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Toxic effect prediction of cefatirizine amidine sodium and its impurities by structure-toxicity relationship of cephalosporins

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ABSTRACT

The three-dimensional (3D) structure-toxicity relationship of cephalosporins was explored by computing the most stable conformations of 33 kinds of cephalosporins in aqueous solution and using the teratogenicity and lethality of these compounds obtained in zebrafish embryo toxicity testing to evaluate their toxic effects. The toxic effect of cefatirizine amidine sodium, a novel cephalosporin which has finished preclinical study, was investigated. It is thought that the teratogenic effect of the triazine ring at the C-3 position is the main toxic effect of cefatirizine amidine. In addition, cefatirizine amidine is no more toxic than cefathiamidine and ceftriaxone. The results of the zebrafish embryo toxicity test combined with gene expression microarray technology were consistent with the prediction. The toxic effects of some potential process-related impurities of cefatirizine amidine were also predicted.

1. Introduction

Cephalosporins are one kind of β-lactam antibiotic derived from the core structure of 7-aminocephalosporanic acid (7-ACA) (Table 1). Since the first cephalosporin was introduced in 1964, four generations of cephalosporins have been brought into clinical use after > 50 years of study (Bryskier, 2000; Hwu et al., 2003; Macheboeuf et al., 2007; Singh, 2004). With the comprehensive understanding of the structure-activity relationship of cephalosporins, the fifth generation of cephalosporins (ceftaroline and ceftobiprole) has been launched and more candidates are undergoing clinical evaluations (Butler and Cooper, 2011). In new drug R & D, only one candidate in 5000 will enter into clinical study on average, yet the candidate might not be approved to hit the market due to safety concerns (Adams and Brantner, 2010). Also, some post-marketing drugs have been withdrawn because of toxic effects (Li, 2001, 2004). The safety concerns of the impurities in drugs should also be highlighted (Alsante et al., 2014). According to the ICH guidelines, the toxicity of the impurities should be evaluated when the content of the impurities exceeds the qualification threshold (0.15% for chemical entities). Therefore, the fast and accurate prediction of toxic effects of both drug candidates and impurities thereof in the early stage becomes a key issue to improve the success rates of new drug R & D.

In a previous study, we investigated the toxic effects of cephalosporins with Zebrafish embryo toxicity testing (Zhang et al., 2015; Zhang et al., 2010; Zhang et al., 2013). We studied both the C-7 and C-3 substituents of cephalosporins and the relationships between the structures of cephalosporins, conformations, absorption, and toxic effects in combination with theoretical calculations. The following conclusions can be proposed preliminarily:

(1) Both the C-7 and C-3 substituents of cephalosporins are toxic functional groups, which are far more toxic than the core structure of 7-ACA, and each toxic functional group may generate toxic effects independently or synergistically (Zhang et al., 2010; Zhang et al., 2013).

(2) The conformational configurations have impacts on the toxic effects; the toxic functional groups with extended form are more likely to generate toxic effects than the folded form ones (Zhang et al., 2013).

(3) The toxic effects of the drugs are both influenced by toxic functional groups and absorption (Zhang et al., 2015; Zhang et al., 2013).

Cefatirizine amidine sodium is a novel cephalosporin that has finished a preclinical study. To evaluate the toxic effects of cefatirizine amidine sodium and its potential impurities, we investigated the toxic effects with Zebrafish embryo toxicity testing and theoretical calculations based on the previously established structure-toxicity relationship of cephalosporins.

