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ORIGINAL RESEARCH

Synthesis, Separation and Crystal Structures of *E* and *Z* Isomers of 3-(2,5-Dimethoxyphenyl)-2-(4-Methoxyphenyl)Acrylic Acid

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Abstract Synthesis, separation and X-ray crystal structures of *E* and *Z* isomers of 3-(2,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylic acid are reported. Separation of *E* and *Z* isomers from a 1:1 mixture has been carried out by selective acidification of their sodium salts carefully controlling the pH of the solution. The structures of *E* and *Z* isomers were confirmed by determining crystal structures of these isomers using single crystal X-ray diffraction. The *E* isomer crystallizes in the $P2_1/c$ space group with $a = 11.493(2)$ Å, $b = 5.5456(11)$ Å, $c = 24.900(5)$ Å, $\alpha = 90°$, $\beta = 92.36(3)°$, $\gamma = 90°$, $Z = 4$. The *Z* isomer crystallizes in the $P2_1/c$ space group with $a = 10.192(2)$ Å, $b = 12.893(3)$ Å, $c = 13.948(3)$ Å, $\alpha = 90°$, $\beta = 92.18(3)°$, $\gamma = 90°$, $Z = 4$. Details of the synthesis and structural characterization and X-ray crystal structure determination of the title compounds are presented.

Keywords *E* and *Z* isomers · Diarylacrylic acid · X-ray · Single crystal structures

Introduction

Gram-positive bacteria such as staphylococci and streptococci are endowed with a multitude of cell-wall anchored proteins that serve as an interface between the microbe and its host. Sortase A (SrtA), a cysteine transpeptidase, participates in secretion and anchoring many of these cell wall proteins by a mechanism conserved in almost the entire class of gram-positive bacteria [1, 2]. Sortase A, because of its control over the cellular location of multiple virulence factors, is an attractive potential target for the development of antibacterial drugs [1–3]. Based on a hit from random screening, Oh et al. have recently reported a novel small-molecule inhibitor (**1**), a diarylacrylonitrile derivative for *S. aureus* SrtA with IC_{50} value of 9.2 μM in vitro [4]. High resolution X-ray crystal structures of *S. aureus* SrtA and its complex with natural substrate (LPETG) have recently been obtained by Narayana and coworkers [5, 6]. As a part of a project aimed at developing inhibitors of SrtA, we were interested in making structural modifications to the identified lead inhibitor **1** (Fig. 1).

Inhibitor **1** has a *Z* diarylacrylonitrile ring system. The aryl ring (ring A) close to the CN group has a methoxy group at the 4-position and the second aryl ring (ring B) has two methoxy groups at the 2′- and 5′-positions. By designing molecules that are variations of this template, we hoped to discover new compounds that will inhibit SrtA with higher binding affinities. Molecular modeling and 'DOCKing' efforts, using the crystal structure of SrtA, helped us position this inhibitor in the enzyme active site. Our computer model of inhibitor **1** in the enzyme active site has revealed a set of interactions that could be exploited for the design of new inhibitors. One of the key interactions is that of the linear CN group present in inhibitor **1** with the guanidine side chain of Arg197 moiety in the active site. We propose to modify this CN group to a more polar COOH group which is expected to result in a salt bridge interaction with Arg197 side chain. This will enhance the binding of the inhibitor in the enzyme active site. With this goal we proposed to make the target carboxylic acid derivative **2**. In this manuscript, we present the

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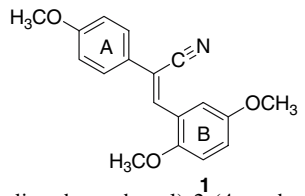

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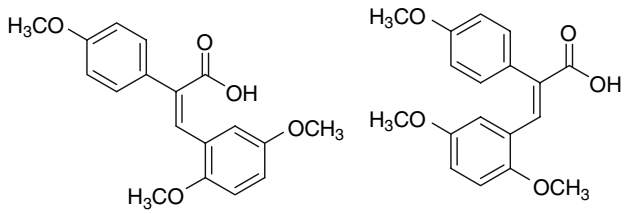
Fig. 1 (*Z*)-3-(2,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylonitrile (1)



2 3

Fig. 2 *Z* and *E* isomers of 3-(2,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylic acid

synthesis and X-ray crystals structures of the target carboxylic acid derivative **2** and its geometrical isomer **3** (Fig. 2).

