Journal of Fluorine Chemistry 132 (2011) 263–268

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Synthesis of *N*-aryl-2,2,2-trifluoroacetimidoyl piperazinylquinolone derivatives and their antibacterial evaluations

Ali Darehkordi [a,*], Mahmood Javanmiri [a,b], Somayeh Ghazi [a,b], Shokrollah Assar [b]

[a] Department of Chemistry, Faculty of Science, Vali-e-Asr University of Rafsanjan, Rafsanjan 77176, Iran
[b] Department of Microbiolog, Immunology and Biology, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

ARTICLE INFO

Article history:
Received 9 December 2010
Received in revised form 1 February 2011
Accepted 2 February 2011
Available online 4 March 2011

Keywords:
Organofluorine
Trifluoroacetimidoyl chloride
Piperazinylquinolone
Norfloxacin
Ciprofloxacin

ABSTRACT

N-substituted trifluoroacetimidoyl chlorides were used for the synthesis of new piperazinylquinolone derivatives. These reactions provided *N*-aryl-2,2,2-trifluoroacetimidoyl piperazinylquinolone derivatives in good yields. Two selected compounds were evaluated for their antibacterial activities. These compounds displayed good antibacterial activities.

1. Introduction

One particularly important area of medicinal researches is the synthesis and application of organofluorine compounds. Organofluorine chemistry has received extensive attention especially in the pharmaceutical industry and in materials science due to the unique properties of fluorinated compounds [1]. Some of the most well known fluorine containing drugs are Prozac® (anti-depressant), Diflucan® (anti-fungal agent), Casodex® (anti-cancer agent) and Desflurane (inhalation anesthetic) [1]. Recently, new application of organofluorine compounds is including their use as potential therapeutics for HIV, cancer or Alzheimer's disease. Accordingly, the synthesis of these molecules is in great demand [2] and the search for new biologically active fluorinated compounds is in the forefront of organic and medicinal chemistry [3]. Trifluoromethylated imines are particularly important as precursor products or as building blocks for the synthesis of biologically active molecules [4].

A new class of synthetic antibacterial agents is oxazolidinones that have a unique mechanism in inhibition of bacterial protein synthesis [5–9].

The first drug in this class, Zybox (linezolid), has been widely accepted as a valuable addition to the chemotherapeutic armamentarium to treat the serious gram-positive bacterial infections [10,11]. The excellent pharmacokinetic properties, high antimicrobial activities, and few side effects that most quinolones demonstrate explain widespread use of oxazolidinones in clinical practice [12]. These compounds have been effective against gram-negative bacteria, while the gram-positive pathogens, such as *Staphylococcus aureus* which resist their effects have become a problem [13–19]. Thus, despite many advances in the fluoroquinolone field, there exists a continuous need for novel quinolones to overcome the limitations of existing drugs. From an SAR viewpoint, antibacterial compounds of both classes feature a heterocyclic amine presented as a popular C-ring in oxazolidinones [5–7] and a mandatory cyclic amine in position 7 of quinolones [20]. In the past few years organofluorine chemistry has returned as an expanding a productive area of research, as can be seen by the increasing number of recent publications, reviews, topics, and monographs [21]. Furthermore, organofluorine chemicals have found a wide range of applications in medicine and agriculture due, in part, to the unique biological properties imparted by the fluorine atom [22].

The 1,4-dihydro-4-oxopyridine-3-carboxylic acids associated with a 5,6-fused aromatic ring is the common chemical feature of bactericidal quinolones (Fig. 1).

In the resulting bicyclic ring, the 1-, 5-, 6-, 7-, and 8-positions are the major targets of chemical variation but, synthetic efforts for improved potency the main focus have been on 7-position [23–25]. Both activity spectrum and pharmacokinetic profiles can be controlled at C-7. The most common substituents are cyclic amino

* Corresponding author. Tel.: +98 3913202147; fax: +98 3913202260.
E-mail addresses: adarehkordi@yahoo.com, darehkordi@mail.vru.ac.ir (A. Darehkordi).

