Carlos Fernández-Galleguillos, Jorge Bórquez, Alejandro Cárdenas and Iván Brito*

Crystal structure of 3-(2-chloro-6-methoxyquinolin-3-yl)-5-phenylisoxazole ($C_{19}H_{13}ClN_2O_2$)

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Abstract

$C_{19}H_{13}ClN_2O_2$, monoclinic, $P2_1/c$ (no. 14), $a = 11.2461(18)$ Å, $b = 15.967(2)$ Å, $c = 9.2864(13)$ Å, $\beta = 106.770(9)^\circ$, $V = 1596.6(4)$ Å³, $Z = 4$, $R_{gt} = 0.0670$, $wR_{ref}(F^2) = 0.1606$, $T = 296(2)$ K.

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The crystal structure is shown in the figure. Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

Source of material

The title compound was prepared by the reaction of 2-chloro-6-methoxyquinolin-3-carbaldehyde (1.0 equiv.) with hydroxylamine solution (1.1 equiv.) in ethanol. Then NaOH was added (1.1 equiv.) to the reaction mixture, which was stirred at room temperature for 45 minutes. The oxime formation was corroborated by thin-layer chromatographic. Chloramine-T trihydrate (1.1 equiv.) was added, followed by $CuSO_4 \cdot 5H_2O$ (0.03 equiv.) and Cu (0.01 equiv.). When a change of color was observed, 10 mL of THF followed by phenylacetylene (1.1

Table 1: Data collection and handling.

Crystal:	Block, colorless
Size:	$0.40 \times 0.20 \times 0.18$ mm
Wavelength:	Cu $K\alpha$ radiation (1.54178 Å)
μ :	2.23 mm^{-1}
Diffractometer, scan mode:	Bruker D8-Venture θ/ψ , φ and ω -scans
θ_{max} , completeness:	58.9° , >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int} :	11188, 2277, 0.149
Criterion for I_{obs} , $N(hkl)_{gt}$:	$I_{obs} > 2 \sigma(I_{obs})$, 1195
$N(param)_{refined}$:	219
Programs:	Bruker programs [1], SHELX [2, 3], OLEX2 [4]

equiv.) were added to the solution and stirred for 8 hours. Once finished, the reaction was filtered to remove copper salts, washed with water, dried with anhydrous Na_2SO_4 . The organic solvent was removed in vacuo and the product was purified by column chromatography (silica gel, petroleum ether/EtOAc) to afford a yield of 77%. Recrystallization from *n*-hexane/EtOAc (8:2) a room temperature yielded colourless crystals.

Analysis: Colourless solid crystalline m.p. 166–168 °C; IR (KBr) ν_{max}/cm^{-1} 2914, 1595, 1569, 821; 1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H, quinoline), 7.98 (d, 1H, J 9.3 Hz, quinoline), 7.90 (dd, 2H, J 7.9, 1.3 Hz, phenyl), 7.52 (m, 3H, phenyl), 7.47 (dd, 1H, J 9.0, 2.7 Hz, quinoline), 7.16 (d, 1H, J 2.7 Hz, quinoline), 7.12 (s, 1H, isoxazol), 3.97 (s, 3H, quinoline- OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (C-isoxazol), 160.5 (C-isoxazol), 158.5 (C-quinoline), 145.3 (C-quinoline), 143.9 (C-quinoline), 138.3 (CH-quinoline), 130.4 (C-quinoline), 129.7 (C-quinoline), 129.0 (CH-phenyl), 127.8 (CH-quinoline), 127.1 (CH-phenyl), 125.8 (CH-phenyl), 124.4 (C-phenyl), 122.8 (CH-quinoline), 105.2 (CH-quinoline), 100.9 (CH-isoxazol), 55.6 (OCH_3 -quinoline); (QTOF-MS) m/z calculated for $C_{19}H_{13}ClN_2O_2$: 336.07; found: 336.81.

Experimental details

H atoms were located in the difference Fourier map, but refined with fixed displacement parameters, using a riding model with C–H distances of 0.93 Å (for aromatic rings) and 0.96 Å (for CH_3 group) with $U(H)$ values of $1.2U_{eq}(C)$ for CH

*Corresponding author: Iván Brito, Departamento de Química, Facultad de Ciencias Básicas, Universidad de Antofagasta, Casilla 170, Antofagasta, Chile, e-mail: ivan.brito@uantof.cl

Carlos Fernández-Galleguillos and Jorge Bórquez: Departamento de Química, Facultad de Ciencias Básicas, Universidad de Antofagasta, Casilla 170, Antofagasta, Chile

Alejandro Cárdenas: Departamento de Física, Facultad de Ciencias Básicas, Universidad de Antofagasta, Casilla 170, Antofagasta, Chile

