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Methyl 1-(4-fluorobenzyl)-1*H*-indazole-3-carboxylate

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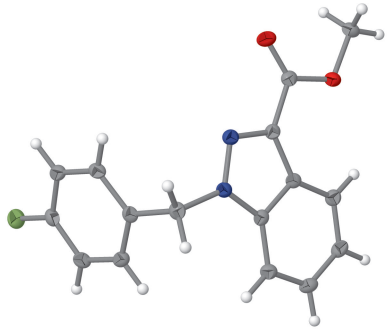
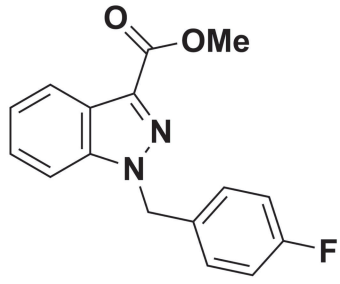
The title compound, $C_{16}H_{13}FN_2O_2$, was synthesized by nucleophilic substitution of the indazole N—H hydrogen atom of methyl 1*H*-indazole-3-carboxylate with 1-(bromomethyl)-4-fluorobenzene. In the crystal, some hydrogen-bond-like interactions are observed.

3D view



Chemical scheme



Structure description

Methyl 1-(4-fluorobenzyl)-1*H*-indazole-3-carboxylate is an intermediate compound of synthetic cannabinoids, a class of compounds with a high potential for abuse as psychoactive substances, acting as the agonist of the cannabinoid type 1 receptor (Longworth *et al.*, 2017; Doi *et al.*, 2018; Cannaert *et al.*, 2020). The molecule is composed of two planar segments connected at a bond angle of 110.90 (8)° at C6. The indazole ring is nearly coplanar with the ester moiety, suggesting that the ester moiety is conjugated with the aromatic ring. Furthermore, the C3—C14 bond distance is 1.4790 (14) Å, which provides further evidence for the existence of conjugation (Fig. 1). The crystal packing of the title compound is displayed in Fig. 2. At the centre of the crystal, two weak hydrogen-bond-like interactions (C13—H13···N2^{ii} and C6—H6*A*···O15^{ii}) are formed between two adjacent molecules related by inversion (Fig. 2) [symmetry operator: (ii) $-x, -y+1, -z+1$]. The hydrogen-donor molecule also acts as acceptor of the same interactions, creating inversion-related dimers. In the extended structure, there are four more non-classical hydrogen-bond-like interactions and a weak C—H···π interaction is also observed (Table 1).

Synthesis and crystallization

The synthesis of methyl 1-(4-fluorobenzyl)-1*H*-indazole-3-carboxylate was described previously (Doi *et al.*, 2018). In a microvial, the resulted compound was dissolved with ethyl acetate at a concentration of 3% (*w*/*v*). The microvial was left at room temperature

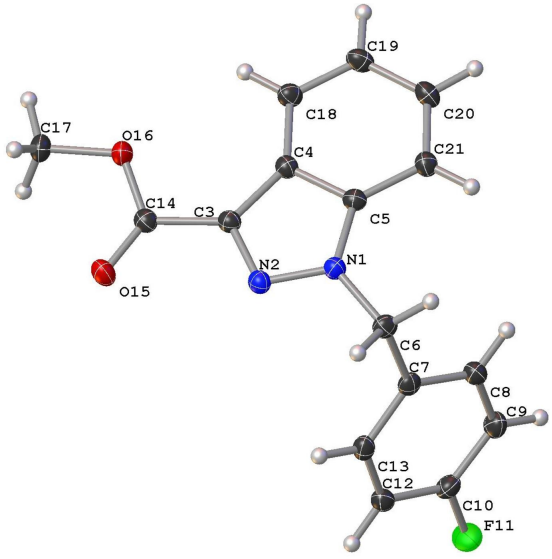


Figure 1
Molecular structure of the title compound, with displacement ellipsoids drawn at the 50% probability level.

for several months, resulting in the formation of several large rod shape crystals in the vial.

Refinement

Crystal, data collection and refinement details are presented in Table 2.

Acknowledgements

The authors would like to sincerely thank Dr Takashi Sato (Rigaku Corporation) for his helpful and fundamental instructions and advice on the measurement, analysis, and interpretation of the results.

