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ORIGINAL PAPER

Synthesis and Crystal Structure of Two Diflunisal Carboxamides

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Abstract The title compounds, 2′,4′-difluoro-4-[(4-methylbenzoyl)oxy]-*N*-[4-nitro-3-(trifluoromethyl) phenyl]-[1, 1′-biphenyl]-3-carboxamide **2a** and 2′,4′-difluoro-4-[(4-chlorobenzoyl)oxy]-*N*-[4-nitro-3-(trifluoromethyl)phenyl]-[1, 1′-biphenyl]-3-carboxamide **2b**, synthesized from diflunisal, a registered anti-inflammatory drug, *via* amidation of carboxlic acid and esterification of phenolic hydroxy group and recrystallized from butanone-ethanol, were confirmed by single-crystal X-ray diffraction [CCDC 753735 and 753736]. The **2a** crystallizes in triclinic space group P$\bar{1}$ with cell parameters $a = 10.562(2)$ Å, $b = 10.696(2)$ Å, $c = 11.061(2)$ Å, $\alpha = 80.503(7)°$, $\beta = 84.722(7)°$, $\gamma = 73.553(7)°$ and $Z = 2$. The **2b** crystallizes in triclinic space group P$\bar{1}$ with cell parameters $a = 9.348(3)$ Å, $b = 11.150(3)$ Å, $c = 11.798(4)$ Å, $\alpha = 106.627(4)°$, $\beta = 93.223(4)°$, $\gamma = 91.579(5)°$ and $Z = 2$. Their packing are stabilized by intermolecular N–H···O hydrogen bonds.

Keywords Diflunisal derivative · Crystal structure · X-ray diffraction · Amidation · Esterification

Introduction

Fluorine-containing drugs, such as tegadifur [1, 2], flutamide [3, 4], ciprofloxacin [5, 6], non-steroid anti-inflammatory drugs [7–9] have been attractive for their special properties. Diflunisal (**1**, CAS 22494-42-4), 2′,4′-difluoro-4-hydroxybiphenyl-3-carboxylic acid, a registered anti-inflammatory drug, has been approved worldwide as therapeutics for the treatment of inflammation and pain [10, 11]. Recently, the modifications of the chemical structure of **1** were studied. For example, 3-(1,3-dihydro-2*H*-isoindol-2-ylcarbonyl)-2′,4′-difluorobiphenyl-4-ol was synthesized and reported to have the H3P-90 inhibition, and H3P-90 in abnormal cells, such as in cancer cells would damage the regulation of signal transduction network [12]. Yu CX reported that esterification or amidation of **1** could increase their solubility and absorption in vivo, and some of them have even better analgesic activity than that of **1** [13]. Some changes in the carboxyl group of **1** also showed good antimycobacterial, antiviral and antimicrobial activities [14]. Roberts found that *O*-aryl esters of **1**, especially lipophilic esters possess large permeability surface area and tissue distribution value [15]. Zhong GX discovered that some amide derivatives of **1** exhibited potent anti-inflammatory, analgesic and anti-tumor activity [16–18].

A convenient synthetic route for title compounds (**2**) was outlined in Scheme 1. Starting from **1**, amidation of carboxlic acid and esterification of phenolic hydroxy group gave the desired product **2**. The anti-tumor activity are affected by the properties of R in compound **2** [18], so the knowledge of the structural characteristic of these analogues is of the utmost importance of the understanding of the quantitative structure–activity relationships (QSARs) underlying their biological activity. Encouraged by the aforementioned information, it was considered valuable to synthesize compounds **2a** and **2b** characterized by X-ray studies.

