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Crystal Structure of a Fluoro Analogue of 3,4-(Methylenedioxy)amphetamine

Jean GUILLON,^{*1} Noël PINAUD,^{*2} Mathieu MARCHIVIE,^{*3} Luisa RONGA,^{*1} Abdelhamid BENAZZOUZ,^{*4} and Stéphane MOREAU^{*1}

^{*1} Université de Bordeaux, UFR des Sciences Pharmaceutiques, INSERM U869, Laboratoire ARNA, 146 rue Léo Saignat, F-33076 Bordeaux Cedex, France

^{*2} Université de Bordeaux, ISM - CNRS UMR 5255, 351 cours de la Libération, F-33405 Talence Cedex, France

^{*3} Université de Bordeaux, ICMCB CNRS-UPR 9048, 87 Avenue du Docteur Schweitzer, 33608 Pessac Cedex, France

^{*4} Université de Bordeaux, Neurodegenerative Diseases Institute, CNRS UMR 5293, 146 rue Léo Saignat, F-33076 Bordeaux Cedex, France

The X-ray crystal structure of 6-fluoro-3,4-methylenedioxyamphetamine hydrochloride, a fluoro analogue of 3,4-(methylenedioxy)amphetamine, was established. It crystallizes in the orthorhombic space group *Pbac* with cell parameters $a = 24.679(4)\text{Å}$, $b = 9.873(4)\text{Å}$, $c = 9.253(5)\text{Å}$, $V = 2254.5(16)\text{Å}^3$ and $Z = 8$. The crystal structure was refined to final values of $R1 = 0.0601$ and $wR2 = 0.1479$. An X-ray crystal structure analysis revealed that each molecule features strong intermolecular N-H...Cl hydrogen bonds.

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Parkinson's disease is due to a dopamine deficiency caused by the degeneration of midbrain dopamine neurons. Current therapies are aimed to substitute dopamine or to directly stimulate postsynaptic dopamine receptors. However, not all patients profit from current therapies to the same extent, even serious side effects such as dyskinesias are complicating the therapy.¹ It has been suggested that methylenedioxy analogues of amphetamine (*i.e.* 3,4-methylenedioxyamphetamine (MDA), MDMA, 3,4-methylenedioxyethylamphetamine (MDE), *N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB)) could represent a novel class of drugs. Thus, MDMA has recently been identified as a potential therapeutic drug against Parkinson's disease in animals.² Furthermore, MDMA may also help to treat people with posttraumatic-stress disorder.² Consequently, new fluoro analogues of 3,4-(methylenedioxy)-amphetamine could be developed and investigated for PET studies in order to further synthesize [¹⁸F]fluoroamphetamines.³ Thus, to prompt investigation into the role of MDMA metabolism, new fluoro analogues of 3,4-(methylenedioxy)-

amphetamine were prepared and characterized. Although electronically very different, the fluoro analogues should be sterically very similar to the non-fluorinated parent compounds.

We report herein on the structural characterization of one of them, *i.e.* the 6-fluoro-3,4-methylenedioxyamphetamine

Table 1 Crystal and experimental data

Chemical formula: C ₁₀ H ₁₃ ClFNO ₂
Formula weight: 233.66
$T = 293(2)\text{K}$
Crystal system: orthorhombic
Space group: <i>Pbac</i>
$a = 24.679(4)\text{Å}$
$b = 9.873(4)\text{Å}$
$c = 9.253(5)\text{Å}$
$V = 2254.5(16)\text{Å}^3$
$Z = 8$
$D_x = 1.377\text{ Mg/m}^3$
Radiation: Cu $K\alpha$ ($\lambda = 1.54180\text{ Å}$)
$F(0\ 0\ 0) = 976$
Crystal size = $0.15 \times 0.10 \times 0.10\text{ mm}^3$
No. of reflections collected = 2138
No. of independent reflections = 2138
No. of reflections used [$I > 2\sigma(I)$] = 1384
θ range for data collection: 3.58 to 70.03°
Data/Restraints/Parameters = 2138/0/139
Goodness-of-fit = 1.062
R indices [$I > 2\sigma(I)$]: $R1 = 0.0601$, $wR2 = 0.1479$
R indices (all data): $R1 = 0.0993$, $wR2 = 0.1730$
$(\Delta/\sigma)_{\text{max}} = 0.001$
$(\Delta\rho)_{\text{max}} = 0.336\text{ Å}^{-3}$
$(\Delta\rho)_{\text{min}} = -0.232\text{ Å}^{-3}$
Structure determination: SHELXS-97 ⁴
Refinement: SHELXL-97 ⁴
CCDC deposition number: 891819

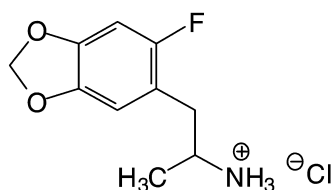


Fig. 1 Chemical structure of 6-fluoro-3,4-methylenedioxyamphetamine hydrochloride.

