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2-Amino-6-(1-imidazolylmethyl)-4-(3,5,5-trimethyl-2-pyrazolin-1-yl)-1,3,5-triazine and 2-amino-6-(1-benzimidazolylmethyl)-4-(3,5,5-trimethyl-2-pyrazolin-1-yl)-1,3,5-triazine hemihydrate

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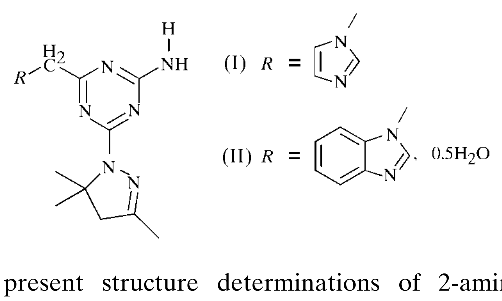
The two title compounds, $C_{13}H_{18}N_8$ and $C_{17}H_{20}N_8{\cdot}0.5H_2O$, possess similar molecular shapes, with the pyrazoline moiety and *s*-triazine ring located approximately in one plane, and the imidazole or benzimidazole ring nearly perpendicular to the *s*-triazine nucleus. In both crystal structures, despite there being a large number of accessible hydrogen-bond acceptor sites, only one H atom from the NH_2 group is involved in hydrogen bonding; the molecules are assembled into discrete centrosymmetric dimers *via* a pair of nearly linear N—H···N hydrogen bonds.

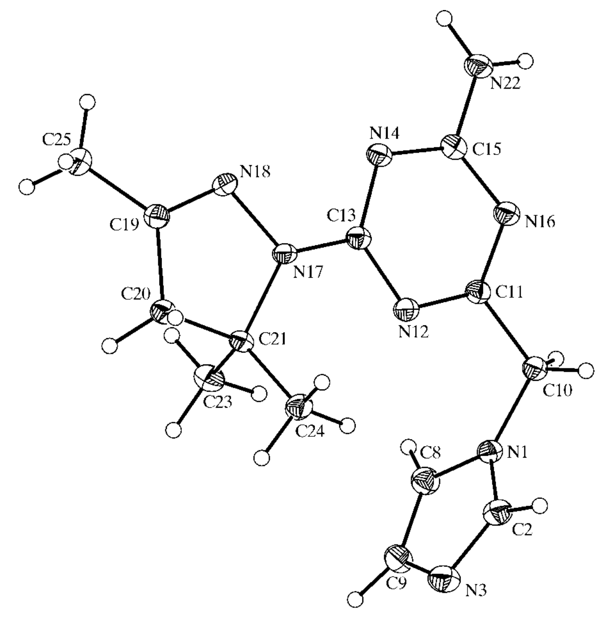
Comment

Molecules with 2,4-diamino-1,3,5-triazine skeletons are known to possess diverse biological activities. Recently, it has been demonstrated that some 2-amino-4-(3,5,5-trimethyl-2-pyrazolino)-1,3,5-triazine derivatives caused considerable growth inhibition in distinct tumor cell lines, showing that these compounds may be useful in the development of new chemotherapeutic agents (Brzozowski *et al.*, 2000; Brzozowski & Sączewski, 2002).

