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Novel heterocyclic inhibitors of matrix metalloproteinases: three 6*H*-1,3,4-thiadiazines

Jörg Schröder,[a] Herbert Wenzel,[a] Hans-Georg Stammler,[b] Anja Stammler,[b] Beate Neumann[b] and Harald Tschesche[a]*

[a]Universität Bielefeld, Fakultät für Chemie, Abteilung Biochemie I, 33615 Bielefeld, Germany, and [b]Universität Bielefeld, Fakultät für Chemie, Abteilung Anorganische Chemie III, 33615 Bielefeld, Germany
Correspondence e-mail: harald.tschesche@uni-bielefeld.de

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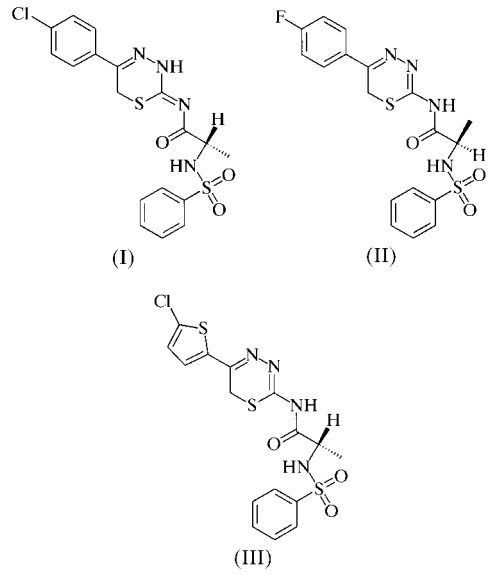
The title compounds, (2*S*)-*N*-[5-(4-chlorophenyl)-2,3-dihydro-6*H*-1,3,4-thiadiazin-2-ylidene]-2-[(phenylsulfonyl)amino]propanamide, $C_{18}H_{17}ClN_4O_3S_2$, (I), (2*R*)-*N*-[5-(4-fluorophenyl)-6*H*-1,3,4-thiadiazin-2-yl]-2-[(phenylsulfonyl)amino]propanamide, $C_{18}H_{17}FN_4O_3S_2$, (II), and (2*S*)-*N*-[5-(5-chloro-2-thienyl)-6*H*-1,3,4-thiadiazin-2-yl]-2-[(phenylsulfonyl)amino]-propanamide, $C_{16}H_{15}ClN_4O_3S_3$, (III), are potent inhibitors of matrix metalloproteinases. In all three compounds, the thiadiazine ring adopts a screw-boat conformation. The molecules of compound (I) show a short intramolecular $N_{Ala}—H\cdots N_{exo}$ hydrogen bond [N···N 2.661 (3) Å] and are linked into a chain along the *c* axis by $N_{endo}—H\cdots S_{endo}$ and $N_{endo}—H\cdots O_{Ala}$ hydrogen bonds [N···S 3.236 (3) and N···O 3.375 (3) Å] between neighbouring molecules. In compound (II), the molecules are connected antiparallel into a chain along the *a* axis by $N_{exo}—H\cdots O_{Ala}$ and $N_{Ala}—H\cdots N_{endo}$ hydrogen bonds [N···O 2.907 (6) and N···N 2.911 (6) Å]. The molecules of compound (III) are dimerized antiparallel through $N_{exo}—H\cdots N_{endo}$ hydrogen bonds [N···N 2.956 (7) and 2.983 (7) Å]. The different hydrogen-bonding patterns can be explained by an amido–imino tautomerism (prototropic shift) shown by different bond lengths within the 6*H*-1,3,4-thiadiazine moiety.

Comment

Inhibitors of matrix metalloproteinases (MMPs) can provide useful treatments for diseases associated with excessive degradation of the extracellular matrix, such as osteoarthritis (Cawston, 1996), rheumatoid arthritis (Bläser *et al.*, 1996), periodontal disease (Overall *et al.*, 1987), multiple sclerosis (Yong, 1999) and tumour metastasis (Chambers & Matrisan, 1997). Recent efforts by a number of laboratories working in the area have provided several classes of MMP inhibitors, which have been extensively reviewed by Becket & Whittaker (1998). The value of thiadiazines as MMP inhibitors has, however, not hitherto been recognized. To investigate this heterocyclic system further and to establish the inhibitor structures for ligand–protein docking experiments, single-crystal X-ray diffraction studies were carried out on the three title compounds, *viz*. (I), (II) and (III).



