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Phosphine derivatives of sparfloxacin – Synthesis, structures and *in vitro* activity

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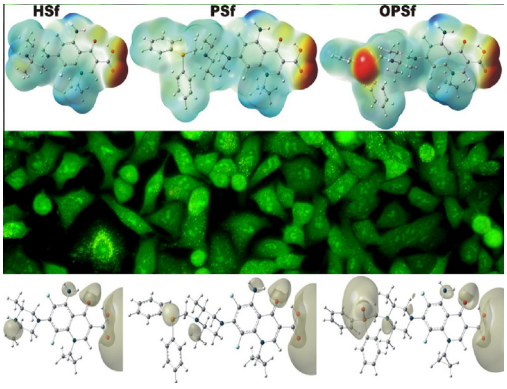
HIGHLIGHTS

- We synthesized two sparfloxacin derivatives: phosphine (**PSf**) and its oxide (**OPSf**).
- Molecular structure of **OPSf** was determined using X-ray analysis.
- DFT calculations were performed for all the compounds.
- Antibacterial activity was studied against several reference and clinical strains.
- **OPSf** exhibited a high cytotoxic activity against CT26 and A549 cancer lines.

GRAPHICAL ABSTRACT

Two derivatives of sparfloxacin: aminomethyl(diphenyl)phosphine and its oxide were synthesized and characterized by NMR spectroscopy, MS and elemental analysis. Their molecular structures were determined using DFT and X-ray analysis. The phosphine oxide was found cytotoxic *in vitro* against CT26 and A549 cancer cell lines.



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ABSTRACT

We synthesized two derivatives of sparfloxacin (**HSf**): aminomethyl(diphenyl)phosphine (**PSf**) and its oxide (**OPSf**). The compounds were characterized by NMR spectroscopy, MS and elemental analysis. In addition, the molecular structures of the compounds were determined using DFT and X-ray (**OPSf**) analysis. The antibacterial activity of **HSf** and both derivatives was tested against four reference and fifteen clinical Gram-positive and Gram-negative strains of bacteria (sensitive or resistant to fluoroquinolones). The results showed that the activity of **PSf** was similar to or higher than the activity of **HSf**, while **OPSf** was found significantly less active. The compounds were also tested *in vitro* toward the following cancer cell lines: mouse colon carcinoma (CT26) and human lung adenocarcinoma (A549). Regardless of the can-

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Aminomethylphosphine
Cytotoxicity
Antimicrobial activity

cer cell line, derivatization of **HSf** resulted in the gradual increase of cytotoxicity. **OPSf** exhibited the highest one (4 h – incubation time: IC50(CT26) = 51.0 ± 1.2; IC50(A549) = 74.9 ± 1.4 and 24 h: IC50(CT26) = 109.2 ± 8.8; IC50(A549) = 52.7 ± 9.2).

Introduction

Fluoroquinolones (FQs) belong to one of the most commonly prescribed classes of antibiotics in the world and are used extensively for treatment of many bacterial infections, both in human and veterinary medicine [1]. This class of antibiotics prove to be useful not only as antibacterial or antimalarial agents; they also exert immunomodulation and antitumor effects [2–4]. Therefore they are a popular subject of structural modifications, which can alter their biological activity and often help overcome microbial quinolone-resistance [5]. Structural modifications of the fused ring system have already resulted in four commercially available generations of these antibiotics [6]. Another interesting approach is adding substituents at the secondary nitrogen atom of the piperazine ring [7–12].

Numerous literature reports confirming that phosphines and their metal complexes exhibit promising antimicrobial, anticancer and antiarthritic properties [13–21] further justify such modifications. In addition, compounds bearing Ph_2P- or $Ph_2P(O)$-structural motifs (*i.e.* $Ph_2PCHR^1R^2$, $Ph_2(O)PCH\ R^1R^2$, $Ph_2P–N\ R^1R^2$, $Ph_2(O)P–N\ R^1R^2$) have proved to be potent inhibitors of the Kv1.5 potassium channel in the possible treatment of atrial fibrillation [22].

