Novel N-2-(Furyl)-2-(Chlorobenzyloxyimino) Ethyl Piperazinyl Quinolones: Synthesis, Cytotoxic Evaluation and Structure-Activity Relationship

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Abstract

Quinolone antibacterials are one of the most important classes of pharmacological agents known as potent inhibitors of bacterial DNA gyrase and topoisomerase IV that efficiently inhibit DNA replication and transcription by generating several double-stranded DNA break. Some quinolone derivatives demonstrated inhibitory potential against eukaryote topoisomerase II and substantial dose-dependent cytotoxic potential against some cancerous cells. In present study, synthesis and cytotoxic activity evaluation of new series of N-pipearzinyl quinolones containing N-2-(furyl-2 or 3-yl)-2-(chlorobenzyloxyimino) ethyl moiety 7a-i have been studied. Reaction of quinolone with 2-bromo-1-(furan-2 or 3-yl)ethanone-O-substituted chlorobenzyloxime in DMF in presence of NaHCO₃ at room temperature, gave the title compounds N-2-(furan-2 or 3-yl)-2-(chlorobenzyloxyiminoethyl) quinolone 7a-i. Synthesized compounds were further evaluated in-vitro against three human breast tumor cell lines. Preliminary screening indicated that compound 7 g demonstrated significant growth inhibitory potential against all evaluated cell lines. The results of structure-activity relationship study exhibited that quinolone derivatives are superior in cytotoxic potential compared to 1,8-naphthyridone series. Furthermore, ethyl quinolone derivatives were more potent cytotoxic agents comparing with cyclopropyl quinolones.

Keywords: Furl; N-pipearzinyl quinolones; Cytotoxic activity.

Introduction

Quinolones are bicyclic ring structures containing 4-oxo-1,4-dihydroquinoline core and different substituted moieties at N-1 position and demonstrate a wide range of pharmacological effects (1-3). Some important quinolone derivatives (e.g. ciprofloxacin) containing various substitutes at different positions of quinolone central core, have been primarily known as potent antibacterial agents that target type II bacterial topoisomerases (DNA gyrase and topoisomerase IV) and efficiently
inhibit DNA replication and transcription by generating several double-stranded DNA breaks (4-6). Several researches have indicated that some quinolone derivatives display inhibitory potential against eukaryote topoisomerase II. Therefore, in addition to antibacterial activity, some members of quinolones demonstrated substantial dose-dependent growth inhibitory potential against some cancerous cells (7-10). Moreover, a variety of cytotoxic mechanism such as apoptotic induction and inhibition of tubulin polymerization have been postulated as a plausible mechanism responsible for anticancer activity of cytotoxic quinolones (11-13).

According to above findings and based on ciprofloxacin and norfloxacin core (Figure 1), several novel quinolone derivatives were synthesized and displayed significant anticancer activity. Structure-activity relationship study of cytotoxic quinolones demonstrated that substitution of aromatic moieties at C-7 position of quinolone central nucleus mainly affect the anticancer activity of these compounds and enhances selectivity toward type II of human topoisomerase rather than bacterial type (9, 14, 15). Chemical structure of some potent cytotoxic quinolones containing aromatic and heteroaromatic substitutes at C-7 position such as 7-pyridinyl (WIN57294) and 7-hydroxyphenyl (CP-115, 953) are demonstrated in Figure 1 (9). Moreover, 7-pyrazinyl derivatives of tricyclic quinolones such as isothiazoloquinolones A-65281 (Figure 1) induces significant DNA-breakage mediated by calf thymus topoisomerase II and demonstrated cytotoxic potential nearly as potent as etoposide (16). We have previously reported cytotoxic activity of N-substituted pyrazinyl quinolone derivatives of ciprofloxacin type containing $N$-(furyl-2-yl)-2 (chlorobenzyloxyimino) ethyl moiety, $N$-[2-(5-chlorothiophen-2-yl)-2-oxoethyl] or $N$-[2-(5-chlorothiophen-2-yl)-2-oxyiminoethyl]pyrazinyl moiety against some human tumor cell lines (17, 18). The results indicate that introduction of aforementioned substitutes into pyrazinone ring of quinolone derivatives resulted in enhanced cytotoxic potential in some cases. In continuation of our ongoing research program on finding the potent anticancer scaffolds (19-23) and in attempt to construct structure-activity relationship of these type of cytotoxic quinolones, in the current study, we report the synthesis and cytotoxic activity of novel derivatives of 6-fluoroquinolone 3-carboxylic acid and 6-fluoro-1,8-naphthyridone 3-carboxylic acid core containing $N$-2-(2-furyl)-2-(chlorobenzyloxyimino)ethyl or $N$-2-(3-furyl)-2-(chlorobenzyloxyimino)ethyl piperazinyl pendant.

