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Methyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

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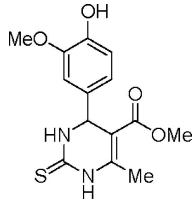
Key indicators: single-crystal X-ray study; T = 294 K; mean σ(C–C) = 0.004 Å; R factor = 0.043; wR factor = 0.115; data-to-parameter ratio = 12.5.

The title compound, $C_{14}H_{16}N_2O_4S$, was synthesized by the reaction of 4-hydroxy-3-methoxybenzaldehyde, thiourea and methyl 3-oxobutanoate in ethanol under reflux. The crystal structure is stabilized mainly through intermolecular N—H···S and O—H···O hydrogen bonds. The tetrahydropyrimidin-2-one ring is twisted.

Related literature

For related literature, see: Atwal *et al.* (1989, 1991); Kappe (1993); Kappe & Fabian (1997); Rovnyak *et al.* (1992).



Experimental

Crystal data

$C_{14}H_{16}N_2O_4S$
M_r = 308.35
Triclinic, $P\overline{1}$
a = 7.267 (3) Å
b = 8.863 (3) Å
c = 12.002 (5) Å
α = 103.234 (7)°
β = 90.318 (7)°
γ = 106.710 (6)°
V = 718.6 (5) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.24 mm^{-1}
T = 294 (2) K
0.24 × 0.20 × 0.18 mm

Data collection

Bruker SMART CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 1997)
T_{min} = 0.944, T_{max} = 0.958
3781 measured reflections
2531 independent reflections
1753 reflections with $I > 2\sigma(I)$
R_{int} = 0.025

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.115
S = 1.03
2531 reflections
202 parameters
2 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}

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

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···O2^{i}	0.82	2.14	2.905 (3)	155
O3—H3···O4	0.82	2.16	2.614 (3)	115
N1—H1···O1^{ii}	0.891 (10)	2.166 (12)	3.039 (3)	166 (2)
N2—H2···S1^{iii}	0.894 (10)	2.435 (12)	3.312 (2)	167 (2)

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

Data collection: *SMART* (Bruker, 1997); cell refinement: *SAINT* (Bruker, 1997); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Bruker, 1997); software used to prepare material for publication: *SHELXTL*.

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: HG2303).

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supplementary materials

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Methyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Z.-H. Shang and J. Ha

Comment

Dihydropyrimidinones (DHPMs) and their derivatives exhibit a wide range of biological activities such as antibacterial, antiviral, antitumor and anti-inflamatory actions (Kappe, 1993). These compounds also exhibit pharmacological activities as calcium channel blockers, antihypertensive agents, and neuropeptide Y(NPY) antagonists (Atwal *et al.*, 1989, 1991; Rovnyak *et al.*, 1992; Kappe & Fabian, 1997). The structure of the title compound (Fig. 1.) was synthesized by the reaction of 4-hydroxy-3-methoxybenzaldehyde, thiourea and methyl 3-oxobutanoate in ethanol under reflux. The tetrahydropyrimidin-2-one ring is twisted [C3—N2—C4—C5= 35.0 (3) °]; the phenyl ring is almost perpendicular to the tetrahydropyrimidin-2-one ring [C3—N2—C4—C8=-90.7 (3)° and C8—C4—C5—C2=98.9 (3)°]. The crystal structure is stabilized mainly through intermolecular N—H···S and O—H···O hydrogen bonds.

Experimental

A solution of methyl 3-oxobutanoate (1.74 g, 15 mmol), 4-hydroxy-3-methoxybenzaldehyde (1.52 g, 10.0 mmol) and thiourea (0.76 g, 10 mmol) in ethanol (10 ml) was heated under reflux in the presence of a catalytic amount of HCl for 5 h. The reaction mixture was cooled and filtered. the product was recrystallized from ethanol to afford the pure product. The title product was dissolved in 100 ml absolute ethanol and crystals suitable for X-ray analysis were grown by slow evaporation of the absolute ethanol solution at room temperature over a period of 15 d.