Experimental Section

Synthesis

Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. IR spectra were taken with Brucker Vector-22 and Bomen MB-104 instruments. All ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 300 MHz spectrometer using TMS as internal standard. The values of chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Elemental analyses were performed by Atlantic Microlab, Norcross, Georgia and the results are within $\pm$0.4% of theoretical values. Reactions were monitored by TLC (Whatmann, Si gel, UV 254, 25 μM plates). The solvents used for reactions were purchased as anhydrous in Sure-Seal^{TM} bottles from Aldrich chemical company. The chemicals used are purchased from Aldrich, Lancaster or Fisher chemical companies and used as received.

(*E*)-3-(2,5-Dimethoxyphenyl)-2-(4-Methoxyphenyl)Acrylic acid (3)

To a solution of 4-methoxyphenylacetic acid, **4** (2 g, 12 mmol) in acetic anhydride (7 mL) and 2,5-dimethoxybenzaldehyde, **5** (2 g, 12 mmol) and Et_3N (1.4 mL) were added and the resulting mixture was stirred at room temperature for 5 min. The reaction mixture was then heated at 140 °C for 24 h. TLC (EtOAc/hexanes, 1:1) indicated the completion of the reaction. The reaction mixture was allowed to attain room temperature and acetic anhydride was completely removed under reduced pressure using a rotary evaporator. The residue obtained was stirred with 1N NaOH solution (75 mL) for 12 h. The reaction mixture was then diluted with water (75 mL) and washed with chloroform (3× 30 mL). The aqueous layer was cooled to 0 °C and acidified by slow addition of conc. HCl. The resulting solid was filtered under suction, washed with water and dried. This crude product was recrystallized from a mixture of EtOAc and hexanes (1:1) to afford the *E* isomer of 3-(2,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylic acid, **3** (2.5 g, 66%); m.p. 195 °C. ^{1}H NMR ($CDCl_3$) δ 3.32 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 6.35 (s, 1H), 6.76–6.79 (m, 2H), 6.87–6.97 (m, 2H), 7.14–7.22 (m, 2H) and 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.3, 55.5, 56.4, 112.1, 114.3, 114.5, 117.8, 124.0, 127.9, 131.1, 131.5, 137.0, 152.7, 153.2, 159.4 and 173.6; IR (neat): ν 2,459–3,329 cm^{-1}; 1,677 cm^{-1}; MS (ES^{+}) *m/z* 313 (M–H). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.63; H, 5.82.

(*Z*)-3-(2,5-Dimethoxyphenyl)-2-(4-Methoxyphenyl)Acrylic Acid (2)

The *E* isomer of the acid, **3** (1.2 g, 3.8 mmol) was dissolved in acetonitrile (100 mL) and was irradiated with UV light (λ = 254 nM, Rayonet RPR-2000 reactor) for 4 h. TLC ($CHCl_3$/MeOH, 9:1) and ^{1}H NMR indicated that the isomerization is complete and it is a 1:1 mixture of *E–Z* isomers. The solvent was completely removed under reduced pressure to obtain the *E–Z* mixture. The *E–Z* mixture (750 mg, 2.39 mmol) was dissolved in 1N NaOH (80 mL) and stirred for 30 min. The insoluble impurities were filtered off. The filtrate was acidified by careful drop wise addition of glacial acetic acid (The pH was monitored using a pH meter). A light yellow solid was precipitated at the pH of 4.8–5.0. This was filtered off and dried to furnish 285 mg (38%) of the *E* isomer (**3**). The filtrate was then further acidified by careful drop wise addition of 6N HCl until a pH of 3.3–3.5. An off-white solid precipitated at this pH. This was filtered under suction and dried to furnish the *Z* isomer of 3-(2,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylic acid, **2** (299 mg, 40%); m.p. 102 °C; ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3H), 3.78 (s, 3H), 3.84 (s, 3H), 6.80–6.83 (m, 2H), 6.86–6.94 (m, 2H), 6.95–7.0 (m, 1H), 7.14 (s, 1H) and 7.39–7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.5, 55.8, 55.9, 111.9, 114.1, 114.7, 115.2, 125.7, 128.6, 128.9, 129.9, 134.1, 151.6, 153.4, 159.8 and 175.5; IR (neat): ν 2,452–3,312 cm^{-1}; 1,677 cm^{-1}; MS (ES^{+}) *m/z* 313 (M–H). Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.40; H, 5.76.

