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Five analogs of the active metabolite of leflunomide

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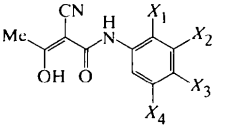
Abstract

The title compounds, 2-cyano-3-hydroxy-*N*-(4-bromophenyl)but-2-enamide, $C_{11}H_9BrN_2O_2$ (LFM-A1), 2-cyano-3-hydroxy-*N*-(2-fluorophenyl)but-2-enamide, $C_{11}H_9FN_2O_2$ (LFM-A7), 2-cyano-3-hydroxy-*N*-(3-bromophenyl)but-2-enamide, $C_{11}H_9BrN_2O_2$ (LFM-A9), 2-cyano-3-hydroxy-*N*-(3-chlorophenyl)but-2-enamide, $C_{11}H_9ClN_2O_2$ (LFM-A10), and 2-cyano-3-hydroxy-*N*-(3-fluorophenyl)but-2-enamide, $C_{11}H_9FN_2O_2$ (LFM-A11), are analogs of A77 1726, the active metabolite of the immunosupressive drug leflunomide, which is known to act in part by inhibiting the tyrosine kinase epidermal growth factor receptor (EGFR) [Mattar, Kochhar, Bartlett, Bremer & Finnegan (1993). *FEBS Lett.* **334**, 161–164]. The molecular structures of the title compounds are very similar and they display similar crystal packing and hydrogen-bonding networks. All five molecules are approximately planar; the dihedral angles between the phenyl ring and the plane defined by the N—C—C=C—CH_3 group are 4.8 (8)° for LFM-A1, 12.5 (2)° for LFM-A7, 6.2 (6)° for LFM-A9, 5.5 (3)° for LFM-A10 and 4.4 (3)° for LFM-A11. The intramolecular hydrogen bond between the O atoms observed in all the compounds locks them into a planar conformation and may contribute to a conformation which is favorable for binding the shallow ATP-binding pocket of EGFR.

Comment

The epidermal growth factor receptor (EGFR) is a membrane-associated tyrosine kinase which serves as an endogenous negative regulator of apoptosis in breast-cancer cells (Uckun *et al.*, 1998). Consequently, the development of new potent anti-breast-cancer drugs has emerged as an exceptional focal point for translational research in the treatment of breast cancer (Abrams *et al.*, 1994). A77 1726 is the primary metabolite of the isoxazole leflunomide [*N*-(4-trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide] and is an anti-inflammatory agent with pleiotropic effects (Parnham, 1995; Xu *et al.*, 1995, 1996; Bertolini *et al.*, 1997). A77 1726 was recently shown to inhibit the EGFR kinase at micromolar concentrations (Mattar *et al.*, 1993). In a systematic effort to design potent inhibitors of this receptor family protein tyrosine kinase (PTK) as anti-breast cancer agents, we have constructed a three-dimensional homology model of the EGFR kinase domain and used advanced docking procedures for the rational placement of chemical groups with defined sizes at multiple modification sites on A77 1726 (LFM) (Ghosh *et al.*, 1998). Based on the modeling studies, A77 1726, along with some of its designed analogs, were synthesized and tested for their kinase inhibitory activity on EGFR. This study is the first report of the structural characterization of five such LFM analogs which target the EGFR tyrosine kinase.



LFM-A1 : $X_1 = X_2 = X_4 = H, X_3 = Br$
LFM-A7 : $X_2 = X_3 = X_4 = H, X_1 = F$
LFM-A9 : $X_1 = X_3 = X_4 = H, X_2 = Br$
LFM-A10 : $X_1 = X_3 = X_4 = H, X_2 = Cl$
LFM-A11 : $X_1 = X_2 = X_3 = H, X_4 = F$

The atom numbering scheme and molecular conformation adopted by the molecules are shown in Figs. 1–5. The molecular structures of the title compounds are very similar and they display similar crystal packing and hydrogen-bonding networks. All five structures are approximately planar and there is no significant difference in the corresponding bond distances and angles in the five structures. All bond lengths except the C8—C11 and C11≡N11 bonds are consistent with values for similar types of bonds reported in the Cambridge

† Member of the Drug Discovery Program.

