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# (*E*)-8-(3-Chlorostyryl)-1,3,7-trimethylxanthine, a caffeine derivative acting both as antagonist of adenosine A2A receptors and as inhibitor of MAO-B

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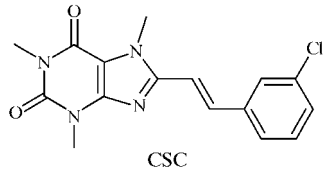
In the crystal structure of (*E*)-8-(3-chlorostyryl)-1,3,7-trimethylxanthine (CSC) [systematic name: (*E*)-8-(3-chlorostyryl)-1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,6-dione], $C_{16}H_{15}ClN_4O_2$, the xanthine ring and the lateral styryl chain are coplanar. The crystal packing involves mainly parallel stacking of these planar molecules. The electrostatic potential calculated on the crystal structure conformation confirms the pharmacophore elements associated with MAO-B inhibition.

## Comment

(*E*)-8-(3-Chlorostyryl)-1,3,7-trimethylxanthine (CSC) (Fig. 1) is a caffeine derivative that acts both as an antagonist of adenosine A2A receptors and as an inhibitor of MAO-B, offering novel therapeutic benefits in patients diagnosed with neurodegenerative disorders, such as Parkinson's disease (Castagnoli *et al.*, 2003; Petzer *et al.*, 2003). The crystal structure reported here will be the starting point for three-dimensional quantitative structure–activity relationship and docking studies, which may aid in the future design of potent A2A receptor antagonists that also possess monoamine oxidase B (MAO-B) inhibitory activity.

The bond lengths (Table 1) within the xanthine ring are systematically intermediate between single and double C—C and/or C—N bonds. Analysis of the torsion angles revealed that the molecule adopts an almost planar conformation; the xanthine ring is coplanar with the lateral styryl moiety, which adopts an all *trans* conformation (Table 1).




CSC

Crystal cohesion of CSC is mainly assumed by stacking interactions involving the five-membered (imidazole-type) ring, C4/C5/N7/C8/N9, and the benzene ring, C17–C22. In particular, there are a pair of five-membered rings stacked across $(0, 1, \frac{1}{2})$ and a pair of benzene rings stacked across $(0, \frac{1}{2}, 1)$. The distance between the centroids of the C4/C5/N7/C8/N9 ring in the molecules at $(x, y, z)$ and $(-x, 2-y, 1-z)$ is 3.637 (2) Å, with an interplanar spacing of 3.402 (2) Å; the separation between the centroids of the benzene rings of the molecules at $(x, y, z)$ and $(-x, 1-y, 2-z)$ is 3.707 (2) Å, with an interplanar spacing of 3.551 (2) Å. Propagation of these stacking interactions by successive inversions then generates a chain along $[01\bar{1}]$.

The coplanar conformation adopted by CSC is in agreement with our previously determined MAO-B pharmacophore (Wouters *et al.*, 1997; Wouters, 1998; Ooms *et al.*, 2003). The molecular electostatic potential (MEP) around the molecule (Fig. 2) was calculated (*ab initio*, RHF 6-31G* basis set) using the crystal structure conformation. The features of the MEP map conform with stereoelectronic elements already found among other families of reversible MAO-B inhibitors. In particular, the MEP map identifies three attractive potential wells that show a high degree of similarity compared with other MAO-B inhibitors. These attractive potential wells generated by the two carbonyl groups and atom N9 of the xanthine ring define a unique pharmacophoric pattern similar to that observed among diazaheterocyclic groups of reversible MAO-B inhibitors (Wouters *et al.*, 1997; Wouters, 1998). This fact suggests that the heteroatoms of the xanthine ring can stabilize this new family of reversible MAO-B inhibitors with appropriate hydrogen-donor residues found within the MAO-B active site.

