J Chem Crystallogr (2008) 38:461–466
DOI 10.1007/s10870-008-9343-9

COMMUNICATION

The Syntheses and Crystal Structures of Metronidazole-derived Compounds

Huan-Qiu Li · Zhu-Ping Xiao · Rui-Qin Fang · Hai-Liang Zhu

Received: 31 May 2006 / Accepted: 27 March 2008 / Published online: 15 April 2008

Abstract Metronidazole (MET-OH), widely used as an antibacterial agent, is found to have some side effects on human bodies. Due to these disadvantages, people have been looking for its modification compounds for substituents. In this article, four MET-OH derivatives were designed, prepared, and structurally characterized by single crystal X-ray diffraction. These compounds are MET-OTs (**1**), MET-Br (**2**), MET-Cl (**3**), and MET-I (**4**). X-ray structure analyses revealed that, **1** crystallized in the monoclinic system with space group $P2_1/c$, with $a = 16.1178$, $b = 7.5473$, $c = 13.4161$ Å, $V = 1520.3$ Å^3, $\beta = 111.3210^o$ and $Z = 4$. **2** crystallized in the monoclinic system with space group $P2_1/c$, with $a = 12.079$, $b = 11.089$, $c = 6.380$ Å, $V = 847.1$ Å^3, $\beta = 97.57^o$ and $Z = 4$. **3** crystallized in the monoclinic system with space group $P2_1/c$, with $a = 12.098$, $b = 11.007$, $c = 6.295$ Å, $V = 830.3$ Å^3, $\beta = 97.886^o$ and $Z = 4$. **4** crystallized in the triclinic system with space group $P1$, with $a = 6.192$, $b = 7.740$, $c = 10.001$ Å, $V = 457.9$ Å^3, $\alpha = 89.073$, $\beta = 86.903$, $\gamma = 73.097^o$ and $Z = 2$.

Keywords Metronidazole (MET-OH) · Crystal structure · Halogenations · 4-Methyl-benzenesufonyl chloride

Introduction

MET-OH (Scheme 1) is one of the nitroimidazole derivatives that are an extremely important class of compounds. It is extensively used in the treatment of anaerobic infections and is under continuing investigation [1, 2]. Though widely used as an antibacterial medicine, it also has some side effects [3]. For example, the metabolism products of MET-OH can combine with nerve cell RNH, which may strengthen the excitement of the bronchus myocardial nerve fiber controlled by the RNH, extend the capillary vessel and increase the transparence, consequently it would cause the nervous system, respiration system, cardiovascular system, immune system(... etc. to work abnormally.

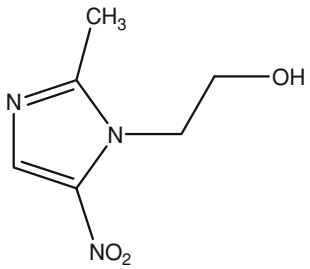
In order to overcome its disadvantages, a variety of compounds related to MET-OH with less toxicity needed to be synthesized. There is a hydroxyl group in the molecule of MET-OH, thus there are definitely lots of modifying measurements starting from this group. For example, changing the structure to the Tinidazole (Scheme 2) can make it more effective in the treatment of anaerobic fungus and diseases infected by ectosarc [4, 5]. However, as it is not so easy to change the hydroxyl directly into other functional groups, the hydroxyl group can be designed to be remodeled to -OTs group or halogen group firstly, consequently, the introduction of other more complex groups would become convenient. There some reports on the halogenations of the hydroxyl group in the literature [6–8], but the reaction condition is rather strict and the yield is rather low, here a more convenient and effective way to replace the hydroxyl group is presented and the structures of four intermediates (Scheme 3) were determined by X-ray crystallography report.

