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SYNTHESES AND CRYSTAL STRUCTURES OF METHYL 2-(4-(2-(4-((TERT-BUTOXYCARBONYL)AMINO)PHENYL)ACETAMIDO)PHENYL)ACETATE

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Abstract

The asymmetric unit of the title compound, $C_{22}H_{26}N_2O_5$, contains 1,2-diphenylethane-1,2-diimine and diisobutyl groups, with the dihedral angle between the phenyl rings being 89.23 (5)°. In the crystal, the molecules are elongated along the c-axis direction and stacked along the b-axis direction. Neither intra- or intermolecular hydrogen bondings nor aromatic π--π stacking interactions are observed. The volume of the crystal voids and the percentage of free space were calculated to be 53.38 $Å^3$ and 6.03%, showing that there is no large cavity in the crystal packing. Hydrogen bonding, N-H…O, π–π, C—H⋯π(ring) and van der Waals interactions are the dominant interactions in the crystal packing.

Keywords: methyl 2-(4-(2-(4-((tert-butoxycarbonyl)amino)phenyl)acetamido)phenyl)acetate; intermolecular hydrogen bonds; crystal structure; π-stacking;

1. Introduction

The molecule consists of a methyl ester group attached to a central acetic acid backbone, which is further substituted with aromatic rings and functional groups. The core structure features a phenyl ring linked via an acetamido group to another phenyl ring, which is further substituted with a tert-butoxycarbonyl (Boc) protected amino group. The Boc group serves as a protective moiety during synthesis, preventing undesired reactions at the amino site. γ-Amino acids are important components of α,γ-peptide hybrids, which are resistant towards enzymatic degradation and, as a result, display useful biological activity, including antibiotic, antiviral and anticancer properties. The acids are also important elements of foldamers. In comparison with the α-amino acids, they show significant flexibility due to the two additional single bonds between the carboxylic and amine functions. Still, their oligomers form well defined conformations in solutions, in particular helical ones in the case of monosubstituted γ-amino acids [1,2]. Thus, the structures and common conformations of γ-amino acids and their derivatives are of interest.

Protection of amino functionalities utilizing bulky tert-butylcarboxy groups is a common synthetic strategy in drug dicovery research programmes [3]. Typically, mono-substituted derivatives are formed from reactions of anilines and di-tert-butyldicarbonate, with di-substitution generally inhibited by the poorer nucleophilic character of the intermediate secondary carbamate.

2. Materials and methods

2.1. General Information

A survey of the Cambridge Structural Database (CSD, July 2025 update) [4] revealed 12 structures similar to the title compound (1Z,2Z)-N1 ,N20 -diisobutyl-1,2-diphenylethane-1,2-diimine.

2.2. Preparation and Characterization of Compounds

(3R)-4-((tert-Butoxycarbonyl)amino-)-3-benzyl-butanoic acid was obtained from racemic (±)-3-aminomethyl-4-phenylbutanoic acid hydrochloride, which was synthesized following earlier published procedure [5], with some modifications. Ethyl (±)-3-nitromethyl-4-phenylbutanoate was hydrolyzed and then hydrogenated using 10% Pd/C to get acid, which was transformed into Boc-derivative and purified by crystallization from ethyl acetate/hexane. The synthesis of methyl 2-(4-(2-(4-((tert-butoxycarbonyl)amino)phenyl)acetamido)phenyl)acetate involves multiple steps, including protection, coupling, and deprotection reactions. Initially, the Boc-protected amino phenyl derivative is prepared through amination of the corresponding phenyl precursor. Subsequently, this intermediate is coupled with the acetic acid derivative using peptide coupling reagents such as EDCI or DCC in an appropriate solvent like dichloromethane or DMF. The methyl ester is introduced via esterification reactions, often employing methyl iodide or methyl alcohol under acidic or basic conditions. Purification of the final compound is achieved through column chromatography or recrystallization.

