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N-(2-Fluoroethyl)-3β-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2α-carboxamide: a new cocaine derivative with equatorially attached ligands[1]

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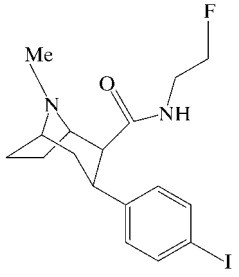
In the title compound, $C_{17}H_{22}FIN_2O$, both the amide and the iodophenyl substituents of the tropane ring lie in equatorial positions. The crystal packing is determined by N—H···O and C—H···F intermolecular hydrogen-bonding interactions.

Comment

The dopamine transporter (DAT) is a widely accepted marker for the integrity of the presynaptic dopaminergic system (Innis *et al.*, 1993). A markedly reduced DAT density has been demonstrated in brains from patients with degenerative brain disorders such as Parkinson's and Alzheimer's disease. When combined with positron emission tomography (PET) or single photon emission tomography (SPECT), radioligands binding specifically to the DAT are potentially useful as non-invasive



(I)

in vivo imaging tools for studying the various illnesses and evaluating the degrees of success of their treatments (Schenk, 2002; Torres *et al.*, 2003). Therefore, the development and evaluation of suitable radioligands are required. Cocaine analogues are known to result in the best effects (Singh, 2000). The structure of the title amide derivative, (I) (Krebs *et al.*, 2003), of the established radioligand β-CIT (Carroll *et al.*, 1991) is described here.

The molecular structure of (I) shows the usual piperidine chair conformation (Fig. 1). The absolute configuration was determined from anomalous dispersion effects by refining the Flack (1983) parameter. Both the amide and the iodophenyl group are attached equatorially to the central tropane ring, adopting 2α- and 3β-positions, respectively. The relevant torsion angles are C1—C2—C15—N2 = 86.3 (4)° and C2—C3—C9—C10 = 60.2 (5)°. The related molecular structures of cocaine (Hrynchuk *et al.*, 1982) and cocaine salts (Shen *et al.*, 1975; Zhu *et al.*, 1999) show corresponding torsion angles for their methoxycarbonyl groups of −61, −46 and −17°, respectively. In (I), the phenyl ring and the best plane through the amide group (atoms C15, O1, N2 and C16) are perpendicular, with a dihedral angle of 89.2 (1)°. The N8—C1 and

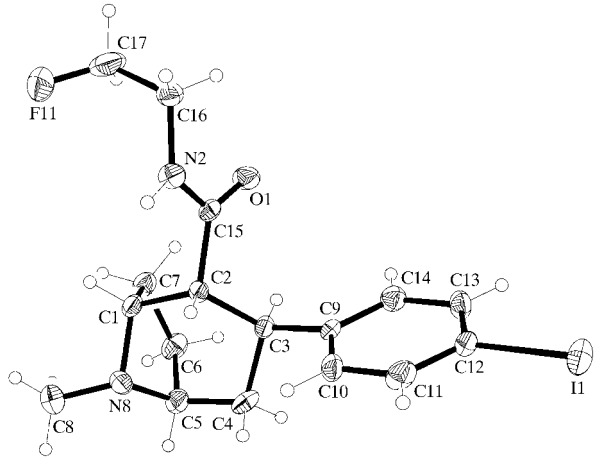


Figure 1
The molecular structure of (I). Only one position is shown for the disordered F atom. Displacement ellipsoids are drawn at the 50% probability level.

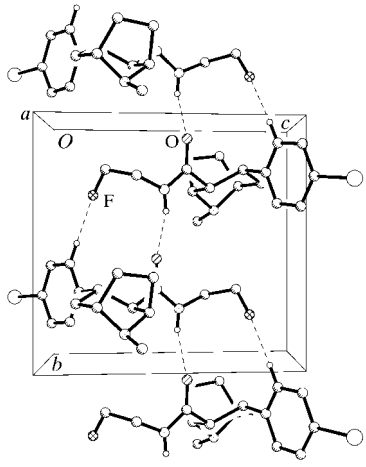


Figure 2
The crystal packing in (I), viewed along [100], with hydrogen bonds indicated by dashed lines. O atoms are dotted and F atoms cross-hatched. Only one position (F11) of the disordered F atom is shown and H atoms not involved in hydrogen bonding have been omitted.