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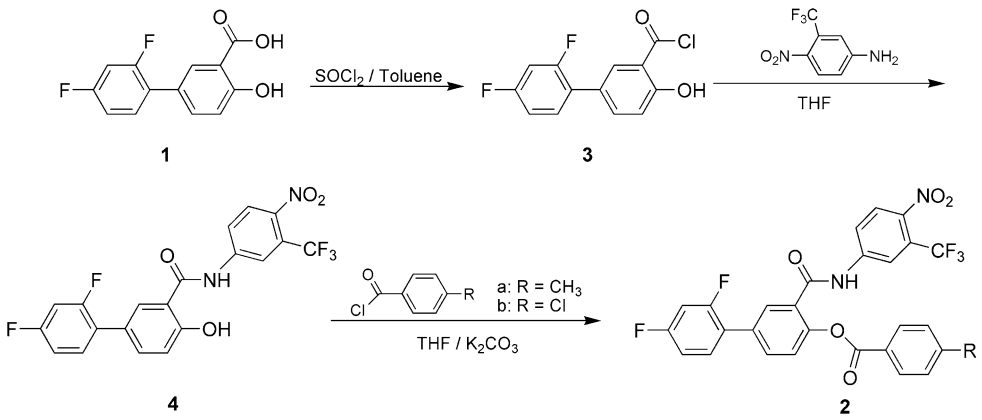
Scheme 1 Route of synthesis of diflunisal carboxamides **2**



Experimental

2′,4′-Difluoro-4-Hydroxy-*N*-[4-Nitro-3-(Trifluoromethyl)phenyl]-[1,1′-Biphenyl]-3-Carboxamide (**4**)

A mixture of compound diflunisal **1** 12.7 g (0.05 mol) and $SOCl_2$ 11.9 g (0.1 mol) in 70 ml toluene was reacted for 7 h at 80 °C prior to work up to give compound **3**. The compounds **4** (18.2 g) was prepared by reaction of **3** with 4-nitro-3-(trifluoromethyl)phenylamine 10.3 g (0.05 mol) and K_2CO_3 12.4 g (0.05 mol) in 120 ml THF at room temperature for 12 h, in 83% total yields based on the diflunisal. Recrystallized with butanone to get white solid. m.p. 175–176 °C. ^{1}H NMR ($CDCl_3$): δ 6.96 (t, 1H, J = 8.5 Hz, 3′-H), 6.99 (t, 1H, J = 8.5 Hz, 5′-H), 7.16 (d, 1H, J = 8.5 Hz, 5-H), 7.40 (q, 1H, J = 8.5 Hz, 6′-H), 7.63 (d, 1H, J = 8.0 Hz, 6-H), 7.68 (s, 1H, 2-H), 8.05 (d, 1H, J = 8.0 Hz, 5″-H), 8.09 (s, 1H, 2″-H), 8.11 (d, 1H, J = 8.0 Hz, 6″-H, 8.29 (s, 1H, –NH), 11.30 (s, 1H, –OH). MS: *m/z* 438(M^+, 12.93), 233(100), 232 (89.69), 204 (18.02), 177 (28.11), 151 (25.23), 63 (4.45), 53 (16.24); Anal. Calcd. for $C_{20}H_{11}F_5N_2O_4$: C, 54.81; H, 2.53; N, 6.39. Found: C, 54.69; H, 2.48; N, 6.30 [18].

2′,4′-Difluoro-4-[(4-Substitutedbenzoyl)oxy]-*N*-[4-Nitro-3-(Trifluoromethyl)phenyl]-[1,1′-Biphenyl]-3-Carboxamide(**2**)

A solution of 4-substituted benzoyl chloride (0.02 mol) in THF (20 mL) was added dropwise into a solution of **4** 8.77 g (0.02 mol) and K_2CO_3 2.77 g (0.02 mol) in $CHCl_3$ (60 ml) at room temperature, and the reaction was allowed to processed with stirring for an additional about 12 h (monitored by TLC). After filtrating and evaporation of THF in vacuum, the crude material was washed with alcohol, recrystallized with butanone and ethanol to afford crystal **2**.