X-ray Data Collection and Solution

A suitable single crystal of each compound was glued on a glass fiber with epoxy and aligned upon an Enraf Nonius CAD4 single crystal diffractometer under aerobic conditions. Standard peak search and automatic indexing routines followed by least squares fits of 25 accurately centered reflections resulted in accurate unit cell parameters for each. The space groups of the crystals were assigned on the basis of systematic absences and intensity statistics. All data collection was carried out using the CAD4-PC software [7], and details of the data collections are given in Table 1. The analytical scattering factors of the complex were corrected for both $\Delta f'$ and $i\Delta f''$ components of anomalous dispersion. All data were corrected for the effects of absorption and for Lorentz and polarization effects.

All crystallographic calculations were performed with the Siemens SHELXTL-PC program package [8]. All heavy atom positions were located using Direct Methods with carboxylic acid hydrogen atoms located in difference Fourier maps. Full matrix refinement of the positional and anisotropic thermal parameters for all these atoms versus F^2 was carried out. All other hydrogen atoms were placed in calculated positions with the appropriate molecular geometry and the d(C–H) = 0.96 Å. The isotropic thermal parameter associated with each hydrogen atom was fixed equal to 1.2 times the U_{eq} of the atom to which it was bound. Selected bond lengths and angles for complexes **2** through **3** are given in Table 2; selected dihedral angles and torsion angles are given in Table 3. Crystallographic data for all complexes have been deposited with the Cambridge Crystallographic Database (**2**: CCDC 620355; **3**: CCDC 620356).

Table 1 Crystal and structure refinement data for compounds **2** and **3**

	2	**3**
Empirical formula	$C_{21}H_{21}O_5$	$C_{18}H_{18}O_5$
CCDC deposit no.	620355	620356
Formula weight	353.38	314.32
Temperature	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Unit cell dimensions	a = 10.192(2) Å	a = 11.493(2) Å
	b = 12.893(3) Å	b = 5.5456(11) Å
	c = 13.948(3) Å	c = 24.900(5) Å
	β = 92.18(3)°	β = 92.36(3)°
Volume	1831.6(6) Å^3	1585.6(5) Å^3
Z	4	4
Density (calculated)	1.175 mg/m^3	1.317 mg/m^3
Absorption coefficient	0.085 mm^{-1}	0.096 mm^{-1}
F(000)	685	664
Crystal size	0.4 × 0.5 × 0.8 mm^3	0.2 × 0.2 × 0.7 mm^3
θ range for data collection	2.00–22.46°	2.36–22.48°
Index ranges	$-10 \le h \le 10$, $-13 \le k \le 0$, $-14 \le l \le 1$	$-12 \le h \le 12$, $-5 \le k \le 0$, $-1 \le l \le 26$
Reflections collected	2717	2222
Independent reflections	2379 [R(int) = 0.0340]	2062 [R(int) = 0.0565]
Completeness to θ = 22.48°	100.00%	99.90%
Absorption correction	None	None
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2379/0/244	2062/0/216
Goodness-of-fit on F^2	1.03	1.002
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0453, w$R2$ = 0.1200	$R1$ = 0.0662, w$R2$ = 0.1565
R indices (all data)	$R1$ = 0.0776, w$R2$ = 0.1373	$R1$ = 0.1639, w$R2$ = 0.1913
Extinction coefficient	0.015(2)	0.0023(17)
Largest diff. peak and hole	0.189 and −0.185 e Å^{-3}	0.207 and −0.188 e Å^{-3}

