# organic compounds

# Ethyl 3-(10-bromoanthracen-9-yl)-5-methyl-1,2-oxazole-4-carboxylate

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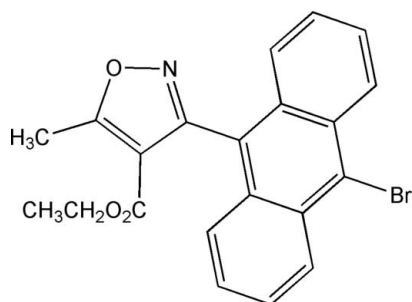
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In the title compound, $C_{21}H_{16}BrNO_3$, the mean planes of the anthracene tricycle and isoxazole ring are inclined to each other at a dihedral angle of 72.12 (7)°. The carboxy group is slightly out of the isoxazole mean plane, with a maximum deviation of 0.070 (5) Å for the carbonyl O atom. In the crystal, pairs of weak C—H···O hydrogen bonds link the molecules into dimers, and weak C—H···N interactions further link these dimers into corrugated layers parallel to the *bc* plane.

## Related literature

For the synthesis of anthryl isoxazoles, see: Mosher & Natale (1995); Zhou *et al.* (1997); Han & Natale (2001); Rider *et al.* (2010); Mirzaei *et al.* (2012). For related structures, see: Mosher *et al.* (1996); Han *et al.* (2002, 2003); Li *et al.* (2006, 2008). For the antitumor activity of aryl isoxazole amides (AIMs), see: Han *et al.* (2009); Gajewski *et al.* (2009); Balasubramanian *et al.* (2011); Neidle (2012); Kohn *et al.* (2012); Shoemaker (2006).



## Experimental

### Crystal data

| | |
|---|---|
| $C_{21}H_{16}BrNO_3$ | $V = 1729.77$ (4) Å$^3$ |
| $M_r = 410.26$ | $Z = 4$ |
| Monoclinic, $P2_1/c$ | Mo $K\alpha$ radiation |
| $a = 8.8437$ (1) Å | $\mu = 2.40$ mm$^{-1}$ |
| $b = 16.7099$ (2) Å | $T = 100$ K |
| $c = 11.7157$ (2) Å | $0.49 \times 0.47 \times 0.38$ mm |
| $\beta = 92.419$ (1)° | |

### Data collection

| | |
|---|---|
| Bruker SMART BREEZE CCD diffractometer | 34958 measured reflections |
| Absorption correction: multi-scan (*SADABS*; Bruker, 2008) | 4290 independent reflections |
| | 4128 reflections with $I > 2\sigma(I)$ |
| $T_{min} = 0.39$, $T_{max} = 0.47$ | $R_{int} = 0.020$ |

### Refinement

| | |
|---|---|
| $R[F^2 > 2\sigma(F^2)] = 0.025$ | 237 parameters |
| $wR(F^2) = 0.074$ | H-atom parameters constrained |
| $S = 1.05$ | $\Delta\rho_{max} = 0.51$ e Å$^{-3}$ |
| 4290 reflections | $\Delta\rho_{min} = -0.39$ e Å$^{-3}$ |

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

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| C2—H2···N1$^{i}$ | 0.95 | 2.54 | 3.4305 (19) | 155 |
| C4—H4···O2$^{ii}$ | 0.95 | 2.58 | 3.1990 (18) | 123 |

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

Data collection: *APEX2* (Bruker, 2008); cell refinement: *SAINT* (Bruker, 2008); data reduction: *SAINT*; program(s) used to solve structure: *SHELXL97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXS97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *OLEX2* and *publCIF* (Westrip, 2010).

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# Ethyl 3-(10-bromoanthracen-9-yl)-5-methyl-1,2-oxazole-4-carboxylate

**Chun Li, Michael J. Campbell, Matthew J. Weaver, Nathan S. Duncan, Janet L. Hunting and Nicholas R. Natale**

## 1. Introduction

The aryl isoxazole amides (AIMs) (Han *et al.*, 2009; Gajewski *et al.*, 2009) have significant activity in the National Cancer Institutes 60 cell line screen (Kohn *et al.*, 2012; Shoemaker *et al.*, 2006) comparable to several agents in general medical practice, such as fluorouridine and bleomycin. Our working hypothesis for developing the structure activity relationship (SAR) of AIMs to improve their anti-tumor efficacy is focused on the quadruplex DNA conformations (Balasubramanian *et al.*, 2011; Neidle, 2012). To more accurately inform our G-4 - small molecule docking studies, we rely on crystallographic determinations of AIMs.

