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ORIGINAL PAPER

An efficient reduction of azide to amine: a new methodology to synthesize ethyl 7-amino-1-ethyl-6,8-difluoroquinolone-3-carboxylate and its spectroscopic characterization

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Abstract Most of the quinolone antibacterial research has been focused on the functionality at C-7 position where the nature of substituents is responsible for antibacterial spectrum, potency, bioavailability, and side effects of the quinolones. Then, a 7-amino-fluoroquinolone could be the starting point of a wide variety of potentially useful compounds like tetracyclic and tricyclic quinolones or secondary amines with side chain derivatives. This attracted our attention to synthesize a 7-azide-fluoroquinolone, which could be converted to amine performing a photochemical reaction using CuI as catalyst. FT-IR and H^1 NMR spectra of the final product, ethyl 7-amino-1-ethyl-6,8-difluoroquinolone-3-carboxylate, suggests the formation of dimers, a feature already observed in norfloxacin.

Keywords Anti-infective compound · Aminofluoroquinolone dimer · π–π interaction · 7-amino-fluoroquinolone · 7-azide-fluoroquinolone

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Introduction

Quinolones have received great attention due to biological and pharmacological activities not only as potential antibacterial, antitumor, and anticancer agents but also as important and useful starting materials for the synthesis of other fused heterocyclic systems. The evolution of quinolones has been possible due to modifications in the quinolone nucleus through the addition of various substituents at the N-1, C-5, C-6, C-7, and C-8 positions and the formation of fused rings, being positions 5, 6, 7, and 8 (Ahmed and Daneshtalab 2012; Boteva and Krasnykh 2009; Mitscher 2005; Naeem et al. 2016; Soni 2012) the major targets. These modifications altered the biological activities, pharmacokinetics, and metabolic properties of the quinolones and provided a better understanding of structure–activity relationships in quinolone compounds (Bolon 2011; Richter et al. 2005).

Different mechanisms of action concerning quinolone drugs against bacterial infection that involve inhibition of DNA gyrase and cell penetration have been proposed (Aldred et al. 2014, 2012; Khodursky and Cozzarelli 1998; Shen et al. 1989). One of these hypotheses suggests the existence of a complex that occurs between dimers of quinolone molecules with DNA chains and DNA gyrase where the cooperativity and the high binding affinity are derived from the strong intermolecular drug–drug interactions. That complex prevents the DNA replication and conducts to cell death. Recently, studies show how the intermolecular interactions between aromatic ring π orbitals play an important role in the quinolone packing in solid state (Mafra et al. 2012), indicating that these molecules have a tendency to self-associate.

A difluoroquinolone derivative with an amino at the position 7 could be used as an intermediate compound to

generate tetracyclic and tricyclic quinolones by fusing rings between the 6 and 7, or 7 and 8 positions (Glushkov et al. 1990; Zahra et al. 2007), or secondary amines with side chain derivatives, showing in either case a favorable increase in antibacterial activity (Zhang et al. 2004) or in treatments against cancer cell lines without cytotoxicity to normal cells (Al-Trawneh et al. 2010).

Nevertheless, the synthesis of 7-amino-quinolone obtained so far, is from a sodium amide by S_NAr (Bunneti and Kearley 1971) but limited by the kind of halogen bonded to the aromatic ring, being fluorine atom the less reactive of halides (Hartwing et al. 2007). Another method involves the reduction of a nitro group by hydrogen gas (Facchinetti et al. 2015), but offers a not friendly environment and requires special equipment. An alternative, and understudied, method is a reduction of the azide group that seems to be a simple, regio- and stereo-selective strategy when combined with the use of a photoreactor (Leyva et al. 2008).

Thus, we are reporting the synthesis of ethyl 7-amino-1-ethyl-6,8-difluoroquinolone-3-carboxylate by a Gould-Jacobs cyclization process followed by alkylation, substitution, and reduction, as well as its spectroscopic characterization, and the preliminary theoretical studies as a tool for understanding the formation of quinolone dimers. This work belongs to an ongoing program focused to identify novel, potent, and broad-spectrum antibacterial and anticancer agents.

Experimental

Instruments

The melting points were obtained with a Fisher–Johns melting point apparatus. The UV–Vis spectra were performed on a Shimadzu UV-2401 PC UV–Vis spectrophotometer using methanol as solvent and 1 cm path quartz cells. The IR spectra were recorded in a Thermo Nicolet iS10 FTIR spectrophotometer using the attenuated total reflectance (ATR) technique. The NMR spectra were obtained on a Varian Gemini 200 and a Mercury 400 MHz spectrometer using TMS as internal standard.

Synthesis

Hydrolysis reaction

The ester-quinolone ***2*** (1.32 mmol) was mixed with 2 N NaOH (3 mL) at 110–120 °C for 30 min; then, it was cooled to room temperature and 1:1 HCl (3 mL) was added. The resulting solid was filtered, washed with distilled water, and dried in vacuum to obtain a solid ***3***.

Difluoroborylation

The ester-quinolone ***2*** (1.32 mmol) and diphenyl ether (6 mL) were added slowly inside a round flask at 200 °C. Then, $BF_3{\cdot}OEt_2$ (1.58 mmol) was added and allowed it to react for 20 min. The formed solid ***4*** was filtered and washed with *n*-hexane.

