Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(5):295-301

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis and crystal structure studies of amino derivatives of 4-chlorophenacyl benzoate

C. S. Chidan Kumar[1*], Chin Wei Ooi[2], R. Venkatachalapathy[3], Siddegowda Chandraju[4], Ching Kheng Quah[2] and Hoong-Kun Fun[2,5]

[1]*Department of Engineering Chemistry, Alva's Institute of Engineering & Technology, Visvesvaraya Technological University, Mijar, Moodbidri 574225, Karnataka, India*
[2]*X-ray Crystallography Unit, School of Physics, Universiti Sains Malaysia, Penang 11800, Malaysia*
[3]*Department of Chemistry, D. V. S. College of Arts & Science, Shimoga, Karnataka, India*
[4]*Department of Sugar Technology & Chemistry, Sir M. Visvesvaraya PG Center, University of Mysore, Tubinakere 571402, Karnataka, India*
[5]*Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia*

ABSTRACT

*Phenacyl benzoates attract commercial importance due to their various applications in the field of synthetic and photo-chemistry. They play vital role as protecting groups for carboxylic acids in organic synthesis. These are also the photosensitive blocking groups with the ease of cleaving under mild conditions. Amino derivatives of 4-chlorophenacyl benzoate (**2a-c**) are synthesized by reacting 4-chlorophenacyl bromide with ortho-, meta- and para-amino substituted benzoic acids separately using a slight excess of potassium carbonate in N,N-dimethyformamide medium at room temperature. These reactions offered convenience, mild conditions, high purity and good yield.*

Key words: Benzoates, synthesis, crystal structure, high yield and purity.

INTRODUCTION

Phenacyl benzoate is a derivative of an acid which is formed by the reaction between an acid and a phenacyl bromide. They play a key role as protecting groups for carboxylic acids in organic synthesis and biochemistry [1,2]. The advantage of using these photosensitive blocking groups is that they can easily be cleaved under completely neutral and mild conditions [1-3] and therefore used for the identification of organic acids. Phenacyl bromide derivatives have found vital application for decades in the field of synthetic chemistry [4] such as in the synthesis of imidazoles and oxazoles [5] as well as benzoxazepine [6].

Encouraged with the above observations and in continuation of our work [7], the present study was focused to study the substituent effect on the geometrical features, to understand the molecular conformation and intermolecular interactions which holds the assembly of molecules in the crystal lattice. For the present work, we have synthesized those 4-chlorophenacyl benzoates with strong activating $-NH_2$ group at different positions (*–o*, *–m* and *–p*) on the phenyl ring.

EXPERIMENTAL SECTION

Chemicals and instrumentation

The reagents and solvents for the synthesis were obtained from the Sigma Aldrich Chemical Co., and were used as received without additional purification. Melting point was determined by Stuart Scientific (UK) apparatus. The purity of the compound was confirmed by thin layer chromatography using Merck silica gel 60 F254 coated aluminium plates.