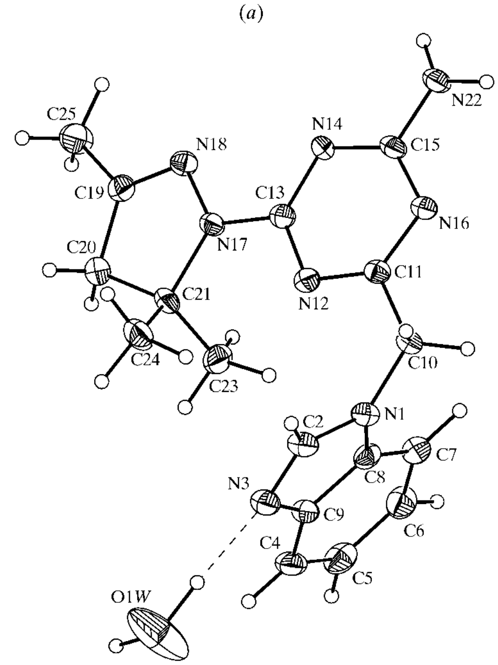


The present structure determinations of 2-amino-6-(1-imidazolylmethyl)-4-(3,5,5-trimethyl-2-pyrazolin-1-yl)-1,3,5-triazine, (I), and 2-amino-6-(1-benzimidazolylmethyl)-4-(3,5,5-trimethyl-2-pyrazolin-1-yl)-1,3,5-triazine hemihydrate, (II), are part of our research program on structure–activity relationships for this series of compounds. So far, only the crystal structure of one derivative, *viz*. 2-amino-4-(3,5,5-trimethyl-2-pyrazolin-1-yl)-6-chloromethyl-1,3,5-triazine, (III), has been reported (Brzozowski *et al.*, 2000).

The molecular structures of (I) and (II) are shown in Fig. 1. Bond lengths and bond angles for (I) and (II) (Tables 1 and 3) show good agreement. The *s*-triazine moiety exhibits a typical pattern of bond angles, with N—C—N angles greater than 125° and C—N—C angles less than 115°. In both compounds,



(*a*)



(*b*)

Figure 1
The molecular structure of (*a*) compound (I) and (*b*) compound (II), with displacement ellipsoids shown at the 50% probability level.

the C11—N12 and C11—N16 bonds are the shortest in the *s*-triazine ring, and the C15—N16 and C13—N12 bonds are the longest. The *s*-triazine ring geometry compares well with some other 2,4-diamino-1,3,5-triazine derivatives (Perrakis *et al.*, 1993; Brzozowski *et al.*, 2000; Gidaspov *et al.*, 2002). The triazine rings, including atoms N22, C10 and N17 of the substituents, are virtually coplanar, the maximum deviations from planarity being 0.0041 (7) and 0.0252 (16) Å in (I) and (II), respectively, when all these atoms are included in the calculation of the best plane.

The conformational features of (I) and (II) are generally very similar (Tables 1 and 3). The molecules of (I), (II) and (III) show a *Z* configuration at the partially double C13—N17 bond. The pyrazoline moiety and *s*-triazine ring lie approximately in one plane, whereas the benzimidazole and imidazole rings are nearly perpendicular to the *s*-triazine nucleus [the dihedral angles are 87.10 (4) and 80.09 (5)° for (I) and (II), respectively]. Interaction of these heteroaromatic substituents with the two methyl groups bound to atom C21 of the pyrazoline fragment results, most probably, in a characteristic bent shape of the molecules, with the dihedral angles between the pyrazoline and imidazole planes being 76.71 (5) and 77.87 (8)°, and the N12—C11—C10—N1 torsion angles 17.25 (14) and 13.1 (3)° in (I) and (II), respectively. The bonds to pyrazoline atom N17 are not strictly coplanar, and atom N17 deviates by 0.1582 (11) Å from the plane defined by atoms C13, N18 and C21 in (I), whereas this deviation is 0.106 (2) Å in (II). The endocyclic torsion angles of the 3,5,5-trimethylpyrazoline moiety indicate an envelope conformation of the five-membered ring in (I) (Table 1) and a strongly flattened envelope in (II) (Table 3).