Refinement

Carbon-bound H atoms were positioned geometrically, with C—H =0.93–0.96 Å, and refined in a riding model, with U_{iso}(H)= 1.2Ueq(carrier). The positional parameters of the nitrogen-bound H atoms were refined freely, with U_{iso}(H)=1.2Ueq(N).

Figures

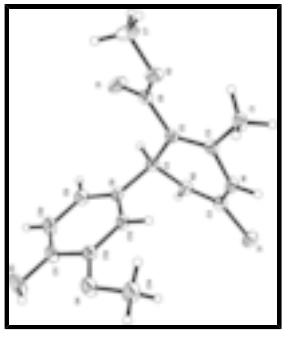


Fig. 1. The molecular structure of (I), drawn with 30% probability ellipsoids.

Fig. 2. The formation of the title compound.

Methyl 4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-thioxo- 1,2,3,4-tetrahydropyrimidine-5-carboxylate

Crystal data

$C_{14}H_{16}N_2O_4S$	$Z = 2$
$M_r = 308.35$	$F_{000} = 324$
Triclinic, $P\overline{1}$	$D_x = 1.425$ Mg m^{-3}
Hall symbol: -P 1	Melting point: 235-236 K
$a = 7.267$ (3) Å	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
$b = 8.863$ (3) Å	Cell parameters from 1119 reflections
$c = 12.002$ (5) Å	$\theta = 2.9$–25.9º
$\alpha = 103.234$ (7)º	$\mu = 0.24$ mm^{-1}
$\beta = 90.318$ (7)º	$T = 294$ (2) K
$\gamma = 106.710$ (6)º	Prism, colourless
$V = 718.6$ (5) Å^3	0.24 × 0.20 × 0.18 mm

Data collection

Bruker SMART CCD area-detector diffractometer	2531 independent reflections
Radiation source: fine-focus sealed tube	1753 reflections with $I > 2\sigma(I)$
Monochromator: graphite	$R_{int} = 0.025$
$T = 294$(2) K	$\theta_{max} = 25.0$º
φ and ω scans	$\theta_{min} = 1.8$º
Absorption correction: multi-scan (SADABS; Bruker, 1997)	$h = -8 \rightarrow 8$
$T_{min} = 0.944$, $T_{max} = 0.958$	$k = -10 \rightarrow 10$
3781 measured reflections	$l = -14 \rightarrow 7$

Refinement

Refinement on F^2	Secondary atom site location: difference Fourier map
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.043$	H atoms treated by a mixture of independent and constrained refinement
$wR(F^2) = 0.115$	$w = 1/[\sigma^2(F_o^2) + (0.0524P)^2 + 0.1382P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.03$	$(\Delta/\sigma)_{max} = 0.001$
2531 reflections	$\Delta\rho_{max} = 0.21$ e Å^{-3}
202 parameters	$\Delta\rho_{min} = -0.25$ e Å^{-3}
2 restraints	Extinction correction: none

