Can Functionalization of Quinoline Derivatives Be Exploited to Control Quinolines Cytotoxic Effects?

Zahra Hami,1 and Ramin Zibaseresht2,3,*

1Department of Toxicology, Faculty of Medicine, AJA University of Medical Sciences, Tehran, IR Iran
2Biomaterial Laboratory, Faculty of Medicine, AJA University of Medical Sciences, Tehran, IR Iran
3Department of Chemistry and Physics, Faculty of Sciences, Maritime University of Imam Khomeini, Nowshahr, Mazandaran, IR Iran

*Corresponding author: Ramin Zibaseresht, Biomaterial Laboratory, Department of Toxicology, Faculty of Medicine, AJA University of Medical Sciences, Tehran, IR Iran. Tel: +98-2188377783, Fax: +98-2188020193, E-mail: rzi12@uclive.ac.nz

Received 2017 July 17; Accepted 2017 October 29.

Abstract

Background: Quinoline and its variety of derivatives have long been studied for their biological activities such as anticancer, anti-tumor, anti-inflammatory, and antioxidant properties.

Objectives: As part of our research, we are interested in the synthesis and development of heterocyclic compounds such as quinoline derivatives and poly-pyridyl materials that might have potential biological activities. Particularly, anti-cancerous and anti-bacterial properties of such compounds are of our interest.

Methods: A previously synthesized mixture of two quinoline derivative isomers (7-methylquinoline and 5-methylquinoline (A + B)) and other four quinoline derivatives (7-methyl-8-nitro-quinoline (C), 7-(3-trans- (N,N-dimethylamino) ethenyl)-8-nitroquinoline (D), 8-nitro-7-quinolinecarbaldehyde (E), and 8-Amino-7-quinolinecarbaldehyde (F)) were selected to evaluate their in vitro cytotoxicity against human epithelial colorectal carcinoma (Caco-2) cultured cells by MTT assay. The IC_{50} values for the mixture and other compounds were calculated by SigmaPlot 12.0 software.

Results: Compounds (A + B), (C), (D), (E), and (F) showed IC_{50} values of 2.62, 1.87, 0.93, 0.53, and 1.140 \mu M, respectively.

Conclusions: Our investigation suggested that all compounds were cytotoxic against Caco-2 cell lines. We observed that the previously synthesized quinoline derivatives (A + B), (C), (D), (E), and (F) in a reaction sequence show an influence in cytotoxicity against Caco-2 cell lines. Based on our observations, we concluded that functionalization of the quinoline derivatives we studied resulted in a change in cytotoxic activities of the compounds. Therefore, the functionalization strategy we employed for the quinoline derivatives could be useful in controlling the cytotoxic level of such compounds.

Keywords: Quinoline Derivatives, Functionalization, Caco-2, Cytotoxicity

1. Background

Quinoline and its derivatives have received considerable attention because of their potential activities such as anticancer (1-9), anti-inflammatory (10-12), anti-oxidant, and other biological activities (13-17).

A variety of research have demonstrated that quinoline and its derivatives have shown cytotoxic activity by inhibiting PI3K-PKB, epidermal growth factor receptor, mitogen-activated protein kinase, ALK5, platelet-derived growth factor, or non-receptor tyrosine kinase (18).

Bingul et al. investigated the synthesis of some quinoline derivatives and showed their anti-cancer activity against neuroblastoma cells (19). In another study, Meshram et al. showed that some quinoline derivatives they had prepared were toxic to human cell line HL-60 (myeloid leukemia) and U937 (leukemic monocyte lymphoma) (20). To the best of our knowledge, in all articles we reviewed in literature, the authors have reported the syntheses of quinoline derivatives and investigated their cytotoxic properties against different human cancer cell lines. Here, we have an intention to investigate the possibility of deliberately increasing the cytotoxicity of quinoline derivatives using functionalization reaction methods.

Since there is a growing interest in the development of new quinoline-based compounds for their potential cytotoxicity against cancer cells, in continuation of part of our work for the preparation of such class of molecules, we reported the synthesis of some quinoline derivatives ear-
lier (21). In that project, we developed a synthetic route for the preparation of a novel terpyridine ligand. The synthetic route involved the preparation of some quinoline derivatives as key materials for the preparation of a terpyridine ligand. Herein, we report the anti-cancer activity of the synthesized quinoline-based molecules and investigate the role of functionalization methods we employed in the level of cytotoxicity of such chemicals.