**Experimental**

**Chemistry**

A Kofler hot stage apparatus was used for the measurement of reported melting. The IR spectra were recorded on a Nicolet FT-IR Magna 550 spectrometer. The $^1$HNMR spectra were recorded on Bruker FT-500 MHz spectrometer and chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane. Mass spectra were recorded on an Agilent Technology (HP) mass spectrometer operating at an ionisation potential of 70 eV. Analytical thin layer chromatography (TLC) on Merck silicagel 60 F254 plates using various mobile phases of different polarities was performed in order to confirm the purity of final products.

**General method for the synthesis of O-benzyloximes derivatives 5a-f**

To a mixture of hydroxylamine hydrochloride (0.4 mol), Sodium carbonate anhydrous (0.6 mol) in 185 mL H$_2$O was dropped ethyl chloroformate (0.23 mol). After completion of the reaction, precipitate was extracted with diethyl ether to give N-hydroxyurethane 1. Stirring a mixture of compound 1 (0.68 mol) and chlorobenzyl chloride derivatives (0.42 mol) in 50 mL EtOH gave chlorobenzyl carbethoxy hydroxamate derivatives 2a-c. Compound 2a-c (40 mmol) and sodium hydroxide (80 mmol) in 120 mL EtOH gave chlorobenzyl carboxylic acid hydroxamate derivatives 2a-c. Compound 2a-c was filtered off, dried, and recrystallized from ethanol and water. Compounds 5a-f were prepared from 2-bromo-(furan -2 or 3- yl)-ethanone 4a-b (1 mmol) and substituted O-benzylhydroxylamine hydrochlorides 3a-c (2 mmol) in methanol (10 mL) at room temperature for 3 days (Scheme 1) (19).
General method for the synthesis of N-2-(2 or 3-furyl)-2-(chlorobenzyloxyimino) ethyl quinolone (7a-i)

A mixture of 2-bromo-1-(furan-2 or 3-yl) ethanone O-2-chlorobenzyl oxime derivatives 5a-f (0.55 mmol), quinolone derivatives 6a-c (0.5 mmol) and NaHCO₃ (0.5 mmol) in DMF (5 mL) was stirred at room temperature for 6-9 days. After completion, water (20 mL) was added and the precipitate was filtered off, washed with water and recrystallized from EtOH-CHCl₃ to give target compounds 7a-i.

7-(4-(2-(benzyloxyimino)-2-(furan-3-yl) ethyl) piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid 7a (18)

Yield 54%; m.p. 217 - 218 °C; 'HNMR (500 MHz, DMSO-d₆): 1.40 (t, 3H, J = 7 Hz, CH₃), 3.23-3.32 (m, 4H, piperazine), 3.58-3.65 (m, 4H, piperazine), 3.62 (s, 2H, CH₂), 4.58 (q, 2H, J = 7 Hz, CH₂-CH₃), 5.20 (s, 2H, OCH₂), 6.71 (s, 1H, furyl), 7.17 (d, 1H, J = 7.1Hz, H₂), 7.29-7.43 (m, 5H, phenyl), 7.70 (s, 1H, furyl), 7.93 (d, 1H, J = 13.2Hz, H₅), 8.25 (s, 1H, furyl), 8.95 (s, 1H, H₂), 15.34 ppm (s, 1H, COOH). IR (KBr): 1681,
1619 (C=O). MS m/z 532 (M+, 5), 425 (12), 332 (100), 139 (26).