Primary atom site location: structure-invariant direct methods

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 $F^2 > 2\text{sigma}(F^2)$ 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	0.31510 (9)	0.62332 (8)	0.54227 (6)	0.0388 (2)
O1	−0.2713 (3)	1.0669 (2)	0.66422 (19)	0.0483 (6)
O2	−0.0006 (2)	1.26508 (18)	0.72514 (16)	0.0363 (5)
O3	−0.2544 (3)	0.6472 (3)	1.06798 (17)	0.0574 (6)
H3	−0.1590	0.6879	1.1137	0.086*
O4	0.0976 (2)	0.8131 (2)	1.04330 (16)	0.0443 (5)
N1	0.2938 (3)	0.9175 (2)	0.63172 (19)	0.0328 (5)
N2	0.0090 (3)	0.7232 (2)	0.58519 (18)	0.0297 (5)
C1	0.3447 (4)	1.2034 (3)	0.6602 (3)	0.0434 (7)
H1A	0.2761	1.2743	0.6432	0.065*
H1B	0.4397	1.1945	0.6058	0.065*
H1C	0.4071	1.2469	0.7363	0.065*
C2	0.2072 (3)	1.0404 (3)	0.6530 (2)	0.0294 (6)
C3	0.1972 (3)	0.7589 (3)	0.5887 (2)	0.0296 (6)
C4	−0.0958 (3)	0.8260 (3)	0.6518 (2)	0.0275 (6)
H4	−0.2191	0.8051	0.6087	0.033*
C5	0.0173 (3)	1.0000 (3)	0.6617 (2)	0.0264 (6)
C6	−0.0997 (4)	1.1106 (3)	0.6815 (2)	0.0305 (6)
C7	−0.1091 (4)	1.3800 (3)	0.7458 (3)	0.0521 (8)
H7A	−0.1830	1.3699	0.6765	0.078*
H7B	−0.0224	1.4880	0.7697	0.078*
H7C	−0.1944	1.3587	0.8048	0.078*
C8	−0.1382 (3)	0.7839 (3)	0.7652 (2)	0.0261 (6)
C9	−0.3190 (4)	0.6940 (3)	0.7815 (2)	0.0346 (6)
H9	−0.4169	0.6633	0.7233	0.042*
C10	−0.3575 (4)	0.6485 (3)	0.8831 (2)	0.0405 (7)
H10	−0.4811	0.5878	0.8935	0.049*
C11	−0.2150 (4)	0.6924 (3)	0.9683 (2)	0.0354 (6)
C12	−0.0310 (3)	0.7810 (3)	0.9522 (2)	0.0304 (6)
C13	0.0065 (3)	0.8277 (3)	0.8523 (2)	0.0290 (6)
H13	0.1298	0.8892	0.8425	0.035*

C14	0.2913 (4)	0.8916 (4)	1.0324 (3)	0.0513 (8)
H14A	0.3376	0.8273	0.9697	0.077*
H14B	0.3663	0.9054	1.1021	0.077*
H14C	0.3026	0.9959	1.0179	0.077*