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doi:10.1016/j.jfluchem.2011.02.002

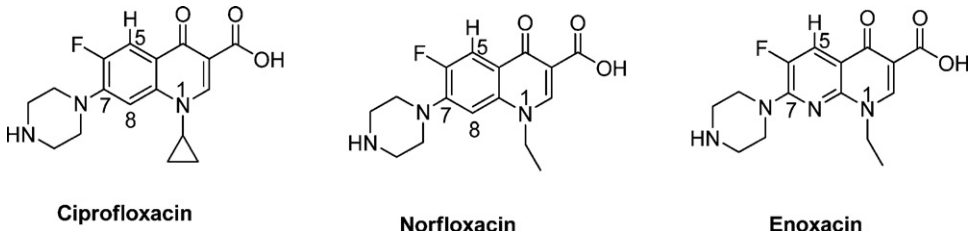


Fig. 1. Common pharmacophore of quinolones and structure of some piperazinylquinolones.

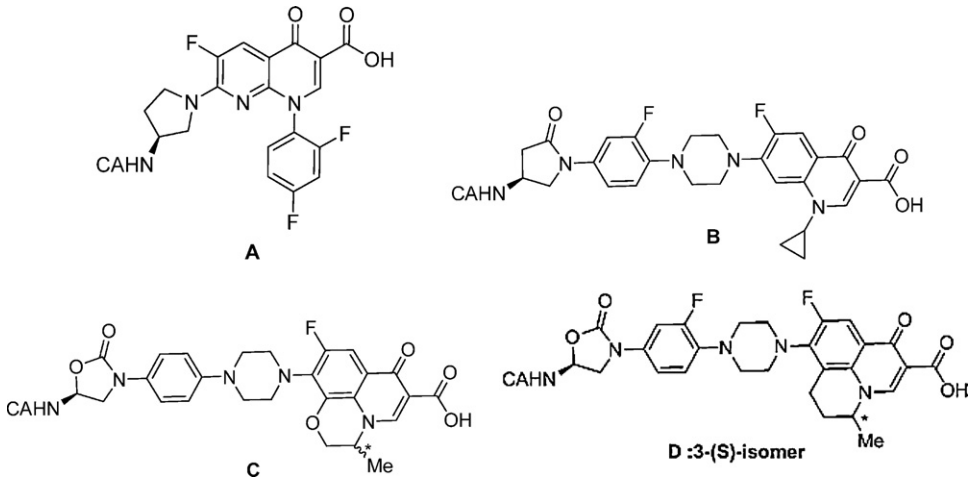


Fig. 2. *N*1-linked tosufloxacin **A** (inactive against gram-positive strains), lactam **B** oxazolidinones **C**, and **D** incorporating ciprofloxacin, ofloxacin, and levofloxacin quinolone substructures linked via a piperazine group (highly potent against gram-positive strains).

groups, for example, piperazine and pyrrolidine rings and other groups have been less successful. Piperazine rings are particularly common (e.g., ciprofloxacin, norfloxacin or enoxacin) and confer potency against gram-negative bacteria [25–29].

In this research *N*-aryltrifluoroacetimidoyl chlorides were selected as an *N*-link to quinolones derivatives in order to improve antibacterial properties.

2. Results and discussion

2.1. Chemistry

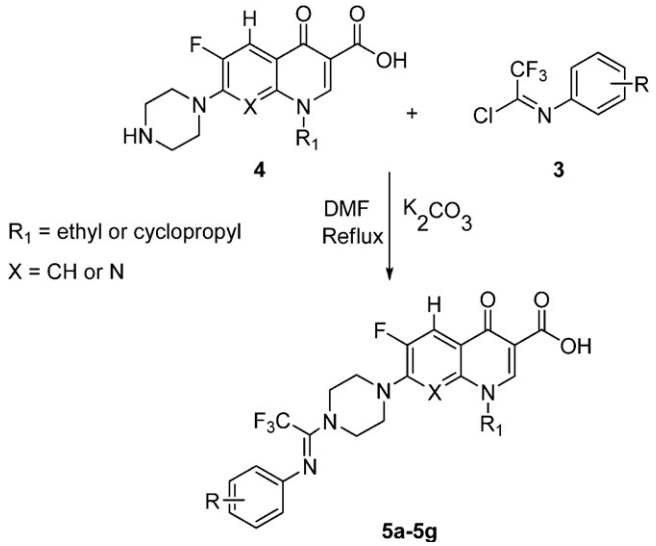
Trifluoromethylated compounds are of particular interest as the strong electron-withdrawing effect of CF_3 group contributes to a number of biologically important molecular properties. For example it results in significant increase in lipophilicity of the molecule, which is a very important feature in drug delivery. The different medicinal applications of fluorinated organic molecules are widespread [1].