Table 2 Selected bond lengths (Å) and angles (°) for **2** and **3**

	2	3
C(3)–C(4)	1.473(3)	1.469(6)
C(1)–O(1)	1.294(3)	1.305(5)
C(1)–C(2)	1.497(3)	1.485(6)
C(2)–C(3)	1.332(3)	1.340(6)
C(2)–C(10)	1.486(3)	1.475(6)
C(1)–O(2)	1.226(3)	1.227(5)
C(3)–C(2)–C(10)	125.2(2)	124.3(4)
O(2)–C(1)–C(2)	121.9(2)	121.3(4)
O(1)–C(1)–C(2)	115.3(2)	116.5(5)
C(3)–C(2)–C(1)	119.5(2)	119.3(4)
C(10)–C(2)–C(1)	115.3(2)	116.4(4)
C(2)–C(3)–C(4)	127.2(2)	129.6(4)
C(5)–C(4)–C(3)	122.0(2)	118.8(4)
C(11)–C(10)–C(2)	121.4(2)	121.5(4)
C(15)–C(10)–C(2)	121.9(2)	121.9(5)
C(9)–C(4)–C(3)	119.3(2)	123.5(5)
O(2)–C(1)–O(1)	122.8(2)	122.3(5)

Table 3 Selected dihedral angles (°) and torsion angles (°) for compounds **2** and **3**

	2	3
C(4)–C(9) ring, C(10)–C(15) ring	53.87	70.37
C(10)–C(15) ring, alkene[a]	16.62	73.88
C(4)–C(9) ring, alkene[a]	37.28	19.00
Alkene[a], carboxylic acid[b]	66.85	6.74
C(2)–C(3)–C(4)–C(5)	−37.82	161.40

[a] Alkene defined by plane through C(2)–C(3)–H(3)

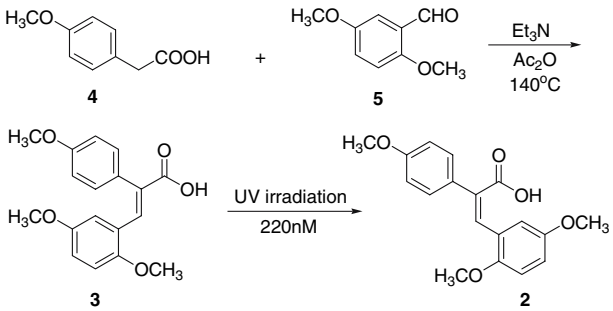
[b] Carboxylic acid defined by plane through O(2)–C(1)–O(1)

Results and Discussion

Synthesis

Our initial attempt to make compound **2** was by directly hydrolyzing the CN group present in inhibitor **1**. Inhibitor **1** was prepared according to the reported literature procedure [4]. Attempts were made to hydrolyze the cyanide group present in inhibitor **1** to corresponding carboxylic acid by treatment with con HCl [9]. However, this reaction did not yield the expected product possibly because the staring material underwent polymerization under strongly acidic conditions. Basic hydrolytic conditions were also attempted for this transformation without significant success.

We then decided to make the target compound **2** by a more traditional method of condensing 4-methoxyphenyl acetic acid with 2,5-dimethoxybenzaldehyde in the presence of a base [10]. The literature indicates that this reaction leads only to the formation of the *E* isomer (**3**). So, the isomerization of the product from an *E* to *Z* form would be a necessary step. We used a modified literature procedure [11] to make the *E* isomer (**3**) by the condensation of 4-methoxyphenyl acetic acid (**4**) and 2,5-dimethoxybenzaldehyde (**5**) in the presence of triethyl amine in acetic anhydride (Scheme 1).



Scheme 1 Synthesis of *E* and *Z* isomers of 3-(2,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylic acid

This reaction resulted in the formation of only *E* isomer (**3**) in excellent yield. A solution of **3** in acetonitrile was irradiated with UV light ($\lambda = 254$ nM, Rayonet RPR-2000 reactor) for 4 h to obtain a 1:1 mixture of *E* and *Z* isomers of 3-(2,5-dimethoxyphenyl)-2-(4-methoxyphenyl)acrylic acid. This mixture was converted to corresponding sodium salts by dissolving in 1N NaOH solution. This solution was then acidified with acetic acid by carefully controlling the pH of the solution by using a pH meter. The *E* isomer (**3**) precipitated out at the pH of 4.8–5.0. This was filtered off and the filtrate was further acidified with 6N HCl. The *Z* isomer (**2**) precipitated out at the pH of 3.3–3.5. In order to confirm the stereochemistry of the isomers, they were crystallized by slow evaporation from the solvent combination of benzene and hexanes and structures were determined by X-ray crystallography.