H1	0.4218 (15)	0.947 (3)	0.632 (2)	0.037 (7)*
H2	−0.066 (3)	0.6219 (16)	0.556 (2)	0.044 (8)*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0328 (4)	0.0352 (4)	0.0451 (5)	0.0123 (3)	0.0001 (3)	0.0002 (3)
O1	0.0286 (11)	0.0344 (10)	0.0798 (16)	0.0103 (8)	−0.0030 (10)	0.0086 (10)
O2	0.0356 (10)	0.0243 (9)	0.0473 (12)	0.0085 (8)	−0.0015 (9)	0.0056 (8)
O3	0.0382 (12)	0.0775 (15)	0.0423 (13)	−0.0137 (11)	0.0001 (10)	0.0260 (12)
O4	0.0270 (10)	0.0600 (12)	0.0381 (12)	−0.0040 (9)	−0.0035 (9)	0.0181 (10)
N1	0.0205 (11)	0.0300 (11)	0.0424 (14)	0.0033 (9)	0.0021 (10)	0.0036 (10)
N2	0.0245 (11)	0.0242 (11)	0.0342 (13)	0.0036 (9)	0.0008 (9)	−0.0007 (9)
C1	0.0324 (15)	0.0310 (14)	0.062 (2)	0.0009 (12)	0.0139 (14)	0.0130 (14)
C2	0.0298 (14)	0.0250 (13)	0.0304 (15)	0.0045 (11)	0.0035 (11)	0.0056 (11)
C3	0.0257 (13)	0.0318 (14)	0.0278 (15)	0.0056 (11)	0.0000 (11)	0.0041 (11)
C4	0.0220 (12)	0.0249 (12)	0.0321 (15)	0.0042 (10)	−0.0023 (11)	0.0040 (11)
C5	0.0261 (13)	0.0226 (12)	0.0286 (14)	0.0044 (10)	0.0005 (11)	0.0063 (10)
C6	0.0308 (15)	0.0283 (13)	0.0318 (15)	0.0061 (11)	0.0012 (12)	0.0094 (11)
C7	0.065 (2)	0.0315 (15)	0.062 (2)	0.0245 (15)	−0.0072 (17)	0.0028 (15)
C8	0.0214 (12)	0.0202 (12)	0.0342 (15)	0.0043 (10)	0.0033 (11)	0.0036 (11)
C9	0.0252 (13)	0.0346 (14)	0.0378 (16)	0.0017 (11)	−0.0037 (12)	0.0057 (12)
C10	0.0237 (14)	0.0418 (15)	0.0469 (18)	−0.0062 (12)	0.0062 (13)	0.0127 (13)
C11	0.0301 (14)	0.0355 (14)	0.0340 (16)	−0.0026 (12)	0.0047 (13)	0.0111 (12)
C12	0.0247 (13)	0.0269 (13)	0.0352 (16)	0.0021 (10)	0.0004 (12)	0.0064 (11)
C13	0.0210 (12)	0.0254 (13)	0.0370 (16)	0.0007 (10)	0.0050 (11)	0.0084 (11)
C14	0.0249 (15)	0.070 (2)	0.052 (2)	0.0020 (14)	−0.0022 (14)	0.0169 (17)

