



Joined X-ray, spectroscopic and theoretical study of potential antibacterial cyano group containing fluoroquinolone drugs precursors with the focus on the conformational behavior



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ABSTRACT

Conformational behavior of 3-fluorophenylaminoethylene precursors of potential antibacterial fluoroquinolone drugs are investigated by the comparison of obtained experimental X-ray structures, IR vibrational frequencies and UV-vis transitions with B3LYP/6-311++G** theoretical calculations. Theoretical investigations of the conformational behavior are extended for the rotational energy barriers between ZZa-EZa and ZZa-ZEa conformers which are investigated along with the change of bond critical points characteristics and delocalization indices of quantum theory of atoms in molecules (including atomic and formal functional group charges). Subsequently, molecular dynamics simulations are presenting a critical assessment of the dynamics of distinguished dihedral angles which are related to the conformational behavior.

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1. Introduction

3-Fluorophenylaminoethylene derivatives are well known precursors of (fluoro)quinolones which have a broad spectrum of biological action, e.g. antibacterial activity [1–4], anti-HIV [5,6] or antimycobacterial [7–10] effects. 3-fluorophenylaminoethylene derivatives represent a specific group of push-pull ethylene system containing electron-withdrawing groups (cyano, esters, etc.) on one side of the chain and electron-donor group (fluorophenylamino) on the other one [11]. These push-pull ethylenes prefer the *anti* (a) orientation of 3-fluorophenylamino group with respect to the C=C double bond of ethylene comparing to the *syn* (s) orientation [12–15]. Intramolecular hydrogen bond between the

amino hydrogen and carbonyl oxygen from the alkoxy carbonyl (methyl/ethyl ester) group is found to be a key feature for the stabilization of the energetically preferred conformer [16]. Hence, the E or Z isomers (alkoxy carbonyl C=O group in *trans* or *cis* position towards the amino group) are expected to be the most abundant for the conformational analysis of such compounds. Notably, the geometry of closely related compounds in the crystal structure is found in the *anti* [17] and/or ZZa [18] conformation.

Previously, we have studied push-pull system with different substituents ($R_1 = R_2 = -COOC_2H_5$, $-COOCH_3$ and $-COCH_3$ [19] as well as $R_1 = -CN$ and $R_2 = -COCH_3$) [20], where the outcome of the conformational analysis was critically confronted with the obtained X-ray structures and supported by molecular dynamics (MD) simulation [19]. Consequently, the theoretical investigation of conformational analysis, vibrational spectra, electronic transitions, and NMR chemical shifts were analyzed with respect to the

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experimentally measured spectra and the found crystal structures [21]. Further attention was paid to a detailed interpretation of the IR and Raman spectra based on the experimental and theoretical results of studied compounds and the interpretation of the calculated spectra in terms of potential energy distributions (PED) [22] $C \cdots \pi$, $N \cdots \pi$, $O \cdots \pi$ and $C-H \cdots \pi$ intermolecular interactions [18,23,24] and/or the crystal structure determination [17,24,25] in similar push-pull compounds have been investigated as well. Nevertheless, published results based on the theoretical calculations, X-ray structure determination and spectral analysis of the studied precursors including conformational behavior exploration are still scarce.

Herein, DFT conformational analysis of ethyl 2-cyano-3-(3-fluorophenylamino)prop-2-enoate (**P1**), methyl 2-cyano-3-(3-fluorophenylamino)prop-2-enoate (**P2**) and 2-[(3-fluorophenylamino)methylidene]propanedinitrile (**P3**) push-pull compounds is reported, i.e. $R_1 = -CN$ and $R_2 = -COOC_2H_5$, $-COOCH_3$. Structures of the studied fluoroquinolone precursors are summarized in Table 1 and the particular conformers of **P1** and **P2** are shown in Fig. 1. The outcome of the conformational analysis is critically confronted with the obtained X-ray structures. Rotational ZZa-EZa and ZZa-ZEa barriers characterization is enriched with monitoring the change in parameters of Quantum Theory of Atoms In Molecules (QTAIM) analysis [26–28], i.e. Bond Critical Point (BCP) characteristics, Delocalization Indices (DI) as well as atomic and formal functional group charges. Molecular dynamics (MD) simulations with and without Molecular Mechanics (MM) solvent molecules are compiled with a critical assessment of the dynamics of distinguished dihedral angles and of the conformational behavior in general. Consequently, the theoretical conformational analysis, vibrational spectra and electronic transitions are compared to the experimentally determined X-ray structures and/or measured spectra.