## 2. Experimental

### 2.1. Synthesis and crystallization

To a suspension of anthracene-9-carbaldehyde (10.0 g, 48.49 mmol; Sigma-Aldrich, 97%) in THF:Ethanol:H2O (135 mL:67.5 mL:67.5 mL) was dissolved sodium acetate (3.5 eq., 13.92 g, 169.7 mmol) and hydroxylamine hydrochloride (2 eq, 6.7387 g, 96.974 mmol). The reaction was covered and let stir at room temperature until TLC showed no starting material remained (ca. 96 hours). The solution was then transferred to a separatory funnel and washed 4 x 350 mL Brine and the combined aqueous layers washed 2x100 mL $CHCl_3$, dried over sodium sulfate, filtered, and the solvent removed under vacuum to yield anthracene-9-carbaldehyde oxime (99%). ^{1}H NMR($CDCl_3$) $\delta$ 9.22 (s, 1H), 8.51 (s, 1H), 8.42 (d, J=8.66 Hz, 2H), 8.03 (d, J=8.16 Hz, 2H), 7.55 (m, 4H).

The anthracene-9-carbaldehyde oxime (10.516 g, 47.53 mmol) was taken up in 200 mL of chloroform at room temperature, to which solution was added pyridine (10 mol%, 0.38 mL) and recrystallized NCS (1.1 eq., 7.197 g, 52.28 mmol). The solution brought to 40°C for three hours then cooled to room temperature. The organic layer was washed with 4x450 mL Brine and 4x300 mL $H_2O$, then the aqueous layer washed with 2x300 mL $CHCl_3$, dried with sodium sulfate, filtered, and the solvent removed under reduced pressure to yield the nitrile oxide. The intermediate was purified only through extractive isolation using brine and $CHCl_3$ and taken on to the next reaction as is. To a solution of the nitrile oxide in absolute ethanol (230 mL) was added 1.4 equivalents of ethylacetoacetate. In a separate flask was added 115 mL absolute ethanol and 2.341 g Na(s). Once the sodium dissociation had completed, the warm solution was added to the nitrile oxide and the mixture was allowed to stir at room temperature under argon for 20 hours until TLC in 4:1 Hex/EtOAc revealed all nitrile oxide had been consumed. Finally, the ethanol was removed via rotary evaporation and the solid chromatographed using 4:1 Hex/EtOAc ($R_f$=0.56). Ethyl 3-(anthracen-9-yl)-5-methylisoxazole-4-carboxylate. Yield 97%. ^{1}H NMR(400 MHz, $CDCl_3$) $\delta$ 8.59 (s, 1H), 8.06 (d, J=7.91 Hz, 2H), 7.66 (d, J=8.16 Hz, 2H), 7.41-7.50 (m, 4H), 3.70 (q, J=7.15, 14.31 Hz, 2H), 2.93 (s, 3H), 0.33 (t, J=7.15 Hz, 3H). Spectral data are in accord with those reported previously (Mirzaei *et al.*, 2012).

Ethyl 3-(anthracen-9-yl)-5-methylisoxazole-4-carboxylate (4.88 g, 14.73 mmol) was taken up in 80 mL DMF to which was added a solution of recrystallized N-Bromosuccinamide (NBS) (1.1 eq, 2.884 g, 16.203 mmol) dissolved in 80 mL DMF. The solution was brought to 40°C and let stir for 5 hours where upon the solution was poured into 1200mL ice/water which was allowed to stir for 2 hours, in which the product precipitated out. Product was filtered, dissolved in $CH_2Cl_2$, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. Yield 88%, $^1$H NMR(CDCl$_3$) $\delta$ 8.62 (d, J=8.91 Hz, 2H), 7.60-7.67 (m, 4H), 7.61 (m, 2H), 3.72 (q, J=7.03, 14.18 Hz, 2H), 2.94 (s, 3H), 0.39 (t, J=7.15, 14.31 Hz, 3H); $^{13}$C NMR(CDCl$_3$) $\delta$ 176.28, 161.23, 160.21, 131.31, 130.01, 128.03, 127.04, 126.50, 125.87, 125.18, 123.62, 111.40, 60.14, 13.41, 12.89. Spectral data are in accord with those reported previously (Han *et al.*, 2003), the crystals were obtained by slow evapotation from a methylene chloride and heptane solution.
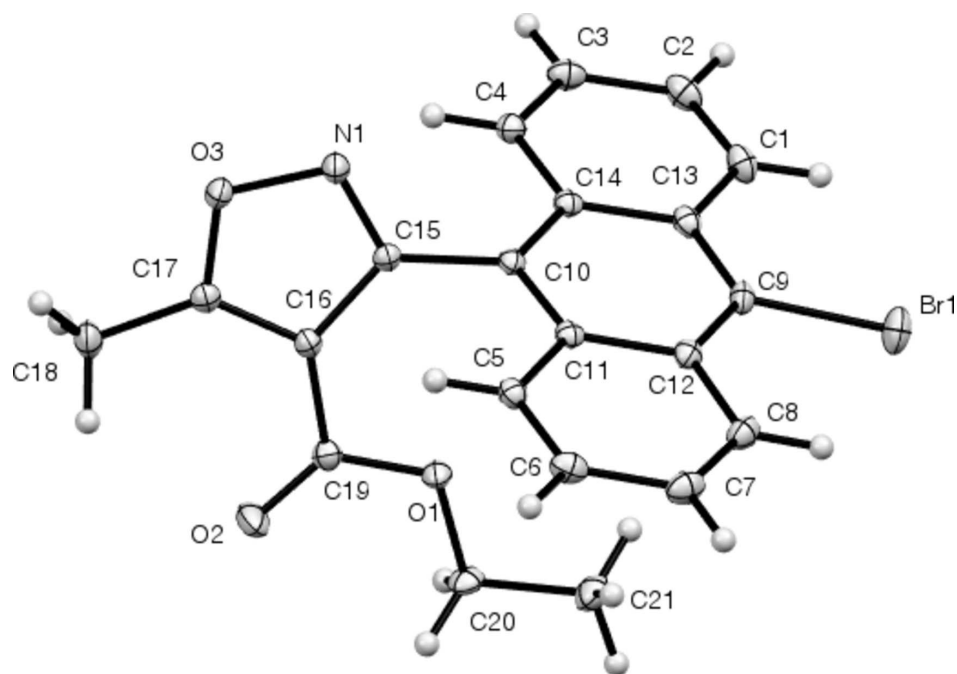
## 2.2. Refinement

