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N-(4-Methoxyphenyl)-*N*′-(5-nitro-1,3-thiazol-2-yl)urea

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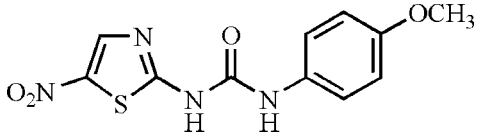
Key indicators: single-crystal X-ray study; T = 150 K; mean σ(C–C) = 0.003 Å; R factor = 0.050; wR factor = 0.145; data-to-parameter ratio = 14.9.

The title compound, $C_{11}H_{10}N_4O_4S$, is a derivative of *N*-(4-methoxybenzyl)-*N*′-(5-nitro-1,3-thiazol-2-yl)urea (AR-A014418), a known glycogen synthase kinase 3β (GSK-3β) inhibitor. All non-H atoms in the molecule are essentially coplanar, with an r.m.s. deviation of 0.045 Å and a maximum deviation of 0.115 (2) Å for the carbonyl O atom. In the crystal structure, molecules are linked *via* N—H···O hydrogen bonds into one-dimensional chains along [101].

Related literature

For background information on the preparation and activity of AR-A014418, see: Bhat *et al.* (2003); Inestrosa *et al.* (2006). For the radiolabelling procedure of AR-A014418 with carbon-11, see: Vasdev *et al.* (2005). For the crystal structure of AR-A014418, see: Vasdev *et al.* (2007).



Experimental

Crystal data

$C_{11}H_{10}N_4O_4S$
M_r = 294.29
Monoclinic, $P2_1/n$
a = 6.8740 (3) Å
b = 12.5840 (7) Å
c = 14.6861 (5) Å
β = 101.622 (3)°
V = 1244.34 (10) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.28 mm^{-1}
T = 150 K
0.28 × 0.24 × 0.22 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*SORTAV*; Blessing, 1995)
T_{min} = 0.718, T_{max} = 0.948
8106 measured reflections
2825 independent reflections
1979 reflections with $I > 2\sigma(I)$
R_{int} = 0.053

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.145
S = 1.07
2825 reflections
190 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.51 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2N···O4^{i}	0.86 (3)	1.97 (3)	2.817 (3)	168 (3)
N3—H3N···O3^{i}	0.87 (3)	2.30 (3)	3.168 (2)	174 (2)

Symmetry code: (i) $x+\frac{1}{2}, -y+\frac{3}{2}, z+\frac{1}{2}$.

Data collection: *COLLECT* (Nonius, 2002); cell refinement: *DENZO-SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO-SMN*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXTL* (Sheldrick, 2008).

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: SU2205).

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supporting information

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N-(4-Methoxyphenyl)-*N*′-(5-nitro-1,3-thiazol-2-yl)urea

Alan J. Lough, Justin W. Hicks, John F. Valliant, Alan A. Wilson and Neil Vasdev

S1. Comment

N-(4-methoxybenzyl)-*N*′--(5-nitro-1,3-thiazol-2-yl)urea (AR-A014418, Bhat *et al.*, 2003) is a selective glycogen synthase kinase-3*β* (GSK-3*β*) inhibitor (Inestrosa *et al.*, 2006). Our initial work on AR-A014418 was to radiolabel this compound with carbon-11 at the methoxy position for positron emission tomography (PET) imaging of brain pathologies (Vasdev *et al.*, 2005). To our surprise, [^{11}C]-AR-A014418 had insignificant brain uptake in rodents despite literature precedence (Bhat *et al.*, 2003). To further understand the role of AR-A014418 and GSK-3*β*, a single-crystal X-ray structure of AR-A014418 was obtained (Vasdev *et al.*, 2007) and overlaid with the structural determination of the co-crystal of GSK-3*β* and AR-A014418 (Bhat *et al.*, 2003). For that structure, the benyzl ring was bent out of the binding pocket of the kinase. We now endeavour to explore the binding affinity of an analogous molecule which has reduced flexibility (*i.e.* the benzyl group is replaced with a phenyl group). Biological assays are underway to determine whether the increased rigidity decreases the binding affinity for GSK-3*β*. Data from these biological studies as well as the crystal structure determinations will assist in designing future ligands for imaging GSK-3*β* with PET.