Compounds (I) and (II) have practically identical abilities to form classical hydrogen bonds. Each molecule contains one NH_2 group, which may act as a twofold hydrogen-bond donor, and five potentially good hydrogen-bond acceptors (atoms N3, N12, N14, N16 and N18; however, atom N12 can be excluded from this list, as access to the lone pair in its sp^2 orbital is hindered by the bulky substituents on atoms C11 and C13 of the *s*-triazine ring). The number of hydrogen-bond acceptors in these molecules greatly exceeds that of donors. In the crystal structure of (III), which lacks one N-acceptor site when compared with the title compounds, the molecules are assembled into tapes *via* $R_2^2(8)$ hydrogen-bond motifs generated by N—H···N interactions between the NH_2 group and triazine atoms N14 and N16 (Brzozowski *et al.*, 2000). Such one-dimensional assemblies are a characteristic supramolecular feature of many 2-aminopyrimidines (Aäkeroy *et al.*, 1998; Krische *et al.*, 1998, 2000). However, no such tapes were found in the crystal structures of (I) and (II). The molecules of (I) form centrosymmetric dimers *via* a pair of nearly linear N22—H22*A*···N14^{i} hydrogen bonds (Fig. 2 and Table 2; symmetry codes are defined in Table 2), and this is the only conventional hydrogen bond in this structure. The amine group interacts only very weakly with pyrazoline atom N18 in the same dimer. C20—H20*A*···N3^{iii} interactions join the dimers into one-dimensional networks, which are further organized into closely packed layers, parallel to the $(\bar{2}11)$ plane, *via* π–π stacking interactions between the imidazole moieties [the interplanar distance is 3.305 (5) Å; Fig. 2]. Neighbouring layers are further connected *via* weak C2—H2···N18^{ii} interactions between the imidazole and pyrazoline moieties. Interestingly, the C2···N18^{ii} vector is oriented nearly perpendicular to the pyrazoline ring plane, indicating that this weak hydrogen bond is accepted by the lone pair in the *p* orbital and not by that of the sp^2 orbital of atom N18.

We were unable to obtain (II) in the anhydrous form. When recrystallized from a hot saturated toluene solution, (II) formed a hemihydrate. The water molecules lie in special positions of twofold symmetry and act as double proton donors in O—H···N hydrogen bonds and as double proton acceptors in C—H···O hydrogen bonds (Table 4). It is interesting that, despite the presence of water molecules and differences in the overall molecular packing, the molecules of (II) are joined together by a set of weak and strong interactions that are similar to those observed in (I). Molecules of (II) are connected into centrosymmetric dimers *via* pairs of nearly linear N22—H22*A*···N14^{iv} hydrogen bonds (Fig. 3 and Table 4; symmetry codes are defined in Table 4). Furthermore, π–π stacking interactions between the benzimidazole rings [the interplanar distance is 3.323 (2) Å] and weak C2—H2···

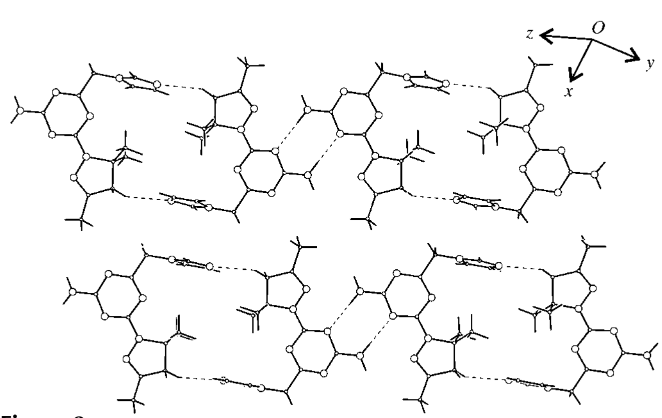


Figure 2
A closely packed layer of hydrogen-bonded molecules in (I).

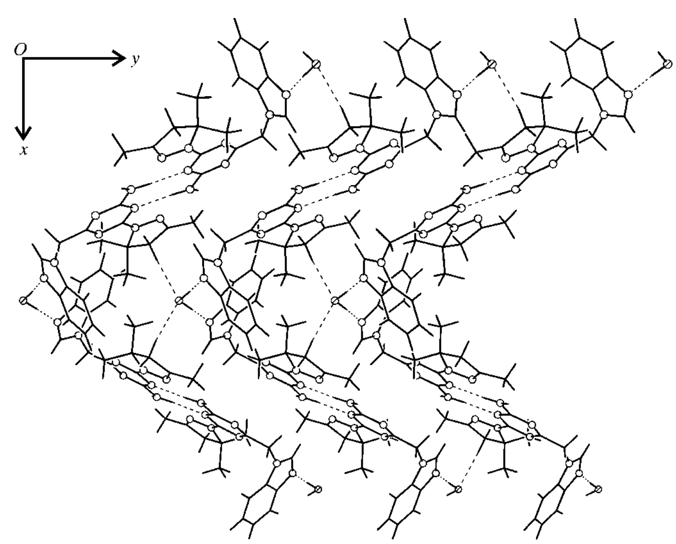


Figure 3
The hydrogen-bonding network in (II).

