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1-(2-Fluorobenzyl)-1-(2-fluorobenzyl-oxy)urea

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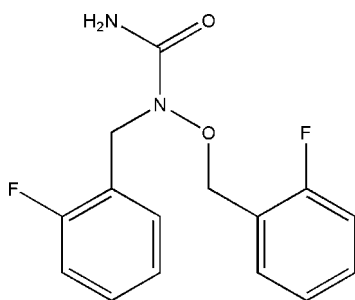
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Key indicators: single-crystal X-ray study; $T = 296$ K; mean $\sigma(\text{C}-\text{C}) = 0.006$ Å; R factor = 0.080; wR factor = 0.260; data-to-parameter ratio = 14.6.

In the title hydroxyurea derivative, $\text{C}_{15}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_2$, the dihedral angle between the two benzene rings is $48.64(19)^\circ$. The urea group forms dihedral angles of $48.1(2)$ and $79.2(2)^\circ$ with the two benzene rings. In the crystal, inversion dimers linked by pairs of $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds occur, and further $\text{N}-\text{H}\cdots\text{O}$ links lead to chains of molecules.

Related literature

For general background, see: Krakoff *et al.* (1968); Young *et al.* (1967) and Yu *et al.* (1974). For related structures, see: Howard *et al.* (1967); Thiessen *et al.* (1978); Armagan *et al.* (1976); Berman & Kim (1967); Larsen *et al.* (1966); Nielsen *et al.* (1993).



Experimental

Crystal data

$\text{C}_{15}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_2$
 $M_r = 292.28$

Monoclinic, $P2_1/c$
 $a = 5.196(5)$ Å

$b = 30.11(3)$ Å
 $c = 9.059(8)$ Å
 $\beta = 102.110(16)^\circ$
 $V = 1386(2)$ Å³
 $Z = 4$

Mo $K\alpha$ radiation
 $\mu = 0.11$ mm⁻¹
 $T = 296(2)$ K
 $0.34 \times 0.13 \times 0.07$ mm

Data collection

Bruker APEXII area-detector diffractometer
Absorption correction: none
8214 measured reflections

2416 independent reflections
1042 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.051$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.080$
 $wR(F^2) = 0.260$
 $S = 1.02$
2416 reflections

166 parameters
H-atom parameters constrained
 $\Delta\rho_{\text{max}} = 0.39$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.37$ e Å⁻³

Table 1

Hydrogen-bond geometry (Å, °).

$D-\text{H}\cdots A$	$D-\text{H}$	$\text{H}\cdots A$	$D\cdots A$	$D-\text{H}\cdots A$
$\text{N2}-\text{H2C}\cdots\text{O2}^{\text{i}}$	0.86	2.05	2.910 (5)	174
$\text{N2}-\text{H2D}\cdots\text{O2}^{\text{ii}}$	0.86	2.32	3.079 (5)	148

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

Data collection: APEX2 (Bruker, 2004); cell refinement: SAINT (Bruker, 2004); data reduction: SAINT; program(s) used to solve structure: SHELXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008); molecular graphics: ORTEP-3 for Windows (Farrugia, 1997); software used to prepare material for publication: publCIF (Westrip, 2009).

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: XU2472).

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supporting information

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1-(2-Fluorobenzyl)-1-(2-fluorobenzoyloxy)urea

Xi Mai, Hong-Ying Xia, Yu-Sheng Cao, Xiao-San Lu and Xiao-Niu Fang

S1. Comment

The anticancer drug hydroxyurea, which has been used in cancer chemotherapy for many years, has shown to impair DNA synthesis by inhibiting the enzyme ribonucleotide reductase (RNR) (Krakoff et al., 1968). Many hydroxyurea derivatives have been designed and synthesized, which inhibit RNR by the same mechanism. We designed and synthesized *N'*-unsubstituted *N*-hydroxyurea derivative, 1-(2-fluorobenzyl)-1-(2-fluorobenzoyloxy)urea. Then we used the compound to make the antitumor activity test in vitro for lymphoid leukemia L1210 through the classic MTT assay. Results show that it has higher inhibition ratios than *N*-hydroxyurea. This seems to be not much in good agreement with the early structure-activity studies of Young et al. (1967) and Yu et al. (1974). As a serial study of such a complex, the title compound was synthesized and its crystal structure is reported here.

