Genotoxicity of quinolone antibiotics in chlorination disinfection treatment: formation and QSAR simulation

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Abstract Lots of unexpected disinfection by-products were formed during the chlorination disinfection of contaminated water bodies, leading to a potential threat to human health and ecological safety. In this study, SOS/umu assay was used to trace the genotoxicity variation of 20 quinolone compounds during the chlorination disinfection. Furthermore, two- and three-dimensional quantitative structure-activity relationship models were developed based on the electronic and hydrophobic properties of the quinolones, which were used to quantify the impact of the different structural features of the compounds on their genotoxicity variation. The results revealed that quinolones bearing hydrophilic substituents with less H-bond donors and negative charge at the 1-position of the quinolone ring exhibited a positive correlation with genotoxicity elevation. More notably, the chlorination of quinolones in both ultrapure water and secondary effluent matrices provided comparable levels of genotoxicity, indicating that our research

could potentially be used to evaluate the environmental risk of quinolone antibiotics in chlorination disinfection treatment.

Keywords Quinolone · Chlorination · Disinfection · Genotoxicity · QSAR · CoMSIA

Abbreviations

STPs	Sewage treatment plants
FAC	Free available chlorine
DBPs	Disinfection by-products
DMSO	Dimethyl sulfoxide
4-NQO	4-Nitroquinoline- <i>N</i> -oxide
<i>GeF</i>	Genotoxicity formation
CoMFA	Comparative molecular field analysis
CoMSIA	Comparative molecular similarity index analysis
PLS	Partial least squares procedure
LOO	Leave-one-out procedure
Q^2	Cross-validated correlation coefficient
N	Optimal number of components
R^2	Correlation coefficient
<i>SEE</i>	Standard error of estimate
F	Fisher test value
M	Dipole moment of each molecule
PSA	The polar surface area

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Introduction

Quinolones are an important class of synthetic antibiotics, which have been used extensively during the last few decades for the treatment of a range of diseases in both humans and animals. Significant quantities of quinolones have consequently entered directly or indirectly into the environment via a multitude of different pathways. Tens of quinolones have

been found in variety of different environmental matrices, including surface water (Kolpin et al. 2002; Kim et al. 2009; Li et al. 2012; Bu et al. 2013), as well as municipal sewage and hospital wastewater (Hartmann et al. 1998; Thomas et al. 2007; Seifrtova et al. 2008). For example, a total of 118 pharmaceuticals have been observed in urban wastewater samples, with ciprofloxacin and ofloxacin being the most frequently detected of these compounds at concentrations as high as 14 and 32 $\mu\text{g/L}$, respectively (Verlicchi et al. 2012). Quinolones have also been detected following secondary biological treatment processes because of incomplete elimination during the treatment of the wastewater, with the residual levels of ciprofloxacin in secondary effluents ranging from 0.13 to 0.64 $\mu\text{g/L}$ (Golet et al. 2003; Costanzo et al. 2005; Watkinson et al. 2007). It has been reported that the total concentration of detectable quinolones could reach $1.01 \pm 0.22 \mu\text{g/L}$ in the secondary effluents from Chinese sewage treatment plants (STPs) (Jia et al. 2012). The occurrence of quinolones in these aquatic environments has raised particular concern because of their long-term input, low susceptibility to biodegradation, and the formation of antimicrobial resistance (Harris et al. 2012; Johnning et al. 2015; Xu et al. 2015; Bajaj et al. 2016; Varela et al. 2016). Furthermore, quinolones have been reported to exhibit significant genotoxic and mutagenic potential toward a large proportion of the bacteria against which they have been tested (Mamber et al. 1993; Hartmann et al. 1998; Hu et al. 2007; Khadra et al. 2012; Li et al. 2014). Since most quinolones in the aquatic environment are released from the effluents of municipal STPs, the removal efficiency of quinolone antibiotics in STPs plays a crucial role in controlling their role as pollutants (Jia et al. 2012).

