Journal of Chemical Crystallography
https://doi.org/10.1007/s10870-018-0725-3

ORIGINAL PAPER

Synthesis and Crystal Structures of Ethyl 2-(4-Methoxyphenyl)-1*H*-benzo[*d*]imidazole-5-carboxylate Dihydrate and Its Building Block 4-Fluoro-3-nitrobenzoic Acid

Keng Yoon Yeong[1,2] · Tze Shyang Chia[3] · Ching Kheng Quah[3] · Soo Choon Tan[1]

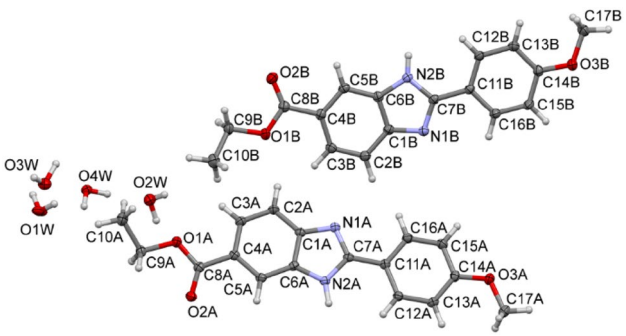
Received: 25 November 2015 / Accepted: 11 August 2018

Abstract

The title compound, ethyl 2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole-5-carboxylate dihydrate (**5**), was synthesized and its crystal structure was studied by single-crystal X-ray diffraction technique. Compound **5** is crystallized in the centrosymmetric triclinic space group $P\bar{1}$ with $Z=4$ and $Z'=2$, and unit-cell parameters of $a=8.9190$ (3) Å, $b=12.6888$ (4) Å, $c=14.7111$ (5) Å, $\alpha=98.4855$ (10)°, $\beta=101.6379$ (9)°, $\gamma=95.4346$ (10)° and $V=1599.43$ (9) Å^3. Its starting material, 4-fluoro-3-nitrobenzoic acid (**1**), is crystallized in the non-centrosymmetric monoclinic space group $P2_1$ and $Z=4$ with unit-cell parameters of $a=3.7170$ (4) Å, $b=12.6475$ (13) Å, $c=15.5237$ (15) Å, $\alpha=90°$, $\beta=91.9786$ (16)°, $\gamma=90°$ and $V=729.35$ (13) Å^3. It was noted that strong hydrogen bonds play important roles in the crystal packing of both compounds, especially in **5**, in which the co-crystallized water molecules act as both strong hydrogen bond donor and strong hydrogen bond acceptor.

Graphical Abstract

Two molecule of compound **5** crystallized in a non symmetrical manner with four co-crystallized water molecules which play an important role in the crystal packing as strong hydrogen-bond donors.



Keywords Benzimidazole · Crystal structure · Hydrogen bonding · Cyclization

Introduction

4-Fluoro-3-nitrobenzoic acid is a fundamental building block for various pharmacologically important heterocycles such as di- or tri-substituted benzimidazoles [1–3]. In recent years, many medicinal chemistry research bearing the benzimidazole scaffold related to cancer therapeutics [4], inflammation [5] and bacterial growth inhibition [6] have been published. We have recently demonstrated the

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10870-018-0725-3) contains supplementary material, which is available to authorized users.

✉ Keng Yoon Yeong
yeong.kengyoon@monash.edu

Extended author information available on the last page of the article

Published online: 14 August 2018

anticancer effect of novel substituted benzimidazole derivatives based on the ethyl 2-phenyl-1*H*-benzo[*d*]imidazole-5-carboxylate scaffold through the inhibition of sirtuin activity [7]. Although the synthesis of the title compound, ethyl 2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole-5-carboxylate dihydrate (**5**) has been previously published [8], no crystal data was reported. Herein, we now would like to report the first resolved crystal structure of **5** which was synthesized using a different reaction route. The first crystal structure of the starting material, 4-fluoro-3-nitrobenzoic acid (neat) is also reported. The structure of the compounds was elucidated using various techniques such as NMR, elemental analysis, direct infusion-MS and unambiguously ascertained through single-crystal X-ray crystallography.