X-ray Crystal Structures

The crystal structures of **2** and **3** exhibit a number of features that differ from one another as shown in Figs. 3 and 4.

However, one important feature that the two compounds share is the presence of intermolecular hydrogen bonding between the carboxylic acid groups in adjacent molecules in the crystal lattice (Figs. 5 and 6). In contrast, there is no intramolecular hydrogen bonding between the carboxylate groups and the adjacent methoxy groups in either compound that would possibly affect the conformation of their enzymatic binding sites.

When investigating the relative conformations of the two compounds, several differences are seen. Table 3 gives

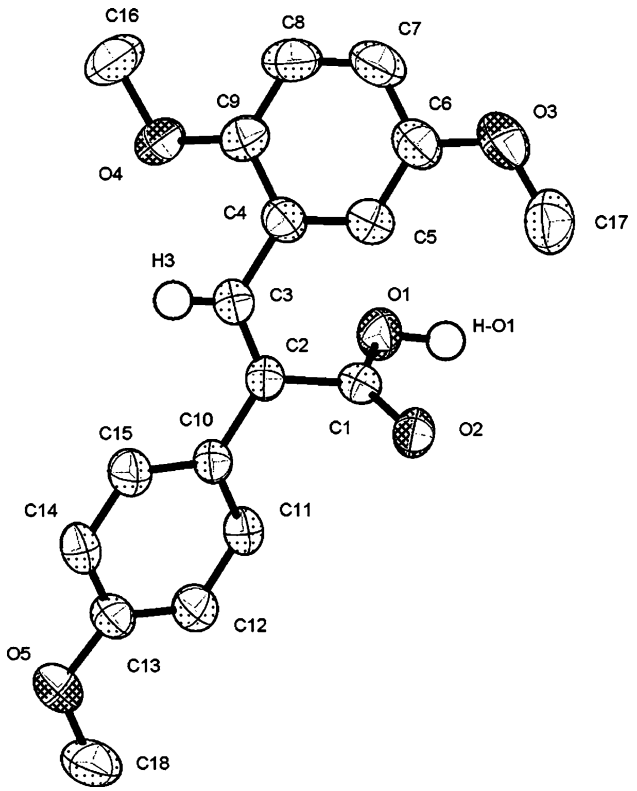


Fig. 3 ORTEP [13] drawing of the molecular structure of the *Z* Isomer, **2**. Thermal ellipsoids are drawn at 50% and nonspecific hydrogens are omitted for clarity

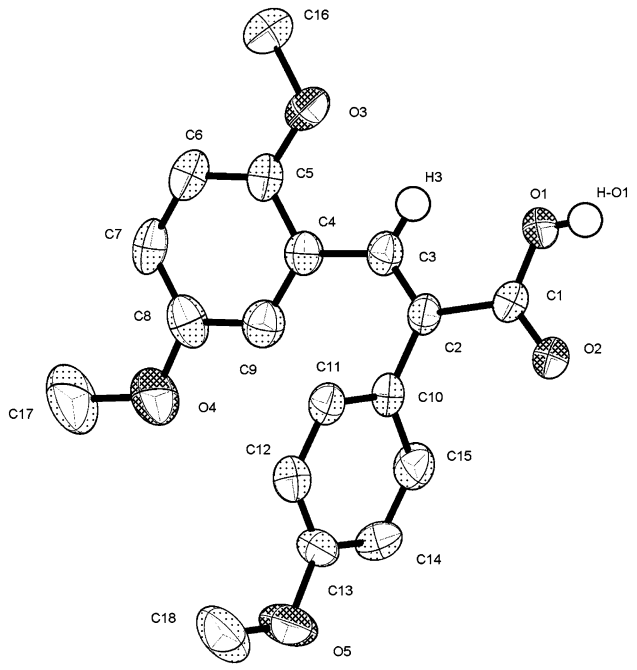


Fig. 4 ORTEP [13] drawing of the molecular structure of the *E* Isomer, **3**. Thermal ellipsoids are drawn at 50% and nonspecific hydrogens are omitted for clarity