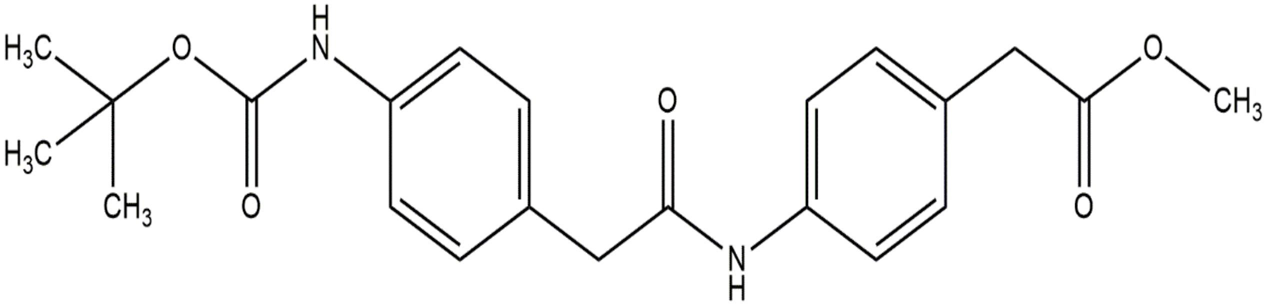

Fig. 1. Scheme

Data Collection

APEX2 (Bruker, 2005) [6]; cell refinement: SAINT-Plus (Bruker, 2008) [7]; data reduction: SAINT-Plus; program(s) used to solve structure: SHELXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008) [8,9]; molecular graphics: PLATON (Spek, 2009) [10] and Mercury (Macrae et al., 2006) [11]; software used to prepare material for publication: PLATON.

2.3. Structure Solution and Refinement

All H atoms were located in difference Fourier maps but finally their positions were determined geometrically, except H5 that was freely refined. H atoms were refined as riding on their carriers with C-H= 0.95 Å for aromatic CH groups, 0.97 Å for CH_2 groups, 0.96 Å for methyl groups and N—H = 0.86 Å for the amide group, and with $U_{iso}(H) = 1.2U_{eq}(C,N)$, except for methyl group where $U_{iso}(H) = 1.5U_{eq}(C)$. The absolute structure was known from the synthetic procedure and is confirmed by the Flack parameter of 0.05 (15).

3. Structural Commentary

he asymmetric unit of (I) contains 1,2-diphenylethane-1,2- diimine and diisobutyl groups (Fig. 1). One of the isopropyl groups (C20–C22) is disordered over two sets of sites with occupancies of 0.759 (7)/0.241 (7). In the dibenzyl moiety, there are no unusual bond distances or inter-bond angles. In the 1,2-diimine and diisobutyl moieties, the bond angles C1—N1—C9 [120.48 (11)°] and C2—N2—C19 [118.82 (12)°], and N1—C9—C10 [110.35 (11)°], N2—C19—C20 [112.00 (13)°] and N2—C19—C20A [114.3 (3)°] are significantly different. The same is true for the torsion angles C9—N1—C1—C2 [2.99 (19)°] and C19—N2—C2—C1 [0.8 (2)°], and C9—N1—C1—C3 [178.88 (11)°] and C19—N2—C2—C13 [179.18 (12)°]. The C —N distances [1.335 (2)–1.464 (2)Å] are in the normal range and are in good agreement those in similar reported structures [12,13]. The bond angles around the N1 and N2 atoms [359.3 (4)° and 360.07 (1)°, respectively], show sp^3 hybridization of the atoms. The presence of the carbonyl group linking the A and B rings contracts the bond angles C2—C1—C6 and C20—C15—C16 [118.17 (2) and 119.43 (2)°, respectively] and expands the bond angles C3—C4—C5 and C17—C18—C19 [121.04 (2)° and 121.51 (2)°, respectively]. These are shown qualitatively in a least-squares overlay plot (Fig. 3).

3.1 Supramolecular features

In the crystal, the molecules are elongated along the c-axis direction and stacked along the b-axis direction (Fig. 4). Neither intra- or intermolecular hydrogen bonding's nor N-H…O interactions are observed. In contrast, the packing of molecule consists of N-H…O hydrogen bonds to adjacent fumarate anions, forming extended hydrogen bonded chains. Three weak C-H…π(ring) interactions (Table 2) may help to consolidate of the packing.

