Synthesis and Crystal Structures of the Derivatives of Butyrate and 1,3-Dioxane; Allyl 2-acetyl-3-(phenylamino)butanoate, 2,6-Dimethyl N-(4-methylphenyl)-1,3-dioxan-4-amine and N-(3,5-Diflourophenyl)-2,6-dimethyl-1,3-dioxan-4-amine

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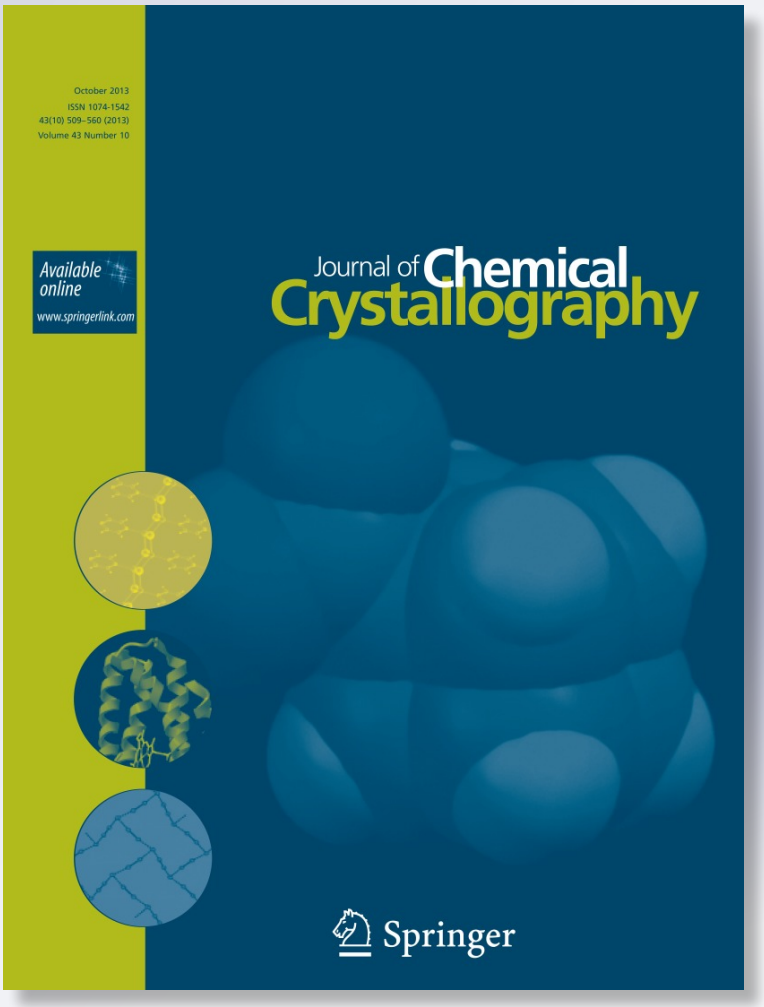

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ORIGINAL PAPER

Synthesis and Crystal Structures of the Derivatives of Butyrate and 1,3-Dioxane; Allyl 2-acetyl-3-(phenylamino)butanoate, 2,6-Dimethyl *N*-(4-methylphenyl)-1,3-dioxan-4-amine and *N*-(3,5-Diflourophenyl)-2,6-dimethyl-1,3-dioxan-4-amine

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Abstract Butyrate derivatives of allyl 2-acetyl-3-(phenylamino)butanoate (**1**) and 1,3-dioxane derivatives of 2,6-dimethyl *N*-(4-methylphenyl)-1,3-dioxan-4-amine (**2**) and *N*-(3,5-diflourophenyl)-2,6-dimethyl-1,3-dioxan-4-amine (**3**) were synthesised. Their structures were characterized by FTIR (**1**) ^{1}H NMR, ^{13}C NMR spectroscopic techniques and single crystal X-ray diffraction. The compound (**1**) crystallizes in the triclinic crystal system with the space group p-1 with a = 10.0874(5) Å, b = 10.1751(5) Å, c = 14.1930(8) Å, α = 82.429(4)°, β = 77.482(4)°, γ = 80.820(4)°, v = 1396.77 (13) Å^3. The compound (**2**) crystallizes in the monoclinic space group $P2_{1/C}$ with unit cell dimensions a = 9.8454(3) Å, b = 13.3032(4) Å, c = 10.1967(3) Å, α = 90°, β = 114. 821(2)°, γ = 90°, v = 1212.15(6) Å^3. The compound (**3**) crystallizes in the triclinic space group p-1 with unit cell dimensions a = 9.65630(10) Å, b = 11.2266(2) Å, c = 11.2658(2) Å, α = 83.7710(10)°, β = 79.1770(10)°, γ = 77.1290(10)°, v = 1166.59(3) Å^3.