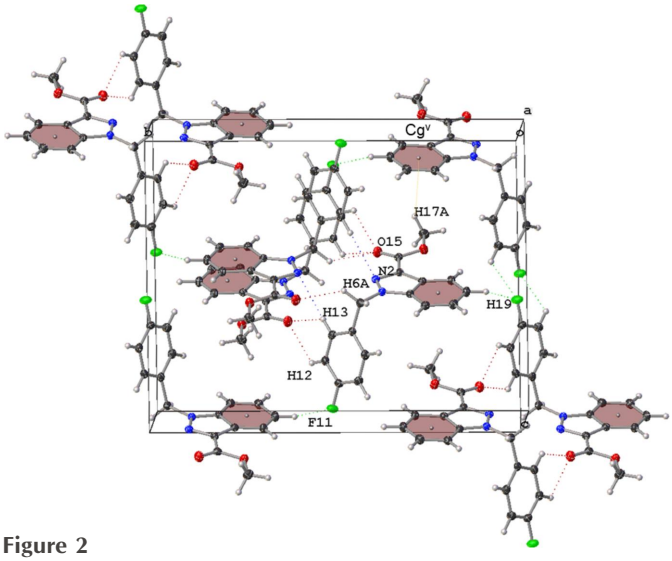


Figure 2
The crystal packing of the title compound.

Table 1
Hydrogen-bond geometry (Å, °).

Cg is the centroid of the C4/C5/C18–C21 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H6*A*···O15^{i}	0.99	2.67	3.3417 (13)	125
C12—H12···O15^{ii}	0.95	2.61	3.2190 (12)	123
C13—H13···O15^{ii}	0.95	2.62	3.2339 (12)	123
C13—H13···N2^{i}	0.95	2.62	3.4578 (13)	148
C19—H19···F11^{iii}	0.95	2.73	3.3840 (13)	127
C9—H9···F11^{iv}	0.95	2.59	3.2577 (12)	127
C17—H17*A*···*Cg*^{v}	0.98	2.95	3.8114 (12)	148

Symmetry codes: (i) $-x+1, -y+1, -z+1$; (ii) $-x, -y+1, -z+1$; (iii) $-x+\frac{1}{2}, y-\frac{1}{2}, -z+\frac{3}{2}$; (iv) $-x+1, -y+1, -z+2$; (v) $x-\frac{3}{2}, -y-\frac{1}{2}, z-\frac{3}{2}$.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{16}H_{13}FN_2O_2$
M_r	284.28
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	100
a, *b*, *c* (Å)	5.04322 (3), 18.11509 (13), 14.46487 (10)
β (°)	90.4600 (6)
V (Å^3)	1321.45 (2)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.88
Crystal size (mm)	0.32 × 0.13 × 0.12
Data collection	
Diffractometer	XtaLAB Synergy, Single source at home/near, HyPix-Arc 100
Absorption correction	Gaussian (*CrysAlis PRO*; Rigaku OD, 2023)
T_{min}, T_{max}	0.626, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	47493, 2732, 2666
R_{int}	0.035
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.627
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.031, 0.078, 1.03
No. of reflections	2732
No. of parameters	192
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.30, −0.18

Computer programs: *CrysAlis PRO* (Rigaku OD, 2023), *SHELXT2018/2* (Sheldrick, 2015*a*), *SHELXL2018/3* (Sheldrick, 2015*b*), and *OLEX2* (Dolomanov *et al.*, 2009).

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References

Cannaert, A., Sparkes, E., Pike, E., Luo, J. L., Fang, A., Kevin, R. C., Ellison, R., Gerona, R., Banister, S. D. & Stove, C. P. (2020). *ACS Chem. Neurosci.* **11**, 4434–4446.
Doi, T., Tagami, T., Takeda, A., Asada, A. & Sawabe, Y. (2018). *Forensic Toxicol.* **36**, 51-60.
Dolomanov, O. V., Bourhis, L. J., Gildea, R. J., Howard, J. A. K. & Puschmann, H. (2009). *J. Appl. Cryst.* **42**, 339–341.