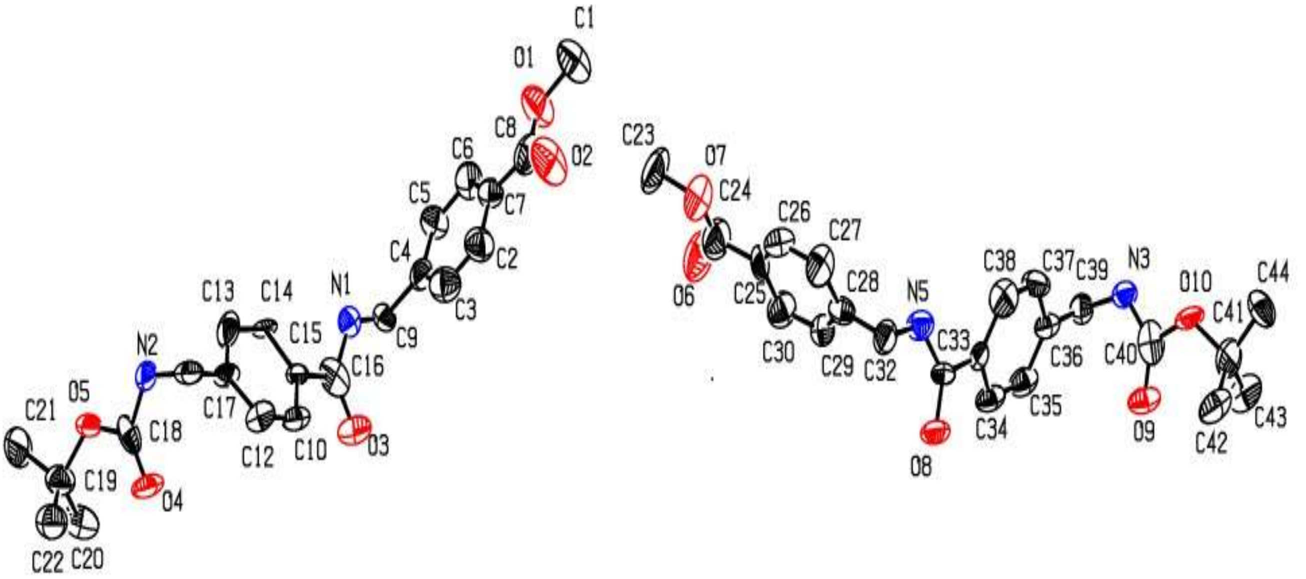

Fig. 2. The molecular structure of the title compound, with atom labels and 50% probability displacement ellipsoids.