Keywords Synthesis · Single crystal · X-ray diffraction · Hydrogen bond · Crystal structure · Ring motif

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Introduction

Butyrate (butanoate) controls colonic tumour cells and promotes healthy colonic epithelial cells [1]. Dietary fibres play a major role in colon cancer. The fatty acids produced from butyrate by fermentable fibres mimics the role of dietary fibres in colon cancer [2]. The bacterial fermentation of dietary fibres in colonic lumen shows butyrate as a major metabolite. In inflammation mediated ulcerative colitis and colorectal cancer, butyrate exhibits promising preventive and therapeutic potential. The mechanism has been suggested that butyrate enhances apoptosis of T cells in the colonic tissue and thereby eliminates the source of inflammation production of *N*-butyrate, an antineoplastic agent which inhibits proliferation and induces differentiation in a variety of transformed cell types in vivo [3]. *N*-butyrate has been shown to induce antigen-specific nonresponsiveness in CD41 T cells in vivo [4]. In pharmaceutical preparations, oxygen heterocycles plays a vital role as basic building blocks. Dioxane rings are frequently encountered in structural motifs in many bioactive molecules such as cytotoxic agents [5], derivatives of 2-substituted 1,3-dioxanes (antimuscarinic agents) [6] as a novel activator of low density lipoprotein receptor promoters [7] and 2,2-diphenyl-1,3-dioxane derivatives as effective agents against multidrug resistance [8]. The excellent biological and pharmacological role of butyrate and 1,3 dioxane prompted us to synthesize three novel compounds, namely, allyl-2-acetyl-3-(phenylamino)butanoates,

2,6-dimethyl *N*-(4-methylphenyl)-1,3-dioxan-4-amine and *N*-(3,5-difluoro phenyl)-2,6-dimethyl-1,3-dioxan-4-amine with butanoate and 1,3 dioxane as one of the structural motifs. Further, the structural elucidation of the three compounds helps us to understand the conformational features of these molecules which are essential for the structural activity investigations of these pharmaceutical preparations.

Experimental

Instrumentation

Solvents and reagents were purchased from Aldrich and used without further purification. Melting points were taken on Elchem Microprocessor-based DT apparatus in open capillary tubes and were corrected relative to benzoic acid. Fourier Transform Infrared Spectra were obtained on an Avatar-330 FTIR spectrometer (Thermo Nicolet) using KBr pellets. The NMR spectra were recorded on a Bruker Avance 200 and 300 MHz. The purity of the compounds was confirmed by thin layer chromatography using Merck silica gel 60 F_{254} coated aluminium plates.

X-Ray Crystallography

A single crystal suitable for X-ray diffraction was mounted on glass fibres. The crystal was placed in the cold stream of an Oxford Cryosystems Cobra open-flow nitrogen cryostat [9] operating at 100.0 (1) K and the diffraction data were collected on Bruker SMART APEXII CCD area-detector diffractometer with Mo–Kα radiation (λ = 0.71073 Å) The data for these compounds were processed with SAINT and corrected for absorption using SADABS [10]. The structures were solved by direct methods using the program SHELXTL [11] and refined by full-matrix least squares technique on F^2 using anisotropic displacement parameters using SHELXTL [11] program. All geometrical calculations were carried out using the program PLATON [12]. The molecular graphics were drawn using SHELXTL [11] program. The N-bound hydrogen atoms was located in a difference Fourier map and refined freely [0.81(3)–0.95(4) Å]. The remaining hydrogen atoms were fixed at calculated positions with a common isotropic displacement parameters set to 1.2 (1.5 for methyl groups) times the equivalent isotropic U values of the parent carbon atoms. A rotating group model was applied to the methyl groups.

Table 1 The crystal data and parameters for structure refinement of (**1**), (**2**) and (**3**)