Longworth, M., Banister, S. D., Boyd, R., Kevin, R. C., Connor, M., McGregor, I. S. & Kassiou, M. (2017). *ACS Chem. Neurosci.* **8**, 2159–2167.
Rigaku OD (2023). *CrysAlis PRO*. Rigaku Inc., Tokyo, Japan.
Sheldrick, G. M. (2015*a*). *Acta Cryst.* A**71**, 3–8.
Sheldrick, G. M. (2015*b*). *Acta Cryst.* C**71**, 3–8.

full crystallographic data

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Crystal data

$C_{16}H_{13}FN_2O_2$
M_r = 284.28
Monoclinic, $P2_1/n$
a = 5.04322 (3) Å
b = 18.11509 (13) Å
c = 14.46487 (10) Å
β = 90.4600 (6)°
V = 1321.45 (2) Å^3
Z = 4
$F(000)$ = 592
D_x = 1.429 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54184 Å
Cell parameters from 29913 reflections
θ = 3.9–79.9°
μ = 0.88 mm^{-1}
T = 100 K
Block, clear light colourless
0.32 × 0.13 × 0.12 mm

Data collection

XtaLAB Synergy, Single source at home/near, HyPix-Arc 100 diffractometer
Radiation source: fine-focus sealed X-ray tube, Enhance (Cu) X-ray Source
Graphite monochromator
Detector resolution: 10.0000 pixels mm^{-1}
ω scans
Absorption correction: gaussian (CrysAlisPro; Rigaku OD, 2023)
T_{min} = 0.626, T_{max} = 1.000
47493 measured reflections
2732 independent reflections
2666 reflections with $I > 2\sigma(I)$
R_{int} = 0.035
θ_{max} = 75.3°, θ_{min} = 3.9°
h = −6→6
k = −21→22
l = −18→18

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.031
$wR(F^2)$ = 0.078
S = 1.03
2732 reflections
192 parameters
0 restraints
Primary atom site location: dual
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0369P)^2 + 0.532P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}
Extinction correction: SHELXL-2018/3 (Sheldrick 2018), $Fc^*=kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Extinction coefficient: 0.0027 (3)

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Refinement. All the H atoms were included using a riding model starting from calculated positions (aromatic C—H = 0.95 Å, methylene C—H = 0.99 Å, and alkyl C—H = 1.00 Å). The U_{iso}(H) values were fixed at 1.2 times the equivalent U_{eq} value of the parent C atoms (1.5 times for the methyl group).

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
F11	0.20188 (14)	0.51087 (4)	0.93308 (4)	0.03075 (18)
O16	0.11216 (15)	0.25606 (4)	0.38007 (5)	0.02287 (18)
O15	0.03249 (15)	0.37833 (4)	0.38349 (5)	0.02512 (19)
N1	0.65913 (16)	0.38193 (5)	0.56604 (6)	0.01720 (19)
N2	0.45483 (16)	0.39395 (5)	0.50783 (6)	0.01800 (19)
C5	0.71051 (19)	0.30814 (5)	0.57692 (7)	0.0168 (2)
C4	0.52753 (19)	0.27022 (5)	0.52017 (7)	0.0170 (2)
C3	0.37458 (19)	0.32774 (5)	0.47872 (7)	0.0172 (2)
C7	0.63589 (19)	0.46374 (5)	0.70088 (7)	0.0180 (2)
C6	0.7843 (2)	0.44440 (6)	0.61369 (7)	0.0194 (2)
H6A	0.786848	0.487719	0.571991	0.023*
H6B	0.970040	0.431674	0.629647	0.023*
C12	0.2762 (2)	0.52949 (6)	0.77426 (7)	0.0201 (2)
H12	0.131495	0.562982	0.771153	0.024*
C13	0.4240 (2)	0.51310 (5)	0.69631 (7)	0.0191 (2)
H13	0.380134	0.535846	0.639021	0.023*
C14	0.1556 (2)	0.32536 (6)	0.41015 (7)	0.0185 (2)
C18	0.5330 (2)	0.19243 (6)	0.51774 (7)	0.0200 (2)
H18	0.411852	0.165588	0.480012	0.024*
C21	0.9019 (2)	0.27162 (6)	0.63117 (7)	0.0198 (2)
H21	1.025145	0.297972	0.668632	0.024*
C10	0.3461 (2)	0.49563 (6)	0.85637 (7)	0.0212 (2)
C20	0.9017 (2)	0.19570 (6)	0.62728 (8)	0.0226 (2)
H20	1.028026	0.168985	0.663067	0.027*
C8	0.7006 (2)	0.43131 (6)	0.78554 (7)	0.0219 (2)
H8	0.845925	0.398046	0.789401	0.026*
C19	0.7187 (2)	0.15640 (6)	0.57148 (8)	0.0225 (2)
H19	0.723970	0.103984	0.571045	0.027*
C9	0.5551 (2)	0.44705 (6)	0.86433 (7)	0.0242 (2)
H9	0.598636	0.424934	0.922035	0.029*
C17	−0.0982 (2)	0.24943 (6)	0.31188 (8)	0.0250 (2)
H17A	−0.046710	0.275111	0.255159	0.038*
H17B	−0.260822	0.271534	0.336094	0.038*
H17C	−0.129430	0.197143	0.298222	0.038*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
F11	0.0376 (4)	0.0365 (4)	0.0183 (3)	0.0086 (3)	0.0041 (3)	−0.0015 (3)
O16	0.0232 (4)	0.0211 (4)	0.0241 (4)	0.0026 (3)	−0.0085 (3)	−0.0028 (3)
O15	0.0253 (4)	0.0218 (4)	0.0281 (4)	0.0045 (3)	−0.0065 (3)	0.0027 (3)