In our previous papers, we have described ciprofloxacin (**HCp**) and norfloxacin (**HNr**), the 2nd generation fluoroquinolones, modified to the novel aminomethyl(diphenyl)phosphine derivatives (Ph_2PCH_2**Cp**; **PCp** and Ph_2PCH_2**Nr**; **PNr**) and phosphine oxides ($Ph_2P(O)CH_2$**Cp**; **OPCp** and $Ph_2P(O)CH_2$**Nr**; **OPNr**). We have also demonstrated their diversified biological activity [13,14]. This prompted us to undertake studies on the derivatives of a 3rd generation fluoroquinolone antibiotic, sparfloxacin (**HSf**, Fig. 1). **HSf** is known for a broad spectrum of microbial activity against various Gram-positive and Gram-negative bacteria, including major emerging pathogens associated with community-acquired pneumonia such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Staphylococcus maltophilia* as well as *Staphylococcus aureus* [23]. Moreover, **HSf** is a promising modulating agent in combination with anticancer drugs for future preclinical and clinical studies. It has been proven that **HSf** inhibits HERG – one of the potassium channels, which are essential proteins for the regulation of cell proliferation [24]. HERG is overexpressed in a wide range of tumors, including colon carcinoma, what makes **HSf** and its prospective modifications an attractive subject of investigations.

Experimental

Materials

Reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques. $PPh_2(CH_2OH)_2Cl$ was synthesized according to a literature procedure [25]. Sparfloxacin, Ph_2PH, calf thymus DNA (CT DNA), human serum albumin (HSA) and other small chemicals and solvents were purchased from Sigma–Aldrich (Germany) and used without further purifications. Mueller Hinton Agar and Mueller Hinton medium were purchased from BioCorp (Poland). All cell culture fluids were purchased from IMMUNIQ (Poland). All solvents were deaerated prior to use.

Methods

NMR spectra were recorded on a Bruker AMX 500 spectrometer with traces of solvent as an internal reference for ^1H and ^{13}C spectra and 85% H_3PO_4 in H_2O as an external standard for ^{31}P. The signals in the spectra are defined as: s = singlet (∗ – strongly broadened signal), d = doublet, dd – doublet of doublets, t = triplet and m = multiplet. Chemical shifts are reported in ppm and coupling constants are reported in Hz. Elemental analyses were performed on a Vario EL3 CHN analyzer for C, H, and N, and they were within 0.4% of the theoretical values. Mass spectra were recorded on a Bruker Daltonics micrOTOF-Q mass spectrometer equipped with electrospray ionization (ESI) source and operated in positive ion mode.

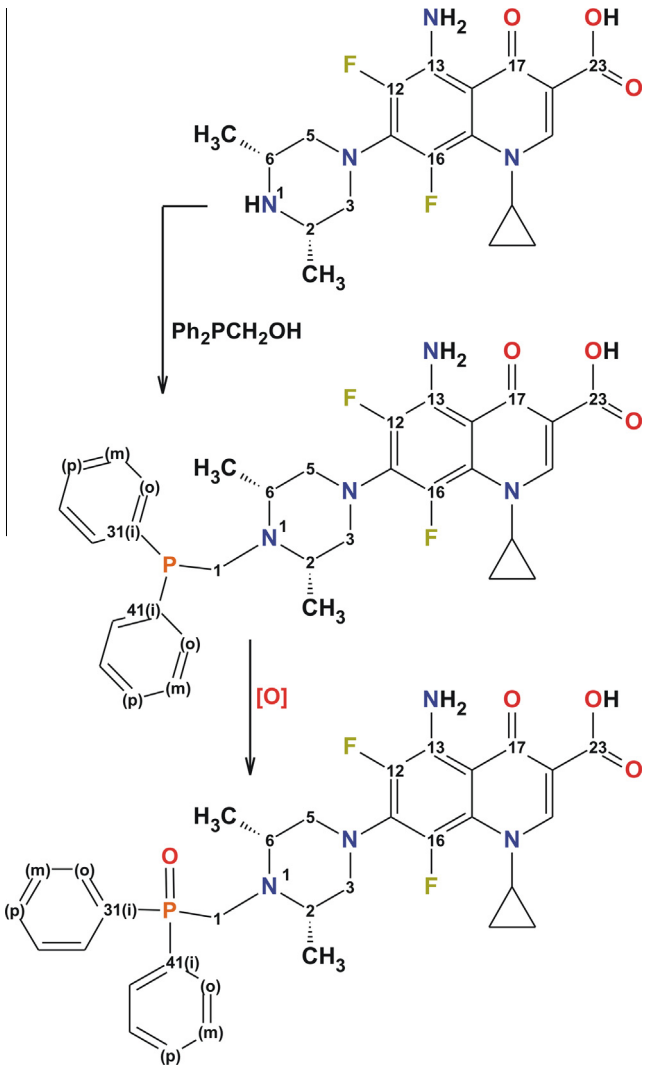

Fig. 1. Scheme of the synthesis route of **PSf** and **OPSf**.