Parameters	Compound (**1**)	Compound (**2**)	Compound (**3**)
Molecular formula	$C_{15}H_{19}$ N O_3	C_{13} H_{19} N O_2	C_{12} H_{15} F_2 N O_2
Molecular weight	261.31	221.29	243.25
Crystal system	Triclinic	Monoclinic	Triclinic
Space group	P-1	P 2_1/c	P-1
a (Å)	10.0874(5)	9.8454(3)	9.65630(10)
b (Å)	10.1751(5)	13.3032(4)	11.2266(2)
c (Å)	14.1930(8)	10.1967(3)	11.2658(2)
α (°)	82.429(4)	90	83.7710(10)
β (°)	77.482(4)	114.82(2)	79.1770(10)
γ (°)	80.820(4)	90	77.1290(10)
v ($Å^3$)	1396.77(13)	1212.15(6)	1166.59(3)
Z	4	4	4
Dcalc (g cm^{-3})	1.243	1.213	1.385
Crystal dimensions (mm)	0.34 × 0.11 × 0.09	0.49 × 0.30 × 0.28	0.50 × 0.26 × 0.19
μ (mm^{-1})	0.086	0.081	0.115
Radiation λ (Å)	0.71073	0.71073	0.71073
Tmin/Tmax	0.9711/0.9927	0.9616/0.9776	0.9451/0.9791
Reflections measured	1958	3815	9625
Ranges/indices (h, k, l)	−11, 11; −12, 12;−16, 16	−14, 14; −20, 20; −15, 15	−12, 12; −14, 12;−14, 14
θ limit (°)	1.48–25.00	2.28–32.62	1.84–27.50
Unique reflections ($I > 2\sigma(I)$)	14018	16637	22944
Parameters	355	152	319
Goodness of fit on F2	1.016	1.043	1.031
R1[$I > 2\sigma(I)$], wR2 (all data)	0.0646, 0.1664	0.0532, 0.1391	0.0376, 0.1058

Table 2 The geometry of the hydrogen bonds (Å, °)

D H···A	d(D–H)	d(H···A)	d(D···A)	<(D–H···A)
Compound (**1**)				
N1A–H1NA···O2B[a]	0.95(4)	2.10(4)	3.050(4)	179(3)
N1B–H1NB···O2A[a]	0.81(3)	2.27(3)	3.044(4)	161(3)
C1A–H1AA···O3B[b]	0.9500	2.6000	3.545(4)	173.00
C7A–H7AA···O3B[b]	1.0000	2.5600	3.531(4)	165.00
C1B–H1BA···O3A[b]	0.9500	2.5700	3.511(4)	173.00
C7B–H7BA···O3A[b]	1.0000	2.4400	3.416(4)	166.00
Compound (**2**)				
C5–H5A···O1[c]	0.9500	2.4700	3.3394(15)	152.00
Compound (**3**)				
N1A–H1NA···O1A[c]	0.876(17)	2.359(17)	3.2105(14)	164.4(15)
C8A–H8AA···O2A[d]	0.9900	2.4800	3.4496(15)	167.00
N1B–H1NB···O1B[e]	0.862(17)	2.575(17)	3.4223(14)	167. 5(15)
C8B–H8BB···O2B[f]	0.9900	2.6000	3.5787(15)	172.00
C4B–H4BA···O1A[g]	0.9500	2.5700	3.4202(16)	150.00

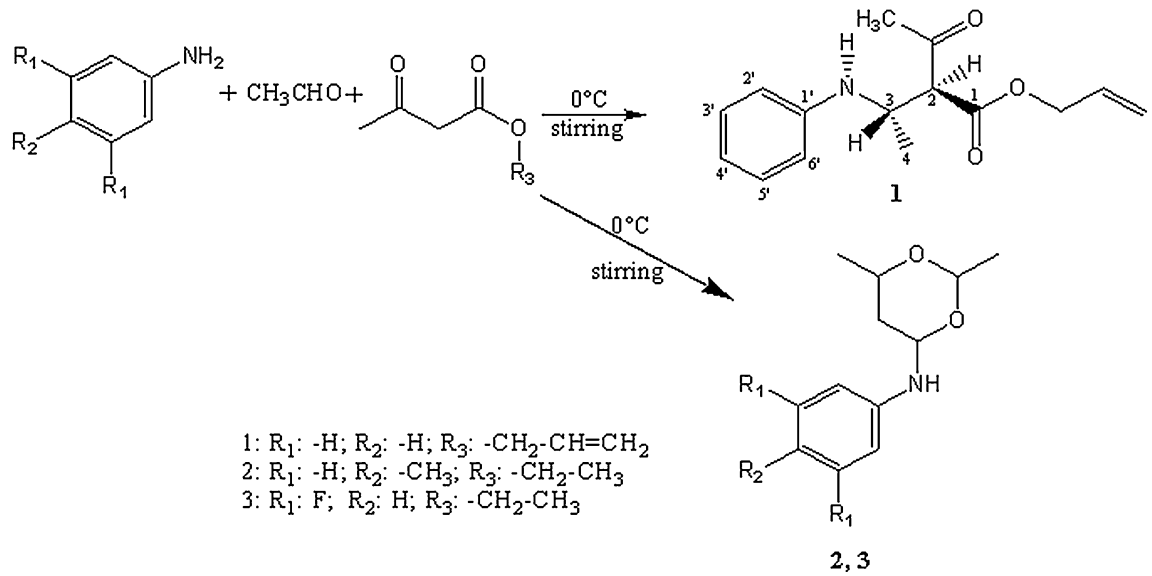
Symmetry code: [a][1 − x, 1 − y, 1 − z]; [b][−x, 1 − y, 1 − z]; [c][1 − x, −y, 1 − z]; [d][1 − x, −y, 1 − z]; [e][1 − x, 1 − y, −z]; [f][−x, 1 − y, 1 − z]; [g][x, −1 + y, z]

The crystallographic data are given in Table 1. Hydrogen bonding interactions are shown in Table 2. The scheme of the synthesis of the compounds and plausible reaction mechanism are shown in Schemes 1 and 2.