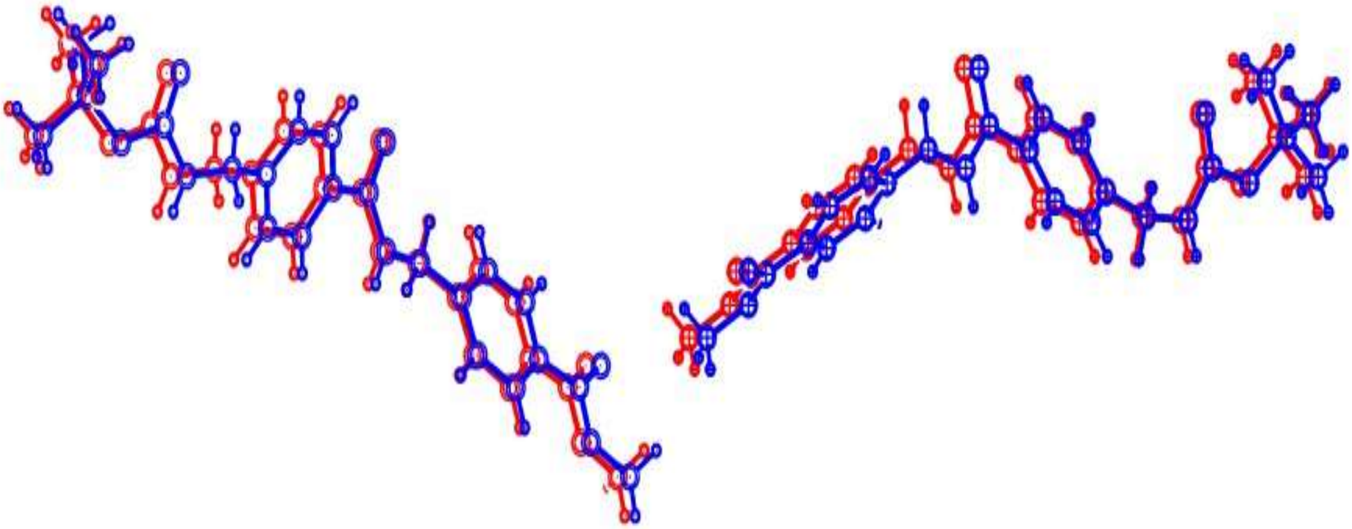

Fig. 3. A least-squares-fit overlay of the title compound.

