

2-[(3-Chloro-2-methylphenyl)amino]quinoline-3-carboxylic acid

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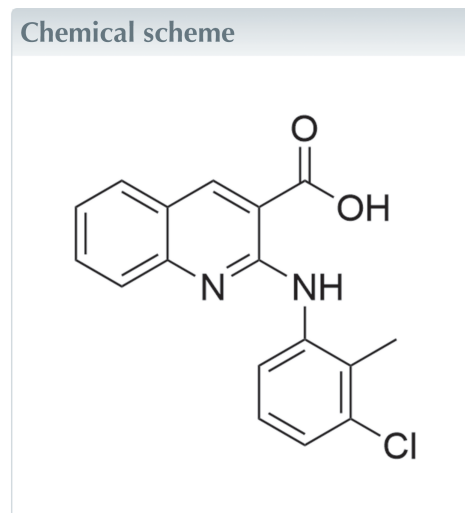
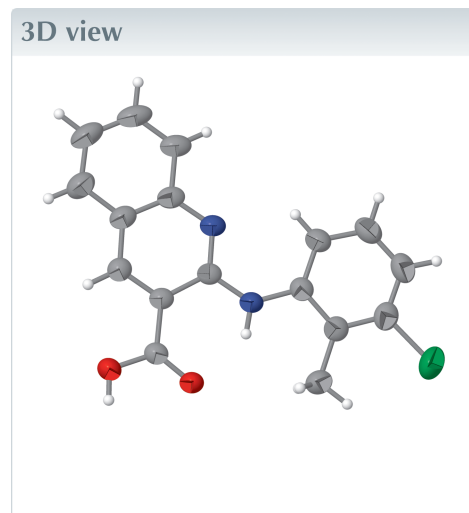
Received 27 May 2026

Accepted 29 May 2026

Edited by I. Brito, University of Antofagasta, Chile

Keywords: synthon; hydrogen bond; acid–acid dimer; single crystal.**CCDC reference:** 2558014**Structural data:** full structural data are available from iucrdata.iucr.org

The title compound, $C_{17}H_{13}ClN_2O_2$, is an analogue of fenamic acid-type non-steroidal anti-inflammatory drugs. It was prepared from 2-chloroquinoline-3-carboxylic acid and 3-chloro-2-methylaniline *via* palladium-catalysed Buchwald–Hartwig cross-coupling to afford the methyl ester intermediate, followed by alkaline hydrolysis. The molecule adopts a nearly planar conformation with a dihedral angle of $7.17(5)^\circ$ between the quinoline ring system and the substituted phenyl ring. Adjacent molecules form centrosymmetric carboxylic acid dimers *via* pairwise $O-H\cdots O$ hydrogen bonds.



Structure description

Non-steroidal anti-inflammatory drugs (NSAIDs) are mainstream clinical medicines with anti-inflammatory, analgesic and antipyretic activities. Fenamate-type diarylamine derivatives serve as important lead scaffolds for anti-inflammatory drug discovery (Luan *et al.* 2017). However, traditional fenamate molecules suffer from high conformational flexibility and disordered crystal packing, resulting in poor polymorphic stability and unstable pharmacological performance, which limits their clinical application (Uzoh *et al.* 2012). Replacing the benzene ring with a quinoline fused-ring moiety may enhance molecular conjugation and planarity, thus optimizing the molecular packing characteristics. To further explore the regulatory effects of substituents on molecular structures and solid-state properties, the title quinoline-based fenamate derivative was constructed by introducing a 3-chloro-2-methyl disubstituted group onto the N-aryl ring. The substituent effects on molecular conformations, hydrogen-bonding interactions and crystal packing were investigated, providing theoretical support for structural modification of this class of anti-inflammatory derivatives.