Experimental

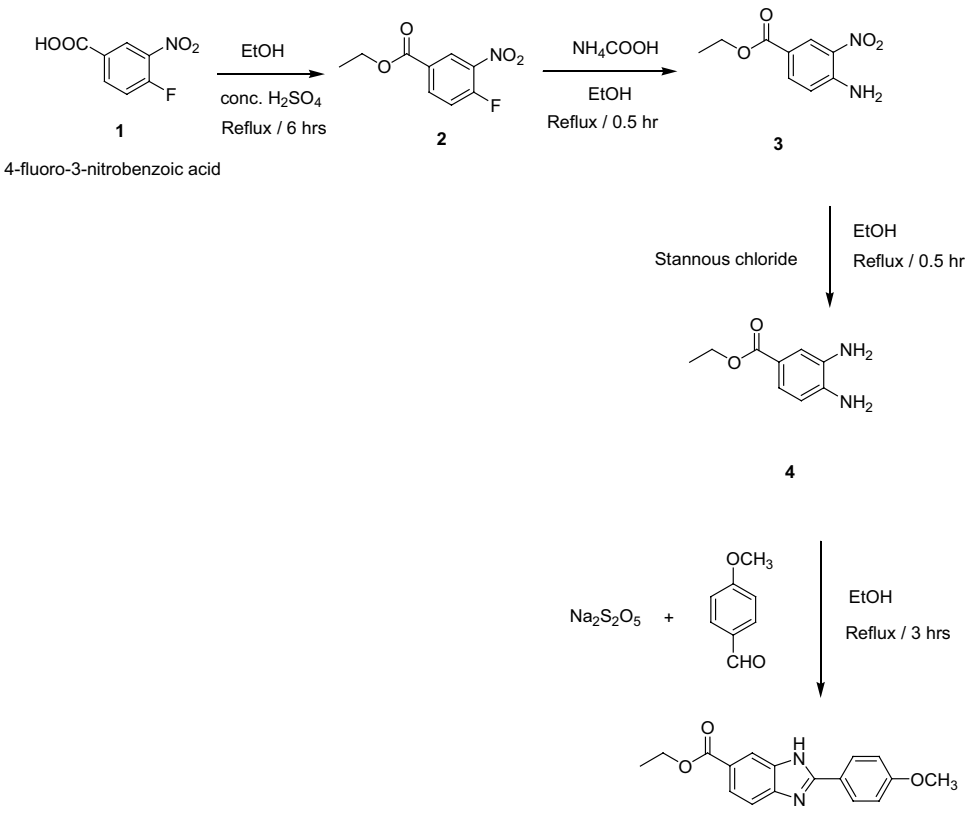
Chemistry

All reagents were used as supplied without prior purification. Melting points were determined on a Gallenkamp MFB-595-010M melting point apparatus. Elemental analyses were performed on a Perkin Elmer 2400 Series II CHN elemental analyzer. ^{1}H NMR was performed on a Bruker Avance 500 spectrometer in $CDCl_3$. Mass spectra were recorded on a Varian 320-MS TQ LC/MS in positive electrospray ionization (ESI) mode. Crystal structure analysis was carried out using a Bruker SMART APEX II DUO CCD area-detector diffractometer.

Synthesis of Ethyl 2-(4-Methoxyphenyl)-1*H*-benzo[*d*] imidazole-5-carboxylate Dihydrate (5)

The synthetic scheme of **5** utilized a facile and efficient sequential one-pot protocol (Scheme 1) in mild reaction conditions, similar to the published method in the previous report [7]. One major advantage of this synthesis is that it does not require any purification steps prior to obtaining the final product **5**. Apart from that, expensive catalysts were also not needed during the course of the reaction making it highly scalable. Briefly, 4-fluoro-3-nitrobenzoic acid **1**, was esterified in the presence of catalytic sulfuric acid in ethanol by refluxing for 6 h to afford ethyl 4-fluoro-3-nitrobenzoate **2**. Ammonium formate was subsequently added into the solution, and the mixture stirred at room temperature for 0.5 h. The resultant intermediate, ethyl 4-amino-3-nitrobenzoate **3**, was then reduced to ethyl 3,4-diaminobenzoate **4** using stannous chloride. Cyclization of intermediate **4** with 4-anisaldehyde and catalytic amounts of sodium metabisulfite proceeded in a fast and smooth manner to afford final compound **5** in good yield (90%). Recrystallization of crude product **5** in ethyl acetate yielded light brown crystals, which are suitable for X-ray crystallographic analysis. Melting