S_NAr by N_3 group

In a round flask with DMF (4.2 mL), the quinolone ***2***, ***3***, or ***4***, (3.44 mmol) was solved increasing gradually the temperature up to 60 °C. After then, NaN_3 (4.12 mmol) was slowly added and keep reacting for 30 min. Subsequently, ice water (10 mL) was poured into the flask reaction, the solid ***5a–c*** was filtered, washed with cold water, and crystallized from methanol.

N_3 reduction to amine

In a round flask, the azide-quinolone ***5a*** (312.9 μmol) was mixed with trifluoroacetic acid (625.8 μmol), CuI (5 μmol %), and methanol (2 mL). The mixture was irradiated with 350 nm light for 3 days in a Southern New England Rayonet Photoreactor. After that, saturated $NaHCO_3$ (3 mL) was added and the product extracted with $CHCl_3$ (10 mL × 3). The solvent was removed using a rotary evaporator to yield a solid from which ***6a*** was purified by preparative TLC chromatography with silica gel using a mixture of ethyl acetate/*n*-hexane.

Computational calculations

Pairs of amino-quinolone ***6a*** molecules were initially arranged as starting geometries where the closeness of appropriate groups could form dimers interacting by intermolecular hydrogen bonds and/or π–π interactions. The geometry of molecule ***6a*** and the arranged pairs were optimized, without constraints, using the PM6-DH+ method, which include Korth's corrections (Korth 2010). Vibration frequency calculations were carried out at the regular PM6 method (Stewart 2007). All calculations were performed with the MOPAC 2009 package of programs (MOPAC2009).

Results and discussion

Synthesis

A general procedure for the synthesis of 7-azide-1-ethyl-6,8-difluoroquinolone-3-substituted (***6a***: R=CO_2R, ***6b***: CO_2H, ***6c***: CO_2BF_2) is presented as a Gould–Jacobs

cyclization process, starting from 2,3,4-trifluoroaniline ***1***, followed by *N*-alkylation to produce the 1-ethyl-6,7,8-trifluoroquinolone-3-carboxylate ***2*** (Fig. 1). This intermediate has a carbon with high electrophilic character that allows the introduction of an azide group at C-7 position, resulting the 7-azide-6,8-difluoroquinolone, ***5*** (Leyva and Leyva 2007). However, the nucleophilic displacement of the fluorine atom from **2** could be enhanced by the transformation of the ester into a carboxylic acid ***3*** or a boron complex ***4*** (Hermecz et al. 1998). In both cases, a high regioselectivity occurred.

Then, the azide is reduced to amine giving ethyl 7-amino-1-ethyl-6,8-difluoroquinolone-3-carboxylate ***6a*** by a photochemical reaction using CuI as catalyst. Moreover, this reduction has a useful increase in efficiency: a 46% yield compared to 20% previously reported (Leyva et al. 2008) since the generated nitrene could be intercepted by a nucleophile such as methanol or undergone polymerization to form tar (Leyva et al. 2008), but is comparable with the reduction of a nitro group bonded to quinolone, 60–70% yield (Facchinetti et al. 2015).

The azide reduction reaction has been studied using different catalysts such as: $CeCl_3{\cdot}7H_2O$/NaI (Bartoli et al. 2008) and $AlCl_3{\cdot}6H_2O$/Fe (Zhen et al. 2006), or different solvents like acetonitrile or ethanol; however, in our case they did not allow us to obtain the 7-amino-quinolone.

Therefore, the reduction of a 7-azide-quinolone by a photochemical reaction results in a mild reaction method requiring reagents as trifluoroacetic acid and CuI, in catalytic amounts, and aqueous methanol at room temperature without pretreatment using UV radiation to react, avoiding the use of anhydride solvents or inert atmosphere.

The products ***3–6*** were characterized by UV–Vis, FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. Their corresponding spectra can be found in the supplementary data and the main spectral features are shown in Table 1.

Spectroscopy

Regarding the 7-azide-6,8-difluoroquinolone-3-carboxylate ***5a*** and its derivatives (***5b***, ***5c***), the azide group is observed in IR spectroscopy at 2127 cm^{-1} due to the N–N stretching vibration (Fig. 2); it has a strong intensity in the azide-quinolone esters ***5a*** and ***5c*** due to the dipole moment present in the N–N bond of aromatic azides that is favored by the resonance structures ***5a*** and ***5c*** (Fig. 3); however, in the azide-quinolone carboxylic acid ***5b***, this band has an unusual behavior because the unpaired electrons in the nitrogen atom could conjugate with the carbonyl group present in the quinolone ring, resulting in lowering the N–N absorption intensity being the predominant resonance structure ***5b***. Then, the azide group in the azide-quinolone