All H atoms were placed at geometrically calculated positions and included in the refinement in the riding model approximation, with C—H lengths of 0.95 (aromatic CH), 0.98 (CH$_3$) and 0.99 (CH$_2$) Å. Idealized methyl groups were refined as rotating groups. $U_{iso}$ of the H atoms was set at 1.5$U_{eq}$ of the parent C atom for the methyl group and at 1.2$U_{eq}$ for the remaining H atoms.
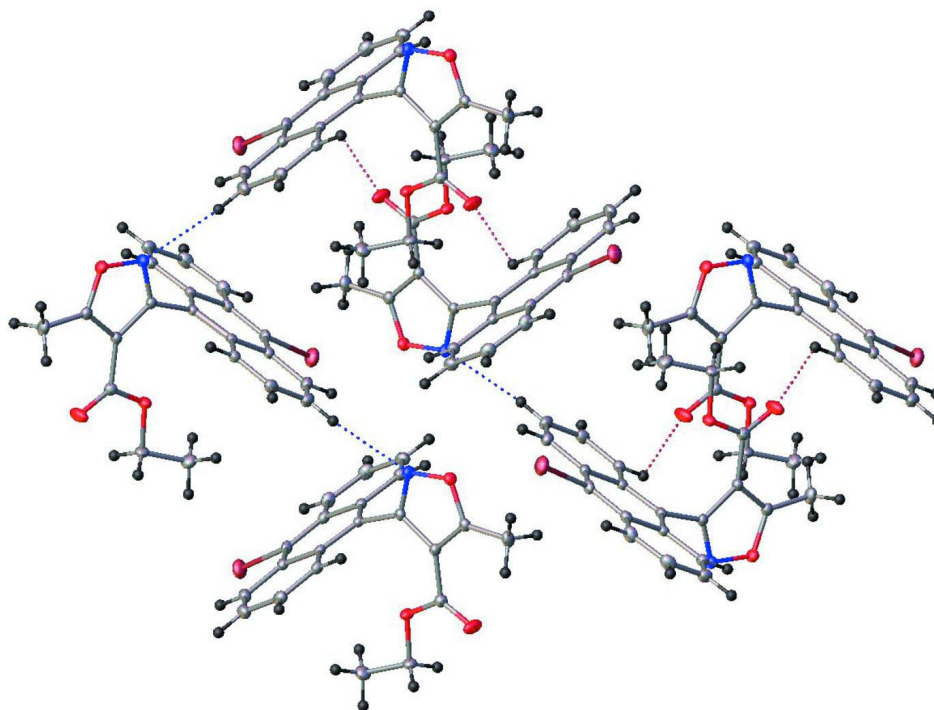
## 3. Results and discussion

