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Ethyl 3-[3-amino-4-methylamino-*N*-(pyridin-2-yl)-benzamido]propanoate

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Keywords: crystal structure; dabigatran etexilate; hydrogen bonding; oral anticoagulant.

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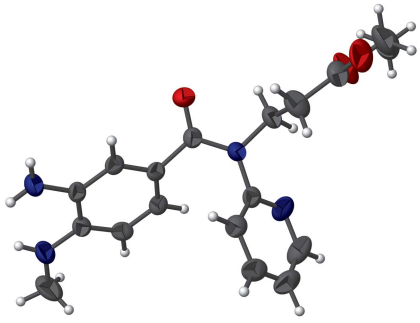
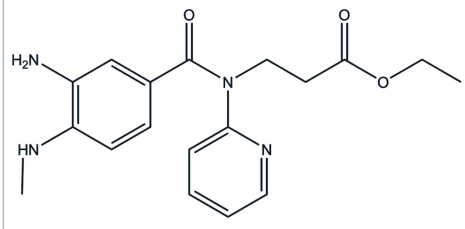
Structural data: full structural data are available from iucrdata.iucr.org

In the title compound, $C_{18}H_{22}N_4O_3$, the benzene ring is twisted by 63.29 (15)° with respect to the pyridine ring. In the crystal, molecules are linked by N—H···O hydrogen bonds and C—H···π interactions, forming slabs parallel to the *ac* plane.

3D view



Chemical scheme



Structure description

The title compound (Fig. 1), an important intermediate of dabigatran etexilate, has attracted much attention due to its oral anticoagulant properties (Chen *et al.*, 2013).

The benzene ring forms a dihedral angles of 63.29 (15)° with the pyridine ring. The mean plane through the C15/C14/N3 fragment makes dihedral angles of 83.5 (3) and 56.0 (3)° with the pyridine and benzene rings, respectively. The N2—C5 bond [1.386 (3) Å] is slightly shorter than the N1—C4 bond [1.412 (4) Å], which implies that the –NH–CH_3 group is a stronger electron-donating group compared to the NH_2 group, thus resulting in a slightly shorter bond length.

In the crystal, molecules are linked by N—H···O hydrogen bonds (Table 1). The N1—H1*B*···O2^{ii} hydrogen bond leads to the formation of chains along [101], while the N1—H1*A*···O1^{i} hydrogen bond and C—H···π interaction link the molecules to form slabs parallel to the *ac* plane (Table 1 and Fig. 2).

Synthesis and crystallization

The title compound was synthesized by the procedures reported by Chen *et al.* (2013). Single crystals were obtained from methanol solution.

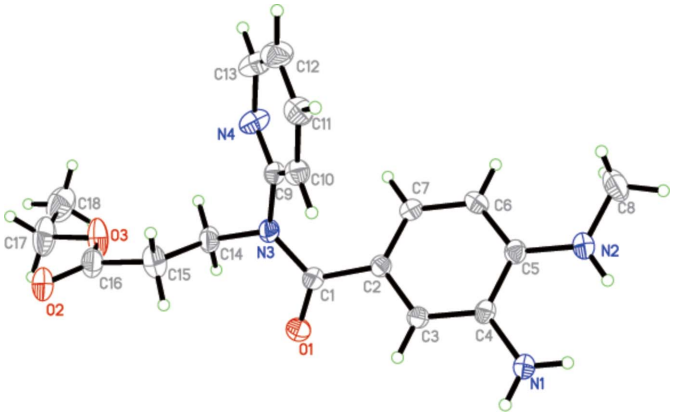


Figure 1
The molecular structure of the title compound, showing the atom labelling. Displacement ellipsoids are drawn at the 50% probability level.

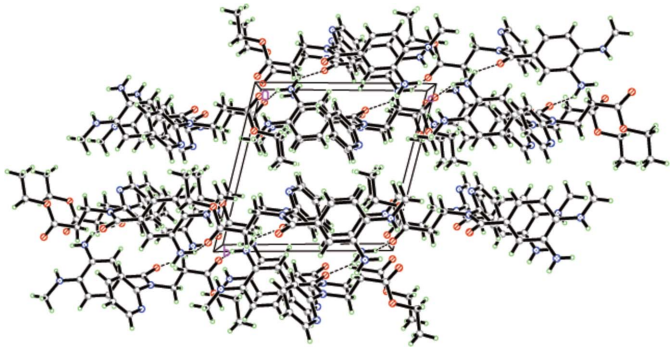


Figure 2
A view along the *c* axis of the crystal packing, with hydrogen bonds shown as dashed lines (see Table 1).