The shortage of freshwater resources represents a growing problem in many countries throughout the world, as existing supply routes continue to be stretched by population growth and economic development. Extensive practical experience has shown that wastewater reclamation and reuse represents a feasible and attractive way to relieve issues surrounding the supply of freshwater (Asano 1996; Chu et al. 2004). Conventional secondary treatment, however, cannot remove all the chemical and pathogenic contaminants present in wastewater, except for some advanced treatment techniques (Niu et al. 2012; Mahdi-Ahmed and Chiron 2014). A disinfection process is required to guarantee the safety and quality of the water, and this practice applies not only to conventional secondary treatment but also to reclamation treatment. Free available chlorine (FAC) has been used extensively as a disinfectant for reducing pathogenic risk because of its strong oxidation potential. Some organic and inorganic substances in wastewater, however, can react with FAC to generate toxic disinfection by-products (DBPs) (Ashbolt 2004), resulting in adverse impact on human health and ecological safety. Several antibiotics by chlorination has been reported in the literature with respect to their removal efficiencies and transformation

pathways (Dodd et al. 2004; Dodd et al. 2005; Li and Zhang 2012; El Najjar et al. 2013). It is currently not possible to detect all of the toxic DBPs individually even with advanced monitoring techniques, and the biological effects have consequently been used as an alternative way to represent the formation of toxic DBPs as a whole following the chlorination process (Wang et al. 2007a).

The short-term SOS/umu test is based on the ability of genotoxic agents to induce the expression of the umuC-gene in response to genotoxic lesions in the DNA (ISO 2000). Reifferscheid and Heil (1996) demonstrated that the SOS/umu test can be used as an important and reliable tool for the assessment of a compound's genotoxicity and reported a concordance of approximately 90 % with the Ames test. The SOS/umu test is particularly useful for determining the umuC-dependent mutagenic potentials of chemicals in the context of environmental pollution. The purpose of the current study is to measure the genotoxicity variation of chlorination systems containing quinolones using SOS/umu test. Previous studies in this area have indicated that the chemical substituents on the quinolone ring impacted not only the potency and spectrum of the antibacterial activities of these compounds (Domagala 1994) but also the primary active sites during the chemical reactions (Zhang and Huang 2005; De Witte et al. 2009; Li et al. 2011). Furthermore, the quinolone skeleton remains intact during the chlorination process (Dodd et al. 2005; El Najjar et al. 2013). Based on these observations, it is reasonable to assume that the differences in the genotoxicity of the compounds formed during the chlorination disinfection process are dependent on the chemical substituents on the quinolone ring. With this in mind, the quantitative structure-activity relationship (QSAR) techniques could be applied to explore the relationship between the different substituents on the quinolone ring and their genotoxicity during the chlorination process. The results of the current study could be used to provide useful information for evaluating the potential environmental risk associated with the chlorination of quinolones.

Materials and methods

Reagents and solutions

The 20 quinolone antibiotics used in the current study are listed in Fig. S1. These compounds were purchased from Sigma-Aldrich (St Louis, MO, USA) and the National Institute for Food and Drug Control of China (Beijing, China). All of the reagents were purchased as reagent grade (purity >97 %) and used directly without purification. Stock solutions of the quinolones were prepared in ultrapure water, which was produced using a Milli-Q ultrapure water system (Millipore, Billerica, MA, USA).

Chlorination disinfection treatment

Considering the residual level of quinolones in secondary effluent of STPs (ca. $\mu\text{g/L}$ level), and the operating parameters required for a practical chlorination disinfection treatment process (i.e., 0.3–22 mg/L FAC dose and 30–60 min retention time) (Krasner et al. 2009), the chlorination reaction was set up as follows: Each of the quinolone stock solution was diluted by phosphate buffer solution (0.02 M, pH 7) to prepare working solution (1.0–1.0 mM), and the dilution rate reached to 100 times at least. Then, the working solution was placed into a 200-mL amber borosilicate glass bottle, and 10 equivalents of FAC was added to trigger reaction, the mixed solution kept constant stirring at 25 °C over a period of 60 min. Phosphate buffer solution (0.02 M) was used to maintain the reaction at pH 7. The reaction was quenched with 1 M sodium sulfite solution, freeze-dried, and extracted with a 1:1 (v/v) mixture of methanol/acetone (10 mL). The supernatant was collected and dried under a stream of N_2 to give a residue, which was dissolved in dimethyl sulfoxide (DMSO) prior to being tested for its genotoxicity. The chlorination experiment was conducted in triplicate for each quinolone compound.