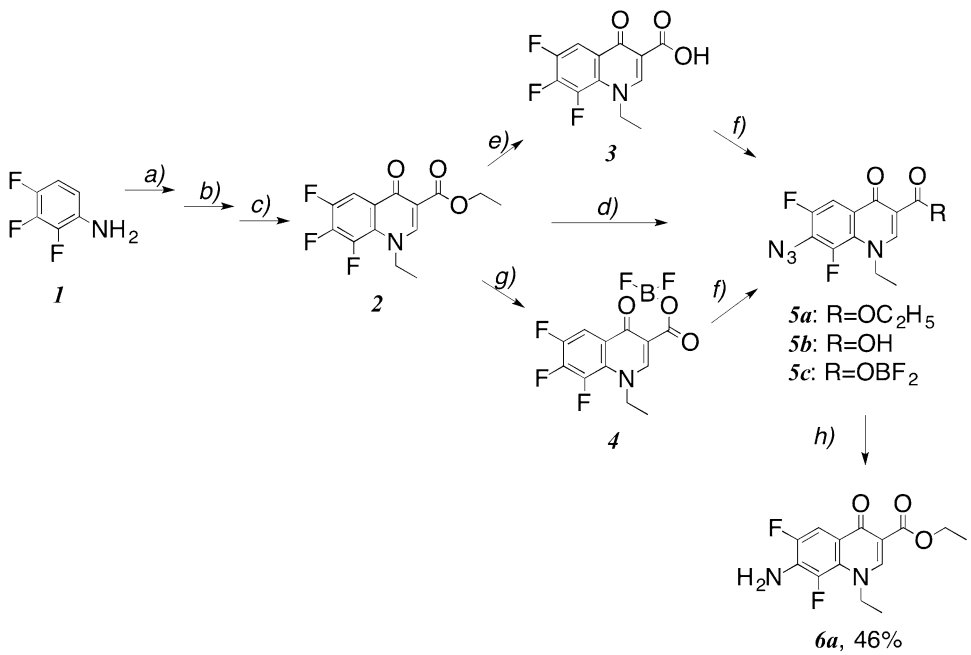

Fig. 1 Synthesis of ethyl 7-amino-1-ethyl-6,8-difluoroquinolone-3-carboxylate ***6a***

a) EMME, 110-120 °C, 2h. *b*) diphenylether, 250 °C, 6h. *c*) Iodoethane, K_2CO_3, DMF, 80-90 °C, 8h. *d*) NaN_3, CH_3COCH_3/H_2O, 60 °C, 6h. *e*) NaOH 2N, HCl (1:1), 110-120 °C, 2h. *f*) NaN_3, DMF, 60 °C, 30 min. *g*) $BF_3{\cdot}OEt_2$, diphenylether, 200 °C, 30 min. *h*) UV, MeOH, F_3CCO_2H, CuI, 3 days.