X-ray Crystallography

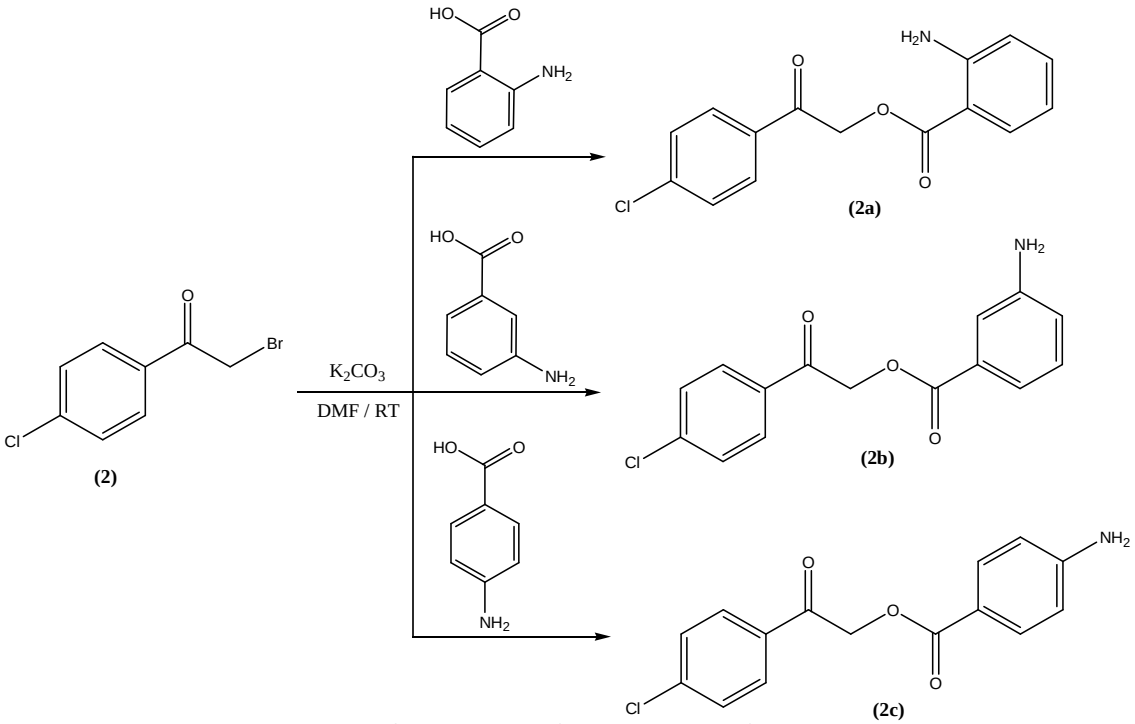
X-ray analysis was done using either Bruker SMART Apex II or Apex DUO CCDC diffractometer. The data were processed with SAINT and corrected for absorption using SADABS [8]. The structures were solved by direct method using the program SHELXTL [9], and were refined by full-matrix least squares technique on F^2 using anisotropic displacement parameters. The crystallographic data of compound **2a** and **2b** were collected at 100.0(1) K using the Oxford Cryosystem Cobra low temperature attachment [10] whereas compound **2c** was collected under room temperature. The non-hydrogen atoms were refined anisotropically. All N bound H atoms were located from the difference map and were fixed at their found positions with U_{iso} (H) = 1.2 U_{eq} (N). [N—H = 0.88(2)-0.90(3) Å]. The hydrogen atoms bounded to C atoms were positioned geometrically [C—H = 0.93 or 0.97 Å] with U_{iso} (H) = 1.2 U_{eq} (C). The crystallographic data for the reported compounds are given in Table 1. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre. CCDC No: 944073, 944074 and 944075 for compounds **(2a)**, **(2b)** and **(2c)** respectively. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 IEZ, UK. Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

Table 1: Crystal data and parameters for structure refinement of 2a, 2b and 2c

Compound	2a	2b	2c
CCDC	944073	944074	944075
Molecular formula	$C_{15}H_{12}ClNO_3$	$C_{15}H_{12}ClNO_3$	$C_{15}H_{12}ClNO_3$
Molecular weight	289.71	289.71	289.71
Temperature/K	100	100	297
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_1/c$	$P2_12_12_1$
a (Å)	14.9029 (17)	7.993 (2)	5.2076 (9)
b (Å)	9.6590 (11)	10.725 (3)	8.2380 (13)
c (Å)	9.2955 (12)	16.701 (4)	31.941 (5)
α (°)	90	90	90
β (°)	93.503 (3)	110.801 (10)	90
γ (°)	90	90	90
V (Å^3)	1335.6 (3)	1338.4 (6)	1370.3 (4)
Z	4	4	4
D_{calc} (g cm^{-3})	1.441	1.438	1.404
Crystal Dimensions (mm)	0.75 × 0.41 × 0.10	0.39 × 0.38 × 0.06	0.72 × 0.50 × 0.20
μ (mm^{-1})	0.29	0.29	0.28
Radiation λ (Å)	0.71073	0.71073	0.71073
Reflections measured	10360	11660	8896
Ranges/ indices (h, k, l)	-12, 19; -11, 12; -12, 12	-10, 10; -12, 13 ; -15, 21	-5, 7; -11, 11; -45, 29
θ limit (°)	2.5-27.5	2.3-27.5	2.6-30.3
Unique reflections	3050	3057	4100
Observed reflections ($I > 2\sigma(I)$)	2488	2273	3074
Parameters	189	181	189
Goodness of fit on F^2	1.05	1.07	1.02
R1, wR2 ($I \geq 2\sigma(I)$)	0.039, 0.117	0.066, 0.186	0.046, 0.139