The aryl isoxazole amides (AIMs) (Han *et al.*, 2009; Gajewski *et al.*, 2009) have significant activity in the National Cancer Institutes 60 cell line screen, (Kohn *et al.*, 2012; Shoemaker, 2006) comparable to several agents in general medical practice, such as fluorouridine and bleomycin. Our working hypothesis for developing the structure activity relationship (SAR) of AIMs to improve their anti-tumor efficacy is focused on the quadruplex DNA conformations (Balasubramanian *et al.*, 2011; Neidle *et al.*, 2012). To more accurately inform our G-4 - small molecule docking studies, we rely on crystallographic determinations of AIMs. In previous studies we have determined that the dihedral angle between the isoxazole and the C-3 aryl is approximately orthogonal (Mosher *et al.*, 1996; Li *et al.*, 2008), and we have postulated that this is a critical feature in the biological activity of the AIMs. The anthracenyl group is almost perpendicular to the isoxazole plane in ethyl 3-(10′-chloroanthracenyl)-5-(1″-phenyl-2″-hydroxyethylenyl)isoxazole-4-carboxylate [85.51 (4)°] (Li *et al.*, 2006), which is similar to analogous anthracenyl isoxazole structures in the Cambridge Structural Database, i.e. ethyl 3-(10′-chloro-9′-anthracenyl)-5-methyl-4-isoxazolcarboxylate [74.3°] (Han *et al.*, 2003; CSD refcode EZENEC), ethyl 3-(10′-chloro-9′-anthracenyl)-5-(2-phenylethyl)-4-isoxazolecarboxylate [78.5°] (Han *et al.*, 2002; CSD refcode MUQMOA). This AIM analog represents a key intermediate in future synthesis and SAR studies, and our progress will be reported in due course.

## Computing details

Data collection: *APEX2* (Bruker, 2008); cell refinement: *SAINT* (Bruker, 2008); data reduction: *SAINT* (Bruker, 2008); program(s) used to solve structure: *SHELXL97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXS97* (Sheldrick, 2008); molecular graphics: OLEX2 (Dolomanov *et al.*, 2009); software used to prepare material for publication: OLEX2 (Dolomanov *et al.*, 2009) and *publCIF* (Westrip, 2010).

**Figure 1**

The molecular structure of titled compound, with atom labels and 50% probability displacement ellipsoids for non-H atoms.



**Figure 2**

A portion of the packing diagram viewed in [100]. Weak intermolecular C—H···O and C—H···N hydrogen bond interactions are shown as dashed lines.

### Ethyl 3-(10-bromoanthracen-9-yl)-5-methyl-1,2-oxazole-4-carboxylate

*Crystal data*

| | |
|---|---|
| $C_{21}H_{16}BrNO_3$ | $F(000) = 832$ |
| $M_r = 410.26$ | $D_x = 1.575$ Mg m$^{-3}$ |
| Monoclinic, $P2_1/c$ | Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å |
| $a = 8.8437$ (1) Å | Cell parameters from 330 reflections |
| $b = 16.7099$ (2) Å | $\theta = 0.3$–27.5° |
| $c = 11.7157$ (2) Å | $\mu = 2.40$ mm$^{-1}$ |
| $\beta = 92.419$ (1)° | $T = 100$ K |
| $V = 1729.77$ (4) Å$^3$ | Prism, translucent yellow |
| $Z = 4$ | $0.49 \times 0.47 \times 0.38$ mm |

*Data collection*

| | |
|---|---|
| Bruker SMART BREEZE CCD diffractometer | 4290 independent reflections |
| Radiation source: 2 kW sealed X-ray tube | 4128 reflections with $I > 2\sigma(I)$ |
| $\pi$ and $\omega$ scans | $R_{int} = 0.020$ |
| Absorption correction: multi-scan (*SADABS*; Bruker, 2008) | $\theta_{max} = 28.3°$, $\theta_{min} = 2.1°$ |
| | $h = -11 \rightarrow 11$ |
| $T_{min} = 0.39$, $T_{max} = 0.47$ | $k = -22 \rightarrow 22$ |
| 34958 measured reflections | $l = -15 \rightarrow 14$ |

*Refinement*

| | |
|---|---|
| Refinement on $F^2$ | Primary atom site location: structure-invariant direct methods |
| Least-squares matrix: full | |
| $R[F^2 > 2\sigma(F^2)] = 0.025$ | Hydrogen site location: inferred from neighbouring sites |
| $wR(F^2) = 0.074$ | |
| $S = 1.05$ | H-atom parameters constrained |
| 4290 reflections | $w = 1/[\sigma^2(F_o^2) + (0.0448P)^2 + 1.2294P]$ where $P = (F_o^2 + 2F_c^2)/3$ |
| 237 parameters | |
| 0 restraints | $(\Delta/\sigma)_{max} = 0.002$ |
| | $\Delta\rho_{max} = 0.51$ e Å$^{-3}$ |
| | $\Delta\rho_{min} = -0.39$ e Å$^{-3}$ |

*Special details*

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

**Refinement**. Refinement of $F^2$ against ALL reflections. The weighted $R$-factor $wR$ and goodness of fit $S$ are based on $F^2$, conventional $R$-factors $R$ are based on $F$, with $F$ set to zero for negative $F^2$. The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating $R$-factors(gt) *etc*. and is not relevant to the choice of reflections for refinement. $R$-factors based on $F^2$ are statistically about twice as large as those based on $F$, and $R$-factors based on ALL data will be even larger.

