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2-[(2,5-Dimethylphenyl)amino]quinoline-3-carboxylic acid

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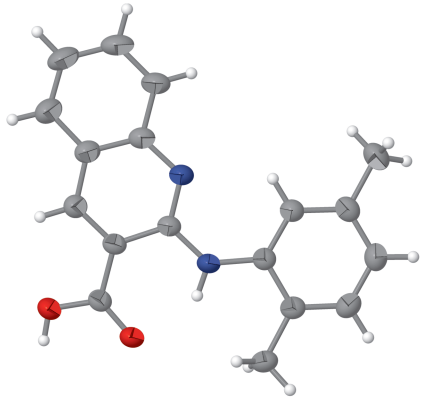
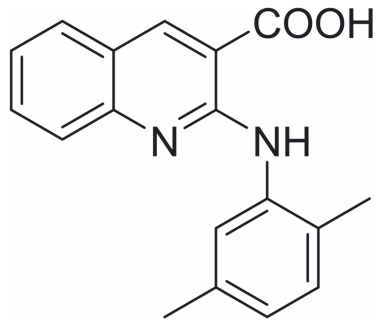
The title compound, $C_{18}H_{16}N_2O_2$, was synthesized *via* a two-step route with the Buchwald–Hartwig cross-coupling reaction. The quinoline ring system and phenyl ring of the molecule are nearly coplanar with a dihedral angle of 6.51 (5)°. In the crystal, adjacent molecules form carboxylic acid dimers *via* intermolecular hydrogen bonding.

3D view



Chemical scheme



Structure description

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of medicines that exert antipyretic, analgesic, and anti-inflammatory effects by inhibiting cyclooxygenase (COX). They are widely used in the treatment of rheumatoid arthritis, osteoarthritis, and acute pain (Vishwakarma & Negi, 2020). Classic NSAIDs such as ibuprofen, naproxen, and flurbiprofen all contain an arylpropionic acid or arylacetic acid structure, and their efficacy is closely related to the carboxyl group in the molecule (Astrvatham *et al.*, 2019). However, these drugs usually suffer from poor water solubility, variable bioavailability, and gastrointestinal adverse effects. In recent years, studies have shown that the polymorphism of solid drugs directly affects their solubility, dissolution rate, stability, and even biological activity (Bindu *et al.*, 2020). For example, different polymorphs of ibuprofen exhibit significantly different dissolution behaviors, which in turn affect *in vivo* absorption (Zhou *et al.*, 2024). Therefore, systematic studies on the polymorphism of NSAIDs are of great significance for optimizing formulation processes, improving therapeutic efficacy, and circumventing patents (Ley *et al.*, 2025). Research on drug polymorphism holds promise for discovering new crystal forms of drugs, thereby enhancing their druggability and providing a solid scientific basis for generic drug development. Furthermore, clarifying the polymorphic behavior of intermediates or products can provide key guidance for subsequent formulation screening, helping to select the thermodynamically stable crystal form with the best bioavailability, thereby reducing the risk of efficacy fluctuations caused by crystal form transformation.