Synthesis of amino derivatives of 4-chlorophenacyl benzoate'

4-Chlorophenacyl benzoate derivatives were obtained *via* two-step reaction reported earlier [11]. 2-bromo-1-(4-chlorophenyl)ethanone (0.002 mol) was reacted with amino substituted benzoic acids (0.003 mol) in presence of potassium carbonate in dimethyl formamide (10 ml) and stirred at room temperature for about 2 h (Scheme 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice-cold water. The solid obtained was filtered and washed with water, recrystallized with ethanol and dried to get the pure product **(2a-c)**.



Scheme 1: Reaction scheme for the synthesis of amino derivatives of 2-chlorophenacyl benzoate

RESULT AND DISCUSSION

*X-ray Single Crystal Structure Description of Compounds **2a**, **2b** & **2c***

X-ray quality crystals of the compounds, 2-(4-chlorophenyl)-2-oxoethyl 2-aminobenzoate (**2a**), 2-(4-chlorophenyl)-2-oxoethyl 3-aminobenzoate (**2b**) and 2-(4-chlorophenyl)-2-oxoethyl 4-aminobenzoate (**2c**) were obtained from their solution in acetone/methanol (1:1 v/v) by the slow evaporation method. Fig. 1 shows the molecular structures of the compounds, which differ from each other with respect to the -NH_2 substituent at different positions (*–o*, *–m* and *–p*) on the benzene ring. H-bonding interactions are listed in Table 2. The compounds crystallize in monoclinic system, space group $P2_1/c$ (**2a** and **2b**) and orthorhombic system, space group $P2_12_12_1$ (**2c**). The two benzene rings are almost perpendicular to each other in all compounds as indicated by the dihedral angles of 83.08 (8)° in compound **2a**, 83.45 (15)° in compound **2b** and 76.97 (10)° in compound **2c** . Among the three, the compound **2a** appears unique with S(6) ring motif which is generated by the intra-molecular N—H…O bond as shown in Fig. 1.

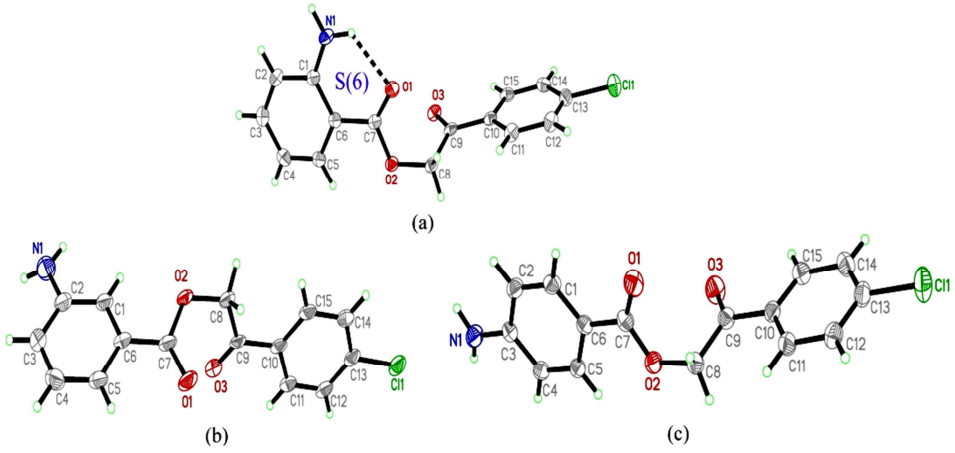
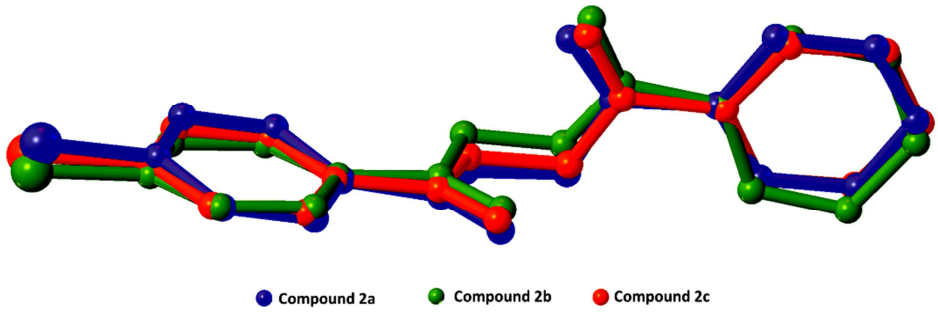


