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(4*S*)-4-(Methoxycarbonylmethylamino-carbonyl)-4-(3,4,5-trimethoxybenzamido)-butanoic acid

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Key indicators

Single-crystal X-ray study
T = 298 K
Mean σ(C–C) = 0.004 Å
R factor = 0.061
wR factor = 0.155
Data-to-parameter ratio = 13.6

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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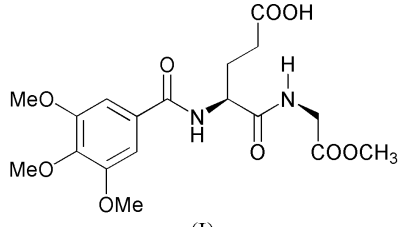
The title compound, $C_{18}H_{24}N_2O_9$, was synthesized by the condensation of *N*-(3,4,5-trimethoxybenzoyl)glutamic acid anhydride with L-glycine methyl ester hydrochloride in dichloromethane solution. The structure is stabilized by intermolecular hydrogen bonds.

Comment

Aminopeptidase N (APN) is a member of the membrane-bound zinc-dependent exopeptidase family, which is involved in the metabolism of angiotensin III in the brain and peripheral organs. The over-expression of APN is involved in several pathological conditions, including cancer (Yoneda *et al.*, 1992), leukemia, diabetic nephropathy (Bedir *et al.*, 1996), rheumatoid arthritis (Shimizu *et al.*, 2002), angiogenesis (Sato, 2004) and central nervous system diseases such as Alzheimer's disease (Sloane *et al.*, 2002). This has led to a search for APN inhibitors (APNIs) as potential therapeutic agents. Unfortunately, no such effective agents exist at the present time.



(I)

Antineoplaston A-10 (3-phenylacetylamino-2,6-piperidinedione) is the first chemically identified APNI and has potential utility in breast cancer treatment (Badria, Mabed, El-Awadi *et al.*, 2000; Badria, Mabed, Khafagy & Abou-Zeid, 2000). A-10 and its metabolites have shown promising cytostatic responses when challenged on tumor tissue cultures or when administered to human patients with hepatocellular carcinoma (Abou-Zeid *et al.*, 2001).

Compound (I), one of the novel L-iso-glutamine derivatives synthesized in our laboratory, can serve as a potential anti-tumor agent (Wang *et al.*, 2003). It displays normal peptide geometry; the bond lengths and angles are unexceptional. The crystal structure is stabilized by intermolecular O—H···O and N—H···O hydrogen bonds; there are also weak C—H···O interactions (Table 1).

Experimental

Starting from 3,4,5-trihydroxybenzoic acid, *via* a three-step reaction, the key intermediate *N*-(3,4,5-trimethoxybenzoyl)glutamic acid anhydride was obtained according to the literature method (Fan,

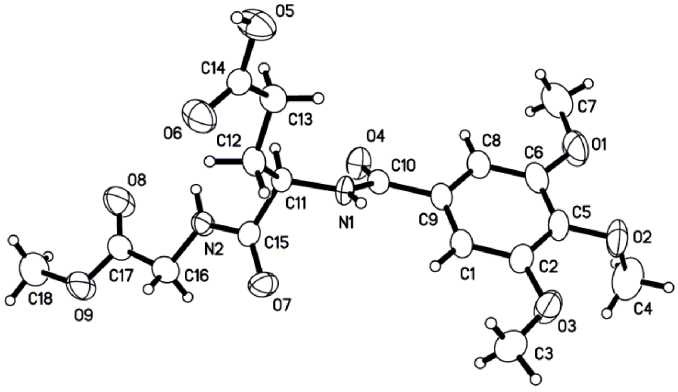


Figure 1
View of the molecule of (I), showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 30% probability level. H atoms are represented by small spheres of arbitrary radii.

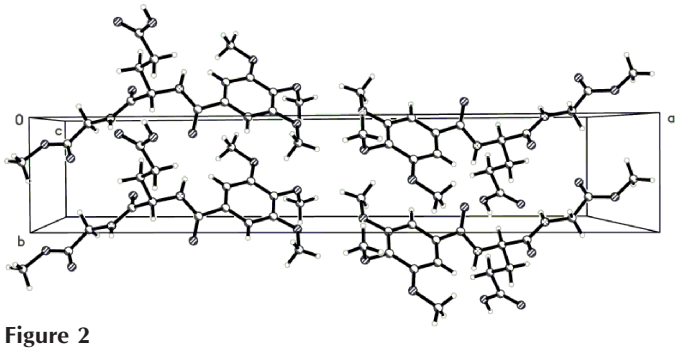


Figure 2
The molecular packing of (I), viewed along the *c* axis.