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å$^2$)*

| | *x* | *y* | *z* | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| Br1 | 0.65922 (2) | 0.19002 (2) | 0.12783 (2) | 0.02178 (7) |
| O1 | 0.29601 (12) | 0.46676 (6) | 0.02087 (8) | 0.0145 (2) |
| O2 | 0.14962 (15) | 0.57548 (8) | −0.00887 (10) | 0.0261 (3) |
| O3 | 0.06569 (12) | 0.53843 (6) | 0.34089 (9) | 0.0145 (2) |
| N1 | 0.15853 (14) | 0.46963 (7) | 0.35626 (10) | 0.0142 (2) |
| C1 | 0.31314 (18) | 0.19895 (9) | 0.06508 (13) | 0.0166 (3) |

| | | | | |
|---|---|---|---|---|
| H1 | 0.3800 | 0.1580 | 0.0424 | 0.020* |
| C2 | 0.16567 (19) | 0.19731 (9) | 0.02681 (13) | 0.0187 (3) |
| H2 | 0.1310 | 0.1554 | −0.0224 | 0.022* |
| C3 | 0.06357 (17) | 0.25744 (9) | 0.05964 (12) | 0.0167 (3) |
| H3 | −0.0390 | 0.2555 | 0.0323 | 0.020* |
| C4 | 0.11134 (17) | 0.31807 (8) | 0.13019 (12) | 0.0135 (3) |
| H4 | 0.0412 | 0.3577 | 0.1520 | 0.016* |
| C5 | 0.52484 (16) | 0.45590 (8) | 0.35132 (12) | 0.0141 (3) |
| H5 | 0.4571 | 0.4969 | 0.3725 | 0.017* |
| C6 | 0.67305 (17) | 0.45991 (9) | 0.38810 (12) | 0.0171 (3) |
| H6 | 0.7075 | 0.5034 | 0.4345 | 0.020* |
| C7 | 0.77617 (17) | 0.39918 (10) | 0.35718 (13) | 0.0191 (3) |
| H7 | 0.8791 | 0.4022 | 0.3834 | 0.023* |
| C8 | 0.72856 (16) | 0.33668 (9) | 0.29027 (13) | 0.0175 (3) |
| H8 | 0.7993 | 0.2969 | 0.2701 | 0.021* |
| C9 | 0.52055 (16) | 0.26791 (8) | 0.17830 (12) | 0.0133 (2) |
| C10 | 0.31823 (15) | 0.38718 (8) | 0.23963 (11) | 0.0111 (2) |
| C11 | 0.46912 (15) | 0.39100 (8) | 0.28134 (11) | 0.0116 (2) |
| C12 | 0.57441 (16) | 0.32977 (8) | 0.24980 (12) | 0.0132 (3) |
| C13 | 0.36915 (16) | 0.26146 (8) | 0.13894 (11) | 0.0126 (2) |
| C14 | 0.26560 (16) | 0.32284 (8) | 0.17184 (11) | 0.0114 (2) |
| C15 | 0.21490 (15) | 0.45584 (8) | 0.25655 (11) | 0.0111 (2) |
| C16 | 0.16273 (15) | 0.51365 (8) | 0.17353 (11) | 0.0118 (2) |
| C17 | 0.06993 (15) | 0.56274 (8) | 0.23177 (12) | 0.0128 (2) |
| C18 | −0.02091 (17) | 0.63431 (9) | 0.19866 (13) | 0.0184 (3) |
| H18A | −0.1080 | 0.6384 | 0.2474 | 0.028* |
| H18B | −0.0567 | 0.6295 | 0.1186 | 0.028* |
| H18C | 0.0419 | 0.6824 | 0.2081 | 0.028* |
| C19 | 0.19946 (16) | 0.52302 (8) | 0.05278 (12) | 0.0139 (3) |
| C20 | 0.34574 (17) | 0.47134 (9) | −0.09567 (12) | 0.0162 (3) |
| H20A | 0.4147 | 0.5174 | −0.1044 | 0.019* |
| H20B | 0.2578 | 0.4778 | −0.1500 | 0.019* |
| C21 | 0.42720 (19) | 0.39376 (10) | −0.11786 (13) | 0.0211 (3) |
| H21A | 0.4647 | 0.3944 | −0.1954 | 0.032* |
| H21B | 0.3571 | 0.3488 | −0.1102 | 0.032* |
| H21C | 0.5126 | 0.3878 | −0.0624 | 0.032* |