2. Objectives

The main aims of this research were to investigate the cytotoxicity effect of some quinoline derivatives against cancer cell line and to demonstrate the possibility of the toxicity control of such molecules by functionalization methods in a reaction route.

3. Methods

3.1. Materials

Compounds 7-methylquinoline (A) and 5-methylquinoline (B) as mixture, 7-Methyl-8-Nitroquinoline (C), 7-(β-trans- (N, N-dimethylamino) ethenyl)-8-nitroquinoline (D), 8-Nitro-7-quinolinecarbaldehyde (E), and 8-Amino-7-quinolinecarbaldehyde (F) were synthesized as previously described (21). 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) was purchased from Sigma (St Louis, MO, USA). Dulbecco's modified eagle's medium (DMEM), RPMI 1640 medium, and penicillin/streptomycin solution were obtained from Gibco Invitrogen (Carlsbad, CA, USA). Human epithelial colorectal carcinoma (Caco-2) cells were provided by Pasteur Institute, Tehran, Iran.

3.2. Methods

In vitro cytotoxicity study by MTT assay (22): Caco-2 cells (human epithelial colorectal carcinoma cells) were cultured in a medium consisting of RPMI-1640, Dulbecco's modified Eagle medium (DMEM), heat-inactivated fetal bovine serum (FBS), and penicillin-streptomycin in a ratio of 50:34:15:1 at 37°C in a humidified incubator with 5% CO₂. Stock solutions of the test compounds were prepared in DMSO solvent and diluted 100 folds with the culture medium. The cells were seeded in 96-well transparent plates at 10,000 cells per well. After 24 hours, the old medium was removed and Caco-2 cells were exposed to the test compounds at concentrations ranging from 0.1 - 1000 µg/mL. After 48 hours incubation, 20 µL of MTT solution (5 mg/mL) was added to each well of the plates and the plates were then maintained in incubator. After 4 hours, 100 µL DMSO solvent was added to each well to dissolve the purple formazan crystals and then the plates were read on a Synergy HT Microplate Reader (Bio-Tek Instruments, Winooski, VT) at 570 nm with the reference wavelength at 690 nm. The IC₅₀ values were calculated by SigmaPlot 12.0 software.

4. Results

To study the effect of functionalization reactions of quinoline derivatives on their cytotoxicity, the previously prepared compounds (i.e. a mixture of two quinoline derivative isomers (7-methylquinoline and 5-methylquinoline (A+B) and four quinoline derivatives (7-methyl-8-nitro-quinoline (C), 7-(β-trans- (N, N-dimethylamino) ethenyl)-8-nitroquinoline (D), 8-nitro-7-quinolinecarbaldehyde (E), and 8-Amino-7-quinolinecarbaldehyde (F) were synthesized as previously described (21)). 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) was purchased from Sigma (St Louis, MO, USA). Dulbecco's modified eagle's medium (DMEM), RPMI 1640 medium, and penicillin/streptomycin solution were obtained from Gibco Invitrogen (Carlsbad, CA, USA). Human epithelial colorectal carcinoma (Caco-2) cells were provided by Pasteur Institute, Tehran, Iran.

3.2. Methods

In vitro cytotoxicity study by MTT assay (22): Caco-2 cells (human epithelial colorectal carcinoma cells) were cultured in a medium consisting of RPMI-1640, Dulbecco's modified Eagle medium (DMEM), heat-inactivated fetal bovine serum (FBS), and penicillin-streptomycin in a ratio of 50:34:15:1 at 37°C in a humidified incubator with 5% CO₂. Stock solutions of the test compounds were prepared in DMSO solvent and diluted 100 folds with the culture medium. The cells were seeded in 96-well transparent plates at 10,000 cells per well. After 24 hours, the old medium was removed and Caco-2 cells were exposed to the test compounds at concentrations ranging from 0.1 - 1000 µg/mL. After 48 hours incubation, 20 µL of MTT solution (5 mg/mL) was added to each well of the plates and the plates were then maintained in incubator. After 4 hours, 100 µL DMSO solvent was added to each well to dissolve the purple formazan crystals and then the plates were read on a Synergy HT Microplate Reader (Bio-Tek Instruments, Winooski, VT) at 570 nm with the reference wavelength at 690 nm. The IC₅₀ values were calculated by SigmaPlot 12.0 software.