7-(4-(2-(4-chlorobenzyloxyimino)-2-(furan-3-yl) ethyl) piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid 7b

Yield 85%; m.p. 248–250 °C; 1HNMR (500 MHz, DMSO-d6): 1.40 (t, J=7 Hz, 3H, CH3), 2.62-2.70 (m, 4H, piperazine), 3.23-3.30 (m, 4H, piperazine), 3.64 (s, 2H, CH2), 4.57 (q, J=7.0 Hz, 2H, CH2), 5.20 (s, 2H, OCH2), 6.56-6.70 (m, J=3.3 Hz, 1H, furyl), 7.15 (d, J=7.15 Hz, 1H, furyl), 7.43-7.49 (m, 4H, benzyl), 7.74 (s, 1H, furyl), 7.92 (d, J=13.2 Hz, 1H, H2), 8.95 (s, 1H, H2), 15.14 ppm (s, 1H, COOH); IR (KBr): 1629 (C=O). MS m/z 566 (M+, 2), 332 (40), 316 (21), 233 (25), 125 (100).

7-(4-(2-(2-chlorobenzyloxyimino)-2-(furan-3-yl) ethyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid 7c

Yield 66%; m.p. 230-231 °C; 1HNMR (500 MHz, DMSO-d6): 1.40 (t, J=6.8 Hz, 3H, CH3), 2.45-2.76 (m, 4H, piperazine), 3.23-3.53 (m, 4H, piperazine), 3.61 (s, 2H, CH2), 4.56 (q, J=6.8Hz, 2H, CH2), 5.27 (s, 2H, OCH2), 6.50 (d, J=3.2 Hz, 1H, furyl), 6.98 (d, J=3.2 Hz, 1H, furyl), 7.14 (d, J=6.8 Hz, 1H, furyl), 7.30-7.40 (m, 4H, benzyl), 7.55 (t, J=3.2 Hz, 1H, furyl), 7.89 (d, J=13.2 Hz, 1H, H2), 15.29 ppm (s, 1H, COOH); IR (KBr): 1714, 1629 (C=O). MS m/z 566 (M+, 2), 318 (19), 234 (24), 141 (100).

7-(4-(2-(3-chlorobenzyloxyimino)-2-(furan-3-yl) ethyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid 7f

Yield: 66%; m.p. 230–231 °C; 1HNMR (500 MHz, DMSO-d6): 1.30 (t, J=6.3 Hz, 3H, CH3), 2.53-2.59 (m, 4H, piperazine), 3.57 (s, 2H, CH2), 3.70-3.80 (m, 4H, piperazine), 4.46 (q, J=6.7 Hz, 2H, CH2), 5.13 (s, 2H, OCH2), 6.68 (bs, 1H, furyl), 6.95 (bs, 1H, furyl), 7.68-7.86 (m, 4H, benzyl), 7.74 (bs, 1H, furyl), 8.06 (d, J=13.5Hz, 1H, H2), 8.94 (s, 1H, H2), 15.14 ppm (s, 1H, COOH); IR (KBr): 1720, 1634 (C=O). MS m/z 566 (M+, 6), 319 (14), 234 (33), 141 (100).
2.50-2.52 (m, 4H, piperazine), 2.98 (s, 2H, CH₂), 3.28-3.34 (m, 4H, piperazine), 3.82-3.89 (m, 1H, cyclopropyl), 5.22 (s, 2H, OCH₂), 6.63-6.65 (m, 1H, furyl), 6.89-6.98 (m, 1H, furyl), 7.31-7.41 (m, 3H, benzyl), 7.55 (d, J=6.9 Hz, 1H, H₆), 7.76-7.83 (m, 1H, furyl), 7.90 (d, J=13.1Hz, 1H, H₇), 8.67 (s, 1H, H₅), 15.13 ppm (s, 1H, COOH); IR (KBr): 1712, 1624 (C=O). MS m/z 578 (M⁺, 7), 481 (100). 7-(4-(2-(3-chlorobenzyloxyimino)-2-(furan-3-yl)ethyl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid 7i Yield: 35%; m.p. 278–280 °C; ¹H NMR (500 MHz, DMSO-d₆): 1.37 (t, J=6.9 Hz, 3H, CH₃), 2.48-2.59 (m, 4H, piperazine), 3.33 (s, 2H, CH₂), 3.74-3.80 (m, 4H, piperazine), 4.46 (q, J=6.9 Hz, 2H, CH₂), 5.22 (s, 2H, OCH₂). 6.95 (d, J=1.5Hz, 1H, furyl), 6.97 (d, J=1.5 Hz, 1H, furyl), 7.31-7.45 (m, 3H, benzyl), 7.75 (t, J=1.5 Hz, 1H, furyl), 8.04 (d, J=13.5 Hz, 1H, H₇), 8.49 (s, 1H, benzyl), 8.95 (s, 1H, H₅), 15.30 ppm (s, 1H, COOH); IR (KBr): 1719, 1634 (C=O). MS m/z 567 (M⁺, 3), 319 (19), 234 (41), 141 (100).