The molecular structure of the title compound is shown in Fig. 1. All non-hydrogen atoms in the molecule are essentially co-planar with a r.m.s. deviation of 0.045 Å and a maximum deviation of 0.115 (2)Å for atom O1.

In the crystal symmetry related molecules are linked via N—H···O hydrogen bonds, to form one-dimensional chains propagating along [101] (Table 1, Fig. 2).

S2. Experimental

The title compound, $C_{11}H_{10}N_4O_4S$, was obtained by heating equimolar amounts of 2-amino-5-nitrothiazole (0.65 mmol) and 4-methoxyphenyl isocyanate (0.65 mmol) in dry *N*,*N*-dimethyl formamide (5 ml) in a Biotage Initiator Microwave for 1 h at 403 K under nitrogen. Upon cooling, the reaction mixture was partitioned between ethyl acetate and water and the aqueous layer was further extracted with more ethyl acetate (15 ml). The combined organic layers were washed with brine (3 × 30 ml), dried ($MgSO_4$), filtered, and concentrated prior to purification by silica chromatography (Biotage Isolera Flash system, 98% dichloromethane and 2% methanol). $C_{11}H_{10}N_4O_4S$ was obtained as a red solid in 39% yield (not optimized). X-ray quality crystals were obtained by slow evaporation of a solution of the title compound in ethyl acetate/hexane (50/50) containing 5% ethanol. ^{1}H NMR (DMSO d_6, 400 MHz) δ 11.75 (s, 1 H, NH), 9.28 (s, 1H, NH), 8.53 (s, 1H, thiazole), 7.41 (d, J = 8.9 Hz, 2H, Ar), 6.91 (d, J = 8.9 Hz, 2H, Ar), 3.73 (s, 3H, CH_3). HRMS (ESI) m/z calcd for $C_{11}H_{11}N_4O_4S$, 295.0495; found 295.0483 (M^++H), m.p. = 454–456 K.

S3. Refinement

H atoms bonded to C atoms were placed in calculated positions with C—H = 0.95Å or 0.98Å for methyl groups and included in the refinement with U_{iso}(H) = 1.2U_{eq}(C) or 1.2U_{eq}(C_{methyl}). H atoms bonded to N atoms were refined independently with isotropic displacement parameters.

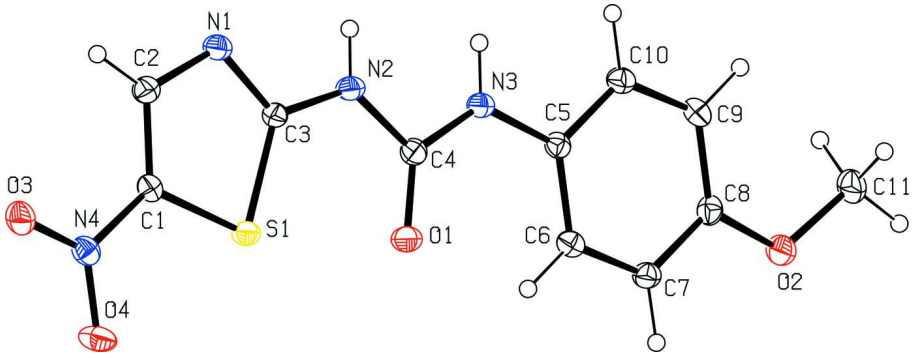

Figure 1

The molecular structure of the title compound with probability ellipsoids drawn at the 30% level.