N1	0.0187 (4)	0.0158 (4)	0.0171 (4)	0.0004 (3)	−0.0013 (3)	0.0006 (3)
N2	0.0189 (4)	0.0187 (4)	0.0163 (4)	0.0013 (3)	−0.0001 (3)	0.0014 (3)
C5	0.0170 (4)	0.0165 (5)	0.0171 (5)	0.0003 (4)	0.0025 (4)	0.0006 (4)
C4	0.0160 (4)	0.0183 (5)	0.0168 (5)	0.0005 (4)	0.0012 (4)	0.0009 (4)
C3	0.0179 (5)	0.0169 (5)	0.0168 (5)	0.0008 (4)	0.0009 (4)	0.0009 (4)
C7	0.0190 (5)	0.0151 (5)	0.0199 (5)	−0.0037 (4)	−0.0022 (4)	−0.0014 (4)
C6	0.0202 (5)	0.0165 (5)	0.0216 (5)	−0.0027 (4)	−0.0004 (4)	−0.0010 (4)
C12	0.0209 (5)	0.0168 (5)	0.0224 (5)	0.0009 (4)	−0.0028 (4)	−0.0008 (4)
C13	0.0218 (5)	0.0166 (5)	0.0189 (5)	−0.0022 (4)	−0.0039 (4)	0.0018 (4)
C14	0.0184 (5)	0.0197 (5)	0.0172 (5)	0.0009 (4)	0.0011 (4)	0.0013 (4)
C18	0.0195 (5)	0.0174 (5)	0.0230 (5)	−0.0009 (4)	−0.0001 (4)	−0.0004 (4)
C21	0.0180 (5)	0.0216 (5)	0.0199 (5)	0.0007 (4)	−0.0015 (4)	0.0005 (4)
C10	0.0255 (5)	0.0208 (5)	0.0173 (5)	−0.0008 (4)	0.0003 (4)	−0.0034 (4)
C20	0.0202 (5)	0.0221 (5)	0.0255 (5)	0.0043 (4)	−0.0018 (4)	0.0042 (4)
C8	0.0236 (5)	0.0187 (5)	0.0235 (5)	0.0032 (4)	−0.0043 (4)	−0.0007 (4)
C19	0.0227 (5)	0.0162 (5)	0.0287 (5)	0.0019 (4)	0.0007 (4)	0.0019 (4)
C9	0.0315 (6)	0.0231 (5)	0.0179 (5)	0.0023 (4)	−0.0053 (4)	0.0019 (4)
C17	0.0231 (5)	0.0284 (6)	0.0234 (5)	0.0017 (4)	−0.0082 (4)	−0.0035 (4)

Geometric parameters (Å, º)