The conformations of the *N*—H and C=O bonds in the structure of 1-(2-fluorobenzyl)-1-(2-fluorobenzoyloxy)urea (Fig. 1) are anti to each other, similar to that observed in *N*-hydroxyurea (Howard et al., 1967; Thiessen et al., 1978; Armagan et al., 1976; Berman & Kim, 1967; Larsen et al., 1966), 1-hydroxy-1-methylurea (Nielsen et al., 1993), 1-hydroxy-3-methylurea (Nielsen et al., 1993) and other hydroxyurea derivatives. The bond parameters in *N*-(phenylmethoxy)-urea are similar to those in above hydroxyurea derivatives, but the length of the carbonyl bond (C=O) is obviously shorter (< 1.25 Å). This may be related with the hydroxy group's etherification. The urea *N*—(C=O)—*N* group forms a dihedral angle of 48.1 (2) and 79.2 (2)° with the two benzene rings respectively. Intermolecular *N*—H···*O* hydrogen bonding presents in the crystal structure (Table 1).

S2. Experimental

The title compound was prepared by the reaction of 1-(2-fluorobenzoyloxy)urea (1.3 mmol) and 1-(chloromethyl)-2-fluorobenzene (1.3 mmol) in methanol (10 ml) in the presence of potassium hydroxide (1.7 mmol). After refluxing for 14 h, the mixture was distilled in the reduced pressure at 308 K. The resulting crude solid was filtered and washed by trichloromethane repeatedly, then recrystallized in acetone and trichloromethane mixture (5:2), filtered. Colorless needle-shaped single crystals used for X-ray structure determination were recrystallized from the mixed solvent acetone and *N*-hexane (3:13) at room temperature for one week.

S3. Refinement

H atoms were placed in calculated positions with C—H = 0.93 (aromatic), 0.97 Å (methylene) and *N*—H = 0.86 Å, and were refined in riding mode. The $U_{\text{iso}}(\text{H})$ values were set at $1.2U_{\text{eq}}(\text{C},\text{N})$.