Despite of many advances in the fluoroquinolone field, there exist continuous needs for novel quinolones to overcome the limitations of available drugs.

Design of a tether connecting the oxazolidinone and quinolone pharmacophores is critical for antibacterial activity. Thus, *N*1-linked tosufloxacin analogue A (Fig. 2) is inactive. In contrast, oxazolidinones B, C, and D (Fig. 2) incorporating ciprofloxacin, ofloxacin, and levofloxacin quinolone substructures linked via a piperazine group are highly potent against gram-positive strains [27].

The results of MIC tests against both gram-positive and gram-negative bacteria revealed that ciprofloxacin derivatives (R = cyclopropyl and X = CH) were more active than norfloxacin and enoxacin derivatives (R = ethyl and X = CH or N). These data confirm that the effect of changes in the side-chain of the 7-piperazinyl ring mainly depends on the substituent at $N-1$ position [28].

According to this information *N*-aryltrifluoroacetimidoyl chlorides were selected as an *N*-link to quinolone derivatives in order to improve antibacterial properties of them. *N*-aryltrifluoroacetimidoyl chlorides can be prepared by several procedures [29]. In this research a one-pot synthesis of imidoyl halides was described which consists of refluxing a mixture of trifluroacetic acid and a primary amine in carbon tetrachloride in the presence of triethylamine and triphenylphosphine. Work up and distillation provided the desired imidoyl chlorides in good to excellent yields [29]. We also reported the synthesis of *N*-aryltrifluoroacetimidoyl phthalimide and succcinimide by using imidoyl chlorides [30].



Scheme 1. Substitution reaction of acetimidoyl chlorides with piperazinylquinolones.

Table 1
Synthesis of piperazinylquinolone derivatives.

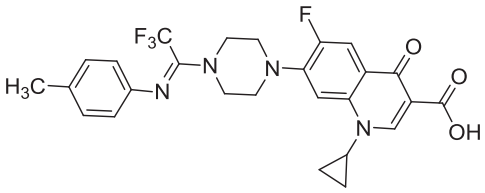
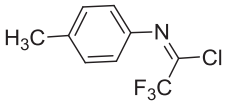
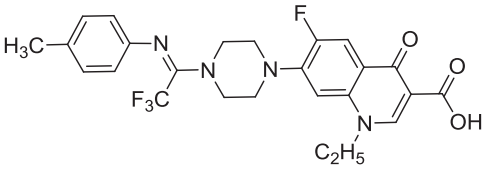
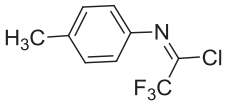
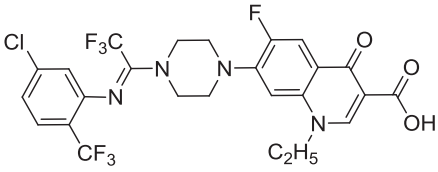
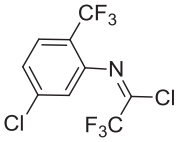
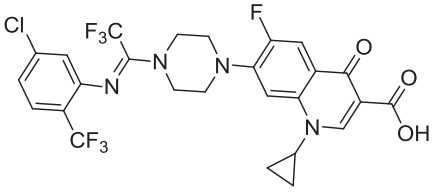
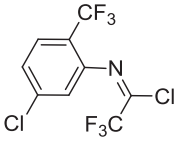
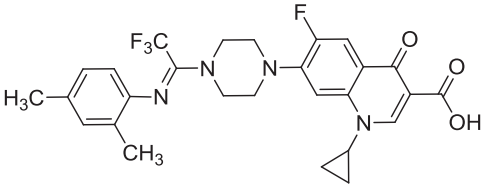
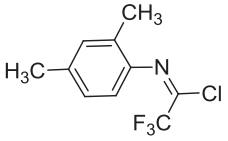
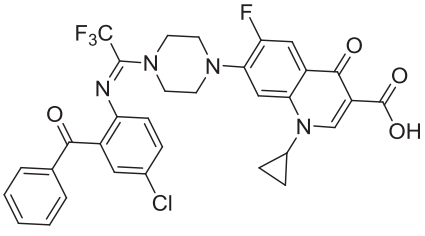
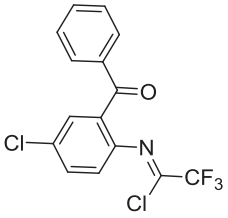
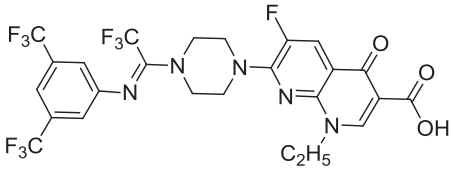
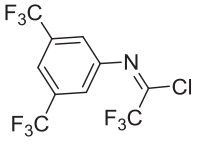
Entry	Product	Acetimidoyl chloride	Yield (%)
5a			86
5b			83
5c			80
5d			85
5e			72
5f			70
5g			60