Experimental

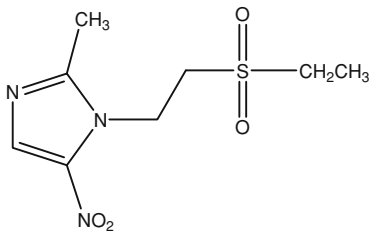
Materials and Physical Measurements

All chemicals and reagents used in current study were of analytical grade. MET-OH was purchased from Chan Zhou

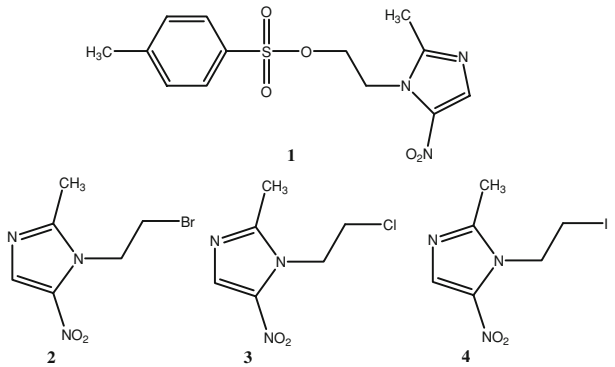
H.-Q. Li · Z.-P. Xiao · R.-Q. Fang · H.-L. Zhu (✉)
Engineering Research Center for Clean Production of Textile Dyeing and Printing, Ministry of Education, Wuhan University of Science and Engineering, Wuhan 430073, P. R. China
e-mail: zhuhl@nju.edu.cn



Scheme 1 Structure of Metronidazole



Scheme 2 Structure of Tinidazole



Scheme 3 Structures of compounds **1**–**4**

Dongsheng Company, Chan Zhou, P. R. China. TLC was run on the silica gel coated aluminum sheets (silica gel 60 GF_{254}, E. Merk, Germany) and visualized in UV light (254 nm). All the NMR spectra were recorded on a Bruker DRX 500 model Spectrometer in either DMSO-d_6 or $CDCl_3$. Chemical shifts (δ) for ^{1}H-NMR spectra are reported in parts per million to residual solvent protons. Melting points were measured on a Boetius micro melting point apparatus.

Preparations

Synthesis of 2-(2-methyl-5-nitro-imidazol-1-yl)-ethyl ester toluene-4-sulfonate (1) (Scheme 4)

MET-OH (3.14 g, 20 mmol) and Et_3N (3.0 mL, 22 mmol) were dissolved in CH_2Cl_2 (20 mL), and 4-methyl-benzenesufonyl chloride (3.83 g, 20.1 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred at 0 °C for 5 h, and 30 mL of ice water was added, the layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The organic layer was combined and washed with saturated $NaHCO_3$, and dried with anhydrous Na_2SO_4 for 0.5 h. Removal of the solvent gave a slight-yellow crystal of compound **1** (5.89 g, 18.1 mmol). Yield: 90%; Mp: 155–157 °C; ^{1}H NMR (DMSO-d_6): 2.40 (s, 3H, Ar–CH_3); 2.49 (s, 3H, –CH_3–); 4.38 (t, J = 9.72 Hz, 2H, N–CH_2–); 4.55 (t, J = 9.80 Hz, 2H, O–CH_2–); 7.38 (d, J = 7.97 Hz, 2H), 7.59 (d, J = 8.30 Hz, 2H); 7.92 (s, 1H).

Synthesis of 1-(2-bromoethyl)-2-methyl-5-nitro-1H-imidazole (2) (Scheme 4)

Compound **1** (6.54 g, 20.1 mmol) was dissolved in 30 mL of anhydrous DMF and the solution was stirred at 100 °C for 15 min. Then NaBr (5.2 g, 50 mmol) in anhydrous DMF (20 mL) was carefully added, after the mixed solution was stirred at 100 °C for 4 h, the mixture was cooled to 20 °C, and the solvent was removed under reduced pressure. The residue was suspended in EtOH (100 mL) and filtered, the solvent was removed under reduced pressure, and the residue was chromatographed. Elution with EtOAc gave an oil which recrystallized from EtOAc/petroleum ether (3/1) to give 1-(2-bromoethyl)-2-methyl-5-nitro-1H-imidazole (**2**) (3.28 g, 14 mmol). Mp: 78.5–79.5 °C; Yield: 70%; ^{1}H NMR (DMSO-d_6): 2.50 (s, 3H, –CH_3–); 3.51 (t, J = 8.68 Hz, 2H, N–CH_2–); 4.61 (t, J = 8.51 Hz, 2H, –CH_2–); 8.05 (s, 1H).