Structural Database (Allen & Kennard, 1993). The C8—C11 bond length is 1.427 (8) Å in LFM-A1, 1.426 (4) Å in LFM-A7, 1.426 (5) Å in LFM-A9, 1.425 (4) Å in LFM-A10 and 1.424 (3) Å in LFM-A11, which are slightly longer than the expected $Csp^2—Csp^1$ bond length of 1.416 Å. The C≡N11 bonds are shorter than the expected C≡N bond length of 1.165 Å [1.143 (8) Å in LFM-A1, 1.144 (3) Å in LFM-A7, 1.136 (5) Å in LFM-A9, 1.146 (3) Å in LFM-10, 1.144 (2) Å in LFM-A11]. A similar situation has been observed in the crystal structure of the leflunomide metabolite analog α-cyano-β-hydroxy-*N*-(2,5-dibromophenyl)but-2-enamide (LFM-A13) where C8—C11 = 1.438 (6) Å and C11≡N11 = 1.146 (6) Å (Ghosh *et al.*, 1999). The dihedral angles between the phenyl ring and the plane defined by the N—C—C=C—CH_3 group are are 4.8 (8)° for LFM-A1, 12.5 (2)° for LFM-A7, 6.2 (6)° for LFM-A9, 5.5 (3)° for LFM-A10 and 4.4 (3)° for LFM-A11.

The hydrogen-bonding parameters for the five compounds LFM-A1, LFM-A7, LFM-A9, LFM-A10 and LFM-A11 are listed in Tables 2, 4, 6, 8 and 10, respectively. Of the four hydrogen-bond forming groups present in these molecules, two (the hydroxyl group and the carbonyl oxygen) are involved in an intramolecular hydrogen bond in all the compounds. For LFM-A1, LFM-A9, LFM-A10 and LFM-A11 there is an intermolecular hydrogen bond between the remaining two groups: the amine nitrogen (N1) and the cyano nitro-

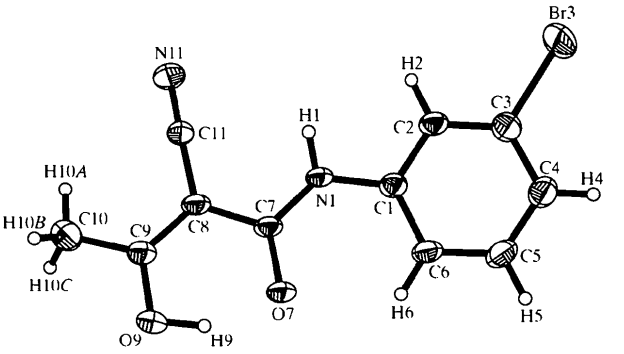


Fig. 3. The molecular structure of LFM-A9 showing the atomic numbering. Displacement ellipsoids are drawn at the 30% probability level. H atoms are displayed as small circles of an arbitrary radius.

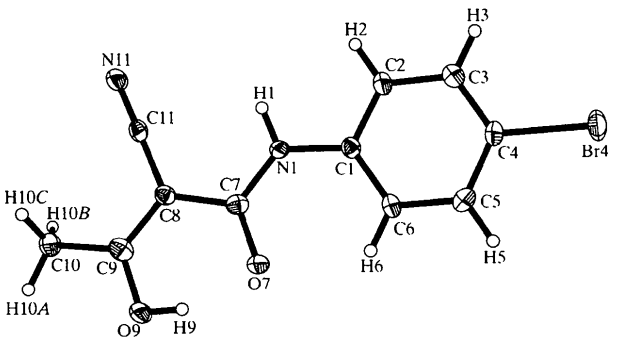


Fig. 1. The molecular structure of LFM-A1 showing the atomic numbering. Displacement ellipsoids are drawn at the 30% probability level. H atoms are displayed as small circles of an arbitrary radius.

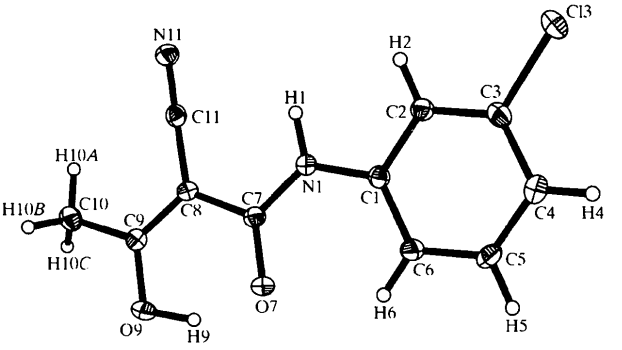


Fig. 4. The molecular structure of LFM-A10 showing the atomic numbering. Displacement ellipsoids are drawn at the 30% probability level. H atoms are displayed as small circles of an arbitrary radius.