Scheme 1 Synthesis protocol of benzimidazole derivative **5**



point: 188–189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (3H, t, J = 6.9 Hz), 3.88 (3H, s), 4.53 (2H, t, J = 6.9 Hz), 7.06 (2H, d, J = 9 Hz), 7.47 (1H, d, J = 9 Hz), 7.75 (2H, d, J = 9 Hz), 8.04 (1H, dd, J = 1.5 Hz, 9 Hz), 8.54 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): 14.69, 56.22, 61.45, 109.75, 109.98, 121.12, 122.18, 123.40, 150.05, 151.59, 168.67. ESI-MS: m/z 297.1 $[M+H]^+$. Anal. Calc. for $C_{17}H_{16}N_2O_3$: C, 68.88; H, 5.50; N, 4.47%. Found: C, 68.90; H, 5.41; N, 4.50%.

Single-Crystal X-Ray Structure Determination

X-ray data of **1** and **5** were collected by using Bruker SMART APEX II DUO CCD area-detector diffractometer [9] with Mo Kα radiation (λ = 0.71073 Å). The sample temperature was kept at 100 (1) K by using Oxford Cryosystems Cobra open-flow nitrogen cryostat [10]. Data reduction and absorption correction were performed by using SAINT and SADABS programs [9]. The crystal structures were solved by direct methods and refined by full-matrix least-squares techniques on F^2 using SHELXTL package [11, 12]. The carboxylic H atoms of **1** were located from difference Fourier map, fixed at found positions (AFIX 3) and refined with $U_{iso}(H) = 1.5 \times U_{eq}(O)$. The H atoms attached to water molecules and benzimidazole N atom in **5** were located from difference Fourier map and refined freely [d(O–H) = 0.84 (2)–0.95 (2) Å; d(N–H) = 0.874 (19) and 0.92 (2) Å]. The C-bound H atoms were calculated geometrically and refined with $U_{iso}(H) = 1.2 \times U_{eq}(C)$ for methine or methylene group, and $U_{iso}(H) = 1.5 \times U_{eq}(C)$ for methyl group. A rotating group model (AFIX 137) was applied to the methyl group. The crystal data, data collection and structure refinement details of compounds **1** and **5** are tabulated in Table 1.

Table 1 Crystal and structure refinement data for compounds **1** and **5**

	1	**5**
CCDC deposition number	1437965	1437966
Chemical formula	$C_7H_4FNO_4$	$C_{17}H_{16}N_2O_3{\cdot}2(H_2O)$
Formula weight	185.11	332.35
Crystal system	Monoclinic	Triclinic
Space group	$P2_1$	$P\bar{1}$
a (Å)	3.7170 (4)	8.9190 (3)
b (Å)	12.6475 (13)	12.6888 (4)
c (Å)	15.5237 (15)	14.7111 (5)
α (°)	90	98.4855 (10)
β (°)	91.9786 (16)	101.6379 (9)
γ (°)	90	95.4346 (10)
Volume (Å^3)	729.35 (13)	1599.43 (9)
Z, D_x (Mg m^{-3})	4, 1.686	4, 1.380
μ (mm^{-1})	0.16	0.10
F(000)	376	704
Crystal size (mm^3)	0.28 × 0.15 × 0.08	0.33 × 0.24 × 0.13
θ_{max}, θ_{min} (°)	28.2, 1.3	28.2, 1.4
hkl range	$-4 \le h \le 4$	$-11 \le h \le 11$
	$-16 \le k \le 16$	$-16 \le k \le 16$
	$-20 \le l \le 20$	$-19 \le l \le 19$
Measured reflections	18113	49050
Independent reflections	3488	7833
Reflections with $I > 2\sigma(I)$	2966	6577
R_{int}	0.049	0.030
T_{min}, T_{max}	0.673, 0.790	0.917, 0.960
Parameters/restraints	235/1	477/0
$R[F^2 > 2\sigma(F^2)]$	0.044	0.041
$wR(F^2)$	0.099	0.114
S	1.08	1.04
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.31, −0.33	0.34, −0.30