The title compounds (Figs. 1, 2 and 3) consist of a 6*H*-1,3,4-thiadiazine system, a *p*-substituted phenyl ring or 5-chloro-substituted thiophene ring, and an amide-linked *N*-phenylsulfonyl-substituted D- or L-alanine residue. The three rings do not share a common plane and the thiadiazine ring deviates from planarity. The puckering of this ring system may be described by the amplitude and phase coordinates introduced by Cremer & Pople (1975) and Evans & Boeyens (1989). The puckering parameters for (I), (II) and molecules 1 and 2 of (III) are Q = 0.567 (3), 0.618 (2), 0.634 and 0.665 Å, θ = 70.6 (3), 69.9 (2), 109.5 and 70.5°, and φ = 39.9 (3), 33.1 (3), 217.1 and 35.9°, respectively. Thus, the thiadiazine moiety

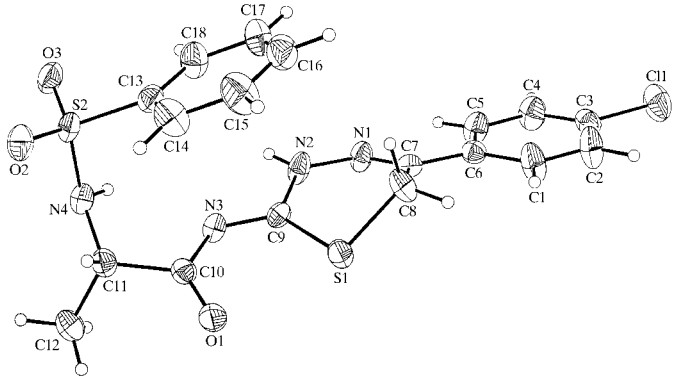


Figure 1
The molecular structure of (I) showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

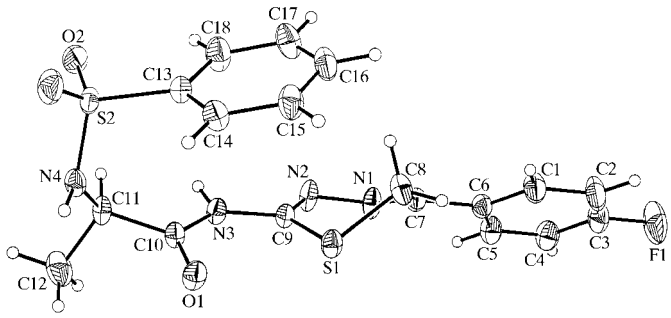


Figure 2
The molecular structure of (II) showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

assumes a screw-boat conformation in all compounds (Boeyens, 1978). The large φ value for molecule 1 in the unit cell of (III) indicates that the direction of the ring distortion is towards an inverted screw-boat conformation.

In compounds (I) and (II), there are two distinct S1—C8 and S1—C9 bond lengths, which can be attributed to typical S—Csp^3 and S—Csp^2 bonds [average values 1.819 (19) and 1.751 (17) Å; Allen *et al.*, 1992]. The two molecules of compound (III) show similar S—C bond lengths. This corresponds to the 6*H* tautomeric form of the thiadiazine ring (Novikova *et al.*, 1991). The endocyclic C9—N2 distance in (II) is shorter than the exocyclic C9—N3 distance and corresponds to an N=Csp^2 bond. The same applies to the two molecules of compound (III). In contrast with this trend, the endocyclic C9—N2 distance in (I) is slightly longer than the exocyclic C9—N3 distance and corresponds to an N—Csp^2 bond. These systematic bond differences resemble the characteristic pattern of bond-length changes introduced by an amido–imino tautomerism (prototropic shift) within the 6*H*-1,3,4-thiadiazine moiety.