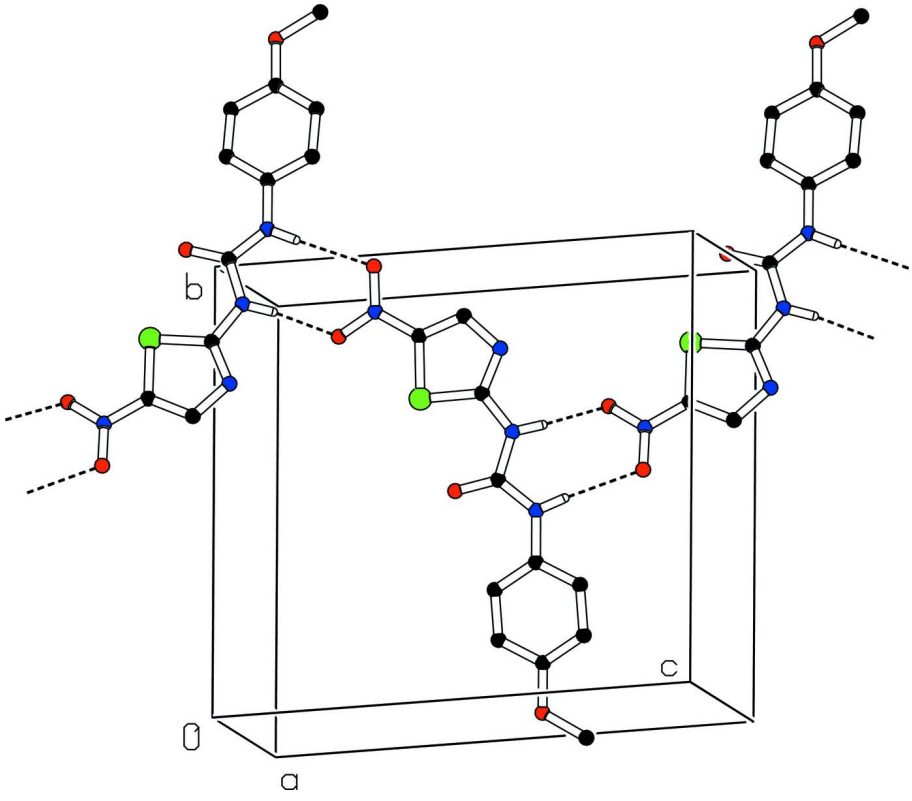

Figure 2

Part of the crystal structure of the title compound with hydrogen bonds drawn as dashed lines.

i>N-(4-Methoxyphenyl)-N′-(5-nitro-1,3-thiazol-2-yl)urea

Crystal data

$C_{11}H_{10}N_4O_4S$
$M_r = 294.29$
Monoclinic, $P2_1/n$
Hall symbol: -P 2yn
$a = 6.8740\ (3)$ Å
$b = 12.5840\ (7)$ Å
$c = 14.6861\ (5)$ Å
$\beta = 101.622\ (3)°$
$V = 1244.34\ (10)$ Å^3
$Z = 4$
$F(000) = 608$
$D_x = 1.571$ Mg m^{-3}
Melting point: 454 K
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 3592 reflections
$\theta = 2.6–27.5°$

μ = 0.28 mm^{-1}
T = 150 K

Block, red
0.28 × 0.24 × 0.22 mm

Data collection

Nonius KappaCCD diffractometer
Radiation source: fine-focus sealed tube
Graphite monochromator
Detector resolution: 9 pixels mm^{-1}
φ scans and ω scans with κ offsets
Absorption correction: multi-scan (*SORTAV*; Blessing, 1995)
T_{min} = 0.718, T_{max} = 0.948

8106 measured reflections
2825 independent reflections
1979 reflections with $I > 2\sigma(I)$
R_{int} = 0.053
θ_{max} = 27.5°, θ_{min} = 2.8°
h = −8→8
k = −14→16
l = −17→19

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.145
S = 1.07
2825 reflections
190 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 atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0755P)^2 + 0.3053P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.51 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 expr ession 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}
S1	0.12900 (8)	0.68571 (5)	0.41433 (3)	0.0246 (2)
O1	0.2254 (2)	0.48461 (14)	0.47569 (10)	0.0306 (4)
O2	0.5006 (3)	0.00530 (13)	0.62455 (11)	0.0340 (4)
O3	−0.0126 (3)	0.97318 (14)	0.33409 (11)	0.0347 (4)
O4	0.0063 (3)	0.82488 (15)	0.25900 (11)	0.0367 (5)
N1	0.2026 (3)	0.79137 (16)	0.57084 (12)	0.0277 (5)
N2	0.2668 (3)	0.61085 (16)	0.58904 (13)	0.0268 (5)
H2N	0.327 (4)	0.627 (2)	0.6449 (19)	0.042 (8)*
N3	0.3514 (3)	0.44014 (16)	0.62860 (13)	0.0253 (5)
H3N	0.380 (4)	0.466 (2)	0.6845 (19)	0.037 (8)*
N4	0.0257 (3)	0.87648 (16)	0.33258 (13)	0.0270 (5)
C1	0.0930 (3)	0.82155 (19)	0.41566 (14)	0.0232 (5)