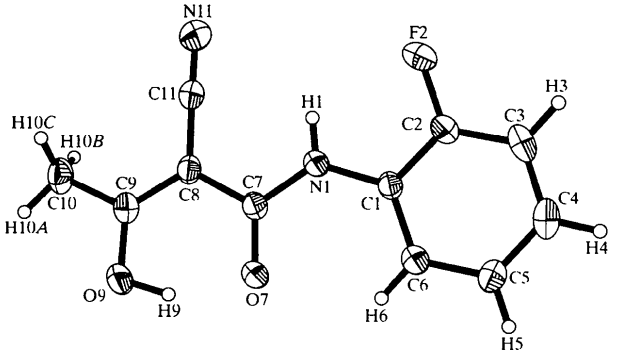


Fig. 2. The molecular structure of LFM-A7 showing the atomic numbering. Displacement ellipsoids are drawn at the 30% probability level. H atoms are displayed as small circles of an arbitrary radius.

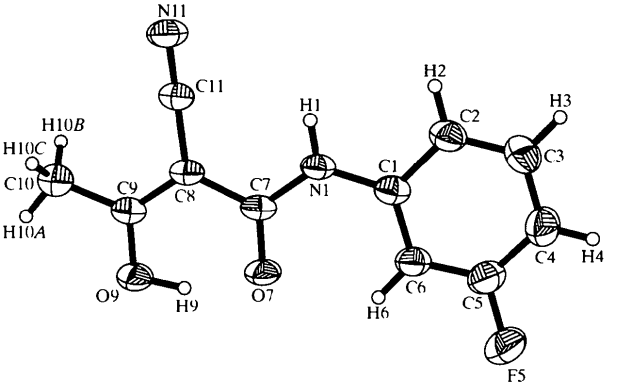


Fig. 5. The molecular structure of LFM-A11 showing the atomic numbering. Displacement ellipsoids are drawn at the 30% probability level. H atoms are displayed as small circles of an arbitrary radius.

gen (N11) of the centrosymmetrically related molecule. For LFM-A7 only the O7···O9 intramolecular hydrogen bond is present and the nitrile group is not involved in a hydrogen bond. A second intermolecular hydrogen bond is also observed between the hydroxyl group (O9) and the carbonyl oxygen (O7) in LFM-A9. A similar intramolecular hydrogen bond has also been observed between the hydroxyl group and the carbonyl-O atom in the crystal structure of the leflunomide metabolite analog, α-cyano-β-hydroxy-*N*-(2,5-dibromophenyl)but-2-enamide (LFM-A13) (Ghosh *et al.*, 1999). The intramolecular hydrogen bond observed in the crystal structures of these leflunomide metabolite (LFM) analogs locks them in an approximately planar conformation and may contribute to their ability to fit favorably into the shallow triangular binding pocket of EGFR. This is supported by the detailed molecular docking studies which revealed that the LFM analogs were predicted to bind to the catalytic site of EGFR in a planar conformation (Ghosh *et al.*, 1998).

Experimental

Single crystals of LFM-A1 and LFM-A9 were obtained by slow evaporation from acetonitrile, and crystals of LFM-A7 were obtained by slow evaporation from tetrahydrofuran (THF). Crystals of LFM-A10 were obtained by liquid–liquid diffusion from THF/ether and crystals of LFM-A11 were obtained by liquid–liquid diffusion from chloroform/diethyl ether.

Compound LFM-A1

Crystal data

$C_{11}H_9BrN_2O_2$
M_r = 281.11
Triclinic
$P\bar{1}$
a = 4.9906 (2) Å
b = 9.3735 (3) Å
c = 11.8869 (1) Å
α = 77.394 (2)°
β = 86.404 (2)°
γ = 88.065 (2)°
V = 541.47 (3) Å^3
Z = 2
D_x = 1.724 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 1833 reflections
θ = 1.76–25.01°
μ = 3.781 mm^{-1}
T = 173 (2) K
Plate
0.42 × 0.08 × 0.02 mm
Colorless

Data collection

Siemens SMART CCD area-detector diffractometer
ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996*a*)
T_{min} = 0.300, T_{max} = 0.955
2741 measured reflections
1836 independent reflections