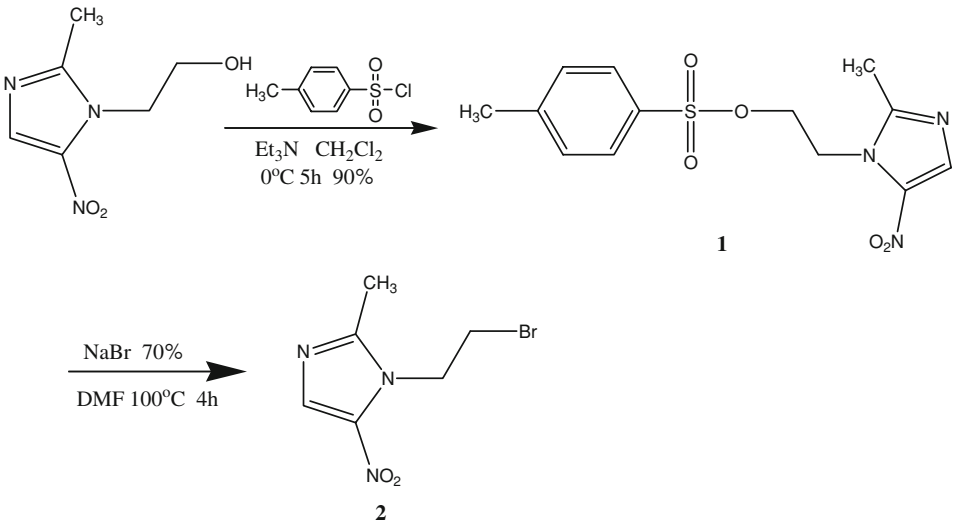
Synthesis of 1- (2-chloroethyl)-2-methyl-5-nitro-1H-imidazole (3) (Scheme 5)

MET-Cl was synthesized as the literary method [9] with slight changes. MET-OH (4.71 g, 30 mmol) was dissolved in $SOCl_2$ (11 mL, 0.15 mol), and the solution was stirred at 70 °C for 6 h and cooled. The solvents and excess $SOCl_2$ were then removed under reduced pressure. Compound **3** (4.98 g, 26.3 mmol) was obtained as a yellow crystal. Yield: 88%; Mp: 78.5–79.5 °C; ^{1}H NMR (DMSO-d_6): 2.49 (s, 3H, –CH_3–); 3.69 (t, J = 9.75 Hz, 2H, N–CH_2–); 4.95 (t, J = 9.88 Hz, 2H, –CH_2–); 8.35 (s, 1H).

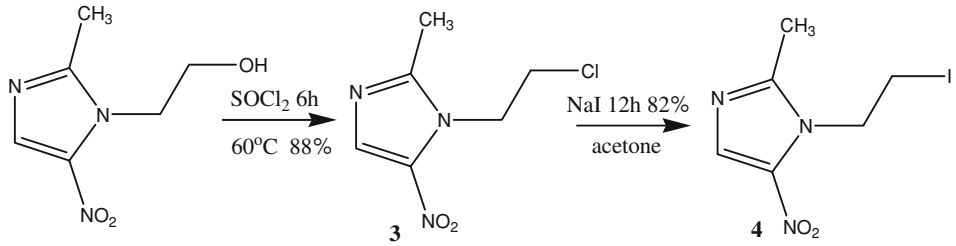
Synthesis of 1-(2-iodo-ethyl)-2-methyl-5-nitro-1H-imidazole (4) (Scheme 5)

MET-I was synthesized as the literary method [10] with slight changes. Compound **3** (10.43 g, 55.0 mmol) was dissolved in 30 mL of anhydrous acetone; the solution was stirred at 90 °C for 15 min. Then NaI (9.0 g, 60.0 mmol) in anhydrous acetone (20 mL) was carefully

Scheme 4 The synthetic route of compounds **1** and **2**



Scheme 5 The synthetic route of compounds **3** and **4**



added. After the mixed solution was stirred at 90 °C for 12 h, the solvents were removed and the residue recrystallized from chloroform gave compound **4** (12.70 g, 45.2 mmol) as a yellow solid. Yield: 82%; Mp: 78.5–79.5 °C; ^{1}H NMR (DMSO-d_6): 2.59 (s, 3H, –CH_3–); 3.89 (t, J = 11.25 Hz, 2H, N–CH_2–); 4.64 (t, J = 11.15 Hz, 2H, –CH_2–); 7.99 (s, 1H).