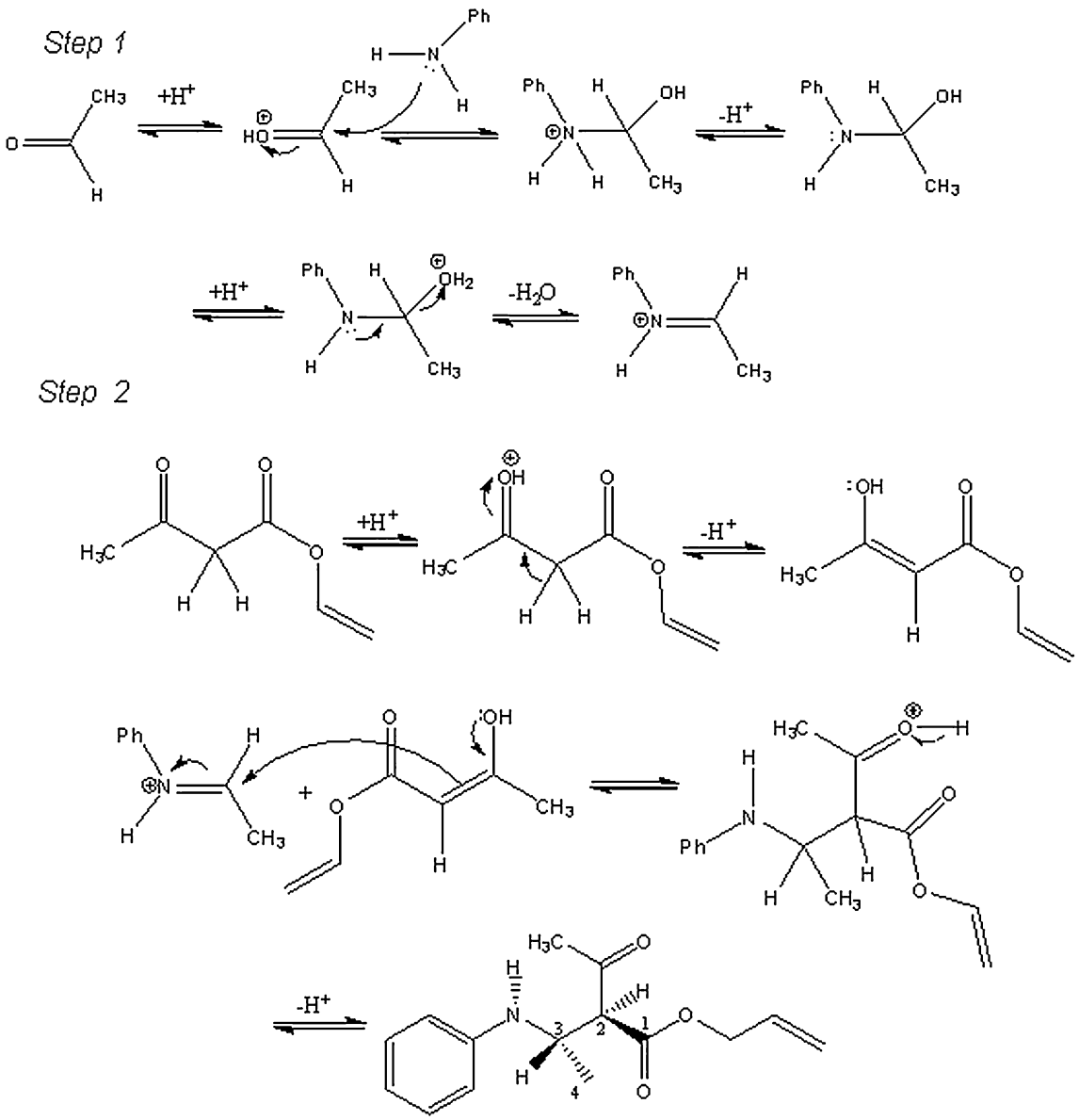
Synthesis

General Procedure for the Synthesis of Allyl 2-acetyl-3-(phenylamino)butanoate

To a mixture of aniline (1 mmol) and allylacetoacetate (1 mmol), acetaldehyde (1.5 mmol) was added in dropwise and stirred for about 4 h at 0 °C. The progress of the reaction was monitored by thin layer chromatography. After confirming that the reaction was completed, the reaction mixture was washed with petroleum ether and the resultant product was dissolved in diethyl ether and allowed to evaporate for solid formation. The solid product obtained was recrystallized with diethyl ether; m.pt: 78–80 °C. Yield: 85 %. White crystalline solid; m.p: 78–80 °C (diethyl ether). IR spectrum, ν, cm^{-1}: 3328 (–NH), 1703 (–CO), 1729 (–COOEt); ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.27 (t, 3H, $J = 4.5$ Hz, –C $\underline{H_3}CH$); 2.25 (s, 3H, –C $\underline{H_3}CO$); 3.69



Scheme 1 Synthesis of allyl 2-acetyl-3-(phylamino)butanoate (**1**). 2,6,-dimethyl *N*-(aryl)-1,3-dioxan-4-amines (**2**, **3**)



Scheme 2 Plausible reaction mechanism for the formation of allyl 2-acetyl-3-(phenylamino)butanoate (**1**)

(d, 1H, $J = 4.5$ Hz); 3.80 (bs, 1H, –NH); 4.27 (m, 1H); 4.63 (bs, 1H) 5.82–5.94 (m, 2H); 6.25 (d, 2H, *ortho* in aryl), 6.74 (d, 1H, *para* in aryl), 7.18 (d, 2H, *meta* in aryl).

General Procedure for the Synthesis of 2,6-Dimethyl N-(4-methylphenyl)-1,3-dioxan-4-amine

To a mixture of toulidine (1 mmol) and ethylacetoacetate (1 mmol), acetaldehyde (1.5 mmol) was added in dropwise and stirred for about 4 h at 0 °C. The progress of the reaction was monitored by thin layer chromatography. After confirming that the reaction was completed, the reaction mixture was washed with petroleum ether and the resultant product was dissolved in diethyl ether and allowed to evaporate for solid formation. Solid product obtained was recrystallized with diethyl ether; m.pt: 116–118 °C. Yield: 89 %.