Table 1 Spectral data of newly prepared compounds

Compound	Spectral data
3	UV–Vis (CH_3OH) λ/nm: 216 (π → π*, C=O carboxylic acid), 236 (π → π*, C=O ketone), 261, 271 (π → π*, C=C aromatic), 313 (η → π*, C=O carboxylic acid), 324 (η → π* C=O, ketone).
	FT-IR (ATR) ν/cm^{-1}: 3550–3300 (O–H carboxylic acid), 1703 (C=O carboxylic acid), 1686 (C=O ketone), 1615 (C=C vinyl), 1540, 1445 (C=C aromatic), 1372, 1251 (C–O carboxylic acid), 1203, 1016 (C–N).
	^{1}H NMR (DMSO-d_6) δ/ppm: 1.41 (t, J_{HH} = 7.00 Hz, 3H), 4.56 (c, J_{HH} = 7.00 Hz, 2H), 7.87 (d, $J_{HF\ ortho}$ = 10.50 Hz, 1H), 8.90 (s, 1H), 12.02 (s, 1H).
	^{13}C NMR (DMSO-d_6) δ/ppm: 176.2 (ketone), 166.1 (carboxylic acid), 151.3, 107.2 (vinyl), 141.1, 127.5, 126.7, 125.4, 118.8, 107.1 (aromatic), 53.9 (methylene), 16.3 (methyl).
4	UV–Vis (CH_3OH) λ/nm: 217 (π → π*, C=O ester), 240 (π → π*, C=O ketone), 245 (π → π*, C=C aromatic), 313 (η → π*, C=O ester), 327 (η → π*, C=O ketone).
	FT-IR (ATR) ν/cm^{-1}: 3667 (C=O overtone), 1722 (C=O ester), 1677 (C=O ketone), 1652 (C=C vinyl), 1613, 1494 (C=C aromatic), 1321, 1189 (C–O ester), 1056, 1189 (C–N).
	^{1}H NMR (DMSO-d_6) δ/ppm: 1.42 (t, J_{HH} = 7.00 Hz, 3H), 4.60 (q, J_{HH} = 7.00 Hz, 2H), 8.24 (t, $J_{HF\ orto}$ = 9.00 Hz, 1H), 9.02 (s, 1H).
	^{13}C NMR (DMSO-d_6) δ/ppm: 175.89 (ketone), 165.52 (ester), 152.40, 108.94 (vinyl), 151.9, 127.5, 126.7, 125.4, 110.3, 108.2 (aromatic), 53.9 (methylene), 16.1 (methyl).
5a	UV–Vis (CH_3OH) λ/nm: 210 (π → π*, C=O ester), 249 (π → π*, C=O ketone), 257 (π → π*, C=C aromatic), 276 (η → π*, azide), 314 (η → π*, C=O ester), 324 (η → π*, C=O ketone).
	FT-IR (KBr) ν/cm^{-1}: 2127 (N_3), 1682 (C=O ester), 1640 (C=O ketone), 1617 (C=C vinyl), 1601, 1474 (C=C aromatic), 1319, 1301 (C–O ester).
	^{1}H NMR ($CDCl_3$) δ/ppm: 1.41 (t, J_{HH} = 7.20 Hz, 3H), 1.54 (t, J_{HH} = 7.00 Hz, 3H), 4.37 (q, J_{HH} = 7.20 Hz, 2H), 4.40 (q, J_{HH} = 7.00 Hz, 2H), 8.09 (dd, $J_{HF\ ortho}$ = 11.00 Hz, $J_{HF\ para}$ = 2.40 Hz, 1H), 8.39 (s, 1H).
	^{13}C NMR ($CDCl_3$) δ/ppm: 171.4 (ketone), 165.1 (ester), 151.0, 109.3 (vinyl), 154.0, 145.3, 142.8, 126.8, 125.7, 110.6 (aromatic), 61.2, 53.5 (methylene), 16.1, 14.3 (methyl).
5b	UV–Vis (CH_3OH) λ/nm: 216 (π → π*, C=O carboxylic acid), 238 (π → π*, C=O ketone), 263, 269 (π → π*, C=C aromatic), 312 (η → π*, C=O carboxylic acid), 322 (η → π*, C=O ketone).
	FT-IR (ATR) ν cm^{-1}: 3550-3300 (O–H carboxylic acid), 2136 (azide), 1707 (C=O carboxylic acid), 1686 (C=O ketone), 1614 (C=C vinyl), 1539, 1444 (C=C aromatic), 1249 (C–O carboxylic acid), 1202, 1046, 1015 (C–N).
	^{1}H NMR (DMSO-d_6) δ/ppm: 1.41 (t, J_{HH} = 7.00 Hz, 3H), 4.57 (q, J_{HH} = 7.00 Hz, 2H), 7.89 (dd, $J_{HF\ ortho}$ = 10.00 Hz, $J_{HF\ para}$ = 1.5 Hz, 1H), 8.91 (s, 1H), 12.01 (brs, 1H).
	^{13}C NMR (DMSO-d_6) δ/ppm: 176.2 (ketone), 166.1 (carboxylic acid), 151.3, 107.1 (vinyl), 143.1, 141.2, 127.5, 125.4, 117.9, 107.3 (aromatic), 54.0 (methylene), 16.3 (methyl).
5c	UV–Vis (CH_3OH) λ/nm: 217 (π → π*, C=O ester), 276 (π → π*, C=C aromatic), 325 (η → π*, C=O ester), 337 (η → π*, C=O ketone).
	FT-IR (ATR) ν/cm^{-1}: 3667 (C=O overtone), 2127 (azide), 1719 (C=O ester), 1678 (C=O ketone), 1614 (C=C vinyl), 1516, 1466 (C=C aromatic), 1320, 1255 (C–O ester), 1196, 1128 (C–N).
	^{1}H NMR (DMSO-d_6) δ/ppm: 1.54 (t, J_{HH} = 7.00 Hz, 3H), 4.61 (q, J_{HH} = 7.00 Hz, 2H), 8.23 (d, $J_{HF\ ortho}$ = 11.50 Hz, 1H), 9.42 (s, 1H).
	^{13}C NMR (DMSO-d_6) δ/ppm: 176.0 (ketone), 165.6 (ester), 152.1, 108.9 (vinyl), 151.9, 127.5, 126.7, 125.4, 110.3, 108.0 (aromatic), 57.8 (methylene), 16.8 (methyl).
6a	Uv–Vis (CH_3OH) λ/nm: 213 (π → π*, C=O ester and ketone), 274 (π → π*, C=C aromatic), 313 (η → π*, C=O ester), 324 (η → π*, C=O ketone).
	FT-IR(ATR) ν/cm^{-1}: 3503, 3434, 3318, 3199 (N–H), 3246 (N–H overtone), 1717 (C=O ester), 1691 (C=O ketone), 1645 (C=C vinyl), 1620, 1579 (C=C aromatic), 1085 (C–N amine), 795 (N–H oop).
	^{1}H NMR ($CDCl_3$) δ/ppm: 1.41 (t, J = 7.1 Hz, 3H), 1.53 (t, J = 7.1 Hz, 3H), 4.32 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 8.09 (dd, $J_{HF\ ortho}$ = 11.00 Hz, $J_{HF\ para}$ = 2.40 Hz, 1H), 8.39 (s, 1H).
	^{13}C NMR ($CDCl_3$) δ/ppm: 171.4 (ketone), 165.1 (ester), 151.0, 109.3 (vinyl), 154.0, 145.3, 142.8, 126.8, 125.7, 110.6 (aromatic), 61.2, 53.5 (methylene), 16.1, 14.3 (methyl).

ester ***5a*** could be reduced to an amine group with lower byproducts.

The amino-quinolone ***6a*** showed interesting spectroscopic results that caught our attention. In IR spectroscopy, it is common to observe two bands for primary amines in the range from 3500 to 3300 cm^{-1} as a result of N–H stretch vibration. In our case, a second pair of bands between 3500 and 3100 cm^{-1} was observed (Fig. 7,

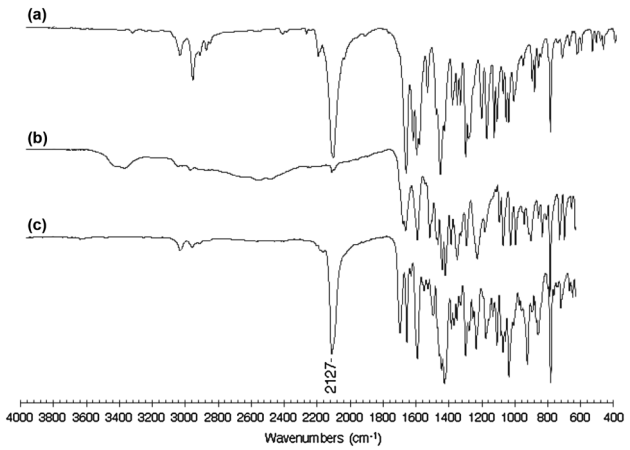

Fig. 2 IR spectra of the azide-quinolone ester ***5a*** and its derivatives ***5b*** and ***5c***