Table 2
Antibacterial activity of ciprofloxacin, vancomycin, **5a** and **5c**.

Type of bacteria reagents	*Staphylococcus aureus*	*Escherichia coli*	*Klebsiella pneumonia*
5c	39 mm	30 mm	33 mm
5a	31 mm	32 mm	30 mm
Ciprofloxacin	–	26 mm	27 mm
Vancomycin	17 mm	–	–

Here, we describe preparation of *N*-aryl-2,2,2-triflouroacetymidoyl piperazinylquinolone derivatives from *N*-substituted trifluoroacetimidoyl chlorides which chlorine is replaced with nitrogen.

Thus, the reaction of equimolar quantities of norfloxacin or ciprofloxacin with *N*-substituted trifluoroacetimidoyl chlorides and K_2CO_3 under reflux for 18–20 h resulted in the formation of *N*-aryl-2,2,2-trifluoroacetymidoyl piperazinylquinolone derivatives **5** in 60–86% yields (Scheme 1 and Table 1).

In trifluoroacetimidoyl norfloxacin, trifluoroacetimidoyl ciprofloxacin and trifluoroacetimidoyl enoxacin compounds, hydroxyl (OH), carbonyl (C=O), and imino (C=N) groups, in IR spectra appeared in 3409–3429, 1718–1724, and 1620–1631 cm^{-1}, respectively. The ^1H NMR spectra of these compounds showed a singlet signal at 15.07–15.15 (COOH) and multiplet signals at 3.20–3.57 ppm assigned for the protons of piperazine ring. ^{19}F NMR spectra of trifluoroacetimidoyl norfloxacin, ciprofloxacin and enoxacin showed peaks at −73.85 to −76.15 ppm for CF_3 imidoyl groups, and at −121.80 to −125.29 ppm corresponding to fluorine atom of quinoline rings, while CF_3 group attached to the trifluoroacetimidoyl aromatic rings appeared at −58.79 to −60.41 and −66.21 ppm.

2.2. Biology

Ciprofloxacin and vancomycin are both specific drugs which are routinely used as antibacterial drugs. Therefore, growth restriction zones of the bacterial such as *Escherichia coli*, *Klebsiella pneumoniae* and *S. aureus* indicate sensitive to *N*-4-methyl (phenyl)-2,2,2-trifluoroacetimidoyl ciprofloxacin *and N*-(5-chloro-2-(trifluoromethyl) phenyl)-2,2,2-trifluoroacetimidoyl norfloxacin. As shown in Table 2 among the synthesized compounds, **5a** and **5c** were found to be effective against the growth of these bacteria with a concentration of 10–15 μg/mL.

These compounds would have promising antibacterial effects, although more experiments to examine reproducibility and effective dose are required.

3. Conclusion

In conclusion, a series of *N*-aryl-2,2,2-trifluoroacetimidoyl piperazinylquinolone derivatives were synthesized by the reaction of *N*-aryltrifluoroacetimidoyl chlorides with norfloxacin, ciprofloxacin and enoxacin, under mild conditions. We selected *N*-aryltrifluoroacetimidoyl chloride as an *N*-link to quinolone derivatives in order to improve their antibacterial properties. The selected compounds were evaluated for their antibacterial activities. These compounds displayed good antibacterial activities. Further studies on biological activities of these compounds are in progress.

4. Experimental

4.1. Chemistry

4.1.1. General experimental procedures

All reactions were performed with magnetic stirring in flame-dried glassware with dry and distilled solvents.