Results and Discussion

The starting material, 4-fluoro-3-nitrobenzoic acid (**1**), is a common fundamental building block for numerous heterocyclic compounds such as benzimidazoles and benzodiazenes. The single-crystals of **1** were successfully recrystallized from isopropanol. Compound **1** is crystallized in the non-centrosymmetric monoclinic space group $P2_1$ and

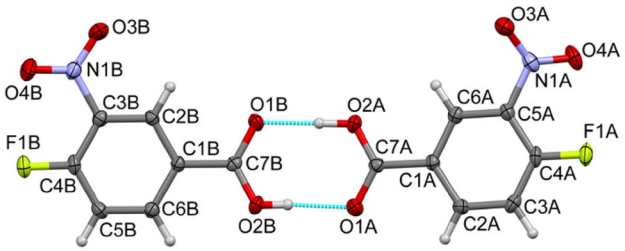


Fig. 1 The ORTEP diagram of **1**

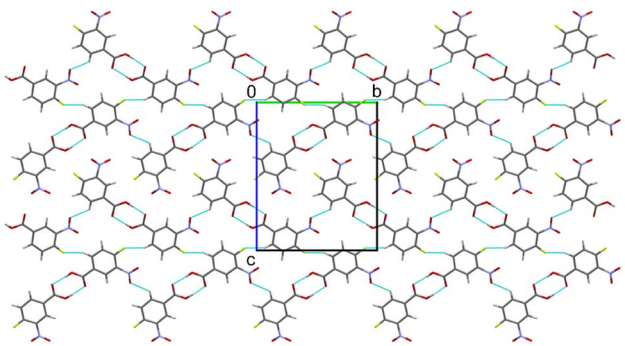


Fig. 2 The partial crystal packing of **1** shows two supramolecular tapes with intermolecular hydrogen bonds (cyan lines) viewed along a-axis. (Color figure online)

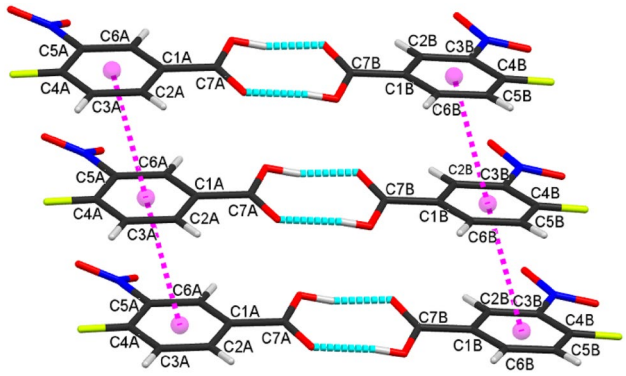


Fig. 3 The intermolecular π···π interactions (magenta lines) of **1**. (Color figure online)