^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (J, Hz): 1.29 (t, 3H, $J = 4.8$ Hz); 1.37 (d, 3H, $J = 3.2$ Hz); 1.48 (q, 1H, $J = 11.2$ Hz); 1.85 (d, 1H, $J = 12.8$ Hz); 3.84 (bs, 1H); 4.38 (d, 1H, $J = 8.8$ Hz) 4.84–4.90 (m, 2H); 6.74–6.83 (m, 3H, aryl protons). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 21.07 (methyl carbon in dioxane ring), 21.51 (methyl carbon in dioxane ring), 38.53 (methylene carbon in dioxane ring), 72.02, 81.52, 96.69, (three CH carbons in dioxane rings) 103.75, 110.87, 114.56, 130.02, 153.37 (aryl carbons).

General Procedure for the Synthesis of N-(3,5-difluoro phenyl)-2,6-dimethyl-1,3-dioxan-4-amine

To a mixture of 2, 4-difluoroaniline (1 mmol) and ethylacetoacetate (1 mmol), acetaldehyde (1.5 mmol) was added in dropwise and stirred for about 4 h at 0 °C. The progress of the reaction was monitored by thin layer chromatography. After conforming that the reaction was completed, the reaction mixture was washed with petroleum ether and the resultant product was dissolved in diethyl ether and allowed to evaporate for solid formation. Solid product obtained was recrystallized with diethyl ether; m.pt: 94–96 °C. Yield: 88 %.

^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.29 (t, 3H, $J = 5.6$ Hz); 1.38 (d, 3H, $J = 4.4$ Hz); 1.44 (q, 1H, $J = 12.0$ Hz); 1.82 (d, 1H, $J = 12.0$ Hz); 2.25 (2, 3H); 3.84 (bs, 1H); 4.22 (bs, 1H); 4.86 (d, 1H, $J = 3.6$ Hz); 4.94 (t, 1H, $J = 9.8$ Hz); 6.66 (d, 2H, $J = 7.8$ Hz); 7.01 (d, 2H, $J = 7.8$ Hz). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 20.55 (methyl carbon at aryl); 21.12 (methyl carbon in dioxane ring), 21.56 (methyl carbon in dioxane ring), 38.78 (methylene carbon in dioxane ring), 72.04, 81.96, 96.65 (three CH carbons in dioxane rings), 114.46, 128.47, 129.80, 142.74 (aryl carbons).