*Atomic displacement parameters (Å²)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| Br1 | 0.01713 (9) | 0.01729 (9) | 0.03139 (10) | 0.00372 (5) | 0.00673 (6) | −0.00296 (5) |
| O1 | 0.0174 (5) | 0.0153 (5) | 0.0111 (4) | 0.0030 (4) | 0.0040 (4) | 0.0021 (4) |
| O2 | 0.0333 (7) | 0.0279 (6) | 0.0175 (5) | 0.0158 (5) | 0.0050 (5) | 0.0084 (4) |
| O3 | 0.0153 (5) | 0.0136 (5) | 0.0146 (5) | 0.0031 (4) | 0.0024 (4) | −0.0010 (4) |
| N1 | 0.0152 (6) | 0.0125 (5) | 0.0150 (5) | 0.0029 (4) | 0.0015 (4) | 0.0002 (4) |
| C1 | 0.0210 (7) | 0.0129 (6) | 0.0162 (6) | −0.0005 (5) | 0.0036 (5) | −0.0019 (5) |
| C2 | 0.0237 (8) | 0.0157 (7) | 0.0167 (7) | −0.0045 (5) | 0.0010 (6) | −0.0026 (5) |
| C3 | 0.0169 (7) | 0.0167 (6) | 0.0162 (6) | −0.0039 (5) | −0.0020 (5) | 0.0016 (5) |
| C4 | 0.0143 (7) | 0.0125 (6) | 0.0135 (6) | 0.0005 (5) | 0.0004 (5) | 0.0020 (5) |
| C5 | 0.0157 (6) | 0.0142 (6) | 0.0124 (6) | 0.0002 (5) | 0.0003 (5) | 0.0002 (5) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C6 | 0.0177 (7) | 0.0183 (7) | 0.0150 (6) | −0.0038 (5) | −0.0016 (5) | −0.0002 (5) |
| C7 | 0.0128 (6) | 0.0222 (7) | 0.0219 (7) | −0.0011 (5) | −0.0023 (5) | 0.0041 (6) |
| C8 | 0.0121 (6) | 0.0175 (7) | 0.0227 (7) | 0.0020 (5) | 0.0006 (5) | 0.0028 (5) |
| C9 | 0.0131 (6) | 0.0108 (6) | 0.0162 (6) | 0.0029 (5) | 0.0042 (5) | 0.0010 (5) |
| C10 | 0.0123 (6) | 0.0110 (6) | 0.0101 (5) | 0.0013 (5) | 0.0013 (4) | 0.0018 (4) |
| C11 | 0.0126 (6) | 0.0115 (6) | 0.0106 (6) | 0.0000 (5) | 0.0012 (4) | 0.0019 (4) |
| C12 | 0.0124 (6) | 0.0128 (6) | 0.0143 (6) | 0.0008 (5) | 0.0015 (5) | 0.0033 (5) |
| C13 | 0.0147 (6) | 0.0107 (6) | 0.0126 (6) | 0.0001 (5) | 0.0024 (5) | 0.0014 (5) |
| C14 | 0.0125 (6) | 0.0111 (5) | 0.0107 (6) | −0.0004 (5) | 0.0013 (5) | 0.0021 (5) |
| C15 | 0.0108 (6) | 0.0104 (6) | 0.0122 (6) | −0.0010 (5) | −0.0003 (4) | −0.0007 (4) |
| C16 | 0.0114 (6) | 0.0111 (6) | 0.0129 (6) | 0.0004 (5) | −0.0005 (4) | 0.0004 (5) |
| C17 | 0.0121 (6) | 0.0120 (6) | 0.0144 (6) | −0.0012 (5) | −0.0008 (5) | −0.0009 (5) |
| C18 | 0.0179 (7) | 0.0135 (6) | 0.0235 (7) | 0.0043 (5) | −0.0016 (5) | −0.0019 (5) |
| C19 | 0.0132 (6) | 0.0145 (6) | 0.0139 (6) | 0.0001 (5) | 0.0006 (5) | −0.0001 (5) |
| C20 | 0.0207 (7) | 0.0175 (7) | 0.0106 (6) | −0.0008 (5) | 0.0049 (5) | 0.0010 (5) |
| C21 | 0.0246 (8) | 0.0213 (7) | 0.0180 (7) | 0.0028 (6) | 0.0063 (6) | −0.0027 (6) |