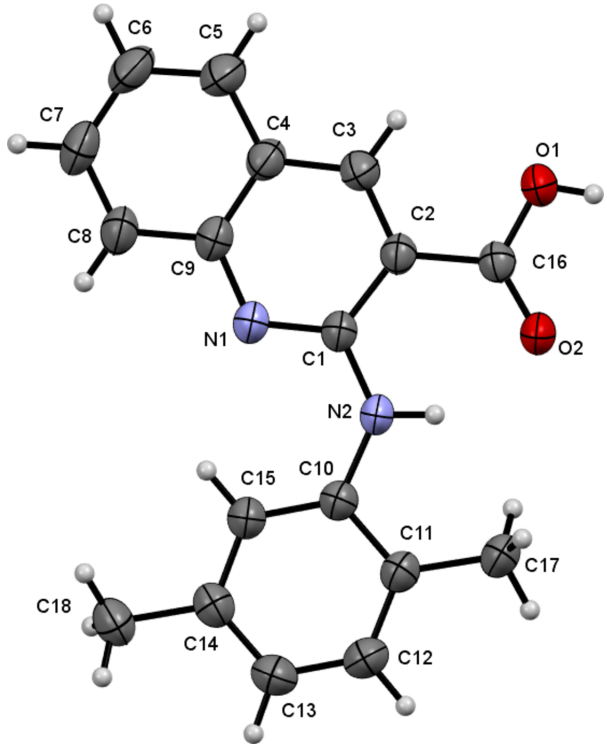


Figure 1
The molecular structure of the title compound with displacement ellipsoids drawn at the 50% probability level.

In the title compound (Fig. 1), the two aromatic moieties are nearly coplanar with a dihedral angle of 6.51 (5)°. In the crystal (Fig. 2), adjacent molecules form carboxylic acid dimers *via* intermolecular hydrogen bonding (Table 1).

Synthesis and crystallization

The target compound 2-[(2,5-dimethylphenyl)amino]-quinoline-3-carboxylic acid was synthesized (Fig. 3) *via* a two-step route with the Buchwald–Hartwig cross-coupling reaction. In the first step, methyl 2-chloroquinoline-3-carboxylate reacted with 2,5-dimethylaniline in toluene for 24 h using $Pd(OAc)_2$/BINAP as the catalytic system and Cs_2CO_3 as the base. The intermediate methyl 2-[(2,5-dimethylphenyl) amino]quinoline-3-carboxylate was obtained by extraction followed by column chromatography. In the second step, the above intermediate was hydrolyzed in an aqueous ethanol solution containing KOH for 6 h. After the reaction, the mixture was acidified, and the target product was isolated by extraction and purified by column chromatography. Pure 2-[(2,5-dimethylphenyl)amino]quinoline-3-carboxylic acid was dried for 8 h. Single crystals were obtained by slow evaporation of an ethanol solution at room temperature.

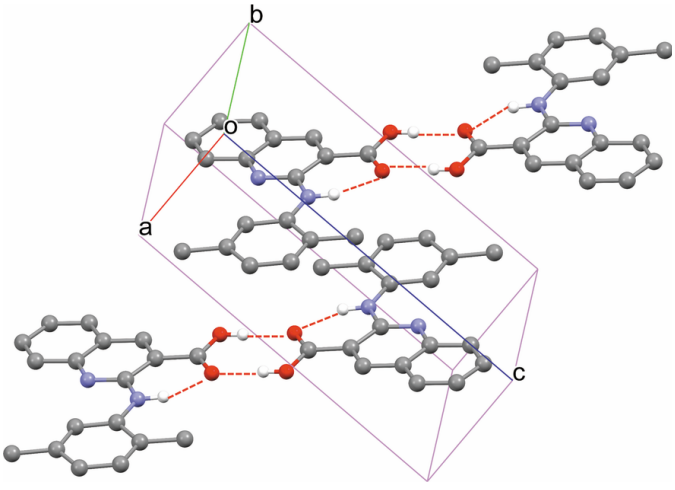


Figure 2
Packing of the molecules in the title compound (for clarity, H atoms not involved in hydrogen bonding are omitted).

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···O2	0.86	1.96	2.6925 (13)	142
C15—H15···N1	0.93	2.30	2.9134 (15)	123
O1—H1···O2^{i}	0.82	1.85	2.6702 (12)	178

Symmetry code: (i) $-x-1, -y+1, -z+1$.

Table 2
Experimental details.