Results and Discussion

Crystal Structure Description (**1**)

In the crystal structure of allyl-2-acetyl-3-(phenylamino)butanoate (Fig. 1), the asymmetric unit comprises of two crystallographically independent molecules with similar geometries. The phenyl ring system in both the molecules is planar with the maximum deviation from planarity of −0.006(3) Å for atom C5A in molecule A and 0.003(3) Å for atom C1B in molecule B. The structure adopts an extended conformation, with all of the main chain torsion angles associated with the butanoate and amino groups close to *trans*. The crystal structure consists of three planar subunits viz. the phenyl amine (C1A–C6A/N1A; C1B–C6B/N1B), acetyl (C8A/C14A/O2A/C15A; C8B/C14B/O2B/C15B) and butanoate (C8A–C9A/O1A/O3A/C10A–C12A; C8B–C9B/O1B/O3B/C10B–C12B) groups. The phenyl amine group (C1A–C6A/N1A; C1B–C6B/N1B) is almost orthogonal to the acetyl unit (C8A/C14A/O2A/C15A; C8B/C14B/O2B/C15B) with the dihedral angle of 88.54(16)° in molecule A and 87.85(16)° in molecule B. The phenylamino ring (C1A–C6A/N1A; C1B–C6B/N1B) forms dihedral angles of 10.72(15)° and 0.9(3)° with the butanoate unit (C8A–C9A/O1A/O3A/C10A/C11A–C12A; C8B/C9B/O1B/O3B/C10B/C11B–C12B) in molecules A and B respectively. The acetyl unit (C8A/C14A/O2A/C15A; C8B/

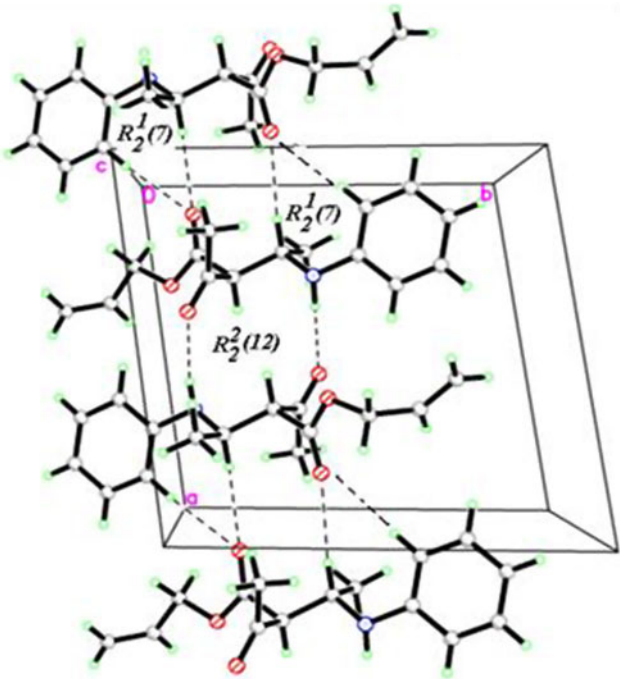


Fig. 2 Crystal packing of compound (**1**) with intermolecular hydrogen bonding patterns shown as *dashed lines*

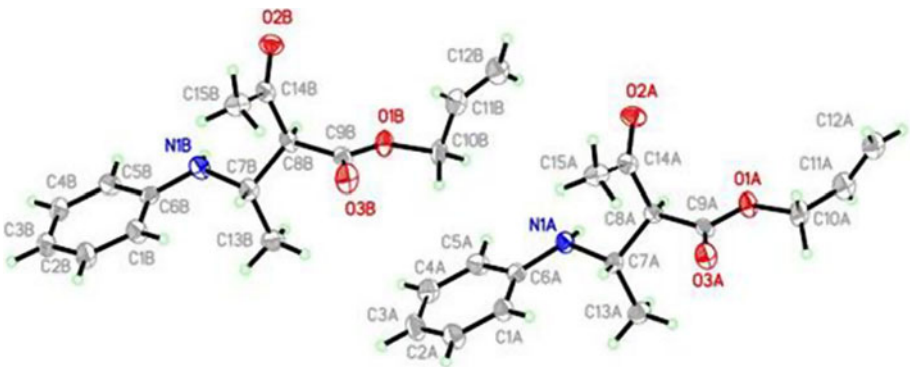


Fig. 1 Thermal ellipsoidal plot of compound (**1**), *ellipsoids* are drawn at the 50 % probability level

C14B/O2B/C15B) is inclined at an angle of 86.2(2)° and 68.0(2)° with the butanoate unit in the molecules A and B. The crystal packing is stabilized by intermolecular C–H···O and N–H···O hydrogen bonds in a head to tail fashion. One of the butanoate oxygen atom is involved in the bifurcated intermolecular hydrogen bonding with the adjacent molecule forming dimers with a ring motif $R_2^1(7)$ [13]. The amino hydrogen atoms in the molecules forming hydrogen bonding with acetyl oxygen atom make a ring of motif $R_2^2(12)$ and linking the adjacent dimers to form chains along [100] (Fig. 2).