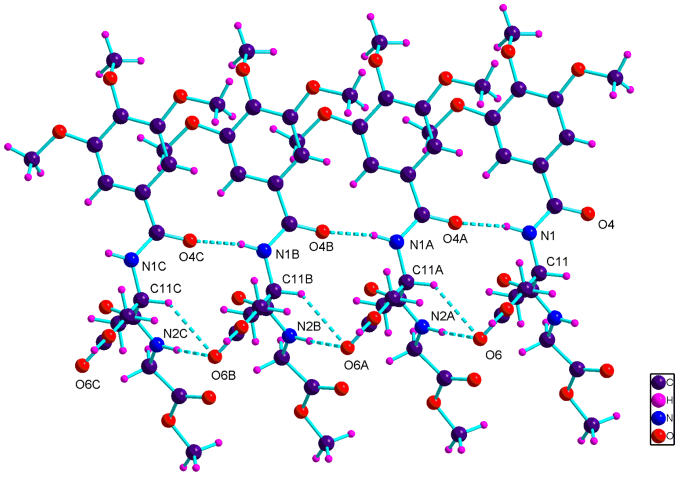


Figure 3
Part of the crystal structure of (I), showing the formation of intermolecular hydrogen bonds (dashed lines). The molecule containing atom N1*A* is related to the molecule containing atom N1 by a unit-cell translation along *b*. Further unit-cell translations along *b* yield the molecules containing N1*B* and N1*C*.

1992) (m.p. 423–425 K, 55% yield). IR (KBr, ν cm^{-1}): 3310.0 (NH), 2945.1 (CH), 1777.0 and 1640.7 (O═C—O—C═O), 1504.2 (NH), 1239.6 and 1129.6 (C—O). ESI-MS (*m*/*z*): 323.8 [*M*—H]$^+$. To a suspension of *N*-(3,4,5-trimethoxybenzoyl)glutamic acid anhydride (3.23 g, 10 mmol) and L-glycine methyl ester hydrochloride (2.5 g, 20 mmol) in dichloromethane (30 ml) was added triethylamine (5 ml). The resulting solution was stirred at room temperature for 2 h. The excess solvent was removed under reduced pressure. The residue was diluted with distilled water and acidified to pH 2 with 2*M* hydrochloric acid. After two days, colorless crystals of (I) were obtained (m.p. 442–445 K, 74% yield). Analysis found: C 52.60, H 5.96, N 6.69%; calculated for $C_{18}H_{24}N_2O_9$: C 52.42, H 5.87, N 6.79%. ^{1}H NMR (DMSO-d_6, p.p.m.): δ 8.45 (*d*, 1H, J = 7.5 Hz, NH), 8.38 (*t*, 1H, *J* = 5.4 Hz, NH), 7.23 (*s*, 2H, Ar—H), 4.47 (*m*, 1H, CH), 3.88 (*d*, 2H, *J* = 5.4 Hz, CH_2), 3.83 (*s*, 6H, 2-OCH_3), 3.69 (*s*, 3H, OCH_3), 3.62 (*s*, 3H, $COOCH_3$), 2.34 (*t*, 2H, *J* = 8.0 Hz, CH_2), 2.06, 1.92 (2 × *m*, 2H, CH_2). ESI-MS (*m*/*z*): 412.8 [*M*—H]$^+$.

Crystal data

$C_{18}H_{24}N_2O_9$	D_x = 1.399 Mg m^{-3}
M_r = 412.39	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 1522 reflections
a = 27.665 (9) Å	θ = 2.2–22.0°
b = 5.1444 (16) Å	μ = 0.11 mm^{-1}
c = 13.907 (4) Å	T = 298 (2) K
β = 98.401 (5)°	Block, colorless
V = 1958.0 (11) Å^3	0.25 × 0.15 × 0.10 mm
Z = 4	

Data collection

Bruker SMART CCD area-detector diffractometer	R_{int} = 0.041
φ and ω scans	θ_{max} = 25.5°
9819 measured reflections	h = −33 → 26
3619 independent reflections	k = −6 → 6
2497 reflections with $I > 2\sigma(I)$	l = −16 → 16

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0676P)^2 + 0.7151P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.061	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.155	$\Delta\rho_{max}$ = 0.33 e Å^{-3}
S = 1.04	$\Delta\rho_{min}$ = −0.20 e Å^{-3}
3619 reflections	
267 parameters	
H-atom parameters constrained	

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O5—H5···O7^{i}	0.82	1.85	2.667 (3)	174
N2—H2···O6^{ii}	0.86	2.38	3.193 (3)	157
N1—H1···O4^{iii}	0.86	2.25	3.060 (3)	157
C11—H11···O6^{ii}	0.98	2.52	3.313 (3)	138
C18—H18*B*···O6^{iv}	0.96	2.47	3.014 (4)	116

Symmetry codes: (i) $x, -y+\frac{5}{2}, z-\frac{1}{2}$; (ii) $x, y-1, z$; (iii) $x, y+1, z$; (iv) $-x, y-\frac{3}{2}, -z+\frac{3}{2}$.

H atoms were positioned geometrically (with orientation to fit the observed electron density for the carboxylic O—H) and refined with a riding model [O—H = 0.82 Å, N—H = 0.86 Å, C—H = 0.93–0.98 Å, and U_{iso}(H) = xU_{eq}(carrier atom), where x = 1.5 for methyl H atoms and x = 1.2 for all other H atoms.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SAINT* (Bruker, 1997); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL* (Sheldrick, 2001); software used to prepare material for publication: *SHELXTL*.

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