Herein, 2-[(3-chloro-2-methylphenyl)amino]quinoline-3-carboxylic acid (Fig. 1) was synthesized by a two-step route using 2-chloroquinoline-3-carboxylic acid and 3-chloro-2-methylaniline as starting materials, applying the palladium-catalyzed Buchwald–Hartwig

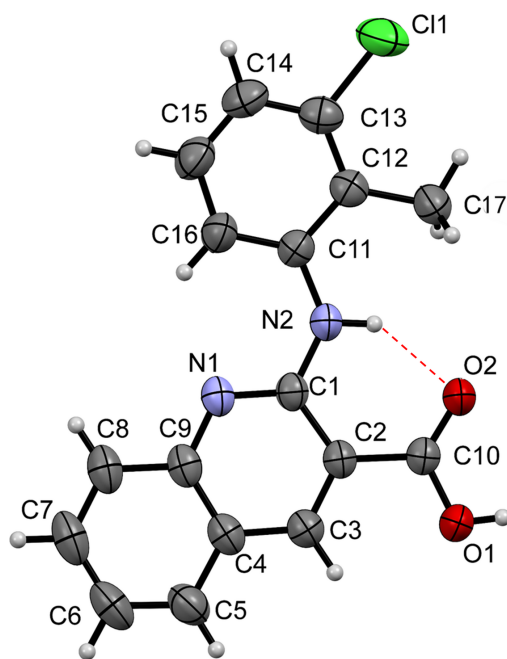


Figure 1
Molecular structure of the title compound, with displacement ellipsoids drawn at the 50% probability level.

cross-coupling, followed by alkaline hydrolysis, acidification and purification (Janke *et al.* 2019). A strong intramolecular N–H···O hydrogen bond is present in the molecule (Table 1), with a donor–acceptor distance of 2.6919 (13) Å and a bond angle of 140°. This interaction effectively restricts the free rotation of aromatic rings, yielding an approximately planar molecular conformation with a dihedral angle of 7.17 (5)° between the quinoline ring system and the substituted benzene ring.

In the crystal, adjacent molecules self-assemble into centrosymmetric carboxylic acid dimers through pairwise O–H···O hydrogen bonds. The donor–acceptor distance is

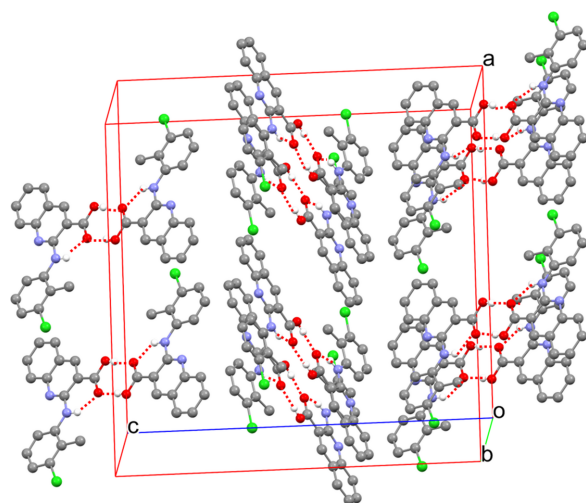


Figure 2
Packing of the molecules in the title compound (for clarity, H atoms not involved in hydrogen bonding are omitted).

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

<i>D</i> –H··· <i>A</i>	<i>D</i> –H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> –H··· <i>A</i>
O1–H1···O2 ⁱ	0.82	1.83	2.6532 (13)	177
N2–H2···O2	0.86	1.97	2.6919 (13)	140

Symmetry code: (i) $-x + \frac{1}{2}, -y + \frac{5}{2}, -z + 1$.

Table 2
Experimental details.

Crystal data	
Chemical formula	C ₁₇ H ₁₃ ClN ₂ O ₂
<i>M_r</i>	312.74
Crystal system, space group	Monoclinic, <i>C2/c</i>
Temperature (K)	298
<i>a</i> , <i>b</i> , <i>c</i> (Å)	27.6987 (4), 4.97483 (8), 24.2475 (4)
β (°)	97.6652 (8)
<i>V</i> (Å ³)	3311.36 (9)
<i>Z</i>	8
Radiation type	Cu <i>K</i> α
μ (mm ⁻¹)	2.11
Crystal size (mm)	0.22 × 0.17 × 0.13
Data collection	
Diffractometer	XtaLAB Synergy R, DW system, HyPix
Absorption correction	Multi-scan (<i>CrysAlis PRO</i> ; Rigaku OD, 2024)
<i>T_{min}</i> , <i>T_{max}</i>	0.747, 1.000
No. of measured, independent and observed [<i>I</i> > 2 σ (<i>I</i>)] reflections	15744, 3303, 2939
<i>R_{int}</i>	0.020
(<i>sin</i> θ / λ) _{max} (Å ⁻¹)	0.630
Refinement	
<i>R</i> [<i>F</i> ² > 2 σ (<i>F</i> ²)], <i>wR</i> [<i>F</i> ²], <i>S</i>	0.038, 0.119, 1.08
No. of reflections	3303
No. of parameters	201
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{\max}$, $\Delta\rho_{\min}$ (e Å ⁻³)	0.17, -0.35