Crystal data	
Chemical formula	$C_{18}H_{16}N_2O_2$
M_r	292.33
Crystal system, space group	Triclinic, $P\overline{1}$
Temperature (K)	299
a, b, c (Å)	4.80942 (7), 11.8944 (2), 12.9466 (2)
α, β, γ (°)	88.9803 (13), 85.8751 (12), 84.4910 (12)
V (Å^3)	735.24 (2)
Z	2
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.70
Crystal size (mm)	0.21 × 0.05 × 0.04
Data collection	
Diffractometer	XtaLAB Synergy R, DW system, HyPix
Absorption correction	Multi-scan (*CrysAlis PRO*; Rigaku OD, 2024)
T_{min}, T_{max}	0.805, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	7863, 2904, 2659
R_{int}	0.021
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.629
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.039, 0.118, 1.07
No. of reflections	2904
No. of parameters	203
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.22, −0.16

Computer programs: *CrysAlis PRO* (Rigaku OD, 2024), *SHELXT* (Sheldrick, 2015*a*), *SHELXL2018/3* (Sheldrick, 2015*b*), *OLEX2* (Dolomanov *et al.*, 2009) and *Mercury* (Macrae *et al.*, 2020).

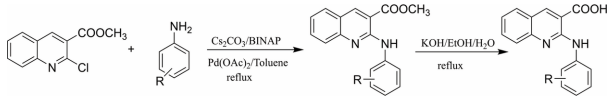


Figure 3
Synthesis of the title compound.

Refinement

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

Acknowledgements

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full crystallographic data

IUCrData (2026). **11**, x260546 [https://doi.org/10.1107/S2414314626005468]

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Crystal data

$C_{18}H_{16}N_2O_2$
M_r = 292.33
Triclinic, $P\overline{1}$
a = 4.80942 (7) Å
b = 11.8944 (2) Å
c = 12.9466 (2) Å
α = 88.9803 (13)°
β = 85.8751 (12)°
γ = 84.4910 (12)°
V = 735.24 (2) Å^3
Z = 2
$F(000)$ = 308
D_x = 1.320 Mg m^{-3}
Cu $K\alpha$ radiation, λ = 1.54184 Å
Cell parameters from 2760 reflections
θ = 3.4–74.8°
μ = 0.70 mm^{-1}
T = 299 K
Needle, clear dark yellow
0.21 × 0.05 × 0.04 mm

Data collection

XtaLAB Synergy R, DW system, HyPix diffractometer
Radiation source: Rotating-anode X-ray tube, Rigaku (Cu) X-ray Source
Mirror monochromator
Detector resolution: 10.0000 pixels mm^{-1}
ω scans
Absorption correction: multi-scan (CrysAlisPro; Rigaku OD, 2024)
T_{min} = 0.805, T_{max} = 1.000
7863 measured reflections
2904 independent reflections
2659 reflections with $I > 2\sigma(I)$
R_{int} = 0.021
θ_{max} = 76.0°, θ_{min} = 3.4°
h = −5→5
k = −14→14
l = −16→16

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.118
S = 1.07
2904 reflections
203 parameters
0 restraints
Primary atom site location: dual
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0644P)^2 + 0.1121P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: SHELXL2018/3 (Sheldrick 2015b), $Fc^* = kFc[1+0.001xFc^2\lambda^3/\sin(2\theta)]^{-1/4}$
Extinction coefficient: 0.0035 (12)

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. The position of the H atom in O and the position of the H atom in C are obtained from the differential Fourier diagram. The geometric positioning of the H atom is C—H = 0.93 for the aromatic group and the geometric positioning of the H atom is O—H = 0.82 for the methyl group.

