

**(Z,Z)-3,6-Bis[(3,4,5-trimethoxyphenyl)-  
methylene]piperazine-2,5-dione****Wendy A. Loughlin, Raymond L. Marshall,† Kathryn E. Fairfull-Smith (née Elson) and Peter C. Healy\***

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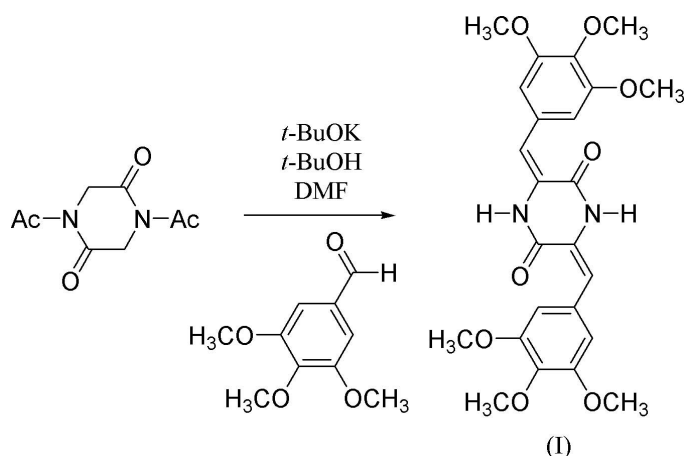
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**Key indicators**Single-crystal X-ray study  
 $T = 295\text{ K}$   
Mean  $\sigma(\text{C}-\text{C}) = 0.005\text{ \AA}$   
 $R$  factor = 0.052  
 $wR$  factor = 0.189  
Data-to-parameter ratio = 13.4For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.

The title compound,  $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_8$ , is a derivative of neihumicin, a cytotoxic antibiotic from *Micromonospora neihuensis*. The compound crystallizes as discrete molecules with crystallographic inversion symmetry. Intermolecular  $\text{N}-\text{H}\cdots\text{O}$  hydrogen bonds yield polymeric chains along the  $c$  axis. The trimethoxyphenylmethylene side chain is found to be in a  $Z$  configuration about the  $\text{C}=\text{C}$  double bond.

**Comment**

$\alpha,\beta$ -Unsaturated amino acid derivatives are present in many natural products, several of which exhibit biological properties. For example, neihumicin, produced by *Micromonospora neihuensis*, is a cytotoxic antibiotic (Wu *et al.*, 1988; Yang *et al.*, 1988). A structure–activity relationship (SAR) of piperazine-2,5-dione derivatives of neihumicin has been carried out (Yokoi *et al.*, 1988). We report here the first solid-state structural elucidation of the title compound, (I), a neihumicin derivative from the reported SAR study. Compound (I) was obtained by a modification of the procedure (Gallina & Liberatori, 1973) where 1,3-diacetyl piperazine-2,5-dione (Marcuccio & Elix, 1984) was condensed with 3,4,5-trimethoxybenzaldehyde in the presence of a strong base, namely potassium *tert*-butoxide.

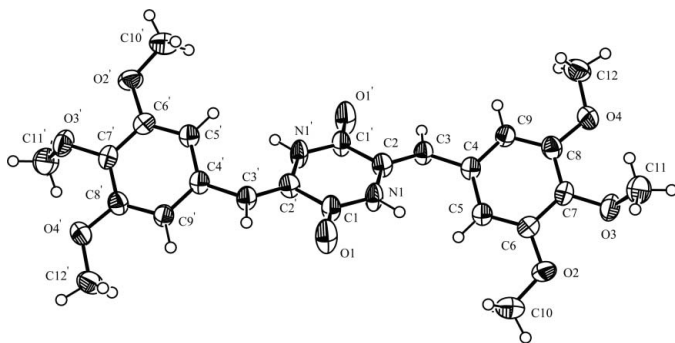


The crystal structure of (I) consists of discrete molecules with a crystallographic centre of symmetry located at the centre of the piperazine ring, such that the asymmetric unit consists of half the molecule (Fig. 1). The trimethoxyphenylmethylene side chain is found to be in the  $Z$  configuration about the  $\text{C}=\text{C}$  double bond. The molecules are linked along the  $c$  axis by an  $R_2^2(8)$   $\text{N}-\text{H}\cdots\text{O}$  interaction (Bernstein *et al.*, 1995) between the amide and carbonyl oxygen groups (Table 2 and Fig. 2). This interaction presumably stabilizes the planar