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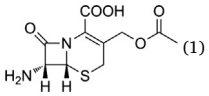
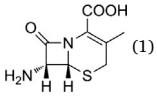
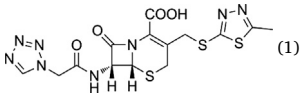
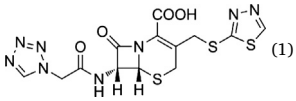
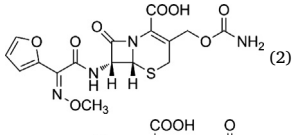
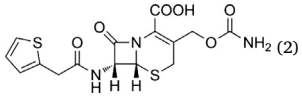
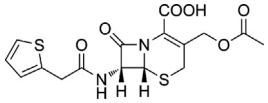
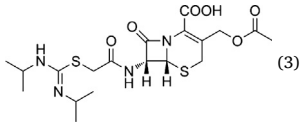
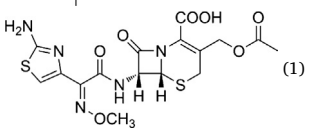
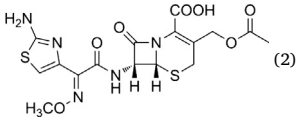
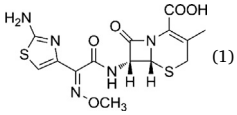
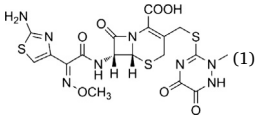
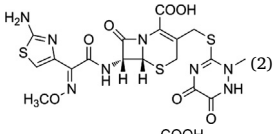
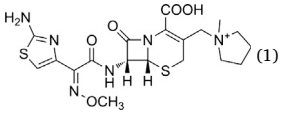
Table 1
The chemical structures, zebrafish embryo toxicity testing (6–72 hpf) results and theoretical computation results of 32 kinds of cephalosporins.

No.	Name	Structure[a]	TC_{50}/LC_{50} (mmol/L)	TPSA ($Å^2$)	Note
1	7-ACA	 (1)	19.4/49.5	120.494	
2	7-ADCA	 (1)	10/10	91.368	
3	Cefazolin	 (1)	0.15/4.0	166.910 (conformation 1) 161.293 (conformation 2) 131.328 (conformation 3)	The relative energies of these three conformers are 0, 0.2 and 1.1 kcal/mol
4	Ceftezole	 (1)	0.15/4.5	167.793 (conformation 1) 163.531 (conformation 2) 137.085 (conformation 3)	The relative energies of these three conformers are 0.2, 0 and 2.2 kcal/mol
5	Cefuroxime	 (2)	−/5.5	173.286 (conformation 1) 179.394 (conformation 2)	The relative energies of these two conformers are 0 and 0.4 kcal/mol
6	Cefoxitin	 (2)	7.7/27.1	143.147 (conformation 1) 140.219 (conformation 2)	The relative energies of these two conformers are 0 and 0.5 kcal/mol
7	Cefalotin	 (1)	2.9/14.1	121.316	
8	Cefathiamidine	 (3)	−/16.3	109.984 (neutral) 131.609 (anion)	
9	Cefotaxime	 (1)	30/54.1	183.344 (conformation 1) 188.758 (conformation 2)	The relative energies of these two conformers are 0.04 and 0 kcal/mol
10	(*E*)-cefotaxime	 (2)	6/13.8	158.034	
11	Cefetamet	 (1)	5.1/11	154.368 159.292	The relative energies of these two conformers are 0.1 and 0 kcal/mol
12	Ceftriaxone	 (1)	17/24	218.102 (keto tautomer conformation 1) 222.809 (keto tautomer conformation 2) 217.936 (enol tautomer conformation 1) 223.084 (enol tautomer conformation 2)	The relative energies of these two keto conformers are 0.23 and 0.0 kcal/mol; the relative energies of these two enol conformers are 0.17 and 0.0 kcal/mol
13	(*E*)-ceftriaxone	 (2)	3.4/5.1	202.020 (keto tautomer) 197.774 (enol tautomer)	
14	Cefepime	 (1)	19.1/−	151.828 (conformation 1) 157.453 (conformation 2)	The relative energies of these two conformers are 0 and 0.41 kcal/mol

(*continued on next page*)