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

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	−0.35770 (17)	0.61275 (7)	0.41684 (7)	0.0472 (2)
H1	−0.479882	0.599790	0.461771	0.071*
O2	−0.23465 (17)	0.42979 (7)	0.44090 (6)	0.0456 (2)
N1	0.4312 (2)	0.45264 (8)	0.20624 (7)	0.0415 (3)
N2	0.2069 (2)	0.33488 (8)	0.32298 (8)	0.0437 (3)
H2	0.070482	0.332918	0.369511	0.052*
C1	0.2313 (2)	0.43900 (9)	0.27944 (8)	0.0360 (3)
C2	0.0353 (2)	0.53280 (9)	0.31657 (8)	0.0362 (3)
C3	0.0700 (2)	0.63768 (10)	0.27559 (9)	0.0429 (3)
H3	−0.050859	0.699194	0.298862	0.052*
C4	0.2853 (2)	0.65434 (10)	0.19880 (9)	0.0428 (3)
C5	0.3314 (3)	0.76093 (12)	0.15430 (12)	0.0604 (4)
H5	0.221114	0.825172	0.177780	0.072*
C6	0.5367 (3)	0.77007 (13)	0.07711 (12)	0.0641 (4)
H6	0.565416	0.840374	0.047888	0.077*
C7	0.7041 (3)	0.67368 (13)	0.04186 (11)	0.0585 (4)
H7	0.841604	0.680419	−0.011595	0.070*
C8	0.6686 (3)	0.57010 (12)	0.08475 (10)	0.0510 (3)
H8	0.783743	0.507189	0.061076	0.061*
C9	0.4577 (2)	0.55755 (10)	0.16501 (9)	0.0396 (3)
C10	0.3639 (2)	0.23006 (9)	0.30574 (9)	0.0392 (3)
C11	0.2930 (2)	0.14151 (10)	0.37352 (9)	0.0426 (3)
C12	0.4354 (3)	0.03583 (11)	0.35730 (11)	0.0518 (3)
H12	0.390172	−0.023759	0.400831	0.062*
C13	0.6432 (3)	0.01616 (11)	0.27818 (11)	0.0532 (3)
H13	0.733864	−0.055992	0.269038	0.064*
C14	0.7167 (3)	0.10343 (11)	0.21262 (10)	0.0459 (3)
C15	0.5758 (2)	0.21017 (10)	0.22698 (9)	0.0436 (3)
H15	0.623613	0.269343	0.183389	0.052*
C16	−0.1953 (2)	0.51938 (9)	0.39614 (8)	0.0365 (3)
C17	0.0690 (3)	0.15969 (11)	0.46105 (10)	0.0519 (3)
H17A	0.101986	0.224403	0.500077	0.078*
H17B	0.073923	0.094170	0.505505	0.078*
H17C	−0.111249	0.172065	0.433234	0.078*
C18	0.9457 (3)	0.08438 (12)	0.12718 (11)	0.0586 (4)
H18A	0.919523	0.141436	0.074471	0.088*
H18B	0.938963	0.011242	0.097787	0.088*
H18C	1.124263	0.088331	0.154902	0.088*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0412 (5)	0.0431 (5)	0.0534 (5)	0.0014 (3)	0.0146 (4)	0.0031 (4)
O2	0.0426 (4)	0.0430 (5)	0.0478 (5)	−0.0009 (3)	0.0145 (3)	0.0055 (4)
N1	0.0430 (5)	0.0402 (5)	0.0397 (5)	−0.0053 (4)	0.0101 (4)	0.0021 (4)
N2	0.0438 (5)	0.0379 (5)	0.0460 (5)	−0.0023 (4)	0.0172 (4)	0.0046 (4)
C1	0.0355 (5)	0.0381 (6)	0.0339 (5)	−0.0050 (4)	0.0038 (4)	0.0008 (4)
C2	0.0330 (5)	0.0404 (6)	0.0346 (5)	−0.0040 (4)	0.0019 (4)	0.0015 (4)
C3	0.0399 (6)	0.0404 (6)	0.0466 (6)	0.0001 (4)	0.0037 (5)	0.0042 (5)
C4	0.0410 (6)	0.0431 (6)	0.0440 (6)	−0.0059 (5)	0.0008 (5)	0.0081 (5)
C5	0.0599 (8)	0.0465 (7)	0.0715 (9)	−0.0028 (6)	0.0101 (7)	0.0167 (7)
C6	0.0665 (9)	0.0556 (8)	0.0692 (9)	−0.0152 (7)	0.0087 (7)	0.0243 (7)
C7	0.0580 (8)	0.0679 (9)	0.0493 (7)	−0.0190 (7)	0.0125 (6)	0.0115 (6)
C8	0.0519 (7)	0.0553 (7)	0.0447 (7)	−0.0115 (6)	0.0126 (5)	0.0025 (6)
C9	0.0392 (6)	0.0455 (6)	0.0345 (5)	−0.0091 (5)	0.0012 (4)	0.0031 (5)
C10	0.0391 (6)	0.0359 (6)	0.0418 (6)	−0.0045 (4)	0.0041 (4)	0.0000 (4)
C11	0.0425 (6)	0.0401 (6)	0.0449 (6)	−0.0081 (5)	0.0051 (5)	0.0009 (5)
C12	0.0571 (7)	0.0380 (6)	0.0587 (8)	−0.0062 (5)	0.0067 (6)	0.0071 (5)
C13	0.0554 (7)	0.0382 (6)	0.0630 (8)	0.0034 (5)	0.0068 (6)	−0.0009 (6)
C14	0.0445 (6)	0.0455 (6)	0.0459 (6)	−0.0003 (5)	0.0048 (5)	−0.0044 (5)
C15	0.0450 (6)	0.0400 (6)	0.0439 (6)	−0.0029 (5)	0.0084 (5)	0.0018 (5)
C16	0.0327 (5)	0.0405 (6)	0.0357 (5)	−0.0021 (4)	0.0006 (4)	−0.0004 (4)
C17	0.0580 (8)	0.0431 (7)	0.0526 (7)	−0.0102 (5)	0.0160 (6)	0.0049 (5)
C18	0.0585 (8)	0.0562 (8)	0.0560 (8)	0.0074 (6)	0.0148 (6)	−0.0047 (6)