F11—C10	1.3601 (12)	C12—H12	0.9500
O16—C14	1.3459 (13)	C12—C13	1.3887 (15)
O16—C17	1.4477 (12)	C12—C10	1.3801 (15)
O15—C14	1.2047 (13)	C13—H13	0.9500
N1—N2	1.3432 (12)	C18—H18	0.9500
N1—C5	1.3704 (13)	C18—C19	1.3767 (15)
N1—C6	1.4653 (13)	C21—H21	0.9500
N2—C3	1.3329 (13)	C21—C20	1.3765 (15)
C5—C4	1.4090 (14)	C10—C9	1.3770 (15)
C5—C21	1.4046 (14)	C20—H20	0.9500
C4—C3	1.4259 (13)	C20—C19	1.4135 (15)
C4—C18	1.4098 (14)	C8—H8	0.9500
C3—C14	1.4790 (14)	C8—C9	1.3900 (15)
C7—C6	1.5129 (14)	C19—H19	0.9500
C7—C13	1.3943 (14)	C9—H9	0.9500
C7—C8	1.3946 (14)	C17—H17A	0.9800
C6—H6A	0.9900	C17—H17B	0.9800
C6—H6B	0.9900	C17—H17C	0.9800
C14—O16—C17	114.47 (8)	O15—C14—O16	123.86 (9)
N2—N1—C5	111.93 (8)	O15—C14—C3	124.86 (9)
N2—N1—C6	119.68 (8)	C4—C18—H18	120.9
C5—N1—C6	128.23 (8)	C19—C18—C4	118.24 (9)
C3—N2—N1	106.36 (8)	C19—C18—H18	120.9
N1—C5—C4	106.64 (8)	C5—C21—H21	121.7
N1—C5—C21	130.70 (9)	C20—C21—C5	116.59 (10)
C21—C5—C4	122.66 (9)	C20—C21—H21	121.7

C5—C4—C3	103.78 (8)	F11—C10—C12	118.50 (9)
C5—C4—C18	119.27 (9)	F11—C10—C9	118.41 (9)
C18—C4—C3	136.95 (9)	C9—C10—C12	123.09 (10)
N2—C3—C4	111.28 (9)	C21—C20—H20	119.1
N2—C3—C14	117.47 (9)	C21—C20—C19	121.78 (10)
C4—C3—C14	131.23 (9)	C19—C20—H20	119.1
C13—C7—C6	119.54 (9)	C7—C8—H8	119.6
C13—C7—C8	119.06 (9)	C9—C8—C7	120.80 (10)
C8—C7—C6	121.36 (9)	C9—C8—H8	119.6
N1—C6—C7	110.90 (8)	C18—C19—C20	121.45 (10)
N1—C6—H6A	109.5	C18—C19—H19	119.3
N1—C6—H6B	109.5	C20—C19—H19	119.3
C7—C6—H6A	109.5	C10—C9—C8	118.12 (10)
C7—C6—H6B	109.5	C10—C9—H9	120.9
H6A—C6—H6B	108.0	C8—C9—H9	120.9
C13—C12—H12	121.0	O16—C17—H17A	109.5
C10—C12—H12	121.0	O16—C17—H17B	109.5
C10—C12—C13	117.95 (9)	O16—C17—H17C	109.5
C7—C13—H13	119.5	H17A—C17—H17B	109.5
C12—C13—C7	120.97 (9)	H17A—C17—H17C	109.5
C12—C13—H13	119.5	H17B—C17—H17C	109.5
O16—C14—C3	111.28 (8)		

Hydrogen-bond geometry (Å, º)

Cg is the centroid of the C4/C5/C18–C21 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H6*A*···O15^{i}	0.99	2.67	3.3417 (13)	125
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C9—H9···F11^{iv}	0.95	2.59	3.2577 (12)	127
C17—H17*A*···*Cg*^{v}	0.98	2.95	3.8114 (12)	148

Symmetry codes: (i) −*x*+1, −*y*+1, −*z*+1; (ii) −*x*, −*y*+1, −*z*+1; (iii) −*x*+1/2, *y*−1/2, −*z*+3/2; (iv) −*x*+1, −*y*+1, −*z*+2; (v) *x*−3/2, −*y*−1/2, *z*−3/2.