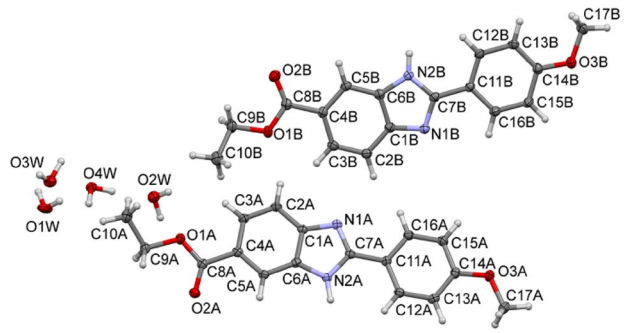


Fig. 4 The ORTEP diagram of the asymmetric unit of **5**

$Z = 4$. The asymmetric unit of **1** consists of two crystallographically independent acid molecules (*A* and *B*), which are connected into a homodimer *via* strong intermolecular O–H···O hydrogen bonds (Fig. 1). The *meta*-substituted nitro groups are twisted away from the attached phenyl rings with dihedral angles of 28.1 (3)° and 13.0 (4)° for molecules *A* and *B*, respectively. In the crystal, acidic homodimers are joined by weak intermolecular C–H···O and C–H···F hydrogen bonds into infinite linear tapes along crystallographic *b*-axis (Fig. 2). The crystal structure of **1** is further stabilized by intermolecular π···π stacking interactions (Fig. 3) along *a*-axis, involving the centroids of phenyl rings between two molecules *A* and between two molecules *B* with a centroid···centroid separation of 3.7170 (18) Å (symmetry codes: $x-1$, *y*, *z*; $x+1$, *y*, *z*). These π···π stacking interactions of **1** involved parallel-displaced phenyl rings with slippages of 1.417 and 1.466 Å. The multi-component complexes of **1** with two active pharmaceutical ingredients, viz., caffeine and theophylline, were recently reported [13–15] and deposited in the Cambridge Structural Database [16] with reference codes of ARIFUE, ZEKPIR and ZEKPIR01. The characteristic carboxylic acid···carboxylic acid homodimer of **1** is absent in the crystal structures of these three complexes. Instead, the acid molecule forms heterodimer with caffeine or theophylline molecule through strong intermolecular O–H···N hydrogen bond between carboxyl and imidazole groups in the complexes. In addition, in the crystals of ZEKPIR and ZEKPIR01, two adjacent acid···theophylline heterodimers are interconnected by a pair

Table 2 Hydrogen bond geometry (Å, °) (*D*: donor, *A*: acceptor) for crystals of compounds **1** and **5**

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*	Symmetry code
1					
O2*A*–H1*O2*···O1*B*	0.95	1.68	2.609 (3)	168	*x*, *y*, *z*
O2*B*–H2*O2*···O1*A*	0.84	1.79	2.625 (3)	173	*x*, *y*, *z*
C2*A*–H2*AA*···O3*B*	0.95	2.59	3.290 (4)	131	*x*, $y-1$, *z*
C6*B*–H6*BA*···F1*B*	0.95	2.46	3.266 (4)	143	$-x-1$, $y-1/2$, $-z$
5					
N2*A*–H1*N2*···O1*W*	0.92 (2)	1.84 (2)	2.7357 (14)	164.1 (17)	$-x+1$, $-y+1$, $-z+1$
N2*B*–H2*N2*···O4*W*	0.87 (2)	2.01 (2)	2.8750 (15)	173.4 (17)	$-x$, $-y+1$, $-z$
O1*W*–H1*W1*···N1*B*	0.84 (2)	2.03 (2)	2.8613 (15)	174 (2)	$x+1$, $y-1$, *z*
O1*W*–H2*W1*···O4*W*	0.83 (3)	1.95 (3)	2.7794 (15)	174 (2)	*x*, *y*, *z*
O2*W*–H1*W2*···O3*W*	0.87 (3)	1.90 (3)	2.7647 (15)	174 (2)	$x-1$, *y*, *z*
O2*W*–H2*W2*···O2*A*	0.90 (2)	1.91 (2)	2.8035 (13)	174.5 (18)	$-x+1$, $-y+1$, $-z+1$
O3*W*–H1*W3*···N1*B*	0.92 (2)	2.05 (2)	2.9586 (16)	168 (2)	$x+1$, $y-1$, *z*
O3*W*–H2*W3*···O2*B*	0.95 (2)	1.86 (2)	2.7979 (14)	169.7 (19)	$-x+1$, $-y+1$, $-z$
O4*W*–H1*W4*···N1*A*	0.88 (2)	1.99 (2)	2.8622 (14)	171.4 (18)	*x*, $y-1$, *z*
O4*W*–H2*W4*···O2*W*	0.90 (2)	1.80 (2)	2.6946 (14)	176 (2)	*x*, *y*, *z*
C15*A*–H15*A*···O3*W*	0.95	2.57	3.3419 (16)	138	$x-1$, $y+1$, *z*
C17*A*–H17*C*···*Cg*2	0.98	2.76	3.5578(16)	139	$-x$, $-y+2$,$-z+1$