5. Discussion

We have previously reported the synthesis and characterization of some quinoline derivatives (Figure 2) (21). As shown in Figure 1, the cytotoxic activities of the quinoline derivatives against Caco-2 cell lines highly depend on the functional groups attached to the quinoline core structure. Nitration reaction of the mixture (A + B) resulted in a product with a nitro group ortho to a methyl group in compound A (Figure 2) (21). However, compound B remained unreacted and it was separated from the reaction mixture consequently. Based on our observations, the nitro derivative C is more cytotoxic than the mixture (A + B) against Caco-2 cell line. In the next step, the reaction of C with N, N-dimethylformamide dimethyl acetal (DMFDMA) gave the derivative D (21). The cytotoxic activity of compound D was also determined against Caco-2 cell line. We observed that compound D was more toxic than the mixture C (IC₅₀ values of 0.929 and 1.871 µM, respectively). Oxidation reaction of D produced the nitro-aldehyde derivative E. We again observed an increase in cytotoxicity of E against Caco-2 cell line (IC₅₀ value, 0.535 µM). A decreased cytotoxic activity was observed during the cytotoxicity evaluation of the amine-aldehyde quinoline derivative F as the product of a reduction reaction of derivative E using Fe catalyst in an acidic medium (Figure 3).
We observed that the previously synthesized quinoline derivatives (A + B), (C), (D), (E), and (F) in a reaction sequence showed an influence in cytotoxicity against Caco-2 cell lines. Based on our evaluation, nitro-aldehyde quino-
line derivative (E) showed the highest cytotoxicity against the cultured cells compared to the other compounds we studied. An increase in cytotoxicity was observed from the mixture (A + B) to the compounds (C), (D) and (E), in sequence, while a decrease in cytotoxicity was demonstrated from the nitro-aldehyde derivative (E) to its corresponding amine-aldehyde derivative (F). The latter trend we observed is consistent with the literature values in which the aromatic amine derivatives were less toxic than their corresponding nitro compounds (23). The change in cytotoxic activities of the compounds showed that functionalization of the quinoline derivatives we studied can be used as a method to control cytotoxicity of such compounds.

Acknowledgments

The authors gratefully acknowledge Dr. S. J. Hosseini Shokouh, Dr. Sh. Iravani, and Dr. A. Khoshdel for their generous support.

Footnotes

Authors’ Contribution: All authors contributed to experimental design, data acquisition, and manuscript preparation, and approved the final manuscript.

Financial Disclosure: The authors declare no financial disclosure.

Funding/Support: This work was financially supported by grants from AJA University of Medical Sciences.

References

1. Ahmed NS, Badahdah KO, Qassar HM. Novel quinoline bearing sulfonamide derivatives and their cytotoxic activity against MCF7 cell line. Med Chem Res. 2017;26(6):1201–12. doi: 10.1007/s00044-017-1850-9.

2. Sun M, Ou J, Li W, Lu C. Quinoline and naphthalene derivatives from Saccharopolyspora sp. YM M13568. J Antibiott (Tokyo). 2017;70(3):320–2. doi: 10.1038/ja.2016.142. [PubMed: 27899791].

3. Kouznetsov VV, Sojo F, Rojas-Ruiz FA, Merchan-Arenas DR, Arvelo F. Synthesis and cytotoxic evaluation of 7-chloro-4-phenoxoquinolines with formyl, oxime and thiosemicarbazone scaffolds. Med Chem Res. 2016;25(1):2718–27. doi: 10.1007/s00044-016-1688-6.

4. Mohamede ASI, Elnearby MAA, Eldine SM. 2,4-cycloaddition reactions: preparation and cytotoxicity of novel quinoline and pyrrolo[3,4-f]quinoline derivatives. Int J Pharm Pharm Sci. 2015;7(12):64–8.