2. Experimental methods

The single-crystal diffraction data for studied compounds were collected at 298.0(1) K on an Oxford Diffraction Kappa geometry Gemini R diffractometer equipped with Ruby CCD area detector using monochromated Mo-K α radiation. Data collection and reduction was performed with Oxford Diffraction CrysAlis PRO version 1.171.37.35 software suite [29]. Crystal structures were

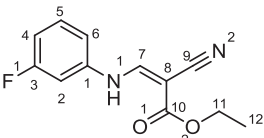
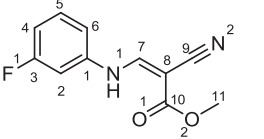
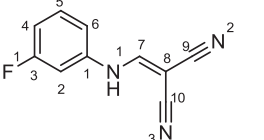
solved by direct methods with SHELXS-2013 [30] and refined by least-squares procedure on F^2 with SHELXL-2014 [31]. All non-hydrogen atoms were refined anisotropically. DIAMOND program was used for the molecular graphics [32]. Crystals of **P1** were prepared by dissolving the powder sample in just enough hot solvent (dimethyl sulfoxide, DMSO, for synthesis, Mikrochem, Slovakia) to form a saturated solution first and subsequently the crystallization was performed by a slow evaporation of the solvent at room temperature. Crystals of **P2** were crystallized out of chloroform ($CHCl_3$, for analysis, Mikrochem, Slovakia) by a slow diffusion of vapors of antisolvent (hexane, for synthesis, Mikrochem, Slovakia) in closed beaker. The powder sample of **P3** was dissolved in DMSO to form saturated solution. Crystallization of **P3** was then performed via a slow diffusion between a double layer of water (antisolvent) into DMSO solution of **P3** in the narrow test tube. All of the crystals of the studied compounds were colorless and precipitated after few weeks. The crystal data and final parameters after refinement are summarized in Table 2.

Experimental details of FT-IR and UV-vis measurements (including NMR shifts presented in the Supplementary Materials) are described in Plevová et al. [21].

3. Computational details

The geometry optimization was performed at the B3LYP/6-311++G** [33–36] level of theory using Gaussian09 [37] program package. Solvent effects of DMSO and $CHCl_3$ solutions were approximated by Integral Equation Formalism Polarizable Continuum Model (IEFPCM) [38,39] and a full conformational analysis of the fluoroquinolone precursors under study was performed. Vibrational analysis was used to confirm that the optimal geometry corresponds to the energy minimum (no imaginary vibrations) and to obtain the vibrational spectra. TD-DFT electronic transitions [40,41] were computed for each relevant conformer using the same solvent as in the experimental measurements (DMSO and $CHCl_3$). The 50 lowest electron excitations from the ground state were accounted for. ^{13}C , 1H and ^{19}F NMR chemical shifts (see Supplementary Materials) were calculated using the Individual Gauges for Atoms in Molecules (IGAIM) [42,43] and the Gauge-Including Atomic Orbital (GIAO) [44–47] approaches as embedded in Gaussian09. TMS (1H , ^{13}C NMR) and $CFCl_3$ (^{19}F NMR) were employed as NMR standards in the determination of theoretical

Table 1
Overview of the fluoroquinolone precursors under study.

| Abbreviation | Structure | Systematic name |
|--------------|---|--|
| P1 |  | ethyl 2-cyano-3-(3-fluorophenylamino)prop-2-enoate |
| P2 |  | methyl 2-cyano-3-(3-fluorophenylamino)prop-2-enoate |
| P3 |  | 2-[(3-fluorophenylamino)methylidene]propanedinitrile |

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