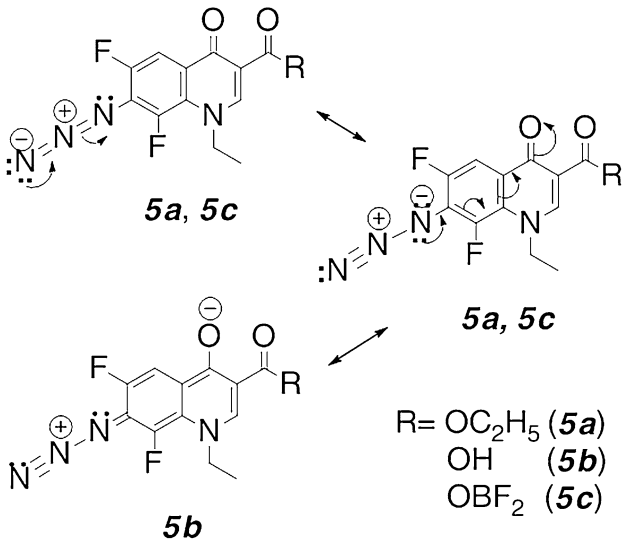

Fig. 3 Predominant resonance structures of the azide-quinolone esters (***5a***, ***5c***) and the carboxylic acid (***5b***)

spectrum a) indicating the presence of two different amino groups bonded to the fluoroquinolone ring. Probably the formation of dimers by the overlapping of two molecules of quinolone ***6a***, caused by π–π interactions and/or intermolecular hydrogen bonds, could have originated additional bands in the IR spectrum. The self-association of quinolone-based antibiotics like norfloxacin, explained as π–π interactions, has been proposed as an explanation for the inhibition of DNA gyrase (Shen et al. 1989). The close-related antibiotic ciprofloxacin, in anhydrous or hydrated forms, also associates in the solid state (Mafra et al. 2012). Norfloxacin and ciprofloxacin even co-crystalize in a 1:1 stoichiometric proportion (Vitorino et al. 2013).

In the ^{1}H NMR spectrum of ***6a*** (Fig. 4, spectrum a), a single kind of amino group at 4.32 ppm was only detected. This behavior was observed only when $CDCl_3$ was used as a dissolvent, instead of DMSO-d_6, for the NMR analysis. In an attempt to show the intermolecular interactions of these compounds in solution, we conducted a ^{1}H NMR spectrum of ***6a*** at different $CDCl_3$ concentrations. Figure 4 shows that the signal corresponding to NH_2 shifts slightly downfield as the concentration of ***6a*** increases from 3.5 to 14 mg of 6***a***/0.5 mL of $CDCl_3$ (spectra a, b, c and d). This fact shows a weak interaction of ***6a*** molecules. However, an estimate of the shift caused by hydrogen bonding is observed when tetrabutylammonium fluoride (TBAF) is added (0.1–1 molar equivalents, spectra e, f and g) (Tapia-Juárez et al. 2014; Thordarson 2011). A significant shift of the NH_2 signal, explained by the strong hydrogen bond with fluoride ions, firmly suggests that dimers' hydrogen bonds would be weak.

Computational studies

We performed semiempirical calculations as a preliminary tool for a theoretical understanding of the formation of quinolone dimers. The starting structures used to evaluate the possible formation of dimers are shown in Fig. 5, where ***6a*** is a single molecule of amino-quinolone and **p1**, **p2**, and **p3** are three different pairs of ***6a*** molecules stacked in different orientations. In pairs **p1** and **p3** the ester groups of both molecules are on opposite sides whereas in pair **p2** the ester groups are on the same side. Figure 6 shows the optimized geometries of molecule ***6a*** and five different dimers of ***6a*** molecules, **d1**–**d5**. Two views of each dimer are shown in Fig. 6. Molecule ***6a*** belongs to the C_1 point group with the amine and ethyl groups out of the plane of the aromatic ring. In dimers **d1** and **d4** two N–H···O(C) intermolecular hydrogen bonds, between the amino group from a ***6a*** molecule and oxygen from the ester group of the second ***6a*** molecule, seem holding the dimer. Similar dimers containing possible hydrogen bonds between an amino group and a carbonyl from the ester group were also obtained and labeled as **d2** and **d5**. The optimization of pair **p3** gave the dimer **d3** where the aromatic rings keep the highest degree of parallelism among the five dimers found, suggesting π–π interaction as the source of the **d3** dimer stability.