Refinement

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

Acknowledgements

We are very grateful for the financial support from the National Natural Science Foundation of China (grant No. 21371031).

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

*Cg*2 is the centroid of the C2–C7 benzene ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*A*···O1^{i}	0.86	2.31	3.035 (3)	142
N1—H1*B*···O2^{ii}	0.86	2.41	3.018 (4)	128
C12—H12*A*···*Cg*2^{iii}	0.93	2.79	3.566 (4)	142

Symmetry codes: (i) $-x, -y, -z+1$; (ii) $x-1, y, z-1$; (iii) $x+1, y, z$.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{18}H_{22}N_4O_3$
M_r	342.39
Crystal system, space group	Triclinic, $P\overline{1}$
Temperature (K)	293
a, *b*, *c* (Å)	8.3380 (17), 10.435 (2), 10.885 (2)
α, β, γ (°)	102.95 (3), 97.94 (3), 97.51 (3)
V (Å^3)	901.2 (3)
Z	2
Radiation type	Mo *K*α
μ (mm^{-1})	0.09
Crystal size (mm)	0.20 × 0.10 × 0.10
Data collection	
Diffractometer	Enraf–Nonius CAD-4
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	3550, 3305, 1996
R_{int}	0.025
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.603
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.063, 0.192, 1.01
No. of reflections	3305
No. of parameters	226
No. of restraints	1
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.35, −0.25

Computer programs: *CrystalClear* (Rigaku, 2005), *SHELXS97* and *SHELXL97* (Sheldrick, 2008) and *ORTEP-3 for Windows* (Farrugia, 2012).

References

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full crystallographic data

IUCrData (2017). **2**, x161941 [https://doi.org/10.1107/S2414314616019416]

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Crystal data

$C_{18}H_{22}N_4O_3$
$M_r = 342.39$
Triclinic, $P\overline{1}$
$a = 8.3380$ (17) Å
$b = 10.435$ (2) Å
$c = 10.885$ (2) Å
$\alpha = 102.95$ (3)°
$\beta = 97.94$ (3)°
$\gamma = 97.51$ (3)°
$V = 901.2$ (3) Å^3
$Z = 2$
$F(000) = 364$
$D_x = 1.262$ Mg m^{-3}
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 445 reflections
$\theta = 2.4$–22.8°
$\mu = 0.09$ mm^{-1}
$T = 293$ K
Block, brown
0.20 × 0.10 × 0.10 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Radiation source: fine-focus sealed tube
$\omega/2\theta$ scans
3550 measured reflections
3305 independent reflections
1996 reflections with $I > 2\sigma(I)$
$R_{int} = 0.025$
$\theta_{max} = 25.4°$, $\theta_{min} = 2.0°$
$h = 0 \rightarrow 10$
$k = -12 \rightarrow 12$
$l = -13 \rightarrow 12$
3 standard reflections every 200 reflections
intensity decay: 1%

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.063$
$wR(F^2) = 0.192$
$S = 1.01$
3305 reflections
226 parameters
1 restraint
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.35$ e Å^{-3}
$\Delta\rho_{min} = -0.25$ e Å^{-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.