Chlorination treatment on secondary effluents

Two secondary effluent samples were collected from two different STPs in Beijing, China. The physicochemical properties of the two water samples were analyzed in accordance with standard methods (APHA 1998). To effectively simulate the chlorination conditions used in conventional disinfection processes in STPs, four quinolones were randomly selected as targets to respectively perform chlorination treatment in two secondary effluents with the following operating parameters:

20 mL of each effluent sample was spiked with 0.56–1.12 mg/L (0.0028 mM) of the quinolones and 2 mg/L (0.028 mM) of FAC (about 10 equivalents to quinolones), and the resulting mixture was agitated for 60 min. All of the water samples were treated directly without adjusting their pH conditions. The water samples were then subjected to the treatment method described above in “Chlorination disinfection treatment” section. The chlorination treatment of each targeted quinolone compound in both secondary effluent matrices was conducted in duplicate.

Genotoxicity assay

The SOS/umu assay for short-term genotoxicity screening was carried out according to the standard ISO protocol (Oda et al. 1985; ISO 2000). The test *Salmonella typhimurium* TA1535/pSK1002 was donated by Professor Oda (Japan). Each extracted sample from the previous chlorination treatment was challenged with *S. typhimurium* in triplicate. For each test, a series of 4-nitroquinoline-*N*-oxide (4-NQO) solutions were set as positive controls to obtain a dose-response curve. The genotoxicity of each sample was converted to its equivalent value relative to the 4-NQO reference, and the values are shown in the Supplementary Data (Table S1). The exposure concentration of DMSO, which was used as a co-solvent for evaluating the genotoxicities of the samples, was set at 0.1 % (v/v). The genotoxicity changes of samples collected prior to chlorination after quinolone compounds spiked in and samples collected at the end of chlorination treatment were determined. And an index defined as genotoxicity formation (*GeF*) was proposed to describe the genotoxicity changes quantitatively. Taking ofloxacin as an example, the *GeF*_{ofloxacin} value can be defined as follows

$$GeF_{\text{ofloxacin}} = \frac{\text{the genotoxicity value after chlorination}}{\text{genotoxicity value before chlorination}} \quad (1)$$

Using this equation, a *logGeF* value greater than zero indicates an increase in the genotoxicity during the chlorination treatment, whereas a *logGeF* value of less than zero indicates a decrease in the genotoxicity. Furthermore, the higher the *logGeF* value, the greater the genotoxicity following the chlorination treatment process. Details of the calculation methods used to determine the *logGeF* values have been provided in the Text S1 and Fig. S2.

2D-QSAR method

The molecule structure descriptors for the quinolones used in the current study were obtained using the ADRIANA. Code program (Ver2.2.4, Molecular Networks GmbH, Germany). A total of 155 2D descriptors were calculated for the quinolones

to provide an adequate representation of their shape, topological and global molecular properties. All of the descriptors were selected as independent variables, whereas the *logGeF* values were selected as dependent variables. A stepwise multiple linear regression method was used to establish the fitting models.

3D-QSAR method

All of the molecular modeling techniques and 3D-QSAR analyses were performed using version 8.0 of the SYBYL software (Tripos Inc., USA). The structures of the 20 quinolones used in the current study were fully geometry-optimized using the Tripos force field. An energy gradient convergence criterion of 0.005 Kcal/mol/Å was used to achieve energy

minimization. Partial atomic charges were assigned using the Gasteiger-Hückel formation to calculate the electrostatic potential. Ofloxacin, which displayed the most significant changes in its genotoxicity, was selected as the template molecule. All of the other molecules were superimposed onto OFL according to the database alignment rules, and a 3D view of the aligned molecules is shown in Fig. S3.

The overlapped molecules were placed in a 3D cubic lattice with a 2-Å grid (Lu et al. 2010). For the comparative molecular field analysis (CoMFA) model, the steric and electrostatic fields were calculated using a standard Tripos force field. An sp^3 carbon atom with a charge of +1.0 was used as a probe to generate the energies of the steric and electrostatic fields. A default energy value of 30 kcal/mol was used to avoid an infinity of energy values inside the molecules. The comparative molecular similarity index analysis (CoMSIA) model was generated based on the same lattice box. Given that this model represents an extension to the CoMFA approach, five fields, including steric, electrostatic, hydrophobic, H-bond donor, and acceptor fields, were calculated using the standard settings (Klebe and Abraham 1999; Hou and Xu 2001).

Statistical analysis was performed using the partial least squares (PLS) procedure, and cross-validation was achieved by the leave-one-out (LOO) procedure. The cross-validated correlation coefficient (Q^2) allows for the predictive capacity of the model to be quantified and should be greater than 0.5. The optimal number of components (N) was employed to allow for the validation of the PLS analysis, generate the final model, and derive a contour map. The correlation coefficient R^2 was used to represent the self-consistency of the model and should be greater than 0.9. The standard error of estimate (SEE) and the Fisher test (F) values were also calculated.