The intermolecular distance between the aromatic rings of each dimer molecule is about 3.3 Å, as shown in Table 2; the values are the two closest distances between pairs of atoms, where each atom in a pair is located in one of the almost parallel aromatic rings. The interring distance is comparable to the distance reported for the benzene dimer, the simplest system stabilized by π–π interactions, in parallel displaced conformation, about 3.4–3.6 Å (Sinnokrot et al. 2002). On the other hand, the possibility of hydrogen bonds stabilizing dimers is suggested by the H-acceptor (O) interatomic distances (Table 2) in dimers

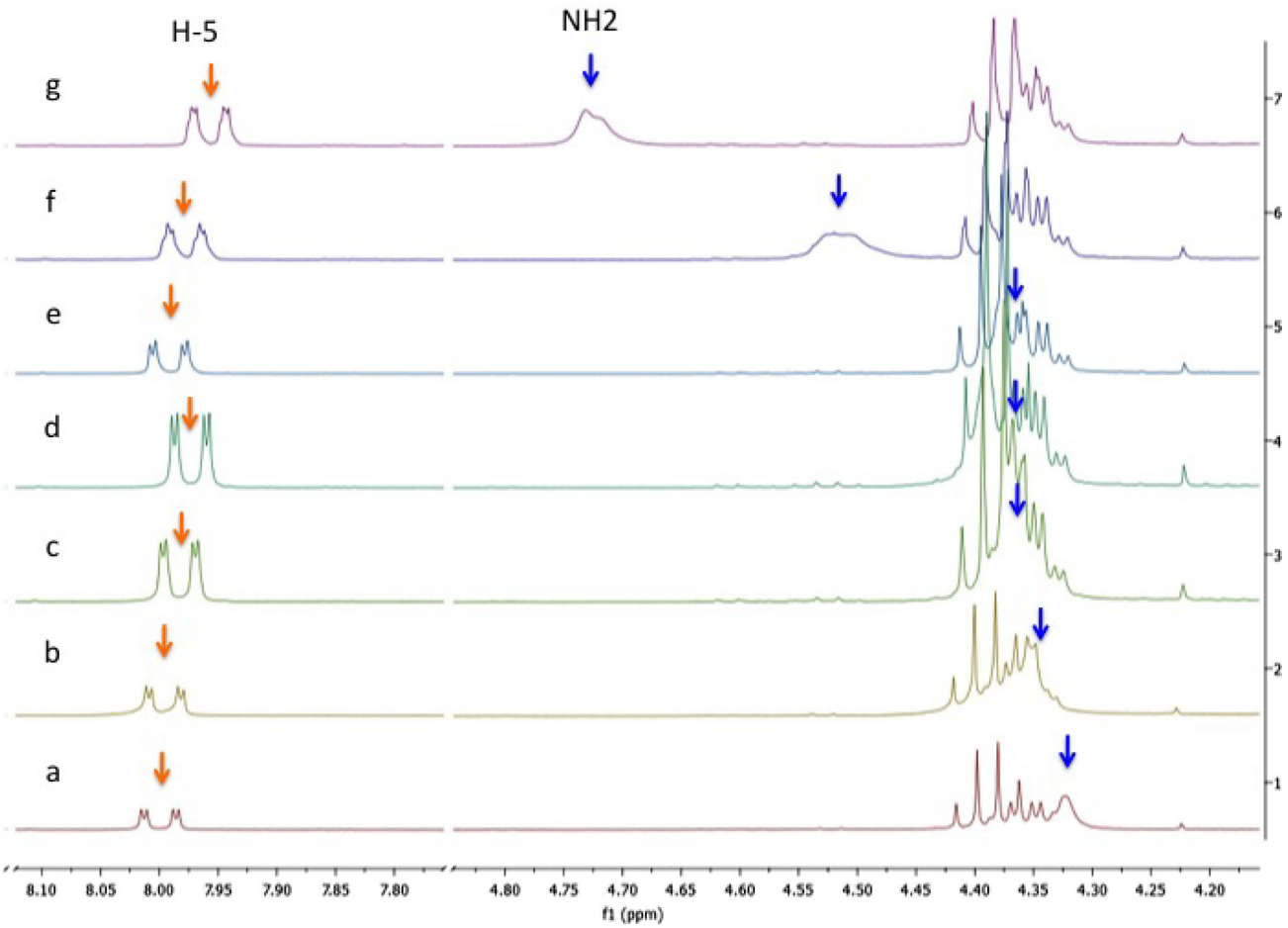

Fig. 4 ^{1}H NMR spectra of 7-amino-quinolone ***6a*** (mg) in $CDCl_3$ (0.5 mL): **a** 3.5 mg, **b** 7 mg, **c** 10.5 mg, **d** 14 mg. Addition of tetrabutylammonium fluoride (molar equivalents) to 3.5 mg ***6a***/0.5 mL $CDCl_3$: **e** 0.1 mol eq, **f** 0.5 mol eq, and **g** 1 mol eq