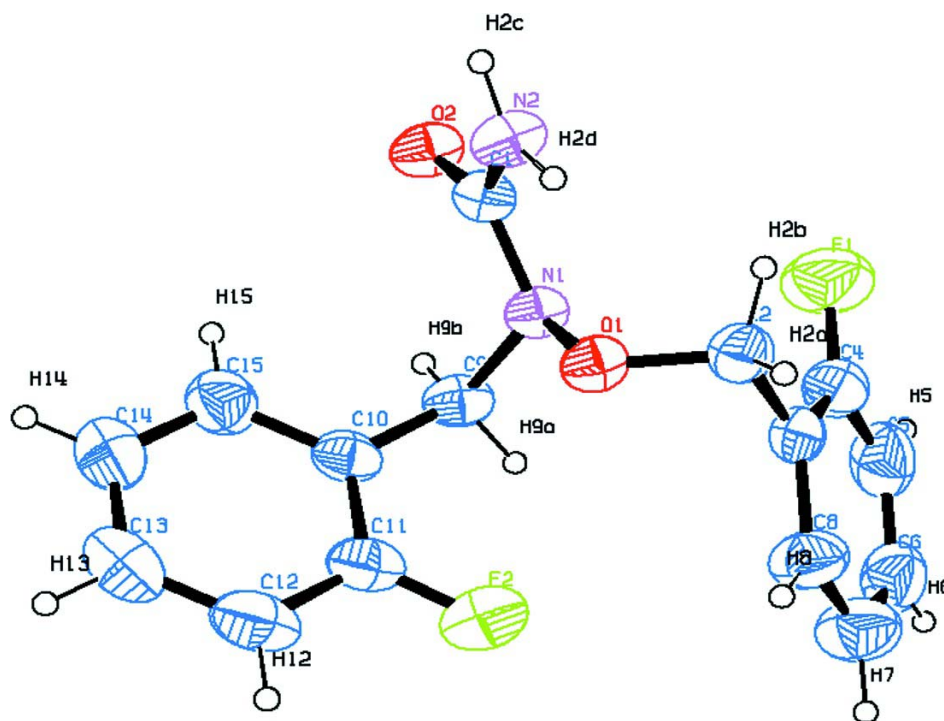


Figure 1

Molecular structure of the title compound showing the atom labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

1-(2-fluorobenzyl)-1-(2-fluorobenzyloxy)urea

Crystal data

$C_{15}H_{14}F_2N_2O_2$

$M_r = 292.28$

Monoclinic, $P2_1/c$

Hall symbol: $-P\ 2ybc$

$a = 5.196\ (5)\ \text{\AA}$

$b = 30.11\ (3)\ \text{\AA}$

$c = 9.059\ (8)\ \text{\AA}$

$\beta = 102.110\ (16)^\circ$

$V = 1386\ (2)\ \text{\AA}^3$

$Z = 4$

$F(000) = 608$

$D_x = 1.401\ \text{Mg m}^{-3}$

Melting point: 414.0 K

Mo $K\alpha$ radiation, $\lambda = 0.71073\ \text{\AA}$

Cell parameters from 1260 reflections

$\theta = 2.4\text{--}19.3^\circ$

$\mu = 0.11\ \text{mm}^{-1}$

$T = 296\ \text{K}$

Needle, colourless

$0.34 \times 0.13 \times 0.07\ \text{mm}$

Data collection

Bruker APEXII area-detector
diffractometer

Radiation source: fine-focus sealed tube
Graphite monochromator

φ and ω scans

8214 measured reflections

2416 independent reflections

1042 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.051$

$\theta_{\text{max}} = 25.0^\circ$, $\theta_{\text{min}} = 2.4^\circ$

$h = -6 \rightarrow 6$

$k = -35 \rightarrow 35$

$l = -10 \rightarrow 10$

Refinement

Refinement on F^2
 Least-squares matrix: full
 $R[F^2 > 2\sigma(F^2)] = 0.080$
 $wR(F^2) = 0.260$
 $S = 1.02$
 2416 reflections
 166 parameters
 0 restraints
 Primary atom site location: structure-invariant
 direct methods

Secondary atom site location: difference Fourier
 map
 Hydrogen site location: inferred from
 neighbouring sites
 H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.14P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.39 \text{ e } \text{\AA}^{-3}$
 $\Delta\rho_{\min} = -0.37 \text{ e } \text{\AA}^{-3}$

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 (\AA^2)

	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
C10	0.2248 (6)	0.40316 (12)	0.5643 (3)	0.0675 (13)
C11	-0.0040 (7)	0.38153 (11)	0.4930 (4)	0.0829 (15)
C12	-0.1631 (6)	0.40007 (16)	0.3653 (4)	0.106 (2)
H12	-0.3162	0.3856	0.3175	0.127*
C13	-0.0935 (9)	0.44024 (17)	0.3089 (4)	0.118 (2)
H13	-0.2000	0.4526	0.2235	0.141*
C14	0.1352 (10)	0.46187 (12)	0.3803 (5)	0.119 (2)
H14	0.1818	0.4887	0.3426	0.142*
C15	0.2944 (7)	0.44333 (12)	0.5080 (5)	0.0938 (17)
H15	0.4474	0.4578	0.5557	0.113*
C3	0.1504 (7)	0.31233 (9)	0.9537 (4)	0.0677 (13)
C4	0.3952 (7)	0.29896 (13)	1.0354 (4)	0.0867 (16)
C5	0.4847 (6)	0.25614 (15)	1.0185 (5)	0.108 (2)
H5	0.6484	0.2472	1.0732	0.130*
C6	0.3294 (9)	0.22670 (10)	0.9199 (5)	0.1050 (19)
H6	0.3893	0.1980	0.9086	0.126*
C7	0.0846 (9)	0.24007 (11)	0.8383 (5)	0.113 (2)
H7	-0.0192	0.2204	0.7723	0.135*
C8	-0.0049 (6)	0.28289 (12)	0.8552 (4)	0.0964 (18)
H8	-0.1686	0.2918	0.8005	0.116*
C1	0.3969 (8)	0.43961 (14)	0.9001 (5)	0.0581 (11)
C2	0.0492 (10)	0.35829 (16)	0.9702 (6)	0.0767 (14)
H2A	-0.1322	0.3564	0.9812	0.092*
H2B	0.1512	0.3716	1.0615	0.092*
C9	0.3958 (9)	0.38360 (15)	0.7028 (5)	0.0675 (13)