Figure 1: Molecular structure of compounds (a) 2a, (b) 2b and (c) 2c, with atom numbering schemes. Displacement ellipsoids are drawn at the 50% probability level in compounds 2a and 2b and 30% probability level in compound 2c. The dashed line represents the intramolecular hydrogen bonds

The conformations of the three compounds are very analogous as illustrated in Fig. 2(a). The r.m.s. value for the overlay between all non-H atoms in the compounds **2a**/**2b**, **2a**/**2c** and **2b**/**2c** are 0.233, 0.319 and 0.229 Å, respectively, when terminal amide groups at different positions (-o, -m and –p) on the phenyl rings are excluded. In the compound **2b**, a weak intermolecular C12—H12A···N1 hydrogen bond(Table 2) between the nitrogen atom of the terminal amide group and one of the carbon atoms of the chloro-substituted benzene ring ensures a

favorable orientation that the atoms N1 and C12 are on the same side in the crystal packing (Fig. 4a) which causes the benzene ring plane to rotate by nearly 180º with respect to the compounds **2a** and **2c** (Fig. 2b).

(a)



(b)

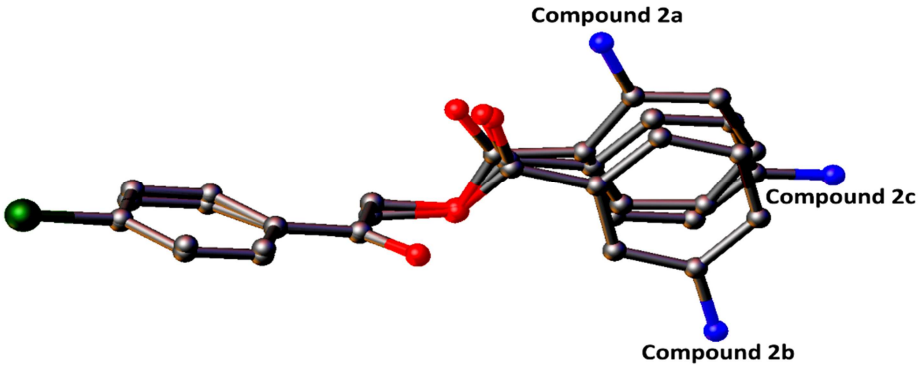


Figure 2: (a) Overlay of all non-H atoms, excluding the terminal amide groups. (b) Overlays were calculated using the 4-chlorobenzoate moiety in compounds 2a, 2b and 2c. Hydrogen atoms have been removed for clarity

In compound 2a and 2b, molecules are linked *via* intermolecular N1—H…O3 hydrogen bonds into zig-zag chains (Fig. 3 and Fig. 4a) running along *c* and *b* axis, respectively. However molecules in compound 2c are connected with intermolecular N1—H…O1 hydrogen bonds into C(8) chain motifs along *b*-axis as shown in Fig. 5a. In the crystal packing of all the three compounds, the neighboring zig-zag chains are aligned in anti-parallel fashion. These anti-parallel chains are further interconnected into 2D corrugated sheet running along (011) *via* weak intermolecular C8—H8B…O1 hydrogen bonds in compound 2a, generating $R_2^2(10)$ graph-set motifs [12] (Fig. 3). Formation of two-dimensional framework (Fig. 4b) and two-molecules-thick two dimensional network (Fig. 5b) parallel to the *ab* plane *via* intermolecular N1—H2…O1 and C12—H12A…N1 hydrogen bonds in compound 2b and intermolecular N1—H2N1…N1 hydrogen bonds in compound 2c are observed. In addition, the crystal structure stability of compound 2b is consolidated by C—H…π interactions, involving the C8 atom and the centroid of the benzene rings (C1-C6 and C10-C15) and weak π−π stacking interactions are also observed between C10-C15 benzene rings. The distance between the centroids of interacting rings is 3.753(2) Å with the symmetry code -x, 1-y, -z. All above interactions as well as Van der Waals interactions play significant roles in stabilizing these three crystal structures.