Results and discussion

The genotoxicity variation of the 20 quinolones during the chlorination disinfection process was determined using SOS/umu assay, and their $\log GeF$ values are shown in Table 1. The results revealed that the majority of the compounds tested exhibited low $\log GeF$ values, although several compounds with complex structures did give relatively high $\log GeF$ values following the chlorination process.

2D-QSAR analysis

A statistical model involving the $\log GeF$ values and the physicochemical descriptors was obtained using a step-wise multiple linear regression analysis. This process can be described as follows:

$$\log GeF = 14.10 (\pm 2.62) - 0.41 (\pm 0.14)$$

$$\times \mu - 12.36 (\pm 1.99) \times R_{\text{complexity}}$$

$$+ 1.98 (\pm 0.57) \times q^- + 0.03 (\pm 0.01) \times PSA \quad (2)$$

$$N = 20, R^2 = 0.84, R^2_{\text{adj}} = 0.80, SE = 0.60, F = 20.03, p < 0.001.$$

where N represents the number of compounds, R^2 is the multiple correlation coefficient, R^2_{adj} is the multiple correlation coefficient adjusted by the degree of freedom, SE is the standard error, F is the F -test value for the analysis of the variables, and p is the significance. A plot of the observed versus the calculated $\log GeF$ values is shown in Fig. 1.

The dipole moment (μ) of each molecule, which describes the net polarity and represents the charge separation in the molecule, contributes a negative contribution to the $\log GeF$ value. The dipole moments of the quinolone molecules can be attributed to the carbonyl groups (C^+-O^-) at the 3- and 4-positions of the quinolone ring. The carbonyl groups of the quinolone molecules can also result in permanent polarization, which can lead to a dipole-dipole-type interaction between two or more molecules through hydrogen-bonding interactions (Pillai et al. 2005). The descriptor $R_{\text{complexity}}$ represents the ring complexity proposed by Gasteiger and Jochum (1979) and reflects the significant impact of the substituents on the properties of the ring. The descriptor q^- represents the most negative atomic charge in the molecule. The polar surface area (PSA) of a molecule is defined as the sum surface area over all of the polar atoms (primarily oxygen and nitrogen atoms as well as their attached hydrogen atoms) (Ertl et al. 2000).

The descriptors involved in Eq. (1) can be divided into two different types. The first type, including q^- , is used to describe the electronic properties of the molecule. The second type, including μ , $R_{\text{complexity}}$, and PSA , is used to describe the hydrophobic properties of the molecule. Both types of descriptors made a significant contribution to changes in the genotoxicity of the quinolones following chlorination. The specific contributions of the different substituents of the quinolone ring on the $\log GeF$ values following the chlorination process, in terms of their properties and positions, however, remain unclear. 3D-QSAR methods (using CoMFA and CoMSIA methods) can be used to complement 2D-QSAR methods and can deliver significant improvements in terms of the interpretation of the model.

3D-QSAR analyses

CoMFA and CoMSIA statistical results

The statistical results of the CoMFA model are shown in Table 2. Leave-one-out analysis gave a cross-validated Q^2 value of 0.58 for three optimal components. The correlation

Table 1 Physiochemical properties of 20 quinolones and their genotoxicity formation values in chlorination ($\log GeF$) involved in the 2D- and 3D-QSAR models