Crystal Structure Description (**2**)

In the molecular structure of compound (**2**) (Fig. 3), the 2,6-dimethyl *N*-(4-methylphenyl)-1,3 dioxan-4-amine, the tolyl ring (C1–C6) system is inclined at an angle of 61.73(6)° with the dioxan ring system (C7–C9/O1/C10/O2). The dioxan ring adopts the chair conformation with the ring puckering parameters of Q2 = 0.0234(12) Å, Q3 = 0.5756(11) Å, Q = 0.5760(11) Å, θ = 2.30(12)° and φ = 253(3)° [14]. The mean plane of the tolyl ring is planar with mean deviation from planarity being 0.009(14) Å for atom C2. The methyl group attached to the tolyl ring is deviated from the mean plane by 0.034(13) Å for atom C13. In the crystal packing, the molecules are linked together by intermolecular C–H···O hydrogen bonds, forming dimers with graph set motif generating $R_2^2(16)$ rings (Fig. 4).

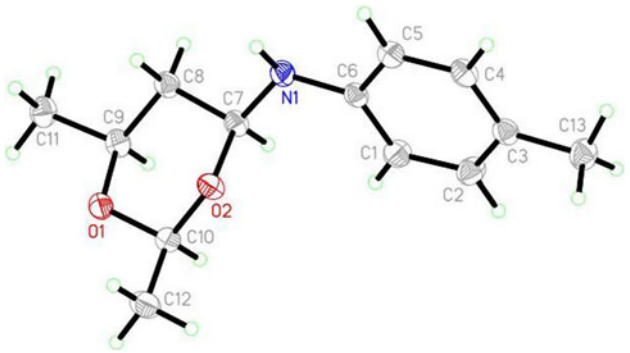


Fig. 3 ORTEP diagram of (**2**) drawn at 50 % *ellipsoids* for non-hydrogen atoms

Crystal Structure Description (**3**)

In the molecular structure of compound (**3**) (Fig. 5), the asymmetric unit comprises of two crystallographically independent molecules with similar geometries. The difluorophenyl ring system (C1A–C6A; C1B–C6B) is inclined at an angle of 45.50(6)° with the dioxan ring system (O1A/C10A/O2A/C7A–C9A; O1B/C10B/O2B/C7B–C9B) in molecule A and 50.52(6)° in molecule B, respectively. In molecule A, the dioxan ring adopts the chair conformation with the ring puckering parameters of Q2 = 0.0699(12) Å, Q3 = −0.5571(12) Å, Q = 0.5615(12) Å, θ = 172.86(12)° and φ = 140.1(10)°. The corresponding values in molecule B are 0.0408(12) Å, 0.5688(12) Å, 0.5702(12) Å, 4.05(12)° and 333.9(17)°. In the crystal packing, the molecules are linked together by C–H···O and N–H···O hydrogen bonds in a tail to tail fashion forming dimers with graph set motif $R_2^2(8)$. The adjacent molecules are linked by C–H···O hydrogen bonds forming chains along [−101] (Fig. 6).