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**Figure 1**

View of the title compound, with the atom numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level. H atoms are included with arbitrary radii. The symmetry code of the primed atoms is  $(1 - x, -y, 1 - z)$ .

conformation of the piperazine ring. The C3—C4 and C1—C2<sup>i</sup> [symmetry code: (i)  $1 - x, -y, 1 - z$ ] distances of 1.466 (5) and 1.486 (5) Å are close to the value of 1.48 Å expected for a single bond between two *sp*<sup>2</sup>-hybridized C atoms (Allen *et al.*, 1987). Analogous C3—C4 and/or C1—C2 bond lengths with intramolecular and intermolecular hydrogen-bond stabilization, respectively, have been observed with indolydene piperazine-2,5-diones (Katritzky *et al.*, 1989) and the cyclic dipeptide of dehydrophenylalanine (Ajo *et al.*, 1985). The methoxy groups on atoms C6 and C8 are coplanar with the benzene ring. The group on C7, however, lies significantly out of the plane, with a C11—O3—C7—C8 angle of 69.4 (5)°. The benzene ring is twisted about the C3—C4 bond with respect to the piperazine ring, with a C2—C3—C4—C5 torsion angle of 37.3 (7)°.

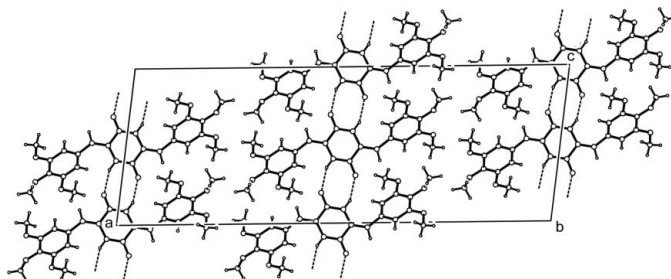
## Experimental

Potassium *tert*-butoxide (0.224 g, 2.00 mmol) in *tert*-butanol (2 ml) was added to a stirred solution of 3,4,5-trimethoxybenzaldehyde (0.392 g, 2.00 mmol) and 1,4-diacetylpiperazine-2,5-dione (0.4 g, 2.0 mmol) in dry DMF (4.0 ml) at 273 K. The mixture was stirred at room temperature for 24 h and worked up as described elsewhere (Gallina & Liberatori, 1973), giving compound (I) as a yellow powder (329 mg, 35%). Yellow crystals of (I) [m.p. 529–530 K (decomposed); literature 528–529 K (Sonn, 1925) and 533–535 K (Yokoi *et al.*, 1988)] were isolated by slow evaporation of a DMF solution of (I). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, p.p.m.): δ<sub>H</sub> 8.25 (2H, *brs*, NH), 6.96 (2H, *s*, 1'-H), 6.59 [4H, *s*, *o*-C<sub>6</sub>H<sub>2</sub>(OCH<sub>3</sub>)<sub>3</sub>], 3.89 (18H, *s*, 6 × OCH<sub>3</sub>); ESMS<sup>+</sup> 469 (M—H<sup>+</sup>, 100%); ESMS<sup>+</sup> 477 (MLi<sup>+</sup>, 70%).