*Cg*2 is the centroid of C1*A*–C6*A* ring

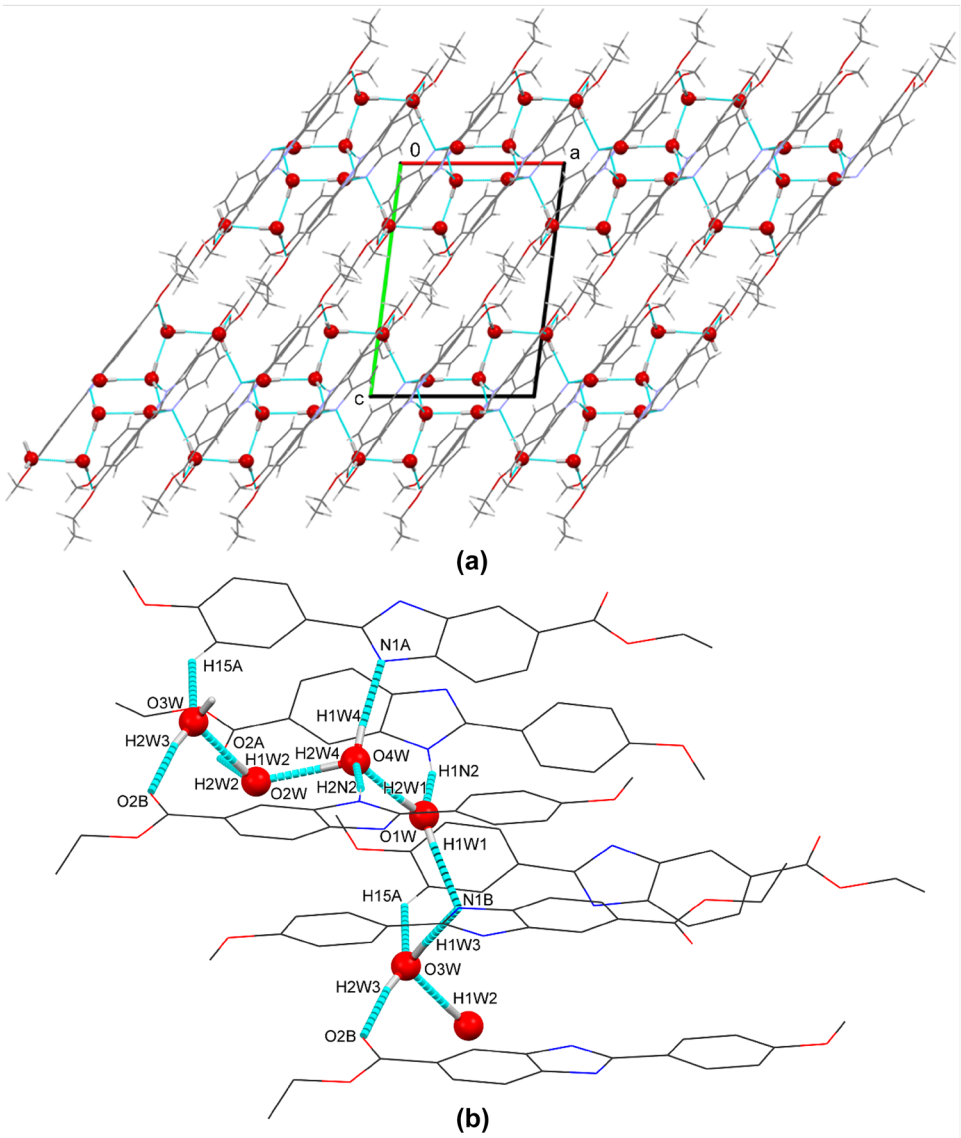


Fig. 5 **a** The partial crystal packing of **5** with co-crystallized water molecules (red balls) and hydrogen bonds (cyan lines) viewed along *c*-axis. **b** The water molecules of asymmetric unit and their neighbouring molecules in short contacts. (Color figure online)

of strong intermolecular N–H···O hydrogen bonds into an acid···theophylline···theophylline···acid heterotetramer. The N atoms of imidazole group of these two complexes act as strong donor of N–H···O hydrogen bond and strong acceptor of O–H···N hydrogen bond as compared to ARIFUE, in which the strong donating NH group is replace by a weak donating N–CH_3 group.