Chemicals and solvents were purchased from Merck AG and Aldrich Chemical companies. The trifluoroacetimidoyl chloride **3** was prepared according to the literature. Melting points were determined with a Bammstead electrothermal. IR spectra (KBr) were obtained on a Matson-1000 FT-IR spectrometer. The proton and carbon-13 NMR spectra were recorded by a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.7 MHz, respectively, using Me_4Si as an internal standard (chemical shifts in δ, ppm). ^{19}F NMR spectra were taken on Brucher AM-300 (282 MHz) spectrometer using $CFCl_3$ as external standard. Element analyses (C, H, and N) were performed by a Heracus CHN-O-Rapid analyzer. The mass spectra were run on a Finnigan TSQ-70 spectrometer (Finnigan, USA) at 70 eV. Merck silica gel 60 F254 plates were used for analytical TLC.

4.1.2. General procedure for synthesis of N-aryl-2,2,2-trifluoroacetimidoyl piperazinylquinolone derivative

A mixture of piperazinylquinolone 4 (1 mmol) and K_2CO_3 (26 mg, 1 mmol) in DMF (10 mL) was stirred at room temperature for 10 min and then a solution of *N*-aryl-2,2,2-trifluoroacetimidoyl chloride **3** (1 mmol) in DMF (10 mL) were added successively. The mixture was refluxed for 18–24 h. After consumption of piperazinylquinolone (monitored by TLC), $NaHCO_3$ (20 mL, 10%) was added and the resulting solids were washed with water and recrystallised from DMF to give *N*-aryl-2,2,2-trifluoroacetimidoyl piperazinylquinolone compounds.

4.1.3. N-4-methyl (phenyl)-2,2,2-trifluoroacetimidoyl ciprofloxacin (5a)

Yellow-brownish solid; mp: 186 °C, IR KBr (ν_{max}, cm^{-1}): 3424 (–COOH), 3043–2929 (C–H aromatic), 2849–2795 (CH-aliphatic), 1720 (C=O), 1624, 1527 (C=N, C=C). ^{19}F NMR (DMSO-d_6, 282 MHz); δ (ppm): −123.16 (1F, s), −73.41(3F, CF_3, s). ^1H NMR (DMSO-d_6, 500 MHz); δ (ppm): 1.26–1.31 (m, 4H,), 2.20 (s, 3H, CH_3), 3.30 (br, 4H, piperazine ring), 3.37 (m, br, 4H, piperazine ring), 3.76–3.81 (m, 1H, cyclopropyl ring), 6.69 (br, 2H, H phenyl ring) 7.07 (d, 2H, H phenyl ring), 7.51 (s, 1H, H_8-quinoline), 7.80 (d, 1H, H_5-quinoline, $J_{H,F}$ = 13.1 Hz), 8.59 (s, 1H, H_2-quinoline), 15.07 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6 300 MHz); δ (ppm): 7.48 (CH_2 cyclopropyl ring), 20.28 (CH_3), 35.74 (CH cyclopropyl), 48.70, 49.11 (CH_2 piperazine ring), 104.28, 106.37, 110.74, 117.64, 118.73, 119.27 (CF_3, q, J_{C-F} = 277.2 Hz), 119.99, 129.12, 131.80 (CF_3-ring, q, J_{C-F} = 274.31 Hz), 138.93 (C=N, q, J_{C-C-F} = 42.2 Hz), 142.51, 147.75, 151.73, 153.72, 165.68, 176.14. Anal. calcd. for $C_{26}H_{24}F_4N_4O_3$: C, 60.46; H, 4.68; N, 10.85. Found: C, 60.37; H, 4.59; N, 10.69%.