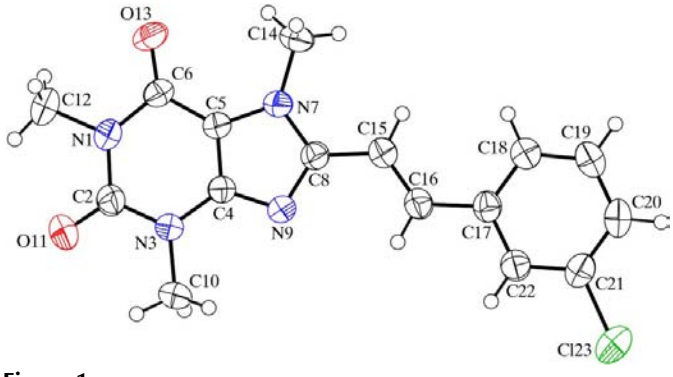



**Figure 1**
The molecular conformation of CSC, showing the atomic numbering scheme and displacement ellipsoids at the 50% probability level.

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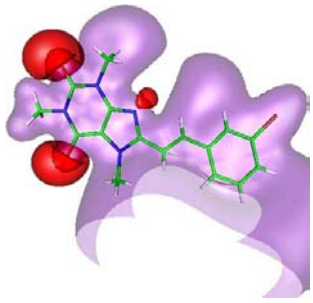

**Figure 2**
The molecular electostatic potential (MEP) calculated around CSC (*ab initio*, RHF 6-31G* basis set) using the crystal structure conformation.

## Experimental

CSC was obtained from 5,6-diamino-1,3-dimethyluracil and (*E*)-3-chlorocinnamic acid according to the general procedure reported by Jacobson *et al.* (1993) [m.p. 478 K, literature 478 K (Jacobson *et al.*, 1993)]. Crystals were grown at room temperature by slow evaporation from a solution of CSC in methanol.

*Crystal data*

$C_{16}H_{15}ClN_4O_2$
$M_r$ = 330.77
Triclinic, $P\overline{1}$
$a$ = 8.244 (1) Å
$b$ = 8.319 (1) Å
$c$ = 12.722 (1) Å
$\alpha$ = 77.864 (7)°
$\beta$ = 77.502 (6)°
$\gamma$ = 66.214 (5)°
$V$ = 772.05 (15) Å$^3$
$Z$ = 2
$D_x$ = 1.423 Mg m$^{-3}$
Cu $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta$ = 4–45°
$\mu$ = 2.33 mm$^{-1}$
$T$ = 298 K
Prism, colourless
0.32 × 0.30 × 0.10 mm

*Data collection*

Enraf–Nonius CAD-4 diffractometer
$\theta/2\theta$ scans
Absorption correction: analytical (de Meulenaer & Tompa, 1965)
$T_{min}$ = 0.523, $T_{max}$ = 0.801
3240 measured reflections
3015 independent reflections
2776 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.016
$\theta_{max}$ = 71.8°
$h = -10 \rightarrow 0$
$k = -10 \rightarrow 9$
$l = -15 \rightarrow 15$
3 standard reflections
frequency: 60 min
intensity decay: 1%

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.132
$S$ = 1.03
3015 reflections
209 parameters
H-atom parameters constrained
$1/[\sigma^2(F_o^2) + (0.0756P)^2 + 0.2615P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.012
$\Delta\rho_{max}$ = 0.33 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.40 e Å$^{-3}$
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0124 (13)

**Table 1**
Selected geometric parameters (Å, °).

| | | | |
|---|---|---|---|
| N1—C2 | 1.399 (2) | N7—C5 | 1.380 (2) |
| N1—C6 | 1.399 (2) | N7—C8 | 1.356 (2) |
| N3—C2 | 1.375 (2) | N9—C4 | 1.347 (2) |
| N3—C4 | 1.375 (2) | N9—C8 | 1.342 (2) |
| N7—C8—C15—C16 | −178.8 (2) | C15—C16—C17—C18 | 0.0 (3) |
| C8—C15—C16—C17 | 179.9 (2) | | |

H atoms were refined using a riding model. For the methyl groups (C10, C12 and C14), C—H distances were fixed at 0.96 Å, with $U_{iso}$(H) = 1.5$U_{eq}$(C). All other C—H distances were fixed at 0.93 Å, with $U_{iso}$(H) = 1.2$U_{eq}$(C).

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS*; data reduction: *HELENA* (Spek, 1997); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2001); software used to prepare material for publication: *PLATON*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1409). Services for accessing these data are described at the back of the journal.

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