[†] To whom correspondence should be addressed.
E-mail: jean.guillon@u-bordeaux.fr

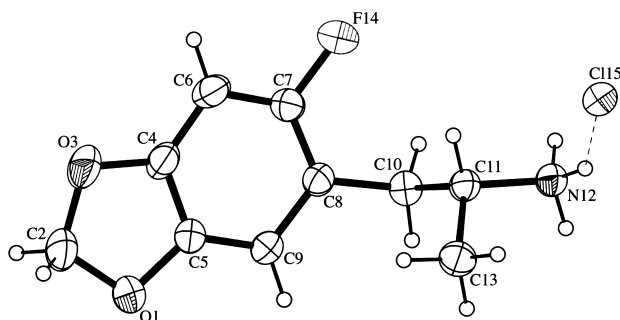


Fig. 2 ORTEP view of the crystal structure of 6-fluoro-3,4-methylenedioxyamphetamine with our numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

hydrochloride (Fig. 1). Colourless crystals having dimensions of $0.15 \times 0.1 \times 0.1 \text{ mm}^3$ suitable for X-ray diffraction analysis were obtained by slow crystallization from an ethanol-water solution at $+20^\circ\text{C}$. The molecular structure of 6-fluoro-3,4-methylenedioxyamphetamine hydrochloride is depicted in Fig. 2. Crystal and experimental data are given in Table 1.

Crystallographic data of this compound were collected at 293 K with an Enraf-Nonius CAD-4 diffractometer with monochromatic $\text{Cu-K}\alpha$ radiation ($\lambda = 1.54178 \text{ \AA}$). The collected data were reduced using the NONIUS CAD4 software and all reflections were used for unit-cell refinement. The crystal structure was solved by direct methods and successive Fourier difference syntheses with the SHELXS-97 program.⁴ The refinement of the crystal structure was performed on F^2 by weighted anisotropic full-matrix least squares methods using the SHELXL97 program.⁴ The absorption correction was performed using psi-scan method.⁵ All non-H atoms were refined anisotropically. The H atom positions were calculated from the atomic coordinates of the non-H atoms to which H atoms are linked. The positions were confirmed by difference Fourier synthesis. H atoms were included for structure factor calculations, but not refined.

Crystallographic data have been deposited in the Cambridge Crystallographic Data Centre (CCDC 891819). Copies of these data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/data_request/cif

Bond distances and valence angles for the aromatic ring and the ethylamine side chain are close to expected values and reasonable agreement with those reported for amphetamine derivatives.⁶⁻⁹ The torsion angle $\text{C}(7)\text{-C}(8)\text{-C}(10)\text{-C}(11)$ was found at 74.9° , and the antiperiplanar torsion angle $\text{C}(8)\text{-C}(10)\text{-C}(11)\text{-N}(12)$ was -170.7° showing that the ethylamine chain was nearly fully extended. Moreover, this extended side chain was nearly planar with respect to the atoms $\text{C}(8)\text{-C}(10)\text{-C}(11)\text{-N}(12)$, with a RMS deviation of 0.057 \AA and maximal deviation from the plane of 0.058 \AA for $\text{C}(10)$. The interplanar

Table 2 Hydrogen-bonding geometry (\AA , $^\circ$)

<i>D</i> -H... <i>A</i>	H-A	<i>D</i> -A	<i>D</i> -H... <i>A</i>
N(12)-H(12a)...Cl(15, I)	2.410	3.188(3)	146.02
N(12)-H(12c)...Cl(15, II)	2.290	3.167(3)	168.60
N(12)-H(12b)...Cl(15, III)	2.286	3.170(4)	172.33

Symmetry codes: I (x, y, z), II ($1.5-x, 1-y, 1/2+z$), III ($x, 1.5-y, 1/2+z$).

dihedral angle between the benzene ring and the side chain was found at 77.76° . The $\text{C}(7)\text{-F}(14)$ bond was noticed at $1.376(4) \text{ \AA}$, as typically observed for $\text{C}_{\text{ar}}\text{-F}$ bonds.¹⁰ The C-C distances within the six-membered rings are in the range of 1.366 to 1.390 \AA , consistent with the aromatic character of the ring system. Average C-C and C-N single bond distances were observed at 1.514 and 1.502 \AA , respectively. In accordance with the previously described amphetamine ammonium salts,⁸⁻⁹ the C-N^+ bond was found longer than the standard C-N bond.¹⁰ Pertinent distances for the hydrogen bonds were given in Table 2. The N atom is fully protonated, and the nitrogen atoms were involved in intermolecular hydrogen bonds with chloride ions: *i.e.* the hydrogen bonds link $\text{N}(12)\text{-H}(12)\text{-Cl}(15)$ with $\text{N}\cdots\text{Cl}$ distances of 3.167 , 3.170 and 3.188 \AA within the *bc* plane. The cohesion of the network is ensured in the *a* direction by weaker hydrogen like interaction between hydrogen of the aromatic 6-membered ring and the oxygen atoms of the methylenedioxy moiety of another molecule. Such interactions link together the 2D networks developed within the *bc* plane by the strong $\text{NH}_3^+\cdots\text{Cl}^-$ H-bonds.

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