**Cytotoxic activity**

- The cytotoxic activity of target compounds 7a-i was assessed in vitro against a panel of three human cancer cell lines including MCF-7, MDA-MB-231 and T47D. The percentage of cell growth was evaluated using MTT colorimetric assay in comparison with untreated controls. For each compound, the 50% absorbance of each well was measured by plate reader (Biotek Instruments, Winooski, Vt.) at a test wavelength of 492 nm. Three independent experiments in triplicate were performed for determination of sensitivity to each compound. The IC₅₀ were calculated by linear regression analysis, expressed in mean ± SD.
Inhibitory concentration (IC\textsubscript{50}) was determined and reported in Table 1. The corresponding data for etoposide was included for comparison. On the basis of obtained IC\textsubscript{50} values, most of synthesized compounds demonstrated potent to moderate cytotoxic potential especially against T47D cell line (IC\textsubscript{50} = 2.20-39.08 \mu M). However, most of evaluated derivatives were almost inactive against MDA-MB-231 cell line (IC\textsubscript{50} > 100 \mu M). The most promising compound

\textbf{Scheme 1.} Synthesis of N-2-(furyl)-2-(chlorobenzyloxyimino)ethyl quinolones (6a-i). Reagents and conditions: A) Na\textsubscript{2}CO\textsubscript{3}, H\textsubscript{2}O, rt; B) Na, EtOH, rt; C) 1. NaOH, H\textsubscript{2}O, heat, 2. EtOH, HCl; D) MeOH, rt; E) DMF, NaHCO\textsubscript{3}, rt.
of this series 7g, ethyl quinolone derivative (X=CH and R=Et) containing 3-furyl moiety (Ar=3-furyl) and 3-chloro phenyl (Y=3-Cl), demonstrated significant growth inhibitory potential against all evaluated cell lines (the corresponding IC_{50} values against MCF-7, MDA-MB-231 and T47D cells were 3.03, 11.90 and 2.20 μM, respectively). Moreover, 7 g demonstrated superior cytotoxic activity compared to reference compound, etoposide (the corresponding IC_{50} values against MCF-7, MDA-MB-231 and T47D cells were 7.9±Quinolone derivatives were more potent cytotoxic agents than 1, 8-naphthyridones in most cases; e.g ethyl quinolone compound 7 g (Ar=3-furyl, Y=3-Cl) was found to be most potent cytotoxic derivative. However, its 1-ethyl 1,8-naphthyridinone counterpart 7i was almost inactive against MCF-7 and MDA-MB-231 (IC_{50}>100μM) and showed weak growth inhibitory potential toward T47D cells (IC_{50}=39.08μM).