H9A	0.3850	0.3515	0.6953	0.081*
H9B	0.5769	0.3919	0.7050	0.081*
F1	0.5413 (8)	0.32477 (14)	1.1264 (5)	0.1447 (16)
F2	-0.0789 (8)	0.34425 (11)	0.5430 (4)	0.1243 (13)
N1	0.3293 (6)	0.39708 (11)	0.8446 (4)	0.0594 (10)
N2	0.2206 (7)	0.46056 (11)	0.9610 (4)	0.0693 (11)
H2C	0.2563	0.4863	1.0015	0.083*
H2D	0.0704	0.4485	0.9601	0.083*
O1	0.0624 (5)	0.38636 (9)	0.8448 (3)	0.0635 (9)
O2	0.6157 (6)	0.45452 (10)	0.8966 (4)	0.0719 (10)

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C10	0.062 (3)	0.080 (3)	0.062 (3)	0.000 (3)	0.018 (2)	-0.019 (2)
C11	0.080 (4)	0.097 (4)	0.071 (4)	-0.010 (3)	0.014 (3)	-0.025 (3)
C12	0.095 (4)	0.139 (6)	0.080 (4)	-0.020 (4)	0.008 (4)	-0.029 (4)
C13	0.132 (6)	0.145 (6)	0.070 (4)	0.005 (5)	0.006 (4)	0.003 (4)
C14	0.141 (6)	0.123 (5)	0.084 (5)	-0.021 (5)	0.006 (4)	0.016 (4)
C15	0.092 (4)	0.111 (4)	0.080 (4)	-0.015 (3)	0.020 (3)	-0.001 (3)
C3	0.071 (3)	0.072 (3)	0.064 (3)	-0.015 (3)	0.021 (3)	0.002 (2)
C4	0.084 (4)	0.091 (4)	0.077 (4)	-0.011 (3)	-0.003 (3)	0.006 (3)
C5	0.106 (5)	0.111 (5)	0.102 (5)	0.010 (4)	0.007 (4)	0.036 (4)
C6	0.127 (5)	0.083 (4)	0.108 (5)	0.007 (4)	0.031 (4)	0.016 (4)
C7	0.106 (5)	0.097 (5)	0.121 (5)	0.000 (4)	-0.009 (4)	-0.008 (4)
C8	0.108 (4)	0.067 (4)	0.104 (4)	-0.001 (3)	0.000 (3)	-0.011 (3)
C1	0.050 (3)	0.064 (3)	0.059 (3)	0.004 (2)	0.008 (2)	-0.006 (2)
C2	0.075 (3)	0.082 (3)	0.076 (3)	-0.015 (3)	0.023 (3)	-0.006 (3)
C9	0.056 (3)	0.070 (3)	0.080 (3)	0.004 (2)	0.022 (2)	-0.021 (2)
F1	0.140 (3)	0.135 (3)	0.133 (3)	-0.026 (3)	-0.031 (2)	-0.013 (2)
F2	0.134 (3)	0.105 (3)	0.129 (3)	-0.038 (2)	0.016 (2)	-0.019 (2)
N1	0.049 (2)	0.061 (2)	0.069 (2)	-0.0016 (16)	0.0145 (17)	-0.0087 (18)
N2	0.054 (2)	0.063 (2)	0.096 (3)	-0.0041 (18)	0.027 (2)	-0.018 (2)
O1	0.0480 (17)	0.0676 (19)	0.077 (2)	-0.0041 (14)	0.0176 (15)	-0.0076 (15)
O2	0.0490 (18)	0.074 (2)	0.095 (2)	-0.0078 (16)	0.0216 (16)	-0.0186 (16)