5. Sidoryk K, Switalska M, Jaromin A, Cmoch P, Bujak I, Kaczmarska M, et al. The synthesis of indol[2,3-b]quinoline derivatives with a guanidine group: highly selective cytotoxic agents. Eur J Med Chem. 2015;105:208–19. doi: 10.1016/j.ejmech.2015.10.022. [PubMed: 26496013].

6. Jhanwar D, Sharma J. Use of quinoline derivatives in cancer treatment. Int J Pharm Res Bio Sci. 2015;4(2):3130–48.

7. Ghorbab MM, Ragab FA, Heiba HI, Nissam YM, Ghorab WM. Novel brominated quinoline and pyrimidoquinoline derivatives as potential cytotoxic agents with synergistic effects of gamma-radiation. Arch Pharm Res. 2012;35(8):1335–46. doi: 10.1007/s12272-012-0803-6. [PubMed: 22941476].

8. 24th ACS National Meeting amp; Exposition. August 19-23, 2012; Philadelphia, PA. U.S. 2012.

9. V. Kouznetsov V, A. Rojas Ruiz F, Y. Vargas Mendez I, P. Gupta M. Simple C2-substituted quinolines and their antitumor activity. Lett Drug Des Discov. 2012;9(7):580–6. doi: 10.1016/j.ldd.2009.03-5454.

10. Jeena V, Naidoo S. Synthesis of 2,4-disubstituted quinoline derivatives via A3-coupling: An ecoscale evaluation. Synthesis. 2017;49(12):2621–31. doi: 10.1055/s-0036-1588176.

11. Mukherjee S, Pal M. Medicinal chemistry of quinolines as emerging anti-inflammatory agents: an overview. Curr Med Chem. 2013;20(35):4386–410. [PubMed: 23862668].

12. Kreutzberger A. Condensed heterocycles as structure characteristics in inflammation inhibitors. Disch Apoth Ztg. 1972;11(4):606–13.

13. Wen D, Guo J, Jiang F, Huang C, Zhao Z, Lu G, et al. A rapid and sensitive UHPLC-MS/MS method for quantification of 883b1 in plasma and its application to bioavailability study in rats. J Pharm Biomed Anal. 2017;134:71–7. doi: 10.1016/j.jpba.2016.11.001. [PubMed: 27886572].

14. Silverman R. The organic chemistry of drug design and drug action. San Diego: Academic Press; 1992.

15. Thompson LA, Ellman JA. Synthesis and Applications of Small Molecule Libraries. Chem Rev. 1996;96(1):555–600. doi: 10.1021/cr9402081. [PubMed: 8847657].

16. Franzen RG. Recent advances in the preparation of heterocycles on solid support: a review of the literature. J Comb Chem. 2000;2(3):295–214. doi: 10.1021/cc000002f. [PubMed: 10872921].

17. Foley M, Tilley L. Quinoline antimalarials: mechanisms of action and resistance and prospects for new agents. Pharmacol Ther. 1998;79(1):57–87. doi: 10.1016/S0163-7258(98)00012-6. [PubMed: 9791345].

18. Solomon VR, Lee H. Quinoline as a privileged scaffold in cancer drug discovery. Curr Med Chem. 2013;20(10):1488–508. [PubMed: 23428895].

19. Binigul M, Tan O, Gardner CR, Sutton SK, Arndt GM, Marshall GM, et al. Synthesis, Characterization and Anti-Cancer Activity of Hydrazide Incorporating a Quinoline Moiety. Molecules. 2016;21(7). doi: 10.3390/molecules2107096. [PubMed: 27428941].

20. Moshmann TM. Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. J Immunol Methods. 1988;123(1-2):55–61. doi: 10.1016/0022-1759(89)90303-4.
23. Razo-Flores E, Donlon B, Lettinga G, Field JA. Biotransformation and biodegradation of N-substituted aromatics in methanogenic granular sludge. *FEMS Microbiol Rev.* 1997;20(3-4):525-38. doi: 10.1111/j.1574-6976.1997.tb00335.x. [PubMed: 9340000].