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

2.6532 (13) Å and the bond angle is 177°. These dimers further adopt a layered packing pattern (Fig. 2). The centroid-to-centroid distance between adjacent aromatic rings is 4.9749 (7) Å, hence no effective π – π stacking interactions are observed.

Synthesis and crystallization

The title compound was synthesized in two steps using a Buchwald–Hartwig cross-coupling reaction followed by hydrolysis (Fig. 3). The compound was purified by column chromatography. Pale-yellow transparent block-shaped single crystals suitable for single-crystal X-ray diffraction measurements were grown by slow evaporation of an anhydrous ethyl acetate solution at ambient temperature.

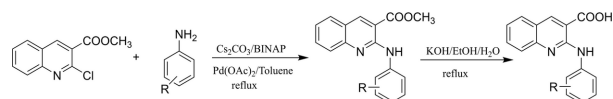


Figure 3
Synthesis of the title compound.

Refinement

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

Acknowledgements

YJZ and SL thank the Graduate Innovation Fund of WIT for financial support.

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full crystallographic data

IUCrData (2026). **11**, x260570 [<https://doi.org/10.1107/S2414314626005705>]

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Crystal data

$C_{17}H_{13}ClN_2O_2$	$F(000) = 1296$
$M_r = 312.74$	$D_x = 1.255 \text{ Mg m}^{-3}$
Monoclinic, $C2/c$	Cu $K\alpha$ radiation, $\lambda = 1.54184 \text{ \AA}$
$a = 27.6987 (4) \text{ \AA}$	Cell parameters from 11991 reflections
$b = 4.97483 (8) \text{ \AA}$	$\theta = 3.7\text{--}75.3^\circ$
$c = 24.2475 (4) \text{ \AA}$	$\mu = 2.11 \text{ mm}^{-1}$
$\beta = 97.6652 (14)^\circ$	$T = 298 \text{ K}$
$V = 3311.36 (9) \text{ \AA}^3$	Block, clear light yellow
$Z = 8$	$0.22 \times 0.17 \times 0.13 \text{ mm}$

Data collection

XtaLAB Synergy R, DW system, HyPix diffractometer	$T_{\min} = 0.747, T_{\max} = 1.000$
Radiation source: Rotating-anode X-ray tube, Rigaku (Cu) X-ray Source	15744 measured reflections
Mirror monochromator	3303 independent reflections
Detector resolution: $10.0000 \text{ pixels mm}^{-1}$	2939 reflections with $I > 2\sigma(I)$
ω scans	$R_{\text{int}} = 0.020$
Absorption correction: multi-scan (CrysAlisPro; Rigaku OD, 2024)	$\theta_{\max} = 76.4^\circ, \theta_{\min} = 4.6^\circ$
	$h = -34 \rightarrow 34$
	$k = -6 \rightarrow 6$
	$l = -29 \rightarrow 29$

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.038$	$w = 1/[\sigma^2(F_o^2) + (0.0732P)^2 + 0.6877P]$
$wR(F^2) = 0.119$	where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.08$	$(\Delta/\sigma)_{\max} = 0.001$
3303 reflections	$\Delta\rho_{\max} = 0.17 \text{ e \AA}^{-3}$
201 parameters	$\Delta\rho_{\min} = -0.35 \text{ e \AA}^{-3}$
0 restraints	
Primary atom site location: dual	