[1] Dedicated to Professor Karsten Krohn on the occasion of his 60th birthday.

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N8—C5 bond lengths of 1.472 (5) and 1.486 (7) Å, respectively, compare well with the values of 1.460 (7) and 1.467 (6) Å in cocaine. The same is valid for C2—C15, with values of 1.518 (5) and 1.509 (6) Å in (I) and cocaine, respectively, but the C15═O1 bond of 1.229 (5) Å in (I) is longer than the corresponding distance of 1.188 (5) Å in cocaine.

The crystal packing of (I) shows two intermolecular hydrogen bonds (Table 2) between molecules related by a twofold screw axis, thus generating a chain in the *b* direction (Fig. 2).

Experimental

Triethylamine (28 mg, 0.28 mmol) was added at 273 K over 10 min to a stirred mixture of the carboxylic acid of *β*-CIT (98 mg, 0.264 mmol), fluoroethylamine (29 mg, 0.29 mmol) and diethylcyanophosphonate (47 mg, 0.29 mmol) in dimethylformamide (1 ml). The mixture was stirred at 273 K for 30 min and then at room temperature for 1 h. It was then diluted with AcOEt and washed with H_2O, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over K_2CO_3. Column chromatography of the resulting residue (EE:MeOH:Et_3N = 8.5:1:0.5; R_F = 0.62; EE is acetic acid) gave colourless crystals of the amide (99 mg, 90%, m.p. 418 K). Recrystallization from CH_2Cl_2–Et_2O (1:1) yielded crystals of (I) suitable for X-ray analysis. Spectroscopic analysis: ^{1}H NMR (250 MHz, $CDCl_3$, *δ*): 1.69–2.31 [*m*, 6H, $2CH_2$ (H6, H7), H4*α*, H5], 2.41 (*s*, 3H, CH_3), 3.17–3.42 (*m*, 4H, H2, H3, H1, H4*β*), 4.08–4.48 [*m*, 4H, $F(CH_2)_2$], 6.18 (*d*, 1H, NH), 7.04 (*d*, 2H, C_6H_4), 7.56 (*d*, 2H, C_6H_4); ^{13}C NMR (250 MHz, $CDCl_3$, *δ*): 22.98 (CH_2), 26.38 (CH_2), 36.72 (CH_3), 39.81 (CH_2), 40.75 (CH), 53.77 (CH), 62.37 (CH), 65.36 (CH), 81.37 (CH_2), 84.68 (CH_2), 92.23 (CI), 130.30, 137.98, 143.27 (C_6H_4), 172.30 (C═O).

Crystal data

$C_{17}H_{22}FIN_2O$
M_r = 416.27
Monoclinic, $P2_1$
a = 8.9837 (8) Å
b = 9.5600 (8) Å
c = 10.1222 (9) Å
β = 98.225 (2)°
V = 860.39 (13) Å^3
Z = 2
D_x = 1.607 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3506 reflections
θ = 2.3–28.3°
μ = 1.87 mm^{-1}
T = 120 (2) K
Block, colourless
0.40 × 0.20 × 0.12 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Bruker, 2002)
T_{min} = 0.574, T_{max} = 0.799
7235 measured reflections
4021 independent reflections
3602 reflections with $I > 2\sigma(I)$
R_{int} = 0.031
θ_{max} = 28.4°
$h = -11 \rightarrow 12$
$k = -12 \rightarrow 11$
$l = -11 \rightarrow 13$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.031
$wR(F^2)$ = 0.071
S = 1.00
4021 reflections
211 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0344P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 1.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.63 e Å^{-3}
Absolute structure: Flack (1983), 1741 Friedel pairs
Flack parameter = −0.02 (2)

Table 1
Selected geometric parameters (Å, °).