N18[vi] interactions between the benzimidazole and pyrazoline rings are observed. The C20—H20*A*···N3 interaction that is present in (I) is replaced in (II) by two hydrogen bonds involving the water molecule, *viz*. C20—H20*A*···O1*W*[v] and O1*W*—H1*W*···N3. Thus, as in (I), despite there being a large number of potential hydrogen-bonding sites, only one amine H atom is involved in hydrogen bonding.

Experimental

Compound (I) was prepared according to the procedure described by Brzozowski & Sączewski (2002). For the preparation of (II), finely powdered NaOH (1.6 g, 0.04 mol) and 4-bromomethyl-6-(3,5,5-trimethyl-4,5-dihydro-1*H*-pyrazolyl)-1,3,5-triazin-2-amine[6] (3.0 g, 0.01 mol) were added successively to a solution of benzimidazole (2.36 g, 0.02 mol) in dimethyl sulfoxide (10 ml). The reaction mixture was stirred vigorously at 308–313 K for 2 h and then poured into cold water (50 ml). The crude product that precipitated was separated by suction and purified by crystallization from methanol/water to give (II) in 76% yield (m.p. 402–404 K). IR (cm^{-1}): 3424, 1664, 1544, 1472, 1440, 1376, 1196; ^{1}H NMR (DMSO-d_6): δ 0.92 (*s*, 6H, CH_3), 1.87 (*s*, 3H, CH_3), 2.62 (*s*, 2H, CH_2), 5.26 (*s*, 2H, CH_2), 6.9 (*s*, 2H, NH_2), 7.1–7.25 (*m*, 2H, aromatic), 7.4–7.5 (*m*, 1H, aromatic), 7.6–7.7 (*m*, 1H, aromatic), 8.24 (*s*, 1H, CH). The single crystal used for X-ray analysis was obtained by slow evaporation of a toluene solution of (II).

Compound (I)

Crystal data

$C_{13}H_{18}N_8$
M_r = 286.35
Triclinic, $P\bar{1}$
a = 8.2493 (7) Å
b = 9.4564 (7) Å
c = 9.7050 (8) Å
α = 93.221 (5)°
β = 105.342 (5)°
γ = 106.191 (6)°
V = 694.20 (10) Å^3
Z = 2
D_x = 1.370 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 3986 reflections
θ = 4–25°
μ = 0.09 mm^{-1}
T = 110 (2) K
Block, colourless
0.40 × 0.40 × 0.30 mm

Data collection

Kuma CCD diffractometer
ω scans
5098 measured reflections
2448 independent reflections
2275 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 25.0°
$h = -9 \rightarrow 6$
$k = -11 \rightarrow 11$
$l = -10 \rightarrow 11$

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

C11—N12	1.3248 (14)	N14—C15	1.3459 (14)
C11—N16	1.3338 (14)	C15—N22	1.3424 (15)
N12—C13	1.3565 (14)	C15—N16	1.3567 (15)
C13—N14	1.3489 (14)	N17—N18	1.4105 (12)
C13—N17	1.3570 (14)	N18—C19	1.2823 (15)
N12—C11—N16	127.53 (10)	C15—N14—C13	114.31 (9)
C11—N12—C13	114.03 (9)	N14—C15—N16	125.69 (10)
N14—C13—N12	125.10 (10)	C11—N16—C15	113.34 (9)
N12—C11—C10—N1	17.25 (14)	C19—C20—C21—N17	20.89 (10)
C11—C10—N1—C2	−101.91 (12)	C20—C21—N17—N18	−21.73 (11)
N17—N18—C19—C20	2.52 (13)	C21—N17—N18—C19	13.10 (12)
N18—C19—C20—C21	−16.22 (13)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N22—H22*A*···N14[i]	0.905 (17)	2.085 (17)	2.9906 (14)	179.0 (15)
N22—H22*A*···N18[i]	0.905 (17)	2.626 (16)	3.0712 (14)	111.2 (12)
C2—H2···N18[ii]	0.957 (15)	2.574 (15)	3.4491 (15)	152.1 (12)
C20—H20*A*···N3[iii]	0.988 (15)	2.547 (15)	3.3782 (15)	141.6 (11)