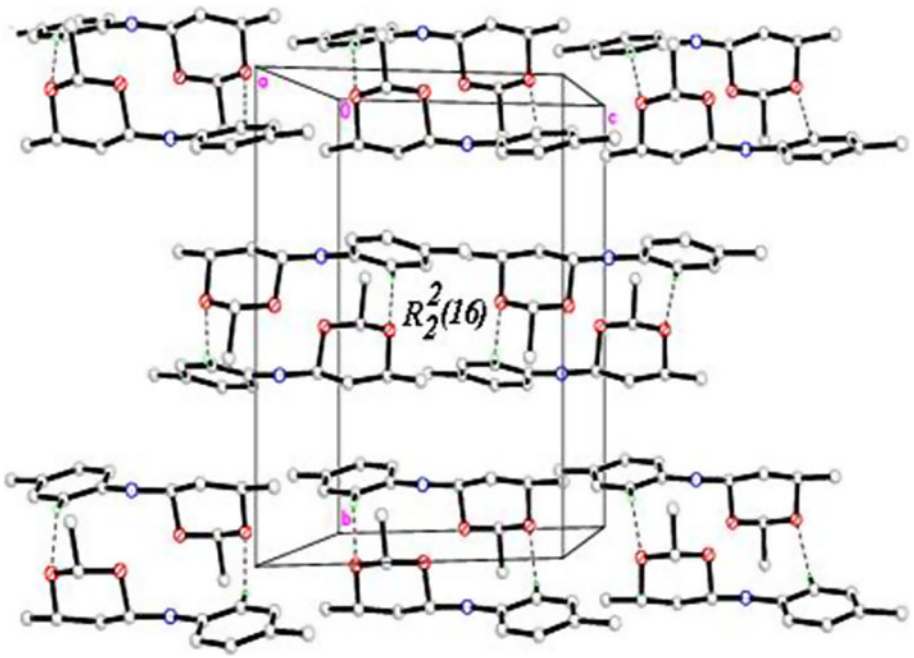


Fig. 4 Crystal packing of compound (**2**) with intermolecular hydrogen bonding patterns showing ring motif $R_2^2(16)$. H atoms not involved in the crystal packing have been omitted for clarity

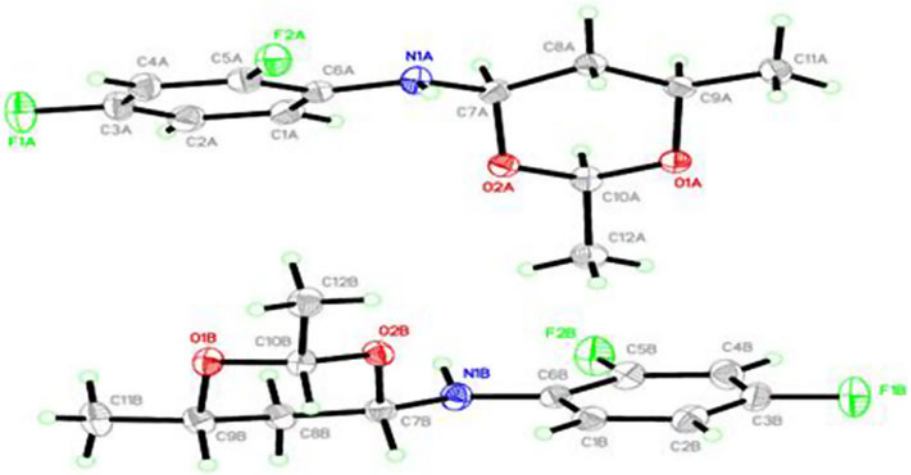


Fig. 5 Molecular structure of compound (**3**), showing the atom labelling scheme and 50 % probability level

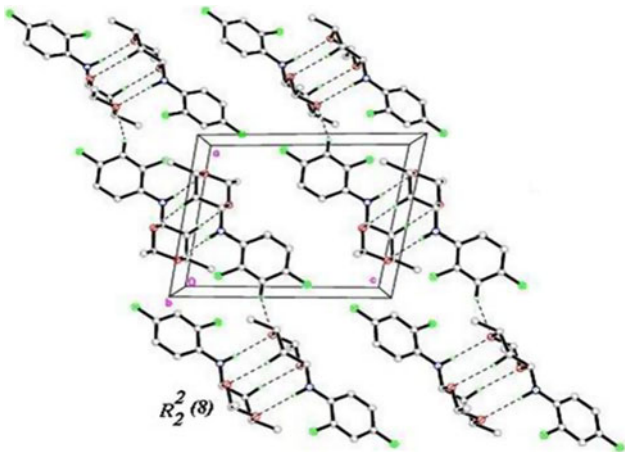


Fig. 6 Crystal packing of compound (**3**) with intermolecular hydrogen bonding patterns showing a ring of motif $R_2^2(8)$. H atoms not involved in the crystal packing have been omitted for clarity

Conclusions

The compounds allyl-2-acetyl-3(phenylamino)butanoate (**1**), 2,6-dimethyl *N*-(4-methylphenyl)-1,3-dioxan-4-amine (**2**) and *N*-(3,5-diflourophenyl)-2,6-dimethyl-1,3-dioxan-4-amine (**3**) have been synthesized and characterized by IR(1), ^{1}H NMR and ^{13}C NMR. The crystal structures of the three compounds were elucidated by single crystal X-ray diffraction. The conformational geometry of the molecules has been extensively investigated. Further, the structural elucidation of the three compounds helps to understand the conformational features of the molecules which are essential for the structural activity investigations of these pharmaceutical preparations. The hydrogen bonding interactions with ring motifs consolidate the crystal packing in the solid state. Further studies are in progress to assess the anti-proliferation activity of allyl-2-acetyl-3(phenylamino)butanoate and the bioactivity of 1,3-dioxane derivatives.

Supplementary material

CCDC 915689, 915690 and 915691, contains the supplementary crystallographic data for this paper. The data can be obtained free of charge at http://www.ccdccam.ac.uk/const/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336033 or email: deposit@ccdc.cam.ac.uk.

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