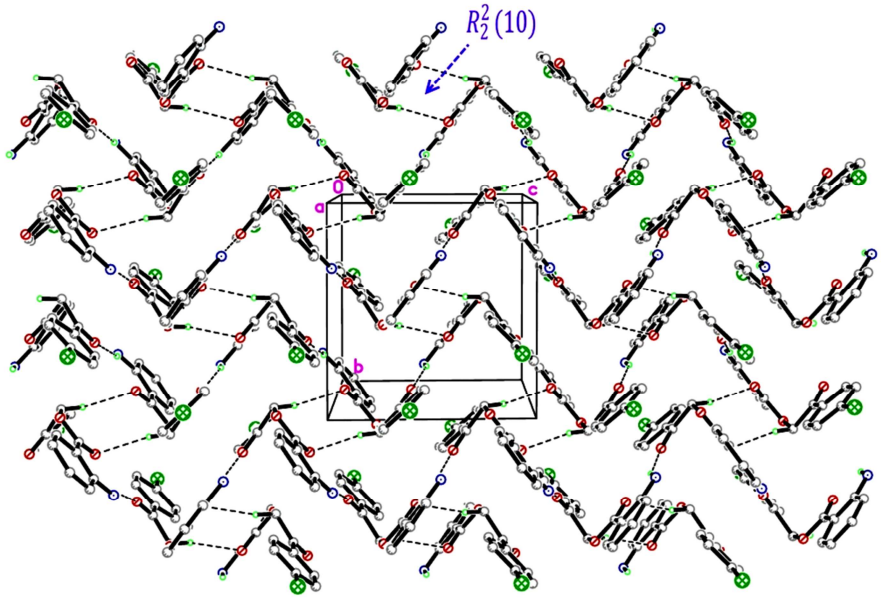
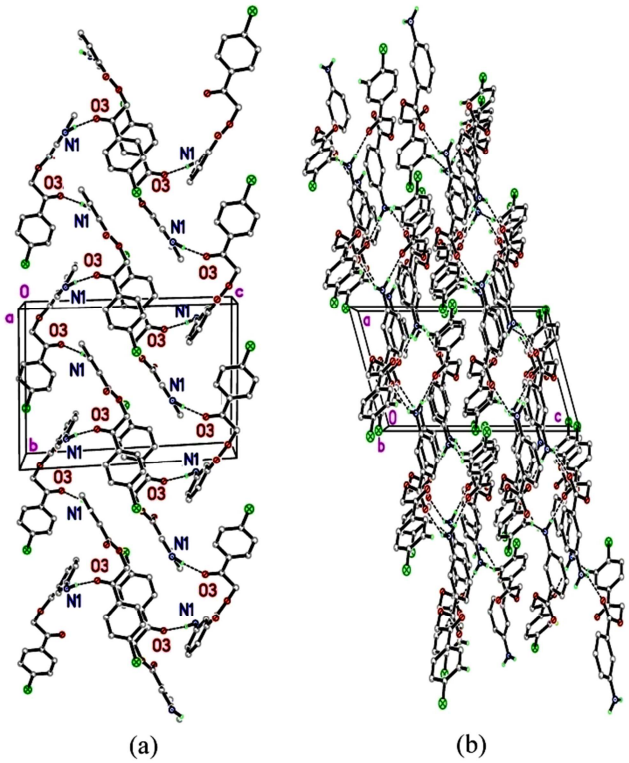