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	x	y	z	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
Cl1	0.17596(15)	−0.06489(9)	0.02408(16)	0.0712(6)
O1	0.6291(4)	0.1976(3)	−0.3235(4)	0.0733(13)
O2	0.2765(4)	0.1596(2)	0.4132(4)	0.0707(12)
N1	0.3151(4)	−0.0117(3)	−0.1336(5)	0.0574(13)
N2	0.3396(5)	0.1461(3)	0.3031(5)	0.0688(15)
C1	0.2735(5)	0.0090(4)	−0.0221(6)	0.0551(16)
C2	0.3923(5)	0.0426(4)	−0.1745(5)	0.0517(15)
C3	0.4266(5)	0.1212(3)	−0.1037(6)	0.0490(14)
C4	0.5052(5)	0.1745(3)	−0.1522(6)	0.0568(16)
H4	0.5262	0.2264	−0.1066	0.068*
C5	0.5513(6)	0.1507(4)	−0.2665(6)	0.0570(16)
C6	0.6806(6)	0.2718(4)	−0.2434(7)	0.084(2)
H6A	0.7386	0.2964	−0.2892	0.126*
H6B	0.7225	0.2578	−0.1407	0.126*
H6C	0.6152	0.3110	−0.2464	0.126*
C7	0.5203(6)	0.0717(4)	−0.3348(6)	0.0630(17)
H7	0.5539	0.0555	−0.4111	0.076*
C8	0.4427(6)	0.0191(4)	−0.2916(6)	0.0655(17)
H8	0.4225	−0.0325	−0.3389	0.079*
C9	0.3769(5)	0.1399(3)	0.0150(6)	0.0551(15)
H9	0.3957	0.1912	0.0636	0.066*
C10	0.3022(5)	0.0855(4)	0.0616(6)	0.0530(15)
C11	0.2604(6)	0.1042(4)	0.1959(6)	0.0571(16)
C12	0.1636(5)	0.1236(4)	0.3664(6)	0.0549(16)
C13	0.1492(6)	0.0889(4)	0.2317(6)	0.0618(17)
H13	0.0798	0.0604	0.1735	0.074*
C14	0.0862(6)	0.1302(3)	0.4665(6)	0.0571(16)
C15	−0.0326(6)	0.0995(4)	0.4251(7)	0.0714(19)
H15	−0.0633	0.0745	0.3312	0.086*
C16	−0.1079(7)	0.1047(4)	0.5187(8)	0.086(2)
H16	−0.1889	0.0846	0.4873	0.103*
C17	−0.0620(8)	0.1396(5)	0.6576(9)	0.088(2)
H17	−0.1113	0.1415	0.7225	0.106*
C18	0.0555(8)	0.1719(4)	0.7027(8)	0.092(2)
H18	0.0852	0.1965	0.7971	0.111*
C19	0.1302(7)	0.1678(4)	0.6079(7)	0.079(2)
H19	0.2099	0.1901	0.6383	0.095*

in aromatic moiety and 1.5*U*_{eq}(C) for CH₃ group. The low resolution is due to very poor crystal quality.

Discussion

Quinolines and their derivatives are important heterocycles that possess a variety of commercial applications, such as pharmaceuticals, fragrances and dyes [5]. These nitrogen compounds are widely found in many natural products, such as the alkaloids isolated from the bark of the cinchona tree [6], to the antitumoral agent dynemicin A [7]. In recent years quinoline derivatives fused and/or substituted with heterocyclic rings were demonstrated to have significant biological activities. The insertion of the benzimidazole ring at

4-position showed antimicrobial and antifungal activity [8]. The substitution of a triazole ring at 3-position of the 2-chloro-quinoline derivatives enhances antimicrobial and antifungal properties [9]. In addition, antimicrobial and antituberculosis activity was found by insertion of the oxazole [10] and isoxazol ring in the quinoline core [11]. In the title molecule, the fragments 5-phenylisoxazole and 3-(2-chloro-6-methoxyquinolin-3-yl) are planar and make a dihedral angle of 36.8(2)°. In the crystal structure the molecules are linked by weak π - π interactions $\text{Cg1-Cg2}^i = 3.797(2)$ Å [$\text{Cg1} = \text{C2/C3/C4/C5/C7/C8}$; $\text{Cg2}^i = \text{N1/C1/C2/C3/C9/C10}$, symmetry code (i) = 1 − *x*, −*y*, −*z*].

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References

1. Bruker. *APEX3*, SAINT Bruker AXS Inc., Madison, WI, USA (2016).
2. Sheldrick, G. M.: Crystal structure refinement with SHELXL. *Acta Cryst.* **C71** (2015) 3–8.
3. Sheldrick, G. M.: SHELXT – Integrated space-group and crystal-structure determination. *Acta Crystallogr.* **A71** (2015) 3–8.
4. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H.: OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Crystallogr.* **42** (2009) 339–341.
5. Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. A.: A cycloaddition approach toward the synthesis of substituted indolines and tetrahydroquinolines. *J. Org. Chem.* **64** (1999) 3595–3607.
6. Kouznetsov, V. V.; Vargas, M. L. Y.; Melendez, G. C. M.: Recent progress in the synthesis of quinolines. *Curr. Org. Chem.* **9** (2005) 141–161(21).
7. Smith, A. L.; Nicolaou, K. C.: The enediyne antibiotics. *J. Med. Chem.* **39** (1996) 2103–217.
8. Garudachari, B.; Satyanarayana, M. N.; Thippeswamy, B.; Shivakumar, C. K.; Shivananda, K. N.; Hegde, G.; Isloor, A. M.: Synthesis, characterization and antimicrobial studies of some new quinoline incorporated benzimidazole derivatives. *Eur. J. Med. Chem.* **54** (2012) 900–906.
9. Katgaonkar, A. H.; Shinde, P. V.; Katgaonkar, A. H.; Pasale, S. K.; Shingate, B. B.; Shingare, M. S.: Synthesis and biological evaluation of new 2-chloro-3-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl) quinoline derivatives *via* click chemistry approach. *Eur. J. Med. Chem.* **45** (2010) 3142–3146.
10. Eswaran, S.; Adhikari, A. V.; Kumar, A. J.: New 1,3-oxazolo [4,5-*c*]quinoline derivatives: Synthesis and evaluation of antibacterial and antituberculosis properties. *Eur. J. Med. Chem.* **45** (2010) 957–967.
11. Mao, J.; Yuan, H.; Wang, Y.; Wan, B.; Pak, D.; He, R.; Franzblau, S. G.: Synthesis and antituberculosis activity of novel mefloquine-isoxazole carboxylic esters as prodrugs. *Bioorg. Med. Chem. Lett.* **20** (2010) 1263–1268.