Results and Discussion

Syntheses of the Four MET Derivatives

In this paper, four MET derivatives: **1**, **2**, **3**, and **4** were synthesized from the metronidazole. Treatment of MET-OH with TsCl gave **1**, treatment of **1** with sodium bromide in DMF gave **2**, treatment of MET with thionychloride gave **3**, treatment of **3** with sodium iododide in anhydrous acetone gave **4**.

When the hydroxyl group was changed to -OTs, the ratio of the starting materials had great effect on the yield of the reaction. Both triethylamine and pyridine could act as the base in the reaction, the less poisonous triethylamine is chosen as the base in our study. The use of equivalent of triethylamine in the reaction is the most optimal, and dichloromethane is found to be the best solvent for the reaction that produced the highest yield. The bromization reaction with the intermediate **1** has also been carried out, the cheap sodium bromide is used as the brominating agent in DMF in place of phosphorus tribromide in the organic solvent, in thus condition the reaction could be easier to handle, which also supplied a new valuable method for the bromization.

As to the chlorination of the hydroxyl group, dichlorosulfoxide has been used as the chlorination reagent, the reaction is homogeneous and the reaction condition is milder in comparison to the literatures, the selectivity is also very good. The less poisonous dichlorosulfoxide compared to benzene is employed as the solvent and thus the reaction proceed under a comparatively low temperature, which made the reaction more controllable and milder.

Crystal Structures of Compounds **1–4**

Diffraction intensities for complexes **1–4** were collected on a CCD area detector diffractmeter equipped with graphite-monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation. The intensities were collected using the 2θ scan mode with variable scan speed. Crystal data were corrected for Lorentz and polarization effects during data reduction using XSCANS [11–13]. All the non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated geometrically and allowed to ride on their parent carbon atoms. Analytical expressions of neutral-atom scattering

Table 1 Crystallographic and experimental data for compounds **1–4**

Compound	**1**	**2**	**3**	**4**
Formula	C_{13} H_{15} N_3 O_5 S	$C_6H_8BrN_3O_2$	$C_6H_8ClN_3O_2$	$C_6H_8IN_3O_2$
FW	325.34	234.06	189.60	281.05
Crystal shape/color	Block/colorless	Prism/colorless	Prism/colorless	Prism/Pale yellow
Crystal size/mm	0.20 × 0.10 × 0.10	0.40 × 0.30 × 0.10	0.38 × 0.35 × 0.30	0.40 × 0.35 × 0.35
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	*P2₁/c*	*P2₁/c*	*P2₁/c*	P1
a/Å	16.1178	12.079	12.098	6.192
b/Å	7.5473	11.089	11.007	7.740
c/Å	13.4161	6.380	6.295	10.001
α/°				89.073
β/°	111.3210(10)	97.57	97.886	86.903
γ /°				73.097
V /Å^3	1520.3	847.1	830.3	457.9
Z	4	4	4	2
T/ K	292	293	298	298
μ/mm^{-1}(Mo-K*α*)	0.240	4.815	0.42	3.46
D_x/mg m^{-3}	1.421	1.835	1.517	2.039
Reflections/parameters	3469/201	1647/109	1895/110	1553/110
F(000)	680	464	429	675
T_{max}	0.9764	0.6445	0.890	0.298
T_{min}	0.9536	0.2490	0.850	0.265
θ range /°	2.71/27.50	1.70/25.95	1.70/28.33	2.04/25.00
Index range (*h*, *k*, *l*)	−20/20, −9/9, −17/17	−14/14, −13/0, 0/7	−16/14, −14/14, −6/8	−7/7, −7/9, −10/11
Reflections collected	3469	1647	1895	1553
Independent reflections	1647	960	1328	1410
Goodness of fit on F^2	1.051	1.050	1.004	1.060
R_1, wR_2 [I ≥ 2*σ*(I)][a)]	0.0485, 0.0598	0.0659, 0.1251	0.0503, 0.0711	0.0391, 0.0423

factors were employed, and anomalous dispersion corrections were incorporated. The crystallographic data were listed in Table 1.

Figures 1–4 gives a perspective view of the molecular structures of **1–4** together with the atomic labeling system. Counpound **1–3** crystallized monoclinically with space group *P2₁/c*, while MET-I **4** crystallized in the triclinic system with space group *P1*. For compound **1**, the imidazole ring (plane I) and the benzene ring (plane II) both are well-defined planes with an average deviation of 0.0010 Å for the former and 0.0051 Å for the later. The dihedral angles between the basal planes are as follows: 3.9° between plane I and the nitro plane; 10.3° between plane I and plane II; and 7.3° between the nitro plane and plane II.