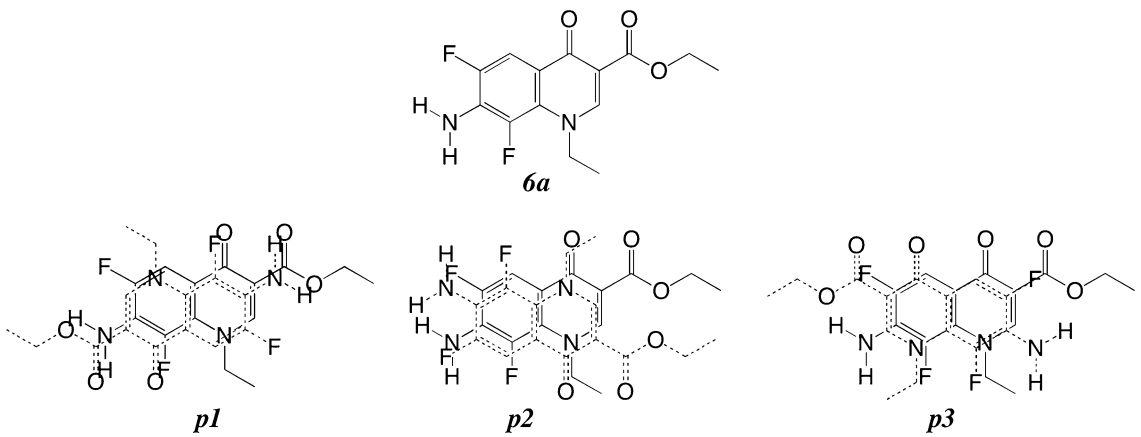

Fig. 5 Starting structures for theoretical study

d2 and **d5**, 1.91–1.93 Å, and **d1** and **d4**, 1.95–2.03 Å; however, a better indicator of hydrogen bonds is the donor (N)-acceptor (O) distance, 2.82–2.94 Å, but it is 0.2–0.3 Å larger that the limit for strong O–H···O hydrogen bonds (Gilli et al. 1994) indicating weak bonds; moreover, being here heteroatoms (N, O) the bonds would be even weaker, discouraging hydrogen bonds as the main source of dimers' stability. This behavior leaves π–π interaction as the possible source of dimers' stability, as Mafra et al. (2012) reported for quinolone rings.

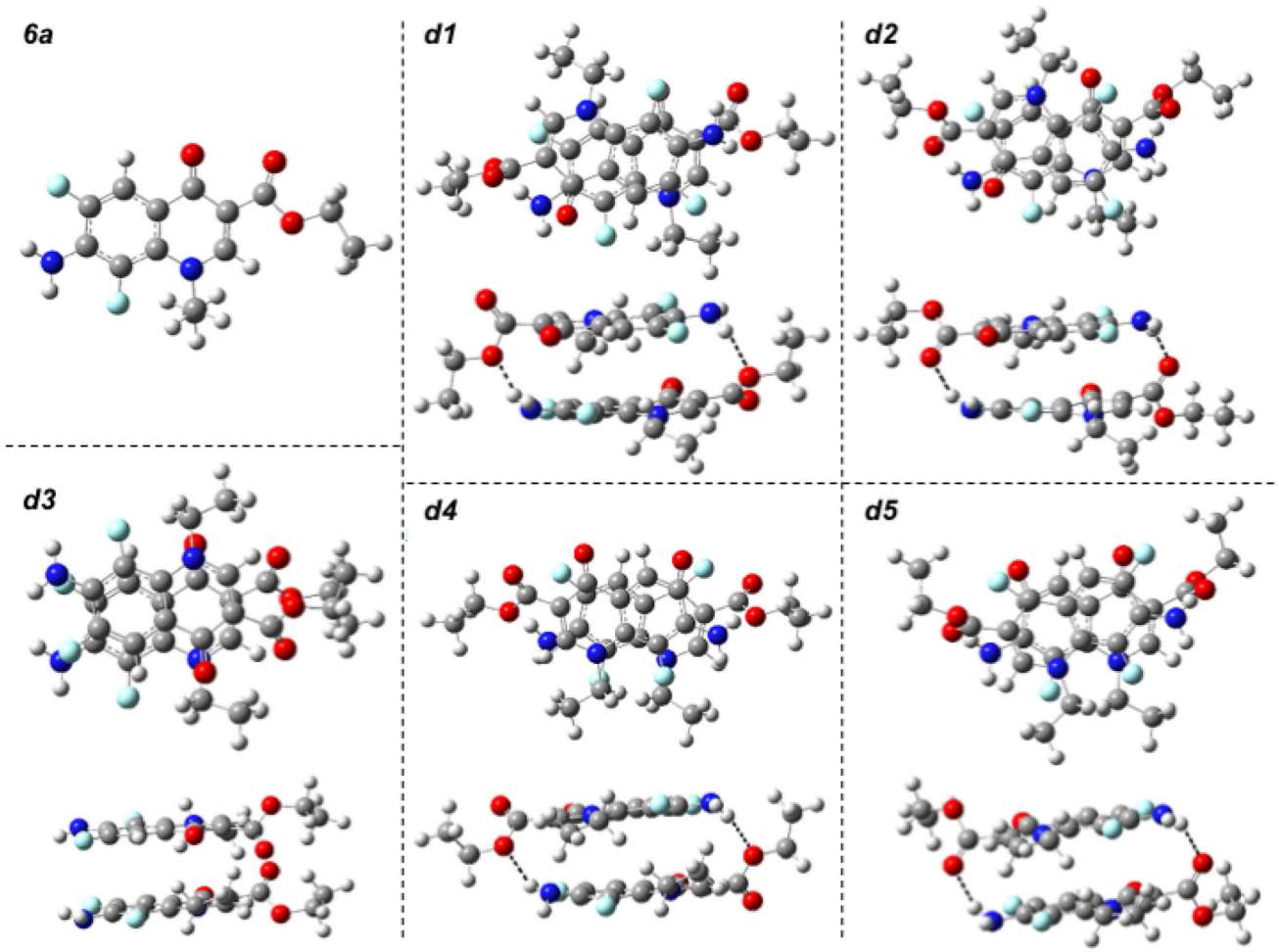

Fig. 6 Optimized geometries (PM6-DH+) of the monomer ***6a*** and five dimers (**d1**–**d5**). A top view and a side view are shown for each dimer

Table 2 Geometric parameters (PM6-DH+) and stretching frequencies (PM6) calculated for dimers **d1–d5**