Compound **2a** (R = CH_3): yield 84%, yellowish crystalline solid, m.p. 178–179 °C. ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, CH_3), 6.97 (t, 1H, J = 8.5 Hz, 3′-H), 7.01 (t, 1H, J = 8.5 Hz, 5′-H), 7.39 (d, 2H, J = 8.0 Hz, 3‴,5‴-H), 7.41 (d, 1H, J = 8.5 Hz, 5-H), 7.48 (q, 1H, J = 8.5 Hz, 6′-H), 7.61 (s, 1H, 2″-H), 7.78 (d, 1H, J = 8.5 Hz, 6-H), 7.92 (d, 1H, J = 8.0 Hz, 6″-H), 8.06 (d, 1H, J = 8.5 Hz, 5″-H), 8.13 (d, 2H, J = 8.0 Hz, 2‴,6‴-H), 8.19 (s, 1H, 2-H), 8.89 (s, 1H, –NH). MS: *m/z* 556 (M^+, 0.11), 391 (0.52), 351 (2.09), 232 (3.89), 204 (5.86), 175 (6.04), 119 (100.00), 91 (56.85); Anal. Calcd. for $C_{28}H_{17}F_5N_2O_5$: C, 60.44; H, 3.08; N, 5.03. Found: C, 60.29; H, 3.02; N, 4.93.

Compounds **2b** (R = Cl): yield 79%, yellowish crystalline solid, m.p. 198–200 °C. ^{1}H NMR ($CDCl_3$): δ 6.97 (t, 1H, J = 8.5 Hz, 3′-H), 7.01 (t, 1H, J = 8.5 Hz, 5′-H), 7.39 (d, 1H, J = 8.5 Hz, 5-H), 7.48 (q, 1H, J = 8.5 Hz, 6′-H), 7.54 (d, 2H, J = 8.5 Hz, 3‴,5‴-H), 7.76 (d, 1H, J = 8.0 Hz, 6-H), 7.77 (s, 1H, 2″-H), 7.93 (d, 1H, J = 8.5 Hz, 6″-H), 7.99 (d, 1H, J = 8.5 Hz, 5″-H), 8.04 (s, 1H, 2-H), 8.15 (d, 2H, J = 8.5 Hz, 2‴,6‴-H), 8.56 (s, 1H, -NH). IMS: *m/z* 576 (M^+, 0.08), 420 (3.14), 371 (1.29), 232 (4.31), 204 (4.99), 175 (6.03), 139 (100), 111 (26.33), 75 (9.67). Anal. Calcd. for $C_{27}H_{14}ClF_5N_2O_5$: C, 56.22; H, 2.45; N, 4.86. Found: C, 56.11; H, 2.36; N, 4.79.

Crystal Structure Determination of **2**

Single-crystal X-ray diffraction measurement for **2a** of dimensions 0.37 mm × 0.37 mm × 0.20 mm was carried out Rigaku AFC10 Saturn 724 + diffractometer with graphite-monochromated MoKa radiation (λ = 0.71073Å) [19]. Intensity data were collected up to a θ_{max} of 27.49° by the $\omega/2\theta$ scan. A total of 11876 reflections were collected, resulting in 5345 independent reflections of which 3845 had $I > 2\sigma(I)$ and these are considered as observed. The ranges of *h, k, l* are $-13 \le h \le 13$, $-13 \le k \le 13$, $-14 \le l \le 14$.

A single crystals of **2b** of dimensions 0.57 mm × 0.37 mm × 0.37 mm was chosen for X-ray diffraction studies on the same instrument. Intensity data were collected up to a θ_{max} of 27.49° by the $\omega/2\theta$ scan. A total of 11915 reflections were collected, resulting in 5320 independent reflections of which 4197 had $I > 2\sigma(I)$ and these