In the molecules of compound **2–4**, the imidazole ring in each molecule is planar, with an average deviation of 0.0023 Å for compound **2**, 0.0016 Å for compound **3** and 0.0079 Å for compound **4**. The nitro N atom lays 0.059 Å of **2** (0.060 Å for **3**, 0.017 Å for **4**) above the plane. The two other groups attached to the ring are located on the opposite side of the plane, with displacements of 0.097 (for

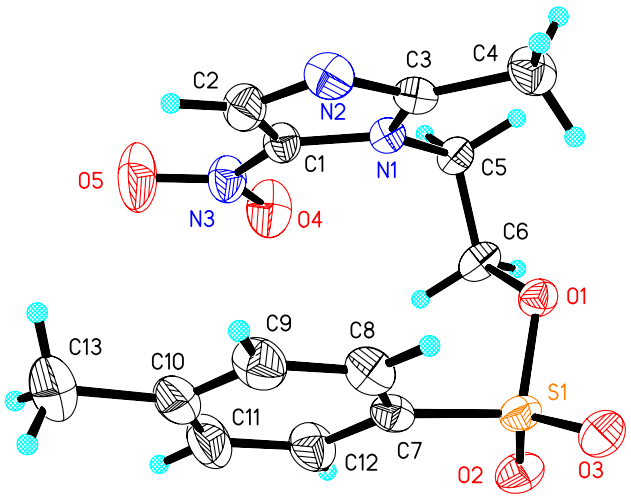


Fig. 1 Molecular structure of 1. The displacement ellipsoids are drawn at the probability level

C2) and 0.022 Å (for C3) from the plane of the ring of compound **2**, 0.144 (for C4) and 0.004 Å (for C6) of compound **3**, 0.229 (C5) and 0.027 Å (C4) of compound **4**,

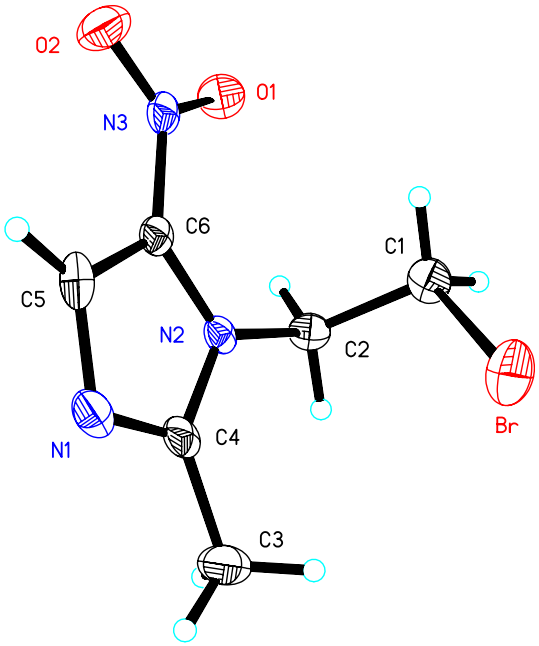


Fig. 2 Molecular structure of 2. The displacement ellipsoids are drawn at the probability level

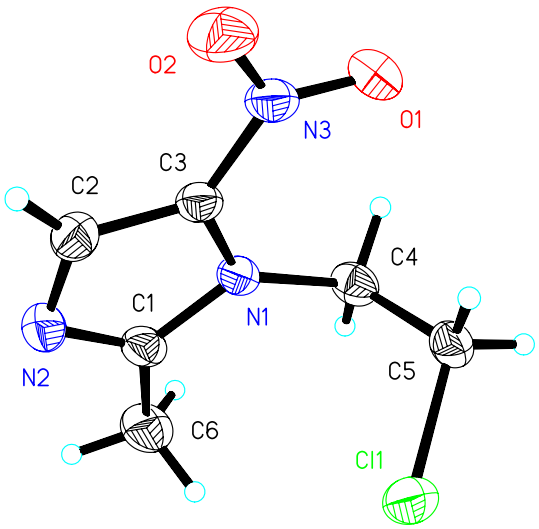


Fig. 3 Molecular structure of 3. The displacement ellipsoids are drawn at the probability level

respectively. The dihedral angle between the imidazole ring and the nitro plane is 6.6° for **2** (6.5° for **3**, 6.6° for **4**).