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

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.2166 (3)	0.1355 (2)	0.65272 (19)	0.0547 (6)
N1	−0.0262 (3)	−0.0047 (2)	0.1767 (2)	0.0445 (6)
H1A	−0.0624	−0.0731	0.2028	0.053*
H1B	−0.0635	0.0012	0.1008	0.053*
C1	0.3201 (3)	0.1803 (3)	0.5971 (3)	0.0385 (7)
N2	0.0901 (3)	0.2199 (3)	0.0943 (2)	0.0515 (7)
H2A	0.0084	0.1615	0.0497	0.062*
C2	0.2749 (3)	0.1894 (3)	0.4627 (3)	0.0353 (7)
O2	0.6824 (3)	0.0688 (3)	1.0268 (3)	0.0793 (8)
N3	0.4777 (3)	0.2287 (2)	0.6610 (2)	0.0399 (6)
C3	0.1552 (3)	0.0899 (3)	0.3803 (3)	0.0356 (7)
H3A	0.1154	0.0160	0.4084	0.043*
O3	0.6338 (4)	0.2761 (3)	1.0443 (2)	0.0796 (9)
C4	0.0943 (3)	0.0979 (3)	0.2585 (3)	0.0354 (7)
N4	0.7219 (3)	0.3610 (3)	0.6602 (3)	0.0565 (8)
C5	0.1541 (3)	0.2097 (3)	0.2156 (3)	0.0379 (7)
C6	0.2708 (4)	0.3093 (3)	0.2993 (3)	0.0413 (7)
H6A	0.3096	0.3845	0.2728	0.050*
C7	0.3308 (3)	0.2995 (3)	0.4209 (3)	0.0397 (7)
H7A	0.4095	0.3676	0.4750	0.048*
C8	0.1558 (5)	0.3243 (4)	0.0416 (3)	0.0773 (12)
H8A	0.0954	0.3143	−0.0427	0.116*
H8B	0.1472	0.4089	0.0952	0.116*
H8C	0.2692	0.3202	0.0367	0.116*
C9	0.6160 (3)	0.2519 (3)	0.6011 (3)	0.0379 (7)
C10	0.6416 (4)	0.1628 (3)	0.4945 (3)	0.0439 (7)
H10A	0.5646	0.0865	0.4561	0.053*
C11	0.7814 (4)	0.1880 (3)	0.4461 (3)	0.0518 (8)
H11A	0.8008	0.1291	0.3740	0.062*
C12	0.8924 (4)	0.3007 (4)	0.5044 (4)	0.0620 (10)
H12A	0.9888	0.3202	0.4733	0.074*
C13	0.8578 (4)	0.3840 (4)	0.6098 (4)	0.0690 (11)
H13A	0.9330	0.4612	0.6491	0.083*
C14	0.5114 (4)	0.2464 (3)	0.8003 (3)	0.0475 (8)
H14A	0.4104	0.2557	0.8337	0.057*
H14B	0.5888	0.3282	0.8385	0.057*
C15	0.5797 (5)	0.1331 (4)	0.8390 (3)	0.0655 (10)
H15A	0.4958	0.0541	0.8098	0.079*
H15B	0.6709	0.1160	0.7947	0.079*
C16	0.6378 (4)	0.1525 (4)	0.9788 (3)	0.0599 (9)
C17	0.6878 (6)	0.3086 (5)	1.1817 (3)	0.0847 (14)
H17A	0.7971	0.2879	1.2014	0.102*
H17B	0.6137	0.2571	1.2208	0.102*
C18	0.6888 (6)	0.4523 (5)	1.2312 (4)	0.0952 (15)
H18A	0.7242	0.4766	1.3223	0.143*

H18B	0.7628	0.5024	1.1921	0.143*
H18C	0.5801	0.4716	1.2115	0.143*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0435 (13)	0.0743 (16)	0.0496 (13)	−0.0010 (11)	0.0100 (11)	0.0272 (12)
N1	0.0462 (15)	0.0471 (15)	0.0367 (14)	−0.0005 (12)	−0.0029 (11)	0.0137 (11)
C1	0.0357 (16)	0.0398 (16)	0.0391 (16)	0.0055 (13)	0.0030 (13)	0.0108 (13)
N2	0.0542 (17)	0.0577 (17)	0.0418 (15)	0.0017 (13)	−0.0019 (13)	0.0212 (13)
C2	0.0284 (14)	0.0419 (16)	0.0388 (16)	0.0093 (12)	0.0059 (12)	0.0143 (13)
O2	0.0681 (17)	0.094 (2)	0.0817 (19)	0.0158 (15)	−0.0147 (14)	0.0491 (17)
N3	0.0369 (14)	0.0513 (15)	0.0321 (13)	0.0058 (11)	0.0041 (11)	0.0137 (11)
C3	0.0306 (15)	0.0371 (16)	0.0419 (16)	0.0068 (12)	0.0049 (12)	0.0153 (13)
O3	0.103 (2)	0.101 (2)	0.0398 (14)	0.0422 (17)	−0.0046 (14)	0.0235 (14)
C4	0.0308 (15)	0.0403 (16)	0.0347 (15)	0.0096 (12)	0.0026 (12)	0.0081 (13)
N4	0.0394 (15)	0.0587 (18)	0.0618 (18)	−0.0022 (13)	0.0067 (13)	0.0026 (14)
C5	0.0354 (16)	0.0432 (17)	0.0374 (16)	0.0112 (13)	0.0051 (13)	0.0123 (14)
C6	0.0456 (17)	0.0386 (16)	0.0446 (17)	0.0073 (14)	0.0130 (14)	0.0174 (14)
C7	0.0344 (16)	0.0411 (17)	0.0409 (17)	0.0009 (13)	0.0033 (13)	0.0094 (13)
C8	0.105 (3)	0.077 (3)	0.052 (2)	−0.001 (2)	0.005 (2)	0.035 (2)
C9	0.0347 (15)	0.0392 (16)	0.0409 (16)	0.0077 (13)	0.0013 (13)	0.0143 (13)
C10	0.0427 (18)	0.0427 (18)	0.0472 (18)	0.0100 (14)	0.0077 (14)	0.0113 (15)
C11	0.050 (2)	0.055 (2)	0.058 (2)	0.0177 (17)	0.0181 (16)	0.0182 (17)
C12	0.0394 (19)	0.069 (2)	0.086 (3)	0.0152 (18)	0.0211 (19)	0.027 (2)
C13	0.043 (2)	0.059 (2)	0.094 (3)	−0.0072 (17)	0.005 (2)	0.009 (2)
C14	0.0495 (19)	0.058 (2)	0.0350 (17)	0.0111 (15)	0.0008 (14)	0.0157 (15)
C15	0.081 (3)	0.069 (2)	0.051 (2)	0.021 (2)	0.0042 (19)	0.0235 (18)
C16	0.052 (2)	0.079 (3)	0.055 (2)	0.0171 (19)	0.0002 (17)	0.030 (2)
C17	0.091 (3)	0.126 (4)	0.039 (2)	0.043 (3)	−0.001 (2)	0.018 (2)
C18	0.086 (3)	0.126 (4)	0.061 (3)	0.016 (3)	−0.003 (2)	0.008 (3)