Geometric parameters (Å, º)

O1—C16	1.3150 (13)	C5—C6	1.364 (2)
O2—C16	1.2281 (13)	C6—C7	1.400 (2)
N1—C1	1.3199 (14)	C7—C8	1.3631 (19)
N1—C9	1.3621 (15)	C8—C9	1.4149 (15)
N2—C1	1.3633 (14)	C10—C11	1.4102 (16)
N2—C10	1.4070 (14)	C10—C15	1.3954 (15)
C1—C2	1.4549 (15)	C11—C12	1.3844 (18)
C2—C3	1.3672 (16)	C11—C17	1.5099 (16)
C2—C16	1.4765 (14)	C12—C13	1.3855 (19)
C3—C4	1.4087 (16)	C13—C14	1.3852 (18)
C4—C5	1.4135 (17)	C14—C15	1.3894 (17)
C4—C9	1.4095 (17)	C14—C18	1.5078 (17)
C1—N1—C9	119.30 (10)	N1—C9—C8	118.53 (11)
C1—N2—C10	131.81 (9)	C4—C9—C8	118.43 (11)
N1—C1—N2	119.81 (10)	N2—C10—C11	115.75 (10)
N1—C1—C2	121.83 (10)	C15—C10—N2	124.25 (10)
N2—C1—C2	118.36 (9)	C15—C10—C11	120.00 (11)
C1—C2—C16	122.98 (10)	C10—C11—C17	121.81 (11)
C3—C2—C1	117.75 (10)	C12—C11—C10	117.80 (11)

C3—C2—C16	119.27 (10)	C12—C11—C17	120.38 (11)
C2—C3—C4	121.26 (11)	C11—C12—C13	121.98 (11)
C3—C4—C5	123.55 (12)	C14—C13—C12	120.32 (11)
C3—C4—C9	116.75 (11)	C13—C14—C15	118.79 (11)
C9—C4—C5	119.68 (11)	C13—C14—C18	121.21 (11)
C6—C5—C4	120.36 (14)	C15—C14—C18	120.00 (11)
C5—C6—C7	120.03 (12)	C14—C15—C10	121.09 (11)
C8—C7—C6	120.95 (12)	O1—C16—C2	114.30 (9)
C7—C8—C9	120.51 (13)	O2—C16—O1	121.77 (9)
N1—C9—C4	123.04 (10)	O2—C16—C2	123.92 (10)

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
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