1473 reflections with $I > 2\sigma(I)$
R_{int} = 0.032
θ_{max} = 25.01°
h = −5 → 5
k = −10 → 11
l = 0 → 14

Refinement

Refinement on F^2
$R(F)$ = 0.064
$wR(F^2)$ = 0.166
S = 1.043
1836 reflections
150 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.1065P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.010
$\Delta\rho_{max}$ = 1.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.99 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °) for LFM-A1*

Br4—C4	1.913 (6)	N11—C11	1.143 (8)
O7—C7	1.250 (7)	C7—C8	1.468 (9)
O9—C9	1.321 (7)	C8—C9	1.366 (9)
N1—C7	1.349 (8)	C8—C11	1.427 (8)
N1—C1	1.421 (8)	C9—C10	1.482 (9)
C7—N1—C1	127.5 (5)	C9—C8—C11	117.1 (6)
C6—C1—N1	124.2 (5)	C9—C8—C7	120.7 (5)
C2—C1—N1	116.6 (5)	C11—C8—C7	122.1 (5)
C3—C4—C5	121.2 (6)	O9—C9—C8	121.6 (6)
C3—C4—Br4	120.5 (5)	O9—C9—C10	114.1 (5)
O7—C7—N1	122.2 (6)	C8—C9—C10	124.3 (6)
O7—C7—C8	118.7 (5)	N11—C11—C8	178.5 (7)
N1—C7—C8	119.2 (5)		

Table 2. *Hydrogen-bonding geometry (Å, °) for LFM-A1*

D—H···A	D—H	H···A	D···A	D—H···A
O9—H9···O7	0.84	1.74	2.487 (6)	148
N1—H1···N11^{i}	0.89 (6)	2.20 (6)	3.079 (7)	170 (5)

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

Compound LFM-A7

Crystal data

$C_{11}H_9FN_2O_2$
M_r = 220.20
Monoclinic
$P2_1/c$
a = 8.9641 (8) Å
b = 14.1215 (12) Å
c = 8.3270 (7) Å
β = 101.023 (2)°
V = 1034.64 (15) Å^3
Z = 4
D_x = 1.414 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 2755 reflections
θ = 2.31–25.04°
μ = 0.111 mm^{-1}
T = 298 (2) K
Plate
0.50 × 0.35 × 0.15 mm
Colorless

Data collection

Siemens SMART CCD area-detector diffractometer
ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996*a*)
T_{min} = 0.947, T_{max} = 0.984
5017 measured reflections
1788 independent reflections

1319 reflections with $I > 2\sigma(I)$
R_{int} = 0.029
θ_{max} = 25.04°
h = −10 → 10
k = 0 → 16
l = 0 → 9

Refinement

Refinement on F^2
$R(F) = 0.056$
$wR(F^2) = 0.147$
$S = 1.202$
1788 reflections
148 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0645P)^2 + 0.1748P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.007$
$\Delta\rho_{max} = 0.36$ e Å^{-3}
$\Delta\rho_{min} = -0.27$ e Å^{-3}
Extinction correction: *SHELXTL-Plus* (Sheldrick, 1996*b*)
Extinction coefficient: 0.011 (3)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 3. *Selected geometric parameters (Å, °) for LFM-A7*

F2—C2	1.359 (3)	N11—C11	1.144 (3)
O9—C9	1.319 (3)	C7—C8	1.455 (3)
O7—C7	1.246 (3)	C8—C9	1.371 (3)
N1—C7	1.355 (3)	C8—C11	1.426 (4)
N1—C1	1.408 (3)	C9—C10	1.488 (3)
C7—N1—C1	128.8 (2)	C9—C8—C11	119.6 (2)
C2—C1—N1	117.7 (2)	C9—C8—C7	120.7 (2)
C6—C1—N1	125.1 (2)	C11—C8—C7	119.8 (2)
F2—C2—C3	119.6 (2)	O9—C9—C8	122.2 (2)
F2—C2—C1	117.0 (2)	O9—C9—C10	113.8 (2)
O7—C7—N1	121.8 (2)	C8—C9—C10	124.0 (2)
O7—C7—C8	120.9 (2)	N11—C11—C8	178.0 (3)
N1—C7—C8	117.3 (2)		