C2	0.1399 (3)	0.8632 (2)	0.50308 (15)	0.0267 (5)
H2A	0.1292	0.9369	0.5153	0.032*
C3	0.2033 (3)	0.69504 (18)	0.53334 (15)	0.0224 (5)
C4	0.2790 (3)	0.50759 (19)	0.55815 (15)	0.0243 (5)
C5	0.3832 (3)	0.32879 (18)	0.62462 (15)	0.0223 (5)
C6	0.3583 (3)	0.2717 (2)	0.54193 (15)	0.0245 (5)
H6A	0.3153	0.3064	0.4839	0.029*
C7	0.3970 (3)	0.1640 (2)	0.54544 (15)	0.0258 (5)
H7A	0.3791	0.1245	0.4892	0.031*
C8	0.4620 (3)	0.11186 (19)	0.63008 (15)	0.0253 (5)
C9	0.4842 (4)	0.1688 (2)	0.71214 (16)	0.0281 (6)
H9A	0.5265	0.1342	0.7702	0.034*
C10	0.4439 (4)	0.2773 (2)	0.70889 (16)	0.0277 (5)
H10A	0.4583	0.3164	0.7651	0.033*
C11	0.5519 (4)	−0.0525 (2)	0.70992 (17)	0.0360 (6)
H11A	0.5715	−0.1276	0.6965	0.054*
H11B	0.4446	−0.0460	0.7445	0.054*
H11C	0.6749	−0.0236	0.7472	0.054*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0269 (3)	0.0260 (4)	0.0198 (3)	0.0001 (2)	0.0024 (2)	−0.0017 (2)
O1	0.0405 (10)	0.0273 (10)	0.0225 (9)	0.0016 (8)	0.0028 (7)	−0.0024 (7)
O2	0.0482 (11)	0.0242 (9)	0.0304 (9)	0.0047 (8)	0.0097 (8)	0.0018 (7)
O3	0.0418 (11)	0.0279 (10)	0.0335 (10)	0.0046 (8)	0.0057 (8)	0.0080 (8)
O4	0.0450 (11)	0.0437 (12)	0.0193 (8)	0.0073 (9)	0.0015 (7)	−0.0019 (8)
N1	0.0368 (12)	0.0251 (11)	0.0214 (10)	0.0020 (9)	0.0059 (8)	−0.0009 (8)
N2	0.0352 (12)	0.0240 (11)	0.0205 (10)	0.0011 (9)	0.0040 (8)	−0.0033 (9)
N3	0.0315 (11)	0.0238 (11)	0.0204 (10)	0.0003 (9)	0.0048 (8)	−0.0014 (9)
N4	0.0239 (11)	0.0318 (12)	0.0250 (10)	0.0008 (9)	0.0041 (8)	0.0044 (9)
C1	0.0226 (12)	0.0249 (13)	0.0223 (11)	0.0005 (10)	0.0049 (9)	0.0036 (10)
C2	0.0310 (13)	0.0242 (13)	0.0246 (12)	0.0003 (10)	0.0046 (9)	−0.0005 (10)
C3	0.0241 (12)	0.0231 (13)	0.0206 (11)	−0.0022 (9)	0.0063 (8)	−0.0015 (9)
C4	0.0243 (12)	0.0251 (13)	0.0247 (12)	−0.0007 (10)	0.0079 (9)	−0.0009 (10)
C5	0.0206 (11)	0.0247 (13)	0.0226 (11)	−0.0003 (9)	0.0070 (8)	0.0002 (10)
C6	0.0233 (12)	0.0285 (14)	0.0219 (11)	0.0006 (10)	0.0051 (9)	0.0007 (10)
C7	0.0253 (12)	0.0293 (14)	0.0233 (11)	−0.0025 (10)	0.0063 (9)	−0.0030 (10)
C8	0.0257 (12)	0.0214 (12)	0.0309 (12)	0.0006 (10)	0.0105 (9)	0.0002 (10)
C9	0.0310 (13)	0.0314 (14)	0.0231 (11)	0.0006 (11)	0.0087 (9)	0.0044 (10)
C10	0.0338 (14)	0.0273 (13)	0.0235 (12)	0.0006 (11)	0.0097 (10)	−0.0020 (10)
C11	0.0477 (16)	0.0261 (14)	0.0345 (14)	0.0045 (12)	0.0089 (11)	0.0074 (11)