*Geometric parameters (Å, º)*

| | | | |
|---|---|---|---|
| Br1—C9 | 1.8996 (13) | C8—H8 | 0.9500 |
| O1—C19 | 1.3340 (17) | C8—C12 | 1.4290 (19) |
| O1—C20 | 1.4539 (16) | C9—C12 | 1.4013 (19) |
| O2—C19 | 1.2073 (18) | C9—C13 | 1.4017 (19) |
| O3—N1 | 1.4197 (15) | C10—C11 | 1.4031 (18) |
| O3—C17 | 1.3435 (17) | C10—C14 | 1.4043 (19) |
| N1—C15 | 1.3097 (18) | C10—C15 | 1.4853 (18) |
| C1—H1 | 0.9500 | C11—C12 | 1.4420 (19) |
| C1—C2 | 1.361 (2) | C13—C14 | 1.4384 (19) |
| C1—C13 | 1.4314 (19) | C15—C16 | 1.4332 (18) |
| C2—H2 | 0.9500 | C16—C17 | 1.3636 (19) |
| C2—C3 | 1.415 (2) | C16—C19 | 1.4731 (18) |
| C3—H3 | 0.9500 | C17—C18 | 1.4832 (19) |
| C3—C4 | 1.363 (2) | C18—H18A | 0.9800 |
| C4—H4 | 0.9500 | C18—H18B | 0.9800 |
| C4—C14 | 1.4316 (19) | C18—H18C | 0.9800 |
| C5—H5 | 0.9500 | C20—H20A | 0.9900 |
| C5—C6 | 1.364 (2) | C20—H20B | 0.9900 |
| C5—C11 | 1.4342 (19) | C20—C21 | 1.511 (2) |
| C6—H6 | 0.9500 | C21—H21A | 0.9800 |
| C6—C7 | 1.422 (2) | C21—H21B | 0.9800 |
| C7—H7 | 0.9500 | C21—H21C | 0.9800 |
| C7—C8 | 1.362 (2) | | |
| | | | |
| C19—O1—C20 | 116.66 (11) | C9—C12—C11 | 118.01 (12) |
| C17—O3—N1 | 109.05 (10) | C1—C13—C14 | 118.32 (13) |
| C15—N1—O3 | 105.62 (11) | C9—C13—C1 | 123.80 (13) |
| C2—C1—H1 | 119.5 | C9—C13—C14 | 117.85 (12) |
| C2—C1—C13 | 121.07 (14) | C4—C14—C13 | 118.50 (12) |
| C13—C1—H1 | 119.5 | C10—C14—C4 | 121.59 (13) |
| C1—C2—H2 | 119.7 | C10—C14—C13 | 119.86 (13) |