Geometric parameters (Å, °)

S1—C3	1.667 (3)	C4—C5	1.501 (3)
O1—C6	1.196 (3)	C4—C8	1.503 (4)
O2—C6	1.329 (3)	C4—H4	0.9800
O2—C7	1.438 (3)	C5—C6	1.454 (3)
O3—C11	1.353 (3)	C7—H7A	0.9600
O3—H3	0.8200	C7—H7B	0.9600
O4—C12	1.358 (3)	C7—H7C	0.9600
O4—C14	1.401 (3)	C8—C9	1.368 (3)
N1—C3	1.353 (3)	C8—C13	1.384 (3)
N1—C2	1.384 (3)	C9—C10	1.376 (4)
N1—H1	0.891 (10)	C9—H9	0.9300
N2—C3	1.310 (3)	C10—C11	1.359 (4)
N2—C4	1.457 (3)	C10—H10	0.9300
N2—H2	0.894 (10)	C11—C12	1.382 (3)
C1—C2	1.485 (3)	C12—C13	1.359 (4)

C1—H1A	0.9600	C13—H13	0.9300
C1—H1B	0.9600	C14—H14A	0.9600
C1—H1C	0.9600	C14—H14B	0.9600
C2—C5	1.334 (3)	C14—H14C	0.9600
C6—O2—C7	116.6 (2)	O2—C6—C5	114.3 (2)
C11—O3—H3	109.5	O2—C7—H7A	109.5
C12—O4—C14	118.0 (2)	O2—C7—H7B	109.5
C3—N1—C2	123.9 (2)	H7A—C7—H7B	109.5
C3—N1—H1	117.5 (16)	O2—C7—H7C	109.5
C2—N1—H1	117.1 (16)	H7A—C7—H7C	109.5
C3—N2—C4	124.5 (2)	H7B—C7—H7C	109.5
C3—N2—H2	121.0 (17)	C9—C8—C13	119.0 (2)
C4—N2—H2	112.6 (18)	C9—C8—C4	120.1 (2)
C2—C1—H1A	109.5	C13—C8—C4	120.8 (2)
C2—C1—H1B	109.5	C8—C9—C10	120.7 (2)
H1A—C1—H1B	109.5	C8—C9—H9	119.7
C2—C1—H1C	109.5	C10—C9—H9	119.6
H1A—C1—H1C	109.5	C11—C10—C9	119.9 (2)
H1B—C1—H1C	109.5	C11—C10—H10	120.0
C5—C2—N1	118.1 (2)	C9—C10—H10	120.0
C5—C2—C1	128.7 (2)	O3—C11—C10	119.5 (2)
N1—C2—C1	113.2 (2)	O3—C11—C12	120.7 (2)
N2—C3—N1	115.2 (2)	C10—C11—C12	119.9 (3)
N2—C3—S1	123.90 (19)	O4—C12—C13	126.3 (2)
N1—C3—S1	120.90 (18)	O4—C12—C11	113.5 (2)
N2—C4—C5	108.29 (19)	C13—C12—C11	120.2 (2)
N2—C4—C8	110.69 (19)	C12—C13—C8	120.3 (2)
C5—C4—C8	113.99 (19)	C12—C13—H13	119.8
N2—C4—H4	107.9	C8—C13—H13	119.8
C5—C4—H4	107.9	O4—C14—H14A	109.5
C8—C4—H4	107.9	O4—C14—H14B	109.5
C2—C5—C6	126.2 (2)	H14A—C14—H14B	109.5
C2—C5—C4	120.1 (2)	O4—C14—H14C	109.5
C6—C5—C4	113.7 (2)	H14A—C14—H14C	109.5
O1—C6—O2	122.3 (2)	H14B—C14—H14C	109.5
O1—C6—C5	123.3 (2)		
C3—N1—C2—C5	18.8 (4)	C4—C5—C6—O2	160.2 (2)
C3—N1—C2—C1	−159.8 (2)	N2—C4—C8—C9	−102.9 (2)
C4—N2—C3—N1	−18.7 (4)	C5—C4—C8—C9	134.8 (2)
C4—N2—C3—S1	162.42 (19)	N2—C4—C8—C13	73.6 (3)
C2—N1—C3—N2	−10.7 (4)	C5—C4—C8—C13	−48.7 (3)
C2—N1—C3—S1	168.2 (2)	C13—C8—C9—C10	0.5 (4)
C3—N2—C4—C5	35.0 (3)	C4—C8—C9—C10	177.1 (2)
C3—N2—C4—C8	−90.7 (3)	C8—C9—C10—C11	−0.3 (4)
N1—C2—C5—C6	−178.8 (2)	C9—C10—C11—O3	179.9 (2)
C1—C2—C5—C6	−0.4 (5)	C9—C10—C11—C12	−0.7 (4)
N1—C2—C5—C4	1.7 (4)	C14—O4—C12—C13	−4.9 (4)
C1—C2—C5—C4	−180.0 (3)	C14—O4—C12—C11	175.3 (2)