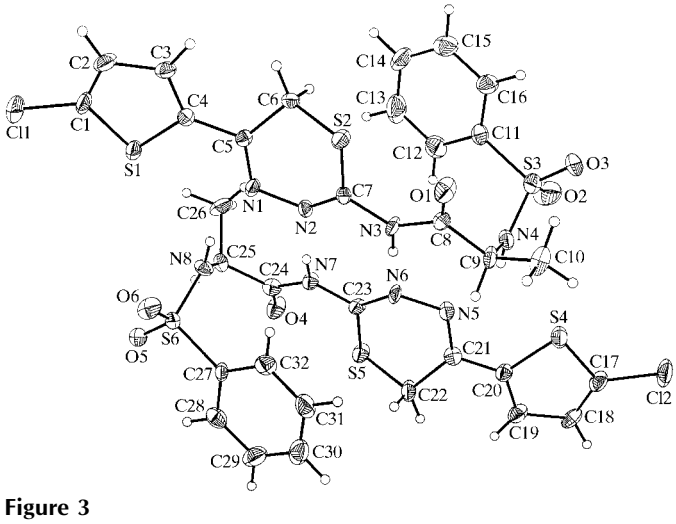
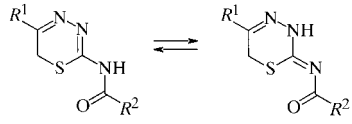


Figure 3
The molecular structure of (III) showing the two independent molecules and the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

As shown in the scheme below, the geometry of compounds (II) and (III) is consistent with the tautomer on the left-hand side, while the geometry of (I) is closer to that of the tautomer on the right-hand side. Consequently, the endocyclic N atom close to the exocyclic N atom is a hydrogen-bond acceptor in (II) and (III), and a hydrogen-bond donor in (I). The opposite applies to the exocyclic N atom, which is a hydrogen-bond donor in (II) and (III), and a hydrogen-bond acceptor in (I). This contributes to the different hydrogen-bonding patterns in the crystal structures of the three compounds.



Experimental

The syntheses and spectroscopic data of the title compounds will be published elsewhere. Crystals of all three compounds suitable for diffraction analysis were obtained by slow crystallization from solutions in methanol/acetonitrile (5:1).

Compound (I)

Crystal data

$C_{18}H_{17}ClN_4O_3S_2$
M_r = 436.93
Orthorhombic, $P2_12_12$
a = 15.600 (4) Å
b = 20.764 (6) Å
c = 5.826 (3) Å
V = 1887.1 (12) Å^3
Z = 4
D_x = 1.538 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 21 reflections
θ = 2.3–11.3°
μ = 0.453 mm^{-1}
T = 173 (2) K
Needle, colourless
1.00 × 0.30 × 0.15 mm

Data collection

Siemens $P2_1$ diffractometer
Wyckoff scans
6296 measured reflections
3154 independent reflections (plus 2337 Friedel-related reflections)
4278 reflections with $I > 2\sigma(I)$
R_{int} = 0.031
θ_{max} = 30°
$h = -21 \rightarrow 21$
$k = -29 \rightarrow 29$
$l = -8 \rightarrow 8$
3 standard reflections
every 100 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.051
$wR(F^2)$ = 0.123
S = 1.020
5491 reflections
263 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0588P)^2 + 0.3217P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.33 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0119 (13)
Absolute structure: Flack (1983)
Flack parameter = −0.09 (9)

Table 1
Selected geometric parameters (Å, °) for (I).

S1—C9	1.726 (3)	N2—C9	1.338 (3)
N1—C7	1.284 (4)	N3—C9	1.321 (3)
N1—N2	1.389 (3)		
C9—N2—N1	128.6 (2)		

Table 2
Hydrogen-bonding and short-contact geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2N···S1^{i}	0.82 (4)	2.72 (4)	3.236 (3)	122 (3)
N2—H2N···O1^{i}	0.82 (4)	2.56 (4)	3.375 (3)	173 (4)
N4—H4N···N3	0.90 (3)	2.31 (3)	2.661 (3)	103 (2)

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

Compound (II)

Crystal data

$C_{18}H_{17}FN_4O_3S_2$
M_r = 420.48
Orthorhombic, $P2_12_12_1$
a = 9.675 (19) Å
b = 12.704 (19) Å
c = 15.606 (15) Å
V = 1918 (5) Å^3
Z = 4
D_x = 1.456 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 20 reflections
θ = 2.6–11.5°
μ = 0.315 mm^{-1}
T = 173 (2) K
Needle, colourless
1.0 × 0.6 × 0.6 mm