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|---|---|---|---|
| C1—C2—C3 | 120.64 (13) | N1—C15—C10 | 120.96 (12) |
| C3—C2—H2 | 119.7 | N1—C15—C16 | 111.28 (12) |
| C2—C3—H3 | 119.8 | C16—C15—C10 | 127.76 (12) |
| C4—C3—C2 | 120.50 (14) | C15—C16—C19 | 130.21 (12) |
| C4—C3—H3 | 119.8 | C17—C16—C15 | 104.43 (12) |
| C3—C4—H4 | 119.5 | C17—C16—C19 | 125.33 (12) |
| C3—C4—C14 | 120.97 (13) | O3—C17—C16 | 109.62 (12) |
| C14—C4—H4 | 119.5 | O3—C17—C18 | 117.14 (12) |
| C6—C5—H5 | 119.3 | C16—C17—C18 | 133.24 (13) |
| C6—C5—C11 | 121.34 (13) | C17—C18—H18A | 109.5 |
| C11—C5—H5 | 119.3 | C17—C18—H18B | 109.5 |
| C5—C6—H6 | 119.9 | C17—C18—H18C | 109.5 |
| C5—C6—C7 | 120.18 (14) | H18A—C18—H18B | 109.5 |
| C7—C6—H6 | 119.9 | H18A—C18—H18C | 109.5 |
| C6—C7—H7 | 119.7 | H18B—C18—H18C | 109.5 |
| C8—C7—C6 | 120.54 (13) | O1—C19—C16 | 111.34 (12) |
| C8—C7—H7 | 119.7 | O2—C19—O1 | 124.46 (13) |
| C7—C8—H8 | 119.3 | O2—C19—C16 | 124.19 (13) |
| C7—C8—C12 | 121.36 (14) | O1—C20—H20A | 110.5 |
| C12—C8—H8 | 119.3 | O1—C20—H20B | 110.5 |
| C12—C9—Br1 | 118.94 (10) | O1—C20—C21 | 106.36 (11) |
| C12—C9—C13 | 123.32 (12) | H20A—C20—H20B | 108.6 |
| C13—C9—Br1 | 117.72 (10) | C21—C20—H20A | 110.5 |
| C11—C10—C14 | 121.29 (12) | C21—C20—H20B | 110.5 |
| C11—C10—C15 | 120.00 (12) | C20—C21—H21A | 109.5 |
| C14—C10—C15 | 118.41 (12) | C20—C21—H21B | 109.5 |
| C5—C11—C12 | 118.23 (12) | C20—C21—H21C | 109.5 |
| C10—C11—C5 | 122.15 (12) | H21A—C21—H21B | 109.5 |
| C10—C11—C12 | 119.57 (12) | H21A—C21—H21C | 109.5 |
| C8—C12—C11 | 118.36 (13) | H21B—C21—H21C | 109.5 |
| C9—C12—C8 | 123.60 (13) | | |
| | | | |
| Br1—C9—C12—C8 | −1.87 (19) | C10—C15—C16—C19 | −2.4 (2) |
| Br1—C9—C12—C11 | 176.22 (10) | C11—C5—C6—C7 | 0.1 (2) |
| Br1—C9—C13—C1 | 1.24 (19) | C11—C10—C14—C4 | 179.20 (12) |
| Br1—C9—C13—C14 | −176.59 (9) | C11—C10—C14—C13 | −3.33 (19) |
| O3—N1—C15—C10 | −179.64 (11) | C11—C10—C15—N1 | −75.68 (17) |
| O3—N1—C15—C16 | 0.03 (15) | C11—C10—C15—C16 | 104.71 (16) |
| N1—O3—C17—C16 | −0.55 (15) | C12—C9—C13—C1 | 179.42 (13) |
| N1—O3—C17—C18 | 179.89 (11) | C12—C9—C13—C14 | 1.6 (2) |
| N1—C15—C16—C17 | −0.35 (16) | C13—C1—C2—C3 | −0.3 (2) |
| N1—C15—C16—C19 | 178.00 (13) | C13—C9—C12—C8 | 179.97 (13) |
| C1—C2—C3—C4 | 0.0 (2) | C13—C9—C12—C11 | −1.9 (2) |
| C1—C13—C14—C4 | 0.65 (19) | C14—C10—C11—C5 | −179.58 (12) |
| C1—C13—C14—C10 | −176.89 (12) | C14—C10—C11—C12 | 2.97 (19) |
| C2—C1—C13—C9 | −177.91 (14) | C14—C10—C15—N1 | 110.56 (15) |
| C2—C1—C13—C14 | −0.1 (2) | C14—C10—C15—C16 | −69.05 (18) |
| C2—C3—C4—C14 | 0.6 (2) | C15—C10—C11—C5 | 6.85 (19) |
| C3—C4—C14—C10 | 176.60 (13) | C15—C10—C11—C12 | −170.60 (12) |

| | | | |
|---|---|---|---|
| C3—C4—C14—C13 | −0.9 (2) | C15—C10—C14—C4 | −7.13 (19) |
| C5—C6—C7—C8 | 0.3 (2) | C15—C10—C14—C13 | 170.34 (12) |
| C5—C11—C12—C8 | 0.29 (19) | C15—C16—C17—O3 | 0.54 (15) |
| C5—C11—C12—C9 | −177.91 (12) | C15—C16—C17—C18 | −179.99 (15) |
| C6—C5—C11—C10 | −177.89 (13) | C15—C16—C19—O1 | 0.5 (2) |
| C6—C5—C11—C12 | −0.4 (2) | C15—C16—C19—O2 | −178.75 (15) |
| C6—C7—C8—C12 | −0.4 (2) | C17—O3—N1—C15 | 0.32 (14) |
| C7—C8—C12—C9 | 178.20 (14) | C17—C16—C19—O1 | 178.55 (13) |
| C7—C8—C12—C11 | 0.1 (2) | C17—C16—C19—O2 | −0.7 (2) |
| C9—C13—C14—C4 | 178.60 (12) | C19—O1—C20—C21 | −169.06 (12) |
| C9—C13—C14—C10 | 1.06 (19) | C19—C16—C17—O3 | −177.91 (12) |
| C10—C11—C12—C8 | 177.84 (12) | C19—C16—C17—C18 | 1.6 (2) |
| C10—C11—C12—C9 | −0.36 (19) | C20—O1—C19—O2 | 1.5 (2) |
| C10—C15—C16—C17 | 179.29 (13) | C20—O1—C19—C16 | −177.73 (11) |

*Hydrogen-bond geometry (Å, º)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| C2—H2···N1[i] | 0.95 | 2.54 | 3.4305 (19) | 155 |
| C4—H4···O2[ii] | 0.95 | 2.58 | 3.1990 (18) | 123 |

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