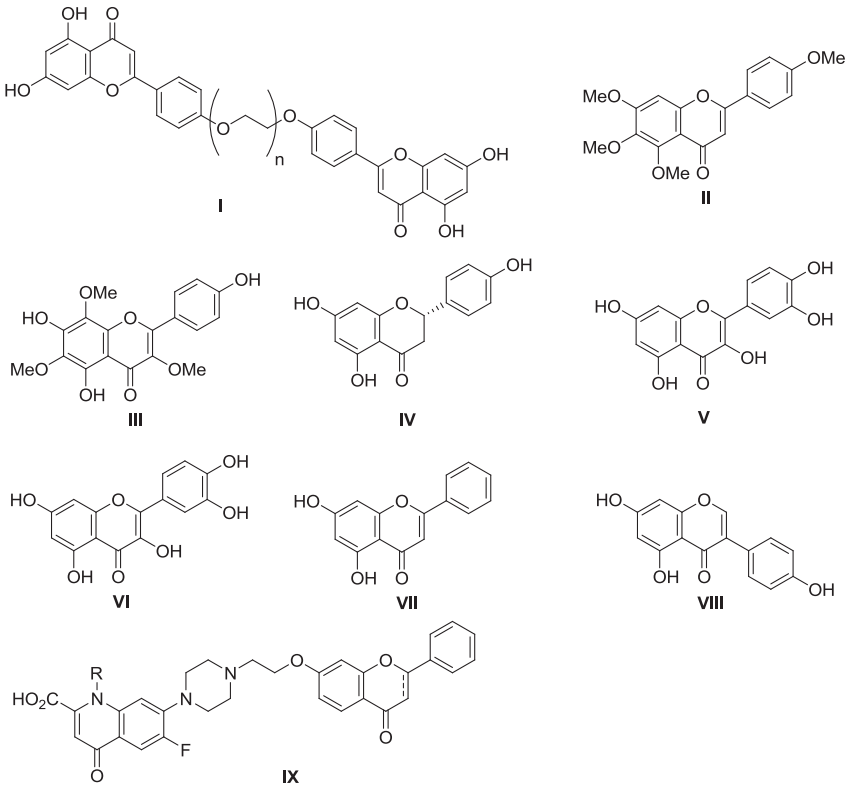


Scheme 1. Structures of some flavonoids and efflux pump modulators, and the scaffold of a Flox–Flav hybrid.

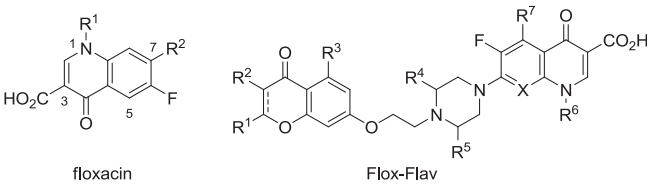
chrysin (**VII**) [13] and genistein (**VIII**) [19]) were also identified as effective inhibitors of the multidrug transporters from the MRP family.

Drug resistant bacteria constitute one of the main reasons for chemotherapy failure, which in turn becomes a primary driver for antibacterial research and development [1]. As widely known, discovery of novel agents against new bacterial targets is regarded a risky business endeavor [20]. Therefore, most development activities are focused on expanding existing antibiotic classes [21]. Recently, some fluoroquinolone hybrids were synthesized and reported as good anticancer and antimicrobial agents [22–24]. Based on this inspiration and inhibition properties of some flavonoids against efflux pumps, hybrid analogues (**IX**) of flavonoidfloxacin were designed for expecting to reduce the grave problem of fluoroquinolone resistance.

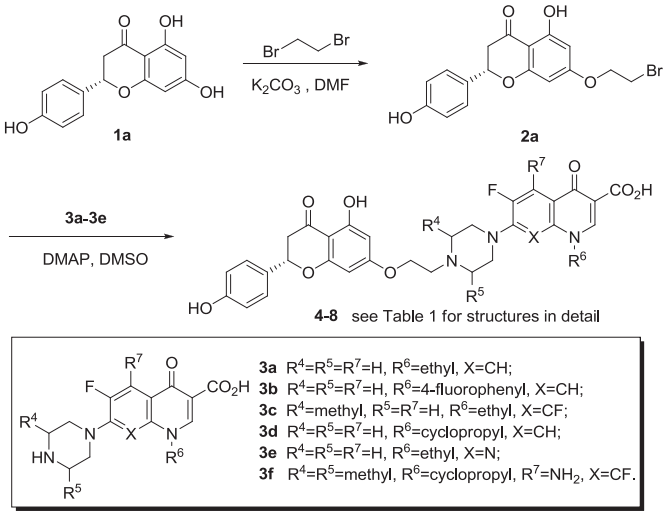
2. Results and discussion

2.1. Chemistry

Structure–activity relationship studies of fluoroquinolone antibacterial agents have been widely reviewed and have demonstrated a high tolerance for structural variations at the 7-position (Scheme 2), including alkylations at the terminal nitrogen of the piperazine moiety [25–27]. Specifically, it appears that increasing bulkiness of the C-7 substituent leads to the enhancement of the antibacterial potency against Gram-positive bacteria and the activity against efflux-mediated resistant mutants [28]. On the basis of this information and together with the inhibitory activity of flavonoids against efflux pumps, a series of hybrids of floxacin and flavonoid (Flox–Flav) were therefore synthesized for antibacterial evaluation against resistant bacteria (Scheme 2). Flox–Flavs **4**–**24** were prepared by direct coupling of commercial floxacins with



Scheme 2. General structures of a fluoroquinolone and a Flox–Flav hybrid.



Scheme 3. The synthetic route for Flox–narigenins.