Table 1 Crystal data and experimental crystallographic details

Compound	**2a**	**2b**
R	CH_3	Cl
Empirical formula	$C_{28}H_{17}F_5N_2O_5$	$C_{27}H_{14}ClF_5N_2O_5$
Formula weight	556.44	576.86
Temperature (K)	93(2)	93(2)
Wavelength	$\lambda = 0.71073$ Å	$\lambda = 0.71073$ Å
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
Cell dimensions		
a (Å)	10.562(2)	7.6199(13)
b (Å)	10.6958(17)	32.133(6)
c (Å)	11.061(2)	9.8079(17)
α (°)	80.503(7)	90
β (°)	84.722(7)	94.048(2)
γ (°)	73.553(7)	90
Volume (Å^3)	1180.7(4)	2395.5(7)
Z	2	2
Density(calculated) (Mg/m^3)	1.565	1.604
Absorption coefficient (mm^{-1})	0.134	0.222
$F000$	568	1176
Crystal size	0.37 × 0.37 × 0.20 mm	0.53 × 0.37 × 0.37 mm
θ range for data collection	3.21–27.48	3.28–27.48
Index ranges	$-13 \le h \le 13$,	$-9 \le h \le 9$,
	$-13 \le k \le 13$,	$-41 \le k \le 36$,
	$-14 \le l \le 14$	$-12 \le l \le 12$
Reflections collected	11876/5345	19174/5479
	[R(int) = 0.0268]	[R(int) = 0.0295]
Independent reflections	5345	5479
Completeness to $\theta = 27.48$	98.6%	99.8%
Absorption correction	Empirical	Empirical
Max. and min. transmission	0.9737 and 0.9524	0.9228 and 0.8906
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	5345/0/366	5479/0/365
Goodness-of-fit on F^2	1.000	0.999
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0363$,	$R1 = 0.0338$,
	$wR2 = 0.0741$	$wR2 = 0.0752$
R indices (all data)	$R1 = 0.0562$,	$R1 = 0.0433$,
	$wR2 = 0.0805$	$wR2 = 0.0795$
Largest diff. peak and hole (e Å^{-3})	0.331 and −0.223	0.379 and −0.376
CCDC deposit no.	753735	753736

are considered as observed. The ranges of h, k, l are $-11 \le h \le 12$, $-14 \le k \le 14$, $-15 \le l \le 15$.

The details of crystal data and refinement are given in Table 1.

Results and Discussion

Both structures were solved by direct methods procedures as implemented in SHELXS97 program. [20] The positions of all the non-hydrogen atoms were included in the full-matrix least-squares refinement using SHELXL97 program [21].

Table 2 gives the bond distances and angles of non-hydrogen atoms for **2a** and **2b**, respectively. Figure 1 represents the ORTEP diagram [22] of the molecule **2a** and **2b** with thermal ellipsoids at 50% probability. H atoms were included at calculated positions and refined using a riding model. H atoms were given isotropic displacement parameters equal to 1.2 times (1.5 times for methyl) the