Geometric parameters (Å, º)

S1—C3	1.723 (2)	C1—C2	1.364 (3)
S1—C1	1.728 (2)	C2—H2A	0.9500
O1—C4	1.227 (3)	C5—C10	1.385 (3)

O2—C8	1.373 (3)	C5—C6	1.391 (3)
O2—C11	1.431 (3)	C6—C7	1.381 (3)
O3—N4	1.246 (3)	C6—H6A	0.9500
O4—N4	1.245 (2)	C7—C8	1.397 (3)
N1—C3	1.332 (3)	C7—H7A	0.9500
N1—C2	1.349 (3)	C8—C9	1.384 (3)
N2—C3	1.356 (3)	C9—C10	1.391 (3)
N2—C4	1.384 (3)	C9—H9A	0.9500
N2—H2N	0.86 (3)	C10—H10A	0.9500
N3—C4	1.353 (3)	C11—H11A	0.9800
N3—C5	1.421 (3)	C11—H11B	0.9800
N3—H3N	0.87 (3)	C11—H11C	0.9800
N4—C1	1.398 (3)		

C3—S1—C1	86.27 (11)	C10—C5—C6	120.0 (2)
C8—O2—C11	117.49 (19)	C10—C5—N3	116.5 (2)
C3—N1—C2	109.40 (18)	C6—C5—N3	123.5 (2)
C3—N2—C4	124.68 (19)	C7—C6—C5	119.0 (2)
C3—N2—H2N	115.2 (19)	C7—C6—H6A	120.5
C4—N2—H2N	118.6 (19)	C5—C6—H6A	120.5
C4—N3—C5	128.5 (2)	C6—C7—C8	121.3 (2)
C4—N3—H3N	117.8 (18)	C6—C7—H7A	119.4
C5—N3—H3N	113.6 (18)	C8—C7—H7A	119.4
O4—N4—O3	122.61 (19)	O2—C8—C9	124.7 (2)
O4—N4—C1	117.3 (2)	O2—C8—C7	115.9 (2)
O3—N4—C1	120.09 (19)	C9—C8—C7	119.4 (2)
C2—C1—N4	127.3 (2)	C8—C9—C10	119.5 (2)
C2—C1—S1	112.58 (17)	C8—C9—H9A	120.3
N4—C1—S1	120.16 (17)	C10—C9—H9A	120.3
N1—C2—C1	114.6 (2)	C5—C10—C9	120.8 (2)
N1—C2—H2A	122.7	C5—C10—H10A	119.6
C1—C2—H2A	122.7	C9—C10—H10A	119.6
N1—C3—N2	119.29 (19)	O2—C11—H11A	109.5
N1—C3—S1	117.15 (17)	O2—C11—H11B	109.5
N2—C3—S1	123.53 (17)	H11A—C11—H11B	109.5
O1—C4—N3	126.7 (2)	O2—C11—H11C	109.5
O1—C4—N2	121.2 (2)	H11A—C11—H11C	109.5
N3—C4—N2	112.05 (19)	H11B—C11—H11C	109.5

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2*N*···O4^{i}	0.86 (3)	1.97 (3)	2.817 (3)	168 (3)
N3—H3*N*···O3^{i}	0.87 (3)	2.30 (3)	3.168 (2)	174 (2)

Symmetry code: (i) $x+1/2, -y+3/2, z+1/2$.