Geometric parameters (Å, º)

O1—C1	1.223 (3)	C7—H7A	0.9300
N1—C4	1.412 (4)	C8—H8A	0.9600
N1—H1A	0.8600	C8—H8B	0.9600
N1—H1B	0.8600	C8—H8C	0.9600
C1—N3	1.371 (4)	C9—C10	1.375 (4)
C1—C2	1.487 (4)	C10—C11	1.363 (4)
N2—C5	1.386 (3)	C10—H10A	0.9300
N2—C8	1.424 (4)	C11—C12	1.364 (5)
N2—H2A	0.8600	C11—H11A	0.9300
C2—C7	1.377 (4)	C12—C13	1.365 (5)
C2—C3	1.394 (4)	C12—H12A	0.9300
O2—C16	1.187 (4)	C13—H13A	0.9300
N3—C9	1.421 (4)	C14—C15	1.494 (4)
N3—C14	1.469 (3)	C14—H14A	0.9700

C3—C4	1.378 (4)	C14—H14B	0.9700
C3—H3A	0.9300	C15—C16	1.492 (5)
O3—C16	1.333 (4)	C15—H15A	0.9700
O3—C17	1.450 (4)	C15—H15B	0.9700
C4—C5	1.409 (4)	C17—C18	1.474 (6)
N4—C9	1.320 (4)	C17—H17A	0.9700
N4—C13	1.342 (4)	C17—H17B	0.9700
C5—C6	1.387 (4)	C18—H18A	0.9600
C6—C7	1.380 (4)	C18—H18B	0.9600
C6—H6A	0.9300	C18—H18C	0.9600