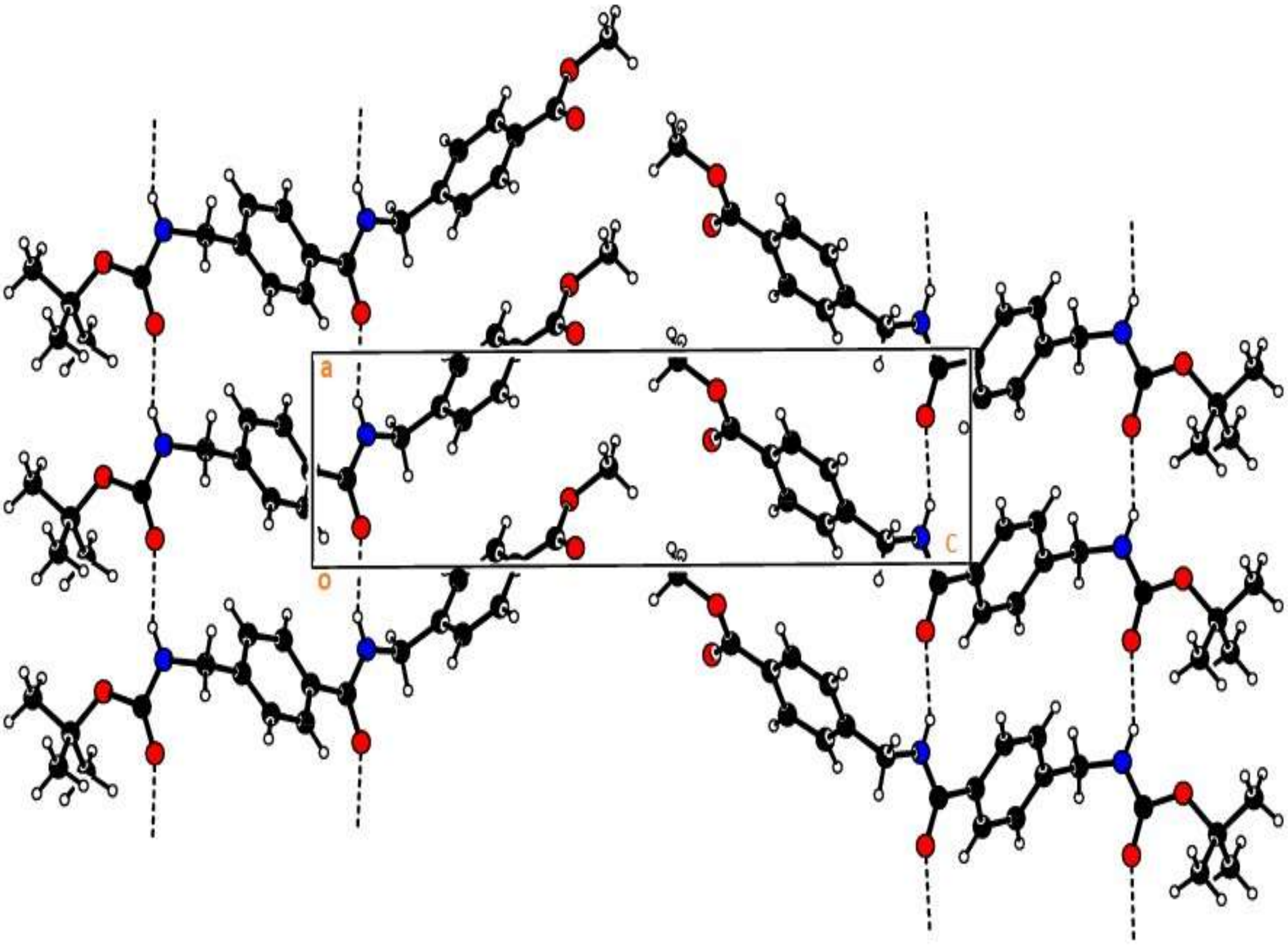

Fig. 4. Part of the crystal structure viewed along the [010] direction. Hydrogen bonds are shown as dashed lines

Table 1 The selected Bond length (Å) and Bond angles (˚)

Atom	Length(Å)	Atom	Angles(°)
O1-C1	1.49(2)	C1-O1-C2	117(2)
O4-C18	1.21(2)	C17-N2-C18	118.6(2)
N1-C10	1.36(2)	O2-C2-C3	127.4(2)
C3-C4	1.35(2)	C4-C3-C8	120.3(2)
O1-C2	1.34(2)	O3-C10-N1	119.3(2)
O5-C18	1.35(2)	O4-C18-N2	125.9(2)
C6-C9	1.49(2)	C20-C19-C22	110.1(2)
O6-C24	1.21(3)	C18-O5-C19	120.6(2)
O9-C40	1.23(2)	O1-C2-O2	121.0(2)
C25-C26	1.34(2)	C2-C3-C4	116.5(2)
O7-C23	1.46(2)	C3-C4-C5	120.8(2)
C28-C29	1.36(2)	O5-C18-N2	108(2)
C36-C39	1.48(2)	O5-C19-C22	109.9(2)
N5-C32	1.35(2)	C21-C19-C22	109.3(2)

Table 2 Hydrogen-bond geometry (Å ,°).

D-H…A	D-H	H…A	D…A	D-H…A
N1-H1…O3i	0.86	2.17	2.963(2)	154
N5-H5…O8i	0.86	2.15	2.943(2)	153
N2-H2…O4i	0.86	2.14	2.930(2)	153
N3-H3…O9i	0.86	2.16	2.944(2)	152

Symmetry code: i = 1+x,y,z

Table 3 Crystal Data and Details of the Structure Determination

Parameters	Title of compound
Empirical formula	C22 H26 N2 O5
Formula weight	398.45
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 5.177 (10) Å, α= 77.11°.
	b = 9.936 (6) Å, β= 89.73 (13)°.
	c = 20.87 (6) Å, γ = 89.92(7)°.

Volume	1047
Z	2
Density (calculated)	1.264 cm^{-3}
Absorption coefficient	0.090 mm^{-1}
F(000)	424
Crystal size	0.32 x 0.22 x 0.18 mm^3
Theta range for data collection	2.0 to 27.2°.
Index ranges	-6<=h<=6, -11<=k<=12, -26<=l<=26
Reflections collected	7983
Independent reflections	1853 [R(int) = 0.063]
Completeness to theta = 25.99°	95.10%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7486 and 0.6077
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7983 / 0 / 523
Goodness-of-fit on F2	0.89
Final R indices [I>2sigma(I)]	R1 = 0.0965, wR2 = 0.1343
R indices (all data)	R1 = 0.093, wR2 = 0.3173
Largest diff. peak and hole	0.21, -0.19 e.Å^{-3}

4. Acknowledgment

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