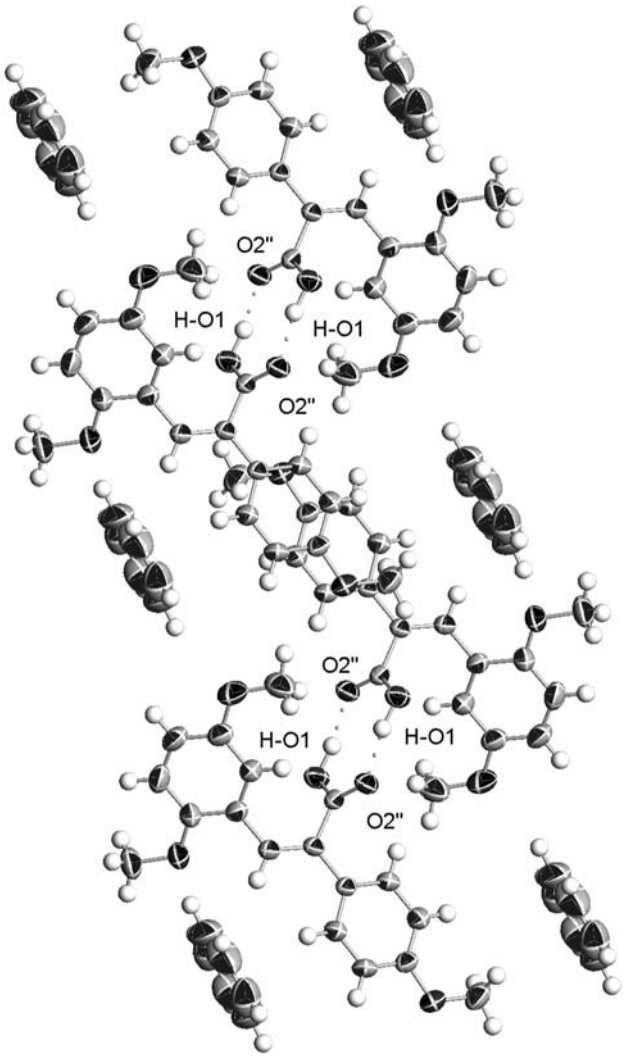


Fig. 5 ORTEP [13] Packing Diagram of the molecular structure of the *Z* Isomer, **2**, showing intermolecular hydrogen bonding. Thermal ellipsoids are drawn at 50%

selected dihedral angles and torsion angles for specific sections of each molecule. From this data, one can see that the *E* isomer (**3**) is considerably more sterically hindered by the interaction between the two rings causing them to twist out of plane with one another. This is demonstrated by the 70.37° dihedral angle between the planes of the two rings as well as the torsion angle of 161.40° about the C(3)–C(4) bond. This conformation also shows little or no interaction between the dimethoxy ring and the carboxylate group which results in the alkene double bond and the carboxylate group being coplanar (dihedral angle = 6.74°) and thus conjugated. In contrast, the *Z* isomer (**2**) is much more planar overall. However, increased interaction between the dimethoxy ring and the carboxylate group results in the carboxylate group twisting out of plane and thus lessens the amount of conjugation (dihedral angle = 66.85°).

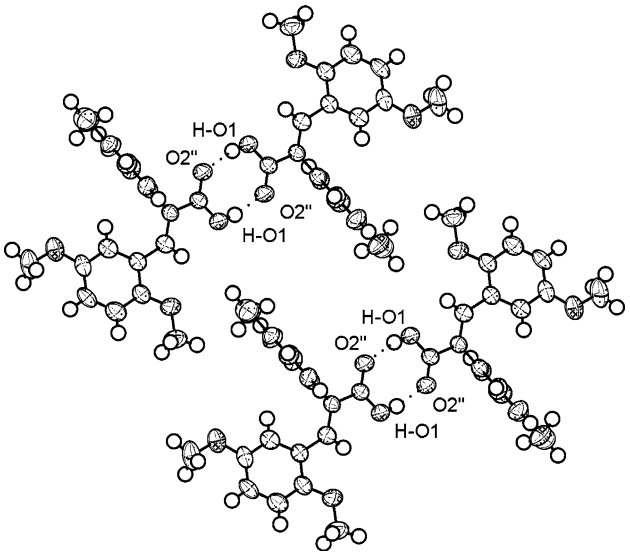


Fig. 6 ORTEP [13] Packing Diagram of the molecular structure of the *E* Isomer, **3**, showing intermolecular hydrogen bonding. Thermal ellipsoids are drawn at 50%