4.1.4. N-4-methyl (phenyl)-2,2,2-trifluoroacetimidoyl norfloxacin (5b)

Yellow-brownish solid; mp: 194 °C, IR KBr (ν_{max}, cm^{-1}): 3409 (–COOH), 2922–3048 (C–H aromatic), 2853–2798 (CH-aliphatic), 1718 (C=O), 1620, 1579 (C=N, C=C). ^{19}F NMR (DMSO-d_6, 282 MHz); δ (ppm): −123.13 (1F, s), −73.26 (3F, CF_3, s). ^1H NMR (DMSO-d_6, 500 MHZ); δ (ppm): 1.53 (t, 3H, J = 7.2 Hz, –CH_3 ethyl), 2.24 (s, 3H, CH_3), 3.55 (br, 4H, piperazine), 3.58 (m, br, 4H, piperazine), 4.40 (q, 2H, J = 7.2 Hz, –CH_2– ethyl), 6.67 (br, 2H, H phenyl ring) 7.07 (d, 2H, H phenyl ring), 7.38 (s, 1H, H_8-quinoline), 7.54 (d, 1H, H_5-quinoline, $J_{H,F}$ = 13.1 Hz), 8.63 (s, 1H, H_2-quinoline), 15.07 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6 300 MHz); δ (ppm): 14.21 (–CH_3 ethyl), 20.34 (1C, CH_3), 52.14 (CH_2 ethyl), 45.54, 49.00 (CH_2 piperazine ring), 104.32, 106.37, 110.90, 116.96, 118.85, 119.48 (CF_3, q, J_{C-F} = 277.2 Hz), 122.55, 123.15, 129.19, 131.76, 138.93, 144.49 (C=N, q, J_{C-C-F} = 43.1 Hz), 147.78, 151.78, 154.51, 165.80, 180.59. Anal. calcd. for $C_{25}H_{24}F_4N_4O_3$: C, 59.52; H, 4.80; N, 11.11. Found: C, 59.50; H, 4.79; N, 11.15%.

4.1.5. N-(5-chloro-2-(trifluoromethyl) phenyl)-2,2,2-trifluoroacetimidoyl norfloxacin (**5c**)

Yellow-brownish solid; mp: 206 °C, IR KBr (ν_{max}, cm^{-1}): 3429 (–COOH), 2922–3055 (C–H aromatic), 2886–2783 (CH-aliphatic), 1720 (C=O), 1631, 1583 (C=N, C=C). ^{19}F NMR (DMSO-d_6, 282 MHz); δ (ppm): −127.17 (1F, s), −76.47 (3F, CF_3, s), −-58.79 (3F, CF_3, s). ^1H NMR (DMSO-d_6, 500 MHz); δ (ppm): 1.56 (t, 3H, J = 7.2 Hz, –CH_3 ethyl), 3.43 (br, 4H, piperazine), 3.66 (m, br, 4H, piperazine), 4.47 (q, 2H, J = 7.2 Hz, –CH_2– ethyl), 7.31 (br, 2H, H phenyl ring), 7.59 (s, 1H, H_8-quinoline), 7.94 (s, 1H, H phenyl ring) 7.60 (d, 1H, H_5-quinoline, $J_{H,F}$ = 13.0 Hz), 8.66 (s, 1H, H_2-quinoline), 15.14 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6 300 MHz); δ (ppm): 14.25 (–CH_3 ethyl), 52.18 (CH_2 ethyl), 49.12, 52.32 (CH_2 piperazine ring), 105.82, 109.17, 112.31, 118.76, 118.85, 120.44 (CF_3, q, $J_{C–F}$ = 278.0 Hz), 122.75, 123.55, 129.89, 132.48, 139.63 (C=N, q, $J_{C–C–F}$ = 44.0 Hz), 144.87 (C=N, q, $J_{C–C–F}$ = 44.0 Hz), 148.78, 155.74, 156.65, 165.97, 179.19. Anal. calcd. for $C_{25}H_{20}ClF_7N_4O_3$: C, 50.65; H, 3.40; N, 9.45. Found: C, 50.69; H, 3.52; N, 9.46%.

4.1.6. N-(5-chloro-2-(trifluoromethyl)phenyl)-2,2,2-trifluoroacetimidoyl ciprofloxacin (**5d**)

Yellow-brownish solid; mp: 214 °C, IR KBr (ν_{max}, cm^{-1}): 3424 (–COOH), 2929–3043 (C–H aromatic), 2795–2849 (CH-aliphatic), 1720 (C=O), 1624, 1527 (C=N, C=C). ^{19}F NMR (DMSO-d_6, 282 MHz); δ (ppm): −127.32 (1F, s), −76.53 (3F, CF_3, s), −60.41 (3F, CF_3, s). ^1H NMR (DMSO-d_6, 500 MHz); δ 1.22–1.30 (m, 4H, CH_2 cyclopropyl), 3.20 (br, 4H, piperazine), 3.29 (m, br, 4H, piperazine), 3.55–3.85(m, 1H, cyclopropyl), 7.57 (br, 2H, H phenyl ring) 7.90 (br, 2H, H phenyl ring), 7.59 (s, 1H, H_8-quinoline), 7.94 (s, 1H, H phenyl ring) 8.65 (d, 1H, H_5-quinoline, $J_{H,F}$ = 13.1 Hz), 8.97 (s, 1H, H_2-quinoline), 15.10 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6 300 MHz) δ (ppm): 7.54 (CH_2 cyclopropyl ring), 35.89 (CH cyclopropyl), 46.27, 47.29 (CH_2 piperazine ring), 103.04, 106.79, 111.00, 117.92, 119.23, 119.89 (CF_3, q, $J_{C–F}$ = 277.6 Hz), 124.70,130.47, 139.03, 144.01, 146.26 (C=N, q, $J_{C–C–F}$ = 43.0 Hz) 148.05 151.80, 153.79, 165.72, 176.30. Anal. calcd. for $C_{26}H_{20}ClF_7N_4O_3$: C, 51.63; H, 3.33; N, 9.26. Found: C, 51.46; H, 3.32; N, 9.19%.