The selected bond distances and bond angles in **1–4** given in Table 2 are discussed as below. The crystal structures of compounds **2**, **3** and **4** are quite similar, they all consist of an imidazole ring, a nitro plane, and a halogen atom. As shown in table 1, the bond lengths of C–X are 1.897, 1.791 and 2.163 Å in **2**, **3**, and **4**, respectively, which well correspond to the size of the halogen atom and all conform to the normal value for the C–X bond. While for

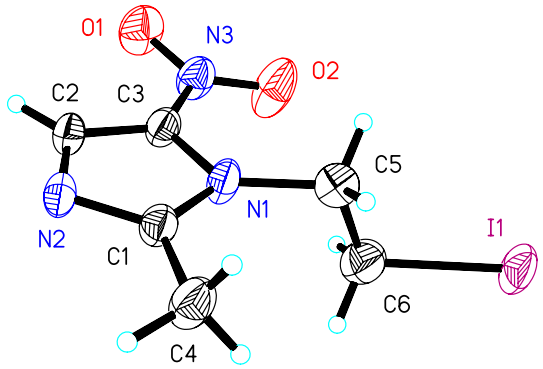


Fig. 4 Molecular structure of 4. The displacement ellipsoids are drawn at the probability level

Table 2 Selected bond lengths (Å) and angles (°) for **1–4**

MET-OTs (1)			
C(2)–C(1)	1.357	C(1)–N(3)	1.407
C(1)–N(1)	1.381	C(3)–N(1)	1.353
C(2)–N(2)	1.348	C(5)–N(1)	1.469
C(3)–N(2)	1.318	C(6)–O(1)	1.462
O(1)–C(6)–C(5)–N(1)	−63.35	O(5)–N(3)–C(1)–N(1)	5.3
O(4)–N(3)–C(1)–N(1)	2.9		
MET-Br (2)			
C(5)–C(6)	1.368	C(4)–N(2)	1.348
C(5)–N(1)	1.355	C(6)–N(3)	1.413
C(6)–N(2)	1.383	C(2)–N(2)	1.455
C(4)–N(1)	1.327	C(1)–Br(1)	1.897
Br(1)–C(1)–C(2)–N(2)	59.2	O(1)–N(3)–C(6)–N(2)	4.8
O(2)–N(3)–C(6)–N(2)	−176.1		
MET-Cl (3)			
C(2)–C(3)	1.366	C(1)–N(1)	1.365
C(2)–N(2)	1.343	C(3)–N(3)	1.407
C(3)–N(1)	1.382	C(4)–N(1)	1.465
C(1)–N(2)	1.339	C(5)–Cl(1)	1.791
Cl(1)–C(5)–C(4)–N(1)	60.3	O(1)–N(3)–C(3)–N(1)	4.4
O(2)–N(3)–C(3)–N(1)	−175.94		
MET-I (4)			
C(2)–C(3)	1.348	C(1)–N(1)	1.358
C(2)–N(2)	1.345	C(3)–N(3)	1.414
C(3)–N(1)	1.385	C(5)–N(1)	1.516
C(1)–N(2)	1.334	C(6)–I(1)	2.163
I(1)–C(6)–C(5)–N(1)	−179.9	O(2)–N(3)–C(3)–N(1)	8.3
O(1)–N(3)–C(3)–N(1)	−171.4		

compound **1**, the bond length of C–O is 1.462 Å, which is the shortest because the size of O atom is smaller than that of the halogen atoms.