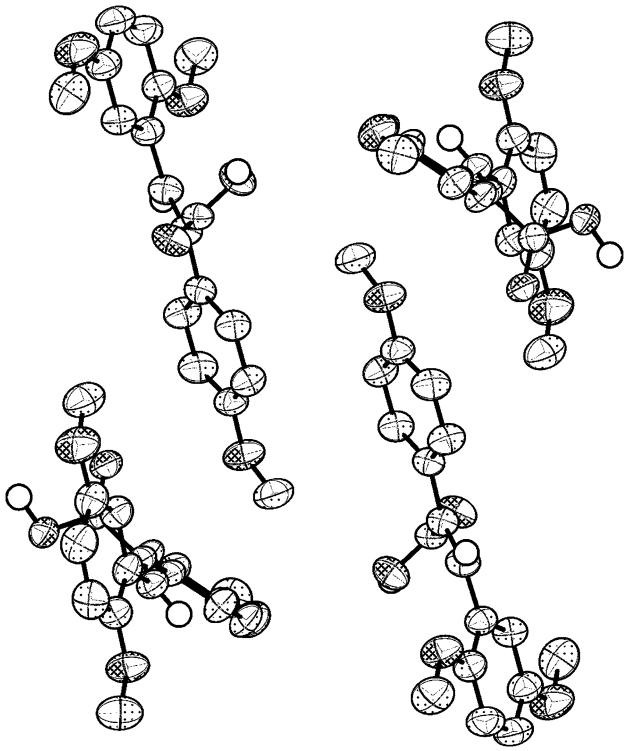


Fig. 7 ORTEP [13] Packing Diagram of the molecular structure of the *Z* Isomer, **2**, showing intermolecular π–π stacking. Thermal ellipsoids are drawn at 50%

One final point of interest is the manner in which these compounds stack in the crystal lattice with respect to the two rings. The *Z* isomer (**2**) exhibits π–π stacking (Fig. 7) between adjacent molecules in the unit cell whereas this is not seen in the *E* isomer (**3**). The interplanar distance between interacting rings of 3.423 Å is consistent with previous work done on purine rings by Bugg et al., who found the distances of interacting rings in stacked structures to be 3.879 Å [12]. The presence of this interaction in the *Z* isomer (**2**) is likely due to the increased planarity of the molecule, which allows for the rings to orient themselves on one another to stack throughout the lattice. The *E* isomer (**3**) has the rings twisted much more out of plane with one another preventing adjacent molecules from π–π stacking.

References

1. Cossart P, Jonquières R (2000) Proc Natl Acad Sci USA 97:5013–5015
2. Navarre WW, Schneewind O (1999) Microbiol Mol Biol Rev 63:174–229
3. Supuran CT, Scozzafava A, Clare BW (2002) Med Res Rev 22:329–372
4. Oh KB, Kim SH, Lee J, Cho WJ, Lee T, Kim S (2004) J Med Chem 47:2418–2421
5. Zong Y, Bice T, Ton-That H, Schneewind O, Narayana SVL (2004) J Biol Chem 279:31383–31389
6. Zong Y, Mazmanian SK, Schneewind O, Narayana SVL (2004) Structure 12:105–112
7. CAD4-PC Ver. 1.2 (1988) Enraf Nonius Co, Delft, The Netherlands
8. Sheldrick GM (2001) SHELXTL NT Ver. 6.12. Bruker AXS, Madison, WI
9. Newkome GR, Arai S, Fronczek FR, Moorefield CN, Lin X, Weis CD (1993) J Org Chem 54:898–903
10. Ohsumi K, Nakagawa R, Fukuda Y, Hatanaka T, Morinaga Y, Nihei Y, Ohishi K, Suga Y, Akiyama Y, Tsuji T (1998) J Med Chem 41:3022–3032
11. Royer R, Bodo B, Demerseman P, Clavel JM (1971) Bulletin de la Societe Chimique de France 2929–2933
12. Thewalt J, Bugg CE (1972) Acta Cryst B 28:871–879
13. Burnett MN, Johnson CK (1996) ORTEP-III: Oak ridge thermal ellipsoid plot program for crystal structure illustrations, Oak Ridge National Laboratory Report ORNL-6895