No.	$\log GeF$ (Ex- p.)	2D-QSAR					3D-CoMSIA(2)		
		μ (D)	R_{com}	q^-	PSA	$\log GeF$ (Cal.)	Res.	$\log GeF$ (Cal.)	Res.
Balofloxacin	-1.06	7.220	1.125	-0.630	100.700	-0.72	-0.34	-1.14	0.08
Ciprofloxacin	-1.00	8.598	1.105	-0.615	86.600	-1.47	0.48	-1.19	0.2
Danofloxacin	-3.01	9.245	1.211	-0.622	76.500	-3.39	0.38	-2.97	-0.04
Difloxacin	-1.09	7.240	1.091	-0.626	76.500	-1.09	0	-1.11	0.02
Enrofloxacin	-2.89	9.515	1.105	-0.616	76.500	-2.18	-0.7	-2.80	-0.08
Fleroxacin	-1.97	6.386	1.125	-0.626	76.500	-1.16	-0.81	-2.11	0.14
Gatifloxacin	-1.36	9.102	1.105	-0.627	100.700	-1.24	-0.12	-1.43	0.07
Levofloxacin	-3.78	8.843	1.263	-0.628	90.600	-3.42	-0.35	-3.90	0.13
Lomefloxacin	-1.38	7.798	1.125	-0.621	86.600	-1.4	0.02	-1.28	-0.1
Nadifloxacin	-1.75	7.871	1.263	-0.629	97.600	-2.8	1.05	-1.76	0.01
Norfloxacin	-1.14	8.675	1.125	-0.622	86.600	-1.76	0.62	-1.36	0.22
Ofloxacin	-3.97	8.843	1.263	-0.625	90.600	-3.41	-0.56	-3.90	-0.07
Pazufloxacin	-3.83	8.300	1.313	-0.634	108.100	-3.25	-0.58	-3.87	0.04
Pefloxacin	-3.08	9.614	1.125	-0.635	76.500	-2.5	-0.57	-2.86	-0.21
Rufloxacin	-3.23	8.794	1.263	-0.621	76.500	-3.84	0.62	-3.08	-0.14
Sarafloxacin	0.23	6.261	1.091	-0.626	86.600	-0.36	0.59	0.38	-0.15
Sparfloxacin	0.11	6.805	1.105	-0.608	109.500	0.028	0.082	0.21	-0.1
Cinoxacin ^a	-0.43	7.792	1.308	0.619	110.600	-0.41	-0.02		
Enoxacin ^a	-0.83	9.220	1.105	-0.613	97.900	-1.35	0.52		
Pipemidic acid ^a	-0.50	6.606	1.125	-0.630	109.200	-0.19	-0.31		

All compounds were used as the training set in the 2D-QSAR

μ dipole moment in Debye, R_{com} $R_{complexity}$, q^- most negative atomic charge in the solution molecule, PSA polar surface area, Exp. experimental (actual) value, Cal. calculated value from QSAR models, Res. residue between the experimental and calculated values

^a Rejected compounds to 3D-QSAR because of their naphthyridone core

coefficient R^2 was determined to be 0.97 for the non-cross-validated PLS analysis. The correlation between the observed and calculated values is shown in Fig. 1, and the steric and electrostatic contour maps are shown in Fig. S4.

The results of CoMSIA(1) are shown in Table 2 and revealed that the H-bond donor, hydrophobic, and electrostatic fields made the greatest contribution to the $\log GeF$ value,

whereas the steric and H-bond acceptor fields made a much smaller contribution. Based on these results, we constructed a second CoMSIA model known as CoMSIA(2), which excluded the steric and H-bond acceptor fields. A cross-validated Q^2 value of 0.69 was obtained with five optimal components, together with an R^2 value of 0.99. The F and SE values were 242.81 and 0.15, respectively. A plot of the observed values

Fig. 1 Plot of observed vs calculated values for QSAR models

Table 2 Summary of 3D-QSAR models

Model	Q^2	R^2	SE	F	NC	Contribution				
						S ^a	E ^b	H ^c	D ^d	A ^e
CoMFA	0.58	0.97	0.26	139.41	3	0.749	0.251			
CoMSIA(1)	0.66	0.98	0.18	223.91	4	0.062	0.148	0.301	0.463	0.026
CoMSIA(2)	0.69	0.99	0.15	242.81	5		0.177	0.342	0.481	

^a Steric field^b Electrostatic field^c Hydrophobic field^d H-bond donor field^e H-bond accept field

versus the calculated values is shown in Fig. 1. Statistical analysis of this model revealed that a reliable CoMSIA(2) model had been successfully developed.

Interpretation of CoMSIA(2) contour maps

An electrostatic contour map of the CoMSIA(2) model is shown in Fig. 2a. The red contours represent the negatively charged areas of the molecule that favored an increase in genotoxicity, and the blue contours represent the positively charged areas of the molecule that favored an increase in the genotoxicity. A large red contour surrounded the 1-position of the quinolone ring, indicating that substituents bearing negative charge in this region would afford a high level of

genotoxicity. This result was supported by sarafloxacin (bearing a strong electron-withdrawing *p*-fluorophenyl group at the 1-position), which had a higher *logGeF* value than those of norfloxacin and ciprofloxacin (bearing electron-donating ethyl and cyclopropyl groups at the 1-position, respectively).