### Crystal data

C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub>  
*M<sub>r</sub>* = 470.47  
 Monoclinic, C2/c  
*a* = 35.204 (3) Å  
*b* = 5.282 (6) Å  
*c* = 12.738 (4) Å  
 β = 97.503 (15)°  
*V* = 2348 (3) Å<sup>3</sup>  
*Z* = 4

*D<sub>x</sub>* = 1.331 Mg m<sup>-3</sup>  
 Mo Kα radiation  
 Cell parameters from 25 reflections  
 θ = 18.5–19.9°  
 μ = 0.10 mm<sup>-1</sup>  
*T* = 295 K  
 Plate, yellow  
 0.50 × 0.20 × 0.05 mm


**Figure 2**

Packing diagram of the title compound, projected on to the *ac* plane. Dashed lines indicate hydrogen bonds.

### Data collection

Rigaku AFC-7R diffractometer  
 ω–2θ scans  
 Absorption correction: none  
 2106 measured reflections  
 2070 independent reflections  
 1094 reflections with  $I > 2\sigma(I)$   
*R*<sub>int</sub> = 0.037

θ<sub>max</sub> = 25.0°  
*h* = 0 → 41  
*k* = 0 → 6  
*l* = –15 → 15  
 3 standard reflections  
 every 150 reflections  
 intensity decay: 0.3%

### Refinement

Refinement on *F*<sup>2</sup>  
*R* [*F*<sup>2</sup> > 2σ(*F*<sup>2</sup>)] = 0.052  
*wR* (*F*<sup>2</sup>) = 0.189  
*S* = 1.03  
 2070 reflections  
 154 parameters  
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0815P)^2 + 4.1485P]$   
 where  $P = (F_o^2 + 2F_c^2)/3$   
 (Δ/σ)<sub>max</sub> = 0.001  
 Δρ<sub>max</sub> = 0.23 e Å<sup>-3</sup>  
 Δρ<sub>min</sub> = –0.23 e Å<sup>-3</sup>  
 Extinction correction: none

**Table 1**

Selected geometric parameters (Å, °).

O1—C1	1.229 (5)	O4—C12	1.429 (6)
O2—C6	1.365 (5)	N1—C1	1.349 (5)
O2—C10	1.426 (6)	N1—C2	1.412 (4)
O3—C7	1.365 (5)	C1—C2 <sup>i</sup>	1.486 (5)
O3—C11	1.425 (6)	C2—C3	1.330 (5)
O4—C8	1.362 (5)	C3—C4	1.466 (5)
C6—O2—C10	117.5 (3)	N1—C2—C1 <sup>i</sup>	116.6 (3)
C7—O3—C11	115.6 (3)	O2—C6—C5	125.0 (3)
C8—O4—C12	118.1 (3)	O2—C6—C7	114.5 (3)
C1—N1—C2	125.6 (3)	O3—C7—C6	119.1 (3)
O1—C1—C2 <sup>i</sup>	120.9 (3)	O3—C7—C8	121.7 (3)
N1—C1—C2 <sup>i</sup>	117.8 (3)	O4—C8—C7	115.9 (3)
O1—C1—N1	121.3 (3)	O4—C8—C9	124.2 (4)
N1—C2—C3	125.7 (3)		

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

**Table 2**

Hydrogen-bond geometry (Å, °).

<i>D</i> —H... <i>A</i>	<i>D</i> —H	H... <i>A</i>	<i>D</i> ... <i>A</i>	<i>D</i> —H... <i>A</i>
N1—H1...O1 <sup>ii</sup>	0.90	2.10	2.934 (5)	154

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

H atoms were constrained as riding atoms, with C—H set to 0.95 Å. *U*<sub>iso</sub>(H) values were set to 1.2*U*<sub>eq</sub> of the parent atom.

Data collection: *MSC/AFC7 Diffractometer Control Software* (Molecular Structure Corporation, 1999); cell refinement: *MSC/*

*AFC7 Diffractometer Control Software*; data reduction: *TEXSAN for Windows* (Molecular Structure Corporation, 2001); program(s) used to solve structure: *TEXSAN for Windows*; program(s) used to refine structure: *TEXSAN for Windows* and *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *TEXSAN for Windows* and *PLATON* (Spek, 2003).

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