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

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.096
S = 1.08
2834 reflections
262 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0495P)^2 + 0.2587P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.015
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

Compound (II)

Crystal data

$C_{17}H_{20}N_8 \cdot 0.5H_2O$
M_r = 345.42
Monoclinic, $C2/c$
a = 22.5030 (14) Å
b = 8.3217 (6) Å
c = 18.4269 (12) Å
β = 94.667 (5)°
V = 3439.2 (4) Å^3
Z = 8
D_x = 1.334 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 4283 reflections
θ = 4–50°
μ = 0.09 mm^{-1}
T = 100 (2) K
Needle, colourless
0.35 × 0.10 × 0.05 mm

Data collection

Kuma CCD diffractometer
ω scans
8348 measured reflections
3035 independent reflections
1805 reflections with $I > 2\sigma(I)$
R_{int} = 0.048
θ_{max} = 25.1°
$h = -26 \rightarrow 26$
$k = -9 \rightarrow 9$
$l = -20 \rightarrow 21$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.045
$wR(F^2)$ = 0.093
S = 0.93
3035 reflections
251 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0337P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

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

C11—N12	1.324 (3)	N14—C15	1.349 (3)
C11—N16	1.335 (3)	C15—N22	1.345 (3)
N12—C13	1.357 (3)	C15—N16	1.359 (3)
C13—N14	1.344 (3)	N17—N18	1.412 (2)
C13—N17	1.355 (3)	N18—C19	1.278 (3)
N12—C11—N16	127.6 (2)	C13—N14—C15	114.01 (19)
C11—N12—C13	114.1 (2)	N14—C15—N16	126.1 (2)
N14—C13—N12	125.2 (2)	C11—N16—C15	112.91 (19)
N12—C11—C10—N1	13.1 (3)	C19—C20—C21—N17	9.4 (2)
C11—C10—N1—C2	−93.8 (3)	C20—C21—N17—N18	−10.4 (2)
N17—N18—C19—C20	0.1 (3)	C21—N17—N18—C19	7.0 (2)
N18—C19—C20—C21	−6.6 (3)		

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

D—H···A	D—H	H···A	D···A	D—H···A
O1W—H1W···N3	0.85	2.04	2.894 (2)	176
N22—H22A···N14^{iv}	0.90	2.09	2.991 (3)	179
N22—H22A···N18^{iv}	0.90	2.61	3.035 (3)	110
C20—H20A···O1W^{v}	0.96	2.54	3.415 (3)	152
C2—H2···N18^{vi}	0.96	2.60	3.443 (3)	147

Symmetry codes: (iv) $\frac{1}{2}-x, \frac{5}{2}-y, -z$; (v) $x, 1+y, z$; (vi) $x, y-1, z$.

In both (I) and (II), all H atoms were located from difference Fourier maps. In (I), H atoms were refined freely, with isotropic displacement parameters. In (II), H atoms were placed in positions calculated from the standarization of C—H, N—H and O—H bond lengths (0.96, 0.90 and 0.85 Å, respectively) and during refinement were constrained to ride on their parent atoms. The U_{iso} value of the unique H atom of the water molecule was set equal to $1.2U_{eq}$(O1W); the isotropic displacement parameters of the remaining H atoms were refined.

For both compounds, data collection: *CrysAlis CCD* (Oxford Diffraction, 2000); cell refinement: *CrysAlis CCD*; data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *Stereochemical Workstation Operation Manual* (Siemens, 1989); software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA1035). Services for accessing these data are described at the back of the journal.

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