C4—N1—H1A	120.0	C10—C9—N3	122.2 (3)
C4—N1—H1B	120.0	C11—C10—C9	119.1 (3)
H1A—N1—H1B	120.0	C11—C10—H10A	120.5
O1—C1—N3	119.9 (3)	C9—C10—H10A	120.5
O1—C1—C2	120.6 (2)	C10—C11—C12	119.3 (3)
N3—C1—C2	119.5 (2)	C10—C11—H11A	120.4
C5—N2—C8	121.9 (3)	C12—C11—H11A	120.4
C5—N2—H2A	119.0	C11—C12—C13	118.0 (3)
C8—N2—H2A	119.0	C11—C12—H12A	121.0
C7—C2—C3	118.6 (3)	C13—C12—H12A	121.0
C7—C2—C1	122.7 (3)	N4—C13—C12	124.0 (3)
C3—C2—C1	118.3 (2)	N4—C13—H13A	118.0
C1—N3—C9	124.7 (2)	C12—C13—H13A	118.0
C1—N3—C14	118.6 (2)	N3—C14—C15	113.1 (3)
C9—N3—C14	116.4 (2)	N3—C14—H14A	109.0
C4—C3—C2	121.9 (3)	C15—C14—H14A	109.0
C4—C3—H3A	119.1	N3—C14—H14B	109.0
C2—C3—H3A	119.1	C15—C14—H14B	109.0
C16—O3—C17	117.4 (3)	H14A—C14—H14B	107.8
C3—C4—C5	119.3 (3)	C16—C15—C14	115.9 (3)
C3—C4—N1	120.7 (3)	C16—C15—H15A	108.3
C5—C4—N1	120.0 (2)	C14—C15—H15A	108.3
C9—N4—C13	116.7 (3)	C16—C15—H15B	108.3
N2—C5—C6	122.1 (3)	C14—C15—H15B	108.3
N2—C5—C4	119.5 (3)	H15A—C15—H15B	107.4
C6—C5—C4	118.3 (2)	O2—C16—O3	123.7 (3)
C7—C6—C5	121.6 (3)	O2—C16—C15	124.5 (4)
C7—C6—H6A	119.2	O3—C16—C15	111.7 (3)
C5—C6—H6A	119.2	O3—C17—C18	107.8 (3)
C2—C7—C6	120.3 (3)	O3—C17—H17A	110.2
C2—C7—H7A	119.8	C18—C17—H17A	110.2
C6—C7—H7A	119.8	O3—C17—H17B	110.2
N2—C8—H8A	109.5	C18—C17—H17B	110.2
N2—C8—H8B	109.5	H17A—C17—H17B	108.5
H8A—C8—H8B	109.5	C17—C18—H18A	109.5
N2—C8—H8C	109.5	C17—C18—H18B	109.5
H8A—C8—H8C	109.5	H18A—C18—H18B	109.5

H8B—C8—H8C	109.5	C17—C18—H18C	109.5
N4—C9—C10	123.0 (3)	H18A—C18—H18C	109.5
N4—C9—N3	114.7 (3)	H18B—C18—H18C	109.5
O1—C1—C2—C7	136.9 (3)	C5—C6—C7—C2	−0.3 (4)
N3—C1—C2—C7	−40.0 (4)	C13—N4—C9—C10	1.3 (5)
O1—C1—C2—C3	−34.9 (4)	C13—N4—C9—N3	177.4 (3)
N3—C1—C2—C3	148.3 (3)	C1—N3—C9—N4	140.7 (3)
O1—C1—N3—C9	163.5 (3)	C14—N3—C9—N4	−45.4 (3)
C2—C1—N3—C9	−19.6 (4)	C1—N3—C9—C10	−43.2 (4)
O1—C1—N3—C14	−10.3 (4)	C14—N3—C9—C10	130.7 (3)
C2—C1—N3—C14	166.6 (2)	N4—C9—C10—C11	−0.8 (4)
C7—C2—C3—C4	1.1 (4)	N3—C9—C10—C11	−176.5 (3)
C1—C2—C3—C4	173.2 (2)	C9—C10—C11—C12	0.1 (5)
C2—C3—C4—C5	−0.1 (4)	C10—C11—C12—C13	0.0 (5)
C2—C3—C4—N1	179.6 (2)	C9—N4—C13—C12	−1.3 (5)
C8—N2—C5—C6	8.7 (5)	C11—C12—C13—N4	0.7 (6)
C8—N2—C5—C4	−174.3 (3)	C1—N3—C14—C15	98.0 (3)
C3—C4—C5—N2	−178.3 (2)	C9—N3—C14—C15	−76.3 (3)
N1—C4—C5—N2	2.0 (4)	N3—C14—C15—C16	172.1 (3)
C3—C4—C5—C6	−1.2 (4)	C17—O3—C16—O2	0.1 (6)
N1—C4—C5—C6	179.1 (2)	C17—O3—C16—C15	−179.8 (3)
N2—C5—C6—C7	178.4 (3)	C14—C15—C16—O2	173.4 (4)
C4—C5—C6—C7	1.4 (4)	C14—C15—C16—O3	−6.6 (5)
C3—C2—C7—C6	−0.9 (4)	C16—O3—C17—C18	174.3 (3)
C1—C2—C7—C6	−172.7 (2)		

Hydrogen-bond geometry (Å, º)

Cg2 is the centroid of the C2–C7 benzene ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*A*···O1^{i}	0.86	2.31	3.035 (3)	142
N1—H1*B*···O2^{ii}	0.86	2.41	3.018 (4)	128
C12—H12*A*···*Cg2*^{iii}	0.93	2.79	3.566 (4)	142

Symmetry codes: (i) −*x*, −*y*, −*z*+1; (ii) *x*−1, *y*, *z*−1; (iii) *x*+1, *y*, *z*.