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.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (\AA^2)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
C11	0.05724 (2)	0.47003 (12)	0.64179 (2)	0.08519 (19)
O1	0.31240 (3)	1.13616 (19)	0.52322 (4)	0.0517 (2)
H1	0.295888	1.243453	0.503101	0.078*
O2	0.23926 (3)	1.00467 (18)	0.54053 (4)	0.0498 (2)
N1	0.30894 (4)	0.4131 (2)	0.65151 (4)	0.0446 (2)
N2	0.23512 (4)	0.5993 (2)	0.61329 (4)	0.0461 (3)
H2	0.221813	0.709601	0.588480	0.055*
C00H	0.13698 (5)	0.7379 (3)	0.58383 (6)	0.0592 (4)
H00A	0.152806	0.905160	0.594516	0.089*
H00B	0.102309	0.761483	0.580278	0.089*
H00C	0.146033	0.680377	0.548826	0.089*
C1	0.28489 (4)	0.5914 (2)	0.61842 (4)	0.0398 (3)
C2	0.30970 (4)	0.7816 (2)	0.58646 (4)	0.0400 (3)
C3	0.35948 (5)	0.7756 (3)	0.59269 (5)	0.0466 (3)
H3	0.376165	0.895091	0.572572	0.056*
C4	0.38588 (5)	0.5910 (3)	0.62913 (5)	0.0482 (3)
C5	0.43749 (5)	0.5861 (3)	0.63887 (7)	0.0636 (4)
H5	0.455480	0.704892	0.620105	0.076*
C6	0.46074 (6)	0.4060 (4)	0.67600 (7)	0.0699 (4)
H6	0.494581	0.404376	0.682981	0.084*
C7	0.43373 (6)	0.2248 (3)	0.70336 (6)	0.0658 (4)
H7	0.449972	0.101335	0.727994	0.079*
C8	0.38385 (6)	0.2244 (3)	0.69483 (5)	0.0562 (3)
H8	0.366614	0.101220	0.713457	0.067*
C9	0.35855 (5)	0.4118 (2)	0.65761 (5)	0.0445 (3)
C10	0.28369 (4)	0.9822 (2)	0.54854 (5)	0.0405 (3)
C11	0.20208 (5)	0.4583 (2)	0.64160 (5)	0.0436 (3)
C12	0.15239 (5)	0.5282 (3)	0.62760 (5)	0.0462 (3)
C13	0.11928 (5)	0.3953 (3)	0.65606 (6)	0.0541 (3)
C14	0.13227 (6)	0.2027 (3)	0.69635 (6)	0.0614 (4)
H14	0.108869	0.119319	0.714622	0.074*
C15	0.18075 (6)	0.1376 (3)	0.70868 (6)	0.0628 (4)
H15	0.190216	0.007937	0.735593	0.075*
C16	0.21570 (5)	0.2618 (3)	0.68171 (5)	0.0543 (3)
H16	0.248298	0.214214	0.690344	0.065*

Atomic displacement parameters (\AA^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C11	0.0481 (2)	0.1171 (4)	0.0934 (3)	0.0027 (2)	0.0205 (2)	0.0133 (3)
O1	0.0459 (5)	0.0534 (5)	0.0560 (5)	0.0025 (4)	0.0072 (4)	0.0183 (4)
O2	0.0420 (5)	0.0501 (5)	0.0562 (5)	0.0036 (4)	0.0028 (4)	0.0170 (4)
N1	0.0476 (6)	0.0440 (5)	0.0410 (5)	0.0062 (4)	0.0014 (4)	0.0040 (4)
N2	0.0419 (5)	0.0469 (6)	0.0485 (5)	0.0033 (4)	0.0023 (4)	0.0134 (4)
C00H	0.0480 (7)	0.0663 (9)	0.0632 (8)	0.0113 (6)	0.0071 (6)	0.0121 (7)