4.1.7. N-(3,5-dimethyl (phenyl))-2,2,2-trifluoroacetimidoyl ciprofloxacin (**5e**)

Yellow-brownish solid; mp: 203–205 °C, IR KBr (ν_{max}, cm^{-1}): 3425 (–COOH), 2956–3054 (C–H aromatic), 2884–2780 (CH-aliphatic), 1715 (C=O), 1628, 1588 (C=N, C=C). ^{19}F NMR (DMSO-d_6, 282 MHz); δ (ppm): −122.19 (1F, s), −74.37 (3F, CF_3, s), ^1H NMR (DMSO-d_6, 500 MHz); δ (ppm): 1.16 (m, 2H, CH_2-cyclopropyl), 1.30 (m, 2H, CH_2-cyclopropyl), 2.87 (br, 4H, piperazine), 3.32 (m, br, 4H, piperazine), 3.78 (m, 1H, H-cyclopropyl), 6.55 (s, 2H, H phenyl) 6.90 (s, 1H, H phenyl ring), 7.54(s, 1H, H_8-quinoline), 7.93 (s, 1H, H phenyl ring), 7.85 (d, 1H, H_5-quinoline, $J_{H,F}$ = 13.1 Hz), 8.62 (s, 1H, H_2-quinoline), 15.12 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6 300 MHz); δ (ppm): 7.56 (CH_2 cyclopropyl ring), 35.87 (CH cyclopropyl), 46.34, 47.78 (CH_2 piperazine ring), 105.01, 108.73, 113.23, 115.16, 117.95, 119.43 (CF_3, q, $J_{C–F}$ = 276.2 Hz), 120.82, 124.81 (CF_3-ring, q, $J_{C–F}$ = 271.4 Hz), 125.17, 128.19, 129.97, 133.87 (C–CF_3-attached the ring, q, $J_{C–C–F}$ = 33.1 Hz), 139.93, 144.09, 144.99, 145.01 (C=N, q, $J_{C–C–F}$ = 42.2 Hz), 148.85, 152.83, 155.09, 168.12 (C=O), 173.62 (C=O). Anal. calcd. for $C_{27}H_{20}F_{10}N_4O_3$: C, 50.79; H, 3.16; N, 8.78. Found: C, 50.88; H, 3.23; N, 8.61%.