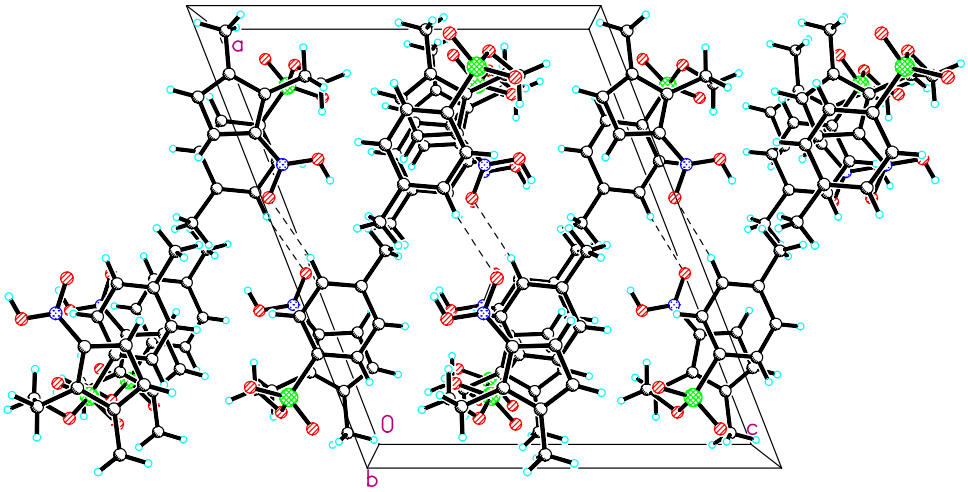


Fig. 5 The packing structure of compound **1** along the b-axis showing hydrogen bonds

In the imidazole ring, the double bond lengths of C–N are 1.318, 1.327, 1.339, and 1.334 Å; the double bond lengths of C–C are 1.357, 1.368, 1.366, and 1.348 Å in **1**, **2**, **3**, and **4**, respectively, typical of double bonds. The packing structure of compound **1** along the b-axis showing hydrogen bonds was listed in Fig. 5.

For compound **1**, the O(1)–C(6)–C(5)–N(1), O(5)–N(3)–C(1)–N(1), and O(4)–N(3)–C(1)–N(1) torsion angles in the central part of the molecule are −63.35, 5.3, and 2.9°, respectively. Correspondingly, they are 59.2, 4.8, −176.1; 60.3, 4.4, −175.94; −179.9, 8.3, −171.4° in compounds **2**, **3**, and **4**, respectively, and these are all in agreement with the values found in the analogous compound. Though the compounds **2**, **3** and **4** are iso-structures, the compound **4** crystallizes in a different crystal system with different set of unit cell parameters, while the isomorphism is clearly seen in **2** and **3** compounds. One of the causing factors is that N–C–C–X torsion angle. In the **2** and **3** compounds it is the gauche+ range whereas it got transformed to trans region in **4**.

Supplementary Material

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) (E-mail: deposit@ccdc.cam.ac.uk) as supplementary material and the CCDC numbers are 609616 (MET-Br) & 609617 (MET-OTs).

References

1. Cavalcanti JCM, De Abreu FC, Oliveira NV, De Moura MABF, Chaves JG, Alves RJ, Bertinaria M, Fruttero R, Goulart MOF (2004) Bioelectrochemistry 63:353–357
2. Welch DE, Vatne RD (1968) J Med Chem 11:370–371
3. Pope AJ, Toseland N, Rushant B (1998) Digest Dis Sci 43:109–119
4. Ando T, Minami M, Mizuno T, Watanabe O, Ishiguro K, Ina K, Kusugami K, Nobata K, Nishiwaki T, Tsuzuki T, Shimada M, El-Omar E, Goto H (2005) Helicobacter 10:379–384
5. Crossley M, Thordarson P, Hunter N, Yap B, Collyer CA (2006) Pct Int Appl 85 pp
6. Kajfez F, Sunjic V, Kolbah D, Fajdiga T, Oklobdzija M (1968) 1-Substitution in 2-methyl-4(5)-nitroimidazole. I. J Med Chem 11:167–169
7. Hay MP, Lee HH, Wilson WR, Roberts PB, Denny WA (1995) J Med Chem 38:1928–1941
8. Clayton R, Ramsden CA (2005) Synthesis 16:2695–2700
9. Pi WX, Yang YM, Li HQ, Zhu HL (2005) Acta Crystallogr E E61:o2880–o2881
10. Yang YM, Li HQ, Shi L, Zhu HL (2005) Acta Crystallogr E, E61:o2882–o2883
11. Sheldrick GM (1997a) SHELXL97 and SHELXS97. University of Göttingen, Germany
12. Sheldrick GM (1997b) SHELXTL. Version 5.1. Bruker AXS Inc., Madison, Wisconsin, USA
13. Siemens (1996) SMART and SAINT. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA