Ecotoxicology and Environmental Safety 136 (2017) 111–118

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

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

Analysis of positions and substituents on genotoxicity of fluoroquinolones with quantitative structure-activity relationship and 3D Pharmacophore model

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ARTICLE INFO

Keywords:
Fluoroquinolones
Genotoxicity
Quantitative structure-activity relationship
Full factorial experimental design
Pharmacophore model

ABSTRACT

The genotoxicity values of 21 quinolones were studied to establish a quantitative structure-activity relationship model and 3D Pharmacophore model separately for screening essential positions and substituents that contribute to genotoxicity of fluoroquinolones (FQs). A full factor experimental design was performed to analyze the specific main effect and second-order interaction effect of different positions and substituents on genotoxicity, forming a reasonable modification scheme which was validated on typical FQ with genotoxicity and efficacy data. Four positions (1, 5, 7, 8) were screened finally to form the full factorial experimental design which contained 72 congeners in total, illustrating that: the dominant effect of 5 and 7-positions on genotoxicity of FQs is main effect; meanwhile the effect of 1 and 8-positions is a second-order interaction effect; two adjacent positions always have stronger second-order interaction effect and lower genotoxicity; the obtained modification scheme had been validated on typical FQ congeners with the modified compound has a lower genotoxicity, higher synthesis feasibilities and efficacy.

1. Introduction

Fluoroquinolones (FQs) are an important emerging group of antibacterial agents that have been extensively used in clinical applications for human and veterinary diseases since the first type of FQ was synthesized in the 1980s (Denadai and Cass, 2015; Martinez et al., 2006; Mitscher, 2005; Philipp et al., 2012). They always possess a broad spectrum of activity for various Gram-positive and Gram-negative bacteria, mycobacteria, and parasites. They also prevent the synthesis of bacterial DNA because of the presence of an F atom and piperazinyl group that can improve drug penetration into the bacterial cell (Gao et al., 2015; Lin et al., 2016; Speltini et al., 2011; Sturini et al., 2015). Due to their excessive addition in feed, FQs have been detected in various environmental samples via excretion (urine or feces), such as hospital sewage, treated sewage, surface water bodies and so on (Turiel et al., 2005; Gao et al., 2012), leading to an adverse threat to the ecosystem and human health (Ebert et al., 2011).

Genotoxicity is one of the primary adverse effects of FQs that limits their further application, such as the effects of ciprofloxacin (CIP) in rat tenocytes (Chang et al., 2012), gemifloxacin (GAT) in human breast cells (Chen et al., 2014), and moxifloxacin hydrochloride (MOX) in human corneal cells (Oum et al., 2014). Previous studies have illustrated that the genotoxicity mechanism of FQs mainly contains two approaches: inhibited the bacterial DNA gyrase, blocked the DNA replication and cell division (Khobursky and Cozzarelli, 1998; Suh and Lorber, 1995); inhibited the topoisomerase IV by the induction of SOS pathway for DNA repair (Hu et al., 2007). Thus, the SOS/umu bioassay has been used to evaluate the ability of detected samples to induce DNA damage.

To date, the large consumption and potential ecological risk of FQs make the acquisition of adequate data and a rapid/sensitive screening technique more essential to evaluate their environmental threat to humans and other organisms, which is difficult to realize just relaying on experimental values (in vivo) (Zhang et al., 2015). The quantitative structure-activity relationship (QSAR) model has provided a valuable approach in researching and supplying data on toxicity and other various environmental behaviours, and it has been successfully adopted for FQs (Alaa et al., 2011; Li et al., 2010; Minovski et al., 2011; Tang et al., 1988). However, the descriptors involved in previous QSAR models for the genotoxicity of FQs were mainly quantum mechanical properties, topologic descriptors (Agrawal et al., 2000), 2D molecular descriptors (Minovski et al., 2012), or a combination of these descriptors (Li et al., 2014), which were all abstract and could not reflect the detailed effect of each position on the genotoxicity of the FQ.

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http://dx.doi.org/10.1016/j.ecoenv.2016.10.036
Received 14 March 2016; Received in revised form 26 October 2016; Accepted 27 October 2016
Available online 08 November 2016
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Thus, the relationship between the substituent positions and the complete molecular genotoxicity is still unclear. In addition, previous research always only focused on the preformation promotion of the established QSAR model, searching different modelling methods by introducing different descriptors, and predicting the genotoxicity of undetected FQs. Among this research, substituent characteristics have only been discussed separately, without analysis of the second-order interaction effects of different substituent groups, substituent numbers and substituent positions on the genotoxicity of FQs.

Full factorial experimental design is considered to be an important analysis method for assessing the risk of compounds by the EPA (Svensgaard and Hertzberg, 1994), and it has been widely used in the field of environmental chemistry to quantize the strength of the single (main effects) and combined effects (second-order interaction effects) attributed to each target factor, but it is scarcely involved in the theoretical analysis for organic compounds. Jiang and Li have introduced the full factorial experimental design for PCBs (Jiang and Li, 2015) and PBDEs (Jiang and Li, 2016) based on their molecular structure characteristics, including: the same structure frame (biphenyl for PCBs and diphenyl ether for PBDEs) and similar substituent characteristics (different substituent are located at each substituent position), presenting the feasibility of the application and accuracy of the full factorial experimental design. The aim of this paper is to establish a QSAR model and a 3D Pharmacophore model to screen dominant substituent positions for the full factorial experimental design, which is used to analyze the main effect and second-order interaction effect of dominant positions and substituents on the genotoxicity of FQs.

2. Methods and data

2.1. Experimental genotoxicity values

The genotoxicity values (the lowest observed effective concentration, LOEC) of 21 quinolones cited in this paper were measured via the SOS/umu protocol (SIO 13829) by Li et al. (2014) who used the engineered bacterium *Salmonella thyphimurium* TA1535/Psk1002 as an indicator. Although there are 2 congeners not belonging to the FQs, they both have a similar basic structure to that of the FQs, but they have less influence on establishing a QSAR model for FQs. The LPEC value of each quinolone was converted to a *p*LOEC (-lg LOEC) value for convenient analysis and the values are listed in Table 1. The general geometry and specific number of each position for FQs are shown in Fig. 1.

2.2. QSAR modelling

Using the interval-sampling method, the experimental *p*LOEC values of the 21 quinolones were sequenced from big to small, and quinolones with the order number of 3n +5 (n=0, 1, 2, 3) were put into a testing set. The final QSAR model (17 samples in the modelling set and 4 samples in testing set) was established via the stepwise regression method to predict the *p*LOEC values of other FQs which were used in the latter full factorial experimental design.

The performance of the established QSAR model was validated in terms of its fitness, robustness and predictive ability in this paper. For fitness, the conventional square of the correlation coefficient (R^2) and Fisher test values (F) were selected as evaluation indices. For robustness, the correlation coefficient during leave-one-out cross-validation (q^2), prediction error sum of squares (*PRESS*) and the Y-randomization test technique were used to evaluate the robustness. The lower values of R^2 and R_{cv}^2 obtained from the Y-randomization test always reveal better robustness (Tropsha et al., 2003; Afantitis et al., 2006). The conventional square of correlation coefficient produced by the testing set (R_{pre}^2) was the basic descriptor for evaluating the predictive ability. Meanwhile, Tropsha et al. considered a QSAR model to have good predictive ability, if the following conditions were satisfied (Golbraikh and Tropsha, 2002; Tropsha et al., 2003):

$$R_{CVext}^2 > 0.5,\ R_{pre}^2 > 0.6$$

$$0.85 \le k \le 1.15 \text{ or } 0.85 \le k' \le 1.15$$

The detailed definitions of $R2$ CVext, k and k' are presented below:

$$R_{CV\text{ext}}^2 = 1 - \frac{\sum_{i=1}^{test}(y_i - \tilde{y}_i)^2}{\sum_{i=1}^{test}(y_i - \overline{y}_{tr})^2}$$

$$k = \frac{\sum y_i \tilde{y}_i}{\sum \tilde{y}_i^2},\ k' = \frac{\sum y_i \tilde{y}_i}{\sum y_i^2}$$

where y_i are the experimental values, $\tilde{y}_i$ are the predicted values from the QSAR model, and $\overline{y}_{tr}$ is the average value of the dependent variables of the training set. The four quinolones in the testing set were labelled with the superscript symbol "#" and are shown in Table 1.

Geometries of all of the quinolones were first optimized using density functional theory (DFT) at the level of B3LYP/6–31+G(d) via Gaussian 09 software that has been used successfully in FQs (Rimarčíka et al., 2011). Then, quantum chemical descriptors (used as independent variables for QSAR modelling) were calculated at the same level and contained the following: the energy of the highest occupied molecular orbital (E_{HOMO}, eV); the energy of the lowest unoccupied molecular orbital (E_{LUMO}, eV); E_{LUMO}-E_{HOMO} (ΔE, eV); total energy (*TE*, eV); dipole moment (μ, Debye); the atomic partial Mulliken charge on typical atoms (q_{N1}, q_{C2}, q_{C3}, q_{C4}, q_{C5}, q_{C6}, q_{C7}, q_{C8}, q_{C9}, q_{C10}, q_{O11}, q_{C12}, q_{O13}, q_{O14}, q_{H15}, q_{F16}, e); mean polarizability (α, 10^{-30} esu); anisotropy polarizability ($\Delta\alpha$, 10^{-30} esu); approxpolarizability (α_{xx}, α_{yy}, α_{zz}, α_{xy}, α_{xz}, α_{yz}); molar volume (V, cm^3/mol).

2.3. 3D pharmacophore model

In this paper, the 3D pharmacophore model for *p*LOEC was generated via the Catalyst HypoGen module of Accelrys Discovery Studio V2.5 (DS, www.accelrys.com) based on the optimal geometries of the 21 quinolones obtained above. A maximum of 255 diverse conformers was generated for each quinolone by using the best flexible conformation generation module (Chen and Foloppe, 2008; Mittal et al., 2014). Five common features including hydrogen bond acceptor (A), hydrogen bond donor (D), hydrophobic (H), hydrophobic aromatic (Ha) and ring aromatic (R) were applied to generate hypotheses (the feature value must be set between 0 and 5).

The quality of the established pharmacophore model was mainly validated by two important calculated cost values: fixed cost and null cost, both of which were presented in bit units. A significant pharmacophore model should have a value of the total cost that is close to the fixed cost and far from the null cost, and the value of the configuration which enumerates that the entropy of the hypothetical space must be less than 17 (Arooj et al., 2011; Nayana et al., 2009). Based on these criteria described above, the best pharmacophore model for *p*LOEC was confirmed and used to analyze the critical pharmacophore features.

2.4. Full factorial experimental design

Different substituent positions were assumed to be factors and different types of functional groups at each position were taken as levels. The number of factors was determined by screening essential substituent positions from the established QSAR model and 3D pharmacophore model, while the number of levels was based on the substituent characteristics of the 21 given quinolones. Thus, the final full factor experimental table could be formed using the experimental design module of the Minitab software to analyze the main and second-order interaction effects of each position and functional group on the *p*LOEC values of FQs, leading to a reasonable modification scheme.

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