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Chemosphere 62 (2006) 641–649

CHEMOSPHERE

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A QSAR study of acute toxicity of *N*-substituted fluoroacetamides to rats

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Received 22 December 2004; received in revised form 26 April 2005; accepted 1 May 2005
Available online 5 July 2005

Abstract

Acute toxicity in vivo toward rats, of nineteen *N*-alkyl and *N*-cycloalkyl fluorocetamides [F–CH_2–C(O)–NH–R] was correlated with their structure-dependent properties. Used descriptors are: molecular weights (M_w) and heat of formation (ΔH_f) of compounds; molar refractivity (CMR), lipophilicity (Clog *P*), Broto lipol values, virtual log *P*, molecular lipophilic potential (MLP), Van der Waals surfaces (VdW SAS) and hydropathicity surface (ILM) of whole molecules; Taft steric parameters (E_s); E_s values with Hancock corrections (E_s^{CH}) and Verloop sterimol (B_5) and (L) parameters of alkyl and cycloalkyl residues; superdelocalizabilities and electron densities on the [NH–C(O)–CH_2–F] fragment. Strong quantitative structure–activity relationships were assessed. Obtained correlation suggested that lipophilicity, shape and bulkiness of the alkyl and cycloalkyl substituents, particular nearest vicinity of the amide nitrogen, as well charges on the amide moiety are the main factors that influence on the acute toxicity of studied compounds toward rats. Mechanism of toxic action was proposed.

Keywords: Acute toxicity; Rats; *N*-alkyl fluoracetamides; QSAR

1. Introduction

One of the current interests in medicinal chemistry and toxicology is the classification of chemical substances with the respect to their toxicity toward living systems. Quantitative structure–activity relationships (QSAR) have provided a valuable tool in research on the toxicity of organic chemicals.

The toxicity of derivatives of fluoroacetic acid to insects and rodents is well known (Metcalf, 1966; Zhu et al., 2002). Fluoroacetamide is an active insecticide, but it is less toxic and acts more slowly than sodium fluoroacetate (Alekseev and Turov, 1967). In addition, various *N*-substituted and *N*,*N*-disubstituted fluoroacetamides (Takeuchi and Ishida, 1962) and *N*-methylenefluoroacetamide derivatives (Pianka and Polton, 1965) have been

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0045-6535/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.chemosphere.2005.05.005

tested as insecticides and rodenticides. Related compounds have been also studied (Ishii, 1976).

N-alkyl fluoroacetamides also exert antischistosomal activity (Chen et al., 1982a,b). It was shown that *N*-ethyl fluoroacetamide inhibit the aconitase (E.C. 4.2.1.3) from *Schistosoma japonicum* and exerts antischistosomiasis activity (Huang et al., 1980).

It is also known that *N*-alkyl haloacetamides act as alkylating agents (Kanstrup et al., 1993; Jablonkai, 2003). Structure–activity relationships of fifteen *N*-alkyl bromoacetamides in their action toward *S. aureus* were described previously (Hansch and Lien, 1971). Minimum bactericidal concentration (MBC) was correlated with lipophilic ($\log P$), steric E_s and electronic σ' values. Very good correlation was obtained ($r = 0.980$).

The aim of this work was to correlate the acute toxicity in vivo toward rats, of group of nineteen *N*-alkyl and *N*-cycloalkyl fluorocetamides with their structure related properties. The toxicity results will also complement the toxicity database for the risk assessments of the studied compounds.

2. Materials and methods

2.1. Chemistry

Nineteen *N*-alkyl and *N*-cycloalkyl fluoroacetamides (listed in Table 1) were synthesized, using the known Schotten–Baumann reaction by acylation of the corresponding amines with fluoroacetyl chloride in the presence of a concentrated aqueous solution of potassium hydroxide, purified by recrystalization/microdistillation and characterized by melting point, elemental analysis, ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry (Miščević et al., 1992; Jeremić et al., 1995).

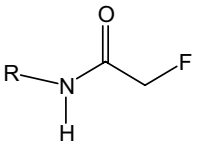
2.2. Animals

The male adult Wistar rats, average mass 200–250 g, were used. Animals were kept in cages (10 rats per cage) at room temperature under a 12-h light/dark cycle with food and water available ad libitum.

2.3. Acute toxicity

The acute toxicity (LD_{50}) was evaluated as described by Miller and Tainter (1994). In brief, freshly prepared aqueous solutions of *N*-substituted fluoroacetamides were used. The method involved the administration of five different doses of the aqueous solutions to five groups of rats (six rats per group). The mortality in each group was recorded in 24 h. The LD_{50} was than estimated and the obtained results are listed in Table 1.

Table 1
Acute toxicity of *N*-alkyl and *N*-cycloalkyl floroacetamides



Compound no.	R–	*C* (mg/kg)	*C* (M/kg)	log(1/*C*)
1	*n*-Propyl–	7	5.88×10^{-05}	4.2310
2	*n*-Butyl–	6	4.51×10^{-05}	4.3462
3	*n*-Pentyl–	8	5.44×10^{-05}	4.2648
4	*n*-hexyl–	7	4.34×10^{-05}	4.3623
5	(1-Methyl)ethyl–	72	6.04×10^{-04}	3.2187
6	(1-Methyl)propyl–	104	7.81×10^{-04}	3.1073
7	(1,2,2-Trimethyl)propyl–	150	9.30×10^{-04}	3.0313
8	(1-Methyl)butyl–	118	8.02×10^{-04}	3.0960
9	(1,4-Dimethyl)pentyl–	250	1.43×10^{-04}	2.8457
10	(1,1-Dimethyl)ethyl–	132	9.91×10^{-04}	3.0038
11	(2-Methyl)propyl–	29	2.18×10^{-04}	3.6620
12	(2,2-Dimethyl)propyl–	70	4.76×10^{-04}	3.3228
13	(3-Methyl)butyl–	13	8.83×10^{-05}	4.0539
14	(1,1,3,3-Tetramethyl)butyl–	300	1.59×10^{-03}	2.8000
15	Cyclopropyl–	9	7.68×10^{-05}	4.1144
16	Cyclobutyl–	10	7.62×10^{-05}	4.1178
17	Cyclopentyl–	31	2.14×10^{-04}	3.6705
18	Cyclohexyl–	130	8.17×10^{-04}	3.0880
19	Cyclohepthyl–	200	1.15×10^{-04}	2.9376