Geometric parameters (Å, °)

C10—C11	1.3900	C5—H5	0.9300
C10—C15	1.3900	C6—C7	1.3900
C10—C9	1.497 (6)	C6—H6	0.9300
C11—F2	1.301 (4)	C7—C8	1.3900
C11—C12	1.3900	C7—H7	0.9300
C12—C13	1.3900	C8—H8	0.9300
C12—H12	0.9300	C1—O2	1.229 (5)
C13—C14	1.3900	C1—N2	1.324 (5)
C13—H13	0.9300	C1—N1	1.394 (5)
C14—C15	1.3900	C2—O1	1.429 (6)

C14—H14	0.9300	C2—H2A	0.9700
C15—H15	0.9300	C2—H2B	0.9700
C3—C4	1.3900	C9—N1	1.457 (6)
C3—C8	1.3900	C9—H9A	0.9700
C3—C2	1.499 (6)	C9—H9B	0.9700
C4—F1	1.264 (4)	N1—O1	1.424 (4)
C4—C5	1.3900	N2—H2C	0.8600
C5—C6	1.3900	N2—H2D	0.8600
C11—C10—C15	120.0	C5—C6—H6	120.0
C11—C10—C9	120.3 (3)	C6—C7—C8	120.0
C15—C10—C9	119.7 (3)	C6—C7—H7	120.0
F2—C11—C12	117.9 (3)	C8—C7—H7	120.0
F2—C11—C10	122.1 (3)	C7—C8—C3	120.0
C12—C11—C10	120.0	C7—C8—H8	120.0
C11—C12—C13	120.0	C3—C8—H8	120.0
C11—C12—H12	120.0	O2—C1—N2	124.2 (4)
C13—C12—H12	120.0	O2—C1—N1	119.4 (4)
C14—C13—C12	120.0	N2—C1—N1	116.4 (4)
C14—C13—H13	120.0	O1—C2—C3	113.0 (4)
C12—C13—H13	120.0	O1—C2—H2A	109.0
C13—C14—C15	120.0	C3—C2—H2A	109.0
C13—C14—H14	120.0	O1—C2—H2B	109.0
C15—C14—H14	120.0	C3—C2—H2B	109.0
C14—C15—C10	120.0	H2A—C2—H2B	107.8
C14—C15—H15	120.0	N1—C9—C10	114.9 (3)
C10—C15—H15	120.0	N1—C9—H9A	108.6
C4—C3—C8	120.0	C10—C9—H9A	108.6
C4—C3—C2	121.0 (3)	N1—C9—H9B	108.6
C8—C3—C2	119.0 (3)	C10—C9—H9B	108.6
F1—C4—C5	118.2 (4)	H9A—C9—H9B	107.5
F1—C4—C3	121.8 (4)	C1—N1—O1	112.3 (3)
C5—C4—C3	120.0	C1—N1—C9	119.0 (4)
C4—C5—C6	120.0	O1—N1—C9	110.4 (3)
C4—C5—H5	120.0	C1—N2—H2C	120.0
C6—C5—H5	120.0	C1—N2—H2D	120.0
C7—C6—C5	120.0	H2C—N2—H2D	120.0
C7—C6—H6	120.0	N1—O1—C2	110.1 (3)

Hydrogen-bond geometry (\AA , $^\circ$)

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N2—H2C \cdots O2 ⁱ	0.86	2.05	2.910 (5)	174
N2—H2D \cdots O2 ⁱⁱ	0.86	2.32	3.079 (5)	148

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