N2—C4—C5—C2	−24.8 (3)	O3—C11—C12—O4	0.7 (4)
C8—C4—C5—C2	98.9 (3)	C10—C11—C12—O4	−178.6 (2)
N2—C4—C5—C6	155.6 (2)	O3—C11—C12—C13	−179.1 (2)
C8—C4—C5—C6	−80.8 (3)	C10—C11—C12—C13	1.6 (4)
C7—O2—C6—O1	−3.0 (4)	O4—C12—C13—C8	178.8 (2)
C7—O2—C6—C5	179.6 (2)	C11—C12—C13—C8	−1.3 (4)
C2—C5—C6—O1	163.2 (3)	C9—C8—C13—C12	0.3 (3)
C4—C5—C6—O1	−17.2 (4)	C4—C8—C13—C12	−176.2 (2)
C2—C5—C6—O2	−19.4 (4)		

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O3—H3···O2^{i}	0.82	2.14	2.905 (3)	155
O3—H3···O4	0.82	2.16	2.614 (3)	115
N1—H1···O1^{ii}	0.891 (10)	2.166 (12)	3.039 (3)	166 (2)
N2—H2···S1^{iii}	0.894 (10)	2.435 (12)	3.312 (2)	167 (2)

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

Fig. 1

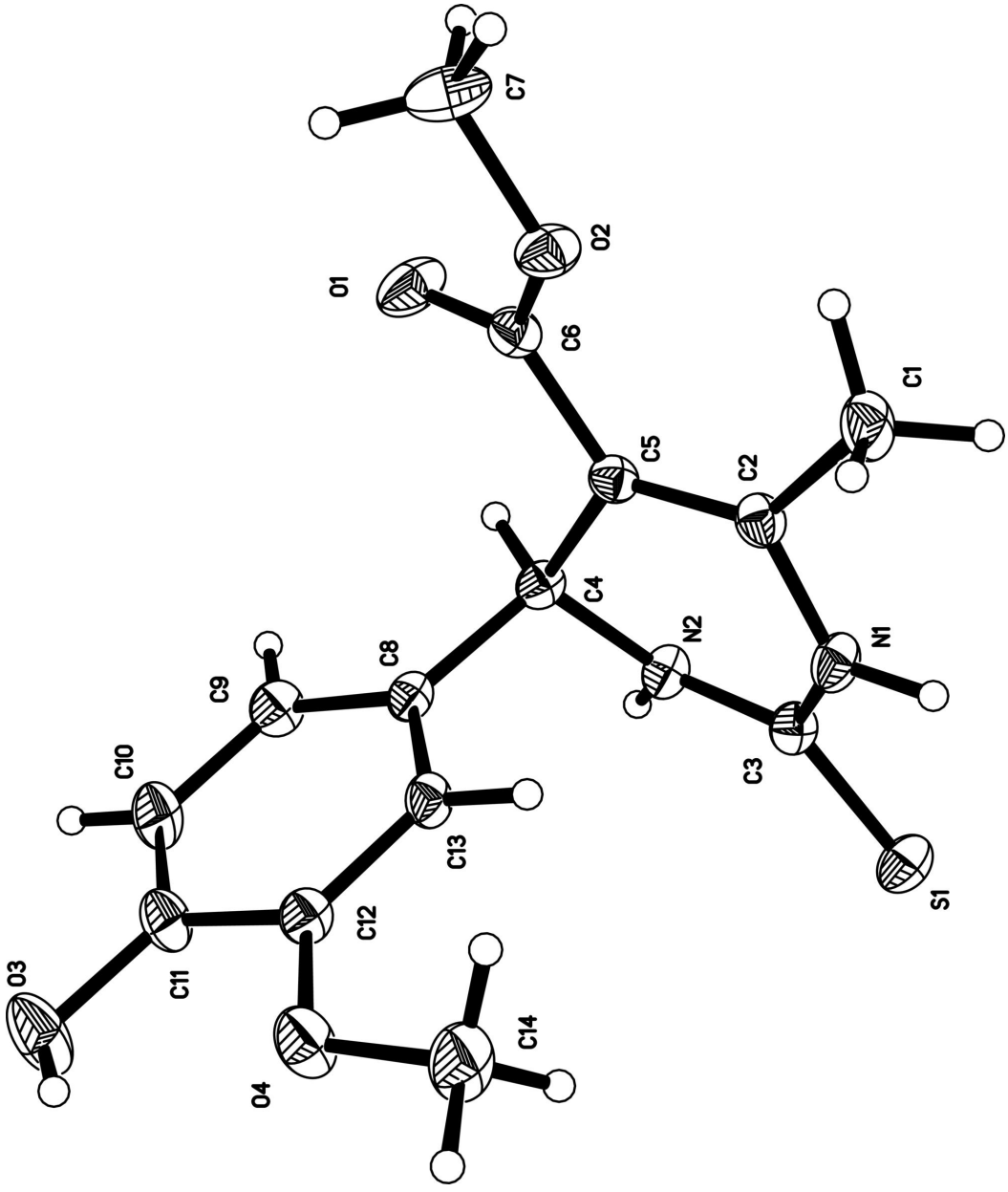
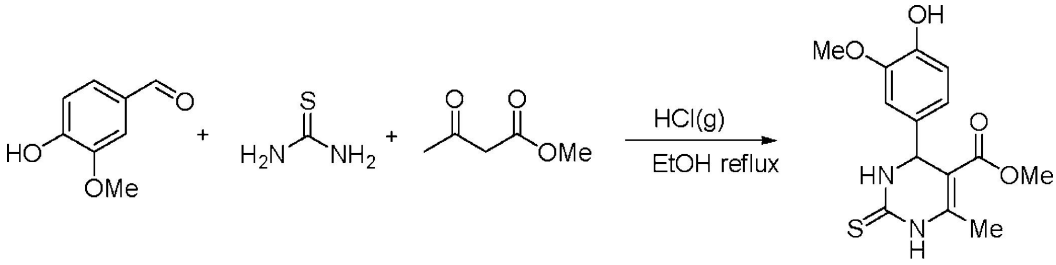


Fig. 2



(**I**)