Compound **5** is crystallized in the centrosymmetric triclinic space group $P\bar{1}$ with $Z = 4$ and $Z' = 2$. The asymmetric unit of **5** (Fig. 4) consists of two major ethyl 2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole-5-carboxylate molecules and four co-crystallized water molecules, which play an important role in the crystal packing as strong hydrogen bond donors (Table 2). The molecular geometries of both major molecules are similar after an inversion with a RMSD of 0.0875 Å. The phenyl ring and benzimidazole ring are almost co-planar as indicated by dihedral angles of 1.61 (5)° and 0.23 (5)°. The terminal ethyl groups are twisted away from the planar parent molecules with C8–O1–C9–C10 torsion angles of 160.99 (11)° and − 165.84 (12)°. All water molecules in the crystal lattice are treated with full occupancy since their U_{eq}(O) values are in the range from 0.0205 (2) to 0.0334 (3) Å^2. In the crystal of **5**, molecules are joined by strong intermolecular N–H···O_{water}, O_{water}–H···N, O_{water}–H···O and O_{water}–H···O_{water} hydrogen bonds into two-dimensional networks parallel to crystallographic *ac*-plane (Fig. 5). The networks are further stabilized by weak intermolecular C–H···O_{water}, C–H···π (Table 2) and π···π interactions ($Cg1\cdots Cg1^{i} = 3.5442$ (7), $Cg5\cdots Cg6^{ii} = 3.7277$ (8), $Cg5\cdots Cg7^{iii} = 3.6684$ (8), $Cg6\cdots Cg5^{ii} = 3.7276$ (8) and $Cg7\cdots Cg5^{iii} = 3.6684$ (8) Å. *Cg*1, *Cg*5, *Cg*6 and *Cg*7 are the centroids of N1*A*/C1*A*/C6*A*/N2*A*/C7*A*, N1*B*/C1*B*/C6*B*/N2*B*/C7*B*, C1*B*–C6*B* and C11*B*–C16*B* rings, respectively. Symmetry codes: (i) $-x+1, -y+2, -z+1$; (ii) $-x, -y+2, -z$;

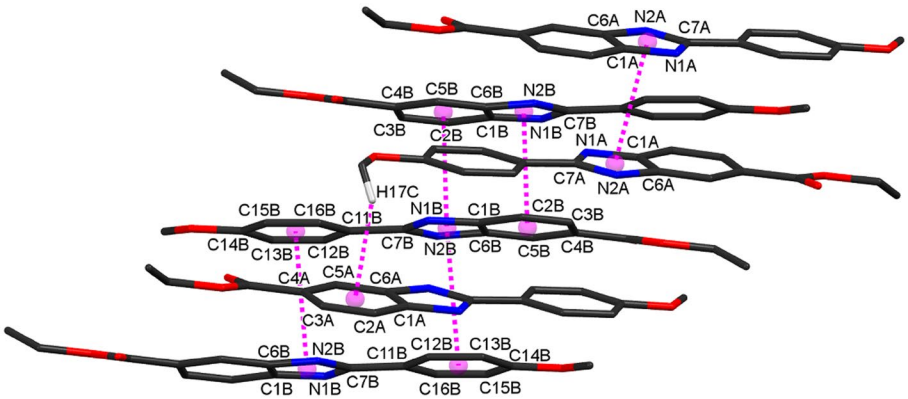


Fig. 6 The intermolecular C–H···π and π···π interactions (magenta lines) of **5**. (Color figure online)

(iii) $-x-1, -y+2, -z$). These π···π stacking interactions of **5** (Fig. 6) involved parallel-displaced phenyl rings with slippages of 0.647, 1.536, 1.235, 1.530 and 1.257 Å.

Conclusion

The crystal structures of ethyl 2-(4-methoxyphenyl)-1*H*-benzo[*d*]imidazole-5-carboxylate and its starting material, 4-fluoro-3-nitrobenzoic acid have been analysed by X-ray diffraction technique. These studies also serve to establish unambiguously the crystal packing of these two compounds. The molecules of **1** are connected *via* strong intermolecular O–H···O hydrogen bonds into homodimers, which are further joined by weak intermolecular C–H···O and C–H···F hydrogen bonds into infinite linear tapes along crystallographic *b*-axis. The water molecules play essential role in the crystal packing of **5**, in which the molecules are joined by strong intermolecular N–H···O_{water}, O_{water}–H···N, O_{water}–H···O and O_{water}–H···O_{water} hydrogen bonds into two-dimensional networks parallel to crystallographic *ac*-plane. The redundant π···π interactions of **1** and **5** contributed to the stabilization of their crystal structures.

Supplementary Material

CCDC 1437965 and 1437966 contain the supplementary crystallographic data of **1** and **5**, respectively, in this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +441223 336033).