The hydrophobic contour map is depicted in Fig. 2b. The yellow and white colored regions of the contour map represent the areas of the quinolone ring that favor hydrophobic and hydrophilic groups, respectively. A large white area surrounded the 7-position, which suggested that the introduction of hydrophilic substituents at this position would lead to a significant increase in the genotoxicity of the compounds following the chlorination treatment. This result was in agreement with the steric map provided by the CoMFA model (Fig. S4a),

Fig. 2 Contour maps for CoMSIA(2) model. **a** Electrostatic field. **b** Hydrophobic field. **c** H-donor field

Table 3 Parameters of two secondary effluents samples

	pH	NH ₃ -N (mg/L)	COD (mg/L)	DOC (mg/L)	UV ₂₅₄ (/cm)	Gene toxic ^a
1#	6.75	2.28	8.37	2.30	0.128	no
2#	8.67	6.85	11.16	3.94	0.140	no

^a Gene toxic effect was tested with SOS/umu assay

in that small groups at the 7-position favored high levels of genotoxicity. Variations in the *logGeF* values of the quinolones could be attributed to the hydrophilicity of the substituent at the 7-position. Quinolones bearing an *N*-methylated piperazine group exhibited lower levels of both hydrophilicity and genotoxicity, as evidenced by the compound pairs sarafloxacin/difloxacin, ciprofloxacin/enrofloxacin, and norfloxacin/pefloxacin (Fig. S1). This result correlated well with the positive contribution of the polar surface area descriptor in the 2D-QSAR model.

The H-bond donor properties are shown in Fig. 2c. The cyan contours represent the regions of the quinolone structure where the introduction of hydrogen bond donating substituents led to an increase in the genotoxicity, and the purple contours represent areas where the inclusion of hydrogen bond donating substituents led to a decrease in the genotoxicity. A large purple contour appeared in the region where the H-bond donors derived from amine groups made a negative contribution on the genotoxicity.

Validation of genotoxicity formation in secondary effluent matrices

To determine whether similar genotoxicity patterns would be observed following the conventional chlorination process, four quinolones were randomly selected and subjected to the two secondary effluents from two STPs, Beijing. The physicochemical characteristics of those two secondary effluents #1 and #2 are listed in Table 3. The *logGeF* values of the four quinolones measured in the two secondary effluents as well as

ultrapure water system are shown in Fig. 3. In the two secondary effluents, the *logGeF* values of three quinolones were slightly reduced, except for gatifloxacin in secondary effluent #2. Using two secondary effluents as controls for umu/SOS toxicity test, parameters of dissolvable organic carbon levels and UV₂₅₄ spectrum (Li et al. 2000) were excluded, and ammonia nitrogen (NH₃-N) was identified as a critical parameter accounts for the decrease of *logGeF* values. It was envisaged that the NH₃-N consumed FAC quickly (Qiang and Adams 2004), leading to the formation of inactive chloramine, which would in turn lead to a reduction in the formation of toxic by-products in most cases (Wang et al. 2007b).

Environmental implication

Previous work in this area implied that the antibacterial activities of quinolones could be retained even after the chlorination disinfection process. This retention of activity was attributed to the quinolone skeleton remaining intact through the chlorination process, although the corresponding biological data has not been reported (Dodd et al. 2005). With respect to 18 of the quinolones investigated in the current study, Hu et al. (2007) reported a negative relationship between the minimum inhibitory concentrations (MIC₅₀) of these compounds against *Streptococcus pneumoniae* and their genotoxic potentials (based on the SOS/umu assay). The results of the current study indicated that the genotoxic potentials of most of the quinolone derivatives were reduced significantly following the chlorination disinfection treatment and gave low antibacterial activities. This result suggested that the chlorination disinfection of quinolone-containing wastewater would not only decrease the potential risk but also eliminate the occurrence of drug resistance in bacterial pathogens.

Conclusions

The genotoxicity of 20 quinolones formed in chlorination disinfection treatment was measured using the SOS/umu assay, and an index of genotoxicity formation (GeF) was used to evaluate the genotoxicity changes of the compounds. 2D- and 3D-QSAR models were established to estimate the contributions of the different chemical substituents on the quinolone skeleton to the genotoxicity. These models suggested that the presence of hydrophilic substituents containing less H-

Fig. 3 Genotoxicity formation values (*logGeF*) of quinolones in different matrices

bond donors or negative charge at the 1-position of the quinolone ring would lead to an increase in the genotoxicity after the chlorination process. Furthermore, the result was successfully applied to secondary effluents of STPs, and the present research implied that the chlorination disinfection treatment of quinolone-containing wastewater could potentially reduce its ecological impact.

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