4.1.8. N-(5-chlorobenzophenone)-2,2,2-trifluoroacetimidoyl ciprofloxacin (**5f**)

Yellow-brownish solid; mp: 198–200 °C, IR KBr (ν_{max}, cm^{-1}): 3430 (–COOH), 2925–3056 (C–H aromatic), 2889–2788 (CH-aliphatic), 1760, 1727 (C=O), 1630, 1587 (C=N, C=C). ^{19}F NMR (DMSO-d_6, 282 MHz); δ (ppm): −125.29 (1F, s), −73.85(3F, CF_3, s). ^1H NMR (DMSO-d_6, 500 MHz); δ (ppm): 1.24 (m, 2H, CH_2-cyclopropyl), 1.36 (m, 2H, CH_2-cyclopropyl), 2.87 (m, br, 4H, piperazine), 3.59 (m, br, 4H, piperazine), 3.78 (m, 1H, cyclopropyl) 7.43–7.45 (br, 6H, H phenyl ring), 7.94 (s, 1H, H_8-quinoline), 8.10 (s, 1H, H phenyl ring), 7.82 (d, 1H, H_5-quinoline, $J_{H,F}$ = 13.0 Hz), 8.52 (s, 1H, H_2-quinoline), 15.12 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6 300 MHz); δ (ppm): 7.56 (CH_2 cyclopropyl ring), 35.87 (CH cyclopropyl), 46.34, 47.78 (CH_2 piperazine ring), 105.01, 108.73, 113.04, 113.23, 115.16, 117.95, 120.44 (CF_3, q, $J_{C–F}$ = 278.1 Hz), 120.82, 125.17, 128.19, 128.66, 129.97, 133.87, 139.93, 144.09, 144.72, 144.99, 146.78 (C=N, q, $J_{C–C–F}$ = 43.3 Hz), 146.96, 148.85 152.83, 155.09, 167.02 (C=O), 177.19 (C=O), 198.55 (C=O), Anal. calcd. for $C_{32}H_{25}ClF_4O_4$: C, 59.96; H, 3.93; N, 8.74. Found: C, 60.12; H, 4.03; N, 8.42%.

4.1.9. N-(3,5-bistrifluoromethyl (phenyl))-2,2,2-trifluoroacetimidoyl enoxacin (**5g**)

Yellow-brownish solid; mp: 141–145 °C, IR KBr (ν_{max}, cm^{-1}): 3419 (–COOH), 2920–3047 (C–H aromatic), 2881–2776 (CH-aliphatic), 1732 (C=O), 1636, 1582 (C=N, C=C). ^{19}F NMR (DMSO-d_6, 282 MHz); δ (ppm): −128.14 (1F, s), −78.63 (3F, CF_3, s), −66.21 (6F, $2CF_3$, s). ^1H NMR (DMSO-d_6, 500 MHz); δ (ppm): 1.57 (t, 3H, J = 7.2 Hz, –CH_3 ethyl), 3.50 (br, 4H, piperazine), 3.67 (m, br, 4H, piperazine), 4.43 (q, 2H, J = 7.2 Hz, –CH_2– ethyl), 7.31 (br, 2H, arom), 7.56 (s, 1H, H_8-quinoline), 7.62 (s, 1H, arom), 7.58 (d, 1H, H_5-quinoline, $J_{H,F}$ = 13.0 Hz), 8.64 (s, 1H, H_2-quinoline), 15.13 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6 300 MHz); δ (ppm): 14.23 (–CH_3 ethyl), 53.08 (1C, CH_2 ethyl), 49.65, 52.53 (CH_2 piperazine ring), 105.82, 109.17, 113.45, 115.60, 118.76, 120.85 (CF_3-imidoyl, q, $J_{C–F}$ = 278.1 Hz), 122.75, 123.55, 124.35, 127.00 (CF_3-ring, q, $J_{C–F}$ = 272.1. Hz), 129.89, 132.88 (C–CF_3-attached the ring, q, $J_{C–C–F}$ = 33.1 Hz), 136.41, 138.96, 139.63, 145.87 (C=N, q, $J_{C–C–F}$ = 43.3 Hz), 148.78, 151.74, 155.74, 165.53, 175.17 (C=O). Anal. calcd. for $C_{25}H_{19}F_{10}N_5O_3$: C, 47.86; H, 3.05; N, 11.16. Found: C, 47.67; H, 2.98; N, 11.21%.

4.2. Biology

4.2.1. Material and method

The 0.01 g of synthesized powder (anti-bacterial compounds tested) was dissolved in 200 μL DMSO and then blank discs were soaked with 40 μL of the above solution containing different compounds. Discs were put at 60 °C for 30 min to get dried. *E. coli*, *K. pneumonia* as gram-negative bacteria and *S. aureus* as gram-positive were obtained from Persian Type Culture Collection (PTCC) with 1037, 1290 and 1189 codes respectively and cultured. Antibiogram test performed according to Kirby-Bauer method on Mueller Hinton Agar (Merck, Germany). In case of *Staphylococcus*, vancomycin and in cases of *Klebsiella* and *Escherichia* we used ciprofloxacin as positive controls (Padtan Teb, Iran). Two prepared (**5c**, **5a**, as mentioned) discs with positive controls tested. After 18 h, the diameter of inhibition zones were measured (mm) and reported as shown in Table 2.

Acknowledgment

We gratefully acknowledge, the Vali-e-Asr University of Rafsanjan Faculty Research Grant for financial support.

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