Table 4. *Hydrogen-bonding geometry (Å, °) for LFM-A7*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O9—H9···O7	0.82	1.81	2.540 (2)	147

Compound LFM-A9

Crystal data

$C_{11}H_9BrN_2O_2$
$M_r = 281.11$
Triclinic
$P\bar{1}$
$a = 5.2782$ (2) Å
$b = 10.2335$ (4) Å
$c = 11.5754$ (4) Å
$\alpha = 69.792$ (1)°
$\beta = 78.592$ (1)°
$\gamma = 75.837$ (1)°
$V = 564.49$ (4) Å^3
$Z = 2$
$D_x = 1.654$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 2560 reflections
$\theta = 1.89$–$25.04°$
$\mu = 3.627$ mm^{-1}
$T = 298$ (2) K
Sword
0.50 × 0.25 × 0.10 mm
Colorless

Data collection

Siemens SMART CCD area-detector diffractometer
ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996*a*)
$T_{min} = 0.264$, $T_{max} = 0.713$
3713 measured reflections
1926 independent reflections
1499 reflections with $I > 2\sigma(I)$
$R_{int} = 0.034$
$\theta_{max} = 25.04°$
$h = -6 \rightarrow 6$
$k = -11 \rightarrow 12$
$l = 0 \rightarrow 13$

Refinement

Refinement on F^2
$R(F) = 0.056$
$wR(F^2) = 0.156$
$S = 0.988$
1926 reflections
155 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.1095P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.006$
$\Delta\rho_{max} = 0.89$ e Å^{-3}
$\Delta\rho_{min} = -0.94$ e Å^{-3}
Extinction correction: *SHELXTL-Plus* (Sheldrick, 1996*b*)
Extinction coefficient: 0.005 (4)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 5. *Selected geometric parameters (Å, °) for LFM-A9*

Br3—C3	1.894 (4)	N11—C11	1.136 (5)
O7—C7	1.262 (4)	C7—C8	1.459 (6)
O9—C9	1.321 (5)	C8—C9	1.369 (6)
N1—C7	1.345 (5)	C8—C11	1.426 (5)
N1—C1	1.417 (5)	C9—C10	1.488 (6)
C7—N1—C1	129.2 (3)	C9—C8—C11	118.8 (4)
C2—C1—N1	117.2 (3)	C9—C8—C7	120.4 (3)
C6—C1—N1	123.4 (4)	C11—C8—C7	120.7 (3)
C2—C3—Br3	119.0 (3)	O9—C9—C8	121.8 (4)
C4—C3—Br3	119.4 (3)	O9—C9—C10	113.6 (4)
O7—C7—N1	122.1 (4)	C8—C9—C10	124.6 (4)
O7—C7—C8	119.3 (3)	N11—C11—C8	178.8 (5)
N1—C7—C8	118.6 (3)		

Table 6. *Hydrogen-bonding geometry (Å, °) for LFM-A9*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O9—H9···O7	0.93 (5)	1.63 (5)	2.491 (5)	153 (5)
O9—H9···O7^{i}	0.93 (5)	2.63 (5)	3.149 (4)	116 (4)
N1—H1···N11^{ii}	0.76 (5)	2.42 (5)	3.170 (5)	168 (4)

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

Compound LFM-A10

Crystal data

$C_{11}H_9ClN_2O_2$
$M_r = 236.65$
Triclinic
$P\bar{1}$
$a = 5.2955$ (4) Å
$b = 10.0638$ (7) Å
$c = 11.2503$ (8) Å
$\alpha = 103.951$ (2)°
$\beta = 102.516$ (1)°
$\gamma = 105.121$ (2)°
$V = 536.13$ (7) Å^3
$Z = 2$
$D_x = 1.466$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 2236 reflections
$\theta = 1.95$–$25.02°$
$\mu = 0.341$ mm^{-1}
$T = 173$ (2) K
Needle
0.45 × 0.06 × 0.04 mm
Colorless

Data collection

Siemens SMART CCD area-detector diffractometer
ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996*a*)
$T_{min} = 0.862$, $T_{max} = 0.987$
3410 measured reflections
1829 independent reflections
1415 reflections with $I > 2\sigma(I)$
$R_{int} = 0.031$
$\theta_{max} = 25.02°$
$h = -6 \rightarrow 6$
$k = -11 \rightarrow 11$
$l = 0 \rightarrow 13$