Molecule	Ring to ring distance (Å)	H—acceptor (O) distance (Å)	Donor (N)–acceptor (O) distance (Å)	N–H stretching frequency (cm^{-1})
d1	3.15–3.31	1.95	2.94 (ester)	2676
		2.02	2.89 (ester)	2707
				2780, 2797
d2	3.15–3.28	1.93	2.89 (CO)	2648
		1.91	2.84 (CO)	2658
				2786, 2815
d3	3.29–3.36			2804 (2), 2811, 2815
d4	3.28–3.30	1.96	2.89 (ester)	2676
		2.03	2.91 (ester)	2710
				2810, 2822
d5	3.32–3.33	1.91, 1.92	2.82 (2) (CO)	2655, 2657
				2819 (2)
6a[1]				2804, 2809

[1] Stretching frequencies of **6a** are added as reference

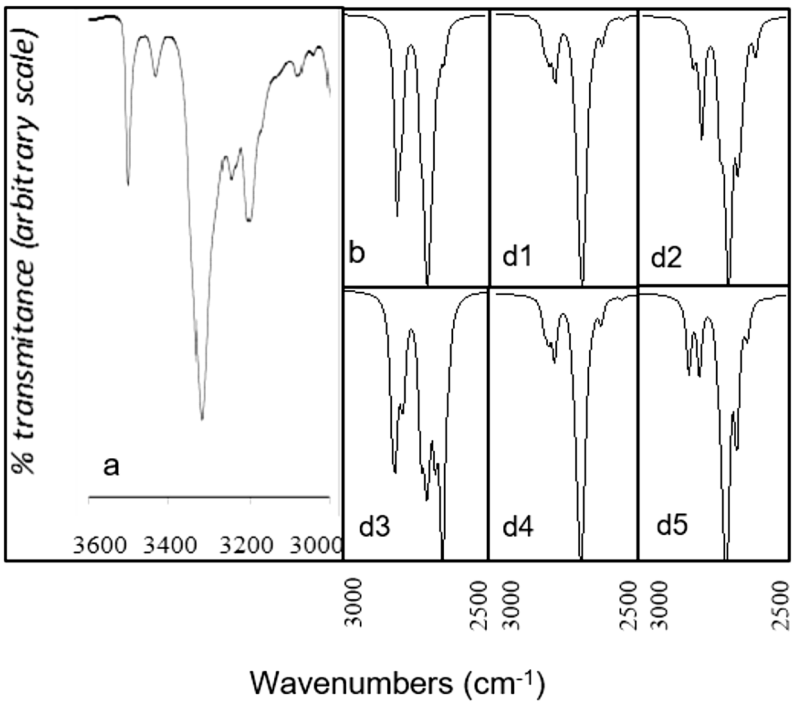

Fig. 7 IR spectra in the N–H stretching region. **a** Experimental for ***6a***. **b** Calculated for ***6a***. Calculated for dimers (**d1**–**d5**)

Regarding vibration frequencies, the experimental IR spectrum of ***6a*** is shown in Fig. 7a, whereas the calculated IR spectra of ***6a*** and dimers **d1**–**d5** are shown in Fig. 7b, d1–d5, with their calculated N–H stretching frequencies reported in Table 2. Figure 7 shows IR spectra in the N–H stretching region. For ***6a*** the experiment shows a medium peak at 3318 cm^{-1} and four small peaks at 3199, 3246, 3434, and 3503 cm^{-1}; all of them could be attributed to a complex variety of N–H stretching modes. In contrast, the calculated spectrum of ***6a*** (within the PM6 approximation) gives only two medium peaks in the 2700–2800 cm^{-1} region; however, only the 2804 and 2809 cm^{-1} frequencies belong to N–H bonds; the system about 2700 cm^{-1} belongs to C–H stretching bonds. Clearly, the experiment indicates more than two kinds N–H bonds suggesting the formation of dimers of ***6a*** molecules with non-equivalent N–H bonds.

The calculated IR spectra for dimers **d1**–**d5** show multiple bands with different intensity from 2540 to 2830 cm^{-1}; such behavior is closer to what is experimentally observed, although the calculated values are smaller than the experimental ones. Even as the possibility of hydrogen bonds lies in the weak type, by geometry considerations, the closeness of an oxygen atom to an H–N bond does shift the calculated H–N stretching frequency to lower values, as expected from the weakening of the H–N bond (Kovács et al. 2002; Vega-Rodríguez, et al. 2013). Table 2 shows lower H–N stretching frequencies (a 100–170 cm^{-1} decrease) in dimers **d1**, **d2**, **d4,** and **d5** compared to the values in single ***6a*** molecules. For dimer **d3**, with no oxygen near an H–N bond, the four H–N stretching frequencies are in the range 2804–2815 cm^{-1}, as in isolated ***6a*** molecules.

From our first level (semiempirical) approximation to the calculated IR spectra of five dimers of ***6a*** molecules, the features of their H–N stretching frequencies resemble the experimental spectrum.

Conclusions

We have developed a facile and general synthesis of 7-azide-3-substituted fluoroquinolones by direct nucleophilic substitution of 1-ethyl-6,7,8-trifluoroquinolone with sodium azide. This intermediate is highly reactive and easily reduced to the corresponding 7-amino-1-ethyl-6,8-difluroquinolone. The last compound, by the use of standard procedures, could be used to develop new chemical libraries of fluoroquinolones such as tetracyclic and tricyclic quinolones or secondary amines with side chain derivatives. The FT-IR and H^1 NMR studies, besides characterizing the final compound, suggest the synthesized ethyl 7-amino-1-ethyl-6,8-difluoroquinolone-3-carboxylate associates in dimers.

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