Acknowledgements The authors wish to express their gratitude and appreciation to Pharmacogenetics and Novel Therapeutics Research Cluster, Institute for Research in Molecular Medicine, Universiti Sains Malaysia, Penang for supporting this work. This work was funded through Research Grant No. RUC (1001/PSK/8620012).

Compliance with Ethical Standards

Conflict of interest The authors hereby declare there is no conflict of interests.

References

1. Yoon YK, Ali MA, Wei AC, Choon TS, Osman H (2014) A one-pot tandem synthesis of diversified 1,2-disubstituted benzimidazoles. Tetrahedron Lett 55:4697–4700
2. Kommi DN, Kumar D, Bansal R, Chebolu R, Chakraborti AK (2012) "All-water" chemistry of tandem *N*-alkylation–reduction–condensation for synthesis of *N*-arylmethyl-2-substituted benzimidazoles. Green Chem 14:3329–3335
3. Yeh WB, Lin MJ, Sun CM (2004) Combinatorial synthesis of biheterocyclic benzimidazoles by microwave irradiation. Comb Chem High Throughput Screen 7:251–255
4. Easmon J, Puerstinger G, Roth T, Fiebig HH, Jenny M, Jaeger W, Heinisch G, Hofmann J (2001) 2-benzoxazolyl and 2-benzimidazolyl hydrazones derived from 2-acetylpyridine: a novel class of antitumor agents. Int J Cancer 94:89–96
5. Lazer ES, Matteo MR, Possanza GJ (1987) Benzimidazole derivatives with atypical antiinflammatory activity. J Med Chem 30:726–729
6. Yoon YK, Ali MA, Wei AC, Choon TS, Ismail R (2015) Synthesis and evaluation of antimycobacterial activity of new benzimidazole aminoesters. Eur J Med Chem 93:614–624
7. Yoon YK, Ali MA, Wei AC, Choon TS, Shirazi AN, Parang K (2015) Discovery of a potent and highly fluorescent sirtuin inhibitor. Med Chem Commun 6:1857–1863
8. Ji YH, Bur D, Häsler W, Schmitt VR, Dorn A, Bailly C, Waring MJ, Hochstrasser R, Leupin W (2001) Tris-benzimidazole derivatives: design, synthesis and DNA sequence recognition. Bioorg Med Chem 9:2905–2919
9. Bruker (2009) APEX2, SAINT and SADABS. Bruker AXS Inc, Madison
10. Cosier J, Glazer AM (1986) A nitrogen-gas-stream cryostat for general X-ray diffraction studies. J Appl Cryst 19:105–107
11. Sheldrick GM (2008) A short history of SHELX. Acta Cryst A64:112–122
12. Sheldrick GM (2015) Crystal structure refinement with SHELXL. Acta Cryst C71:3–8
13. Singaraju AB, Iyer M, Haware RV, Stevens LL (2016) Caffeine co-crystal mechanics evaluated with a combined structural and spectroscopic approach. Cryst Growth Des 16:4383–4391

14. Singaraju AB, Nguyen K, Gawedzki P, Herald F, Meyer G, Wentworth D, Swenson DC, Stevens LL (2017) Combining crystal structure and interaction topology for interpreting functional molecular solids: a study of theophylline cocrystals. Cryst Growth Des 17:6741–6751
15. Kakkar S, Bhattacharya B, Reddy CM, Ghosh S (2018) Tuning mechanical behaviour by controlling the structure of a series of theophylline co-crystals. CrystEngComm 20:1101–1109
16. Groom CR, Bruno IJ, Lightfoot MP, Ward SC (2016) The Cambridge Structural Database. Acta Cryst B72:171–179

Affiliations

Keng Yoon Yeong[1,2] · Tze Shyang Chia[3] · Ching Kheng Quah[3] · Soo Choon Tan[1]

[1] Institute for Research in Molecular Medicine, Universiti Sains Malaysia, 11800 USM, Penang, Malaysia

[2] School of Science, Monash University Malaysia Campus, 47500 Bandar Sunway, Selangor, Malaysia

[3] X-ray Crystallography Unit, School of Physics, Universiti Sains Malaysia, 11800 USM, Penang, Malaysia