Refinement

Refinement on F^2
$R(F) = 0.051$
$wR(F^2) = 0.136$
$S = 1.024$
1829 reflections
154 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0809P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.003$
$\Delta\rho_{max} = 0.27$ e Å^{-3}
$\Delta\rho_{min} = -0.33$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 7. *Selected geometric parameters (Å, °) for LFM-A10*

Cl3—C3	1.746 (3)	N11—C11	1.146 (3)
O9—C9	1.318 (3)	C7—C8	1.468 (3)
O7—C7	1.251 (3)	C8—C9	1.382 (4)
N1—C7	1.355 (3)	C8—C11	1.425 (4)
N1—C1	1.421 (3)	C9—C10	1.482 (4)
C7—N1—C1	128.2 (2)	C9—C8—C11	118.6 (2)
C6—C1—N1	124.5 (2)	C9—C8—C7	120.3 (2)
C2—C1—N1	116.0 (2)	C11—C8—C7	121.1 (2)
C2—C3—Cl3	118.2 (2)	O9—C9—C8	121.2 (2)
C4—C3—Cl3	119.8 (2)	O9—C9—C10	114.4 (2)
O7—C7—N1	122.4 (2)	C8—C9—C10	124.4 (2)
O7—C7—C8	119.6 (2)	N11—C11—C8	179.0 (3)
N1—C7—C8	118.0 (2)		

Table 8. *Hydrogen-bonding geometry (Å, °) for LFM-A10*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O9—H9···O7	0.90 (4)	1.65 (4)	2.497 (3)	155 (4)
N1—H1···N11^i	0.88 (3)	2.27 (3)	3.131 (3)	166 (2)

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

Compound LFM-A11

Crystal data

$C_{11}H_9FN_2O_2$
$M_r = 220.20$
Monoclinic
$P2_1/c$
$a = 4.7724$ (1) Å
$b = 24.1536$ (1) Å
$c = 9.1565$ (2) Å
$\beta = 95.9370$ (1)°
$V = 1049.81$ (3) Å^3
$Z = 4$
$D_x = 1.393$ Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 4918 reflections
$\theta = 1.69$–$25.02°$
$\mu = 0.110$ mm^{-1}
$T = 298$ (2) K
Prism
0.50 × 0.45 × 0.40 mm
Colorless

Data collection

Siemens SMART CCD area-detector diffractometer
ω scans
Absorption correction: empirical (*SADABS*; Sheldrick, 1996*a*)
$T_{min} = 0.947$, $T_{max} = 0.957$
6832 measured reflections
1851 independent reflections
1394 reflections with $I > 2\sigma(I)$
$R_{int} = 0.030$
$\theta_{max} = 25.02°$
$h = -5 \rightarrow 5$
$k = 0 \rightarrow 28$
$l = 0 \rightarrow 10$

Refinement

Refinement on F^2
$R(F) = 0.053$
$wR(F^2) = 0.170$
$S = 1.070$
1851 reflections
154 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.1094P)^2 + 0.0458P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.005$
$\Delta\rho_{max} = 0.437$ e Å^{-3}
$\Delta\rho_{min} = -0.186$ e Å^{-3}
Extinction correction: *SHELXTL-Plus* (Sheldrick, 1996*b*)
Extinction coefficient: 0.020 (7)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 9. *Selected geometric parameters (Å, °) for LFM-A11*

F5—C5	1.355 (3)	N11—C11	1.144 (2)
O7—C7	1.249 (2)	C7—C8	1.470 (3)
O9—C9	1.315 (2)	C8—C9	1.372 (3)
N1—C7	1.350 (3)	C8—C11	1.424 (3)
N1—C1	1.414 (3)	C9—C10	1.483 (3)
C7—N1—C1	127.50 (17)	C9—C8—C11	118.11 (18)
C6—C1—N1	123.97 (18)	C9—C8—C7	120.21 (17)
C2—C1—N1	117.28 (18)	C11—C8—C7	121.66 (17)
F5—C5—C6	118.2 (2)	O9—C9—C8	121.59 (19)
F5—C5—C4	117.8 (2)	O9—C9—C10	114.05 (19)
O7—C7—N1	122.33 (19)	C8—C9—C10	124.36 (18)
O7—C7—C8	118.89 (17)	N11—C11—C8	179.6 (2)
N1—C7—C8	118.78 (17)		