Figure 3: Crystal packing of compound 2a with intermolecular hydrogen bonding shown as dashed lines. Hydrogen atoms not involved in intermolecular interactions have been omitted for clarity



(a) (b)

Figure 4: (a) Anti-parallel zigzag chains mediated by N1—H…O3 hydrogen bonds in compound 2b. (b) Packing diagram of compound 2b with N—H…O and C—H…N intermolecular hydrogen bonds shown as dash lines. For clarity sake, hydrogen atoms not involved in hydrogen bonding have been omitted

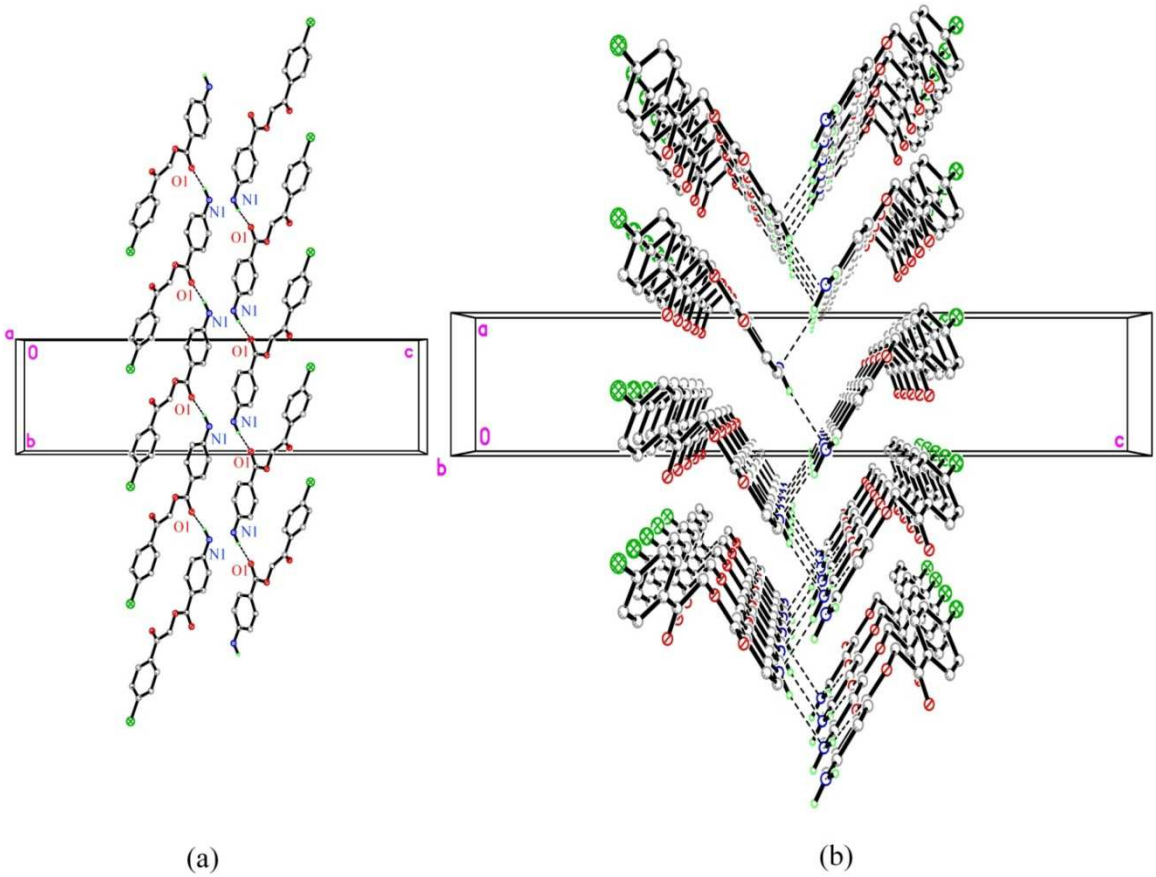


Figure 5: (a) View showing the C(8) chain motifs pack in anti-parallel pattern running along *b*-axis *via* intermolecular N1—H…O1 hydrogen bonds in compound 2c. (b) Crystal structure of compound 2c with intermolecular hydrogen bonding patterns shown as dashed lines. Hydrogen atoms not participating in intermolecular interactions have been omitted for clarity

