Structure Investigation of New Lidocaine Analogs with Local Anesthetic Activity

P. Serda [1], G. Navarrete-Vázquez [2],M. Markiewicz [3],
T. Librowski [4], B. Filipek [4], G. Mogilski [4], Sz. Nowak [5],D. Trots [6]

[1]Regional Laboratory of Physicochemical Analysis and Structural Research,
Jagiellonian University, Ingardena 3, PL-30-060 Krakow, Poland,
[2]Facultad de Farmacia, Universidad Autónoma
del Estado de Morelos, Cuernavaca, Mor. 62210, México
[3]Department of Chemistry Jagiellonian University, Krakow, Poland
[4]Department of Pharmacodynamics,
[5]Laboratory of Pharmacobiology,
Department of Cytobiology and Histochemistry,
Collegium Medicum, Jagiellonian University, Medyczna 9, PL 30-688
Kraków, Poland
[6]DESY-HASYLAB, Notkestrasse 85, Hamburg, Germany

The search for new potential drugs with local anesthetic activity is an important task both from practical and theoretical viepoints. The investigated compounds were designed to increase the half-life and also the metabolic stability of lidocaine. The design of the compounds was based on the biological activity predictions made by the computer software PASS® [1] (prediction of activity spectra for substances). The accuracy of prediction is reported to be as high as 85%.

Figure 1: Structural formulae of two studied lidocaine analogs, JCB-1 and JCB-3.

In the synthesis of *N*-(2,6-dichlorophenyl)-2-cycloalkylamine-1-ylacetamides (denoted JCB-1 and JCB-3) certain molecular modifications with respect to lidocaine molecular structure were undertaken. The replacement of methyl groups by chlorine was done in order to increase the half-life, liposolubility and reduce drug metabolism. Also the transformation of alkyl substituents into cyclic analogs was done for the same purpose. A comparison of their local anesthetic activity [2] with that of lidocaine as a reference compound is given in Table 1.

Compound	Concentration (%)	Inhibition of pain reaction (%)					
		5 min	15 min	30 min	60 min	240 min	24 h
LID	**1.0%**	65.72 [c]	59.34 [b]	56.77 [b]	36.1 [a]	12.81	0
JCB-1	**1.0%**	86.8 [d]	60.00 [b]	68.91 [c]	53.0 [b]	46.99 [d]	0
JCB-3	**1.0 %**	87.64 [d]	70.67 [d]	61.00 [c]	16.77	62.77 [c]	0

[a] $p < 0,05$ [b] $p < 0,02$ [c] $p < 0,01$ [d] $p < 0,001$

Table 1: Local anesthetic activity (infiltration anesthesia) of the investigated compounds.

The compounds appear only in micro-crystalline form with grain size too small for single crystal diffraction – hence, the crystal structure could be determined only from powder diffraction. Synchrotron radiation HRPD was a method of choice for structure solution and phase analysis.

Powder diffraction patterns of JCB-1 and JCB-3 samples were recorded on B2 beamline at DESY-HASYLAB. The experiments were done in high-resolution mode and Debye-Scherrer (capillary) geometry. The capillary diameter was 0.7 mm. For beam conditioning a Si (111) double flat-crystal monochromator and a Ge (111) analyser crystal in front of the single counter was used. The wavelength was determined via 6 reflections of Si 640b standard reference material to 1.19014 Å.

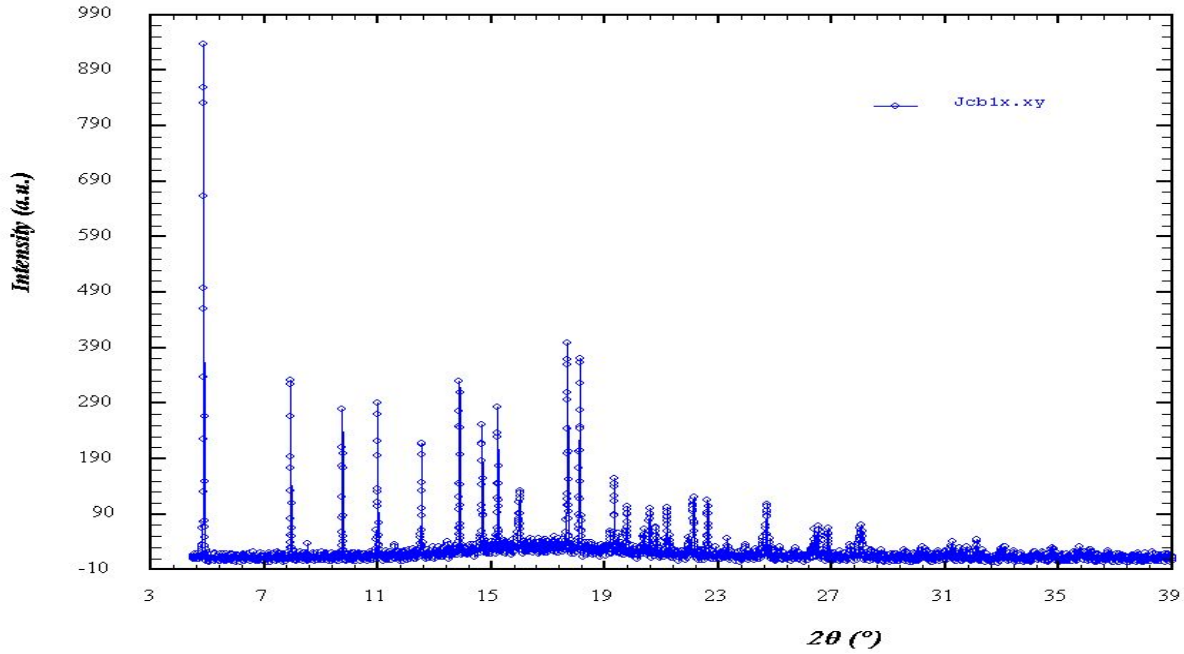

Figure 2: High-resolution powder pattern of the JCB-1 sample.

The pattern for JCB-1 was indexed using TREOR90 [3] program to yield the following lattice constants: *a*=8.9778, *b*=10.8929, *c*=13.9916 Å, orthorhombic system, with figure of merit M(20)=89, F(20)=204. Structure solution via global optimization is in progress. The starting molecular model was obtained from quantum-mechanical calculations. A systematic search of the conformational space was done by varying all four free torsion angles. During the search, all conformers were optimized in the Dreiding 2.21 force field (Gasteiger charges). The conformers with their RMS differing by more than 2Å were saved and then used to approximate the shape of molecules in the crystalline state.

Acknowledgements
The measurements were carried out under DESY - HASYLAB: I-20070138 EC proposal. This work was supported by the Contract RII3-CT-2004-506008 (IA-SFS) of the European Commission.

References

[1] E. Bülbring, J. Wajda, J. Pharmacol. Exp. Ther., 85, 78-84 (1945)
[2] A. Sadym, A. Lagunin, D. Filimonov, V. Poroikov. SAR QSAR Environ Res. 14, 339-47 (2003)
[3] P. E. Werner, L. Eriksson, M. Westdahl, J. Appl. Cryst. 18, 367-370 (1985)