C1	0.0438 (6)	0.0381 (6)	0.0365 (5)	0.0030 (5)	0.0016 (4)	-0.0006 (4)
C2	0.0428 (6)	0.0384 (6)	0.0379 (5)	0.0037 (5)	0.0019 (4)	0.0000 (4)
C3	0.0438 (6)	0.0478 (7)	0.0480 (6)	0.0021 (5)	0.0050 (5)	0.0023 (5)
C4	0.0442 (7)	0.0505 (7)	0.0484 (6)	0.0084 (5)	0.0002 (5)	-0.0032 (5)
C5	0.0454 (7)	0.0704 (9)	0.0735 (9)	0.0082 (7)	0.0025 (6)	0.0019 (7)
C6	0.0471 (8)	0.0819 (11)	0.0765 (10)	0.0207 (7)	-0.0073 (7)	-0.0049 (8)
C7	0.0661 (9)	0.0672 (9)	0.0585 (8)	0.0262 (8)	-0.0125 (7)	-0.0020 (7)
C8	0.0630 (8)	0.0548 (7)	0.0478 (7)	0.0162 (6)	-0.0034 (6)	0.0019 (6)
C9	0.0497 (7)	0.0442 (6)	0.0376 (5)	0.0092 (5)	-0.0014 (5)	-0.0054 (5)
C10	0.0439 (6)	0.0383 (6)	0.0387 (5)	0.0015 (5)	0.0035 (5)	0.0012 (4)
C11	0.0465 (7)	0.0421 (6)	0.0419 (6)	-0.0016 (5)	0.0056 (5)	0.0008 (5)
C12	0.0475 (7)	0.0466 (6)	0.0448 (6)	0.0009 (5)	0.0074 (5)	-0.0032 (5)
C13	0.0490 (7)	0.0612 (8)	0.0534 (7)	-0.0026 (6)	0.0115 (5)	-0.0063 (6)
C14	0.0648 (9)	0.0666 (9)	0.0558 (8)	-0.0103 (7)	0.0189 (6)	0.0051 (7)
C15	0.0714 (9)	0.0633 (9)	0.0540 (7)	-0.0057 (7)	0.0090 (7)	0.0158 (7)
C16	0.0548 (7)	0.0549 (7)	0.0520 (7)	-0.0016 (6)	0.0029 (6)	0.0131 (6)

Geometric parameters (Å, °)

C11—C13	1.7470 (15)	C4—C5	1.4175 (19)
O1—C10	1.3138 (14)	C4—C9	1.4088 (19)
O2—C10	1.2253 (15)	C5—C6	1.369 (2)
N1—C1	1.3158 (15)	C6—C7	1.395 (3)
N1—C9	1.3623 (16)	C7—C8	1.369 (2)
N2—C1	1.3682 (15)	C8—C9	1.4163 (17)
N2—C11	1.4029 (16)	C11—C12	1.4162 (18)
C00H—C12	1.5087 (18)	C11—C16	1.3952 (17)
C1—C2	1.4525 (16)	C12—C13	1.3867 (19)
C2—C3	1.3674 (17)	C13—C14	1.381 (2)
C2—C10	1.4777 (15)	C14—C15	1.375 (2)
C3—C4	1.4094 (18)	C15—C16	1.384 (2)
C1—N1—C9	119.40 (11)	N1—C9—C8	118.60 (12)
C1—N2—C11	131.02 (10)	C4—C9—C8	118.46 (12)
N1—C1—N2	119.80 (11)	O1—C10—C2	114.17 (10)
N1—C1—C2	121.82 (11)	O2—C10—O1	122.03 (10)
N2—C1—C2	118.38 (10)	O2—C10—C2	123.79 (11)
C1—C2—C10	123.09 (10)	N2—C11—C12	115.89 (11)
C3—C2—C1	117.96 (10)	C16—C11—N2	123.92 (12)
C3—C2—C10	118.95 (11)	C16—C11—C12	120.19 (12)
C2—C3—C4	120.97 (12)	C11—C12—C00H	120.85 (12)
C3—C4—C5	122.89 (13)	C13—C12—C00H	122.41 (12)
C9—C4—C3	116.87 (12)	C13—C12—C11	116.74 (12)
C9—C4—C5	120.22 (12)	C12—C13—C11	119.89 (11)
C6—C5—C4	119.76 (16)	C14—C13—C11	116.37 (11)
C5—C6—C7	120.05 (15)	C14—C13—C12	123.74 (13)
C8—C7—C6	121.58 (13)	C15—C14—C13	118.15 (13)
C7—C8—C9	119.91 (15)	C14—C15—C16	121.10 (13)

N1—C9—C4	122.94 (11)	C15—C16—C11	120.08 (13)
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Hydrogen-bond geometry (Å, °)

<i>D</i> —H \cdots <i>A</i>	<i>D</i> —H	H \cdots <i>A</i>	<i>D</i> \cdots <i>A</i>	<i>D</i> —H \cdots <i>A</i>
O1—H1 \cdots O2 ⁱ	0.82	1.83	2.6532 (13)	177
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