Table 2 Selected lengths (Å) and bond angles (°) of **2a** versus **2b**

Bond length	**2a**	Bond length	**2b**
C(17)–C(20)	1.506(2)	Cl(1)–C(17)	1.7375(16)
F(1)–C(1)	1.3564(17)	F(1)–C(1)	1.3554(17)
F(2)–C(3)	1.3650(17)	F(2)–C(3)	1.3592(18)
F(3)–C(28)	1.3468(17)	F(3)–C(27)	1.3449(17)
F(4)–C(28)	1.3415(18)	F(4)–C(27)	1.3465(17)
F(5)–C(28)	1.3430(18)	F(5)–C(27)	1.3394(18)
O(1)–C(13)	1.3662(17)	O(1)–C(13)	1.3548(18)
O(1)–C(10)	1.4005(18)	O(1)–C(10)	1.4076(17)
O(2)–C(13)	1.2093(18)	O(2)–C(13)	1.2098(19)
O(3)–C(21)	1.2206(18)	O(3)–C(20)	1.2220(17)
O(4)–N(2)	1.2316(18)	O(4)–N(2)	1.2314(16)
O(5)–N(2)	1.2244(18)	O(5)–N(2)	1.2304(17)
N(1)–C(21)	1.3738(19)	N(1)–C(20)	1.3682(19)
N(1)–C(22)	1.4017(19)	N(1)–C(21)	1.4038(18)
N(1)–H(1N)	0.878(19)	N(1)–H(1N)	0.883(18)
N(2)–C(25)	1.473(2)	N(2)–C(24)	1.4700(18)
Band angle	**2a**	Band angle	**2b**
C(18)–C(17)–C(16)	117.76(15)	C(18)–C(17)–C(16)	121.90(15)
C(18)–C(17)–C(20)	120.25(15)	C(18)–C(17)–Cl(1)	119.47(13)
C(16)–C(17)–C(20)	122.00(15)	C(16)–C(17)–Cl(1)	118.63(13)
C(13)–O(1)–C(10)	122.52(11)	C(13)–O(1)–C(10)	117.18(12)
C(21)–N(1)–C(22)	126.73(13)	C(20)–N(1)–C(21)	125.84(12)
C(21)–N(1)–H(1N)	114.4(12)	C(20)–N(1)–H(1N)	119.0(12)
C(22)–N(1)–H(1N)	117.5(12)	C(21)–N(1)–H(1N)	115.2(12)
O(5)–N(2)–O(4)	124.34(14)	O(5)–N(2)–O(4)	124.26(12)
O(5)–N(2)–C(25)	118.46(14)	O(5)–N(2)–C(24)	118.27(12)
O(4)–N(2)–C(25)	117.14(14)	O(4)–N(2)–C(24)	117.38(13)
F(1)–C(1)–C(2)	117.24(14)	F(1)–C(1)–C(2)	117.20(14)
F(1)–C(1)–C(6)	118.77(14)	F(1)–C(1)–C(6)	118.96(13)
F(2)–C(3)–C(2)	118.08(15)	F(2)–C(3)–C(2)	117.62(14)
F(2)–C(3)–C(4)	118.40(14)	F(2)–C(3)–C(4)	119.38(14)
F(3)–C(28)–C(24)	110.40(12)	F(3)–C(27)–C(23)	111.07(12)
F(4)–C(28)–F(3)	105.89(12)	F(3)–C(27)–F(4)	105.97(12)
F(4)–C(28)–F(5)	107.50(12)	F(5)–C(27)–F(4)	107.10(12)
F(5)–C(28)–F(3)	106.18(12)	F(5)–C(27)–F(3)	106.12(12)
F(4)–C(28)–C(24)	113.02(13)	F(4)–C(27)–C(23)	112.33(12)
C(9)–C(10)–O(1)	122.74(14)	C(9)–C(10)–O(1)	117.94(13)
C(11)–C(10)–O(1)	115.48(13)	C(11)–C(10)–O(1)	120.39(12)
O(2)–C(13)–O(1)	122.93(14)	O(2)–C(13)–O(1)	122.86(13)
O(2)–C(13)–C(14)	126.85(14)	O(2)–C(13)–C(14)	124.56(14)
O(1)–C(13)–C(14)	110.21(12)	O(1)–C(13)–C(14)	112.58(13)
C(27)–C(22)–N(1)	123.88(14)	C(26)–C(21)–N(1)	122.48(14)
C(23)–C(22)–N(1)	116.72(13)	C(22)–C(21)–N(1)	117.96(12)
C(26)–C(25)–N(2)	116.65(13)	C(25)–C(24)–N(2)	116.16(13)
C(24)–C(25)–N(2)	122.51(14)	C(23)–C(24)–N(2)	122.16(13)

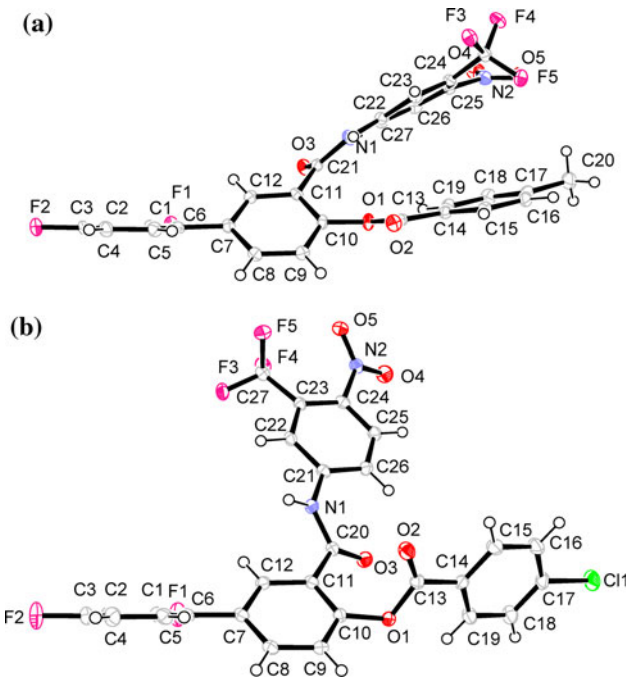


Fig. 1 ORTEP of **2a** (*the upper molecule*) versus **2b** molecules at 50% probability

equivalent isotropic displacement parameters of their parent atoms, and C–H distances were set to 0.95 Å for the benzene H atoms and 0.98 Å for the methyl H atoms. After refinement, the hydrogen atoms were placed at chemically acceptable positions.