I1—C12	2.107 (3)	C2—C15	1.518 (5)
C15—O1	1.229 (5)	C2—C3	1.539 (5)
N2—C15	1.346 (5)	C3—C9	1.520 (5)
N2—C16	1.454 (5)	C16—C17	1.484 (6)
N8—C8	1.457 (5)	C17—F11	1.284 (6)
N8—C1	1.472 (5)	C17—F12	1.230 (9)
N8—C5	1.486 (7)		
C15—N2—C16	121.3 (3)	N2—C15—C2	114.3 (3)
C15—C2—C3	111.1 (3)	N2—C16—C17	112.3 (3)
C9—C3—C2	112.6 (3)	F11—C17—C16	116.9 (4)
O1—C15—N2	122.6 (3)	F12—C17—C16	121.2 (6)
O1—C15—C2	123.1 (3)		
C15—C2—C3—C9	71.2 (4)	C1—C2—C15—O1	−91.7 (4)
C2—C3—C9—C10	60.2 (5)	C1—C2—C15—N2	86.3 (4)

Table 2
Hydrogen-bonding geometry (Å, °).

F11 and F12 are the disorder components of the same F atom.

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2B···O1^{i}	0.86	2.28	3.061 (4)	151
C14—H14A···F11^{ii}	0.93	2.37	3.284 (7)	167
C10—H10A···F12^{i}	0.93	2.54	3.41 (1)	156

Symmetry codes: (i) $1-x, y+\frac{1}{2}, 1-z$; (ii) $1-x, y-\frac{1}{2}, 1-z$.

The largest residual electron-density peak lies 0.98 Å from atom I1. The F atom is disordered and was refined with a split model over two positions, with an occupancy of 0.638 (9) for F11 and 0.362 (9) for F12. H atoms were placed in calculated positions, riding on their attached C or N atoms, with U_{iso}(H) = 1.2U_{eq}(C,N) or 1.5U_{eq}(CH_3). Methyl groups were allowed to rotate but not to tip or distort.

Data collection: *SMART* (Bruker, 2002); cell refinement: *SAINT* (Bruker, 2002); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Bruker, 2002); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1554). Services for accessing these data are described at the back of the journal.

References

Bruker (2002). *SMART* (Version 5.62), *SAINT* (Version 6.02), *SHELXTL* (Version 6.10) and *SADABS* (Version 2.03). Bruker AXS Inc., Madison, Wisconsin, USA.

Carroll, F. I., Gao, Y., Rahman, M. A., Abraham, P., Parham, K., Lewin, A. H., Boja, J. W. & Kuhar, M. J. (1991). *J. Med. Chem.* **34**, 2719–2725.

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.

Hrynchuk, R. J., Barton, R. J. & Robertson, B. E. (1982). *Can. J. Chem.* **61**, 481–487.

Innis, R. B., Seibyl, P., Scanley, B. E., Laruell, M. & Abi-Dargham, A. (1993). *Proc. Natl Acad. Sci. USA*, **90**, 11965–11969.

Krebs, B., Bier, D., Shiver, W., Holschbach, M. & Coenen, H. H. (2003). *J. Labelled Compd Radiopharm.* **46**, S53.

Schenk, J. O. (2002). *Prog. Drug Res.* **59**, 113–131.

Shen, M., Ruble, J. R. & Hite, G. (1975). *Acta Cryst.* B**31**, 2706–2709.

Singh, S. (2000). *Chem. Rev.* **100**, 925–1024.

Torres, G. E., Carneiro, A., Seamans, K., Fiorentini, C., Sweeney, A., Yao, W. D. & Caron, M. G. (2003). *J. Biol. Chem.* **278**, 2731–2739.

Zhu, N., Harrison, A., Trudell, M. J. & Klein-Stevens, C. L. (1999). *Struct. Chem.* **10**, 91–103.