Table 2: Hydrogen bond geometries for compounds 2a, 2b and 2c

D—H···*A*	*d*(*D*—H) (Å)	*d*(H···*A*) (Å)	*d*(*D*···*A*) (Å)	*Angle* (*D*—H···*A*) (°)
(2a)				
N1—H1N1···O1	0.889 (19)	2.077 (19)	2.6914 (18)	1254 (16)
N1—H1N1···O3	0.889 (19)	2.296 (19)	3.0900 (18)	148.7 (16)
C8—H8B···O1^{ii}	0.97	2.53	3.4913 (19)	169
(2b)				
N1—H1···O3^{iii}	0.88	2.06	2.939 (4)	173
N1—H2···O1^{iv}	0.88	2.41	3.147 (4)	142
C12—H12A···N1^{v}	0.93	2.62	3.506 (5)	159
(2c)				
N1—H2N1···N1^{vi}	0.90(3)	2.37 (3)	3.257 (2)	170 (2)
N1—H1N1···O1^{vii}	0.88(2)	2.13 (2)	2.967 (2)	160 (2)

Symmetry code: (i) x, −y+1/2, z+1/2; (ii) −x+2, −y+1, −z+1; (iii) −x+2, y−1/2, −z+1/2; (iv) −x+1, y, z; (v) x−1, y+1, z; (vi) x+1/2, −y+5/2, −z+2; (vii) x, y+1, z.

CONCLUSION

Synthesis, single-crystal X-ray diffraction studies and reducing power assay of 2-(4-chlorophenyl)-2-oxoethyl 2-aminobenzoate **(2a)**, 2-(4-chlorophenyl)-2-oxoethyl 3-aminobenzoate **(2b)** and 2-(4-chlorophenyl)-2-oxoethyl 4-aminobenzoate **(2c)** have been described. The reaction offered convenient, mild conditions, high purity and good yield. The crystal structure stability is consolidated by C—H…π interactions and weak π−π stacking interactions in compound **2b** whereas the stability is mainly due to Van der Waals interactions in compounds **2a** and **2c**.

Acknowledgements
The authors thank the Malaysian Government and Universiti Sains Malaysia (USM) for the Research University Individual Grant (1001/PFIZIK/811278). The authors extend their appreciation to The Deanship of Scientific Research at King Saud University for the researchgroup Project No. RGP VPP-207.

REFERENCES

[1] R Ruzicka; M Zabadal; P Klan, *Synth. Commun*., **2002**, 32, 2581–2590.
[2] JK Litera; AD Loya; P Klan, *J. Org. Chem*., **2006**, 71, 713–723.
[3] JC Sheehan; K Umezaw., *J. Org. Chem.*, **1973**, 38, 3771–3773.
[4] JB Rather; E Reid, *J. Am. Chem*., Soc., **1919**, 41, 75–83.
[5] W Huang; J Pian; B Chen; W Pei; X Ye, *Tetrahedron*., **1996**, 52, 10131–10136.
[6] SS Gandhi; KL Bell; MS Gibson, *Tetrahedron*., **1995**, 51, 13301– 13308.
[7] CS Chidan Kuma; HK Fun; M Tursun; CW Ooi; S Chandraju; CK Quah; C Parlak, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, **2014**, 124C, 595-602.
[8] Bruker; APEX2; SAINT; SADABS. Bruker AXS Inc., Madison, Winconsin, USA; **2009**.
[9] GM Sheldrick, *Acta Cryst*., **2008**, A64, 112-122.
[10] J Cosier, AM Glazer, *J Appl Cryst*., **1986**, 19, 105–107.
[11] CS Chidan Kumar; TS Chia; S Chandraju; CW Ooi; CK Quah; HK Fun, *Z. Kristallogr*., **2014**, 229(4), 328-342.
[12] J Bernstein; RE Davis; L Shimoni; NL Chang, *Angew. Chem. Int. Ed. Engl*., **1995**, 34, 1555-1573.