From Fig. 1, the atoms of C1–C6, F1 and F2 are almost coplanar, deviating from the mean plane within 0.005(12) and 0.0139(13) Å, respectively for **2a** and **2b**. The different *para*-substituent of the benzene rings C14–C19 can cause the distinct configuration. In **2a**, the benzene ring C14–C19 and C20, O1 are almost coplanar deviating within 0.0703(12) Å, and the deviation of the carbonyl O2 from the plane is 0.1441 (17) Å. But the atoms C13, C14, O1 and O2 lie on the same plane. By contrary, in **2b**, the atoms C13–C19, O1, O2 and Cl1 are coplanar, deviating from the mean plane within 0.0448(9) Å. There is an interesting phenomenon that both adjacent substituent (C10 and C11 of the parent ring) remove away or reverse each other, and the reason may be the Cl atom showing greater repulsive force to the triflurometyl group than methyl group.

From Fig. 2, [23] intermolecular hydrogen bonding (Table 3) helps to stabilize the crystal structure. In both crystal packing, N–H···O hydrogen bonds contribute to the formation of the crystals. In **2a** and **2b,** two molecules form stacks in a head-to-tail manner by N1–H1···O2 intermolecular hydrogen bonds to form dimer, and those dimers interact other dimers to form network.

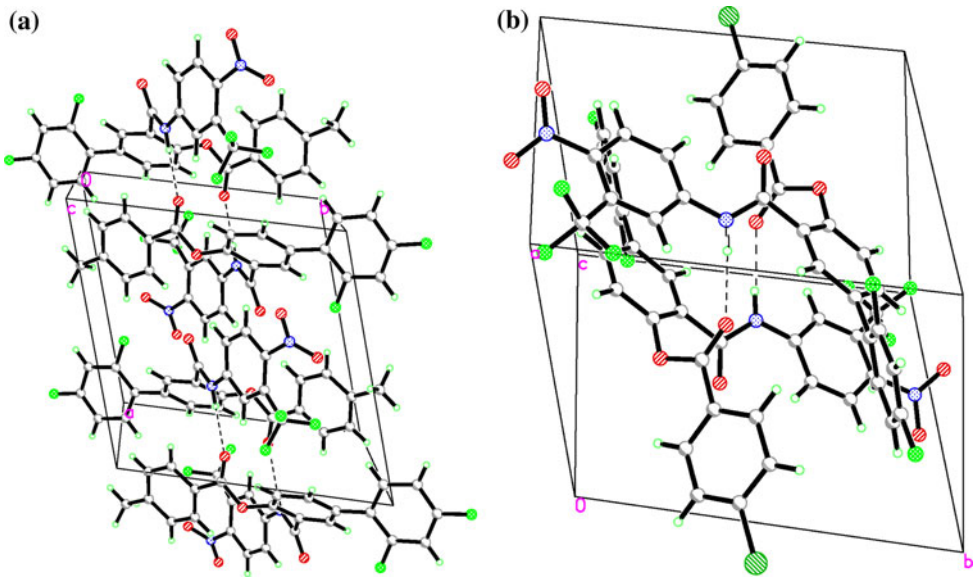


Fig. 2 Packing of **2a** (*the upper molecule*) versus **2b** down *c* and *a*-axis, respectively *Dashed lines* represent the hydrogen bonds

Table 3 Hydrogen-bonding geometry (Å, °)

Compound	D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
2a	N1–H1···O2[a]	0.878	2.101(0)	2.967(1)	168.75(2)
2b	N1–H1···O2[b]	0.883	2.071(0)	2.950(1)	173.53(1)

Symmetry codes: (a) $-x$; $1-y$; $1-z$; (b) $1-x$, $1-y$, $1-z$

As a result, the similar molecules **2a** versus **2b** show some distinct configuration which maybe affect on the anti-tumor activity which are worth to research the SARs in the future.

Supplementary Material

CCDC-753735 and 753736 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk.

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