Ethyl quinolones demonstrated high cytotoxic potential over cyclopropyl quinolones; e.g. compound 7 g was potent cytotoxic agent

Table 1. Structures and in-vitro cytotoxicity of compounds 7a-i against three different human breast cancer cell lines assessed by MTT reduction assay^a.

| Compound | X | Ar | Y | R | MCF-7 IC_{50} (μg/ml) | MDA-MB-231 IC_{50} (μg/ml) | T47D IC_{50} (μg/ml) |
|----------|---|----|---|---|---------------------|----------------------------|---------------------|
| 7a | CH |  | H | Et | 5.30±4.7 | >100^b | 7.00±5.09 |
| 7b | CH |  | 4-Cl | Et | 12.35±1.7 | >100 | 8.70±2.5 |
| 7c | CH |  | 2-Cl | Et | 7.50±1.1 | >100 | 7.60±2.1 |
| 7d | N |  | 2-Cl | Et | >100 | >100 | 10.05±1.6 |
| 7e | CH |  | 4-Cl | Et | 11.40±2.7 | 65.4±5.4 | 10.90±1.9 |
| 7f | N |  | 4-Cl | Et | 10.05±1.9 | 77.00±6.3 | 15.20±1.1 |
| 7g | CH |  | 3-Cl | Et | 3.03±1.5 | 11.90±2.6 | 2.20±1.5 |
| 7h | CH |  | 3-Cl |  | >100 | >100 | 12.35±1.6 |
| 7i | N |  | 3-Cl | Et | >100 | >100 | 39.08±8.4 |
| Etoposide | --- | --- | --- | --- | 7.9± | 11.1± | 8± |

^a Values represent the mean±SD of three different experiments.
^b Compounds were tested at the maximum final concentration of 100 μg/mL.
of these series (the corresponding IC<sub>50</sub> values against MCF-7, MDA-MB-231 and T47D cells were 3.03, 11.90 and 2.20 μM, respectively). While its cyclopropyl quinolone counterpart 7h was inactive against MCF-7 and MDA-MB-231 cancer cells (IC<sub>50</sub>&gt;100 μM) and showed moderate cytotoxic potential against T47D cells (IC<sub>50</sub>=12.35μM).

Considering the substituted moiety on the oxime pendant (Ar group), no significant differences were observed between cytotoxic potentials of 2-furyl and 3-furyl derivatives; i.e. compound 7e, ethyl quinolone derivative containing 3-furyl substitute on the oxime pendant (Y=4-Cl) and its 2-furyl counterpart 7b, demonstrated potent cytotoxic potential against MCF-7 (7b (IC<sub>50</sub>=12.35 μM) and 7e (IC<sub>50</sub>=11.40 μM)) and T47D cells (7b (IC<sub>50</sub>=8.70μM) and 7e (IC<sub>50</sub>=10.90μM)). Both compounds were almost inactive against MDA-MB-231 cells.

## Conclusion

In conclusion, a novel series of 6-fluoro quinolone 3-carboxylic acid and 6-fluoro-1,8-naphthyridone 3-carboxylic acid derivatives containing N-2-(2-furyl)-2-(chlorobenzyloxyimino)ethyl or N-2-(3-furyl)-2-(chlorobenzyloxyimino)ethyl piperazinyl pendant attached to the central core was synthesized and evaluated against three different human cancer cell lines. The most promising compound of ethyl quinolone series, 7 g, demonstrated significant growth inhibitory potential against all evaluated cell lines. The results of structure-activity relationship study demonstrated that quinolone derivatives are superior in cytotoxic potential compared to 1,8-naphthyridone series. Furthermore, ethyl quinolone derivatives were more potent cytotoxic agents than cyclopropyl quinolones.

## Acknowledgment

This work was supported by grants from the Young Researchers and Elite Club, Isfahan Branch, Islamic Azad University and the research council of Tehran University of Medical Sciences grant number 93-02-92-26357.

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لینک های مفید

- عضویت در خبرنامه
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