Data collection

Siemens $P2_1$ diffractometer
Wyckoff scans
6306 measured reflections
3169 independent reflections (plus 2102 Friedel-related reflections)
4615 reflections with $I > 2\sigma(I)$
R_{int} = 0.045
θ_{max} = 30.06°
$h = -13 \rightarrow 13$
$k = -17 \rightarrow 17$
$l = -21 \rightarrow 21$
3 standard reflections
every 100 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.128
S = 1.011
5271 reflections
262 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0722P)^2 + 0.8564P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.34 e Å^{-3}
$\Delta\rho_{min}$ = −0.43 e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = −0.12 (8)

Table 3
Selected geometric parameters (Å) for (II).

S1—C9	1.752 (4)	N1—N2	1.404 (3)
S1—C8	1.816 (3)	N2—C9	1.296 (4)
N1—C7	1.291 (4)	N3—C9	1.403 (3)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3N···O1^{i}	0.90 (4)	2.01 (4)	2.907 (6)	174 (3)
N4—H4N···N2^{ii}	0.88 (5)	2.06 (5)	2.911 (6)	163 (4)

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

Compound (III)

Crystal data

$C_{16}H_{15}ClN_4O_3S_3$
M_r = 442.95
Monoclinic, $P2_1$
a = 10.613 (4) Å
b = 11.193 (4) Å
c = 16.399 (5) Å
β = 102.48 (3)°
V = 1902.0 (11) Å^3
Z = 4
D_x = 1.547 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 19 reflections
θ = 2.2–12.0°
μ = 0.556 mm^{-1}
T = 173 (2) K
Needle, colourless
0.40 × 0.15 × 0.15 mm

Data collection

Siemens $P2_1$ diffractometer
Wyckoff scans
7536 measured reflections
3566 independent reflections (plus 3183 Friedel-related reflections)
4676 reflections with $I > 2\sigma(I)$
R_{int} = 0.054
θ_{max} = 25.05°
$h = -12 \rightarrow 12$
$k = -13 \rightarrow 13$
$l = -19 \rightarrow 19$
3 standard reflections
every 100 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.061
$wR(F^2)$ = 0.125
S = 1.016
6749 reflections
489 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0364P)^2 + 0.5602P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.35 e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter = −0.03 (11)

Table 5
Selected geometric parameters (Å) for (III).

S2—C7	1.750 (6)	S5—C23	1.755 (6)
S2—C6	1.805 (7)	S5—C22	1.817 (7)
N1—C5	1.286 (8)	N5—C21	1.292 (8)
N1—N2	1.407 (7)	N5—N6	1.423 (7)
N2—C7	1.286 (8)	N6—C23	1.288 (8)
N3—C7	1.395 (8)	N7—C23	1.396 (8)

Table 6
Hydrogen-bonding and short-contact geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3N···N6	0.88	2.09	2.956 (7)	168
N4—H4N···S4	0.88	2.77	3.456 (5)	136
N4—H4N···N5	0.88	2.08	2.842 (7)	145
N7—H7N···N2	0.88	2.11	2.983 (7)	172
N8—H8N···N1	0.88	2.04	2.882 (7)	160

H atoms on N atoms in (I) and (II) were refined isotropically. Other H atoms in (I) and (II), and all H atoms in (III), were included in calculated positions using a riding model, with U(H) = 1.2U_{eq}(C) for CH_2 and CH groups, and U(H) = 1.5U_{eq}(C) for CH_3 groups, and C—H distances in the range 0.95–1.00 Å. The torsion angles of the CH_3 groups were refined.

For all compounds, data collection: *P3*/*VMS* (Siemens, 1989); cell refinement: *P3*/*VMS*; data reduction: *SHELXTL-Plus* (Sheldrick, 1990*a*); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990*b*); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997); software used to prepare material for publication: *SHELXL*97 and *PLATON* (Spek, 1990).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV1070). Services for accessing these data are described at the back of the journal.

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