Table 10. *Hydrogen-bonding geometry (Å, °) for LFM-A11*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O9—H9···O7	0.98 (3)	1.56 (3)	2.483 (2)	156 (2)
N1—H1···N11^i	0.87 (2)	2.30 (2)	3.134 (3)	163 (2)

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

The H atoms attached to N and O atoms were located from a difference map, and were refined isotropically (molecules LFM-A9, -A10, -A11), by using a riding model (LFM-A7) or a combination of both (-A1, riding H9, refining H1). All H atoms attached to C atoms were placed in ideal positions and refined using a riding model with aromatic C—H = 0.96 Å, methyl C—H = 0.98 Å, and with fixed isotropic displacement parameters equal to 1.2 (1.5 for methyl-H atoms) times the equivalent isotropic displacement parameter of the atom to which they were attached. The methyl groups were allowed to rotate about their local threefold axis during refinement.

For all compounds, data collection: *SMART* (Siemens, 1996*a*): cell refinement: *SAINT* (Siemens, 1996*b*); data reduction: *SAINT*; program used to solve structure: *SHELXTL-Plus* (Sheldrick, 1996*b*); program used to refine structure: *SHELXTL-Plus*; molecular graphics: *SHELXTL-Plus*; program used to prepare material for publication: *SHELXTL-Plus*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DA1089). Services for accessing these data are described at the back of the journal.

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Inhibitor of HIV-1 reverse transcriptase: *N'*-(5-bromo-2-pyridyl)-*N*-[2-(2,5-dimethoxyphenyl)ethyl]thiourea

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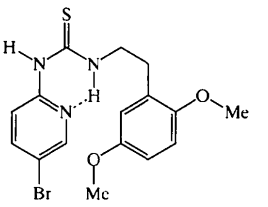
Abstract

The crystal structure of the title compound, $C_{16}H_{18}BrN_3O_2S$ (HI-236), a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase, revealed an intramolecular hydrogen bond between a thiourea N atom and the pyridyl-N atom [N—H···N = 2.671 (3) Å, graph-set motif $S_1^1(6)$] that imparts a more rigid conformation to the molecule. A second hydrogen bond between a thiourea N atom and the thiocarbonyl-S atom [N—H2···S = 3.403 (2) Å, graph-set motif $R_2^2(8)$] was observed between inversion-related molecules of HI-236. The first-level hydrogen-bond graph-set notation for HI-236 was determined to be $S_1^1(6)R_2^2(8)$.

Comment

We recently reported the anti-human immunodeficiency virus (HIV) activity of a thiourea derivative, *N'*-(5-bromo-2-pyridyl)-*N*-[2-(2,5-dimethoxyphenyl)-ethyl]thiourea (HI-236, wild type $HTLV_{IIIB}$ IC_{50}p24 $< 0.001\ \mu M$) (Mao *et al.*, 1999). The identification of HI-236 was aided by structure-based drug design methods which relied on the construction of a composite binding pocket to represent the available binding space in the non-nucleoside inhibitor (NNI or NNRTI) binding site of HIV reverse transcriptase (RT) (Mao *et al.*, 1998, 1999; Sudbeck *et al.*, 1998; Vig *et al.*, 1998*a*,*b*). HI-236 was highly effective against the multidrug-resistant HIV-1 strain RT-MDR (IC_{50} = 5 n*M*) which contains mutations at RT residues Val-74, Leu-41, Ala-106, and Tyr-215 (Mao *et al.*, 1999).



HI-236

The X-ray crystal structure of HI-236 (Fig. 1) showed that the molecule contains an intramolecular hydrogen bond between N3—H3*A* and N1 that locks the molecule into a more rigid conformation and imparts a more compact molecular shape. The presence of this hydrogen bond is consistent with modeling studies undertaken to predict how the inhibitor could bind to the NNI binding site of HIV RT. Modeling studies which docked the HI-236 molecule into the binding site of RT showed that the compact conformation resulting from the hydrogen bond would allow the molecule to easily fit into the NNI binding site (Mao *et al.*, 1999). An extended conformation resulting from a 180° rotation about the N2—C6 bond, however, would hinder the binding of HI-236 in the NNI binding site of RT. An approximation of the dihedral angle between the two aromatic ring planes in the crystal structure of HI-236 can be described by the N3—C7—C8—C9 dihedral angle which was observed to be 66°.

† On the Drug Discovery Program.